Dear Josh:—
Brink will probably show you this,
but I wanted to make sure you see it. As appears
in my letter to Brink, I am unsure of myself in this
field. Perhaps if I have seriously erred in any respect,
you might be willing to correct my mistakes. I'd be glad
if you would do so, directly to Brink.
Your nice letter arrived this morning. I'll answer later.
Very best, as always, to you & Esther, Tracy

October 16, 1953

Dr. R. A. Brink
Managing Editor, Genetics
Genetics Building
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Madison 6, Wisconsin

Dear Dr. Brink:

It is not easy, believe me, for an outsider to form a well-founded judgment in the difficult field represented by Appleyard's paper. I therefore submit the following comments with genuine humility and full recognition that my lack of firsthand experience with the material probably renders me to some extent unfit for this job. On the other hand, there is at present apparently such a deep and vigorous split of viewpoint and opinions among workers in the field that there may be some compensating advantages to consulting an outsider. For that reason I have less hesitation in commenting.

Page 1, paragraph 2 - Objection might be raised to the impression created by this paragraph. He identifies asymmetry of recombination with the donor-acceptor hypothesis of Hayes. This is not the only possible hypothesis and another has been proposed by the Lederbergs and Cavalli. Further, he identifies F^+ with donor and F^- with acceptor, without reference to the discoverers and namers of F^+ and F^- (the Lederbergs and Cavalli). On the whole, it seems to me that the portrayal of the situation is not a just representation of "our current picture." It is only one side of the picture, but it entails bringing in work of the other side (F^+ and F^-) without credit or reference.

On the main body of the paper I have no comments to make, but the discussion (pp. 11-13) seems to me to be open to the following criticisms and comments:

(1) Since lysogenicity for both lambda-s and lambda-cl are closely linked to gal, the chromosome determines both the carriage of pro-lambda and the kind of lambda released. From this he concludes that lysogenicity is not due to cytoplasmic lambda under genic control. But if the two kinds of lambda were controlled by two closely linked genes, respectively, the observations would not be incompatible with cytoplasmic localization of lambda. Hence, I cannot see that this possibility is excluded, or even rendered improbable.

(2) A major fact in the discussion is that lysogenicity interferes with recombination and that the interference is greater in double lysogenics than in single lysogenics. This is held to favor the view that something extra is attached at or near the gal locus in lysogenics, more

in double lysogenics. I admit that this is a possible interpretation, but is it not also true that the frequency of crossing over varies with many physiologic and environmental conditions and that change in frequency need not be due to mechanical interference of the kind he postulates? If recombination is here due to crossing over or something like it, then change in its frequency might be a result of physiologic, rather than mechanical, disturbances due to the presence of prophage. He seems to reject this possibility without explanation. Why? Is the disturbance in recombination confined to gal?

(3) Throughout this argument he also has an implied, but unstated, assumption which needs to be made explicit, for, when stated, it reveals a weakness in the argument. He believes that prophage is attached over a region, or at least at more than one point. In this way he accounts for the possibility of carrying more than one kind of prophage. Further, his argument about mechanical interference with recombination is based on greater interference by two prophages than by one. This therefore implies that when one prophage is present it is attached at only one point, or at least over a smaller region than is occupied by two kinds of prophage. But it is not clear why this should be so unless the different kinds of prophage are specifically restricted to different chromosome regions. And if that is so, then my argument above about cytoplasmic localization of prolambda, each kind under the control of a different locus, must be admissible. If there is no specialization of the chromosome region involved, then the whole region should be available for one kind of prophage when only one kind is present and should be shared by two kinds of prophage when two kinds are present. In both cases, the region of chromosome occupied would be the same. This leaves no mechanical basis left for greater interference with recombination by two kinds of prophase than by one, and my argument for physiologic interference is strengthened. So, regardless of which alternative is accepted, Appleyard's discussion seems to me to be defective.

(4) He cites in his argument a point made in an as yet unpublished paper, namely, that in double lysogenics one can obtain recombination of the characters of the carried prophages. This is believed to support the view that they are carried in adjacent positions on the chromosome. Of course I have not seen this paper and it may be unfair to question the argument; but since it is cited here as a relevant point, I raise a doubt about the argument. As I understand the biology of lysogenics, there is occasional spontaneous loss of prophage and occasional spontaneous lysis. Would not this provide ample possibility for occasional recombination of phage characters in the usual way without any necessity of resorting to adjacent position in the chromosome to explain it?

(5) As part of his argument for the mechanical interference in recombination, he tries to show that the interference evidenced by reduction in the frequency of gal "transfer" is not due to lethality of the

missing recombinants through induction of lambda maturation in these. The argument appears to me to involve some or all of the following assumptions, which are implied but not stated: (a) a single lysogenic is resistant to action of lambda of a different kind; (b) if a cell carries a prolambda, i.e., if it is lysogenic, then it must be in a condition suitable to receive and carry another kind of lambda as a second lysogenic; (c) if one kind of prolambda is carried in "attached" position, introduction of another lambda (or prolambda) will not result in inducing maturation of lambda. Not being an expert in this field, I am not sure whether all of these assumptions are sound, but I have the impression they are not. If I am correct in this and in concluding that the assumptions are implied, then the argument is unsound and differential survival is an alternative explanation of the apparent interference with recombination.

From the above comments, you will see that I have grave doubts about the validity of the discussion and the main conclusions in the paper. If my criticisms are sustained by another referee or admitted by the author, it seems to me that thorough revision of the discussion and conclusions might fairly be called for. The facts in the paper I do not question, and these are of sufficient interest and importance to warrant publication in Genetics. As I see the situation, there are two main facts: (1) recombination does not occur between the loci involved in double lysogenicity (or in crosses between the two single lysogenics); (2) the apparent frequency of "transfer" of gal is reduced in lysogenics, more so in double lysogenics. A paper adequately setting forth these facts and soundly discussing their significance would be worthy of publication in Genetics; but I believe the present manuscript does not soundly discuss them.

Yours,

T. M. Sonneborn

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