Joshua Lederberg on Bacterial Recombination

Mark Johnston[1]
Department of Biochemistry and Molecular Genetics, University of Colorado School of Medicine, Aurora, Colorado 80045
ORCID ID: 0000-0002-4932-7229 (M.J.)

ORIGINAL CITATION

Gene Recombination and Linked Segregations in *Escherichia coli*
Joshua Lederberg
GENETICS September 1, 1947 **32**: 505–525

This paper describes the first genetic analysis of bacteria. Before its publication, most scientists wondered if bacteria even had genes. Many thought bacteria to be a distinct form of life, separate from higher organisms like *Drosophila* and maize, which were known to follow Mendel's principles of heredity. But when George Beadle and Edward Tatum showed in 1941 that *Neurospora* obeys Mendel's laws (Beadle and Tatum 1941), and 2 years later Salvador Luria and Max Delbrück reported in *GENETICS* that bacterial mutations arise at random (Murray 2016), microorganisms began to shed their outsider status. Then, when Avery, McLeod, and McCarty identified DNA as the substance that stably converts one form of *Pneumococcus* bacteria to another (Avery *et al.* 1944), many scientists came to realize that bacteria have conventional genes.

One of those scientists was Joshua Lederberg, who in 1944 was studying for a doctor of medicine (MD) degree at Columbia College and working in the lab of Francis Ryan. Lederberg had read Avery's paper and was excited by the prospect of probing the chemical nature of the gene. He wondered if DNA transformation could be investigated using the powerful genetic tools of *Neurospora*, which Ryan had brought to Columbia from his postdoctoral stint with Beadle and Tatum. But when Lederberg tried to repeat Avery's experiments in *Neurospora* he was foiled by the high reversion rate of the nutritional mutant on hand in Ryan's lab, leaving him with no way to identify rare transformants.

doi: 10.1534/genetics.116.190637
Image of Joshua Lederberg in 1946 courtesy of University of Wisconsin-Madison Archives.
[1]Address for correspondence: Anschutz Medical Campus, University of Colorado School of Medicine, Mail Stop 8101, P.O. Box 6511, Aurora, CO 80045. E-mail: Mark.Johnston@ucdenver.edu

Lederberg decided to take a different tack. Instead of trying to replicate DNA transformation in an existing model organism, why not establish a new system for genetic analysis of bacteria? The conventional wisdom was that bacteria do not engage in sex, which would make standard genetic analysis impossible. There had been a few attempts to detect genetic exchange in bacteria, but the results were inconclusive. Lederberg decided to give it another try. Why not? He knew he had nothing to lose: he did not need to complete a research project to receive his MD degree.

Lederberg chose to use *Escherichia coli* for these experiments and started the painstaking process of mutagenizing cells and screening them for nutritional requirements. By July 1945, he was ready to attempt to detect sex in bacteria. Ryan had just learned that Tatum was moving to Yale University, and he suggested that Lederberg collaborate with Tatum on the project.

Lederberg's plan was elegantly simple: mix bacteria that have different nutritional requirements and select for recombinants with no nutritional requirement. If each strain requires multiple different nutrients, the chance of it spontaneously reverting to wild type is miniscule; anything that grows in the absence of nutritional supplements must be a recombinant. This would allow him to select for individuals—expected to be rare—that had undergone a genetic exchange.

Lederberg arrived at Tatum's lab in April 1946 and got right down to work. He mixed one mutant that required threonine, leucine, and thiamin with another that required biotin, phenylalanine, and cysteine. When he plated about a billion cells on media lacking those nutrients, about 100 colonies grew! It took him and Tatum 6 weeks to convince themselves that the result was real and not due to cross-feeding

or DNA-mediated transformation. In July, Lederberg presented his observations to the phage group at Cold Spring Harbor (Max Delbrück was as skeptical as ever). They announced their discovery (without supporting evidence) in a brief "Letter to *Nature*" (Lederberg and Tatum 1946), later presenting the supporting data in the *Journal of Bacteriology* (Tatum and Lederberg 1947). Over the course of just a few months, Lederberg had shown that *E. coli* is sexual, transforming bacteria from a biological curiosity into an indispensable tool for genetic analysis.

Lederberg's *GENETICS* paper (essentially an abstract of his PhD thesis) described the ratios of the eight traits segregating in his crosses, which clearly showed that the responsible genes were linked. He concluded that there is only a single chromosome in *E. coli*, and he presented the organism's first genetic map. The 1947 paper established that "the segregational behavior of mutant factors seems to be closely analogous to that of higher forms, and seems to compel their admission into the same arena as the genes of *Drosophila*." Lederberg had ushered bacteria into the circle of life.

For these discoveries, Lederberg was awarded—at the tender age of 22—a faculty position at the University of Wisconsin and then a share of the 1958 Nobel Prize in Physiology or Medicine (along with Beadle and Tatum). He never received his MD degree because he was unwilling to abandon such exciting research. He recognized the importance—and the potential—of his discovery; we are proud it was first fully documented in the pages of *GENETICS* (Ankenbauer 1997; Milkman 1997; Gratia 2000; Falk 2010).

Literature Cited

Avery, O. T., C. M. Macleod, and M. McCarty, 1944 Studies on the chemical nature of the substance inducing transformation of pneumococcal types: induction of transformation by a desoxyribonucleic acid fraction isolated from pneumococcus TYPE III. J. Exp. Med. 79: 137–158.

Beadle, G. W., and E. L. Tatum, 1941 Genetic control of biochemical reactions in *Neurospora*. Proc. Natl. Acad. Sci. USA 27: 499–506.

Murray, A., 2016 Salvador Luria and Max Delbrück on random mutation and fluctuation tests. Genetics 202: 367–368.

Lederberg, J., and E. L. Tatum, 1946 Gene recombination in *Escherichia coli*. Nature 158: 558.

Tatum, E. L., and J. Lederberg, 1947 Gene recombination in the bacterium *Escherichia coli*. J. Bacteriol. 53: 673–684.

Further Reading in *GENETICS*

Ankenbauer, R. G., 1997 Reassessing forty years of genetic doctrine: retrotransfer and conjugation. Genetics 145: 543–549.

Crow, J. F., 2008 Joshua Lederberg, 1925–2008: a tribute. Genetics 178: 1139–1140.

Falk, R., 2010 Mutagenesis as a genetic research strategy. Genetics 185: 1135–1139.

Gratia, J.-P., 2000 André Gratia: a forerunner in microbial and viral genetics. Genetics 156: 471–476.

Milkman, R., 1997 Recombination and population structure in Escherichia coli. Genetics 146: 745–750.

Other *GENETICS* Articles by J. Lederberg

Cavalli-Sforza, L. L., and J. Lederberg, 1956 Isolation of preadaptive mutants in bacteria by sib selection. Genetics 41: 367–381.

Cook, A., and J. Lederberg, 1962 Recombination studies of lactose nonfermenting mutants of *Escherichia coli* K-12. Genetics 47: 1335–1353.

Lederberg, E. M., and J. Lederberg, 1953 Genetic studies of lysogenicity in *Escherichia Coli*. Genetics 38: 51–64.

Lederberg, J., 1947 Gene recombination and linked segregations in *Escherichia Coli*. Genetics 32: 505–525.

Lederberg, J., 1948 Gene control of beta-galactosidase in *Escherichia coli*. Genetics 33: 617.

Lederberg, J., 1956 Linear inheritance in transductional clones. Genetics 41: 845–871.

Lederberg, J., 1961 A duplication of the Hl (flagellar antigen) locus in *Salmonella*. Genetics 46: 1475–1481.

Lederberg, J., 1987 Gene recombination and linked segregations in *Escherichia coli*. Genetics 117: 1–4.

Lederberg, J., 1989 Replica plating and indirect selection of bacterial mutants: isolation of preadaptive mutants in bacteria by sib selection. Genetics 121: 395–399.

Lederberg, J., 1991 The gene (H.J. Muller 1947). Genetics 129: 313–316.

Lederberg, J., 1994 The transformation of genetics by DNA: an anniversary celebration of Avery, MacLeod, and McCarty (1944). Genetics 136: 423–426.

Lederberg, J., 1996 Genetic recombination in *Escherichia coli*: disputation at Cold Spring Harbor, 1946–1996. Genetics 144: 439–443.

Lederberg, J., 1999 J. B. S. Haldane (1949) on infectious disease and evolution. Genetics 153: 1–3.

Lederberg, J., and T. Iino, 1956 Phase variation in *Salmonella*. Genetics 41: 743–757.

Lederberg, J., L. L. Cavalli, and E. M. Lederberg, 1952 Sex compatibility in *Escherichia Coli*. Genetics 37: 720–730.

Makela P. H., J. Lederberg, E. M. Lederberg, 1962 Patterns of sexual recombination in enteric bacteria. Genetics 47: 1427–1439.

Morse, M. L., E. M. Lederberg, and J. Lederberg, 1956a Transduction in *Escherichia Coli* K-12. Genetics 41: 142–156.

Morse, M. L., E. M. Lederberg, and J. Lederberg, 1956b Transductional heterogenotes in *Escherichia coli*. Genetics 41: 758–779.

Nester, E. W., M. Schafer, and J. Lederberg, 1963 Gene linkage in DNA transfer: a cluster of genes concerned with aromatic biosynthesis in *Bacillus Subtilis*. Genetics 48: 529–551.

Communicating editor: C. Gelling