OAK RIDGE NATIONAL LABORATORY
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NUCLEAR DIVISION

POST OFFICE BOX X
OAK RIDGE, TENNESSEE 37830

N G Anderson

March 22, 1971

Dr. Joshua Lederberg
Department of Human Genetics
Stanford University Medical School
Palo Alto, California

Dear Josh:

Between work on zonal centrifuges and clinical analyzers for the SKYLAB, we have been working on the problem of the origin of the variable sequence in antibodies, mostly via theoretical models. One has to strain very hard indeed to make any model based on somatic mutations credible, and my conclusion is that it can't and doesn't work. The same is true of the simple germ line theory which states that we have evolved a gene for each distinct antibody which has only an antibody producing function. The conclusion that no present theory was tenable has therefore been my starting point. It seemed to me that there must be a dead simple basis for the entire process of recognition of foreignness and I set out to find it. The results are described in the enclosed paper. I would appreciate your reaction to it. So far, biochemists and structural chemists understand the idea and a few are busy exploring it. My immunologist friends mostly don't catch on, and some also appear to dislike the idea of not having a number of theories to choose between (i.e., of solving the problem).

The most important result of the idea of cellular perfect sets has been the realization that a special type of sequencing of cell protein groups would be required during differentiation as mutually forbidden surfaces were expressed in different cell types. This suggested that many early proteins would be antigens in the adult, which turns out to be true even in isogenic strains. This in turn led to the realization that tumor specific transplantation antigens may all be early fetal proteins. From there to immunizing against tumor challenge with fetal antigens was a direct and logical step. It works with all the tumors we have tried, and we now have an expanding program to evolve both methods of early cancer detection and therapy based on it.

All aspects of this work is being reviewed in a small symposium here on May 23-25. If you are interested, we would like to have you attend.

It's rather odd to have gotten a firm experimental hold on a tough problem using a theoretical approach that seems to have so little appeal.

Let us know if you can come.

As ever,

Norman

NGA:jdr

Norman G. Anderson, Director
Molecular Anatomy (MAN) Program