Dose-Rate Effects Generated from Repair and Regeneration

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A general effect for cell proliferation has been incorporated into Roesch's survival equation (Accumulation Model). From this an isoeffect formula for the low dose-rate regimen is obtained. The prediction for total doses equivalent to 60 Gy delivered at the constant dose-rate over 7 days agrees well with the dose-time data of Paterson and of Green, when the parameter ratio A/B ($\approx a\mu/2\beta$ where μ is the repair rate) is chosen to be 0.7 Gy/h. When a constant proliferation rate and known facts of division delay are assumed, an isoeffect relation between low dose-rate treatment and acute dose-rate treatment can be derived. This formula in the regimens where proliferation is negligible predicts exactly the data of Ellis that 8 fractions of 5 Gy/day for 7 days are equivalent to continuously applied 60 Gy over 7 days, provided the A/B ratio is 0.7 Gy/h and the a/β ratio is 4 Gy. Overall agreement between the clinical data and the predictions made by the formula at the above parameter values suggests that the biologcal end points used as the tolerance level in the studies by Paterson, Green, and Ellis all agree and they are not entirely the early effects as generally assumed. The absence of dose-rate effects observed in the mouse KHT sarcoma can better be explained in terms of a large value for the A/B ratio. Similarly, the same total dose used independently of the dose-rate to treat head and neck tumors by Pierquin can be justified.

Key Words: Cell survival, Dose-rate effects, Repair, Proliferation, Isoeffect formula

INTRODUCTION

The potential benefits of being able to predict tumor and normal tissue responses to therapeutic radiation at both low and high dose-rates are significant and widereaching. To develop this ability, an initial step is to quantify the therapeutic effects of the received doses. A major difficulty associated with this task, however, originates at the low dose-rate end where both damage repair and cell proliferation enhance the dose-rate effect. The effects of proliferation for tissue survival in fractionated therapy have been given earlier[1] without the effect of division delay[2,3]. Thus, to meet these needs, it is critical to find the effects of repair and proliferation of target cells in both low dose-rate and fractionated regimens. The tolerance

dose, which is defined as the maximum dose tolerated by a tissue, should increase with the growth rate of the target cells.

Since the delivery schedule of radiation determines the degree of repair and regeneration, the teatment time or the fraction time interval becomes an important variable. The NSD and CRE formulas[4~7] do give the treatment time for continuous and factionated application of radiation. These formulas possess an appeal of simplicity, but their validity has been questioned, particularly with respect to their treatment time dependence of tolerance dose[8].

In contrast, a formulation based on cell survival not only gives the isoeffective dose as a function of fractionated dose, but it also takes into account the dependence on the speed of apparent tissue reaction. Hence, a single formula is applicable to multiple clinical situations. The importance of the tissue reaction speed in radiation therapy has been emphasized, and a formula based on this understanding for the fractionated regimen has been derived[9]. In this work of Withers, Thames, and Peters, the ratio of cells' 'one-hit' radiosensitivity (a) to 'two-hit' sensitivity (β) of the LQ (linear-

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quadratic) model becomes the parameter representing the tissue reaction speed. Their work, however, does not include the effects of regeneration, slow repair[10,11], recruitment, redistribution along the cell cycle, and hence does not take into account the entire dependence of isoeffect dose on the treatment time. This time dependence is not important when the effect of regeneration on the tolerance dose is delayed so long that a therapy session is completed before the effect becomes significant. When the tissue regeneration response is acute, however, the treatment time is important even for the fractionated regimen.

The need for the time dependence or time factor is particularly severe when an isoeffect relationship involves continuous irradiation treatment. Such a relationship is needed, for example, when clinical situations dictate a necessity for supplementing brachytherapy with fractionated irradiation. The therapeutic value of very low dose-rate radiation received by normal and tumor tissues at distance from the source has to be known in order to boost the region with an optimal amount of external beam radiation.

Liversage[12] has derived a formula for the above purpose. However, his formula is valid in only special schedules. Dale[13] has used the Accumulation Model of Roesch[14,15] to derive a formula for the same purpose. O'Donoghue[16] applied Dale's work to fit the data of Green[4] and Paterson[17]. Yet, this low dose-rate counterpart of the LQ model has not been exploited. Furthermore, no formula proposed so far has, however, taken into account the proliferation of tumors and regeneration of normal tissues.

The theory described below incorporates intratherapy cell proliferation as well as the effect of relevant damage repair. The effect of repair portion on survival is identical to the Accumulation Model of Roesch[14,15]. However, the effects of proliferation and division delay on the net number of surviving cells is new. In order to determine the effect of proliferation in the therapeutic regimens, it is essential to study the dose and dose-rate effects of radiation on proliferation; the rate of proliferation depends on the dose fractionation schedule and on the dose-rate for continuous irradiation. It is our understanding that the radiation-altered rate in cell division constitutes the fractionation and dose-rate dependence of net survival and of the total dose. This point needs to be elaborated.

As given above, the dose-rate effect of cell proliferation can be understood from the elongation of cell cycle time for cells undergoing continu-ous irradiation. Cell cycles are lengthened by division delay induced by radiation. It has been known that the percent increase in the cell cycle time due to a high dose-rate X-ray pulse is proportional to the magnitude of the dose. From the division delay determined by short duration high dose-rate irradiation, it is possible to derive the division delay expected for protracted low dose-rate irradiation. This is shown in the following section. This is important in writing an isoeffect relations for continuous and fractionated radiations and the isoeffect relationship between continuous radiation of different dose-rates.

The proliferation term in the survival equation is comprised of dose-rate dependent and independent terms. The dose-rate effect produced by proliferation is important because it can be greater than the dose-rate effect produced by the repair-dependent term. At very low dose-rates encountered in interstitial implant therapy empolying sources such as I-125, the rate of proliferation is relatively simple. Under continuous irradiation, sparse population of surviving cells makes their growth close to exponential, excluding the effects of division delay, recruitment, and reoxygenation. At dose-rates close to the critical dose-rate, the cell division rate is nearly zero, and its dose-rate dependence becomes more complicated. Analysis of this phenomenon requires separate investigation.

THEORETICAL PRELIMINARIES

1. Growth-Survival Equation for a Homogeneous Cell Population Subjected to Extended Irradation

When a population of n cells receives a pair of radiation pulses far apart in time, their survival can be predicted from their ability to survive the individual pulses. As the separation of the two pulses is shortened, the number of surviving cells decrease as predicted from the split-dose experiment. It is not difficult to see that the additional death is caused by synergistic interaction of the two pulses of radiation. When the two pulses are separated by a long time, the memory of the first pulse is largely erased in surviving cells by the time the second pulse arrives.

Consider a pulse of radiation at time t_1 lasting a time interval of dt_1 and an earlier pulse of radiation at $t_2(t_2 < t_1)$ lasting an interval of dt_2. A sublethal lesion produced at t_1 converts a fraction of cells which had received only sublethal damage at t_2 into clonogenically dead cells. This additional death due to the interaction of the two infintesimal radia-

tion effects gives rise to

$$k(t_2-t_1)\times r(t_1)dt_1 \times r(t_2)dt_2 \qquad (1)$$

in which $r(t)$ is the dose-rate at t. The function k in Eq. (1) is the probability for the lethal conversion of unrepaired sublethal damage. This is the product of the rate of conversion of sublethal damage into lethality and the probability that sublethal damage remains unrepaired at a given time. The probability of having unrepaired sublethal damage after a time interval t is not a simple exponential function of t. This is because of the occurrences of sublethal damage of different severity and also because of their uneven distribution. Nevertheless, since this function is a monotonically decreasing function of time, it will be approximated to be an exponential function of time as was assumed by Roesch[14,15]:

$$k(t_1-t_2)=2\beta e^{-\mu(t_1-t_2)} \qquad (2)$$

where β is proportional to the rate of conversion of sublethality into lethality and μ is the repair rate of sublethal damage. Elkind's split-dose experiments confirm at least qualitative validity of Eq. (2).

Let us write the net change in the clonogenic cell number into two terms, the proliferation term and the inactivation term:

$$dn(t)=dn_g-dn_x \qquad (3)$$

$\dfrac{dn_g}{dt}$ is the rate of proliferation, and $\dfrac{dn_x}{dt}$ is the rate of total lethal conversion. The latter term is, in turn, made up of two contributions, the single-hit lethal damage made at the rate of α per Gy, and the conversion of sublethal damage into lethality discussed above. Therefore,

$$\frac{dn_x(t)}{n(t)}=\alpha r \, dt+2\beta r^2\int_0^t dt_1 e^{-\mu(t-t_1)}dt \qquad (4)$$

where μ may be considered the rate of repair of the sublethal lesions.

The rate of proliferation $\dfrac{dn_g}{dt}$ for a given tissue generally depends on the time beginning from the irradiation and on the number of cells. The cell number fraction is increased by proliferation at the time rate, γ:

$$\frac{dn_g(t)}{n(t)}=\gamma(t)dt \qquad (5)$$

The proliferation rate γ is a product of the growth fraction g and average division rate c:

$$\gamma=gc \qquad (6)$$

By inserting Eqs. (4) and (5) into Eq. (3), the fractional change in the cell number is

$$\frac{dn(t_1)}{n(t_1)}=\gamma(n,t)dt_1-\alpha r \, dt_1$$
$$-2\beta r^2\int_0^{t_1}dt_2 e^{-\mu(t_1-t_2)}dt_1 \qquad (7)$$

where the cell number (and density) and time dependence of growth rate is indicated. Eq. (7) can be integrated:

$$n(t)=n_0 e^{-\alpha rt-\frac{2\beta r^2}{\mu}t\left\{1+\frac{e^{-\mu t}-1}{\mu t}\right\}}+\int r(t)dt \qquad (8)$$

This is, apart from the proliferation term, the result of the Accumulation Model of Roesch[14,15]. When the dose-rate is low and the treatment time is long, the term inside the brackets is nearly 1. Furthermore, if the rate γ is independent of t, hence of n,

$$n(t)=n_0 e^{-\alpha rt-\frac{2\beta r^2}{\mu}t+rt} \qquad (9)$$

This equation is adequate for low dose-rate brachytherapy.

The high and low dose-rate survival data obtained by Mitchell et al.[18] are satisfactorily explained using Eq. (8) with a constant γ[19]. This and the studies of survival of stationary cells at assorted dose-rates[20,21] indicate the fundamental correctness of the assumptions used in deriving Eq. (8).

In the limit of short interval irradiation which fractionated high dose-rate therapy requires, Eq. (8) leads to the linear-quadratic (LQ) model[22,23], and the dose-rate dependence of survival disappears from the equation. Thus, the LQ model predicts that the surviving fraction following an acute irradiation of dose Da is:

$$\log f=-\alpha D_a-\beta D_a^2 \qquad (10)$$

in which α and β are constant indicators of the weight of the linear and square dependence on the dose, respectively. When the acute dose of radiation is fractionated into identical doses of magnitude d Gy, which are equally spaced in time so that the repair of sublethal damage is the same in each interval, it can be assumed that the survival curve segment repeats itself each time a fraction is given except at the beginning of the schedule. Since the effects are, thus, additive, such a series of equal fractions would give rise to a straight overall survival curve except near the beginning of a fractionated schedule. However, during the interval between a pair of adjacent fractions, some cells may undergo mitosis. Such proliferation during therapy must be taken into consideration. Thus, from Eq. (8)

$$\log f=N\left(\int_0^\Delta \gamma dt-\alpha d-\beta d^2\right) \qquad (11)$$

where γ is the time rate of fractional increase in cell population during each time fraction of Δ hours, and d is the fractional dose of high dose-rate in the

course of N fractions. Eq. (11) can be shown from Eq. (8) by taking the limit of short irradiation interval t.

2. Dose and Dose-Rate Dependence of Division Rate

Both short and long (compared to cell generation time) duration irradiation alter the rate of cell division via the division delay caused by G_2 arrest. For the short duration irradiation, the division delay depends on the phase of cell cycle in which radiation is given[24]. For an asynchronous cell population, the division delay of the population is the average of the delay suffered by cells at different cell ages, and for long duration irradiation also, the overall delay is the cell-age average. It is known that the average percent increase in the cell generation time due to a high dose-rate X-ray pulse is proportional to the magnitude of the dose[24]. It is about 10% of the cell generation time per Gy up to 10 Gy[25]. For continuous irradiation, the increase in cell generation time is related to the 'unwasted' portion of the dose received during the period. An increased cell generation time is translated into a slowed division rate. Thus, the division rate depends on the fractionation schedule and dose-rate. Below, we show this explicitly.

a. Fractionated radiation

It is simple to find the division rate as a function of dose if this dose is delivered in an interval short compared to the repair time. Of course, this is the case for fractionated therapeutic radiation. The division rate may be assumed constant following the division delay. The actual division rate decreases gradually, but since the fractionation interval is not much longer than the typical cell generation time, it is a good approximation to work with a time-averaged, constant division rate. The growth fraction, g, also depends on the dose-rate and time due to recruitment and cell loss change. These are neglected here but will be dealt with in a subsequent paper. Thus, for the present purpose, the proliferation rate γ is the division rate multiplied by a constant growth fraction.

If z is the division delay per Gy, zd is the division delay caused by a dose fraction of size d Gy. The average growth per single fractionation interval Δ is equal to free growth (γ_0) over and interval $\Delta - zd$. Thus,

$$\int_0^\Delta \gamma dt = \int_{zd}^\Delta \gamma dt = \gamma_0(\Delta - zd) \quad \text{only for } \Delta > zd,$$
$$= 0 \text{ for } \Delta < zd. \tag{12}$$

As shown in APPENDIX 2, the division delay per Gy averaged over a cell cycle, z_{av}, is:

$$z_{av} = z_p \frac{1 - e^{-\rho t_p}}{\rho \tau_f} \tag{13}$$

where z_p is the division delay per Gy of radiation given at the cell age t_p, and t_p is the last time point of G_2 at which division delay can be induced. t_p is slightly shorter than the cell cycle time τ_f.

b. Continuous radiation

If τ_0 is the cell cycle time in the absence of radiation and τ_c is the same in the presence of continuous irradiation of constant dose-rate r for a cell system, then the cell cycle time is lengthened by ry_{av}:

$$\tau_c - \tau_0 = ry_{av} \tag{14}$$

where y_{av} is given by:

$$y_{av} = z_p \frac{1 - e^{-\rho t_p}}{\rho \tau_c} \tag{15}$$

where differs from Eq. (13) only by the denominator.

Since the proliferation rate in the absence of radiation,

$$\gamma_0 = g \frac{\ln 2}{\tau_0},$$

and in the presence of radiation,

$$\gamma_c = g \frac{\ln 2}{\tau_c}, \tag{16}$$

may be substituted into Eq. (14), the cell-cycle-averaged growth rate is

$$\gamma_c = \frac{\gamma_0}{1 + r\eta}$$
$$\approx \gamma_0(1 - r\eta) \tag{17}$$

where

$$\eta = \frac{z_p \gamma_0}{\rho \ln 2}(1 - 2^{-\rho/\tau_c}). \tag{18}$$

In the low dose-rate limit of our interest, γ_c does not differ very much from γ_0, the growth rate in the absence of radiation. In such a case, γ_c in the exponent of 2 can be replaced with γ_0. This equation agrees well with the growth curves obtained by Mitchell for the low dose-rates[19]

3. Slow repair

Travis and Tucker[11] have reanalyzed the existing data[10] for the onset on radiation pneumonitis and arrived at a new variant of the LQ survival model. In order to explain the slow repair observed by Field et al.[10], they had to incorprate a new term γT in the isodose expression of the survival model. When this term is equally broken up into contributions from individual fractionation intervals, the slow repair term is the same as the proliferation term above except for the absence of the delay term. Thus, the formalism given above for proliferation is applicable to slow repair in the

context discussed in the article of Travis and Tucker. Therefore, Eqs. (11) and (12) with the delay function $z=0$ are useful for tissues which exhibit slow repair.

RESULTS

1. Isoeffect Formula in the Low Dose-Rate Regimen

The relationship between the treatment time and dose-rate can be obtained from Eq. (8). If T and T_s denote the treatment time at a dose-rate in question and at the reference dose-rate (in our case 0.357 Gy/h), respectively, then the treatment time may be expressed as:

$$\frac{T}{T_s} = \frac{ar_s + b_s r_s^2 - \gamma_{0s}}{ar + br^2 - \gamma_0} \tag{19}$$

in which

$$a = a + \gamma_0 \eta,^* \tag{20}$$

$$b = \frac{2\beta I}{\mu},$$

and

$$b_s = \frac{2\beta I}{\mu} \tag{21}$$

where the correlation factor I is:

$$I = 1 + \frac{e^{-\mu T} - 1}{\mu T}$$

and

$$I_s = 1 + \frac{e^{-\mu T_s} - 1}{\mu T_s}. \tag{22}$$

The factor I is equal to 1 for most practical purposes of continuous brachytherapy. Even if the repair kinetic parameter μ takes a very low value of 0.2 per hour, it reaches 0.9 for treatment of 2 days and 0.97 for 1 week treatment. At the fast repair rate of $\mu = 4$, I reaches 0.99 after merely 1 day. Thus,

$$b_s \doteqdot b.$$

Therefore, Eq. (19) leads to the following isoeffect relationship:

$$\frac{D}{D_s} = \frac{a + br_s - \gamma_{0s}/r_s}{a + br - \gamma_0/r} \tag{23}$$

in which D_s is a reference dose which is given continuously at a chosen rate. If the total treatment time is not long compared with the *in vivo* regeneration delay, then γ_0 terms in both the numerator and the denominator in Eqs. (19) and (23) may be dropped in comparison to other terms.

The dose-rate dependence of the proliferation terms in Eq. (23) can be expanded in a power series of $r - r_s$ and the proliferation term can be effective-
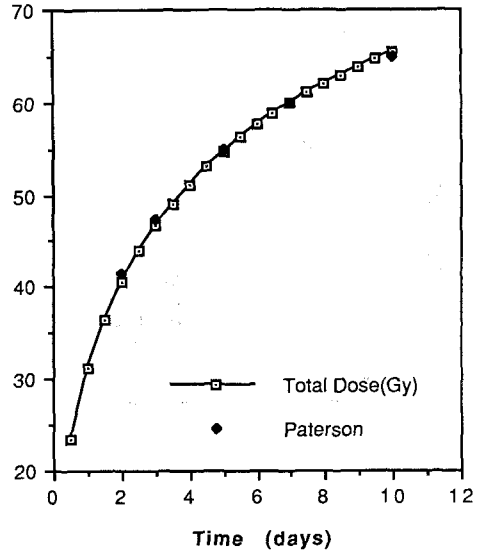
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*The effect of division delay is incorporated into a by substituting Eq. (17) into Eq. (8). See Eq. (27) below. At low dose-rates a is not significantly greater than α.
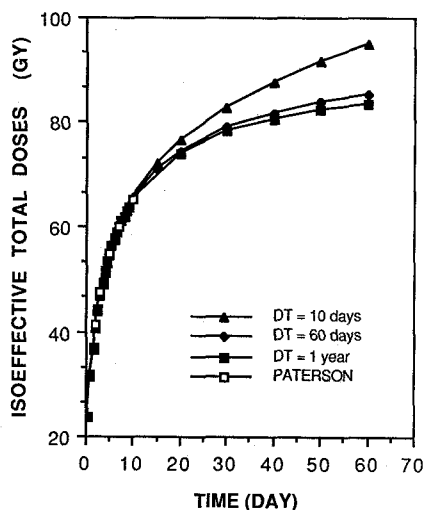

Fig. 1. Isoeffect curves for low dose-rate therapy. With the choice of 0.7 Gy/h for the value of A/B, the total dose is plotted as a function of the required time to deliver the dose. The agreement with the data of Paterson[17] is excellent.

ly incorporated into a and b.

Thus, by collecting the new coefficients of dose-rate r, new parameters A and B can be defined. Thus, Eq. (23) can be rewritten in the neighborhood of r_s:

$$\frac{D}{D_s} = \frac{A/B + r_s}{A/B + r} \tag{24}$$

in which A is no longer simply related to a except for the situation where proliferation effects can be neglected.

When one substitutes into Eq. (24) the following values for the reference dose and for the reference dose-rate,

$$D_s = 60 \text{ Gy}$$
$$r_s = 0.357 \text{ Gy/h},$$

and another data set from clinical data published by Ellis[4] and Hall[26,27], one obtains a value of about 0.7 Gy/h for A/B. With this choice of A/B, the isoeffect curve is drawn in Fig 1. The data attributed to Paterson[17] and the calculated curve from the present theory nearly coincide exactly (within 1%). Let us suppose that the proliferation effect is negligible in the dose-rate range where Paterson and Green has obtained their data. Then, $a = A$ and $b = B$. This assumption is justified by the outcome of the calculation which uses this assumption in Eq. (23). Namely, the substitution of a set of assorted

Fig. 2. Isoeffect curves for proliferatng tissues
With the choice of 0.71 for the value of a/b and 0.27 for a (this value for a is obtained from analyzing the cell survival data of both Bedford and Hall[34] and also Mitchell et al.[18]),the curves of the equipotent total dose vs. the required time to deliver it are drawn. The upper curve refers to the tissue doubling time (abbreviated as DT in the legend) of 10 days and the lower two curves refer to the tissue doubling time of 60 days and 1 year. The data given by Paterson[17] nearly coincide with the calculated curves where they are available.

Fig. 3. Isoeffect curves at various values of A/B
The equipotent total doses are plotted relative to the dose at 0.357 Gy/h (assumed to be 60 Gy) for a given value of A/B ratio. As the A/B ratio is increased, one obtains a family of flattening isoeffect curves. This decrease in the slope of the isoeffect curves indicates a lesser dependence of the total dose on the dose-rate. Tissues which respond fast to the action of radiation and may repair the damage fast also so that most of reparable damage is repaired would fall into this category. On the other hand, a smaller A/B indicates a relative importance of the dose-rate dependent term and refers to a slowly responding tissue.

proliferation rates, the found values for A and B into Eq. (23) extrapolates the isoeffect curve of Paterson as shown in Fig 2. The isoeffect curves of different growth rates do not diverge until the dose-rate is decreased to 25 cGy/h. It is interesting to note that Paterson's data are terminated at the dose-rate where the proliferation begins to contribute toward the total dose. Below the dose-rate of 25 cGy/h, the isodose does depend on the rate of proliferation. Much below this dose-rate the isodose is a sharply increasing function of the proliferation rate.

It was determined in the APPENDIX 1 that the A term gives the dose-rate independent portion of survival/growth curve and the B term contributes to the dose-rate dependence of survival/growth. If the value of this ratio is increased, one obtains a family of flattening isoeffect curves, and when A/B is decreased, the curves become steeper (see Fig. 3). The decrease in the slope of the isoeffect curves as A/B is increased indicates a lesser dependence
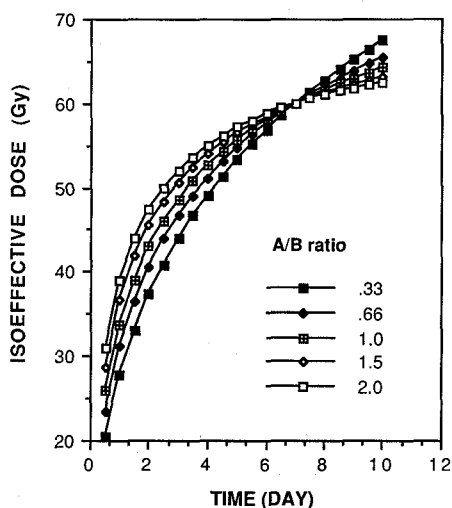
of the total dose on the dose-rate and the characteristics of fast-reacting tissue. When A/B is decreased, the curve exhibits the characteristics of a slow-reacting tissue.

The time dose-rate relation of Eq. (19) can be written in the same spirit. Thus,

$$\frac{T}{T_s} = \frac{Ar_s + B_s r_s^2}{Ar + Br^2}. \tag{25}$$

The time can be plotted as a function of r with the A/B ratio varied around the best fit for Paterson's data. The log-log plot of this relation is given in Fig. 4. Note that the curve is not a straight line but possesses a slow downward turn at the 168 hour point. Curiously, a similar turn is observable in Hall's plots[27] of clinical data of Green and of Paterson.

2. Derivation of an Isoeffect Formula Connecting Continuous and Fractionated Regimens

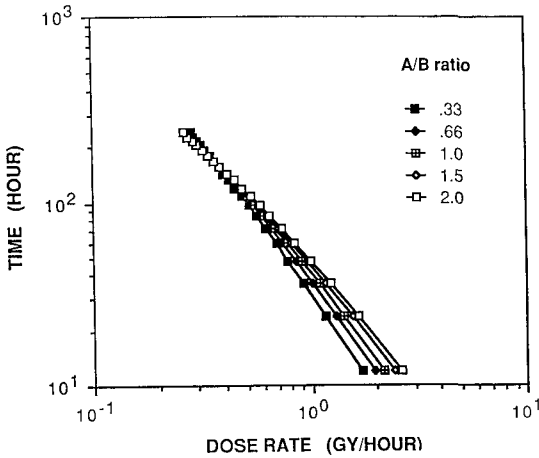When the proliferation rate is assumed to be

Fig. 4. Time-dose-rate isoeffect relation

The curves correspond to the log-log plot of the dose-rate vs. the treatment time required to achieve the same end point at the same values of A/B as chosen in Fig 2. Observe that the isoeffect curves are not a straight line. The curves corresponding to the data of Paterson and to $A/B=0.66$ are essentially the same and similar to the plots given by Orton[6].

Table 1. Prediction of Total Doses Equivalent to 60 Gy at 0.357 Gy/h

Fractional dose (Gy)	Total dose (Gy)
.85	
	75.5
1.15	
	71.1
1.20	
	70.4
1.60	
	65.4
1.80	
	63.1
2.00	
	61.0
2.50	
	56.3
3.00	
	52.3
3.50	
	48.8
4.00	
	45.8
5.00	
	40.0

It is reasonable to equate the proliferation effect in the continuous regimen of dose-rate .357 Gy/h to that of the equipotent plan for the same duration but in the fractionated regimen. An 8 equal-fraction acute doses given for 7 days, which is equivalent to constant irradiation over the same period at the dose-rate of 0.357 Gy/h, is computed to be 5 Gy each (the last line). This is exactly the value clinially observed by Eillis[28]. This 8 fraction 40 Gy treatment is equivalent to 30 fraction 60 Gy treatment if the α/β theory and a value of 4 Gy for the ratio are used.

constant following the division delay between fractions, the surviving fraction can be obtained from Eq. (11). For two schedules of fractional doses of d_1 and d_2, their total doses D_1 and D_2 are related by the following equation if they are to be isoeffective:

$$\frac{D_1}{D_2}=\frac{\gamma_0(\Delta_2-z_{av}d_2)/d_2-\alpha-\beta d_2}{\gamma_0(\Delta_1-z_{av}d_1)/d_1-\alpha-\beta d_1} \tag{26}$$

where Δ's are the time span beween a pair of adjacent fractional doses. One should note here that the alpha-beta theory[9] follows only when the overall growths for the entire therapy duration are the same for the two plans.

For constant continuous irradiation, it can be shown from Eqs. (9) and (17) that

$$\log f=T(\gamma_0(1-\eta r)-ar-br^2) \tag{27}$$

where T is the treatment time for constant dose-rate therapy. By equating Eqs. (11) and (27) at the same survival fraction, one can show the isoeffect relationship between the schedule of N fractions at d Gy and the schedule of continuous T-hour treatment at a constant dose-rate. The correlation factor I is equal to 1 at the low dose-rates where growth is important. Thus,

$$\frac{D_f}{D_c}=\frac{\alpha+2\beta r/\mu-\gamma_0(1/r-\eta)}{\alpha+\beta d-\gamma_0(\Delta/d-z_{av})} \tag{28}$$

where D_f and D_c denote the total doses equally

potent but for the regimens of fractionation and continuous low dose-rate, respectively, and they are:

$$D_f=Nd$$

and

$$D_c=Tr.$$

Eq. (28) can be solved explicitly for the acute dose d in terms of the dose-rate of continuous irradiation, or vice versa. When the proliferation terms are included into the parameters, A and B as in Eq. (24), the fraction size d of a N fraction course which is equivalent to a T hours' continuous irradiation of constant dose-rate r is:

$$d=\frac{\alpha}{2\beta}\left(-1\pm\sqrt{1+4\frac{T}{N}\left(\frac{A}{\alpha}r+\frac{r^2}{\alpha/\beta}\right)\frac{\beta}{\alpha}}\right). \tag{29}$$

When the parameter takes the following values:

$$\frac{\alpha}{\beta} = 4 \text{ Gy} \tag{30}$$

$$\frac{A}{B} = 0.7 \text{ Gy/h} \tag{31}$$

the 8 equal-fraction acute doses given for 7 days, which is equivalent to constant irradiation over the same period at the dose-rate of 0.357 Gy/h, is computed to be 5 Gy each since $T/N = 21$ hours in Eq. (29). This is exactly the value clinically observed by Ellis[28].

When the durations of treatment regimens are different, however, the cancellation of proliferation terms would not be legitimate unless the proliferation rate of the tissue in question is very low. Nevertheless, this 8 fraction 40 Gy treatment is computed to be equivalent to 30 fraction 60 Gy treatment if the same values for the parameter ratios as given in Eqs. (30) and (31) are assumed (see Table 1). Therefore, the overall consistency leads one to conclude that the value 0.7 Gy/h for A/B is equivalent to 4 Gy for α/β.

DISCUSSION

The low dose-rate isoeffect formula represented by Eq. (24) explains the existing data extremely well. Eq. (24) is similar in appearance to the isoeffect relation of Withers et al.[8]. This latter relation is applicable to fractionated acute doses and not to continuous low dose-rate doses. We have shown that, apart from the proliferation dependent terms, these relations are two opposite limiting cases of a more general relation Eq. (23), which is valid over a wide range of dose-rates. The general survival equation represented by Eq. (8) is a proliferation-corrected model of Roesch[14,15] and others[21]. Some of the low and high dose-rate survival curves of Mitchell et al. can be reasonably fitted by Eq. (8) after correcting for the exaggerated survival of multicell colonies[19].

The isoeffect data obtained by Green and also those attributed to Paterson agree very well with the predictions of Eq. (24), provided A/B is chosen to be around 0.7 Gy/h (The implication of this particular value will be discussed in this and subsequent paragraphs). If this ratio is increased, the theoretical isoeffect curves become less steep. The flattening curves indicate that the total dose applied to reach a certain clinical value depends less critically on the number of days treated and therefore, on the dose-rate. Such slow dependence of isoeffect doses on the dose-rate would occur in tissues in which sublethal damage is repaired well

to permit less of its lethal conversion. When the biological end point for the isodose is the tumor control instead of normal tissue tolerance, the A/B ratio is generally greater and the dose-rate dependence will be slower. On the other hand, the smaller the A/B ratio, the steeper the isoeffect curve becomes. This signifies the increased importance of the dose-rate dependent term and the slow repair of sublethal damage which can lead to greater cell death by a lethal conversion. As the repair kinetics slows, cell death by compounded sublethal hits becomes increasingly important.

Applying the concept underlying Eq. (24), one can explain the absence of dose-rate effects observed in the mouse KHT sarcoma[29] in terms of a large value for the A/B ratio. Similarly, dose-rate independent choices for the total doses used to treat head and neck tumors by Pierquin[30] can be justified on the basis of high A/B ratio for the tumors. The survival curves obtained by Hill and Bush show no shoulder, even those taken at high dose-rates. This is an indication that the β value for this tumor is very small. Thus, B is also small, making the A/B ratio large. Reoxygenation cannot explain the absence of the shoulder for high dose-rate survival, and cannot lower the survival for low dose-rates also because it takes hours before lethally hit cells lose their respiratory function.

Equating α and A, we have obtained results which are consistent with several clinical data sets. This consistency depends critically on the choice of value 4 Gy for the α/β ratio, which corresponds to the value of 0.7 Gy/h for A/B. Elsewhere we have also shown that the NSD/CRE formulation and a growth-incorporated $\alpha - \beta$ theory are equivalent in clinically important doses and dose-rates if α/β ratio is 4.5 Gy and γ/β ratio is 1.5 Gy^{2}Day^{-1} [31]. O'Donoghue obtained $\alpha/\beta = 3$ for the best fit of Paterson's curve using Dale's formula [13, see also 32]. This indicates that, in obtaining their data, Paterson, Ellis, and Green might all have used the same biological end point for the tolerance level. This end point is closer to the late effect of a tissue than to the early effect. This is also consistent with the statement by the originator of the NSD formula: "the NSD concept·····aimed to provide a one-figure estimate in rets, based on deductive and inductive reasoning, of the late effects of normal connective tissue"[33].

Thus, the biological end point used by Paterson, Ellis, and Green corresponds to an approximate α/β ratio of 4 Gy in the isoeffect formula for the tissue tolerance. In the constant low dose-rate regimen,

the same biological end point corresponds to an A/B ratio of 0.7 Gy/h in the low dose-rate formula. If proliferation does not play a critical role as in an accelerated schedule, the ratio $2\dfrac{A/B}{\alpha/\beta}=2\times(0.7/4)=0.35$ per hour is equal to the repair rate μ. This value is rather low but not far off from the value 0. 46 per hour found by a different analysis of direct experiments[13].

The assumption made to derive Eq. (9) is the approximation the low dose-rate allows. In the low dose-rate limit, any valid survival model should lead to Eq. (9) for the surviving number of cells, as shown in APPENDIX 1. The proliferation dependent terms contain a dose-rate dependent term and they can be expanded in the powers of the dose-rate. Growth rate, growth fraction, division delay, and cell loss factor all depend on the dose-rate. At sufficiently low dose-rates, however, any term beyond quadratic in the dose-rate in the series expansion can be neglected. Only when A and B are equal to α and $2\beta/\mu$, respectively *and* when the proliferation term is unimportant, our formulas are reduced to those found by Dale[13].

The isoeffect formula of Withers et al.[9] predicts the total doses required to achieve the same response among schemes utilizing distinct sets of uniformly fractionated doses. The total dose predicted by this theory depends on two variables: the fractional dose d and the tissue responding speed, α/β ratio. In NSD formulation the total dose depends on the total time of delivery as well as the total number of fractions. Thus, unlike the formula of Ellis, the $\alpha-\beta$ theory does not depend on the total time of delivery of fractional doses. The reason for the absence of the time factor is simple: the theory does not explicitly take into account the dynamic changes occurring during therapy such as proliferation, cell loss, cell cycle redistribution, cell cycle delay, and recruitment of stationary cells into the cycling population.

Difficulties in predicting the outcome of irradiation at *very* low dose-rates arise from determining proliferation, lethal conversion of sublethal lesions, and other dynamic terms. We have given a first-order approximation for the proliferation and division delay in isoeffect formulas. For the tissues proliferating during irradiation particularly at protracted low dose-rates and and for the tissues fast-responding with respect to regeneration, the tolerance dose is greater than that of the same tissues but non-proliferating. For most normal tissues, having a low turnover rate, the division delay

per Gy is longer than the duration for typical brachytherapy. Then, proliferation is not important. There are exceptions, however. Permanent implant therapy is effective for many half lives of isotopes involved. For rapidly regenerating tumors, proliferation must be taken into consideration.

For tumor control, determination of the additional dose to counter proliferation is desirable, but not a trivial matter. First, the proliferation rate of the tumor is not easy to estimate. Second, even if the proliferation rate is known in the absence of irradiation, it is difficult to predict the growth in the presence of protracted irradiation because of the cell arrest in a cell cycle phase and radiosensitivity changes due to this effective elongation of cell cycle. Thus, it is clear that the effectiveness of low dose-rate radiation in cell killing and cell arrest must be known as a function of the dose and the dose-rate. However, it is difficult to determine the net cell survival experimentally without knowing the rate of cell multiplication. Hence, a serious dilemma exists in the problem. The circular problem can be overcome if there is a theory governing cell survival and proliferation in low dose-rate range. This goal has partially been met by the present work.

In order to test the validity of Eq. (28), the isoeffect formula connecting the equipotent doses of the continuous and fractionated regimens, we assumed the equality of our parameter A and α of the linear-quadratic model. a (or A) should be distinct from α because of possible difference in the quality of radiation for the high and low dose-rate regimens and because of the dissimilarity in the effects of division delay. They can also differ because of different cell cycle redistribution effects. When an acute dose is applied for a short time, the cell cycle is not affected *during* the irradiation time. On the other hand, during a protracted irradiation including fractionated plans, altered cell cycle can change the cell sensitivity to subsequent irradiation. Thus, it is inconceivable that the survival curve in each regimen can be summarized just with two parameters and that one in each set is perfectly preserved throughout the wide range of the dose-rate.

Nevertheless, if α is also obtained by clinical data but not from a single-dose in vitro survival curve, the 'spill-over' effect would be *similar* for both α and A.

CONCLUSION

A general form for cell proliferation has been incorporated into Roesch's survival equation (Accumulation Model). In the high dose-rate limit, the equation leads to an LQ model modified for proliferation.

When a constant proliferation rate and known facts of division delay are assumed, three practical isoeffect formulas can be obtained: one relating a total dose in the low dose-rate regimen to another in the same regimen, the second formula relating a total dose in the fractionated regimen to another in the same regimen, and the third relating a total dose in the low dose-rate regimen to another in the fractionated regimen.

Independent of the proliferation term, the prediction of total doses equivalent to 60 Gy delivered at the constant dose-rate over 7 days agrees well with the dose-time data of Paterson and of Green, when the parameter ratio $A/B (\approx \alpha\mu/2\beta$ where μ is the repair rate) is chosen to be 0.7 Gy/h.

Applying this latter formula, one can explain the absence of dose-rate effects observed in the mouse KHT sarcoma on the basis of a large value for the A/B ratio. Similarly, a dose-rate independent choice for the total doses used to treat head and neck tumors by Pierquin can be justified on the basis of a high A/B ratio for the tumors.

An isoeffect relationship between low and acute dose-rate treatments can be derived. This formula predicts exactly the data of Ellis that 8 fractions of 5 Gy/day for 7 days are equivalent to continuously applied 60 Gy over 7 days, provided the A/B ratio is 0.7 Gy /h and the α/β ratio is 4 Gy. From this result we find that the repair rate μ is equal to 0.35 per hour.

Overall agreement between the clinical data and the predictions made by the formula at the above parameter values suggests that the biological end points used as the tolerance level in the studies by Paterson, Green, and Ellis all agree and they are not entirely the early effects as generally assumed.

If exponential growth is assumed and the known dose dependence of cell cycle elongation (= division delay) is used, radiation cell survival and isoeffect formulas are applicable in the low dose-rate range for tissues exhibiting regenerative response during therapy.

APPENDIX

1. Low Dose-Rate Approximation

An alternative approach leading to Eq. (9) will be given without any assumption with regard to the repair kinetics. The sublethal damage and its repair are important, but no assumption is necessary for the low dose-rate with regard to the kinetics of fading damage.

A continuous irradiation may be considered as a succession of many but small discrete pulses of radiation. The final outcome of such irradiation cannot, however, be decomposed into a sum of the effects of the small radiation pulses. This is because sublethal lesions produced by different radiation pulses can interact to give rise to a lethal damage. In the limit of low dose-rate, such interaction of lesions with be less likely to occur.

Thus, the fractional change in the cell number(n) in a tissue may be expanded in the series of powers of the dose-rate r.

$$\frac{1}{n(t)}\frac{dn}{dt} = gG - Ar - Br^2 + O(r^3) \tag{A1}$$

The first term in the right hand side of Eq. (A1) represents the growth/loss term with G denoting the dose-rate independent growth rate including cell loss rate and g the growth fraction. A is the weight of dose-rate independent term and B is the same but linear in dose-rate for cell survival. Both parameters A and B may contain contributions from the radiation-induced changes in the proliferation rate and in the growth fraction. In subsection 1 of RESULTS section, a concrete example of such a 'spill-over' is discussed; the contribution from the division delay has the linear dose-rate dependence and it should be absorbed into A. If the growth fraction is zero, the second term comes from the single-hit killing and the third term originates from cell killing by a pairwise interaction of sublethal cellular lesions in the context of the Accumulation Model of Roesch. We shall assume at this point that any term containing the dose-rate in the power equal to or higher than 3 is negligible. We adopt 'hour' as the unit of our time and 'Gray' for the radiation dose. Henceforth the dimension of G is inverse hour (h^{-1}), the dimension of A is inverse Gray (Gy^{-1}), and the same of B is, then, $h \cdot Gy^{-1}$.

Therefore, in the low dose-rate limit, the number of surviving cells is obtained by integrating Eq. (A1):

$$n(t) = n(O)e^{\int gGdt - Art - Br^2t} \tag{A2}$$

To conform to the spirit of linear time-

dependence, we assumed gG to be constant in time. Such a linear dependece of the growth on time has been osberved for low dose-rates by Mitchell et al.[18] This equation can also be derived in the limit of low dose-rate using a more general expression formulated in the context of specific models. Thus, we made the contact with Eq.(9) of the main text.

When a constant dose-rate radiation is applied for a time inerval of t, the total dose D is given by

$$D = rt \tag{A3}$$

Thus, the time of irradiation may be expressed in terms of the total dose D and the dose-rate r:

$$t = D/r.$$

Then, Eq. (A2) may be expressed in terms of the total dose and the dose-rate.

$$N(D, r) = N(O) e^{gGD/r - AD - BrD} \tag{A4}$$
$$-\log f = D(A + Br - gG/r) \tag{A5}$$

It is important to notice here that the logarithm of the surviving fracton, $\log f = \log N/N(O)$ has the dose-rate dependent slope:

$$\frac{\partial \log f}{\partial D} = gG/r - A - Br. \tag{A6}$$

Thus, A provides the dose-rate independent slope to the survival curve while the proliferation and B terms provide the dose-rate dependence.

2. Repair Kinetics of Lesions Giving Rise to G_2 Arrest

The cellular lesions leading to G_2 arrest are repaired until the lesion is expressed. The kinetics of the decay of surviving lesions are needed to determine the cell age dependence of the effectiveness of the lesions leading to G_2 arrest. For simplicity, we shall assume a decay rate of ρ for an exponential function of the time between the creation (t_x) of a lesion and the expression (t_p) of the mitotic delay.

$$e^{-\rho(t_p - t_x)} \tag{A7}$$

Then, the number $\nu_q(D)$ of the damage lesions which are produced by a radiation dose of D given at the cell age of t_x but survive to add to the G_2 arrest is:

$$\nu(D) = Dqe^{-\rho(t_p - t_x)} \tag{A8}$$

where q is the number of the lesions produced per unit dose of radiation and the lesions are repaired at the rate of ρ. Thus, the delay per Gy is given by.

$$z = z_p e^{-\rho(t_p - t_x)} \tag{A9}$$

where z_p is the division delay per Gy of radiation given at t_p, and t_p is the last time point of G_2 at which division delay can be induced and t_p is slightly shorter than the cell cycle time.

The superposed effect of division delays scored by individual cells in an asynchronous population is an average of delays suffered by cells irradiated at all points t_x along the cell cycle.

Thus,

$$\frac{1}{\tau_c} \int_0^{\tau_c} dt_x \int_{2d}^{\Delta} dt\gamma$$
$$= \gamma_0 \left(\Delta - \frac{z_p(1 - e^{-\rho t_p})}{\rho \tau_c} d \right) \text{ only for } t_1 < zd \tag{A10}$$

where τ_c is the cell cycle time. Hence,

$$z_{av} = z_p \frac{(1 - e^{-\rho t_p})}{\rho \tau_c}. \tag{A11}.$$

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국문초록 =

재생과 증식에 기인하는 선량률 효과

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Roesch의 생존 방정식속에 세포증식으로 일어나는 생존증가를 가장 일반적 형식으로 포함시킨 식을 유도하고 이 식으로부터 저선량률 방사선에만 적용되는 동결과선량식 (isoeffect formula)을 유도하였다. 이 저선량률식이 파라메터 하나로 결정해주는 총선량은 Paterson과 Green에 의하여 얻어진 실험 임상결과와 일치한다. 이 파라메터와 선량률효과 사이의 관계의 의의를 논하였다. 또한 고선량률 분절(fractionation) 치료와 동저선량률 계속치료를 연락하는 동결과 선량식을 유도 사용하여, Ellis가 잰 실험결과와 비교하였다. 그 결과, Ellis와 Paterson이 쓴 'tolerance'의 표준이 α/β의 비 4 Gy에 해당하는 것임이 밝혀졌다. 그러므로 이들의 'tolerance'의 표준은 'early effect'에만 두고 본것이 아님을 알 수 있다.

개념적인 면에서도, 아래와 같은 새로운 견해가 나올 수 있다. KHT sarcoma의 생존선도(survival curve)에 선량률효과가 보이지 않는 이유로 α/β의 비가 큰 점을 들을 수 있다. 이것은 이 survival curve에 어깨(shoulder)가 보이지 않는 것으로도 증명이 된다. Pierquin이 선량률에 무관하게 head and neck tumor치료에 같은 총선량을 쓴 것을 정당화시킬 수 있다.