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October 15<sup>th</sup> 1956.

Dear Prof. Lederberg,

Thank you for your interesting letter of October 12<sup>th</sup>. Enclosed is the manuscript of a paper that I read at the Symposium on Antibiotics held in Milan September 10<sup>th</sup> to 14<sup>th</sup> and a few reprints describing some earlier work on the penicillin problem. We also have a paper in the press on the "autolytic" protoplast formation in staphylococci which will appear in the Journal of General Microbiology vol. 16, No. 1. By "autolysis" we mean the reversal of the processes of synthesis. We observe, for instance, that the cell walls isolated from staphylococci (that have been harvested from rapidly growing cultures) will spontaneously digest themselves if placed in a medium at appropriate ionic strength and pH: they also digest themselves under the same conditions when they are still in situ round the intact protoplast of the staphylococcus provided that the protoplast is protected by the presence of very high concentrations of sucrose. We have used the term "autolysis" to mean spontaneous degradation without reference to whether the cell is "dead" or not. We would not like to attempt to define the word "dead".

I was very interested by your remarks about the "L-forms", especially as Weibull suggested in the Symposium on Bacterial Anatomy held by the Society for General Microbiology last April that the "L-forms" might be naked protoplasts. It is most interesting, therefore, that you have succeeded in getting an "L" growth of your coli protoplasts. As you probably know, McQuillen has obtained a kind of proliferation

of protoplasts of B. megaterium which seems to be by budding instead of binary fission. I am ~~also~~ enclosing a speculative little note on <sup>a</sup>the possible reason for the different mode of division in protoplast and intact cell.

As to the "weird mixture" of malonate and arabinose, I cannot see that this is weirder than penicillin and sucrose! The reason for using arabinose is that it is not metabolised and does not penetrate the plasma-membrane rapidly. Malonate may be substituted by a number of other salts at the same ionic strength, but malonate seems to work best, partly I suspect, because it helps to inhibit residual respiration, but mainly because it cannot penetrate the membrane and acts as quite a good buffer. There is nothing magical about it — at least, no more magical than penicillin!

I still feel that the mechanism of action of penicillin is not completely explained. For one thing, in experiments that we have been doing for the last year, we have not been successful in preparing protoplasts of gram-positive penicillin-sensitive bacteria as you have been able to do with the "penicillin-insensitive" coli. There may be experimental reasons for this failure, but at present we are unable to think what they may be.

I will let you know of any further development of our work along these lines as it comes to hand, and I shall be most interested to hear about your progress in return.

Yours sincerely,