Theory of Radiation Effect on Cell Populations in Intestinal Epithelium

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ABSTRACT

Some simple mathematical models were developed to analyze the kinetics of the cell populations in the intestinal epithelium after an exposure to ionizing radiation. For the proliferative cells in crypt a logistic proliferation was assumed and for the functional cells in villus the compartment was assumed to be a first in-first out type. A feedback mechanism is introduced between the two compartments. Mechanisms of the effects of radiation on the system were considered by cell deaths, including delayed deaths, and by mitotic delay. The calculated results showed reasonable amount of over-shoot in the cell numbers in the recovery period and were in general consistent with the experiment.

INTRODUCTION

As a simple cell renewal system, the intestinal epithelium has been described...
in many papers\textsuperscript{1-6}. The system has a high radiosensitivity and a high potentiality for repair. Therefore the intestinal epithelium is one of the most useful system for quantitative study in cell population kinetics. The effects of radiation on self-renewing cell populations were mathematically described by Sacher and Trucco in general form\textsuperscript{7}. The authors have tried to apply their model to the intestinal epithelium of mice with some modifications. The mathematical work reported in this paper is a part of a project where the effects of radiation delivered partially to abdominal region are being studied on the intestinal epithelium of mice. It will be shown here that the last model in the text has satisfactory properties compared with the experimental results.

**MODELS WITHOUT FEEDBACK MECHANISM**

The two-compartment model given by Sacher and Trucco\textsuperscript{7} describes a self-renewing cellular system of the proliferative (mitotic) and the functional (postmitotic) cells. In case of intestinal epithelium, cells in crypt are proliferative and cells in villus are functional. Their model is as follows,

\begin{align*}
\frac{dN_0(t)}{dt} &= P_0N_0(t) \left\{ A - N_0(t) \right\} \\
\frac{dN_1(t)}{dt} &= k \left\{ A_1N_0(t) - AN_1(t) \right\}
\end{align*}

where

\begin{align*}
N_0(t) &\text{: number of proliferative cells} \\
N_1(t) &\text{: number of functional cells} \\
P_0, k, A, A_1 &\text{: constants.}
\end{align*}

The compartment for villus is reasonably assumed to be a “first in-first out” type from the tracer experiment\textsuperscript{2,4-5}. By “first in-first out” the authors mean that every cell stays a definite time in villus or that cells entered earlier leave the villus earlier. The transit time (or life span) of the cells in villus may be 2 to 3 days in conventional mice\textsuperscript{4}. Accordingly we have the following model in which the term for a random loss is explicitly added in the proliferative compartment.

**Model I:**

\begin{align*}
\frac{dN_0(t)}{dt} &= P_0N_0(t) \left\{ A - N_0(t) \right\} - P_1N_0(t) \\
\frac{dN_1(t)}{dt} &= P_1N_0(t) - P_1N_0(t - b)
\end{align*}

where

\begin{align*}
P_1, b &\text{: constants.}
\end{align*}

The effect of single exposure to the system will be given as initial conditions as follows,

\begin{align*}
N_0(0) &= N_0 \left\{ 1 - (1 - e^{-\alpha D})^m \right\}
\end{align*}
where $\bar{N}_0$ and $\bar{N}_1$ are the stationary state values of $N_0(t)$ and $N_1(t)$, respectively.

The initial condition (5) is a typical multi-target model. There is no reason to choose a multi-target model instead of a multi-hit model. However, it is hard to discriminate both models with experiment and then multi-target model was assumed for the sake of mathematical simplicity.

In order to take reproductive deaths or delayed deaths into account, as a trial function an exponential distribution is assumed for delayed deaths in the second model.

Model II:

\begin{align*}
\frac{dN_0(t)}{dt} &= P_0 N_0(t) \left\{ A - N_0(t) \right\} - a N_0(1 - e^{-aD})^m e^{-a t} - P_1 N_0(t) \\
\frac{dN_1(t)}{dt} &= -P_1 N_0(t) - P_1 N_0(t - b)
\end{align*}

where

- $\alpha$: constant.

The second term in the right side of equation (8) corresponds to delayed deaths and it shows that the total number of dying cells after an exposure is again given by multi-target model as follows.

$$\int_0^\infty \alpha \bar{N}_0(1 - e^{-aD})^m e^{-a t} dt = \bar{N}_0(1 - e^{-aD})^m$$

The initial conditions for equations (8) and (9) are

$$N_0(0) = \bar{N}_0$$

$$N_1(t) = \bar{N}_1 \quad \text{for} \quad t \leq 0$$

The third model has a correction factor for the mitotic delay due to radiation in the proliferative term as follows.

Model III:

\begin{align*}
\frac{dN_0(t)}{dt} &= P_0 \left[ 1 - e^{-c} \right] N_0(t) \left\{ A - N_0(t) \right\} - a \bar{N}_0(1 - e^{-aD})^m e^{-a t} - P_1 N_0(t) \\
\frac{dN_1(t)}{dt} &= P_1 N_0(t) - P_1 N_0(t - b)
\end{align*}

where

- $c$: constant.
The initial conditions for equations (10) and (11) are the same as those for Model II. For the numerical solutions, the parameter values are tentatively given as follows.

\[ P_0 = 0.01 \text{ day}^{-1}, \quad a = 0.01 \text{ R}^{-1} \]
\[ N_0 = 100, \quad D = 1000 \text{ R} \]
\[ N_1 = 300, \quad m = 10 \]
\[ C = 4.6 \text{ day}^{-1}, \quad P_1 = 1.0 \text{ day}^{-1} \quad (12) \]
\[ A = 200, \quad b = 3 \text{ days} \]
\[ \alpha = 2.3 \text{ day}^{-1}. \]

Our preliminary experiments show that the exposure of 1000 R to the abdominal region of mice is non-lethal in 30-day observation. The numerical calculations were done with computer, Tosbac-3400, in National Institute of Radiological Sciences. The calculated results were shown in Fig. 1. In the top of Fig. 1, the approximately linear decrease of cell numbers in villus is a characteristic response of “first in-first out” compartment in the higher dose where the differentiation from the proliferative compartment is temporarily negligible. The recovery in villus follows that in crypt with some delay. A mechanism of delayed death produces less depression in cell numbers than in Model I (See the middle in Fig. 1). In the bottom of Fig. 1 one will see that an addition of factor for mitotic delay severely decreases the cell numbers in both compartments. None of the above models shows an over-shoot in cell numbers.

**MODEL WITH FEEDBACK MECHANISM**

An over-shoot phenomenon in cell numbers and in weight of intestine is commonly observed after single exposure to sublethal dose. In order to reproduce the over-shoot, we will introduce a feedback mechanism. The feedback mechanism will be such that a decrease in cell numbers in villus stimulates the proliferations in crypt and that an increase in cell numbers in villus suppresses the proliferations in crypt. A model with the following correction factor to the parameter \( A \) has a feature of the feedback mechanism mentioned above.

**Model IV :**

\[
\frac{dN_0(t)}{dt} = P_0(1 - e^{-\alpha t})N_0(t) \left\{ A e^{-\frac{N_1^2(t)}{N_1^2}} - N_0(t) \right\} - \alpha N_0(1 - e^{-\alpha D}) e^{-\alpha t} - P_1 N_0(t) \quad (13)
\]
\[
\frac{dN_1(t)}{dt} = P_1 N_0(t) - P_1 N_0(t - b) \quad (14)
\]

where

\( f \): constant.
The initial conditions for equations (13) and (14) are the same as those for Model II. The solutions of (13) and (14) with \( f = 0.5, \ A = 329.7 \) and with the parameters in (12) were shown in Fig. 2. The over-shoot in cell numbers in crypt seems to be reasonable compared with the experiment on rat\(^8\). If the changes in the intestinal weight mostly reflect the changes in cell numbers in villus, the general trend of cell numbers in villus may be consistent with the experiment on mice\(^1\). In Fig. 3, \( N_0(t) \) is plotted against \( N_1(t) \) where initial values of \( N_0(0) \) and \( N_1(0) \) are normalized to 100. The curve in Fig. 3 shows how the system changes with time after an exposure. An arrow on the curve indicates the direction of the changes. The system initially stands at the point of \( N_0(0) = 100 \) and \( N_1(0) = 100 \). After an exposure \( N_0(t) \) decreases rapidly and then \( N_1(t) \) begins to decrease. Any value of \( N_0(t) \) or \( N_1(t) \) larger than 100 means an over-shoot. As the time lapses, the curve converges to the point of \( N_0(t) = 100 \) and \( N_1(t) = 100 \) which shows a complete recovery of the system.

**DISCUSSION**

The Model IV presented in the previous section still has many ambiguities, though it has some satisfactory properties. In particular almost no information on the feedback function and on the delayed death distribution is available at present. At the exposure of 1000 R, the extrapolation numbers, 1, 5 and 10 produce no significant changes in the cell population kinetics by the Model IV. In the second compartment for villus, changes in life span of the cells, \( b \), shift the minimum or the maximum of \( N_1(t) \) in Fig. 3 back and forth. In all the calculations with Model II, III and IV, \( N_0(0) \) is assumed to be 100 cells. Since the equation (13) is non-linear with respect to \( N_0(t) \), \( N_0(0) \) values other than 100 require some modifications on the parameters, \( P_0 \) and \( A \) in order to get the identical solutions. By changing the dose in the Model IV, one will see that a larger decrease in cell number produces a larger over-shoot in recovery period.

The over-shoot phenomena can also be seen in splenic weight\(^8\) and in some
cells of hematopoietic organ after irradiation\textsuperscript{9} or after injection of anti-thrombocyte serum\textsuperscript{10}. The model with the feedback mechanism may possess an essential feature in the dynamics of the cell renewal system.

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