MODEL FOR THE ^{224}Ra-PROTRACTION EFFECT

Peter G. Groer and John H. Marshall

It was pointed out by Spiess and Mays[1] that for a fixed total dose the observed incidence of bone sarcomas in German children and adults exposed to ^{224}Ra was higher the lower the dose rate. Two mathematical models that exhibit a protraction effect are presented in this report. Both models replace cells killed by α radiation with normal endosteal cells. This regeneration of cells increases the total number of cells at risk and leads thus to the production of more tumor cells during the longer time periods corresponding to the lower dose rates.

The model for the induction of bone sarcomas by ^{226}Ra presented in the previous paper should also describe the induction of sarcomas by ^{224}Ra and should, therefore, explain the "protraction effect."[1] We felt that a replacement of killed endosteal cells might provide an explanation for this effect. We described the replacement process in two different ways:

1. Delayed Replacement

Any endosteal cell killed by radiation from internally deposited ^{224}Ra or ^{226}Ra will not be replaced instantaneously. On the average, a time τ will elapse after which the killed cell will be replaced. If $M_0(t)$ denotes the number of normal endosteal cells at risk, the following differential equation will describe this process:

$$\dot{M}_0(t) = \kappa F M_0(t-\tau) - \kappa F M_0(t) , \qquad (1)$$

where κ is the probability per rad that a cell will be killed and F is the dose rate function (rads/unit time). Equations of the form (1) are differential equations with a retarded argument.[2–4]

In radiation biology an equation of this type was considered by Sievert[5] who also pointed out the great variety of solutions for such equations.[5] A solution of (1) can be found by the "method of continuation"[4] if an initial function is given over a certain time interval. This "initial function" replaces the initial value used for ordinary differential equations. Assuming for simplicity a constant dose rate F, one obtains a solution of (1) in the following manner. In the interval $(0,\tau)$ the solution of (1) is

$$M_0(t) = M_0(0)\ \exp(-\kappa F t)\ . \qquad (2)$$

No replacement takes place. For the next interval $(\tau, 2\tau)$ the term $\kappa F M_0(t-\tau)$ can be calculated from Eq. (2) and so on for all subsequent intervals. Proceeding in this fashion one obtains

$$\dot{M}_0(t) = \kappa F(M_0(0)\, e^{-\kappa F(t-\tau)} - M_0(t)\ )$$

$$(\tau \le t \le 2\tau)$$

$$M_0(t) = M_0(0)\, e^{-\kappa F t}\ \{\, 1 + \kappa F(t-\tau)\, e^{\kappa F t}\} \ ,$$

and by induction the general expression

$$M_0(t) = M_0(0)\ \exp(-\kappa F t)\{\, 1 + \kappa F(t-\tau)\ \exp(\kappa F t)$$

$$+ (\kappa F)^2\ \frac{(t-2\tau)^2}{2!}\ \exp(2\kappa F\tau) + \ldots \qquad (3)$$

$$+ (\kappa F)^{n-1}\ \frac{(t-(n-1)\tau)^{n-1}}{(n-1)!}\ \exp(\ (n-1)\kappa F\tau)\ \}$$

for $(n-1)\tau \le t \le n\tau$.

The asymptotic form of Eq. (3) for $t \to \infty$ has so far not been found. The expression (3) for $M_0(t)$, if used to express $M_2(t)$ (see Eq. (10)–(13) of the previous paper for a definition of the M_i's), shows a protraction effect since more M_2 cells will be present the longer the radiation acts (the smaller F), because more and more terms of the series in Eq. (3) will be used the longer the irradiation period. To illustrate this fact, consider the following example. The total dose D shall be delivered over periods of τ and 2τ. In the first case we find for the total number of M_2 cells produced by D,

$$M_2(\tau) = M_0(0)\ \sigma^2 D^2\ \exp(-\kappa D)/2\ .$$

In the second case we find for the total number of M_2 cells generated by D over a period of 2τ:

$$M_2(2\tau) = M_0(0)\ \sigma^2 D^2\ \exp(-\kappa D)/2 + M_0(0)\ \sigma^2\ \kappa D^3\ \exp(\kappa D/2)/3\ .$$

Since the second term on the right is positive, more M_2's have been produced

by D over the longer time period.

2. Restoring Replacement

In this model the delay time until a killed cell is replaced is neglected. Instead an average rate of replacement, ρ, is introduced and the replacement rate depends on the deviation from the equilibrium value. The differential equation for $M_0(t)$ describing this form of replacement is

$$\dot{M}_0(t) = \rho\left(M_0(0) - \sum_{i=0}^{2} M_i(t)\right) - \kappa F M_0 - \sigma F M_0 \,. \qquad (4)$$

All M_i's except M_0 can be neglected because of their smallness. This yields

$$\dot{M}_0(t) = \rho\left(M_0(0) - M_0(t)\right) - \kappa F M_0 - \sigma F M_0 \,. \qquad (4a)$$

Integrating Eq. (4a) for F = const gives the following expression for $M_0(t)$:

$$M_0(t) = M_0(0)\exp\left(-(\rho + \kappa F + \sigma F)t\right)$$

$$+ M_0(0)\rho\left\{\left(1 - \exp\left(-(\rho + \kappa F + \sigma F)t\right)\right)/(\rho + \kappa F + \sigma F)\right\} . \qquad (5)$$

Using expression (5), an expression for $M_2(t)$ can be derived, solving the differential equations (10)–(13) given in the previous paper. The resulting $M_2(t)$ is quite complex and will not be given here in its explicit form since the derivation is straightforward.

A computer evaluation of $M_2(t)$ using different values of F (dose rate) showed a protraction effect (see Table 1).

We will attempt to fit the observed protraction effect[1] using either model for replacement of cells in conjunction with the other differential equations given earlier. It will probably not be possible to differentiate between the two models using the existing data for ^{224}Ra in man.

TABLE 1. Protracted Production of Tumor Cells[a]

F, rad/day	T, days	$M_2(t)/M_0(0)$
0.1	10^4	9.0×10^{-5}
1	10^3	5.0×10^{-5}
10	10^2	9.1×10^{-6}

[a] $\rho = 0.01\ \text{day}^{-1}$; $\sigma = 10^{-8}\ \text{rad}^{-1}$; $\lambda = 3 \times 10^{-5}\ \text{day}^{-1}$; $\kappa = 0.01\ \text{rad}^{-1}$.

References

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