

Reflections

Lederberg and the ‘Cellularity’ of Bacteria

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Joshua Lederberg will surely be remembered for his stellar contributions to microbial genetics and his sage intervention in public affairs concerning exobiology, infectious diseases, epidemiology, and bioterrorism. Not so well known is his emphatic mission to spell out that bacteria are cells and not something else. This brief sketch examines some of his contributions to bacterial cytology.

During the first century of modern microbiology (ca. 1850-1950), the cellular nature of bacteria (and, by modern extension, archaea) was not universally embraced. Even those who accepted it might have asked: *Are bacteria cells like all other cells, or are they something quite different?* One reason for their perplexity is clear; bacteria are generally small and, with some exceptions, look nearly uniform and structureless under the optical microscope, the main tool available at the time. In fact, hardly anything is less revealing of internal structures than the most widely used method for rendering bacteria visible, the Gram stain. Most bacteria contain large numbers of ribosomes which, being acidic, avidly bind basic dyes, thus obscuring internal structures.

By the mid 1940's, it was evident that bacteria should indeed be considered cells, but Lederberg believed that it was still necessary to dispel any lingering doubts. Most likely, it was his discovery of bacterial conjugation (see article by R Jayaraman in this issue) that swept away the remaining hesitancy about bacteria being cells. If only cellular organisms have sex, and if bacteria are sexually-endowed, then bacteria must be cells. But if so, what are their cellular attributes? Early in his career, Lederberg had taken an interest in bacterial cytology, a bent that was somewhat unusual among bacterial geneticists. He took note of the developing work on cell walls and membranes and fleetingly even endorsed a claim by Ed DeLamater [1] that bacterial ‘nuclei’ divide by mitosis. Rather bravely, DeLamater (my PhD mentor) later withdrew this claim [2]. Much bacterial structure remained to be discovered, but the door was opened for bacteria to take their place among all cells, no longer relegated to the sidelines as some biological oddity.

Lederberg published several articles on the cytological investigations pursued in his laboratory. He tried to observe bacterial mating and the details of conjugation at the cellular level [3] (reproduced in the Classics section), processes that are still being investigated [4]. He made the important discovery that penicillin induces the formation of spheroplasts. The announcing



Box 1. Articles by Lederberg Directly Related to Bacteria Cytology

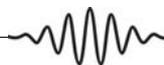
- J Lederberg, Single-cell isolations of diploid heterozygous *Escherichia coli.*, *J. Bacteriol.* Vol.61, pp.351–355, 1951.
- J Lederberg and J St Clair, Bacterial protoplasts induced by penicillin, *Proc. Natl. Acad. Sci. USA*, Vol.42, pp.574–577, 1956.
- J Lederberg, Conjugal pairing in *Escherichia coli*, *J. Bacteriol.*, Vol.71, pp.497–498. 1956.
- M R Zelle and J Lederberg, Protoplasts and L-type growth of *Escherichia coli.*, *J. Bacteriol.*, Vol.75, pp.143–160, 1958.
- J Lederberg, Mechanism of action of penicillin, *J. Bacteriol.*, Vol.73, pp.144, 1957.
- J Lederberg, Bacterial reproduction, *Harvey Lect.*, 1957–1959, Vol.53, pp.69-82.
- J Lederberg, The microbe's contribution to biology – 50 years after, *Int. Microbiol.*, Vol.9, pp.155-6, 2006.

paper [5] offers a promissory sentence about spheroplasts: “*Their possible genetic applications are being studied in this laboratory*”. Surely, he must have intended to use protoplast fusion as an alternative form of conjugation. In time, this was put to use by others to achieve genetic recombination, especially in the actinomycetales (see [6] for a review).

There is not much written record of the subtleties of researchers' attitudes towards the developments in this field, then called bacterial cytology. As a graduate student working in this area in the early 1950's, it was my business to follow its developments. Most of what I write is based on my own memory. To ensure that it is not faulty, I called upon Robert Murray, one of the founders of bacterial cytology. He replied:

“You are right in saying that Lederberg really had in mind that bacteria were real cells. I know this because both C. F. Robinow and I spent time with him before and while he was at Wisconsin; he was very much interested in the cellularity of bacteria. I am pretty sure that a good part of the stimulus came, as it did for me, from reading Rene Dubos' book, The Bacterial Cell [7], and thinking about the micrographs in the addendum in that book by Robinow. Lederberg implies that indebtedness in the foreword he wrote for a compendium of classic papers, Microbiology: a Centenary Perspective, (unfortunately not all I would have put in) edited by Joklik et al. and put out by ASM Press in 1999 [8]. Look at his second page where he states: “A major conceptual turning point was the publication of Dubos book in 1945 just in the midst of the wave of discovery of spontaneous mutation, of genetic transformation, of (conjugal) genetic recombination – i.e., sex “in bacteria, and soon after virus-mediated transduction.” My, that was discovery plus, something special that came to a mind prepared to think hard about experiments that told one something.”

This was not just a youthful aberration; Lederberg's convictions about bacteria being cells



continued unabated. Late in life, he re-affirmed this interest in his essay entitled ‘The Microbe’s Contribution to Biology – 50 Years After’ [9]. He reiterated:

“By 1956, there were strenuous debates about the place that bacteria could occupy in any (scala naturae) comprehensive scheme. Rene Dubos was nearly unique in his serious reference to “cells”. Most writers were impressed by the bacteria’s apparent deficit in mitotic spindles, then cytokinesis, or indeed, of many of the organelles that routinely populate larger cells and organs. The bacteria were routinely swept under the rug in biology textbooks, which in turn were subdivided into those covering botany or zoology”.

In a recent letter [10], Marlyn H Witte uncovered a homework assignment for high school student researchers that she shared with Lederberg. In his response, he had scribbled: “*Are not bacteria ‘cells’?*”

Suggested Reading

- [1] E D DeLamater, The mitotic mechanism in bacteria, *Cold Spring Harbor Symp Quant Biol.*, Vol.18, pp.99–100, 1953.
- [2] E D DeLamater, Withdrawal of the concept of the occurrence of classical mitosis in bacteria, *Nature*, Vol.195, pp.309–310, 1962.
- [3] J Lederberg, Conjugal pairing in *Escherichia coli.*, *J Bacteriol.*, Vol.71, pp.497–498, 1956.
- [4] A Babic, A B Lindner, M Vulic, E J Stewart and M Radman, Direct visualization of horizontal gene transfer, *Science*, Vol.319, pp.1533–1536, 2008.
- [5] J Lederberg and J St Clair, Bacterial protoplasts induced by penicillin, *Proc. Natl. Acad. Sci. USA*, Vol.42, pp.574–577, 1956.
- [6] D A Hopwood, Genetic studies with bacterial protoplasts, *Ann. Rev. Microbiol.*, Vol.35, pp.237–272, 1981.
- [7] R Dubos, *The Bacterial Cell*, Harvard Univ. Press., Cambridge, USA, 1945.
- [8] W K Joklik *et al*, *Microbiology: A Centenary Perspective*, ASM Press, Washington DC, USA, 1999.
- [9] J Lederberg, *Int. Microbiol.*, Vol.9, pp.155–156, 2006.
- [10] M H Witte, Joshua Lederberg’s Interest in Ignorance, *Science*, Vol.320, p.1159, 2008.

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