May 1, 1957

Dr. Werner Maas
Department of Pharmacology
New York University - College of Medicine
550 Fifth Avenue
New York City, New York

Dear Werner,

My plans are changed. I am going now to Gatlinburg but will return from there to Chicago instead of going on to New York. Thus I will not be able to see you on Monday.

I like your postulate: "Inducers, there ain't such a thing!" more and more. I think the plan that you should now write a Note or an article which would include some of your results on arginine synthesis -- perhaps all those which you have obtained before you started collaborating with Gorini (unless, of course, you should want Gorini to be a co-author and include all your results). This paper should also review the facts relating to histidine synthesis and orotic acid synthesis (provided these are published), and end up with the conclusion that there is really no evidence to show that such a thing as an inducer exists at all. Just how much caution you want to put into the conclusion that inducers just don't exist is a matter for your own personal decision. I personally believe they do not exist.

Concerning β-galactosidase synthesis, there is one simple experiment which remains to be done which by itself would decide the question of whether there is an inducer operating in this system. This experiment is as follows: Milt finds that all of the constitutive mutants secrete a gunk, presumably a polysaccharide. If this gunk is composed of galactose, then there may be an inducer. If it is composed of glucose and contains no galactose, then there is no inducer. I have proposed to Novick and Milt that this experiment be done and that the three of us publish a paper on β-galactosidase synthesis, basing a new interpretation of all

Brown
~~Observed~~ facts on this one experiment. If they agree, then this is how I would prefer to handle the matter. OTHERWISE, I would be perfectly willing to stick my neck out and publish my current interpretation of the apparent induction of β-galactosidase on the basis of the evidence of published experiments. I would then go on from there and predict the outcome of a number of simple experiments on the basis of my current ideas. I feel, however, that this way of proceeding would not be the nice thing to do. After all, without knowing the facts presented by Milt in New York -- which were all developed by Milt and Aaron -- I would not have been in a position to reach my current conclusions. I hope, therefore, that Milt and Aaron will go along with my proposal on how to publish.

If a manuscript on β-galactosidase is ready by the time you are ready with your manuscript, we would try to get it published at the same time and in the same place as yours. However, I would suggest that your paper go in as soon as it is written and that the publication not be delayed waiting until we are ready with a reasoned analysis of the β-galactosidase system. I have asked Novick and Weiner not to discuss our half-baked ideas with outsiders even though my confidence that these ideas are correct is very great.

Because of my schedule I will have to do all the writing that needs to be done in the next two weeks. Therefore, please hurry up with your part of the writing also. One must not prolong a situation where one is inhibited from discussing freely one's ~~his~~ ideas with others, and the sooner we get out of it the better.

Sincerely,

Leo Szilard

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P.S. Because Dr. Szilard had to leave for Gatlinburg, this letter was not read by him after being transcribed.

May 7, 1957

Dr. Werner Maas
Department of Pharmacology
New York University College of Medicine
550 First Avenue
New York City, New York

Dear Werner,

I have now returned from Gatlinburg to Chicago and I am writing to you because I may have misled you just a bit in my last letter. Since I wrote that letter I have again looked at the β-galactosidase system. This system is really complicated and only further experiments will tell us what is going on there. However, it now looks to me that one probably cannot explain the inducing effect of TMG solely on the grounds that it inhibits an enzyme which makes the inhibitor -- UDP Gal. Accordingly, I can no longer say that the constitutive mutant must secrete a glucose derivative rather than a galactose derivative.

I have now decided to stop thinking any further about this system. One should come back to it after one has a theory of enzyme induction, and may then use the β-galactoside story to confirm the theory. By your challenging statement that all the inducer ever does is to inhibit an enzyme that makes an inhibitor, you have stimulated me to think about the whole general problem of enzyme induction, and I shall continue to think about it for the next two weeks.

I propose to write down my current thoughts on the subject and then sit back and look at the whole thing, and I should like to urge you to do the same. I expect to be in New York for two days in the second half of May, and we can then compare notes and see whether our thinking has moved along parallel lines or otherwise. I believe that you ought to try to go beyond just jotting down your thoughts and get a manuscript ready for

publication, and base it on all the facts that are available to you at present. You may publish your conclusions either alone or - if the experiments which you have done jointly with Gorini need to be used in order to strengthen your case, then - you may publish jointly with Gorini.

I have asked Milt to write down all of the known facts about the β-galactosidase system on a sheet of paper, and as soon as I receive this from him, I shall send you a copy. However, I have little hope that he will do this. For apart from a possibly subconscious inhibition, both he and Novick are completely absorbed for the moment in studying the permease. I expect to have a longer talk with him on Sunday and will then try to barter some ideas which I have against a list of his facts.

I shall call you over the telephone as soon as I get to New York in about two weeks or so, and I hope you will have a paper ready by then.

Sincerely,

Leo Szilard

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P.S. I just talked to Milt and I hope to send off a list of facts to you tomorrow.

May 9, 1957

Dr. Werner Maas
Department of Pharmacology
New York University College of Medicine
550 First Avenue
New York City

Dear Werner,

I saw Milt yesterday dictating a first draft of the Facts of Life concerning β-galactosidase for the purpose of sending it to you, so I hope you will receive the list before long.

In the meantime the following situation has developed here. I now understand the synthesis of β-galactosidase. There are three major thoughts which enter into this. One was provided by Milt when he postulated that β-galactosidase is not contained in the bacterium for the purpose of splitting lactose on the rare occasions when the bacterium is milk fed, but rather is an enzyme which the bacterium uses to build cell wall out of galactose residues. Inhibition of an enzyme which makes the inhibitor by the inducer, TMG, plays a role in this phenomenon, and the thought that this might occur was provided by you. I believe, however, that in addition TMG acts as an inducer which enhances the rate of production of an enzyme, and that by assuming that this is so we can now understand everything. I shall discuss this with you when I see you.

In the meantime I am merely writing to say the following: I shall be very glad to publish an interpretation of β-galactose synthesis - if I can convince you and Milt that my interpretation is correct - jointly with you and Milt; inasmuch as this interpretation makes use of both Milt's and your suggestions, the participation of both of you would be fully justified, if you wish to participate. I should be glad to prepare a rough outline which I would discuss with Milt before going to New York, and then you and I could see what further changes ought to be made in it. I told Milt of this plan and we might be able to

get together over this weekend when I hope to convince him that I am right; or else we will have to defer this get-together to the following weekend. The way this shapes up in my mind at present would be as follows: You might write up, either alone or jointly with Gorini, whatever ideas you wish to present concerning the control of enzyme synthesis which are involved in the biosynthetic pathways leading to an amino acid, and draw such general conclusions from it as you may wish. This paper I hope you will have ready - at least in outline - by the time I get to New York, and I would like to take a copy of it with me to Washington and brood over it further.

I have made some ~~considerations~~ of enzyme synthesis which I am writing down and I may be able to leave a manuscript with you when I see you in New York.

The paper which you and Milt and I might write on β-galactosidase synthesis would illustrate how such thoughts as you and Gorini might have developed and how such thoughts as I may develop on the general problem of enzyme synthesis might be applied to the interpretation of a concrete case such as the synthesis of β-galactosidase. I realize, of course, that you feel a decision must ~~wait on~~ my convincing you of the correctness of my ideas on the subject, and I propose to do this by oral argument. In the meantime, however, you might mull over the general proposition and let me know what you think about it when I get to New York.

With kindest regards,

Sincerely,

Leo Szilard

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DEPARTMENT OF PHARMACOLOGY

OREGON 9-3200

May 16, 1957

Dr. Leo Szilard
The Quadrangle Club
University of Chicago
Chicago 37, Illinois

Dear Dr. Szilard:

After coming back to New York I discussed our idea with Luigi, and after having many discussions about it, we have now arrived at the following notions.

It seems to us that a generally accepted concept today is that the inducer is an integral part of the enzyme-forming apparatus, not only for inducible enzymes, but for other enzymes as well. This idea has sprung from the work of the Monod School. Our work and other experiments on feed-back inhibitions of enzyme synthesis suggests strongly that no inducer is necessary for enzyme formation. Certain metabolites inhibit enzyme synthesis and certain others may stimulate it, though at the moment there is no clear-cut evidence in any of the feed-back systems for the latter type. However, if we regard "inducers" such as TMG as stimulators in our sense, we may say that they act either by removing an inhibition, or directly, by accelerating enzyme synthesis. Which-ever way they act, does not affect our basic picture, that of an enzyme-forming machinery which can function perfectly well without an inducer. Yet I feel quite sure that some of the cases of "inducer" action in the β-galactosidase system will turn out to be due to release of feed-back inhibition.

As far as publications are concerned, we are not clear about a future course of action. Much as we like the idea of applying the notions of release of feed-back inhibition to inducible enzymes and thus do away with the unphysiological teleology which has crept into the thinking in this field, we hate to publish such a hypothesis without some definite experimental evidence. We now have some data which permit us to conclude that in the case of arginine biosynthesis, and more specifically for the enzyme we have been studying, the substrate, ornithine, is not a necessary part of the enzyme-forming apparatus. We could write a note, using these data as our starting point, and expand our notions to other enzyme systems. If Milton has gone far enough with his experiments, the Chicago Group could publish a note simultaneously. We do feel that such notes should be published quite soon, rather than to wait ~~until the~~ for the final extensive papers. At any rate, I shall write down my ideas on the evidence we can adduce for our notion during the next few days and we can then discuss the question of publication when you are here.

Sincerely yours,

Werner Maas

P.S. Thank you for your letters of May 1, 7, 9, and 13. There are many points in them which I haven't touched upon above, especially those regarding Milton's experiments and would like very much to talk about when you come.

Robert Wagner
H.K. Mitchell