February 14, 1946

Dr. Van R. Potter
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Dear Van;

Have just returned from a trip east whose major purpose was to attend the gene-panel symposium called by the NRC. I was told that I would receive a sizable grant to prosecute the program I submitted. Haven't as yet received official word on it however.

I have seen the Thomas paper in the December 22 issue of Nature and found its major interest in the fact that still another person working on different materials problems has come to the same general conclusions. With reference to the Theysen and Morris work I may say that we confirmed it soon after its publication by producing giant cells with the use of camphor. We did not retain the strains since physiologically they were not very different from normal. Should it be desirable to do something with them, it will be relatively easy to recover them. It is my feeling that the analogy drawn by Thomas between these types and cancer cells is not sufficiently fundamental to warrant the expenditure of much effort on them at present without some further evidence for a closer connection.

With reference to your second letter, after overcoming my feeling of awe at the large number of coincidences in thinking that has been going on in various laboratories I got a real good spontaneous laugh. The reasons for this you will see from the enclosures. One is part of a letter I sent to Dr. L. J. Stadler (the corn geneticist) in December and the other is the pertinent part of the paper I gave at the recent gene symposium called by the National Academy in New York. We have arrived at exactly the same conclusions once again. Let me know what you think about it. I have a short paper coming out in Science giving the pertinent results. I am also including three abstracts which we sent in the Fed. Proc. for the Spring Meetings which you may find of interest.

With reference to Miss Zorzoli, she is a Ph. D. in experimental embryology with little or no background in biochemistry or enzymology, an omission she is eager to rectify. She is a pleasant and competent person who will probably not set the world on fire but is capable of producing sound results.

At the New York Conference, after I had finished giving my paper A. J. Muller following a very flowery set of bouquets thrown in my direction, mentioned that in a Pilgrim lecture he gave in London last November he had proposed the same theory as to the role of the nucleoproteins--also Mirsky had come to the same conclusions from his experiments.

By the way there is to be a very interesting gene-in-microorganism syposium at Cold Spring Harbor beginning July 2. Will you be east for the Gibson Island symposium?

Re: my review: It isn't due until late fall. In the meantime I contracted to write a chapter in a new series on "Advance in Genetics" that will come out early next year.

Sincerely yours,

S. Spiegelman

SS:MM

Quotation from letter to Dr. L. J. Stadler December 26, 1945

"I had set myself the task of finding the sufficient conditions for the 'autosynthetic' type of kinetics in order to see what could be concluded. Of course the most trivial is the so-called autocatalytic type exemplified by the pepsinogen pepsin transformation. This however is of little real interest to us (I still believe in spite of Beadle's excellent review) since pepsinogen already contains inherently all the specificty of pepsin and besides the transformation is spontaneous. Another kind, however, is the formation of energy accumulators, i. e. units which contain in their structure energy richbonds the energy of which can be used for the further synthesis of similar units. The bonds in such units would confer a type of specificity not merely on themselves, but far more important on the energy contained in the enrgy rich bonds, so as to earmark it for certain uses, or for the synthesis of only particular kinds of structure. The stereochemistry would determine to a large extent the type of compound to which such energy could be effectively transferred. It is relatively easy to show that the growth kinetics of such units would be of the autosynthetic type without involving the concept of 'autocatalysis' in the usual non-energetic sense of the term.

Disregarding the fancy mathematical trimmings the whole thing boils down to this; in the synthesis of any compound, simple or complex, which requires energy, the energy required for the synthesis must be made specific for the particular compound being formed. Put this way it sounds almost trivial and probably is, but it has many experimental implications. It means fundamentally that it will be unlikely that we will find a general energy pool in cells which can be tapped directly for all kinds of synthetic activity. It means that while the energy obtained from the catabolic breakdown of such things as carbohydrate and fats may be similar it must be transferred to many diverse accumulators each of which supplies the energy for a specific type of synthetic reaction. And the more complex the product the severer the restraints on the specificity of its energy donators. It means that if we can find the immediate energy donator for a particular synthetic reaction we will have at the same time found the determinator of the specificity of the product of the reaction. From this point of view the problem of energy supply and specificity become one and the same. The implications of this for the problem of gene control over enzymatic constitution are obvious.

At any rate from all this you can see why I went in the direction I did. I was not surprised to find therefore that our search for the energy used in enzyme formation led us past the relatively simple and non-specific energy rich compounds of the ATP group and ended up in the very much more complex nucleoproteins. I believe we are on the right track and have the right methods and will end up with a much more unified picture of gene action than we had last year. It begins to look like gene nucleoprotein enzyme with the nucleoprotein as the more likely autosynthetic unit in the cytoplasm than the enzyme. We are a long ways off but we sure have fun.

The results of the experiments in which P turnover in the different fractions was studied under different conditions may then by briefly summarized by the following:

1. The phosphate turnover in the classical glycolytic system is necessary but not sufficient for enzyme formation (as well as nitrogen assimilation).

2. The phosphate bond energy in the form of adenosinetriphosphate is not directly available for enzyme formation.

3. The phosphate bond energy of the above compound had to be transferred to the nucleoprotein fraction before it could be used for enzyme or protein synthesis in general.

4. Arrangement of conditions which left the phosphate turnover in the glycolytic system intact but hindered the flow of phosphate to the nucleoprotein fraction stopped enzyme formation.

5. Compounds and conditions which increased phosphate turnover is the nucleoprotei fraction increased the rate and extent of enzyme formation.

6. Prevention of flow of P from the nucleoprotein fraction stops enzyme formation.

The above conclusions are based on experiments with only one enzyme in one strain. It is imperative to extend these experiments to other strains and enzymes.

These results make understandable, in terms of a common factor, a whole host of isolated findings collected during the study of the phsyiology of the adaptive process.

Of greater importance however is the implication that in the synthesis of a complex compound upon which rigid restrictions of specificity are imposed, a non-specific source of energy (as e. g. adenosinetriphosphate) is not adequate. It may well be therefore that the source of energy and <u>specificity</u> come from the same compound and the experiments indicate that this compound is a protein nucleotide.

These experiments also raise the obvious question of whether we were not studying, in our earlier experiments, the self-duplication of these protein-nucleotide units rather than melibiase. On theoretical grounds, the former would more likelu be the cytoplasmic self-duplicating units since they contain the necessary energy. The melibiase enzyme would appear to be self-duplicating if its synthesis closely followed those of the corresponding protein-nucleotide units.