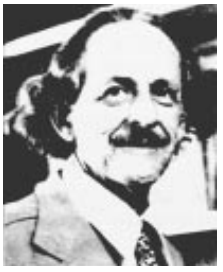


Current Comments®

EUGENE GARFIELD
INSTITUTE FOR SCIENTIFIC INFORMATION®
3501 MARKET ST., PHILADELPHIA, PA 19104

Go to reprint: "Gene Recombination in Escherichia coli"

Postmature Scientific Discovery and the Sexual Recombination of Bacteria—The Shared Perspectives of a Scientist and a Sociologist

Number 3 January 16, 1989

Forty-three years ago Joshua Lederberg and Edward L. Tatum, then at the Osborn Botanical Laboratory, Yale University, New Haven, Connecticut, published a landmark paper in *Nature* reporting the discovery of bacterial sex.[1] Its importance convinced me to reprint the piece here. Recently we have also reprinted reminiscences by Lederberg, now president, The Rockefeller University, New York, on his work in genetics,[2] but as an aspiring sociologist of science I was even more attracted to the paper that he coauthored with Harriet Zuckerman, Department of Sociology, Columbia University, New York, in the December 18, 1986, issue of *Nature*. In this paper, which we are also reprinting here, Zuckerman and Lederberg view this discovery from a sociological point of view.[3] In reading this remarkable "case study" of the Lederberg-Tatum discovery of bacterial sex, my thoughts resonated to their analysis of "postmature scientific discovery."

Some *Current Contents*® readers may not be aware that Harriet and Josh coined this term as a parallel to "premature discovery," the phenomenon described by Gunther S. Stent, professor of molecular biology, University of California, Berkeley, and others[4,5] that we have discussed on many occasions. (A prototypical example is the case of botanist Gregor Mendel.[6]) Indeed, we at ISI® have used citation analysis to study cases of premature discovery. These longitudinal studies have covered many years of data and focus especially on delayed recognition, one aspect of prematurity, as in the cases of Peter D. Mitchell[7,8] and the Higgs boson.[9,10] Currently we are preparing an essay that deals with the topic of delayed recognition. It will appear in the next few months.

Some time ago sociologist Robert K. Merton, Columbia University, honored me by writing the foreword to my book *Citation Indexing—Its Theory and Application in Science, Technology, and Humanities*.[11] There, he reflected on the possibility that the *Science Citation Index*® was an "inevitable" discovery. In a recent publication, he has also mentioned the reprint on postmature scientific discovery that follows as an example of "sociological autobiography"—combining the complementary advantages of both Insider and Outsider perspectives, while minimizing the disadvantages of each.[12] Reading the Zuckerman-Lederberg definition of postmature discovery made me realize the interesting relationship between these: the inevitability of discovery and postmaturity. Language plays tricks on us—inevitability of discovery seems the right way to describe, for example, simple techniques that are so "obvious" once they are invented. In patent law, "inevitability" is often expressed by the phrase "obvious to anyone versed in the art." Many a patent application has been denied on that principle.

Both the inevitable "discovery" of citation indexing and the postmature discovery of bacterial sex show the three attributes

specified by Zuckerman-Lederberg. In retrospect, (1) it must be judged to have been technically achievable at an earlier time with methods then available; (2) it must be judged to have been understandable, capable of being expressed in terms comprehensible to working scientists at the time; and (3) its implications must have been capable of having been appreciated.[3]

In an era of Big Science, with goals such as the conquest of cancer, AIDS, and so on, it is important to understand the limitations of science, but also to understand how its development may be accelerated. When I first entered the field of information science, it was a tenet of our missionary zeal that information technology could have a significant catalytic effect on discovery and its application. While intuition tells us that this has indeed been the case, this assertion is difficult to prove. Whether the "social" engineering of science through better understanding of the discovery process (social science) can claim similar efficiencies remains to be seen. But certainly the management of the global science enterprise will pay a small price for the continued investigation of such processes that might accelerate both research and technology transfer. Zuckerman and Lederberg have made an important contribution to that process.

* * * * *

My thanks to Peter Pesavento for his help in the preparation of this essay.

REFERENCES

1. **Lederberg J & Tatum E L.** Gene recombination in *Escherichia coli*. *Nature* 158:558, 1946.
2. **Garfield E.** The impact of basic research in genetic recombination—a personal account by Joshua Lederberg. Parts 1&2. *Current Contents* (24):3-17, 13 June 1988; (25):3-14, 20 June 1988.
3. **Zuckerman H & Lederberg J.** Postmature scientific discovery? *Nature* 324:629-31, 1986.
4. **Stent G S.** Prematurity and uniqueness in scientific discovery. *Sci. Amer.* 227(6):84-93, December 1972.
5. **Barber B.** Resistance by scientists to scientific discovery. *Science* 134:596-602, 1961.
6. **Garfield E.** Premature discovery or delayed recognition—why? *Essays of an information scientist.* Philadelphia: ISI Press, 1981. Vol. 4. p. 488-93.
7. ----------. The 1976 articles most cited in 1976 and 1977. 2. Physical sciences. *Ibid.*, p. 115-26.
8. Mitchell, Peter D. (Wasson T, ed.) *Nobel Prize winners.* New York: Wilson, 1987. p. 713-5.
9. **Veltman M J G.** The Higgs boson. *Sci. Amer.* 255(5):76-82, 1986.
10. **Garfield E.** How to use citation analysis for faculty evaluations, and when is it relevant? Part 2. *Op. cit.*, 1984. Vol. 6. p. 363-72.
11. **Merton R K.** Foreword. (Garfield E.) *Citation indexing—its theory and application in science, technology, and humanities.* New York: Wiley, 1979. p. v-ix.
12. ----------. Some thoughts on the concept of sociological autobiography. (Riley M W, ed.) *Sociological lives. Vol. 2. Social change and the life course.* Newbury Park, CA: Sage, 1988. p. 17-21.

 Back to Introduction

Gene Recombination in *Escherichia coli*

Analysis of mixed cultures of nutritional mutants has revealed the presence of new types which strongly suggest the occurrence of a sexual process in the bacterium *Escherichia coli*.

The mutants consist of strains which differ from their parent wild type, strain *K*-12, in lacking the ability to synthesize growth-factors. As a result of these deficiencies they will only grow in media supplemented with their specific nutritional requirements. In these mutants single nutritional requirements are established at single mutational steps under the influence of *X*-ray or ultra-vio-

let[1,2]. By successive treatments, strains with several requirements have been obtained.

In the recombination studies here reported, two triple mutants have been used: *Y*-10, requiring threonine, leucine and thiamin, and *Y*-24, requiring biotin, phenylalanine and cystine. These strains were grown in mixed culture in 'Bacto' yeast-beef broth. When fully grown, the cells were washed with sterile water and inoculated heavily into synthetic agar medium, to which various supplements had been added to allow the growth of colonies of various nutritional types. This procedure readily allows the detection of very small numbers of cell types different from the parental forms.

The only new types found in 'pure' cultures of the individual mutants were occasional forms which had reverted for a single factor, giving strains which required only two of the original three substances. In mixed cultures, however, a variety of types has been found. These include wild-type strains with no growth-factor deficiencies and single mutant types requiring only thiamin or phenylalanine. In addition, double requirement types have been obtained, including strains deficient in the syntheses of biotin and leucine, biotin and threonine, and biotin and thiamin respectively. The wild-type strains have been studied most intensively, and several independent lines of evidence have indicated their stability and homogeneity.

In other experiments, using the triple mutants mentioned, except that one was resistant to the coli phage *T1* (obtained by the procedure of Luria and Delbrück[3]), nutritionally wild-type strains were found both in sensitive and in resistant categories. Similarly, recombinations between biochemical requirements and phage resistance have frequently been found.

These types can most reasonably be interpreted as instances of the assortment of genes in new combinations. In order that various genes may have the opportunity to recombine, a cell fusion would be required. The only apparent alternative to this interpretation would be the occurrence in the medium of transforming factors capable of inducing the mutation of genes, bilaterally, both to and from the wild condition. Attempts at the induction of transformations in single cultures by the use of sterile filtrates have been unsuccessful.

The fusion presumably occurs only rarely, since in the cultures investigated only one cell in a million can be classified as a recombination type. The hypothetical zygote has not been detected cytologically.

These experiments imply the occurrence of a sexual process in the bacterium *Escherichia coli*; they will be reported in more detail elsewhere.

This work was supported in part by a grant from the Jane Coffin Childs Memorial Fund for Medical Research.

Joshua Lederberg*
E. L. Tatum

Osborn Botanical Laboratory,
Yale University,
New Haven, Conn.
Sept. 17.

*Fellow of the Jane Coffin Childs Memorial Fund for Medical Research.

[1]Tatum, E. L., *Proc. Nat. Acad. Sci.*, **31**, 215 (1945).
[2]Tatum, E. L., Cold Spring Harbor, Symposia Quant. Biol., vol. 11 (in the press, 1946).
[3]Luria, S. E., and Delbrück, M., *Genetics*, **28**, 491 (1943).

Postmature scientific discovery?

Harriet Zuckerman and Joshua Lederberg

New scientific discoveries do not always flow directly from those made just before. Rather, several varieties of discontinuity can be identified in the growth of science. Premature discoveries are those that scientists do not attend to in a timely way and are retrospectively described as having been "ahead of their time". These have been examined by Barber[1] and Stent[2]. Here, we suggest that there are also postmature discoveries, those which are judged retrospectively to have been 'delayed'. We analyse the arguments that the discovery of bacterial sex was postmature and take up the cor-

relative questions of how the problem was identified and why Lederberg and Tatum[3,4] were likely candidates for making it when they did.

This paper draws on documents, published and private, and analyses by the sociologist-observer and the scientist-participant. Our dialectic procedure departs from most oral histories[5,6]: first, the procedure was iterative: as new discussion raised further possibilities, we both searched for relevant documentation; and second, we both identified the underlying analytic questions and articulated tentative answers to them. We felt that personal reminiscence had to be validated by contemporary documents and other testimony as oral history and autobiography are prone to "unconscious falsification"[7].

Continuities and discontinuities

Scientific growth, usually broadly incremental, can at important times be episodic and discontinuous. Premature discoveries, one conspicuous form of temporal discontinuity in science, are either passively neglected or actively resisted at the time they are made. Mendel's discovery of particulate inheritance in 1865, lost to view for thirty-five years, is the best-known historical case. Discoveries can be premature because they are conceptually misconnected with 'canonical knowledge'[2], are made by an obscure discoverer, are published in an obscure place, or are incompatible with prevailing religious and political doctrine. Barriers between disciplines imposed by specialization of inquiry also contribute to neglect or resistance[1,8-10]. Although the character and sources of premature discoveries have received some analytical attention[8,11], the pattern of postmature discoveries has not been identified, much less systematically studied.

For a discovery to qualify as postmature, for it to evoke surprise from the pertinent scientific community that it was not made earlier, it must have three attributes. In retrospect, it must be judged to have been technically achievable at an earlier time with methods then available. It must be judged to have been understandable, capable of being expressed in terms comprehensible to working scientists at the time, and its implications must have been capable of having been appreciated.

Both prematurity and postmaturity can be recognized only by retrospection. They differ in that prematurity is a matter of actual historical observation while postmaturity is a matter of retrospective conjecture. Such formulations would seem to smack of 'Whig History', the inclination, according to Butterfield, "to produce a story which is the ratification if not the glorification of the present"[12]. But, they are designed to serve quite the contrary purpose. The ideas of premature and postmature discovery provide convenient handles for analysing discontinuities in the growth of scientific knowledge, and support a nonlinear and complex model of advancement in scientific understanding.

Postmature discoveries are not all of a piece. One class results from pre-emption of scientists' research attention. For example, Linus Pauling observed that there was "no reason why" he, himself, could not have discovered the alpha helix eleven years earlier than he actually did "after a few hours of work". In fact, he was preoccupied in the interval by other seemingly more important and feasible inquiries[13,14]. Another class of postmature discoveries answers questions not previously recognized by scientists to be problematic. Certain assumptions, beliefs and images[15] which are also indispensable for the organization of scientific thought can, in specific cases, impede perception of lines of inquiry. For example, Weinberg notes that physicists neglected to pursue quantum field theory further in the 1930s because prevailing images, conceptual schemes and attitudes toward theory and empirical evidence stood in the way[16]. In our case study, both cognitive and social processes obstructed the thinking of scientists about recombination in bacteria.

Sources of neglect

Why was recombination in bacteria not perceived as problematic before 1946? How had asexuality in bacteria come to be an unquestioned 'truth' and how was that view perpetuated?

Before 1870, many believed that the different shapes bacteria assumed were varieties of the same organism, which changed under varying conditions. Indeed, the doctrine of polymorphism or bacterial plasticity became the basis for extravagant claims about variability through most of the nineteenth century. By 1872, Ferdinand Cohn concluded that the various shapes bacteria took were not different forms of the same organism; they were monomorphic and did not change during their short lifetimes[17]. Yet reports of variation continued until 1881 when Robert Koch introduced a simple and effective means for growing pure cultures. Koch's pure-culture method, which became a symbol of modern bacteriology with its phobia of contamination, together with Cohn's doctrine of monomorphism rapidly changed bacteriologists' views about variation.

The two were consolidated into what was called the Cohn-Koch Dogma, which discouraged for years the study of the problems of morphology, inheritance and variation in bacteria[18].

Cohn was convinced that bacteria were primitive plants which could "only reproduce by asexual means" and in 1875 characterized all bacteria as *Schizomycetes* or 'fission fungi'. With every use of that label, bacteriologists were reminded that these organisms reproduced only by fission and that they were simple primitive plants, a tradition that had begun with Leeuwenhoek's first observation of bacteria in 1675. Labels, categories, nomenclature and taxonomies usually help to organize scientific thought but can also delay the reexamination of fallacious traditions, thus becoming self-fulfilling prophecies[19]. In the end, the emergence of medical microbiology as a science depended on the doctrinal base laid down by Cohn and the pure culture methods of Koch. Nonetheless, monomorphic doctrine, when strictly construed, threw out the baby of bacterial variation with the dirty bath water of contamination. It was widely assumed that observations of bacterial variation had to result from contamination. Bacteriologists took experiments involving variation to be error-prone and disreputable[20]. Such experiments were to be avoided as having great procedural difficulty and little intellectual merit. With the strong incentives in science for avoiding problems notorious for leading to irreproducible results, very few scientists would elect to undertake them.

Bacteria occupied an ambiguous place in the hierarchy of living organisms. To many, these organisms appeared so primitive that they could not yet have evolved 'differentiated genes'. This image also reinforced the use of bacteria as exemplars of pre-genic levels of organization for physico-chemical analysis. Once such complex imagery becomes established, special provocation is needed to splinter away one or more of its elements.

Disciplinary emphases and the division of labour among the sciences also diverted attention from the problem of bacterial sexuality. Bacteriologists were principally concerned with problems in medical pathology rather than issues like the biology of bacterial reproduction. Geneticists were no more interested in bacterial reproduction than bacteriologists. They were occupied with larger organisms in which the products of crossing were readily observed. Thus, disciplinary division of labour and the careful choice of organisms for inquiry, both generally conducive to the development of scientific knowledge, contributed in this instance to neglect of bacterial recombination. It has been argued, however, that 'disciplinary dogmatism' and 'disciplinary monopoly' have only rarely impeded the development and diffusion of scientific innovation[21].

Members of the Delft School of Microbiology, in the early part of this century, did bridge the gap between bacteriology and genetics. Clearly separating themselves from the medical bacteriologists who maligned bacteria, they believed that progress in fundamental microbiology depended on people who 'loved' microbes[22]. Martinus Beijerinck, the main figure in the group, seems now to have been the most likely candidate for investigating bacterial sex. He rejected prevailing dogma on bacterial invariability, promptly cited deVries' finding on plant mutations and offered some of the first coherent challenges to strict monomorphism[23]. He also developed 'enrichment culture' methods, forerunners of the selective techniques used later in discovering bacterial recombination. Moreover, he was better informed than most microbiologists about work on plant hybridization which would have been useful in planning any investigation of sex in bacteria. Beijerinck and the Delft School were likely candidates for investigating bacterial sex, but they did not. In fact, Beijerinck strongly supported the Cohnian dogma of schizomycetes. Thus the problem of sexual recombination still fell between disciplinary schools[24].

Significance of bacterial sex

By the 1930s, developments were under way that led biologists to reexamine how bacteria related to other forms of life and whether bacteria really had genes. Important among these developments was the unification in biological thought of Mendelian genetics, quantitative population theory and Darwinian evolution, particularly the notion of species being Mendelian breeding populations or isolated gene pools. The idea that sexuality was, itself, an evolved genetic system proved particularly provocative, with illustrations drawn from simple and complex plant life. Dobzhansky's monograph, "*Genetics and the Origin of Species*"[25], was widely read as the definitive reinterpretation of Darwinian theory of evolution and focused interest on the details of breeding systems as the key to understanding evolutionary development. This, in turn, sharpened interest in understanding the evolution of organisms, like bacteria, believed to be devoid of sexual mechanisms.

The biochemical analysis of microbial nutrition, especially by Knight and Lwoff[18], was another

major impetus to reexamining the relationship of bacteria to other forms of life. In particular, the discoveries that the biochemistry of microbes paralleled in many details that of higher organisms inspired Beadle and Tatum's work on *Neurospora* in 1941[26]. They showed *Neurospora's* usefulness as a research material for studying the genetic control of an organism's development through the encoding of specific enzymes, known as the 'one-gene-one-enzyme' hypothesis. This marriage of biochemistry and genetics had particular significance for the Lederberg–Tatum work[27,28].

There was also renewed speculative interest in a biochemical theory of the origin of life. "*The Origin of Life on Earth*"[29] by the Russian biochemist, Oparin, became available in English in 1944, as did "*What is Life?*"[30] by the physicist, Schrödinger. Both focused attention on questions that demanded the integration of the biology of viruses and microbes with the more traditional biology of plants and animals.

The connections between these independent developments were not always apparent at the time. But one event did call attention to their common message: the discovery by Avery, MacLeod and McCarty[31] in 1944 which identified DNA as the transforming principle that changed rough non-pathogenic pneumococci into smooth virulent ones.

The scientific significance of that discovery has been examined in detail[32-38]. For our purposes, it highlighted two important questions: what was the structure of bacterial genes and how were they transferred? Thus the work by Avery *et al.* made the question of bacterial sex newly consequential. Dubos[39] makes it clear that had sexual reproduction been observed, it would have been understood and appreciated. But bacteria were so widely assumed not to reproduce sexually that no one considered this problem to be important. Dogma prevailed over focused curiosity.

Structural contexts

In retrospect, Lederberg's position in the communication network and his not yet having a career in science seem consequential for his identifying the problem of bacterial sex, for his developing a method for its investigation and for his being in a position to do the research. Tatum was led to the problem independently for somewhat different reasons[27]. Lederberg was unenthusiastic about classical genetics when he arrived at Columbia College in 1941. His interest in "understand[ing] the chemical nature of life" led him to spend much of the next four years studying chemistry, cytology and physiological embryology. But he was not ignorant of classical genetics and the Columbia biologists were well connected with the New York network of scientific communication about genetics. Dobzhansky was a central figure. Arthur Pollister was in close touch with researchers at the Rockefeller Institute. Alfred Mirsky worked at both institutions. Lederberg not only learned quickly about the neo-Darwinian developments described earlier but he also heard about the work of Avery *et al.* from Mirsky and promptly read their paper. If the Avery *et al.* work sharpened Lederberg's interest in bacterial reproduction, Dubos' review of the inconclusiveness of evidence on sexual reproduction sharpened his scepticism; the cognitive and structural elements were coalescing.

In Lederberg's second year at Columbia he met Francis Ryan, an assistant professor, who had just completed a postdoctoral fellowship at Stanford with Beadle and Tatum. It was Ryan who first told him about the work on biochemical genetics and who persuaded him that chemistry and genetics were not as far apart as he had thought[27]. It was also Ryan who generously provided Lederberg with laboratory facilities, catalysed his association with Tatum, and, most importantly, encouraged, educated and socialized him as a scientist. Columbia provided Lederberg with a multifaceted and advantageous structural context for his scientific development and for the initiation of a high-risk, high-stakes research programme.

Lederberg's plan for research was well worked out by July 1945, when he was a second-year student at Columbia Medical School but continued to work in Ryan's laboratory. The research might have been pursued at Columbia, but Ryan and Lederberg both recognized that an association with Tatum would be valuable. In particular, his experience in microbial biochemistry could help broaden Lederberg's education beyond the opportunities available on Morningside Heights. Furthermore, Tatum, then in the process of moving to Yale, was rapidly becoming recognized as a scientific leader. He could provide Lederberg with better access not only to information, research materials and fellowship support, but also to the invisible college of the emerging scientific discipline of biochemical genetics. The impact of such informal ties between investigators on the directions and pace of scientific research has yet to be properly investigated.

Lederberg's status as a medical student was less an obstacle to his investigating bacterial sex than might be supposed. Though much of his time was spent on course work, he was not subject to the

constraints that apply in the early years of study for the PhD. He did not, like ordinary graduate students, have to choose a research problem that would be suitable for a thesis and publication. Being marginal[40] to the biological research enterprise, he could afford to take on a high-risk problem. The search for bacterial sex was definitely high-risk; it was not one likely to produce useful and publishable findings. After all, not observing bacterial recombination would scarcely demonstrate that it did not exist. The risk of a negative finding using *E. coli* is now known precisely; bacterial recombination being observed in only five percent of all strains with the techniques used in 1946.

For a different set of reasons, Tatum could also afford research on a high-risk problem at the time. He had a variety of projects in process in his laboratory and could manage to take a long-shot experiment that required little time and little money. For both men, bacterial recombination was a good gamble; failure would have low marginal costs for each but promised large if prospectively improbable returns. High-risk investigations are not equally feasible for all scientists. They fall to the comparatively well-established or to those who are marginal as Lederberg was in 1946. Those who solve high-risk problems, having chosen them in the first place, may more often come from the ranks of the well established than from neophytes thus contributing to the accumulation of advantage[41]. Risk-taking in science is a matter not only of psychological daring but also of position in the social structure[14,42].

After a brief correspondence, Tatum invited Lederberg to work at Yale. He arrived in March 1946; genetic recombination in *E. coli* was experimentally observed early in May. The results were so arresting that Tatum arranged for Lederberg to present them at the Cold Spring Harbor Symposium to be held in July. The publications which followed[3,4,43] did not merely describe the results of the initial laboratory investigation. They are the product of critical discussion of those results at that meeting and of follow-up experiments done immediately afterwards[27]. The dynamics of organized scepticism in science[44] can be observed in the records of that meeting and later in responses to the papers announcing the discovery. Even as first published, discoveries are not simply reports of events initially observed in the laboratory[45,46] but often are also the outcomes of exchange between contributors and their critics. Treating scientific contributions as the results of inquiry, criticism and subsequent work makes problematic the custom of designating this or that scientist as the exclusive contributor and focusses attention on the operation of organized scepticism and its effect on shaping the meaning and assessment of those contributions.

Conclusions

Was the investigation of sexual recombination in bacteria postmature, that is, conducted significantly later than it could have been? The problem was obscured for decades by the Cohn–Koch dogma of monomorphism and the conviction that bacterial variation resulted only from contamination. This was so even for Beijerinck and members of the Delft School who did not subscribe to strict monomorphism, knew how to mark microbial strains by their fermentative and nutritional characteristics (the basis of Lederberg's design), knew about Mendelian segregation in plants, and might have appreciated the significance of sexual recombination in bacteria were it observed. But, they were committed to the view that bacteria reproduced only by fission and did not consider the phenomenon problematic. In principle, the investigation was technically feasible by 1908, as demonstrated by Browning's[47] use of drug resistance as a selective marker, an early anticipation of the Lederberg–Tatum work. But Browning dealt with a different organism, reported a negative result, and used terminology not readily transferable to the case of bacterial recombination. In the 1930s, bacterial sex was still viewed as unlikely, even as a disputable idea. Yet had it been demonstrated experimentally, it would have been understood and appreciated by geneticists and possibly even by bacteriologists.

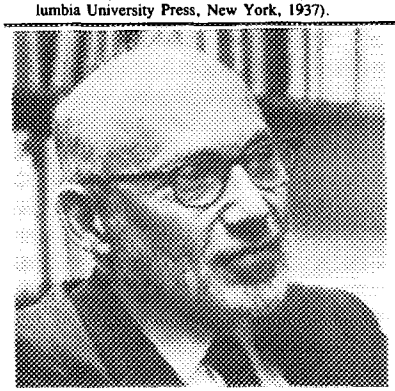
This case study suggests that problem identification and selection in science have features deserving further analysis. First, the solutions to two classes of problems are apt to be postmature: those which do not survive competition for scientists' attention when they first appear because they seem insignificant, unfeasible or both and those which are obscured by prevailing cognitive commitments or have no socially and cognitively defined disciplinary home. Second, in calculating the probable returns on selecting problems for investigation, scientists assess the likelihood of error and this contributes to the continuing neglect of certain problems that have a history of being error-prone. Third, the feasibility of addressing high-risk problems in science and so of making major advances in this way is not equal for all investigators; they are left largely to the well-established who can afford them and to others who have a

smaller stake, for structural reasons, in their immediate record of publication. What scientists define as problematic and worthy of investigation are the products of interactions between cognitive and social processes.

Research supported by NSF Foundation (SES 80-08609), the Russell Sage Foundation and the Center for Advanced Study in the Behavioural Sciences.

Harriet Zuckerman is at the Department of Sociology, Columbia University, New York, New York 10027, USA and Joshua Lederberg is at The Rockefeller University, 1230 York Avenue, New York, New York 10021, USA.

1. Barber, B. *Science* **134,** 596–602 (1961).
2. Stent, G.S. *Sci. Am.* **227,** 12, 84–93 (1972).
3. Lederberg, J. & Tatum, E.L. *Nature* **158,** 558 (1946).
4. Lederberg, J. & Tatum, E.L. *Cold Sp. Harb. Symp.* **9,** 113–114 (1946).
5. Nevins, A. *Wilson Lib. Bull.* **60,** 607–615 (1966).
6. Bension, S. in *Modern Methods in the History of Medicine* (ed. Clarke, E.) 286–365 (Athlone, London, 1971).
7. Sarton, G. *The Study of the History of Mathematics* **35** (Harvard University Press, Cambridge, 1936).
8. Merton, R.K. *The Sociology of Science* 371–382 (University of Chicago Press, 1973).
9. Garfield, E. *Essays of an Information Scientist (1979–80)* 488–493 (ISI, Philadelphia, 1981).
10. Cole, S. *Am. J. Sociol.* **76,** 286–306 (1970).
11. Garfield, E. *Current Comments* **1717,** 3–10 (1985).
12. Butterfield, H. *The Whig Interpretation of History* (W.W. Norton, New York, 1965).
13. Pauling, L. *Nature* **248,** 769–771 (1974).
14. Zuckerman, H. *Sociol. Inq.* **48,** 65–95 (1978).
15. Holton, G.J. *Thematic Origins of Scientific Thought: Kepler to Einstein.* (Harvard University Press, Cambridge, 1973).
16. Weinberg, S. *Daedalus* **106,** 17–35 (1977).
17. Geison, G.L. in *Dict. Sci. Biog.* **3,** (ed. Gillispie, C.C.) 335–41 (Scribner's, New York, 1971).
18. Dubos, R.J. *The Bacterial Cell* **135** (Harvard University Press, Cambridge, 1945).
19. Merton, R.K. *Social Theory and Social Structure* 475–490 (Free Press, New York, 1968).
20. Zuckerman, H. in *Deviance and Social Change* (ed. Sagarin, E.A.) 87–138 (Sage Publications, Beverly Hills, California, 1977).
21. Ben-David, J. in *Culture and Its Creations* (eds Ben-David, J. & Clark, T.) 255–65 (University of Chicago Press, Chicago, 1977).
22. *Kluyver, Albert Jan: His Life and Work.* (eds Kamp, A.R., La Rivière, J.W.M. & Verhoeven, W.) **186** (Amsterdam, North Holland, 1959).
23. Beijerinck, M. *Versl. Akad. Wetensch. (Amsterdam)* **9,** 310 (1901).
24. Aronson, N. *Why Weren't Vitamins Discovered Earlier?* (unpublished, 1984).
25. Dobzhansky, T.G. *Genetics and the Origin of Species* (Columbia University Press, New York, 1937).
26. Beadle, G.W. & Tatum, E.L. *Proc. natn. Acad. U.S.A.* **27,** 499–506 (1941).
27. Lederberg, J. *Nature* **324,** 627–631 (1986).
28. Lederberg, J. & Tatum, E.L. *A. Rev. Genet.* **13,** 1–5 (1979).
29. Oparin, A.I. *The Origin of Life on Earth* Trans. Ann Synge (Academic, New York, 1957).
30. Schrödinger, E. *What is Life? The Physical Aspect of the Living Cell* (Cambridge University Press, Cambridge, 1962).
31. Avery, O.T., MacLeod, C.M. & McCarty, M. *J. exp. Med.* **79,** 596–602 (1944).
32. Judson, H.F. *The Eighth Day of Creation: Makers of the Revolution in Biology* (Simon & Schuster, New York, 1979).
33. McCarty, M. *The Transforming Principle: Discoveries That Genes Are Made of DNA* (Norton, New York, 1986).
34. Olby, R.C. *The Path to the Double Helix* (University of Washington Press, Seattle, 1974).
35. Dubos, R.J. *The Professor, The Institute and DNA* (Rockefeller University Press, New York, 1976).
36. Fruton, J.S. *Molecules and Life: Historical Essays on the Interplay of Chemistry and Biology* (Wiley, New York, 1972).
37. Lederberg, J. *Nature* **239,** 234–236 (1972).
38. Cohen, J.S. & Portugal, F.H. *Persp. Biol. Med.* **18,** 204–207 (1975).
39. Dubos, R.J. *The Bacterial Cell* **181,** (Harvard University Press, Cambridge, 1945).
40. Gieryn, T.F. & Hirsch, R.F. *Soc. St. of Sci.* **13,** 87–106 (1983).
41. Merton, R.K. *The Sociology of Science* 439–59 (University of Chicago Press, Chicago, 1973).
42. Mulkay, M.J. *The Social Process of Scientific Innovation: A Study in the Sociology of Science,* 49–51 (Macmillan, London, 1972).
43. Tatum, E.L. & Lederberg J. *J. Bact.* **53,** 673–684 (1947).
44. Merton, R.K. *The Sociology of Science* 267–278 (University of Chicago Press, Chicago, 1973).
45. Latour, B. & Woolgar, S. *Laboratory Life: The Social Construction of Scientific Facts.* (Sage Publications, Beverly Hills, 1979).
46. Knorr-Cetina, K. *The Manufacture of Knowledge: An Essay on the Constructivist & Contextual Nature of Science* (Pergamon, Oxford, 1981).
47. Browning, C.H. *J. Path. Bact.* **12,** 166–190, (1908).



Joshua Lederberg

Harriet Zuckerman