THE UNIVERSITY OF WISCONSIN
MADISON 6

DEPARTMENT OF MEDICAL GENETICS
SCHOOL OF MEDICINE

DEPARTMENT OF GENETICS
COLLEGE OF AGRICULTURE

Please Reply To
GENETICS BUILDING
UNIVERSITY OF WISCONSIN
MADISON 6, WISCONSIN

December 26, 1958

Professor Leo Szilard
Quadrangle Club
University of Chicago
Chicago 37, Illinois

Dear Dr. Szilard:

Dr. Lederberg showed me your papers on aging, and I read them with great interest. The theory has the merit of being concrete and quantitative so that there are several possible tests.

One way in which the theory seems unrealistic to me is in distinguishing so sharply between early acting lethals and faults. I have the opposite impression that most mutants cause reduced viability at several ages. The fact that there is a very low death rate from 10-20 years doesn't need to cause any trouble; this may simply be a particular resistant period when cellular events that would otherwise have an effect do not. There are numerous examples of mutants in man and Drosophila that reduce both early viability and adult longevity.

If there is a relation between early and late mortality, some of the calculations that Morton, Muller, and I have done are relevant (PNAS 42: 855. 1956). We found from mortality rates in consanguineous marriages that the average human carries the equivalent of about 4 recessive lethals causing death from birth to early adulthood. Of course, we can't distinguish between 4 lethals or 8 with probability 0.5 of causing death, etc. These studies were done on data gathered in rural France some years ago when the environment was presumably more rigorous than now. Slatis (Am. J. Human Gen. December 1958) has reported a value about half this large from current Chicago data.

Children of consanguineous marriages would have Ar homozygous faults, where A = 1/32 for cousin marriage, or 1/8 for sib mating. On your hypothesis I assume these would die as embryos and there would be no reduction in adult longevity. This would provide one test of the hypothesis. I know of no information on longevity in inbred humans, but there may be mouse data.

What would be the mathematical consequences of redefining r to mean the number of "fault equivalents", where a fault equivalent means n mutants each with 1/n probability of causing a cell death when combined with an aging hit or when homozygous?

Another possible modification of the hypothesis is to assume that aging hits are also affected by radiation. Without speculating on the nature of an aging hit, I should think that many hypotheses would be such that radiation would be expected to increase their frequency. I haven't thought through the quantitative consequences of this (probably you have), but it would lead one to expect a smaller reduction in longevity in the progeny than in the irradiated parents. This same consequence is to be expected if, as I suspect, some faults also increase the probability of early death.

In any event I think it is most important to compare life shortening in irradiated parents with that of their offspring. If the animals were irradiated in a single dose very early in embryology it would increase the likelihood that germinal and somatic tissues are equally responsive.

It is possible that the environmental similarities of identical twins are sufficient to lead to a serious underestimate of non genetic scattering. A possible check is provided by 2-egg twins, whose intra-pair variance in number of faults should be half that of a randomly chosen unrelated pair. At the same time their environmental similarity should be about the same as identical twins.

For example, if the average difference in fraternal twins is 8 years (I don't know how you made the calculation on p. 11 going from death over age 60 to those over 40, so this is only a guess) this would correspond to a standard deviation of the difference of 10, or a variance of 50 for a single individual. Subtracting 10 for the environmental variance leaves 40 which is approximately half the genetic variance, 96-10=86, of unrelated individuals.

As far as experimental tests go, a comparison of longevity of progeny and radiated parents ought to be very informative particularly if, as you suggest, other signs of aging are looked for. I would like to add to this the longevity of sib mated progeny of irradiated parents, and the comparison of hybrids with inbred lines. An especially critical consequence of your hypothesis, because of its easy testability, is the absence of an effect of inbreeding on longevity.

If you are ever near Madison, I hope you will stop in.

Sincerely,

James Crow

James F. Crow
Professor

JFC/ew

P. S. On page 6, equation (10), there is a small typographical error. The quantity under the radical should have 1/m substituted for 4 m.

P.P.S. One might look for somatic mosaics in animals known to carry heterozygous recessive factors - hair color genes perhaps.

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Dr. Leo Szilard

Another possible modification of the hypothesis is to assume that aging hits are also affected by radiation. Without speculating on the nature of an aging hit, I should think that many hypotheses would be such that radiation would be expected to increase their frequency. I haven't thought through the quantitative consequences of this (probably you have), but it would lead one to expect a shorter reduction in longevity in the progeny than in the irradiated parents. This same consequence is to be expected if, as I suspect, some faults also increase the probability of early death.

In any event, I think it is most important to compare life shortening in irradiated parents with that of their offspring. If the animals were irradiated in a single dose very early in embryology it would increase the likelihood that germinal and somatic tissues are equally responsive.

It is possible that the environmental similarities of identical twins are sufficient to lead to a serious underestimate of non genetic scattering. A possible check is provided by egg twins, whose intra-pair variance in number of facets should be half that of a randomly chosen unrelated pair. At the same time their environmental similarity should be about the same as identical twins.

For example, if the average difference in fraternal twins is 4 years (I don't know how you made this calculation on p. 12 going from death over age 70 to those over 70, so this is only a guess) this would correspond to a standard deviation of the difference of 10, or a variance of 50 for a single individual. Subtracting 10 for the environmental variances leaves 40 which is approximately half the genetic variance, 80, estimated for individuals.

As far as experimental tests go, a comparison of longevity of progeny and radiated parents ought to be very informative particularly if, as you suggest, other signs of aging are looked for. I would like to see this the longevity of sibmated progeny of irradiated parents. The comparison of hybrids with inbred sibmates. The experimental arguments of your hypothesis, because of its easy sustability, is the absence of an effect of inbreeding on longevity.

If you are ever near Madison, I hope you will stop in.

Sincerely,

James F. Crow
Professor

JFC/ew

P. S. On page 6, equation (10), there is a small typographical error. The quantity under the radical should have 1/n substituted for 4 n.

COPY

January 5, 1959

Dr. James F. Crowe
Genetics Building
University of Wisconsin
Madison 6, Wisconsin

Dear Dr. Crowe:

Many thanks for your thoughtful letter of December 26th. I am moving about at present and, being away from my office, I am forced to restrict myself to making just a few comments on the points which you raised. Some of these you will find in the attached copy of a letter which I have written to H. J. Muller.

Concerning the longevity of inbred lines, I have adopted the view that inbred lines, because they are homozygous for a number of "weak" genes, suffer during differentiation and morphogenesis a maldevelopment. Accordingly, for such inbred strains, the value of the critical surviving fraction, f*, should be appreciably higher than for the hybrid strain, derived from crossing two inbred strains. Their life expectancy should be appreciably shorter than that of the F_1 hybrid.

You raise the question whether I don't underestimate the non-genetic scattering of the ages of death in the general population by failing to take into account the social inhomogeneity of the population.

A priori, it is conceivable that the social inhomogeneity of the population might introduce considerable scattering in the values of f*. Before I wrote my paper, I had the same apprehension and, therefore, in the first version of my manuscript, I based my considerations on the observed mean age difference at death of dizygotic female twins. I obtained τ=6.15 years for n=2.5. This is very close to the value which I derived in my paper from the observed distribution of the ages of death of the white female population (i.e., τ=6 years for n=2.5). Accordingly, I concluded that the effect of social

inhomogeneity on the distribution of the ages of death can be neglected for the white female population of the United States. Therefore, I decided to discuss my theory in terms of the life tables rather than in terms of the data relating to dizygotic female twins. I am now preparing, however, a second paper in which I shall include the discussion of dizygotic female twins.

I am, for the time being, not prepared to accept any of the "modifications" which you suggest in your letter and I propose to hold on to the view that the rate of aging is affected by the inherited faults and that it is not affected by recessive lethals, which are not cell lethals.

I am now trying to see whether the second approximation of the theory may give a better fit for the life tables than does the first approximation presented in the paper.

Enclosed you will find an excerpt, dated December 9th, 1958, which might perhaps interest you. The paper itself will appear in the January issue of the Proceedings of the National Academy of Science.

With kind regards -

Sincerely,

Leo Szilard

Enclosure