

THE UNIVERSITY OF CHICAGO

CHICAGO 37 • ILLINOIS

THE ENRICO FERMI INSTITUTE  
FOR NUCLEAR STUDIES

May 8, 1959

Dr. Jonas Salk  
The Medical School  
The University of Pittsburgh  
Pittsburgh, Pennsylvania

Dear Salk:

We are reappraising the need to discuss with our Russian colleagues the problem posed by the bomb. As you may remember we called off the meeting which was scheduled for last September in Moscow. At this time the response on this side of the Atlantic appears to be stronger and more favorable than it was last fall. Hans Bethe and Alvin Weinberg (Director of the Oak Ridge National Laboratory) are joining the Committee of the American Academy of Arts and Sciences which is responsible for this operation.

Roger Revelle (Director of the University of California in La Jolla) has joined both the overseeing committee and the operating committee. For the time being Revelle and I are jointly operating, the general idea being that I may soon resign as Chairman and Revelle may then take over the Chairmanship.

We had a dinner meeting in Washington, D. C., for the purpose of discussing ~~the~~ procedures, (Roger Revelle,

Jerome Wiesner, Alvin Weinberg, Victor Weiskopf, Richard Leghorn, Harrison Brown, and E. P. Wagner), and subsequently Revelle and I called at the State Department. We have a tentative plan of holding a meeting of about fifteen American scientists over the weekend of June 5-7, in New York, Princeton, New Jersey, or Washington, D. C. We propose to discuss on this occasion not procedures but substance. You will be advised if the meeting is definitely scheduled.

Let me now turn to another subject. I wonder whether you would consider setting up the research operation about which you spoke to me at some place other than Pittsburgh. If so, please read the enclosed memorandum concerning conversations which I had with Jim Watson (Harvard) and Roger Revelle. Revelle has asked me to find out whether you might be willing to consider La Jolla. As you know, the University of California is setting up a Graduate School of Science and Engineering at La Jolla, of which Roger Revelle will be the Chancellor or Provost, or whatever you call the top man. At present, he is the Director of it. He is also Director of the Scripps's Institute of Oceanography at La Jolla which is part of the University of California.

They have started building up their physics department and are in the process of making appointments. They have also started building up their Chemistry Department and, as you

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Next, they have planned to build up their Department for Micro-biology with emphasize on Molecular Biology.

They have not scheduled the building of an undergraduate college. They would like to embrace the first two years of medical school which is limited to the basic biological sciences, but have not so far approached the Regents about this. The establishment of clinical departments corresponding to the last two years of the medical school is not being discussed as yet. In order to make it easier, however, to establish such departments later on, concrete proposals have now been made to build a large hospital, which was supposed to have been built in San Diego, in La Jolla instead.

I know La Jolla very well and think it is an excellent place. I have no doubt that you would like Revelle and that you and he would think alike concerning the need to keep such a research institute, as you have in mind, out of the clutches of the Regents.

Please let me have your reaction to the enclosed memorandum, provided that you have reached the point of considering sites other than Pittsburgh. Frankly, I see no possibility of getting many first-class people to move to Pittsburgh.

You can reach me in care of Robert B. Livingston,

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National Institutes of Health, Bethesda 14, Maryland, (Telephone, OLiver 6-4000, extension 3501), or at the Dupont Plaza Hotel in Washington where I am staying.

If we actually schedule a meeting for the weekend of June 5-7, there would be an excellent opportunity for you to have an informal discussion with Revelle on that occasion.

With kind regards,

Sincerely,



Leo Szilard

P. S. Recently <sup>1/3</sup> had an idea on how to approach the problem of aging. Attached you will find a one ~~page~~ article which represents a fairly good summary of the paper that I published. Naturally, it is not entirely correct. I am now working on a second paper, mainly concerned with conclusions of the theory which could be tested experimentally with comparative ease.

## AMERICAN NEWSLETTER

# A theory of how we age

from JOHN LEAR, our American correspondent

AGEING is plainly a matter of arithmetic. We add one year to another until our time expires. Everyone knows this, and insurance salesmen earn a pleasant living by averaging out the figures and cajoling the rest of us into wagering where we as individuals fit into the scheme. But only a very imaginative man would think of systematizing these mathematics into one equation to comprehend the interval between the cradle and the grave. In all of American science, there are few minds creatively abundant enough to put such a thought into action if the idea did strike. One of these rare intellects graces the disarming corpulence of Dr. Leo Szilard, who has used it to work out mankind's first scientific theory of how we grow old.

It seems to me inevitable that this latest of the Hungarian-born theorist's long line of brilliances will in time be recognized as a major contribution to human thought. It appears, however, with almost innocuous modesty in the pages of the January, 1959, *Proceedings of the National Academy of Sciences*. A dry and frugal footnote tells us that the work was done while Dr. Szilard—ordinarily occupied with the affairs of the University of Chicago's Enrico Fermi Institute of Nuclear Studies—was serving as a consultant to the basic research programme of the National Institute of Mental Health at Bethesda, Maryland. The NIMH is, of course, keenly conscious of the relationship between advancing age and mental illness at a time when the population of this country is ageing markedly.

"This paper represents an attempt to describe a hypothetical biological process that could account for the phenomenon of ageing", the introductory sentence says. "Ageing manifests itself in much the same general manner in all mammals, and we are in a position to learn enough about the ageing of mammals to be able to test the validity of a theory that leads to predictions of a quantitative kind—as does the theory here presented."

Dr. Szilard's thinking takes off from the fact that the basic hereditary unit in our makeup, the gene, can be responsible for the synthesis of a specific protein molecule, and that this molecule in many instances has a specific catalytic function

in one of the chemical processes of the body. When the gene mutates, the change renders the gene incompetent to bring about the process for which it ordinarily would be responsible. When the bundle of changes inside us grows sufficiently large, we are incapacitated, we are crippled, and ultimately we die.

How do we begin to die? Just where does the mysterious stroke of death originate? The theory assumes not one all-powerful, felling blow but a series of minor hits. The hits occur at random, with a speed that remains constant from the moment we are born. One hit disables one chromosome, to the extent of knocking out one of the working partners of a pair of genes harnessed to a given biological task. The chromosome continues to function, however, until the second partner also suffers a hit.

Each of us possesses altogether about 15,000 genes. The Szilard theory assumes that only 3,000 of these are important to the healthy life of an adult. To distinguish these effective operatives from all the other genes, the 3,000 are dubbed "vegetative" genes and the mutants of these "vegetatives" are called "faults".

If this were the whole story, the variation in the length of our lives would depend entirely on accidents, murders and wars. But this is not the whole story. The whole story begins generations before we are conceived. It is handed down in the genes of our forebears. By the time the chromosomes containing the 3,000 "vegetative" genes reach us, a certain number of hereditary "faults" have already occurred. In terms of age, it is as though we have already been scraped by the edge of Father Time's scythe before we emerge from the womb. Some of us are born relatively old people.

Whatever individual age one of us has at the beginning of his own phase of the eternal process known as life, that age increases progressively with the number of "vegetative" genes that are disabled by the mysterious hits of time against the species. The progression is not entirely steady, for the really "old" newborn die off rapidly in the first year of existence and then at a slower rate to the age of ten years. After that time, inherited "faults" increase the death rate "only in conjunction with the hits of time, and they increase it appreciably only above 40 (years

of age)". From then on, the surviving fraction of vital genes "decreases with age at an accelerating rate".

Here Dr. Szilard begins his ageing equation by writing the symbol "f" to represent the surviving fraction of genes. When "f" reaches a certain critical value, symbolized as "f\*", "the individual . . . dies . . . within the year".

"Thus, in its crudest form," Dr. Szilard notes, "the theory postulates that the age at death is uniquely determined by the genetic makeup of the individual."

This, however he adds at once, "cannot be strictly true, for, if it were true, identical twins would die within one year of each other". And the fact is that female identical twins die at differing intervals averaging out to three and a half years. So the reasoning has been refined to account for the variance in manifold ways, including the shielding effects of environmental conditions "prevailing at present in the United States, where essentially no adult dies for lack of food or shelter and no adult has a reduced propensity to procreate because of his inability to provide food or shelter for his offspring".

In underpinning his theory mathematically, Dr. Szilard takes a hypothetical, genetically perfect, white female and designates her age of death as the "life-span of the (human) species". He finds that she, at 50 years of age, would have the same physiological age as today's average woman of 35 years. Her most probable age of death would be 92 years, twelve years greater than the age at which the average woman dies today.

The Szilard equation encompasses other women by postulating a basic time interval of the ageing process and defining this interval as the difference between the life-expectancy of the genetically perfect woman and a woman whose genetic makeup includes one "fault".

Dr. Szilard stipulates that genes "vegetatively" incapacitated by the hits of age are not thus rendered impotent in their power to duplicate themselves in future generations.

Experiments are now under way in mice to provide supporting evidence for the ageing theory, mice being better than hamsters or dogs for the purpose because the number of their chromosome pairs is closer to the number of man's.

From: Leo Szilard

May 7, 1959

Memorandum on conversations with Jim Watson on May 4, and with Roger Revelle on May 5, regarding the hypothetical possibility of convincing Jonas Salk to set up a research institute for basic and applied biology at La Jolla in loose affiliation with the University of California at La Jolla.

On May 4, I happened to meet Jim Watson by accident. I had previously heard from Francis Crick that Watson has been thinking a lot about the cancer problem and so I asked him about this. Watson explained to me his reasons for believing that, with the techniques at hand, it should now be possible to obtain relevant information about the nature of cancer. As the conversation continued it turned out that he was actively exploring the possibility of setting up a research laboratory staffed with people who are interested in the basic problems of biology, but who are also sufficiently interested in applied problems to enjoy cooperating with each other on the problem of cancer.

On an earlier occasion, I, myself, had given some thought to the question of what it would take to create a research institute in which people, mainly interested in basic biological research, ~~also~~ would take an interest in some of the major problems of public health and medicine.

Watson and I were agreed that in order to make such an operation successful one would have to create conditions which would make it possible to get practically every one who is desirable to join. One necessary condition for this would be to set up the institute in California in the Berkeley, Palo Alto, or La Jolla area. Next Watson and I attempted to define what kind of people would be desirable. For this purpose we proceeded to list the following names: Kalckar, Berg, Mitchison (Edinburgh), Dulbecco, Khorana (Vancouver) Meselson (Cal Tech), Jacob (Paris), Smith (of Markham & Smith), Tom Anderson (Philadelphia), Lenox, Stent (Berkeley), and Pardee (Berkeley).

Watson and I also agreed that more men whose main interest is anti-body formation, delayed hypersensitivity, and tissue transplantation ought to be added.

Apparently Jim Watson and I think alike on what kind of people it would take to get a successful research operation going.

I mentioned to Jim Watson that Jonas Salk had been thinking of perhaps setting up a somewhat similar research institute and that his thinking on what it would take to create conditions in which scientists could work happily in the field of basic biological research might come rather close to our own thinking on this subject. I told Jim Watson


that Salk realizes that such a research institute should be affiliated with a university but should not be run by the Board of Trustees of the university or be subject to the numerous rules under which the university operates.

In conclusion, I told Jim Watson that perhaps we ought to look for a university in California which would invite Salk to set up an institute along the lines along which he had been thinking in the last few years. In many respects the ideal location would be La Jolla where the University of California is in the process of building up a graduate school which might include the first two years of medical school centering on the basic biological sciences. I told Jim Watson that knowing Roger Revelle, who is the Director of this operation at La Jolla, it is my guess that he and Jonas Salk would quickly reach a meeting of the minds on what needs to be done and how it should be done.

I saw Roger Revelle on May 5 on another matter and I made use of this opportunity to review with him my conversation with Jim Watson. I also told him what I knew of Salk's reluctance of setting up a research institute under the domination of a university. I found on all the points which I touched an enthusiastic response on the part of Revelle, including even the people whom Jim Watson and I have hastily listed. Revelle asked me to contact Salk and find out whether he would be willing, in principle, to consider setting up an



institute at some place other than Pittsburgh. Revelle thought that it would be comparatively easy to obtain at La Jolla a tract of land, as a gift, upon which such an institute could be built, if Jonas Salk were willing to set up such an operation at La Jolla. I told Revelle that I would explore this and let him know if it appears desirable that he and Jonas Salk get together early in June.

cc: Jim Watson  
Roger Revelle  
Jonas Salk 

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