Preprint

Fishberg

25 July 1963

THE AGING PROCESS AND THE "COMPETITIVE STRENGTH" OF SPERMATOZOA*

by Leo Szilard
The University of Chicago, Chicago, Illinois

In a paper, printed in 1959, I presented a theory of the nature of the aging process in mammals, that attributes aging to changes which take place within the chromosomes of the somatic cells.[1.)] I postulated in particular that in spontaneous random events, designated as "aging hits", a whole chromosome, or a large fraction of a whole chromosome, is rendered non-functional. In the case of Man I estimated an average of one aging hit over a period of six years for a somatic cell, containing 46 chromosomes (23 chromosome pairs). This theory makes quantitative predictions which, if correct, ought to be capable of experimental verification.

If one assumes that the chromosomes contained in the spermatogonia of the male do not escape such aging hits, then one may be led to entertain speculations of the following kind:

Let us assume that each spermatozoon, contained in the ejaculated semen of a male, possesses a certain "competitive strength" and that in the mating process spermatozoa which have a "competitive strength" that is markedly below normal lose out - in the competition for reaching and fertilizing a mature ovum - to spermatozoa which possess full competitive strength. Let us further assume that a spermatozoon derived from a spermatogonium which, because of the advancing age of the individual, no longer contains an intact diploid set of chromosomes, has a markedly reduced competitive strength and, accordingly, a markedly reduced chance of fertilizing an ovum in the natural mating process.

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If such a selection takes place in the natural mating process, then the ova are safeguarded against being fertilized by a spermatozoon that carries a chromosome which has become non-functional as a result of an "aging hit".

It would seem of interest to test the validity of these assumptions by experiments of the following general type:

Let us assume, for the sake of argument, that we have available two strains of a mammalian species, a strain A and an isogenic strain B. Let us further assume that these two strains differ from each other with respect to one gene locus, which controls an easily visible phenotypic character and that strain A is homozygous at this locus for a dominant allele, while strain B is homozygous at this locus for an allele which is recessive.

Let us now select a young male A and a number of males B_1, B_2, B_3, who differ in age, their ages being t_1, t_2, t_3, ... One set of experiments consists in inseminating young females of strain B, who are all of the same age, with semen which is composed of a mixture of spermatozoa of two individuals, a male A and of one, or another, of the males B. Within the offspring of each female B, that has been inseminated with a mixture of spermatozoa of two individuals, those derived from the male A and those derived from one of the males B can be distinguished from each other; those derived from A show the phenotypic character of the dominant allele, while those derived from a male B (homozygous for the recessive allele) do not show the dominant phenotypic character.

What is of interest to us here is the ratio of the number of offspring of male A and number of offspring of a male B, derived from inseminations of

B females with mixtures of spermatozoa of A and B_1, of spermatozoa A and B_2, of spermatozoa A and B_3 etc. We shall designate these ratios as

$$\left[\frac{A}{B_1}\right] = \beta_1 \; ; \; \left[\frac{A}{B_2}\right] = \beta_2 \; ; \; \left[\frac{A}{B_3}\right] = \beta_3 \; ; \; etc.$$

In order to simplify the interpretation of these ratios β it is assumed that in all experiments the sperm mixtures used for insemination contain the same number of spermatozoa A and ~~spermatozoa~~ B.

If the males A and B_1 are of equal age and if the genetic difference between them is "irrelevant", then we ought to have $\beta_1 \approx 1$. This is what we would expect to find if the strain A is genetically identical with the isogenic strain B - except for one "irrelevant" gene locus which controls the visible phenotypic character, used for distinguishing the offspring of the male A from the offspring of a male B.

If experiments of the sort described above are carried out, we would then expect that if we use males B_1, B_2, B_3 of increasing ages t_1, t_2, t_3 etc., the ratios β will increase, and more particularly we would expect that, for equal increments of age, these ratios will increase by the same factor.

Further, we would expect that if we inseminate a number of females B with the mixed semen of the same pair of males A and B at different points in time, distributed over a time interval of a few years, the ratios β will remain the same.

On the basis of ~~my~~ the theory ~~mm~~ (1), one may venture to predict how the ratios β ~~will~~ might increase for increasing ages t_1, t_2, t_3 ... t_i...t_k... of the males B. According to the theory we ~~must~~ might expect:

$$\frac{\beta_k}{\beta_i} = e^{\gamma(t_k - t_i)}$$

For Man in particular the theory predicts for μ the value of

$$\mu = 1/6 \text{ years}$$

For other species of mammals the theory predicts as a rough approximation for the value of μ

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where t_∞ is the lifespan of the species, expressed in years, and m is the number of chromosome pairs of the species (the number of the chromosomes in the haploid set).

For example we may expect for any species of mammals for which the chromosome number is about the same as for Man ($\beta \approx 20$), if the age difference, $t_k - t_i$, amounts to about one-fifth of the life-span, t_∞.

A qualitatively similar, but quantitatively different, result must be expected if a spermatozoon may possess full competitive strength, even if the spermatogonium from which it is derived does not have an intact diploid set of chromosomes, ~~as long as~~ provided that the spermatozoon itself carries an intact haploid set of chromosomes. If this were the case, the values of μ would be half of the values given above.

It may be assumed that the general considerations discussed above would also hold for birds, and it is conceivable that they would also hold for reptiles.

In the case of cold-blooded vertebrates, like reptiles, it would be of interest to carry out an experiment which is not feasible in the case of either mammals or birds:

In the case of such cold-blooded animals, a male A and a male B could be maintained at temperatures which differ by, say, 10° C. If the male B, for instance, were maintained at the higher temperature, then we would expect that the ratios β would increase with time, if females ~~were~~ are inseminated with mixtures of the sperm of the same pair of males A and B at different points in time, distributed over a time interval of a few years. For equal intervals of time the ratios β would increase by the same factor.

It must be pointed out for the sake of conceptual clarity that ~~the concept of~~ the competitive strength of spermatozoa must not be equated with the concept of the viability of spermatozoa. We designate a spermatozoon as viable if in the natural mating process, or in artificial inseminations which simulate the conditions of the natural mating (fertilization) process, the spermatozoon is capable of reaching an ovum and of giving a viable zygote by fertilizing that ovum, provided that the ovum has not already been fertilized by another spermatozoon which was faster in reaching it. One may obtain a measure of the number of viable spermatozoa, contained in a given ejaculate of a male, by inseminating females with 1 cc (a constant volume) samples of highly diluted semen and determining the probability of obtaining a pregnancy as a function of the dilution factor. (See the Appendix).

counting like blood corp. 2

It is reasonable to expect that the number of viable spermatozoa contained in the ejaculates of males may also decrease with age. The theory does not permit, however, to make quantitative predictions with the same assurance in this regard, as in regard to the decrease of the number of spermatozoa which possess full competitive strength.

For this reason, priority ought to be given to experiments with mixtures of spermatozoa of the kind described above, and arrangements for experiments

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If these experiments should bear out our predictions, they would throw light on the nature of the aging process, and at the same time they would furnish an explanation as to why the male ejaculates millions of spermatozoa in the mating process when it takes only one single spermatozoon to fertilize an ovum.

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We may write for the probability, P_{conc}, for a pregnancy to result from an insemination with 1 cc of the undiluted semen of a given male

$$P_{conc} = \alpha\left(1 - e^{-n}\right) \text{ where } \alpha < 1$$

and where n denotes the number of viable spermatozoa thatreach a mature ovum, and can give a viable zygote by fertilizing that ovum, provided that no other spermatozoa have reached and fertilized that ovum earlier.

Similarly we may write for the probability, P_{dil}, of obtaining a pregnancy if 1 cc of the semen, diluted by a factor D, of the same individual is inseminated

$$P_{dil} = \alpha\left(1 - e^{-n/D}\right)$$

Because we have

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we may write

$$n = D \ln \frac{1}{1 - P_{dil}/P_{conc}}$$

and for $\frac{P_{dil}}{P_{conc}} \ll 1$ we may write

$$n \approx D \frac{P_{dil}}{P_{conc}}$$

It should be noted that the number n is not the number of viable spermatozoa contained in 1 cc of the undiluted semen, rather it is a very much smaller number. However, n is proportional to the number of viable spermatozoa contained in 1 cc of the undiluted semen, and the factor of proportionality will be the same in all the experiments, here envisaged, provided the inseminated females are isogenic, are of the same age, and have the same physiological, as well as anatomical, vaginal, cervical, uterine, tubular and ovarian conditions.

We may directly compare, $n(E)$ and $n(F)$, measures of the number of viable spermatozoa contained in 1 cc of the semen of two different males E and F, by diluting their semen with a suitable factor D, inseminating a number of females with 1 cc samples of the diluted semen of E and inseminating a number of other females with 1 cc samples of the diluted semen of F. We may then write for the ratio of the probability $P(E)$ ~~for~~ of obtaining a pregnancy in an insemination of the diluted sperm of E and the probability $P(F)$ of obtaining a pregnancy in an insemination of the diluted sperm of F

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The End.

1. Concentration of sperm varies with male + individual condition.
2. Therefore number of total sperm competitive + other should be determined.
3. Relative competitive strength might vary quite strongly between ♂♂ of various genotype and specially in mixture where they can influence each other chemically
4. All right if only 1 sperm needed for fertilization (if no mass effect).
5. Is ♀♀ a neutral recipient? or does it prefer sperm from certain source?
6. Does place of contact on ♀♀ play role?

7. 2. young

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In the case of such cold-blooded animals, a male A and a male B could be maintained at temperatures which differ by, say, 10° C. If the male B, for instance, were maintained at the higher temperature, then we would expect that the ratios β would increase with time, if females ~~were~~ are inseminated with mixtures of the sperm of the same pair of males A and B at different points in time, distributed over a time interval of a few years. For equal intervals of time the ratios β would increase by the same factor.

It must be pointed out for the sake of conceptual clarity that ~~the concept of~~ the competitive strength of spermatozoa must be distinguished from ~~not be equated with~~ the concept of the viability of spermatozoa. We designate a spermatozoon as viable if in the natural mating process, or in artificial inseminations which simulate the conditions of the natural mating process, the spermatozoon is capable of reaching an ovum and of giving a viable zygote by fertilizing that ovum, provided that the ovum has not already been fertilized by another spermatozoon which was faster in reaching it. One may obtain a measure of the number of viable spermatozoa, contained in a given ejaculate of a male, by inseminating females with 1 cc samples of highly diluted semen and determining the probability of obtaining a pregnancy as a function of the dilution factor. (See the Appendix).

It is reasonable to expect that the number of viable spermatozoa contained in the ejaculates of males may also decrease with age. The theory does not permit, however, to make quantitative predictions with the same assurance in this regard, as in regard to the decrease of the number of spermatozoa which possess full competitive strength.

~~For this reason~~, In the circumstances, priority ought to be given to experiments with mixtures of spermatozoa of the kind described above, and arrangements for experiments

along these lines are now under discussion.

If these experiments should bear out our predictions, they would throw light on the nature of the aging process, and at the same time they would furnish an explanation as to why the male ejaculates millions of spermatozoa in the mating process when it takes only one single spermatozoon to fertilize an ovum.

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References:

1. Leo Szilard, Proc. Nat. Acad. Sc. (USA) Vol. 45, pp. 30-45, 1959

APPENDIX

One can obtain a measure of the number of viable spermatozoa contained per cc in an ejaculate of a given male in the following manner: One inseminates a number of females each, say, with 1 cc of the undiluted semen of that male and one determines the probability of obtaining pregnancies. This probability is then compared with the probability of obtaining pregnancies when a number of other females are inseminated with 1 cc of semen, diluted by a factor D, of the same male.

We may write for the probability, P_{conc}, for a pregnancy to result from an insemination with 1 cc of the undiluted semen of a given male

$$P_{conc} = \alpha\left(1 - e^{-n}\right), \text{ where } \alpha < 1$$

and where n denotes the number of viable spermatozoa thatreach a mature ovum, and can give a viable zygote by fertilizing that ovum, provided that no other spermatozoa have reached and fertilized that ovum earlier.

Similarly we may write for the probability, P_{dil}, of obtaining a pregnancy if 1 cc of the semen, diluted by a factor D, of the same individual is inseminated

$$P_{dil} = \alpha\left(1 - e^{-n/D}\right)$$

Because we have

$$e^{-n} \ll 1$$

we may write

$$n = D \ln \frac{1}{1 - P_{dil}/P_{conc}}$$

and for $\frac{P_{dil}}{P_{conc}} \ll 1$ we may write

$$\cancel{n \approx D \frac{P_{dil}}{P_{conc}}} \qquad n = D\,\frac{P_{dil}}{P_{conc}}$$

It should be noted that the number n is not the number of viable spermatozoa contained in 1 cc of the undiluted semen, rather it is a very much smaller number. However, n is proportional to the number of viable spermatozoa contained in 1 cc of the undiluted semen, and the factor of proportionality will be the same in all the experiments, here envisaged, provided the inseminated females are isogenic, are of the same age, and have the same physiological, as well as anatomical, ~~vaginal, cervical, uterine, tubular and ovarian conditions~~ conditions of the vagina, cervix, uterus, tubes and ovaries.

We may directly compare, $n(E)$ and $n(F)$, measures of the number of viable spermatozoa contained in 1 cc of the semen of two different males E and F, by diluting their semen with a suitable factor D, inseminating a number of females with 1 cc samples of the diluted semen of E and inseminating a number of other females with 1 cc samples of the diluted semen of F. We may then write for the ratio of the probability $P(E)$ ~~for~~ of obtaining a pregnancy in an insemination of the diluted sperm of E and the probability $P(F)$ of obtaining a pregnancy in an insemination of the diluted sperm of F

$$\frac{P(E)}{P(F)} = \frac{1 - e^{-n(E)/D}}{1 - e^{-n(F)/D}}$$

where $n(E)$ is a measure at the number of viable spermatozoa per cc in the undiluted semen of E, and $n(F)$ is a measure of the number of viable spermatozoa per cc in the undiluted semen of F.

In order to obtain reasonably accurate information concerning the relative numbers of viable sperm of the two males E and F, from $P(E)$ and $P(F)$, it is necessary to choose the diluting factor D sufficiently high.

For sufficiently high dilutions we have

$$\frac{n(E)}{n(F)} \approx \frac{P(E)}{P(F)}$$

In order to illustrate the conceptual difference between the "competitive strength" of a spermatozoon and the "viability" of the spermatozoon, we may consider a spermatozoon that is derived from a spermatogonium in that one or several chromosomes have suffered aging hits, but carries a haploid set of chromosomes which are unaffected by aging hits. On the basis of the assumptions described above, this spermatozoon might have a markedly reduced "competitive strength" and might therefore lose out in the competition with spermatozoa which are in possession of full competitive strength, and yet conceivably this spermatozoon might be fully viable, in terms of the definition given above.

The End.