January 20,1950.

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Dear Pete:

Thanks for your note of information on the mutability of 58-278 (which was isolated at Stanford, although I did some work on it at OBL). Here is one instance, at least, where recombination has been of some use.

The augmentation of the mutation rate is certainly remarkable. It raises the question whether the S^r mutation generally is a single step from S^s. There seem to me to be a number of possibilities, which you have probably considered already. As you may know, Esther has been working on the very similar problem of the genetic control of mutability, but at the Lac locus. Judging from her results, 58-278 may differ from K-12 in any of the following significant respects:

1. It may carry an allele of S, say S^m, which is itself sensitive, but with a higher mutation rate to S^r. This can be verified if 478 x S^r gives sensitive prototrophs all of which are mutable.

2. It may carry the standard S^s allel, but also a modifier "Ms", which may act either a) to increase the intrinsic mutability of the S locus, or b) interacts with mutations other than S^r [at S or other loci] so that they are phenotypically resistant, which they otherwise would not be. On this hypothesis, 478 x S^r will give some stable sensitive prototrophs. Also, on this hypothesis, one might expect that some S^r stocks, if crossed to S^s, will yield some mutable sensitive recombinants. This would be true, in particular, of 478 S^r.

~~The fact that all 24 prototrophs tested from your cross were S^m tends to support (1); for this is precisely the behavior of the S locus:~~ very many ~~prototrophs like the B_1 parent.~~ —This is not write: ighore it

I have in press with J. Bact. a note on using inhibitors to select for recombinants in bacteria (K-12 in particular). Streptomycin and azide were used in the experiments which consisted of $Az^r S^s$ x $Az^s S^r$, and recovering $Az^r S^r$ recombinants by plating the mixtures into a medium with both compounds. Streptomycin worked very well indeed, because of the typically low mutation rate, single-step resistance, and low background, but azide was at best a poor expedient, although most of the dual resistants recovered were demonstrably recombinants. If you can suggest another inhibitor comparable to streptomycin in its desirable characteristics, which will work well with enterobacteriaceae, and does not "cross-resist" with streptomycin, I would be grateful for the suggestion.

Some months from now, we will be starting some work on the mechanism of spontaneous mutation. I had planned to use streptomycin resistance, but 10^{-10} is an inconveniently low rate. Would it be intruding on your plans if we used 58-278 for these experiments?

Sincerely,

Joshua Lederberg