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Dear Tracy:

I shall try to answer some of the questions raised in your letter in some order.

Firstly, I cannot give you, with any degree of certainty, Lindegren's stand on the cytogene hypothesis since it varies from one day to the next. All I do know is this, that in the discussions that I heard, he postulates that the non-Mendelian results can be explained by a gene-to-gene transfer, that is to say, from the positive to the negative locus. As a matter of fact he has a paper in press on that. I do not know when it is coming out.

As far as my own attitude is concerned, I have stated publicly, both in Stockholm and at Oxford, that the plasmagene hypothesis which I proposed at Cold Spring Harbor last year is still the one most acceptable to the data at hand. Insofar as the melibiose case is concerned, it seems to me necessary to reserve judgment on its significance for several reasons (and these I have also stated publicly).

1) It is quite evident that there are factors other than substrate which influence the transmission of a character and until these other factors are delineated, it will not be possible to exert adequate control over the phenomena. Experimentally, this is what we are trying to do at present.

2) The second reason is not unconnected with the first but is an important one to note. Even in the so-called "good" pedigrees these non-Mendelian phenomena crop up with varying frequency. It is obvious therefore that it is extremely difficult under such conditions to set up an adequate control in an experiment designed to test the effect of any substance or condition on Mendelian inheritance. The fact that non-Mendelian results are obtained cannot be taken as evidence that the substance or condition being tested is affecting the transmission mechanism in the absence of a truly exhaustive set of controls. Here again, it is clear that only when we know and can control the factors which underly these peculiar results will we be able to draw any definite

conclusions as to the nature of the phenomena. In other words, my attitude is that the melibiose experiments cannot be accepted as conclusive evidence for the existence of plasmagenes although they suggest that one should look in this direction for the causal agent.

With reference to the last point you raised, that is to say, my "distinctive contribution" to the theory and to the evidence for it. As I have indicated in my discussion of it (See for example the Cold Spring Harbor paper) I certainly do not take any credit for the term or the concept of plasmagenes. I have talked this very problem over with Darlington and he also agrees that the plasmagene concept is a very old one which has been kicking around the biological literature for quite some time and that none of us can claim credit in any way for invoking it. However, actually there is, as far as I know, no well-defined theory of plasmagenes. Their existence has been postulated at various times by different people to explain a whole host of apparently unconnected phenomena which cannot be encompassed within the usual classical Mendelian concept of what the gene is, and what it does, and how it does it.

I believe that I have proposed, not a plasmagene theory but a theory of gene action which involves plasmagenes. It differs in several respects from previous discussions which have made mention of plasmagenes and their properties. In my instance, the need for postulating the existence of a unit like the plasmagene arose from the study of the normal processes involved in the formation of enzymes. The critical difference between the plasmagene concept which I have used from others that I have seen, is that in my theory of gene action which I proposed at Cold Spring Harbor, the plasmagene is not a special or unique or isolated cytoplasmic component in the sense that it is outside the normal physiological processes. On the contrary, it is assumed to be an integral part of the enzyme-synthesizing system and is presumed to be the normal link by means of which genes can effect control over protein formation in the cytoplasm.

This same theory permits us to understand the role of substrates in modifying the enzymatic constitution of cells. As to the evidence that our work has provided for the "plasmagene theory of gene action", I think the following can be cited: 1) that enzyme formation in the cytoplasm is inherently autosynthetic on the grounds of the kinetics of enzyme synthesis; 2) that enzyme formation involves a type of competitive interaction which is to be expected from competing, self-duplicating units; 3) an experimental confirmation of two consequences of this hypothesis, one involving the formation of enzyme in the absence of substrate utilization which we have succeeded in doing in two different ways and, second, the formation of enzyme in the absence of substrate or analog by minimizing the severity of the competitive interaction in the cytoplasm.

To summarize then, I would say that if I have made any "distinctive contributions", it has been to incorporate the plasmagene into a well-defined theory of gene action which is sufficiently detailed to permit adequate description of how genes can control enzymatic constitution in the cytoplasm. This same theory permits us to understand how other substrates and conditions which we have experimentally tested can modify the nature of this control and specifically, how substrate can evoke the homologous enzymatic activity.

Finally, I should like to emphasize that these points which I have made involve conclusions and facts which are independent of the melibiose case.

I hope this statement is what you are looking for. I am not particularly concerned about credit and certainly do not want any which I do not deserve. If this helps keep the facts straight, then my time was well spent.

I am looking forward eagerly to seeing you during your visit to St. Louis. I do not think I shall be able to get out to Columbia as we have a new arrival at home (a girl this time), and I have to stay close to home base for a while.

Sincerely yours,

S. Spiegelman

ss/b