

## THE ROCKEFELLER UNIVERSITY

New York, N.Y. 10021

October 31, 1972

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Dear Josh,

I was not instrumental in acquainting Harriet Taylor with Avery's work. I know that she made contact with him entirely on her own after the publication of his paper.

There has not yet been a satisfactory account of the pneumococcus episode in the history of molecular and cell biology. Stent did a good deal to start the record of confusion concerning the attitude of geneticists to the pneumococcus work; Wyatt added to the confusion; Olby hardly clarified the record.

In the last paragraph of your note in Nature you refer to "the failure of other microbiologists and geneticists to explore the Griffith phenomenon between 1928 and World War II." You are, of course, aware of the papers by Dawson and Alloway, both of whom died not long after they left the Institute. This work (or most of it) was done in Avery's laboratory but these men were surely not mere assistants. Dawson's contribution was an essential and imaginative step and should be attributed primarily to him.

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Dawson was a more vigorous person than anyone else who worked on the problem. Alloway made the first bacterial extracts in 1931. The point of view towards transformation was described in this way: "The experimental evidence now available seems to indicate that any R strain of pneumococcus has potentially the function of elaborating any one of the specific capsular polysaccharides: - the particular one being determined by a particular stimulus of a specific nature. ...this potential function latent in the living R cells may be specifically activated by the addition to an appropriate medium of a bacterial extract prepared from a given specific type of pneumococcus. Under these conditions, the R forms irrespective of their type derivation again elaborate a capsular material identical in specificity with that of the type of pneumococcus from which the extract was prepared."

I have read all the reports (from which the above quotation was taken) made to the Board of Scientific Directors of the Rockefeller Institute on pneumococcus work from 1928 to 1954 so that I have a clear picture of what happened and what was going on in the minds of the investigators. After the second of Alloway's fine papers in 1932 there was, as you know, no publication until 1944. During this period Avery's lab was a very active place. Bacterial transformation was only one of many interests. In the reports Avery frequently speaks of what a significant phenomenon transformation is, but it is clear that it did not have a position of the highest priority among his interests. Rogers (1932) took

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up the transformation problem after Alloway left (1931). Then in 1934 Colin MacLeod came and went on with the work. Colin had other interests as well, so that in some years of the reports there is no mention of transformation. Until McCarty came (1941) not much of significance was accomplished. In 1941 Avery, MacLeod and McCarty collaborated in a study of bacterial virulence, in which there is no mention of transformation. In 1942 (MacLeod having left) McCarty took up the problem of transformation with vigor. It is curiously striking how little was done on transformation from the departure of Alloway (1931) to 1942, and also how quickly McCarty accomplished what was published in 1944. He did what could have been done after Alloway's departure in 1931. It is also curious how when Dr. Homer Swift retired in 1946, McCarty dropped work on transformation and accepted the appointment to continue Swift's work on rheumatic fever and hemolytic streptococci.

Studies on transformation were continued by Rollin Hotchkiss and Harriet Taylor. Hotchkiss' very fine work on the chemical nature of the transforming agent and on transformation with respect to resistance to streptomycin and penicillin is fully described in the reports. It has been said that his experiments on the independent transfer of penicillin resistance clearly established that a gene fragment was transferred. The reports on this work by Hotchkiss show that for several years his conception

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of transformation was different from this; he was thinking of the induction of specific mutations. In 1950-51 he said, "These results strengthen the impression that transformation is a means of inducing artificially changes closely analogous to those spontaneous ones that are now generally considered bacterial mutations." In 1951-52 he said that cells "may acquire mutant characters at rates far higher than those at which the same character can appear as a spontaneous mutation." In his Cold Spring Harbor paper (1951, page 459) Hotchkiss expressed the same view. Much the same opinion had been expressed by Dobzhansky in 1941: "If this transformation is described as a genetic mutation - and it is difficult to avoid so describing it - we are dealing with authentic cases of induction of specific mutations by specific treatments - a feat which geneticists have vainly tried to accomplish in higher organisms." Hotchkiss' report for 1952-53 shows that by this time he had finally arrived at a clear, straightforward point of view: he speaks of the transforming agent as having the "fundamental properties of a gene," and in the report for 1953-54 he speaks of "the gene-like activity of transforming agents."

It is striking that others had come to this point of view years before Hotchkiss did. You have referred to Wright and Muller. As for myself, after discussing the chemistry of the transforming agent, I wrote: "Since it is now known that the material derived from the heat-killed cells that is effective in

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pneumococcus transformation contains DNA, this is in itself evidence for considering the process to be essentially a hybridization. In those cells which can be studied cytologically all the DNA is localized in chromosomes and the essential role of chromosomal material in hybridization is well-known. It is remarkable in the pneumococcus transformation that part of the DNA-containing material is derived from heat-killed cells, and that before being used for "hybridization" it can be examined chemically." (In "Genetics in the 20th Century" edited by L.C. Dunn, 1950, The Macmillan Co., New York page 133.)

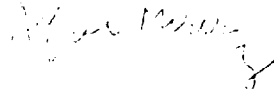
In "Phage and the Origins of Molecular Biology", 1966 Hotchkiss gave a charming and rambling account of the history of the transforming agent. However, this account (compared with what I have read in the reports (including those by Hotchkiss)), is often obscure and incomplete. In the 1966 account Hotchkiss recounted several interesting conversations, but there was one that he did not give that I remember clearly. He gave a lecture at the Institute on his work concerning the transformation of pneumococci with respect to penicillin resistance. This lecture was one of our regular Friday afternoon meetings, attended by practically the whole staff. In this lecture Hotchkiss spoke of mutations to antibiotic resistance in pneumococci and how these could be induced by DNA. In the discussion at the end of the lecture I said that he was dealing with "a sexual phenomenon" rather than with the induction of mutations. I met Sam Granick

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as we all walked out of the room and he said to me, "Do you really mean a sexual phenomenon?" To this I replied, "I certainly do." Next day when I was taking lunch (In those days we all came in on Saturdays and there was often some discussion about the Friday lecture.) Hotchkiss came over to where I was sitting and said, "I think you are right."

These notes are meant for you personally. At some time in the future I am planning to publish an account of the pneumococcus episode in the hope of setting the record straighter than it now is.

Yours sincerely,



AEM:ggl

Alfred E. Mirsky  
Professor