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December 16, 1940.

Dr. Wm. C. Boyd,
Department of Biochemistry,
Boston University, School of Medicine,
80 East Concord Street,
Boston, Mass.

Dear Boyd:

Your letter interested me greatly and I certainly envy you your courage in writing a book on immunology -- it will surely involve a prodigious amount of work. I'll be very glad, of course, to look over your antigen-antibody chapter if you care to send it, but I must warn you that I've already promised to do the same for another friend who is also writing an Immunochemistry.

As for the comments of your scientist friend, there is little I can add to what I have already written, nor do I think anything that has happened since has weakened the arguments advanced then (esp. Bact. Revs. '39,3,49).

"a". The first sentence sums up beautifully prevailing misconceptions regarding specific bacterial agglutination: first, that of antigen-antibody combination as a single, static process, followed by a second aggregative process for which, I submit, there exist only assumed, but not real, analogies. If "it is generally agreed" that this is the process, it illustrates all the more clearly the harm wrought by dragging in assumed analogies. If, as stated in the second sentence, combination is correctly accounted for by the mutual multivalence theory, as I prefer to call it, separation of specific antigen-antibody combination into two steps represents an unnecessary complication.

b. I have found no sound evidence in the literature that electrostatic repulsion and cohesive force have anything whatsoever to do with specific bacterial agglutination. I know of no useful prediction as to the process based on these two, to me entirely gratuitous assumptions, whereas, making use of the principles already referred to (also J. Exp. Med. 37, 63, 855) one can readily predict, when a little information is available, whether or not agglutination will take place.

1. I do not question the experimental facts cited, merely their interpretation. The agglutination of a sensitized, salt-free suspension may be better predicted on the basis of the

neutralisation of well-known Coulomb force effects than by the introduction of a special and vague concept such as "cohesive force."

2. It seems to me that Mudd and Jeffe's old experiments (J. Gen. Physiol. 35, 18, 599 ) as well as our own above referred to, showed that electrophoresis measurements and "potential" would be of influence only in the sense that too large Coulomb forces might impede the completion of specific aggregation.

c. The apparently arbitrary separation of specific agglutination from other agglutinations is a convenience because antigen-antibody interaction supplies a clue as to mechanism that is lacking in the other types. I believe that as the factors promoting particulation in other systems come to be as well understood as those responsible for specific bacterial agglutination these other systems will show real analogies in place of those which now have to be assumed. One can visualize hydrogen-bonding or other secondary valence forces as connecting links. I still feel that the shifting of emphasis in agglutination from demonstrated chemical interaction of "generally agreed" multivalent components to the assumed physical analogies has impeded the understanding of the process, and still is, according to your friend's comments.

I think we are likely to have a very stimulating conference in March. In a few days I hope to be able to send out a tentative program.

Looking forward to seeing you then, if not before, and with greetings to Dr. Hooker,

Sincerely yours,

MH/m Michael Heidelberger.