MEMORIAL RESOLUTION
ESTHER MIRIAM LEDERBERG
(1922-2006)

Esther Miriam Lederberg, emeritus professor of microbiology and immunology, at Stanford University died November 11, 2006. She was born Esther Miriam Zimmer in the Bronx borough of New York City on December 16, 1922. Esther won a scholarship to attend Hunter College. She initially intended to study literature, but to everyone's surprise, she majored in biochemistry instead. After her graduation from Hunter in 1942, she came to Stanford University to study genetics. Esther worked part time as a biology teaching assistant to support herself, and it is said that she supplemented her modest earnings by dining on frogs' legs from dissection class. She earned her master's degree in genetics from Stanford in 1946.

Soon afterwards she met the brilliant young microbiologist, Joshua Lederberg, and joined him as his wife and as his research associate at the University of Wisconsin, Madison where she received a Ph.D. in 1950. Joshua Lederberg and Edward Tatum had showed that the bacterium *Escherichia coli* entered a sexual phase, during which it could share genetic information through cell-to cell contact (bacterial conjugation). This was a revolutionary discovery and, for the first time, permitted some mapping of the *E. coli* chromosome. Joshua Lederberg, while still a medical student received his Ph.D. from Yale University in 1947, but instead of returning to medical school, he took a faculty position at Wisconsin where he and Esther formed an extraordinary team.

Esther published her first seminal discovery of a bacterial virus she called lambda in 1950. The lambda phage and its relatives became a useful model for studying the biology of all viruses and was an essential tool for studying gene regulation and genetic recombination. Lederberg's phage was "temperate" and lived silently in the chromosome of the bacterium. It is a testimony to Esther's extraordinary talents of observation, and as Louis Pasteur once noted the possession of a "prepared mind," that Lederberg first suspected that *E. coli* carried a silent virus by noticing that some bacterial colonies looked as if they were "moth eaten." Only when lambda-infected bacteria became stressed did the phage become virulent and replicated at the expense of its bacterial host, bursting out and seeking new healthy bacterial cells to maintain its life cycle. This work eventually laid the foundation for showing how bacterial viruses can transfer genes between even dissimilar bacteria. Moreover, in time, the lambda phage became the laboratory model for studying animal viruses that have a similar lifestyle such as the herpes virus and some tumor viruses.

In 1952, Esther and Josh Lederberg made a brilliantly simple discovery of a technique that became known as replica plating. This method was essential in the study of bacterial genetics, more specifically in the selection of mutants from among hundreds of bacterial colonies on a plate. This method offered an accessible way to study how

chromosomes behave, how mutations occur and how these changes can be easily tracked in the laboratory. It is said that the initial feasibility experiment employed the powder puff from Esther's compact to validate the technique.

In practice a sterilized square of velvet is pressed onto a glass dish containing hundreds of colonies, each of which is derived from a single bacterium. By pressing the velvet, like pressing a rubber stamp onto an ink pad, the tiny fibers of the velveteen acted like hundreds of tiny inoculating needles. The pad was carefully kept in the same orientation and was used to inoculate a series of agar plates containing different growth elements, containing antibiotics or supplemented with essential nutrients such as amino acids and vitamins. If the replica plate lacked a specific nutrient, only the mutant unable to make a colony would not appear on the replica of the original culture. Similarly if the replica dish contained an antibiotic, only a mutant that was resistant to that antibiotic would flourish. The technique definitively proved that antibiotic resistance was already spontaneously present in the colonies and was not, as many scientists believed at the time, developed only by exposure to the antibiotic.

During her time in Wisconsin Esther Lederberg also discovered the fertility factor, F, and published the work with Joshua and Luigi Luca Cavalli-Sforza. F was the mediator of bacterial conjugation and possessed surprising phage-like similarities, although it was clearly not a virus. Subsequently, this led to the understanding that bacteria possessed a battery of mobile genetic elements, plasmids, transposons and viruses, freely shared among even diverse microbes, which served as a major source of biological variation and as a foundation for the evolution of bacterial specialization ranging from nitrogen fixation to bacterial pathogenicity. In 1956, the Society of Illinois Bacteriologists awarded Joshua Lederberg and Esther Lederberg the Pasteur Medal, for "their outstanding contributions to the fields of microbiology and genetics." It was this work, as well as his discovery of bacterial conjugation and bacterial transduction with Norton Zinder, that won Joshua Lederberg the Nobel Prize in 1958.

The following year Esther came back to Stanford when Joshua became the founder and chairman of the Department of Genetics. Despite her independent seminal contributions in Joshua's laboratory, which surely led, in part, to his Nobel Prize, Esther was not offered a faculty position at Stanford but rather was named a research associate in the Department of Medical Microbiology (renamed the Department of Microbiology and Immunology in 1980). In order to receive a faculty appointment, the story goes, Esther and two other women went to the dean to demand he appoint at least one woman to the faculty. She got the job, for which she was overqualified, because only she was willing to accept an untenured post.

Esther and Joshua were divorced in 1966. Esther remained at Stanford and worked on a variety of research projects dealing with the genetics of bacteria with her colleagues in the Department of Microbiology and Immunology, as well as with Stanley N. Cohen in the Genetics Department. Cohen has said about Esther, "She was a very keen observer and picked up biological phenomena that would have escaped the eyes and intellects of most other people." Their work together, published in 1974 describing a method of

transforming *Salmonella* is widely cited even today. The late 1960s and early 1970s were a remarkable period in the field of bacterial genetics, and Esther, who was considered one of the great pioneers in the field, was much in demand for her advice, insight and for the remarkable collection of mutant bacterial and viral strains she had created in her laboratory.

Esther invariably arrived at a meeting carrying what appeared to be an enormous shopping bag from which often protruded sheets of music and her beloved musical instrument, a recorder. She also kept notebooks, snacks and heaven knows what else in this portable closet she lugged into the meeting hall. Esther also always had a camera. It was not a fancy camera, and in later years it was one of those throw-away devices. After a meeting, it was common to receive in the mail a number of prints of pictures that Esther had recorded at these meetings. She was a kind of Boswell of bacterial genetics and bacterial plasmids, and her collection of photographs still exists (http://www.estherlederberg.com/home.html).

By the mid-70s, because of the burgeoning field of recombinant DNA and biotechnology, Esther was asked to take on the role of curator of plasmids worldwide by an international committee of scientists. She agreed. Because of her knowledge and the high regard in which she was held by her colleagues, Esther was entrusted with keeping the plasmids in a collection she kept here at Stanford. She distributed these to investigators around the globe. She was particularly helpful to young investigators and to those in foreign countries who were just starting out in science. She was also the arbiter of contentious quarrels among scientists about how plasmids and the jumping genes they carried were named. Scientists can be especially difficult about their pet names for things, and they resist using any nomenclature that is not their own. Esther always prevailed in bringing difficult investigators into line because she had the patience to wear them down. Also, no one could out talk or out argue Esther -- it was possibly a Talmudic tradition in which she was raised as a girl. Esther managed the plasmid reference center until her retirement as the first female professor in the Department of Microbiology and Immunology in 1985.

On a personal level, after her divorce in 1966, she started a group for divorced women at Stanford. She had already founded the Mid-Peninsula recorder orchestra, and she further developed her interest in medieval dance and renaissance and baroque music. In 1989, Mathew Simon, an engineer new to Stanford, went to a meeting and asked if there was anyone who knew about early music. Esther overheard him. They married in 1993 when she was 70. He and her brother, Benjamin Zimmer, survive her.

Following her death there were several tributes to Esther from scientists who testified in their recollections about Esther's insight and help. Notable among these were Sir Gus Nossal from Australia and the Nobel Laureate Werner Arber. There was also a reawakened realization that Esther Lederberg was a brilliant scientist who participated and was a major contributor to some of the most important discoveries in genetic science under circumstances of the time when these discoveries were often credited to the male member of a research team. Esther had to face a number of hurdles that had been placed in

her way by the times. She did so with extraordinary grace, gentleness and with a respect and love for science that is important to remember and emulate, especially at this time when the pursuit of basic knowledge is becoming so very difficult. Esther Zimmer Lederberg has an assured place in the history of science. It will not be forgotten so long as there is a civilization.

Committee:

Stanley Falkow (Chair)
Lucy Tompkins