1155 East 57th Street
Chicago 37, Illinois
July 13, 1949

Dr. A. Novick
Hopkins Marine Station
Pacific Grove, California

Dear Novick,

Thanks for your letter. Enclosed is the present version of our paper. I made changes following suggestions received from Konrad Bloch and Westheimer.

I am making a few control experiments with Lee at the moment but expect to leave Chicago Friday noon. You can reach me at Stead's Ranch, Estes Park, Colorado.

If you think the paper should now go to Muller for submission to the Proceedings, write me to Estes Park and I will immediately send it from there to Muller. Also let me know if any changes in phrasing are deemed necessary, and state which of the changes are important enough to warrant a delay in case I should have difficulty in getting the changes typed at Estes Park.

I have asked Cross to send you the slides. If you do not get them in time you had better shout about it.

Hope that you have a grand time.

Yours,

Leo Szilard

m
Encl.

THE UNIVERSITY OF CHICAGO
CHICAGO 37 · ILLINOIS
INSTITUTE OF RADIOBIOLOGY AND BIOPHYSICS

Aug 8, 1949

Dear Szilard,

The Cal Tech situation seems difficult. I had hoped to leave for Chicago before then. I have reservations for the 4th of Sept. If Delbruck's baby should be late, no telling how late it will be before we can visit. I would suggest that we go to Cal Tech as soon as convenient for you. It would be a shame, though, to miss Delbruck.

Luria was here a few days ago for one day. He is dictating his book to Mani Delbruck. He had no more information about when the baby might come then we do. Apparently Delbruck will be away for 2 weeks starting with the birth of the baby.

I would prefer to keep my reservation for Chicago as I am eager to get back.

Regarding Delbruck and T2(4) I certainly approve of leaving it in his hands. Tell him we would like all of our experiments to be taken up by such noble hands.

Muller's letter sounded very disturbing. Does he need more than glance at the paper? I feel that something is bothering him. I looked into the Journal

situation here. Apparently we would be disowned if we published in Jour Soc Exptl Biol & Med. It is despised here. People suggested Jour of Bacteriology, Jour of General Physiology, Jour of Gen Microbiology, and Jour of ~~Comp~~ Cell and Comp Physiology. Also Science. I looked at the latest issues of all. The fastest is the Proceedings of Nat Acad Sci which is 2 months on the average. The others are about 4 months behind except for Jour Gen Microbiol which is 6 to 9 months and is also English. I couldn't tell about Science. So even if Muller takes a month this is still the fastest. Could we ask Delbruck, who I hear is a member of Nat Acad, to submit it or is this not politic?

I gave a seminar on the subject last week and it was well received. Bernie Davis liked it very much. He had a few ideas as to what we should do next. I haven't talked to van Niel about it yet as he seems so busy and tired that I feel like a criminal at the thought of disturbing him.

I got a letter from Howard Ted today. He has been getting some interesting results on B/1, t + low conc of trypsin with and without gelatine. I do not completely understand the results yet. After a few days I'll write again when I am not in such a rush to get the letter off to you.

The real estate office wired us that it has an apartment for us in Chicago at half our present rent and in an identical building one block down.

Best regards
Aaron

P.S. These people have'nt a phone yet. Our home address is 307 Pacific St., Monterey, Calif. Any messages can also reach me thru the lab as Bernie Davis will take them to me. I plan to go to San Francisco Friday the 12th and come back here Monday the 14th. On Tuesday, in S.F. I can be reached care of Jake's mother, Emma Chalkley at the Fairmount Hotel.

The Stanley

MEMORANDUM

To Dr. Szelard Date August 25, 1949

I have obtained at reservation for Dr. and Mrs. Novick at the Ambassador Hotel, Denver, Colo. for September 5. The room has a tub bath and rents for $4.50 per day. The Ambassador has agreed to hold the room for them until 9:00 P.M.

If the Novick's plans should be changed, please notify the Ambassador.

Signed Henry M. Lynch

DOMESTIC SERVICE
Check the class of service desired; otherwise this message will be sent as a full rate telegram

FULL RATE TELEGRAM		SERIAL	
DAY LETTER		NIGHT LETTER	X

WESTERN UNION

1206

W. P. MARSHALL, PRESIDENT

INTERNATIONAL SERVICE
Check the class of service desired; otherwise this message will be sent at the full rate

FULL RATE		LETTER TELEGRAM	
VICTORY LETTER		SHIP RADIOGRAM	

NO. WDS.-CL. OF SVC.	PD. OR COLL.	CASH NO.	CHARGE TO THE ACCOUNT OF	TIME FILED
18 N.L.	Pd.			

Send the following message, subject to the terms on back hereof, which are hereby agreed to

NIGHT LETTER

DOUGHERTY CHEMICALS
86-28 131st STREET
RICHMOND HILL 18, N.Y., N.Y.

PLEASE QUOTE PRICE OF 3-METHYL URACIL. REPLY AIR MAIL, INSTITUTE OF RADIOBIOLOGY AND BIOPHYSICS, UNIVERSITY OF CHICAGO.

AARON NOVICK

Institute of Radiobiology and Biophysics
The University of Chicago
July 2, 1951

5650 Ellis Avenue

November 19, 1951

Dr. Katherine Brehme Warren
The Biological Laboratory
Long Island Biological Association
Cold Spring Harbor, L.I., New York

Dear Dr. Warren:

We wondered if it were possible to add a few lines to our manuscript in proof, to read as follows:

"The authors wish to express their gratitude to Dr. George H. Hitchings of the Wellcome Research Laboratories, who very kindly put at their disposal many of the purine and pyrimidine derivatives used in these experiments. The authors gratefully acknowledge the support of this work by a grant from the National Institutes of Health of the United States Public Health Service."

Hope this is not too much inconvenience.

With best regards,

Sincerely yours,

Aaron Novick

AN/sds

cc: Dr. Szilard

DR. SZILARD

1 gram DL Citrulline

Nutritional Biochemicals Corp.
ATTN: Mr. Mann
21010 Miles Ave,
Cleveland 28, Ohio

INCLUDE IN WIRE: Confirming Purchase Order #11705 being sent by Miss Zeuch of U. of C. Purchasing Department.

65
10
75¢

X
35 words

Pd.

NUTRITIONAL BIOCHEMICALS CORP. NIGHT LETTER
ATTENTION: MR. MANN
21010 MILES AVENUE
CLEVELAND 28, OHIO

KINDLY SEND ONE GRAM OF DL CITRULLINE AIRMAIL TO INSTITUTE OF RADIOBIOLOGY AND BIOPHYSICS ATTENTION DR. NOVICK, UNIVERSITY OF CHICAGO. CONFIRMING PURCHASE ORDER 11705 BEING SENT BY MISS ZEUCH OF UNIVERSITY OF CHICAGO PURCHASING DEPARTMENT.

AARON NOVICK

Institute of Radiobiology & Biophysics
5650 Ellis Avenue
January 11, 1952

cc: Sophie Lender

MEMORIAL CENTER

FOR CANCER AND ALLIED DISEASES

444 East 68th Street, New York 21, N. Y.

Memorial Hospital • James Ewing Hospital, department of hospitals, city of new york • Strang Cancer Prevention Clinic
Sloan-Kettering Institute for Cancer Research • Sloan-Kettering Division, cornell university medical college

February 25, 1953

Mr. Aaron Novick
Institute of Radiobiology and Biophysics
University of Chicago
808 South Wood Street
Chicago, Illinois

Dear Mr. Novick:

I would appreciate very much your sending me reprints of the following articles:

"Experiments with the Chemostat on Spontaneous Mutations of Bacteria", Proc. of the Nat. Academy of Sciences, 36, No.12, pp 708-719, December, 1950.

"Description of the Chemostat", Science, 112, No.2929, pp 715-716, December 15, 1950.

"Genetic Mechanisms in Bacteria and Bacterial Viruses I. Experiments on Spontaneous and Chemically Induced Mutations of Bacteria Growing in the Chemostat", Cold Spring Harbor Symposia on Quant. Biol., XVI, 1951.

Thank you.

Sincerely yours,

John S. Laughlin

John S. Laughlin
Department of Physics

Also send Nature paper

JSL:mh

3.3.53

Chicago, March 6, 1953

Dr. Patrick H. Hume
Wilkinson, Huxley, Byron and Hume
First National Bank Building
Chicago 3, Illinois

Dear Dr. Hume,

Dr. Leo Szilard has been out of town for some time and has asked me now to reply to your letter of December 8, 1952.

I enclose a photostat of our application. We will not be able to take any further action, pending a decision on the part of the ONR as to whether they consider this patent Government property.

Sincerely yours,

Enclosure

Aaron Novick

AN/llt

February 2, 1954

Dr. Aaron Novick
Institut Pasteur
Paris, France

Dear Novick:

I Assumed you got one letter from me which I wrote in response to yours. I should have thought that by now the appointment of Evans as head of the joint departments of Biochemistry and Biophysics would have been made official. However, I talked with Goffron yesterday over the telephone in order to check and it seems that the situation is confused. According to rumor, Zirkle and Bloom do not like the idea of a joint department and that they would prefer an independent department of Biophysics with Zirkle as head. According to rumor, Zirkle has an offer from somewhere which strengthens his bargaining position and Evans had a conversation with him which was not satisfactory to Evans. In the meantime, both Westheimer and Bloch have received and accepted an offer from Harvard. I thought you should know all this so that in case you have to decide between returning to Chicago and accepting someother position, you should be aware of the situation at Chicago as it looks at present.

I expect to see Monod while he is over here and he will probably have news from you but you might drop me a line just the same when an occasion arrises.

Yours,

Leo Szilard

LS:sj

Institut Pasteur
28, RUE DU Dr ROUX - PARIS XV
TÉL. SÉGUR 01-10

Gaffron
Ky 37797

PARIS, le 8 February, 1954

Dear Szilard,

I was very depressed to learn from your letter that Bloch and Westheimer were leaving Chicago. This is too large a fraction of the good people to lose at once.

And the news about the administrative problems in Chicago were no more cheering. To set up a separate department with Zirkle as head would be going back to 1945 and the old Institute. Is there anything we can do to influence the University in this decision? One only has to compare the Biochemistry department with the Institute to make things very clear. I should think Coggeshall would be happy that Zirkle has another offer. This provides a very polite way of ending this business. As you knew and can judge from these disconnected remarks, I am very unhappy about the turn of events. I trust Gaffron feels the same way.

Your first letter was very cheering as you urged me to spend my time talking and thinking rather than trying to turn out a publication. Cheering because I was beginning to feel a little guilty about my activities. Lwoff even teased me a little about always making theories on the drop of a hat. But he is really very understanding and I think approves of the way I have been spending my time. I have become a general consultant here on experiments in progress, manuscripts, and Monod's lectures. Jacob is the best by far of the young French workers. He did not make much of an impression at Cold Spring Harbor, but I find him very good. Last week he did an experiment which I think you will find amusing. He induces mutations to virulence in lambda phage (K-12) by growing them in irradiated bacteria (UV). If he incubates the bacteria in broth prior to infection, the rate of mutation rises to a maximum at 20 minutes and then falls off rapidly. I am sure that the photoreactivability will fall off rapidly after 20 min. We think that this is when mutations occur in irradiated bacteria also.

I gave two seminars here, one on mutations and one on our regulation experiments. Both went well but I was particularly pleased with the good response the regulation experiments received.

From here the U.S. seems an unhappy place. The political events of the last few months in the U.S. frighten everyone here. By the way Spanel's advertisement received very much favorable publicity in France. In fact it was so widely quoted that one busines used it as the basis for its own ad. I enclose a copy.

Nick Visconti has been in Paris a few times and we have talked about all kinds of things that he might do. He wants to leave phage and is thinking about Economics. I urged him to call you

Institut Pasteur
28, RUE DU Dr ROUX - PARIS XVe
TÉL. SÉGUR 01-10

PARIS, le

while he is in the States (after March 1). He has arranged a trip to Italy for me with expenses paid to visit a large pharmaceutical company owned by a friend of his in Milan. I will go some time after Easter when Visconti has returned. It sounds like a very interesting company. Nick introduced me to the owner when he was in Paris a few weeks ago. I think if one ever has a bold idea this is the kind of company to do business with. The owner has plenty of money and he seems to be seeking something interesting to do.

Maaloe and Westergaard have arranged also to have part of my expenses paid to Copenhagen with a lecture.

We have been hearing regularly from the Felds in Rome. They have been having much trouble with their daughter having diahhorea, apparently due to an inability to digest starch.

Our baby is thriving and I have been very well though Jane has not been. But all the wives here seem to be ill. I really love the feel of being in Europe, and am already unhappy about the thought of returning. People here constantly ask me why we stay in Chicago. Both Monod and Lwoff have offered to look around for places for me in the States. When you talk with Monod you might discuss this with him. He is staying with the Pappenheimers.

Many thanks again for the news even if it was so sad, and I look forward to your next letter.

Aaron

Aaron Novick

February 24, 1954

Dr. Aaron Novick
Institut Pasteur
Paris, France

Dear Novick:

I heard the other day from Nickerson in Princeton and indirectly (through Bernie) from Waksmann that you may expect shortly to have an offer from him. Yesterday I ran into Heidelberger who told me that he is considering to retire to the Waksmann Institute at the end of the next school year (one year before he is due for retirement at Columbia). He was just about to go down to New Brunswick to look the place over. Enclosed you will find a copy of a letter which I received from Moon.

I heard all of Monet's talks at Columbia except one and if time permits, I shall send you a memorandum on one aspect which relates to protein synthesis.

I hope you continue to have a nice time.

Sincerely,

Leo Szilard

LS:sj

Enc.

March 29, 1954

Dr. Aaron Novick
c/o Lwoff
Institut Pasteur
Paris, 15, France

Dear Novick:

I just received your letter of March 11th on my return to New York. I immediately called Bernie Davis in the hope that he might know what chances you would have in New Brunswick if you held out for tenure. Bernie has left for Paris and I assume you will take up the whole issue with him at once.

Just how important tenure is, in this instance, I do not know. Nickerson spoke very highly of you when I saw him in Princeton and after all they will have to keep somebody working in that huge place.

When would the six years which Chicago sets as a limit for assistant professors be up for you? If this is very soon then they could not very well expect you to refuse New Brunswick unless they offer you an associate professorship. Perhaps they would do that if you play your cards well. Perhaps you would have to take a rather positive stand to Zirkle's proposal in order to be successful in this. How would it be to write to Franck at this point? Gaffron is leaving Chicago for England today.

It is conceivable that New Brunswick would meet such an offer from Chicago by raising their bid but this would depend on whether Waksman can get the University to make long-range commitments. He really ought to be getting a few positions with tenure but not very many; this is perhaps one more reason for putting the heat on now.

I am afraid these oracles I am emitting here are not very helpful.

I was moved by your saying that you would like to continue working with me if this could possibly be arranged. I would very much like this of course (in some setting other than Chicago) provided that the organizational set-up is such that you are on your own and

that your independence cannot be questioned. I am convinced that you need this independence now not only for the sake of "advancement" but also for the sake of your own inner-development.

Unfortunately I am rather at a loss concerning my own plans.

Yours,

Leo Szilard

LS:j

March 11, 1954

Dear Szilard,

Many thanks for including the copy of Moon's letter in your last letter. I found it particularly interesting in the light of a letter which I have received from Zirkle. I am quite unhappy about the manoeuvering tactics of Zirkle and Bloom — fearing they would set the clock back eight years at least. On the other hand I hesitate to say anything to them in opposition for fear such statements would be held against me in the future.

Just the other day I got the offer from Wakeman — an Associate Membership at $7590 with a three year contract. I have just written him, not discouragingly, but yet not accepting as yet. I am also writing to Coggeshall.

I find writing these letters very difficult because I can not really make up my own mind. The fact is that I am not happy about either Chicago or Rutgers. Not only is Chicago very uncertain in terms of its very existence, but the city is such a disgusting place to live, as you well know. On the other hand I fear that Rutgers is not the kind of University atmosphere that one likes, particularly in these times.

Moreover I find it hard to make up my mind because of my uncertainty about your plans. I would like very much to continue working with you if this can possibly be arranged.

I am also unhappy about the Rutgers appointment because of its being stated as three years. ~~From~~ At my age, ~~now~~ I feel I should expect offers with tenure although I have no a priori intent of staying permanently. I have asked Waksman about this.

To go back to science for a minute. Did you see the note of George Gamow in Nature about the Watson-Crick DNA model? He shows quite nicely that there are "holes" in the structure, each of which conceivably ~~each~~ holds one amino acid. There are 32 possible holes of this kind, but only 20 unique since 12 are in a mirror-image relationship with 12 others. This number 20, he points out is roughly the number of amino-acids. I trust that by now someone has tried to see which amino acids might go into which holes.

I learned from Mel Cohen that you had a talk with him. He is very good I think and has boundless energy in the lab. His galactosidase system is very nice and really easy to work with. Unhappily P_Z (the protein immunochemically similar to the enzyme G_Z) is too difficult to determine. We have begun a few experiments together - one I hope may show whether the bacterium knows how to make the odd pyrimidine in T_2 or whether this information is carried in by T_2.

By the way there is, as you probably know, much talk about "synchronizing" bacterial divisions.

I have heard rumors of a number of successes. A few months ago I too had thought about the problem and even did a couple of experiments. The idea is the following. The destribution of bacteria at various stages of the division cycle should be different if for example the bacteria are growing at some "unlimited" fast rate as compared to bacteria growing tryptophane limited. I imagine in the latter case, tryptophane limitation, the bacteria are ~~randomly~~ uniformly destributed since reactions involving tryptophane uptake probably occur continuously throughout the life cycle. But in the case where they are growing very fast, there is the chance that a very small number of processes, ideally one, limit the growth rate. Then the population will be mostly made up of bacteria at this stage of development. (By the way this difference in relative time spent at various stages might very well explain Maaw's expt's in the breeder giving a high mutation rates). If one shifts suddenly from the fast rate to a slow tryptophane limited rate one should have a synchronized population. I needed a chemostat to do the expts - the bactogen being too clumsy to operate.

Please let me know how you feel about the relative merits of Chicago & Rutgers. I guess I really had hoped for something in the west.

Best regards

Aaron

THE UNIVERSITY OF CHICAGO
CHICAGO 37 · ILLINOIS
INSTITUTE OF RADIOBIOLOGY AND BIOPHYSICS

Thursday
Mar 24, 1955

Dear Szilard,

I have not written sooner because of some difficulties I had with the expt. On Tuesday I ~~saw at~~ did 2 expts - at 4×10^{-4} M and at 1×10^{-4} M at $\tau = 1.9$ hrs and using B/N/1,0 (this for the first time). To my great dismay, I found a fall in bacterial density. I have repeated the expts using TMG sterilized by filtration and the density is maintained. I enclose graphs obtained at 5×10^{-4} M and at 5×10^{-5} M. I am still sleepy from the hours spent taking readings so I'll withhold comment. By the way I haven't given this much thought, but would not your theory have difficulty explaining an expt. in which TMG is added only to the growth tube - where the enzyme rises and then finally falls - whereupon one adds TMG again and finds that the rate of synthesis is that which corresponds to the concentration of enzyme at the time of addition.

By the way have you heard of the results of Dunn & Smith, Nature, Feb 28 (I think)

who find that Escherichia coli 6 Thymineless
mutant, will incorporate ~~amino~~ methyl amino
purine to the extent of 30% - instead of thymine
in its DNA. This is bad for Watson-Crick

Hope we see you soon.

Aaron

P.S. The fact that the linear slope is increased
much more than by the increase in inducer
concentration (in the present expt) makes me
more suspicious of an extracellular factor.

Oct 19, 1954

Dear Szilard,

Several days ago it was announced that Mort Gordgins was taking a leave of absence as dean of the social sciences to be in charge of "Special Projects" for Kingston. Chauncey Harris of the Geography dep't was made acting dean.

Today someone told me in "great confidence" that Mort was very ill – a terminal case. I do not know at all how reliable this story is – and if true I am sure he must not know. I ran into him several weeks ago and he seemed in quite good spirits.

I am very angry that people should spread such stories – and I only write this to you because of your obvious interest. [redacted]

Monod wrote urging me to take up the study of the kinetics of enzyme induction in the chemostat and when I receive the strains from him I will start. Unfortunately the inducer, thiomethylgalactoside, must be synthesized as Monod's supply is exhausted.

People tell me that Teller's popularity is at an all time low because of this book on the hydrogen bomb by the Luce people. I heard that when Rabi talked with him at Los Alamos Rabi insisted on having witnesses present.

Best regards to all and will we see you soon?

Cairns

P.S. Koch (a biochemist here) finds that caffeine and some of the other compounds interfere with the reaction Adenosine + phosphate ⇌ adenine + ribose-phosphate

CHICAGO
JUN 5
11 PM
1955
18
ILL.

THIS SIDE OF CARD IS FOR ADDRESS

Dr. Leo Szilard
Kenyon Crown Hotel
420 W. 116th St.
N.Y.C., N.Y.

Ça marche! (Flasks)

Activity with 10^{-3} M TMG	195
Activity after 10^4 fold multiplication in "F"	<0.1
Activity after 10^4 fold multiplication in "F" + 10^{-5} M TMG	175
Activity after 10^4 fold mult in 2×10^{-5} M TMG	~200
Activity of uninduced after 10^4 fold mult in 10^{-5} M TMG	2.6
Ditto after 10^4 in $2 10^{-5}$ TMG	29

Will get with lower TMG and also ~~longer~~ greater multiplication.

Aaron

June 28, 1955

Dear Szilard,

It occurred to me that the flask experiments are not so interesting in the light of the fact that bacteria concentrate inducer from the medium proportional to their enzyme content. This means that for low inducer concentrations the synthetic rate will depend on enzyme concentration and may in fact be proportional to it. The resulting apparent exponential is then not the reflection of some self-duplicating process. The only good evidence for a self-duplicating process lies in the linear rise in the Chemostat where the duplication rate must be very close to the bacterial growth rate.

By the way I now agree with your argument about the intercept being necessarily greater than 2 if it is the "RNA" which is self-reproducing.

I have arranged to use a Beckman here and have seat for chemicals and cuvettes. I'll repeat the flask expts, but with less enthusiasm than before.

Best regards

Aaron

General

June 25, 1957

Dr. Aaron Novick
Biological Laboratory
Cold Spring Harbor
New York

Dear Novick,

I am sending you under separate cover Stent's manuscript. My own manuscript which I had prepared for publication I decided not to publish. It turns out that the basic idea (that trinucleotides carrying one amino acid are the intermediates in protein synthesis), was put forward by Crick in the discussion at a meeting which took place in February, 1956, and was recently published in the Biochemical Society Symposium, No. 14, Cambridge University Press. Reference to this idea is also contained in Crick's paper in the May issue of the Proceedings of the National Academy (U.S.A.), which reached me just in the nick of time.

The second half of my manuscript, which relates to the rate of protein synthesis, I shall probably incorporate in the next manuscript, which is in preparation. My additional idea that trinucleotides of the ribose variety carry each a sequence of three amino acids in the form of acid anhydrides on a phosphate which hangs on the (2) carbon of the ribose, I am temporarily abandoning for the following reason:

The past week which I spent in Denver I got hold of a manuscript of Brenner's, in which were collected the known amino acid sequences. According to my postulate, there ought to have been ten sequences of three amino acids -- in this sample -- occurring twice. This is not in fact the case, and therefore the facts do not bear out my postulate. It was a nice try anyway.

I hope it is not too warm and humid in Cold Spring Harbor. With kind regards to Jane and you,

Yours,

m

Leo Szilard

Pumpkin

LONG ISLAND BIOLOGICAL ASSOCIATION
COLD SPRING HARBOR, NEW YORK

BIOLOGICAL LABORATORY

Aug 20, 1957

Dear Szilard,

I'm writing principally to call your attention to the phage meeting to be held at Cold Spring Harbor on August 27, 28, 29. Although I know of no unusual results the meeting should be pleasant and stimulating, sessions to be held in the morning only so that afternoon and evenings are free for discussion. Among others Stent, Garen, Hershey, Luria, many good Japanese and others will be there.

We have been having a pleasant summer, despite a siege of minor ailments.

I'm somewhat disturbed about Milt, as I have not received a single letter from him all summer. I've been eager to have certain results to no avail. I've called several times and only gotten more promises and excuses. I wonder if you have been in contact with him, mostly to be sure he is O.K.

I plan to go to Woods Hole on Sept 4 for several days to attend a meeting of the Soc. of Gen'l Physiologists on regulation of metabolic activity. You might enjoy these meetings, too. We will return to Chicago immediately afterwards getting to Chicago about Sept 10. What are your plans.

Best regards
Aaron

August 22, 1957

Dr. Aaron Novick
Biological Laboratory
Long Island Biological Association
Cold Spring Harbor, New York

Dear Novick,

Many thanks for your letter of August 20th. I would like to attend the phage meeting, but I will probably not be able to make it. I am supposed to be in Cambridge on the 12th of September to visit with Crick et al., and on the 23rd in Heidelberg to give a talk at Richard Kuhn's place, and on the 7th of October in Berlin.

Milt is unchanged. I have not seen much of him. I drop in at his laboratory on occasion to ask him some specific question. I find this is the only way to get hold of him. I have given up making dates with him since he is not able to keep them, and at best he telephones five minutes before the date to say that he cannot make it. I have the impression that his experiments are going well though I have only a vague notion of what he is doing. He is very busy now, of course, preparing to leave, and also for about a week he was upset because he had an animal cell tumor pushing on one of his teeth which was painful. It was excised and there is nothing to worry about, but he had to make several visits to the dentist to have the tooth repaired.

I regret to say that we might miss each other, since I might have to leave before September 10th.

Yours,

Leo Szilard

m

December 12, 1958

Minutes of Meeting Held December 8, 1958
Between Representatives of American Sterilizer
and Marc Wood International, Inc., to Discuss
Licensing of the Monod Patents

The meeting was held at 2:30 P.M., December 8, 1958, at the offices of Marc Wood International, Inc., 30 Rockefeller Plaza, New York 20, N. Y.

Attending were Messrs. Jewell, Barry and Perkins of American Sterilizer and Messrs. Wood, Le Lievre and Yates of Marc Wood International.

At the outset it was agreed that copies of the minutes of this meeting should be sent to Drs. Monod, Novick, Cohn and Szilard.

I. Apparatus Patent

Mr. Le Lievre opened the discussion by explaining that C.N.R.S., Institut Pasteur, and the above bacteriologists had decided to form a joint venture,to be represented by Marc Wood International. The members of the joint venture were prepared to cooperate with Dr. Monod in the grant of a general license under the Monod process patent, U.S. No. 2,822,319, to American Sterilizer and to reserve to AS and its customers and licensees the exclusive benefit of the consulting services of the individual bacteriologists, in so far as such services relate to this process. However, a condition of the offer was the taking by American Sterilizer of a license under the Monod apparatus patent, U.S. No. 2,686,754. This condition was simply a question establishing future relations on a proper basis and showing business good faith.

Mr. Jewell indicated that American Sterilizer was not opposed to such a condition in principle, but was concerned about who would prosecute infringers. American Sterilizer was already aware of 2 or 3 competitors who are now infringing the Monod apparatus patent.

Mr. Le Lievre appreciated their reluctance to defend a patent in which they had no confidence, but pointed out that manufacturers of the apparatus could be prosecuted as contributory infringers of the process patent. Mr. Jewell asked whether this would be true even if the purchasers were

scientific laboratories. Mr. Le Lievre affirmed that it was, that there was no exception in their favor even if they were operating the equipment for production of substances used for further research as distinguished from research with a view to improving the device itself.

The terms of a license under the apparatus patent were outlined by Mr. Wood who indicated that the minimum acceptable to Dr. Monod was no cash, no guaranteed annual minima but a 5% royalty on the net selling price of each apparatus retroactive to the first equipment sold.

Mr. Jewell indicated that these terms probably offered the basis for an agreement but that it would be necessary to reconsider the contract with Mr. Rinderer to whom, at Dr. Cohn's insistence, American Sterilizer now pays a royalty on all Biogen units sold. The reason for paying a royalty to Mr. Rinderer was that it was said Dr. Monod's design would not work without foaming unless Mr. Rinderer's modifications were incorporated. However, Mr. Yates recalled that in a previous meeting Dr. Monod had denied this and had claimed that a unit using his own design worked excellently in his laboratory in Paris for someone who understood the theory of the process.

The terms of the agreement between AS and Mr. Rinderer included $12,000 cash plus a 3% royalty based on Biogen units costing approximately $12,800 without accessories. These terms were intended to compensate him also for the promotional work he had done which had resulted in several orders being almost booked at the time of the Agreement. If Mr. Rinderer's royalty ultimately proved to be an economic obstacle, Mr. Le Lievre believed that it might perhaps be in part deducted from Dr. Monod's royalty.

II. Process Patent

1. Mr. Jewell and Mr. Perkins prefaced the discussion of the process patent by pointing out that Seagram's and Anheuser Busch have done work on continuous fermentation since the late 1940's and that Standard Oil of N. J. and The Texas Co. have patents in the same field dating from that era. These patents would not necessarily have turned up in the patent office during Dr. Monod's application since they related to the petroleum field. Mr. Le Lievre stated that it was obviously impossible to answer these remarks at this time and that the discussion would have to proceed on the assumption that the Monod process patent was of interest to AS.

2. The mechanics by which AS would exploit the Monod process patent under a general license were outlined by Mr. Wood:

a. AS representatives in the course of their travels would seek out the problems of prospective licensees.

b. AS's research department would conduct a feasibility test.

c. The results of this test would be submitted to the prospect with a proposal to pursue the matter further on a joint basis. Concurrently with this proposal, AS would induce the prospect to take a paying option for a monthly fee to be agreed upon.

d. The study of a possible application of the Monod process patent might lead to the design and/or manufacture of equipment by AS and/or the prospect.

To summarize, income would be derived from:

a. Option fees,

b. License agreements,

c. The manufacture of special equipment ("special" meaning equipment other than the Biogen).

3. Terms of a general exclusive license to AS:

a. An initial option period of 6 months would be granted for a consideration of $200 per month.

b. A possible 6 months extension of this option period would be granted, if required, for a consideration of $500 per month.

c. Upon exercise of the option, AS would pay the joint venture $25,000 in cash.

d. AS would collect option fees and royalties from its sublicensees and turn 60% of such income over to the joint venture (except for the Biogen for which a 5% royalty under the apparatus patent is included in the price and payable to the joint return). The royalty

charged by AS would be 5% of the cost to the sublicensee of equipment used to practice the Monod process or developed with the assistance of the venture. When feasible, AS would charge a cent-per-pound royalty on the products obtained with such equipment (at rates approved by the venture) in lieu of the 5% on cost royalty, or, even better, the 5% royalty would be deemed a cash advance against the per-pound royalty.

The reason for allowing AS only 40% of the royalties so collected is that AS stands to make an additional profit on any equipment which it may sell to the sublicensees.

e. AS would guarantee the joint venture minimum annual income from option fees and royalties of $12,000 for the first year, $24,000 for the second and each subsequent year. Mr. Le Lievre pointed out that these minima could be easily earned by granting options to a few sublicensees per year. He also called attention to the fact that the $25,000 upon exercise of the option was payable at the beginning of the first license year, while the $12,000 minimum was payable at the end of such year.

Mr. Jewell noted the foregoing terms but was unable to say whether his associates in Erie would react favorably to them. He realized, however, that AS would have at least 6 months under the option in which to find out whether a general licensing program would be feasible and to check into the history of continuous culture processes. This was no less than each customer would want to do before taking a sublicense. In any case, if AS ultimately decided not to exercise the option it would state fully its reasons.

In the course of the meeting Mr. Jewell stated his understanding that Dr. Novick and Dr. Cohn might be under obligations which may conflict with the arrangements described in these minutes, by virtue of having received grants from universities and/or the United States government. Mr. Jewell also pointed out that Dr. Novick was currently under retainer from AS as a consultant. It was suggested that Drs. Novick and Cohn review this question and that each of them should notify MWI of the extent of his freedom to render the contemplated services.

Dan files

UNIVERSITY OF OREGON
EUGENE, OREGON

INSTITUTE OF MOLECULAR BIOLOGY

February 9, 1959

Dr. Leo Szilard
The Quadrangle Club
1155 East 57th Street
Chicago 37, Illinois

Dear Szilard:

I am sending enclosed the proposals Monod has made. They are agreeable to me.

Best regards,

Aaron

Aaron Novick

AN:tdm

Enclosures

P.S. Also enclose minutes of meeting between Amer. Sterilizer Co and Monod's representatives.

AGREEMENT made this day of , 1959 by and between JACQUES MONOD of 28 rue de Docteur Roux, Paris, France (hereinafter called the Inventor)

COHN of , NOVICK of , and SZILARD of (hereinafter collectively called "the Associates"), CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE, an agency of the French Government having offices at 13 Quai Anatole France, Paris, France (hereinafter called CNRS), INSTITUT PASTEUR having offices at 28 rue du Docteur Roux, Paris, France and MARC WOOD INTERNATIONAL, INC., a corporation of the State of Delaware having offices at 30 Rockefeller Plaza, New York 20, New York (hereinafter called MWI):

W I T N E S S E T H:

WHEREAS, the Inventor is the owner of U. S. patents nos. 2,686,754 and 2,822,319 covering respectively the apparatus and processes for the industrial cultivation of micro-organisms (hereinafter called the "Patents");

WHEREAS, the Associates assisted the Inventor in the development of the machines necessary for the exploitation of the inventions;

WHEREAS, the Inventor and Associates worked in the laboratories of, and with facilities of Institut Pasteur;

WHEREAS, the Inventor and Associates were supplied with funds by CNRS to finance the development of the Patents; and

WHEREAS, the Inventor, the Associates, CNRS and Institut Pasteur desire to organize a joint venture under the laws of the Republic of France with MWI as Manager, for the purpose of obtaining in the United States of America and the Dominion of Canada the maximum development of the machines and processes covered by the Patents;

NOW, THEREFORE, the parties hereby unite in a joint venture and agree to exercise their best efforts to carry out the above-mentioned purposes, as follows:

1. The Inventor contributes for the duration of the joint venture and of any contract executed by the joint venture the benefit of the proceeds of the exploitation of said Patents. Title to such Patents shall remain in the Inventor.

2. The Inventor and the Associates agree to contribute for the duration of the joint venture and of any contract executed by the joint venture their knowledge and know-how concerning the machines and processes described in said Patents, and more generally, concerning the field of industrial cultivation of microorganisms. Each such party undertakes, within the limits of his available time, to render consulting services with respect to said Patents and field to any licensee under said Patents, its sublicensees and customers, and to no other party in the United States and Canada. Compensation for such services shall be fixed by the party or parties rendering the same in agreement with the beneficiary thereof.

3. MWI is hereby designated to act as Manager of the Joint Venture, and as compensation therefor shall be entitled to 20% of the gross receipts of the joint venture.

4. The Manager of the joint venture shall collect all amounts due to the joint venture, shall pay out of such amounts all expenses of the joint venture (including the Manager's compensation and necessary expenses and disbursements such as legal fees, travelling expenses, cables, long distance telephone calls, etc.), and shall remit the remainder to the several joint venturers annually on or before February 15, or at more frequent intervals, in the proportions set forth in paragraph 5 hereof. The Manager shall account to the joint venturers on or before February 15 of each year for the preceding calendar year; provided that for the first period of operations hereunder such

account shall be for the period commencing with the execution of this Agreement and terminating on the next December 31.

5. The respective interests of the parties hereto, including their share of income after the deduction of all expenses, are as follows:

Monod	18%
Novick	18%
Cohn	18%
Szilard	18%
CRNS	14%
Institut Pasteur	14%

6. It is expressly agreed that each party shall retain title to any assets and know-how contributed by him to the joint venture. The Inventor and each of the Associates shall benefit exclusively from any fees for consulting services paid to him by any licensee.

7. This joint venture shall continue until terminated by mutual agreement or until fulfillment or failure of its purpose. Upon termination, any moneys and divisible property remaining on hand shall be distributed in the proportions stipulated in paragraph 5 hereof. Any indivisible property shall remain in joint ownership. The appointment of MWI as Manager of the joint venture shall continue in effect for the duration of said venture.

8. This Agreement is personal to the parties hereto and may not be assigned, except that a corporation or institution may assign it to any corporation or institution succeeding to or purchasing a substantial part of its business and good will and that the monetary benefits accruing to an individual shall accrue to his estate in case of death.

9. Any notice called for by this Agreement shall be served by a party on the other parties by registered air mail addressed to such other parties at the addresses

given at the beginning of this Agreement, or at such other addresses as any party may hereafter designate in writing.

10. This Agreement and performance hereunder shall be governed in all respects by the laws of the Republic of France. Any controversy or claim arising out of or relating to this Agreement, or any breach hereof, shall be submitted by the parties to arbitration in Paris in accordance with the rules of the International Chamber of Commerce of Paris, and judgment upon any award so rendered may be entered in any court having jurisdiction thereof.

IN WITNESS WHEREOF, the parties have executed or caused this Agreement to be executed in their name by their duly authorized representatives,

_____
Jacques Monod

_____
Cohn

_____
Novick

_____
Szilard

CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

By_____

INSTITUT PASTEUR

By_____

MARC WOOD INTERNATIONAL, INC.

By_____

Denver, Colorado
February 19, 1959

Dr. Aaron Novick
Institute of Molecular Biology
University of Oregon
Eugene, Oregon

Dear Novick:

Many thanks for your letter. I do not know what my schedule will be. I doubt that I will go to the Pittsburgh meeting and I might hang on mostly West in the next few months, with the exception of one trip East on an as yet undetermined date.

Concerning the draft agreement which you sent me, I should say this: I have no intention to consult with anybody else in this field. It seems to me that the arrangement proposed by Monod is a very generous one. My only hesitation is that under as yet unforeseeable circumstances I might be embarrassed by an obligation of not to consult in a given field. For this reason I would prefer to sign the agreement as it stands, with the proviso that I shall be free to withdraw from it, and that if I do, I forfeit all income from the agreement. My share could then be divided up among those who will remain a party to the agreement. If this proviso were acceptable, I should then be glad to sign the agreement as it is. If this proviso is unacceptable, I would have to think more about the unexpected contingencies that might arise and in which the agreement might become embarrassing to me, unless I can withdraw from it. Among these is, above all, the possibility that I might join the National Institute of Health.

Sincerely yours,

Leo Szilard

June 22, 1959

Dr. Aaron Novick
Institute of Molecular Biology
The University of Oregon
Eugene, Oregon

Dear Novick:

Don't bother please about the reprint mailing list which you have lost. However, if in time you manage to assemble one again, keep a copy for me. You may send it to me later on when I ask for it again.

I am leaving for Europe tomorrow to attend the Fourth Pugwash Meeting in Baden near Vienna.

From copies of letters sent to me by Mel Cohn and Monod, I see they are having some trouble in arriving at an agreement. I am writing to authorize you to accept, in my absence, any modification of the agreement which is limited to a change in the financial terms but does not impose any additional personal obligations on me. Please feel free to put my signature under any such agreement if my signature should be required. This will avoid unnecessary delay if you have trouble reaching me.

With kindest regards.

Sincerely,

Leo Szilard

December 24, 1959

Mr. John S. Yates
Marc Wood International, Inc.
30 Rockefeller Plaza
New York 20, New York

Dear Mr. Yates:

I am writing in connection with the Joint Venture agreement among the Associates (Monod, Szilard, Cohn, Rinderer, Novick, the CRNS, and the Institut Pasteur).

I would like clarification about the benefits accruable to an individual's estate in the event of his death. Although the agreement does state in paragraph 8 ". . . . that the monetary benefits accruing to an individual shall accrue to his estate in case of death", I am concerned that this might be limited by some service required of an individual by the agreement, as in paragraph 2, for example.

My question is made urgent by the fact that Prof. Leo Szilard has become ill and feels that he must prepare a will. I would like to be able to offer him assurance that any monetary benefits would accrue to his estate in the absence of any service on his part.

I suggest that this be done by the appendment to our Agreement of a statement signed by all of us making clear beyond any doubt that benefits would accumulate to an estate as well as to a living member. Could you prepare such a statement and circulate it for signature?

I would like to have this matter settled as soon as possible and would, therefore, be grateful for the earliest possible assistance.

Sincerely,

Aaron Novick

AN:ret
cc: Dr. Jacques Monod
Dr. Melvin Cohn
Mr. F. Rinderer
Dr. Leo Szilard

UNIVERSITY OF OREGON
EUGENE, OREGON

INSTITUTE OF MOLECULAR BIOLOGY

January 7, 1960

Dr. Leo Szilard
St. Moritz Hotel
New York, New York

Dear Szilard:

I enclose the copies of the Group's Agreement for signature as well as a stamped envelope so that you can send it on to Melvin Cohn. I understand that you received a copy of Yates' letter to me of January 5 in which he replies to my letter of December 14 regarding the disposition of a member's monetary benefits in the event of his death. My lawyer friends here agree with Yates but I will get this spelled out more clearly, if you wish.

I am interested to see your antibody paper especially before I come East. I expect to be in New York the last week in February and look forward to seeing you.

Best regards.

Sincerely,

Aaron

Aaron Novick

Encl.

UNIVERSITY OF OREGON
EUGENE, OREGON

INSTITUTE OF MOLECULAR BIOLOGY

January 15, 1960

Dr. Leo Szilard
St. Moritz Hotel
New York, New York

Dear Leo:

I have just received from Howard Green your two manuscripts. I have read the first and am about to start the second. I found the first extremely interesting, especially since it crystallizes much of my own vague speculation. I have two remarks which I want to make right away. More comments will follow later.

The first has to do with when regulation occurs. We have done the following experiment: bacteria in a test tube are permitted to become starved for phosphate. Under these conditions they began to make large quantities of phosphotase, the RNA falls, and the DNA rises. We added TMG during this period of phorphorus starvation and observed an immediate production of β-galactosidase at a rate at least equal to that of a control with excess phosphate. This was done with ML3 (a permeaseless strain) and at a TMG concentration which gives 10% of the maximum rate. We would like to conclude that, if the templates* contain phosphorus, they are already present before inducer is added, and that regulation occurs at the point of enzyme synthesis.

Another point is some evidence which may contradict some of your ideas. This is an observation at the Institut Pasteur reported by Jacob, Schaeffer, and Wollman in a paper entitled "Episomic Elements in Bacteria" to be given at the Tenth Symposium of the Society for General Microbiology in London, April, 1960. I quote the pertinent paragraph from pages 34-35 of their ms:

"One may also wonder whether the regulation of the heterocatalytic functions of the galactose determinants is disturbed when these determinants are incorporated into a phage genome. Preliminary experiments suggest that this might be the case (G. Buttin, unpublished). In wild E.coli K12, the synthesis of galactokinase occurs only in the presence of an external inducer which is likely to release a specific repression as in the case of β-galactosidase. When non-lysogenic gal^- mutants are infected with λ-gal^+ phages, it is observed that, after a short lag, the infected cells are able to manufacture the enzyme constitutively.

*or enzyme forming units

that is in the absence of any external inducer. Such a constitutive synthesis occurs even in conditions of single infection, in which the defective λ-gal appears (of Arber, 1958) not to multiply vegetatively. If, however, lysogenic gal^- mutants, carrying a prophage λ, are infected with $\lambda\text{-gal}^+$ phage, no constitutive synthesis of enzyme is observed, unless the cells are exposed to a dose of U.V. light which releases immunity and initiates phage development. In the same way, in heterogenotes carrying a λ-gal prophage, which synthesize galactokinase only in the presence of inducer during growth, U.V. irradiation initiates a constitutive synthesis during the latent period. These results suggest that, when incorporated into a phage genome, the hetero-catalytic functions of the gal determinants may escape the normal system of bacterial regulation and perhaps become submitted in some way to the phage system of repression which determines immunity. If confirmed by further experiments, this would support the hypothesis that repression systems operate by regulating the expression of groups of determinants which are structurally associated in the genetic material."

I am eager to discuss these matters with you and hope to be in New York soon.

Best regards,

Aaron

Aaron Novick

UNIVERSITY OF OREGON
EUGENE, OREGON

INSTITUTE OF MOLECULAR BIOLOGY

1-19-60

Dear Szilard,

I am enjoying your antibody ms very much. Its clear precision of thought is beautiful. One question is raised by Dubert's expt. If he immunizes an animal with human serum albumin and then later challenges it with sulfanilic acid coupled to human serum albumin, will he get more anti-sulfanilic acid than in a control (not previously immunized with human serum albumin)? I expect he might because if the feedback system requires the concentration of the antigen at the site of synthesis there ~~might~~ would be a lot more sulfanilic acid brought in with the human serum albumin.

Best regards,

Sam

UNIVERSITY OF OREGON
EUGENE, OREGON

INSTITUTE OF MOLECULAR BIOLOGY

Dear Szilard,

According to Monod and Cohn (Advin Enzymology) melibiose has zero activity as a complexant of β-galactosidase (measured by inhibition of hydrolysis of ONPG). Another hard blow is the observation of Buttin, Jacob, and Monod that galactokinase is normally repressed when the gene is in the chromosome but that it becomes derepressed when it is attached to a defective λ phage in process of active multiplication. Thus the specificity of the control is through an operator and not directly on the gene. I enclose a copy of their paper which appeared in the Comptes

(over)

Rendues of March 24, 1960.

Pres Medical

Andre Bouvier
254 Faubourg St Honoré
90 Tablets

Best regards,

Ann

DG 428 Bayer

French: 8950 RP
SPECIA

3 Tablets a day week or
Months. —
blood count

MEMORANDUM ON X-RNA

July 19, 1956 [0]

From: Szilard

To: Jacob
Meselson
Brenner
Watson
Gros
Novick
Levinthal

This memorandum is concerned with the issue of whether the production of the short-lived high molecular weight X-RNA which has been observed by Jacob, Meselson and Brenner (unpublished) is, in general, under the control of repressors or whether it is not.

It seems to me that it should be possible to answer this question simply by determining the rate kinetics of the appearance ~~which~~ of labelled uracil ~~goes~~ in high molecular weight RNA - both X-RNA and Ribosomal RNA. The experiment is as follows:

Let us add, at zero time, labelled uracil to a growing bacterial culture and let us determine how much label is subsequently present in the high molecular weight RNA fraction, as a function of time. In this RNA fraction the label ought to increase initially fast and reach an apparent plateau of some height A, within a rather short period of time. Subsequently, the label will increase more slowly and we shall designate by B the height which it will reach within one generation time, τ. We shall designate by $\frac{\delta}{2}$ the time it takes for the label initially to rise to the height $\frac{A}{2}$.

Let us now see what we should expect regarding the values A, B and S if the production of X-RNA molecules by the corresponding genes is not under the control of repressors, but rather each gene makes the corresponding X-RNA at the same full rate in a growing bacterial culture.

Let us for the sake of argument make the following assumptions:

(1) The molecular weight of the X-RNA is about equal to the molecular weight of the corresponsing DNA molecule;

(2) The total weight of the Ribosomal RNA is, say, 4 times the weight of the metabolically active DNA molecules in toto.

In these circumstances, we should expect roughly speaking to have

$$\frac{4A}{B} = \frac{S}{L}$$

If this is what we find then we would expect the repressors to control the rate at which each X-RNA molecule produces the corresponding protein molecule.

If, on the other hand, all the X-RNA molecules make protein at the full rate and the rate of the production of X-RNA molecules by the genes is controlled by repressors then we should expect to find

$$\frac{4A}{B} << \frac{S}{L}$$

UNIVERSITY OF OREGON
INSTITUTE OF MOLECULAR BIOLOGY
EUGENE, OREGON

August 11, 1960

Dear Leo,

I have been meaning to send you the enclosed copy of part of a letter from Tomizawa, but a series of visitors and other distractions have kept me from writing. What is additionally impressive about the Tomizawa letter is the fact that in the past he has been apolitical, having little enthusiasm or interest in politics.

François Jacob visited us a few weeks ago. Goodness, he has an impressive number of facts and ideas. His experiment with Brenner on the "message RNA" excites me very much, and I wish I had done it. This breakthrough should lead to the clarification of all kinds of problems in the next few months.

I talked with Jacob about the repressor and was interested to see that he comes to the conclusions you proposed in your PNAS paper. That is, that the repressor is composed of two parts – one containing the specificity (the RNA moiety) and one containing the information for the need (the metabolic moiety). He proposed that our temperature mutant (inducible at low temperature, constitutive at high) has a thermolabile coupling enzyme. I am pleased by all this. Incidentally, I guess we did discuss the fact that the Szilard paradox about the effect of growth rate on rate of induction

at suboptimal inducer can be understood even in the consideration of transition from one z^+ to another. I would say that the transition occurs with no overshoot (which is what we are finding) because although the repressor concentration increases at longer z^+, the new value is reached very quickly because the metabolic moiety has a short mean life. The original Pardee, Monod, Jacob expts where the i^+z^+ genes are put into an i^-z^- cytoplasm show that the repressor level rises only slowly. This is explained by saying that it is the RNA moiety which is rising slowly. Thus the RNA part must be relatively stable.

I hope this is not too muddy. If you are in the mood please call me collect as I would enjoy discussing these things.

Life here is very pleasant and if it were not for the ever-continuing threat of catastrophe I would be quite pleased. I am dismayed at the pressures to resume bomb-testing as well as the general lack of comprehension in the public at large. The Conventions did not encourage me.

The children are growing rapidly now. David reads constantly and I am privately very pleased by their intellectuality.

Please give my greetings to Trudy.

Love

Cara

UNIVERSITY OF OREGON
INSTITUTE OF MOLECULAR BIOLOGY
EUGENE, OREGON

September 8, 1960

John S. Yates
Vice President
Marc Wood International Inc.
30 Rockefeller Plaza

Dear Mr. Yates:

I wish to acknowledge your letter of August 12 and state that I approve in principle of Mr. Rinderer's proposal. To my best knowledge Professor Szilard would also approve. Regarding the specific problem of any share we have in royalties from American Sterilizer we both would like to do as have the CNRS, the Pasteur Institute, and Dr. Monod and contribute our shares toward setting up the laboratory.

Your suggestion that the group hold a plenary meeting is a wise one. I do not think it will be convenient for Dr. Szilard to attend, and I wonder if the meeting could be held here on the west coast since Monod, Cohn, and myself will be here.

Sincerely,

Aaron Novick
Director

cc: Professor Leo Szilard

lru

Dear Leo,

I am somewhat dubious about the proposed arrangement, but I think we ought to accede to Monod and Cohn who feel it is OK.

Best regards,
Aaron

Chemin

V-14

September 13, 1960.

Professor Aaron Novick,
Institute of Molecular Biology,
University of Oregon,
Eugene, Oregon,

Dear Novick,

I have a copy of your letter addressed to Mr. Yates dated September 8, 1960. Please note that I and Trude, to whom I have assigned my income from this arrangement, accede to the arrangement proposed by Mr. Rinderer, provided that it does not involve any refunding of royalties already received by us.

Yours,

Leo Szilard

March 16, 1961

Professor Ed Novitski
The University of Oregon
Eugene, Oregon

Dear Dr. Novitski:

Attached you will find a memorandum which might perhaps interest you. If you have any data from which I might deduce whether the ratio of boys to girls at birth falls off strongly with the number of siblings if one disregards the sex of the last born, I should be very grateful if you would let me know. For the next few weeks I shall be in Washington, D. C., staying at the Hotel Du-pont Plaza, and I might try to find such data here through the Bureau of the Census or the National Office of Vital Statistics, unless you know where I might find such data.

With kind regards,

Sincerely,

Leo Szilard

cc: H. J. Muller
Leo Goodmann

15 December 1961

Professor Aaron Novick
Institute of Molecular Biology
University of Oregon
Eugene, Oregon

Dear Professor Novick:

Enclosed I am sending some advertising material, "About the Author" and a glossy photograph. Enclosed is also a copy of my speech. It is the latest version but not the final version. I suggest that this version be duplicated rather than any other older versions.

With kindest regards.

Yours,

Leo Szilard

Washington, D. C.
March 3, 1962

Professor Aaron Novick
Institute for Molecular Biology
The University of Oregon
Eugene, Oregon

Dear Novick:

The attached letter is meant for you and those others whose names are listed in the memo, "The Next Step". I should be very grateful to you for reading the attached letter and the enclosures, and for advising me as soon as possible whether you are willing to serve as an Associate.

I hope very much that you are not going to disqualify yourself from serving on the Board of Directors of the Council.

Sincerely,

Leo Szilard

Hotel Dupont Plaza
Washington 6, D. C.
Telephone: HUdson 3-6000

Enclosures

P.S. I am enclosing the revised and final version of my speech, which will be printed in the April issue of the Bulletin of the Atomic Scientists.

LS

UNIVERSITY OF OREGON
INSTITUTE OF MOLECULAR BIOLOGY
EUGENE, OREGON

6 April 1964

Dear Leo,

I am sending enclosed a copy of a letter I have just sent to Jacob. I am also sending a copy to Ed Lennox, who may be able to clarify some of the places where I am obscure or unclear.

I keep feeling that things are very close to being understood even though there are still so many possible models.

Please give my greetings to Trudy.

As ever,

Sam

See also François NOVICK → Jacob April 6, 1964

UNIVERSITY OF OREGON
INSTITUTE OF MOLECULAR BIOLOGY
EUGENE, OREGON

16 April 1964

Dear Leo,

I want to add a few remarks about Jack Sadler which I may not have expressed in my phone call.

1) He has the attractive virtue of great enthusiasm for good ideas. If someone offers him an idea better than his own he has no psychological difficulties and will work enthusiastically on the better idea.

2) He was raised in the West and has the cheerful open personality of westerners, but he also has gained by the years he spent at Oxford.

3) He thinks about the consequences of ideas and has played a very important role in our work. In fact it was his experiments and ideas which convinced me that the repressor "turns-over."

4) We are currently working on a number of quite complex experiments and he is very able to keep on top of them all.

I believe he would be a valuable addition to your community (Brenner liked him very much).

He will make no commitment until after he has visited La Jolla.

I'm looking forward to seeing your pre-print on the nervous system work.

Please give my best to Trudy and to Suzanne and Mel.

Best regards,

Aaron

File: Persons

(503) 342-1411
ext 1481
Los Angeles
via Dr. Paul Boyer
from Biochem Dept.
U.C.L.A.

UNIVERSITY OF OREGON
INSTITUTE OF MOLECULAR BIOLOGY
EUGENE, OREGON

16 April 1964

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He will make no commitment until after he has visited La Jolla.

I'm looking forward to seeing your pre-print on the nervous system work.

Please give my best to Trudy and to Suzanne and Mel.

Best regards,

Aaron

John Richard Sadler

Born Jan. 13, 1934 in Edgemont South Dakota

Graduated from Lovell Public High School, Lovell, Wyoming June 1952

Graduated from Reed College, June 6, 1956 major in chemistry

Awarded Rhodes Scholarship - Wyoming & Brasenose College Oxford in January 1956

Received Honours Degree in Chemistry from Oxford U. in 1958

Received D. Phil from Oxford U. in July 1961:

Thesis Topic. Aspects of C_2 metabolism in micro-organisms.

Thesis Advisor. Dr. Hans L. Kornberg (now Prof. at U. of Leicester)

Married Jutta Renate Tecklenburg in Lichterfelde, West Berlin July 28, 1961

A son, Wilfrid Jörg Sadler, born July 7, 1963.

Publications

1) Acetate Metabolism in Escherichia coli. Kornberg H.L. Phizackerley P.J.R., & Sadler, J.R. in Biochem. J. 1959
2) The oxidation of Glycollate in Micro-organisms. Kornberg & Sadler, Nature (Lond.) 1960
3) Synthesis of Cellular Material from Acetate in E. coli Kornberg, Phizackerley & Sadler Biochem. J. 1960

P.T.O.

41) Glycollate Catabolism: A Dicarboxylic Acid Cycle.
Kornberg & Sadler, Biochem J. 1961

4) Oxidation of Glycollate via a Dicarboxylic Acid Cycle. Kornberg & Sadler Biochem J. 1961

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Plans for Research

I would like to use the Fellowship to carry out researches on the genetics and physiology of microorganisms. I would like to work in several laboratories doing work closely related to my own.

Professor Leo Szilard and myself have developed a device called the Chemostat that is proving to be useful to the study of genetics, adaptation, and physiological regulation of microorganisms. Our studies to date have been largely concerned with spontaneous and induced mutations and more recently with the regulation of intermediary metabolism of bacteria.

I propose first to work with Professor R. Y. Stanier at the University of California on adaptive processes in bacteria. The principal plan is a study of the relationship between the rate of adaptation to a substrate and the concentration of that substrate. Professor Stanier has learned a great deal about a system of adaptive oxidative enzymes in Pseudomonas. This system combined with the Chemostat technique should teach us something of the mechanism of enzymic adaptation and its genetic basis.

As a second part of my plan I would like to work with Professor J. Monod at the Institut Pasteur in a study of the enzymic constitution of bacteria. The research contemplated is a study of the enzymic composition of bacteria growing at different rates.

Although our knowledge of particular biosynthetic pathways is rapidly increasing, practically nothing is known of the mechanisms that determine the relative rates of synthesis of the various constituents of living material. It is these mechanisms I hope to begin to study during the course of a Fellowship.

I propose to spend one year on such a Fellowship and hope to obtain results suitable for publication.

3. My predoctoral research was carried out under Professor Frank H. Westheimer of the Department of Chemistry of the University of Chicago, from 1941 to 1943, in the field of physical organic chemistry. The principal subject of study was an investigation of the kinetics and mechanism of the oxidation of isopropyl alcohol by chromic acid.

After receiving my Ph.D., I worked with the Manhattan Project from 1943 to 1945. My principal teachers and colleagues included James Franck, Otto Stern, and Frederick Seitz. Research carried out was concerned with the effects of radiation on the chemical and physical properties of various materials.

During 1946 and 1947, I collaborated with Professor Herbert L. Anderson, Institute for Nuclear Studies, University of Chicago, at the Argonne National Laboratory in an investigation of certain nuclear properties of H^3 and He^3.

In 1947 I joined the Institute of Radiobiology and Biophysics of the University of Chicago and worked with Professor Leo Szilard in the field of microbial genetics and physiology. In 1949 I was made an Assistant Professor of Biophysics at the Institute of Radiobiology and Biophysics. Our principal studies have included the effects of visible light on ultraviolet bacteria, phenotypic confusion in the bacterial viruses, and, most recently, a study of spontaneous and induced mutations in bacteria.

Aaron Novick

4. List of publications:

The kinetics of the oxidation of isopropyl alcohol by chromic acid. Journal of Chemical Physics 11, 506 (1943). With F. H. Westheimer. University of Chicago.

Magnetic moment of the triton. Physical Review 71, 372 (1947). With H. L. Anderson. Argonne National Laboratory.

Half-life of tritium. Physical Review 72, 972 (1947). Argonne National Laboratory.

Magnetic moment of He^3. Physical Review 73, 919 (1948). With H. L. Anderson. Argonne National Laboratory.

Experiments on light-reactivation of ultra-violet inactivated bacteria. Proceedings of the National Academy of Sciences 35, 591 (1949). With Leo Szilard. University of Chicago.

Experiments with the Chemostat on spontaneous mutations of bacteria. Proceedings of the National Academy of Sciences 36, 708 (1950). With Leo Szilard. University of Chicago.

Description of the Chemostat. Science 112, 715 (1950). With Leo Szilard. University of Chicago.

Virus strains of identical phenotype but different genotype. Science 113, 34 (1951). With Leo Szilard. University of Chicago.

Experiments on spontaneous and chemically induced mutations of bacteria growing in the Chemostat. Cold Spring Harbor Symposia on Quantitative Biology, vol. 16 (in press). With Leo Szilard. University of Chicago.

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6 April,

Dear Francois,

I am sorry to be so slow to reply to your letter, but I have been hoping to have unequivocal results at any moment and, of course, I have not found them.

When I got back to Eugene in February I became convinced, mostly by Jack Sadler, to take the possibilty of turn-over of repressor seriously. The only new results he had were temperature shift experiments with i^{ts} RS1 (i^P) in chemostats. He used C-source limitation since we found that under N-source limitation the bacteria cannot stand the temperature change 30→42°. Sadler found that $\frac{dz}{dB}$ increased much more sharply with fall in B/B in the chemostat, which would mean either a much higher power dependence for $\frac{dz}{dB}$ as $f(R)$ or a faster turn-over per generation. We have also made further comparisons of haploids with homozygous diploids, as I described earlier. These seemed to favor turn-over, but the question is still very open.

On this basis we have gone ahead to consider what turn-over might mean. The most obvious model, which we talked about many times in Paris, is that the repressor is composed of a protein (the i gene product) and an RNA (which might be the structure messenger). Such a model can explain a number of results and does lead to testable expectations. It is these we have been considering.

First, we realized that this picture could be used to explain the heterogeneity we found in the Eugene temperature-sensitive mutant (i^E). Here it appeared that although all of the repressor could be inactivated by heating at 44° at lower temperatures a decreasing fraction could be heat-inactivated, no matter how long the time of heating. This heterogeneity can be explained by assuming two steps in the thermal inactivation. First, there is melting of the RNA component, a step which is fast but only occurs above a specified temperature depending on the length of the RNA. Second, is the inactivation of the protein which is heat-sensitive in the Eugene strain. Now, if turn-over of repressor involves a break-down of the RNA part - say enzymatically from one end - and if the complex protein-RNA retains repressor activity down to some specified RNA size, there will be a heterogeneity among repressor molecules determined by the length of the associated RNA. And, obviously, this is the heterogeneity

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which would account for the behavior of i^E.

A test of this picture is based upon the further hypothesis that induction involves the dissociation of the protein-RNA complex in the presence of inducer. It follows that the heterogeneity in the population of repressor molecules should be eliminated in the presence of inducer, and one should expect to be able to heat inactivate all of the repressor in $5\ i^E$ in the presence of inducer even at lower temperatures where normally a substantial fraction is heat-stable. So we did the experiment of heating i^{ts} at 37° (in a q^- strain) with and without inducer present during heating. Upon return to 25°, the sample heated with inducer had an initial $\frac{dz}{dB}$ close to maximal while the other sample had a $\frac{dz}{dB}$ ten to twenty times lower. A long time ago we had looked for thermal stabilization of repressor by inducer, but we got negative results and overlooked the possibility of sensitization by inducer.

A further test we have been trying with less clear results is this. Following transfer of i^s from 30° to growth at 42° there is a relatively rapid rise in $\frac{dz}{dB}$ which reaches 0.1 of maximum in about a doubling time. If this is the result of turn-over of the RNA moiety with subsequent loss of the protein part because it remains blocked by a stub of residual RNA, one should be able to find this protein — or reveal it — by dissociating off the inactive RNA with inducer. For this, Sadler isolated a mutant of the kind we discussed — temperature-sensitive like i^s but i^+ rather than i^s. In the experiment we shift a culture from 30° to 42°. After 1.2 doublings, $\frac{dz}{dB}$ rises from 0.0005 (2000 units of repressor) to 0.1 (10 units of repressor). We add IPTG for 3 minutes at 42°, remove very fast by filtration and washing — all at 42° — and continue to grow at 42°. On the basis of the present model we expect there to be $2^{-1.2} = 0.43$ of the i^s protein left when the association ceases with most RNA the repressor level should rise to $0.43 \times 2000 = 860$ which should give a drop in $\frac{dz}{dB}$ from 0.1 to 0.001. We were elated to discover that there was a substantial fall in $\frac{dz}{dB}$ as a result of the brief exposure to IPTG, but we cannot yet rule out the possibility that there is a high rate of repressor formation even at 42° in the presence of inducer and [illegible]

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repressor which gives the drop in $\frac{dz}{dt}$. This will require some careful controls which we are trying.

I also expected to be able to do a similar experiment with the T.S. alkaline phosphatase mutant of Ballant. From his experiments, one might speculate that the R2 gene product is analogous to the c product in the mutant i^E. It is not inactivated by heating in buffer like with i^E because the RNA has a higher melting point. No repressor is made at higher temperatures because the protein is inactivated before it finds an RNA. We would predict that if the bacteria are starved for phosphorus at low temperature, the repressor should be dissociated and the protein part susceptible to inactivation by brief heating in buffer. We tried this and it worked. We are now trying to work out the best conditions to show this effect most clearly.

If there is some truth to the present model one should expect constitutive mutants mapping near z which are recessive. Since you never have found any of these, I would guess that maybe such mutants are necessarily z^- or y^- or possibly both. If only z^- or y^- could they not have been over-looked? In our enthusiasm we are isolating some z^- and some y^- mutants to see if we can find some which are recessive constitutives for y or z.

If this model is still alive when you are at Harvard for your lectures it would be wonderful to discuss them with you. I have forgotten the exact dates of your stay there and would appreciate getting them from you so that I can try to get east then.

Except for Jan getting a new boss there is not much new here. We had a visit from Sidney Brenner last week in which he astonished everyone by an up-to-the-minute expert understanding of everything being done by Stahl, Stent, Benzer and myself. He really is an institute in himself.

Please give my warmest greetings to Lise & the children.

As ever,

Aaron