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Dear Tracy:

Judging from your letter of the 28th, I would guess we have very much the same prospects for GOM. I can fully appreciate your sense of harassment by your own immediate writing obligations. Like your students, I will also welcome the publication of your accumulated research findings.

I am making only one commitment to GOM, by which you can judge the pace which I hope to keep. That is that I am not going to undertake any other review or writing jobs, except for research findings of course, that would constitute distractions from GOM. From past experience, I would guess that we are about equally tempted to write in general terms when there seems to be a free moment. If these temptations can be disciplined on focussed on this particular objective, I think it will be accomplished in its own good time. Mr. Freeman was here yesterday and assured me that his interest, at least, was not deflected by the prospects that this would be a long term job.

Of course I had fully expected that as joint authors we would have to be jointly responsible for each chapter. My selfish interest in this collaboration has been the education that I expected to get out of it. If we have each set 10 years as our personal limits, together we can perhaps cut that in half. But as a practical matter we ought each to take responsibility for the early drafts of each chapter.

Don't take my outline too seriously- it was not intended to be complete. But the more I think of it, the more obvious it becomes that the "general section" will have to follow the special sections, although the latter will have to be written so as the support the former. I have a feeling now that we have a sufficient mutual understanding that we should go ahead and put together the special sections as occasion permits, and that the enterprise will develop a momentum and structure of its own. The one way that I am going to get to think about the genetics of the protozoa will be to see your drafts on it. You have the advantage of the demands of the lecture-room for a penetration of bacteriology, but perhaps I can still do something of the same service. Anyhow, as I wrote in my last letter, I am not going to go ahead without you, but will proceed conservatively on the assumption that we are still together on it.

Our Salmonella material and technique has finally gotten to the point where we can study the genetics of flagellar phase variation, one thus of the things I've had my sights on from the beginning of this work. Things are still quite hazy, but I thought you might be interested in the picture that is developing. The symbol -X refers to transduction to; X- is the converse.

Most of the work has been done with typhimurium (i:1,2), paratyphi b (b:1.2) and abony (b: enx). The phase of a culture in a given experiment is underlined.

The first question was whether the alternative phases are "genotypically digferent". Apparently they are: A) <u>ixixxxxxx b:enx -X i;12 gives b:12</u>; B b:<u>eax -X i:12 gives i:enx</u>

xhoxxxxtx1200xxxtereneroceponeroceponeroceptrt200x000ceccoct2

Also, in another system, i and b were readily transducible from these phases, but not from i:12 or b:12.

However, I do not think that phase variation is likely to be a mutation between alternative alleles. In A) above, when **b** is transduced, it does not carry over the latent in potentiality, and in B), when enx is transduced, the result has i, not b for its other phase.

The kind of picture that I get out of this differs slightly from the Paramecium antigen story. I would regard b, i and 12, enx as representatives of alleles at each of two loci, respectively. In general, throughout the Salmonella group, one phase is "specific#--a,b,c,d...., the other "non-specific "12,15,17,enx...,", and it is quite exceptional for a type to have a specific antigen in both phases, or ma a "non-specific" antigen in both phases, although each of one group occurs in almost any combination with each of the other. Then there must be a mechanism which ensures that the "activity of each locus" (to speak very loosely) excludes the other more or less indefinitely. The switch mechanism might be thought of as analogous to the cytoplasmic states. Its suppressive effect seems, however, the be inseprable from the locus itself, in transduction. The best analogy for this is Dis in McClintock's corn, but, of course, self-perpetuating gene states do not have to be explained on a particle basis any more than do cytoplasmic states. The alterbative direction is to question whether transduction really is axaakmar exclusively a nuclear phenomenon, but even so one would expect to find some separation of the latent specificity from its non- or inactivator unless these were rather firmly bound together. It has been suggested that the activated state is some sort of expansion or reduplication of material still bound to the locus, but it is evident by now that all these speculations are far beyond the data.

I just received a batch of reprints from Inoki, and some time ago, a letter from him. He seems to be afraid that he had offended you--but I put this down to hypersensitivity on his part. What do you think of his system?

Sincerely.

Joshua Lederberg

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