

The "Chromosomal-Function-Loss" theory of the aging process and the dependence of the sex ratio at birth on the age of the father.

Sir,

Recently, I have attempted to develop a general theory of aging, applicable to mammals.⁽¹⁾ This theory assumes that, during the life time of the animal, whole chromosomes, which are contained in the somatic cells, suffer a total loss of function in a single random event. It further assumes that the probability of such an event remains constant throughout lifetime and that it is the same for all individuals of a given species.

On the basis of the U.S. life tables I have derived the frequency with which such a random event occurs in Man and found that on the average one chromosome, of the haploid chromosomal set of the somatic cell, suffers such a "hit" in about twelve years. If we assume that this holds also for the spermatogonia in Man, we should then expect that the ratio of boys and girls at birth decreases with the age of the father. This conclusion is based on the following notions:

If the X chromosomes in a spermatogonium suffer an aging hit, then the cell is eliminated; if the Y chromosomes in a spermatogonium suffer an aging hit, then the cell remains fully functional and will give rise to spermatozoa, but only to spermatozoa which contain an X chromosome.

The length of the Y chromosomes amounts to about 2 % of the total length of the haploid set of the autosomes⁽²⁾ and on this basis we may perhaps assume that an average of 2 % of the Y chromosomes of the spermatogonia suffer an aging hit in a 12 year period. Thus, we are then led to conclude that the ratio, at birth, of boys and girls should decrease by 2 % for a 12 years' increase in the age of the father, and that it should decrease by 4 % for a 24 years' increase.

Professor Peter B. Medawar has very kindly transmitted to me statistical figures for 1956 for England and Wales, showing the dependence of the ratio of boys and girls on the age of the mother. These ratios, for the age group of the mother indicated, and for the sample sizes given in brackets, are as follows:

Under 20 (~19,000) 107.4 ; 20 - 24 (~100,000) 106.4 ;
25 - 29 (~110,000) 105.6 ; 30 - 34 (~70,000) 105.3 ;
35 - 39 (~35,000) 104.8 ; 40 - 44 (~10,000) 102.6 .

Because there is a strong correlation between the age of the father and the age of the mother these data are in good qualitative agreement with the prediction of our theory of the aging process.

In view of the small samples involved on which data of this type are based, it would be hardly worth while to attempt a

quantitative analysis in the hope of obtaining a quantitative confirmation of the prediction of the theory. For a more sophisticated analysis of birth data of this type the reader is referred to the work of those⁽³⁾ who attempt to separate the influence of the age of the father and the age of the mother on the sex ratio at birth.

~~The excess of boys over girls, conceived by young fathers, indicates that the probability of failure to be included in the spermatozoon must be higher for the X chromosome than for the Y chromosome; it is not possible, ^{however} to say on a theoretical ^{grounds just} basis how large an excess to expect. *on this basis*~~

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November 21, 1959.

- Leo Szilard*
- (1) Proc. Nat. Acad. Sc., U.S.A., Vol. 45 pp 32-45 Jan. 1959
 - (2) J.H. Tijo and T.T. Puck, Proc. Nat. Acad. Sc., U.S.A., Vol. 44 p. 1229, 1959
 - (3) E. Novitsky and A.W. Kimball, Amer. J. Human Genetics 1958.

The "Chromosomal-Function-Loss" theory of the aging process: H
The dependence of the sex ratio at birth on the age of the father
and other implications.

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Recently I have attempted to develop a general theory of aging applicable to mammals. (1) This theory assumes that, during the lifetime of the animal, whole chromosomes, which are contained in the somatic cells, suffer a total loss of function in a single random event. It further assumes that the probability of such an event remains constant throughout lifetime and that it is the same for all individuals of a given species.

From the U.S. life tables I have derived on the basis of the theory the frequency with which such a random event occurs in Man and found that on the average one chromosome, of the haploid chromosomal set of the somatic cell, suffers such a "hit" in about twelve years. If we assume that this holds also for the spermatogonia in Man, we should then expect that the ratio of boys and girls at birth decreases with the age of the father. This conclusion is based on the following notions:

We may assume that any cell of the male becomes non-functional if the X chromosome for which the cell is hemizygous suffers an aging hit, ^{that is,} i.e., the absence of the X chromosomes is lethal for the somatic cell in the male. The absence of the Y chromosome is not lethal for the somatic cell and, as a matter of fact, it need not be lethal even for the zygote; there exist individuals whose cells contain one X chromosome and no Y chromosome and these exhibit Turner's Syndrome.

Accordingly, if the X chromosome in a spermatogonium suffers an aging hit, then the cell is eliminated; if the Y chromosome in a spermatogonium suffers an aging hit, then the cell remains fully functional and will give rise to spermatozoa, but only to spermatozoa which contain an X chromosome.

The length of the Y chromosomes amounts to about 2% ^{per cent} of the total length of the haploid set of the autosomes (2) and on this basis we may perhaps assume that an average of 2% ^{per cent} of the Y chromosomes of the spermatogonia suffer an aging hit in a 12-year period. Thus, we are led to conclude that the ratio, at birth, of boys and girls should decrease by 2% ^{per cent} for a 12-years² increase in the age of the father,

and that it should decrease by 4 ^{per cent} % for a 24-years^r increase.

One may compute on the basis of birth data ⁽³⁾ for the United States, 1955, the dependence of the ratio of boys and girls on the age of the father. For the age-group of the father indicated and for the sample sizes - for boys alone or girls alone - given in brackets, the ratios are as follows:

- 15 - 19 years (~46,000): 106.7; 20 - 24 years (~410,000): 105.7;
- 25 - 29 years (~590,000): 105.0; 30 - 34 years (~440,000): 105.0;
- 35 - 39 years (~250,000): 105.0; 40 - 44 years (~120,000): 104.1;
- 45 - 49 years (~45,000): 103.6.

These data do not take into account the age of the mother, and there is of course a strong correlation between the age of the father and the age of the mother. What one would want to know is the dependence of the sex ratio at birth on the age of the father, for a fixed age of the mother. However, if one tabulates the available data on this basis the sample sizes become too small.

From the above quoted data it would appear that the ratio of boys and girls does fall with increasing age of the father but that it does not fall linearly with the age of the father, as the theory would demand. We can not say as yet whether data of this type contradict the theory because the sample sizes are too small, but they may conceivably contradict the theory when sufficiently large samples become available.

We propose to turn now to certain other implications of the theory. It is tempting to postulate that a spermatozoon which is derived from a spermatogonium in which an autosome has suffered an aging hit, may have a ^{finite, but} much smaller chance of reaching and fertilizing the ovum, than a spermatozoon which is derived from a spermatogonium in which none of the autosomes have suffered an aging hit. On this basis we may then ^{further} assume that a spermatozoon carrying an autosome that has suffered an aging hit, or a spermatozoon that is missing an autosome, will fertilize the ovum only rarely, and that on these rare occasions there will be an early abortion. Accordingly, the number of early abortions should increase with the age of the father.

The theory permits us ^{to} predict ^{the} fraction p of the spermatozoa that carry a haploid set of chromosomes which have remained un-hit, as a function of the age of the male, and we may write:

$$p = e^{-\frac{\text{age}}{2\tau}}$$

where τ is the average time-interval between aging hits suffered by the diploid sets of chromosomes. In the case of Man we have $\tau = 6$ years.

Because only the fraction p of the spermatozoa may be expected to lead to a successful pregnancy, it is possible experimentally to test the prediction of the theory in animals for which ^{we have} adequate methods ~~have been worked out~~ for artificial insemination.

In general we may expect, for the young male, that the number of spermatozoa that need to be inseminated in order to have a high probability for a successful pregnancy, is only a small fraction of the number of the spermatozoa contained in one ejaculate. In order to test the prediction of the theory one would need to determine for young males, age (1), the number of spermatozoa that must be inseminated in order to obtain a successful pregnancy with a given low probability. The theory then predicts that in an old male, age (2), the number of spermatozoa used in insemination must be higher by a factor of p_1/p_2 in order to obtain a successful pregnancy with the same probability. For p_1/p_2 we may write:

$$p_1/p_2 = e^{\frac{age(2) - age(1)}{2\tau}}$$

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- (1) Leo Szilard, ^{U.S.} Proc. Nat. Acad. Sci., U.S.A., Vol. 45 pp. 32-45 Jan. (1959)
- (2) J.H. Tijo and T.T. Puck, ^{U.S.} Proc. Nat. Acad. Sci., U.S.A., Vol. 44 p. 1929 (1959)
- (3) "Vital Statistics of the U.S.", Vol. 1 p. 213 (1955).

December 21, 1959.

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Recently I have attempted to develop a general theory of aging applicable to mammals.⁽¹⁾ This theory assumes that, during the life time of the animal, whole chromosomes, which are contained in the somatic cells, suffer a total loss of function in a single random event. It further assumes that the probability of such an event remains constant throughout lifetime and that it is the same for all individuals of a given species.

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~~On the basis of~~ the U.S. life tables I have derived *on the basis of the theory* the frequency with which such a random event occurs in Man and found that on the average one chromosome, of the haploid chromosomal set of the somatic cell, suffers such a "hit" in about twelve years. If we assume that this holds also for the spermatogonia in Man, we should then expect that the ratio of boys and girls at birth decreases with the age of the father. This conclusion is based on the following notions:

ovum
somatic
We may assume that any cell of the male becomes non-functional if the X chromosome for which the cell is hemizygous suffers an aging hit, i. e. the absence of the X chromosome is lethal for the cell in the male. The absence of the Y chromosome is not lethal for the cell and, as a matter of fact, it need not be lethal even for the zygote; there exist individuals whose cells contain one X chromosome and no Y chromosome and these exhibit Turner's Syndrome.

Accordingly, if the X chromosome in a spermatogonium suffers an aging hit, then the cell is eliminated; if the Y chromosome in a spermatogonium suffers an aging hit, then the cell remains fully functional and will give rise to spermatozoa, but only to spermatozoa which contain an X chromosome.

The length of the Y chromosomes amounts to about 2 % of the total length of the haploid set of the autosomes⁽²⁾ and on this basis we may perhaps assume that an average of 2 % of the Y chromosomes of the spermatogonia suffer an aging hit in a 12 year period. Thus, we are ~~then~~ led to conclude that the ratio, at birth, of boys and girls

should decrease by 2 % for a 12 years' increase in the age of the father, and that it should decrease by 4 % for a 24 years' increase. X

Professor Peter B. Medawar has very kindly transmitted to me statistical figures for 1956 for England and Wales, showing the dependence of the ratio of boys and girls on the age of the mother. These ratios, for the age group of the mother indicated, and for the sample sizes given in brackets, are as follows:

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Because there is a strong correlation between the age of the father and the age of the mother these data are in good qualitative agreement with the prediction of our theory of the aging process.

In view of the small samples involved on which data of this type are based, it would be hardly worth while to attempt a quantitative analysis in the hope of obtaining a quantitative confirmation of the prediction of the theory. For a more sophisticated analysis of birth data of this type the reader is referred to the work of those⁽³⁾ who attempt to separate the influence of the age of the father and the age of the mother on the sex ratio at birth.

It is tempting to postulate that a spermatozoon which is derived from a spermatogonium in which an autosome has suffered an aging hit, may have a much smaller chance of reaching and fertilizing the ovum, than a spermatozoon which is derived from a spermatogonium in which none of the autosomes have suffered an aging hit. On this basis we may then assume that a spermatozoon carrying an autosome that has suffered an aging hit, or a spermatozoon that is missing an autosome, will fertilize the ovum only rarely, and that on these rare occasions there will be an early abortion. Accordingly, the number of early abortions ^{sh} would increase with the age of the father. ~~It is not possible, however, to make a quantitative prediction in this regard on the basis of the theory.~~

The theory permits us to predict, ~~however,~~ the fraction p of the spermatozoa that carry a haploid set of chromosomes which have

remained un-hit, as a function of the age of the male, and we may write

$$p = e^{-\frac{age}{2\tau}}$$

where τ is the average time interval between aging hits suffered by the diploid sets of chromosomes. In the case of Man we have $\tau = 6$ years.

Because only the fraction p of the spermatozoa ^{may be expected to} ~~can~~ lead to a successful pregnancy, it is possible experimentally to test the prediction of the theory in animals for which adequate methods have been worked out for artificial insemination.

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In general we may expect, ~~that~~ for the young male, that the number of spermatozoa that need to be inseminated in order to have a high probability for a successful pregnancy, is only a small fraction of the number of the spermatozoa contained in one ejaculate. In order to test the prediction of the theory one would need to determine for young males, age (1), ~~group~~ the number of spermatozoa that must be inseminated in order to obtain a successful pregnancy with a given low probability, ~~for instance 30%~~. The theory then predicts that in an old male, age (2), the number of spermatozoa used in insemination must be higher by a factor of p_1/p_2 in order to obtain a successful pregnancy with the same probability. For p_1/p_2 we may write:

$$p_1/p_2 = e^{\frac{age(2) - age(1)}{2\tau}}$$

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(3) (4) E. Novitzky and A.W.Kimball, Amer.J.Human Genetics, 1958.

Vital Statistics of the U.S. Vol 10 pp. 268-275
Vol I p 213 1955

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The dependence of the sex ratio at birth on the age of the father

and other implications of the chromosomal
function-loss theory of the aging process
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and that it should decrease by 4 % for a 24 years' increase.

One may compute on the basis of birth data⁽³⁾ for the United States, 1955, the dependence of the ratio of boys and girls on the age of the father. For the age group of the father indicated and for the sample sizes - for boys alone or girls alone - given in brackets, the ratios are as follows:

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These data do not take into account the age of the mother and there is of course a strong correlation between the age of the father and the age of the mother. What one would want to know is the dependence of the sex ratio at birth on the age of the father, for a fixed age of the mother. However, if one tabulates the available data on this basis the sample sizes become too small.

From the above quoted data it would appear that the ratio of boys and girls does fall with increasing age of the ^{parents} father but that it does not fall linearly with the age of the father, as the theory would demand. We can not say as yet whether data of this type contradict the theory because the sample sizes are too small, but they may conceivably contradict the theory when sufficiently large samples become available.

We propose to turn now to certain other implications of the theory. - It is tempting to postulate that a spermatozoon which is derived from a spermatogonium in which an autosome has suffered an aging hit, may have a ^{finite but} much smaller chance of reaching and fertilizing the ovum, than a spermatozoon which is derived from a spermatogonium in which none of the autosomes have suffered an aging hit. On this basis we may then ^{further} assume that a spermatozoon carrying an autosome that has suffered an aging hit, or a spermatozoon that is missing an autosome, will fertilize the ovum only rarely, and that on these rare occasions there will be an early abortion. Accordingly, the number of early abortions should increase with the age of the father.

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where τ is the average time interval between aging hits suffered by the diploid sets of chromosomes. In the case of Man we have $\tau=6$ years.

Because only the fraction p of the spermatozoa may be expected to lead to a successful pregnancy, it is possible experimentally to test the prediction of the theory in animals for which ^{we have} adequate methods ~~have been worked out~~ for artificial insemination.

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Insert 1.

We may assume that ^{Some} the spermatogonia are lost ~~at a certain~~ ~~rate~~ and are replaced by other spermatogonia undergoing division. If spermatogonia which lack a functioning Y chromosome divide at the same rate as spermatogonia which ^{carry} a functioning Y chromosome, then the ratio, at birth, of boys and girls would decrease by 2% for a 12 years increase in the age of the father, and by 4% for a 24 years increase. However, if the spermatogonia which lack a functioning Y chromosome undergo divisions at a somewhat lower rate, then the ratio of boys and girls would initially, ~~for young fathers,~~ decrease with the father's age at the rate quoted above, but the ratio would approach a fixed value with increasing age of the father.

Insert 2.

From the above quoted data it would appear that the ratio of boys and girls does fall with increasing age of the father. ~~but~~ it will not be possible ^{however,} to draw ~~any~~ conclusions which are ^{relevant} ~~of interest~~ from the point of view of the theory until data based on larger samples become available.