

January 16, 1952

Dear Cavalli:

I should have waited for your reply to my letter of the 26th Dec., which is possibly in the mails now, but a number of interesting things have developed in the past weeks with respect to the "fertility problem". In my last letter I mentioned briefly our old data on sterile combinations. The necessity of responding to the suggestions in your letter resuscitated this old question in my mind, and I hope you will not mind that I have taken up the problem again. I am most ready to acknowledge my indebtedness to you for raising the question again, and for providing the seeds of a new viewpoint on the problem. It happens that the time was ripe (for me, personally)-- I had been tied down for a few months with literary assignments, and have been eager to approach a fresh problem. I hope you will consider favorably the possibility of some collaboration, with the advantages of mutual fertilization.

It will help to use some symbols. Let us assume (as I did not previously) that you are correct in regarding the TL- series as self-incompatible, and symbolize this as F-. Let us assume further that Mrs. Lederberg's incompatible BM-derivative (W-1800, and others) carries the same F- factor. K-12, 679, 58-161 etc. are F+, as are prototrophs and auxotrophs extracted from F+ x F- crosses (either in the usual way, or through heterozygous diploids, or by mixed sm-nutritional selection.) Then F+ x F+ and F+ x F- are fertile; F- x F- are sterile. In the TL series, 679 is F+ (as is 679-183); 679-680 is F-, as are all of its clonal descendants. Rather than heterothallism, the scheme suggested to me that an "F+ hormone" was involved, required for sexual reproduction. I set out to test this by growing BM- Lac+ S^S F+ [58-161] together with BM- Lac- S^R F- [W-1607]. The mixture was then plated with TLB₁- Lac+ S^S F- [Y-10]. In addition to the expected Lac+ S^S prototrophs, there were also many Lac- S^R, Lac-S^S etc. I thought this confirmed the hormone concept, and set out to test filtrates of various sorts from F+, and F+ with F-, cultures to see if they would activate the F- x F- cross. No success. The experiment was repeated several times with various similar designs, and it always worked: when grown in presence of F+ the F- was also crossable to F-. A number of the exceptional prototrophs were examined, in the expectation that they would be F- (having come from F- parents), but they proved to be F+ by cross with W-1177. The paradox was resolved meanwhile by the rather incredible discovery that the W-1607 [F-] grown with 58-161, and recovered by colony isolation on EMB lactose or by selection with streptomycin, became persistently and heritably F+. If this experiment is correct [I am trying to repeat it now in a variety of combinations], F+ is transmitted not only cytoplasmically, in agreement with both your and my genetical observations, but also extracellularly. In the cited experiments, 6 out of 7 W-1607 colonies had become F+. Of course, possible selective differentials have not yet been considered. If this transmission occurs at all generally, you should be able to confirm it with your stocks. I am sending a few key cultures under separate cover; I hope that a revision will not have to accompany them. I have convinced myself that lambda is (probably) not the agent of transmission of F+, and that F+/F- has nothing to do with the aberrant linkage behavior of extracted TLB₁- stocks.

Another line that may not be too fruitful is the effect of aeration. We had observed a long time ago that well-aerated cultures appeared to be infertile. The effect now seems to be as if the aeration of 58-161 made it behave like F-. I have not, however, been able to modify other F+ cultures in the TL line, and the effect itself is not entirely consistent. Whether the modification of 58-161 is heritable cannot yet be stated. I thought to test your Hfr for unusual potency in producing "F+ hormone", but my stock seems to have lost its Hfr quality altogether. For adequate proof that F- is a self-incompatibility factor, complementary auxotrophs should be prepared from an F- prototroph, such as your TLB₁ reversion, although perhaps your present argument is already strong. Let me know what you think of a joint disposal of this problem, and your criticisms of these ideas.

Your letter of the 8th was received after this was sealed. Thanks you for your kind offices with respect to the Congress. I shall have to try to see if something can be worked out.

Yours sincerely,

Joshua Lederberg