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I am still pondering how much more (or less) personal detail should be here — and still be an honest report. any comment would be most welcome! J.L.

The biochemical unity of life, the doctrine of comparative biochemistry, was the guiding principle of Edward L. Tatum's scientific career. His molding of that principle into a systematic method of biochemical genetic analysis has helped to transform contemporary experimental biology. The exploitation of these principles in research on the fungus, Neurospora, and the bacterium Escherichia coli, were instrumental in making these favored research materials for the most fundamental investigations of the nature and action of the gene in the living cell. His most important investigations were all collaborative efforts, speaking to the facility with which he could combine his own perspectives as a comparative biochemist with those from other disciplines and of other personalities. His scientific achievements were appropriately recognized by his election to the National Academy of Sciences in 1952 and the Nobel Prize in Physiology and Medicine in 1958 (shared with G.W. Beadle and J. Lederberg). A more enduring legacy has been the everyday use of experimental mutation analysis of biochemical pathways in modern biology since then.

It's OK - The balance is good. As a graduate student he seemed rather lonely and troubled, always kind and able to enjoy the pranks of others but never a prankster himself. One felt that his affectionate nature and the fact that he had always lived at home had made it difficult for him to emerge from adolescence. But I see no value in including such observations — I just thought they might interest you. (PB)

Edward Lawrie Tatum was born at Boulder,Colorado on December 14, 1909, the first son of Arthur L. and Mabel Webb Tatum. At that time his father was instructor in chemistry at the University of Colorado. In rapid succession the Tatum family moved to Madison,Wisconsin; Chicago,Illinois; Philadelphia,Pennsylvania; Vermillion,South Dakota; and back to Chicago by 1918. In the process, the elder Tatum had held a succession of teaching positions, earned a Ph.D. in physiology and pharmacology from the University of Chicago, and an M.D. from Rush Medical College. By 1925 he had settled at the University of Wisconsin at Madison as Professor of Pharmacology.

Edward, having the advantage both of this remarkable family background, and some schooling at the University of Chicago Experimental School, then continued his education at Wisconsin, earning a bachelor's degree in 1931 and a Ph.D. in microbiology in 1934. His graduate studies, and a year's postdoctoral research were in the wave of extraordinary developments in the physiology and nutrition of bacteria under the* leadership of E.B. Fred (later president of the University of Wisconsin), ~~and~~ W.H. Peterson, and Marv Johnson. During that time, Tatum also collaborated with H.G. Wood, Esmond Snell, and Claude Fromageot, publishing an extensive series of pioneering studies on the role of vitamins in bacterial nutrition. His dissertation, published 1936, comprised the isolation of a thiaminlike substance from natural products, and the demonstration that thiamin was an essential growth factor for propionic acid bacteria. At this point in the development of the subject, vitamins had long been recognized to share a role in the

(per your letter!)

* leadership isn't quite the right word. Fred was already hopelessly out of touch with intellectual developments in microbiology. (over)

nutrition of animals, man, and yeast. The 1936 paper appears to be the first of a multitude that showed that many bacterial species also had diverse requirements for the same substances proven to be so crucial for animal and human nutrition. His dissertation also comprised a study of the enzymatic racemization of lactic acid by toluenized cell suspensions of Clostridium butylicum. Coming from a laboratory of international distinction, these studies were already recognized by contemporary reviewers in the course of his graduate studies.

In 1936 Tatum won a fellowship of the General Education Board to take him, with his wife (the former June Alton) and infant daughter, for a year to Fritz Kogl's laboratory at Utrecht, Netherlands. Kogl 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 recognized for animals).

By Tatum's own account, his brief time at Utrecht (concerned with efforts to isolate further growth factors for staphylococci) never reached a sharp research focus. The most important event was his meeting a fellow from Finland, Nils Fries who was using the newly available biotin to demonstrate the specific nutritional requirements of an ever wider range of fungi. Fries and Kogl were also able to demonstrate striking examples of mutual nutritional repair of complementary deficits in mixed cultures of various fungi. Similar phenomena had recently been reported by Lwoff and Lwoff for the exchange of hemin and nicotinic-adenosine-dinucleotide between different species of Hemophilus. Tatum's report to the General Education Board also records his gratification at having met 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. All three had also commented on 'variational' changes in the nutrition of bacteria as reflecting the evolution of their biochemical competence. They had not, as yet, adopted the language or conceptual framework of genetics which would have described such variations as gene mutations affecting biosynthetic enzymes.

That same year, G.W. Beadle was on the point of moving from Harvard to Stanford, planning a research program in physiological genetics. Tatum's professors at Wisconsin were looking out for possible positions for him, and forwarded Beadle's solicitation for a research associate "biochemist to work on hormone-like substances that are concerned with eye pigments in Drosophila." (But their preferred recommendation concerned research on the chemical microbiology of butter: "This field is certainly getting hot.") Evidently Dean Fred had also decided to try to keep him for Wisconsin, but found that Tatum had already cabled his acceptance of the position offered by Beadle. We can only speculate whether the drive for a novel and more independent role, mere fortune or his own foresight was predominant in his choosing insect eyes

over dairy microbiology (whose contemporary economic importance was manifest.) That he would have been influenced in some measure by the challenges of comparative biochemistry is at least plausible in the light of future events.

Was he already so keen on comp. biol.?

Having joined Beadle at Stanford, Tatum was engaged between 1937 and 1941 in the arduous labors of extracting pigment-precursors from Drosophila larvae. Earlier transplantation experiments of Ephrussi and Beadle had demonstrated that a diffusible substance produced by wild-type flies was critically lacking in the mutant strain. A significant short-cut emerged from a discrepancy between the published report of Ephrussi and Chevais, and Tatum and Beadle's own experience. According to the former, normal eye-color could be restored in cultures supplemented with tryptophane; however, Tatum could not confirm this except 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 also 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 underlay this perspective. 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 kynurenine. (Butenandt had noted a publication from a Japanese biochemist that kynurenine was one of the products of metabolism of tryptophane in the dog and tested the substance for eye color hormone activity on that well founded speculation).

I don't know - I wasn't in touch - but sounds like busy-work. Ed had seen too much of that at the ag school. He had to get out while getting was possible.

This jarring experience, to have such painstaking work overtaken in so facile a fashion, contributed to the impetus on Beadle and Tatum's part to seek another organism more tractable than Drosophila for biochemical studies of gene action.

In Winter Quarter 1941, Tatum, although a research associate without teaching responsibilities, had volunteered to develop and offer a then unprecedented course in comparative biochemistry for the benefit of graduate students in biology and chemistry. In the course of his lectures,* Tatum ~~recalled Fries's continuing work on the nutrition of fungi - which now embraced a number of Ascomycete species that could be cultivated on well defined media.~~ recounted the nutrition of yeasts and fungi, some of which exhibited well-defined blocks in vitamin biosynthesis. Beadle, attending these lectures, recalled the elegant work on the segregation of morphological mutant factors in Neurospora that he had heard from B.O. Dodge (in a seminar at Cornell in 1932), work that was followed up by C.C. Lindegren at Cal Tech. The conjunction was that Neurospora had an ideal life-cycle for genetic analysis with the immediate manifestation of segregating genes in the string of ascospores. From Fries's work it seemed likely that it could also be cultured readily on a well

*Lucky find: Carlton Schwerdt's original notes for the course!

Neat!

defined medium. In the event, it was soon established that Neurospora required only biotin as a supplement to an inorganic salt-sucrose medium; and it did indeed prove to be an ideal organism in which to seek mutations with biochemical effect demonstrated by nutritional requirements. By February 1941, the team was X-raying Neurospora and seeking these mutants.

In those days graduate students were not subjected to the technological displacement of some of the methods, that have since been developed, for seeking nutritional mutants in microorganisms; and it was a painstaking task to examine the isolates from irradiated parents, one by one, for their nutritional properties. Until the 299th culture had been tested, one could not know whether the speculation would succeed but with that famous #299 - which proved to be a pyridoxin-deficient mutant - Neurospora began to occupy the center of the stage as an object of genetic experimentation. By May the same year, Beadle and Tatum were ready to submit their first report (to the Proceedings of the National Academy of Sciences) of these revolutionary methods.

In that same year Tatum was recruited to the regular faculty of Stanford's Biology Department as an assistant professor and was encouraged to undertake an increasingly independent role in keeping with that academic station. The succeeding couple of years were ones of fulfillment of the promise of this new organism and of the concept that underlay its exploitation. 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. Tatum's own work gravitated towards the analysis of specific biochemical pathways, in particular the biosynthesis of tryptophane.

The biosynthesis of tryptophane, possibly harking back to the Drosophila eye-color-hormone problem, remained one of Tatum's central interests. Among the early additions to the Neurospora library were mutants that were blocked at various stages of tryptophane formation and could thus help to verify the pathway. At one point, Tatum and Bonner inquired whether the dismutation of tryptophane by an E. coli preparation was a simple reversal of the synthetic reaction. While this analogy has been complicated by further knowledge, we now know that there are indeed interesting similarities between the tryptophane-cleaving enzyme and one sub-unit of the synthetase. Perhaps equally important, in order to perform these studies Tatum retrieved strain K-12 of E. coli from the Bacteriology Department's long-standing stock collection; and by this accident K-12 came to be the object of further genetic experimentation. Its name will reappear shortly in our story.

With Beadle's encouragement he also mobilized his familiarity with bacteria to attempt to use Acetobacter and E. coli in a fashion similar to Neurospora for biochemical

analysis. No matter that there was no theoretical or experimental basis at that time to expect bacteria to have a genetic organization similar to that of higher organisms! In fact, Tatum's prompt demonstration of the ease with which biochemical mutants of a similar sort could also be induced in E. coli was itself strong provocative evidence that bacteria did have genes, at least in this sense, analogous to those of Neurospora and other organisms.

During 1944-45, the laboratories were also recruited into an OSRD-sponsored multi-laboratory search for improved strains of Penicillium needed for the practical development of the new antibiotic. Although Stanford did make significant improvements in yield, these were in practise outstripped by developments with other strains elsewhere.

By this time the team of Beadle and Tatum had become world-famous, Nevertheless, exigencies of finance and of academic politics in the Biology department and the University left little proximate promise for Tatum's academic future at Stanford, and he left in 1945 for Yale University.
Beadle and the formidable team that he had assembled also left Stanford en bloc, in 1946, to reshape the program of Biology at Caltech.

Tatum's role at Yale was a tenured chair for the development of a biochemically oriented microbiology program within the Department of Botany. This progression was also a serendipitous break for Lederberg who at that time was a medical student at Columbia continuing research on Neurospora with Francis J. Ryan. Ryan had been one of Tatum's postdoctoral fellows in 1941-42 and introduced Lederberg's own proposals for the study of genetic recombination in bacteria by correspondence with Tatum. In the event, Lederberg was able to join Tatum at New Haven, to work under his supervision in the spring of 1946 while Tatum was organizing his new department. That speculation also worked out beyond the wildest expectations; and the discovery of genetic recombination in E. coli could be reported in June 1946 by Tatum and Lederberg, vindicating Tatum's gamble that indeed E. coli did have genes!

The choice of 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 made it possible to avert a number of technical difficulties that would have confused the interpretation of searches for recombinational phenomena. 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. 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. This serendipity cannot rationally be attributed to any personal skill or insight on Tatum's part. On the other hand, the style of his receptivity to the 'far-out' proposals of a medical student to visit his laboratory was

typical of the combination of human generosity and scientific vision that characterized his career.

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. He was still to be disappointed in the level of commitment to the expansion of biochemically oriented research in a department that was still heavily dominated by the morphological-systematic traditions. In 1948, Douglas Whitaker having assumed a new level of leadership in biological research at Stanford, Tatum accepted a call to return as full professor to the department that had neglected to offer him a first promotion just three years earlier.

[Yale Ph.D.s]

From this time forward Tatum pursued and supervised a variety of research projects which were generally a reconciliation of his students' and fellows' prior interests, with his own particular biochemical insights. He became increasingly interested in the analogy between mutagenesis and the carcinogenesis in an early anticipation of the currently famous Ames screening test. If the induction of nutritionally dependent mutants in Neurospora was in fact a rather laborious way to demonstrate mutagenicity of a chemical compound, it at least had the by-product of adding to the library of useful strains for biochemical pathway analysis. While 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 mutants could be obtained and propagated, Tatum generally left the exploitation of this material to the students; it was plain that Neurospora was indeed his first love throughout his career. In addition his leaned over backwards to give his intellectual heirs the utmost leeway for their own development.

[Summarize which degrees were completed in this era.]

During this decade (1948-58) Stanford was also to be the seat of a courageous, self-conscious bid to become a major national center of scholarship, concomitantly with the emergence of California in economic, demographic and political influence. Although the new President, J.E.Wallace Sterling had been a historian, scientific and technical developments were warmly nurtured under his strong leadership -- exemplified by the adventurous and ambitious program to reconstruct the school of medicine at the Stanford campus. This was to transform a hospital-based school in San Francisco, that had had little more than a nominal relationship to the academic life of the university, into a national center for medical and biological research. Like the analogous development of the school of engineering, this institution-building was possible only by virtue of the postwar assumption of federal responsibility for the vigorous development of high technology and its scientific foundations.

In his role as spokesman for the rapidly emerging discipline of biochemistry, Tatum played a substantial role in the development of scientific policy at Stanford, and with his subsequent membership on the National Science Board nationally as well. 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, which would take full effect in 1959 with the construction of the new medical center. However, just at this time, conflicts in his domestic life overshadowed his professional plans, and he resigned from Stanford effective January 1957, coincidentally with the foundering of his first marriage. Speaking just from his own standpoint, the very depth of his feelings for family life and children made these events especially painful for everyone concerned.

By this time, Whitaker had left Stanford to become academic vice-president at Rockefeller and take a leading role in its transformation from research institute to university. He seized to opportunity to ask Tatum to join him there in the role that would embrace the remainder of Tatum's career.

In New York, Tatum married Viola Kantor whom he had met as a staff employe at the National Foundation/March of Dimes, to which he continued to give a great deal of time as scientific adviser. They differed in almost every imaginable measure -- age, ethnic and religious background, education, temperament -- but were the happiest of couples, sharing a domesticity that was to be marred only by Viola's death in 1974 from cancer at a tragically young age.

As a professor at Rockefeller, Tatum was less concerned with institutional affairs than at Stanford, but played an increasingly important part on the national scene -- especially as a member of the National Science Board. There he was especially concerned about strengthening programs for fellowships, and other measures to bolster support for younger people entering scientific work. He was also Chairman of the Board of the Cold Spring Harbor Biological Laboratory, through a period of fiscal crisis and interpersonal turbulence that -- according to one of his associates -- were the most grievous episodes of his life.

Nicely handled!

In his own laboratory, Tatum was especially notable for nurturing independent-minded fellows in the pursuit of their own ideas. He ~~would have been~~ was prouder of them as individuals than of any specific contributions he might have added to their research. They include: Shatkin, Reich, Gross ....

His younger colleagues on the faculty, like Norton Zinder, have acknowledged a similar debt.

[Can this be stated better?]

His personal research interests during this phase centered on the use of Neurospora as a model of genetic control of development. The effects of inositol-deprivation, or of 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, 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 gene-environmental interactions that lead to morphological elaboration. Yet to be found in this type of material are quasi-stable epigenetic states, such as are expressed in higher plant and animal cells in tissue culture, for which the power of biochemical genetic analysis would be extraordinarily helpful.

Tatum's last paper, with .. Mishra, is undoubtedly the most controversial. It reports that RNA from wild-type Neurospora can transform the inositol mutant, engendering inositol-positive forms which segregate in crosses like chromosomal markers. If this work can be confirmed in other laboratories, it will certainly give Neurospora still a new role in experimental biology.

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 doggedly clung. Perhaps the deepest paradox was his unremitting commitment to cigarette smoking, the most destructive act of his life towards any person, namely himself. His death on November 7, 1975 from heart failure complicated by progressive, chronic emphysema, can be squarely attributed to that uninterrupted habit.

[Would Ed NOT have wanted this reference to his health?]
~~[I have no information on his 3d marriage.]~~

The imperative of balancing critical scientific objectivity, personal ambition, and one's interdependence on others, which some scientists may take a lifetime or longer to learn, was engrained in Ed Tatum's ethos from the beginning. He did not lack for misfortune in his personal environment; but we may hope there was some compensation, that few scientists have had so many others look to them so warmly as father and brother.

[Bibliographic note: problems of documentation
Initial discovery
History of Stanford Univ., Medical School
Grateful to mAny for documents and reminiscences
Archives collected and deposited.]

Summary references on Neurospora, K-12,....

The tribute that is owing to Francis Ryan and Ed Tatum needs a larger frame than this article to be justly recorded. At a time when the public image of scientific fraternity is so problematical, it is important to record the survival of norms{ 13 } and behavior exemplifying mutual respect, helpfulness, consideration, and above all a regard for the advance of knowledge, even in a system that inevitably puts a high premium on competition and self-assertion. I have never encountered the extremities that Jim Watson painted in his self-caricature of ruthless competition (The Double Helix), which is hardly to argue that they do not take place. However, even by the most optimistic normative standards, the generosity and selflessness of my own teachers stand out as examples to be emulated, and to pass on to those whom I might in turn have the privilege to influence. Perhaps the greatest tribute to their skill as teachers is that they have made it impossible, to this day, for me to dissect my own innovation and creativity from the ideas that they may have planted and certainly nourished in the course of my learning and collaboration with them.

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