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DAY LETTER

[sent by phone 5/15/52]

Mr. Alan Garen
Perkins Hall #62
Harvard University
Cambridge, Mass. – phone Eliot 4-9537

Institute in the position to guarantee you $4,000 for one year starting October first in case your efforts to obtain fellowship should fail. Because it is not likely that this offer could be renewed for another year and because of the general situation here, we two believe that from an objective point of view Cold Spring Harbor would be a better place for you for the coming year. Should you decide to accept our offer, we would of course be personally happy to have y here. Letter confirming Institute's offer is beir mailed to you.

Aaron Novick & Leo Szilard

Perkins Hall 62
Harvard Univ.
Cambridge, Mass.
May 15, 1952

Dear Dr. Szilard:

I have been thinking over the talks we had in Chicago about my plans for the fall, and I have now decided that at this time Cold Spring Harbor would probably be the best place for me to work. The major reason for this decision is that I would like to continue concentrating on phage problems for a little while, and as you indicated to me phage will not be a prime concern in your laboratory. I have many regrets about not coming to Chicago (assuming that it could have been arranged) since I like the unusually stimulating and pleasant atmosphere of the laboratory. I hope it may still be possible to work with you sometime in the future.

I am very grateful that you arranged for my trip to Chicago and were able to spend so much time discussing this question of a job with me. My entire stay in Chicago was extremely enjoyable and I want to thank you again for making all of it possible.

I plan to pass through Chicago en route to Denver about June 8 and I hope to be able to see you again at that time.

Best regards,

Alan Garen

Alan Garen

5650 Ellis Avenue

May 22, 1952

Mr. Alan Garen
Perkins Hall #62
Harvard University
Cambridge, Massachusetts

Dear Garen:

Your letter of May 15th crossed our telegram which you will have received in the meantime as well as Harrison Davies' letter to which our telegram referred.

While I regret your decision, I also have to say that I would have made the same decision if I had been in your place, particularly if I had wanted to work on phage.

After a while it should become clearer in what field of work our laboratory in Chicago is going to settle down, and then the place might have more attraction for you and others in similar position.

With kind regards,

Sincerely,

Leo Szilard

LS/sds

5650 Ellis Avenue

April 3, 1952

Mr. Alan Garen
Perkins Hall #62
Harvard University
Cambridge, Massachusetts

Dear Garen:

I discussed your letter with Novick and Harrison Davies, who is Acting Director of the Institute. Everybody here would be very happy if you came here, but the Institute has at present no funds. It is possible that the sum of $2,500, which is now earmarked for another purpose, will become free either within two weeks or by the end of July, and this is the only fund which could be used to supplement other sources of income which you might have. Why not find out for sure whether or not you are eligible for a post-doctoral fellowship with the U.S. Public Health Service and if not, apply for a predoctoral fellowship and hope to get it supplemented from somewhere? I understand the situation for postdoctoral Public Health Service fellowships is quite favorable.

Whether Chicago is a good place for you to come at this time I do not know. Novick has applied for a fellowship, and if he gets it he will leave in March (a year from now) and will be away

for a year. My own plans have not yet crystallized. Fox I expect will be here, and the Institute is also trying to get Zinder, but whether or not it will succeed I do not know.

I am sorry I cannot give you a more encouraging picture and that it took so long to get this much clarified.

Sincerely yours,

Leo Szilard

LS/sds

cc: Harrison Davies

April 8, 1952

Dear Dr. Szilard:

I was happy to hear that it would be possible for me to come to the Institute this year. Despite the discouraging aspects of your letter I still feel that the Institute should be a valuable place for a period of research.

I will apply this month for two post-doctoral fellowships, from the Public Health Service and the Damon Runyon Fund for Cancer Research. I am enclosing a statement about the Runyon fellowship program since you may not be familiar with it. I gather from your letter that it is all right for me to list your laboratory as the place where the research is to carried out. I will send you a copy of the proposed research program which I must submit with the applications so that you can make any necessary revisions.

Best regards,

Alan

Alan Garen

Perkins Hall #62
Harvard Univ.
Cambridge, Mass.
April 10, 1952

Dear Dr. Szilard:

The next two deadlines for Public Health Service fellowships are May 1 and August 1. Since applications which are filed in August will be acted on by September 15 I think it would be adviseable for me to postpone applying until then. My chances for obtaining a fellowship may be better at that time as I will have completed my degree requirements and published another paper.

In the meantime I want to apply for the Runyon fellowship. I know nothing about these fellowships except what is contained in the circular I sent you, but if taken at face value they sound good. In order for me to complete the application it is necessary that you furnish the material requested in parts 2 and 3 of the instruction sheet which I have enclosed. Please return the page of the application to me so that I can submit it with the remaining pages.

There is a question on the Runyon application which asks for a description and title of the proposed research program. I would like to have your advice on this point. My idea was to participate in your studies on bacterial mutations and possibly also include mutations in phage.

Sincerely,

Alan

Alan Garen

5650 Ellis Avenue

April 18, 1952

Mr. Alan Garen
Perkins Hall #62
Harvard University
Cambridge, Massachusetts

Dear Garen:

I have studied your document relating to the Damon Runyon Memorial Fund and also the fellowship application form, and I find it difficult to answer the question concerning "the pertinence of the work you wish to do to cancer". It is quite true that the Committee on Growth has given grants for work of the kind in which you are interested, but I have no reason to believe that this holds for the Damon Runyon Memorial Fund. So unless you can get information to the contrary from this fund, I believe it would be unwise to apply for this fellowship on the basis of wanting to come to our laboratory and do the kind of work we are doing at present.

Concerning the U.S. Public Health fellowship, I wonder whether it wouldn't be wise for you to apply for a predoctoral fellowship now in the hope that some supplementary funds can be found for you. In this respect the chances in Chicago are somewhat better than when I last wrote you. As far as Chicago is concerned, I believe the fastest way for you to get anywhere would be for you to come here and give a talk in our Institute. If you want to do this, Harrison Davies, the Acting Director of our Institute, will send you an official invitation and state that you will be reimbursed for your travelling expenses from Boston and return. You could come sometime after May 7th, and you should probably come as soon as possible after that date.

If you want to apply for a predoctoral U.S. Public Health fellowship now, your deadline is May 1st and you would have to move quite fast. If you get the fellowship and if Chicago cannot supplement it, you could, of course, refuse to take it and apply for a postdoctoral fellowship by August 1st.

It seems now certain that Novick will be away from Chicago for a year beginning March of next year. I am returning to you enclosed all the material which you sent me since I won't be doing anything with it anyway until I hear from you.

If you decide to apply for a predoctoral U.S. Public Health fellowship by May 1st and if you want me to write a letter as sponsor, you will have to furnish me with all the information that I might want to include. This you had better address to our secretary, Mrs. Shirley D. Sykes, so that if I am out of town, as I might be for a week between now and May 1st, she can contact me.

Concerning your visit to Chicago, you had also better write to Shirley Sykes, who will then take it up with Dr. Harrison Davies and set the final date.

With best wishes,

Sincerely yours,

Leo Szilard

LS/sds
Enclosures
cc: Harrison Davies

Perkins Hall #62
Harvard Univ.
Cambridge, Mass.
April 21, 1952

Dear Dr. Szilard:

You are probably correct in feeling that the Runyon fellowship would not apply to me. I was thinking in terms of the broad policy which is used for American Cancer Society grants, but the Runyon committee may be more clinically oriented. I will write for more specific information about their program and in the meantime not bother with that application any further.

I would like to go ahead and apply for a Public Health predoctoral fellowship as you suggest, but I wonder whether I am eligible for one. My impression is that on the predoctoral level the fellowship is intended to cover work done towards a degree. However, by the time I hope to come to Chicago all of my requirements for a degree, including the thesis, should be completed, so that I can not state that the research program to be carried out in your laboratory is a part of my degree plan. In fact one of the questions on the Public Health application asks what degree is being sought from the institution where the fellowship will be granted, and I am at a loss to answer it.

Unfortunately there is very little time left before the May 1st deadline, but if you still feel that I should apply for the Public Health fellowship despite this difficulty I mentioned, please let me know immediately, as I believe that the deadline can be met. As a sponsor, you are asked to furnish the following statements:

a) that satisfactory arrangements have been made with you and that the institution will provide the necessary facilities if a fellowship is awarded.

b) an evaluation of my general background, research ability, and research promise.

If you require any information from me for part b) I will of course be glad to furnish it.

As for giving a talk at the Institute, I would like to very much although I have some misgivings whether the talk would justify the expenditure. My subject would primarily cover the equilibrium studies on Ti adsorption which I discussed with you last summer in Denver plus a few new ideas, and I don't know how familiar the people at the Institute are with this data. However if Dr. Davies and you feel that this material is of sufficient interest, I could come to Chicago on almost any date you suggest, although a Friday or a Monday would be most convenient for me.

With best regards,

Alan

Alan Garen

April 21, 1952

Mrs. Shirley Sykes
Institute for Radiobiology and Biophysics
University of Chicago
Chicago, Illinois

Dear Mrs. Sykes:

I am addressing my letter for Dr. Szilard to you as he suggested, since there was the possibility that he might be out of town this week. I hope Dr. Szilard will be able to answer my question about the Public Health fellowship as soon as possible. The deadline for applying is only a few days off and I can not submit the application until I hear from him.

I am alsosupposed to contact you about giving a talk at the Institute. Well, as I wrote to Dr. Szilard in the enclosed letter, I should like very much to do so. My subject would cover some equilibrium and kinetic studies on bacteriophage adsorption and their significance for the mechanism of adsorption. I could come to Chicago at almost any time, but I would prefer to make it on a Friday or a Monday if that can be arranged.

Sincerely,

Alan Garen

Alan Garen

April 25, 1952

Mr. Alan Garen
Perkins Hall #62
Harvard University
Cambridge, Massachusetts

Dear Garen:

In view of what you write me about the predoctoral Public Health fellowship, I am inclined to drop my suggestion and fall back on your idea of your applying in August for a postdoctoral fellowship, either for Chicago or for some other suitable place.

I talked to Puck about the Runyon fellowships and he tells me they are no less liberal in interpreting the meaning of the term, cancer research, than the Committee on Growth. In these circumstances, I see no objection to your filing an application with them on the basis of the kind of work which you might want to do in Chicago. Just what that work should be we could perhaps discuss when you come here.

The best dates for your talk appear to be either Monday, May 5th, at 3:30 pm, or Monday, June 2nd, at 3:30 pm. The earlier date would be pref erable if you can make it. You may consider this as an official invitation with your traveling expenses paid from Chicago to Boston and return. You will have a small ad hoc selected audience mixed of chemists and biologists, and it is not necessary for you to say anything new but rather to present the basic ideas and results of the work which you did with Puck on phage absorption.

With best wishes,

Sincerely,

Leo Szilard

LS/sds

cc: T.N.D.

1/9

April 27, 1952

Dear Dr. Szilard:

Thanks for the invitation to speak at the Institute. I can make it at the earlier date on Monday, May 5th, and I probably will arrive in Chicago on Sunday. If I am not able to contact you on Sunday I will be at the Institute early Monday morning.

I am enclosing a copy of the discussion from the paper I am now completing. I would like you, Novick, and Fox to look it over if you have time so that I can discuss it with you before the talk Monday. It is not in a finished form and there are several new ideas which may require some revision. In addition certain conclusions from the first two papers in this series have been drastically changed. However I feel that the overall picture of the adsorption reaction which is developed in this discussion is both plausible and consistent, and I plan to have the talk revolve around it.

Best regards,

Alan

Alan Garen

Discussion:

It is now possible to analyze the reversible attachment reaction between T1 bacteriophage and E. Coli host cells in the light of a variety of data. Experiments of both a kinetic and equilibrium nature have revealed these facts about the reaction:

a. The influence of ionic strength:

As shown in figures 2 and 3, both the equilibrium constant and the forward and reverse reaction rates are extremely sensitive to ionic strength. At low ionic strengths the equilibrium lies far towards dissociation, but when the ionic strength is raised to a value of $\mu = .001$ the equilibrium shifts drastically in favor of the associated state. The rate of association, k1, exhibits a similar trend, changing from an immeasureably slow rate at low ionic strengths to a value which is close to the theoretical collision frequency at $\mu = .004$. Conversely, the rate of dissociation, k2, decreases in this region. At still higher ionic strengths the situation is reversed; the equilibrium constant and k1 fall rapidly while k2 increases.

b. The influence of temperature:

There is essentially no temperature-dependence of either the equilibrium constant or the reaction rates in a medium where $\mu = .004$, indicating that both the heat of reaction and the activation energy are negligible. The calculated entropy change however has a large positive value.

All of these facts can be integrated into the following reaction scheme:

In a medium of low ionic strength the virus and cell each carry an excess surface charge of like sign which sets up an

electrostatic barrier to their interaction. This barrier is sufficiently high so that there is no measureable rate of interaction at low ionic strengths, and the system exists almost entirely in the dissociated state. As the ionic strength is increased a diffuse layer of oppositely-charged ions surrounds the reactants and eventually neutralizes their excess surface charge. Consequently the electrostatic barrier is eliminated and collisions between viruses and cells can occur readily, limited only by the diffusion velocity of the virus.

The overall energy barrier or activation energy existing at a given ionic strength may be resolved into two components; an electrostatic term Ee for the repulsive effect of like surface charge, and a chemical term Ec for the intersurface bonds which form on association. The rate of association is then described by a modified Arrhenius equation:

$k1 = Z\, e^{-(Ee + Ec)/RT}$, where Z is the theoretical collision frequency.

It is known from temperature-dependence studies on k1 that at an ionic strength $\mu = .004$ both Ee and Ec are essentially zero. It seems reasonable to assume that Ec is also zero at lower ionic strengths since the same association bonds should be involved, and thus to attribute the energy barrier in this region entirely to the electrostatic term Ee. On this assumption a minimum value of Ee at $\mu = 0$ can be calculated as follows:

$$k1_{(37^\circ C,\, \mu=0)} \leq 3 \times 10^{-12} \text{ cc}^3 \text{ mm.}^{-1}$$

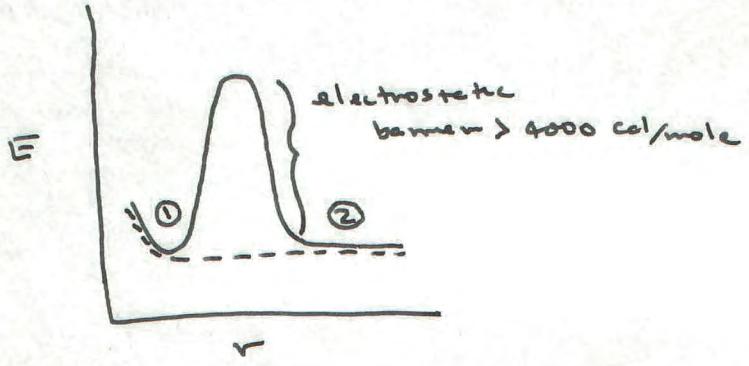
$$k1_{(37^\circ C,\, \mu=.004)} = 3 \times 10^{-9} \text{ cc}^3 \text{ mm.}^{-1}$$

$$k1_{(\mu=0)} / k1_{(\mu=.004)} = e^{-Ee(\mu=0)/RT}$$

$$Ee_{(\mu=0)} \geq 4000 \text{ cal./mole or } 10^{-20} \text{ cal./particle}$$

This result shows that under conditions of zero ionic strength and a temperature of 37°C only those viruses which possess kinetic energy in excess of at least 10^{-20} calories are able to penetrate the electrostatic barrier and reach the cell surface. The probability of doing so is less than one in a thousand.

The fact that there is no significant heat of reaction indicates that the energy of the system when the reactants are in the dissociated state is close to the energy of the associated state. In figure 4 the energy of the system is sketched qualitatively as a function of the distance of separation of the reacting virus and cell, in accordance with the reaction scheme outlined so far.



Solid curve for $n = 0$
dashed curve for $n = .004$
① ≡ associated state
② ≡ dissociated state

The question now arises why T1, bacteriophage can succeed in reversibly attaching to host cells to such an extent that equilibrium may lie far in the direction of association. Since nothing is gained energetically from association, the explanation must rest entirely with the entropy factor. Equilibrium measurements have yielded the unusually high value of +60 entropy units for the standard entropy change of the attchment reaction. If the reaction consisted simply of an association of a virus with a cell, the number of degree of freedom of the system would decrease, causing the entropy change to be negative instead of positive. However if the reaction also involved solvated water molecules which were released into the medium when the virus and cell surfaces united, this could account for the observed entropy change. Similar results on the binding of organic anions to bovine serum albumin were interpreted in this manner by Klotz and Urquhart ( ). An alternative explanation whereby the degrees of freedom of the virus would increase when it is attached to the cell seems unlikely, since the virus comes off the cell

in an unaltered state and this would preclude any serious rearrangement of its configuration during attachment. Equation 1 for the reversible attachment reaction can now be generalized to include the postulated dehydration effect:

(6) $V(H_2O)x + B(H_2O)y \underset{k_2}{\overset{k_1}{\rightleftharpoons}} V \cdot B(H_2O)z \quad nH_2O$

where $n = x+y-z$

The high value of the entropy change shows that n is large, and since n is a measure of the number of reacting sites, multi-bond formation is indicated by this reaction mechanism.

Some recent experiments provide important information about the chemistry of the attachment reaction. Hershey and Chase, using radioactive T2 bacteriophage, have demonstrated that the surface of this virus consists almost exclusively of a protein membrane which is responsible for attachment( ), and it seems likely that this finding also applies to T1. Furthermore Weidel succeeded in isolating the cell wall of E. Coli B to which bacteriophage attach and in showing that it is a complex phospholipoprotein material( ). Thus protein groups certainly from the virus and probably also from the cell, must be involved in the attachment reaction.

If equation 6 is correct, then the entrance of water molecules into the reaction throws still more light on the chemical nature of the attachment bonds. Pauling has shown that the total number of water molecules bound to a protein corresponds closely to the number of positive and negative ionic groups, indicating that water is bound at these ionic sites. It is also to be expected on theoretical grounds that water dipoles would react primarily with ionic groups, since ion-dipole forces are stronger than other forces which might cause hydration. Therefore in order to dislodge sovated water molecules from the virus and cell surfaces as suggested by equation 6 , ionic groups would have to participate in the intersurface bonds that are formed. This conclusion is consistent with the high collision efficiency of the attachment reaction, which is a characteristic property of simple ionic association reactions.

The preceding line of reasoning has now arrived at a picture of the reversible attachment reaction in which the reacting sites are identified as ionic groups, probably carboxyl and amino to a large extent, from the surface protein material of the virus and cell. It should be possible to subject this proposed reaction mechanism to a direct and simple test, by utilizing the techniques which have been developed for chemically modifying proteins ( ). In this manner carboxyl or amino groups may be specifically covered up with non-ionic reagents, and the theory predicts that if this is done to the virus or cell reversible attachment will be drastically repressed.

The beautiful electron micrographs of bacteriophage attached to their host cells which Anderson recently obtained ( ) show that T1, like other members of the T system possessing tail-like structures, attaches in the tail-first position only. This result at first appears incompatible with the high collision efficiency of the reaction. If only the single tail-first configuration can lead to attachment, then only the small fraction of random virus-cell collisions which occur in this fashion should contibute to the rate of reaction., and the collision efficiency should be correspondingly low. However under the preparative techniques used in electron microscopy all of the viruses appearing in the picture are attached <u>irreversibly</u>. Therefore the tail-first configuration may only relate to the irreversible reaction and have nothing to do with the reversible reaction preceding it. Probably reversible attachment occurs after any random collision, and during the virus's 30 second reversible sojurn on the cell surface its position changes continually as a result of thermal oscillations. At some instant before its 30 seconds are up, the virus finds itself in a tail-first position and procedes to the irreversible step before leaving the cell surface.

It is of interest in this connection to calculate a lower limit for the rate of the irreversible step, k3. The calculation depends on the fact that the rate of reversible attachment equals the rate of irreversible attachment within the limits of accuracy of the measuring techniques. As a first approximation it is apparent that k3 is greater than k2, but a more quantitative comparisom is desired. The equation for this calculation is derived in an appendix to this paper, and the result shows that k3 is more than twenty times as rapid as k2 at an ionic strength of $\mu = .004$. Thus less then 0.3 seconds is required for a reversibly bound virus to react irreversibly. However k3 may be a composite of two separate rates; first the rate at which the virus can move into the proper tail-first position, and second the rate of the irreversible chemical reaction. Either factor could be rate-limiting for k3.

Finally the behaviour of the reversible reaction rates at high ionic strengths remains to be accounted for. In this region k1 decreases rapidly and k2 simultaneously increases. This effect can not be attributed to the diffuse ionic atmosphere surrounding the reactants, which only neutralizes their excess surface charge. Certain data from a previous paper pertain directly to this point( ). It was shown that when Tl attaches to a glass surface instead of a bacterial surface, the efficiency of the reaction also increases at first with increasing ionic strength, but after reaching a maximum the attachment levels off and does not decrease at high ionic strengths as it does when bacteria are used. The difference in behaviour at high ionic strength must be caused by a specific reaction between the ions in the medium and the cell surface. The ions apparently can attach to the same ionic sites on the cell as are used

by the virus, but only after the ionic concentration becomes sufficiently great do the ions begin to compete successfully with the virus for these sites. Either ions or virus can be bound to cell sites, but are mutually exclusive. Such competition would explain both the observed increase in k1 and decrease in k2 at high ionic strengths.

PURDUE UNIVERSITY
BIOPHYSICAL LABORATORY
LAFAYETTE, INDIANA

Nov 21, 1955

Dear Szilard,

I have been thinking about your suggested experiment and have also checked that there is an adequate supply of nucleosides in the laboratory. But I am afraid that I will not be able to do the necessary preliminary experiments for at least the next three weeks. I am now swamped in finishing K12 experiments that were left over from Cold Spring Harbor days and may soon be antiquated by Jacob's work (he is a frighteningly efficient competitor), and also in setting up new experiments on protein synthesis in infected cells which is supposed to be the reason I am at Purdue.

Nevertheless I hope you proposed visit was not strictly contingent on being able to run that experiment. Benzer and I would be happy to see you at any time. As you know my apartment is at your disposal. All I require is a day's warning to make some effort at cleaning.

with best regards,

Alan Garen

June 7th. 1960.

Dr. Alen Garen,
Department of Biology,
Massachusetts Institute of Technology,
Cambridge, Mass.

Dear Garen,

I have sent the attached letter and memorandum to Alex Rich. Would you pass it on to Cy also.

If you get to New York again call me over the telephone and if you know what position you will accept, write me a postcard.

With kindest regards,

Sincerely,

Leo Szilard.

Enclosures:

Perkins Hall #62
Harvard Univ.
Cambridge, Mass.

Dear Dr. Szilard,

I left directly from Calumet City on Saturday to catch a plane for Boston and did not have a chance to say goodbye to you, Aaron, and Maurie. Thanks again for helping to make the two days I spent in Chicago so enjoyable and stimulating.

As you know I am now trying to decide on a place to work starting this fall. So far there are two tentative possibilities - with Hershey and Visconti at C.S.H. and with Luria at Urbana. I am also very interested in the program at your laboratory and I would like to know what opportunity exists, if any, for joining your group. I intend to apply for fellowships from the American Cancer Society and Public Health Service, but since my degree will not be granted officially until June, 1953 I may not be able to obtain a fellowship for the fall of this year, and in that case I would need financing from some other source.

My best regards to Aaron, Janie, Maurie, and Sophie.

Sincerely,

Alan

Alan Garen

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Nutla neo synthaphyllin? 65/16

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