February 5, 1956

Dear Norton:

Thanks very much for sending your precis. I wish I could be more help at this stage, but it is written so compressedly I would almost have to write it out in detail in order to discuss it point-by-point, and I am sure you want to do this task yourself. When it gets to that stage, I will be very happy to give it the test-bomb treatment. However, I think I could get the main drift of your argument here, though you overestimate your reader's ability to guess at the gaps in your description, tables, etc. The following are then some preliminary suggestions; style and content are intermixed.

Terminology of types., There is some possible confusion here between genotypes, which govern several alternative potentialities, and reactions. A table (see appendix) would be the easiest way out, and may help to avoid contradictions like "2" where immune cells produce phage. I would also defer the generalization that "all strains... contain homologous genetic material". You could say that Lwoff had defined prophage as the so&so, and you were broadening the definition to include that genetic material of a lysogenic or a sensitive bacterium which can be shown to be homologous with the genome of a temperate phage. If you are agreeable, I would like to consult with you on the details of this generalized definition, in hopes of having one that would be compatible with our conception of pro-lambda as equivalent to an exogenote in our system. (We would need something along these lines, that the phage genome is that which is regularly included in the infective particle; the prophage is the corresponding material which is propagated in a lysogenic bacterium..., but I haven't worked this through in detail). The logical alternative would be factitious, to accept Lwoff's definition (i.e. as the difference between a lysogenic and a sensitive bacterium, which is perhaps one locus of the prophage in the broader sense) and invent a new term (latent genophage!) for the broader meaning. Please note: abort is a v.i. according to my dictionary.

Neither Larry nor I could see why immunity had to be subdivided into homo- and hetero-logous. What is your definition, actually? If you have A(Plv_2), does this show homologous or heterologous immunity in re Plv_2^+? As they are written, the definitions are too complex: they lump the inducibility pattern with the response to infection so that I could not readily unta inducibility ngle them, and Ihad better wait to see this polished before discussing further.

The paragraph "The major point for consideration..."follows logically from the definition of prophage. Again and throughout, it would be better if you could spell out your experimental results, and reserve as much of the discssuinn or the end as possible.

I don't agree with your definition of host--induced-modification, if you mean it as a generalization. How would it fit Luria's T4 case, for example? You have every right to propose the hypothesis for the immediate examples. In general, don't be in a hurry to pack everything into one sentence, and make sure you have expressed each idea. I don't think you will have too many literary problems if

you do this. I am sure a large audience can understand the principles and the experiments, but if I am already having so much trouble following you, you can see that you will have make sure that you are making complete statements of your facts and ideas.

—On Experimental: Should you document the strains by published references? What does "P22 as given" mean, grown on A? I assume you will be giving your phage cross data in this paper, or at least prior to its publication.

What does assorts at random mean for the output of P1 on B (p.3)? Does this mean half the output, or half the mutant (non-P1) output?

p.3 Strain B.... This is the heart of the story, and I am delighted it has worked out so well. However, I think you have to show that C differs from A, e.g., in noy giving mutants under UV conditions, or at least not the typical pattern. Aren't you going to mention this point in regard to A? Otherwise, the reader will wonder whether A and C are not equivalent. As matters stand, one could argue that C has merely lost a selective (compatibility) factor that brings out the mutants. I thought you had delysogenized a B($P1_{mut}$); if so you should get that particular mutant back.

Actually, I wonder if at least part of the story wouldn't be cleaner if you used strain A rather than B, and uv/uv to elicit recombination, rather than an even vaguer compatibility system. Of course, if you can tie everything together, all the better.

p.4 "D" had me puzzled for a long time. I then realized you must mean that D was a de-lysogenized B(P5), not B(P1) as stated.

If you can document your characterization of the phages as AA', etc., you should have a very neat story. Why is there an infinte series? There are nine theoretical possibilities, considering just one marker per chromosome. If necessary, I would synthesize bacteria that had just one mutant marker on each chromosome, and could through the cycles with them, though I doubt this is necessary. You already have phage that corresponds to:

CC', CB' BC' BB' AC'

Perhaps a simpler approach still would be to delysogginize PLT22, and deal only with it, C and B. There is every expectation (if I understand correctly) that C and A will have the same general modificational behavior, and differ only in a few marker alleles that you are not concerned about here anyhow. This stock should, of course, resemble C. (This is a confusing point of symbolology; it might be better to reserve "C" for P22, and call the delysogenized B(P1) B_C or the like. (I'm not too happy about this expedient either.)

This is about all I can do at this stage. The two principal suggestions are to verify your C as CC' by uv-crosses (with the phages); to simplify the system by using a delysogenized (I almost typed deloused) P22 in place of A. From this pair, you should generate only 4 principle combinations, and a complete analysis should show what happens in every combination of phage and bacteria. When you get this rounded out some more, I will be happy to see it if you want to take the time.

I've been busy myself with Hfr types, having worked out methods to pick out many more. It all started when I finally realized that Hayes' Hfr must be different in segregation behavior from Cavalli's, and sure enough it is. I was misled before by the fact that Hayes' stock had largely reverted to F+ (as Cavalli's used to). While I was in the middle of this, and had been isolating some new one's from UV'd W-6, I got a note from Jacob that they've been doing much the same thing, indeed believe that CROSSING of F+ is due to Hfr mutants. For a number of reasons, I don't believe this is true, though Hfr mutants might explain some exceptionally fertile clones.

What concerns me more is the reason behind the variability in segregation pattern, which may be as simple as chromosome rearrangement. One reason I doubt that Hfr mutants play a predominant role in F+ fertility is ~~that~~ constancy of elimination behavior of F+ (as tested qualitatively in diploids) as compared to the likely variability of many of the new Hfr's (which, however, still have to be tested in diploids). The original F+ and Hfr CAVALLI are rather alike in this respect, which is why the issue had not come up before here, but at least we can now understand why Francois et al and we could not agree on details of syngamic elimination, etc. The whole story is obviously coming to a rapid boil, now that the fancies of F+vectors have been disposed of.

Sincerely & best regards,