November 2, 1956

Dear Dr. Mitchell:

I want to thank you for the "shower of reprints and mss." you have taken the trouble to send me. I am greatly interested in your approach to many problems of common interest, and this material makes it much easier to catch up on background reading.

I had two reasons last Spring (ie. just before the Bact. Anatomy Symposium) for following up the hunch that L-forms and protoplasts might be related: a) the hope of clearing up the biological significance of a very murky subject, and b) the hope that protoplasts might be used very effectively in genetic-physiological investigation. Professor Spiegelman has been exploiting one aspect of the latter, with very encouraging results, i.e., in demonstrating "synpoietic" effects of RNA from Lac+ strains in provoking lactase synthesis in protoplast preparations of various Lac- mutants. I had hoped we could make similar trials with DNA in transduction experiments, but these have so far failed: the problem may be to create a system which is sufficiently permeable to DNA and still viable (i.e. capable of clonal growth). Clearly there are innumerable ways to try such experiments, and we are continuing with them. Unfortunately, there is no authentic report of DNA-transduction in genetically favorable strains of enteric bacteria.

It had occurred to me that the phasic changes in pneumococci which underly their "competence" as recipients in transformation (cf. Hotchkiss, Proc Nat Acad Sci 40:49, 1954) might be related to a stretching of the cell wall— which must be very close to what you have in mind in your letter and discussion in the B.A. Symposium. Would it be possible to encourage you to investigate pneumococci from this point of view, by your biophysical techniques? This is almost a unique system where the uptake of DNA can be demonstrated, and it has not been well defined at all as a biophysical problem.

Penicillin-induced protoplasts and L-colonies have retained their F+ quality and, in large measure their ability to mate. However, the protoplasts may not be completely denuded: for example they show a prominent capsule in india-ink preparations. The capsule is invisible in phase-contrast ;whether it represents the remains of the wall of an augmentation of the normal K- antigen has to be determined, probably by Tomscik's methods. I am not clear whether other authors have studied protoplasts in this fashion, but am suspicious that some of the "haloes" in published photographs may be more than the usual phase-optical artefact. If the wall-constituents are partly retained, it may explain why we have not yet obtained irreversible L colony types (accepting the primer hypothesis, which is one of several possibilities).

I am hopeful of visiting Edinburgh next March, and of taking advant of the occasion to discuss these questions at first hand. Professor W dington should be cognizant of these plans.

Yours sincerely,