University on the Heights

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Francis J. Ryan

by Joshua Lederberg

A great university is measured by the caliber of the men it can attract and maintain in a free community of scholars. In my own scientific career, one great man was a pre-eminent formative influence—Francis J. Ryan, professor of Zoology at Columbia University. Ryan was a Columbia man throughout: A.B. (1937), Ph.D. (1941), and then a professor until a sudden fatal heart attack in 1963 at the age of forty-seven.

I first met Ryan when I was a Columbia College sophomore in 1942. He had just returned from a year's postdoctoral re-

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JOSHUA LEDERBERG, *1944 College student at Columbia College of Physicians and Surgeons from 1944 to 1946, and Ph.D. from Yale in 1947, was a Nobel laureate in 1958 in physiology and medicine for research in genetics of bacteria. He is now at Stanford.*

search fellowship at Stanford. He had intended to work on embryological physiology in frogs, but there he met G. W. Beadle and E. L. Tatum, who were rapidly pushing ahead after their first epochal findings in the biochemical genetics of Neurospora. He was perhaps foolhardy to bring this botanical material—the red bread mold—back to a department of Zoology, but he was too good a biologist to be deterred by niceties like plant versus animal in deciding how to study fundamental issues of life. Besides, this mold grew so quickly that it would put up a good race with a lame snail. So one could pretend to imbue it with the animal virtue of locomotion.

The excitement of a biochemical approach to genetics was infectious, and I soon begged him for a chance to learn the tricks of this new game. He arranged a laboratory job for me, glassware washing at first; later, technical work in microbiology, that not only helped me through that year of college, but taught me much of the discipline of laboratory research. Above all, it gave me the opportunity to sharpen my adolescent thinking against one of the most versatile, most generous minds I would ever encounter. In retrospect, I can perceive more clearly what a unique quality he had for focusing on his students' development even at the expense of a professorial ego. He rarely instructed me about anything, but would often lead me into an intellectual trap, then challenge me to find my own way out of it.

In 1944, Avery, McCarty, and MacLeod of the Rockefeller Institute published their historic paper on the identification of DNA as the "transforming factor" in certain bacteria. This work aroused great interest as a strong indication that the gene was composed of DNA. It was not yet conclusive for it

was still controversial whether bacteria could even be thought of as having a genetics. The details of this bacterial "transforming factor" still left very reasonable questions about its analogy to the genes of higher organisms with well-defined chromosomes, like Neurospora, fruit flies, or man. In a bull session, Ryan and I soon agreed that it would be exciting to try experiments on the possibility of a similar transforming effect of DNA in Neurospora.

The advantage of Neurospora was that, on the one hand, it could be easily manipulated as laboratory material for microbial genetics. Experiments that would take years with mice, and months with fruit flies, could be done in a few days. Furthermore, one could perform biochemical tests with billions of individual cell nuclei in a small flask. On the other hand, Neurospora could be cross-bred (unlike, as we then thought, other simpler microbes) and apparent genetic changes subjected to thorough analysis by test crosses, in close analogy to the genetics of other well-studied organisms.

The experimental design was impeccable—but it never worked. In fact, to this day we have no very clear example of the incorporation of purified DNA molecules into existing chromosomes of cells of higher forms. If we failed to achieve our original aims, however, there were several useful by-products. For one thing, we discovered the occasional occurrence of spontaneous reversions of a mutant gene back to the original normal type, and it was an occasion of great pride to co-author this with Ryan as my debut in scientific publication. Far more important, this work laid the methodological groundwork for systematic searches for rare genetic events occurring in large cell populations.

One day I suggested that we ring the changes on our ex-

perimental approach. Instead of trying to make Neurospora imitate a phenomenon recently worked out in bacteria, we could use similar methods to inquire whether bacteria had genetic mechanisms similar to Neurospora.

Ryan immediately perceived the potentialities of this approach, and thereafter spared no effort to create the opportunity for me to explore them. We did start some experiments on bacterial recombination at Columbia, but they were inconclusive. (Later we were to know that the particular strains of bacteria we used then were inappropriate, but there could have been no way to tell this beforehand.)

By this time, I had begun my training at Columbia Medical School, while continuing part-time research with Ryan at Morningside Heights. By a fortunate coincidence, the midquarter of the junior year was allocated to elective work, and Ed Tatum had just then taken a chair at Yale University. During 1945, Ryan had learned that Tatum had already initiated some similar steps toward a bacterial genetics, having already published a brief note on biochemical mutants of *Escherichia coli* in 1944. Ryan suggested that I ask Tatum to sponsor me as a research fellow at Yale to pursue this work —and of course must have recommended me to him, for I was promptly accepted.

When I met Tatum, I found he had already been thinking along similar lines for some time, but his active work on the problem had been disrupted by moving and the reorganization of a new laboratory. I arrived in New Haven in March 1946, just when he was restarting his own work. This is not the place to recount that happy story; briefly, the fellowship lengthened into a year's leave, and eventually into a dropout from Columbia Medical School. My research with Tatum

went too well to be interrupted, and Columbia courses were readily accepted for credit toward a Yale Ph.D. In fact, I was officially registered for elective work (off campus) in the Columbia M.D. program while doing the research that became my Yale Ph.D. dissertation in 1947. Fortunately, these technicalities were overlooked at the time.

To my regret, I had only occasional visits with Ryan after that, but they were always a lift to the spirit and a challenge to the mind.

In 1958, I was somewhat bewildered to find myself in Stockholm on a platform with Beadle and Tatum, to share a Nobel Prize of which my part was based on these studies on genetic recombination in bacteria. Perhaps only a knowledgeable circle knew, as we did, of Ryan's part in them. Any such awards are bound to be arbitrary, and a thoughtful observer will always look for the teacher behind the student.

In many ways Ryan was ahead of his time; but he also insisted on keeping a firm hold on traditional biology as well as its innovations in biochemistry and microbiology. He was also keenly alert to the human uses and misuses of scientific knowledge: for him, biology was one of the essential humanities. Some of his insights into modern biology were too advanced to get the priority they deserved, even taking account of the pressure of legitimate but conflicting demands on the resources of a great university. The winds of change are blowing again, and he might now look forward with greater confidence that the university he loved so well would regain its historic pre-eminence in research and teaching about the fundamentals of life.