CARNEGIE INSTITUTION OF WASHINGTON
DEPARTMENT OF GENETICS
COLD SPRING HARBOR, LONG ISLAND, N.Y.

July 17, 1947.

Dear Lederberg,

With regard to the experiments on delayed effect, I dont think it is possible at this stage to discriminate between the possibility that the end point mutants are the result of delayed alteration of the genotype, and that they are the delayed phenotypic expression gene mutations produced earlier.

In the untreated material all that can be said with certainty is that there is an excess of mutations associated with the lag and early logarithmic growth phases. These may be the result of a genuine high mutation rate or they may be the delayed expression of gene changes occurring in the resting stage. I am sure that they are <u>not</u> a mere accumulation of gene changes occurring at the normal rate during the growth prior to the resting stage which have failed to express themselves phenotypically, as it would take twenty generations at least to produce the observed numbers of the excess.

The experiments done with irradiated material are not terribly critical as the results seem to depend on the design of the experiment. They do however cast doubt on the concept of the end point mutants as the result of a finite number of changes. In those experiments which I have done there is a fixed or slightly rising number of delayed mutations occurring as the result of each generation. After a certain number of generations this fixed increment is obscured by the spontaneous mutations which become more numerous as the population increases. This imposes a practical limit on the determination of the end point number, and true end point number may be greater than estimated or may be infinite in which case the concept is meaningless. A better description might be "induced mutation

rate per clone per generation" since such a figure seems to remain pretty constant over the period of growth during which it can be measured.

I would not like to be quoted on induced mutations as the work I have done has not been sufficiently detailed; the work on spontaneous mutations is now pretty conclusive, however, and may be quoted if your review covers that aspect of the subject. It would naturally be better if we could have a chat about these things, and I wish very much that you would have a chance to visit us before you leave.

A number of us have been wondering if it would be possible to induce you to come here for a few days and to show us your techniques, as we ought to know whether the induced mutations we are working with behave the same as other genes. This would of course mean inducing mutants in K-12 and doing recombination studies to make sure that they are not just some peculiar surface phenomenon.

However, you will probably hear further about this from Mrs. Witkin if she is able to make the necessary arrangements at this end.

All best wishes,

Sincerely,

Howard Jukes