A Model For Radiation Injury (6)
— Whole Body Injury —

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放射線障害の模型（6）
全身障害

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（昭和40年4月20日受付）

致死線量領域に於ける全身障害を定義するために，放射線感受性の個体差は正規分布をし，死亡により一部の動物が失われても生存群は同じ正規分布に再分布すると仮定した．この模型によると全身障害は死亡率から容易に計算される．死亡数の時間的分布，全身障害及び放射線感受性の個体差の間の定量的関係が確立された．死亡数の時間的分布が二つの極大を持つ場合には，最初の極大の直後に全身障害の回復があることが示された．全身障害の極大と死亡数の時間的分布の極大は一般的には一致しないが，それらが一致する条件は死亡率に対する条件として与えられた．致死線量以下の領域に関しては従来は30日半致死線量が用いられてきたが，時刻に対する不明確の問題がある．したがつて半致死線量としての条件を満たすような30日より短かい観察期間が望まれることが知られた．

I. Introduction

It has been a great problem so long time to determine the pattern of the whole body injury. One of its basic difficulties lies in the experimental definition of the whole body injury. One approach to this is so-called paired-dose method[1-4]. After an exposure of the conditioning dose to the population, it is determined how the $LD_{50}(30)$s of the population change daily by the additional test exposures.

Comparing them with the $LD_{50}(30)$ of the control groups, the whole body injury will be defined as follows,

$$I_w = LD_{50}(30) \text{ of control} - LD_{50}(30) \text{ of irradiated} \quad (1)$$

In the above definition, the additivity of the injuries from the conditioning dose and from the test dose is assumed and also at present without such assumption of the additivity, any formulation can hardly be done. But the measure of $LD_{50}(30)$ may involve another ambiguity of the time. It comes from the fact that the time of exposure to the test dose is different from the time at death.

Another definition of the whole body injury[5] consists of the informations from single conditioning dose and from a continuous irradiation until death. The formula will be given asfollows,

$$D_R = D_C \times \frac{MASo - MASc}{MASo} \quad (2)$$

D_R : Residual injury
D_C : Conditioning dose
MASo : Mean after survival of the control group
MASc : Mean after survival of the group received conditioning dose

In this definition, there is still an ambiguity on the time when the residual injury must be referred.

Assuming the time pattern of the whole body injury, the method to test the validity of the assumption with the experimental data may be called an indirect definition of the whole body injury. The accordance of the result from the assumption with the experimental data shows the consistency between them but the assumption could not be the unique conclusion of the experimental data. Another assumption may still be consistent with the same experimental data. Most simple assumption is the exponential recovery function[6] for the whole body injury induced by single exposure. By Blair[7-11] irreparable part was added to the exponential recovery function. Mewissen et al.[12] have proposed an idea for latent injury to explain "wasted radiation". The other simple assumption is linear recovery function by Tyler et al[13,14]. These models are mostly concerned with the recovery process which happens immediately after the single exposue. For the amplification of the whole body injury there is a model presented by Neary[15].

Most elegant method to determine the whole body injury has been proposed by Brues et al[16-19]. The method has given the way how to calculate the whole body injury from the data on continuous irradiation until death. The experimental curve on dose-rate versus mean survival time will give enough informations to calculate the whole body injury and the injury will be obtained by graphical differentiation of some curve with time. In acute radiation death, the daily death distribution is sometimes clearly bimodal[20-24] and the mean survival time of the distribution is hardly determined as a good statistic. Then it will be impossible to infer the whole body injury from the mean survival time in such case. In this paper, a model for the whole body injury in the acute radiation death will be presented and it will consistently explain the time pattern of the whole body injury, the daily death distribution and the individual fluctuation in radiosensitivity.

II. Model for whole body injury

In the previous papers[25,26], a vector-matrix representation of the whole body injury has been presented. In the mathematical representation the whole body injury is constructed with the injuries of each organ and the interactions among the organs. The formula for the whole body injury is as follows,

$$I_w = \sum_{i=1}^{n} w_i \left(I_{ii} + \sum_{j=1}^{n} A_{ij} I_{jj} + \sum_{j,k}^{n} B_{ij} A_{jk} I_{kk} + \sum_{j,k,l}^{n} B_{ij} B_{jk} A_{kl} I_{ll} + \cdots \right) \quad (3)$$

I_w : Whole body injury
I_{ii} : Intrinsic injury of the i-th organ
A_{ji}, B_{ij} : Interaction from the j-th organ to the i-th organ
W_i : Essentialness of the i-th organ to survive

Also in the previous paper[26] it is suggested that the plateau[27-34] in the graph of dose versus survival time in the acute radiation death may ocur with a particular time pattern of the whole body injury (See Fig. 1 and Fig. 2).

(1) Definition of the whole body injury

The individual fluctuation in radiosensitivity and the whole body injury determine the daily death distribution. To establish the quantitative relation among the individual fluctuation in radiosensitivity,

Fig. 1. Schematic diagram of whole body injury

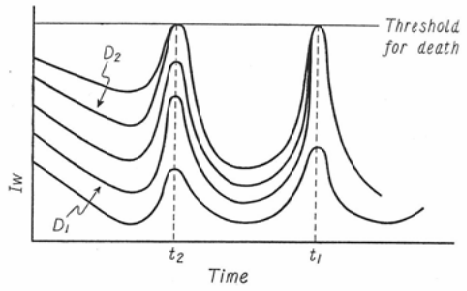
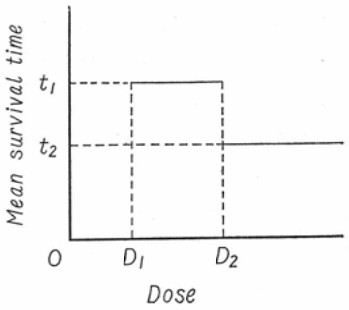


Fig. 2. Mean survival time and cause of death



the whole body injury and the daily death distribution, the following two assumptions were used.

(a) The individual fluctuation in radiosensitivity has a normal distribution

(b) When the sensitive group in the above distribution is lost by the radiation death, remaining survivals re-distribute in the same type as before

In Fig. 3 the control group has the normal distribution around the mean background injury which is induced by some natural disturbances. If the radiation is delivered to the group, the whole body injury increases and the injury of the relatively sensitive group exceeds the lethal injury I_L. In this case the number of animals died is expressed in the shaded area. Using the above assumptions the complete model is shown at three dimensions in Fig. 4 where the single lethal dose is given at time zero. The line connecting

Fig. 3. Individual fluctuation in radiosensitivity and lethal injury I_L

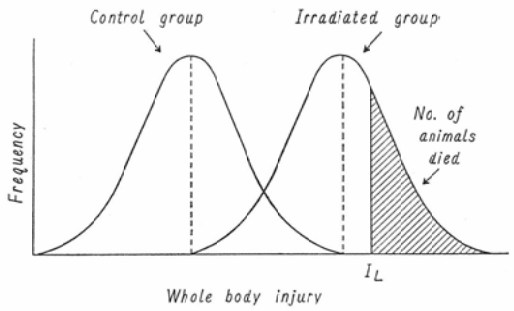
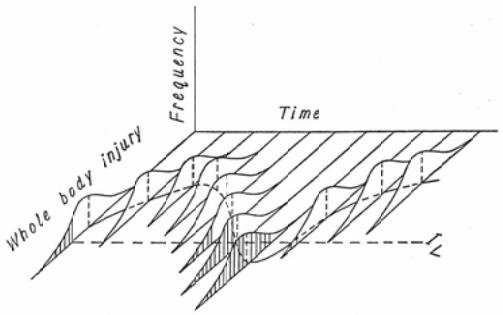


Fig. 4. A model for whole body injury



the center of the distribution indicates the time pattern of the mean whole body injury of the survivals at each time. In this example, the whole body injury has a recovery process immediately after the irradiation and then an amplification. Its daily death distribution is bimodal as shown in the shaded area. Normalizing the area under the normal distribution to 1, the shaded area corresponds exactly to the age specific mortality defined as follows,

$$\text{Age specific mortality } m(t) = \frac{N(t) - N(t+\Delta t)}{N(t)} \qquad (4)$$

$N(t)$: Number of survivals at time t

Accordingly, the mean whole body injury will be claculated from the observed age specific mortality. In the calculation one can set the variance of the normal distribution to 1 without losing the generality of the model, because the whole body injury is still written in arbitrary unit. Detailed calculations of the

whole body injury from the age specific mortality are divided into two cases.

(a) $m(t)<0.5$

$$Y=0.5-m(t)$$

$$Y=\frac{1}{\sqrt{2\pi}}\int_0^x e^{-\frac{x^2}{2}}dx$$

(b) $m(t)>0.5$

$$Y=m(t)-0.5$$

$$Y=\frac{1}{\sqrt{2\pi}}\int_0^x e^{-\frac{x^2}{2}}dx$$

The values X corresponding to Y are tabulated in usual statistical tables. In the case m (t) >0.5, negative sign shall be put to the X for convenience. A theoretical example of the daily death distribution and the whole body injury is shown in Fig. 5. Recovery and amplification of the whole body injury will be shown in terms of the age specific mortality as follow.

$\frac{dm(t)}{dt} < 0$: Recovery

$\frac{dm(t)}{dt} > 0$: Amplification

Therefore a monotonic increase of Gompertz[15,16] function indicates an amplification of the whole body injury.

Fig. 5 Daily death distribution and whole body injury

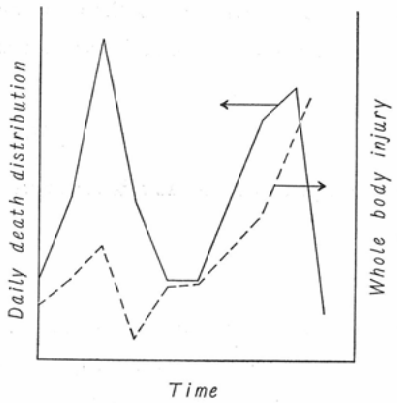
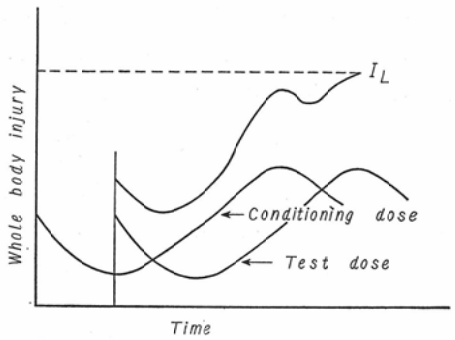


Fig. 6 Additivity of injuries



On the other hand, one cannot get any information on the age specific mortality without zero in the sublethal range. In this case it will be necessary to use some definition analogous to equation (1). In general LDx(y) has two conditions to be a good statistic. At first x must be fifty percent to secure the highest confidence. In the second place, y must be chosen to make an accurate count of the deaths such that the death distribution is minimum at y. If the whole body injury of the conditioning dose changes daily in complicated form, the superposition of the injury from the test dose on that from the conditioning dose gives rise to such aninjury as shown in Fig. 6. Accordingly the difference defined in equation (1) has an ambiguity on the time when the residual injury must be referred. To avoid the ambiguity, any other y, earlier than 30 days, will be much better.

(2) The relation between the distribution of the individual fluctuation in radiosensitivity and the daily death distribution.

If one can know the whole body injury induced by single lethal dose, one can show how the individual fluctuation in radiosensitivity determines uniquely the daily death distribution. In Fig. 4 let the observation time $t_0, t_1, \cdots t_n$ in equal time intervals and the shaded area at t_i, P_i. P_i is the age specific mortality and it means the probability of death at t_i. If the number of the animals at t_0 is equal to N_0, the numbers of survivals and deaths at each time will be given as follow,

Time	No. of deaths	No. of survivals
t_0	0	N_0
t_1	N_0P_1	$N_0(1-P_1)$
t_2	$N_0P_2(1-P_1)$	$N_0(1-P_1)(1-P_2)$
t_3	$N_0P_3(1-P_1)\ (1-P_2)$	$N_0(1-P_1)\ (1-P_2)\ (1-P_3)$
⋮	⋮	⋮
t_n	$N_0P_n\prod_{i=1}^{n-1}(1-P_i)$	$N_0\prod_{i=1}^{n}(1-P_i)$

Therefore number of deaths at interval $t_{n-1}<t\leq t_n$ will be given as follows,

$$M(t_n)=N_0P_n\prod_{i=1}^{n-1}(1-P_i) \tag{5}$$

The whole body injury and the individual fluctuation in radiosensitivity determine the P_i and the P_i determines uniquely the daily death distribution through the equation (5)

(3) The relation between the whole body injury and daily death distribution

In general the maximum of the daily death distribution does not coincide with that of the whole body injury. The necessary and sufficient condition for the maximum in the daily death distribution is as follows (See Appendix I),

$$\frac{P_{n-1}}{1-P_{n-1}} < P_n > \frac{P_{n+1}}{1+P_{n+1}} \tag{6}$$

The necessary and sufficient condition for the coincidence of the both peaks in the daily death distribution and in the whole body injury is as follows (See Appendix II),

$$\frac{P_{n-1}}{1-P_{n-1}} < P_n > P_{n+1} \tag{7}$$

In conclusion the model mentioned above explains consistently the whole body injury, the daily death distribution and the individual fluctuation in radiosensitivity. The whole body injury is easily estimated from the age specific mortality. In sublethal range, $LD_{50}(y)$ with proper y determines the whole body injury. Quantitative relations among the above three quantities are established.

III. Discussions

The assumption of the normal distribution for the individual fluctuation in radiosensitivity may be conventional and rather arbitrary. The only reason for the choice is that there is no particular reason to choose other distributions. In target thoery Poisson distribution is unique conclusion from the randomness of hits. The binominal distribution comes necessarily from the mechanism of heredity in genetics. In any case these three distributions are almost same in some limiting case. In the second assumption of re-distribution in section II the following facts were assumed.

(a) The variance of the distribution is constant.

(b) When a portion of the distribution is lost by deaths, its sharp edge is not maintained.

Another comparable assumptions to these are as follow,

(a) The constant vaiance and no re-distribution

(b) The variable variance and re-distribution

(c) The variable variance and no re-distribution

The above three cases are shown in Fig, 7, 8, and 9. In case of (a) and (c), the line connecting the center of the distribution does not express the mean whole body injury of the survivals at each time. The whole body injury will be expressed by the line connecting the center of gravity of the area corresponding to the survivals. In this way the assumptions may approach to those in section II. With an accuracy of biological experiment it may be hard to discriminate the small changes in the variances. But these discussions lead to a serious difficulty on some sort of uncertainity. As seen so far there are three factors to

Fig. 7 Model (a) for whole body injury

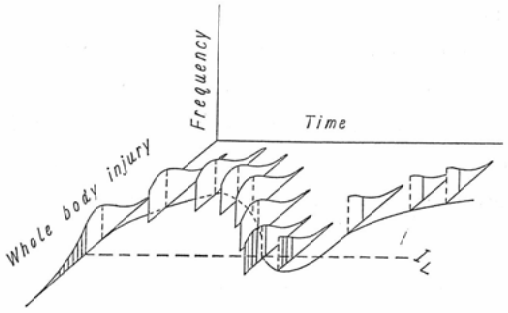


Fig. 8 Model (b) for whole body injury

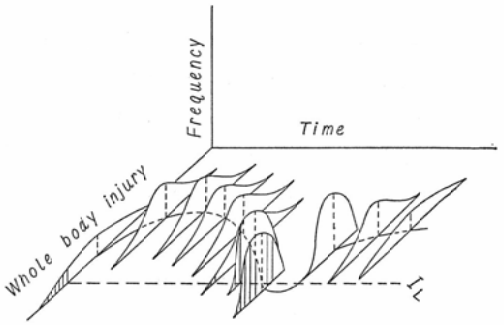


Fig. 9 Model (c) for whole body injury

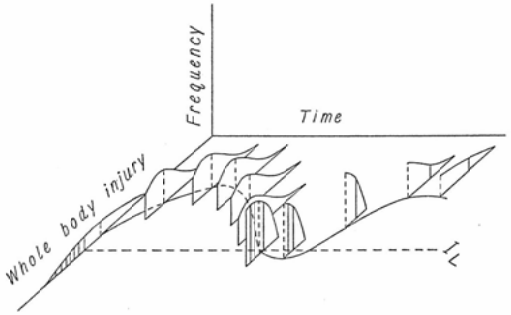
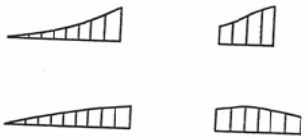


Fig. 10 Uncertainty in shapes



be determined, namely the whole body injury, the daily death distribution and the individual fluctuation in radiosensitivity. These three factors are related to one another in the model. The directly observable quantity is only the daily death distribution. Therefore one of the rest two factors should be assumed. In experiment one can only know the shaded area in Fig. 4 and no information for the shape of the area. For example if the areas are the same, one cannot discriminate the cases shown in Fig. 10. Some sort of data pertaining to the above discussion seems to be obtainable from the experiment on LD_{50} (30)[20,35].

In Fig. 4 I_w exceeds the lethal injury I_L at some time. If the age specific mortality exceeds 50% in this model, the mean whole body injury is always larger than I_L. This fact may come from the assump-

tion of the re-distribution and from the discontinuity of the observation time.

The quantitative changes in the whole body injury may involve the qualitative changes in detail. In the vector-matrix representation of the whole body injury.

$$I_w = \vec{W} \cdot \vec{I} = \vec{W}(\vec{I_0} + A\vec{I_0} + BAI_0^{\rightarrow} + BBA\vec{I_0} + \cdots$$

the each component of the scalar products shows how much the component contributes to the whole body injury. The contribution will change by time and the informations on the above discussion will be necessary to test the validity of the additivity assumption.

In practice it will not be easy to choose proper $LD_x(y)$ for some animals discarding the conventional $LD_{50}(30)$. For smaller y, the test dose should be relatively high and it may be difficult to detect the small changes of the conditioning dose or to detect the small conditioning dose itself. On the other hand the conditioning dose should be small not to cause death before the test dose.

Some experiments designed by this model wih 10^4 fishes will be reported in the next paper.

Summary

A model has been presented to explain consistently the whole body injury, the daily death distribution and the individual fluctuation in radiosensitivity. The whole body injury is easily estimated from the age specific mortality with the model. Quantitative relations among the above three factors are established. In general the maximum of the daily death distribution does not coincide with that of the whole body injury. The change in the age specific mortality is almost parallel with the whole body injury.

Appendix

I. The necessary condition for the maximum of the daily death distribution will be obtained as follows,

$$M(t_{n-1}) < M(t_n) > M(t_{n+1})$$

$$N_0 P_{n-1} \prod_{i=1}^{n-2}(1-P_i) < N_0 P_n \prod_{i=1}^{n-1}(1-P_i) > N_0 P_{n+1} \prod_{i=1}^{n}(1-P_i)$$

Dividing with $N_0 \prod_{i=1}^{n=2}(1-P_i)$,

$$P_{n-1} < P_n(1-P_{n-1}) > P_{n+1}(1-P_n)(1-P_{n-1})$$

From the first inequality,

$$\frac{P_{n-1}}{1-P_{n-1}} < P_n$$

From the second inequality,

$$P_n > P_{n+1} - P_{n+1}P_n$$

$$P_n(1+P_{n+1}) > P_{n+1}$$

$$P_n > \frac{P_{n+1}}{1+P_{n+1}} \qquad (1)$$

Accordingly,

$$\frac{P_{n-1}}{1-P_{n-1}} < P_n > \frac{P_{n+1}}{1+P_{n+1}}$$

The sufficient condition will be obtained in the same manner.

II. The necessary condition for the coincidence of the both peaks in the daily death distribution and in the whole body injury will be obtained as follows. The necessary condition for the maximum in the whole body injury is,

$$P_{n-1} < P_n > P_{n+1} \qquad (2)$$

Considering the eqations (1) and (2),

$$\frac{P_{n-1}}{1-P_{n-1}} < P_n > P_{n+1}$$

The sufficient condition will be obtained in the same manner.

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