SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
RESEARCH UNIT OF MEMORIAL CENTER
FOR CANCER AND ALLIED DISEASES
410 EAST 68TH STREET
NEW YORK 21, NEW YORK

May 6, 1953

Dr. Leo Szilard
Department of Biophysics
University of Chicago
Chicago, Illinois

Dear Doctor Szilard:

One of my friends related to me your talk at the New York Bacteriologists' Meeting a few months ago. It was in connection with suspended animation and I found it very humorous. I stopped in at the University of Colorado on my way back from the American Chemical Society Meeting and Ted Puck and Leonard Lerman told me that you had a whole host of such fantasies. As a matter of fact, they thought that some of them were published, such as "Grand Central Station", "My Trial as a War Criminal", and so forth. I wonder if you have reprints available which you could send me, or if you could give me the references, I would be very interested in looking them up.

Very sincerely yours,

David Pressman

David Pressman, Ph. D.
Head, Section of Immunochemistry

DP/mm

July 24, 1953

Dr. David Pressman
Head, Section of Immunochemistry
Sloan-Kettering Institute for Cancer Research
410 East 68th Street
New York 21, New York

Dear Dr. Pressman:

Enclosed you will find two reprints in which you expressed interest in your letter of May 6. It was very nice hearing from you and I hope to see you some time when I am in New York.

Sincerely

Leo Szilard

LS:jda

Enc. 2

The Quadrangle Club
The University of Chicago
Chicago 37, Illinois
August 29, 1956

Dr. David Pressman
Roswell Park Memorial Institute
663 North Oak Street
Buffalo 3, New York

Dear Pressman:

A short while ago I thought of an experiment on the formation of antibodies which, I believe, would enable us to decide one of the issues which appear to be quite crucial today. For the sake of brevity, I shall reduce this issue to the following simple question: An antigen F is injected into a rabbit and subsequently another antigen F' is injected which is so closely related to F as to evoke an anamnestic response but yet not identical with F. Which of the two antigens determines the specificity of the antibody produced in the anamnestic response?

My present tentative guess is that the specificity of the antibody is determined by F which is injected first and not by F' which evokes the anamnestic response. If this were established as a fact beyond the shadow of a doubt, we would then be on much firmer ground in planning further experiments on the mechanism of the antibody formation.

The proposed experiment is as follows: We take a soluble hapten a, couple it to a protein P and thus obtain an antigen which we may call A. We then inject a rabbit with this antigen A and obtain an antibody which we may designate [A] . Subsequently we inject the same rabbit again with the same antigen A and obtain in the anamnestic

response an antibody which we may call $[A(A)]$. The letter in the brackets, ( ), indicates the antigen which was injected first (which in this particular case happens to be identical with the antigen that was injected second).

Further we make a substitution in the hapten a to obtain the hapten a', we couple a' to the same protein P and thus obtain antigen A'. In injecting a rabbit twice with this antigen, we obtain in the anamnestic response the antibody $[A'(A')]$.

Next we determine the binding energies of the antibodies $[A(A)]$ and $[A'(A')]$ for the haptens a and a'. One may designate these four binding energies as follows:

$[A(A)]$-a; $[A(A)]$-a'; $[A'(A')]$-a; $[A'(A')]$-a'

We may thus write for the ratios, r_1 and r_2, of the binding energies for these two antibodies

$$\frac{[A(A)]\text{-a}}{[A(A)]\text{-a'}} = r_1 [A(A)] \qquad \frac{[A'(A')]\text{-a}}{[A'(A')]\text{-a'}} = r_2 [A'(A')]$$

I believe it is almost a foregone conclusion that r_1 will be larger than 1, and r_2 will be smaller than 1, provided two suitable soluble haptens were chosen.

The main part of the experiment is now as follows: We inject into a rabbit the antigen A and evoke the anamnestic response with antigen A'. In the anamnestic response we then obtain an antibody which we shall designate as $[A'(A)]$ to indicate that the antibody was obtained

by injecting A' into a rabbit which was previously immunized by A. Similarly we prepare the antibody A(A') by injecting first A' and obtaining the antibody in the anamnestic response evoked by A. We are now interested in the ratios of the binding energies of each of these two antibodies for the haptens a and a'. These ratios may be designated by

$$\frac{A'(A) \quad -a}{A'(A) \quad -a'} = r_3 \quad A'(A)$$

$$\frac{A(A') \quad -a}{A(A') \quad -a'} = r_4 \quad A(A')$$

If the antigen used in the first injection determines the specificity of the antibody formed in the anamnestic response evoked by a related antigen, then we should expect r_3 to be larger than 1 and r_4 to be smaller than 1. Moreover we should expect

$$r_3 = r_1 \quad \text{and} \quad r_4 = r_2$$

This assumes that all the rabbits are identical which is, of course, not the case. But while the binding energy of one of these antibodies to one of the haptens may vary greatly from rabbit to rabbit, the ratio of the binding energies of one of these antibodies to the two haptens will vary much less from rabbit to rabbit, and perhaps will not vary at all. Therefore, it may take in our experiments comparatively few rabbits to establish the mean value for the ratios r.

What I now want to ask you is:

(1) What do you think of this experiment?

(2) Should we attempt to collaborate on it?

If you like the experiment and think we should collaborate on it, we might do well to keep in mind the following: For people to be certain on such a crucial issue, it would be well to have an independent confirmation of the result as soon as possible. Therefore, we might as well arrange our collaboration in such a manner that we get the result and its independent confirmation at the same time.

Recently I talked with Dr. David W. Talmage, who is at the Medical School of this University, about the anamnestic response, and found his views rather in line with my own preconceived notions. The thought of the experiment herein described arose from the desire to prove or disprove the correctness of these views. I assume, therefore, that Dr. Talmage would be willing to collaborate in the proposed experiment.

One possible way in which we might proceed, if this meets with your approval, might be as follows: You might prepare in Buffalo a suitable pair of soluble haptens, a and a', and the corresponding antigens, A and A'. Half of the amount prepared you could send to Chicago.

All the relevant antibodies would be prepared simultaneously in Buffalo and in Chicago. For the measurement of the binding energies half of the amount of the antibodies prepared in Chicago would be sent to you, and you could send half of the amount of the antibodies prepared in Buffalo.

An added attraction of this procedure would be that we in Chicago need not know the identity of the antibodies which were sent to us from Buffalo and you need not know the identity of the antibodies sent to you from Chicago. This somewhat childish embroidery might help to convince the sceptics if the results obtained should come out too good to be true.

As soon as I hear from you, I will discuss the issues involved with Dr. Talmage, and subsequently I could stop over in Buffalo on my way to New York to discuss with you whatever there is to discuss, including the choice of haptens. I am frequently away from Chicago but if you send your letter or telegram to me in care of Mrs. N. Mann, The Enrico Fermi Institute for Nuclear Studies, The University of Chicago, it will be forwarded faster than if you sent it to my regular address at the Quadrangle Club.

Your talk at Ann Arbor, as well as that of Coons, provided the basic stimulation for the contents of this letter, and I hope to see you again soon either in connection with this matter or otherwise.

With kind regards - also to your wife.

Sincerely,

Leo Szilard

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In place of hog.

Albumin coupled hapten does not precipitate with $(NH_4)_2SO_4$ so that antigen remains in solution while globulin (antibody) falls out.

J* for label

J adrandye

egg albumine + a as antigen

bovine albumine + a ~~as~~

~~xx~~ + J* as reagent

precipitate with Ammon sulfate

control: non antibody ~~bovine~~ albumine + iodine labeled + a egg albumine precipitated

STATE OF NEW YORK

ROSWELL PARK MEMORIAL INSTITUTE

BUFFALO 3, N. Y.

August 31, 1956

Dr. Leo Szilard
c/o Mrs. N. Mann
The Enrico Fermi Institute for Nuclear Studies
The University of Chicago
Chicago, Illinois

Dear Leo:

Thanks for your letter of August 29. I just received it and have not been able to go through it very carefully.

I am on my way to a U.S.Public Health Service Study Section meeting in San Francisco and shall be gone for over a week.

When I return, I shall give your letter serious thought and write you accordingly.

With kindest regards, I am,

Very sincerely yours,

David

David Pressman, Ph.D.
Director of Cancer Research
in Biochemistry

DP:DZ

STATE OF NEW YORK

ROSWELL PARK MEMORIAL INSTITUTE

BUFFALO 3, N. Y.

September 14, 1956

Dr. Leo Szilard
c/o Mrs. N. Mann
The Enrico Fermi Institute for Nuclear Studies
The University of Chicago
Chicago, Illinois

Dear Leo:

I have just returned from San Francisco and I'm getting ready to go off to the American Chemical Society meetings in Atlantic City this next week. Then I hope to get down to work.

I agree that the experiment which you have outlined does have value. However, there is still a great deal which we do not know about the preparation of antibody against haptenic substances; for example, we have normally been injecting each rabbit many times before getting sera which had enough anti-hapten antibody to be useful. We have never injected a rabbit only once with a coupled antigen, waited some time and then given it a second injection, which is the way the experiment should be carried out.

I talked the experiment over with Dr. Nisonoff of this laboratory, and I think the best thing for us to do would be to inject several rabbits with a coupled protein; wait a matter of four weeks, and then inject a second time in order to see if we do get decent antibody formation with a second injection of the homologous antigen. If we get good results with this, then we would be in a position to pursue the problem further.

Although it would be nice to carry on the problem in two laboratories as you have suggested, I think, in view of the probable hindrances to the work due to unknown factors, it would be much simpler not to be involved with another laboratory. If you feel that you would like to pursue this more vigorously right from the beginning, by all means, feel free to do so.

I do hope that you will see fit to drop in and visit us at Roswell Park, and shall look forward to seeing you.

In connection with the specificity of the secondary response, I would like to call to your attention a paper entitled, "The Specificity of the Secondary Response to Protein Antigens" by Frank Dixon and Paul Maurer, appearing in the Journal of Immunology, 64, 418 (1955).

Very sincerely yours,

David Pressman

David Pressman, Ph.D.
Director of Cancer Research
in Biochemistry

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