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Prof. Dr. J. Lederberg,
Department of Genetics,
Genetics Building,
The University of Wisconsin,
Madison 6, Wisc.,
U.S.A.

Dear Dr. Lederberg,

First of all, once more my congratulations for your Nobelprize. We are all happy about it here.

Thank you so much for your kind letter. I appreciated the 'postscript'. I would quite agree the two weakest points in the cell selection idea are 1) the maintenance of immense numbers of separate clones for each type of antibody, and 2) the normal change of the cell population through mutation.

Several points still appear strange: Tolerance can only be maintained in the continued presence of antigen. An experiment is at present made by my colleague Boyden, who castrated animals. It is supposed that these animals might now possibly form antibodies against testes material, since the corresponding cell clones are no longer under the antigens inhibiting pressure.

Your modification of the cell selection theory represents a definite improvement. What is still missing is an explanation for the actual mode of action of the antigenic stimulus, especially so in the characteristic secondary response. I am afraid my 'peptide hypothesis' in this respect is no good. This would suggest 2 stages, a specific and non-specific one. In the former the antigen is acting in the primary response on a selected number of cells only, because these cells have a higher affinity for it. The antigen is pynocytosed and degraded to several peptides (evidence available). These peptides, carrying perhaps the specific grouping, act now as stimulus for cell proliferation (how?). The relatively few multiplying cells will form and release antibody, which they produce naturally anyway. Part of this antibody will then be fixed by many more cells on their surface, so that upon reencounter with antigen in secondary response many more cells can adsorb out specifically the stimulating agent. In this situation now the other 'non-specific' mechanism could contribute significantly to the rapid increase in antibody population: the 'non-specific' stage: antigen will react with antibody, the complex in context with complement will give rise to toxic reactions, ending in the release of the hosts' own 'endotoxins' (Landy, Shear). This potent agents will stimulate additionally the antibody production resp. cell proliferation in already established fashion (see Bacterial Endotoxins, Tb-lipopolysaccharide peptide).

These seemingly somewhat far fetched working hypotheses are liable to several tests, e.g. artificial production of polypeptides from antigen, testing the growth stimulatory effect on sensitised cells as compared with normals in

tissue culture, their effect on increased production of antibody in vivo and in vitro. Test for increased surface antibodies after primary stimulus etc. Study of antibody production in dependance of host's own 'endotoxins'.

Quite another way of looking at antibody production is to suppose that antibody production is going on all the time, but we do not know of this as all the antibody species are continuously degraded (seems rather wasteful!). What antigen does is actually only to protect the antibody from its usual rapid intracellular breakdown and in doing so it appears as there is antibody de novo synthesized. Boyden and I are testing this queer and probably wrong idea at the present.

My colleague Spärck, who is involved in the cellular aspects of antibody formation (1-cell-1 antibody idea) has been away for several months in the States and is just only now again settling down to this problem. We will inform you on any progress along these lines. I think the great difficulty will be, that even if you have succeeded in isolation of clones in tissue culture of various cell strains, they will a) probably undergo further mutation, b) have passed the proper stage in their development for suitable antibody production (transiency).

A new more chemical approach we have recently started. We want to synthesize antibody in vitro in a cell free system. The method is based on the incorporation of C^{14} amino acids into de novo formed specific antibody, isolated by specific precipitation with carrier and comparison with non-immunized controls. The method works with intact cells, but damage to cells reduces this antibody formation to a level too low to be of significance under the present conditions. This also Humphrey (Bioch.J., 1958) has shown. We feel, however, that progress can be made using additional energy generating systems etc. Many clues as to the mechanism of antibody production could be obtained with a cell free system and how it could be influenced by ag, ag/ab complexes, ab etc.

Another approach to antibody production we have just started based on the following working hypothesis: obviously a hapten, although a carrier of specificity, can not 'produce' antibodies. But it can perhaps induce slight antibody formation or start at least some stages in it. Therefore upon giving this hapten in a complete antigenic form later, we might obtain a response of the secondary type. Also the reverse of this is under study.

When I saw you again in Wisconsin last spring I had already lost my heart to California, how commonplace; and decided to take even a shoe cleaners job in San Francisco. I greatly appreciate and am thankful for your recent indications as to possibilities for a collaboration in Stanford. No doubt, in case of realisation, the profit would be entirely on my side. One difficulty is certainly that I am bound by contract with the World Health Organization until December, 1959. Furthermore, I could probably not overcome the difficulty to leave and come back to the present job.

With best regards,

Ernst Sorkin

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