

January 5, 1952

Dear Dr. Felix:

Your most interesting (and kind) air letter arrived this noon, but I regret that the "air parcel" has not, as of this evening. I am afraid your confidence in our postal system is misplaced. You may be interested that your cablegram was delivered, via phone, about 8 AM Friday (our time). I thought that "air parcel" might have meant air freight or air express, especially as you seemed so confident of its time of arrival, but neither the postoffice nor our airport has had any word of it. I shouldn't be surprised if the delay is ~~was~~ at customs at New York or Milwaukee. May I thank you for the very considerable trouble you have taken on my account!

I am sorry that the account of my letter of the 13th Dec. was so unexplicit, as I fear I may have led you into a misapprehension. PLT-22 appears to be strictly an O-specific phage. It is adsorbed by almost all cultures carrying the XII somatic antigen, and by no others. There is still some uncertainty about the special role of XII<sub>2</sub>, which may account for inconsistencies with *S. paratyphi* A and *S. abortus-bovis*, which have still to be cleared up. Wherever it has been possible to test the point, all *Salmonellas* that adsorb PLT-22 are subject to the transduction of genetic traits from it, whether or not the phage is capable of lysing or establishing a symbiotic relationship with a given host. (PLT-22 has, for example, almost no overt effect on several *S. typhi* strains, except for transduction). Non-O variants lose, at once, their capacity to adsorb PLT22 and to suffer transduction by it. JSK Boyd has characterized PLT22 as an "A1" type in his classification; Stocker and I have confirmed that the other A phages of typhimurium will also transduce genetic traits, though with a lesser efficiency than PLT-22. The host-range of PLT-22 restricts our experiments to the XII-bearing types, so it is a natural interest to look for other phages that will extend the scheme. For technical reasons, it would be preferable to test phages that include our marked typhimurium strains in their host-range. A number of rough-specific phages have been tested, but none has so far been capable of mediating transduction. These are the isolates to which my letter hastily referred.

Thank you for referring me to the history of *S. typhi* H-901; you've caught me napping on this. I have not, so far, given Vi determinations the emphasis they deserve in our work: in fact, the reason for using H901 was the hope of avoiding what seemed at the time a complication. Actually, the strain of *S. typhi* cited on p. 692 of our paper was *S. typhi* Watson V, as received some five years ago from Kauffmann, and maintained without special regard for maintaining the Vi status. At the time of the experiment, the culture was still Vi (by colony appearance and Vi-agglutination), but most or all of the i products of typhimurium --x typhi were Vi-negative. I suspect that non-Vi cells have a higher affinity for O phages, so that their descendants are more likely to be represented in the ~~transductions~~ transductions. Rather than explore this story at the time, and in view of my inexperience with the Vi problem, I decided to switch to the non-Vi H-901 (as received severally from Kauffmann, Edwards and Boulgakov). I was ignorant of the Vi history of H-901, having had the impression (acc'd'g to Booy & Wolff, e.g.) that this was unshakably non-Vi. We have made no attempts to transduce the Vi character, and in view of the complications you site, as well as the developments of your work with Anderson, it is just as well we did not undertake this prematurely. I was especially interested to have your comment on other experiments on this question. Booy & Wolff's and Creze's

experiences did not seem to tally with ours, as the alterations must have occurred with a frequency of several percent to have been discernable without special techniques. Perhaps killed bacteria exert a selective effect favoring Vi-carrying variants, but if so, it may not be necessary to invoke an inductive effect as well. In our experiments, only about  $10^{-7}$  or  $10^{-6}$  of the treated bacteria, at most, are influenced in a given trait so that specific selection is essential. In addition, it seems improbable that Booy and Wolff's procedure, heating washed bacteria, and almost impossible that Creze's (boiling for 10 minutes) could have left significant amounts of phage. These considerations would not rule out phenomena quite different from transduction-via-phage.

One point in your account of O 901 is discrepant with our experience. We have had no difficulty in repeatedly isolating O-H (d:-) from the strains recorded as O-901 in our possession (rec'd from Kauffmann and Boulgakov). Our experiments involve the most stringent selection for motility, rather heavy inoculation of plates of soft agar-gelatin, so that the recovery of O-H may not be strictly inconsistent with your experience. If it is, it is possible that we did not have an authentic culture, and would be happy to have one from you.

Your discussion (Symp. Virus Multipl.) was as interesting as your letter. (Perhaps I can apologize for this logorrhea by suggesting that it is contagious.) I do not at all "dislike" the trend of these remarks, although I am not sure that they are irreconcilable with the subjects of your criticism. You are certainly justified in complaining of the uncritical generalization from "phage T2" to "viruses". I suspect that the rediscovery of lysogenicity by America may temper previous haste. The only useful function of calling phages, bacterial viruses, is to attract the attention of virologists to the ideas and techniques that have been developed in phage science. I find much the same difficulty with the equally knotty question of viruses vs. plasmagones in the minds of geneticists (and have complained of this in my recent review Cell Genetics...) A situation like that of kappa in Paramcium, or sigma in Drosophila despite its obvious significance in any broad approach to heredity is ignored by many geneticists, "relegated to pathology" as someone put it, as soon as the suggestion that these might be viruses or the like is entertained. Thus, the unique possibilities of applying the methodology of microbiology to problems of heredity are needlessly discounted.

I will need pretend or attempt to refute the endogenous origin of phage by any detailed speculation. If phages are ultimately derived, qua parasites, from fragments of bacteria the question of endogenous vs. exogenous devolves mostly on a question of how long ago. Since, to use the parasite terminology, an extrinsic particle can establish a symbiotic relationship with a bacterium it has not recently seen before, the present existence of such symbioses does not tell us much of their own antiquity or ~~idiosyncrasy~~ idiogenesis. Again, the parasitologist can, rather speciously perhaps, explain any novel occurrence of bacteriophage in a bacterial culture by invoking a prior, cryptic, symbiosis. Your remarks on the remarkable parallelism of phage to bacterial receptors may serve to stimulate some speculation, and ultimately some study. Would it be inconceivable that the phage does not develop this specificity fortuitously, but that it borrows the bacterium's own machinery to manufacture the phage's skin, but this is somehow inside-out! This would still, at once, be consistent with what Luria called "parasitism at a genetic level", and with the facts of phenotypic host-induced modification. The development of such an adaptation may strain the imagination no more than organic evolution in other forms. Teleologically speaking, a phage particle requires some mark to recognize host bacteria whose overall internal organization is sufficiently familiar as to be likely to support its development; the superficial, i.e., antigenic properties of the bacterium might be the most accessible marks of this kind. By the way, our own casual observations suggest that the Sertic-Boulgakov phage suppresses the flagella primarily by lysing or otherwise killing ~~within~~ flagellated cells. Thus it can be used to select for O variants, although many of these prove to be rather unstable (some are quite stable).

You are doubtless well acquainted and equally weary with the repeated arguments for phage-virus-parasite. I am not clear whether you are objecting simply to the uncritical and narrow application of this theorem. In particular, do you regard "bacteriophages are endogenous products of the bacterial cell" as the only basis on which they may be "specific self-reproducing units which form part of the genetic makeup of the bacterium" (p. 4, Symp. Disc.). The last proposition is hardly distinguishable from "parasitism at a genetic level". The trick word is again, perhaps, "endogenous". I think it can be argued that such units might equally well be descended in some fashion from other organisms, so that the symbiotic adaptation is secondary, as it doubtless is in lichens. If one puts the same question to chloroplasts, one runs into the same difficulties as with phage. My review hoped not to explain away the difficulties, but to point out that these problems must still engage the interest of geneticist and virologist, microbiologist and enzymologist alike, or we will never get to the root of them.

Your remarks p.5, anticipating genetic studies on lysogenicity, have been fully borne out. Mrs. Lederberg and I have a paper in press demonstrating that the phage associated with E. coli K-12, lambda, behaves in crosses precisely as if it were a chromosomal determinant. This may mean that whenever lambda is released it carries with it a fragment of the bacterial chromosome by means of which it recognizes its appropriate site. I will admit that parasitism at so intimate a genetic level does strain the imagination. The chief argument for retaining this notion is that one can with less strain visualize the further evolution of phage into a more independent organism. If all phages, and not merely lambda, prove to have unique localizations on bacterial chromosomes, I would have to admit that they have not, in fact, evolved in this way.

Yours sincerely,

Joshua Lederberg