# THEORETICAL APPROACH TO LIFE SPAN SHORTENING INDUCED BY RADIATION (3)
# — A MODEL FOR RADIATION INJURY —

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## 放射線と寿命についての考察（3）
## ── 放射線障害の模型化 ──

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国際放射線防護委員会の現在の関心は混合被曝の際に於ける許容量を決定することである．一方，筆者等は寿命短縮の線量，効果関係の解析を進めてきたが，混合被曝による寿命短縮の問題について障害の模型化を試みた．その際全身障害を器官のレベルで理解することに主眼を置き，可成り複雑な障害機構を含みうる模型化を行うことができた．各器官の複雑な生理学的相関を考慮するために，その数式化に行列とベクトルを用い，それによりフィード・バック機構も容易に含めることができた．筆者等の模型を現在の実験データと比較し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．

### 1. Introduction

Life shortening by radiation has been studied by many authors as a late effect, and this type of low dose effect is one of the important criteria for maximum permissible level of ionizing radiations. Recently ICRP[1–3] (International Commission on Radiological Protection) has been interested in so called "mixed radiation problems". The analyses given so far on the life shortening were done by using mostly injury function and no one dealt with the radiation injury in organ level. In this paper we have 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.

### 2. Assumptions and Formulation

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 we have used the following assumptions.

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

ii) 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 we may mean 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,

$$I_i = I_{ii} + I_{ai} \qquad (1)$$

where $I_{ii}$ is the intrinsic injury of the i-th organ and $I_{ai}$ is the interaction injury of the organ. If we deal with n organs, $I_i$ is understood as i-th component of n-dimentional "injury vector" $\vec{I_0}$ for the sake of simplicity. If the i-th organ receives no radiation, $I_{ii}$ vanishes but $I_i$ is not necessarilly zero owing to the second term of $I_{ai}$.

The next step of the formulation is how to make $I_{ai}$ from $I_{11}$, $I_{22}$,......$I_{nn}$, keeping the self-consistency in the model. In this paper we deal with the only quasi-stationary state[4] of the body in view point of physiological state. On the other hand, non-stationary state may require a dependence of $I_{ai}$ on the $I_i$ and in such case it is almost impossible to build a model. Nevertheless we must follow the time course of the injury and then the only way to solve this question is to regard the time course of the injury as step-wise changes between the quasi-stationary states.

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 the 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,

$$I_i = I_{ii} + \sum_{j=1}^{n} A_{ij} I_{jj} \qquad (2)$$

$$A_{ij} = 0, \text{ if } i = j \qquad (3)$$

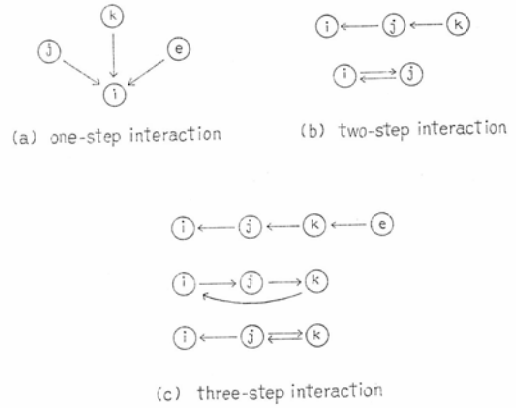


Fig. 1. Types of interaction between organs

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 hormonal controls may be included in the two-step interaction as shown in Fig. 1, (b). Considering both types of interactions, $I_i$ has following form,

$$I_i = I_{ii} + \sum_{j=1}^{n} A_{ij} I_{jj} + \sum_{j.k}^{n} B_{ij} A_{jk} I_{kk} \tag{4}$$

$$B_{ij} = 0, \text{ if } i = j \tag{5}$$

The reason why we use the $B_{ij}$ pifferent 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 way, including the higher order interaction, $I_i$ takes the following from,

$$I_i = I_{ii} = + \sum_{j=1}^{n} A_{ij} I_{jj} + \sum_{j,k}^{n} B_{ij} A_{jk} I_{kk} + \sum_{j,k,l}^{n} B_{ij} B_{jk} A_{kl} I_{ll} + \cdots \tag{6}$$

Each of the two types of interaction coefficient forms the "interaction matrix" as follows,

$$\mathbf{A} = \begin{pmatrix} 0 & A_{1,2} \cdots A_{1,n} \\ A_{2,1} & 0 & \vdots \\ \vdots & \ddots & \vdots \\ A_{n,1} & \cdots\cdots & 0 \end{pmatrix} \tag{7}$$

$$\mathbf{B} = \begin{pmatrix} 0 & B_{1,2} \cdots B_{1,n} \\ B_{2,1} & 0 & \vdots \\ \vdots & \ddots & \vdots \\ B_{n,1} & \cdots\cdots & 0 \end{pmatrix} \tag{8}$$

Using the matrices, equation (6) can be rewritten as follows,

$$\vec{I} = \vec{I_0} + \mathbf{A}\,\vec{I_0} + \mathbf{BA}\,\vec{I_0} + \mathbf{BBA}\,\vec{I_0} + \cdots \tag{9}$$

While each component of the vector in equation (9) shows the total injury of each organ, injury of whole body must be made by taking the weighted summation of each $I_i$.

$$I_w = \sum_{i=1}^{n} w_i I_i \tag{10}$$

or

$$I = \vec{W} \cdot \vec{I} \tag{11}$$

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[5]. Using the equations (9) and (11), we have the final equation as follows,

$$I_w = \vec{W} \cdot \vec{I} = \vec{W}\,(\vec{I_0} + \mathbf{A}\vec{I_0} + \mathbf{BA}\vec{I_0} + \mathbf{BBA}\vec{I_0} + \cdots \tag{12}$$

or

$$= \sum_{i=1}^{n} w_i\,(I_{ii} + \sum_{j=1}^{n} A_{ij} I_{jj} + \sum_{j,k}^{n} B_{ij} A_{jk} I_{kk} + \sum_{j.k,l}^{n} B_{ij} B_{jk} A_{kl} I_{ll} + \cdots \tag{13}$$

In case of the life shortening, lethal threshold injury[6] would be understood as a limit for $I_w$. Then when $I_w$ exceeds the lethal threshold injury, the animal dies and the each term $w_i$ $I_i$ in equation (10) may give some information on the mode of death.[7,8]

### 3. Experimental data pertaining to the model

As mentioned before, available data on radiobiology and radiology do not permit us to estimate the parameter A,B or $\vec{I_0}$ but we will show what types of phenomena may be dealt with this model.

Blair[9] has given attention to a relation between $LD_{50}$ (30)s from whole body and partial body irradiations[10-12]. If a whole body is divided into n sections, the $LD_{50}$ (30)s which are obtained by exposure of each section have following relation with the $LD_{50}$ (30) of whole body.

$$\frac{1}{R_w}=\frac{1}{R_1}+\frac{1}{R_2}+\cdots+\frac{1}{R_n} \qquad (14)$$

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

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

This equation was compatible with the experiment with n=2. To apply our model for n=2, we assumed $I_{ii}$ as follows,

$$I_{ii}=c_iD_i+d_iD_i^2 \qquad (15)$$

$D_i$: dose delivered to i-th part of the body

$c_i$, $d_j$: constants

When only part 1 is exposed with dose of $R_1$, using equation (13) and one-step interaction,

$$I_W=(w_1+w_2A_{2,1})\ (c_1R_1+d_1R_1^2) \qquad (16)$$

When only part 2 is exposed with dose of $R_2$,

$$I_W=(w_1A_{1,2}+w_2)\ (c_2R_2+d_2R_2^2) \qquad (17)$$

When whole body is exposed with dose of Rw,

$$I_W=(w_1+w_2\ A_{2,1})\ (c_1R_W+d_1R^2{}_W)+(w_1A_{1,2}+w_2)\ (c_2R_W+d_2R^2{}_W) \qquad (18)$$

Using above three equations,

$$\frac{R_W+\alpha_1R^2{}_W}{R_1+\alpha_1R_1^2}+\frac{R_W+\alpha_2R^2{}_W}{R_2\ +\alpha_2R_2^2}=1 \qquad (19)$$

$\alpha_i \equiv d_j/c_i$

If $d_i=0$, equation (19) reduces to Blair's equation (14).

Then the equation (14) does not show that there is no interaction between part 1 and part 2.

Effects of radiation on many organs were comprehensively studied to determine the RBE and for other purposes[13-18]. Data on weight loss of spleen, thymus, and testis show that $I_i$ may have logarithmic dependence on dose if one assumes the measure of the injury as the weight loss (per cent) of its organ. An example for the weight loss (per cent) of spleen at five days after exposure is given below.

$I_i=-137.46+73.86\log D$

$I_i$ : weight loss (per cent) of spleen

D: rads of $Co^{60}$

Kohn[19] has studied the abscopal (indirect) effect on testicular weight loss by whole body and partial body irradiations. The testicular weight loss by whole body irradiation was almost the same as the weight loss by irradiation of testes with the same dose. In this case $I_i$ may come mostly from $I_{ii}$ and then $A_{ji}$ or $B_{ij}$ would be small. Many other data [7,20,21] obtained by partial body irradiation gave information wether $A_{ij}=0$ or not. Hormonal controls such as in neuro-endocrine system[22] propose much more definite ideas on A and B but the difficulty is left in the definition of $I_{ii}$ which will be discussed later.

Some informations on $\vec{W}$ are obtained in the proposed modes of acute lethality[7,8]. As for $I_w$ of the life shortening, so many formula[23–37] were proposed but none of them went into the organ level. In this field of study, much interest was placed on the kinetics of recovery as a whole body. An example of $I_w$ given by Blair[6] was as follows,

$$Iw=\frac{(A-\alpha)}{\beta}\gamma\ (1-e^{-\beta t})+\alpha\gamma t \qquad (20)$$

$\alpha$: constant for irreparable injury
$\beta$: recovery constant
$\gamma$: dose rate
A: constant for sensitivity

Difficulties lying in the interpretation of $I_w$ mentioned above by organ level surely come from the extraordinary complexity both in the damage of organ and in the interaction of organs.

## 4. Discussions

In this kind of theoretical approach to radiation injury, one should go into the detail of complex responses of the organs to ionizing radiation. The typical example of this sort of problems is seen in the responses of anterior pituitary to a stress[22]. If an ionizing radiation may act as a stress, secretion of ACTH increases and secretion of gonadotropic hormone, prolactin and growth hormone decreases. It is hardly possible to express these complicated responses of pituitary with a quantity $I_{ii}$. Of course we will able to give $A_{ji}$ to each secretion of hormones but the product $A_{ij}\ I_{ij}$ would not correspond to the biological reaction unless $I_{jj}$ is properly chosen in the sense mentioned above. The second difficulty rises in the assumption for the common measure of injury of many organs. If we give an attention to a particular function, the common measure of the injury may be properly determined.

In this paper, almost nothing was mentioned on the dependence of $I_w$, $\vec{I}$ and $\vec{I_0}$ upon dose and time. Research for these dependencies is under way to analyse the data on recovery[38,39] and "wasted radiation"[39].

To understand a whole body injury by radiation on the level of organs, one should give careful considerations on the many types of interactions between organs. The model for radiation injury including the interactions has necessarily the vector-matrix form.

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