May 28, 1953

Dear Luca:

Your letter of the 19th and manuscript arrived 2 days ago. It is unfortunate that we have to work under such pressure of time; in better circumstances, I am sure that the tasks would be far more pleasurable.

On the whole, the ms. is in quite good shape, and with the exception of the biometric problem at issue between us, I would not be distressed to see it published just as is. However, I have marked a number of points for your attention, all in red pencil to make them more conspicuous. Most of these are formalities, or improvements in phraseology, of which your judgment must be final. In two places, I have suggested softening a phrase to mitigate possible personal criticisms. The points to which I ask your special consideration are marked*, but again I will acquiesce to your considered judgment.

We seem each to have become rigidly convinced on the question raisedon p. 8, which perhaps means that I am no longer really thinking about it. Perhaps I have not fully understood your point. I am willing to admitnthat several parameters might be needed to describe the response of a population, one of these possibly describing the distribution of potential resistance among the cells, about another parameter, their mean response (or probability of forming a resistant colony). Such parameters may have values corresponding to what you call internal inhomogeneity. But if the parameters are the same from culture to culture, i.e., if these can be regarded as unbiassed samples from the same universe, I contend that these samples will have to show a Poissonian distribution. Of course, if the cultures are not unbiassed samples, i.e., if for any underlying reason of environment or heredity, the individual variates (cells) are correlated within cultures with respect to any parameter (mean or ~~xxxxxxx~~ moment), then e.g. a negative binomial might ensue. But this is not, as I would call it. <u>internal</u> heterogeneity, but a modification of Hinshelwood's proposals of uncontrolled or even accidental variation in the state (i.e. the parameters) of one culture as against another.

I have best been able to convince myself of the conclusion by taking the extreme cases. Consider two "species" of bacteria, of which one has a probability = 0 of becoming resistant, while the second has a probability =1. Then of course, so long as the second species is rare, replicate cultures among which the proportion of the two species is subject pnly to random or sampling error, will give a Poisson distribution. To postulate a non-random variation in the proportion of species is to bring in some specific factor, different from tube to tube, responsible for the difference (e.g. common heredity). The same consideration should apply to a system of numerous species, each with a charecteristic probability of survival.

In fact, the problem seems quite analogous to Fisher's treatment of "the relation between the number of species and the number of individuals in a random sample of an animal population" (J. Animal Ecol. 12:42, 1943 or paper 43 in the collection "Contributions to Mathematical Statistics" "In strictly parallel samples, i.e. equivalent sampling processes applied to homogeneous material, the numbers caught of each individual species will be distributed in a Poisson series, and it easily follows that the same is true of the aggregate number of all species...."

I am not sure of the Greenwood-Yule paper to which you refer. Professor Crow showed me the J. Roy. Stat. Soc. 83, 1920, concerning the distribution of accidents among <u>workmen</u>. It readily follows that an appropriate spread of accident-liability among different individuals tested over a period of time long enough to permit cumulation will lead to a negative-binomial distribution of accidents among individuals

He does not treat directly the problem of the distribution of accidents among factories (of uniform size) which would be more relevant to the present problem. I can imagine that there would be a distortion of the Poisson distribution even here, _if_ the observations were continued long enough to include repeated injuries by one person, but this is only because the repeated occurrences are correlated with each other. In our present problem, if there is even a transient persistence of characteristic response through one or more cells divisions (as might be expected of cell size) adeviation from the Poisson would be expected, but I assume that even this vestige of heritability is denied. This is ~~xxxxx~~ a point, however, that L&D did not adequately consider, as they distinguished only the extremes of full heritability versus entire ~~randomness~~ non-correlation of relatives, and Hinshelwood would likely be in favor of an intermediate. or better _/Yudkin

Perhaps this is what you had in mind.

The results with B are interesting indeed. I had thought we had tested B,(auxotrophs x Hfr) with negative results, but I rather suspect that several cultures are masquerading under the name B, and this may account for differences. Id the fact of crossability itself, in your material, confirmed? I did not fully understand your marginal note.

I hope you will not hold me to my (not entirely serious) proposal of a book, but if I could manage to as little work on it as for the preparation of this paper I would be glad to help. The thought of more literary work just now is rather terrifying! But perhaps time will help relieve this.

June-October are the least pleasant months of the year, but by all means start preliminary enquiries. I can almost certainly raise the funds for a supplementary salary ($250-300/mo.) but will know more surely in a couple of months. There are some other vexatious problems of lab. space, but we will surely find some way of accomodating both of you, regardless of contingencies. On the whole, I would think WHO would be both more likely to support a short-term fellowship, and also would be useful in disposing of fuss with passport-visa problems. Make sure that an extra salary here would be unobjectionable both to WHO and to the US consular authorities.

As you have probably guessed, I have temporarily turned over most of the Hfr work to Nelson, while I finished some Salmonella problems. I am nearly ready to go back to cytology of Hfr X F-,(which had given some promising results),and am sure that we will not get so far as to preclude a very active collaboration on it if you can get here next year, a possibility to which I look forward with anticipated pleasure. His most recent experiments, by the way, show that S^t (and therefore certainly F+) Het Mal- Lac- X Y10 or XY10 S^r give ~~xxxxxxx~~ diploids, about 90% Mal+ Lac+/-, and 10% Mal-/. Lac+/-. There is therefore certainly ~~xxxxxxx~~ an elimination of the contribution of the _F+_ parent in 10% of the diploids, in confirmation of previous data. We are currently trying to clean up with some real data the suppositions on the role of F polarity on elimination, as the basis of the effects on segregation (cf. p.727 paragraph 2 of our Genetics paper), since we know have Het M- F- stocks (by passage through motility agar. On this point, a single experiment in Novick's chemostat seems to show that prolonged cultivation at great dilution is sufficient to yield F-, as may possibly explain the motility agar effect, but this result needs to be substantiated).

Have you received the filter as yet? Thank you for the ca. 200 reprints of the JGM paper, received during several days this week. I am not sure how freely to distribute these. Probably, I will get most of the US-originating requests. I do not wish to ask for any part of your supply, but it will help me to judge how well the "market" can be saturated if I know how many you have purchased, and how many will be left after you complete a routine mailing(Unless you advise me to the contrary, I assume that you will be distributing yourself to a general list which would probably be congruent with my own.)

I regret that there was only one copy of the ms. with your letter. If you can send ~~an a~~ a second (perhaps with those changes to which you would accede) it would be appreciated, but not indispensable. I will try to refrain from perpetuating the discussion.

I will return the tear-sheets of your paper for the Biochemical Congress in Paris in the near future. Could you get for me the full name, publisher, and price so that I can get our library to buy the volume? [Please do not consider assuming this burdeh yourself!]

Unfortunately, I have to think of two other mss. along with this one, so my mind is not so clear on other issues that may have accumulated. I assume that you will be increasingly busy (if not frantic!) with the forthcoming meetings. I will wait for your acknowledgment of this before trying to collect our past correspondence and resume in a more coherent way.

Only one person seems to be going to Europe this summer from this department, one of my students (Miss Helen Byers). I intend to ask her to bring back the printed materials from the Congress for me, if possible. If there is any comparable favor I can ask of her, please let me know-- but she will probably be flying, and may be tight for baggage weight.

Yours sincerely,

Joshua Lederberg