A MODEL FOR RADIATION INJURY (7)
— Paired-dose Method —

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放射線障害の模型(7)
二回照射法

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(昭和41年11月11日受付)

哺乳動物における放射線による全身障害の評価は，主に LD_{50} (30) 又は平均寿命を用いて行われてきた．前照射を行つた動物について経時的に LD_{50} (30) を求め，対照群の LD_{50} (30) と比較する方法が2回照射法と呼ばれるものである．通常，対照群の LD_{50} (30) から前照射群の LD_{50} (30) を引いたものが，LD_{50} (30) を決定するために行つた2度目の照射時の障害と定義されている．この場合照射時と50%死亡率が観察される時期の間には30日間の観察期間があるので上記の如く定義される障害が，いかなる時期の障害を表わすかについては問題が残つている．筆者等は上記の定義による障害が2度目の照射時の障害を正しく表わすための条件を理論的に求めた．それによると前照射による障害が指数関数的に増巾される時に2回照射法が正しく障害を定義することが知られた．2回照射法による実験データは障害の増巾ではなく，指数関数又は線型の回復があることを示している．従って，通常の2回照射法で定義される障害は2度目の照射時の障害を表わしているとは考えられない．

経時的な死亡数分布や平均寿命を用いた障害の評価は，急性死の各モードに対応した障害の増巾と回復があることを示唆している．これらの障害の増巾と回復が指数関数で近似されると仮定すると，2回照射法によるデータの新しい解釈が生まれる．それによると2回照射法により定義される障害は2度目の照射から30日後の障害の状態の指標となる．従来の解釈によれば，LD_{50} (30) に関与するのは主として骨髄障害で，照射24時間後から回復が見られることになるが，実際の骨髄死は2週間後を中心に生じている．特に注意したいのは死亡率を指標とする限り，その障害はあくまで全身障害であり，又は決定器官の障害の全身障害への反映と解釈すべきであり，器官レベルの障害ではない．筆者等の解釈は，2回照射の30日後に前照射による障害が回復の状態にあるとするもので，死のモードとの関連から考えても矛盾がないように思われる．

I. Introduction

To estimate the whole body injury induced by radiation, $LD_{50}(30)$s[1)-9)] and mean survival times[10)-15)] have been used so far. The residual injury induced by a conditioning dose has been determined by the so-called paired-dose method as follows. Large groups of animals were exposed to an initial sublethal dose of radiation and at various time intervals thereafter they were divided into subgroups and given graded doses of radiation in order to determine the $LD_{50}(30)$. The extent to which the LD_{50} was lower than the value for the control group then gave a measure of the amount of the damage remaining from the first exposure. Most of data[1)-9)] by the paired-dose method have shown a simple recovery in the post-irradiation period. On the other hand the deaths associated with the $LD_{50}(30)$ are believed due primarily to hematopoietic damage[1)]. The bone marrow death occurs around two weeks after exposure though the paired-dose method shows a recovery in the period. A problem in the paired-dose method exists in the fact that the time of exposure to the test dose is not identical with the time at death. Therefore there will be a great ambiguity how the difference of $LD_{50}(30)$s adequately expresses the residual injury at the time of delivery of test dose. In this paper we will discuss the theoretical fundations of the paired-dose method and some interpretations on the difference of LD_{50}s will be given by an exponential model.

II. Theoretical fundations of the paired-dose method

The population of animals we treat has a fluctuation in radiosensitivity. The animal which dies at the median survival time will be chosen as a representative animal and we will consider the whole body injury of the above representative animal. $LD_{50}(\alpha)$ is defined as the dose which gives median survival time of α. Conventional value for α is 30 days in mammals. The following three assumptions were used in this paper.

1. In fractionated exposure the whole body injury of each exposure is additive one another at any time.

2. When the whole body injury of an animal accumulates to the lethal threshold, the animal will die.

3. The whole body injury is described in a form of separation of variables with dose and time.

A whole body injury induced by conditioning dose D_0 and test dose D^i has a following relation with that of control induced by single dose D^c when the representative animal dies at $t_1+\alpha$ after the conditioning dose.

$$I_w(D_0,\ t_1+\alpha)+I_w\ (D^i,\ \alpha)\ =I_w\ (D^c,\ \alpha)=\ I_L \tag{1}$$

where

D_0	:	Conditioning dose
D^i	:	$LD_{50}(\alpha)$ of irradiated group
D^c	:	$LD_{50}(\alpha)$ of control group
t_1	:	Time when test dose D^i is given
$I_w(D,\ t)$	:	Whole body injury of representative animal at time t when dose D is given at time zero
α	:	Median survival time
I_L	:	Lethal threshold.

A theoretical example of whole body injuries induced by the paired-dose method was given in Fig. 1. The broken line indicates an injury induced by conditioning dose and the dotted line indicates an injury by test dose in Fig. 1. The solid line which is the sum of broken and dotted lines indicates total injury. The broken-dotted line indicates an injury of single exposure. The conventional definition of residual injury is as follows,

$$I_w(D^0,\ t_1)=\ D^c-D^i \tag{2}$$

In general the above equation cannot be induced from the equation (1). We will try to find the condition on $I_w(D,\ t)$ with which one can induce the equation (2) from the equation (1). From the third assumption mentioned above, the equation (1) is rewritten as follows,

$$F(D_0)f(t_1+\alpha)=F(D^c)f(\alpha)-F(D^i)f(\alpha) \qquad (3)$$

If the functions $F(D)$ and $f(t)$ satisfy the following equations, one can reasonably obtain the equation (2) from the equation (1).

$$F(D)=D \qquad (4)$$

$$f(t_1+\alpha)=f(t_1)f(\alpha) \qquad (5)$$

From the equation (5), it follows that,

$$f(t)=a^{\lambda t}=e^{(\lambda \log a)t} \qquad (6)$$

a, λ: positive constants

The conclusion is that the difference of $LD_{50}(\alpha)$s between control and preirradiated group indicates the residual injury at the time of delivery of test dose if the whole body injury is expressed by $I_w(D, t)=De^{(\lambda \log a)t}$. In Fig. 2 the whole body injuries were illustrated. On the other hand, if $I_w(D, t)\neq De^{(\lambda \log a)t}$, the difference of $LD_{50}(\alpha)$s could not be considered as the residual injury. The conditions of (4) and (5) are sufficient conditions and not necessary conditions. However it is unlikely that any other simple functions of $F(D)$ and $f(t)$ may satisfy the equation (2).

Fig. 1. Whole body injury by paired doses

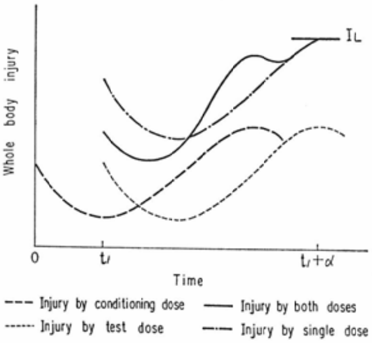
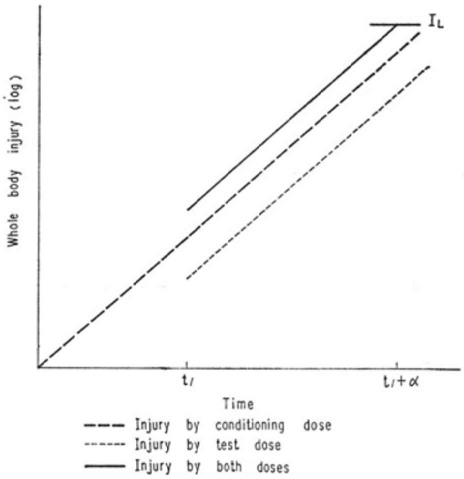


Fig. 2. Whole body injury of exponential amplification



III. Exponential model for recovery and amplification

As shown in the preceding section the paired-dose method gives the residual injury when the whole body injury is expressed by simple amplification of exponential type. We will discuss the informations given by the paired-dose method when the above conditions are not satisfied with the whole body injury. For the sake of simplicity it is assumed that the whole body injury is expressed by $I_w(D, t)=De^{\pm\lambda t}$, $\lambda>0$. Following three cases were considered.

A. Recovery followed by amplification

$$I_w(D, t)=De^{-\lambda t} \qquad \text{for } 0\leqq t\leqq t_0 \qquad (7)$$

$$I_w(D, t)=De^{-\lambda t_0}.\ e^{\lambda'(t-t_0)} \qquad \text{for } t_0\leqq t \qquad (8)$$

B. Amplification followed by recovery

$$I_w(D,\ t)=De^{\lambda t} \qquad \text{for } 0 \leqq t \leqq t_0 \tag{9}$$

$$I_w(D,\ t)=De^{\lambda t_0}.\ e^{-\lambda'(t-t_0)} \qquad \text{for } t_0 \leqq t \tag{10}$$

C. Recovery followed by amplification and recovery

$$I_w(D,\ t)=De^{-\lambda t} \qquad \text{for } 0 \leqq t \leqq t_0 \tag{11}$$

$$I_w(D,\ t)=De^{-\lambda t_0}.\ e^{\lambda'(t-t_0)} \qquad \text{for } t_0 \leqq t \leqq t_0+t'_0 \tag{12}$$

$$I_w(D,\ t)=De^{-\lambda t_0}.\ e^{\lambda' t'_0}.\ e^{-\lambda''(t-t_0-t'_0)} \qquad \text{for } t_0+t'_0 \leqq t \tag{13}$$

A. Recovery followed by amplification

Based on the equations (7)and (8) the whole body injuries were shown in Figs 3 and 4. The time t_1 when the test dose D^i is given is either $t_1 \leqq t_0$ or $t_1 > t_0$, but the difference $D^c - D^i$ becomes the same function on time t_1. Median survival time α cannot be in $0<\alpha<t_0$ since the control animal may not die in the recovery range. At $t_1+\alpha$ the following equation holds from the equation (1).

Fig. 3. Whole body injury of recovery and amplification

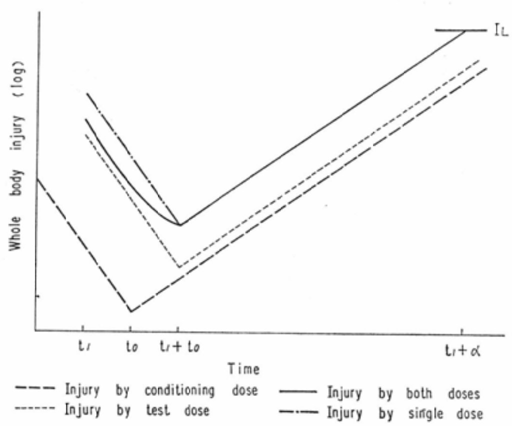
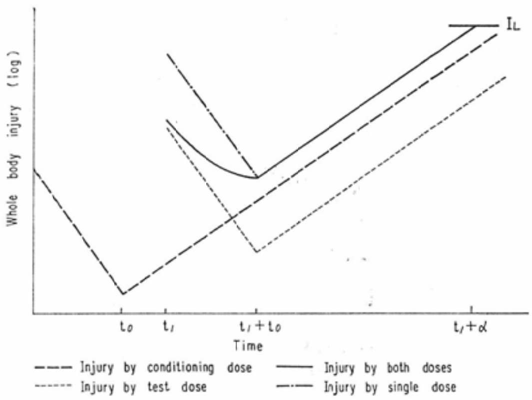


Fig. 4. Whole body injury of recovery and amplification



$$D_0e^{-\lambda t_0}.\ e^{\lambda'(t_1+\alpha-t_0)}+D^ie^{-\lambda t_0}.e^{\lambda'(t_1+\alpha-t_1-t_0)}$$
$$=D^ce^{-\lambda t_0}.\ e^{\lambda'(t_1+\alpha-t_1-t_0)}=I_L \tag{14}$$

Then the difference of $LD_{50}(\alpha)$s between control and irradiated animals is expressed as follows,

$$D^c-D^i=D_0e^{\lambda' t_1} \tag{15}$$

Fig. 5. Whole body injury of amplification and recovery

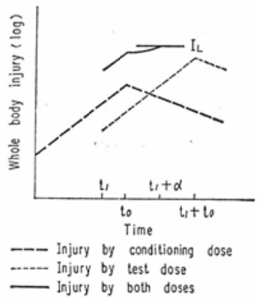
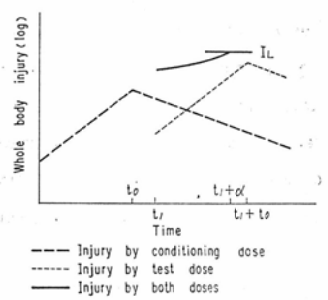


Fig. 6. Whole body injury of amplification and recovery



In this case the difference of $LD_{50}(\alpha)$s increases exponentially with time t_1 and no information is given on λ.

B. Amplification followed by recovery

In case of amplification followed by recovery, there are three types of possibility for choice of t_1 and α. Only meaningful case is $t_0 < \alpha + t_1 < t_0 + t_1$. The time t_1 is either $t_1 \leqq t_0$ or $t_1 > t_0$ as shown in Figs. 5 and 6. In both cases the difference $D^c - D^i$ becomes the same function on time t_1. At $t_1+\alpha$, the following equation holds from the equation (1).

$$D_0 e^{\lambda t_0} .\ e^{-\lambda'(t_1+\alpha-t_0)} + D^i e^{\lambda\alpha} = D^c e^{\lambda\alpha} = I_L \tag{16}$$

Then the difference of $LD_{50}(\alpha)$s is expressed as follows,

$$D^c - D^i = D_0 e^{(\lambda+\lambda')(t_0-\alpha)} .\ e^{-\lambda' t_1} \tag{17}$$

Accordingly the difference of $LD_{50}(\alpha)$s decreases exponentially with time t_1 and with recovery constant λ'. In particular,

$$D^c - D^i = D_0 \tag{18}$$

$$\text{if } (\lambda+\lambda')\ (t_0-\alpha) = \lambda' t_1 \tag{19}$$

Though the equation (18) shows no recovery in the sense of the conventional paired-dose method, the actual recovery with λ' exists.

C. Recovery followed by amplification and recovery

Based on the equations (11), (12) and (13), the whole body injuries were showen in Figs. 7, 8 and 9.

Fig. 7. Whole body injury of recovery, amplification and recovery

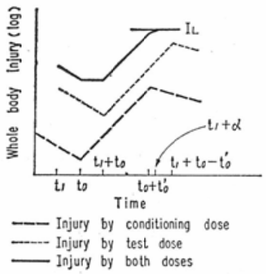


Fig. 8. Whole body injury of recovery. amplification and recovery

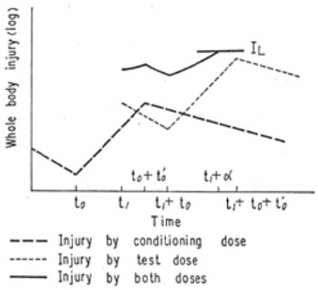
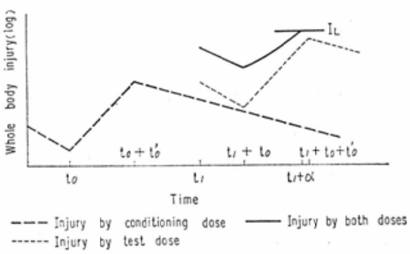


Fig. 9. Whole body injury of recovery. amplification and recovery



Whenever the test dose D^i is given, the difference $D^c - D^i$ becomes the same function on time t_1. At $t_1 + \alpha$, the following equation holds from the equation (1).

$$\begin{aligned} &D_0 e^{-\lambda t_0}.\ e^{\lambda' t_0'}.\ e^{-\lambda''(t_1+\alpha-t_0-t_0')} + D^i e^{-\lambda t_0}.\ e^{\lambda'(t_1+\alpha-t_1-t_0)} \\ &= D^c e^{-\lambda t_0}.\ e^{\lambda'(t_1+\alpha-t_1-t_0)} = I_L \end{aligned} \tag{20}$$

Then the difference of $LD_{50}(\alpha)$s is expressed as follows,

$$D^c - D^i = D_0 e^{\lambda'(t_0+t_0'-\alpha)}.\ e^{-\lambda''(\alpha-t_0-t'_0)}.\ e^{-\lambda'' t_1} \tag{21}$$

Accordingly the difference of $LD_{50}(\alpha)$s decreases exponentially with t_1 and recovery constant λ''. The first recovery constant λ does not appear in the equation (21). No recovery in appearance will also be seen if the following equation holds.

$$\lambda'(t_0+t_0'-\alpha) - \lambda''(\alpha-t_0-t_0') = \lambda'' t_1 \tag{22}$$

In all the cases of A, B and C the difference of $LD_{50}(\alpha)$s was expressed as follows,

$$D^c - D^i = aD_0 e^{bt_1} \qquad a,\ b\text{: constants} \qquad (23)$$

where b is determined by the fact that I_w (D_0, $t_1+\alpha$) is either in the stage of recovery or in the stage of amplification. In general the dependence of D^c-D^i on t_1 is not determined by the state of the whole body injury when the test dose D^i is given.

IV. Discussions

The conventional paired-dose method gives a reasonable residual injury when the whole body injury is expressed by simple increasing function of exponential type. Most of data on mammal have shown exponential or linear recovery from conditioning dose by paired-dose method[1)-9)]. As was shown in the preceding section, if the injury recovers exponentially, the paired-dose method does not give a reasonable residual injury at the time of the test exposure. Experimental evidences that the difference of LD_{50} (30)s between control and irradiated groups decreases exponentially with t_1 may be interpreted with the equation (17) or (21). Namely, the injury induced by the conditioning dose is recovering around 30 days instead of recovery at t_1. The new interpretation may also be supported with the impulse lethality function by Sacher[15)] and the bimodal daily death distributions[16)-19)].

In addition, if the whole body injury has an irreparable part, it is easy to show that the residual injury at the time of delivery of test dose cannot be estimated by the paired-dose method. An easy way to avoid the difficulty associated with the paired-dose method is to use so small α that the time of exposure to the test dose may almost coincide with the time of death. In such case one may be restricted in a mode of instantaneous death. As far as one accepts the assumptions in the section II, it is desirable that the data by the paired-dose method so far published shall be reconsidered and that the observation period α, as well as the time of delivery of test dose, shall be made variable in future experiments by the paired-dose method. With such experiments, it will be possible to obtain much more reasonable interpretations for the informations given by the paired-dose method.

A model given by the authors for the whole body injury has been previously published[20)] and the model have shown how to calculate the mean whole body injury in survivors from age specific motrality. The mean whole body injury in survivors is slightly different from the whole body injury of the representative animal mentioned in this text. The point of age specific mortality of fifty per cent is more critical than that of accumulated mortality of fifty per cent in the model. If we define $ASM_{50}(\alpha)$ as the dose which gives the age specific mortality of fifty per cent at time α, the analogous discussions as above can be made with $ASM_{50}(\alpha)$ instead of $LD_{50}(\alpha)$.

Summary

A residual injury induced by the conditioning dose is usually estimated by the so-called paired-dose method. Theoretical fundation of the paired-dose method and the informations given by the method are discussed. The paired-dose method gives the residual injury at the time of delivery of test exposure when the whole body injury increases exponentially. If the whole body injury has recovery and amplification of both exponential type, the difference of $LD_{50}(\alpha)$s between control and conditioned groups gives an information on the whole body injury at the time α instead of the time of delivery of test dose.

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