CHÂTEAU DE BELLE-VUE
F - 30210 CASTILLON DU GARD
(66) 37.00.75

Dr. Jamie Cunliffe,

22 August 1983

Dear Dr. Cunliffe,

Earlier this month I received your letter of 9th July with inclusions A,B,C, and D, which was forwarded to my address here in Castillon. A copy of manuscript A was sent to Dr. B. Kickhöfen, Freiburg, the Editor in Chief of the European Journal of Immunology.

I am impressed by your encompassing and erudite description of the immune system, and by the perseverance with which you derive a far-reaching theoretical construction from e few elementary concepts. As you point out, the most important of these concepts is the "inversion" of T-killer cell functions. This inverted function is conferred upon phagocytic cells, as explained on page 2, and in Table 1. The phagocyte, according to this thesis, is intrinsically aggressive, but is triggered to non-aggressiveness by "recognising" self, or self/self, as you say.
Lymphocytes, on the other hand, are triggered to aggressiveness (and B-cells to antibody production) by recognising non-self. This property requires a large repertoire of receptors, a repertoire that may be called "complete", in the sense that virtually any "foreign" macromolecule can be recognised by receptor-ligand binding. I am missing, in your theory, a consideration of the fact that antibody molecules and antibody-like B-cell receptors display, in their variable regions, molecular surface profiles (idiotypes) which present "foreign" antigenic determinants (idiotopes) against which the system is capable of making antibodies. Considering the huge receptor repertoire which can recognise all idiotopes, we may postulate that the idiotypic repertoire is likewise complete, in the sense that the system itself possesses a set of idiotopes similar to virtually the entire universe of foreign antigens. I have exploited this concept in proposing a "Network Theory" (Annales Immunol. Inst. Pasteur, 1974, 125 C, p. 373). An enormous experimental idiotype literature has since arisen.

This is only to emphasize that lymphocytes (the role of which you relegate to a slave function orchestrated by phagocytes) can be triggered when recognising non-self. You now introduce a "phagocyte receptor repertoire" which recognises self/self. You specify that "recognition" involves complementary molecules (LIGANDs - RECEPTORs) which bind together rather like substrates to enzymes.

p.t.o.

I now repeat the argument I already made in 1960 (Annual Review of Microbiology, vol.14, p.348), namely: why should a "healthy self cell" be recognised, if the only action upon "recognition" must be to leave that cell in peace? I trust that you realise the cogency of this argument. "Recognition" requires LIGAND-RECEPTOR binding. Though this binding is reversible, we would have to accept that in a healthy animal, phagocytes are continuously engaged in binding and unbinding to and from healthy cells. A phagocyte that has just unbound from a healthy cell is quite likely to bind again to that same cell a moment later or, if it drifts away, to bind to another healthy cell, unbind, etc.
I find this an unattractive concept, as specified in the middle block of your Table 6, and I prefer to regard as the true elementary property of the immune system its ability to recognise non-self by members of its huge repertoires of molecular receptors, Thus I relegate the role of phagocytes to a "slave function" orchestated by this enormous capacity of lymphocytes to recognise "foreign".

I do not expect to convince you. Considering the large amount of synthetic thought that you have brought to bear on these problems, I would suggest that you submit your essay to another journal, such as the "Journal of Theoretical Biology".

I am sending a copy of this letter to Dr. Kickhöfen, and to you I send my kindest regards.

Yours sincerely,

Niels Jerne

N.K. Jerne