Marine Biological Lab.,
Woods Hole, Mass.,
August 29, 1947.

Dear Dr. Mather,

You would, I think, have been not a little amused could you have observed my mental gyrations during the past few days over the question of two- and four- strand crossing-over. You have been, of course, entirely correct in asserting that there should be no difference . My fallacy consisted of attending entirely to the distribution of breaks on the chromatids in the tetrad, which one might suppose to show interactions in the four-strand case. If one considers the distribution of breaks on the strands recovered, one realizes that it makes no difference what combinations of cos led to them, they will still be distributed on the strands Poisson-wise. It was the identity of $2\sinh x / e^x = 1 - e^{-2x}$ that led to this realization, the first term having come from my 2-; the second from my four- strand analysis. So, you were not quite right in remarking that I had entered into crossing-over theory "truly and well", considering this inexcusable blunder. Please accept my thanks for having helped me out of it. The formulae of the two strand case are, of course, essentially the same as Haldane's $x_{12} = x_1 + x_2 - 2x_1 x_2$, as can be shown from the addition formula for $\tanh (x_1 + x_2)$.

The specific problem becomes very much easier to handle, since the crossovers in each segment will be distributed Poissonwise with a mean proportional to the length of the segment. In the case at hand, the ratio of triple-types to total prototrophs will be:
$$\frac{(1 - e^{-2ax})(1 - e^{-2bx})(1 - e^{-2cx})}{1 - e^{-2x}}$$
where a,b,c are the proportions of the segments, and x the map distance.

You are quite right also about the futility of this type of detailed analysis in view of the approximations that must be made of no interference. A priori, however, I had absolutely no conception of the final estimate of the map distance, and if it had proven to be much greater than it was, some sort of correction for multiple crossovers would have to be made. This was particularly cogent since I was using the multiple-crossover frequency itself to measure the distance! There does not seem to be anything that can be done about chromosome chiasma interference, but it may cancel itself out- although it will bias the single- as against multiple break chromatids, it will also tend to even out the distribution of such multiple breaks as do occur and make them more effective in producing the "triple" types. I am not sure that chromatid interference would have any effect; complete interference would be equivalent simply to juxtaposing two two-strand dyads, and would have no effect.

When referring to zygotes previously, I had in mind the fact that the combining cultures are mixed just before being poured into hardening agar. The gametes produced by a single zygote should therefore be kept in one place, and under certain circumstances give rise to mixed colonies.

The crossover algebra has not been as useful in my own work as I had hoped. It is of course applicable under any restraints one cares to formulate: non-sister strand c.o., chromatid or chromosome interference, competitive pairing in multisomics, etc. One need merely place the appropriate restrictions on the subscripts of adjacent crossover-symbols. It would be mostvuseful probably in such a system as Lindegren's analysis of interference in Neurospora.

I shall be leaving Yale this Fall, and am taking a post as Asst. Prof. in Genetics at the University of Wisconsin, Madison, Wisc., starting in the middle of September. Very satisfactory conditions for a program of research in microorganisms are being established there, and there is a rapidly growing interest in such departments as biochemistry and bacteriology in the implications of genetic research for their work. The prospects for fruitful collaborations there look very good, and were the main reason for my going out there.

The linkage work has been written up and sent to Genetics, where it should appear in the September issue. Your encouragement and assistance have been invaluable- and I hope, fruitful.

With best regards from my wife,

Yours sincerely,

Joshua Lederberg.