

December 14, 1952

Dr. Lawrence L. Weed  
Army Medical Center  
Washington 12, D.C.

Dear Dr. Weed:

Thank you for your kindness in letting me see your manuscript on B/Cu. I am returning it herewith.

You asked for my critical comments. The only serious criticism that occurs to me is the discrepancy between the introductory paragraph, with its emphasis on the unelucidated role of environment in heredity, and the actual content of the paper which makes only a passing reference to the genetic aspects of the phenomenon. In particular, as you say yourself, it is very difficult to prove whether the B/Cu form is actually induced, or simply selected, by the Cu but this is the crux of the general introduction. It might be added that most bacterial geneticists are more optimistic about their understanding of the "environment-heredity" question, and that, to me, at least your paper's greatest interest would be in exposing a possible exception opposed to the bulk of serious experimental findings on environmentally "induced" hereditary changes. As, again, you have pointed out yourself Ephrussi's work on petites-colonies mutations in yeast provides a very sound precedent. But it would be a mistake to confuse the intense interest in this exceptional phenomenon with its role in yeast inheritance, the preponderant mass of which is fairly ordinary mendelism, and therefore not so exciting. Dr. Spicer has the impression that you have a rather more explicit case for specific induction of B/Cu than is presented in this ms.

I have some additional notes which are questions rather than criticisms.

p. 2 : B/Cu can hardly be related to L-forms if their microscopic morphology is typically bacilliform. [I have been culturing some of Dienes' Proteus L-type growth, and its microscopic appearance is unmistakable.] The L-forms present such a confusing story that such a correlation does noone any benefit unless there is some substantial basis for it. [I've fallen into this trap myself, cf. Cold Spring Harbor Symposium, 16:438-439, 1951].

p.4 Inoculum  $5 \times 10^7$  B, in what volume? Presumably 10 ml from the size tube used.

p/6 Spicer and I were both surprised at your serology: I had thought that B was as rough as could be, and would be most interested to see a verified O and K diagnosis. The lactose story is confusing. Does B/Cu grow any better in glucose? Apparently not, if "a similar inoculum...would have remained small". Does it appear more likely that reversion occurs more promptly on lactose medium. Could the small colony form be due to a growth factor deficiency, inefficiently provided by the usual complete media? If there is a specific lactase effect, it should be easy to test for the formation of lactase using nitrophenyl galactoside--I will send you some if warranted.

p.7 foot. I could not understand just what you meant. Which correlations are erratic--and there must be some explanation.

Bibliography:

4. 1'Institut  
5. Klieneberger-Nobel  
12. Kelner  
20. 639-700??
14. Not "Gleerupska University,"  
But Gleerupska University-Bokhandeln,  
(I.E. Gleerupska, University Bookstore)
- Probably a more intelligible reference  
would be Acta pathologica, Suppl. 62.  
for the identical publication.
- ?? Where's Colwell, C?A. 1946 Small colony variants of E. coli.  
J. Bact. 52:417-422. Her story is almost as certainly related  
to yours, as L-forms are not.

I will see what I can do now with Cu and with naphthaquinone on crossable strains of E. coli, and will let know what goes from there. We should wait for this before any serious discussions, I think.

Your suggestion of a visit to this lab. is appealing. However, we are very cramped for space in the immediate future. Some remodelling is planned for this Spring which may relieve this situation to some extent. I would much prefer a longer visit that would permit some real progress on a problem, over a shorter one. Do you think you could arrange an extended assignment? (10-15 weeks).

Of course we did run into each other at P&S. But as you know, I never did return to P&S after taking a research leave at Yale for what was to have been a few months. Instead, I came here in 1947 after getting my Ph.D. at Yale.

Sincerely,

Joshua Lederberg

*P.S. I will start what I hope  
will be an exchange of papers.*

*The enclosed may be of particular interest.*