October 28, 1952

Dear Morton:

I hope all of the cultures will have arrived safely— let me know if any replacements are needed.

Some sort of picture of phase variation is emerging from experiments with abony -x typhimurium. [-x signifies transduction to, x- transinduction by]. SW-535 is not entirely satisfactory: its motility and phase-variation are somewhat erratic. I have been using LT-2.

In general, FA from phase 2 shows no trace of the phase 1 factors. This was apparent in your typhimurium^{II} -x typhi, and even more strikingly in tym^{II} -x SW-543 and abony^{II} -x SW-543. To the extent of a limited number of tests this also holds up in abony -x tym. In many cases, the second phase evidently cannot be maintained in a monophasic type such as SW-543 or typhi. [the 1,2 phase in SW-534 and -588 may be exceptional, see below]. The following results have been obtained with abony -x LT-2^{I}:

abony^{II} -x : enx ⟵ i

abony^{I} -x : b ⟵ 1,2

If this result can be generalized, we have the following conclusions:

1) The alternative phase is not inherent in the transduced allele
2) The alternative phase is not represented in any active form in the FA
3) The alternative phase is retained in an inactive state in the recipient cell.
4) The specific and non-specific are, in general, homologues at two distinct loci, but are not allelic to each other
5) Monophasicity may be accounted for in some cases by the unsuitability of the residual genotype for the expression of the alternative phase. In other cases, it may have to do with the frequency of the shift itself.

The consideration of 2) with 3) leads to a paradox. In previous thinking, I had speculated about a phase-shifting locus whose mutation determined the expression of either phase; one could imagine a "cytoplasmic state" mechanism in similar terms. But whatever type of suppression of one locus is involved is not separable from it by transduction. If we accept that transduction is confined to nuclear factors, usually single, we have to infer more or less permanent gene states, mutually exclusive as between the two loci. This sounds rather like McClintock. One can also imagine that one locus is replicated many fold, either into the cytoplasm (gene-initiated plasmagenes) or at the locus itself, like Huskins' lamellae. I don't want to go too far in speculative

analogies with somatic differentiation until the facts are more thoroughly established. I am fairly convinced, however, that phase variation is not a mutation in the ordinary sense, but a semi-permanent inactivation, of some sort, of one of a pair of loci— the inactivation being so closely associated with the locus that it is not separated by transduction.

I had thought that the monophasic behavior of SW-543 H^+ could be understood by its inability to sustain the 1,2 phases. Stocker showed, however, that SW-534 -x 543 gave 1,2, and I have confirmed this, also ruling out the possibility of contamination. SW-534 itself reverts occasionally to give the 1,2 phase (e.g. SW-588). More recently, I have gone back to what I regarded as SW-703 (i.e. Edwards #3) which should be equivalent to SW-533, the source of SW-534. However, FA (SW-703) either II or I gave only b, and no 1,2 from SW-543.

It is rather important, therefore, to trace the history of these cultures accurately. Unfortunately, at the time these experiments were done, not too great care was taken to identify the serotypes. In the lyophil collection, there is an envelope labelled S. paratyphi B, with no other designation. I have assumed that this represents Edwards #3, on the one hand, and the parent of 534, SW-533 on the other. Is there any possibility that this is incorrect? To add to the confusion, there was a contaminating Salmonella, so far untypable, in the stock culture of "Paratyphi B #3", but I don't think this is related to the present question. At any rate, it would help to clear this up if you could send back to me any cultures that you may have under the designation SW-533, or Edwards 3, or any others that might be confused with these. Please also record how they have been labelled in your hands, and perhaps the situation can be clarified.

Sincerely,

Joshua Lederberg

P.S. Thanks for the check, which has been forwarded. It will help.