January 7, 1957

Dr. H. Kalckar
Dr. K. Kurahashi
National Institutes of Health
Bethesda 14, Md.

Dear Herman,
Dear Kiyoshi:

Please forgive us for writing double. And best wishes to Barbara and you, Herman. We are very sorry you will not be able to visit in the near future. Would it be easier to arrange on our funds, Herman?

We have been very much pleased by the way these Gal studies have been going, but for the same reason it would be most disappointing if they were interrupted before the climax. Is there any way we can encourage you to follow the 'straight and narrow path'? This is, of course, a matter of opinion, but it seems inescapable that the Gal_3^- mutant is crucial to the analysis. We have now learned that it belongs to both the Gal_1 and the Gal_2 cistrons. That is, Gal_3^- shows position effect with <u>both</u> groups of mutants. It is therefore obvious that we should learn, on the biochemical side, whether <u>both</u> enzymes are missing. If so, we will be willing to concede the likelihood of the hypothesis that each ~~mitmum~~ cistron does correspond to an enzyme, which is a principle that has been speculated on elsewhere, but nowhere else has any likelihood of such exact proof. This result might also lead to ~~xgx~~ the conclusion that on the 'nucleotide keyboard', the different functional segments are not so well separated as Demerec has supposed, but may overlap one another. In that case, Gal_3^- would be a point in the overlapping segment:

[Speculative drawing]

kinase

.....

1 4 6 7 3 2 8

transferase

We do not actually have much direct evidence on the sequences, but are working to develop the necessary methods, so that it will be possible to correlate three kinds of information: 1) enzymatic defect 2) cistron relations and 3) linkage sequence. Nowhere else has this been so possible, but it does mean hard work for everyone.

We assume you did get the Gal_3^- strain(s) -- they were left for you with Dr. Reaume.

Kiyoshi-- what are your plans for next year? Would it help this project

if you could come to Madison for a year? If this would interest you, let me know what you would need (e.g. are now getting) by way of salary, and I will see what might be done between Genetics and the Enzyme Institute.

There are two other things we want to press you for: 1) [long standing] the quantitative data relating relative enzyme activity to total protein of the various extracts, so we can judge, e.g., the 'constitutiveness' of the different enzymes, and the extent of the defect in the mutants. 2) -please,please,please a definite protocol on the galactose-inhibition experiment. We very much want to use your method for the preliminary screening of many of our mutants, but did not succeed in one rough trial. So won't you tell us your exact medium, the preparation of the inoculum, the period of observation, and so forth. Please. We aren't trying to study the mechanics of galactosemic syndromes, as you are, but we should take ~~my~~ advantage of any method for screening the mutants.

This is a long letter, so we will summarize the principal points, and hope you have time for comment or reply:

1. The critical importance of Gal$^-_3$ in the enzyme-genetic analysis.
2. Your exact method for showing inhibition by galactose.
3. The quantitative data on activity:protein ratios in various preps.

With best wishes for the new year*

Yours,

Esther M. and Joshua Lederberg

*It is of course also the anniversary of our collaboration. We think we have no reason to regret the fruitfulness of it.