June 5, 1953

<u>Personal</u>

Professor E. L. Tatum
c/o Symposium, L.I. Biol. Lab.
Cold Spring Harbor, L.I., N.Y.

Dear Ed:

This letter follows your phone call by just a few minutes. This was so unexpected that I may not have been as articulate as I might. I am touched that you, and other friends, should have thought to call, and am sorry to miss another occasion to see you. As I said, we probably want to spend rather a quiet summer (especially with moving to a house). We would have loved to visit California again (and conceivably still might). When we heard ~~[illegible]~~ might leave a house vacant for a summer trip, we thought this might be a means of settling somewhere for a month— I guess Esther and I have had our fill of just driving around: we spent last summer driving through Ontario, Quebec, the Gaspe, Maritimes.....

From the tone (if not the fact) of your call, I wonder if hidden or ulterior motives are being read into our <u>not</u> coming. In fact, I seem to get this response generally. This is nonsense. I do remember what a mess the 1951 symposium turned out to be, and how tired we were after it, and I admit I am relieved in a way to be out of it. If we had not had such a phenomenally busy time of it this last Spring, and to look forward to the same for the rest of the summer, we probably would have gone.

I specially would not want you to think there is any reason to modify any of the technical conclusions of our work, as published in 1947, 1951 or 1952 (except insofar as the F-polarity sheds light on the determination of segmental elimination). Hayes was kind enough to send a draft of his ms.— it is a good presentation, and those details of his present views with which I do not agree can probably best be worked out between ourselves. Of course, I think that you or I will accept a <u>vectorial</u> picture of K-12 recombination when someone actually brings up some positive evidence of cell-free transmission, as against all of the negative data already accumulated (Atchley; Davis; Texas;...&T&L). [Cf. Genetics 32:521, 1947]. If Hayes (and Watson) add many more chromosomes to the number which can be jointly "transferred", they are soon going to end up with a whole nucleus.

The main points at issue seem to be 1) whether "elimination", as of Mal-S segments, is pre- or post-zygotic, and 2) whether the "F+ agent" is also the vector of genetic material. Until the F+ agent is separated from the cells, (2) cannot be decided; at least so long as one postulates a variable probability of association of the two elements, any circumstantial evidence of their separability

(v. Genetics 37:720-30, 1952, at 725, lines 10ff, 37-38, 727 lines 39ff, and in Hayes' experiments, the effect of streptomycin) can easily be explained away. (1) is a question that bothered us when the peculiarities of the diploids first became apparent. In 1949 (PNAS 35:181) it was already stated that the diploids from M-F+ x TLB1-F-Lac-Xyl-Mal- [F status now added] were usually hemizygous Mal-, but occasionally Mal+, and never Malv. One has to infer from this statement also the result of many other explicit experiments in which Mal+ prototrophs were selected as such, and were never heterozygous for Mal. On the other hand, in a similar cross (CSH '51 tables 6 and 8, of 28 Lac*v* diploids, 15 were Mtl*v* and 8 were Mtl+, so that "the Mtl+ chromosome is transferred along with the Lac+ chromosome from the F+ parent" to at least 3/4's of the diploids, if not all of them as I imagine is actually the case. This is very far from a random concordance.

But perhaps the most dritical evidence is also already indicated in table 6 (left column). The parents can now be~~/~~ written as M-Het F+ Mal+ S^r x TLB_1- F- Mal-S^s. ~~[illegible]~~
Of 38 classifiable Mtl*v* diploids, 30 were indeed Mal- S^s, in accord with the F- parent. However, 6 (no negligible proportion) were Mal+ [and reverse crosses, such as in table 8, have shown that this class also is hemizygous], like the F+ parent. Subsequent experiments under the same conditions have shown that platings of F+ & F- mixtures ~~together with~~ do not allow crossing of these with other F- cells (Genetics 37:724, line 3-6), as has been verified in this particular type of cross. But the remote possibility of an artificial reversal of F polarity is even more ~~decsi~~ decisively discounted by the two hemizygous crossovers, Mal+ S^s in which the hemizygous segment is derived in part from the F+ parent, in part from the F-. We have to conclude from these results the elimination is post-zygotic, and occurs only after there has been an opportunity for crossing-over between the entire gametic contributions. In these two crossovers, the(F+) Mal+ factor has escaped elimination by crossing-over; I assume that the other 6 Mal+'s are also crossovers, this time not between Mal and S, but between both and a third locus (F?) at which the breakage occurs.
These results are quite typical of a large series of experiments. Most were done several years ago, although the F character is on record. Tom Nelson and I have been repeating them with comparable results. In addition, he has done some of these crosses with the F+ parent heavily treated with streptomycin, presumably eliminating ~~the~~ its competence as F-. The results are much less extensive (owing to very low yields from such experiments in our hands) but still comparable.

There is another line of approach on which there has been little comment so far: haploid x diploid crosses (cf. CSH p. 425). The polarity of these crosses is often 2n.F+ x 1n.F-, but ~~their progeny are~~ the resulting prototrophs are almost all diploid, and in this case usually <u>not</u> deficient even for Mal-S. These "F+ agents" would have had to carry quite a burden!

Well, Ed, you see what happens when I get started. There are actually very few factual results at issue (though we do not get Hayes' picture with Hfr crosses: the B_1-M linkage is still 10%), and some of the interpretive differences are semantic. I hope you will not also have misunderstood our 4-armed linkage map as representing an <u>X-chromosome</u> (vs. an X-configuration at diakinesis).

I hope we will get to see each other again 'fore too long. Give my best to Aaron and so many others.

Sincerely

Joshua Lederberg

P.S. I have written Hayes many times about these points, but we seemed not to talk the same language; at least, neither he nor Watson answered them in their recent paper. I am looking forward to meeting Hayes (in Madison's quiet atmosphere) to talk them over.