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ON THE NATURE OF THE AGING PROCESS

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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 are in a 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 can be responsible for the synthesis of a specific protein molecule, which in many cases has a known enzymatic activity. When we speak later of a mutant, or "incompetent," form of a gene, we mean an altered form of the gene, which cannot 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 inactive. The "hit" need not destroy the chromosome in a physical sense. (See note 1 added in proof.)

We assume that the "aging hits" are random events and that the probability that a chromosome of a somatic cell 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 remaining able to fulfil their function in the organism) decreases with age. On the basis of our assumptions, spelled out below, the "surviving" fraction of the somatic cells decreases with age at an accelerating rate.

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 that individual may die within a period of one year will come 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 substantially before the organism loses its capacity to live, perhaps to 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 true, for, if it were true, identical twins would die within one year of each other. In fact, the mean difference between the ages at death of female identical twins can be estimated to be about 3.5 years. 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 that 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. There may be in man perhaps 15,000 genes. There may be a larger number of specific DNA molecules which are inherited from generation to generation, but we designate as "genes" here only those DNA molecules which would handicap the individual if present in a mutant 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 abundance of mutant forms of genes in the population may not correspond to the steady state under present conditions.

We may assume that the "genes" somehow affect differentiation and morphogenesis during the embryonic development of the individual and that a mutant form

of a gene may cause, with a certain probability—appreciable even in the heterozygote—a developmental abnormality of the individual.

We assume that among the 15,000 genes, there are perhaps 3,000 genes 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.

We postulate that, in the course of aging, a somatic cell remains functional as long as, out of each pair of homologous vegetative genes, at least one of the two genes is competent and active and that the cell ceases to be functional when both genes are out of action. Accordingly when a chromosome suffers an aging hit, the cell will cease to be functional if the homologous chromosome has either previously suffered an aging hit or if it carries a fault.

According to the views here adopted, the main reason why some adults live shorter lives and others live longer is the difference in the number of faults 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 by n). From the observed distribution of the ages at death, between seventy and ninety years of age, we shall be led to conclude that we have $n > 2$. For $n = 2$ we would obtain from the crude theory for the critical surviving fraction of the somatic cells $f^* \backsimeq 1/4$. For $n = 4$ we would obtain $f^* \backsimeq 1/12$. On this basis we shall be led to conclude that we have $n < 4$.

We shall, for the purposes of our discussion, adopt, as a reasonable value, $n = 2.5$, and then we obtain $f^* \backsimeq 1/6$, which would seem 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 a function of her age.

We designate by ξ the average number of "aging hits" that have been suffered by a chromosome of a somatic cell, and we may write

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

where 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."

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

$$f = [1 - (1 - e^{-\xi})^2]^{m-r} . e^{-r\xi} \tag{2}$$

or

$$\ln f = (m - r) \ln [1 - (1 - e^{-\xi})^2] - r\xi. \tag{3}$$

For $\xi \ll 1$ we may write, from equation (3), neglecting $m\xi^4$ and $r\xi^3$, etc.,

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

Writing

$$\rho = \frac{r}{2m}, \tag{5}$$

we may write

$$\ln \frac{1}{f} = m[\xi + \rho]^2.[1 - (\xi + \rho)], \tag{6}$$

provided $r \ll x \ll 2m$ (i.e., $\rho \ll \xi - 1$)

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

where $\eta = \xi + \rho$. In place of equation (7) we may write, in our approximation,

$$f = [1 - (1 - e^{-\eta})^2]^m \tag{8}$$

We may also write inversely

$$\eta = \ln \frac{1}{1 - \sqrt{1 - f^{1/m}}}, \tag{9}$$

or, expanding,

$$\eta = \sqrt{\frac{1}{m} \ln \frac{1}{f}} + \frac{1}{2m} \ln \frac{1}{f}. \tag{10}$$

According to the assumption of the crude theory, f, the surviving fraction of the somatic cells, reaches the critical value f^* at the age of death, which we designate by t_r. Further, we designate by x_r the average number of aging hits suffered *in toto*, up to the age of death, by the m pairs of homologous chromosomes of the somatic cells. Thus we have, at the age of death,

$$x_r = \frac{t_r}{\tau} = 2m\xi \tag{11}$$

and

$$\eta = \frac{x_r + r}{2m}. \tag{12}$$

Accordingly, we may write at the age of death, where we have $f = f^*$, from equation (8),

$$\ln \frac{1}{f^*} = \frac{(x_r + r)^2}{4m} \left(1 - \frac{x_r + r}{2m}\right). \tag{13}$$

Similarly, we may write at the age of death, from equation (10),

$$x_r + r = \sqrt{4m \ln \frac{1}{f^*}} + \ln \frac{1}{f^*} \tag{14}$$

or

$$\frac{t_r}{\tau} + r = \sqrt{4m \ln \frac{1}{f^*}} + \ln \frac{1}{f^*}. \tag{15}$$

For the genetically perfect female, for whom we have $r = 0$, we shall designate the age at death by t_0. We shall call t_0 the "life-span" of the species.

From equation (15) we may write for, the life-span, t_0,

$$\frac{t_r}{\tau} + r = \frac{t_0}{\tau} \tag{16}$$

or

$$t_r = t_0 - \tau r \tag{17}$$

or

$$r = \frac{t_0 - t_r}{\tau}. \tag{18}$$

As may be seen from equation (17), the addition of one fault to the genetic makeup of an individual shortens the life of that individual by $\Delta t = \tau$, so that we may write

$$\Delta t \text{ per fault } = \tau. \tag{19}$$

This expresses one of the basic results of our theory. According to equation (19), an individual whose genetic makeup contains one fault more than another individual has a life-expectancy which is shorter by τ, the basic time interval of the aging process. This holds true within the crude theory for individuals who have inherited a small number of faults.

Concerning the life-span, t_0, we may write, from equations (11), (13), and (16),

$$\ln \frac{1}{f^*} = \frac{1}{4m} \left(\frac{t_0}{\tau}\right)^2 \left(1 - \frac{1}{2m} \frac{t_0}{\tau}\right), \tag{20}$$

and, from equations (15) and (16), we may write

$$\frac{t_0}{\tau} = \sqrt{4m \ln \frac{1}{f^*}} + \ln \frac{1}{f^*}. \tag{21}$$

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 thus 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 the number of deaths, P_r, occurring at each age, is given by the Poisson distribution:

$$P_r = \frac{n^r e^{-n}}{r!} \tag{22}$$

where, according to equation (18), we have $r = \frac{t_0 - t_r}{\tau}$ and where n stands for the average number of faults per individual.

The distribution of the ages at death in the population is actually a continuous function of the age. Even though the probability that an individual may die within a year may increase rather steeply as the surviving fraction of his somatic cells approaches the critical value f^*, genetically identical individuals do not all die at the same age. The observed mean age difference at death of identical twins may be regarded as a measure of the scattering of the ages at death, which is left out of account by the crude form of the theory and to which we shall refer as the "non-genetic scattering."

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

$$P(r) = \frac{n^r}{\Gamma_{(r+1)}} e^{-n} \tag{23}$$

where Γ represents the gamma function (which for integral values of $r + 1$ assumes the values of $r!$) and where we have

$$r = \frac{t_0 - t}{\tau}. \tag{24}$$

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

$$d(\text{theor.}) = -\frac{dr}{dt} \frac{n^r}{\Gamma_{(r+1)}} e^{-n}. \tag{25}$$

From equation (24) we obtain

$$-\frac{dr}{dt} = \frac{1}{\tau}. \tag{26}$$

Thus we may write, from equation (25),

$$d(\text{theor.}) = \frac{1}{\tau} \frac{n^r}{\Gamma_{(r+1)}} e^{-n} \text{ per year}, \tag{27}$$

where r is given by equation (24) and where τ is expressed in years.

The approximation used throughout this paper holds for small values of r, which correspond to high ages at death. We may say that at high ages of death the distribution of ages at death in the population is represented by a reversed Poisson distribution (27), where small values of r correspond to high ages at death.

Lower Limit for n.—We shall now proceed to compare the distribution of the ages at death, as given by our formula (27), with the actually observed distribution of the ages at death, as given by the U.S. Life Tables, based on the 1949–50 Census.

For the purposes of this comparison, we shall use Table 6 for white females, which lists the number of deaths per year, in yearly intervals, as a function of age. According to this table, the maximal number of deaths occurs between the eightieth and eighty-first year; the corresponding maximal number of deaths per year is 0.0344 per person.

The distribution of the ages at death is not symmetrical around the age at the maximum, $t^* = 80.5$ years of age; the number of deaths per year fall faster toward higher ages than toward lower ages. Thus the table lists, for the number of deaths per year, 0.0230 per person between the ages seventy and seventy-one and 0.0179 per person between the ages of ninety and ninety-one.

We may derive from this table a "normalized" distribution of the ages at death by forming R(obs.), the ratio of the number of deaths per year and the maximal number of deaths per year, 0.0344. Thus we obtain R(obs.) = 0.667 at 70.5 years of age; R(obs.) = 1 at 80.5 years of age; R(obs.) = 0.520 at 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 equation (27) and the maximal number of deaths per year given by $d(\text{theor.})_{\text{max.}}$:

$$d(\text{theor.})_{\text{max.}} = \frac{1}{\tau} e^{-n} \left\{ \frac{n^r}{\Gamma_{(r+1)}} \right\}_{\text{max.}} . \tag{28}$$

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

$$r^* \backsimeq n - 0.5. \tag{29}$$

Accordingly, we may write

$$R(\text{theor.}) = \frac{d(\text{theor.})}{d(\text{theor.})_{\text{max.}}} = \frac{n^r}{n^{(n-0.5)}} \frac{\Gamma_{(n+0.5)}}{\Gamma_{(r+1)}}. \tag{30}$$

We may now ask for what value of n would the normalized Poisson distribution, R(theor.), fit R(obs.), both above and below 80.5 years of age so that we have for a suitably chosen value of Δr, for $r = r^* + \Delta r$, R(theor.) = 0.667 (the value of R(obs.) at 70.5 years of age) and that we also have, for $r = r^* - \Delta r$, 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 the corresponding value of Δr we obtain $\Delta r = 1.4$. For the corresponding value of τ we may write

$$\tau = \frac{10}{\Delta r} \text{ years}. \tag{31}$$

For $n = 2$ and with $\Delta r = 1.4$, we obtain $\tau = 7.15$ 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 $r = r^* - \Delta r$, then, for $r = r^* + \Delta r$, we have R(theor.) < 0.667 (the value of R(obs.) at 70.5 years of age).

Because there is reason to believe that, below 80.5 years of age, the crude theory gives too low values for R(theor.), we cannot exclude the possibility that we have $n > 2$. Therefore, from the fact that R(theor.) derived from the crude theory fits R(obs.) for $n = 2$ between the ages of 70.5 and 90.5, we may not conclude that we actually have $n = 2$, and we may only conclude that we have

$$n \geqq 2. \tag{32}$$

Approximation of the Poisson Distribution by a Gaussian Relationship between τ and n.— R (theor.) given by equation (30) goes over into a Gaussian for $n \gg 1$. For a Gaussian, the value of R(theor.) = 0.667 (the value of R(obs.) at 70.5 years of age) corresponds to a distance from the maximum of 0.9 σ, where σ is the standard deviation of the Gaussian. Similarly, R(theor.) = 0.520 (the value of R(obs.) at 90.5 years of age) corresponds to a distance from the maximum of 1.14σ. Thus the time interval of 20 years around the maximum corresponds to 2.04σ, and hence we have

$$\sigma = \frac{20}{2.04} \text{ years} = 9.8 \text{ years} \tag{33}$$

Because the variance of a Poisson distribution is given by its mean, n, we may write (for $n \gg 1$)

$$\sigma = \tau\sqrt{n} \tag{34}$$

or

$$\tau = \frac{\sigma}{\sqrt{n}}, \tag{35}$$

and thus we obtain $\tau = \dfrac{9.8}{\sqrt{n}}$ years.

While equation (34) holds, strictly speaking, only for large values of n, the error is small even for $n = 2$.

For $n = 2$ from equation (35) we obtain $\tau = 6.82$ in place of the previously given value of $\tau = 7.15$.

For $n = 2.5$ from (35) we obtain $\tau = 6.2$ years in place of the "correct" value of $\tau = 6.3$ years, which we find by fitting the "normalized" Poisson distribution, as well as possible, to R(obs.).

Thus, for most of our purposes we may use equation (35) for values of n for $n \geqq 2$.

From equation (35) we obtain

$$n\tau = \sigma\sqrt{n}, \tag{36}$$

where $n\tau$ represents the average life-shortening caused by the "load of faults," n. Since the value of σ is empirically fixed, the higher we assume n to be, the higher is the life-shortening effect which we must attribute to it. In this sense, the life-shortening effect of the mutation load increases with $\sqrt{n}$.

Correction of τ for the Non-genetic Scattering of the Ages at Death.—Because the non-genetic scattering of the ages at death has so far not been taken into account by us, the observed distribution of the ages at death may be expected to be actually somewhat broader, and, accordingly, the actual value of τ may be expected to be somewhat lower than the values given above.

The mean age difference at death between female identical twins has been reported by Franz J. Kallman to be about 2.6 years for twins dying above the age of 60. From this value we may estimate, on the basis of the Life Tables, the mean age difference at death of female identical twins who die as adults above the age

of 40 to be 3.4 years. If the distribution of the ages at death of genetically identical individuals resembled a Gaussian, then 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 that of our theoretical distribution of the ages at death. By making such an assumption, for the purposes of this computation, we may then correct the values of τ, given above, as follows:

From the fact that the mean age difference at death of female identical twins may be taken to be about 3.4 years, it follows that the standard deviation of the distribution of their ages at death is about 3 years. Using this value, we find that the non-genetic scattering increases the variance of the distribution of the ages at death by a factor of about 1.1 and, accordingly, the previously given values of τ must be reduced by 5 per cent.

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

We may also write on this basis—within the limits of the approximation—for $n > 2$,

$$\tau = \frac{9.3}{\sqrt{n}} \text{ years.} \tag{37}$$

Substituting this value of τ in equation (16), we obtain

$$\frac{t_0}{\tau} = \frac{t_r}{9.3}\sqrt{n} + r. \tag{38}$$

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 (for white females) the maximal number of deaths per year occurs at 80.5 years of age. Our theory demands (29) that the maximal number of deaths per year should occur for individuals for whom we have $r = n - 0.5$. Accordingly, we may write $t_r = 80.5$ and $r = n - 0.5$. We thus obtain, from equation (38),

$$\frac{t_0}{\tau} = \frac{80.5}{9.3}\sqrt{n} + n - 0.5 \tag{39}$$

and, from equation (20),

$$\ln \frac{1}{f^*} = \frac{1}{4m}\left(\frac{80.5}{9.3}\sqrt{n} + n - 0.5\right)^2\left[1 - \frac{1}{2m}\left(\frac{80.5}{9.3}\sqrt{n} + n - 0.5\right)\right]. \tag{40}$$

From this equation we may now compute for a given value of n the corresponding value of f^*. Thus we obtain for $n = 2$, $f^* \backsimeq 1/4$; for $n = 2.5$, $f^* \backsimeq 1/6$; for $n = 4$, $f^* \backsimeq 1/12$.

On this basis we may then write, by assuming $f^* > 1/12$,

$$n < 4. \tag{41}$$

A value of $f^* \backsimeq 1/6$ would seem to be rather reasonable and, therefore, we shall adopt, as a reasonable value for n, the value of

$$n \backsimeq 2.5, \tag{42}$$

and, as a reasonable value for τ, the corresponding value of

$$\tau = 6 \text{ years.} \tag{43}$$

We shall in the remainder of the paper base all our discussions on these values of n and τ. We cannot exclude, of course, the possibility that n might be somewhat larger and that τ might be somewhat lower.

The "Physiological Age."—The general physiological age may be defined for a given population on the basis of its age-specific death rate; according to our theory, it may be defined as the age of the genetically perfect female who has the same surviving fraction of the somatic cells, f. Accordingly, we may say that two females, whose genetic makeup differs by Δ faults, differ from each other in their physiological age by $r\Delta$ years at sufficiently high ages, as demanded by the approximation used.

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 less 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.

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 equation (36), with $\sqrt{n}$.

A doubling of our load of faults might conceivably occur, in time, through the exposure of the population, generation after generation, to ionizing radiation, in an intensity that doubles the mutation rate.

Such an increase in our load of faults might perhaps occur also as a result of the current practice of controlling the family size. As spelled out below this practice might conceivably eliminate one of the selection pressures which have tended to keep our load of faults low.

We may, on this occasion, 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 above, that the genetically perfect female would at 50 years of age have the same physiological age as the average female 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.

Life-Shortening Effect of Ionizing Radiation on the Adult Offspring of the Exposed Population.—Experiments of W. L. Russell have shown that the offspring of mice which have been exposed to a dose of fast neutrons have a reduced life-expectancy. This has generally been interpreted to mean that exposure of the parents to ionizing radiation induces mutations in the germ cells of the gonads and thus "reduces the viability" of the offspring.

From the point of view of our theory, however, we have to distinguish between that reduction of the life-expectancy of the offspring which is due to an increased mortality of young animals and that reduction which is due to a decrease in the life-expectancy of the adults. All the mutations induced by ionizing radiation may contribute to the former, but only the "faults" contribute to the latter.

In the case of man, at least, it should be possible to make a fairly clean separation between these two categories of life-shortening. In the case of man the U.S. Life

Tables show that the number of deaths per year falls, from an initial high value in the first year of life, to about 40 per 100,000 per year at the age of 10. Moreover, of the few deaths occurring at 10 years of age, a substantial fraction is due to accidents. Thus we are led to believe that, in the heterozygous individual, mutant (incompetent) forms of genes may cause the death of the embryo, or of the infant below 10 years of age, while they do not cause death with an appreciable probability after the tenth year of age, unless they represent "faults." Faults increase the age-specific death rate above 10 years of age only in conjuction with aging hits, and they increase it appreciably only above 40.

If we observe the life-shortening of the adult animal in the offspring of an irradiated population, resulting from the induction of faults by ionizing radiation in one species, we may be able to predict, on the basis of our theory, the life-shortening for another species. This may be seen as follows:

We obtain from equations (19) and (21) for the relationship between the life-shortening, Δt per fault, and for the life-span of the species, t_0,

$$\frac{\Delta t \text{ per fault}}{t_0} = \frac{\tau}{t_0} = \left(\sqrt{4m \ln \frac{1}{f^*}} + \ln \frac{1}{f^*} \cdot \right)^{-1} \tag{44}$$

The right-hand side of the equation contains only the chromosome number m and the critical value f^*. Therefore, if two species of mammals have the same value of f^* and the same chromosome number m, their life-shortening per fault caused by exposure of their parents to ionizing radiation amounts to the same fraction of their life-span. We may call the ratio the "specific life-shortening" of a fault.

If the two species of mammals may be assumed to have also the same number of vegetative genes and if the sensitivity of their genes to the ionizing radiation employed may be assumed to be the same, then the number of faults produced by a given dose of radiation will be the same for the two species. Thus, according to equation (44), the radiation exposure will shorten the lives of the two species by the same fraction of the life-span.

If m, the number of their chromosome pairs, is different for the two species, then the "specific life-shortening" will be larger for the species which has the smaller chromosome number. According to (44), the specific life-shortening increases about inversely with $\sqrt{m}$. The number of chromosome pairs is 11 for the Chinese hamster and 39 for the dog. Therefore, according to (44), the specific life-shortening per fault induced may be expected for the Chinese hamster to be higher than for the dog by a factor of about 2.

The mouse has $m = 20$ pairs of homologous chromosomes and we may therefore estimate the life-shortening of man from the life-shortening of the mouse and vice versa, by postulating that the life-shortening per rep in man and in the mouse amount to about the same fraction of their life-span. (Some authors believe that man is about twice as sensitive to X-rays as the mouse and, if they are correct, then our estimated value for the life-shortening of man would be low by a factor of about two.)

W. L. Russell found that an X-ray dose of 300, as well as a dose of 600 rep, induces 25×10^{-8} gene mutations per rep per locus in the spermatogonia of mice. As-

suming 15,000 loci, we may conclude that an X-ray dose of 667 rep would induce 5 mutations in the diploid offspring of exposed mice. If we assume that one-fifth of the genes are vegetative genes, then 667 rep of X-rays induce on the average one fault in the offspring. Assuming $\tau = 6$ years for man, we may thus expect in man a life-shortening of the adult offspring of $\delta^* = 3.3$ days per rep.

The number of faults induced in the offspring per rep depends on the nature of the ionizing radiation, and may be assumed higher for fast neutrons than for X-rays. Also, in the case of X-rays, the number of faults induced might conceivably depend not only on the total dose but also on the dose rate and be lower for lower dose rates.

The actual value of δ^* ought to be determined experimentally, for the different kinds of ionizing radiations which are of interest, by direct observation of the life-shortening of the adult offspring. Experimental data so far available are inadequate.

If the average mutation rate per gene per generation is 1/60,000 and if we assume for N_1, the number of vegetative genes, $N_1 = 3000$, and for N_t the total number of genes, $N_t = 15{,}000$ then we obtain for μ_1, the spontaneous mutation rate of the haploid set of vegetative genes, $\mu_1 = 0.05$, and for μ_t, the total spontaneous mutation rate of all genes, $\mu_t = 0.25$. We shall use these values for the purposes of our discussion below.

The Life-Shortening Effect of Ionizing Radiation on the Exposed Population.—We may expect ionizing radiation to produce gene mutations in the chromosomes of the somatic cells of an exposed individual and we shall assume that the sensitivity of the genes of the somatic cells is about the same as that of the genes in the spermatogonia and the oogonia. Because a certain fraction of these mutations, perhaps one-fifth of them, affect vegetative genes, faults are induced in the chromosomes of the somatic cells of the exposed individual. It can be shown that an exposure to ionizing radiation which induces on the average one fault per somatic cell must reduce—on this score alone—the life-expectancy of the exposed individual by about τ years. If exposure to ionizing radiation had no other life-shortening effect, the life-shortening, δ, of the individual in the exposed population would be equal to δ^*, the life-shortening of the adult offspring of the exposed population (see note 2 added in proof).

Maternal Selection Pressure against Faults?—It is conceivable that a woman who carries a particular fault in her genetic makeup ceases to be capable of bearing children $\tau = 6$ years earlier, on the average, than her counterpart who lacks that particular fault. This is what one would expect on the assumption that the termination of a woman's reproductive period is determined by her physiological age—if all other factors are equal. If this assumption is correct, then a powerful selection has operated in the past that has tended to keep the load of faults low.

In the past, infant mortality was high, the birth rate was high, and women kept on having children until the end of their childbearing period. Clearly, the maternal selection mentioned above is switched off when women have two or three children between the ages of 18 and 25 and then avoid having further children.

If such a "maternal" selection was the predominating selection of the past, then we may expect that, when this selection ceases to operate, our load of faults may double, in time. 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 still cannot increase by more than $2\mu_1 = 0.1$ per generation. This means that—at the 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 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 woman who does not carry this particular "fault" but who is otherwise identical in her genetic makeup. We now assume that the "physiological age" sets the termination of the reproductive period, and we take for the "most probable duration" of the reproductive period 30 years. Thus the fault singled out "most probably" shortens the reproductive period by one-fifth of its length. The fertility of younger women is higher than that of older women. Near the end of the reproductive period, the (average) time interval between two successive pregnancies might be by a factor $k > 1$ (of perhaps 2 or 3) longer, than the interval between two successive pregnancies, averaged over the whole reproductive period.

If we postulate that this "maternal" selection constitutes essentially the sole selection pressure against faults, then we may write for the mutation equilibrium of the fault, singled out:

$$2\frac{\mu_1}{N_1} = \frac{n}{2 \times 5\, kN_1}, \tag{45}$$

and, for the value of $\mu_1 = 0.05$ per generation, we thus obtain $k = n$. For $n = 2.5$ we have

$$k = 2.5. \tag{46}$$

Under "natural" conditions, for young women the average time interval between two successive pregnancies might be about 1 year; toward the end of the reproductive period it might be about 5 years; and, averaged over the whole reproductive period of about 30 years, it might be about 2 years. These values correspond to $k = 2.5$. This coincidence might, of course, turn out to be fortuitous.

Refinements of the Theory—Specialized Vegetative Genes.—It appears likely that there exist genes which are not essential for the functioning of most of the somatic cells of the adult but each of which is essential for the functioning of one particular kind of specialized somatic cell. We shall call these genes "specialized vegetative" genes, and mutant forms of such genes we shall call "specialized faults."

We shall now single out, for the purposes of our discussion, specialized cells which synthesize a gene product, a particular enzyme, for instance, that serves not the needs of these cells themselves but rather those of the organism as a whole. Such specialized cells might in some cases fulfill their function in the organism by releasing the enzyme into the circulation.

We may in general assume that the normal young person has a considerable reserve of such enzymes, and we shall specifically assume, for the purposes of this particular discussion, that the maximal output of a normal young person is higher than the need of the organism by a factor of about 6.

The maximal output of enzyme by such a specialized cell may be assumed to be

lower by a factor of $^1/_2$ in the heterozygous individual, who has inherited a mutant form of the specialized vegetative gene. Further, it may be shown that, for an individual who has inherited $n = 2.5$ faults, the surviving fraction of the somatic cells is about one-third at 54 years of age. Since, in the heterozygote, the specialized cells under discussion carry one additional fault, the surviving fraction of the specialized cells will reach one-third about 6 years earlier. Thus, at 48 years of age, the maximal output of the enzyme of the surviving specialized cells of the heterozygote will be lower, by a factor of about $^1/_6$, than for a normal young person.

On this basis we may then expect that around 50 years of age there may become manifest, in such heterozygotes, symptoms of disease due to the insufficiency of the output of one kind of specialized cell. The inheritance of diseases of this class may be expected to show a marked degree of dominance.

Speaking more generally, we may expect to see in certain heterozygotes, late in life, narrowly circumscribed degenerative phenomena which are caused by specialized faults they have inherited.

The Number of "Segments" per Chromosome.—Instead of assuming that a whole chromosome is "destroyed" in one aging hit, we might choose to assume that the elementary step in the process of aging consists in the random destruction of one-half of a chromosome. The formulas given above remain then unchanged, except that we have to write $2m$ in place of m. As one may see from equation (40), we then obtain, for the same value of n, a higher value for f^*. Thus for $n = 2.5$ we obtain $f^* \backsimeq {}^1/_3$. Apart from this, the general character of the theory remains unchanged.

However, one might ask at this point whether one could not generalize the theory, presented above, 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, independently of each other. By choosing the value of g larger and larger, we might then gradually change the character of the theory and might end up with a theory which postulates that the aging process consists in a sequence of gene mutations of the chromosomes of the somatic cell.

A theory of this kind would, however, come up against difficulties, which are as follows:

As may be seen from equation (40) (where we now have to write gm in place of m), for a fixed value of f^*, n goes up roughly parallel with increasing g. A very large value of n might, however, be incompatible with the known fertility of consanguinous matings.

Further, as we increase g, we would also increase the difference of the life-expectancy of the female and the male. The male of the species has only one X chromosome, while the female has two. Let us disregard here the possibility that a substantial piece of the X chromosome might be covered, in the male, by genes contained in the Y chromosome. Let us also assume, for the sake of argument, that f^* has the same value for the male as it has for the female. On the basis of these assumptions, we may then identify the male, from the point of view of his life-expectancy, with a female who has suffered g aging hits, prior to birth. Accordingly, we may expect the adult male to live a shorter time, by $g\tau$ years, than the adult female.

Actually, according to the 1949–50 Census, the maximal number of deaths for the

white male occurs between the ages of 77 and 78, i.e., three years earlier than for the white female. This difference is three years less than what we would expect on the basis of our theory, which assumes $g = 1$ and which gives an estimate for τ of $\tau = 6$ years. This discrepancy indicates that perhaps the value of f^* is somewhat larger for the male than for the female.

Because of the possibility that this might be the case, we conceivably have $g = 2$ ($g = 2$ would mean that the elementary process of aging consists in the "destruction" of one-half of a chromosome rather than a whole chromosome).

However, there is no reason to believe that f^* may be very much larger for the male than for the female. Therefore, the observed small difference between the life-expectancy of the female and that of the male may rule out a modification of the theory that assumes $g \gg 1$.

Experimental Test of the Theory.—The most stringent experimental test of the validity of our theory is likely to come from experiments in which one observes a reduction in the life-expectancy of the adult offspring of, say, an irradiated mouse population. Experiments of this sort are needed in order to determine the value of δ^*. Experiments of this sort will also show whether among the different phenomena which generally accompany senescence, such as the graying of the hair, the loss of accommodation of the eye, etc., there are any which are determined by the general physiological age, defined on the basis of the age-specific death rate. Arrangements for experiments along these lines are now under discussion.

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NOTATIONS

f is the fraction of the somatic cells which "survive," in the sense of remaining functional up to a given age.

f^* is the "surviving" fraction of the somatic cells at the age of death.

r is the number of inherited faults.

ρ is the number of inherited faults per chromosome.

n is the average number of faults per person in the population.

τ is the basic time interval of the aging process, defined as the average time interval between two successive aging hits suffered by the chromosomes of the somatic cell.

m is the number of pairs of homologous chromosomes of the female of the species.

x_r is the number of aging hits suffered, on the average, by the chromosomes of the somatic cells up to the age of death, by an individual who has inherited r faults.

t_r is the age, at death, of an individual who has inherited r faults.

t_0 is the life-span of the species, defined as the age at death of the genetically perfect female who did not inherit any faults.

d(theor.) is the number of deaths per year that will occur in a cohort, as given by the theory.

$d(\text{theor.})_{\max.}$ is the highest number of deaths per year that will occur in a cohort, as given by the theory.

R(theor.) is the ratio of the number of deaths per year and the maximal number of deaths per year in a cohort, as given by the theory.

R(obs.) is the ratio of the number of deaths per year and the maximal number of deaths per year in a cohort, as given by the U.S. Life Tables for white females.

σ is the standard deviation of the Gaussian that approximates the observed distribution of the number of deaths per year, between the ages of 70.5 and 90.5.

τ/t_0 is the specific life-shortening per fault of the species.

δ is the life-shortening per rep for a population that has been exposed to ionizing radiation.

δ^* is the life-shortening per rep of the adults in the offspring of a population that has been exposed to ionizing radiation.

μ_1 is the spontaneous mutation rate of the haploid set of vegetative genes per generation.

μ_t is the total spontaneous mutation rate of all genes in the haploid set.

N_1 is the haploid number of vegetative genes of the species.

N_t is the haploid number of all genes of the species.

g is the postulated number of "segments" per chromosome.

NOTES ADDED IN PROOF

1. When we say that an aging hit "destroys" a chromosome of the somatic cell, we mean that that chromosome has been rendered inactive as far as its vegetative functions are concerned, i.e., the genes which the chromosome contains will fail to produce the corresponding gene products. The question whether the chromosome is inactivated in any other sense is left open for the present. Thus it is left open whether, if a cell containing an inactivated chromosome were to duplicate, the inactivated chromosome would or would not duplicate and whether or not it would remain inactive after such a duplication. One might, for instance, imagine that the chromosomes of the somatic cell contain DNA strands which fulfil a vegetative function in the somatic cell by producing the specific gene products but do not duplicate when the cell duplicates. Aging hits would then inactivate these vegetative "copies" rather than the genetic copies. The latter would duplicate when the cell duplicates and would then produce fresh vegetative copies. This is just one of several assumptions which one may make concerning the nature of the aging hits. For the present, we are free to choose among several such *ad hoc* assumptions.

2. 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. Disregarding such other effects, the "surviving" fraction of the somatic cells of an exposed female may be computed 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:

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

for $p/2m \ll 1$ and $p/x \ll 1$ we may write, in analogy to (13)

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

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

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ON THE NATURE OF THE AGING PROCESS

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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 are in a 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 can be responsible for the synthesis of a specific protein molecule, which in many cases has a known enzymatic activity. When we speak later of a mutant, or "incompetent," form of a gene, we mean an altered form of the gene, which cannot 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 inactive. The "hit" need not destroy the chromosome in a physical sense. (See note 1 added in proof.)

We assume that the "aging hits" are random events and that the probability that a chromosome of a somatic cell 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 remaining able to fulfil their function in the organism) decreases with age. On the basis of our assumptions, spelled out below, the "surviving" fraction of the somatic cells decreases with age at an accelerating rate.

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 that individual may die within a period of one year will come 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 substantially before the organism loses its capacity to live, perhaps to 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 true, for, if it were true, identical twins would die within one year of each other. In fact, the mean difference between the ages at death of female identical twins can be estimated to be about 3.5 years. 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 that 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. There may be in man perhaps 15,000 genes. There may be a larger number of specific DNA molecules which are inherited from generation to generation, but we designate as "genes" here only those DNA molecules which would handicap the individual if present in a mutant 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 abundance of mutant forms of genes in the population may not correspond to the steady state under present conditions.

We may assume that the "genes" somehow affect differentiation and morphogenesis during the embryonic development of the individual and that a mutant form

of a gene may cause, with a certain probability—appreciable even in the heterozygote—a developmental abnormality of the individual.

We assume that among the 15,000 genes, there are perhaps 3,000 genes 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.

We postulate that, in the course of aging, a somatic cell remains functional as long as, out of each pair of homologous vegetative genes, at least one of the two genes is competent and active and that the cell ceases to be functional when both genes are out of action. Accordingly when a chromosome suffers an aging hit, the cell will cease to be functional if the homologous chromosome has either previously suffered an aging hit or if it carries a fault.

According to the views here adopted, the main reason why some adults live shorter lives and others live longer is the difference in the number of faults 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 by n). From the observed distribution of the ages at death, between seventy and ninety years of age, we shall be led to conclude that we have $n > 2$. For $n = 2$ we would obtain from the crude theory for the critical surviving fraction of the somatic cells $f^* \backsimeq {}^1/_4$. For $n = 4$ we would obtain $f^* \backsimeq {}^1/_{12}$. On this basis we shall be led to conclude that we have $n < 4$.

We shall, for the purposes of our discussion, adopt, as a reasonable value, $n = 2.5$, and then we obtain $f^* \backsimeq {}^1/_6$, which would seem 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 a function of her age.

We designate by ξ the average number of "aging hits" that have been suffered by a chromosome of a somatic cell, and we may write

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

where 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."

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

$$f = [1 - (1 - e^{-\xi})^2]^{m-r} . e^{-r\xi} \tag{2}$$

or

$$\ln f = (m - r) \ln [1 - (1 - e^{-\xi})^2] - r\xi. \tag{3}$$

For $\xi \ll 1$ we may write, from equation (3), neglecting $m\xi^4$ and $r\xi^3$, etc.,

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

Writing

$$\rho = \frac{r}{2m}, \tag{5}$$

we may write

$$\ln \frac{1}{f} = m[\xi + \rho]^2 \cdot [1 - (\xi + \rho)], \tag{6}$$

provided $r \ll x \ll 2m$ (i.e., $\rho \ll \xi - 1$)

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

where $\eta = \xi + \rho$. In place of equation (7) we may write, in our approximation,

$$f = [1 - (1 - e^{-\eta})^2]^m. \tag{8}$$

We may also write inversely

$$\eta = \ln \frac{1}{1 - \sqrt{1 - f^{1/m}}}, \tag{9}$$

or, expanding,

$$\eta = \sqrt{\frac{1}{m} \ln \frac{1}{f}} + \frac{1}{2m} \ln \frac{1}{f}. \tag{10}$$

According to the assumption of the crude theory, f, the surviving fraction of the somatic cells, reaches the critical value f^* at the age of death, which we designate by t_r. Further, we designate by x_r the average number of aging hits suffered *in toto*, up to the age of death, by the m pairs of homologous chromosomes of the somatic cells. Thus we have, at the age of death,

$$x_r = \frac{t_r}{\tau} = 2m\xi \tag{11}$$

and

$$\eta = \frac{x_r + r}{2m}. \tag{12}$$

Accordingly, we may write at the age of death, where we have $f = f^*$, from equation (8),

$$\ln \frac{1}{f^*} = \frac{(x_r + r)^2}{4m} \left(1 - \frac{x_r + r}{2m}\right). \tag{13}$$

Similarly, we may write at the age of death, from equation (10),

$$x_r + r = \sqrt{4m \ln \frac{1}{f^*}} + \ln \frac{1}{f^*} \tag{14}$$

or

$$\frac{t_r}{\tau} + r = \sqrt{4m \ln \frac{1}{f^*}} + \ln \frac{1}{f^*}. \tag{15}$$

For the genetically perfect female, for whom we have $r = 0$, we shall designate the age at death by t_0. We shall call t_0 the "life-span" of the species.

From equation (15) we may write for, the life-span, t_0,

$$\frac{t_r}{\tau} + r = \frac{t_0}{\tau} \tag{16}$$

or

$$t_r = t_0 - \tau r \tag{17}$$

or

$$r = \frac{t_0 - t_r}{\tau}. \tag{18}$$

As may be seen from equation (17), the addition of one fault to the genetic makeup of an individual shortens the life of that individual by $\Delta t = \tau$, so that we may write

$$\Delta t \text{ per fault } = \tau. \tag{19}$$

This expresses one of the basic results of our theory. According to equation (19), an individual whose genetic makeup contains one fault more than another individual has a life-expectancy which is shorter by τ, the basic time interval of the aging process. This holds true within the crude theory for individuals who have inherited a small number of faults.

Concerning the life-span, t_0, we may write, from equations (11), (13), and (16),

$$\ln \frac{1}{f^*} = \frac{1}{4m} \left(\frac{t_0}{\tau}\right)^2 \left(1 - \frac{1}{2m} \frac{t_0}{\tau}\right), \tag{20}$$

and, from equations (15) and (16), we may write

$$\frac{t_0}{\tau} = \sqrt{4m \ln \frac{1}{f^*}} + \ln \frac{1}{f^*}. \tag{21}$$

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 thus 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 the number of deaths, P_r, occurring at each age, is given by the Poisson distribution:

$$P_r = \frac{n^r e^{-n}}{r!} \tag{22}$$

where, according to equation (18), we have $r = \frac{t_0 - t_r}{\tau}$ and where n stands for the average number of faults per individual.

The distribution of the ages at death in the population is actually a continuous function of the age. Even though the probability that an individual may die within a year may increase rather steeply as the surviving fraction of his somatic cells approaches the critical value f^*, genetically identical individuals do not all die at the same age. The observed mean age difference at death of identical twins may be regarded as a measure of the scattering of the ages at death, which is left out of account by the crude form of the theory and to which we shall refer as the "non-genetic scattering."

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

$$P(r) = \frac{n^r}{\Gamma_{(r+1)}} e^{-n} \tag{23}$$

where Γ represents the gamma function (which for integral values of $r + 1$ assumes the values of $r!$) and where we have

$$r = \frac{t_0 - t}{\tau}. \tag{24}$$

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

$$d(\text{theor.}) = -\frac{dr}{dt} \frac{n^r}{\Gamma_{(r+1)}} e^{-n}. \tag{25}$$

From equation (24) we obtain

$$-\frac{dr}{dt} = \frac{1}{\tau}. \tag{26}$$

Thus we may write, from equation (25),

$$d(\text{theor.}) = \frac{1}{\tau} \frac{n^r}{\Gamma_{(r+1)}} e^{-n} \text{ per year}, \tag{27}$$

where r is given by equation (24) and where τ is expressed in years.

The approximation used throughout this paper holds for small values of r, which correspond to high ages at death. We may say that at high ages of death the distribution of ages at death in the population is represented by a reversed Poisson distribution (27), where small values of r correspond to high ages at death.

Lower Limit for n.—We shall now proceed to compare the distribution of the ages at death, as given by our formula (27), with the actually observed distribution of the ages at death, as given by the U.S. Life Tables, based on the 1949–50 Census.

For the purposes of this comparison, we shall use Table 6 for white females, which lists the number of deaths per year, in yearly intervals, as a function of age. According to this table, the maximal number of deaths occurs between the eightieth and eighty-first year; the corresponding maximal number of deaths per year is 0.0344 per person.

The distribution of the ages at death is not symmetrical around the age at the maximum, $t^* = 80.5$ years of age; the number of deaths per year fall faster toward higher ages than toward lower ages. Thus the table lists, for the number of deaths per year, 0.0230 per person between the ages seventy and seventy-one and 0.0179 per person between the ages of ninety and ninety-one.

We may derive from this table a "normalized" distribution of the ages at death by forming R(obs.), the ratio of the number of deaths per year and the maximal number of deaths per year, 0.0344. Thus we obtain R(obs.) = 0.667 at 70.5 years of age; R(obs.) = 1 at 80.5 years of age; R(obs.) = 0.520 at 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 equation (27) and the maximal number of deaths per year given by $d(\text{theor.})_{\text{max.}}$:

$$d(\text{theor.})_{\text{max.}} = \frac{1}{\tau} e^{-n} \left\{ \frac{n^r}{\Gamma_{(r+1)}} \right\}_{\text{max.}}. \tag{28}$$

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

$$r^* \backsimeq n - 0.5. \tag{29}$$

Accordingly, we may write

$$R(\text{theor.}) = \frac{d(\text{theor.})}{d(\text{theor.})_{\text{max.}}} = \frac{n^r}{n^{(n-0.5)}} \frac{\Gamma_{(n+0.5)}}{\Gamma_{(r+1)}}. \tag{30}$$

We may now ask for what value of n would the normalized Poisson distribution, R(theor.), fit R(obs.), both above and below 80.5 years of age so that we have for a suitably chosen value of Δr, for $r = r^* + \Delta r$, R(theor.) = 0.667 (the value of R(obs.) at 70.5 years of age) and that we also have, for $r = r^* - \Delta r$, 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 the corresponding value of Δr we obtain $\Delta r = 1.4$. For the corresponding value of τ we may write

$$\tau = \frac{10}{\Delta r} \text{ years}. \tag{31}$$

For $n = 2$ and with $\Delta r = 1.4$, we obtain $\tau = 7.15$ 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 $r = r^* - \Delta r$, then, for $r = r^* + \Delta r$, we have R(theor.) < 0.667 (the value of R(obs.) at 70.5 years of age).

Because there is reason to believe that, below 80.5 years of age, the crude theory gives too low values for R(theor.), we cannot exclude the possibility that we have $n > 2$. Therefore, from the fact that R(theor.) derived from the crude theory fits R(obs.) for $n = 2$ between the ages of 70.5 and 90.5, we may not conclude that we actually have $n = 2$, and we may only conclude that we have

$$n \geqq 2. \tag{32}$$

Approximation of the Poisson Distribution by a Gaussian Relationship between τ and n.— R (theor.) given by equation (30) goes over into a Gaussian for $n \gg 1$. For a Gaussian, the value of R(theor.) = 0.667 (the value of R(obs.) at 70.5 years of age) corresponds to a distance from the maximum of 0.9 σ, where σ is the standard deviation of the Gaussian. Similarly, R(theor.) = 0.520 (the value of R(obs.) at 90.5 years of age) corresponds to a distance from the maximum of 1.14σ. Thus the time interval of 20 years around the maximum corresponds to 2.04σ, and hence we have

$$\sigma = \frac{20}{2.04} \text{ years} = 9.8 \text{ years} \tag{33}$$

Because the variance of a Poisson distribution is given by its mean, n, we may write (for $n \gg 1$)

$$\sigma = \tau\sqrt{n} \tag{34}$$

or

$$\tau = \frac{\sigma}{\sqrt{n}}, \tag{35}$$

and thus we obtain $\tau = \dfrac{9.8}{\sqrt{n}}$ years.

While equation (34) holds, strictly speaking, only for large values of n, the error is small even for $n = 2$.

For $n = 2$ from equation (35) we obtain $\tau = 6.82$ in place of the previously given value of $\tau = 7.15$.

For $n = 2.5$ from (35) we obtain $\tau = 6.2$ years in place of the "correct" value of $\tau = 6.3$ years, which we find by fitting the "normalized" Poisson distribution, as well as possible, to R(obs.).

Thus, for most of our purposes we may use equation (35) for values of n for $n \geqq 2$

From equation (35) we obtain

$$n\tau = \sigma\sqrt{n}, \tag{36}$$

where $n\tau$ represents the average life-shortening caused by the "load of faults," n. Since the value of σ is empirically fixed, the higher we assume n to be, the higher is the life-shortening effect which we must attribute to it. In this sense, the life-shortening effect of the mutation load increases with $\sqrt{n}$.

Correction of τ for the Non-genetic Scattering of the Ages at Death.—Because the non-genetic scattering of the ages at death has so far not been taken into account by us, the observed distribution of the ages at death may be expected to be actually somewhat broader, and, accordingly, the actual value of τ may be expected to be somewhat lower than the values given above.

The mean age difference at death between female identical twins has been reported by Franz J. Kallman to be about 2.6 years for twins dying above the age of 60. From this value we may estimate, on the basis of the Life Tables, the mean age difference at death of female identical twins who die as adults above the age

of 40 to be 3.4 years. If the distribution of the ages at death of genetically identical individuals resembled a Gaussian, then 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 that of our theoretical distribution of the ages at death. By making such an assumption, for the purposes of this computation, we may then correct the values of τ, given above, as follows:

From the fact that the mean age difference at death of female identical twins may be taken to be about 3.4 years, it follows that the standard deviation of the distribution of their ages at death is about 3 years. Using this value, we find that the non-genetic scattering increases the variance of the distribution of the ages at death by a factor of about 1.1 and, accordingly, the previously given values of τ must be reduced by 5 per cent.

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

We may also write on this basis—within the limits of the approximation—for $n > 2$,

$$\tau = \frac{9.3}{\sqrt{n}} \text{ years.} \tag{37}$$

Substituting this value of τ in equation (16), we obtain

$$\frac{t_0}{\tau} = \frac{t_r}{9.3}\sqrt{n} + r. \tag{38}$$

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 (for white females) the maximal number of deaths per year occurs at 80.5 years of age. Our theory demands (29) that the maximal number of deaths per year should occur for individuals for whom we have $r = n - 0.5$. Accordingly, we may write $t_r = 80.5$ and $r = n - 0.5$. We thus obtain, from equation (38),

$$\frac{t_0}{\tau} = \frac{80.5}{9.3}\sqrt{n} + n - 0.5 \tag{39}$$

and, from equation (20),

$$\ln\frac{1}{f^*} = \frac{1}{4m}\left(\frac{80.5}{9.3}\sqrt{n} + n - 0.5\right)^2\left[1 - \frac{1}{2m}\left(\frac{80.5}{9.3}\sqrt{n} + n - 0.5\right)\right]. \tag{40}$$

From this equation we may now compute for a given value of n the corresponding value of f^*. Thus we obtain for $n = 2$, $f^* \backsimeq 1/4$; for $n = 2.5$, $f^* \backsimeq 1/6$; for $n = 4$, $f^* \backsimeq 1/12$.

On this basis we may then write, by assuming $f^* > 1/12$,

$$n < 4. \tag{41}$$

A value of $f^* \backsimeq 1/6$ would seem to be rather reasonable and, therefore, we shall adopt, as a reasonable value for n, the value of

$$n \backsimeq 2.5, \tag{42}$$

and, as a reasonable value for τ, the corresponding value of

$$\tau = 6 \text{ years.} \tag{43}$$

We shall in the remainder of the paper base all our discussions on these values of n and τ. We cannot exclude, of course, the possibility that n might be somewhat larger and that τ might be somewhat lower.

The "Physiological Age."—The general physiological age may be defined for a given population on the basis of its age-specific death rate; according to our theory, it may be defined as the age of the genetically perfect female who has the same surviving fraction of the somatic cells, f. Accordingly, we may say that two females, whose genetic makeup differs by Δ faults, differ from each other in their physiological age by $r\Delta$ years at sufficiently high ages, as demanded by the approximation used.

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 less 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.

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 equation (36), with $\sqrt{n}$.

A doubling of our load of faults might conceivably occur, in time, through the exposure of the population, generation after generation, to ionizing radiation, in an intensity that doubles the mutation rate.

Such an increase in our load of faults might perhaps occur also as a result of the current practice of controlling the family size. As spelled out below this practice might conceivably eliminate one of the selection pressures which have tended to keep our load of faults low.

We may, on this occasion, 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 above, that the genetically perfect female would at 50 years of age have the same physiological age as the average female 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.

Life-Shortening Effect of Ionizing Radiation on the Adult Offspring of the Exposed Population.—Experiments of W. L. Russell have shown that the offspring of mice which have been exposed to a dose of fast neutrons have a reduced life-expectancy. This has generally been interpreted to mean that exposure of the parents to ionizing radiation induces mutations in the germ cells of the gonads and thus "reduces the viability" of the offspring.

From the point of view of our theory, however, we have to distinguish between that reduction of the life-expectancy of the offspring which is due to an increased mortality of young animals and that reduction which is due to a decrease in the life-expectancy of the adults. All the mutations induced by ionizing radiation may contribute to the former, but only the "faults" contribute to the latter.

In the case of man, at least, it should be possible to make a fairly clean separation between these two categories of life-shortening. In the case of man the U.S. Life

Tables show that the number of deaths per year falls, from an initial high value in the first year of life, to about 40 per 100,000 per year at the age of 10. Moreover, of the few deaths occurring at 10 years of age, a substantial fraction is due to accidents. Thus we are led to believe that, in the heterozygous individual, mutant (incompetent) forms of genes may cause the death of the embryo, or of the infant below 10 years of age, while they do not cause death with an appreciable probability after the tenth year of age, unless they represent "faults." Faults increase the age-specific death rate above 10 years of age only in conjuction with aging hits, and they increase it appreciably only above 40.

If we observe the life-shortening of the adult animal in the offspring of an irradiated population, resulting from the induction of faults by ionizing radiation in one species, we may be able to predict, on the basis of our theory, the life-shortening for another species. This may be seen as follows:

We obtain from equations (19) and (21) for the relationship between the life-shortening, Δt per fault, and for the life-span of the species, t_0,

$$\frac{\Delta t \text{ per fault}}{t_0} = \frac{\tau}{t_0} = \left(\sqrt{4m \ln \frac{1}{f^*}} + \ln \frac{1}{f^*} \right)^{-1} \qquad (44)$$

The right-hand side of the equation contains only the chromosome number m and the critical value f^*. Therefore, if two species of mammals have the same value of f^* and the same chromosome number m, their life-shortening per fault caused by exposure of their parents to ionizing radiation amounts to the same fraction of their life-span. We may call the ratio the "specific life-shortening" of a fault.

If the two species of mammals may be assumed to have also the same number of vegetative genes and if the sensitivity of their genes to the ionizing radiation employed may be assumed to be the same, then the number of faults produced by a given dose of radiation will be the same for the two species. Thus, according to equation (44), the radiation exposure will shorten the lives of the two species by the same fraction of the life-span.

If m, the number of their chromosome pairs, is different for the two species, then the "specific life-shortening" will be larger for the species which has the smaller chromosome number. According to (44), the specific life-shortening increases about inversely with $\sqrt{m}$. The number of chromosome pairs is 11 for the Chinese hamster and 39 for the dog. Therefore, according to (44), the specific life-shortening per fault induced may be expected for the Chinese hamster to be higher than for the dog by a factor of about 2.

The mouse has $m = 20$ pairs of homologous chromosomes and we may therefore estimate the life-shortening of man from the life-shortening of the mouse and vice versa, by postulating that the life-shortening per rep in man and in the mouse amount to about the same fraction of their life-span. (Some authors believe that man is about twice as sensitive to X-rays as the mouse and, if they are correct, then our estimated value for the life-shortening of man would be low by a factor of about two.)

W. L. Russell found that an X-ray dose of 300, as well as a dose of 600 rep, induces 25×10^{-8} gene mutations per rep per locus in the spermatogonia of mice. As-

suming 15,000 loci, we may conclude that an X-ray dose of 667 rep would induce 5 mutations in the diploid offspring of exposed mice. If we assume that one-fifth of the genes are vegetative genes, then 667 rep of X-rays induce on the average one fault in the offspring. Assuming $\tau = 6$ years for man, we may thus expect in man a life-shortening of the adult offspring of $\delta^* = 3.3$ days per rep.

The number of faults induced in the offspring per rep depends on the nature of the ionizing radiation, and may be assumed higher for fast neutrons than for X-rays. Also, in the case of X-rays, the number of faults induced might conceivably depend not only on the total dose but also on the dose rate and be lower for lower dose rates.

The actual value of δ^* ought to be determined experimentally, for the different kinds of ionizing radiations which are of interest, by direct observation of the life-shortening of the adult offspring. Experimental data so far available are inadequate.

If the average mutation rate per gene per generation is 1/60,000 and if we assume for N_1, the number of vegetative genes, $N_1 = 3000$, and for N_t the total number of genes, $N_t = 15{,}000$ then we obtain for μ_1, the spontaneous mutation rate of the haploid set of vegetative genes, $\mu_1 = 0.05$, and for μ_t the total spontaneous mutation rate of all genes, $\mu_t = 0.25$. We shall use these values for the purposes of our discussion below.

The Life-Shortening Effect of Ionizing Radiation on the Exposed Population.—We may expect ionizing radiation to produce gene mutations in the chromosomes of the somatic cells of an exposed individual and we shall assume that the sensitivity of the genes of the somatic cells is about the same as that of the genes in the spermatogonia and the oogonia. Because a certain fraction of these mutations, perhaps one-fifth of them, affect vegetative genes, faults are induced in the chromosomes of the somatic cells of the exposed individual. It can be shown that an exposure to ionizing radiation which induces on the average one fault per somatic cell must reduce—on this score alone—the life-expectancy of the exposed individual by about τ years. If exposure to ionizing radiation had no other life-shortening effect, the life-shortening, δ, of the individual in the exposed population would be equal to δ^*, the life-shortening of the adult offspring of the exposed population (see note 2 added in proof).

Maternal Selection Pressure against Faults?—It is conceivable that a woman who carries a particular fault in her genetic makeup ceases to be capable of bearing children $\tau = 6$ years earlier, on the average, than her counterpart who lacks that particular fault. This is what one would expect on the assumption that the termination of a woman's reproductive period is determined by her physiological age—if all other factors are equal. If this assumption is correct, then a powerful selection has operated in the past that has tended to keep the load of faults low.

In the past, infant mortality was high, the birth rate was high, and women kept on having children until the end of their childbearing period. Clearly, the maternal selection mentioned above is switched off when women have two or three children between the ages of 18 and 25 and then avoid having further children.

If such a "maternal" selection was the predominating selection of the past, then we may expect that, when this selection ceases to operate, our load of faults may double, in time. 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 still cannot increase by more than $2\mu_1 = 0.1$ per generation. This means that—at the 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 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 woman who does not carry this particular "fault" but who is otherwise identical in her genetic makeup. We now assume that the "physiological age" sets the termination of the reproductive period, and we take for the "most probable duration" of the reproductive period 30 years. Thus the fault singled out "most probably" shortens the reproductive period by one-fifth of its length. The fertility of younger women is higher than that of older women. Near the end of the reproductive period, the (average) time interval between two successive pregnancies might be by a factor $k > 1$ (of perhaps 2 or 3) longer, than the interval between two successive pregnancies, averaged over the whole reproductive period.

If we postulate that this "maternal" selection constitutes essentially the sole selection pressure against faults, then we may write for the mutation equilibrium of the fault, singled out:

$$2\frac{\mu_1}{N_1} = \frac{n}{2 \times 5\, kN_1}, \tag{45}$$

and, for the value of $\mu_1 = 0.05$ per generation, we thus obtain $k = n$. For $n = 2.5$ we have

$$k = 2.5. \tag{46}$$

Under "natural" conditions, for young women the average time interval between two successive pregnancies might be about 1 year; toward the end of the reproductive period it might be about 5 years; and, averaged over the whole reproductive period of about 30 years, it might be about 2 years. These values correspond to $k = 2.5$. This coincidence might, of course, turn out to be fortuitous.

Refinements of the Theory—Specialized Vegetative Genes.—It appears likely that there exist genes which are not essential for the functioning of most of the somatic cells of the adult but each of which is essential for the functioning of one particular kind of specialized somatic cell. We shall call these genes "specialized vegetative" genes, and mutant forms of such genes we shall call "specialized faults."

We shall now single out, for the purposes of our discussion, specialized cells which synthesize a gene product, a particular enzyme, for instance, that serves not the needs of these cells themselves but rather those of the organism as a whole. Such specialized cells might in some cases fulfill their function in the organism by releasing the enzyme into the circulation.

We may in general assume that the normal young person has a considerable reserve of such enzymes, and we shall specifically assume, for the purposes of this particular discussion, that the maximal output of a normal young person is higher than the need of the organism by a factor of about 6.

The maximal output of enzyme by such a specialized cell may be assumed to be

lower by a factor of $^1/_2$ in the heterozygous individual, who has inherited a mutant form of the specialized vegetative gene. Further, it may be shown that, for an individual who has inherited $n = 2.5$ faults, the surviving fraction of the somatic cells is about one-third at 54 years of age. Since, in the heterozygote, the specialized cells under discussion carry one additional fault, the surviving fraction of the specialized cells will reach one-third about 6 years earlier. Thus, at 48 years of age, the maximal output of the enzyme of the surviving specialized cells of the heterozygote will be lower, by a factor of about $^1/_6$, than for a normal young person.

On this basis we may then expect that around 50 years of age there may become manifest, in such heterozygotes, symptoms of disease due to the insufficiency of the output of one kind of specialized cell. The inheritance of diseases of this class may be expected to show a marked degree of dominance.

Speaking more generally, we may expect to see in certain heterozygotes, late in life, narrowly circumscribed degenerative phenomena which are caused by specialized faults they have inherited.

The Number of "Segments" per Chromosome.—Instead of assuming that a whole chromosome is "destroyed" in one aging hit, we might choose to assume that the elementary step in the process of aging consists in the random destruction of one-half of a chromosome. The formulas given above then remain unchanged, except that we have to write $2m$ in place of m. As one may see from equation (40), we then obtain, for the same value of n, a higher value for f^*. Thus for $n = 2.5$ we obtain $f^* \backsimeq {}^1/_3$. Apart from this, the general character of the theory remains unchanged.

However, one might ask at this point whether one could not generalize the theory, presented above, 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, independently of each other. By choosing the value of g larger and larger, we might then gradually change the character of the theory and might end up with a theory which postulates that the aging process consists in a sequence of gene mutations of the chromosomes of the somatic cell.

A theory of this kind would, however, come up against difficulties, which are as follows:

As may be seen from equation (40) (where we now have to write gm in place of m), for a fixed value of f^*, n goes up roughly parallel with increasing g. A very large value of n might, however, be incompatible with the known fertility of consanguinous matings.

Further, as we increase g, we would also increase the difference of the life-expectancy of the female and the male. The male of the species has only one X chromosome, while the female has two. Let us disregard here the possibility that a substantial piece of the X chromosome might be covered, in the male, by genes contained in the Y chromosome. Let us also assume, for the sake of argument, that f^* has the same value for the male as it has for the female. On the basis of these assumptions, we may then identify the male, from the point of view of his life-expectancy, with a female who has suffered g aging hits, prior to birth. Accordingly, we may expect the adult male to live a shorter time, by $g\tau$ years, than the adult female.

Actually, according to the 1949–50 Census, the maximal number of deaths for the

white male occurs between the ages of 77 and 78, i.e., three years earlier than for the white female. This difference is three years less than what we would expect on the basis of our theory, which assumes $g = 1$ and which gives an estimate for τ of $\tau = 6$ years. This discrepancy indicates that perhaps the value of f^* is somewhat larger for the male than for the female.

Because of the possibility that this might be the case, we conceivably have $g = 2$ ($g = 2$ would mean that the elementary process of aging consists in the "destruction" of one-half of a chromosome rather than a whole chromosome).

However, there is no reason to believe that f^* may be very much larger for the male than for the female. Therefore, the observed small difference between the life-expectancy of the female and that of the male may rule out a modification of the theory that assumes $g \gg 1$.

Experimental Test of the Theory.—The most stringent experimental test of the validity of our theory is likely to come from experiments in which one observes a reduction in the life-expectancy of the adult offspring of, say, an irradiated mouse population. Experiments of this sort are needed in order to determine the value of δ^*. Experiments of this sort will also show whether among the different phenomena which generally accompany senescence, such as the graying of the hair, the loss of accommodation of the eye, etc., there are any which are determined by the general physiological age, defined on the basis of the age-specific death rate. Arrangements for experiments along these lines are now under discussion.

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NOTATIONS

f is the fraction of the somatic cells which "survive," in the sense of remaining functional up to a given age.

f^* is the "surviving" fraction of the somatic cells at the age of death.

r is the number of inherited faults.

ρ is the number of inherited faults per chromosome.

n is the average number of faults per person in the population.

τ is the basic time interval of the aging process, defined as the average time interval between two successive aging hits suffered by the chromosomes of the somatic cell.

m is the number of pairs of homologous chromosomes of the female of the species.

x_r is the number of aging hits suffered, on the average, by the chromosomes of the somatic cells up to the age of death, by an individual who has inherited r faults.

t_r is the age, at death, of an individual who has inherited r faults.

t_0 is the life-span of the species, defined as the age at death of the genetically perfect female who did not inherit any faults.

d(theor.) is the number of deaths per year that will occur in a cohort, as given by the theory.

$d(\text{theor.})_{\max.}$ is the highest number of deaths per year that will occur in a cohort, as given by the theory.

R(theor.) is the ratio of the number of deaths per year and the maximal number of deaths per year in a cohort, as given by the theory.

R(obs.) is the ratio of the number of deaths per year and the maximal number of deaths per year in a cohort, as given by the U.S. Life Tables for white females.

σ is the standard deviation of the Gaussian that approximates the observed distribution of the number of deaths per year, between the ages of 70.5 and 90.5.

τ/t_0 is the specific life-shortening per fault of the species.

δ is the life-shortening per rep for a population that has been exposed to ionizing radiation.

δ^* is the life-shortening per rep of the adults in the offspring of a population that has been exposed to ionizing radiation.

μ_1 is the spontaneous mutation rate of the haploid set of vegetative genes per generation.

μ_t is the total spontaneous mutation rate of all genes in the haploid set.

N_1 is the haploid number of vegetative genes of the species.

N_t is the haploid number of all genes of the species.

g is the postulated number of "segments" per chromosome.

NOTES ADDED IN PROOF

1. When we say that an aging hit "destroys" a chromosome of the somatic cell, we mean that that chromosome has been rendered inactive as far as its vegetative functions are concerned, i.e., the genes which the chromosome contains will fail to produce the corresponding gene products. The question whether the chromosome is inactivated in any other sense is left open for the present. Thus it is left open whether, if a cell containing an inactivated chromosome were to duplicate, the inactivated chromosome would or would not duplicate and whether or not it would remain inactive after such a duplication. One might, for instance, imagine that the chromosomes of the somatic cell contain DNA strands which fulfil a vegetative function in the somatic cell by producing the specific gene products but do not duplicate when the cell duplicates. Aging hits would then inactivate these vegetative "copies" rather than the genetic copies. The latter would duplicate when the cell duplicates and would then produce fresh vegetative copies. This is just one of several assumptions which one may make concerning the nature of the aging hits. For the present, we are free to choose among several such *ad hoc* assumptions.

2. 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. Disregarding such other effects, the "surviving" fraction of the somatic cells of an exposed female may be computed 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:

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

for $p/2m \ll 1$ and $p/x \ll 1$ we may write, in analogy to (13)

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

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