Theoretical Approach to Life Span Shortening induced by Radiation (2)

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放射線と寿命についての考察 (2)

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抄　録

放射線は生体のもつ情報量をへらしそれが一定限界に達すると死亡するとし，放射線と情報量減少に関して一定の函数関係を假定することにより一回照射及び連続照射による寿命短縮を説明することを試みた．こゝに言う情報量の減少は老化の目安であり線量に関して2次の項を含むものと假定した．線量と寿命との関係の定式化に際してはPremature aging の立場をとり，長期照射による老化は一回照射による老化の単なる蓄積であると假定した．計算値は Furth et al, Lorenz et al 及び Neary のハツカネズミの実験データと照合された．実験誤差の範囲内で計算値はこれらの実験値と一致した．Accelerated aging の立場で計算を行うと1回照射による寿命短縮を説明できないことが確かめられた．

I. Introduction

An important problem in radiation biology today is that of estimating the hazards for the human populations exposed to ionizing radiation. The life span shortening is an important criterion for the estimation of radiation injury, especially in low dose region. Since any experimental determination on human is precluded, we must rely primarily on the informations obtained from animals.

Life span shortening induced by radiation is thought to be a non-specific phenomenon and generally believed as due to a speeding up of aging by radiation. Many theories on the mechanism of aging have been proposed by Blair[1], Neary[2], Quastler[3], Sacher[4], Szilard[5], Yockey[6], and others. While some of them have discussed survival curves and Gompertz plots, Blair and Neary have tried to analyze the relation between life span shortening and radiation dose.

In our preliminary report[7], survival curves in control animals and mortalities due to single massive exposure were analysed in terms of information theory. It was assumed that there was certain minimum value of the information contents to survive. The differences of radiosensitivities in different animals were interpreted as the differences of

information contents which were decreased by any kind of disturbances, e.g., natural aging, irradiation, intoxication etc.. The distribution of radiosensitivities was assumed to be a normal distribution. The assumption that the decrease of the information contents was linear with age was supported with experiments.

In the present paper a consistent formulation of the life span shortening from single to chronic exposures is discussed with a simple model of aging. Before going to our model two typical theories given by Blair[1] and by Neary[2] will be briefly reviewed below.

2. Blair's and Neary's Theories

Blair has proposed to divide a radiation injury into two parts, namely, reversible and irreversible ones. Assuming proportionality of the injury to the dose and a definite lethal threshold of injury to the animal, he has obtained the following relation between life span and dose rate.

$$\frac{S_0-S}{r} = A+BS \qquad (1)$$

where S_0 and S are mean survival times of control and irradiated animals, respectively, r, dose rate, and A, B, constants.

Data in mice on chronic irradiation until death by Lorenz et al[10], and by Neary[2] are shown in Fig. 1. Ordinate is life span shortening divided by dose rate, $\frac{S_0-S}{r}$, and abscissa is survival time, S.

Fig. 1. Dose rate and life span shortening. Data by Lorenz et al[10] (•)and Neary[2](×) on mice

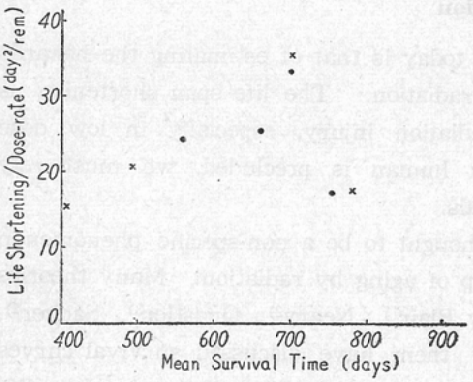
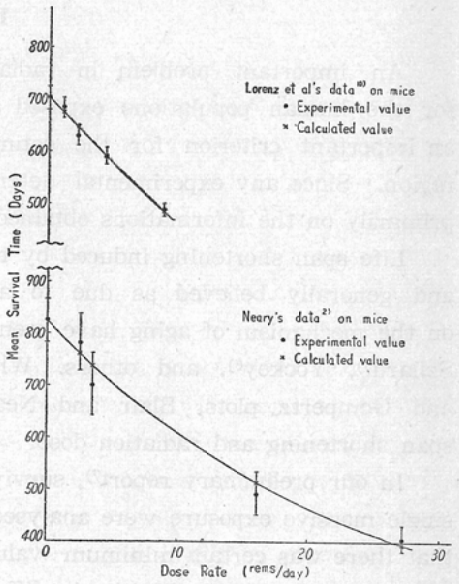


Fig. 2. Analyses on mean survival time in chronic exposure by premature aging.



The linearity predicted by equation (1) is not seen in the region of small life span shortening. On the contrary, an uniform decrease of life span against dose rate is observed even in the region of such small dose rates if one plots mean survival time vs. dose rate as shown in Fig. 2.

Fig. 1 is some sort of differential expression of Fig. 2 and then goes into much more details than the latter with regard to relation between life span shortening and dose rate. That may be the reason why larger fluctuations are observed in the former expression. Thus considering the accuracy of present experiments one may be satisfied with the latter expression.

On the other hand, taking the both ideas of premature and accelerated aging (cf. 5. Discussions), Neary has divided the aging processes into two stages. Primary stage called 'induction' is the period in which intercellular changes are going on but marked physiological impairment cannot be observed. When a certain level of induction change is approached, the second stage of aging sets in rather abruptly. It involves a different level of organization and consists in physiological interaction which proceeds autonomously and autocatalytically when once initiated and which leads to rapid impairment culminat-

Fig. 3. Neary's Model
I_0, I: induction periods of control and irradiated animals, respectively.
S_0, S: mean survival times of control and irradiated animals, respectively.
In this case, $S_0-S=I_0-I$

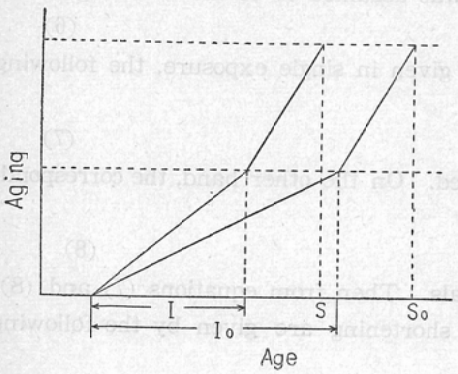
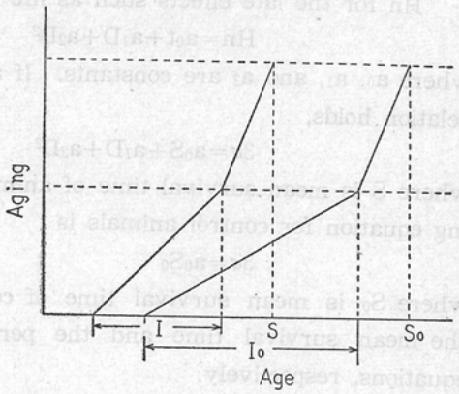


Fig. 4. Neary's Model
I_0, I: induction periods of control and irradiated animals, respectively.
S_0, S: mean survival time of control and irradiated animals, respectively.
In this case, $S_0-S \neq I_0-I$



ing in death; this stage is termed 'development'. He also assumed that the radiation affects the changes only in the induction stage and not in development stage. Accordingly the life span shortening comes from the shortening of the induction stage. This model gives almost the same relation as the equation (1) by Blair and a schematic diagram of the model is shown in Fig. 3. If the beginning of induction will not match with the onset of the irradiation, the formulation by Neary may not be usable (cf. Fig. 4). The coincidence of beginning of induction and irradiation will hardly be

obtained in such experiments.

3. A New Model

The information contents as a measure of viability is determined by the initial entropy H_0 and the noise Hn due to any disturbance as follows,

$$H=H_0-Hn \tag{2}$$

H_0 is a genetically determined quantity and its frequency distribution in animals may be of normal type with the mean $H\mu$ and the variance σ^2.

$$F(H_0)=\frac{1}{\sqrt{2\pi\sigma^2}}\,e^{-\frac{(H_0-H\mu)^2}{2\sigma^2}} \tag{3}$$

The minimum value of H to survive was chosen arbitrarily as $Hd=H\mu-3\sigma$. Hn is a measure of aging due to both natural and radiation-induced.

Natural aging and mortalities of acute death due to massive single exposure have been already analysed by using following equation.

$$Hn=(a_0+a_1D)\,t \tag{4}$$

where a_0 and a_1 are constants, D, dose and t, age of an animal. When we treat the mean life span shortening and the mean per cent life span shortening, H_0 in equation (2) can be replaced by the mean value $H\mu$ as follows,

$$H=H\mu-Hn \tag{5}$$

And then criterion for death is $Hn=3\sigma$.

i) Life shortening by single exposure

Hn for the late effects such as life shortening was assumed to be the following form,

$$Hn=a_0t+a_1D+a_2D^2 \tag{6}$$

where a_0, a_1, and a_2 are constants. If a dose D is given in single exposure, the following relation holds,

$$3\sigma=a_0S+a_1D+a_2D^2 \tag{7}$$

where S is mean survival time of animals irradiated. On the other hand, the corresponding equation for control animals is

$$3\sigma=a_0S_0 \tag{8}$$

where S_0 is mean survival time of control animals. Then from equations (7) and (8), the mean survival time and the per cent life shortening are given by the following equations, respectively.

$$S=S_0-\frac{a_1}{a_0}D-\frac{a_2}{a_0}D^2 \tag{9}$$

$$\frac{S_0-S}{S_0}=\frac{1}{S_0}\frac{a_1}{a_0}D+\frac{1}{S_0}\frac{a_2}{a_0}D^2 \tag{10}$$

ii) Life shortening by chronic exposure

Aging due to the multiple exposures was assumed to be the mere accumulation of aging due to each exposure. If animals are irradiated with dose rate r per day until death, following relation holds.

$$3\sigma=a_0S+a_1rS+a_2r^2S \tag{11}$$

For aging of control,

$$3\sigma = a_0 S_0 \tag{12}$$

Then the mean survival time is

$$S = \frac{S_0}{1 + \frac{a_1}{a_0} r + \frac{a_2}{a_0} r^2} \tag{13}$$

If the radiation effects contain a term of the second order as to dose, a recovery mechanism is automatically included as has been pointed out by Fowler et al[8]. Agings due to total dose D given in single and n times exposures are given by following equations, respectively.

$$Hn = a_0 t + a_1 D + a_2 D^2 \tag{14}$$

$$Hn' = a_0 t + a_1 \left(\frac{D}{n}\right) n + a_2 \left(\frac{D}{n}\right)^2 n$$

$$= a_0 t + a_1 D + a_2 \frac{D^2}{n} \tag{15}$$

$$\therefore\ Hn > Hn' \tag{16}$$

It is well known that to produce the same amount of effect the total dose of fractional exposures is larger than the one of single exposure in radiotherapy and life span shortening. The equation (16) is not inconsistent with these observations.

4. Comparison with Experimental Data

i) Single exposure

The data on LAF_1 mice exposed to a nuclear detonation[9] were analysed by using the equation (9). The constants $\frac{a_1}{S_0\, a_0}$ and $\frac{a_2}{S_0\, a_0}$ were determined by the method of least squares, and the calculated values plotted in Fig. 5. Agreement with the data was good up to 700 r. The same data were plotted in the form of per cent life shortening and the calculated values agreed with them all over the range (cf. Fig. 6).

Fig. 5. Analysis on mean survival time in single exposure by premature aging. Data by Furth et al[9] on mice.

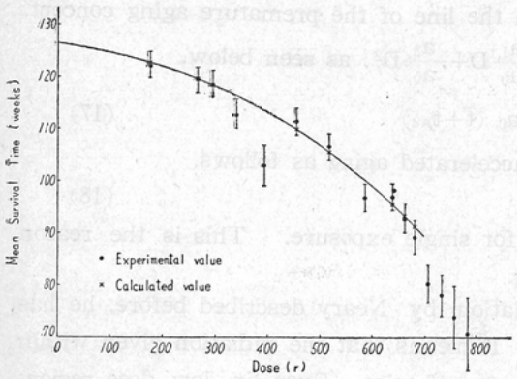
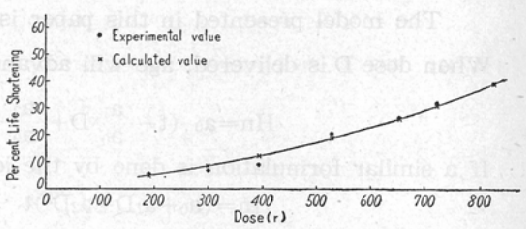


Fig. 6. Analysis on per cent life shortening in single exposure by premature aging. Data by Furth et al[9] on mice.



ii) Chronic exposure

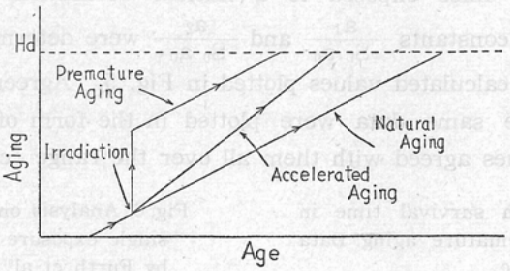
The data on mice chronically exposed to γ ray by Lorenz[10] and Neary[2] were quoted in Fig. 2. The constants $\frac{a_1}{a_0}$ and $\frac{a_2}{a_0}$ in equation (13) were determined again by the method of least squares. The coincidence between calculated and experimental values was good within the range of experimental errors. The experimental value of 0.11 r per day in Lorenz's data was not plotted in Fig. 2 which showed an extension of life span.

5 Discussions

On the mechanism of radiation-induced aging there are two theories at present. One of them, called premature aging, persists that the radiation advances the age abruptly and does not affect the aging process itself. Neary's idea of the development stage may be close to this theory. The phenomenon so-called wasted radiation will be interpreted that the radiation delivered at the period of development does nothing on the aging and can be called wasted.

The second one, called accelerated aging theory, is based on the assumption that the radiation advances the whole processes of the aging. If one plots degree of aging vs. age, radiation contracts the axis of the age with a constant rate. On the contrary, the radiation makes the stepwise advance of axis of the age in premature aging (cf. Fig. 7).

Fig. 7. Premature aging and accelerated aging.



The model presented in this paper is also in the line of the premature aging concept. When dose D is delivered, age will advance by $\frac{a_1}{a_0}D+\frac{a_2}{a_0}D^2$ as seen below.

$$Hn=a_0\ (t+\frac{a_1}{a_0}D+\frac{a_2}{a_0}\ D^2)=\ a_0\ (t+t_{Ad}) \tag{17}$$

If a similar formulation is done by the idea of accelerated aging as follows,

$$Hn=(a_0+a_1D+a_2D^2)t \tag{18}$$

one will get the results shown in Figs. 8 and 9 for single exposure. This is the reason why we have taken the idea of premature aging.

In addition to the trouble in the formulation by Neary described before, he has found 180 days as development stage in mice. It means that the radiation given within 180 days before the death never affects the life span of mice. Even in low dose region, the waste for 180 days does not seem reasonable thinking of whole life span of mice.

Fig. 8. Analysis on mean survival time in single exposure by accelerated aging.

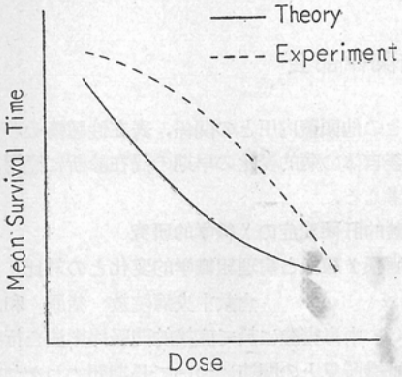
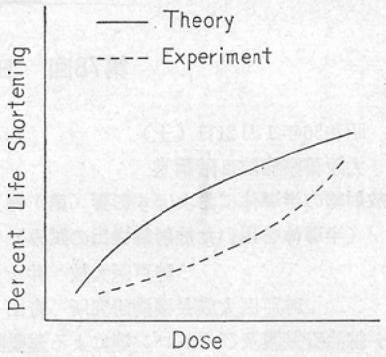


Fig. 9. Analysis on per cent life shortening in single exposure by accelerated aging.



Blair has assumed an age dependency of the lethal threshold of injury, estimating from the changes of $LD_{50}(30)$ for age and no consideration on the natural aging at all. On the contrary we have assumed an age-independent lethal threshold of injury and natural aging term $a_0 t$. Both considerations give the same result as far as the time of death concerns.

The constants $\frac{a_1}{a_0}$ and $\frac{a_2}{a_0}$ estimated from single exposure did not agree with those from chronic exposure even in the order of magnitude. It has to wait for further investigations.

6. References

1) Blair, H.A.: A quantitative description of latent injury from ionizing radiation. Symposium on Information Theory in Biology, 331—340, 1950, Pergamon Press, London. — 2) Neary, G.J.: Aging and radiation. Nature, Vol. 187, No. 4731, 10—18, 1960 — 3) Quastler, H.: Information theory in radiology. Annual Review of Nuclear Science 8, 387—400, 1958 — 4) Sacher, G.A.: On the statistical nature of mortality, with especial reference to chronic radiation mortality. Radiology 67, No. 2, 250—258, 1956 — 5) Szilard, L.: On the nature of the aging process. Proc. Nat'l. Acad. Sci. 45, No. 1, 30—45, 1959 — 6) Yockey, H.P.: On the role of information theory in mathematical biology. Radiation Biology and Medicine ed. by W.D. Claus, 250—282, 1958, Addison-Wesley Publishing Co. Inc.. — 7) Sugahara, T., F. Sato, H. Eto, Y. Takeda, and T. Kankura: Theoretical approach to life span shortening induced by radiation, preliminary report(1).Nippon Acta Radiologica, Tomus XX, Fasc. XI, 2463—2469, 1961 (in Japanese with English résumé). — 8) Fowler, J.F. and B.E. Stern: Dose-rate effects: Some theoretical and practical considerations. Brit. J. Radiol., Vol. XXXIII, No. 390, 389—395, 1960. — 9) Furth, J., A.C. Upton, K.W. Christenberry, W.H. Benedict and J. Moshman: Some late effects in mice of ionizing radiation from an experimental nuclear detonation. Radiology 63, 562—570, 1954 — 10) Lorenz, E., L.O. Jacobson, W.E. Heston, M. Shimkin, A.B. Eschenbrenner, J. Doniger and R. Schweisthal: Effects of long-continued total-body gamma irradiation on mice, guinea pigs, and rabbits. Biological Effects of External X and Gamma Radiation ed. by R.E. Zirkle, 24—148, 1954. McGraw-Hill Book Co. Inc., N.Y..