June 29, 1973

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Dear Dr. Cohen,

I have just read your paper on The Search for the Chemical Structure of DNA and I have some comments.

I was glad to see that you have done justice to P.A. Levene's work. Your remarks on the tetranucleotide hypothesis are on the whole fair, although I think Levene would have been surprised by its prominence in your account. The comment at the bottom of page 10 that the hypothesis was a "scientific catastrophe" by Bentley Glass is surely a gross exaggeration and the "absurd tetranucleotide hypothesis" page 19 from Chargaff is also an obvious over-statement. Chargaff, incidentally, first worked at Mt. Sinai Hospital in New York for some time before he moved to Columbia. I think the comparison between Bergmann's theory and the tetranucleotide is plainly absurd. No more than a passing reference to the tetranucleotide hypothesis is required.

In the J. Gen. Physiol. Vol. 30, page 128, 1946, I gave a good method for preparing DNA, which was widely used for many years, and

still is. This DNA is sold by Nutritional Biochemicals, Cleveland, Ohio and is in their 1971 catalogue, page 23.

I wish to comment particularly on your reference to me, page 39 and reference 143. First of all, the reference to the statement by Ris and myself is entirely irrelevant to the statement that I was "one of the chief opponents to the acceptance of DNA as the transforming substance" and that I "opposed Avery's modest conclusions in the light of their own beliefs in the genetic primacy of proteins." You refer to Chargaff, Stent and Hotchkiss. Why not refer to me? There is in volume 30 of J. Gen. Physiol. at the bottom of page 134 and the top of page 135 a statement of what I thought in 1946. In "Genetics in the 20th Century" edited by L.C. Dunn, 1951 there is a statement of 1951. And in The Scientific American for February, 1953, page 47 there is a further statement.

In 1946 and 1951 I accepted the idea that DNA is part of the transforming material, but asked whether protein is not also necessary. At the time this was an obvious question. It was finally decided by Hotchkiss' work and in 1953 I do not mention the possibility of protein still being there.

An important question concerning the transforming material is how it works. Sewall Wright, H.J. Muller and I considered it to be part of the gene material and many others did. The comments by Stent and Wyatt are really of little account, hardly worth mentioning. I wrote in the book edited by Dunn, page 133, "Since it is now known that the

material derived from the heat-killed cells that is effective in 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."

What was Hotchkiss's attitude? For this I have read the reports made to the Board of Scientific Directors of the Rockefeller Institute on pneumococcus work. After the work by Avery et al, pneumococcus work was taken up by Hotchkiss. His 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 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.

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 äa"sexual phenomenon" rather than with the induction of mutations. I met Sam Granick as weall 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."

In summary, I think that my attitude towards the transforming principle is entirely different from your quote on page 39 and reference 143. From the beginning, I considered DNA as an essential part of the transforming principle and after it was proven by Hotchkiss that there was practically no protein present, (which was my original question) I accepted the conclusion without reservations. I do not consider this being the attitude of an "opponent": I merely asked a question which obviously required an answer. Furthermore relying on Hotchkiss' memory of the events brought you to misleading conclusions. Reading his reports to the B of S D of the RIMR, clearly shows what his point of view was <u>at the time</u>. The quotations from the reports to the Board of Scientific Directors of the Rockefeller Institute which I have given in this letter are for your information, but are not to be quoted without your obtaining the permission of The Archives Office of our Library.

I look forward to hearing from you.

Yours sincerely,

AEM:ggl

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Professor