

November 3, 1958

Dear Sid

Thanks very much for sending me the ms. just received. I will return it in a few days after having taken a bit more time to digest it.

Are your observations related to those of Tremaine, and of Rosenberg et al. which appeared in *J Immunol.*, 79:467 and 81:136 respectively? I am somewhat confused by the terminological obscurities of these reports. I have been quite excited to run into this literature, going right back to Dienes, whose work as an immunologist I had quite forgotten about.

I am still trying to work out my own synthesis of these observations and ideas and am looking forward to the opportunity of having them ground down to more decent acuity by your own advice at close hand. It strikes me that one approach to the problem is still to posit a single molecular species of antibody, but that this antibody must be closely regulated in amount and timing of release if it is to be totally absorbed by the tissues leaving no detectable amounts in the serum. One should in fact suspect that excess serum antibody might inhibit the development of the skin reactions. If so, the function of the adjuvant lipopolysaccharide you discovered might be to inhibit regional antibody production. One should be able to demonstrate this, to a degree, by combining systemic with intradermal immunization; one predicts that this will not give local dermal hypersensitivity of the delayed type, if this proposition has anything to it.

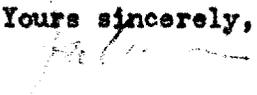
Does your work constitute a detailed criticism of Brent's analogy of the homograft reaction with delayed-type sensitivity? Is there a more far-reaching difference between the latter and the Jones-Mote type besides evanescence? If not, one might have to say that the homograft reaction (e.g. to dissociated epithelial cells) was sometimes evanescent, sometimes not perhaps depending on the intensity and duration of the immunization.

I must admit I was rather provoked by another of the assertions of the Medawar school, and perhaps this is what you have in mind as the basis of your criticism. They seem to believe (viz. *Nature* 1956) that the T(homograft-immunizing) and H(hemagglutinin) functions of the H_2 genes in mice must ~~reflect~~ reflect two different substances, since, e.g., red cells can provoke anti-H without anti-T (at least in their hands). They never thought of the proper experiment, to determine ~~xxxx~~ whether the erythrocyte antigens will provoke anti-T in combination with the generalized stimulus afforded by competent T antigens of different specificity. In general, it seems to me deplorable that this work has not been unified on a theoretical-biological basis with other work in immunology and allergy. I really am looking forward to our association; I experiment I would like to dis-

cuss with you is whether RBC etc. could be made effective T antigens (horrible terminology!) by the use of lipopolysaacharide adjuvants. What had provoked me especially was the presumption that the T antigens were ~~the~~ chromosomes themselves-- an idea that does seem to have gone with the wind on more careful analysis.

On rereading this, I am afraid I have written rather too severely-- my feelings to the trio, including Billingham, are more tender than you might think from this letter.

Yours sincerely,


Joshua Lederberg