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BOOK REVIEW

The Transforming Principle: Discovering that genes are made of DNA

By MACLYN McCARTY. Norton Press, New York, 1985; pp. 252, $ 14.95

On February 1, 1944 the *Journal of Experimental Medicine* published an article from the Rockefeller Institute for Medical Research. It bore the formidable title: "Studies on the chemical nature of the substance inducing transformation of pneumococcal types. Induction of transformation by a desoxyribonucleic acid fraction isolated from pneumococcus type III." This was the dawn of molecular genetics, the first clear demonstration that genetic specificity was inscribed in the chemical structure of DNA.

The authors were Professor O T Avery (1877–1955), and his colleagues Colin MacLeod (1909–1972) and Maclyn McCarty (1911– . . . .). McCarty, the junior author, is now an emeritus professor at The Rockefeller University. His book, an intimate chronicle of the days of discovery, is a result of much urging by his colleagues and myself. He has carefully reviewed laboratory notes and other records to give a critically documented record of what happened in the laboratory, leading to a turning point in 20th century scientific history. His own biography is given in a brief and characteristically modest prefatory chapter: the central actor in the story is DNA.

H. F. Judson's "Eighth Day of Creation" is the definitive history of midcentury molecular biology. Unaccountably, Judson did not interview McCarty, and the present work fills an important gap about the details of the gestation and birth of DNA as we know it today.

Work on pneumococcus transformation began with Fred Griffith's observation of the phenomenon, reported in 1928 in the *Journal of Hygiene*. Killed cells of one pneumococcal serological type, injected into a mouse with live cells of another, "transformed" some of the latter, engendering an infection with live cells of the first type. Avery was initially quite skeptical of the report; but after his fellows insisted on reproducing the experiment in his own laboratory, Avery undertook the long pursuit, spending most of his effort for the next 15 years chasing the substance responsible for the transformation. Much time was spent in developing an *in vitro* assay, and in efforts to isolate and concentrate the "transforming principle". *A priori* judgments favored either the capsular polysaccharide (the phenotypic character itself) or a protein (enzymes having recently been characterized as proteins and the latter therefore the most likely foundation of biological specificity). Before McCarty joined Avery's laboratory, in September 1941, in immediate succession to Colin MacLeod who had left to take the chair of microbiology at New York University, much of the groundwork but little definitive progress had been made.

The book itself should be consulted for all the meticulous details of procedure that McCarty brought to the laboratory work, including a new preparation of crystalline

DNAse that was instrumental in identifying the principle as DNA. By November 1, 1943, the paper was written describing a preparation that contained polymeric DNA, and was free of detectable protein or polysaccharide. Soon after, it was shown that the transforming activity was destroyed by crystalline DNase, but not by other enzymes. The manuscript was remarkably circumspect about the general biological significance of this activity of DNA; together with the publication in a journal of experimental medicine, this may have muted its impact on other biologists.

McCarty notes his own surprise at what he felt was a faint response; but in the same pages he records the numerous lectures Avery and he were asked to give on their new findings, and the explicit mention of the transforming studies in several awards in the interval 1944–1948. In 1946, McCarty was invited to participate in the Cold Spring Harbor Symposium that constituted a major international conference on microbial genetics. This is where I had the pleasure of my first meeting with him. (I was a graduate student at Yale, presenting at the same symposium my own work on crossing in bacteria.) The genetic significance of the pneumococcus transformation was a subject of much speculative discussion that year. It was too soon, however, to generalize from the one case of a polysaccharide phenotype in a pathogenic bacterium to all genes of all other organisms. The 1947 Symposium (devoted to nucleic acids and nucleoproteins) and the one in 1951 (on genes and mutations) also had invited contributions from the Rockefeller Institute laboratory.

In fact, the research at the Rockefeller was particularly well known at Columbia University, where I started my own research. This was largely the result of frequent visits by Alfred Mirsky, and the seminars at Columbia were rife with excited speculation about the biological significance of transformation, and how DNA could be "the gene". In January 1945, impelled by my own reading of the 1944 paper, I began designing experiments in F J Ryan's laboratory looking to the possibility of DNA-mediated transformation in *Neurospora*. These led quite directly to the search for genetic exchange in *E. coli* and the first experiments on bacterial crossing.

Elsewhere, not everyone was instantaneously converted; nor in any rational scientific system should they have been. In my own view at the time, it was precisely the importance of the 1944 claims that demanded they be given the most intense scrutiny. The important question about the function of systemic resistance is not conversion of belief, but the way in which experiments and research programs were shaped by the new claims. By that token, the 1944 paper had a vigorous and effective response culminating, for example, in the exposition of the double helix merely nine years later.

Readers of the *Journal of Genetics* will be interested, but not surprised, to know of J B S Haldane's enthusiasm for the work on transformation. This was voiced in many unrecorded conversations, but also, at length, in his article "Some Alternatives to Sex", *New Biology* 19, 1955. JBS' biographers can also point to his prescient writing: "the nucleus of every . . . cell consists very largely of . . . genes . . . . The chemist may regard them as large nucleoprotein molecules . . . . The precise nature of their activity is uncertain, but . . . strong evidence that they produce definite quantities of enzymes." (*Trans. Oxford Univ. Jr. Sci. Club* 3: 3–11, 1920). It is clear, however, that most geneticists of the era 1900–1950 simply were not equipped to think in any sophisticated way about enzymes. Likewise, few other biochemists could begin to deal with the jargon of heterozygosis and allelomorphism.

These are not the last words to be written about resistance to and acceptance of scientific innovation. "The Transforming Principle" does offer interesting witness on

how these phenomena are perceived by the innovator. The constructive systemic functions of doctrinal skepticism do sometimes conflict with a just allocation of personal credit and reward. Many historical papers in future will be devoted to wrangling over how it happened that the Nobel Prize was never awarded to the foundation work on DNA, when dozens have been earned for its later consequences.

By every account, "The Transforming Principle" stands as one of the most authentic narratives of scientific life, as well as of an epic of discovery, ever to be published. It lacks the flamboyance of other, more dramatic creations. But most scientists will find the human as well as technical ascriptions McCarty gives us as far more congenial to our own experience, and exemplary as role models for our successors.

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