

February 24, 1958

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Dear Dr. James:

Thank you very much for sending me the reprint of your very useful review on the electrochemistry of the bacterial surface.

There was one point that I could not let pass without some discussion, this perhaps being your reason for sending me the review. In your summary on page 139 you suggest that crystal violet has directly induced a modification of the cells of *Aerobacter aerogenes* and that your observations were *more* in support of a modification theory than a ~~proof~~ of natural selections. I must confess that this is one of the very few examples of such chemical modifications that I would be inclined to credit. As you know there are any number of claims of chemically induced resistance to drugs most of which have fallen to the ground on careful analysis. This is all the more reason why I would be pleased to see a really critical analysis of the process by which the changes you describe have occurred.

I am not exactly certain of the grounds on which you principally rely for your conclusions, but your table 8 does seem to furnish very pertinent evidence. If I read it correctly, you would conclude that during the first 1500 minutes or so there simply are no cells of low mobility so that the appearance of a substantial fraction of cells of this type by 2500 minutes would be a sign of direct modifications of cells previously of high mobility. A more detailed quantitative analysis of this evolution might prove to substantiate your interpretation. However as I interpret the histograms samples of some hundred and odd cells were examined for their mobility at this stage. It is therefore still entirely plausible that the culture at time 1500 minutes does contain a proportion of 1% or less of cells of low mobility, and these might then proliferate and be responsible for the increasing proportion of low-mobility cells as time progresses. I would not trouble you with disputatious hypotheses except that it seems to me you have a remarkable opportunity to settle the issue by a further application of your own techniques. Surely it should be possible for you to set up an electrophoretic separation which could discriminate even a minute proportion of organisms with low mobility. In addition you could make known artificial mixtures of the two types previously isolated to establish the sensitivity of the technique. By this means it should be possible to establish upper limits on the natural frequency of the variant type in the untreated population and to determine whether the appearance of the variant during the course of the treatment would be quantitatively inconsistent with the frequency so observed.

JAMES, A.M.

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I would be deeply interested to hear the results of your further experiments along these lines as they are bound to have an important bearing on our own studies on the hereditary determination of mating type in E. coli, which is also a surface property which has some electrokinetic correlates.

Yours sincerely,

Joshua Lederberg
Professor of Medical Genetics

JL/ew