Leo Szilard.

ON THE NATURE OF THE AGING PROCESS

This communication postulates a hypothetical biological process that might account for the phenomenon of aging, as it manifests itself in mammals for instance. The theory derived from it seems to be consistent with all facts, known so far. We postulate that the process of aging consists in the "inactivation" of large pieces of the chromosomes of the somatic cells by random "aging hits". If we were to postulate - on the contrary - that the aging process consists in a sequence of independent gene mutations of the chromosomes of the somatic cells, then we would be lead to conclusions which are not consistent with established facts. We specifically assume on this occasion that a whole chromosome of the somatic cell - rather than, say, one-half of a chromosome - is "inactivated" in an aging hit.

By inactivation of a piece of a chromosome (or a whole chromosome) we mean a process which will render that piece of the chromosome (or that whole chromosome) inactive, in the sense that the genes it contains are incapable of producing the corresponding specific gene products. It is not necessary, and perhaps not permissible, to assume that the "inactivated" piece of the chromosome could not duplicate itself, if the cell containing it were to duplicate, or that it would remain inactive after such a duplication.

We assume that not all genes are needed for the proper functioning of the somatic cells of the adult. The genes needed by the somatic cells we designate as vegetative genes. A mutant form of a vegetative gene, if it is incapable of producing the specific gene product, we designate as a "fault". We postulate that a somatic cell remains functional in the course of aging as long as, out of each pair of homologous vegetative genes, at least one of the two genes remains competent as well as active. A somatic cell ceases to be functional when one of the genes is incompetent and the other becomes inactive. From these assumptions it follows that when a chromosome suffers an aging hit, the somatic

The somatic cells of the human female contain m = 23 pairs of homologous chromosomes. Let us now consider a female who has inherited r faults. If none of the pairs of homologous chromosomes contain more than one fault - a condition likely to be fulfilled if r is small compared to m - then we may write for the "surviving" fraction of her somatic cells at a given age

(1) $$f = \left[1-(1-e^{-\xi})^2\right]^{m-r} \cdot e^{-r\xi}$$

or

(2) $$\ln f = (m-r)\ln\left[1-(1-e^{-\xi})^2\right] - r\xi$$

where ξ designates the average number of hits per chromosome, so that we have

(3) $$\xi = \frac{1}{2m}\,\frac{age}{\bar{c}}$$

$\bar{c}$ is the average time interval between two subsequent aging hits,

cell ceases to be functional if the homqlogous chromosome has previously suffered an aging hit, or if it contains a fault.

Because the total number of aging hits, suffered by the chromosomes of the somatic cell, increases with age, the "surviving" fraction f of the somatic cells falls with increasing age. We postulate that there is a critical "surviving" fraction f*, for which the probability becomes very large that the individual may die within a year. Young adults may be assumed to have a considerable reserve in somatic cells and we assume that f*, the "surviving" fraction of the somatic cells at the age of death, might lie somewhere between 1/3 and 1/12.

Unless an individual is exposed to ionizing radiation which induces faults in the chromosomes of his somatic cells, we may assume that the faults contained by the chromosomes of his somatic cells were inherited. Accordingly, all of his somatic cells contain the same faults. Gene mutations might occur in the chromosomes of the somatic cells of an individual during his lifetime and a certain fraction of the mutant genes thus arising may represent faults, but we assume that we may neglect them for our purposes.

The somatic cells of the human female contain m = 23 chromosome pairs. For a female who has inherited r faults we may write for the "surviving" fraction of her somatic cells at a given age

$$f = \left[2e^{-\xi}(1-e^{-\xi}) + e^{-2\xi}\right]^{m} \cdot \left[1 - e^{-\xi} + e^{-2\xi}\right]^{r} \tag{1}$$

or

$$\ln f = m \ln\left[1-(1-e^{-\xi})^2\right] + r \ln\left[1 - e^{-\xi} + e^{-2\xi}\right] \tag{2}$$

where ξ designates the average number of hits per chromosome

$$\xi = \frac{1}{2m}\,\frac{age}{\tau} \tag{3}$$

τ is the average time interval between two subsequent aging hits,

suffered in toto by the m pairs of homologous chromosomes contained in a somatic cell. We may call this average time interval τ the basic time interval of the aging process. We assume that τ is characteristic for the species and does not differ from individual to individual.

For small values of ξ we may write from (2)

$$\ln \frac{1}{f} = m(\xi^2 - \xi^3) + r(\xi - \xi^2) \tag{4}$$

and if we vary ξ we may write for a fixed value of f from (4)

$$-\frac{dr}{d\varkappa} = 1 - \frac{1}{2}\xi + \frac{r}{\varkappa}(1-\xi) - \left(\frac{r}{\varkappa} + \frac{1}{2}\right)\xi^2 , \tag{5}$$

where $\varkappa$ designates the average number of aging hits suffered in toto by the chromosomes of a somatic cell, i.e. we have

$$\varkappa = \frac{age}{\tau} \tag{6}$$

At high ages and for small values of r where we have $\frac{r}{\varkappa} << 1$ we may write, in the first approximation, from (5)

$$-\frac{dr}{d(age)} = \frac{1}{\tau} \tag{7}$$

The value of the "surviving" fraction f of the somatic cells at a given age depends on r, the number of faults inherited by the individual. For a fixed value of f = f*, the theory thus establishes a relationship between r and t_r, the age at death. Women who have inherited a small number of faults r die, according to the views here adopted, at high ages, so that we have $\frac{r}{\varkappa} << 1$. And in this case we may write for f*, the "surviving" fraction of their somatic cells at the age of death, in the first approximation,

$$\ln \frac{1}{f^*} \approx \frac{1}{4m}\left(\frac{t_r}{\tau} + r\right)^2 \left[1 - \frac{1}{2m}\left(\frac{t_r}{\tau} + r\right)\right] \tag{8}$$

and

$$(9) \qquad \frac{t_r}{\tau} + r \approx \sqrt{4m \ln \frac{1}{f^*}} + \ln \frac{1}{f^*}$$

For the genetically perfect female for whom we have r = o, we designate the age at death with t_o. We shall call t_o the "life span" of the species and we may write from (9) for the age of death.

$$(10) \qquad t_r \approx t_o - \tau r$$

From this it may be seen that the addition of one fault to the genetic make-up of an individual shortens the life of that individual by τ years, so that we may write for the life shortening Δt

$$(11) \qquad \Delta t \text{ per fault} = \tau$$

Accordingly, an adult whose genetic make-up contains one fault more than that of another adult, has a life expectancy which is shorter by τ years, the basic time interval of the aging process. This holds in the approximation of the theory which assumes $\frac{r}{2m} << 1$ and $\frac{r}{x} << 1$.

The average number of faults per person in the population we designate by n and we assume that the faults are distributed in the population at random. The distribution of the number of faults, r, in the population is then given by the Poisson distribution which gives the probability for each value of r, for integral values of r.

Because it is more convenient to think in terms of a continuous distribution of the ages at death than of a discontinuous distribution, we replace the Poisson distribution by a smooth continuous function of r, P(r). For a cohort (a group of persons born in the same year), in which the faults are distributed at random, we write for the number of deaths per year per person born,

$$(11a) \qquad D(\text{theor}) = -\frac{dr}{dt} P(r) = -\frac{dr}{dt} \frac{n^r}{\Gamma(r+1)} e^{-n}$$

or, in the first approximation

$$(12) \qquad D(\text{theor}) \approx \frac{1}{\tau} P(r) = \frac{1}{\tau} \frac{n^r}{\Gamma(r+1)} e^{-n}$$

where Γ represents the Gamma function (which for integral values of r assumes the values of r!) and where we have $\rho = \frac{t_0 - t}{\tau}$.

This formula (12) may be used only for small values of $\rho/2m$. It says that the number of deaths per year, as a function of age, follows an "inverted" Poisson distribution, where small values of r correspond to high ages at death.

By fitting, for a given value of r, this theoretical formula, between the ages of 70 and 90, to the observed number of deaths per year, given by the U. S. Life Tables (1949-50 Census) for white females, we obtain $\tau = \frac{9.8}{\sqrt{n}}$ years. We may correct this value for the non-genetic scattering of the ages at death, which manifests itself in the mean difference of the ages at death (about 3.5 years) of identical female twins. We obtain for the value of τ thus corrected

(13) $$\tilde{\tau} = \frac{9.3}{\sqrt{n}} \text{ years}$$

Further, by determining the value of n, for which (12), giving the number of deaths per year, best fits the data of the Life Tables - between the ages of 70 and 90 - we obtain $n > 2$.

We may obtain an upper limit for n by reasoning as follows: According to the U. S. Life Tables the maximal number of deaths per year occurs for white females between the ages of 80 and 81. Using this information, we may write on the basis of our theory, by substituting in (8)

(14) $$t_\rho = 80.5 \text{ years} \; ; \; \rho = n - 0.5 \; ; \; \tilde{\tau} = \frac{9.3}{\sqrt{n}} \text{ years}$$

It may then be seen from (8) that for values of f* for which we have $f^* > \frac{1}{12}$ we obtain $n < 4$.

For n = 2.5 we obtain $\tilde{\tau}$ = 6 years and for the corresponding value of f^*, we obtain from (8) $f^* \approx \frac{1}{6}$. In our discussion below we shall assume for $\tilde{\tau}$ the value $\tilde{\tau} = 6$ years.

Exposure to ionizing radiation may be assumed to induce gene mutations

both in the chromosomes of the somatic cells and of the germ cells of the gonads. Thus our theory leads us to expect that exposure of a population of mammals to ionizing radiation will shorten the lives of those exposed and also that it will shorten the lives of the adults in the offspring.

In the case of exposed animals it is conceivable that their life is shortened, not only through the induction of gene mutations in the chromosomes of their somatic cells by the ionizing radiation, but perhaps also through some other effects of the ionizing radiation on their somatic cells, which may involve the chromosomes or some other components of the cell. Among such effects might be the breakage of chromosomes which may lead to the loss of a chromosome. However, the theory here presented does not cover the life shortening effect of ionizing radiation which is due to causes other than the induction of gene mutations in the somatic cells of the chromosomes. If we may disregard such other effects, then we may compute the "surviving" fraction of the somatic cells of an exposed female on the basis of the faults induced in the chromosomes of her somatic cells by the ionizing radiation. For a genetically perfect female who is exposed to a dose of ionizing radiation which induces, on the average, p faults per somatic cell, we may write for the "surviving" fraction of somatic cells:

$$f = \left[2e^{-\xi - p/2m}\left(1 - e^{-\xi}\right) + e^{-2\xi}\right]^m, \tag{15}$$

or for small values of $p/2m$ and $p/x << 1$ we may write, in analogy to (8)

$$\ln \frac{1}{f^*} = \frac{1}{4m}\left(\frac{t_p}{\tau} + p\right)^2\left[1 - \frac{1}{2m}\left(\frac{t_p}{\tau} + p\right)\right], \tag{17}$$

where t_p is the age of death of a genetically perfect female who was exposed to a dose of ionizing radiation that induced an average of p faults in the chromosomes of her somatic cells.

On the basis of the assumptions stated above, we may say that, per fault induced, the life shortening of the exposed population and the life shortening of the adult offspring of the exposed population are the same -- in the first approximation. In this approximation, we may write from (9) for the life shortening Δt

$$(18) \qquad \frac{\Delta t \text{ per fault}}{t_0} = \frac{\tilde{\tau}}{t_0} = \frac{1}{\sqrt{4m \ln 1/f^*} + \ln 1/f^*}$$

We shall call this ratio $\frac{\tilde{\tau}}{t_0}$ the "specific life shortening". As one may see from (18) the specific life shortening is roughly inversely proportional to $\sqrt{m}$. Accordingly, one may expect the specific life shortening for the Chinese hamster, for instance, which has m = 11 pairs of homologous chromosomes, to be about twice as high as for the dog, which has about m = 39 pairs of homologous chromosomes - provided that the number of their vegetative genes, and the mutability of their genes (for the ionizing radiation used) are about the same.

From the point of view of our theory, we are on a much firmer ground if we predict the life shortening of the adult offspring of an irradiated population, rather than the life shortening of the irradiated population itself. Clearly in the former case we have to consider only gene mutations or the deletion of one, or several, genes.

Our theory establishes a relationship between the life shortening δ^*, expressed in days per rep, of the adult offspring of the irradiated population and the dose D_0 that induces as many mutations in the offspring as will arise through spontaneous mutations in one generation. We shall refer to D_0 as the "doubling dose". According to our theory we have

$$(19) \qquad D_0 = \frac{2\mu_t}{\delta^* \sqrt{m}} \frac{9.3 \times 365}{} \frac{N_1}{N_t} \text{ rep.}$$

where μ_t is the total spontaneous mutation rate of the haploid sets of genes. N_1 is the haploid number of vegetative genes and N_t is the haploid number of all genes. In deriving (19) we have neglected the induction by X-rays of chromosome deletions which cover more than one gene.

A reasonable set of values for Man might be as follows: $\mu_t = 0.25$; $\delta^* = 6$ days per rep (for single doses of X-rays of the order of 50 rep); $f^* = 1/6$; $n = 2.5$. This set of values would give $D_0 = 36$ rep. --(for single doses of X-rays of the order of 50 rep).

If the population were exposed, generation after generation, to the doubling dose, D_0, the load of faults would double. This means that the life expectancy of the average female would be reduced by $n\tau$ years. Assuming $n = 2.5$ the average life shortening of the female population would amount to about 15 years. If we assume n to be larger than 2.5, this estimated value would have to be increased; it goes up with $\sqrt{n}$.

It would take $\frac{n}{2\mu_t} \frac{N_t}{N_1} = 25$ generations of such radiation exposure to increase the present load of faults by 63%.

We may define the physiological age for a cohort of genetically identical females on the basis of their age specific mortality. According to our theory the physiological age of a female is equal to the chronological age of a genetically perfect female who has the same "surviving" fraction of somatic cells.

There are a number of specific phenomena which generally accompany senescence. Among these are, for instance, the graying of the hair, the loss of accomodation of the eye, and the loss of the ability to bear children. On the basis of our theory it is possible to determine which of the phenomena belonging to this class, (if any), have their onset determined by the physiological age as defined above. This may be done by exposing a population of mice, for instance, to ionizing

radiation and by observing in the adult offspring the reduction of life expectancy, as well as the age of the onset of the various phenomena which generally accompany senescence. According to our theory the physiological age of the offspring is increased by the faults induced. We may conclude from (5) that the amount by which the physiological age is increased, per fault induced, increases with increasing age. For very young animals the increase per fault induced would be very small and towards the end of life it would amount for Man, or mice, to about 6% of the life span. If the physiological age should determine the onset of the graying of the hair, the loss of the accommodation of the eye, or the loss of the ability to bear children, then the age of manifestation would be advanced in the offspring of an irradiated population by an amount, per fault induced, which can be computed on the basis of our theory. This amount depends somewhat on the age at which the phenomenon manifests itself. The advance is somewhat smaller (by about 10%) for phenomena which normally manifest themselves at middle age, rather than at high ages.

It appears likely that the most stringent test of our theory may come from observations focused on the adult offspring of an irradiated population. Arrangement for animal experiments along these lines are now under discussion.

The results here given represent a crude approximation of the predictions of our theory, and the qualifications which have to be made, are presented in a more detailed paper which is in press.(1)

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Part I: On the Effect of "Faults" on the Life Expectancy of the Adult

Introduction

This paper represents an attempt to describe a hypothetical biological process that could conceivably account for the phenomenon of aging. If correct, this theory would permit us to predict the effect on the life expectancy of adults of mutant, incompetent, forms of "vegetative" genes (a certain kind of genes which are described further below). Aging manifests itself in much the same general manner in all mammals and we should be in the position to learn enough about the aging 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.

We know that a gene is responsible for the synthesis of a specific protein molecule, which in many cases has a specific enzymatic activity. When we speak in the following of a mutant, or incompetent, form of a gene, we mean an altered form of a gene, which is not competent to synthesize the protein molecule having a required specific activity.

Our theory assumes that the elementary step in the process of aging is an aging hit, representing a random event, which destroys a chromosome of the somatic cell, in the sense that it renders that chromosome non-competent - even though it may not destroy

it in a physical sense. By saying that a chromosome is made non-competent, we mean that the genes which the chromosome carries were are made non-competent, i.e. incapable of synthesizing the protein molecules for which they are specific in their active form.

The theory assumes that the probability that a chromosome suffers an aging hit remains constant throughout life, and that the rate at which chromosomes of the somatic cells are destroyed is a characteristic of the species, and has the same value for all individuals of this species.

As a result of such an aging process, the number of somatic cells of the organism which remain functional in the sense of being able to fulfill the function that they are supposed to serve decreases with age. And, on the basis of our particular assumpgion spelled out below, it decreases at an accelerating rate. The theory establishes a relationship between the magnitude of the surviving fraction of the somatic cells and the age of the individual at death, by postulating that when f, the surviving fraction of the somatic cells of an individual, approaches some critical value f, the probability that the individual may die within a period of a year becomes very large.

Because the young mammalian organism may be assumed to have a large functional reserve, we may assume that the surviving fraction of the somatic cells of an indiyidual may fall quite substantially before the organism loses capacity to live, Accordingly, we shall in the following tentatively assume

(1)

or

(2)

Fortunately for the theory, only the logarithm of enters into our equations and, therefore, the conclusions

drawn from the theory are not sensitive to the particular assumption that one may make concerning the exact value f.

The precise meaning of the term "critical value, f," will shift as we go from the crudest form of the theory, which we shall discuss first, and the less crude form of the theory, which we shall discuss thereafter.

In the crudest form of the theory, we shall assume that an adult does not die of natural causes until the surviving fraction of his somatic cells comes very close to the critical fraction f* and that the person dies within the year in which this surviving fraction reaches the critical fraction f*. In its crudest form, the theory postulates that the age at death is uniquely determined by the genetic makeup of the individual. Clearly, this cannot be strictly speaking true for if it were true identical twins would die within one year of each other. In fact, the mean difference of the ages at death for female identical twins is about 3 1/2 years. This discrepancy between the crude theory and the observed facts arises from the failure of the crude theory to take into accout that in a cohort of identical individuals the number of deaths per year may be expected to rise as a continuous function with advancing age and that there must be an appreciable number of deaths in years prior to the year in which the surviving fraction of the somatic cells of the individual reaches a critical fraction f.

If not otherwise stated, our discussion here relates to Man and, in particular, to the female of the species.

In the case of Man, the somatic cells of the female contain 23 pairs of homologous chromosomes. The theory assumes that in a genetically perfect female, i.e., the female whose genetic makeup contains every gene in two fully competent copies, a somatic cell remains functional as long as at least one chromosome

out of each pair of homologous chromosomes, escapes being hit. Thus, in a genetically perfect female, a somatic cell ceases to be functional when, in any of the 23 pairs of homologous chromosomes, both chromosomes suffer a "hit." We shall next turn to the effect of the aging process on the "survival" of somatic cells in females who are not genetically perfect, i.e. whose genetic make-up contains mutant forms of genes. As we shall presently see, the "survival" of the somatic cells is not affected by mutant forms of any of the genes, but only of "vegetative" genes - which we shall now proceed to define.

There may be, perhaps, 5,000 or 10,000 genes carried by Man. There may be in Man a much larger number of specific D.N.A. molecules which are inhereited from generation to generation, but of all of these D.N.A. molecules, we designate as genes only those D.N.A. molecules which would handicap an individual for life if it were contained in the genetic makeup of the individual in a mutant form. An individual who is a heterozygote for such a mutant gene might not be handicapped for life under the 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. But, such a heterozygote would have been handicapped (according to our definition of the term "gene") under conditions which were prevalent in the past - up to recent times. The present, presumably low, abundance of mutant forms of genes in the population is due to the selection pressures which have operated in the past.

We may assume that most of the genes somehow affect differentiation and morphogenesis during the embryonic development of the individual and that they may cause with a certain probability, even in the heterozygote, a developmental abnormality of the

individual which results in a handicap for life - under conditions which were prevalent in the past. We shall assume that among the 5,000 (or 10,000) genes, there is a minority of genes, perhaps 1,000 or 2,000, which are important for the functioning of the somatic cells of the adult. We shall call these genes vegetative genes and a mutant form of such a gene we shall designate as a fault. Of the remainder of the genes, we shall assume that they are irrelevant for the functioning of the somatic cells of the adult organism. Concerning the vegetative genes, we postulate that the presence of a competent copy of every one of the vegetative genes is necessary and that the presence of one competent copy of each such gene is sufficient for the proper functioning of a somatic cell of the adult.

From these assumptions it follows that in a female who is not genetically perfect, a somatic cell becomes non-functional when a chromosome is destroyed in the process of aging, provided that the homologous chromosome contains a fault. Because of this, the theory here presented attributed the genetic reason why some adults live shorter and other live longer to the difference in the number of faults contained in the genetic makeup. We shall assume that the faults are distributed at random in the population and we shall thus be able to compute, from the mean number of faults per individual - which we designate with n - the distribution of the ages at deaths in the population. We shall be led to conclude that n is a small number and that we have, presumably

$$2 < n < 4.$$

We shall be led to adopt n = 2.5 as a reasonable value and all of our discussions, if not otherwise stated, will be based on assuming this value for n.

The Surviving Fraction of the Somatic Cells ~~and the Effect of Faults on the Age at Death~~.

We shall now proceed to compute the "surviving" fraction of the somatic cells of a female, who has inherited r faults, as a function of her ~~chronological~~ age. ~~We shall assume that the rate at which chromosomes are hit remains constant throughout the life of the individual and that this rate is characteristic for the species. Designating this rate with~~ $\frac{1}{2m\bar{\tau}}$ ~~we may write for~~ with ξ the average number of aging hits suffered by a chromosome contained in the somatic cell of an individual

(1) $$\xi = \frac{1}{2m}\frac{age}{\bar{\tau}}$$

~~We may be defined~~ as the average time interval between two subsequent aging hits suffered by the two sets of homologous chromosomes contained in a somatic cell. We may call this average time interval $\bar{\tau}$, the basic time interval of the aging process. Let us now single out one homologous pair of chromosomes within a somatic cell. The probability q that aging hits have not caused a loss of function to the cell arising from damage to this particular pair of chromosomes is given by

(2) $$q = 2e^{-\xi}e^{-\rho}(1-e^{-\xi}) + e^{-2\xi}$$

where ρ designates the number of faults per chromosome

(3) $$\rho = \frac{r}{2m}$$

In (2) the first term represents the probability that one of the two chromosomes has not suffered an aging hit and does not contain a fault, whereas the other chromosome has suffered ~~an~~ one or more aging hits. The second term ~~of the expression~~ represents the

probability that neither of the two chromosomes has suffered an aging hit.

In the present paper we shall assume that ~~the average number of faults that n~~, the average number of the faults r in the population, is small, and ~~we~~ also shall restrict our discussion to that ~~fraction~~ part of the population which ~~has~~ inherited ~~a small number of faults r~~ large number of faults. Accordingly, we shall assume $\eta \ll 1$ and we may then write from (2) in the first approximation

(4) $$q \approx 2e^{-\eta}(1-e^{-\eta}) + e^{-2\eta} = 2e^{-\eta} - e^{-2\eta}$$

~~or, writing~~ where $\eta = \xi + \rho$

~~(5)~~ ~~$\eta = \xi + \rho$~~

~~we obtain~~

(5)' $$q \approx 1 - (1-e^{-\eta})^2$$

The probability that the cell has survived because it has remained functional with respect to all m chromosome pairs is thus given by

(6) $$f = q^m = \left(1 - (1-e^{-\eta})^2\right)^m$$

or

(7) $$\frac{1}{m} \ln \frac{1}{f} = \ln \frac{1}{1-(1-e^{-\eta})^2}$$

and we may write inversely

(8) $$\eta = \ln \frac{1}{1 - \sqrt{1 - e^{-\frac{1}{m}\ln \frac{1}{f}}}}$$

~~(For $\eta \ll 1$)~~

~~(8)~~ ~~$\eta \ll 1$~~

We obtain in the second approximation from (6)

(9) $$\frac{1}{m} \ln \frac{1}{f} = \eta^2 - \eta^3$$

and from (8)

$$\eta = \sqrt{\frac{1}{m}\ln\frac{1}{f}} + \frac{1}{2m}\ln\frac{1}{f}$$

For t_r, the age at death for which, according to the assumption of the crude theory, f, the surviving fraction of the cell, reaches the critical fraction f*, we shall designate with x_r the average number of aging hits suffered in toto by the two sets of homologous chromosomes of the somatic cell. ~~Thus that~~ we have

$$x_r = \frac{t_r}{\tau} = 2m\xi$$

and we may write for the age at death

$$\eta = \frac{x_r + r}{2m}$$

We may thus write from (9) for t_r the age at death, where we have f = f*,

$$\ln\frac{1}{f^*} = \frac{(x_r + r)^2}{4m}\left(1 - \frac{x_r + r}{2m}\right)$$

and from (11) we may write

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

or

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

We shall designate with t_o the age at death of the genetically perfect female for whom we have r = o. For the sake of brevity, we shall henceforth refer to t_o as the "life span of the species." From (16) we may write for t_o

~~and from (16) we may write~~

$$\frac{t_o}{\tau} = \left(\sqrt{4m\ln\frac{1}{f^*}} + \ln\frac{1}{f^*}\right)$$

~~and from (14) we may write~~

$$\ln\frac{1}{f^*} = \frac{1}{4m}\left(\frac{t_o}{\tau}\right)^2\left(1 - \frac{1}{2m}\frac{t_o}{\tau}\right)$$

We may write from (16)

$$\frac{t_r}{\tau} + r = \frac{t_0}{\tau} \qquad (17)$$

or

$$t_r = t_0 - \tau r \qquad (18)$$

or

$$r = \frac{t_0 - t}{\tau} \qquad (19)$$

As may be seen from (19) the addition of one fault to the genetic makeup of an individual shortens the life of that individual by ; so that we may write

$$\Delta t = \tau \qquad (20)$$

$$\Delta t \text{ per fault} = \tau \qquad (21)$$

This expresses one of the basic results of the theory here presented.

For the ratio of the life shortening per fault and the life span of the species, we may write

$$\frac{\Delta t \text{ per fault}}{t_0} = \frac{\tau}{t_0} = \frac{\qquad}{\sqrt{4m \ln \frac{I'}{I^*}} + \ln \frac{1}{\rho^*}} \qquad (22)$$

This ratio may be called the "specific" life shortening per fault.

The Life Shortening Effect of Ionizing Radiation:

It is possible experimentally to produce lesions in the DNA molecules contained in the germ cells of the gonads or contained in the somatic cells of the adult animal, by exposing animals to ionizing radiation such as X-rays or fast neutrons. If a lesion is produced in the germ cells happens to lie within a DNA molecule which functions as a gene (in terms of the definition given above) the lesion may render the gene incompetent and thus produce a mutation. If the gene happens to be a vegetative gene, the lesion will produce a fault.

If a lesion is produced in the DNA of a somatic cell, happens to lie in a vegetative gene, then a fault is produced in the nucleus of the somatic cell, and Faults produced in this manner will have the same effect on the surviving fraction of the somatic cells, and, therefore, also on the age of death, as inherited faults.

← The distribution of the ages at death.

The above equations hold within the framework of the crude form of the theory. In this form of the theory, members of one cohort would die only in certain years - at the critical ages, t_r , and the years in which death occurs within one cohort would be separated from each other by time intervals of τ years; no deaths would occur in the intervening years.

Further, if the distribution of the faults in the population is random, then, according to the crude theory, the number of deaths, P_r, occurring at each age, would be given by the Poisson distribution

$$P_r = \frac{n^r}{r!} e^{-n}$$

where, according to (2), we have $r = \frac{t_o - t_r}{\tau}$

and where n stands for the average number of the faults per individual in the population.

The distribution of the ages at death is actually a continuous function of the age. This is, of course, to be expected because, even though the probability that an individual may die within a year increases very steeply as the surviving fraction of his somatic cells approaches the critical value f*, still the probability of his dying within a year must rise as a continuous function rather than a discontinuous function of the surviving fraction of his somatic cells. This fact becomes manifest if one considers the mean age difference at death of identical twins which amounts to about 3-1/2 years. This mean age difference at death may be regarded as a measure of the scattering of the ages at death which the crude form of the theory leaves out of account. Because such a scattering of the ages at death occurs in a group of individuals who are genetically identical, we shall designate it as the non-genetic scattering."

For the time being we shall continue to leave this non-genetic scattering out of account, yet ~~but~~ for the sake of convenience, we shall henceforth describe the distribution of the ages at death by a continuous function of r, P(r) in place of the discontinuous Poisson values. For P(r) we may write

23 ~~(24)~~ $$P(r) = \frac{n^r}{\Gamma(r+1)} e^{-n}$$

where Γ represents the Gamma function (which for integral values of r assumes the values of r!) and where we have

24 ~~(25)~~ $$r = \frac{t_0 - t}{\tau}$$

For the number of deaths occurring within a cohort per unit time we may then write according to our theory

25 ~~(26)~~ $$d(\text{theor}) = +\left|\frac{dr}{dt}\right| \frac{n^r}{\Gamma(r+1)} e^{-n}$$

From ( ) we obtain

26 ~~(27)~~ $$\left|\frac{dr}{dt}\right| = \frac{1}{\tau}$$

Thus we may write from ( )

27 ~~(28)~~ $$d(\text{theor}) = \frac{1}{\tau} \frac{n^r}{\Gamma(r+1)} e^{-n}$$ per ~~unit time~~ year

where r is given by ( ), and where τ is expressed in years.-

Since the approximation used throughout this paper holds for small values of r which correspond to high ages at death, we may now say, ~~on the basis of (28)~~ that the distribution of ages at death in the population ~~must be~~ is represented - at high ages ~~of death~~ - by ~~a sort of~~ like inverted Poisson distribution, i.e. a Poisson distribution where small values of r correspond to high ages at death.

13

Relationship between τ and n - Lower Limit for n

We shall now proceed to compare the distribution of the ages at death as given by our formula ( ), with the actual observed distribution of the ages at death, as given by the Life Tables.

For the purposes of this comparison, we shall use Table 6 for white females, which is based on the 1949-50 census, and lists in the column designated by d_x, the number of deaths per year, in yearly intervals. According to this table, the maximal number of deaths occurs between the 80th and 81st year; the corresponding maximal number of deaths per year is .0344 per person.

The distribution of the ages of deaths is not symmetrical around t^*; the number of deaths per year fall faster towards higher ages than towards lower ages. Thus, the Table lists for the number of deaths per year between the ages 70-71 and 0.0230 per person and between the ages of 90-91 0.0179 per person. We may derive from the column d_x of the Life Tables, which lists the observed number of deaths per year, as a function of age, a normalized distribution of the ages at death by forming, R(obs), the ratio of the number of deaths per year given in the table and the maximal number of deaths per year, 0.0344. Thus we obtain R(obs) = 0.667 at t = 70.5 years of age; R(obs) = 1 at t = 80.5 years of age, and R(obs) = 0.520 at t = 90.5 years of age.

We may similarly obtain from the number of deaths per year given as a function of age by the theory ( ), a normalized distribution of the ages at death, by forming, R(theor), the ratio of the number of deaths per year given by ( ) and the maximal number of deaths per year given by

$$\frac{1}{\tau} P(n)_{max} = \frac{1}{\tau} \left\{ \frac{n^n}{\sqrt{n+1}} e^{-n} \right\}_{max} \quad (29)$$

If we designate with r* the value of r for which this expression becomes maximal, we may write for $n \geq 2$

29 ~~(30)~~ $$r^* = n - \frac{1}{2}$$

Accordingly, we may write

30 ~~(31)~~ $$\frac{1}{t} P(r)_{max} = \frac{n^{(n+0.5)}}{\lfloor n+0.5} e^{-(n-0.5)}$$

and from this and (28) we may write

31 ~~(32)~~ $$R(theor) = \frac{\frac{1}{t}P(r)}{\frac{1}{t}P(r)_{max}} = \frac{n^r}{n^{(n-0.5)}} \frac{\lfloor n+0.5}{\lfloor r+1}$$

Using this formula for R(theor) we may now determine for a given value of n the value of $r = r^* + \Delta r$ for which R(theor) assumes the value of 0.667, i.e. the value of R(obs) at 70.5 years of age. For the value of Δr so obtained we may then write

32 ~~(33)~~ $$\bar{t} = \frac{10}{\Delta r} \text{ years} = 7.15 \text{ years}$$

We find for n = 2: $\Delta r = 1.4$ and $\bar{t} = 7.15$ years ~~and for n = 2.5: $\Delta r = 1.575$ and $\bar{t} = 6.35$ years.~~

Similarly, we may also determine for a given n the value of $r = r^* - \Delta r$, for which R(theor) assumes the value of 0.520, i.e. the value of R(obs) at 90.5 years of age. For this value of Δr we may then also write (33). We thus obtain for n = 2, $\Delta r = 1.4$; $\bar{t} = 7.15$ years; ~~and for n = 2.5, $\Delta r = 1.6$; $\bar{t} = 6.25$ years.~~ ~~(34)~~

We may now ask for what value of n would the normalized Poisson distribution R(theor) given by (31) ~~fit R(obs) both at 70.5 years of age and at 90.5 years of age, In the sense that we have~~ demand that we have or more precisely we require that for $\tau = \tau^* + \Delta\tau$, R(theor) = 0.667 (the value of R(obs) at 70.5 years of age) and that we also have for $\tau = \tau^* - \Delta\tau$ R(theor) = 0.520 (the value of R(obs) at 90.5 years of age).

It turns out that such a fit is possible only for a value of n which is very close to n = 2. For a corresponding value of $\Delta\tau$ we obtain $\Delta\tau = 1.4$ and for the corresponding value of τ we may write:

$$\tau = \frac{10}{\Delta\tau} \text{ years}$$

For values of n which are substantially larger than 2 it is not possible to fit the normalized Poisson distribution R(theor) to R(obs)! In this manner. If R(theor) is made equal to 0.520 (the value of R(obs) at 90.5 years of age) for $\tau = \tau^* - \Delta\tau$, then we have for $\tau = \tau^* + \Delta\tau$ R(theor) > 0.520 (the value of R(obs) at 70.5 years of age).

As may be seen ~~from the above~~ for n = 2 the two values obtained for τ are identical ~~but for n = 2.5 the value~~ obtained when 70.5 years of age is used as ~~a~~ reference point differs from the value obtained when 80.5 years of age is used as ~~a reference point. It may be seen from this and similar computations that~~ R(theor) fits R(obs) within a time range of 20 years centering around 80.5 years of age ~~for a suitable chosen value of~~ $\tau = 6.15$ years.

For values of n ≥ 2, however, R(theor) will deviate from R(obs) no matter ~~how the~~ value of τ ~~is~~ chosen. If τ is so chosen to have R(theor) ≅ R(obs) for ages above 80.5 years of age, then the values of R(theor) will be below the values of R(obs) for ages below 80.5 years of age.

From this we ~~may now~~ conclude that we have n ≥ 2. ~~We shall~~ not conclude, however, that we have n = 2 because our crude theory might well give too low values of R(theor) ~~at ages lower than t* = 80.5~~. We have to expect such a deviation of the values of R(theor), ~~given by~~ the crude theory, because this ~~crude~~ theory assumes that there is no appreciable death in a cohort of genetically identical individuals prior to their critical age. In these circumstances, the considerations given above can ~~be relied on~~ only ~~to set~~ a lower limit for the value of n but not to give ~~an upper limit for~~ its value.

In order to obtain an upper limit for the value of n we shall ~~turn~~ to arguments of a different kind, ~~presented below~~.

From the considerations above, we obtain for values of n > 2 always two different values for τ and we may ~~set the estimated value to be~~ the arithmetic mean of these two values. Thus for n = 2.5 we have $\tau = \frac{6.25 + 6.35}{2} = 6.30$ years. ~~For a larger number of n R(theor) given by ( ) goes over into a Gaussian. For a Gaussian, the value of R(theor) = .667 which corresponds to the value of R(obs) at 70.5 years of age.~~

corresponds to 0.9 σ (where σ is the standard deviation of the Gaussian), and R(theor) = 0.520, i.e. the value of R(obs) at 90.5 years of age, corresponds to 1.14 σ . Thus a time interval of 20 years corresponds to 2.04 σ and hence we have

(34) $\sigma = 9.8$ years

In the case of a Gaussian we may write

(35) $\sigma = \tau \sqrt{n}$

or

(36) $\tau = \frac{\sigma}{\sqrt{n}}$

and thus we obtain

(37) $\tau = \frac{9.8}{\sqrt{n}}$ years

While (35), (36) and (37) should hold, strictly speaking, only for large values of n, the error is small even for n = 2. For n = 2 we obtain from (37) τ = 6.82 in place of the previously given value of τ = 7.15.

Substituting the value of τ from (36) into (18), we obtain for $n \geq 2$

(38) $\frac{t_{n+1}}{9.8} \sqrt{n^2 + \tau} = \frac{t_0}{\tau}$

As may be seen, the two values obtained for τ appear to be identical for n = 2. This means that it is possible to fit the normalized distribution of the ages at death, R(obs), for an interval of twenty years between the ages of 70.5 and 90.5, by the normalized Poisson distribution R(theor) for n = 2. For values of n > 2 it is not possible to make such a fit. If τ is so chosen as to have R(theor) $\approx$ R(obs) between the ages of 80.5 and 90.5, then for ages between 70.5 and 80.5 the values of R(theor) will be appreciably lower than R(obs), for values of n which are substantially larger than two.

From this we conclude, concerning the value of n, that we have $n \geq 2$, rather than that we have n = 2. We do not conclude that we have n = 2 because the latter is necessary because our crude theory might well give too low values of R(theor) below 80.5 years of age. We have to expect such a deviation, for the values of R(theor), derived from the crude theory, because this theory assumes that there is no appreciable death in a cohort of genetically identical individuals prior to their critical age.

In these circumstances, the considerations given above can only set a lower limit for the value of n but cannot give its proper value. In order to obtain an upper limit for the value of n we shall have to turn to arguments of a different kind, presented below.

Approximation by Gaussian - Relationship between τ and n:

R(theor) given by ( ) goes over into a Gaussian for $n >> 1$.

For a Gaussian the value of R(theor) = .667, (i.e., the value of R(obs) at 70.5 years of age) corresponds to 0.9 σ (where σ is the standard deviation of the Gaussian), and R(theor) = 0.520 (i.e. the value of R(obs) at 90.5 years of age) corresponds to 1.14 σ . Thus a time interval of 20 years correspondes to 2.04 σ and

hence we have

(34) $\sigma = 9.8$ years

In the case of a Gaussian we may write

(35) $\sigma = \tau\sqrt{n}$

or

(36) $\tau = \frac{\sigma}{\sqrt{n}}$

and thus we obtain

(37) $\tau = \frac{9.8}{\sqrt{n}}$ years

While (36) holds, strictly speaking, only for large values of n, the error is small even for n = 2.

For n = 2 from (37) we obtain τ = 6.82 in place of the previously given value of τ = 7.15.

For n = 2.5 from (37) we obtain τ = 6.2 years in place of the "correct" value of τ = 6.3 years, that we find by fitting the normalized Poisson distribution as well as possible to R(obs).

Thus for some of our purposes at least, we may use (36) for values of n for n ≥ 2.

(38) ~~(37A)~~ From (36) we obtain $n\tau = \sigma\sqrt{n}$

Correction of τ for the non-genetic Scattering of the Ages at Death of Genetically Identical Individuals:

Because a non-genetic ~~distribution~~ scattering of the ages at death has not been taken into account in our theory, the observed distribution of the ages at death ~~ought to be~~ may be expected somewhat broader than predicted ~~by the theory~~ and, accordingly, the actual value of τ ~~ought to be~~ may be expected to be somewhat lower than the values given above.

The mean age difference at death between female identical twins, dying above the age of 60, has been reported by Franz J. Kallmann to be about 2.6 years. On the basis of the Life Tables, we may exterpolate from this mean age difference at death of identical twins, who die as adults, to be 3.4 years. If the distribution of the ages at death of genetically identical individuals

resembled a Gaussian, the variance of the distribution of the ages at death in the population would be equal to the sum of the variance of this Gaussian and of the theoretical distribution of the ages at death. By making such an assumption, for the purposes of this computation, we may then correct the value of , given above.

From the fact that the mean age difference at death is of female identical twins is 3.4 years, it follows that the standard deviation of the distribution of the ages at death is 3 years. Using this value, we find that the non-genetic scattering here discussed increases the variance of the distribution of the ages at death by a factor of and, accordingly, the previously given values of τ must be reduced by a factor of .95.

Thus, we may now write for the corrected values of for n = 2, τ = 6.8 years; and for n = 2.5, τ = 6 years.

We may also write on this basis - within the limits of error discussed above - for $n \geq 2$

(38) $$\tau = \frac{9,3}{\sqrt{n}} \text{ years}$$

Substituted the value of τ from (38) into ( ) we obtain

(39) $$\frac{t_2}{9.3}\sqrt{n} + r = \frac{t_0}{\tau}$$

Correction of τ for the non-genetic Scattering of the Ages at Death of Genetically Identical Individuals:

Because a non-genetic distribution of the ages at death has not been taken into account in our theory, the observed distribution of the ages at death ought to be somewhat broader than predicted by the theory and, accordingly, the actual value of τ ought to be somewhat lower than the values given above.

The mean age difference at death between female identical twins, dying above the age of 60, has been reported by Franz J. Kallmann to be about 2.6 years. On the basis of the Life Tables, we may exterpolate from this this mean age difference at death of identical twins who die as adults to be 3.4 years. If the distribution of the ages at death of genetically identical individuals resembled a Gaussian, the variance of the distribution of the ages at death in the population would be equal to the sum of the variance of this Gaussian and the variance of the theoretical distribution of the ages at death. By making such an assumption, for the purposes of this computation, we may then correct the value of τ, computed on the basis of the crude theory above by the standard deviation of a Gaussian and obtain for the corrected value

$$\tau_0 \approx 0.95\,\tau \qquad (38)$$

Thus, we may write

$$\tau_0 = 6.8 \text{ years}; \text{ for } n = 2$$

$$\tau_0 = 6 \text{ years}; \text{ for } n = 2.5$$

$$\tau_0 = \frac{9.3}{\sqrt{n}}; \text{ for } n \geq 3$$

Substituting the value of τ from 38 into 18 we obtain

$$\frac{t_r}{9.3}\sqrt{n} + \tau = \frac{t_0}{\tau} \qquad (39)$$

The value of the critical surviving fraction of the somatic cells f* - upper limit for n

In order to compute the critical surviving fraction of the somatic cells f* we shall now make use of the fact that the maximal number of deaths per year occur (for white females) at 80.5 years of age. Our theory demands ( ) that the maximal number of deaths per year should occur for individuals for whom we have $r = n - 0.5$. Accordingly, we may substitute in (39) 80.5 for t_r and $n - 0.5$ for r. We thus obtain from (39) and ( ) from (1) and ( )

$$(40) \qquad \frac{80.5}{9.3}\sqrt{n} + n - 0.5 = \frac{t_0}{\tau} = \sqrt{4n \ln\frac{1}{f^*}} + \ln\frac{1}{f^*}$$

Setting $f^* = 0.26$ or $\ln\frac{1}{f^*} = 1.35$ we obtain $\frac{t_0}{\tau} = 13.75$ and $n =$

Setting $\ln\frac{1}{f^*} = 2$ " " " $n =$ and n

On this basis we may then write

(41) ~~$2 < n < 4$~~

~~For $f^* = 0.26$ we have $\ln f^* = 1.35$, $\frac{t}{\tau_0} = 13.75$, $n = 2$~~

For $n = 2$ we obtain $f^* = 0.260$

$n = 2.5$ we obtain $f^* = 0.135$

$n = 3$ we obtain $f^* = 0.052$

Thus if we assume $0.1 < f^* < 0.25$ we may conclude $2 < n < 3$

$n = 2.5$ would appear as a reasonable assumption, to be used in our further discussion. For the corresponding value of τ we have $\tau =$

The Value of the Critical Surviving Fraction of the Somatic Cells f* - Upper Limit for n:

In order to compute the critical surviving fraction of the somatic cells f* we shall now make use of the fact that the maximal number of deaths per year occur (for white females) at 80.5 years of age. Our theory demands ( ) that the maximal number of deaths per year should occur for individuals for whom we have r = n-0.5. Accordingly, we may substitute in (39) 80.5 for t_r and n - 0.5 for r. We thus obtain from (40) and ( )

(40)

and

(41)

Text

reasonable value

Physiological Age:

There are phenomena that generally accompany senescence. Among these are, for instance, the graying of the hair and the loss of accommodation of the eye. A number of other such general characteristics accompanying senescence might be detected if a systematic search for such phenomena gets under way. For a group of animals, one may expect that the mean age at which such characteristics of senescence appear, to the same quantitatively defined degree, is determined by the mean age at which the surviving fraction of the somatic cells of the animals reaches the same specified value f_1. We accordingly, assume that two females whose genetic makeup differs from each other by Δ faults, differ from each other in physiological age by $\tau\Delta$ years.

Changing the Load of Faults:

If, as a result of living under "modern" conditions our load of faults should, in time, be doubled, then the average adult woman would live $n\tau$ years shorter than she does today.

For n = 2.5 we have $n\tau$ = 15 years. Thus, the physiological age of the average female at 65 would be the same as that of the average 80 year old woman today. Similarly, the physiological age of a woman of 35 would then be that of a 50 year old woman of today.

If we were to assume that $n > 2.5$, then $n\tau$ would amount to more than 15 years because $n\tau$ increases according to ( ) with $\sqrt{n}$.

A doubling of our load of faults might conceivably occur, in time, through the exposure of the population to ionizing radiation, generation after generation, in an intensity that doubles the spontaneous mutation rate. Such a doubling of our load of faults might perhaps occur also as a result of the currently practiced pattern of controlling the family size. This might conceivably

eliminate the most important one of the selection pressures which tend to keep our load of faults low. ~~by counter-balancing the generation of new faults through~~ spontaneously ~~occurring~~ ~~mutations~~ among faults.

Neither of these two considerations need to give rise to alarm, ~~however, for,~~ as we shall show further below, the rate of rise of our load of faults may be expected to be slow; thus in any case we shall have a ~~fairly~~ long period of grace in which we may reflect on how best to cope with the danger involved.

We may in this ~~context~~ connection also ask how much advantage the genetically perfect (faultless) female would have over the average female of today.

Assuming n = 2.5, we may say on the basis of considerations similar to those presented just above that the genetically perfect ~~woman~~ female would at 50 years of age have the same physiological age as the average woman of 35 today. Her most probable age at death would be 92 instead of 80. If n were larger than 2.5 the advantage of the genetically perfect female would be greater.

The Number of "Segments" per Chromosome:

Instead of assuming that a whole chromosome is "destroyed" in each aging hit, we could have assumed that the elementary step in the process of aging consists in the independent, random destruction of one-half of a chromosome. One might then, in this connection, ask whether one might not generalize the theory here presented, by assuming that each chromosome consists of g segments and that the elementary step in the process of aging consists in the random destruction of such segments independent of each other. By choosing the value of g larger and larger, we might then gradually change the character of the theory and, instead of postulating that a large portion of a chromosome is destroyed in an individual aging hit, we might end up by postulating that the aging process consists in a sequence of point mutations of the chromosomes of the somatic cell.

It may be shown, however, that a theory of this kind would not work. This may be seen as follows: The male of the species has only one X chromosome, while the female has two. If we disregard, for the sake of argument, the possibility that in the male a substantial piece of the X chromosome might be covered by genes contained in the Y chromosome, we may say that the male has at birth already received g aging hits. We may then identify the male with a female who has suffered prior to birth g aging hits. Accordingly, we may expect that the adult male has a life expectancy lower by g years than the adult female.

Actually, on the basis of the 1949-50 census, the maximum number of deaths for the white male occurs between the ages of 77 and 78, i.e. that at an age three years below that of the white

female. On the basis of the assumption that we have g = 1, i.e. that a whole chromosome is destroyed in an individual aging hit, the male can be identified with a female who has suffered prior to birth one aging hit, provided that the value of f* is exactly the same for the male as it is for the female. On this basis, we would then expect the male to live 6 years shorter than the female, whereas the observed difference is only 3 years. We cannot, however, exclude the possibility that the value of f* for the male may be somewhat higher than for the female, and, therefore, there is no real discrepancy between our theory and the observed facts.

The point which matters for the purpose of our discussion is rather that the observed difference in the life expectancy of the adult male and the adult female is small, whereas it may be shown that this difference would have to be large if g were a large number.

If g is other than 1, n has to be replaced in our formulae given above by ng. It may be then seen from our formulae that for a fixed value of f*, n increases somewhat faster than g. Since according to ( ) $\bar{c}$ falls with $\frac{1}{\sqrt{n}}$ it follows that ng, the difference between the life expectancy of the male and female, must increase somewhat faster than $\sqrt{g}$. Since the life expectancy of the male is not much smaller than that of the female, we may thus conclude that g cannot be very large.

Because f* might be somewhat smaller for the male than for the female, we would not want to exclude the possibility that g, for instance, might have a value of two, i.e. that the elementary process of aging might consist in the independent destruction of

one-half of a chromosome instead of a whole chromosome. Then if we have n = 2.5 and g = 2, the surviving fraction of the somatic cells at death, f*, would then have a value higher than 1/4, Or, conversely, if we postulate for f*, the value of f* = 1/4, then we would have for n a value which is higher than 2.5, and accordingly, we would have for τ a value of τ < 6 years. As we have seen above, we cannot reduce the value of τ very much below 6 years without having to conclude either that the doubling dose is very low or that the mutation rate μ is very high.

ON THE NATURE OF THE AGING PROCESS

by

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(Submitted by Theodore Puck)

Introduction

This paper represents an attempt to describe a hypothetical biological process that could conceivably account for the phenomenon of aging. Aging manifests itself in much the same general manner in all mammals and we should be in the position to learn enough about the aging 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.

We know that (in general may be a gene ~~is~~ responsible for the synthesis of a specific protein molecule, which in many cases has a known specific enzymatic activity. When we speak in the following of a mutant, or incompetent, form of a gene, we mean an altered form of the gene, which ~~is not competent to~~ can not synthesize the specific protein molecule in its chemically active form.

Our theory assumes that the elementary step in the process of aging is an "aging hit", which "destroys" a chromosome of the somatic cell, in the sense that it renders (all genes carried by that chromosome ~~non-~~competent ~~even though~~ the hit "need ~~may~~ not destroy ~~it~~ the chromosome in a physical sense. ~~By saying that a chromosome has become non-competent, we mean that practically all of the genes carried by that chromosome have become non-competent.~~

We assume that the "aging hits" are random events and that the probability that the chromosome suffers such a "hit" per unit time remains constant throughout life. We

further assume that the rate at which chromosomes of a somatic cell suffer such "hits" is a characteristic of the species and does not vary appreciably from individual to individual.

As a result of an aging process of this nature, the number of the somatic cells of an individual organism which have "survived" up to a given age (in the sense of having remained able to fulfill their function in the organism as a whole) decreases with age. On the basis of our ~~particular~~ assumptions, spelled out below, the "surviving" fraction of the somatic cells decreases with age at an accelerated rate.

~~The~~ Our theory postulates that when f, the surviving fraction of the somatic cells of an individual, approaches a certain critical value f*, then the probability that an individual may die within a period of one year will be close to 1. On this basis, the theory establishes a relationship between the surviving fraction of the somatic cells and the age of death of the individual.

Because the young mammalian organism may be assumed to have a large functional reserve, we shall assume that the surviving fraction of the somatic cells of an individual may fall quite substantially before the organism loses its capacity to live, perhaps to about 1/6. a value somewhere between 1/3 and 1/12.

The precise meaning of the term "critical value, f*", will shift as we go from the crudest form of the theory, which we shall discuss first, to a less crude form of the theory, which we shall discuss thereafter. In the crudest form of the theory, we shall assume that an adult does not die of natural causes until the surviving fraction of his somatic cells comes very close to the critical fraction f* and that he dies at the

critical age, i.e. within the year in which this surviving fraction reaches the critical fraction f*. Thus, in its crudest form, the theory postulates that the age at death is uniquely determined by the genetic makeup of the individual.

Clearly, this cannot be strictly speaking true for, if it were true, identical twins would die within one year of each other. In fact, the mean difference of the ages at death for female identical twins may be estimated to be about 3.5 years. ~~This~~ The discrepancy arises from the failure of the crude theory to take into account that in a cohort of identical individuals the number of deaths per year may be expected to rise as a continuous function with advancing age and an appreciable number of deaths may be expected to occur at ages lower than the "critical age".

* * *

If not otherwise stated, our discussion here relates to Man and, in particular, to the female of the species. In the case of Man, the somatic cells of the female contain m = 23 pairs of homologous chromosomes.

~~The~~ Our theory assumes that in a genetically perfect female, i.e., a female whose genetic makeup contains every gene in two fully competent copies, a somatic cell remains functional as long as at least one chromosome, out of each pair of homologous chromosomes, has escaped being hit. But even in a genetically perfect female, a somatic cell ceases to be functional when, in any of the 23 pairs of homologous chromosomes, both chromosomes suffer a "hit".

We shall next turn to the effect of "aging hits" on the "survival" of somatic cells in females who are not genetically perfect, i.e. females whose genetic makeup contains mutant forms

of genes.

There may be in Man perhaps 5,000 or 10,000 genes. There may be a much larger number of specific D.N.A. molecules which are inherited from generation to generation, but ~~Of these~~, we designate as "genes" ~~/ however /~~ here only those D.N.A. molecules which would handicap the individual if present in a mutant, non-competent, form.

An individual who is a heterozygote for a mutant gene might not necessarily be handicapped under the 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. But, such a heterozygote would have been handicapped (according to ~~our~~ definition of the term "gene") under conditions which were prevalent in the past - up to recent times. The present, presumably low, abundance of mutant forms of genes in the population is due to the selection pressures which have operated in the past.

We may assume that most of the "genes" somehow affect differentiation and morphogenesis during the embryonic development of the individual and that they may cause with a certain - even in the heterozygote appreciable - probability a developmental abnormality of the individual which ~~results in~~ represents a handicap for the individual ~~life~~ under conditions which were prevalent in the past.

We assume that among the 5,000 (or 10,000) genes, there is a minority of genes, perhaps 1,000 or 2,000, which are important for the functioning of the somatic cells of the adult. We shall call these genes "vegetative genes" and a mutant form of such a gene we shall designate as a "fault". Of the remainder of the genes, we shall assume that they are irrelevant for the functioning

Concerning the vegetative genes we postulate that the somatic cell remains functional as long as out of each pair of homologous vegetative genes, one of the two genes is competent and that the cell ceases to be functional when both genes are incompetent.

From these assumptions, it follows that if a chromosome suffers an aging hit, the cell will cease to be functional if the homologous chromosome has either suffered one or more aging hits or if it carries one or more faults.

of the somatic cells of the adult organism.

Concerning the vegetative genes, we postulate that the presence of a competent copy of every one of the vegetative genes is necessary for the proper functioning of a somatic cell of the adult and that the presence of one competent copy of each such gene is sufficient for that purpose.

From these assumptions it follows that a female who is not genetically perfect so that some of her chromosomes contain faults, if a given chromosome contains a fault and the homologous chromosome suffers an aging hit in a somatic cell, then that somatic cell becomes non-functional.

According to the views here adopted, the reason why some adults live shorter and others live longer is primarily determined by the difference in the number of faults that they have inherited. If we assume that faults are distributed in the population at random, then we can compute the distribution of the faults from the mean value of faults per person which we shall designate with n and, further, from the observed distribution of the ages at death between 70 and 90 years of age, we shall be led to conclude that we have $n \geq 2$. For n = 2 we would obtain from the crude theory for the critical surviving fraction of the somatic cells $f^* \approx \frac{1}{4}$. For n = 4 we would obtain $f^* \approx \frac{1}{12}$. On this basis we shall be led to conclude that we have $n < 4$.

We shall, as a basis for our discussions, adopt as a reasonable value n = 2.5 and then we obtain $f^* \approx \frac{1}{6}$ which would appear to be a reasonable value.

The Surviving Fraction of the Somatic Cells:

We shall now proceed to compute the "surviving" fraction of the somatic cells of a female, who has inherited r faults, as

II

10/31/58

ON THE NATURE OF THE AGING PROCESS

by

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Part II: The Production of Faults by Exposure to Ionizing Radiation and through Spontaneous Mutations

If a population of mice is exposed to x-rays, the life expectancy of the mice is shortened, and it has been suspected, for some time, that the irradiation might somehow increase the physiological age of the irradiated animals in the sense of increasing the age specific rate of death uniformly for all causes of death.

The theory here presented leads to attributing the life shortening effect of ionizing radiation in the irradiated animals to the production of point mutations in the genetic substance of the somatic cells. Since a certain fraction of these point mutations will affect "essential vegetative" genes, a certain number of faults are produced in somatic cells and, according to our theory, the life expectancy of the animal ought to be reduced by τ years per added fault per somatic cell.

Experiments of W. L. Russel seem to show that the offspring of mice which have been exposed to a dose of fast neutrons have a reduced life expectancy. This is generally interpreted by saying that exposure of the parents with ionizing radiation produces mutations in the germ cells of the gonads and, therefore, it is a foregone conclusion that the offspring must have reduced viability.

Concerning the reduction of the life expectancy of the offspring of an irradiated population, we have to distinguish from the point of view of our theory that part of the reduction of life expectancy which is due to an increased mortality of the young animals and the part which is due to a reduction in the

life expectancy of the adults. All of the mutations produced by the radiation might contribute to the former, but only the faults are responsible for the latter.

It should be possible to make a clean separation between these two effects because, as the Life Tables show, the number of deaths falls from year to year after birth and by the 10th year of age it is down to about 40 per 100,000. Of these deaths, a substantial fraction is due to accidents. Thus, one is led to believe that mutant, incompetent, forms of genes may, in the heterozygous condition, cause death of the embryo or death of the infant, but they do not cause deaths, with an appreciable probability, after the 10th year of age - at least not in the heterozygous condition. On the basis of our theory, we expect that only faults may enhance the death rate of the adult and they may do it only in conjunction with the aging process. In order to compare the experimental results with the predictions of the theory, these two effects which must both manifest themselves in the offspring of irradiated parents will have to be noted separately.

On the basis of the theory here presented, we are led to believe that the offspring of irradiated parents will have an "increased physiological age" not only in terms of an increase in the age specific death rate which leads to a reduction in the life expectancy of the adult, but also in terms of the reduced chronological age at which general symptoms of senescence appear in some quantitatively defined degree. From the point of view of the theory, the most interesting experiments may therefore be those in which a population of mice or rats are exposed to certain doses of x-rays (or fast neutrons) and in which one determines the age at which various general characteristics of senescence appear in the offspring. One might think of different

general symptoms of senescence which might be singled out for observation in such experiments. It is conceivable that ~~merely~~ even by merely determining the age at which the "hair" turns gray one might ~~obtain~~ obtain significant results.

Arrangements for setting up experiments along these lines, on the offspring of irradiated parents, are at present under discussion.

On the basis of our theory, we must expect (as we shall presently see) that the life shortening produced by a given dose of x-rays in the irradiated animals will ~~amount to~~ represent the same fraction of the total life span for ~~genetically perfect~~ individuals belonging to two different species (if the two species are equally sensitive to X-rays ~~(from a point of view of the production of point mutations in the somatic cells)~~, if the critical value f* is the same for the two species and if the chromosome number m is the same for the two species. ~~This follows from the fact that, according to our theory, the life shortening of a genetically perfect individual by the addition to its somatic cells of one fault - on the average - reduces the life span by tau where tau is given by~~

( )

Thus, we may write

( )

If we compare two species A and B which have different chromosome numbers m_A and m_B then we may write, in the first approximation, for the life shortening per rep

( )

general symptoms of senescence which might be singled out for observation in such experiments. It is conceivable that one might obtain significant results even by merely determining the age at which the "hair" turns gray.

Arrangements for setting up experiments along these lines, on the offspring of irradiated parents, are at present under discussion.

If we observe the life shortening of the adult animal resulting from the induction of a fault by ionizing radiation in one species, we may be able, on the basis of our theory, to predict the life shortening that the induction of a fault ought to produce in the adult animal of another species. This may be seen as follows. We obtain from (21) and from ( ) for the relationship between the life shortening per fault Δt and for the life span of the species t_0

$$\frac{\Delta t \text{ per fault}}{t_0} = \frac{\tau}{t_0} = \frac{1}{\sqrt{4m \ln \frac{1}{f^*}} + \ln \frac{1}{f^*}}$$

The right-hand side of the equation contains only the chromosome number m and the critical value f* for the surviving somatic cells at death. Therefore, if two species of mammals have the same value f* and the same chromosome number m, the life shortening per fault induced by ionizing radiation must amount to the same fraction of their life span. We may call this ratio the specific life shortening effect of a fault.

II page new new 3A

The relationship (22) is important because if we have observed the life shortening effect of a given dose of a certain kind of ionizing radiation in one species of mammals, we may exterpolate from it to another species of mammals.

If the two species of mammals may be assumed to have the same value f, and the same number of vegetative genes, and if the sensitivity of their genes to the ionizing radiation employed is the same, the according to (22) the life shortening effect of radiation exposure will represent the same fraction of the life span for the two species - provided that the chromosome numbers are also the same.

If the chromosome numbers are different, then the "specific life shortening" will be larger for the species which has the smaller chromosome number, and the "specific life shortening" goes inversely with the square root of the chromosome number.

The number of chromosomes m, in the haploid set is 20 for the mouse and 23 for Man, i.e. they are about equal. Accordingly, with the qualifications stated above, we might expect to find the same "specific life shortening" for the mouse and for Man.

The number of chromosomes m in the haploid set is 11 for the Chinese hamster and opossum and 39 for the dog. Accordingly, with the qualifications stated above, the specific life shortening of the Chinese hamster and the opossum may be expected to be higher than that of the dog, by a factor of 2, and higher than that of the mouse, by a factor of about $\sqrt{2}$.

Part II

We shall in this paper extrapolate from the life shortening observed in mice to that which may be expected in Man by assuming that the life shortening per rep in Man and in the mouse amount to the same fraction of the life span. Some authors believe that Man is almost twice as sensitive to X-rays as the mouse and if they are correct, then our extrapolated value for the life shortening of Man might be too low by a factor of about two. Raising the value we use would, however, only strengthen the arguments presented below.

Experiments on the life shortening of adult mice, which are exposed to single doses of X-rays of the order of magnitude of 100 r, indicate that the life expectancy of the adult is mouse is shortened by an amount which is proportionate to the dose. If extrapolated to Man in the manner stated above, these experiments give a life shortening of about 6 days per rep.

47 ~~(69)~~

δ = 6 days per rep

On the basis of the life shortening of δ = 6 days per rep and assuming for n a value of 2.5 and accordingly for $\bar{t}$ a value of $\bar{t}$ = 6 years, we may say that an x-ray dose of 365 rep must result in the production, on the average, of one fault per somatic cell of the exposed individual.

Let us now designate with δ^* the reduction in the life expectancy of the adult offspring of irradiated parents expressed in days per rep, which will occur if a sufficiently long period of time is permitted to elapse between the exposure of the parents and the mating. If we now assume that x-rays produce point mutations in the chromosomes of the immature germ cells of the gonads - in both male and female - with the same effectiveness as they produce point mutations in the genetic substance of the somatic cells, then we may write

48 ~~(70)~~

$\delta^* = \delta$

Accordingly, we would then expect that exposure of both parents to x-ray doses totalling 365 rep would lead, on the average (if a sufficient period of time is permitted to elapse between exposure and mating) to the appearance of one additional fault in the offspring.

Accordingly, such an exposure of the parents should shorten the life expectancy of the adult of the first generation by about $\tau = 6$ years. Further, the physiological age of the first generation ought to be ahead of the chronological age by $\tau = 6$ years and, accordingly, the symptoms which generally accompany senescence ought to set in about 6 years earlier.

The Doubling Dose D_o and the Spontaneous Mutation Rate:

The total dose of X-rays at which one must expose a population in order to produce as many mutations in the offspring as would spontaneously arise in one generation, may be called a doubling dose D_o. The number of mutations produced appear to be proportionate to the total dose, if mice are exposed to single doses of the order of magnitude of 50 rep, and D_o is defined in terms of exposures where the individual doses are of this order of magnitude. An exhaustive effort has been made to determine the doubling dose for mice by W. L. Russell and, in principle at least, a direct determination of the number of mutations produced by X-ray exposures ought to enable us to establish the value of the doubling dose. In such a direct determination, if it were to establish the doubling dose with the desired accuracy, would, however, be difficult. On the basis of such experiments and some more involved considerations, the doubling dose D_o has been variously estimated for Man to be somewhere between 30 and 120 rep. It would be of considerable interest to know the value of this doubling dose D_o because, if generation after generation of the population were persistently exposed to the doubling dose, D_o, our mutation load would in time be doubled. Since an exposure to at least a substantial fraction of the doubling dose generation after generation could conceivably arise from the "practical" use to which atomic energy may be put in the years to come. In a treatise published in 1951, entitled "Our Load of Mutations", H. J. Muller has discussed the deleterious affects that a substantial increase of the mutation rate in the population may be expected to have for future generations. Having this point of view in mind, the paper regards as "optimistic" estimates which would make the doubling dose D_o come out high and it regards as "optimistic" or "conservative" estimates which make the spontaneous mutation rate come out high - in view of the fact that if the

total natural mutation rate is high, then increasing that mutation rate by a fixed amount through the exposure of the population to ionizing radiation would make a comparatively small percentage of change. Subsequent authors have, in general, fallen in line with this terminology.

As we will presently see, however, the theory here presented establishes a connection between the doubling dose D_o and the total spontaneous mutation rate μ_t and in such a way that if we adopt for the doubling dose an estimated value which is high, the total spontaneous rate comes out to be proportionately higher also. Since, Moreover, even if we adopt for the doubling dose D_o within the above-quoted range of its estimated value, the lowest one of D_o =30 rep, the total mutation rate comes out to be $\mu_t = 0.25$ per generation. Following the reasoning of the above-quoted paper of H. J. Muller, this comes to be rather close to what may be regarded as the dangerpoint. Inasmuch as it is easier to protect the population from exposure to ionizing radiation than to adopt measures which will be necessary to counteract the ill effects of too high a spontaneous mutation rate, we shall in the following regard estimates for the doubling dose D_o which make this value come out low (and, accordingly, make the total mutation rate come out tolerable) as the optimistic estimate, rather than the other way around.

In order to see the relationship between the life shortening effect of δ^* days per rep on the offspring of the exposure of the parents to an x-ray dose, D_o, the doubling dose and - the total spontaneous mutation rate per generation - one may reason as follows.

On the one hand, the doubling dose D_o produces a life shortening in the offspring of δ^* days per rep.

On the other hand, the doubling dose D_0 must by definition produce N_1 faults in the haploid set of the genes, where N_1 designates the spontaneously arising faults in the haploid set of genes. Therefore, N_1, the number of faults added to the diploid somatic cells of the offspring of parents who have been exposed to the doubling dose D_0 is given by

(71) faults added per doubling dose = $2\mu_1$

Since one fault produces a life shortening of the adult $\bar{\tau}$ years, we may write for the life shortening in days produced in the offspring caused by the dose D_0 administered to the parents

(72) Life shortening (days) = $365\,\bar{\tau}\,2\mu_1$

And, for S^* the life shortening of the offspring in days per rep we may write

(73) $$S^* = \frac{365\,\bar{\tau}\,2\mu_1}{D_0}$$

or

(74) $$\mu_1 = \frac{1}{2}\,\frac{S^* D_0}{365\,\bar{\tau}}\,N_1$$

If we designate the total number of genes with N_t we may write for μ_t the total mutation rate per generation of the haploid set of genes,

(75) $$\mu_t = \frac{N_t}{N_1}\,\mu_1$$

or, for $2\mu_t$ the total number of new mutations arising spontaneously per generation per individual

(76) $$2\mu_t = \frac{S^* D_0}{365\,\bar{\tau}}\,\frac{N_t}{N_1}$$

A reasonable set of values chosen with the purpose in mind of trying to keep μ_t, the total mutation rate, low might be as follows: $N_1 = 1{,}000$; $N_t = 5{,}000$; $D_0 = 36.5$ rep, $\bar{\tau} = 6$ years. The value of σ^* is ~~experimentally~~ fixed at $\sigma^* = \sigma = 6$ days per rep.

The value of $N_1 = 1{,}000$ is chosen because bacteria may be assumed to have 1,000 genes and there is no reason to believe that the somatic cells of mammals should need a substantially larger number of genes in order to be able to function - at least as microorganisms ~~#~~, in their own right.

Substituting the above values into (74) we obtain

$\mu_1 = 0.05$ or $2\mu_1 = 0.1$ and $\mu_t = 0.25$ or $2\mu_t = 0.5$

$\mu_t = 0.25$ is a rather high total mutation rate. Under ~~the present day conditions~~, we ~~ought to~~ expect our mutation load to rise until a new mutational equilibrium is established. At that point, under the present favorable non-competitive conditions, of each person conceived, a fraction of $e^{-0.5}$ would only survive and the remaining fraction of $1 - e^{-0.5}$ would suffer "genetic death," provided that the individuals eliminated are heterozygous for the mutant gene, rather than homozygous.

Genetic deaths could take the form of death of an individual as an embryo or infant below 10 years of age, it could take the form of failure to procreate even under the present non-competitive conditions. In addition, there might appear, as a new phenomenon, an appreciable number of deaths in young persons above the age of 10 who are homozygous for certain mutant genes.

The worst consequence of an increasing mutation load would, however, probably result - according to the views here adopted - from the increase in the load of faults, which would lead to the onset of senescence at an earlier age.

Since, as may be seen from (76), in our theory, the product

$\nu^* D_0$ is fixed by the value of μ_x, therefore, if the production of point mutations by X-rays falls off at lower dose rates and if it falls off in the same way for the germ cells as it does for the somatic cells, we must expect, at low dose rates, the doubling dose to increase by the same factor by which the life shortening of the irradiated animals decreases,

The mutation rate μ would be higher than the above quoted values if we were to assume that the doubling dose is higher than 36.5 rep, that τ is shorter than 6 years or that N/N_1 is larger than 5.

The mutation rate μ could be lower if N/N_1 were postulated to be less than 5, but we hesitate to assume that the total number of genes is less than 5,000 and we would also hesitate to assume that N_1, the number of essential vegetative genes, is substantially higher than 1,000.

The assumption N = 5,000 corresponds to an average mutation rate per gene of 1 : 25,000 per generation. This is rather on the high side but not out of the range of possibilities. We might shift the average mutation rate per gene per generation to 1/100,000 by assuming N = 25,000 but then we would also have to assume N_1 = 4,000. This is probably as far as one might want to go for it is difficult to imagine that more than 5,000 genes should be essential for the functioning of the somatic cells, in general.

A number of authors believe that when a population of mice is exposed to a very low dose rate, the life shortening effect of a given dose might be 2 or 3 times lower. Similarly, recent experiments by W. L. Russell permit one to suspect that the doubling might be 2 or 3 times higher if x-rays are administered at a very low dose rate. Our estimate for the total spontaneous mutation rate would, however, not change if it should turn out that - at very low dose rates - and are both lower by some factor of 2 or 3 and that the doubling dose is higher by the same factor. This is so because only the product enters into the expression ( ), giving , the total spontaneous mutation rate.

Maternal selection pressure against faults

We might now indulge in attempting to guess at what our total load of mutations might be. In this, we shall follow the reasoning presented by H. J. Muller in 1951 in an article entitled "Our Load of Mutations". Assuming that in the past mutant forms of the important genes had an average persistence of 50 generations, we then obtain a total mutation load of 25. One-fifth, five, will be faults. For the load of faults alone we obtain the value of n = 5. This is twice as high as the value of n = 2.5 which corresponds to $\bar{\tau}$ = 6 years.

It is conceivable, however, that the average persistence of essential vegetative genes was 25 rather than 50 generations and this would reduce the load of faults to n = 2.5. Could there be selection pressure at work that has not been hitherto considered?

It is conceivable that a woman who carries a fault in her genetic makeup ceases to be capable of bearing children $\bar{\tau}$ = 6 years earlier than her counterpart who lacks that particular fault. This is what one would expect on the assumption that the termination of the woman's reproductive period is determined by her physiological age if all other factors are equal. If this assumption is correct, then there was in the past a powerful selection operating that tended to keep the load of faults low. In the past, infant mortality was high and the birth rate was high and women kept on having children until the end of their child-bearing period. Under such circumstances, the selection mechanism mentioned above would be the predominating mechanism. Clearly this selection mechanism is switched off it women have two or three children between the ages of 18 and 25 and then avoid having further children through exercising control over birth control.

If such a maternal selection was indeed the predominating selection mechanism in the past, then, when this selection may cease to operate, we ought to expect that, in time,

our load of faults would double and, as discussed before, senescence would then set in about 15 years earlier.

However, even if we assume the worst in this respect, our load of faults would not increase by more than $2\mu_1 = 0.1$ per year per generation. This means that - at worst - it would take 25 generations for our load of faults to double.

The effect of the "maternal" selection here discussed might be estimated as follows:

Let us single out one particular essential vegetative gene. If a woman carries, as a heterozygote, this particular gene in a mutant form, her physiological age is $\tau = 6$ years higher than that of another female who does not carry this particular "fault" but who is otherwise identical in her genetic makeup. We assume now that the "physiological age" sets the termination of the reproductive period, we take for the "most probable duration" of the reproductive period 30 years. The particular fault thus probably shortens the reproductive period by 1/5 of its length. The fertility of younger women is higher than that of older women. The average time interval between two successive pregnancies might be by a factor k (or perhaps 2 or 3) longer near the end of the reproductive period than the value of this interval averaged over the whole reproductive period.

If we now postulate that the maternal selection above represents the sole selection pressure or a stronly predominating selection pressure against faults, we may write for the mutation equilibrium for the particular fault we are discussing:

$$2\frac{\mu_1}{N_1} = \frac{1}{2}\cdot\frac{1}{5}\cdot\frac{1}{k}\cdot\frac{n}{N_1} \qquad (78)$$

Faults lost due to lost fault reducing φ fecund period.

$= \frac{n}{N_1}$ fraction of veg that are faulty. $\cdot \frac{1}{2}$ chance of conception receiving a fault $\cdot \frac{1}{5}$ fraction of fecund period lost $\cdot \frac{1}{k}$ Prob. of ... at end of fecund per...

longer than average

and for the value of $\mu_1 = 0.05$ per generation
we thus obtain

(79) $k = n$

~~If Under "natural" conditions~~

Under "natural" conditions, the average time interval between two successive pregnancies in young women might be about one year, ~~and~~ towards the end of the reproductive period it might be about five years and ~~the time interval~~ averaged over the whole reproductive period of about 30 years it might be about two years. This ~~would~~ then correspond to ~~X~~ k = 2.5. This coincidence might, of course, turn out to be fortuitous.

X

Refinements of the theory - of the number of segments per chromosome

Refinements of the theory - specialized results

Refinements of the theory ~~- some faults. -~~

To price (mong)

Appendix

$$-P(r)\frac{dx}{dr} = P(r)\left[\frac{1}{1+\frac{4m}{r^2}\ln\frac{1}{kx}} - \frac{4m\ln\frac{1}{kx}}{r^2}\right]$$

$$-P(r)\frac{dx}{dr} = \left[\left(\frac{1}{1+\frac{4m}{r^2}\ln\frac{1}{kx}}\right)^{1/2} - 1\right]P(r)$$

$$P(r)\frac{dt}{dr} = \frac{1}{c}\left[\left(\frac{1}{1+\frac{4m}{r^2}\ln\frac{1}{kx}}\right)^{\frac{1}{2}} - 1\right]P(r)$$

$x = \frac{t}{c}$

I

10/30/58

ON THE NATURE OF THE AGING PROCESS

by

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Part I: On the Effect of Faults on the the Life Expectancy of the Adult

Introduction

This paper represents an attempt to describe a hypothetical biological process that could conceivably account for the phenomenon of aging and that would permit us to predict the effect of mutated, incompetent, genes on the life expectancy of the adult. Aging manifests itself in much the same general manner in all mammals and we should be in the position to learn enough about the aging 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.

This theory assumes that the elementary step in the process of aging is the "destruction" of a chromosome of a somatic cell, in a random process, which somehow renders the whole chromosome "non-competent", even though it may not be destroyed, in a physical sense. It is specifically assumed that the probability that a chromosome is destroyed per unit time remains constant throughout life and that the rate at which chromosomes of the somatic cells are destroyed is a characteristic of the species.

As the result of such an aging process, the fraction of functional somatic cells of the organism decreases with age and, as we shall see, it first decreases more slowly and subsequently it decreases faster. The theory postulates that as the fraction of the surviving somatic cells falls in the course of aging, the probability of dying per unit time increases and that this probability becomes very large when f, the fraction of the

surviving somatic cells falls to a critical value of f = f*. Because the body of the mammalian organism presumably operates with very large reserve, we may assume that the fraction of surviving cells may be quite small and, yet, the organism may continue to live. Accordingly, we shall tentatively postulate for the critical value of the fraction of the surviving cells

(1) $$\frac{1}{3} > f^* > \frac{1}{20}$$

or

(2) $$1 < \ln \frac{1}{f^*} < 2$$

The precise meaning of the term "critical value" f*, is somewhat different in the crudest form of the theory, which we shall discuss first, from that of the term in the less crude form of the theory, which we shall discuss subsequently.

In the crudest form of the theory, we shall assume that an individual - or at any rate, a person above the age of 10 years, does not die of natural causes until the fraction of his surviving somatic cells comes very close to the critical value f* and that a person then dies within the year in which this fraction reaches a critical value. In this crudest form, the theory postulates, concerning the distribution of the ages at death, that the age at death is uniquely determined by the genetic makeup of the individual. If this were true, identical twins would have to die, at least to within one year of each other. In fact, as we shall see, the mean difference of the ages at deaths for female identical twins may be estimated to be about 3-1/2 years. In its crudest form, the theory does not account for the fact that the probability of dying of natural causes must gradually increase for an adult, first more slowly, and later faster, as he approaches the critical age, i.e. the age at which the fraction of the surviving somatic

cells reaches the critical value f*).

If not otherwise stated, our discussion relates to Man ~~in general~~ and to the female of the species in particular. In the case of Man, the somatic cells of the female contain 23 pairs of homologous chromosomes.

The theory assumes that in a genetically perfect female, i.e. a female whose genetic makeup contains every gene in two fully competent copies, ~~the~~ somatic cell remains functional as long as at least one chromosome - out of each pair of homologous chromosomes - remains competent. A somatic cell ceases to be functional ~~if~~ only when both copies ~~of~~ within any of the 23 chromosomes pairs cease to be competent.

We shall ~~now~~ also have to consider how the somatic cells of an ~~individual~~ female will be affected by the aging process if the ~~individual~~ female is not genetically perfect but contains in ~~its~~ her genetic makeup mutant - non-competent - forms of genes.

There may be perhaps 5,000 or 10,000 "important" genes carried by Man. The term "important" is used here in the sense that if one of the pair these genes is present in ~~the~~ a mutant, incompetent, form at conception in the genetic makeup ~~of the heterozygote individual~~ (heterozygous) a child, that individual would be handicapped for life. He might not be handicapped under present living conditions in the United States, when 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. But he would have been handicapped, ~~per~~ by definition of the term "important", under ~~living~~ conditions prevalent in ~~of the past up to - in terms of the evolutionary time scale~~ present contemporaneously times - recent times. The abundance in the population of mutant ~~incompetent~~ forms of such genes is, therefore, ~~at present at a low value~~ due to the selection pressures which have operated in the past - ~~up to recently~~.

We may assume that ~~all~~ most of these important genes somehow affect differentiation or morphogenesis during the embryonic development at the molecular level and that mutant - ~~incompetent~~ - forms of such genes, even if they are "covered", ~~(i.e. in the heterozygous condition)~~.

by competent copy of the gene -- [i.e. even in the heterozygote] may cause, with a sudden probability, a developmental anomaly of the individual which results in a handicap for life.

A great majority of these "important genes", mutant -- incompetent -- form of the gene may even be present in the homozygous condition [i.e. "not covered" by competent copy of the gene] in the somatic cell of the adult, without rendering that somatic cell non-functional.

We assume, however, that among the 5,000 to 10,000 "important" genes, there is at least a minority of genes, perhaps 1,000 or 2,000, which are essential for the functioning of the somatic cells of the adult. We shall call these genes [a sub-class of all the "important" genes] "essential vegetative" genes and a mutant, incompetent, form of such a gene we shall designate as a "fault".

We postulate that, in general, a somatic cell of the adult requires for its proper functioning the presence of each essential vegetative gene in at least one competent copy. We further postulate that one competent copy is enough and that, in general, the somatic cell of the adult will function properly as long as it contains one competent copy of every essential vegetative gene.

From these assumptions it follows that when a chromosome is destroyed, in the course of the process of aging, the cell must cease to become functional if the homologous copy of the chromosome contains a fault.

According to the theory here presented, the "genetic" reason why some adults live shorter and others live longer is due to the difference in the number of faults contained in the genetic makeup. If we assume that the faults are distributed at random in the population of the United States, and if we know the mean number of faults per individual (which we shall designate with n), we are then able to compute the distribution of the ages at death in the population and may then compare it with observed distribution, as given by the life tables.

In case of the population of the United States, or even such a subgroup as white females, the differences in the social

setting in which different individuals live may be expected to introduce a scattering of the individuals' value of f, which should somewhat broaden the distribution of the ages at death. This broadening is in addition to the non-genetic scattering which manifests itself in the mean age differences at death of identical twins, whom we assume to live in the same social setting.

Because this additional broadening cannot be theoretically predicted, there is some advantage in considering a group that may be expected to be homogeneous with respect to the social setting in which its members spend their lives. For this reason, we make use of the observed mean age difference at death of non-identical [dizygotic] twins. The mean age difference of siblings at death may be computed by considering the distribution of faults in a population of siblings and by making a correction for the non-genetic scattering on the basis of the observed mean age difference at death of identical twins. By comparing the predictions of the theory with observed value and from the empirical fact that the number of death per year is maximal [for white females] between the ages of 80 and 81, it is possible to arrive at an estimate for n, the mean value of the faults in the population.

If we assume that the elementary step in the process of aging consists in the destruction of the whole chromosome, we are led to conclude that we have $2 < n < 3$. We also obtain an estimate for τ, the number of years by which one fault shortens the life expectancy of an adult and we have $\quad < \tau < \quad$.

Further below, we shall in passing consider the possibility that the elementary step in the process of aging might be the destruction of one-half of a chromosome rather than a whole chromosome. This assumption would lead to n and τ.

One might be tempted to go even further and to assume that the elementary process of aging consists in the independent destruction of small segments of chromosomes or perhaps even in the independent occurrence of point mutations. If one computes, however, on the basis of such assumptions the difference between the

life expectancy of the female and the male, one obtains differences which are much greater than the observed difference of about three years.

The Effect of a Fault on the Life Expectancy of the Adult:

We shall now proceed to compute the surviving fraction of the somatic cells of an individual as a function of his chronological age -- first, for a genetically perfect female, and next, for a female whose genetic makeup contains r faults.

The Effect of a Fault on the Life Expectancy of the Adult:

"We assume that the rate at which chromosomes are hit in the course of the process of aging does not change throughout the life of the individual and that it is a characteristic of the species. Designating this rate with α, we may write — at any given age — for ξ, the average number of "aging hits", suffered in toto by the chromosomes of a somatic cell of an individual

(3) $$\xi = \alpha \times \text{chron. age}$$

Or, if we write

(4) $$\alpha = \frac{1}{\tau}$$

then we have

(5) $$\xi = \frac{\text{chron. age}}{\tau}$$

τ may be defined as the average time interval between two subsequent aging hits suffered by the chromosomes of the somatic cell. We may call this average time interval τ, the basic time interval of the aging process.

We may now compute for a genetically perfect female - i.e., the female whose genetic makeup contains no faults - the probability that a somatic cell may survive an average of ξ "aging hits" as follows:

If we single out one chromosome pair, the probability that an average of ξ aging hits do not cause loss of function to the cell arising from damage to the chromosome pair which we have singled out may be written as follows:

(6) $$q = 2e^{-\xi}(1-e^{-\xi}) + e^{-2\xi} =$$

In this expression η stands for

(7) $$\eta = \frac{\xi}{2m}$$

Where m represents the number of chromosomes in the haploid set. In expression (6) the first term represents the probability that one of the two chromosomes suffers an aging hit and the other escapes being hit and the second term represents the probability that both chromosomes escape being hit. Expression (6) we may also write in the form

(8) $$q = 1 - (1 - e^{-\eta})^2$$

The probability that an average of ξ aging hits leaves the somatic cell functional with respect to all m chromosome pairs is thus given by

(9) $$f(\eta) = q^m = [1 - (1 - e^{-\eta})^2]^m$$

We shall assume for the purposes of this paper that we have

$$\eta << 1$$

and thus we obtain in the approximation that we choose to use

(10) $$f(\eta) \cong e^{-m(1-e^{-\eta})^2}$$

We may write expression (10) also in the form

(11) $$\ln \frac{1}{f(\eta)} \cong m(1 - e^{-\eta})^2$$

and by expanding (11) we obtain

(12) $$\ln \frac{1}{f(\eta)} \cong m\eta^2\left(1 - \eta + \frac{7}{12}\eta^2 \mp \cdots\right)$$

If we designate the critical value for the fraction of surviving somatic cells with f^* and if we designate with x the average number of hits at which the surviving fraction of the surviving cells falls to the critical value f^* (we might designate x as the

critical number of hits) then we obtain by substituting into (9)

$$\eta = \frac{x}{2m} \tag{13}$$

in (9) we obtain

$$f^* = \left(1 - \left(1 - e^{-\frac{x}{2m}}\right)^2\right)^m \tag{14}$$

or we may write and for small values of $\left(1 - e^{-\frac{x}{2m}}\right)^2$ we may write for the genetically perfect female;

$$\ln \frac{1}{f^*} = m\left(1 - e^{-\frac{x}{2m}}\right)^2 \tag{15}$$

and by expanding this we obtain for the genetically perfect female the Hurwitz approx

where

(16)

as ~~and may be found~~.

and further we may write from (12)

$$\ln \frac{1}{f^*} \doteq \frac{x^2}{4m}\left(1 - \frac{x}{2m} + \frac{7}{12}\frac{x^2}{4m} \mp \cdots\right) \tag{16}$$

For a female who is not genetically perfect and whose genetic makeup contains r faults, the surviving fraction of the somatic cells will be lower for an equal average number of hits. For such a female we may write for the critical number of hits x_r for which the fraction of the surviving cells is given by f^*:

$$f^* = \frac{\left[1 - \left(1 - e^{-\frac{x_r + r}{2m}}\right)^2\right]^m}{\left[1 - \left(1 - e^{-\frac{r}{2m}}\right)^2\right]^m} \tag{17}$$

"Where x_r designates the critical average number of hits x for a somatic cell containing r faults.

For this expression we may write

$$f^* = \frac{e^{-m\left(1 - e^{-\frac{(x_r + r)}{2m}}\right)^2}}{e^{-m\left(1 - e^{-\frac{r}{2m}}\right)^2}} \tag{18}$$

or

$$\ln \frac{1}{f^*} = m\left(1 - e^{-\frac{x_r + r}{2m}}\right)^2 - m\left(1 - e^{-\frac{r}{2m}}\right)^2 \tag{19}$$

or by expanding this, we obtain in second approx.

(20) $$\ln \frac{1}{f^*} = \frac{(x_r+r)^2}{4m}\left(1-\frac{x_r}{2m}\right) - \frac{r^2}{4m}\left(1-\frac{r}{2m}\right)$$

In the consideration to which we propose to turn next, we shall consider only small values of r for which we may neglect the second term in expression (19) so that in our approximation we may now write from (19):

(21) $$\ln \frac{1}{f^*} \approx m\left(1-e^{-\frac{x_m+r}{2m}}\right)^2$$

By expanding this we obtain within the limits of the accuracy of the approximation we propose to use

(22) $$\ln \frac{1}{f^*} \approx \frac{(x_r+r)^2}{4m}\left(1-\frac{x_r}{2m}\right)$$

We may express from (19) inversely $x_r + r$ from f^* and write

(23) $$x_r + r \approx 2m \ln \frac{1}{1-\sqrt{\frac{1}{m}\ln\frac{1}{f^*}}} = \varphi_1(m, f^*)$$

and if we expand this, we obtain in our approximation

(24) $$x_r + r \approx \sqrt{4m \ln \frac{1}{f^*}} + \ln \frac{1}{f^*} = \varphi_2(m, f^*)$$

If we designate with t_r the critical age, i.e. the age at which the surviving fraction of the somatic cells of an individual who has r faults reaches the critical value f^*, we may write

(25) $$x_r = \frac{t_r}{\tau}$$

and thus we obtain from 23

(26) $$\frac{t_r}{\tau} + r \approx 2m \ln \frac{1}{1-\sqrt{\frac{1}{m}\ln\frac{1}{f^*}}}$$

or

(27) $$t_r \approx \tau\left(2m \ln \frac{1}{1-\sqrt{\frac{1}{m}\ln\frac{1}{f^*}}} - r\right)$$

From this equation we may see that -- in our approximation -- each added fault reduces the life time of an individual by τ. This is a basic relationship in the theory here presented. We shall call

the critical age for a genetically perfect female (i.e. a female who has no faults ~~so that we may write~~ r = 0), ~~i.e.~~ the "life span" of the species. For this "life span", we obtain from (27)

(28) $$t_0 = \tau\, 2m \ln \frac{1}{1 - \sqrt{\frac{1}{m} \ln \frac{1}{f^*}}}$$

By introducing t_0 into (27) we obtain

(29) $$t_r = t_0 - \tau r$$

and

(29A) $$r = \frac{t_0 - t_r}{\tau}$$

And from ( ) we obtain

(29B) $$\frac{t_r}{t_0} = \frac{2m \ln \frac{1}{1 + \sqrt{\frac{1}{m} \ln \frac{1}{f^*}}}}{t_0}$$

or

(29C) $$\tau = \frac{\sqrt{4m \ln \frac{1}{f^*}} + \ln \frac{1}{f^*}}{t_0}$$

The equations (29B) or (29C) show that if we compare two species of mammals, A and B, for which the values of f*, the critical fraction of the surviving cells, is about the same and which have about the same chromosome number m, we may write

(29D) $$\frac{\tau(A)}{t_0(A)} = \frac{\tau(B)}{t_0(B)}$$

This relationship may be expressed by saying that the addition of one fault produces a shortening of life which represents in the two different species, the same fraction of the life span of the species.

This is important because it is possible experimentally to introduce faults into the genetic substance of the somatic cells by exposing animals to ionizing radiation and the relationship expressed by (29C) permits to extrapolate the life shortening effect observed in the case of one species of mammals to another species. Such an extrapolation must, of course, either be based on the assumption that the "sensitivity" of the chromosomes of the two species for the radiation employed is the same or else the

"sensitivity" must somehow be determined by an appropriate experiment.

If the haploid chromosome numbers m(A) and m(B) of the two species, A and B, are different, then using the approximation given by (29C) and neglecting the second term in the numerator, we may write

(29E) $$\frac{\tau(A)/t_0(A)}{\tau(B)/t_0(B)} = \sqrt{\frac{m(A)}{m(B)}}$$

This means that the life shortening produced by one added fault in the species of mammals that has a smaller chromosome number than another species of mammals, the life is shortened by a fraction of the life span which is smaller by a factor of than in the species which has a larger chromosome number.

2, the number of chromosomes in the haploid set, is 11 for the Chinese hamster and the opossum, 19 for the cat, 20 for the mouse, 21 for the rat, 22 for the rabbit, 23 for man, and 78 for the dog. Accordingly, assuming that all other things are equal, one should expect for the Chinese hamster, for instance, a percentile shortening of the life span caused by an exposure to, say, a dose of x-rays which is lower by a factor of about $\sqrt{2}$ than the shortening for the mouse, and lower by about a factor 2 than a shortening for the dog.

* * *

Appendix

In an approximation different from that used mostly in this paper, we do not neglect the second term in (19) and thus obtain, in the first approximation

(29F) $$\ln \frac{1}{f^*} = \frac{(X_r + r)^2}{4m} - \frac{r^2}{4m}$$

or

(29G) $$r = \frac{4m \ln \frac{1}{f^*} - X_r^2}{2X_r}$$

or

(29H) $$r = \frac{1}{\tau}\,\frac{t_0^2 - t_r^2}{2t_r}$$

x x x

In the crudest form of the theory, we postulate that a person dies within the year which is centered around the critical time $t = t_r$, when the fraction of his surviving cells reaches the critical value f*. This crudest form of the theory disregards the scattering in the ages of death of individuals who are genetically identical, ~~Such non-genetic scattering~~ which manifests itself in the distribution of the ages at death of identical twins.

As may be seen from (28), in the approximation in which this formula holds, the age of death t_r ~~as given by the crude form of the theory, is reduced~~ by the addition of one fault would reduce τ years, where τ is the basic time interval of the aging process ~~if the number of faults in the genetic makeup of the individual is increased by 1~~. And, similarly, in the less crude form of the theory in which the distribution of the ages at death is a continuous function of the age, we may say that the life expectancy of the adult ~~is reduced~~ by τ years ~~if the number of faults in the genetic makeup of the individual is increased by 1~~. This is one of the basic predictions to which we are led by ~~the~~ this theory ~~here presented.~~

According to the crude ~~form of the~~ theory, members of one cohort would die only in certain years - at the critical ages, t_r, and the years in which death occurs within ~~the~~ one cohort would be separated from each other by time intervals of τ years. No deaths would occur in the intervening years.

Further, if the distribution of the faults in the population is random, then, according to the crude ~~form of the~~ theory, the number of deaths, P_r, occurring ~~in the ages of~~ at each age t_r, would be given by the Poisson distribution

XX (30) $$P_r = \frac{n^r}{r!} e^{-n}$$

where, according to (29), we have $r = \frac{t_0 - t_r}{\beta\tau}$;

and where n stands for the average number of the faults r, distributed at random among the individuals in the population.

The distribution of the ages at death in the population is actually a continuous function. This is due to the fact that the probability of an individual dying rises as a continuous function of age as the fraction of his surviving somatic cells falls with age and approaches the critical value f*. This fact with increasing age causes a non-genetic scattering in the distribution of the ages at death,

which manifests itself in the distribution of the ages at death of identical twins. There should be an additional non-genetic scattering in the ages of death of the population which is due to the inhomogenity of the population with respect to the environment in which different individuals spend their lives.

We shall leave this non-genetic scattering out of account for the moment and merely replace, for the sake of convenience, the discontinuous Poisson distribution for the ages at death given by (29) by the continuous distribution P(r).

XX (31) $$P(r) = \frac{n^r}{\lfloor r+1} e^{-n} \quad ; \quad r = \frac{t_0 - t}{\tau}$$

Where we have r = $\frac{t_0 - t}{\tau}$ and where we may write for d the number of deaths occurring within a year, centered around the chronological age t

XX (32) $$d(gen) = \frac{P(r)}{\tau} \quad ; \quad r = \frac{t_0 - t}{\tau}$$

if τ, the basic time interval, is expressed in years.

Because, as we shall see later, there is actually an appreciable non-genetic scattering of the ages at death, we may not expect this formula to give the correct number of deaths for each year of age. Even a moderate non-genetic scattering will substantially increase the number of deaths occurring per year at ages which are much lower or much higher than the age at which the number of deaths per year is maximum. This is so because the number of deaths per year rises steeply with age at low ages and falls steeply with age at high ages. At the age, or near the age at which the number of deaths per year is maximal, a moderate amount of non-genetic scattering will lower the number of deaths per year given by $\frac{P(r)}{\tau}$, but it will lower it only by a comparatively small amount.

For this reason it should be possible to obtain an estimate for τ by comparing the maximal value for d(gen) with the number of deaths per year, given by the life tables, for the age at which this number attains its maximal value. The actual value of would be expected to be lower.

XX (33) $$d(gen)_{max} = \frac{P_{max}(r)}{\tau}$$

According to the Life Tables based on the 1949-50 census for white females, the maximum number of deaths occurs between the 80th and 81st year. For those alive at 40 years of age, the number of deaths between 80 and 81 is given by

XX (34) $d_{max}(obs) = \frac{3.67}{100} = 0.0367$

Because the ~~xxxx~~ non-genetic scattering must reduce the maximal value for the number of deaths per year which is predicted by (33), we may write

XX (35) $\beta\, d_{max}(gen) = d_{max}(obs)$

where we have $\beta \leq 1$

For $P_{max}(r)$, we may write for values $n \geq 2.5$

XX (36) $P_{max}(r) \approx P(n-\frac{1}{2})$

~~and further for n = 2.5 we may write with, at most, a few percent of error~~ We may further write

XX (37) $P(n-\frac{1}{2}) \approx \frac{0.3989}{\lambda(n)\sqrt{n}} \approx \frac{1}{\lambda(n)\sqrt{2\pi}\sqrt{n}}$

where $\lambda(n) \geq 1$, for $n \geq 3$. For n = 2 we have $\lambda(n) = 0.979$. (Underlined) For n = 2.5 we have $\lambda(n) = 0.985$. Accordingly, we may now write

XX (38) $P_{max}(r) = \frac{0.3989}{\lambda(n)\sqrt{n}} = \frac{\text{from (36) and (37)}}{\lambda(n)\sqrt{2\pi}\sqrt{n}}$

and, further, we may write from (33) and (34)

XX (39) $d_{max}(gen) = \frac{0.3989}{\lambda(n)\sqrt{n}}\frac{1}{\tau} = \frac{1}{\lambda(n)\sqrt{2\pi}\sqrt{n}}\frac{1}{\tau}$

~~or~~

XX ~~(40)~~ $\tau = \frac{0.3989}{d_{max}(gen)} \times \frac{1}{\lambda(n)\sqrt{n}}$ leave = but change!

~~and~~ or from 40 and 35

XX (41) $\tau = \beta \frac{0.3989}{d_{max}(obs)} \frac{1}{\lambda(n)\sqrt{n}} = \beta \frac{1}{d_{max}\,obs} \frac{1}{\sqrt{2\pi}} \frac{1}{\sqrt{n}}$

By substituting ~~this value into~~ from (34) we obtain for $d_{max}(obs) = \frac{3.67}{100}$

XX (42) $\tau = \beta \frac{0.3989}{\frac{3.67}{100}} \frac{1}{\lambda(n)\sqrt{n}} = \beta \frac{10.9}{\lambda(n)\sqrt{n}}$ years

~~Thus we may write~~ for n = 2.5 $\tau \geq 7$ years. ~~and for n = 3~~

(with $\lambda(n) = 0.985$). we obtain $\tau \geq 7$ years

(with $\lambda(n) \geq 1$) we obtain $\tau \geq 6.3$ years

Estimate of the Basic Time Interval of Aging from Data Relating to Female Twins:

In the crudest form of the theory used above, the distribution of the ages at death is determined solely by the genetic makeup of the individuals in the population, i.e. it is determined by the distribution of faults in the population. On the basis of this crudest form of the theory one would have to expect that identical twins must both die within an interval of one year. The crudest form of the theory leads to such a prediction because it neglects the fact that the probability for a person to die becomes appreciable in years which precede the year in which he attains his critical age r (which is determined by the number of faults r). In order to develop a less crude form of the theory we shall now consider the distribution of the ages at death of female identical twins.

The mean age difference at death for identical female twins who die above the age of 60 has been reported by Franz J. Kallman, to have a value of 2.6 years, so that we may write:

$$\overline{\Delta}_{60}(\text{twins}) = 2.6 \text{ years} \qquad (41)$$

From this value we may estimate for the mean age difference of female identical twins who both die above the age of 40

$$\overline{\Delta}_{40}(\text{twins}) = f\,\overline{\Delta}_{60}(\text{twins}) \qquad (42)$$

The value of f we may estimate from the U. S. Life Tables based on the 1949-50 census (using Table 6 for white females, in which the number of deaths are listed in yearly intervals). By computing f on this basis, we obtain $f = 1.31$ so that we then have

$$\overline{\Delta}_{40}(\text{twins}) = 3.4 \text{ years} \qquad (43)$$

we must get

$d_x(\text{obs, corr})_{max} =$

$\left(\frac{100}{13.3}\right)^2$

$\left(\frac{100}{3.67}\right)^2 - \left(\frac{100}{13.3}\right)^2 = 26.22$

$144 - 56.5 = (26.22)^2 = \frac{100}{3.81}$

56.5

6875

$d_x(\text{obs, corr})_{max}$

No data appear to be available concerning the ~~extra~~ shape of the distribution of the ages at death of identical female twins. For that reason, as well as for the sake of convenience, we shall assume that this distribution ~~has the shape of a~~ is Gaussian. Further, we shall assume - in making the transition from the crude form of the theory to/less crude form of the theory - that in a cohort of female identical twins, the maximal number of deaths per year occurs in the year in which the fraction of the surviving cells reaches the critical value f*.

For the standard deviation $\sigma_{(twins)}$ we may write for a Gaussian distribution

(44) $$\sigma_{(twins)} = \frac{\sqrt{\pi}}{2} \cdot \Delta_{(twins)}$$

and thus we obtain for the standard deviation of ~~the~~ this Gaussian, ~~which~~ that describes the distribution of the ages of identical female twins at death

(45) $$\sigma_{(twins)} = 3 \text{ years}$$

The number of deaths per year in a population of female twins will attain a maximal value of

(46) $$d_x(twins)_{max} = \frac{0.3989}{\sigma_{(twin)}} = \frac{13.3}{100} \text{ per year}$$

In order to correct for the non-genetic scattering which manifests itself as described above in the case of female identical twins, we may now revise upward the maximal number of deaths per year obtained from the Life Tables by writing

(47) $$\left(\frac{1}{d_x(ales;corr)_{max}}\right)^2 + \left(\frac{1}{d_x(twins)_{max}}\right)^2 = \left(\frac{1}{d_x(ales)_{max}}\right)^2$$

This then permits us to set a lower limit for beta and we may write beta

$$\beta \geq \frac{d_x(ales\ corr)_{max}}{} = \frac{3.81}{100}$$

and from this we obtain from

(48)

tau =

We may now use this value in order to correct $d_{x\,max}(obs)$, obtained from the life tables, for the non-genetic scattering which manifests itself in the mean age difference at death of female identical twins. We obtain the corrected value $d_{x\,max,corr}$ by writing

(47) $$\left(\frac{1}{d_{x\,max}(obs)_{corr}}\right)^2 + \left(\frac{1}{d_{x\,max}(twins)}\right)^2 = \left(\frac{1}{d_{x\,max}(obs)}\right)^2$$

From this we obtain

(48) $$d_{x\,max}(obs)_{corr} = \frac{3.81}{100}$$

By substituting this value for $d_{x\,max}(obs)$ in (41), we obtain for τ_{corr}, the corrected value of τ

(49) $$\tau_{corr} = \beta \frac{0.3809}{\frac{3.81}{100}} \frac{1}{\lambda(n)\sqrt{n}} = \beta \frac{1}{\sqrt{2\pi}} \frac{\frac{1}{3.81}}{100} \frac{1}{\lambda(n)\sqrt{n}}$$

For n = 2.5 we thus obtain

$$\tau_{corr} < 6.75 \text{ years}$$

We cannot go any further, however, and determine on the basis of theoretical considerations along the line of reasoning so far pursued what the actual value of beta is, i.e. we cannot set an upper limit on beta. The reason for this consists in the fact that the population is inhomogenous with respect to the social setting, in which the individuals are born and in which they spend their lives. This introduces a non-genetic scattering for the critical value for which we are not able to estimate in any direct manner.

For this reason, we shall now adopt a different approach to the problem of determining the value of tau. This approach is based on the observed mean difference at the ages of death of female siblings and in particular of dizygotic female twins.

The mean age difference for dizygotic (non-identical) female twins who die above the ages of 60, $\bar{\Delta}_{60}$ (obs.) has been reported by Franz J. Kallman to have a value of 6.2 years. From this we may estimate for dizygotic female twins who both die above the age of 40 - in the manner spelled out above -

$$\bar{\Delta}_{40}(\text{obs.}) = f\,\bar{\Delta}_{60}(\text{obs.}) = 8.12 \text{ years} \quad (49)$$

where $f = 1.31$

This empirically determined mean age difference of the ages at death of female dizygotic twins may be now corrected on the basis of the empirically obtained mean age difference at death of identical female twins in order to obtain that part of the mean age difference of the ages at death of dizygotic female twins which is purely genetically determined, i.e. which is determined by the distribution of faults in a population of female siblings, and which we may designate with Δ_{40} (allgemein) by writing:

By writing

$$\left[\Delta_{40}(\text{allgemein})\right]^2 = \left[\Delta_{40}(\text{obs.})\right]^2 - \left[\Delta_{40}(\text{id. twins})\right]^2 \quad (50)$$

or

~~(52)~~ ~~(51)~~ (54)

$\Delta_{40}(\text{obs comp.})_{corr} \equiv 7.35$ years

From this empirically determined value, we may then determine the value of τ by writing

~~(55)~~ ~~(52)~~ (53) (56)

$$7.35 \text{ years} = \tau \, \overline{Diff}$$

$$\text{or } \tau = \frac{7.35}{\overline{Diff}} \text{ years}$$

where $\overline{Diff}$ stands for the mean difference in the number of faults in a population of female siblings.

In order to compute the value of $\overline{Diff}$ ( ), we shall assume that the distribution of faults in the population is given by ( ) i.e. a Poisson distribution where the number of faults r has a mean value of n.

A female inherits with a probability of 1/2 each "fault" contained in the genetic makeup of her two parents. Therefore, if the number of "faults" of the two parents ~~in toto~~ is designated with s then the probability $q_i(s)$ that a daughter of such parents has i faults in her genetic makeup is given by

57 ~~(54)~~ $$q_i(s) = \binom{s}{i}\left(\frac{1}{2}\right)^s$$

The probability P_s that the genetic makeup of the two parents contains in toto s faults ~~xi~~ is given by the Poisson distribution which corresponds to a mean value ~~xfx~~ s = 2n

58 ~~(55)~~ $$P_s = \frac{(2n)^s}{s!} e^{-2n}$$

Accordingly, we may write for $\overline{Diff}$, the mean difference in the number of faults in the genetic makeup of female siblings -

59 ~~(56)~~ $$\overline{Diff} = \sum_s P_s \sum_{i,j} |i-j| \, q_i(s) \, q_j(s)$$

For this we may write

60 ~~(57)~~ $\overline{Diff} = \varepsilon(n)\sqrt{\frac{2n}{\pi}}$

where $\varepsilon(n) = 1$ for large values of n. For n = 3 we have $\varepsilon(n) =$. For n = 2.5 we have $\varepsilon(n) = .945$. For n = 2 we have $\varepsilon(n) =$.

On the basis of the crude theory, we may, therefore, write for the mean age difference for female siblings at death from (53)

61 ~~(58)~~ $\overline{\Delta_{40}(gen)} = \tau\ \overline{Diff} = \tau\,\varepsilon(n)\sqrt{\frac{2}{\pi}}\sqrt{n}$

or

62 ~~(59)~~ $\tau = \frac{\overline{\Delta(gen)}}{\varepsilon(n)\sqrt{\frac{2}{\pi}}}\ \frac{1}{\sqrt{n}}$

~~or from ( ) by writing~~ or by substituting $\overline{\Delta_{40}(emp)}_{corr}$ from (52) for $\overline{\Delta(gen)}$ in (59)

63 ~~(60)~~ $\tau = \frac{7.35}{\varepsilon(n)\sqrt{\frac{2}{\pi}}}\ \frac{1}{\sqrt{n}}$ years =

with $\varepsilon(n) = 0.945$

For n = 2.5 this gives

~~(61)~~ $\tau = 6.15$ years

It is of interest to note that for larger values of n, for which $\varepsilon(n) \cong 1$ we may write for $n\tau$

64 $n\tau \cong \frac{7.35}{\sqrt{\frac{2}{\pi}}}\sqrt{n} = 2.93\sqrt{n}$

For n = 3 we would obtain $\tau = 4.7$ years?

Because the distribution of ages at death in the population is affected by a non-genetic scatter due to the scattering of the critical value f which arises from the inhomogenity of the social setting in which individuals are born and in which they spend their lives, it is necessary, for the sake of conceptual clarity, as well as for the sake of the convenience of the computations, to make a specific assumption concerning this kind of non-genetic scattering. A convenient specific assumption which we shall make here is that this kind of non-genetic scattering produces a Gaussian distribution in the value of $X(r)$, the critical number of aging hits for an individual containing r faults. On the basis of this specific assumption, we may now say that a cohort of individuals whose genetic makeup contains r faults will have a maximal number of deaths per year in the year t_r for which the distribution P(r) given in ( ) becomes a maximum. The maximal value of P(r) is attained for $r \approx n - 1/2$.

Since, according to the Life Tables based on the 1949-50 census for white females, the maximum number of deaths per year occurs between the ages of 80 and 81, we may write:

XX (65) $$\frac{80.5}{\tau} + n - 1/2 = X_r + r$$

From this equation, from (63) and from (20) and from the postulated condition $\frac{1}{\rho^*} \ln \frac{1}{\rho^*} \leq 3$ we obtain $n \leq 3$. —

In this manner we obtain an upper limit for n.

For n = 3 we obtain from (63) years.

Lower limit for n.

In order to obtain a lower limit for n, we now turn to the distribution of the ages at death, as given by the 1949-50 census for white females and on the basis of these data we reason as follows:

The number of deaths per year which reaches its maximum -- as stated above -- at 80.5 years of age, does not fall off equally fast on both sides of the maximum; it falls off faster towards higher ages than towards lower ages. Thus, the number of deaths between the ages of 70 and 71 are lower by a factor of 1.5 than the maximal number of deaths per year (i.e. the number of deaths per year between the 80th and 81st years), but the number of deaths per year between 80 and 91 are lower by a factor of 1.925 than this maximal number.

We may now take the distribution of the ages at death as predicted by the crude form of the theory and, in particular, we may take the continuous distribution P(r) given by ( ), and choose n to have some particular value, "n". For such a value of "n", the distribution P(r) will have a maximum for some value r = "r" -- which is close to ("n" -1/2). We first compute the value of "Δ" for which P("r" + "Δ") is lower by a factor of 1.5 than the maximal value of P(r). Subsequently, we compute the value of P("r" + "Δ") with a view of determining by what "factor" it is lower than the maximal value. For high values of n this "factor" will be greater than 1.925. There must be a value of "n" = n* for which this "factor" will be just about 1.925. By following the procedure just described we find for n*, a value slightly above 2. (For "n" = 2 the "factor" is 1.98 in place of 1.925, and for "n" = 2.5 the factor is 1.835).

From this we are led to conclude that the correct value of n is larger than 2.

Our reason for concluding $n > 2$ rather than $n \cong 2$ is based on the following considerations: The observed number of deaths per year between the ages of 40 and 50 are more numerous than one would expect on the basis of a Guassian distribution which has its maximum at 80.5 years of age, which has a maximal value of 3.67/100 and which falls by a factor of 1.5

between the ages of 80.5 and 70.5. This indicates that the non-genetic scattering of the ages at death is no symmetrical, as we have hitherto assumed it to be -- at least in the case of identical twins but that it falls off from its maximal value towards lower ages more slowly than toward higher ages. This might then be, at least in part, the reason why the observed distribution of the ages at death fall by a smaller factor between the ages of 80.5 and 70.5 years than between the ages of 80.5 and 90.5 years. In these circumstances we may only say that n* is greater than 2 and we may not conclude that n* is about equal to 2. ~~XXXXXXX To the above consideration~~ we might ~~also~~ add that it is a priori reasonable from a theoretical point of view to assume that the distribution of the ages at death, ~~which~~ manifests itself in ~~the case of identical twins,~~ falls off ~~more slowly from its maximum towards lower ages than towards higher ages.~~ Our previous assumption that this distribution ~~is~~ symmetrical and ~~may~~ be represented by Guassian was made for the sake of the convenience of certain, particular computations only.

Having thus found that n must lie within the limits of

we shall from here on regard the value of

$$n = 2.5$$

as the "most reasonable" value for n, and will ~~not~~ therefore -- if not otherwise stated -- base all of our subsequent computations on ~~the~~ assumption ~~that it is the right value.~~

For the value of n = 2.5, we have from (63) $\bar{L}$ = 6.15 years. And, further, we obtain from ( ) for

or .

Middle Age

We may define middle age as half of the most probable age at death, which then would come out for white females to be ~~the age of~~ 40.5 years. It is of some interest to compute the fraction of the surviving somatic cells at middle age. For n = 2.5, we obtain from for this fraction

This would then explain why there are so many ~~If this is indeed the correct value, then we may expect to find~~ at middle age an appreciable deterioration of at least some of the physiological functions.

The Reduction Factor of the Last Years.

The factor by which the fraction of surviving cells f decreases for successive intervals τ, increases with increasing age. It is of some interest to know the value of this reduction factor for the last interval which precedes the critical age for death. We may compute R_o, the reduction factor for the last interval ~~of life~~, for females who are likely to die at 80.5 years of age by writing

(66)

and for n = 2.5, we have from ( )

(67)

If R_o, the reduction factor at the end of life, were in fact as large as this, then we may expect that visible signs of senescence may frequently become very marked during the ~~last~~ τ = 6 years of life, just prior to death.

Physiological Age.

There are phenomena that generally accompany senescence. Among these are, for instance, the graying of the hair and the loss of accommodation of the eye. A number of such other general characteristics accompanying senescence might be detected if a systematic search for such phenomena gets under way. For a group of animals, one may expect the mean age at which such characteristics of senescence appear, to a quantitatively defined degree, to be determined by the mean age for the group at which the fraction of the surviving somatic cells of the animals reaches the critical value f*. We shall, accordingly, assume that two females whose genetic makeup differs from each other by faults, differ from each other in physiological age by faults. ~~As may be discussed further below, physiological age as defined on this basis might differ from physiological age~~

defined on the basis of the age specific death rate, particularly if one compares two different strains of animals such as an isogenic strain and a hybrid strain.

Organ Specific Faults:

It is conceivable and it would appear likely that there exist genes which are not essential vegetative genes in the sense defined above because they are not essential for most kinds of somatic cells, but which are, nevertheless, essential for certain specialized somatic cells which serve the needs of the whole body. Because such specialized cells are frequently localized in one organ, we shall, for the sake of brevity, refer to these genes as organ specific genes, and mutant, non-competent forms of these genes we shall designate as organ specific faults.

Such specialized cells as, for instance, those responsible for the secretion of a hormone, are in general not used to their full capacity. However, as a fraction of these specialized cells substantially decreases as a result of the advance of the aging process, the "surviving" specialized cells might be stimulated to their maximum production. If we now consider a person whose genetic makeup contains one fault essential for the functioning of the specialized cells under destruction, the total output of these specialized cells might at an advanced age be decreased for two reasons. First, the masimal output of the cells might be only 1/2 if they contain only one instead of two competent copies of the relevant essential organ specific gene; and, second, - because the cell ceases to be functional when the chromosome containing the only competent copy of the gene is destroyed by an aging hit, the physiological age of the organ is tau years ahead of the general physiological age of the individual, i.e. the fraction of the surviving cell of the organism at death is lowered by a factor of 2 than the fraction of the surviving cell of the body in general (see ( )). Thus, at the age of death, the maximum output of the organ is in toto lowered by a factor of than would be the output of the same organ in an individual of same physiological age who is free from this particular organ specific fault. Since the

reduction factor for the last aging hit is

( )

we may say that the organ affected by an organ specific fault at the time of death is 3 tau = about 18 years older than corresponds to the general physiological age of the individual. For considerations of this sort, this might conceivably explain why the existence of organ specific vegetative phenomena, presumably determined by heredity, which remain latent through middle age and which become manifest beyond middle age.

If the average number of organ specific faults per individual in the population is very small, then such faults may not be expected to have any effect on the shape of the curve describing the distribution of ages at death, but if we had σ = .7 this would mean that one person in two is afflicted with an organ specific fault and one person in four is afflicted with two - in general different organ specific faults. We would then have to take into account the fact that two organ specific faults may not necessarily cause a person to die earlier than if he had only one of these two faults and, thus, the possibility arises that the shape of the distribution of the ages at death might be affected in a manner which, with the general theory of aging here presented, has so far not taken into account.

On Changing the Load of Faults:

If, as a result of living under "modern" conditions our load of faults should, in time, be doubled, then the average adult woman would live $n\tau$ years shorter than she does today.

For n = 2.5 we have $n\tau \approx 15$ years. Thus, the physiological age of the average female at 65 would be the same as that of the average 80 year old woman today. Similarly, the physiological age of a woman of 35 would then be that of a 50 year old woman of today.

If we were to assume that $n \geq 2.5$, then $n\tau$ would amount to more than 15 years,

A doubling of our load of faults might conceivably occur, in time, through the exposure of the population to ionizing radiation, generation after generation, in an intensity that doubles the spontaneous mutation rate. Such a doubling of our load of faults might conceivably occur also as a result of the currently practiced pattern of controlling the family size which might conceivably eliminate the most important of the selection pressures which tend to keep our load of faults low by counterbalancing the generation of new faults through spontaneously occurring mutations.

Neither of these two considerations need to give rise to alarm, however, for, as we shall show below, the rate of rise of our load of faults may be expected to be slow; thus we shall have a fairly long period of grace in which we may reflect on how best to cope with the danger involved.

We may in this context ask also how much advantage the genetically perfect, faultless, female would have over the average female of today.

Assuming n = 2.5, we may say on the basis of considerations similar to those relating to the doubling of the faults - that

the genetically perfect woman would at 50 years of age have the same physiological age as the average woman of 35 today. Her most probable age at death would be ~~95~~ 92 instead of 80 - ~~which it is today~~. of the gen. per. female
If n were larger than 2.5 the advantage would be greater.
~~by gene~~

The Number of Segments per Chromosome and the Difference between the Life Expectancies of the Female and the Male:

Instead of assuming that a whole chromosome is destroyed in each aging hit, we might tentatively choose to assume that the elementary step in the process of aging consists in the random destruction of, say, 1/2 a chromosome, and one might ask if one might not go even further and assume that each chromosome consists of g segments and that the elementary step in the process of aging consists in the random destruction of such segments independently of each other. By making g larger and larger, one might further argue the theory might perhaps gradually change its character. Instead of having to assume that the large portion of a chromosome is destroyed in an individual aging hit, one might perhaps be free to assume that the aging process consists in a sequence of point mutations of the genetic substance of the somatic cell. A theory of this kind would not work and this may be seen as follows.

The male of the species has only one X chromosome in place of the two X chromosomes of the female. If we disregard for the moment the possibility that a substantial part of the X chromosome may be "covered" in the male by genes contained in the Y chromosome, we may say that the male is born with g "aging hits". Accordingly, if we choose for g a value which is large compared to 1, we would expect the adult male to have a substantially lower life expectancy than the adult female.

Actually, on the basis of the 1949-50 census, the maximum number of deaths for white males occurs between the ages of 77 and 78, i.e. at an age three years below that of the white female.

On the basis of the assumption that g = 1, we should expect a difference of tau, about τ 6 years, provided that we can assume the value of f for the male is exactly the same as for the female.

Actually, the value of f* for the male might be somewhat larger than for the female and, therefore, this deviation from the prediction of the theory may not be regarded as serious. The significant point from our discussion here is that the observed difference in the life expectancy of the adult male and the female is small, whereas, if g were large, the difference would be large, assuming that the value of f* for the male cannot be very much larger than the value for the female. That the expected difference between the life expectancy of the female and the male, g tau, is indeed substantially increasing with increasing g may be seen as follows. If g is other than 1 ( ) is replaced by

XX ( ) $$\ln \frac{1}{f^*} = ng\left(1 - e^{-\frac{x+\tau}{2ng}}\right)^2 - ng\left(1 - e^{-\frac{\tau}{2ng}}\right)^2$$

From this it may be seen, in conjunction with ( ) and ( ) that n increases somewhat faster than g. Since, according to ( ) tau falls with $\frac{1}{\sqrt{n}}$, it follows that g tau - the difference between the life expectancy of the female and the male - must increase somewhat faster than $\sqrt{g}$. Thus, in view of the fact that the life expectancy of the male is not much smaller than that of the female, we are led to believe that g cannot be very large. Because, however, f* might well be somewhat smaller for the male than for the female, we would not want to exclude the possibility that g might, for instance, have a value of 2, i.e. that the elementary process of aging might consist in the random destruction of one-half of a chromosome instead of a whole chromosome.

As may be seen from our equations, for a fixed value of n, the value of f* will rise when g is increased, say, from 1 to 2. Thus, if n had a value of 2.5 for g = 1, we would have for f a value of f = $\ln \frac{1}{f^*}$ would fall from about 2 to about 1/3. Similarly, if g is larger than 1 for a fixed value of f*, n will have a larger value than it would have for g = 1 and, accordingly, the corresponding value of tau would be lower.