Joshua Lederberg

1925-2008

(Harald Brüssow)

Source: Wikipedia

Joshua Lederberg was born 1925 in New Jersey into a poor Jewish family that had emigrated from Palestine. A precocious child endowed with voracious reading skills, a phenomenal memory and wide interests, he earned a scholarship for Columbia University, where he studied mold genetics with F. Ryan. The seminal work of O. Avery and colleagues on transformation of *Pneumococcus* bacteria with naked DNA aroused his interest for bacterial genetics. At the time, bacteria were considered as clonal organisms without sex. Lederberg wanted to test whether they showed Mendelian genetics as higher organisms. In a collaboration with E. Tatum at Yale University, who had developed nutritional mutants in *Escherichia coli* strain K-12, Lederberg brought two distinct *E. coli* strains into contact, each showing three but distinct nutritional deficiencies. By plating them on different media, he observed a small, but significant number of colonies that could grow in the absence of all six nutrients needed by the two parental mutant strains, indicating a recombination to wildtype between the two parental strains. Multiple genetic reversions were statistically highly unlikely. Further experiments excluded cross-feeding with nutrients produced by the other strain and also transformation by naked DNA exchanged between the strains was dismissed. Later experiments showed that close physical contact between bacterial cells was needed. Tatum and Lederberg had thus discovered bacterial recombination through a process called conjugation. This observation was a scientific bombshell when first announced at a Cold Spring Harbor meeting.

He got in 1947 a call for an assistant professorship at the University of Wisconsin where, with gifted colleagues, he laid the foundations for bacterial genetics. With N. Zinder he demonstrated that phage P22 could transfer any genetic information from a *Salmonella typhimurium* donor to a recipient strain by a process called generalized transduction. With his wife Esther, he described lysogeny with phage lambda in *E. coli* K-12. They described transfer of bacterial DNA located near the integration site of phage lambda DNA into the bacterial chromosome in a process called specialized transduction. With L. Cavalli he reported an "infectious fertility factor" in *E. coli* K-12 that led to the discovery of plasmids and sex-like conjugation systems. Lederberg developed important technical tools like replica plating of bacterial colonies (with which he demonstrated that mutations occurred spontaneously before exposure to selection conditions) and a color test for enzymatic assays (which later became crucial for the study of the *lac* operon). No wonder that he was elected member of the US Academy of Science in 1957.

In 1957 Lederberg broadened his scientific interests into areas that appeared to outsiders diverse and unlinked but represented work that foreshadowed activities that became topical research areas decades later. As a visiting professor in the lab of the eminent Australian immunologist MacFarlane Burnet, he helped develop the clonal selection theory of antibody production by lymphocytes. He founded with Carl Sagan the field of exobiology (extraterrestrial biology) and advocated at NASA the sterilization of space vehicles before launch to avoid contamination of the moon and also after return from space mission to earth to prevent epidemics with unknown space microbes. He founded the first Medical Genetics department at Wisconsin University where he foresaw developments which became later known as translational medicine.

With such prodigious activities, nobody was surprised that he received together with E. Tatum and G. Beadle the Nobel Prize in 1958 at the age of 33, being one of the youngest Nobel laureate of any discipline. At Standford, Lederberg recruited scientists with diverse expertise that developed new tools that laid the foundation to the fluorescence-activated cell sorter (FACS) and instruments used in 1975 on board of the Viking Landers, designed to detect signs of biological activity on Mars. He also created a Molecular Medicine department at Stanford offering courses in Human Biology.

In the 1960s, Lederberg realized the power of computing, learning himself to write computer programs and, with the eminent chemist C. Djerassi, developed a theory to represent organic molecular structures in graphs. Working wiith early computer scientists, he developed DENDRAL, a dendritic algorithm striving to emulate inductive reasoning through what we would call today artificial intelligence. He formulated the Lederberg principle where a really smart machine can read the literature and spend some time in the real world where the survival of the fittest program is selected. One direct goal of these activities was to deduce chemical structures from mass spectrometric data. His computing efforts also helped in the analysis of the scientific literature by citation indexing. Prophetically he predicted that "biology, in particular, will soon suffocate in the sheer bulk of knowledge about DNA and protein structures, and the complex interactions of the causal chains they initiate, unless new epistemological machinery can be invented."

In 1978 Lederberg became president of the Rockefeller University, a position which he held until his retirement at 65. In parallel to his scientific activities, Lederberg attributed much time to public activities. Between 1966 and 1971, he wrote weekly editorial columns for *The Washington Post* entitled "Science and Man". He served as a science advisor to nine US presidents. He warned on the threats of bioterrorism and emerging and re-emerging infectious diseases and co-chaired a report in 1992, which helped the US Centers for Disease Control and Prevention to expand and to become a central pillar for international public health.

Joshua Lederberg belongs to the towering visionary scientists of the 20th century, laying the foundations of modern biology with nearly prophetic farsightedness. He personified the post-war American liberal feeling the responsibility of an expert to guide government action to improve society. He died in 2008 shortly after signing his last paper.