October 10, 1953

My dear Beale:

In response to your of the 7th, I am sending a pre-print of a paper due to appear shortly in the Journal of Immunology. The more detailed genetic analysis is still in progress, and even those inferences that could be made from the data in that paper were not emphasized.

At first sight, the alternation of phases would seem to be closely analogous to the situation in the Paramecium antigens. It is quite clear that the alternative phases are each represented by a distinct locus seemingly quite unlinked to the other, e.g. S. typhimurium would be $H_1^{i}\ H_2^{1,2}$. The series of "specific " antigens, a, b, c, d, eh, fg, gm,... i, j, k, lv..., r,... then constitute a series of H_1 alleles, while the "non-specific" antigens: 1,2; 1,5; 1,7; enx; enz_{15}; z_6;.... are a series of H_2 alleles. Phase variation is thus not a mutation in the usual sense of a shift from one allelic specificity to another. The chief problem now is how the alternation of phenotype is determined. This is not finally settled, and owing to technical limitations we could probably not distinguish between a determination by cytoplasmic state from that by a third unlinked locus. However, the evidence to date seems to favor a third alternative, namely a change of state at the locus itself. This is seen from experiments of the type:

S. typhimurium ($H_1^{i}\ H_2^{1,2}$) —x S. abony ($H_1^{b}\ H_2^{enx}$), (with b, enx serum for selection)

The only results of such experiments have been either $H_1^{i}\ H_2^{enx}$ and $H_1^{b}\ H_2^{1,2}$, the evidence for two distinct H loci. [The third possible type that the selective conditions would allow would be $H_1^{i}\ H_2^{1,2}$, never found.] The evidence of local determination is that phage from TM cells in the i phase will engender principally the $H_1^{i}\ H_2^{enx}$, while phage from TM ph2 engenders mostly $H_1^{b}\ H_2^{1,2}$. If we accept the principle [based only on rather general evidence] that transduction involves only the transmission of small chromosomal fragments, the difference in the transductions from the two phases would speak for a differentiation local to the genetic factors. Experiments are in progress to seek to generalize these findings, and to test the role of the phase of the recipient cells, but there have been some difficult technical problems. Recently, Bernstein here has confirmed an old and generally discredited report that the two flagellar phases are generally distinguishable, phl being inagglutinable, and ph2 agglutinable by certain basic dyes. This fits nicely the two-locus theory, but we are not yet sure of its more general implications.

You will note the exceptional behavior of the stock CDC-157 recorded in the paper. We have quite good evidence of a duplication of H_1 in this stock, so that it should be represented $H_1^{b}\ H_1^{1,2}$ rather than $H_1^{b}\ H_2^{1,2}$ for typical PB strains. However, the alternation of b:1,2 is extremely sluggish and has impeded the final verification of this notion in certain derived stocks we believe to be, e.g., $H_1^{b}\ H_1^{i}\ H_2^{enx}$.

As ~~you~~ so much of this work is still so tentative, may I ask that it not be quoted as yet (except, of course, for the paper about to appear).

Needless to say, I am deeply interested in your continuing work and look forward to a further ~~exchange~~ exchange of publications.

Yours sincerely,

Joshua Lederberg