S 238 Reply to Gunther Stent, on the alleged "prematurity" of the work of Avery, MacLeod and McCarty in "Prematurity and Uniqueness in Scientific Discovery", Scientific American, December 1972.
(submitted to Scientific American, but not published)

In picturing Avery's work on DNA as an example of a "premature" discovery, and coupling it with the neglect of Mendel between 1865 and 1900, Gunther Stent (December 1972) is augmenting a myth that deserves to be corrected. His statement is "that geneticists did not seem to be able to do much with it or build on it ... had virtually no effect on the general discourse of genetics."

As evidence, he points to the published symposium "Genetics in the 20th Century", in 1950. Textual evidence in that volume is ample to dispose of a parallel between Avery and Mendel; and I can add further history from my own experience of a kind that goes unrecorded in the journals.

However, this letter will be disservice if many omissions of important contributors are taken later as evidence that they are not in mind. Some more relevant detail can be traced from a recent exchange of correspondence in Nature (Wyatt, H.V., Nature 235:86, 1972; Lederberg, J., Nature 239:234, 1972; Olby, R., Nature 239:295, 1972; Pirie, N.W., Nature 240:572, 1972).

To focus first on Stent's remarks the 1950 volume: Mirsky's quarrel in 1950 with the proof of the purity of transforming DNA has been quieted by later evidence, but was consistent with the information then available. It reflected no lack of comprehension of Avery's assertions. Indeed it reflected the conceptual difficulty of thinking of DNA as an informational molecule so long as chemist's perceptions of its structure were dominated by the tetranucleotide model. The X-ray data of that era had contributed to the confusion. For example, Gulland (in 1947) cited Astbury's evidence that "a sodium thymonucleate fiber is ... built to a regular pattern ... based on a sequence of nucleotides that is a multiple of four." But he too was troubled by the evidence of specificity (citing Avery's work via Muller's review), and pointed out that even small departures from statistical regularity could be informationally important. The structure of DNA was the subject of so much assiduous inquiry between 1944 and 1953 precisely because the biologists were trying to do more with it than the chemical traditions seemed to permit. (Chargaff's remarks at the 1947 Cold Spring Harbor Symposium are a notable example.)

Indeed, Mirsky was right on the mark in his biological interpretation of the pneumococcus transformation, "considering the process to be essentially a hybridization". This speculation, which Muller had articulated quite clearly in 1947, in his Pilgrim Lecture, "The Gene", actually went far beyond the existing evidence -- Avery himself was cautious about offering any biological interpretation whatever in 1944. The first clearcut evidence that any factor other than the mucoid capsule could be determined by transferable DNA was published by Hotchkiss in 1951. Meanwhile, other speculations that appeared in the 1950 volume were equally valid: for example, Caspersson and Schultz thought the DNA might be a non-specific regulatory factor, like hertero-chromatin, although other parts of their cytochemical study, e.g. on mitosis, clearly point to the identification of DNA with gene as their working hypothesis.

Beadle refers to "the new knowledge of transforming principles [as] another chapter in genetics, and that promises to be among the most exciting. It has given chemists new incentive to learn about the nucleic acids, compounds which everyone recognizes to be extremely important biologically and about which so little is yet known." Evidently the pneumococcus work was so well known that it did not even require an explicit bibliographic reference!

In my own commentary, I followed Sonneborn in comparing both the pneumococcus transformation and virus lysogenicity to cytoplasmic factors, a hazy forerunner of the episome concept. Today we view the integration of virus genomes into the bacterial chromosome, as a meaningful parallel to the fate of transforming DNA.

Darlington's discussion of chromosomes becoming protectively coated with nucleic acid is most nearly oblivious of the chemistry and specificities of DNA, in stark contrast to the clarity of his speculation about plasmagenes and viruses, and his bold efforts to think ofchromosomes as material, mechanical systems.

More remarkable than the alleged prematurity of the pneumococcus work is the short shrift evidently given to work on bacterial viruses generally. For the general discourse of genetics, this was at the frontier of exploration; was it, therefore, also premature?

Can one find such controversy, such teasing out of alternative interpretations, such provocation of further investigation and hypothesis in the impact of Mendel on biological thought prior to 1900?

Many other texts could be cited, but the mere fact that Avery, McCarty and Taylor were invited to speak at the 1946 Cold Spring Harbor symposium, and that the 1947 symposium was devoted to nucleic acids (with Boivin's participation) testifies to the ferment that these studies had induced. The original transcripts of the discussions at those meetings would be richer sources for the intellectual history of the subject than the sober, edited versions.

Indeed, the paper by Avery, MacLeod and McCarty, published in 1944, had already elicited a number of further investigations within the first five years after its appearance. (That this was perhaps not true within the "phage group" is testimony to a policy that had a certain wisdom at the start -- of ignoring work on systems other than the T phages, and focussing on biometrical and biophysical to the exclusion of biochemical methodology. These paradigms resulted in brilliant successes, and may have led Stent to identify "the general discourse of genetics" with the doctrines of an outstanding group.)

By a similar principle of egocentricity, my own work looms very large in my perceptions of the impact of the 1944 paper. It was enthusiastically brought to my attention in January 1945 by Harriet Taylor (then a graduate student at Columbia, later to work as a postdoctoral fellow with Avery. She is better known by her married name, Ephrussi-Taylor; her premature death by cancer in 1968, in the prime of her career was bitterly lamented by many scientific colleagues as well as her friends.) At that time I had just returned to my undergraduate studies after a brief tour of naval hospital service. Every biologist at Columbia was well aware of the work -- if only on account of Dobzhansky's references to it in his monumental

"Genetics and the Origin of Species"; and I soon appealed to Francis J. Ryan (then an assistant professor of zoology, recently returned from a postdoctoral fellowship with the Neurospora group at Stanford) to work under his supervision on the genetic implications of transformation. (Ryan's early death in 1963 has deprived us another alert witness and an extraordinarily fine human being.) If the Griffith-Avery phenomenon was indeed a gene transfer, we should try to corroborate this either by demonstrating it in a "higher" (we would now say eukaryotic) organism like Neurospora, or by looking for firmer evidence that bacteria have genes and a genetic structure like eukaryotes.

By June 1945, having now started studies at Columbia Medical School, I also began to work on "transforming" Neurospora. We used only the crudest extracts in our first experiments; but no matter, we soon found that the control cultures were also showing spontaneous reversions to the wild type, and this phenomenon needed to be cleared up first. Remarkably, this had not been analyzed previously -- perhaps because reversions were nuisances to be avoided in nutritional studies. These experiments never were productive of the original goal of emulating the pneumococcus transformation. However, they showed how well selective techniques could be applied to nutritionally deficient mutants for genetic analysis. Needless to say, we wrote little of our negative results nor the original motives.

As Medawar has pointed out, scientific papers sacrifice personal truths for the sake of clear exposition of verifiable, public assertions of scientific fact. To that extent, intellectual historians must beware of relying on such documents; they already know how to be skeptical of autobiographical rationalizations.

My medical curriculum included a course in medical bacteriology that taught the inherent absence of sexual reproduction among bacteria. Perhaps for this reason, by early July I began to search for sexual recombinants in E. coli with these selective methods. The following year, a fellowship with E.L. Tatum gave me the intellectual and material environment, and the time, to pursue these studies -- and serendipitously the appropriate strain, E. coli K-12, to carry them to a successful conclusion.

In our first brief published reports, we referred to Avery only in the cautionary sense of having tested the E. coli system for sensitivity to deoxyribonuclease, to verify that free DNA was not involved. Subsequently, both before I left Yale in 1947 and later at Wisconsin, Tatum and I looked hard to find a DNA-transfer system in E. coli, especially among strains sent to us by A. Boivin. However, these evidently lost their competence at Strasbourg as well as in the U.S. before we could confirm those results.

The interpretation, if not the initial discovery, of viral transduction in Salmonella (with N. Zinder) was deeply influenced by the pneumococcus precedent. Indeed we coined the term transduction with the intent of embracing both phenomena as examples of transfer of genes by DNA fragments, whether or not encapsulated in a virus particle.

The Rockefeller group's work was so well entrenched in the general discourse of genetics that I used the 1944 paper throughout my own teaching of genetics at Wisconsin. In 1951, I incorporated it in a reprint anthology published by the University of Wisconsin Press. Needless to say, the 1944 work was also cited in many reviews; or else a later updating article by one of Avery's colleagues might be a more efficient reference. The "pneumococcus transformation" was so well known that it was often cited, or Avery's name used, without a specific reference.

Neither the experimental data relating to the purity of transforming DNA, stated in the 1944 paper, nor the genetic concept of gene transfer which was perhaps implied by it, were immediately accepted by the scientific community. The fact that the critics were wrong in no way demeans their essential function for the integrity of science. The net result of skeptical and inquisitive engagement and valid controversy over those issues was to elevate the level of falsifiable assertion that is the essence of scientific inquiry. Mendel was ignored until his work was rediscovered. Avery was challenged on several fronts, and this helped to spark a conflagration of scientific effort -- to which many others also lent matches and fuel. Popular recognition of Avery's work was delayed, but not egregiously. Had he survived a few years longer, there would be little issue about that, nor then about the alleged prematurity of his work.