Esther Miriam Zimmer Lederberg

Lederberg (December 18, 1922 - November 11, 2006) was an American microbiologist and immunologist and pioneer of bacterial genetics. Notable contributions include the discovery of lambda phage, the relationship between transduction and lambda phage lysogeny, the development of replica plating, and discovery of bacterial fertility factor F.

Lederberg also founded and directed the Plasmid Reference Center at Stanford University, whose collection contained plasmids of all types of genes, coding for antibiotic resistance, heavy metal resistance, virulence, conjugation, colicins, transposons, temperature sensitivity and other unknown factors. (Most of these plasmids have still not been thoroughly studied.)

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Early years

Esther Miriam Zimmer was the first of two children born in the Bronx, N.Y. to David Zimmer and Pauline Geller Zimmer. (A brother, Benjamin Zimmer, followed in 1923.) A child of the Great Depression, her lunch was often a piece of bread topped by the juice of a squeezed tomato.[1]

Zimmer thrived academically. She attended Evander Childs High School in the Bronx, receiving honors for French and graduating at the age of 16. As an undergraduate, Zimmer worked at the New York Botanical Garden, engaging in research on \textit{Neurospora crassa} with Bernard Ogilvie Dodge.[2] She received an A.B. at New York City’s Hunter College, graduating cum laude in 1942, at the age of 20.

After her graduation from Hunter, Zimmer went to work for the Carnegie Institution of Washington (later Cold Spring Harbor Laboratory) as a research assistant to Alexander Hollaender, with whom she worked on \textit{neurospora crassa} as well as publishing her first work in bacterial genetics.[3] In 1944 she won a fellowship to Stanford University, working as an assistant to George Wells Beadle. She traveled west to California, and after a summer studying at Stanford University’s Hopkins Marine Station under Cornelius Van Niel, she entered a master’s program in genetics. While at Stanford she worked with Edward Lawrie Tatum of Yale on bacterial genetics.[4][5] (Note: Tatum and George Beadle later split the 1958 Nobel Prize with her then-husband, Joshua Lederberg.) Stanford awarded her a Master of Arts in 1946.

She married Joshua Lederberg on December 13, 1946, after which she began work on her doctorate at the University of Wisconsin. (Her thesis was "Genetic control of mutability in the bacterium \textit{Escherichia coli}.") Joshua Lederberg accepted a position there as Associate Professor. She completed her doctorate under the sponsorship of R. A. Brink, in 1950: the same year that she discovered the lysogenicity of lambda bacteriophage (see below).
**Professional pioneers**

Esther Lederberg attended the celebrated Cold Spring Harbor Laboratory Symposia on genetics during the late 1940s and 50's, as well as later years.

Lederberg influenced and was influenced by such colleagues and friends as her mentor Edward Lawrie Tatum, George Wells Beadle, Cornelius Van Niel, Barbara McClintock, Salvador Luria, André Lwoff, Jacques Monod, François Jacob, Werner Arber, Erwin Chargaff, Sol Spiegelman, one-time director of Cold Spring Harbor Milislav Demerec, Evelyn M. Witkin, Max Delbrück, Francis Crick, James Watson, Theodosius Dobzhansky, Jim Crow, Luigi Luca Cavalli-Sforza, Enrico Calef, M. B. Yarmolinsky, Mogens Westergaard, Aaron Novick, Bruce A. D. Stocker, Guido Pontecorvo, Bernard Davis, Alfred Hershey, Eugene Nester, Allan Campbell, Alfred Sturtevant, Gunther Stent, Jonas Salk, Tracy Sonneborn, Sydney Brenner, M. Laurence Morse, Julius Adler, Barbara J. Bachmann and many others.[6]

**Contributions to microbiology and genetics**

Lederberg remained at the University of Wisconsin for most of the 1950s. It was there that she discovered lambda phage, did early research on the relationship between transduction and lambda phage lysogeny, discovered bacterial fertility factor F (eventually publishing with Joshua Lederberg and Luigi Luca Cavalli-Sforza), and devised the first successful implementation of replica plating. These four contributions laid the foundation for much of the genetics work done in the latter half of the twentieth century.

**Lambda bacteriophage and transduction**

Esther Lederberg was the first to isolate lambda bacteriophage, a DNA virus, from *Escherichia coli* K-12 in 1950.[7]

Lambda phage genetic material consists of a double-stranded DNA molecule with 5' twelve-base-pair sticky ends (cos sites), which permit circularization of the DNA molecule. It shows a lytic cycle and a lysogenic cycle. Studies on the control of these alternative cycles have been very important for our understanding of the regulation of gene transcription. (The mechanism of integration of lambda DNA into bacterial DNA was first worked out by Esther's colleague and close friend, Allan Campbell, in 1962.[8])

Lambda phage is considered a 'temperate bacteriophage': one whose genome incorporates with and replicates with that of the host bacterium. Uses for lambda include its application as a vector for the cloning of recombinant DNA; the use of its site-specific recombinase, int, for the shuffling of cloned DNAs by the 'Gateway' method; and the application of its Red operon, including the proteins Red alpha (also called 'exo'), beta, and gamma, in the DNA engineering method called recombinering.

Her 1950 lambda phage paper led to an understanding of transduction, which is important not only in explaining the transfer of bacterial resistance, but provides a major mechanism
that can explain modes of evolution.[9]

The intimate relationship between transduction and lambda phage lysogeny was a consequence of this work.[10]

A permanent exhibit in the "DNAtrium" of The Eli and Edythe L. Broad Institute of Massachusetts Institute of Technology honors Esther M. Zimmer Lederberg as the discoverer of lambda phage.

**Bacterial Fertility Factor F**

The Fertility Factor (also known as F Factor) is a bacterial DNA sequence that allows a bacterium to produce a sex pilus necessary for conjugation. The sequence contains 20 tra (for "transfer") genes and a number of other genetic sequences responsible for incompatibility, replication, and other functions. The F Factor is an episome, and can either exist as an independent plasmid or integrate into the bacterial cell's genome.

Esther Lederberg's discovery of F stemmed directly from her discovery of lambda as unexpected plaques on 'lac indicator agar' in the course of experiments on other material. In her own words:

> In terms of testing available markers ... the data showed that there was a specific locus for lysogenicity. ... I explored the notion that there was some sort of 'fertility factor' which if absent, resulted in no recombinants. For short, I named this F.[11]

**Replica plating**

Although there were other less efficient forerunners to the methodology (such as paper, or multipronged arrays using wire brushes, toothpicks, etc.), the problem of reproducing bacterial colonies en masse in the same geometric configuration as on original agar plate was first successfully solved by replica plating, as implemented by Esther M. Zimmer Lederberg.

Anecdotal credit is generally given to Joshua Lederberg for originating the idea of replica plating, but scientists had been struggling for a reliable solution for at least a decade before Esther Lederberg finally implemented it successfully.

Allan Campbell, Eugene Nester and Stanley Falkow all recount how Esther Lederberg provided them with the technical information necessary to successfully use this new methodology. From Alan Campbell:

> Who successfully implemented the technique? Here Esther at least refined the process considerably. I remember (from her and others) that she was the one who went to the fabrics store and selected velvet of the best thickness, pile, etc. to give the cleanest prints.[12]

Eugene Nester said:
I wanted to respond to your question about replica plating and who really invented it. I think it will be very difficult to answer that question in a convincing way. That technique was developed before I ever knew the Lederbergs ... I do know that Esther in all likelihood was responsible for getting the technique to actually work. She emphasized to me how important it was to use a particular kind of Italian velvet (or was it velveteen actually), so in my own mind I believe she was the key person in taking the idea to actual practice.[13]

In Falkow's case, this happened a few years after she first published the replica plating paper. At the memorial for Esther Lederberg, he spoke of the impact of replica plating, and his feelings upon meeting the originator of the technique:

It was brilliantly simple: creative discoveries often are. She thought of using ordinary velveteen from a yard goods store to serve as a kind of rubber stamp. The tiny fibers of the velveteen acted like hundreds of tiny inoculating needles. The pad was carefully kept in the same orientation and used to inoculate a series of agar plates containing different media containing antibiotics or supplemented with essential nutrients such as amino acids and vitamins. Esther and Joshua used this technique as an indirect selective method to prove the spontaneous origin of mutants with adaptive advantages. ...

All of these things foreshadowed our first meeting and I was appropriately in awe of her. I was just starting to use replica plating in my own work and Esther immediately told me what brand of velveteen to look for and to be sure to wash the velveteen before I used them and even what detergent to use to wash them.[12]

Later contributions

Esther Lederberg returned to Stanford in 1959 with Joshua Lederberg. She remained at Stanford for the balance of her research career, founding and directing the Plasmid Reference Center (PRC) at the Stanford School of Medicine from 1976 to 1986.

At first, plasmids were of great interest due to their ability to confer inheritable resistance to antibiotics, thus were referred to as "R-Factors" or "R plasmids". As time passed, the nomenclature was changed to "Plasmids" (in general) to take into account other factors in addition to antibiotic resistance, such as genes for specific activity (gal, lac, ara, etc.) and temperature sensitivity. (For example, plasmid pSC304 used Kretschmer's protocol to establish temperature sensitivity. See P. J. Kretschmer and S. N. Cohen, 1977, J. Bacteriology, 130, 888-899.)

The PRC coordinated closely with the members of the Plasmid Nomenclature Committee (Royston Clowes, Stanley N. Cohen, Rob Curtiss III, Naomi Datta, Stanley Falkow, and Richard P. Novick), assigning prefixes to plasmids, and numbers to Insertion Sequences and Transposons.[14]
She retired from her position in the Stanford Department of Microbiology and Immunology in 1985, but continued to run the PRC for almost another full decade after that.

**Professional honors**

- 1956 Society of Illinois Bacteriologists: Pasteur Award (with Joshua Lederberg; the first time the award was ever given to a *team* of researchers)[15]
- 1969 American Cancer Society Dernham Postdoctoral Fellowship in Oncology (Senior Fellowship)
- President of the Stanford Chapter of SIGMA XI
- Memberships in a number of other scientific societies; frequent invitee to Gordon Conferences; etc.

For a complete list of Esther Lederberg's professional memberships, see [1](http://www.estherlederberg.com/Vita.html).

In 2010, Stanford University dedicated part of Clark Walk to Esther M. Zimmer Lederberg. (Clark Walk is a series of granite blocks that memorialize various Stanford scientists and events in the history of the Stanford School of Medicine, located between the Sherman Fairchild building and the Li Ki Shing Pavilion.)
Esther Lederberg established their own group and worked on bacterial genetics. Studying with Edward Tatum, they discovered sex, or genetic exchange in bacteria, which won him the Nobel Prize shortly after he arrived at Stanford. The process they developed became a way to transfer genetic information between bacteria. Len Herzenberg:

Joshua and Esther Lederberg established their own group and worked on bacterial genetics. Studying with Edward Tatum, they discovered sex, or genetic exchange in bacteria, which won him the Nobel Prize shortly after he arrived at Stanford. The process they developed became a way to transfer genetic information between bacteria.

Stanley Falkow:

A black granite block shows a photograph of Esther Lederberg in the laboratory, a page from one of her notebooks, and quotes from two close colleagues:
Esther Lederberg developed a method of replica plating using velveteen attached to a piston ring. The rings are pressed onto bacterial colonies and then stamped onto a series of plates. She advanced many of the early lab procedures and also discovered lambda phage, which became a widely used tool in microbial genetics.[16]

In this memorial block, Stanford University explicitly attributes its information to the Esther Lederberg Memorial Web Site, "http://www.estherlederberg.com" (http://www.estherlederberg.com/StanFalkowObitElaboration7-26-10.html).

Professional challenges: gender discrimination

Stanley Falkow said of Esther Lederberg that "Experimentally and methodologically she was a genius in the lab."

However, although Esther Lederberg was a pioneer research scientist, she faced significant challenges as a woman scientist in the 1950s and 1960s. These were exacerbated by her collaboration with then-husband Joshua Lederberg.

As Luigi Luca Cavalli-Sforza later wrote, “Dr. Esther Lederberg has enjoyed the privilege of working with a very famous husband. This has been at times also a setback, because inevitably she has not been credited with as much of the credit as she really deserved. I know that very few people, if any, have had the benefit of as valuable a co-worker as Joshua has had.” However, Joshua Lederberg himself failed to mention Esther Lederberg’s name in his Nobel Prize acceptance speech of 1958. Unsurprising that despite the significant effect Esther Lederberg’s work had on twentieth-century microbiology, she was overshadowed by her husband's notoriety.

Esther Lederberg had to fight to gain a position on the Stanford faculty. Retained as a Senior Scientist, in 1974 she was forced to transition to a position as Adjunct Professor of Medical Microbiology “coterminous with research support.” (Adjunct Professors are typically untenured.)

Allan Campbell noted the injustice of Stanford’s attitude toward women scientists in a letter of recommendation for Esther Lederberg, written in 1971: “I think she is a definite asset to the University and merits promotion according to the normal customs of your department (i.e., that your Committee on Women’s Promotions should recommend advancement on the same time schedule as a Committee of Men’s Promotions would advance a male scientist).”

Both in high school and as an undergraduate at Hunter College, her proficiency with languages (French, Spanish), earned her many awards; she also started a French Club newspaper. When Lederberg's instructors learned that she wanted to study science rather than languages, they exerted great effort to persuade her not to go into a field where a woman was not allowed to succeed, with the possible exception of botany. (In fact, her career in science started with three internships doing botanical research at the New York Botanical Garden with B. O. Dodge between 1941 and 1942. She researched heterokaryosis in *Neurospora tetrasperma*.) Lederberg felt that she should pursue her interests, genetics and
microbiology.

Her situation was summed up best, and most publicly, upon Dr. Lederberg’s death in 2006. In his eulogy for Esther Lederberg, Stanley Falkow said that while preparing his remarks he had checked the internet and found “a suggested topic for a term paper to meet the requirements for a passing grade in a bioethics course in Pomona College.” He read:

‘Martha Chase, Daisy Roulland-Dussoix, and Esther Lederberg are women who participated in important discoveries in science. Martha Chase showed that phage genetic material is DNA not protein. Daisy Dussoix discovered restriction enzymes, and Esther Lederberg invented replica plating. Yet each of these discoveries is often credited to the male member of the team (Al Hershey, Werner Arber, and Joshua Lederberg, respectively). Using the resources of the library (at least five sources), write a five page paper that examines how history of science has treated each discovery (generally by Hershey, Arber, and Josh Lederberg, who all received the Nobel prize) and include your own appraisal of how you might have reacted to the reward structure in each case.

The unnamed Professor who posed this question noted that ‘(This one is a challenge! **Feel free to reflect in your paper on why it might be so hard to find relevant information.**)[12][21]

Twenty-first century science historians are beginning to look back on the mid-twentieth century as a time when researchers made great strides in the sciences, but lagged far behind in the area of gender discrimination. For a look at how science historian Pnina Abir-Am highlights the accomplishments of Esther M. Zimmer Lederberg and other under-credited female scientists, see the Brandeis University web site "Scientific Legacies" (http://www.scientificlegacies.org).

**Other interests**

Esther Lederberg had cultural interests that went well beyond science.

**Music**

A lifelong musician, Lederberg was a devotee of Early Music. She was one of the founding members of the Mid-Peninsula Recorder Orchestra (affiliated with the San Francisco Early Music Society) in 1962, serving as its president for several years. At the memorial held for Dr. Lederberg at Stanford University, Frederick Palmer, musical director of the Mid-Peninsula Recorder Orchestra, spoke of Esther’s joy in this music, and her dedication to the MPRO:

One of the frustrations of anyone directing a musical ensemble made up of volunteers is wondering who will show up for rehearsals and if all of the parts will be adequately covered. I never had to worry about Esther. Even after her health began to fail and she was required to use a walker, Esther seldom missed
one of the orchestra's meetings, and she insisted on playing in the concerts that the orchestra presented despite her limited mobility.\[22\]

Always conscious that much of Early Music was really dance music, Lederberg also studied Renaissance and Elizabethan dance.

She loved symphonic music, opera, and the operettas of Gilbert and Sullivan.

**Literature**

Esther's taste in literature was eclectic; her library included both classics and contemporary works by such authors as Gore Vidal, Ursula K. Le Guin, and Margaret Atwood. A scientist who could suspend disbelief enough to actually enjoy some 'science fiction', Esther nevertheless took issue with Michael Crichton's handling of the alien antagonist in his novel, "Andromeda Strain". Her second husband, Matthew Simon, recounts:

Esther commented that "Crichton never got it right." I asked her what she meant, and she replied that if an extraterrestrial life form were caught in an outer space probe and brought back to Earth, whatever would counteract it would with high probability be caught along with it in the same probe, because living things are always surrounded in their environment by those things that counteract it. "They should simply have looked in the same net," she said. "They would have found what they needed to control the alien life form." \[23\]

Lederberg also loved the works of Charles Dickens and Jane Austen, and belonged to societies devoted to studying and celebrating these two authors.\[24\][25]

**Botany and botanical gardens**

Lederberg maintained a lifelong love of botany and botanical gardens. She encouraged the planting of indigenous plants such as poppies and lupins around the Stanford University campus, arguing that as well as being beautiful such plants would not need to be watered—an important consideration to a campus located in the San Francisco Bay Area, which has frequent droughts.


Esther Miriam Zimmer Lederberg died November 11, 2006, from pneumonia and congestive heart failure, at the age of 83.

**Notable papers**


For a list of all known papers authored or co-authored by Esther M. Zimmer Lederberg, see http://www.EstherLederberg.com/Papers.html.

Footnotes

1. ^ "Esther Lederberg Memorial Web Site: Anecdote #5" (http://www.estherlederberg.com/Anecdotes.html)
2. ^ "Esther Lederberg Memorial Web Site: Anecdote #3" (http://www.estherlederberg.com/Anecdotes.html)
10. ^ a b Records (http://www.estherlederberg.com/Records.html)
11. ^ The True History of Fertility Factor F (http://www.estherlederberg.com/HistoryF.html)
12. ^ a b c Deception (http://www.estherlederberg.com/Censorship.html)
14. ^ Correspondence Gateway.html (http://www.estherlederberg.com/EImages/Archive/PRC)
16. ^ See also personal correspondence from Dr. Falkow at http://www.estherlederberg.com/StanFalkowObitElaboration7-26-10.html
23. ^ "Esther Lederberg Memorial Web Site: Anecdote #11" (http://www.estherlederberg.com/Anecdotes.html)
24. ^ "Photograph at Palo Alto Dickens Fellowship"
25. ^ "Photograph at Jane Austen Society of North America, San Francisco"