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The postulates of the LPL (lethal, potentially lethal) model (Curtis, 1983) lead to the conclusion that for low dose rates there will be an interplay between lesion formation and lesion repair, some lesions repairing (or misrepairing) before others are formed. This will be the case when the irradiation time is the same order of magnitude as the repair time. To include this situation, the model must be modified accordingly. This paper presents a more general formulation of the model utilizing differential equations governing lesion formation and elimination that takes low dose rate into account and so can be used for any dose rate.

The present treatment will be valid only for cells not progressing through the cell cycle during the times of irradiation and repair; that is, we assume no fixation points or variation of repair constants with time through the cell cycle.

The differential equations will include a rate of lesion creation (assumed constant). The initial conditions will be that the number of lesions is zero at the start of the irradiation period.

As in the case of the high dose rate treatment, we assume the formation in the radiation field of two types of lesions: one type, n_{PL}, repairing with mean repair constant ε_{PL} (per unit time) or interacting with another lesion of the same type with constant ε_{2PL} to produce a lethal lesion, and the other type of lesion, n_L, irrepairable and lethal. We assume a constant average rate of production per cell nucleus of each type of lesion, K_{PL} for the repairable lesions and K_L for the irrepairable lesions. Since $K_{PL} \cdot t$ and $K_L \cdot t$ are the average total number of repairable and irrepairable lesions created in a time, t, per cell nucleus, and we assume a constant dose rate, $\dot{D}$, we can immediately write the expressions for the rates of formation of the two types of lesions:

$$K_{PL} = \eta_{PL} \dot{D} \text{ and } K_L = \eta_L \dot{D} \text{ where}$$

η_{PL} and η_L are the average rates of formation per unit of absorbed dose per cell nucleus of the repairable and irrepairable lesions, respectively.

The differential equations describing the rates of change with time of the average number of the two types of lesions per cell nucleus, $n_{PL}(t)$ and $n_L(t)$, can be written:

$$\frac{dn_{PL}(t)}{dt} = K_{PL} - \epsilon_{PL} n_{PL}(t) - \epsilon_{2PL} n_{PL}^2(t) \quad (1)$$

$$\frac{dn_L(t)}{dt} = K_L + \epsilon_{2PL} n_{PL}^2(t) \quad (2)$$

We will solve these equations for $n_{PL}(t)$ and $n_L(t)$, with initial conditions $n_{PL}(0) = n_L(0) = 0$, in order to obtain the average number of each kind of lesion per cell at the end of the irradiation time. Then we can use the equations obtained previously (Curtis, 1983) to apply to the final repair time after the irradiation is complete. In those equations, we need only to replace $\eta_L D$ by $n_L(t)$ and $\eta_{PL} D$ by $n_{PL}(t)$ where each function is evaluated at the end of the irradiation time t.

Equation (1) is seen to be of the general Ricotti type, but can be directly integrated. We rewrite equation (1) and integrate:

$$\int_{0}^{n_{PL}} \frac{dn'_{PL}}{(\varepsilon_{2PL}\, n'^{2}_{PL} + \varepsilon_{PL}\, n'_{PL} - K_{PL})} = - \int_{0}^{t} dt' = -t \tag{3}$$

If we let $\varepsilon_o = \left(4\varepsilon_{2PL}\, K_{PL} + \varepsilon^{2}_{PL}\right)^{1/2}$, (4)

we can write the integral immediately from the tables:

$$\frac{1}{\varepsilon_o}\left[\log \frac{2\varepsilon_{2PL}\, n_{PL} + \varepsilon_{PL} - \varepsilon_o}{2\varepsilon_{2PL}\, n_{PL} + \varepsilon_{PL} + \varepsilon_o} - \log \frac{\varepsilon_{PL} - \varepsilon_o}{\varepsilon_{PL} + \varepsilon_o}\right] = -t \tag{5}$$

Simplifying, remembering the definition of ε_o from equation (4), exponentiating each side and solving for n_{PL}, we obtain

$$n_{PL}(t) = \frac{2K_{PL}\left(1 - e^{-\varepsilon_o t}\right)}{\varepsilon_o + \varepsilon_{PL} + (\varepsilon_o - \varepsilon_{PL})e^{-\varepsilon_o t}} \tag{6}$$

Now to solve for $n_L(t)$, we can immediately write from equation (2):

$$n_L(t) = \int_0^t K_L\, dt' + \varepsilon_{2PL}\int_0^t n^{2}_{PL}(t')dt'$$

$$= K_L t + \varepsilon_{2PL} \int_0^t n_{PL}^2(t')dt' \qquad (7)$$

We change variables by letting:

$$x(t) = e^{-\varepsilon_o t} \qquad (8)$$

Then $\frac{dx}{dt} = -\varepsilon_o \, e^{-\varepsilon_o t} = -\varepsilon_o x$ and $dt/dx = -1/\varepsilon_o x$

We can now rewrite equation (7):

$$n_L(t) = K_L t + \frac{\varepsilon_{2PL}}{\varepsilon_o} \int_x^1 \frac{n_{PL}^2(x')\ dx'}{x'} \qquad (9)$$

Looking only at the second term and, substituting equation (8) into equation (6), we have:

$$\int_x^1 \frac{n_{PL}^2(x')dx'}{x'} = 4K_{PL}^2 \left[\int_x^1 \frac{dx'}{x'(a + b\ x')^2} - \int_x^1 \frac{2\ dx'}{(a + b\ x')^2} + \int_x^1 \frac{x'\ dx'}{(a + b\ x')^2} \right] \qquad (10)$$

where we have made the substitutions:

$$a = \varepsilon_o + \varepsilon_{PL} \text{ and } b = \varepsilon_o - \varepsilon_{PL} \tag{11}$$

After again consulting the integral tables, and simplifying, we obtain:

$$n_L(t) = K_L t + \frac{4K_{PL}^2 \varepsilon_{2PL}}{\varepsilon_o} \left[\frac{a^2-b^2}{a^2b^2} \log \frac{a+b}{a+bx} - \frac{b^2 \log x}{a^2b^2} + \frac{(x-1)(a+b)}{ab(a+bx)} \right] \tag{12}$$

From the definitions of a and b [equation (11)] and ε_o [equation (4)] we can write:

$$a + b = 2\varepsilon_o$$

$$a^2 - b^2 = 4\varepsilon_o \varepsilon_{PL}$$

$$ab = 4\varepsilon_{2PL} K_{PL}$$

Then we can rewrite equation (12):

$$n_L(t) = K_L t + \frac{\varepsilon_{PL}}{\varepsilon_{2PL}} \log \frac{2\varepsilon_o}{a+bx} + \frac{(\varepsilon_o - \varepsilon_{PL})^2 t}{4\varepsilon_{2PL}} + \frac{2K_{PL}(x-1)}{a+bx} \tag{13}$$

To obtain $n_{PL}(t)$ in the same notation, we can rewrite equation (6):

$$n_{PL}(t) = \frac{2K_{PL}(1-x)}{a+bx} \tag{14}$$

The sum of these two equations gives the time dependence of the total number of lesions after the start of an irradiation:

$$n_{TOT}(t) = n_{PL}(t) + n_L(t) = K_L t + \frac{\varepsilon_{PL}}{\varepsilon_{2PL}} \log \frac{2\varepsilon_o}{a+bx} + \frac{(\varepsilon_o - \varepsilon_{PL})^2 t}{4\varepsilon_{2PL}} \tag{15}$$

The survival equations from the previous treatment (Curtis, 1983) can be written in general in terms of the initial numbers of lesions at the end of the irradiation:

$$S = \exp\left(-n_{TOT}(T)\right)\left[1 + \frac{n_{PL}(T)}{\varepsilon}\left(1-\exp \varepsilon_{PL}(T-t')\right)\right]^{\varepsilon} \tag{16}$$

where T is the total irradiation time and t'-T is the time for repair after the irradiation is complete and $\varepsilon = \varepsilon_{PL}/\varepsilon_{2PL}$. Written in more conventional terms involving the dose rate, $\dot{D}$ and absorbed dose ($D = \dot{D}T$), we have:

$$S = \exp\left(-n_{TOT}(D/\dot{D})\right)\left[1 + \frac{n_{PL}(D/\dot{D})}{\varepsilon}\left(1-\exp[\varepsilon_{PL}(D/\dot{D}-t')]\right)\right]^{\varepsilon} \tag{17}$$

Here t' is the total time from the beginning of the irradiation to the time beyond which potentially lethal lesions cannot be repaired. This lesion fixation process is an important concept of the LPL model and can be neglected only for cell populations such as those we are considering here that have been given adequate time for repair (i.e., when $t'-T \gg 1/\varepsilon_{PL}$).

Approximations Applying at High and Low Dose Rates

I. High Dose Rate

We define the high dose rate region as that high range of dose rates where the shape of the survival curve does not change appreciably as the dose rate changes. This will be the case when the irradiation time, T, is much less than $2/\varepsilon_0$ and when ε_0^2 is much greater than ε_{PL}^2;

that is, when:

$$T \ll 2/\varepsilon_0 \text{ and } \varepsilon_0^2 \gg \varepsilon_{PL}^2 \qquad (18)$$

This leads to the restriction on the dose rate:

$$\dot{D} \gg \frac{\varepsilon_{PL}^2}{4\eta_{PL}\varepsilon_{2PL}} \qquad (19)$$

The proof of this result is given in the Appendix.

With these restrictions, the survival curve reduces to

$$S = \exp\left[-(\eta_{PL}D + \eta_L D)\right]\left[1 + \frac{\eta_{PL}D}{\varepsilon}\right]^{\varepsilon} \qquad \text{high dose rate} \qquad (20)$$

since $n_{TOT}(T) = \eta_{PL}D + \eta_L D$, and $n_{PL}(T) = \eta_{PL}D$.

We note that there is no dependence on the dose rate; this is the same expression obtained in the earlier treatment (Curtis, 1983).

II. Low Dose Rate

We will define the low dose rate approximation to exist when $\varepsilon_o = \varepsilon_{PL}$. This will be true when:

$$K_{PL} << \frac{\varepsilon_{PL}^2}{2\varepsilon_{2PL}} \text{ or } \dot{D} << \frac{\varepsilon_{PL}^2}{2\eta_{PL}\varepsilon_{2PL}} \tag{21}$$

Proof:

$$\varepsilon_o = (\varepsilon_{PL}^2 + 4\,K_{PL}\,\varepsilon_{2PL})^{1/2} = \varepsilon_{PL}\left(1 + \frac{4\,K_{PL}\,\varepsilon_{2PL}}{\varepsilon_{PL}^2}\right)^{1/2}$$

$$= \varepsilon_{PL}\left(1 + \frac{2\,K_{PL}\,\varepsilon_{2PL}}{\varepsilon_{PL}^2} + \ldots\right)$$

If the inequality of equation (21) holds, the second and succeeding terms are negligible and we have $\varepsilon_o = \varepsilon_{PL}$.

In this case, $b = 0$, $a = 2\varepsilon_{PL}$, and the last two terms in equation (15) vanish. This yields:

$$n_{TOT}(T) = K_L T = \eta_L D \text{ and}$$

$$n_{PL}(T) = \frac{K_{PL}(1 - e^{-\varepsilon_{PL}T})}{\varepsilon_{PL}}$$

Now the survival expression reduces to:

$$S = \exp\,(-\eta_L D)\left[1 + \frac{K_{PL}(1 - e^{-\varepsilon_{PL}T})}{\varepsilon_{PL}\,\varepsilon}\,(1 - e^{-\varepsilon_{PL}(t' - T)})\right]^{\varepsilon} \tag{22}$$

and, remembering that $\varepsilon = \varepsilon_{PL}/\varepsilon_{2PL}$,

$$S = \exp\left(-\eta_L D\right)\left[1 + \frac{K_{PL}\ \varepsilon_{2PL}\ \left(1 - e^{-\varepsilon_{PL}T}\right)}{\varepsilon_{PL}^2}\left(1 - e^{-\varepsilon_{PL}(t'-T)}\right)\right]^{\varepsilon} \qquad (23)$$

But from equation (21), we have assumed that:

$$\frac{2\ K_{PL}\ \varepsilon_{2PL}}{\varepsilon_{PL}^2} << 1$$

and since the two factors involving the exponentials in time are both always less than unity, the second term in the major brackets can be neglected and we have:

$$S = \exp\left(-\eta_L D\right) \qquad \underline{\text{low dose rate}} \qquad (24)$$

Equations (20) and (24) represent the two limits of the survival expression for high and low dose rate respectively in the LPL model. High dose rate is defined as the region of dose rates where $\dot{D} >> \varepsilon_{PL}^2/4\eta_{PL}\varepsilon_{2PL}$ and low dose rate as the region of dose rates where $\dot{D} << \varepsilon_{PL}^2/2\eta_{PL}\varepsilon_{2PL}$.

For intermediate dose rates, equation (16) must be used, with equations (14) and (15) inserted with t = T, the irradiation time. An example of a set of survival curves for various dose rates from 5×10^{-3} to 10^4 Gy/hr is shown in Figure 1. Here the values for the four parameters in the model were chosen to correspond to the experimental data obtained with C_3H-10T1/2 cells in stationary phase (Wells and Bedford, 1983). Specifically, the values chosen were:

$$\eta_L = 0.1366 \text{ Gy}^{-1}$$

$$\eta_{PL} = 0.6 \text{ Gy}^{-1}$$

$$\varepsilon = 9.0 \; (\varepsilon_{2PL} = 0.0556 \text{ hr}^{-1})$$

$$\varepsilon_{PL} = 0.5 \text{ hr}^{-1}$$

Clearly seen are the two limits: the low dose rate limit producing an exponential survival curve with $D_o = 1/0.1366 = 7.32$ Gy, the high dose rate limit occurring for dose rates greater than 100 Gy/hr.

In Figure 2 is shown the dependence of ε_o on the dose rate, calculated for the same set of parameters.

Comparison with Experimental Data

The model has been compared with the experimental data obtained by Wells and Bedford (1983) using C3H-10T1/2 in stationary phase. The values mentioned above were obtained as follows: η_L is simply the reciprocal of the D_o for the exponential curve obtained at very low dose rates. η_{PL} and ε were chosen to yield the survival curve at high dose rate and ε_{PL} was chosen to reflect a characteristic mean repair time of two hours. A comparison between the experimental data and the calculated survival curves is shown in Figure 3.

Summary

The present analysis expands the LPL model to include the effects of dose rates for which lesion formation occurs during the repair (and misrepair) process. In terms of the parameters of the model, three regions of dose rate can be identified:

1. High dose rate: $\dot{D} \gg \varepsilon_{PL}^2/4\eta_{PL}\varepsilon_{2PL}$. Here the survival curve reduces to

$$S = \exp\left[-\eta_{PL}D - \eta_L D\right]\left[1 + \frac{\eta_{PL}D}{\varepsilon}\right]^{\varepsilon}$$

and is not a function of dose rate.

2. Intermediate dose rate: $\dot{D} \sim \varepsilon_{PL}^2/(4\eta_{PL}\ \varepsilon_{2PL})$. Here the survival curve is given by equation (17) and is a function of the dose rate.

3. Low dose rate: $\dot{D} \ll \varepsilon_{PL}^2/2\eta_{PL}\varepsilon_{2PL}$. Here the survival curve is independent of dose rate and reduces to an exponential, $S = \exp(-\eta_L D)$.

APPENDIX

We start with the two general equations for $n_{PL}(T)$ and $n_{TOT}(T)$ [equations (14) and (15)]:

$$n_{PL}(T) = \frac{2n_{PL}\dot{D}(1-x)}{a + bx} \qquad \text{(A1)}$$

$$\text{and } n_{TOT}(T) = n_L D + \frac{\varepsilon_{PL}}{\varepsilon_{2PL}} \log \frac{2\varepsilon_o}{a + bx} + \frac{(\varepsilon_o - \varepsilon_{PL})^2 T}{4\varepsilon_{2PL}} \qquad \text{(A2)}$$

Here $a = \varepsilon_o + \varepsilon_{PL}$, $b = \varepsilon_o - \varepsilon_{PL}$, $x = e^{-\varepsilon_o T}$, and T = the irradiation time.

First we use the restriction of short irradiation times (i.e., $T \ll 2/\varepsilon_o$) to make the approximation $x = 1 - \varepsilon_o T$ and $1 - x = \varepsilon_o T$. Then:

$$n_{PL}(T) = \frac{2n_{PL}\dot{D}\varepsilon_o T}{\varepsilon_o + \varepsilon_{PL} + [(\varepsilon_o - \varepsilon_{PL})(1-\varepsilon_o T)]}$$

$$= \frac{n_{PL}\dot{D}T}{1 - [1/2(\varepsilon_o - \varepsilon_{PL})T]} = n_{PL}\dot{D}T = n_{PL}D \qquad \text{(A3)}$$

We have neglected $1/2(\varepsilon_o - \varepsilon_{PL})T$ in the denominator by invoking the short irradiation time restriction. We note here that if $T \ll 2/\varepsilon_o$, then $T \ll 2/(\varepsilon_o - \varepsilon_{PL})$ since ε_{PL} is always positive and less than or equal to ε_o.

Now from equation (A2), we see that the second term on the right can be simplified by expanding the exponential in the denominator:

$$\varepsilon \log \frac{2\varepsilon_o}{\varepsilon_o + \varepsilon_{PL} + (\varepsilon_o - \varepsilon_{PL})e^{-\varepsilon_o T}}$$

$$= \varepsilon \log \frac{2\varepsilon_o}{\varepsilon_o + \varepsilon_{PL} + (\varepsilon_o - \varepsilon_{PL})(1-\varepsilon_o T)}$$

$$= \varepsilon \log \frac{1}{1-[1/2\ (\varepsilon_o - \varepsilon_{PL})\ T]}$$

$$= \varepsilon \log \left\{1-[1/2(\varepsilon_o - \varepsilon_{PL})T]\right\}$$

We expand the log in a series expansion requiring now that

$T << \frac{4}{(\varepsilon_o - \varepsilon_{PL})}$; remembering the definition of ε, we obtain

$$= -\varepsilon(-1/2[\varepsilon_o - \varepsilon_{PL})T) = \frac{\varepsilon_{PL}(\varepsilon_o - \varepsilon_{PL})T}{2\varepsilon_{2PL}} = \frac{\varepsilon_{PL}\varepsilon_o T}{2\varepsilon_{2PL}} - \frac{\varepsilon_{PL}^2 T}{2\varepsilon_{2PL}} \tag{A4}$$

The third term on the right of equation (A2) can be written:

$$\frac{(\varepsilon_o^2 - 2\varepsilon_o\ \varepsilon_{PL} + \varepsilon_{PL}^2)T}{4\varepsilon_{2PL}} = \frac{\varepsilon_o^2 T}{4\varepsilon_{2PL}} - \frac{\varepsilon_o\ \varepsilon_{PL} T}{2\varepsilon_{2PL}} + \frac{\varepsilon_{PL}^2 T}{4\varepsilon_{2PL}} \tag{A5}$$

Now, upon adding this term to the one derived in equation (A4), we note a cancellation yielding:

$$-\frac{\varepsilon_{PL}^2 T}{2\varepsilon_{2PL}} + \frac{\varepsilon_o^2 T}{4\varepsilon_{2PL}} + \frac{\varepsilon_{PL}^2 T}{4\varepsilon_{2PL}} = \frac{(\varepsilon_o^2 - \varepsilon_{PL}^2)T}{4\varepsilon_{2PL}}$$

Equation (A2) becomes

$$n_{TOT}(T) = \eta_L D + \frac{(\varepsilon_o^2 - \varepsilon_{PL}^2)T}{4\varepsilon_{2PL}} \tag{A6}$$

Now, if we require $\varepsilon_o^2 >> \varepsilon_{PL}^2$, we can write

$$n_{TOT}(T) = \eta_L D + \frac{\varepsilon_o^2 T}{4\varepsilon_{2PL}} \tag{A7}$$

But from the definition of ε_o (equation (4)), we see

$$\varepsilon_o^2 = 4\eta_{PL}\dot{D}\varepsilon_{2PL} + \varepsilon_{PL}^2$$

and if $\varepsilon_o^2 >> \varepsilon_{PL}^2$,

$$4\eta_{PL}\dot{D}\varepsilon_{2PL} + \varepsilon_{PL}^2 >> \varepsilon_{PL}^2$$

$$\frac{4\eta_{PL}\dot{D}\varepsilon_{2PL}}{\varepsilon_{PL}^2} + 1 >> 1$$

So $$\frac{4\eta_{PL}\dot{D}\varepsilon_{2PL}}{\varepsilon_{PL}^2} >> 1 \tag{A8}$$

and the restriction on the dose rate, $\dot{D}$, becomes

$$\dot{D} >> \frac{\epsilon_{PL}^2}{4\eta_{PL}\,\epsilon_{2PL}} \quad \text{(high dose rate)} \tag{A9}$$

Also, from the above inequality, (A8),

$$4\eta_{PL}\dot{D}\;\epsilon_{2PL} >> \epsilon_{PL}^2$$

and we see that ϵ_o^2 reduces to

$$\epsilon_o^2 = 4\eta_{PL}\dot{D}\;\epsilon_{2PL}.$$

Now substituting this expression for ϵ_o^2 into equation (A7), we obtain

$$n_{TOT}(T) = \eta_L D + \frac{4\eta_{PL}\dot{D}\;\epsilon_{2PL}T}{4\epsilon_{2PL}}$$

$$= \eta_L D + \eta_{PL}\dot{D}T = \eta_L D + \eta_{PL}D. \tag{A10}$$

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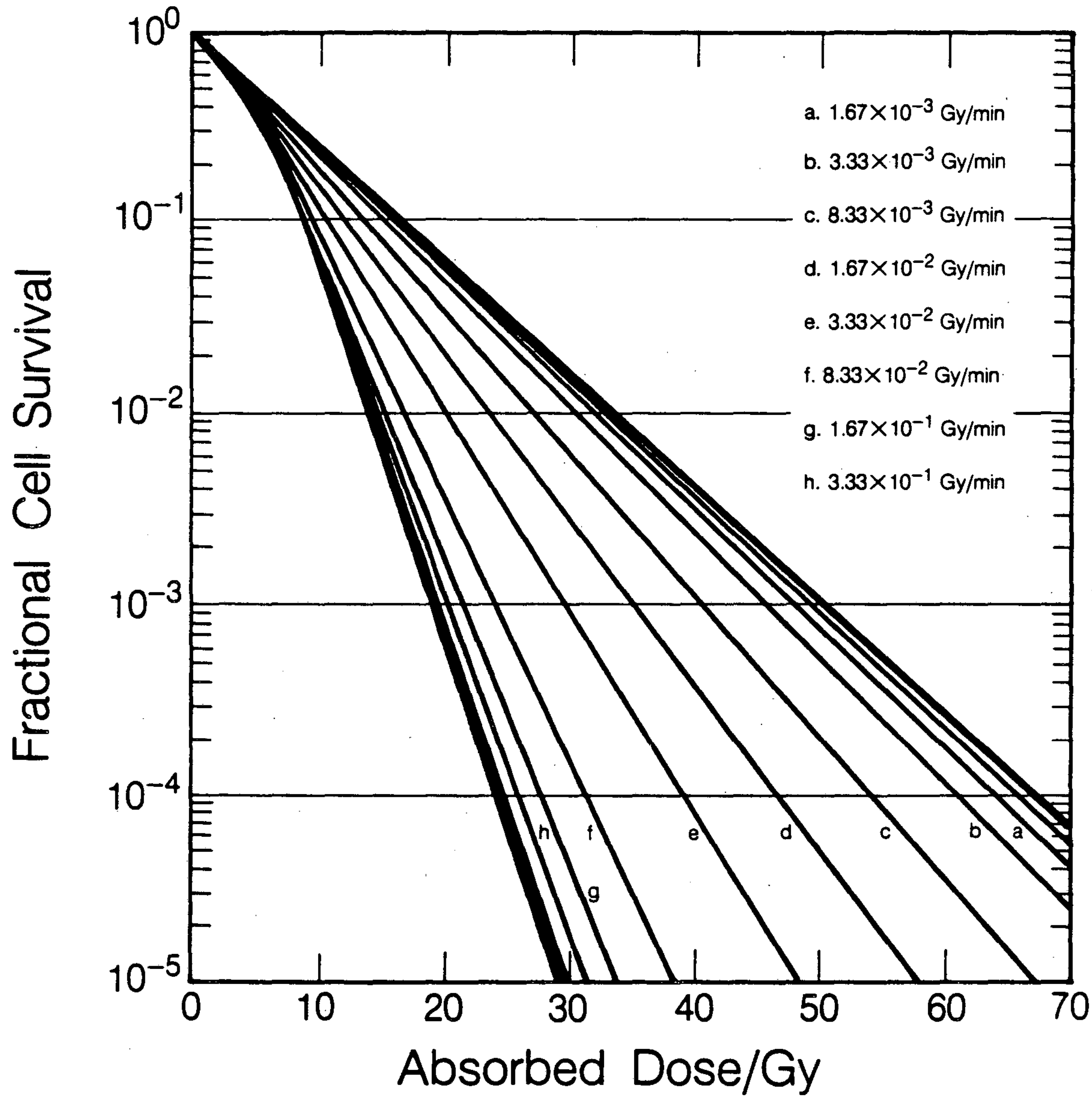
Figure 1: A family of survival curves as calculated from the LPL model. Values of the parameters used are given in the text. At high and low dose rates, the survival curves become independent of dose rate. Curves a through h denote values in the midrange of dose rates where the survival curves are a function of dose rate. (XBL 844-7694)

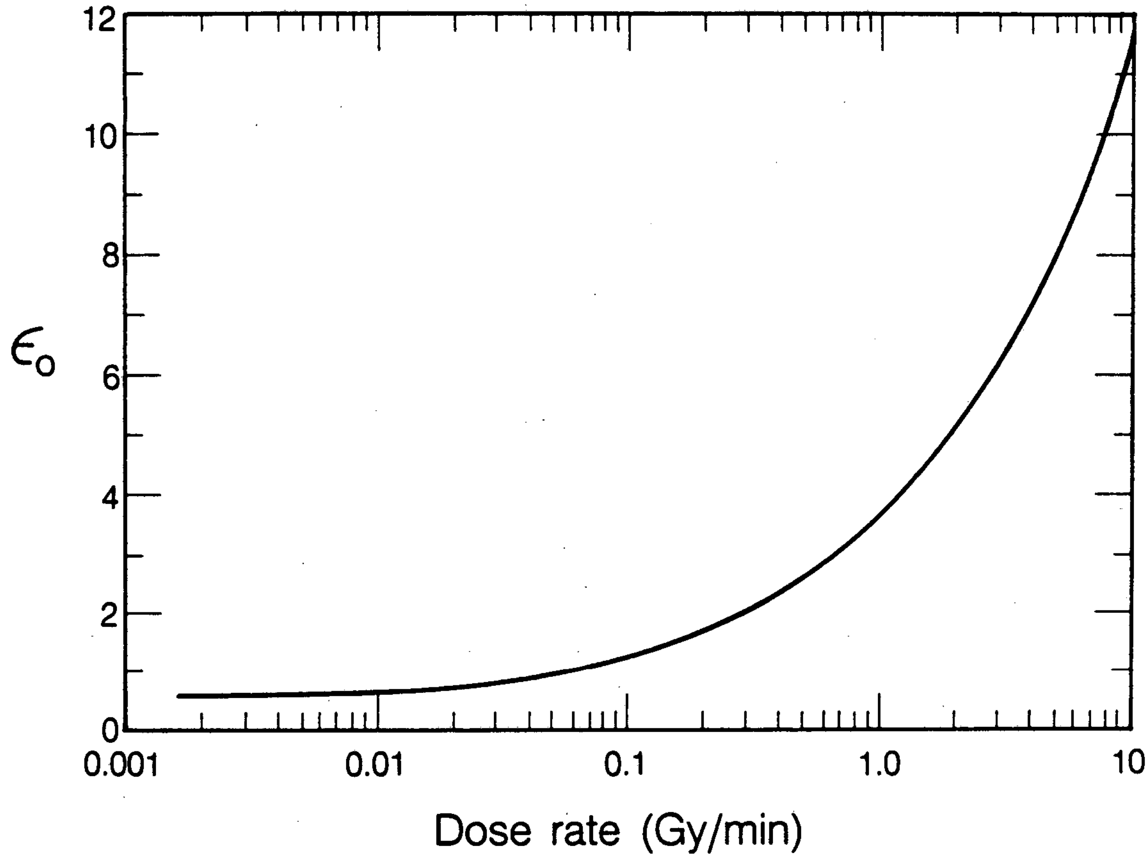
Figure 2: Dependence of ε_0 on the dose rate. Low dose rate conditions occur when ε_0 is constant and equal to ε_{PL}. High dose rate occurs when ε_0 reaches a value of about 5 for the values of the model parameters chosen. (XBL 844-7693)

Figure 3: Comparison of survival curves calculated from the LPL model (solid curves) and the experimental data from C3H10T1/2 density inhibited cells irradiated with ^{137}Cs gamma rays obtained by Wells and Bedford (1983). Parameters in the model are given in the text.
(XBL 8311-4138)



XBL 844-7694

FIGURE 1



XBL 844-7693

FIGURE 2

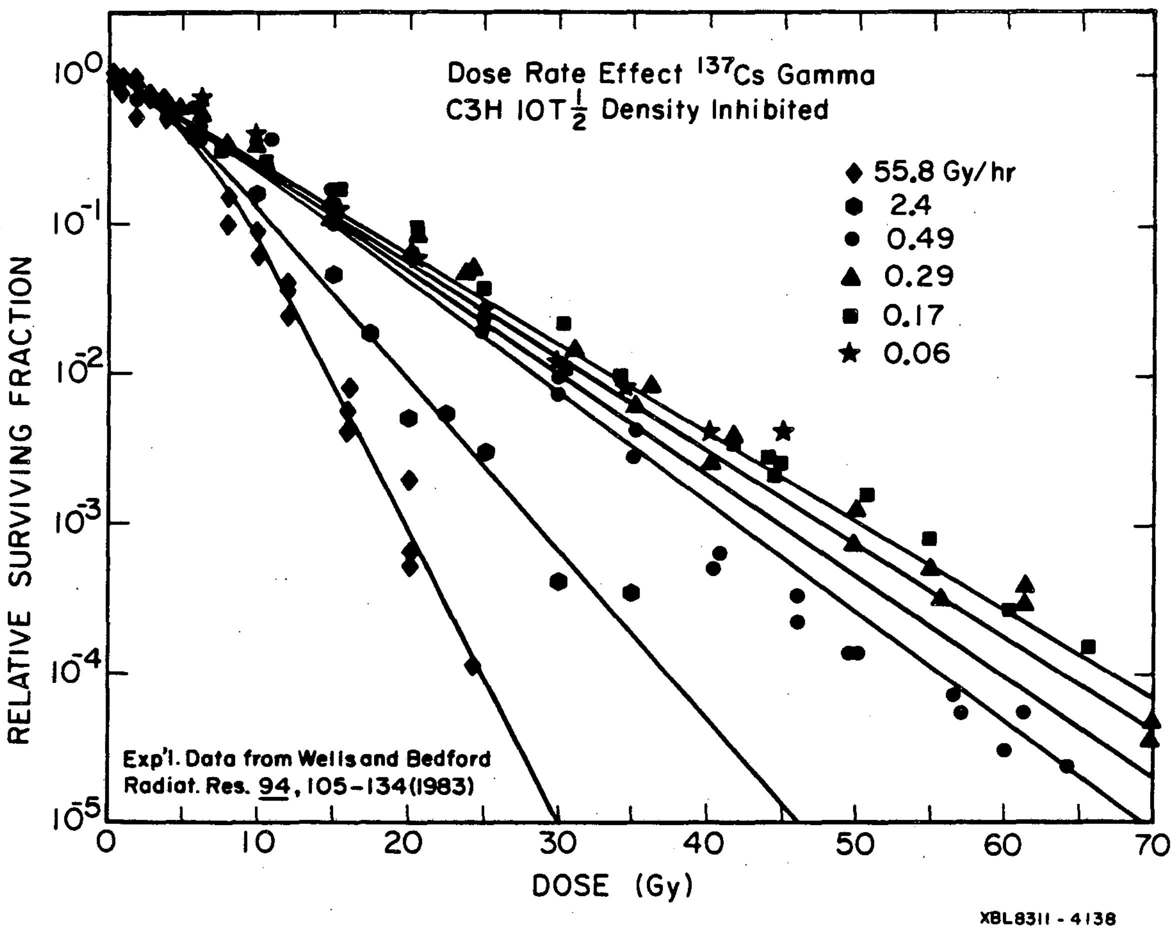

Dose Rate Effect ¹³⁷Cs Gamma
C3H 10T½ Density Inhibited
55.8 Gy/hr
2.4
0.49
0.29
0.17
0.06
RELATIVE SURVIVING FRACTION
DOSE (Gy)
Exp'l. Data from Wells and Bedford
Radiat. Res. 94, 105–134 (1983)
XBL8311 - 4138

FIGURE 3

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