THEORETICAL APPROACH TO LIFE SPAN SHORTENING INDUCED BY RADIATION (4)
— A MODEL FOR RADIATION INJURY —

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放射線と寿命についての考察 (4)
— 放射線障害の模型化 —

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早期及び晩発性障害の広範な現象を統一的に記述し，且つ作用機構の解明の一助となり得るような障害の模型化を試みた．現象論より一歩前進するために全身障害を器官の固有の障害と器官間の相互作用より組み立てた．各種の個体差には正規分布を仮定した．相互作用としてはホメオスタシスを生ずるフィード・バック機構も含ませた．器官の直接作用による固有の障害には時間依存性を与えず，経時的変化は相互作用によると仮定した．全身障害の時間依存性は相互作用が伝達されるためには，ある時間を必要とすることを考慮すれば自動的に模型に組み入れられる．この模型は数学的にはベクトル・マトリツクス形式となる．実験との比較に於いては，死のモード，急性障害からの回復，部分照射による半致死線量，死亡数の時間的分布等を引用しこの模型で如何に記述されるかを議論した．定性的には満足すべき結果を得たが，定量的には可成り多くの問題点が残されている．

I. Introduction

As the peaceful uses of atomic energy increase day to day, the estimation of the hazards for human populations exposed to ionizing radiation becomes an important problem not only in radiology but also in industry. The life span shortening as a late effect is one of criteria for the determination of the maximum permissible dose in ICRP[1]. The occupational exposures are not necessarily whole-body exposures and they are sometimes concomitant exposures to external and to internally deposited sources. Then ICRP[2,3] has been interested in so-called " mixed radiation " problems. At present this kind of estimation of radiation hazards cannot help but use a simple model for radiation injury because of lack of detailed data in such field. Before presenting a model for radiation injury, author will review some of models given so far.

The models for radiation injury given so far may be temporarily classified into two approaches, phenomenological and statistical. The phenomenological approach is mostly

concerned with the population means like a mean survival time and does not say anything on survival curves or types of distribution around mean values. Most widely spread model of this type is Blair's exponential recovery model[4,5] and its schematic diagram is shown in Fig. 1. Principal assumptions adopted by Blair were as follow: (a) the total injury produced by ionizing radiation is proportional to the dose: (b) this injury is reparable in part and irreparable in part: (c) recovery from reparable injury occurs at a rate proportional to its magnitude. The last assumption leads to exponential recovery against time. Experimental data on life shortening and recovery from acute injury produced with sublethal dose were well interpreted with this model. Three parameters were introduced in injury function, namely, radiosensitivity, recovery rate and irreparable portion in whole-body injury. It was suggested that these parameters might be different in different tissues.

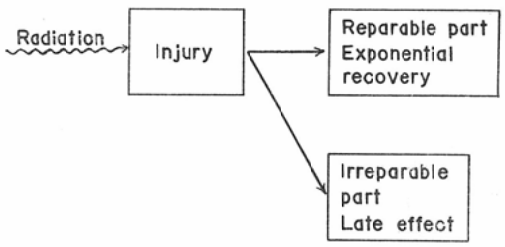

Fig. 1. Block diagram of Blair's model

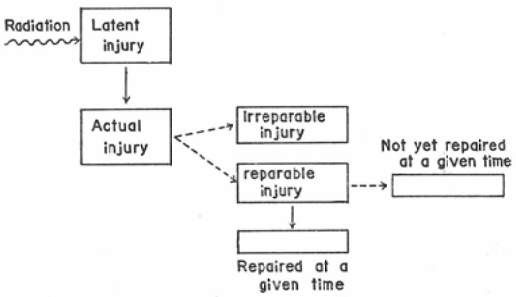

Fig. 2. Block diagram of Mewissen's model

Mewissen et al.[6] modified the Blair's model as shown in Fig. 2. Transformation of latent injury into actual injury at a certain measurable rate was postulated to account for the so-called "wasted radiation". In Mewissen et al.'s model, if one assumes an instantaneous transformation from latent injury to actual injury, the model becomes identical with Blair's model. An attractive feature in formulation of whole-body injury by Mewissen et al. was that the whole-body injury was made of summation of damage to the individual physiological function. Very little is known about the individual physiological process and only two processes known are irreparable and reparable processes. As many experiments had been devoted to test the exponential recovery hypothesis, some modification became necessary to it, particularly in repeated exposures. Following Blair's idea, Mole[7] proposed a formula for injury induced with fractionated exposure and then Storer[8] gave a recovery rate which depended on the number of daily irradiation-dose. His analysis of the effect of repeated exposure on recovery rate has led to the suggestion that repeated exposure causes a progressive decline in recovery. But the recovery-rate seemed to be independent upon the size of exposure and only dependent upon number of exposures.

Analyzing the dependence of LD_{50} (30) on dose-rate, Logie et al.[9] have given the dose-rate dependence to a recovery parameter which was not exactly same as Blair's recovery rate. Using almost the same assumptions as Blair's, Best[10,11] has formulated

the mortality of fractionated exposure with maximum likelihood method. Tyler et al.[12–17] have determined the $LD_{50}(30)$s by changing the exposure time and found that $LD_{50}(30)$ increased linearly with time up to some exposure time. They have proposed linear recovery model instead of exponential recovery according to their findings. The dependence of $LD_{50}(30)$ on exposure time has been also given by Brown et al.[18] and they have shown that both recovery models, linear and exponential, were compatible with their experimental data. Another approach to the ineffectiveness of repeated exposure has been given by Fowler et al[19]. who assumed a dose-squared term in injury function. They formulated the injury function dependent upon number of fractionated exposures but did not give a time course of injury function.

The "wasted radiation" was studied by Neary[20] and special model has been given to the radiation induced aging. Neary divides the intrinsic aging process into two principal successive stages, which between them occupy the whole life-time. First, a stage of intracellular changes probably accompanied by intercellular reactions proceeds insidiously and without marked physiological impairment; this stage is termed "induction". When a certain level of inductive change is approached, the second stage of aging sets in rather abruptly. It involves a different level of organization and consists in physiological interactions which proceed autonomously and autocatalytically when once initiated and which lead to rapid impairment culminating in death; this stage is termed "development". The schematic diagram of Neary's model is given in Fig. 3. It is an essential feature

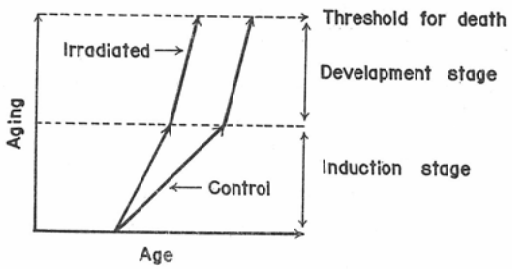

Fig. 3. Neary's model for chronic irradiation

of the model that, after development is triggered off, further inductive change is superfluous; thus radiation during development has comparatively little effect. He also assumes that the radiation affects the changes only in the inductive stage and not in development stage. The irradiation in development stage seemed to be wasted. Accordingly the life span shortening comes from the shortening of the induction stage. Giving an individual fluctuation into development stage, Neary concluded that the Gompertz function was shifted with unchanged slope by chronic irradiation.

Sacher's work[21–23] in this field has introduced two new assumptions to formulate a lethal injury function as follow: (1) the responses of physiologic systems to irradiation, and the interaction between systems, are linear: (2) a lethal process arises which is a weighted sum of the injuries to the consistuent systems. Analyzing data on mean survival

times at various daily dosages, Sacher concluded that the essential assumptions were realistic and that the generalization that might be necessary for a more exact treatment would not make the problem intractable.

On the other hand, almost all the statistisal approaches are based on the line of somatic mutation theory at any rate. Szilard[24] assumes that the elementary step in the process of aging is an "aging hit", which "destroys" a chromosome of somatic cell, in the sense that it renders all genes carried by that chromosome inactive. His theory also postulates that when the surviving fraction of the somatic cells of an individual approaches a certain critical value, then the probability that individual may die within a period of one year will come close to 1.

Using a concept of information theory Yockey[25—28] has induced dose-survival and time-survival curves. In his model radiation destroys DNA in cells and information content or entropy in DNA reduces. When the entropy decreases to some critical value, the animal cannot survive. For survival curves Yockey postulates that the survival curve may be a property of the ensemble of organism rather than the individual. The formulae of survival curves for haploid and diploid organisms could explain some of experimental data. Quastler[29] has also tried to formulate whole-body injury from the damages of body components using analogy to information theory. His theory was similar to multi-target theory and then the genesis of dose-survival curve was not due to the distribution of a sensitivity parameter in the population. In the theory a dose-survival curve came from the mechanisms of action of radiation, analogous to enzyme inactivation by radiation. Quastler's model gave a linear Gompertz function.

To understand the relation of mortality to the dynamics of physiologic function, Sacher[30,31] has given attention to the inherent regulatory capacity of the physiologic processes. In his model aging is interpreted as a secular change in the values of the parameters of regulatory mechanisms. These secular changes are ultimately due to irreversible change in permanent or self-producing macromolecules. Sacher's basic idea is as follows: all dynamic physiologic processes are attended by fluctuation: the magnitude of these fluctuations is determined by the inherent capacity of the specific process and by the magnitude of random disturbances arising both in the environment and within the organism. A parameter to express physiological state of organism was assumed to folloow stochastic differential equation with Gausian random noise disturbance. Then the survival curve was generated from a population in which there was no pre-existing distribution of radiosensitivity. Gompertz function became a linear function of mean physiologic state of a population.

As mentioned above, the phenomenological approaches may explain dose-effect curves but they may not be able to clarify which organ or organ system is responsible for the effects. The statistical approaches based on somatic mutation theory also give no attention to organ specificity. Author tried to establish an overall picture of acute and chronic injury in organ level not in cellular nor in molecular level. In this paper author proposed a model for the radiation injury with consideration on the injury of organs and interaction

between organs. At present the experimental data on this sort of problems are few and we are not able to compare quantitatively the model with the data. The model in this paper has such mathematical form that it may be able to describe a complicated mechanism as shown in Fig. 4[32] in mathematical sense. The mathematical expressions are rather complicated according to the extent of complexity of the problems. In the following section, author will present the general concepts of the model without help of mathematics.

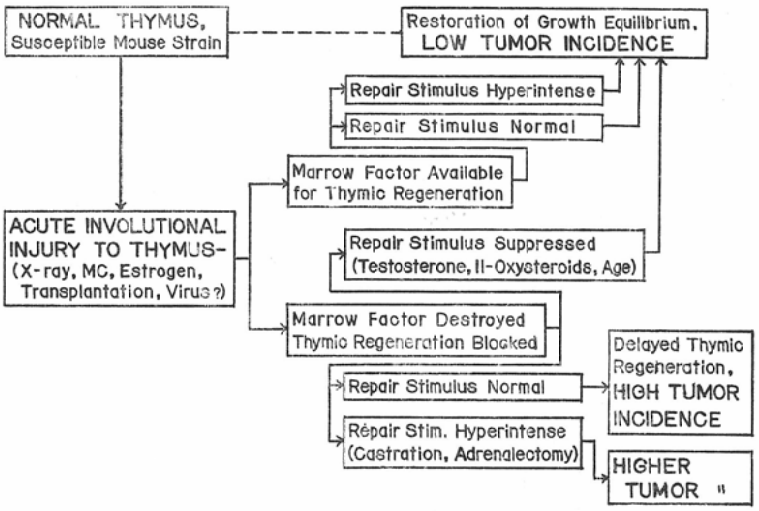

Fig. 4. Schematic diagram of lymphosarcoma induction mechanism

2. Outline of the model

A block diagram of the model is given in Fig. 5. Any kind of radiation will produce injury in the irradiated organs through physical and chemical reactions. Many organs in the organism will interact each other resulting in some recovery or amplification of the initial injury. The whole-body injury will be a weighted summation of each organ injury with regard to essentialness of organs. For example, a case of partial-body irradiatios is illustrated in Fig. 6. Injury in the irradiated portion will affect the other parts of the body as time elapses. Whole-body injury, weighted summation of each injury, will reach some critical value and then the organism will die. Some essential features of the model are described below.

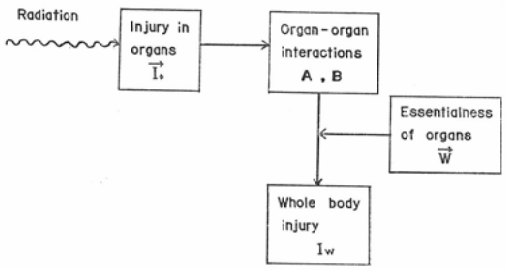

Fig. 5. Block diagram of model

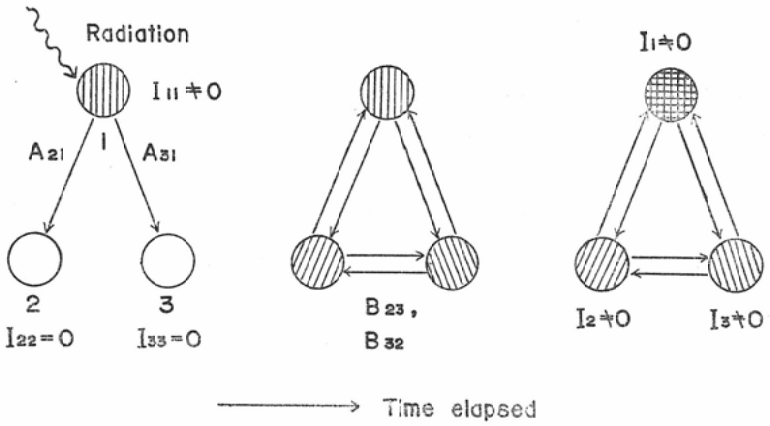

Fig. 6. Partial-body irradiation and organ-organ interactions

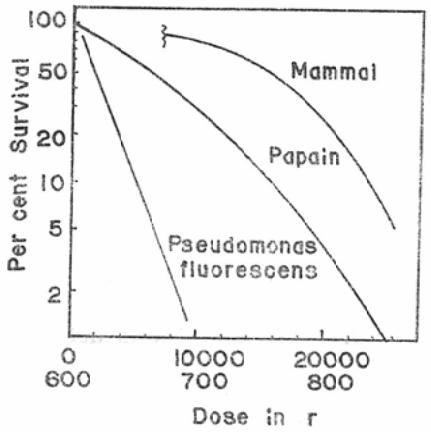

Fig. 7. Per cent survival of enzyme, bacteria and mammals. Dose in upper scale for enzyme and bacteria. Dose in lower scale for mammals 30-day lethality

1) Individual fluctuation. Dose-survival curves shown in Fig. 7. are those for enzyme[33], bacterium[34] and mammal[35], respectively. In the level of molecules or cells, one was used to interprete this type of curves as a result of mechanisms of action but in the level of organisms there are two interpretations as mentioned in the preceding section, one from mechanism of action and the other simply from individual fluctuation in radiosensitivity. Author will take the latter interpretation and some discussion on this problem will be given later. Phenomena from sensitivity distribution and those from population means were strictly divided and treated separately in this model.

2) Organ level. Of course the development of injury in organs will involve many complicated mechanisms in cellular and molecular levels but author will constrain himself in the organ level as far as possible. New parameters concerning organ-organ interactions will play most important role in the model.

3) Time-dependence. Recovery, amplification and compensation of injury were attri-

buted to the organ-organ interactions. Primary injury in irradiated organ was assumed to be constant against time.

4) Injury in organ. Generally injury in organ will be defined as a deviation from normal state in some sense. Injury in one organ will promote recovery or amplification of injury in the other organ. Whether injury in one organ is beneficial or not to the other organ, it will depend upon the states of both organs between which interaction is active. Considering organ-organ interactions and essentialness of organ, "wasted radiation" will be easily solved in organ level.

5) Threshold. When the whole-body injury increases to certain critical value, the animal dies. In other words, when genetically determined information content decreases to a critical value, the animal cannot survive. Age-dependent threshold for death is almost equivalent to the constant threshold including natural aging process to injury in irradiated animal. Author assumes that all animals where whole-body injury reaches the threshold will die and no stochastic process to death.

6) Orthodox method to obtain an injury function is to solve partial differential equations with time and dose assuming some mechanisms of action of radiation. But the differential equations might not have constant coefficients due to complexity of the problem and no solution might be gained by analytical method. In this paper author will not be able to give an injury function explicitly dependent upon time and dose. Author is satisfied with qualitative features of injury function which are compatible with experimental data.

7) Formal theory. The model presented in this paper is a kind of formal theory of radiation injury in the sense that it may give only framework of mechanism of action and the model itself will be to some extent independent upon experimental data because author will not use any particular assumption.

3. Individual fluctuation in radiosensitivity

Using terminology of information theory, differences of radiosensitivity in different animals were interpreted as the differences of information content which would be decreased by any kind of disturbances, e.g., natural aging, irradiation, intoxication etc[36,37]. It is assumed that the form of the distribution of the information content H_o for animals is of normal type at the beginning with mean $H\mu$ and variance σ^2 and that distribution of time at death is also normal type if the deaths come from single cause.

Accordingly frequency distribution of initial information H_o is given as follows.

$$F(H_o) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(H_o - H_\mu)^2}{2\sigma^2}} \qquad (1)$$

Threshold of information content for death H_d will be reasonably chosen as 3σ and thus 99.7 per cent of whole population will be included. Information content of an animal at time t is expressed by using information loss H_n due to any disturbance as follows.

$$H = H_o - H_n \qquad (2)$$

When the information content H decreases up to H_d due to increase of H_n, the

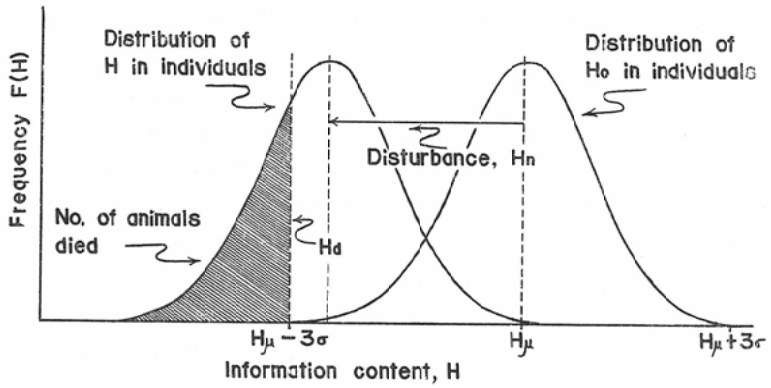

Fig. 8. Distribution of information content in individuals

animal dies. Decrease of information content in the population is illustrated in Fig. 8.

Accumulated mortality for given H_n is calculated by following equation.

$$M(H_n) = \frac{\int_{H_\mu - 3\sigma}^{H_\mu - 3\sigma + H_n} F(H_o)\, dH_o}{\int_{H_\mu - 3\sigma}^{H_\mu + 3\sigma} F(H_o)\, dH_o} \fallingdotseq \int_{H_\mu - 3\sigma}^{H_\mu - 3\sigma + H_n} F(H_o)\, dH_o \qquad (3)$$

Accordingly any type of dependence of H_n upon dose completely determines its dose-mortality curve or dose-survival curve. If H_n is linear with dose, the dose-mortality curve becomes obviously linear in probit paper.

Age specific mortality is also given for any H(t) as follows (See Appendix 1).

$$m(t) = -\frac{d}{dt}\left(\log \int_{H_\mu - 3\sigma + H_n}^{H_\mu + 3\sigma} F(H_o)\, dH_o\right) \qquad (4)$$

Gompertz function is log [m(t)]. The second assumption is equivalent to that the $H_n(t)$ is linear with age. As far as single cause of death is concerned, the accumulated and age specific mortalities are completely specified and both are shown in Fig. 9. on semi-log scale and in Fig. 10 on probit scale. As seen in Fig. 9, author's model does not give a linear Gompertz function for the population in which almost all of members may die of single cause of death. If such case may come true with a particular dose, the relation between two distributions assumed above is easily seen in Fig. 11.

In general a number of causes are concerned with deaths in population, particularly in the late effects and kurtosis and skewness in the distribution of time at death may deviate from those of normal distribution. The distribution of time at death from i-th cause is given as follows.

$$N(t) \cdot P_i(t) = \frac{z_i}{\sqrt{2\pi\sigma_i^2}}\, e^{-\frac{(t - t_i)^2}{2\sigma_i^2}} \qquad (5)$$

If there may be m causes of death in whole life times in a population, age specific mortality and accumulated mortality are given by following equations, where N(t) is

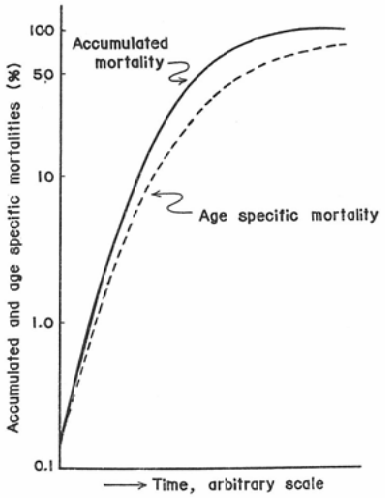

Fig. 9. Two types of expressions for mortality

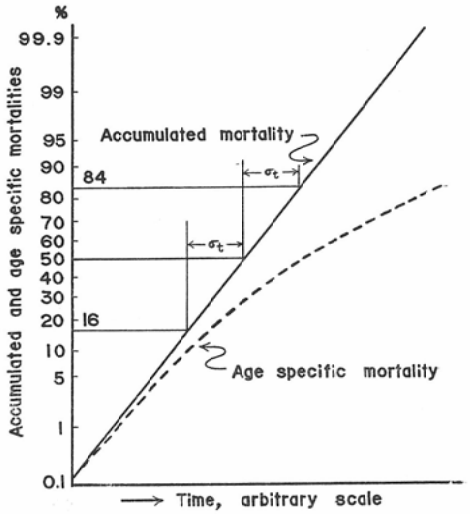

Fig. 10. Two types of expressions for mortality

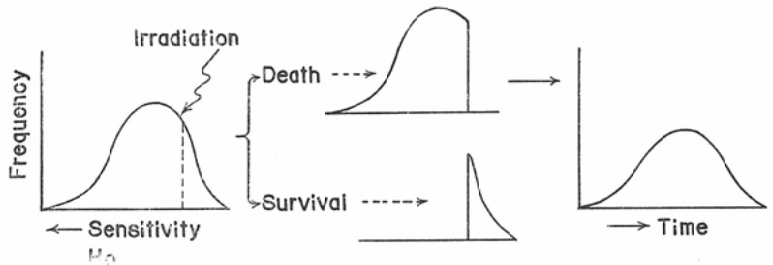

Fig. 11. Distribution of sensitivity and distribution of time at death

number of survivors at t (See Appendix 2).

$$m(t) = \frac{N(t)\,P(t)}{N(t)} = P(t) \tag{6}$$

$$M(t) = \frac{1}{N(o)} \int_0^t N(t)\,P(t)\,dt \tag{7}$$

$$P(t) \equiv \sum_{i=1}^{m} P_i(t) \tag{8}$$

The age specific incidence rate and the final incidence rate are expressed by following equations.

$$\vec{P}(t) = (P_1(t),\ P_2(t),\ \cdots\cdots\ P_m(t)) \tag{9}$$

$$\vec{P} = (P_1,\ P_2,\ \cdots\cdots P_m) \tag{10}$$

$$P_i \equiv \int_T P_i(t)\,dt \tag{11}$$

$$\sum_{i=1}^{m} P_i = 1 \tag{12}$$

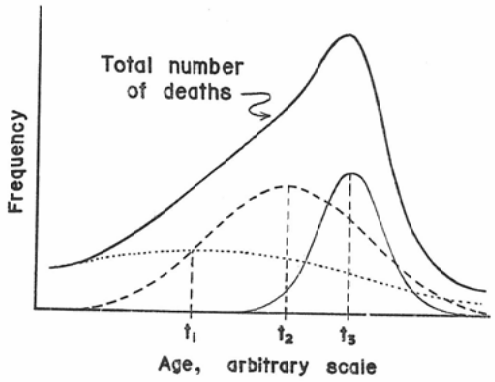

Fig. 12. A distribution of time at death with three causes of death

A theoretical example of distribution of time at death is shown in Fig. 12 where only three causes are encountered. Parameters, t_1, t_2 and t_3 in Fig. 12 are defined in equation (5). Finally, mean survival time is given as follows (See Appendix 3).

$$MST = \frac{1}{N(o)} \int_T t \sum_{i=1}^{m} P_i(t)\, N(t)\, dt \qquad (13)$$

Dependences of each parameter introduced here upon time and dose will be discussed later.

4. Time-independent formula for injury

In the preceding section author developed formulae for phenomena which might be produced from the individual fluctuation in radiosensitivity and in this section author deals with phenomena related to population means. The procedures of formulation of injury will be divided into two steps for convenience' sake, time-independent and time-dependent form, respectively and it will make easy to understand the procedures. In this section, time-independent form will be developed. This form will be finally transformed to time-dependent form in next section.

A radiation injury of whole-body in mammals, such as life shortening, seems to consist in the injuries of many organs and interactions between the organs. In order to form a model for radiation injury author used the following assumptions.

1) Each organ (or part of the body) has common measure of its injury one another.

2) It is possible to divide the injury of an organ into two components. One component is the injury which is due to the direct effect of radiation delivered to the organ. This injury is temporarily called "intrinsic injury". The other component is the "interaction injury" which comes from the interactions between many organs.

By the interactions between organs author means the hormonal or nervous controls of the organs, transport of substance with blood circulation or through cell membranes and so on.

According to the assumptions, an injury of the i-th organ, I_i, is divided into the two components as follows.

$$I_i = I_{ii} + I_{ai} \tag{14}$$

Where I_{ii} is the intrinsic injury of the i-th organ and I_{ai} is the interaction injury of the organ. If there are n organs, I_i is understood as i-th component of n-dimentional "injury vector" $\vec{I}$ for the sake of simplicity. The same for I_{ii} in $\vec{I}_o$. If the i-th organ receives no radiation, I_{ii} vanishes but I_i is not necessarily zero owing to the second term of I_{ai}.

The simplest type of the interaction between the organs is to assume that intrinsic injury I_{jj} of j-th organ directly affects the other organs but does not affect the third organ through the second organ. This type of interaction is called one-step interaction and introducing interaction coefficient A_{ij} from j-th organ to i-th organ, the total injury of i-th organ I_i is expressed as follows.

$$I_i = I_{ii} + \sum_{j=1}^{n} A_{ij} I_{jj} \tag{15}$$

$$A_{ij} = 0, \text{ if } i = j, \tag{16}$$

The meaning of A_{ij} is how much portion of I_{jj} is directly transported to the i-th organ. If A_{ij} is positive, I_i increases as I_{jj} increases.

The feedback mechanisms seen in regulatory systems may be included in the two-step interaction as shown in Fig. 13. Considering both types of interactions, I_i has following form.

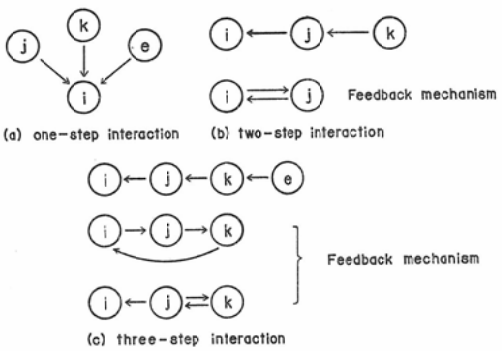

Fig. 13. Types of interaction between organs

$$I_i = I_{ij} + \sum_{j=1}^{n} A_{ij} I_{jj} + \sum_{j,k}^{n} B_{ij} A_{jk} I_{kk} \tag{17}$$

$$B_{ij} = 0, \text{ if } i = j \tag{18}$$

The reason why author uses B_{ij} different from A_{ij} for the second step interaction is that the portion of I_{jj} transported to the i-th organ (A_{ij} I_{jj}) may be different from the portion of A_{jk} I_{kk} transfered to the i-th organ. In the same may, including the higher order interaction, I_i takes the following form.

$$I_i = I_{ii} + \sum_{j=1}^{n} A_{ij} I_{jj} + \sum_{j,k}^{n} B_{ij} A_{jk} I_{kk} + \sum_{l,k,j}^{n} B_{ij} B_{jk} A_{kl} I_{ll} + \cdots \tag{19}$$

In equation (19), it will not be reasonable to take first few terms as an approximation because the term of higher order may sometimes contribute much more than the terms

of lower order do. Each of the two types of interaction coefficient forms the "interaction matrix" as follows.

$$\mathbf{A}=\begin{pmatrix} 0 & A_{1,2}\cdots A_{1,n} \\ A_{2,1} & 0 \\ \vdots & \ddots \vdots \\ A_{n,1}\cdots\cdots & 0 \end{pmatrix} \tag{20}$$

$$\mathbf{B}=\begin{pmatrix} 0 & B_{1,2}\cdots B_{1,n} \\ B_{2,2} & 0 \\ \vdots & \ddots \vdots \\ B_{n,2}\cdots\cdots & 0 \end{pmatrix} \tag{21}$$

Using the matrices, equation (19) can be rewritten as follows.

$$\vec{I}=\vec{I_0}+\mathbf{A}\vec{I_0}+\mathbf{BA}\vec{I_0}+\mathbf{BBA}\vec{I_0}+\cdots \tag{22}$$

While each component of the vector in equation (22) shows the total injury of each organ, injury of whole-body must be made by taking the weighted summation of each I_i.

$$I_w=\sum_{i=1}^{n} w_i I_i \tag{23}$$

or

$$I_w=\vec{W}\cdot\vec{I} \tag{24}$$

The meaning of w_i may depend on what one intends to express with I_w. For example, if I_w is concerned with maximum permissible level, w_i may be the essentialness or indispensability of i-th organ to the wellbeing of the entire body[39]. Using the equations (22) and (24), one has the final equation as follows.

$$I_w=\vec{W}\cdot\vec{I}=\vec{W}\,(\vec{I_0}+\mathbf{A}\vec{I_0}+\mathbf{BA}\vec{I_0}+\mathbf{BBA}\vec{I_0}+\cdots \tag{25}$$

or

$$=\sum_{i=1}^{n} w_i\,(I_{ii}+\sum_{j=1}^{n} A_{ij}I_{jj}+\sum_{j,k}^{n} B_{ij}A_{jk}I_{kk}+\sum_{j,k,l}^{n} B_{ij}B_{jk}A_{kl}I_{ll}+\cdots \tag{26}$$

When I_w exceeds the lethal threshold injury, the animal dies and the each term $w_i \cdot I_i$ in equation (26) may give some information on the mode of death. In equation (26), it is ambiguous how many terms should be included and this problem will be solved in the following section.

5. Time-dependent formula for injury

As mentioned in section 2, (3), I_{ii} is time-independent variable. I_{ii} depends upon dose and only if dose depends upon time like in chronic exposure, I_{ii} depends upon time through dose. The time-dependence of I_w will consist in matrix **A** and **B**, and the procedure to a time-dependent form will be automatically completed by considering the fact that it may take some time for transfer of the interactions between organs. The state of j-th organ which affects the i-th organ at time t is the state some time before t. This has an exact analogy to retarded potential in electromagnetic theory. In this model it is shown schematically in Fig. 14 how to understand a time-dependence of whole-body injury. Shortly after the irradiation an interaction may not go so far from the originated organ. When time becomes available for transfer, many complicated interactions which usually take much time will appear in the organism. Now the time elapsed after irradiation determines

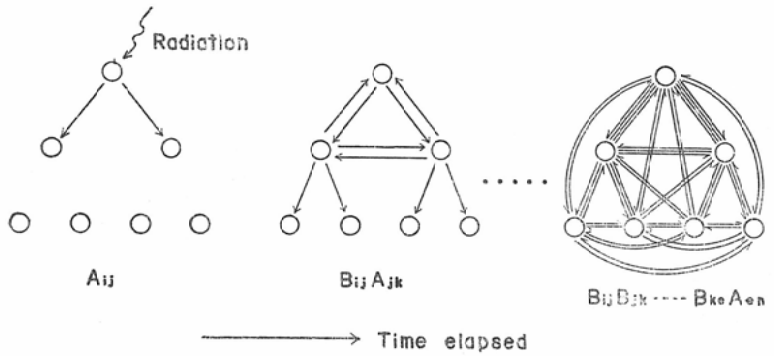

Fig. 14. Time dependent pattern of interactions

the all interactions to be considered, and it means that the elapsed time determines how many terms should be added in equation (26) of the preceding section.

To introduce a retarded time, $t_{ij\cdots 1n}$ will be defined as the time which is needed for transfer of interaction by the way of n,1,·····,j,i and which is temporarily called "transmission time". Obviously following equations hold for transmission times.

$$t_{ij} + t_{jk} = t_{ijk} \tag{27}$$

$$t_{ijk} \neq t_{ik} \tag{28}$$

Using these transmission times, injury in i-th organ will be expressed as follows.

$$I_i(t) = I_{ii} + \sum_{j}^{n} A_{ij}(t - t_{ij})\, I_{jj} + \sum_{j,k}^{n} B_{ij}(t - t_{ij})\, A_{jk}(t - t_{ij} - t_{jk})\, I_{kk} + \cdots \tag{29}$$

$$= I_{ii} + \sum_{j}^{n} A_{ij}(t - t_{ij})\, I_{jj} + \sum_{j,k}^{n} B_{ij}(t - t_{ij})\, A_{jk}(t - t_{ijk})\, I_{kk} + \cdots \tag{30}$$

A simple example of retarded time is given in Fig. 15. In equation (30) the summations will be done under the following conditions.

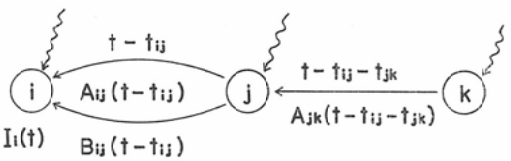

Fig. 15. Retardation of time due to interactions

$$\begin{aligned} &t - t_{ij} > 0 \\ &t - t_{ijk} > 0 \\ &\quad\vdots \end{aligned} \tag{31}$$

In Fig. 16 typical patterns of A_{ij} and B_{ij} are shown. When j-th organ is irradiated and $A_{ij} > 0$, an injury is induced in i-th organ. When i-th organ is irradiated and $B_{ij} \cdot A_{ji} < 0$, the injury in i-th organ is reduced by negative feedback mechanism.

Some special cases of equation (30) will be discussed for comparison with experimental data. "Dose vector" is introduced to express an irradiation pattern in partial-body irradiation as follows.

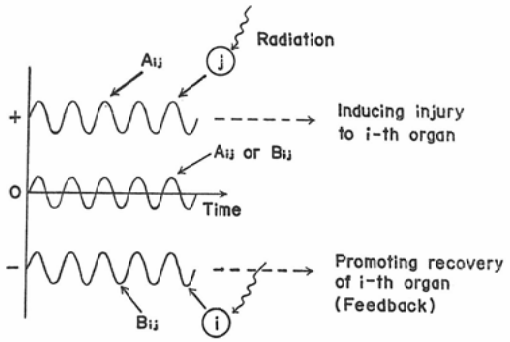

Fig. 16. Typical pattern of A_{ij}, or B_{ij} with time and dose

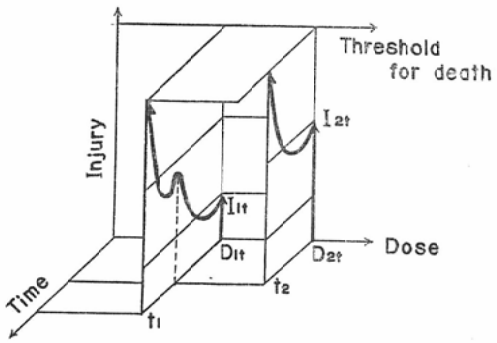

Fig. 17. Typical scheme of radiation death

$$\vec{D} = (D_1, D_2, \cdots\cdots, D_n) \tag{32}$$

D_i is a dose delivered to the i-th organ. An irradiation of only i-th organ and the resulting whole-body injury are given as follow.

$$I_{w1} = I_w(\vec{D_1}), \qquad \vec{D_1} = (D_i \neq 0,\ D_j = 0,\ j \neq i) \tag{33}$$

Similarly, irradiations of j-th organ, and both of i- and j-th organs are given as follow.

$$I_{w2} = I_w(\vec{D_2}), \qquad \vec{D_2} = (D_j \neq 0,\ D_i = 0,\ i \neq j) \tag{34}$$

$$I_{w3} = I_w(\vec{D_3}), \qquad \vec{D_3} = (D_i \neq 0,\ D_j \neq 0,\ D_k = 0,\ k \neq i,\ k \neq j) \tag{35}$$

$$\vec{D_3} = \vec{D_1} + \vec{D_2} \tag{36}$$

Between these three whole-body injuries holds a relation as follows (See Appendix 4).

$$I_{w3} = I_{w1} + I_{w2} \tag{37}$$

If partial-body irradiations with particular doses may produce the same whole-body injury as that of whole-body irradiation, the following relations hold provided that $\mathbf{A}(R_1) \fallingdotseq \mathbf{A}(R_2) \fallingdotseq \cdots\cdots \fallingdotseq \mathbf{A}(R_n) \fallingdotseq \mathbf{A}(R_w)$ and the same for $\mathbf{B}$ (See Appendix 5).

$$I_{wi} = I_w(\vec{D_i}), \qquad \vec{D_i} = (D_i = R_i,\ D_j = 0,\ j \neq i) \tag{38}$$

$$I_{ww} = I_w(\vec{D_w}), \qquad \vec{D_w} = (D_i = R_w,\ i = 1,2, \cdots\cdots n) \tag{39}$$

$$I_{w1} = I_{w2} = \cdots\cdots = I_{wn} = I_{ww} \tag{40}$$

$$\sum_{i=1}^{n} \frac{I_{ii}(R_w)}{I_{ii}(R_i)} = 1 \tag{41}$$

or

$$\frac{I_{11}(R_w)}{I_{11}(R_1)} + \frac{I_{22}(R_w)}{I_{22}(R_2)} + \cdots\cdots + \frac{I_{nn}(R_w)}{I_{nn}(R_n)} = 1 \tag{42}$$

In Fig. 17 three-dimentional expression is given on whole-body injury resulting in death. An animal irradiated with dose D_{1t} at time O has almost instantaneously intrinsic injury I_{1t} as whole-body injury and the whole-body injury changes time to time. Finally the whole-body injury reaches the threshold for death and the animal dies at time t_1. Similar phenomena happen to exposure with dose D_{2t}. Bearing this picture in mind, author will show how the dose-independent survival time in acute radiation death is interpreted in this model. It is assumed that there may be two critical transmission

times in the sense that the terms corresponding to each transmission time, t_1 and t_2, may extraordinarily contribute to the whole-body injury. If these two times do not show any dose-dependence, time-course of whole-body injury in some region of dose takes a form shown in Fig. 18. Obviously in the range, $D_1 < D < D_2$, survival times stay close to t_1 almost independent upon dose and the same for t_2 in some region above D_2. Then dose-survival time curves show two plateaus as shown in Fig. 19.

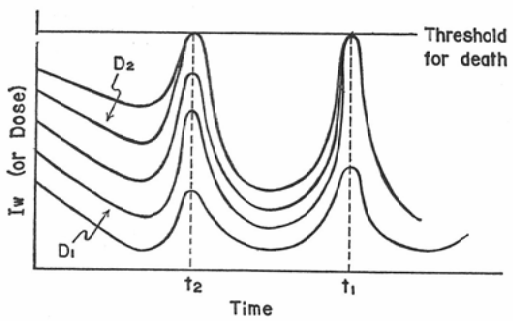

Fig. 18. Schematic diagram of whole-body injury with two special transmission times

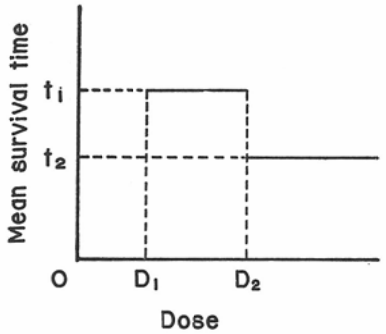

Fig. 19. Mean survival time and cause of death

Thus there may be specific recovery mechanisms corresponding to each plateau.

Organectomy corresponds to decrease the order of **A**,**B**, $\vec{I}$, and $\vec{I}_o$. If i-th organ is ectomized, i-th column and i-th row in **A**, and **B** are swept out and I_i in $\vec{I}$ and I_{ii} in $\vec{I}_o$ are also eliminated.

6. Data pertaining to individual fluctuation in radiosensitivity

First of all author will discuss data on acute injury and then refer to late effects.

1) 30-day lethality and variance. $LD_{50}(30)$ is determined by probit analysis. There

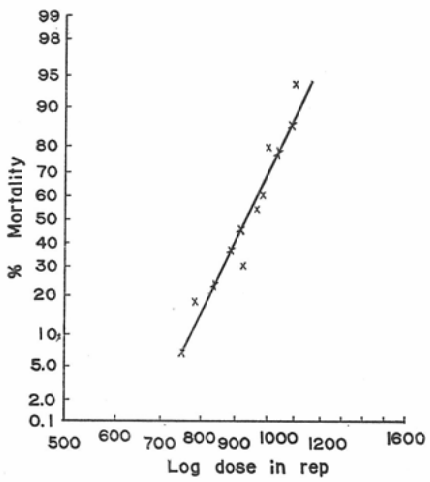

Fig. 20. 30-day mortality curve of mice irradiated with γ-ray.

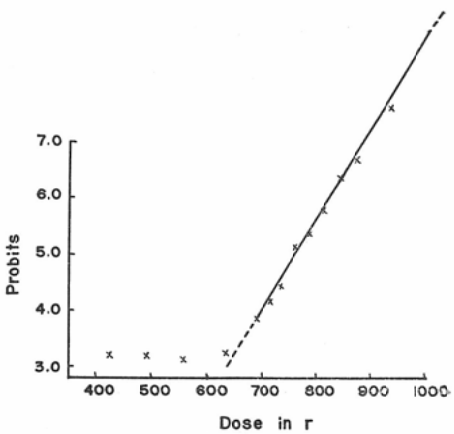

Fig. 21. 30-day mortality versus arithmetic dose

are two types of mortality curve, whether log dose[40–48] or arithmetic dose[13–15,17,35,49–53] shown in Fig. 20 and Fig. 21. The linearity in some region of dose may support the assumption of normal distribution and suggest the H_n of following forms.

$$H_n = aD \qquad \text{arithmetic dose or} \qquad (43)$$

$$H_n = a \log D \qquad \text{log dose} \qquad (44)$$

The slope of dose-mortality curve is a measure of variance defined in equation (1). If the exposure time changes from 10 minutes to 1440 minutes, mortality curve[15] changes as shown in Fig. 22. The longer the exposure time, the smaller the slope of mortality curve. In other words, σ increases as $LD_{50}(30)$ increases. Mice show strain differences[54] in $LD_{59}(30)$ and there is also the same relation between $LD_{50}(30)$ and standard deviation σ.

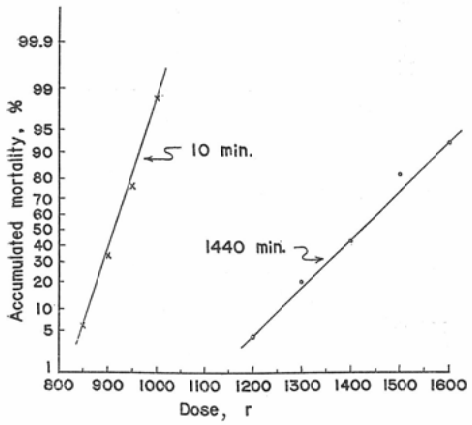

Fig. 22. Probit transtorm of per cent mortality between 9 and 30 days postirradiation in LAF_1 mice versus dose, by exposure time groups.

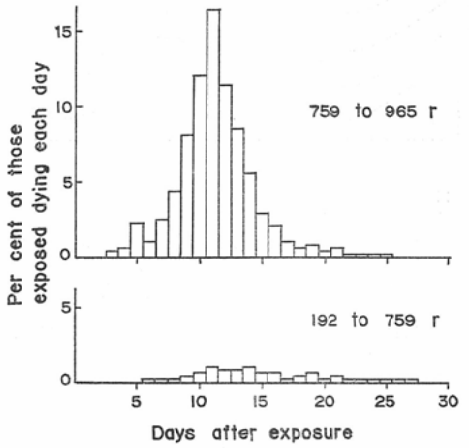

Fig. 23. The pattern of daily deaths of mice

2) Distribution of time at death. A large scale experiment has been done by Cronkite et al[35]. and the distributions of time at death for four dose reanges are quoted in Fig. 23 and Fig. 24.

In the range of 759 to 965 r, cause of death is reasonably assumed to be unimodal, i.e. bone marrow death and to check wether the distribution is of normal type or not,

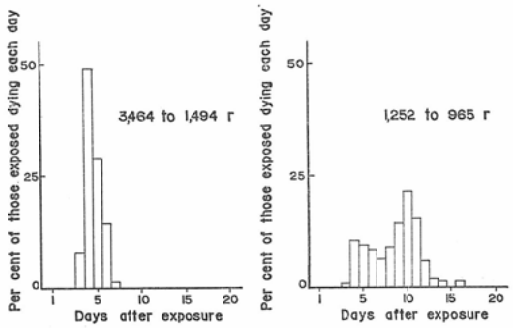

Fig. 24. The pattern of daily deaths of mice

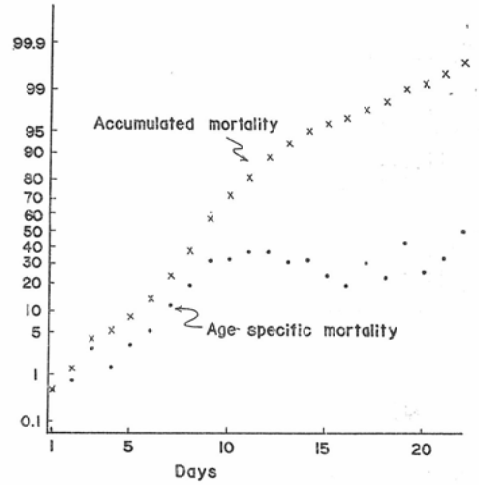

Fig. 25. Mortality of LAF_1 mice exposed to single γ-ray dose

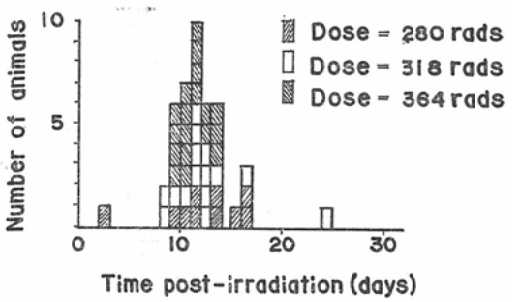

Fig. 26. The pattern of daily deaths of guinea pig

the accumulated mortality is given in probit paper. The linearity seen in Fig. 25 is not so goot but it would not be enough to refuse the assumption of normal distribution. This type of distribution has been found in mouse[15,17,52,55–62], rat[6,43], hamster[51,63], guinea pig[44,64], parakeet[17] and pigeon[17] which have peaks corresponding to bone marrow death or gastro-intestinal death. Lethal exposure to neutrons[40,41,60,61] seems to be different in the distribution of time at death. Another example for guinea pig[44] is given in Fig. 26.

Dunjic et al[43]. have presented linear accumulated mortality in probit versus log time as shown in Fig. 27 which may refuse the assumption.

3) Gompertz function. Almost all types of Gompertz function have been presented which were given for all causes of death in late effects. Some of Gompertz functions are linear[65,66] and others are concave[20] or convex[67,68]. A comprehensive work on delayed effects of atomic radiations in mice was done by Upton et al[69]. and their age distribution of death from all causes of death and that of death from nephrosclerosis are shown in Fig. 28 and Fig. 29. They argued that the frequency distributions were not symmetrical

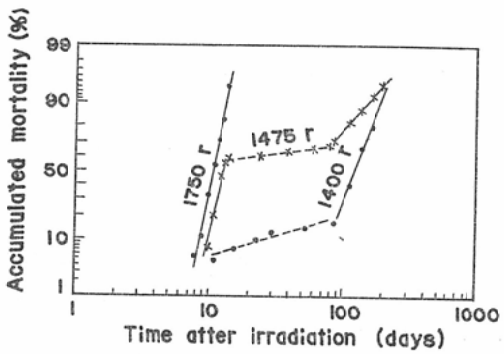

Fig. 27. Incidence of deaths after irradiation of the head in rats.

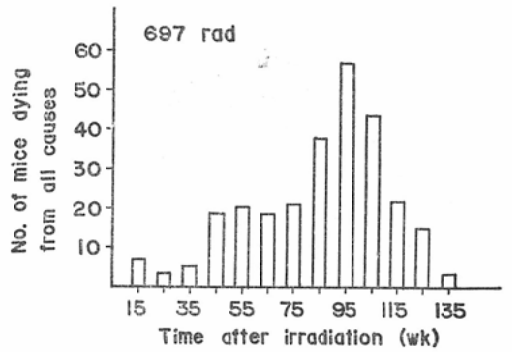

Fig. 28. Age distribution of mortality in mice exposed to gamma rays

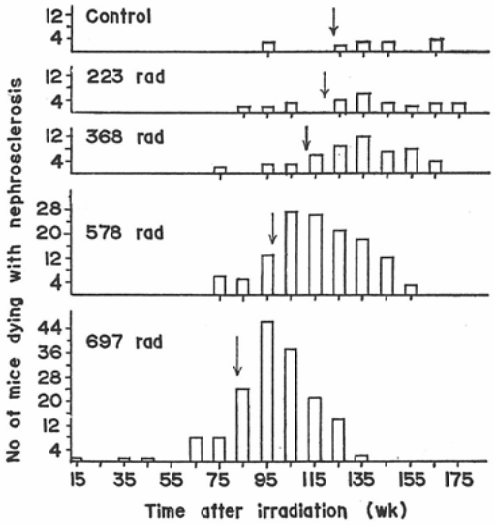

Fig. 29. Age distribution of death with nephrosclerosis in males (arrows indicate mean age at death from all causes in each dose group.

about the mean in Fig. 28 but instead were consistently skewed to the left. The skewness may be interpreted as a superposition of normal distributions as shown in Fig. 12. However it is impossible to test whether the distribution with nephrosclerosis is normal type or not because of small number of deaths. It would be still compatible with the assumption. Kohn et al[67]. reported that in the age 164- and 385-day group with sublethal dose, a linear or approximately linear fit was obtained by plotting probit of cumulated per cent survival against age and that the fit became progressively poorer in the age 550- and 730-day exposure groups, presumably owing to the fact that these experiments began at a time when part of the "distribution" had already been lost. There is no data at present enough to test the hypothesis that the distribution of time at death is normal type if the deaths come from single cause.

7. Data pertaining to population means

In this section author will show some experimental information on the quantities which are introduced to the model in sections 4 and 5.

1) Mode of death. Dose-independent survival times appeared in acute lethality and many works[43,45,50,64,70—81] have been given to explore a relation of the survival time with mode of death. An example[78] of experimental data is shown in Fig. 30. As mentioned in section 5, if critical transmission times distribute separately one another, there appear dose-independent survival times. It is the case in acute lethality, though the transmission times and dose ranges vary species to species. If the dose ranges of two critical transmission times are almost same and if the partial-body irradiation may mask one of the two modes, dose-independent survival times can be separated as seen in oral death[79].

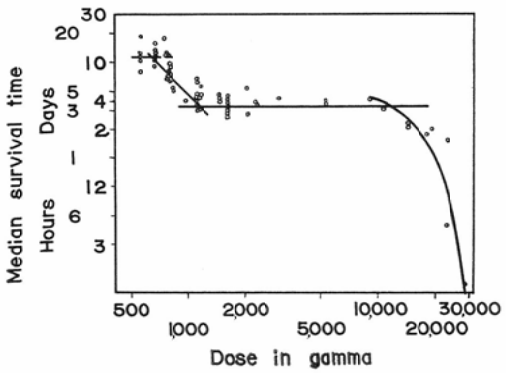

Fig. 30. Survival time of mice after whole-body irradiation. Abscissa-dose in roentgens; ordinate-survival time in hours and days; circle-individual observations.

Dose-dependent survival time between two plateaus comes from individual fluctuation and where the temporal death destribution is bimodal clearly shown in Fig. 24 in section 6. On the other hand, dose-independent survival time is not seen in late effects where many causes of death are associated. Mean survival time of group died from nephrosclerosis decreases with dose as shown in Fig. 29 in section 6. This type of phenomena may seem to come from complicated overlapping of $P_i(t)$ defined by equation (5) in section 3. Then the temporal death distributions in three-dimentional space are shown schematically in Fig. 31 for acute lethality and in Fig. 32 for late effect.

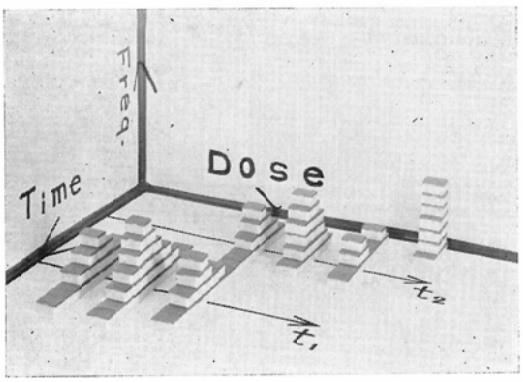

Fig. 31. A temporal death distribution in acute lethality. t_1 and t_2 are critical transmission times.

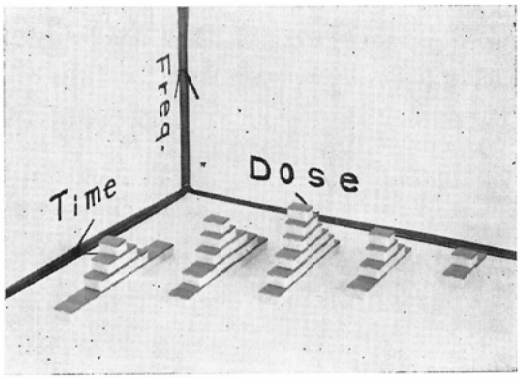

Fig. 32. A temporal death distribution in late effect.

2) Recovery. Paired-dose technique[82] with measure of $LD_{50}(30)$ gave a quantitative method to describe recovery and the existence of recovery from sublethal dose was definitely established by a number of works[9,14—17,41,48,49,51,56,62,65,83—97]. Some of data show a fast recovery component[12,61,83,90,98—100] of order of hours in RT_{50} besides the order of week in RT_{50}. As seen in Fig. 18 in section 5, recovery is directly connected to the mode

of death. There is recovery before or after each dose-independent survival time. Author may infer that the fast recovery component of order of hours might associate with 3.5-day effect and the slow component of order of week might associate with bone marrow death. Recovery mechanism will be interpreted by saying that the interaction injury in some time interval is negative. Swift et al[95]. have reported that considerably lower mortality resulted from x-irradiation of the entire body in mice if the abdomen was exposed 90 minutes prior to or following exposure of the remainder of the body. As shown in Fig. 16 in section 5, if i-th organ is irradiated and if $B_{ij} \cdot A_{ji} < O$, recovery mechanism sets in. The same type of phenomena was reported in number of papers[101—103] and was sometimes called "acquired resistance".

3) Abscopal effects. A typical example of $\mathbf{A} \simeq O$ and $\mathbf{B} \simeq O$ is given in weight loss of testes. Whole-body exposure induces almost same weight loss of testes as exposure of pelvis or testes does[104,105]. The above example is rather exceptional case and most of papers[106—108] report abscopal effects though quantitative description is still difficult. Organectomy may contribute to an injury in three ways: 1. sensitization[109], 2. protection[110], 3. no effect [111]. Negative or positive sign of $B_{ij} \cdots\cdots A_{kl}$ concerning the ectomized organ determines if it acts as sensitization or protection. If A_{ij} or B_{ij} concerning the organ is zero, ectomy induces no effect. Compensation mechanism is seen when one of lungs is irradiated[43]. The intrinsic injury of non-irradiated lung is zero but the interaction injury may arise due to interactions with irradiated lung. This injury, deviation from normal state, may play a role of compensation.

4) $LD_{50}(30)$ from partial-body irradiation. Blair[112] has given attention to a relation between $LD_{50}(30)$s from whole-body and partial-body irradiations. If a whole-body is divided into n sections, the $LD_{59}(30)$s which are obtained by exposure of each section have following relation with the $LD_{50}(30)$ of whole-body.

$$\frac{1}{R_w} = \frac{1}{R_1} + \frac{1}{R_2} + \cdots\cdots\cdots + \frac{1}{R_n} \tag{45}$$

R_w : LD_{50} (30) of whole-body

R_i : LD_{50} (30) of i-th section

It is assumed that I_{ii} takes the following form.

$$I_{ij} = c_i D_i + d_i D_i^2 \tag{46}$$

Equation (41) becomes as follows.

$$\sum_{i=1}^{n} \frac{c_i R_w + d_i R^2_w}{c_i R_i + d_i R^2_i} = 1 \tag{47}$$

Putting $d_i = O$, we get the following relation.

$$\sum_{i=1}^{n} \frac{c_i R_w}{c_i R_i} = \sum_{i=1}^{n} \frac{R_w}{R_i} = 1 \tag{48}$$

or

$$\frac{1}{R_w} = \sum_{i=1}^{n} \frac{1}{R_i} \tag{49}$$

Experimental data[113,114] are given in Table 1 and other data[46,86] also support the

Table 1. $LD_{50}(30)$s for partial-body irradiation

	Whole Body	Abdomen Exposed	Abdomen Shielded
R	650 − 750	1025	1950
Kg·R	175	134	275
1/R	.00143	.00097	.00051

Strain	Whole Body R	Whole Body 1/R	Head Alone R	Body Alone R	Head and Body 1/R + 1/R
Dba	500	.0020	500	1265	.00280
Marsh	570	.00175	1185	1018	.00183
C57	550	.00181	1300	858	.00194
C_3H	492	.00203	1443	735	.00198

equation (49). It shows that the intrinsic injury is linear with dose in the region of lethal dose and does not mean that there is no interaction between body regions.

8. Discussion

The model developed in this paper is a linear model in the sense that the final equation (26) is transformed into following form.

$$I_w = \vec{D} \cdot \vec{I}_o = \sum_{i=1}^{n} D_i I_{ii} \tag{50}$$

$$\vec{D} \equiv (\vec{W} + \vec{W}\mathbf{A} + \vec{W}\mathbf{B}\mathbf{A} + \vec{W}\mathbf{B}\mathbf{B}\mathbf{A} + \cdots\cdots) \tag{51}$$

I_w is linear with I_{ii} and does not contain cross-term of $I_{ii} \cdot I_{jj}$ or squared term of $(I_{ii})^2$. This feature guarantees the equations (37) and (41) in section 5. And there is an assumption that **A** and **B** are the same in I_{w1}, I_{w2} and I_{w3} in equation (37). Kay et al[115]. have reported an induction of polydipsia by partial-body irradiation. In view of the fact that x-irradiation of the kidneys causes polydipsia and x-irradiation of the pancreas causes polydipsia and polyuria, it is curious that x-irradiation of the kidneys plus pancreas or the kidneys plus the liver does not cause either a polydipsia or polyuria. The phenomena are shown schematically in Fig. 33 and it is necessary to modify equation (37). The modification will be done by way of either adjusting parameters **A** and **B** or including cross-terms of $I_{ii} \cdot I_{jj}$. Positive or negative sign of B_{ij} $B_{jk}\cdots\cdots A_{in}$ is one of the difficulties in the model. Law of multiplication of negative number may not hold there and the sign of the product, B_{ij} $B_{jk}\cdots\cdots A_{in}$, may be determined by the biological interest of i-th organ to j-th organ.

Formulations in the preceding sections do not include natural aging process since one is interested in differences between irradiated and control groups. If it is needed, equation (14) in section 4 includes one more term for natural aging process.

Separation of phenomena of individual fluctuation from that of mechanism will leave another problem. If the natural disturbances are uniform for individual organisms, indi-

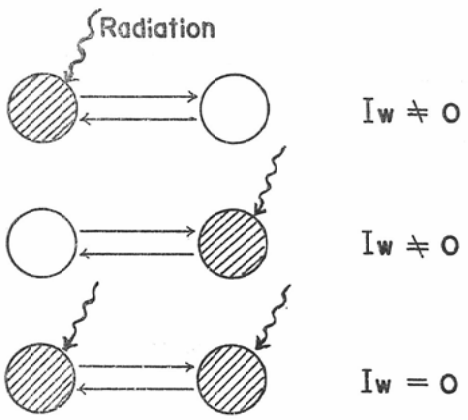

Fig. 33. Partial-body irradiation and special organ-organ interactions

vidual fluctuation is a matter of genetics beyond the works in this paper.

The time-dependence of whole-body injury is expressed by addition or subtraction of terms corresponding to each transmission time in the model and it gives difficulty to describe a chronic exposure. The problem will be left for further studies.

The operation that is carried out in this paper is a transformation in the mathematical sense. The model presented here is still far from adequate for the task of prediction that was assigned at the beginning. An attempt has been made to present some concepts that are felt by the author to be fundamental to an understanding of the factors that govern the stability of living organisms. The logical clarification and experimental implementation of these concepts will, however, require much additional works.

Summary

A mathematical model for radiation injury was developed by assuming organ injury and organ-organ interaction. A normal distribution was assumed for individual fluctuation in radiosensitivity. The time-dependence of the injury was included in the model by considering retardation of transfer of the interaction. The model had a form of vector-matrix. It was compared with experimental data on mode of death, recovery, $LD_{50}(30)$ of partial-body irradiation, temporal death distribution and so on. Some qualitative agreements could be seen in the comparison.

Acknowledgement

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Appendix

1. Survival fraction at time t is given as follows.

$$N(t) = \int_{H_\mu - 3\sigma + H_n(t)}^{H_\mu + 3\sigma} F(H_o)dH_o \qquad (1)$$

Age specific mortality is defined as the probability per unit time of leaving the population and is expressed as follows.

$$m(t) = -\frac{1}{N(t)} \cdot \frac{dN(t)}{dt} = -\frac{d}{dt} \log N(t) \qquad (2)$$

Using equation (1), it follows.

$$m(t) = -\frac{d}{dt}\left(\log \int_{H_\mu - 3\sigma + H_n(t)}^{H_\mu + 3\sigma} F(H_o)\, dH_o \right) \qquad (3)$$

Experimentally, m(t) is calculated by following approximation.

$$m(t) = \frac{1}{2h} \log \frac{N(t-h)}{N(t+h)} \qquad (4)$$

The logarithms used above are all natural logarithms. Age specific mortality is sometimes called force of mortality.

2. $P_i(t)$ is a probability with which animal dies of i-th cause at t since it is normalized both for all causes and whole life time by equations (11) and (12) in section 3. Then equation (6) in section 3 is identical with usual definition of age specific mortality as shown below.

$$m(t) = -\frac{1}{N(t)} \frac{dN(t)}{dt} = \sum_{i=1}^{m} P_i(t) = P(t) \qquad (5)$$

3. Mean survival time is calculated as follows.

$$MST = \frac{\int_T t \sum_{i=1}^{m} P_i(t)\, N(t)\, dt}{\int_T \sum_{i=1}^{m} P_i(t)\, N(t)\, dt} \qquad (6)$$

$$\int_T \sum_{i=1}^{m} P_i(t)\, N(t)\, dt = N(o) \tag{7}$$

4. Whole-body injuries for each exposure are given as follow.

$$I_{w1} = w_i\, I_{ii} + \sum_{p}^{n} W_p\, A_{pi}\, I_{ii} + \sum_{p,k}^{n} W_p\, B_{pk}\, A_{ki}\, I_{ii} + \cdots\cdots \tag{8}$$

$$I_{w3} = W_j\, I_{jj} + \sum_{p}^{n} W_p\, A_{pj}\, I_{jj} + \sum_{p,k}^{n} W_p\, B_{pk}\, A_{kj}\, I_{jj} + \cdots\cdots \tag{9}$$

$$I_{w3} = W_i\, I_{ii} + \sum_{p}^{n} W_p\, A_{pi}\, I_{ii} + \sum_{p,k}^{n} W_p\, B_{pk}\, A_{ki}\, I_{ii} + \cdots\cdots$$

$$+ W_j\, I_{jj} + \sum_{p}^{n} W_p\, A_{pj}\, I_{jj} + \sum_{p,k}^{n} W_p\, B_{pk}\, A_{kj}\, I_{jj} + \cdots\cdots \tag{10}$$

$$= I_{w1} + I_{w2} \tag{11}$$

5. Equation (38) in section 5 is expressed as follows.

$$I_{wi} = W_i\, I_{ii}(R_i) + \sum_{p}^{n} W_p\, A_{pi}\, I_{ii}(R_i) + \sum_{p,j}^{n} W_p\, B_{pj}\, A_{ji}\, I_{ii}(R_i) + \cdots\cdots$$

$$= \left(W_i + \sum_{p}^{n} W_p\, A_{pi} + \sum_{p,j}^{n} W_p\, B_{pj}\, A_{ji} + \cdots\cdots \right) I_{ii}(R_i) = \alpha_i\, I_{ii}(R_i) \tag{12}$$

$$\alpha_i = \frac{I_{wi}}{I_{ii}(R_i)} \tag{13}$$

Using constant α_i, equation (39) in section 5 is rewritten as follows.

$$I_{ww} = \alpha_i\, I_{ii}(R_w) + \alpha_z\, I_{zz}(R_w) + \cdots\cdots \alpha_n\, I_{nn}(R_w) \tag{14}$$

The above equation (14) holds only if $\mathbf{A}(R_1) \fallingdotseq \mathbf{A}(R_2) \fallingdotseq \cdots\cdots \mathbf{A}(R_n) \fallingdotseq \mathbf{A}(R_w)$ and the same for **B**. Substituting α_i in equation (14), it follows.

$$I_w = \frac{I_{w1}\, I_{11}(R_w)}{I_{11}(R_1)} + \frac{I_{w2}\, I_{22}(R_w)}{I_{22}(R_2)} + \cdots\cdots \frac{I_{wn}\, I_{nn}(R_w)}{I_{nn}(R_n)} \tag{15}$$

Using equation (40) in section 5, we get the following equation.

$$1 = \frac{I_{11}(R_w)}{I_{11}(R_1)} + \frac{I_{22}(R_w)}{I_{22}(R_2)} + \cdots\cdots + \frac{I_{nn}(R_w)}{I_{nn}(R_n)} \tag{16}$$