Milan, 16/12/51

My dear Lederberg,

Your experience of mine as a correspondent will, I hope, help you to understand that if I have not replied earlier to your letters, and to the sending of your most exciting CSHS paper has not been a consequence of my being dead in the meanwhile, or of my having dropped bacterial genetics. Neither of these things is true, and, on the contrary, K 12 is still consuming most of my time, even if the later discoveries in your laboratory may have made of it a rather obsolete object for research. I have also had, from the editors, a copy of Microbial Genetics, and was glad to see among the major papers our letter to Nature. I have been doing a great deal of work on the same subject - two papers on it are nearly ready - essentially with a view to confirm the experiments reported in the letter to Nature, and to test the spontaneous origin of mutations in the case of chloromycetin resistance by methods other than the fluctuation test - or complementary to it. The result with which I was most pleased was the creation of a second step resistant by recombination, on drug free media, between two independent and non-allelic first steps. A puzzling result, on the other hand, was that no two allelic independent first steps were obtained; although the number of these tested was not great, it seems likely that the number of genes involved in such resistances is rather high. Also, interactions may be rather complex; however, I have left a detailed analysis of this or similar cases for times when the mating and the genetic system of coli will be more fully elucidated. I have spent a rather long time on this, as I happened to be interested in biometrical genetics - inspite of its unpopularity between geneticists - since a long time. Similar results were obtained with terramycin resistance; which could be easily expected especially in view of the fact that chloromycetin resistant organisms are easily resistant to terramycin, and viceversa.

Since some months I am back to work on maps. Outcrosses of 58-161 and W 677 (or related strains) to W 826 and W 836 had shown segregations which, although not easily understood, were in favor of a chromosome mutation having been induced either in B-M- or T-L-B_1*. By the way, although I have often been using, after your paper, the B-M- designation, I have never found a trace of the biotinless gene; it must have back mutated early in my strains.

Out of the many methods which I have tried to obtain strain

* more probably in the latter

s which one might confidently expect to find homozygous, on crossing, for chromosome arrangements mutations, was the following: an M- strain like a multiply deficient 58-161 (I am actually using a derivative of W 705) was selected for S^r; and on the other hand a prototrophic strain obtained by spontaneous mutation, inspite of the very great difficulty found to get an M+ mutant. An M-sugar negative S^r was then crossed to an M+sugar positive, and viceversa, an M- sugar positive S^r was crossed to a M+ sugar negative, on minimal plus streptomycin. The data I have sofar are essentially confined to the "unmappable" region i.e. all those genes linked with Mal etc., which would never give a linear map in the sindard crosses. All data are in favor of a linear order, but there is one difficulty; in one cross the order is altered in respect to the other cross, in the sense that two genes seem exchanged. I am now starting again with independent mutants.

When a similar technique was applied to T-L-B_1- derivatives, the surprising fact was found that strains T-L-B_1-S^r and T+L+B_1+ (the latter obtained by back mutation from TLB_1-) would never cross together. Therefore I was led to think that a mating-type-like mechanism might exist in K-12; K-12, 58-161 and most other derivatives being homothallic, while W 677 is heterothallic. Homothallism is restored by recombination. In fact, crossing 58-161 S^r to W 677 on minimal + TLB_1, recombinants of TLB_1-S^r types are secured which cross regularly with TLB_1+ strains, etc. I am following the details of the inheritance of this now, first data being in favor of cytoplasmic inheritance.

A conclusion not too far from that one given above concerning mating behaviour of the BM- and TLB_1- strains was reached, in entirely independent way By William Hayes, of Postgraduate Medical Schhol, University of London.

Is there anything new about the cytology of K 12, and especially heterozygotes? We have started having a look at the chromosomes of bacteria here, but find them desperately insignificant.

Your "Microbial Genetics" seems to me excellent, and we shall have it reviewed on our Journal. I hope this letter will reach you in time to bring you best wishes for Xmas and the New Year.

Yours sincerely

P.S. I do not find your name among prospective participants to the IX Congress of Genetics. I hope you will come; I know that also the Microbiology Congress counts on your presence in Italy in 1953.