Dear Albert:

Thank you for sending the chapter. It is a fascinating treatment, and I very much enjoyed the one quick scan I've made so far. You've done a real service in going over this literature-- there are one or two places where I felt you were being a bit tender of someone's feelings and might have wished to be more critical.

I have only a few comments. P.7: Porter's antigenic piece is the one readily crystallized; the antibody pieces are presumably less homogeneous, but I don't think crystallizability is a very good criterion.

p.8 I was not much impressed with the Belser paper. There is no evidence of any inducer-specificity at all, in the sense that antigens evoke specific antibodies. By all present criteria, one induces the same enzyme with a variety of different inducers, and indeed with none at all in constitutive strains. If you want to say that enzymes and antibodies are all stereospecific, I won't argue.

p.11 Your paragraph under mechanisms of antibody formation might give a misleading impression. I don't believe there is any problem in anyone's hands now to get abf from surviving lymphoid cells in culture, when the cells have been taken from immune animals. This is not the same as generating the whole response in vitro, which is what I think you're asking for. I don't believe that the inadequacies of the theories are the cause of experimental difficulties, but the consequence. If we can ever get a selected line of cells to grow at all, we may have in vitro abf, but this alone wouldn't settle the theory.

p.13 This reads very well to me. p.14 I would invoke retention of antigen to account for maintenance of tolerance, at least, and it can still be a factor in the long-term persistence of immunity. But, as you say, the necessity for it is eliminated as a sole basis of 'immunological memory'.

The Cohn-Lennox result is still paradoxical by comparison with the others, or vice versa. I am more than ever inclined to think the difference is the duration of exposure of the animals to the antigens, i.e., that the double reactors are the result of two events in sequence (including even the possibility of phagocytosis of one abf cell by another.)

You asked about the definition of maturity. You are quite right-- by mature I meant at a certain stage of development, i.e., relatively mature, not fully differentiated. It looks now as if fully differentiated plasma cells have a very limited capacity to proliferate, judging from serial transplantation experiments with stimulated cells in newborn hosts.

Of course there might be more than one globulin locus (and p2 is very likely not the same as gamma-). Naturally I wouldn't want to postulate more loci than experimental results require. If there are indefinitely many, all the abf cells will have the same full competence, which leaves no room for selection. This is one of the parameters that we can think of measuring in due course.
Autoimmunity is necessarily some sort of relaxation of autotolerance; this is probably less mysterious on the selection theory than on any other. If for any reason relatively immature cells are allowed to mature with the specifications for making an autoantibody they can never then be stopped. This may be what happens in lupus erythematosus-- i.e. some sort of generalized block to the removal of immature mutants; (perhaps some accessory substances like complement are needed for the removal). In other cases, autotolerance has never developed because the substance involved is normally has no access to the lymphoid cells, e.g., the lens and testis cases. I.E. the lymphoid pool already contains some cells preadapted to make anti-lens antibody. The adjuvant may serve to bring the antigens into the right cells.

I am not certain whether spontaneous hetero- (even iso)gglutinins are very decisive for the selection theory. It is difficult to exclude that cross-reacting antigens, e.g. bacteria, have evoked the 'antibodies'. We would need some animal that would be grown on a strictly synthetic (and bacteria-free!) diet.

The lectins I think are probably carbohydrates (or storage preenzymes) whose specificity corresponds much to that of the blood group factors in a fairly accidental way. That was a clever suggestion, to look for anti-sperm lectins.

Have you got any fairly clean anti-acrosome antibodies? Male-fertility in E. colli is sensitive to periodate, and we are jokingly saying that we are looking for the acrosomal carbohydrate here. Ørskov has an anti-male serum that seems ok; we are setting up to test its effect on fertility, and also to use it for a cytochemical reagent with fluorescent antilglobulin (which would be a nice trick for sperm too! -- has anyone done this?)

With best regards,

[Signature]

Joshua Lederberg

P.S. I haven't heard from your son Steven in years. Since I've lately been interested in Martian flora I'd be curious to know his current views on this. (We had many conversations about this, I think in 154 or was it 51, at Woods Hole.)