January 2, 1956

Dear Luca:

I have finally reached a stage in my own affairs when I can begin to devote real attention to our book. I am very sorry about my long procrastination, but I have simply been overwhelmed with other obligations. I hope that this new year will find you in an equally responsive capacity!

First let me make a new suggestion about procedure. It seems to me that we already have in our outlines a sufficiently clear idea of the general organization. Instead of trying to write the whole book at once in skeleton form, as we have perhaps been starting to do, we should do one chapter at a time, as thoroughly as possible and leave it only when it is essentially done. Then when all the chapters are finished, we can go back over the earlier ones. We can however, each be doing one chapter at a time. I have looked over your long-since sent chapters 1 and 2, and feel that you are getting off to a really good start. Before we go any further, however, I want to ask you if you want to prepare one of these (or any other one) in substantially final form. as far as you are concerned, so that I can address my comments to it. Or do you consider that the versions you sent me last summer should stand for this purpose?

While I wait to hear from you, I will make what progress I can in my own first offering, which will be either the "adaptations of individual organisms" or the "genetic effects of drugs other than adaptation".

By the way, I am a little uncertain of the details of how we agreed to leave the outlines, ~~I we~~ and how the chapters were to be divided. Could you send me a copy of the revised outline, as you understand it? I believe we also had a convention about referring to lines— was it to be the distance in cm from the first writing on each page (which would save counting lines)?

In the lab, a point of some interest. I finally have gotten around to try to check up on Wollman & Jacob, and find that Hayes' Hfr (which they have been using) has very different proprties from yours! For example, in crosses of Hfr_h x Lac-Gal-S^r, almost all of the Lac+S^r recombinants are Gal+, while with your Hfr, almost none are. I have been trying to get at the genetic basis of this difference, but Hfr_h is in an inconvenient genetic background, and, unfortunately seems not to be linked to Gal (in fact I have not been able to get any Hfr_h recombinants. These comments apply to a B_1^- Hfr Az^r S^s "prototroph" (= W2328) received from Hayes a long time ago, and evidently the same stock as the Pastorians use. The parent M- Hfr_hS^r stock, on the other hand, does not seem to show this remarkable behavior. So evidently, the Pastorians are quite right about the high incidence of syngamic induction of Lp^+ in crosses with Lp^s; this does not apply to crosses with your Hfr, and thus we can account for the basic discrepancies. Obviously, Hfr_{luca} much more nearly resembles the typical behavior of, e.g. ordinary F+ than does Hfr_h.

Thanks for the redrawn figures; all is in good order there.

& Happy New year,

P.S. January

On rereading this, I see I should perhaps summarize what I had explicitly asked of you in re the book: 1) Your final version of any one chapter, or your notice that you consider the previously sent draft to be essentially final. 2) Your understanding of the revised chapter outline. I thought I had a copy on which was noted a) the primary division of labor, and b) the revised sequence of chapters, but the paper seems to be lost. We should however stick to the original sheet for designating the chapter numbers.

I also have another favor to ask of you: One of my new students (who started last summer), Alan Richter, has been devoting himself to F, and largely the mechanism by which "motilized" cultures of F+ or Hfr become F-. ((Just before Christmas, by the way, we acted as human chemostats and transferred a rapidly growing culture of Hfr, at low density in broth, over an interval of about 36 hours, but the results are not yet ready on whether this is a satisfactory imitation of the motility experiments.)) Anyhow, Alan seems to have some propensities in this direction for he has already isolated two new Hfr strains, without especially looking for them; both were noticed after UV for another purpose. At any rate one of them is highly unstable and reverts frequently to F+, so frequently that no direct test of its infectivity for F, from the Hfr state, is possible. (However, most recombinants of the Hfr phase x F- are still F-; while the derivative F+ x F- gives recombinants mostly F+, so presumably the Hfr behavior is again coupled with non-infectivity.) It just occurred to us that we (us meaning Alan and me; we = Luca and I) had never thoroughly reviewed the matter of the initial instability of your Hfr. You have sent me Hfr on two occasions. The first one I recorded as W-1033, as you may recall. When this was tested thoroughly later on, it was no longer Hfr, but now F+. This incident is the full extent to which I can corroborate the instability of Hfr. The second shipment of Hfr must have been in early 1953, and recorded as W-1895. This culture and its derivatives have been studied very thoroughly since then, and their has been no evidence whatsoever of its reversion to F+; by motility technique, and once after uv, F- has been isolated from it (some re-infectable; some refractory), but no F+ at all. In the JGM paper, you wrote that Hfr had reverted repeatedly. I would conclude now that the culture changed between about 1951 and 1953 from a revertible to a stable Hfr. The new unstable Hfr of Richter's would tend to support this idea; so far we have not seen any stably Hfr derivatives from it, but we have not had it very long. Naturally, in your efforts to retain Hfr behavior, you would naturally select for a stable derivative, if one occurred. What I want to ask you now is whether you still have your Hfr in its original unstable form, or alternatively whether you can give any more details (perhaps some experimental protocols) illustrative of its former instability after re-isolation. If you would like, we would be happy to exchange cultures with you again. By the way, this unstable Hfr also seems unlinked to Gal; a variety of allelism tests are being set up. I am almost ready to wonder if Hfr is not an ambulatory factor like the Ds/Ac complex in maize, though much simpler ideas are still possible (I am thinking, of course, of the correlation with E, as a working hypothesis).

What are you doing in the lab these days? I have had hardly any time for experiments myself for months, but had been busy in an endless task of developing diploid stocks for crossing and more pedigrees. This is temporarily in abeyance while I'm trying to make sense out of the Hfr_h crosses, as the high Gal-segregation ratio has considerable bearing on the technical problems of the diploids I am trying to develop. Otherwise, I am mostly involved in other affairs in the lab; Larry & Esther's work on Gal-transduction, for example. Nothing very startlingly new there

except we are beginning to understand why the transductional heterogenotes ("partial diploids" which carry a segregating fragment from the donor) do not segbegate for Lp as they do for Gal, e.g., in Gal+ Lp+ --x Gal- Lp^s. The clue we are following now is the fact that this transduction not infrequently gives an "Lp^r" rather than Lp^+. We never before understood where the Lp^r came from but attributed it to secondary damage to the prophage. However, in crosses of an Lp^+ Hfr heterogenote x F- Lp^s Gal-, many of the recombinant heterogenotes also came out Lp^r. (Also, there seems to be a definite coupling ,through the cross, of the fragment and its corresponding chromosome.) There are two further clues: 1) the Lp^r types are invariably unstable, both for the Lp-phenotype and for Gal. Where Gal is homogenotic, this can be told by reversions. 2) Although reorganizations leading to Gal-//Gal- homogenotes, from Gal-//Gal+ heterogenotes, are not infrequent, Lp^s homogenotes have never been seen. To summarize, the Lp^r phenotype never occurs in a haploid; the Lp^s never except in a haploid. This has suggested the hypothesis that the so-called Lp^r is actually the phenotype of the Lp^s in homogenotic form, i.e., as $Lp^s//Lp^s$. Unless you want to invoke dosage compensation (which is perhaps the same idea) this is not simply a, matter of Lp^s in two doses, for $Lp^s//Lp^s$ diploids are still sensitive (though perhaps not so fully as the Lp^s haploid. At any rate, we can explain most of the results with just one postulate, that the initial product of transduction, Lp+//Lp^s is intrinsically unstable (and not unlikely inviable, by growth of the phage) and must go either to Lp+//Lp+ or to Lp^s//Lps , or to a haploid. This would also account for the moderate percentage of transformed clones (20-50%) which are not heterogenotic to begin with. We have hopes of testing some of these ideas by various crosses, but they are almost the first definite notions (whether right or wrong) of how the prophage fits into the story. We would say now that the persistent fragments are segments inclusing the Lp^+ prophage. In the heterogenote, i.e., so long as their peproduction is integrated with that of the bacterium, the whole Gal-Lp complex reproduces chromosome-wise (e.g., in the induction by UV of a heterogenote to give HFT lambda, only about one phage particle is released per cell, and this is often effective in transduction). When the prophage multiplies autonomously, i.e., as a virus, the prophage detaches so that lytic lambda, e.g., has no transducing activity at all. Thus, the phenomenon bears only a remote relationship to transduction in Salmonella. Why non-phage-specific transductions are not also mediated by lambda, I do not know.

We have just lately received your charming gift, the photographic portrayal of Italia, and apprdciate it very much.

With the best, as ever,

Sincerely,

Joshua

P.P.S. Jan. 9.
Before I finally mail this, may I ask you about your experiments with Ceppelini: Did you study the Gal segregation ratios in any crosses of reinfected F-?

Larry asks me to tell you he is furious with you for not answering his letters; he trusts you will have received the ms. of the first Gal-transduction paper. (This is due for Genetics, 41:142-156, 1956,Jan.) As he probably told you, he will be leaving this coming summer to take a position as Asst. Professor of Biophysics at the University of Colorado Medical School, at Denver. Though he will be officially in Puck's department, he will actually have an independent laboratory at the "Colorado Foundation for Research in Tuberculosis!". Actually they are fine people,it is an excellent appointment, and the connection with Tbc. is nominal. As they may also be looking for more senior people too, that was one of the possibilities I had in mind when I asked about your availability.