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Dear Josh:

I am sorry that I can't help you with the penicillin-sensitive strains. Rowley did not leave them with me, and nobody else here seems to know anything about them. I guess you will have to write to Rowley. He was here last March, and I thought he was on his way back to London.

I have just finished reading your commentary given at the Ford Symposium, and I would like to take this opportunity to make some counter-comments. I don't know whether I told you that I thought you did a nice job of this at the meeting --certainly much better than I could have done in the circumstances. In reading the printed version of your remarks, however, I find a number of objectionable points. For one thing, you have by implication ascribed views to me which I do not hold and which were not expressed in my paper. For example, I do not believe that 'specificity is something apart from structure.' To my mind, specificity and structure are inseparable, and I cannot imagine what I said, or what you thought I said, that led you to impute this mystical notion to me. The main question in my mind is whether the gene's contribution to the total structure of an enzyme is in (a) the ordering of amino acids, or (b) the determination of cross-linkages ('folding') in a preformed polypeptide. The view which you seem to ascribe to me ('stamping the specificity on an enzyme') is the same as alternative (b). In fact, I prefer alternative (a), as you can see in my paper. Even so, (b) cannot be criticised on the ground that it divorces specificity from structure.

As far as I am aware, I have never used the expression 'the gene makes the enzyme' in any serious discussion. The statement seems utterly meaningless to me. The gene is simply one component of a system which produces enzymes; our job is to find out what its particular role is.

In the paragraph beginning in the middle of p. 167, you have confused the one-to-one theory, which is a statement of a numerical relationship found in experiments, with the separate question of how we are to interpret this relationship, assuming it to be true. The quotation from Muller merely warns us that we must proceed with caution in our interpretation, a dictum with which I heartily agree. But it says nothing about how we are to establish the validity of the premises. Similarly, the experiments of Gale cannot establish or refute the one-to-one theory, but only the deductions regarding mechanism of enzyme synthesis which are made from it. This distinction, which is an important one, was made sufficiently clear in my paper. No one is more thoroughly convinced than I am that conclusive answers to the problem of protein synthesis cannot be had from studies on intact cells alone.

The last paragraph on p. 167 starts off with the statement that the one-to-

one theory is experimentally indefensible, etc., but later in the same paragraph you say that the recent work is 'almost the first explicit test of it.' Can there be any test of an untestable hypothesis?

Concerning the whole proposition that Max invented in 1946--i.e., that this is a theory which cannot be disproved and that such theories are illegitimate--I could say more than I will try to put into this letter. This proposition seems to rest on the concept of the crucial experiment, which modern writers on scientific method have shown to be spurious. Almost any theory can be preserved in the face of adverse experimental evidence by the addition of supplementary hypotheses. The point at which we decide to abandon the theory depends only on how useful it is in comparison with its alternatives. The Ptolemaic system was abandoned long ago, although no doubt it could still be made to work. The 1st and 2nd laws of thermodynamics, on the other hand, have been shored up repeatedly in order to avoid conflict with experience; it is inconceivable that an experiment could be performed today which would "disprove" them. I interpret your view that the one-to-one theory is a "philosophical necessity" to mean that we are in basic agreement on this point, but you are inconsistent when you proceed to attack it on the above grounds. The only way to attack a philosophical necessity is to show that it is no longer necessary.

With regard to your statement on p. 167 that many pleiotropic mutations are known, you will be interested, as I was--and surprised, too--to hear what Sturtevant said on this point in a course of lectures on the history of genetics which he gave during the winter term. He said that pleiotropic effects are much less common than is generally supposed; and that the idea that most mutations are pleiotropic stems from two sources: (1) de Vries' "mutations" in *Oenothera* and (2) the writings of E. B. Wilson, who decided on theoretical grounds that mutations should be pleiotropic!

I think that the most valuable part of your discussion is your formulation of the alternative interpretation of "mutant enzymes". I am wondering whether you have attempted to think this interpretation through. I agree that we should keep it in mind as an abstract possibility, but I run into difficulties when I try to think about it terms of mechanism.

I had better stop before this attains the length of a symposium paper. I would be glad to hear from you on any of the above points, however.

Best regards,

Yours,



Norman Horowitz