February 15, 1949.

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Dear Ed:

You certainly don't have to worry about receiving any of my publications; the reprints of the Heredity paper simply haven't arrived.; I understand that they're sitting in customs in Milwaukee while our brokers are trying to find a bill of lading that they mislaid while moving their offices! But they should arrive any day now, and I'll send you a set pronto. The penicillin methods, as youhave undoubtedly noticed, are out (in PNAS and in the Dec. JACS). We haven't had quite the phenomenal success with it that Davis reports, but it has certainly turned out to be a very valuable tool both with K-12 and with Salmonella. In S. typhimurium, we have a mutant that bears on alanine synthesis: it grows either on pa. or on tyrosine, better on both, but also responds to a series of phenols, especially in the presence of serine. There also seems to be a response to cyclohexanol + serine. Unfortunately, the mutant is rather unstable, so that we have to do rather laborious controls to eliminate reversions. But these statements seem to be substantiated.

I've written up some of the heterozygote work, substantially with the content of one of my earlier letters to you, so that I don't think it will be especially informative.

Not another word from Boivin. I'm beginning to think that if there's anything to transformations in coli, it may be based on lysogenesis.

Believe it or not, K-12 is lysogenic! This turned up when I noticed some plaques in a culture of a Glucose- mutant streaked out on EMB. I was able to isolate a lysogenic culture, with all the other characteristics of the mutant (which came from Y-10, so it was $TLB_1$-, and sensitive to all the T phages). But this culture was inactive on all the other K-12 derivatives I tried. Finally it turned out, mirabile dictu, that what was peculiar about the Glu mutant was not that it had a phage, but that there were cells sensitive to the phage which is carried by K-12 and most of the derivatives from it. Presumably, the phage had been eliminated from part of the clone, perhaps as a result of the irradiation which was used to produce the mutant, and that lacking the phage (lambda) it was now sensitive to it. So far, I haven't been able to separate lambda from the bacteria, probably due to reabsorption, which makes it look very much like the gamma phages in typhoid that Craigie talked about in his Bact. Revs paper. But we just found this stuff over the weekend, so I don't know much about it yet.

I agree with you that the maltose-utilization paper did not carry a very strong argument about 1:1, and I hope that this bit of propaganda won't be embarrassing, especially to Mike. But I think that a fairly substantial case can be made with the data on hand. Lactase is an enzyme, having been gotten out, and kinetic work done on it by Monod and myself. Since it is absent in cells adapted to maltose, which are fermenting and polymerising maltose, lactase is distinct from any member in the maltase series. Lactase is also distinct from any member of the glucozymase series, for the same reason. Therefore, $Lac_3$- certainly affects at least 2 enzymes, lactase, and (maltase/and/or glucozymase). Somewhat less rigorously, one can also argue that since the suppressor stock does ferment maltose, and not glucose, that "maltase" and glucozymase are also completely distinct. But this argument depends on the assertion that the amylomaltase-phosphorylase mechanism is identical in K-12 and in the suppressor stock in bypassing glucose. This is probably true, but not proven so. If it is then at least 3 enzymes are blocked by $Lac_3$; otherwise, the inability of $Lac_3$-

to use either glucose or maltose is due to a single enzymatic block. But since $Lac_3$- lacks amylomaltase (I hope! I'm not clear whether this has really been established), you would have to pin the block there, and give amylomaltase also a function in glucose utilization! The picture looks like hexokinase is missing (since glucose-1-P is active, and G-6-P is formed from it, while glucose itself is not), but this is dangerous ground until the full story of the complete utilization of maltose is cleared up! I hope that either Mike or I can get around to doing some hexokinase studies on these mutants in a couple of months. I could add to the above that there is a suppressor which permits glucose but not maltose fermentation, but this could operate by a completely different mechanism, so it doesn't prove the separation. Possibly, the best evidence for several enzymatic effects is the temperature sensitive allel of $Lac_3$ which has a different temperature threshold for sorbitol, glucose or maltose, and lactose. If the glucose and maltose blocks are different, that would make four enzymes.

The story on some of the other mutants is getting complexer and complexer. $Lac_1$-, although it shows an inappreciable fermentation of lactose , or content of galactosidase when grown on lactose, does not lack the "genetic specificity" to make this enzyme. It just doesn't make it in response to lactose! Grow the mutant on butyl-galactoside, and the harvested cells ferment lactose beautifully, and have as high or higher a content of galactosidase as wild type under the same conditions! A similar situation holds for $Lac_3$- (?) and ?? for $Lac_5$-. The others haven't produced lactase under any conditions so far tested. On the other hand, lactobionate which is unavailable as an energy source (I don't know yet whether it combines with lactase, but it certainly isn't much split by it) evokes considerable galactosidase from K-12. All of which leads me to think that for adaptive enzymes, the gene impinges in some mysterious way on the competence of the adaptation mechanism, and is not just the source of "specificity" of the enzyme. But this work too is a long way from completion.

The Salmonella work is moving moderately slowly. Prototrophs are irregularly produced from mixtures of multiple mutants. But lysogenicity has turned out to be a very serious problem here. There are several phages involved, and under certain conditions, as yet not too clear, they attack their carrier host, and give suicidal pictures. The problem is to get rid of them, either by moving to new strains, or directly.

You probably have heard something of Esther's progress from other sources. I understand that you may turn up at the Detroit Federation Meetings. If so, let us know just what days you expect to be there, and we'll try to make it there in our "new" ('35 Chev) car at the same time.

I have an opening foraanother student for the Summer or the Fall. If you've got anyone thatf you think is good, but may not have room for yourself, won't you let me know? I'd give a faintly perceptible edge to someone who was interested in bacterial cytology to do some work on the diploid heterozygotes.

Let's hear from you when you've got time. Best regards to your family, the Yale Gang, and to Perk.

Sincerely,

Joshua Lederberg