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26/4/50

Dear Lederberg,

Thank you for your letter, and for strain 123 λ+, which arrived a long ago ; I too was surprised to find no effect in crosses. I have made no great progress with 123; however, growth requirements have been found to be methionine and lysine, on which 123 grows ~~without appreciable effect~~ but with a lag of some 48h (slow growth rate), does this correspond with your findings ?

As I wrote you in my last letter, I had some troubles with recombination which did not occur as usual, in the last months of 1949. I thought I had found a reason for that; but have no more been able to reproduce the failure of recombination, once it started reappearing again. This meant a considerable waste of time ; I am glad it is over now.

Summarizing the results of my work , some have been of little encouragement, some others more interesting: here are some details that might interest you :

1. Hfr . Results of crosses Hfr x Hfr were surprising : no Hfr in the progeny ! I am repeating them now. The interpretation of a Dauermodifkation is always trying.

2. Mating. Hfr proved disappointing under this point of view ; nothing definite has resulted. Some syntrophic growth, which seems unavoidable in mixtures, makes the observation more difficult, but even so it should be possible to see something. This failure may be of some interest in relation to your new hypothesis of small male gametes, which I take from Davis's paper on BMG 2, and in this connection I should like to quote two facts, none of which has much weight per se, but they may give rise to further developments. (In fact some Hfr crosses with few cells of one strain, one sees more recombinants, in some experiments, than colonies on controls with complete of the rarer strain.(*) The other fact is that with microscopical observation in phase contrast, 1500 x. one definitely sees with Hfr crosses some very small motile elements, which I would describe like "free flagella". I entirely agree that/~~both~~/these facts may seem foolish at this stage. The way is probably repetition of Davis's experiment with larger filters and a more efficient strain like Hfr . I am ~~thinking~~ trying something in this line.

(*) unfortunately it is very difficult to reproduce at will such conditions, which destroys nearly all the value of such information

3. Maps . I am looking forward to your paper on segregation announced on Genetics; I feel I am perhaps the only one who still believes in linearity, but I had some results which pointed to a possible way out of the mess. I am inclined to think that the data collected so far (I have seen also Newcombe's data on Sr) can be explained on the hypothesis of linearity only if either a major chromosome mutation has occurred in the building of B-M- or T-L-B_1-, which is not unlikely with use of X-rays , or selection of prototrophs introduces a bias of some sort - not revealed, however, from reciprocal crosses; otherwise, linearity seems untenable. The first hint for a chromosome mutation came from the outcrosses of W 677 and W 705 with W 836 . In the two cases, the relationships between Gal and Lac are reversed; using W 677, Gal is unlinked with Lac, using W 705 it is very closely linked. The markers of W 836 are closely linked between themselves, slightly on the right of M. Gal of 677 and 705 seem allelic (and not alleli to Gal of W 583, which is linked with Lac on the left of it). The easiest interpretation seems that there is an inversion with break points left of M and left of Lac, the orders being : W 677 : B_1 Gal M Lac V_1 LT , and W 705 : B_1 M Gal Lac V_1, the normal order being the last one. Many other markers are linked with Gal : Xyl, Mal of W 677 (not allelic to those of W 705, unfortunately) Ara and S, and should all be within the inversion. The results will be : a) in the cross BM x W 677, or W 836 x W 677, markers within the inversion will recombine only with double c.o. (odd crossovers being normally inviable) giving rise to the observed mess of combinations ; b) there will be an apparent, and partly possibly real negative interference between B_1-M and M-Lac, as is, in fact, found . Also other results follow. Possibly part of the difficult of "diploids" may be due to random segregation of acentrics ? The agreement of data with theory is only qualitative, so far; it is difficult to collect enough data, and it is difficult to test such hypothesis only on the basis of agreement with expectation in view of ignorance on interference . I am trying other ways, now, and should I come to more final conclusions about it, I should like perhaps to ask you the earlier strains T- etc., to trace back the history of the mutation. But it is definitely too early now. At present, I should need instead a replacement of W 826, lost in an accident, and T_6 ; I should also like to have an original K-12; I should very much appreciate a sending of them, and perhaps also strain Y+10, as I am using

as TLB_1- a W 909 reverted for Gal.

4. Antigens. Differences of antigenic type between K-12, W1113, 123 are too small to be of value. However, two and perhaps three strains, antigenically different, and interfertile have been recently found, and serological analysis is in progress; I am developing convenient markers and hope to be able to ship them to you soon. Such strains show also some degree of interfertility with the three mentioned above.

Thank you for the very interesting details of your "diploid" work.

I am sending under separate cover offprints of the letter to Nature; unfortunately I did not correct the proofs, and the alterations you suggested about reference to Professor Tatum, which was insufficient, could not be done. I apologise for this. I am also sending offprint of the abstract of the Stockolm paper, taken from the Proceedings. This paper was quoted by you in your review on Bacterial Variation; unfortunately, in the Abstracts, where you must have taken it from, only my name was given, and not that of my coworker Visconti. This mistake was corrected in the Proceedings. I am adding this, in case it happened to you to quote again the same paper.

A Cambridge statistician, N.T.J.Bailey, has produced some nice methods to deal with selection of prototrophs, estimation of map distances, viabilities etc. He believes that some of his methods may be identical to those you have employed for the analysis of the data of your 1947 paper on Genetics, and would be grateful if he could know more of those methods. Is it possible to get, from Yale University library, a copy of your dissertation ?

Your sincerely

Luigi Cavalli -