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EUGENE GARFIELD

INSTITUTE FOR SCIENTIFIC INFORMATION®  
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## The Impact of Basic Research in Genetic Recombination—A Personal Account by Joshua Lederberg. Part 2. A Discovery Recounted and Evaluated

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Last week we presented the first of two installments of "Genetic recombination in bacteria: a discovery account" by Joshua Lederberg, president, The Rockefeller University, New York.<sup>1</sup> The article originally appeared in the *Annual Review of Genetics* last year.<sup>2</sup> With this second part, the narrative concludes.

In the first part, Lederberg described his beginnings as a scientist. He also introduced the central research effort of his early career, starting in medical school: a search for evidence demonstrating the existence or absence of sexual recombination in bacteria. Bacteria, as Lederberg observed, could not be adopted as models for genetic research until there was some substantiation of the view that they had a genetic system like other organisms. To that end, he applied in the late summer of 1945 to work with biochemist Edward L. Tatum, who was setting up a microbiology lab at Yale University, New Haven, Connecticut.

Tatum generously offered laboratory facilities, the wisdom of his experience, and his collection of double-mutant strains of *Escherichia coli* strain K-12. With these

strains Lederberg promptly demonstrated the recombination process, and the result has been that "K-12" has become a byword in genetic research and biotechnology. For example, in 1987 there were 168 citations to a 1983 review of the genetic map of this organism by Barbara J. Bachmann, Yale University Medical School.<sup>3</sup> Her 1987 reprint of this review, with cumulative bibliography, cites 1,993 articles through 1982.<sup>4</sup>

In 1958 the Nobel Prize in physiology or medicine was awarded to George W. Beadle, then at the California Institute of Technology, Pasadena, and Tatum for "the discovery that the genes regulate stated chemical processes," and to Lederberg for his "discoveries concerning genetic recombination and the genetic apparatus in bacteria."<sup>5</sup>

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*My thanks to Christopher King and Pat Taylor for their help in the preparation of this essay.*

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# GENETIC RECOMBINATION IN BACTERIA: A DISCOVERY ACCOUNT

*Joshua Lederberg*

The Rockefeller University, New York, New York 10021

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Once I was at New Haven, my lab efforts were devoted to rechecking the stability of Tatum's existing double-mutant strains, like 58-161 and 679-183 (biotin-methionine and threonine-proline, respectively). Then, additional mutations such as resistance to virus T1 were also incorporated to allow segregation of unselected markers among the prototrophs selected from the mixed cultures on minimal agar medium. It took about six weeks from the time the first serious efforts at crossing were set up in mid-April to establish well-controlled, positive results. By mid-June, Tatum and I felt that the time was ripe to announce them.

A remarkable opportunity was forthcoming at the international Cold Spring Harbor Symposium. This year, it was to be dedicated to genetics of microorganisms, signalling the postwar resumption of major research in a field that had been invigorated by the new discoveries with *Neurospora*, phage, and the role of DNA in the pneumococcus transformation. Tatum was already scheduled to talk about his work on *Neurospora*. Happily, we were also granted a last minute insertion near the end of the program to permit a brief discussion of our new results (65). (I have found no written record of the precise date; the Symposium was scheduled for the week of July 4, 1946.)

The discussion was lively! The most reasoned criticism was Andre Lwoff's concern that the results might be explained by cross-feeding of nutrients between the two strains without their having in fact exchanged genetic information. He was familiar (94) with nutritional symbiosis in *Hemophilus* (72). [I did not think to counterargue that the apparent cross-feeding (94) was actually a genetic exchange. Indeed, *Hemophilus* is now known to accept DNA in a manner analogous to the transformation system in the pneumococcus (25). This counter hypothesis has not, however, been substantiated.]

Having taken great pains to control the artifacts from cross-feeding, I felt that the indirect evidence we had gathered, especially the segregation of unselected markers, should be accepted as conclusive, and I spent more argument than necessary on whether more direct proofs need be furnished that the purported recombinants were indeed pure strains. Fortunately, Dr. Max Zelle took me aside after the meeting and most generously offered to advise and assist me in the direct isolation of single cells under the microscope, so as to lay such concerns to rest (100).

The Cold Spring Harbor meetings in 1946 (and again in 1947) were also a marvelous opportunity to benefit from new or renewed introductions to outstanding figures in genetics. Many of the scientists were also extraordinarily supportive human beings, both in thoughtfully listening to the logic of my

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experiments, and in offering good advice (personal and technical) about how to respond to criticisms. Discussions with figures like Andre Lwoff, Jacques Monod, Guido Pontecorvo, Maclyn McCarty, Seymour Cohen, Bernard Davis, Boris Ephrussi, Raymond Latarjet, Colin Pittendrigh, Curt Stern, C. B. van Niel, Ernst Caspari, J. F. Crow, M. Demerec, Alex Hollaender, Rollin Hotchkiss, Dan Mazia, Howard Newcombe, Elizabeth Russell, Jack Schultz, Wolf Vishniac, M. J. D. White, Evelyn Witkin—and many others—helped to promote lifelong correspondence, and personal and scientific relationships. I remember most vividly the warmth, interest, and friendship offered by Tracy Sonneborn, H. J. Muller, and Salvador E. Luria; later also by Leo Szilard and J. B. S. Haldane, in discussing the work as it unfolded. It is hard to overestimate the importance of these meetings in sustaining the interpersonal network in science.

The most gratifying evidence of the acceptance of these claims by my scientific colleagues was the trickle (later a torrent) of requests for the cultures of *E. coli* K-12 to enable others to repeat the experiments. The first significant confirmatory publications bore the name of Luca Cavalli-Sforza (14), originally from R. A. Fisher's laboratory at Cambridge and later from Milan and Pavia. This prompted the beginning of an extended transatlantic (and later collegial) collaboration with Cavalli-Sforza that was most gratifying both scientifically and personally.

The only studied holdout was Max Delbrück: he quite curtly expressed his disinterest in the phenomenon for the lack of a kinetic analysis. His admonition was immaterial to the claims on the table; it was, however, the kernel of the methodology later used to such good effect by Wollman & Jacob (99) in showing that fertilization was a progressive entry of the chromosome, taking about 100 minutes for consummation. That story has now been well told in Jacob's personal memoir (36a).

By September 1946 I was scheduled to resume my medical studies at P & S, but this was obviously the most unpropitious time to interrupt the exciting initial progress with crossing in *E. coli*. I was granted another year's leave from P & S and a renewal of my fellowship from the Jane Coffin Childs Fund. The year enabled a consolidation of the preliminary reports and especially the recruitment of many additional genetic markers and the publication of the first linkage map (44). The detailed physical mechanism of crossing was still obscure; it was not, however, mediated by extracellular DNA, for it was quite uninfluenced by the addition of deoxyribonuclease (generously provided by Maclyn McCarty) to the medium. [It would take later discoveries, especially of Hfr (High frequency of recombination) strains by Cavalli-Sforza (13) to open up progress on mechanism.]

A persistent disappointment was the failure of efforts to demonstrate DNA transfer in *E. coli*, which would have completed the paradigmatic aims of the experiment. Boivin & Vendrely had reported such a finding (9), but none of us, Boivin and his collaborators included, was able to reproduce it (R. Tulasne, personal communication; 8), perhaps owing to deterioration of the relevant strains.

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Zoology Dept.  
Columbia University  
New York, N. Y.

19 September 1945

Dr. E. L. Tatum,  
Dept. of Botany,  
Yale University,  
New Haven, Conn.

Dear Sir:

Your recent paper 'X-Ray Induced Mutant Strains of Escherichia Coli' has just come to my attention, and has proven very fascinating. I should be very much obliged to you for reprints of this paper and your preliminary one last summer. I shall take the liberty of writing to you at this length in support of a request that I hope you will entertain.

After doing some work on adaptation (part of which is nearly ready for publication) in Neurospora mutants, it occurred to me that no adequate investigation of a genetic nature had been made to demonstrate the existence or absence of sexual recombination in bacteria. Such things as the distribution of somatic and flagellar antigens in the Salmonella group very strongly suggest that such a process may occur, but no very successful attempt seems to have been made to determine the recombination of bacterial characters. The nutritional mutants described by yourself and Roepke et al. would seem to fill the bill. . . .

I have not yet gone very far in the genetic tests I mentioned (explicitly) on these strains: the methionineless is quite rough therefore possibly not so satisfactory. I had planned to do essentially what you have accomplished: prepare a double mutant by subjecting the prolineless to the same selective procedure used obtaining methionineless, but that seems unnecessary now for a demonstration that independent (X-ray mutable) genes exist. It has seemed to me, however, that despite the apparent stability of the types I now have, and what is I hope adequate technique to eliminate contamination that it would be highly desirable to have genetically marked strains before any attempt was made to perform the experiment. I should therefore be very much obliged to you for cultures of your biotin double mutant series for the purposes of this investigation. . . .

If an investigation of this sort has already occurred to you, please let me know, as I am sure that you can do a much better job and have better facilities for it than I; on the other hand, if your plans do not include work such as this I should appreciate very much the service I ask of you. . . .

Very sincerely yours,

Joshua Lederberg, A.S. V-12 USNR.

Figure 1 Copy of 1945 letter to E. L. Tatum.

Since 1946, *E. coli* K-12 has been the subject of innumerable further investigations, in hundreds if not thousands of laboratories (2). These have substantially revised and enriched our first simple models of the sexual behavior and genetic structure of *E. coli*, though many questions remain open (29, 36a, 37, 53, 55, 56). Many technological applications of gene transfer in *E. coli* have, of course, also emerged. The detailed story of the fructification of the initial discovery is an example of international cooperation and competition that deserves a richer and better informed treatment at some future time.

September 1947 was the next deadline of personal history: I was to return to New York and continue my interrupted medical studies. Ryan also offered me laboratory facilities, and he and Tatum looked hard and partly successfully for some financial support to make all that possible. Meanwhile, Tatum had negotiated with Yale my retroactive registration as a graduate student and had obtained assent from other professors that I had de facto enrolled in a number of their lecture courses and seminars. The work of 1946–1947 became my dissertation, which I had already defended before an international panel of experts. A more serious personal obstacle was obligatory retroactive payment of tuition to Yale University; but the happy result was to qualify for a PhD degree that would, as it turned out, widen my career options. I spent the summer of 1947 at Woods Hole (and the magnificent library of the Marine Biological Laboratory), completing the dissertation. The stacks gave a wonderful opportunity to explore the history of microbiology: how its pioneers had sought to cope with the perplexities of bacterial variability, totally isolated from the intellectual apparatus of modern genetics.

In mid-August, days before the resumption of medical school, I learned from Ed Tatum that the University of Wisconsin had contacted him about an opening in genetics. In a fashion revolutionary for the time, they were seeking a microbial geneticist! He had recommended my name, and as a Wisconsin graduate his word carried great weight there. I have since learned of the controversy that this proposal evoked. Understandably, the appointment of a 22-year old as an assistant professor warranted close examination. Some referees at Cal Tech were still skeptical about the *E. coli* research: a painstaking review by Ray Owen (at Cal Tech, but recently from Wisconsin) did much to allay concerns in that sphere. Most troubling were allusions about character and race—someone with far stronger suits of tact and polish than mine would have been a more compelling nominee to be among the first Jewish professors in a midwestern college of agriculture. (There have been some happy changes in this country over forty years. We still have many burdens of fairness in meeting the cries for equity from other groups subject to discrimination.) It has been enormously gratifying to have learned in later years of the large effort and integrity of support that were offered by R. A. Brink and M. R. Irwin (at Wisconsin) and by E. B. Sinnott (at Yale). It is a measure of their stature that I was, in the event, offered the position; and when I did come to Madison I was given no inkling of what a struggle I had engendered.

The offer posed the deepest dilemma of my career. I was deeply committed to medical research. Two more years of clinical training (and to be meaning-

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ful another two or three of internship and residency) would have reinforced the medical credential, but been a grave (if not total) interruption of research at its most exciting stage. The Wisconsin position was the only one visible for unmitigated support of research in bacterial genetics. That university was furthermore a seat of biochemistry (especially in the Enzyme Institute) and had a long tradition of research in genetics and in microbiology (albeit quite separately up to that point). The Wisconsin Alumni Research Foundation, with income from professors' patents, was a further resource in aiding pioneer research. All this was, however, seated in the College of Agriculture, not Medicine. The medical school at Wisconsin at that time, furthermore, gave little emphasis to research, except for the McArdle Institute for Cancer Research. In short order, I did of course go to Wisconsin, and have never had second thoughts about the wisdom of the choice. The agricultural research context gave me a grounding in practical applications of biotechnology that I have never regretted. I enjoyed a happy collegial association with Brink and Irwin, and shortly thereafter with James F. Crow (whom I had met at the 1947 Cold Spring Harbor symposium) and many other close friends and colleagues, that could be matched at no other time or place. In the long run, however, affiliation with a medical educational and research environment was to be a more compelling vocation. Together with Arthur Kornberg's concurrent move, this was to be the principal attraction of Stanford University, when I was invited to join the new medical school effective February 1959. That opportunity to return to medically centered activities at Stanford, and later at The Rockefeller University in 1978, has substantiated the advice I had from Tatum in 1947. Nevertheless, among my most cherished honorifics are the MD degrees (honoris causa) that I have received from Tufts and from the University of Turin.

"Contrafactual history" is often derided. Nevertheless, if historical analysis is to go beyond the selection of narrative detail and to assert some theoretical depth, it ought ask "what if?" That is, it should make a plausible cause for "postdicting" alternative outcomes, given different hypothetical inputs. There is, of course, no way to verify such speculations; but unless we indulge in them, how can we speak of learning anything from history?

Without the serendipity of *E. coli* K-12, could sexual genetic recombination have remained undiscovered until this day? As we know in retrospect (47), the choice of *E. coli* strain K-12 was lucky; one in twenty randomly chosen strains of *E. coli* would have given positive results in experiments designed according to our protocols. In particular, strain B, which Delbrück and Demerec had insisted upon as a canonical standard, would have been stubbornly unfruitful. Tatum had acquired K-12 from the routine stock culture collection in Stanford's microbiology department when he sought an *E. coli* strain to use as a source of tryptophanase in work on tryptophane synthesis in *Neurospora* (92). The same strain was then in hand when he set out to make single, and then double, mutants in *E. coli* (91). In 1946 I was very much aware of strain specificities and was speculating about mating types (as in *Neurospora*). I have no way to say how many other strains would have been

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tried, or in how many combinations, had the June 1946 experiments not worked out so successfully. K-12 has also been the source of the prototypic extrachromosomal elements, F and lambda.

The serendipitous advantages of K-12 notwithstanding, *E. coli* recombination might have been discovered eventually as a byproduct of studies on the infectious transmission of drug resistance, which has become an important practical problem with many pathogenic bacteria. The development of molecular genetics along other paths would have eased the resistance to conjectures about a genetics of bacteria; it would have reduced the incentives to topple the icons; above all it would have vastly multiplied the number of people seeking their own creativity niches (78) in this general area of work. It is hard to imagine that a bacterial conjugation system would not have been discovered at least by the 1950s or 1960s.

Let us stipulate nondiscovery and ask, only partly tongue-in-cheek, how much regret that resynchronization of history would have entailed. Without the *E. coli* system, the optimistic hypothesis is that other paths would have received still more attention. (We cannot be sure that they would have attracted a compensatory interest.) Delbrück and Hershey had already discovered recombination in viruses (18, 30). The discovery of sex in *E. coli* was not a prerequisite for the work of Hershey & Chase (31) on the role of DNA in the virus life cycle, nor that of Watson & Crick (96) on the structure of DNA. Without the distractions of another genetic system like *E. coli*, even more attention might have been paid to the pneumococcal transformation and the search for more tractable systems like it.

A significant impediment would have been the lack of detailed genetic maps of the bacterial chromosome; but they might well have been built up piecemeal by other methods. Still more likely would have been less emphasis on bacterial genetics and more on the viruses with their simpler structure. It is conceivable that this would have led to even deeper and more rapid advances at the strictly molecular level, perhaps at the price of a scientific natural history of bacteria, of correlating DNA research with classical genetics, and of some practical advances in biotechnology using bacterial hosts.

Other casualties of the deemphasis of bacteria might have been some aspects of phenomena like plasmids, lysogeny, and lysogenic conversion: the incorporation of viruses into the bacterial chromosome (30a, 43, 50, 54). These concepts have achieved some importance as models for oncogenes. Alternatively, some completely different and even more attractive experimental models, unknown to us at the present time, might have emerged.

Historians should ask about the likely consequences of other counterfactuals, stipulated in isolation. They are most provocative if directed at significant discontinuities in the history of science. Besides the further consequences, we can also ask whether such discoveries, perhaps even manifold, are fore-ordained in the contemporary milieu (74, 74a, 74b). What if Avery had not pursued the chemistry of the pneumococcus; if Beadle and Tatum had not thought of fungi for biochemical genetics; if Watson and Crick had not pursued the physical chemistry of DNA? Each of these questions has a

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different genre of answers; on some of them, we might even discover a consensus. These fantasies point to the importance of how attention is focused in the scientific community, a matter as important as, but coupled loosely to, the specific knowledge that is passed on from generation to generation.

Our historical and social understanding does not give us a predictive gauge of the macroeconomics of scientific interest in given fields and the social resources they will attract over periods of time. Every field of enquiry has the latent potential of enormous unforeseeable outcomes. One function of a discovery is to lend credibility to a given avenue of pursuit, and to a new momentum of effort there.

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This memoir is dedicated to Francis J. Ryan and Edward L. Tatum. At a time when the public image of scientific fraternity is so problematical, their lives reflect the survival of norms (74) and behavior exemplifying mutual respect, helpfulness, consideration, and above all a regard for the advancement of knowledge.

Today's popular portrayals of the scientific culture give short shrift to anything but fraud and competition. What contrast to the idealizations by de Kruif and others that inspired my generation! This emphasis may stem in part from the reluctance of scientists to speak out in literary vein, with a few atypical exceptions: outstandingly, June Goodfield in her books and television series (23, 24), which are a renaissance of the de Kruif tradition. The competitive stresses on young scientists' behavior today must be acknowledged. The role modeling and critical oversight of their scientific mentors have also warranted celebration (39, 102). These are now complicated by the disappearance of leisure in academic scientific life, the pressures for funding, and academic structures and a project grant system that give too little weight to the nurture and reassurance of the human resources of the scientific enterprise. The often contradictory demands on the scientific personality are ill understood: antitheses such as imagination vs critical rigor; iconoclasm vs respect for established truth; humility and generosity to colleagues vs arrogant audacity to nature; efficient specialization vs broad interest; doing experiments vs reflection; ambition vs sharing of ideas and tools—all these and more must be reconciled within the professional persona, not to mention other dimensions of humanity (21, 75).

I have never encountered the extremities that Jim Watson painted in his self-caricature of ruthless competition in *The Double Helix* (95), which is hardly to argue that they do not exist. Side by side with competition, science offers a frame of personal friendships and institutionalized cooperation that still qualify it as a higher calling. The shared interests of scientists in the pursuit of a universal truth remain among the rare bonds that can transcend bitter personal, national, ethnic, and sectarian rivalries.

#### ACKNOWLEDGMENTS

Anyone who knows them, and myself, will recognize how far I have been informed by the sociological insights of Robert K. Merton and Harriet A.

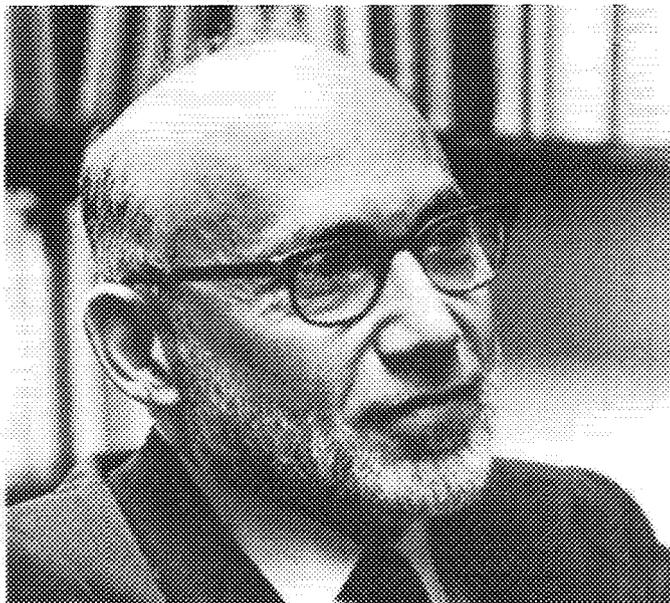
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Zuckerman. Our retrospection was launched in 1974 during a fellowship year on the history and sociology of science at the Center for Advanced Studies in Behavioral Sciences in Stanford, California. My work in 1946 would not have been possible without the willingness of the Jane Coffin Childs Fund for Medical Research to support a calculated risk, in a way that had few parallels then and has had few since. I am indebted to many colleagues who have furnished invaluable documentary sources. The relevant archival materials will be deposited at the Rockefeller Archive Center, Pocantico Hills, New York, whose staff have also been most helpful throughout this effort. This article is taken from an autobiographical work in progress, many years short of publication. I appreciate the editors' assistance in selecting those elements most appropriate for the present readership.

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A number of items of history, briefly touched upon here, have been reviewed more fully: 45, 48–52, 54–56, 60a, 67.

NOTE ADDED IN PROOF An important encyclopedic overview of *E. coli* genetics has just been announced: Neidhardt, F. C., ed. 1987. *Escherichia coli and Salmonella typhimurium: Cellular and Molecular Biology*. Vol. 1, 2. Washington, DC: Am. Soc. Microbiol.



Joshua Lederberg

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