April 28, 1954

Dr. Neal Groman
Department of Microbiology
University of Washington
Seattle 5, Washington

Dear Dr. Groman:

Thank you very much for the manuscript sent under cover of your note of the 7th. It was indeed useful for the discussions at the Oak Ridge meeting, and will be even more so for the formal paper I am now writing as a general review of "genetic recombination in bacteria".

Have you sent, or do you plan to send, this paper to the Journal of Bacteriology? I am interested to know how best to cite it (though personal communication, or to be published, should do) but also as I would like to see it there on behalf of the Journal.

This is a very well written ms., and I could find little to criticize either in form or in substance. My most pressing suggestion on the form is that you delete the section from pp. 7-9 as indicated on the attached review sheet.

As to concept, I hope I will also have clarified my notions of "transduction" as the term applies to the present case vs. Salmonella. To my mind it is far less important that one discuss whether this is a transduction, and better to emphasize the descriptive conclusion that the role of the phage here is quite different. But as I have tried (not altogether successfully) to keep clear, genetic transduction is defined, without reference to the role of phage, as any process of transmission of genetic fragments from one cell to another, as distinct from fertilization, where an intact genome is transmitted to a zygote. Thus the Salmonella case, where a phage acts as the vector of the fragment, and the pneumococcus transformation, wherein no vector seems to be needed other than the hand of the chemist, are both sub-categories of transduction. [The term was developed before it was as clear as now seems that the pn. t. was in fact a transduction in this sense]. What to call conversion depends on how one defines "genetic fragment" — your option. "Transformation" per se means only "change" and has, for example, been applied equally to the mutations from S to R as to the more interesting R to S in pneumococcus,

Yours sincerely,

Joshua Lederberg

Groman— Evidence for the active role of bacteriophage in the conversion of non-toxigenic Corynebacterium diphtheria to toxin production.

P	L	
1	8	"intimately related to" is needlessly vague; I infer you mean "an immediate consequence of".
4	11-14.	This is the same as above. The quantity of phage released by young cultures of lysogenic Salmonella is often (but not always) too small to effect a detectable number of transductions; you have a more sensitive system. I would dele this.
7 to 9	10 3	I think this is overdoing the argument, and likely to do more harm than good, and would therefore leave it all out. Your conclusion is certain on the following brief argument: In Salmonella, the vectorial role of phage is shown by the separability of infective and transductive functions, i.e., not every particle accomplishes any particular transduction. In diphtheria, your well designed experiment failed to separate these activities despite several single-plaque isolations, so that one can conclude that the phage <u>per se</u> invariably transforms the recipient. Since transduction is defined(without reference to phage!!) as a transmission of a hereditary fragment from one cell to another, the question is ~~whether~~ not so much whether conversion is a transduction (which depends now on whether you choose to regard the phage itself as a hereditary fragment) but the role of the phage in the two systems. In Salmonella, the phage is a passive vector; in diphtheria, at the extreme, the (pro-)phage would have to be regarded as the genetic element itself.
5	3	This argument relies on the implicit assumption that the C7 is itself convertible by phage grown on C7 or C4. Otherwise, two possibly <u>non-homologous</u> nontoxigenic strains could still interact by transduction (Cf. restorations of motility in Salmonella in Stocker et al.).
5	last	Is the EOP of this system known?

10-11 Excellent!

11 14 Might be clearer to write "and had not been propagated on C4"...

13 3,4 Again the past perfect "phage (Bh) had been propagated" would be clearer.

16 Discussion of Hyp. 1: The DNASE argument is meaningful only on condition that the accessory factor has to be DNA, which of course it would not. I would leave this out and point merely to the high dilution that you must be able to allow when you recover toxigens from single plaques. This would necessitate an incredible excess of the accessory factor. Hyp. 2 does not mean much except in relation to the criteria that one might employ to separate phage "itself" from each particle. You might find it advantageous to use ultraviolet light which, in Salmonella, attenuates lytic and lysogenizing much faster than transductive function. Your heat expt. (p17) is equally useful; the data should perhaps be recorded in the future

19 10 I do not understand your possible reservations about chromosome-linkage of lambda in E. coli K-12. My wife and I did have to point out the remote possibility that only an indispensable part of the prophage was bound, and the rest still cytoplasmic [though there was no indication of it]. Appleyard (CSH 1953) has since shown that at least one genetic marker of the lambda is similarly bound, and this should clinch it. I agree you have no way of telling about this in diphtheria, and it would be incautious to leap to generalization from this one case.

20 2] Sp. compatibility

20 9-10. This would seem to read that "conversion is an induced change". I am sure such a statement is deletable.

20 14-16. This observation goes back to den Dooren de Jong, I think ("mutilate" colonies).