

November 22, 1958

Professor Sidney Raffel
Department of Medical Microbiology
Stanford University
Stanford, California

Dear Sid:

Thank you for your serious efforts that must have underlain your letter of November 11th. I wish that some of the other nonsense I have to put up to now were nearly as interesting and important as the issues that have come up here.

I hope that you understand that my questions are a reflection of my own unfamiliarity with this field and more often an attempt to get a personal orientation than to make a criticism. I was interested to have you clarify the particular purpose of your article and to explain to me so fully how it related to other current work in the field. Parenthetically I might mention to you that I gave a talk at Harvard last week, one which satisfied a commitment of very long standing, whereat Pappenheimer, seeing me after the lecture, greeted me with the encouraging remark that he had found himself able to disagree with practically every postulate I had made in support of a selection theory of antibody formation. The theory would seem to be either a near miss or a good hit and since I can hardly believe that it can be so rampantly wrong perhaps this is a good omen. How to fit in this transient hypersensitivity into the selection theory may be a ticklish business but perhaps understandable on the basis that the progression of immature cells from a hypersensitive to a reactive state may in some cases be partly reversible so that the cell population which has been built up may give some derivatives that account for the hypersensitivity. I think I would have to agree that these questions are rather too involved to deal with profitably by letter and that it would be best to defer them to more intimate conversation. Your discussion of Tremaine's work does seem to me to touch on the most fundamental issues. Isn't the point just that there is a good experimental basis for the belief that donors which do not show corneal reactivity transfer reactivity in some circumstances to recipients. If this is the case then the corneal nonreactivity must be masked in the donor, perhaps by larger amounts of circulating serum antibody on the premise that small amounts of such antibody may perhaps diffuse to the cornea.

I wasn't thinking so directly of the present paper in connection with Brent so much as our previous discussion about that work.

And I think I may be learning the hard way that some of these questions may not have any very facile answers.

According to our present schedule I will have to reach Palo Alto not later than January 22nd in order to participate in the Medical Genetics Symposium that Kalman is organizing in San Francisco. I hope to be running in to you not long thereafter.

As ever,

Joshua Lederberg

P.S. As I recall Tremaine did not entirely calculate to produce circulating antibodies: her animals were sensitized by intradermal, not intravenous injection. Although she mentions that she did get some circulating antibody it might be of interest to reproduce her results with material from intravenously sensitized animals. I note that she also reported that antiserum did inhibit the reaction and this might again support the idea that the corneal sensitivity is masked by the circulating antibody. An alternative to the idea of reversibility in maturation is the following. While all immature cells are hypersensitive, a fraction of mature cells are reactive, a fraction hypersensitive.

I might add that Byron Waksman gave me no encouragement for the idea that hypersensitive cells were damaged immediately by virtue of reaction with the antigen; but I gather that Rich and you colleague Favour think differently. Have you reached a definite conclusion in your own mind on this question?