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CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA

December 3, 1958

GATES AND CRELLIN LABORATORIES OF CHEMISTRY

Professor Joshua Lederberg
Department of Medical Genetics
School of Medicine
The University of Wisconsin
Madison 6
Wisconsin

Dear Professor Lederberg:

Thank you for the supplement and reprint. I found the material very interesting.

Sorry I don't have more to contribute at present than the resumé of speculations published a couple of years ago. However, in view of additional indirect experimental evidence and more thought, I still think the original ideas are logical and suggest experimental approaches to the problem of antibody synthesis. In our early findings the possible significance of the presence of RNA with most of the fragmented antigen material was not considered. However, when others began to obtain data and to theorize on the role of RNA in protein synthesis I began to think about the significance of the RNA-antigen complex. One possible objection at that time was that our RNA had a molecular weight of about 30,000-50,000 ("soluble" RNA) and most other workers were thinking of protein synthesis in terms of insoluble or microsomal RNA. It is now becoming obvious that this soluble RNA does play an important role in polypeptide formation.

I cannot help but believe that antibody formation depends upon the presence of a small fragment of foreign material (either exogenous or endogenous). The presence of extracellular antibody will depend on analytical methods as well as subtle equilibrium reactions between antigen and antibody within the cell.

The formation of antibody forming clones can of course be explained by "mutation", but it can also be explained by the fragmentation-template idea. For example, the number of fragments or even molecules of antigen retained by each liver cell is quite large (Int. Arch. Allergy 12:70-88 (1958)). When a cell divides there is also a division in the number of antigen particles. However, there is only a definite number of such particles and hence one observes small groups of cells in immune lymph tissue which are producing antibody. It is of interest, that from Al Coons work, one can conclude that the secondary response in immunization, which stimulates clone formation, is the result of either destruction of the initial cell or stimulation of division. I believe that destruction may take place due to a hypersensitive reaction and that antigen fragments are released and picked up by adjacent

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cells. Your studies might answer this question if you use a soluble antigen capable of inducing a secondary response. I cannot explain at present why a single cell or clone (Coon's data also suggests this) forms only a single type of antibody. I would have to determine whether more than one antigen particle could enter any given cell.

Contrary to your apparent apprehension of my skepticism, I seek only the truth, and hope my ideas may help, or at least contribute to, some aspect of the problem. I hope that I have the opportunity of informally discussing this further with you, either at Stanford or the California Institute of Technology, when you get settled on the west coast.

Congratulations on the Nobel Prize and with very best regards.

Sincerely

A handwritten signature in cursive script that reads "Dan H. Campbell". The signature is written in dark ink and is positioned to the right of the typed name.

DHC:mc

Dan H. Campbell
Professor of Immunochemistry