ROUGH DRAFT 5 March, 1964

MEMORANDUM ON THE INDUCTION OF β GALOCTOZYDES sidase.

by Lederberg

I wish to proposed the following model for the induction of β-Galoctozydes sidase which, as far as I can see, is consistent with all experiments which are known to me. so far.

There is a sequence of ~~cytrones on the chromosome~~ cistrons carried by the Lac region which ~~We define the direction of the chromosome which will call~~ go from left to right representing the i gene, the o locus, the z cystone, the y locus, and the acetylesus cystrone. ~~We postulate that transciption~~ and light this region acetylase turns on this order which we shall by definition from "left to right" goes from left to right..... We postulate that the cyntrones of the Messinger RNA (transcription) goes from left to right ..... takes place in the direction from left to right the synthesis of the polypeptide chain on the Messinger (transcription) takes place in the opposite direction as it goes from right to left. We postulate further that the first basis ..... that a number of bases..... that the first number of bases which are at the extreme left of the ..... which are at the left hand side of the i cystone represent a region of the chromosome where in the y type inducible strain the transcription of the Messinger RNA must begin and that if this region is covered by the cp, complimentary

25 22 32
216 17
468
143
325

strain of RNA then no Messinger RNA is produced. There are mutations at the o locus, the oc ± mutents where transcription can also begin at the o locus but ... amount of Messinger RNA is produced. There ~~This~~ may be anything between a few per cent and a full amount of the Messinger RNA produced by the inducible y type strain.

We postulate that the product of the i gene, the z gene, the y gene and the ascetylus gene.....

We postulate that when the Messinger RNA synthesises protein it .... that when the Messinger RNA is ..... the protein synthesized is poly peptide defined by the ascetylus gene. The next poly peptide is defined by the y gene, then comes the z gene and finally the poly peptide is synthesized on the i gene (write locus instead of gene). The poly peptide synthethized at i locus folds up into protein but this protein cannot ..... the protein synthethized is detached from the Messinger RNA whether or not there is an inducer present but the poly peptide synthesized on the i locus folds up into a protein molecule does not detach in the absence of the inducer..... Accordingly in the absence of the inducer the i protein remains sitting on the Messinger RNA and the Messinger RNA to the right of the i locus will be rather farily rapidly destroyed by the virus present in the

cell whereas that part of the Messinger RNA which corresponds to the .... lacks and in particular the far left of the Messinger RNA is protected by the attached I protein. Accordingly in the absence of the inducer there will flow around in the cytoplasm of the cell molecules which are..... into which the i protein is associated a trip of Messinger RNA which is complimentary to the far left end of the i locus. It is assumed that this stretch of RNA recognizes the the homologous stretch of the DNA and absorbs to it, thereby preventing in the absence of the inducer the production of further Messinger RNA by the lack region. I assume that the inducer combines with attached I protein and causes this protein to change itself especially (allosteric) if the inducer is combined with I protein. I assume two things to happen: The I protein is now permitted to detach from the Messinger RNA - a process that might take some time but is also an immediate destruction of the left hand side of the Messinger RNA so that it would no longer recognize the complimentary region of the DNA and would not combine with it or if it has been combined with it it would detached from it.

In order to account for socalled polar mutents which are capable of making the enzyme represented to the left..... represented on the DNA to the left of the point of mutation but not capable of making the enzyme represented to the right of the point of mutation, We have to assume that the DNA ~~dependent~~ are in a-~~synthesized~~ synthethis consistent in polarizing not single RNA bases but rather of tri-nuclear types which correspond to the code words for the various ameno acids and that DNA is not transcribed to the right of the point of mutation. Accordingly, socalled o .... mutations which are point mutations in the three locus that do not make any of the proteins represented to the right from the mutation point should not only prevent the formation of these enzymes but also should prevent the formation of the Messinger RNA, corresponding to these enzymes.

March 5, 1964

MEMORANDUM ON ANTIBODY FORMATION

by Leo Szilard

This memorandum is based on two premises:

(a) In the secondary response the specificity of the bulk of the antibody processed is determined by the antibody..... is determined by the antigen used for the primary ..... is determined by the antigen that is used for the secondary response.

(b) When the primary response is evoked a number of omnipotential cells are induced to form an antibody to the antigen injected and thereafter these cells will produce this antibody at a high rate. If these premises are correct then one of the three postulates listed under 1, 2 and 3 must be correct.

1. The antibody must catalyze the formation of its inducer -- a small molecule which can combine with the antibody molecule whether it is still attached to its messenger RNA and by exerting an allosteric effect on the antibody molecule "in situ" the inducer must permit the antibody to detach from the messenger RNA.

2. There must be for each antibody a specific repressor molecule -- a small molecule which can combine with the antibody which is still attached to its messenger RNA and by exerting an allosteric effect on the antibody molecule

in situ prevents the antibody from detaching from its messenger RNA. Further, the repressor molecule must be able ..... Further, the antibody molecules accumulated in the cytoplasm of the cell must be capable of rather tightly combining their respective repressor molecules.

3. If there are no inducers .... If an antibody does not produce its own inducer and if there are no specific repressors to the antibody that can combine with the free antibody molecules present in the cytoplasm, then the antibody or a precursor of the antibody presumably a monomer ~~f~~ which forms part of the antibody must be able to induce the formation of the antibody by attaching itself to the same or another monomer which is still attached to its messenger RNA and which is destined to form part of the antibody and by exerting an allosteric effect this monomer in situ ~~it~~ must facilitate its detachment from its messenger RNA. Thus, we can for instance imagine that the A ~~gene~~ chain? of an antibody induces ..... Thus, we can for instance imagine that by this mechanism the A ~~gene~~ chain of an antibody induced the formation of its B ~~gene~~ chain and vice versa, the B gene chain antibody induced the formation of its A ~~gene~~ chain.

It would be tempting to assume that the B ~~gene~~ chain induced the formation of the A ~~gene~~ chain only in the presence of the antibody and the same holds for the induction of the B ~~gene~~ chain, by the A ~~gene~~ chain. It would be further tempting to say that if the ~~determining group of the an~~

determining group of the antigen is slightly altered the same B ~~gene~~ chain will induce a slightly different A ~~gene~~ chain and vice versa the same A ~~gene~~ chain will induce a slightly different B ~~gene~~ chain. It would be tempting to assume this because it would then take ..... it would take a much smaller number of cistrons producing A and B ~~genes~~ chains to account for the high specificity of the antibody for the antigen which induces it ~~to~~- but if the antibodies were to owe the high specificity for a the antigen to a mechanism of this sort then it would be difficutl to explain how... why the antigen evoked the secondary response could lead the production of an antibody which fits the antigen used in the primary ..... ionization? rather than the antigen evoking the secondary response.

determining group of the antigen is slightly altered the same B gene will induce a slightly different A gene and vice versa the same A gene will induce a slightly different B gene. It would be tempting to assume this because it would then take ..... it would take a much smaller number of cistrons producing A and B genes to account for the high specificity of the antibody for the antigen which induces it to- but if the antibodies were to owe the high specificity for a the antigen to a mechanism of this sort then it would be difficult to explain how... why the antigen evoked the secondary response could lead the production of an antibody which fits the antigen used in the primary ..... rather than the antigen evoking the secondary response.

Muggleton 6-8558

6 March, 1964

MEMORANDUM ON ALLOTOPY

Allotopy poses a problem because a very large number of different antibodies to different antigens belonging to the same allotype, in the homozygote form allotopy which is difficult to understand if one assumes that each antibody is produced by a different cistron. It is conceivable that this difficulty is closely related to another difficulty which may be phrased as follows: If different antibodies are produced by different cistrons there must be cistrons of the order of magnitude to 100,000 involved in the formation of antibodies to the various antigens which are capable of evoking the formation of an antibody. Considerations put forward by Muller show rather conveniently that, assuming a reasonable mutation rate per cistron the assumption of 100,000 cistrons would lead to an enormous amount of genetic death if cistrons which mutated to incompetence were eliminated by genetic selection. In order to resolve both paradoxes, I propose..... I am ready to assume that the genetic composition of the species is maintained, not by the elimination of a mutated cistron through genetic death, but rather by high mutability ... by mutation equilibrium. Such equilibrium may be maintained if the probability that a cistron undergoes a point of mutation and loses its ability to produce antibody to a certain antigen A is the same as is the probability that one among the

remaining 100,000 cistrons undergoes mutation resulting in an antibody which is specific combining power for antigen A. In this way the genetic position of thespecies will be maintained without an excessive amount of .....

However, if you wish to resolve the paradoxity we will have to go one step further and make the following assumption: Let us assume that there is one gene from which all other capable of forming antibodies are derived and let us assume further that a certain portion of this gene has the normal mutation rate of say 10^{-2} per generation whereas the remainder of the gene has a high mutation rate, say 10^{-2} per generation. Let us further assume that a total mass of the gene is maintained in the face of deletion in the antibody ee forming a region of the genoneme by the propensity of this particular gene to insert copies of itself in the gene.

MEMORANDUM

From: Leo Szilard

28 April, 1964

To:
- Ross Adey
- Joel Elkes
- Donald Glaser
- Clifford Grobstein
- Oscar Hechter
- David Hubel
- Roy John
- Seymour Kety
- Rita Levi-Montalcini
- Robert Livingston
- Oliver Lowry
- Walle J.H. Nauta
- Leslie Orgel
- C.M. Pomerat
- James David Robertson
- Roger Sperry
- Fred Wilt

The enclosed paper, which will appear in the June issue of the Proceedings of the National Academy of Sciences, might perhaps interest you. It is an elaboration of a remark I made at a meeting held February 22-27 at the Salk Institute and it is the first of three instalments. Of the models for the recording and the recall of memory which I have so far seen, those which were sufficiently concrete to be capable of being disproven were manifestly inadequate to explain even Pavlov's basic observations on the conditioned salivary reflex of the dog --not to speak of higher mental functions. The model given in the enclosed paper is sufficiently concrete to be capable of being disproven and it is not obvious that the model is inadequate, even though it might ultimately turn out to be inadequate also.

Any comment which you might care to make will be appreciated. My address is: The Salk Institute for Biological Studies, P.O. Box 9499, San Diego, Calif.

Leo Szilard

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Leo Szilard

MEMORANDUM

From: Leo Szilard 30 April, 1964

To: Roger Revelle
John Isaacs
George Backus
Keith Bruckner
Harry Suhl
Bernd Matthias
Clay Perry
Harold Urey
Jim Arnold
Joe Mayer
Walter Munk
John Singer
Herbert York

The enclosed paper, which will appear in the June issue of the National Academy of Sciences, might perhaps interest you. It is just possible that I have succeeded in guessing right the processes involved in the recording and the recall of a sensory experience.

If you find time to read this paper and if thereafter you think you might like to participate in a discussion of it, please call me at The Salk Institute, 453-4100. I propose to set aside a Saturday morning, 10 - 12.30 or Saturday afternoon 2.30 - 5, for discussing this paper in a small group of those who have read it. If you call me and I am not in, you might talk to Jean Mangan, my secretary, and tell her whether it would be convenient for you to participate in such a discussion. Also if you have a strong preference either for Saturday morning or Saturday afternoon, would you be good enough to indicate this on that occasion?

Leo Szilard

MEMORANDUM

From: Leo Szilard

May 5, 1964

To: Jacques Monod
Seymour Benzer
P.M. Milner
James Olds
D.O. Hebb
Augustus B. Kinsel
Gerard Piel
Robert Galambos
Joshua Lederberg
H.S. Anker

Enclosed is a preprint of a paper which will appear in the June issue of the Proceedings of the National Academy of Sciences. Because authors are limited to eight pages in any one issue of the Proceedings, this preprint is but the first of three instalments.

Had I merely postulated -- as others seem to have done -- that if two neurons fire simultaneously, thereafter the synapse bridging these two neurons has a higher efficacy, then I would not be able to account even for Pavlov's experiments on the conditioned salivary reflex of the dog. As it is, it seems conceivable that the two fundamental postulates of my model might be able to account not only for the peculiarities of all of Pavlov's basic experiments but -- in conjunction with neuron-networks, as yet to be invented -- also for the higher mental functions. This could be true even if the details of the biochemical underpinnings of these two postulates should turn out to be incorrect.

MEMORANDUM

From: Leo Szilard May 5, 1964

To: Warren Weaver
Aaron Novick
Jack Sadler
E.P. Wigner
Edward Teller
George Beadle
H. Stanley Bennett
Michael Fuortes
Leo H. Bartemeier
Cody Webb
D.A. Sholl
Sidney Brenner
H.F.C. Crick

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MEMORANDUM

From: Leo Szilard May 7, 1964

To: Professor Matt Meselson
Professor James Watson
Dr. Frank Brink
Dr. Marc Kac
Dr. Rollin Hotchkiss
Professor Stephen W. Kuffler
Professor B.F. Skinner
Professor Leo Goodman

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Any comments which you might care to make would be appreciated.

MEMORANDUM

From: Leo Szilard

15 May, 1964

To: Sidney Brenner
Francis Crick
Jack Monod

I am sending you under separate cover a copy of Wooldridge's little book. I am particularly impressed by Wooldridge's sense of proportion which manifests itself in the book being remarkably well-balanced. I am enclosing with this memorandum a copy of a letter which I received from Bob Livingston and a copy of a letter which I received from Wooldridge.

Leo Szilard

Enclosures

LS:jm

MEMORANDUM

From: Leo Szilard

20 May, 1964

To: Dr. Herbert Jasper
Professor Tracy Sonneborn
Professor R.W. Doty
Professor H.W. Magoun
Professor W.R. Russel

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Any comment which you might care to make would be appreciated.

Enc.

MEMORANDUM May 27, 1964

Conversation with Charles Gordon Gross, M.I.T. Extension 5767 or 5765.

(1) Most work on fish and reptiles done by M.E. Bitterman, Bryn Mawr College, Penn.

Papers by Bitterman:

(a) On Fish

American Journal of Psychology, pp 542-51, 1961

Journal of Comparative and Physiological Psychology, Volume 54, pp 452-456, 1961

(b) On Turtle

Quarterly Journal of Experimental Psychology, Volume 14, pp 109-112, 1962.

Most papers by Bitterman in American Journal of Psychology and in Journal of Comparative and Physiological Psychology.

BOOKS:

W.H. Thorpe (Part 3) Learning and Instinct in Animals, Harvard University Press - Latest edition late '63 or early '64.

Maier and Schneller, Principles of Animal Psychology, McGraw Hill, 1935 or 1936.

Warner, Warden and Jenkins, Comparative Psychology (3 volumes) 1936 - Textbook

REVIEW ARTICLE: Bitterman, Techniques for the Study of Conditioning in Animals

~~MAGAZINE:~~ The Psychological Bulletin, Volume 59, pp 81-93, 1962.

Bitterman
Tutorials for the Study of Learning
The Psych. Bulletin 59 1962

Warner

21–93

W.H. 5751 Psychological

Thorpe
Part III
Learning & Instinct in Animals
Howard Univ Press 1963/64

Steven-Grover
Gordon-Gordon Gross
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65

M.E. → Bitterman-
Johns Hopkins College
Baltimore

Textbook: Fish
Comp. Psych. 3 Volumes
Warner, Warden and Jenkins 1936

~~Turtle~~

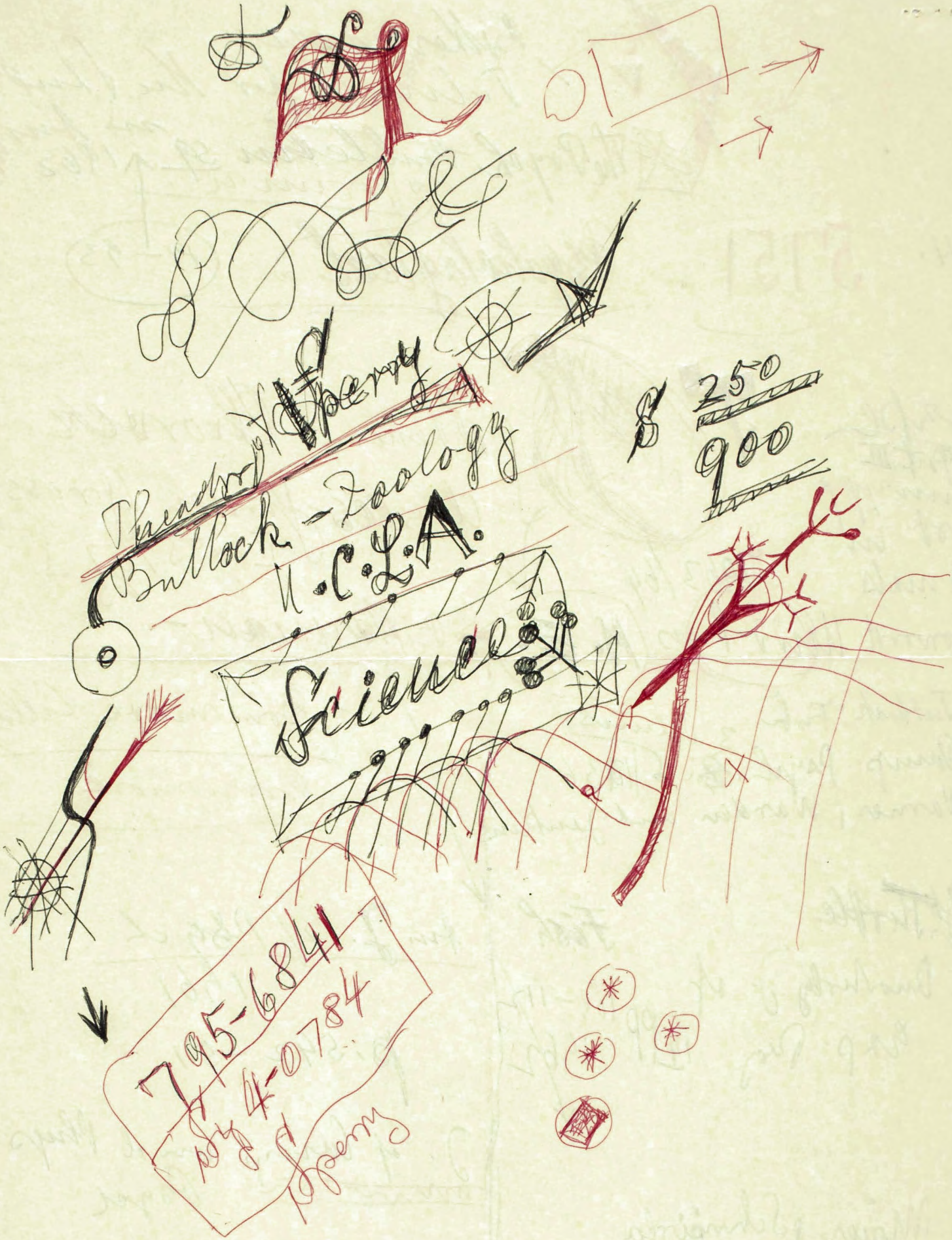
Quarterly J. of Exp. Psy 14 pp 105–112 1962

Fish

Am J. of Psych 1961 p. 542–51

J. of Comp and Phys. Psyc 54 p 452, 456 1961

Maier & Schneirla
Principles of Animal Psy 1936-35
McGraw Hill


Theodore H. Bullock - Zoology
U.C.L.A.
Sciences
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$ 250
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