April 2, 1951

Dear Paul-

If you think there is a substantial possibility of winning an AEC fellowship, I see no reason why you should not proceed as suggested by NRC. Last year, if I am not mistaken, the allocated fellowships in biology exceeded the applicants! It would, of course, be necessary for you to explain the change in your plans. Since the NRC's endorsement is based upon your earlier application, it might do no harm to write to Lapp concerning these changes, and asking whether they would influence the NRC appraisal to AEC. The major obstacle might be your previous tenure of AEC fellowship support, but this is something that you obviously can do nothing about. The most sensible approach, I think, would be to emphasize that the fellowship would broaden your training and experience in a new direction. However, I would not be sympathetic to any gross alteration of your project statement simply to suit AEC. Nevertheless, there would be ample opportunity for the application of radiobiological techniques, and perhaps analysis of radiation responses, in the study we have already discussed, and if you were interested, our project on radiation effects on diploid E. coli might occupy a portion of your time to this end.

The research program I've had in mind would be applicable both for AEC and PHS, and of course turns on the successful isolation of new crossable strains of E. coli. We have about a dozen now, but this particular routine should also be continued and expanded under your direction, both to provide the most diversified material, and to look specifically for evidence of specific compatibility groups (heterothallism). The cultures already isolated prove to be rather diverse in such characters as fermentation reactions; responses to phages and colicins; and somatic antigens. (The latter, I hope, will be the special interest of another postdoctoral applicant). The differential characters of the fullest set of new cultures should be specified as fully as possible, and their range compared with the rather confusing taxonomic groupings. Then, as far as possible, the genetic basis (oligo-, poly-, or extra-genic) of the overt differences should be studied, and these compared with experimentally (i.e. radiation-) induced mutations in the laboratory. For example, the "species" E. coli has been split into varieties "communis" and "communior", based on sucrose-fermentation. Are all of the sucrose-negatives genetically equivalent? What are the genetic factors differentiating them from type positives? Finally, and the most interesting for evolution study, how much genetic differentiation is concealed beneath phenotypic similarity? Experimentally, the sequence Lac$^+$ → Lac$^-$ → Lac$^+$ can sometimes be shown to result in "suppressor" mutations of similar Lac$^+$ phenotype. Is this true of many other phenotypes characteristic of E. coli? The simplest characters to study here would be fermentation capacities and nutritional capacities, the latter particularly since hypomorph or amorph alleles, when unmasked, can be detected for an unlimited number of loci by the simple test of (failure of) growth in synthetic minimal medium.

I hope this is sufficiently detailed for your needs. Although the detailed methodology will be novel to you, the general concepts are closely parallel to those of genetic investigation of the nature of varietal and specific differences in such material as Gossypium.

It was not appropriate for me to make any direct inquiries about Mrs. Levine's status in Zoology. The department is legally unable to make most of its commitments until the enrollment has been established, so that there almost always turn out to be more vacancies later than seems apparent at first. I would like to repeat that I don't know of any worthy students who have been neglected very long in respect to financial support, but the situation for the time being is bound to be very confusing.

Sincerely,

Joshua Lederberg