(*Reprinted from Nature, Vol. 239, No. 5369, p. 234, September 22, 1972*)

Reply to H. V. Wyatt

WYATT's inference[1] that Avery's work on pneumococcal transformation was not well recognized by geneticists in the decade following his 1944 report[2] is somewhat at odds with my own recollection and experience. If we sometimes omitted a specific citation to the original work, this is testimony to his name (like Mendel's) having already become a household word, too familiar to require routine attribution. A more useful reference might be a later review.

In 1946, at the Cold Spring Harbor Symposium, where Tatum and I first reported[3] on recombination in *Escherichia coli*, we were incessantly challenged with the possibility that this was another example of transformation, *à la* Griffith[14] and Avery[2]. In October 1946, we simply referred[4] to negative experiments on transformation with filtrates. These trials were not, in our judgment, detailed enough to warrant comparison with Avery's formidable precedent.

In 1947, we reported[5] on these experiments more fully, including the lack of effect of deoxyribonuclease, and cited Avery[2]. We at no time doubted that geneticists were aware of the pneumococcus studies. In 1951, I included ref. 2 in a collection of reprints intended for graduate students in microbial genetics[6].

One vignette[7] that has not appeared in the scientific literature is that my first laboratory work with F. J. Ryan was an attempt to emulate Avery by transforming *Neurospora* mutants with DNA extract. This was unsuccessful, and was therefore regarded as unworthy of report. These experiments, however, did lead to the finding[8] of reverse-mutations of auxotrophs in *Neurospora*, and the same selective methodology led subsequently to the discovery of recombination in *E. coli*.

Until Hotchkiss[9] had reported the independent transfer of diverse markers by pneumococcal DNA, and comparable phenomena had been elaborated with virus-mediated transduction, the biological interpretation of the underlying phenomena lay in doubt. This was prolonged by the optimism (or obscurantism) of some of my biochemical colleagues who refused to correlate these findings with the tradition of Mendelian genetics. Avery's own a-theoreticism[10], while admirable for its modesty, nevertheless contributed to the postponement of the conceptual synthesis that now identifies "gene" with DNA fragment. This implication was, however, clearly enunciated by some of our most influential geneticists,

such as Muller[11] and Wright[12]. (Wyatt quotes an ambiguous comment from Wright's paper, but omits the crisp assertion: "The results suggest chemical isolation and transfer of a gene . . .".) A history of these interpretations has been embodied in several of my own reviews written during the period[13–15]. Unfortunately, we do not have a comprehensive Citation Index for the period before 1961, which would facilitate the accurate documentation of the influences of the pneumococcus work.

More remarkable than the neglect which is imputed (in my view incorrectly) to Avery's work since 1944, is the failure of other microbiologists and geneticists to explore the Griffith phenomenon[16] between 1928 and World War II. More undisciplined or better informed speculation might have encouraged experiments with a wider variety of genetic markers; these studies were technically possible at least 20 yr before they were attempted. It would also be of interest to know more than Griffith told us by his own bibliography[16] of the conceptual antecedents that may have inspired his experiments. An ancient literature readily available to Griffith, but whose exhumations[17,18] are now themselves rather mouldy, records a number of observations that may deserve further attention, even today. An example is the serological cross-reactions of rickettsia with the bacterial strain, Proteus OX-19. These were naively attributed to a biological relationship, the Proteus strains having been isolated from typhus patients. The relationship may indeed be fortuitous[19], but it has not been studied with modern techniques. For another example, see ref. 20.

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Received March 16, 1972.

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Printed in Great Britain by Flarepath Printers Ltd., St. Albans, Herts.