Joshua Lederberg
Madison, Wisconsin
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Dr. Joseph Leiu
Bristol Laboratories Inc.
Syracuse, New York

Dear Joe:

This is just by way of a brief reply to some of your notes dated June 8th. Unfortunately the mechanism of action of EMB agar has been a profound mystery to us too, in spite of the very extensive use we make of this medium. I therefore am not sure how I would be able to interpret any particular patterns of response but if possible I would like to have a chance to see them if we manage a summer visit. It seems to me quite possible that you are running into inhibitions of acid formation and that these could be fairly simply confirmed by tests in small volumes of liquid media with standard indicators.

I had not until recently appreciated that Cardol really had any scientific basis. If I am going to do some casual experimentation with Chlorizin, I wonder if I should not also include some of this fabulous sodium lauryl sarcosinate, and if you could possibly furnish me with a sample I will be happy to do so.

I am very much interested in your remarks on the inhibition of motility by Neoria and will try sometime to confirm this particular experiment. It would, for example, be a matter of very considerable interest to me, aside from the mechanism of action of the drug, to be able to obtain mutants which are resistant to this agent. I am somewhat discouraged however by the very high levels that would have to be employed. The troubles that you mentioned with motility agar have occasionally happened to us, even with the unaltered medium. I think that if it were possible for you to arrange to add your supplement to sterile tubes and then mix in freshly autoclaved motility agar and then wait 24 to 48 hours for the tubes to dry properly that you might have less difficulty. If you think the trouble is deeper than this and could send me a sample of a particularly troublesome broth, I would be very happy to look at it, and see how this compares with our own experiences. I recall, for example, that we never were able to incorporate materials like methocel into such media because there were specific precipitation effects.

The main point that I wanted to clarify in this response, Joe, has to do with why I think Penide might be synergistic with penicillin. The reason that I brought Penide up at all was the hint that it might function in a relative sense as a competitive inhibitor of penicillinase. If this is the case, then Penide might make penicillin more effective in chemotherapy of infections by penicillinase-producing, resistant organisms. The inhibition of penicillinase would be the main thing that I would be looking for in the design of this experiment and this might be completely independent of antibiotic activity of the compound itself. As I understand it, the principal mechanism of penicillin resistance in naturally occurring organisms, especially the Staphylococci, is the formation of penicillinase. Therefore I would suggest that not only Penide but as large a variety of penicillin-related compounds as possible be screened for their specific function in the inhibition of penicillinase. In fact, this is something which might well be keyed in with your general search for antibiotic activity, although the experiments might well be designed to pick up penicillinase inhibition instead of antibiosis. I had the same thing in mind in referring to Cephalosporin N as another potential compound for this purpose. I know

of practically no attempts to screen for penicillinase inhibiters along these lines and it does not take much imagination to see both the medical and economic possibilities of such a discovery.

I was particularly glad to hear that I had misunderstood the proper channels of your work and that you have considerable leeway in designing the areas of your experimentation.

Yours sincerely,

Joshua

JL:jlg