October 12, 1956

Dr. P. Mitchell
Dept. Zoology
University of Edinburgh
Scotland

Dear Dr. Mitchell:

Thank you for your note and letter of the 5th,

I realize that my "findings" as recorded in the note you saw have been almost if not entirely anticipated by other workers, though perhaps not all the details fitted so coherently as they did in the E. coli/penicillin/sucrose trials. This may be partly due to the greater fragility of the protoplasts in E. coli: they can be prepared in fair yield (1-10%) from Proteus even in dilute media. I have hoped to rectify any possible impression of uniqueness, and also to clarify the implicit hypothesis of penicillin action, by the accompanying "postscript".

Your interesting note offered certain obscurities to my own reading, perhaps because I am not as familiar as I should be with your previously published work. (I would appreciate receiving whatever reprints you can spare on this count!) The malonate-arabinose combination is such a weird mixture it surely was not devised ad hoc, but I don't understand what the specific functions of the components are intended to be. I also am not clear as to your meaning for "autolysis" which connotes, to me, the dissolution of tissue or cellular structure after death.

Dr. Park tells me he has reached identical conclusions as to the mechanism of penicillin action and the role of the accumulated Uridine-diphosphate conjugates from his chemical studies.

Doubtless the main reason these issues were not appreciated sooner was the aura of mysticism that has surrounded the studies of "L-forms"; I am sure you will sympathise with my task of reading and reinterpreting that literature! We have however succeeding in the further propagation of E. coli protoplasts as L-form colonies in penicillin-containing agar (not broth!) and this opens the door to what I hope will be more exact studies of the genetic and physiological significance of these mysterious elements. Unfortunately, our experiments with mixtures of marked strains so far do not encourage the hope for new <u>genetically</u> interesting developments with the L forms. The mechanism of proliferation of L-forms is another issue: at least one process superficially resembling budding (from a small perhaps granular protuberance) has been observed; so far segmentation of a "large body" has not been, in my own material.

Yours sincerely,

Joshua Lederberg
Professor of Genetics

P.S. Dr. Zinder has a note in press, accompanying mine in the PNAS, on lysozyme effects on E. coli. You will be interested in his separation of the development of osmotic fragility from the subsequent sphering.