

This Week's Citation Classic®

Davis B D. Isolation of biochemically deficient mutants of bacteria by penicillin.

J. Amer. Chem. Soc. 70:4267, 1948.

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While Joshua Lederberg and Norton Zinder developed the penicillin method for isolating auxotrophic mutants as part of a flourishing program in bacterial genetics, my simultaneous discovery was the product of a deep desire to get into that new field.

At the end of World War II the US Public Health Service offered me the opportunity to set up a research lab in its newly established Tuberculosis Control Division. I had a medical degree and some background in protein chemistry and immunology (but no research experience with bacteria), so I decided to spend a year working on the tubercle bacillus with René Dubos. Within a few months the bug had begun to work on me, and my mild but protracted case provided me with time to read and to think at length about problems outside my usual range of interest. A review by George Beadle¹ on biochemical mutants of *Neurospora* convinced me that work on such universal aspects of biology would be much more satisfying than work on a small twig on the evolutionary tree. But I knew no genetics.

As often happens, the conviction found its opportunity. An invitation to contribute the chapter on chemotherapy to a textbook edited by Dubos made me aware that the bactericidal action of penicillin depended on cell growth, so when I heard a seminar by Robert Guthrie on mutants with added growth requirements it was immediately obvious that one should be able to use penicillin to isolate such mutants efficiently. And indeed, it worked beautifully with auxotrophic cells added to an excess of wild-type cells. But it was totally ineffective in recovering new auxotrophs from a culture mutagenized by ultraviolet radiation.

After weeks of frustration I decided that the killed cells must be feeding the survivors and hence preventing selection by penicillin, so I introduced the step of intermediate cultivation of the mutagenized culture in rich medium (to permit the survivors to outgrow the killed cells), followed by exposure to penicillin in minimal medium. It worked, but being innocent of genetics, I only later recognized that I had done the right experiment for the wrong reason. (The new mutations were not phenotypically ex-

pressed until the cells had grown enough to go through nuclear segregation and the phenomic lag.)

I first met Lederberg when he came to my lab to present a copy of a letter that he had just submitted to the *Journal of Biological Chemistry* and to offer to request that it be held up if I were willing to submit a similar article for simultaneous publication. While mine was in the mail, the editors informed him that his paper with Zinder could not be accepted because it "does not add to existing fundamental biochemical knowledge"; a few days later I received an identical letter.

In retrospect, I feel that the journal had some justification, for the articles were indeed on a bacteriological method. But at that time the biochemical applications of this class of mutants were so prominent, and the prestige of the *Journal of Biological Chemistry* so high, that we were quite annoyed. Erwin Brand of Columbia's College of Physicians and Surgeons was then encouraging biochemists to use the letters section in the *Journal of the American Chemical Society*, and he was eager to have the penicillin papers in his journal. I browbeat a reluctant Lederberg (if that can be imagined) into accepting this invitation. What is perhaps more interesting is that when the two papers came out side by side, we arranged, at his suggestion, to have the two reprints within the same cover. And while the reason that he advanced for this was "economy," this procedure has always seemed to me a model for how simultaneous independent discoveries might be handled.

A few byproducts of work with the penicillin method include a patent taken out by the government (in order to preempt industrial patenting); the pleasure, for a logophile, of creating a few neologisms (auxotroph, phenomic lag, amphibolic); and an unexpected profitable consultation by a Japanese firm engaged in litigation over the question of whether a "leaky," incompletely blocked mutant should be legally considered an auxotroph.

In 1956 in introductory remarks at a symposium,² I contrasted the intensely competitive atmosphere prevailing in enzymology with the more open and generous relations in microbial genetics, and I suggested that those living in the crowded "cities" might consider moving out to our pleasant, uncrowded "suburbs." Eventually microbial genetics grew into molecular genetics, and our suburbs became very crowded—with the same (and perhaps even more intense) consequences.

[See reference 3 for a recent paper by Davis related to this field.]

1. Beadle G W. Biochemical genetics. *Chem. Rev.* 37:15-96, 1945. (Cited 105 times since 1955.)

2. Davis B D. Introduction: purpose and scope of the symposium. (Gaebler O H, ed.) *Enzymes: units of biological structure and function*. New York: Academic Press, 1956. p. 1-4. (Cited 70 times.)

3. Davis B D, Chen L & Tai P C. Misread protein creates membrane channels: an essential step in the bactericidal action of aminoglycosides. *Proc. Nat. Acad. Sci. USA* 83:6164-8, 1986.