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EDWARD LAWRIE TATUM

1909—1975

A Biographical Memoir by

JOSHUA LEDERBERG

Biographical Memoir

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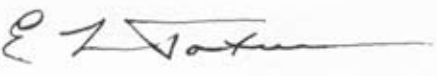

EDWARD LAWRIE TATUM

December 14, 1909–November 7, 1975

BY JOSHUA LEDERBERG

IN THE HISTORY OF BIOLOGY Edward Lawrie Tatum's name is linked with that of George Wells Beadle for their pioneering studies of biochemical mutations in Neurospora.[1] First published in 1941, these studies have endured as the prototype of the investigation of gene action to the present day. A still more enduring legacy is their development of experimental techniques for the mutation analysis of biochemical pathways used daily by modern biologists.

Though this sketch is written as a biography of Edward Tatum, these singular scientific accomplishments were—in practice and attribution—intimately shared with Beadle. Tatum brought to the work a background in microbiology and a passion for the concept of comparative biochemistry; Beadle, great sophistication in "classical genetics" and the leadership and drive to replace the underbrush of vitalistic thinking with a clear-cut, mechanistic view of the gene and the processes of life.

Little more than the bare outlines of Edward Tatum's personal history can be documented, because of his own aversion to accumulating paper and the fact that most of his corre-

[1] George W. Beadle died on June 9, 1989, when this essay was in press. His memoir, by Norman H. Horowitz, is also included in this volume.

spondence was discarded during his various moves. His scientific achievements, however, were largely and appropriately recognized. In 1952 he was elected to the National Academy of Sciences and in 1958, with George Beadle and Joshua Lederberg, won the Nobel Prize in Physiology or Medicine. Tatum was also known for his commitment to nurturing younger scientists, with whom he zestfully enjoyed every aspect of laboratory work. A still more enduring legacy of their work has been the everyday use of experimental mutation analysis of biochemical pathways in modern biology since then.

EDUCATION AND EARLY LIFE

Edward Lawrie Tatum was born in Boulder, Colorado, on December 14, 1909, the first surviving son of Arthur L. (1884–1955) and Mabel Webb Tatum. A twin, Elwood, died shortly after birth. At the time of Edward's birth his father was an instructor in chemistry at the University of Colorado at Boulder, where Mabel Webb's father had been Superintendent of Schools. Arthur's own father, Lawrie Tatum, a Quaker who had settled in the Iowa Territory, had been an Indian agent after the Civil War and written a book, *Our Red Brothers*.

In rapid succession the Tatum family moved to Madison, Wisconsin; Chicago, Illinois; Philadelphia, Pennsylvania; Vermillion, South Dakota; and, back—in 1918—to Chicago. During this period the elder Tatum held a succession of teaching positions while earning a Ph.D. in physiology and pharmacology from The University of Chicago and an M.D. from Rush Medical College. By 1925 he was settled at the University of Wisconsin at Madison as professor of pharmacology in a department that was a major center for the training of professors of pharmacology. Among his research accomplishments were the introduction of picrotoxin as an

antidote for barbiturate poisoning and the validation of arsenoxide (mapharsen) for the chemotherapy of syphilis,[2] the most effective drug for this purpose until the introduction of penicillin.

Edward, having the double advantage of this remarkable family background and the Laboratory School at The University of Chicago, continued his education at Wisconsin, earning a bachelor's degree in 1931. At Wisconsin he came upon the tradition of research in agricultural microbiology and chemistry that was then flourishing under the leadership of E. B. Fred (later president of the University) and W. H. Peterson.[3]

Tatum's first research was a bachelor's thesis (published 1932) on the effect of associated growth of bacterial species Lactobacillus and *Clostridium septicum* giving rise to racemic lactic acid. (In 1936 he demonstrated that the *C. septicum* racemized the d-lactic acid produced by the lactic acid bacteria.) He continued his graduate work at Wisconsin with financial support from the Wisconsin Alumni Research Foundation—the beneficiary of royalties from Steenbock's patents on vitamin D milk. His Ph.D. dissertation (1935) concerned the stimulation of *C. septicum* by a factor isolated from potato, identified as a derivative of aspartic acid and later shown to be asparagine. This was followed by collaborations with H. G. Wood and Esmond E. Snell in a series of pioneering studies

[2] John Patrick Swann, "Arthur Tatum, Parke-Davis, and the Discovery of Mapharsen as an Antisyphilitic Agent," *Journal of the History of Medicine and Allied Sciences*, 40(1985):167–87. F. E. Shideman, "A. L. Tatum, Practical Pharmacologist," *Science*, 123(1956):449. Anonymous, "Profile of a Research Scientist," *Bulletin of Medical Research*, National Society for Medical Research, 8(1954):7–8.

[3] The roots of their work can be traced to Koch, Tollens, and Kossel in Germany. See I. L. Baldwin, "Edwin Broun Fred, March 22, 1887–January 16, 1981," *Biographical Memoirs of the National Academy of Sciences*, Vol. 55, pp. 247–290; and Conrad A. Elvehjem, "Edwin Bret Hart, 1874–1953," *Biographical Memoirs*, Vol. 28, pp. 117–161. See also E. H. Beardsley, *Harry L. Russell and Agricultural Science in Wisconsin* (Madison, Wisconsin: University of Wisconsin Press, 1969).

on the role of vitamins in bacterial nutrition. In 1936 they studied the growth factor requirements of propionic acid bacteria, fractionating one factor from an acetone extract of milk powder. Its physical properties suggested that the factor might be thiamine, and indeed crystalline thiamine was fully active as an essential growth factor.

Vitamins had long been recognized to share a role in the nutrition of animals, man, and yeast. Tatum's work with Snell, Peterson, and Wood initiated a genre of studies showing that many bacterial species had diverse requirements for these identical substances. This was outstanding confirmation of the basic tenet of comparative biochemistry—the evolutionary conservation of biochemical processes—that produced common processes in morphologically diversified species. Tatum's education and doctoral research coincided with the culmination of understanding that all of the basic building blocks of life—amino acids, sugars, lipids, growth factors (and later nucleic acids)—existed in fundamentally similar chemical structures among all forms of life. Hence the most fruitful way to study a problem in animal metabolism might be to begin with a microbe, which might well prove more convenient for experimental manipulation and bioassay and—as the future would show—genetic analysis and alteration.

Tatum then won a General Education Board postdoctoral fellowship that took him, his wife (the former June Alton, a fellow student at Wisconsin), and their infant daughter, Margaret, to Fritz Kögl's laboratory at Utrecht, The Netherlands, for a year. Kögl had just purified and crystallized biotin as a growth factor for yeast, and this enabled and inspired further studies on its nutritional role for other microorganisms. (Not until 1940 was the nutritional significance of biotin for animals recognized.)

By Tatum's own account, his brief time at Utrecht, spent in efforts to isolate further growth factors for staphylococci,

never achieved a sharp research focus. More importantly, he befriended Nils Fries, another research fellow from Uppsala, Sweden, who was using the newly available biotin to define the specific nutritional requirements of an ever wider range of fungi. Fries and Kögl were able to demonstrate striking examples of nutritional symbiosis—the compensation for complementary deficits in mixed cultures of various fungi.

Tatum's report to the General Education Board records his gratification at having been able to meet, as well, A. J. Kluyver at Delft, and B. C. J. G. Knight and P. Fildes in England—then already well known as leading investigators of bacterial chemistry and nutrition from a comparative perspective. (J. H. Mueller at Harvard and A. Lwoff in Paris had also stressed how microbial nutrition reflected evolutionary losses of biochemical synthetic competence—a concept that can be traced to Twort and Ingram in 1911[4]—though they had not as yet adopted the language or conceptual framework of genetics that would eventually describe such variations as gene mutations affecting biosynthetic enzymes.)

THE STANFORD YEARS (1937–1945)

That same year, 1937, Beadle was on the point of moving from Harvard to Stanford. His research program in physiological genetics was to continue the work on the genetics of Drosophila eye pigments that he had initiated in collaboration with Boris Ephrussi, first at Caltech, then in Paris. The Rockefeller Foundation's support of this enterprise was one of Warren Weaver's most foresighted initiatives in the gestation of molecular biology.[5]

Looking out for a possible position for Tatum, his profes-

[4] F. W. Twort and G. L. Y. Ingram, "A Method for Isolating and Cultivating the *Mycobacterium enteritidis chronicae pseudotuberculosae* Johne," and "Some Experiments on the Preparation of a Diagnostic Vaccine for Pseudo-tuberculous Enteritis of Bovines," *Proceedings*, Royal Society, London, Series B, 84(1911–12):517–42.

[5] See also Mina Rees, "Warren Weaver, July 17, 1894–November 24, 1978," *Biographical Memoirs*, Vol. 57, pp. 493–530.

sors at Wisconsin forwarded Beadle's solicitation for a research associate "biochemist to work on hormone-like substances that are concerned with eye pigments in Drosophila." But, practical-minded, they recommended that the young man undertake research on the chemical microbiology of butter, writing him that "this field is certainly getting hot."

With jobs scarce, economic realities weighed as heavily as intellectual appeal in the choice between insect eyes and dairy microbiology. Arthur Tatum, Edward's father, was much concerned that, if his son undertook a hybrid role, he would find himself an academic orphan, disowned by each of the disciplines of biochemistry, microbiology, and genetics. In the event, however, Tatum accepted Beadle's offered position, and the multiple challenges of comparative biochemistry that went with it. Though the economic importance of butter research was far more obvious at the time, it is certain that Edward Tatum could not have chosen better than Drosophila as a means for contributing to the field of biotechnology.

Joining Beadle at Stanford, Tatum was engaged between 1937 and 1941 with the arduous task of extracting pigment-precursors from Drosophila larvae. Ephrussi and Beadle's earlier transplantation experiments had demonstrated that a diffusible substance or hormone produced by wild-type flies was critically lacking in the mutant strain. Yet Tatum and Beadle's own experience differed significantly from the report published by Ephrussi and Chevais. According to this report, normal eye color could be restored in cultures supplemented with tryptophane. Tatum, however, could confirm this only with cultures carrying a bacterial contaminant. Far from discarding such a contaminant as an interfering variable, Tatum cultured the organism (a Bacillus species) to prove that it was a source of the elusive hormone. The interchangeability of growth factors for bacteria and animals and the knowledge that many microbes synthesized vitamins required by other species undoubtedly bolstered this theory.

A. J. Haagen-Smit, whom Beadle had known at Harvard, was now at the California Institute of Technology, and Tatum visited him to learn microchemical techniques, then set out to isolate the "V+ hormone" from the bacterial culture. He succeeded in doing this in 1941, only to be anticipated by Butenandt *et al.* in the identification of V+ as kynurenine. (Butenandt, astutely noting—from a Japanese publication—that kynurenine was a metabolite of tryptophane in dog urine, had tested the substance for eye color hormone activity.) The jarring experience of having their painstaking work overtaken in so facile a way impelled Beadle and Tatum to seek another organism more tractable than Drosophila for biochemical studies of gene action.

Neurospora and the One Gene–One Enzyme Theory

In winter quarter 1941, Tatum (although a research associate without teaching responsibilities) volunteered to develop and teach a then unprecedented comparative biochemistry course for both biology and chemistry graduate students. In the course of his lectures he described the nutrition of yeasts and fungi, some of which exhibited well-defined blocks in vitamin biosynthesis. Attending these lectures, Beadle recalled B. O. Dodge's elegant work on the segregation of morphological mutant factors in Neurospora that he had heard in a seminar at Cornell in 1932,[6] work that was followed up by C. C. Lindegren at Caltech.

Neurospora, with its immediate manifestation of segregating genes in the string of ascospores, has an ideal life-cycle for genetic analysis. Fries's work suggested that Neurospora might also be cultured readily on a well defined medium. It was soon established that Neurospora required only biotin as

[6] See also W. J. Robbins, "Bernard Ogilvie Dodge, April 18, 1872–August 9, 1960," *Biographical Memoirs*, Vol. 36, pp. 85–124.

a supplement to an inorganic salt-sucrose medium and did indeed prove an ideal organism in which to seek mutations with biochemical effects demonstrated by nutritional requirements. By February 1941,[7] the team was X-raying Neurospora and seeking these mutants.

Harvesting nutritional mutants in microorganisms in those days was painstaking hand labor; it meant examining single-spore cultures isolated from irradiated parents for their nutritional properties—one by one. No one could have predicted how many thousands of cultures would have to be tested to discover one that would have a biochemical defect marked by a nutritional deficiency.

Isolate #299 proved to be the first recognizable mutant, requiring as it did pyridoxine. The trait, furthermore, segregated in crosses according to simple Mendelian principles, which foretold that it could in due course be mapped onto a specific chromosome of the fungus. Therewith, Neurospora moved to center stage as an object of genetic experimentation. By May of the same year, Beadle and Tatum were ready to submit their first report of their revolutionary methods to the *Proceedings of the National Academy of Sciences.*

In that report they noted "there must exist orders of directness of gene control ranging from one-to-one relations to relations of great complexity." The characteristics of mutations affecting metabolic steps suggested a direct and simple role for genes in the control of enzymes. The authors

[7] G. W. Beadle, "Recollections," *Annual Revue of Biochemistry,* 43 (1974):1–13. In his chapter, "Biochemical Genetics, Some Recollections," in *Phage and the Origins of Molecular Biology,* eds. J. Cairns, G. S. Stent, and J. D. Watson (Cold Spring Harbor, New York: C. S. H. Biol. Labs, 1966), Beadle confused the 1940–41 meeting of the Society of American Naturalists in Philadelphia, which made no reference to Neurospora, with that of the Genetics Society in Dallas in December 1941. The net effect is to date the Neurospora experiments to 1940 rather than to 1941. H. F. Judson repeated the error in *The Eighth Day of Creation* (New York: Simon & Schuster, 1979), and it is bound to plague future historians.

hypothesized, therefore, that enzymes were primary products of genes. Indeed, in some cases, genes themselves might be enzymes. This was what came to be labelled the one gene–one enzyme theory, the precursor of today's genetic dogma. We shall return to it later.

In that same year Tatum was recruited as an assistant professor to the regular faculty of Stanford's Biology Department, where he developed an increasingly independent research program exploiting the use of Neurospora mutants for the exploration of biochemical pathways. Despite the exigencies of the war effort, an increasing number of talented graduate students and postdoctoral fellows flocked to Stanford to learn the new discipline. Their participation rapidly engendered a library of mutants blocked in almost any anabolite that could be replaced in the external nutrients. Today, that catalog embraces over 500 distinct genetic loci and well over a thousand publications from laboratories the world over.[8]

Anticipating the One Gene–One Enzyme Theory

Would that contemporaries could anticipate what future historians will ask or what errors they will promulgate! How many simple questions we neglect to ask, or fail to record the answers, that might have settled continuing controversies. Among these is the place of Archibald E. Garrod's work and thought in anticipation of the one gene–one enzyme hypothesis. The following discussion is offered in some detail in order to correct some prevalent misconstructions of that history.

In 1908, Garrod published his study of what was then called "inborn errors of metabolism," including alcaptonuria

[8] D. D. Perkins, A. Radford, D. Newmeyer, and M. Bjorkman, "Chromosomal loci of *Neurospora crassa*," *Microbiological Reviews*, 46 (1982):426–570.

in man.[9] This work is sometimes portrayed as a forgotten precursor of Beadle and Tatum's investigation of gene action. Indeed, many geneticists who specialized in maize or Drosophila, including Beadle himself, lamented not knowing of this pioneering work earlier—it having received remarkably little comment from geneticists until after Neurospora was launched in 1941.[10]

Yet Garrod's basic findings on alcaptonuria, which parallel the metabolic blocks in Neurospora mutants, were widely quoted in medical texts. J. B. S. Haldane cited them in a well-read essay in 1937. Tatum likewise referred to them in his course in comparative biochemistry before beginning his own experiments on Neurospora. Beadle, in his Nobel Prize lecture in 1958, was careful to acknowledge these antecedents, though widely quoted reminiscences have blurred the details of just when Beadle and Tatum became aware of Garrod's work.[11]

Haldane, in his 1937 article, cited the difficulty of experimentation on rare human anomalies as an important reason to seek other research paradigms—which Neurospora would eventually provide.[12] But Garrod himself never quite made

[9] "The Croonian Lectures of the Royal College of Physicians," *Lancet* 2(1908):1–7, 73–79, 142–148, 214–220.

[10] H. Harris, ed., *Garrod's Inborn Errors of Metabolism* (Oxford: Oxford University Press, 1963); and B. Childs and C. R. Scriver, eds., *Inborn Factors in Disease by A. E. Garrod* (Oxford: Oxford University Press, 1989), include extensive discussion and bibliography on the history of his ideas. On the neglect of Garrod's work, see also R. Olby, *The Path to the Double Helix* (London, Macmillan Press, 1974).

[11] Though G. W. Beadle implies in *PATOOMB* (*Phage and the Origins of Molecular Biology*, see footnote 7 above), that he and Tatum were unaware of Garrod until perhaps 1945, they referred to Garrod in a paper on their Drosophila-pigment work delivered January 1, 1941 (see *American Naturalist*, 75[1941]:107–16). Garrod's findings were also prominent in Tatum's winter 1941 course on comparative biochemistry at Stanford. I first read about Garrod in Meyer Bodansky's *Introduction to Physiological Chemistry* (New York: Wiley & Sons, 1934), and the late Sewall Wright advised me that he had taught that material in Chicago since 1925.

[12] J. B. S. Haldane, "The Biochemistry of the Individual," in *Perspectives in Biochemistry*, J. Needham and D. E. Green, eds. (Cambridge: Cambridge University

the leap from the anomaly provoked by the mutant gene to the positive functioning of its normal allele. Nor did he recognize enzymes as the direct products of genes in their normal function, but rather referred to mutational anomalies as freaks or aberrations to be compared with the effects of infection or intoxication.

Theoretical biology in Garrod's time believed in "protoplasm" as an almost mystical, living colloid. When altered, genes might influence the workings of that protoplasm but were not yet thought to be the exclusive, or nearly exclusive, seat of hereditary information (to use an anachronistically modern expression).[13] In their 1941 paper, Beadle and Tatum cited the (now quaint) "rapidly disappearing belief that genes are concerned only with the control of 'superficial' characters." It would appear, then, that while Garrod understood how genetic anomalies could assist in the unravelling of metabolic pathways and that biochemical individuality was a hallmark of human nature, he had no comprehensive theory of gene action. Any geneticist, however, would wish to give alcaptonuria—a textbook example of a biochemical genetic defect—full credit as a paradigm on par with the pigment mutation in flowers or in insect eyes.

Before 1941, simple metabolic effects on gene mutation could be inferred in a handful of cases like these, but the vast majority of mutants studied in, say, Drosophila, were complex morphogenetic traits that defied (and still very nearly defy) simple analysis. The experimental material available made it impossible to arrive at any simple theory of gene action. Even more exasperatingly, it offered almost no avenue

Press, 1937). Haldane remarked that "Garrod's pioneer work on congenital human metabolic abnormalities such as alcaptonuria and cystinuria had a very considerable influence both on biochemistry and genetics. But alcaptonuric men are not available by the dozen for research work. . . ."

[13] See J. Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics* (Oxford: Oxford University Press, 1987).

for continued investigation. How frustrated Tatum and Beadle were between 1937 and 1941 in their efforts with Drosophila pigments! It was the conceptual and experimental methodology they developed using nutritional mutants that provided the breakthrough.

Today, four decades later, analyzing developmental and physiological pathways by systematically cataloguing mutants that block them is standard procedure and Beadle and Tatum's papers are rarely cited. Taken for granted, this methodology is yet central to sophisticated studies in physiology, development, and gene action and is of incalculable consequence to biotechnology.

Tryptophane and E. coli *K-12*

The biosynthesis of tryptophane, possibly harking back to Drosophila eye color, remained one of Tatum's central interests. At one point, Tatum and Bonner inquired whether the dismutation of tryptophane into indole + serine was a simple reversal of the synthetic reaction. Though this analogy has been complicated by further knowledge, we now know that there are indeed interesting similarities between the tryptophane-cleaving enzyme and one subunit of the synthetase.

In order to perform studies on tryptophanases, Tatum retrieved a stock strain of *Escherichia coli* from the Stanford Bacteriology Department's long-standing routine strain collection. By this accident, *E. coli* K-12 came to be the object of further genetic experimentation. Its name will reappear shortly in our story.

With Beadle's encouragement, Tatum used his familiarity with bacteria to recruit Acetobacter and *E. coli* as experimental objects for biochemical analysis to parallel Neurospora. Despite the lack of any theoretical or experimental basis for expecting bacteria to have a genetic organization similar to that of higher organisms, Tatum intuitively favored a com-

monality of biological structure to match what comparative biochemistry had revealed in the realm of nutrition. Tatum's prompt demonstration that biochemical mutants like those in Neurospora could also be induced in *E. coli* was, in itself, strong provocation to apply some form of gene theory to bacteria.

As their part in the wartime mobilization during 1944 and 1945, Tatum's laboratory was asked to use its expertise in fungal genetics in an OSRD-sponsored, multi-laboratory search for better penicillin-yielding strains of Penicillium. Though Stanford made significant improvements in yield, their efforts were outstripped by developments elsewhere.

Tatum and Lederberg—Genetic Recombination in Bacteria

The team of Beadle and Tatum by this time had become world famous. But at Stanford, under President Tressider's troubled leadership, the exigencies of finance added to the academic politicking in the Biology Department and left little promise for innovative scientific development. The role of a chemist in a department of biology as then understood was particularly controversial, and C. B. van Niel's unequivocal support for Tatum was of no avail. Despite Tatum's success, his father's foreboding premonition had materialized, and, foreseeing a bleak academic future at Stanford, he sought a post where he could continue to work at the hybrid frontiers of microbiology, genetics, and biochemistry. In 1945, after a trial semester at Washington University in St. Louis, where Carl Lindegren hoped to find a niche for him, Tatum accepted a position at Yale University. A year later Beadle and his formidable team left Stanford *en bloc* to reshape the biology program at Caltech.

At Yale Tatum held a tenured chair and was charged with developing a biochemically-oriented microbiology program with the Department of Botany. His arrival proved a seren-

dipitous break for this author, Joshua Lederberg, then a Columbia medical student studying Neurospora genetics with Francis J. Ryan—an apprenticeship begun at Columbia College in 1942.

In 1941 Ryan had gone to Stanford for a year's postdoctoral fellowship, where he became one of the first disciples of Neurospora biochemical genetics. When he returned to Columbia, he brought back with him his enthusiasm for the new field. At Stanford, Ryan had established a warm friendship with Tatum, and—hearing that he was moving to Yale—sent him Lederberg's proposals for studying genetic recombination in bacteria. On the strength of Ryan's commendation Tatum invited Lederberg to join his laboratory at New Haven starting March 1946, where he was supported financially by the Jane Coffin Childs Fund.

What was to have been a few months' diversion from medical school exceeded Lederberg's wildest expectations. At the Cold Spring Harbor Symposium in July 1946, Tatum's laboratory could report a newly discovered genetic recombination in *E. coli* K-12, vindicating Tatum's gamble that, indeed, *E. coli* had genes![14]

Our use of *E. coli* strain K-12 for these studies derived from Tatum's prior development of single, then double, mutants blocked at different nutritional-biochemical steps. The use of such multiply-marked stocks averted a number of technical artifacts in recombination experiments. Only later did we learn that K-12 itself was a remarkably lucky choice of experimental material: Only about one in twenty randomly chosen strains would have given positive results in experiments designed according to our protocols. In particular, strain B—which had become the standard material for work on bacteriophage—would have been stubbornly unfruitful.

[14] J. Lederberg, "Genetic Recombination in Bacteria: A Discovery Account," *Annual Review of Genetics*, 21 (1987):23–46.

Subsequently K-12 also proved to be a remarkably rich source of the plasmids F and lambda, which have become the objects of major experimental programs in their own right. The serendipity that so often marked Tatum's career cannot be attributed to any personal skill or insight on his part. But his receptivity to "far out" proposals from a medical student visiting his laboratory was typical of the man's unique combination of generosity of spirit and scientific vision.

RETURN TO STANFORD (1948–1956)

During his period at Yale, Tatum also recruited David Bonner to continue joint research on the biosynthesis of tryptophane and bolster the academic program in microbiology. But he was once again disappointed in the University's level of commitment to biochemically-oriented research in a department still heavily dominated by morphological-systematic tradition. In 1948, when Douglas Whitaker took over the leadership of biological research at Stanford, Tatum was persuaded to accept a full professorship in the department that had passed him over just three years before.

From this time forward Tatum, with his particular brand of biochemical insights, pursued and supervised research projects that reconciled a variety of interests introduced by his students and colleagues. In early anticipation of the now famous Ames Screening Test, he became increasingly interested in the analogy between mutagenesis and carcinogenesis.

If the induction of nutritionally dependent mutants in Neurospora was a rather laborious way to demonstrate mutagenicity of a chemical compound, it at least had the advantage of adding to the library of useful strains for biochemical pathway analysis. Many of us felt that *E. coli* was technically superior to Neurospora, both for biochemical and genetic studies (at least in the ease with which vast numbers of mu-

tants could be obtained and propagated; Tatum generally left the exploitation of this material to the students)—and while it was plain that Neurospora was Tatum's first love throughout his career, he leaned over backwards to give his intellectual heirs the utmost leeway for their own development.

During the decade 1948 to 1958, Stanford made a bid to become a major center of scholarship, while California grew in economic, technological, demographic, and political influence. Stanford's then new president, the late J. E. Wallace Sterling, though himself a historian, warmly nurtured scientific and technical development. He supported an ambitious program to reconstruct the School of Medicine on the Stanford campus, transforming a hospital-based school in San Francisco with nominal connection to the University into a major center for medical and biological research.

Under the leadership of Fred Terman, similar institution-building was taking place in Stanford's School of Engineering, nourished by vigorous federal support for science and technology in the wake of World War II. In short order the San Francisco Bay area was transformed into a center for high technology in the electronics and pharmaceuticals industries—a transformation that owed much to Sterling's and Terman's encouragement of University interaction with industry.

With regard to academic policy at Stanford, Tatum proved an energetic spokesman for the rapidly emerging discipline of biochemistry. As a member of the National Science Board he was an influential exponent of predoctoral and postdoctoral fellowship support for creative talent in the new field. In this he no doubt recalled that critical stage in his own career: his postdoctoral experience at Utrecht, that foreshadowed his work with Beadle. He was also a strong advocate of international cooperation among scientists and played an important role in setting up a joint program with Japan.

At Stanford he gave strong encouragement to the development of a new, science-oriented curriculum in medical education and to the whole enterprise—fraught with fiscal and managerial risks—of rebuilding the Medical School. In 1956 he was appointed to head a new Department of Biochemistry, an appointment that would take full effect in 1959 with the completion of the new medical center. Conflicts in his personal life, however, overshadowed his other plans and he left Stanford, separating from his wife and two daughters.

THE ROCKEFELLER INSTITUTE (1957–1975)

In 1953 Detlev Bronk, president of the National Academy of Sciences, left Johns Hopkins to assume the presidency of The Rockefeller Institute in New York, marking the expansion of the Institute into a graduate university. In 1955, Whitaker was recruited from Stanford as vice-president for administration. Between 1953 and 1957, Frank Brink, Keffer Hartline, Paul Weiss, and Fritz Lipmann joined the Institute faculty—not to mention the elevation to full membership of Theodore Shedlovsky, George Palade, and Keith Porter. Tatum was induced to join this illustrious group in 1957, and he remained there until his death in 1975.

In New York, Tatum married Viola Kantor, a staff employee at the National Foundation/March of Dimes where he donated a great deal of time as scientific adviser. This rebuilding of his personal life was, however, to be scarred by Viola's illness and untimely death from cancer in 1974.

As a professor at Rockefeller, Tatum concerned himself with institutional affairs just as he had at Stanford. He was also involved with science policy on a national scale and served on the National Science Board. His special aim was to strengthen fellowship programs and other measures that would bolster support for young people entering scientific work. He was also chairman of the board of the Cold Spring

Harbor Biological Laboratory during a period of fiscal crisis and interpersonal turbulence that, according to one of his associates, was the most grievous episode of his professional life.

THE NOBEL PRIZE (1958)

The Nobel Prize came to Tatum in 1958, a year after his move to the Rockefeller Institute. In his Prize lecture, Tatum reviewed the history of biochemical genetics in his and Beadle's hands. Comparing microbial cultures to populations of tissue cells, he saw cancer as a genetic change subject to natural selection. From this vantage he looked forward to "the complete conquering of many of man's ills, including hereditary defects in metabolism and the momentarily more obscure conditions such as cancer and the degenerative diseases. . . . Perhaps within the lifetime of some of us here, the code of life processes tied up in the molecular structure of proteins and nucleic acids will be broken. This may permit the improvement of all living organisms by processes that we might call biological engineering." Tatum's prophecy erred mainly in its diffidence; the breaking of the genetic code was well under way by 1961, with the reports of M. W. Nirenberg and J. H. Matthaei that matched specific triplets of RNA with individual amino acids in the assembly of polypeptides. These rules of correspondence were the realization in explicit chemical structural terms of the expectations of the one gene–one enzyme theory.

In his own laboratory, Tatum was especially notable for nurturing independent-minded fellows in the pursuit of their own ideas. He was prouder of having cultivated them as gifted investigators than of his own contributions to their research. He strongly encouraged young faculty members at the Rockefeller, like Norton Zinder, and they have acknowledged the debt.

His personal research interests during this phase centered on the use of Neurospora as a model for the genetic control of development. The effects of inositol deprivation or the addition of substances like sorbose on the morphology of the fungus never failed to intrigue him. Features like mycelial branching, subsurface versus aerial hyphae, and the formation of peritheciae and micro- and macro-conidia were thought to be models for the more complex developmental patterns in animal embryogenesis. Such studies are only just now coming into their own.

There is no doubt that mutational alteration of developmental patterns can throw a great deal of light on the interactions between genes and environment that lead to morphological elaboration. This type of material has yet to give us, however, those quasi-stable, epigenetic states—expressed in higher plant and animal cells propagated in tissue culture—whose biochemical genetic analysis would be extraordinarily helpful.

IN CONCLUSION

The ability to balance critical scientific objectivity, personal ambition, and interdependence on others—which some scientists take a lifetime to learn—was ingrained in Ed Tatum from the beginning. Despite misfortune in his personal life, he yet enjoyed the rare and well-earned pleasure of having so many of his fellow scientists look to him warmly as to a father or brother.

At the time of Viola Tatum's death, Ed Tatum's health was already failing, and his friends could only watch with anguish the multiplying pains that attended a life to which he clung with the same doggedness that made him a committed cigarette smoker. He died on November 7, 1975, from heart failure complicated by progressive, chronic emphysema.

Edward Lawrie Tatum was survived by two daughters

from his first marriage: Margaret (Mrs. John Easter) and Barbara. His brother Howard worked for many years with the Population Council doing research on contraception. His late sister, Besse, was married to A. Frederick Rasmussen, professor of microbiology at UCLA.

This memoir was completed more than a decade after Tatum's death—forty-seven years after the climactic initiation of microbial genetics in 1941. Half a century may be almost enough time to see that work in historical perspective and yet allow for some brief overlap to call testimony from contemporaries. My own familiarity with Neurospora, dating to 1942 when Ryan returned from Stanford to Columbia, qualifies me only barely.[15]

The one gene–one enzyme theory that a gene acts by controlling the formation of a specific enzyme in some fairly simple manner was implicit in earlier research on pigment biosynthesis. Before 1941 J. B. S. Haldane's speculative discussion came close but never jelled into a concrete theory that would lead to such effective lines of enquiry. Though the Neurospora work suggested that all biochemical traits could be studied in like fashion, it was Beadle and Tatum who extrapolated—from diverse examples—that all such traits would have an equally direct relationship to the corresponding genes. This fundamental observation is now stated as the DNA sequence providing the information for protein structure (though the numerics are sometimes more complex). Many genes, and sometimes families of enzymes, can be involved in the quantitative regulation and environmental responsiveness of enzyme synthesis. Enzymes are sometimes

[15] Tatum's departure from Stanford in 1957 denied me the chance to be his colleague when I arrived there in 1959. His death in 1975 likewise predated my arrival at The Rockefeller in 1978. In sum, our academic careers ran in curiously parallel but dissynchronous tracks at Wisconsin, Stanford, and Rockefeller. Our sole congruence was at Yale for a year-and-a-half in 1946–47.

complex multi-chain ensembles and can contain nonprotein cofactors requiring the participation of many genes. Understanding the role of RNA as a message intermediary between DNA and protein, the complexities of intervening sequences in RNA, RNA-processing, and post-translational processing came later and required more sophisticated biochemical analysis—but all derived from the concepts and the tools of the Neurospora studies.

Beadle and Tatum's contribution, then, comprised the following:

> 1) A methodology for the investigation of gene-enzyme relationships that exploited experimentally-acquired genetic mutations affecting specific biosynthetic steps.
>
> 2) A conceptual framework—the one gene–one enzyme theory—from which to search for and characterize these mutants. This framework was derived from the model that chromosomal genes contain (substantially) all of the blueprints for development and that enzymes (and other proteins) are the mediators of gene action.
>
> 3) The dethronement of Drosophila as the prime experimental material for physiological genetic research in favor of the fungus Neurospora. This further helped open the way to use of bacteria and viruses in genetic research and the culture of tissue cells as if they were microbes.

These methods and concepts have been the central paradigm for experimental biology since 1941.

Beadle and Tatum shared many awards in addition to the 1958 Nobel Prize in recognition of these innovations. In 1952, Tatum was individually honored by election to the National Academy of Sciences. In 1953 he received the Remsen Award of the American Chemical Society and was elected to the American Philosophical Society. He was president of the Harvey Society (1964–65) and the recipient of at least seven honorary degrees.

He served on the NAS Carty Fund Committee from 1956 to 1961. For the NRC, he took part in a number of panels

and committees having to do with genetics and biology and was a member of the Advisory Committee on the Biological Effects of Ionizing Radiations from 1970 to 1973.

He also did yeoman service on advisory committees for the National Institutes of Health, American Cancer Society, the National Foundation (March of Dimes), and other bodies concerned with the award of fellowships and grants. He was chairman of the Scientists' Institute for Public Information and an advisor to the City of Hope Medical Center, Rutgers University Institute of Microbiology, and Sloan-Kettering Institute for Cancer Research, and a consultant in microbiology for Merck and Co. He worked actively on many scientific publications, including *Annual Reviews*, *Science*, *Biochemica et Biophysica Acta*, *Genetics*, and the *Journal of Biological Chemistry*.

Testifying to a Congressional committee on behalf of the National Science Foundation in 1959, Tatum said:

> "The general philosophy [of the NSF] is concentration on excellence . . . making it possible for [the scientist] to use his capacities, both for research and for training the next generation . . . whether it is a particular research program in a given area, whether it may or may not be immediately practicable in its application . . . freedom to develop the intellectual curiosity and abilities of the individual. . . ."

At this time Beadle and Tatum's legacy is embodied in published work that has influenced biological research through several scientific generations. The original papers are "classics" and taken for granted.

Personal recollections of Tatum are fading, and this report can hardly do justice to his humor, his hobbies (including the French horn), his zest for experiments, his love of microbes, his attachment to students, friends, and family—the trauma of divorce notwithstanding—the tragedy of his final year of bereavement and of an illness that left him gasping for breath. He touched the lives of many young scientists.

The enduring appreciation of his role in their development is the memorial he would have cherished most.

THE TANTALIZINGLY FEW personal papers of Edward Tatum now extant are on deposit at the Rockefeller University Archive Center. I am particularly indebted to Professor Carlton Schwerdt for having preserved and made available his lecture notes on Tatum's 1941 course on comparative biochemistry, to June Alton Tatum for making available to me materials regarding Tatum's life before 1946, and to the staff of the Rockefeller University Archive Center.

I am also indebted to the following important studies for information that appears in this account: R. M. Burian, Jean Gayon, and Doris Zallen, "The Singular Fate of Genetics in the History of French Biology," *Journal of the History of Biology*, 21(1988):357–402, on the Beadle-Ephrussi collaboration that led directly to Beadle and Tatum's work on Drosophila eye color "hormones" and discusses the use of that terminology for what would later be termed "precursors." Lily E. Kay, "Selling Pure Science in Wartime: The Biochemical Genetics of G. W. Beadle," *Journal of the History of Biology*, 22(1989):73–101, reviews the Beadle-Tatum work on penicillin improvement during World War II.

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