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LJFB/LMF 30th July, 1959

Professor Leo Szilard,
Dept. of Biophysics,
The University,
Chicago 37,
Illinois,
U.S.A..

Dear Professor Szilard,

I am enclosing herewith a communication by J.Maynard Smith entitled A NOTE ON SZILARD'S THEORY OF AGEING. I am wondering if you have any comments you would like to make upon it for simultaneous publication; if so perhaps you would be good enough to let me have them when you return Smith's communication.

Yours sincerely,

L. J. F. Brimble

L.J.F.Brimble.

AIR MAIL

Mr. L.J.F. Brimble,
"Nature",
MacMillan and Company Ltd.,
St. Martin's Street,
London, W.C.2.

LJFB/LMF

c/o Dr. H. Coblans,
Scientific Information Service.

29th August, 1959.

Dear Mr. Brimble,

I wish to thank you for your very kind letter of 30th July and I am returning enclosed Mr. Smith's Note together with a Note of my own for simultaneous publication.

I am at present away from my office at the University of Chicago, The Enrico Fermi Institute for Nuclear Studies, as I am spending my vacation in Europe. A letter sent to my Chicago address will reach me, however, with a few weeks' delay.

Yours sincerely,

Leo Szilard

Encs.

K.

A Note on Szilard's Theory of Ageing

by

Leo Szilard

The Enrico Fermi Institute for Nuclear Studies, The University of Chicago, Chicago, Illinois.

In an interesting letter to the Editor appearing in this issue of "Nature" under the above title, J. Maynard Smith refers to the theory of the ageing processes in mammals which I recently proposed ("On the Nature of the Ageing Process", Proc. Nat. Acad. of Science, U.S.A., 45: pp. 30-45, 1959), and he cites observations which may appear to contradict this theory.

All of the observations quoted by Smith relate to fruit flies and they fall into two classes: observations which we may expect to be able to duplicate in the case of mammals and those which we may not. Since I do not propose to discuss here whether the theory might or might not be extended to insects, I am primarily concerned with the former of the two classes.

Smith states that a genetically variable, wild, population of fruit flies has a substantially higher life expectancy than inbred, fairly or wholly homozygous, strains derived from it. He also states that the F_1 hybrid obtained by crossing two different inbred strains has a substantially higher life expectancy than the two inbred strains themselves. Smith holds that these findings are not compatible with the theory of ageing that I proposed.

It is probably true that the observations quoted above could be duplicated with mammals and I am quite prepared to accept this thesis for the sake of argument. As I shall presently show, however, my theory does not preclude that the homozygous inbred strains may have a substantially smaller life expectancy than the wild type strain. Further, the theory demands, that the life expectancy of the F_1 hybrid be appreciably higher than that of the wild type strain, if the wild type strain carries a substantial number of faults. In order to see this, we may consider the following:

At present there is no evidence that a gene may be responsible for anything except for the production of a specific protein molecule which might be endowed with a specific enzymatic activity. In a wild population, a given gene may be present in the form of a variety of alleles and the corresponding enzymes may differ in their turnover number. For the purposes of our discussion here, we shall call an allele "weak" if the turnover number of the corresponding enzyme is small. If this turnover number is very small, the allele might be a recessive lethal. A completely homozygous strain is, of course, free of recessive lethals, but it may contain a number of "weak" alleles.

For the purposes of our discussion here, we shall adopt a somewhat over-simplified picture and we shall disregard the possibility that the enzyme levels in the somatic cells may be determined to some extent by the regulatory mechanisms of the cell, through enzyme induction or otherwise. On this over-simplified basis, we may then say, that the somatic cells of an inbred strain, which is homozygous for a number of "weak" alleles, are impoverished in the corresponding enzymes, as far as their bio-chemical activity is concerned.

Our theory assumes that only a small fraction of the enzymes, less than one-fifth perhaps, is important for the functioning of the somatic cells of the adult, while practically all of the enzymes may be important for differentiation and morphogenesis during the embryonic life of the individual. Accordingly, we may then expect that ~~the~~ an individual of the inbred strain (which is homozygous for a number of "weak" alleles) may be maldeveloped in the sense that it may have a much smaller reserve at birth than the wild type individual, with respect to a number of physiological functions. Thus it is conceivable that an individual belonging to an inbred strain may die at an age at which, f*, the "surviving" fraction of its somatic cells has fallen to, say, $f^* = \frac{1}{2.72} \approx \frac{1}{e}$; whereas and individual belonging to the wild type strain may die at an age at which, f*, the "surviving" fraction of its somatic cells has fallen to about $f^* = \frac{1}{7.4} \approx \frac{1}{e^2}$

We may compute for this case the most probable age at death, for Man, from formula (14) given on page 33 of my paper (loc.cit.) which reads:

$$x_r + r = \sqrt{4m \ln \frac{1}{f^*}} + \ln \frac{1}{f^*}$$

where x_r is the number of ~~faults at age~~ hits at death; r is the number of the inherited faults; m = 23 is the number of chromosome pairs and f* is the surviving fraction of the somatic cells at the age of death.

The (most probable) age at death, t_r, is given by: $t_r = 6 \cdot x_r$ years

For the inbred strain we obtain (t_r) the most probable age at death by writing: r = o and $\ln \frac{1}{f^*} \approx 1$. We thus obtain ~~for the~~ $t_r = 63.6$ years.

For the wild type we obtain t_r, the most probable age at death, by writing: $r = 2$ and $\ln \frac{1}{f^*} \approx 2$. We thus obtain $t_r = 81.5$ years. The actual value for white females in the United States is $t_r = 80.5$ years.

For the F_1 hybrid we obtain t_r, the most probable age at death by writing: $r = o$ and $\ln \frac{1}{f^*} \approx 2$. We thus obtain $t_r = 93.5$ years. This is 12 years more than the value for the wild type.

It may thus be seen that a substantially shortened life expectancy of the homozygous, inbred, strain, as compared with the wild type, <u>need not be inconsistent</u> with the theory. However, an increased life expectancy of the F_1 hybrid ~~in comparison~~ as compared with the wild type strain is <u>a necessary consequence</u> of the theory.

This consequence of the theory could be tested by experiments on short-lived mammals, say mice. In order to render the experiment more sensitive, one may first expose to ionizing radiation a population of "wild" type mice over several generations and may thereby increase the number of faults in the population. Starting with such a wild population, enriched in faults, one would then select two unrelated ~~females~~ families and derive from them two inbred homozygous strains. The theory demands that the F_1 hybrid of these two inbred strains should live appreciably longer than the population from which the two families were selected. Given a suitable opportunity, I propose to arrange for experiments of this sort. A negative result might well prove fatal for the theory.

I should perhaps add at this point that the observed differences in the life expectancy of the male and the female do not provide a usable criterion for the validity of the theory because, f^*, the "surviving" fraction of the somatic cells at death, might differ appreciably for the male and the female.

Smith cites in his note a rather peculiar effect of the temperature on the life expectancy of the male and the female in D.subobscura. It seems to me that any future theory of ageing that may be generally applicable to insects would be put to an unduly severe test, were one to demand that it account for this particular effect.

Because the theory of ageing that I proposed makes quantitative predictions, it is capable of being disproven by experiments and, sooner or later, ~~this~~ such might be its fate. At present I am not aware, however, of any valid observations, which contradicts this theory. In these circumstances, I am not at present disposed to go along with the appraisal of the theory, implied in the last paragraph of Mr. Smith's Note.

L.

29th August, 1958.

c/o Clarendon Laboratory
Parks Road
Oxford

December 3rd 1936

The Editor
Nature

Sir,

enclosed I am sending you the corrected proofs of my paper with the request to forward it to the printers.

A number of changes has proved to be necessary to make the meaning of the paper clearer, and it appeared also necessary to change the summary.

I must apologize for these changes, and should of course be glad to take care of any additional expenses that might be caused by them.

May I again see proofs of the paper before finally releasing it for print, and have perhaps three or four copies instead of the usual two ?

Apologizing once more both for the changes and for the delay caused by my absence

I am

Yours very truly,

(Leo Szilard).

(1.) It is however very improbable that two such anomalies as isomerism and a new type of radiative capture (requiring fast neutrons) should both occur in the same element unless there is a~~n~~ special ~~inherent~~ reason for their combined occurence, because each of these two anomalies - if it exists- must be rare. Since for the time being no such reason is apparent , we have to investigate other alternative interpreatations of our observati

(2.) The generation of the 4½ hr. period by such a non capture process from indium 113 would only be possible if the binding energy of the neutron in this isotope were of ~~the~~ an unexpectedly low value of less than 2.5 m.e.v.

(3.) An estimate of the mass of such a tetra neutron based on current ideas on the neutron-neutron interaction leads to a value which is so much in excess of the lower limit , stateddabove to be 4.016, that the ejection of such a tetra neutron from indium 115 by a 2.5. m.e.v. neutron would appear to be impossible. That the ejection of a double neutron from indium 113 sould account for the generation of of the exceptionally strong 4½ hr. period would seem surprising since the relative abundance[4.)] of this isotope is less than 5½%. The sam difficulty would arise if we attempted to explain the generation of the 4½ hr. periodby a non capture process from indium 113. Such a non capture process is ruled out with certainty as an explanation for any one of the three radioactive bromine isotopes generated in the experiments of Kourtchatow, Myysowsky, and Roussinow[7.)] which raise a problem possibly similar to that of indium.

None ofNdhe of the discussed interpretations of our observations can thus be accepted without additional evidence and indium will be further investigated.

Summary.

Dr. Leo Szilard reports anomalies concerning the generation of a radioactive indium isotope having a half life period of 4 ½ hr. From the experimental evidence one might think that two anomalies, isomerism and a new anomalous type of radiative capture occur in indium. Since each of these anomalies in itself, -if it exists - must be a rare occurence it is difficult to believe that they should both occur for the same element unless there is a special reason for their combined occurence. Alternative interpretations of the observations are investigated including the possibility that a hitherto unknown heavy isotope of the neutron may be ejected from indium by a neutron.

Letter to "NATURE".

ANOMALIES IN THE FERMI EFFECT.

Amaldi, d'Agostino, Fermi, Pontecorvo, Rasetti, and Segre have found[1] that indium shows two radio-active half-life periods (16 sec. and 54 min.) if bombarded by neutrons which have been slowed down by paraffin wax. T. A. Chalmers and I have subsequently reported[2] that indium can also be relatively activated with a period of several hours if irradiated by neutrons from a radon-alpha-particle beryllium source in the absence of hydrogen-containing substances. The two shorter half-life periods seem to arise, to all appearances, from two stable isotopes of indium, 113 and 115, by a process in which the neutron is captures and added to the indium nucleus. These two shorter periods, therefore, should be attributed to two radio-active isotopes of indium, 114 and 116. In these circumstances, it seemed ~~very~~ somewhat difficult to account for a third radio-active half-life period in the case of indium, and we therefore raise the question whether its existence can be explained without a new assumption.

In the present experiments, the behaviour of this third period (the half-life time of which I have now measured, ~~xxx~~ to be 4½ hours) has been investigated by using various sources of neutrons.

Gamma rays from radium C liberated neutrons from beryllium as previously reported[3] and these photo neutrons are efficient in activating elements which transmute into their own isotopes by adding a neutron to the nucleus (radiative capture). By irradiating indium for hours with such photo-neutrons in the absence of hydrogen-containing substances (the presences of which would unduly reinforce the 54 min. period), I obatined activities up to 150 kicks per minute which decayed to less than kicks per minute in hours on the Geiger-Muller Beta-ray counter. These kicks belong entirely to the

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1) Amaldi, D'Agostino and Segre "La Ricerca Anno V, Vol.11, n.9-10.
2) Szilard and Chalmers Nature Vol.135, p.98, 1935.
3) Szilard and Chalmers Nature Vol.134, p.494, 1934.

54 min. period, and no trace is to be found of the 4½ hour period.

By irradiating indium with neutrons from radon-alphaparticle-beryllium sources, or radon-boron sources for about hours, I obtained, 5 minutes after irradiation up to or kicks per minute respectively. About half of the observed kicks belonged to the 4½ hours period in either case.

Using neutrons from a radon-boron source, I compared the intensity of the excitation of the 4½ hour period of indium with that of the 10 min. and 15 h. periods of aluminium, the 2.3. min, period of silicon, and the 2.3 min. period of phosphorus. I find that the 4½ h. period of indium is more than times as intense as any of these other periods. (Incidentally, it is also more intense than the 25 min. period of iodine). The 2.4 h. period of phosphorus is, onthe other hand, ~~xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx~~ about many times as intense as the 4½ h. period of indium.

In the case of the 4½ h. period of indium we know from the chemical evidence[4] that we have to deal with a radio-active isotope of indium. The fact that photo-neutrons do not excite this period in the present experiments indicates, however, that this radio-active indium isotope is not generated from one of the stable indium isotopes by a process in which the neutron is simply added to the nucleus (radiative capture), but is generated from them in some other way ~~from one of the stable indium isotopes~~ by neutrons which are faster than ~~all~~ our photo-neutrons.

The present experiments with neutrons from a radon-boron source, on the other hand, indicate that our radio-active indium isotope arises from the stable indium isotope 115, for it would be very difficult to assume that the 4½ h. period, which, next to the 2.4 h. period of phosphorus, is the strongest observed, should be due to a radio-active indium isotope which arises from the stable indium isotope 113, since the relative abundance of 113 appears to be

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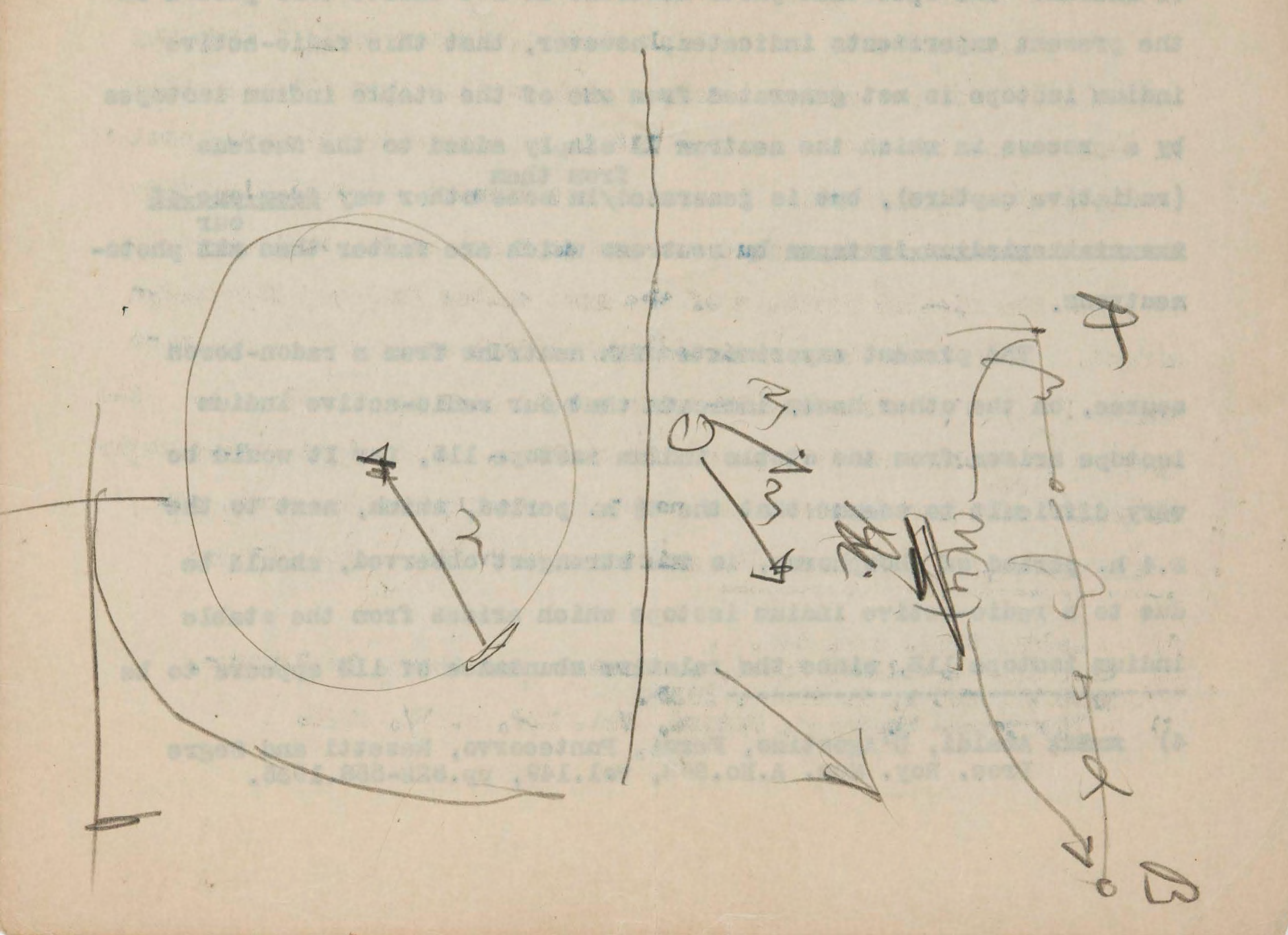
4) ~~xxxx~~ Amaldi, D'Agostino, Fermi, Pontecorvo, Rasetti and Segre Proc. Roy. Soc. A.No.868, vol.149, pp.522-558.1935.



less than 5½ %.[5]

Further, we have to consider that the bulk of the neutrons from a radon-boron source appear to be less fast than a strong group of fast neutrons from a radon-alphapartivle-beryllium source since they are very much less efficient in activating the 2.3 min. period of silicon. This view, first put forward by Amaldi, D'Agostino, Fermi, Pontecorvo, and Segre,[6] finds support in the present experiments which show that the 2.4 h. period of phosphorus, known to be excite by about 3 MEV neutrons[7] is ~~about~~ more than times as strong as the 10 min. and 15 h. period of Al., the 2.3 min. period of Si., and the 2.3 min. period of P. ~~xxxxxxxxxxxxxxxxxxxxxxxxx~~ Therefore it would be difficult to assume that these moderately fast neutrons should produce our radio-active indium isotope in a non-capture process by knocking out a neutron from one of the stable isotopes of indium, This assumption would appear all the more unlikely, as such a non-captu ture process would lead from the abundant stable isotopes of indium 115 to the radio-active isotope 114, which we have already allotted to the half-life periods of either 16 sec. or 54 min.

All thisleads me to think that the indium isotope decaying with the 4½ hour period has a mass number smaller than 115, and that it arises from the indium isotope 115 in a process in which the neutron is captured. Accordingly, I wish to put forward the following view:-

Moderately fast neutrons are captured by the indiu,m nucleus 115, and ~~the~~ a ejected particle of the mass number four and the charge nought. This leads to a radio-active isotope of indium of the mass number 112, which disintegrates with a half-life period of 4½ h. The ejected particle - an isotope of the neutron, which might conveniently be called ~~quatron~~ tetron - has not been observed in the past, and there was no indication of its existence hitherto. The present

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5) Aston, Proc. Roy. Soc.
6) Amaldi, D'Agostino, Fermi, Pontecorvo and Segre, La Ricerca, Anno Vl, Vol 1, h. 11-12. 1935.
7) Bjerge and Westcott, Nature, Vol. 134, p.177, 1934.

experiments, however, seem to give sufficiently strong evidence for its existence to justify attemtps for a direct observation of this particle, and such attempts are now being made.

An exactly analogous explanation might be put foreard in order to explain the generation of three radio-active isotopes of bromine from bromine, which has been discovered recently by Kourtchatow, Myssowsky, Roussinow.[8]. All these three radio-active bromine isotopes can be generated by neutrons which have been slowed down by paraffin wax.[9]

Clarendon Laboratory,

OXFORD.

January 30th. (Leo Szilard).

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8) Kourtchatow, Myssowsky, Roussinow. C.R.200, 1201, 1935.
9) Amaldi, D'Agostino, Fermi, Pontecorvo, Segre, La Ricerca, Anno Vl, Vol.1, n.11-12. 1935.

Be + n

4 0155

4 . 014

11

$A + n = A' + n(4)$

$n(4) + B = B' + n + n$

5½

112 113 114 115 116

16 sec, 54 m

4½ h

2.4h

2.018

4.014

2.018