August 20, 1949.

Mr. N. D. Zinder,
Carnegie Institution,
Cold Spring Harbor, N.Y.

Dear Norton:

I am sorry not to have been able to answer your letter sooner, but have just returned from a trip.

Your data certainly appear to be inconsistent with mine for the frequency of the V_1^r Lac- recombination class, and I don't see offhand just why they should be. I would suggest that you yourself make a direct comparison of crosses not involving SR with those which do.

I am not clear how you crossed the resistants with the dependenisatIf the cross was carried out on streptomycin-lacking medium, I take it that you would have the opportunity of recovering streptomycin-sensitive recombinants unless sr and sd were allelic, but would lose any sd prototrophs. The loss of these sd prototrophs might be expected to bias the segregations of any factors linked to sd, which does seem to be happening (s19 x sd1: you wrote this as Lac+ x Lac+, but I assume that you meant sd1 to be TLB_1- Lac- V_1^r. In this instance, the near absence of V_1^r prototrophs indicates a linkage of sd to V_1.)

Your suggestion that sr may have a "slight" requirement for streptomycin fits the data given very well, but you should control your observations on the Lac V_1 segregations with experiments on the streptomycin sensitive parents. It would be dangerous to assume that the modified responses to streptobiosamine resulted from multiple allelism, without experiments crossing sd's and sr's with ss's (wild type) and looking for exchanges of the modified character (e.g. sr x + might give some recombinant sd's, or the converse.) Is this what you mean by your outcrosses? With regard to crosses of sr x sd on streptomycin medium, I wonder whether you have checked the sd parents to ascertain whether they have any nutritional requirements beyond streptomycin? E.G., will sd-1 grow on minimal + TLB_1 + streptomycin? Will sd x sd give prototrophs on streptomycin medium? But also remember that linkage of sr to appropriate nutritional markers will also give all resistant prototrophs. Instead of using heterozygotes, which are more complex than ever, why not simply do reverse crosses (i.e. BM sr x TLB_1 + and compare with BM + x TLB_1 sr)? I would be interested to try an experiment here with sr in a heterozygote, primarily to ascertain dominance. Demerec has assented to this, and I would appreciate it if you could ask him to take along one or two strains. It would not be especially easy to determine cytoplasmic inheritance with the heterozygotes at the present time because of the possibility of hemizygosity which would also prevent segregation.

The more I have thought on the matter, the more convinced I am that we should dispense with all extraneous issues on the Salmonella program, and devote a lot of time when you return to the production of mutants in one Salmonella strain after another, until one is found with a workable recombination system. Therefore, I think it very well-considered that you are letting the phage problem lie, and hope that we will not be tempted to resurrect it. Don has been turning out mutants from new coli strains at a great rate, and I think that the same procedure should be used with Salmonella.

L. Cavalli has written that he has discovered another coli strain which recombines with K-12. The ice is being broken.

Cavalli has also discovered asderivative of 58-161 which recombines very, very frequently, and using his "Hfr" stock, I have been able to do crosses entirely on complete medium, and get data on unbiased segregations from non-persistent zygotes. The results tie in very well with the conclusions from the mapping of Mal and Gal in prototrophs, and their segregations in the persistent heterozygotes that the segregations are not normal. There is a very definite elimination mechanism which limits the kinds of segregants and recombinants which can be found. Complementary recombinations are not produced with equal frequencies (if at all), and it is impossible now to accept a simple interpretation of any mapping data. Therefore I would not take too seriously your difficulties with Lac and V_1, but agree with Demerec that the important point is the use of recombination to detect allelism. The situation may be parallel to Auerbach's unstable centromere (Genetics Jan. '47) but is still very murky.

Sincerely,

Joshua Lederberg