December 9, 1958.

Dr. Joshua Lederberg
Department of Genetics
University of Wisconsin
Madison, Wisconsin

Dear Dr. Lederberg:

We really appreciate your penetrating comments on the manuscript we sent you last summer entitled "The Direct Estimation of Mutation Rate from Mutant Frequency Under Special Conditions." We were particularly impressed by your comment that phenomic lag during exponential growth would tend to impart an upward bias to the equilibrium mutant frequency. Actually, we had considered this possibility in our own discussion but had rejected it in terms of what now appears to be a misconception. We have generally looked at mutation to respiration deficiency from the particulate loss point of view and assumed that it was largely a pre-mutational loss (i.e., that it was more probable that a bud with no particles would arise from a cell with one or a few particles rather than from a cell with many). This view led us to infer that the newborn mutant would be essentially incapable of phenomic lag divisions. It is now apparent that this inference was based upon the assumption of identity of particles bearing the respiratory enzymes, with particles concerned with their synthesis.

Your comment stimulated us to reexamine the question and to attempt to calculate the upward bias to the equilibrium mutant frequency if phenomic lag did occur. If one assumes that every newborn mutant cell passes through four phenomic lag generations, that respiratory capacity is equally partitioned at each division and that the growth rate with an obligately aerobic C source depends upon respiratory capacity (i.e., the first phenomic lag generation takes the same time as a normal generation, and phenomic lag generation time doubles in each successive generation) then one can calculate, either by arithmetic or algebraic means, that the bias to the equilibrium frequency is 4.78%. It turns out that these assumptions aren't particularly critical so that assuming more than 4 phenomic lag generations does not affect the estimate significantly. You may recall that our estimate of the error arising from plating cells with attached buds was 40% so that these two errors are in part compensating. We are incorporating some of this discussion into our earlier manuscript.
We were further stimulated to see if we could observe phenomic lag directly. The enclosed draft of a manuscript summarizes these experiments. We are still troubled by the possibility that the limited development, which we interpret as the direct observation of phenomic lag, might reflect a pre-mutational rather than a post-mutational event, (i.e. debilitated normal mother cells produce only mutant or debilitated normal offspring and then all debilitated normal cells mutate). Although reasonable arguments can be marshalled maintaining that this possibility is fairly unlikely, we would like to do a critical experiment to disprove it. At present we are discussing some micromanipulative bud stripping experiments to see if there is any evidence for a normal mother cell mutating in the strain which mutates at high frequency.

I know you are very busy but if you can spare the time to read the enclosed note and send us your comments we shall appreciate them. If time doesn’t permit we shall understand.

The entire laboratory joins me in sending our congratulations on the Nobel Award.

Sincerely yours,

Maurice Ogur
Associate Professor
Biological Research Laboratory