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The Linear-Quadratic Model and Most Other Common Radiobiological Models Result in Similar Predictions of Time–Dose Relationships

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One of the fundamental tools in radiation biology is a formalism describing time–dose relationships. For example, there is a need for reliable predictions of radiotherapeutic isoeffect doses when the temporal exposure pattern is changed. The most commonly used tool is now the linear-quadratic (LQ) formalism, which describes fractionation and dose-protraction effects through a particular functional form, the generalized Lea-Catcheside time factor, *G*. We investigate the relationship of the LQ formalism to those describing other commonly discussed radiobiological models in terms of their predicted time–dose relationships. We show that a broad range of radiobiological models are described by formalisms in which a perturbation calculation produces the standard LQ relationship for dose fractionation/protraction, including the same generalized time factor, *G*. This approximate equivalence holds not only for the formalisms describing binary misrepair models, which are conceptually similar to LQ, but also for formalisms describing models embodying a very different explanation for time–dose effects, namely saturation of repair capacity. In terms of applications to radiotherapy, we show that a typical saturable repair formalism predicts practically the same dependences for protraction effects as does the LQ formalism, at clinically relevant doses per fraction. For low-dose-rate exposure, the same equivalence between predictions holds for early-responding end points such as tumor control, but less so for late-responding end points. Overall, use of the LQ formalism to predict dose–time relationships is a notably robust procedure, depending less than previously thought on knowledge of detailed biophysical mechanisms, since various conceptually different biophysical models lead, in a reasonable approximation, to the LQ relationship including the standard form of the generalized time factor, *G*. © 1998 by Radiation Research Society

INTRODUCTION

The rationale for much quantitative radiation biology is the need to predict both dose–response and time–dose relationships. As an example, many of the developments in modern radiotherapy have been driven by the possibility of predicting isoeffect relationships for alternate fractionated or protracted regimens, i.e. when the temporal pattern of the exposure is changed. Such predictions require a mathematical formalism, often, but not always, based on some underlying biophysical model.

The tool most commonly used for such quantitative predictions of time–dose dependences is the linear-quadratic (LQ) formalism (*1–9*). In radiotherapy, the LQ formalism is now used almost universally for calculating isoeffect doses for different fractionation/protraction schemes (*4–8*). In contrast to earlier methodologies, such as NSD or TDF (*10*), which were essentially empirical descriptions of past clinical data, the LQ formalism has become the preferred tool largely because it describes a mechanistically based model, with tumor control and normal-tissue complications attributed specifically to cell killing, The rationale here is that a formalism with a mechanistic underpinning is less likely to be subject to catastrophic failure, as had occasionally happened with empirically based models (*11*).

The LQ model stems from the curvilinear nature of dose–response curves for the log of cell survival—this curvature ultimately being the basis of time–dose effects (*6, 12*). In most expositions of the LQ approach, the curvature is assumed to be related to the production of pairs of primary lesions [often, though not necessarily, associated with DNA double-strand breaks (DSBs) or a subset of DSBs] by two different radiation tracks—two such DSBs being needed to produce a lethal lesion, such as a dicentric chromosome aberration, through binary misrepair. Protracting the exposure time potentially allows the first lesion to be repaired before the second is produced, and the LQ approach quantifies this effect (*6, 9, 12*). This binary misrepair model is the most common mechanistic rationale for the standard LQ formalism, but different biological rationales for the same formalism have also been given (see review in ref. *9*).

It is important to stress here that the standard LQ formalism, as applied to time–dose relationships, is *not* merely a truncated power series in dose. Its key feature here is a specific functional form for the time factor, usually designated by *G*, which takes into account dose protraction or

fractionation. Expressions for special cases of the time factor, G, were derived by Lea and Catcheside (*1*, *2*); a general form was subsequently suggested (*13*) and has since been rederived from several different points of view (*9*). We refer to this general form of the time factor, given explicitly in Eq. (3) below, as the generalized Lea-Catcheside time factor, G.

It has been known for some time that the formalisms describing various other binary misrepair models (e.g. refs. *14*, *15*) also lead to the same generalized Lea-Catcheside time factor, G, in an appropriate approximation, and thus predict virtually the same time–dose relationships as does the LQ approach. This result was demonstrated by several authors (*15–18*) for the repair–misrepair (RMR) model (*14*), the lethal–potentially lethal (LPL) model (*15*) and more general binary misrepair models. The conditions for equivalence are that the dose or dose rate not be too large, and that survival is determined after repair and misrepair have been completed. In light of the conceptual similarities between the LQ model and other binary misrepair models, the fact that the corresponding formalisms make virtually equivalent predictions for dose–time relationships is not, in retrospect, particularly surprising.

The LQ approach, in its general form relating to time–dose effects, has been investigated extensively over several decades and has now received a substantial level of general acceptance. However, debate has continued as to whether the explanation of dose–response curvature and dose protraction effects in terms of binary misrepair is, in fact, correct. Specifically, there has remained a persistent school of thought that the curvature of dose–response relationships, and thus the major effects of dose protraction, might be due to an entirely different biochemical mechanism, "saturable repair", in which the per-lesion repair rate is decreased as the dose—and the production of initial damage—increases (*19–30*). Such a saturable repair mechanism can produce curvilinear dose–response curves, because of decreased repair efficiency with increasing dose, and could also be responsible for dose-protraction effects, through increased repair efficiency when damage arrives piecemeal over the protracted irradiation period.

While binary misrepair models, such as LQ, remain the most plausible basis for the majority of the repair-related dose-protraction effects of relevance in radiotherapy, the alternative, saturable repair approach has not been ruled out definitively. This observation should be of some concern, considering that the LQ formalism is now widely used for applications in radiotherapy. Since saturable repair models appear, *prima facie*, to be quite different from the LQ model, there is the possibility that saturable repair formalisms could make significantly different predictions of fractionation/protraction effects, casting doubt on the validity of current LQ-based isoeffect dose calculations.

In this paper we use analytical techniques to show that, remarkably, the formalisms describing most saturable repair models also lead, in an appropriate approximation, to the same time–dose relationships as does the LQ formalism. This comes about because, as we shall show, these saturable repair formalisms reduce to the specific form of the generalized Lea-Catcheside time factor, G, which describes protraction effects in the LQ approach. Numerical estimates are then given to show that a typical saturable repair formalism makes similar predictions of dose-fractionation effects as does the LQ formalism, at doses relevant to radiotherapy. Specifically, in a comparison of any two practical fractionated external-beam radiotherapy regimens, the predicted isoeffect doses are very similar using either the LQ or the saturable repair formalism. This equivalence of isoeffect doses also holds for calculations aimed at matching tumor control in low-dose-rate brachytherapy, though less so for calculation of isoeffect doses for late effects in brachytherapy.

METHODS

The Effects of Time in the LQ Formalism

Suppose a uniform population of many cells is irradiated with total dose D, delivered acutely or in a fractionated/protracted regimen. We assume here that the cells are not cycling—though the effects of redistribution of cells in the phases of the cell cycle, as well as proliferation, can be considered in extensions to the LQ model (*31*, *32*). The overall regimen can be described by a dose-rate function $\dot{D}(t)$, which tracks the change in dose rate as a function of time into the treatment, and so can represent any possible protracted exposure regimen: acute, fractionated, constant low dose rate, variable low dose rate or a mixture of these.

The LQ model, in its most usual current version, describes cell killing in terms of the following mechanisms:

1. Radiation produces DNA DSBs with a yield proportionate to the dose.
2. These DSBs can be repaired, with first-order rate constant λ (equal to $\ln 2/T_{1/2}$, where $T_{1/2}$ is the repair half-time). In practice, there may be more than one class of DSBs which may be repaired with different rate constants; the LQ formalism can simply be extended to take this into account (*32–34*).
3. In competition with DSB repair, binary misrepair of pairs of DSBs produced from *different* radiation tracks (i.e. different X or γ rays) can produce lethal lesions (often identified as predominantly dicentric chromosomal aberrations), the yield being proportional to the *square* of the dose (see the quadratic term in Eqs. 1 and 2). The two independent radiation tracks can occur at different times during the overall regimen, allowing repair of the first DSB to take place before it can undergo pairwise misrepair with the second; it is this phenomenon which is the heart of the fractionation/protraction dependence in the LQ formalism.
4. In addition, *single* radiation tracks can produce various lethal lesions, possibly by a variety of mechanisms (*9*), the yield being proportional to the dose (the linear term in Eqs. 1 and 2).

Overall, in the LQ formalism, the yield (Y) of lethal lesions and the corresponding survival (S) equation are

$$Y \propto \alpha D + G\beta D^2 \tag{1}$$

and

$$S = \exp[-(\alpha D + G\beta D^2)], \tag{2}$$

where G is the generalized Lea-Catcheside time factor, which accounts quantitatively for fractionation/protraction; it is important to note that G

acts only on the quadratic component, as described in point 3 above. The generalized time factor has the form (*5*, *13*)

$$G = (2/D^2) \int_{-\infty}^{\infty} \dot{D}(t)dt \int_{-\infty}^{t} e^{-\lambda(t-t')} \dot{D}(t')dt'. \quad (3)$$

Generically, the term after the second integral sign refers to the first of a pair of DSBs required to produce a lethal lesion—the exponential term describing the reduction in numbers of such DSBs through repair. Similarly, the term after the first integral sign refers to the second DSB, which can interact with DSBs produced earlier that still remain after repair.

The time factor, G, can be calculated for any fractionation/protraction scheme, and systematically accounts for the effects of protracting the dose delivery in any way. G can take values from zero to one, with $G = 1$ for a single acute dose. The interpretation of $G < 1$ is a reduction in cell killing due to repair which occurs *during* continuous low-dose-rate irradiation and/or between fractions.

Two special cases, which illustrate the main features of the general expression (Eq. 3), are (a) for continuous irradiation consisting of a constant dose rate D/T for time T; then (*2*)

$$G = [2/(\lambda T)^2][\theta - 1 + \lambda T], \quad (4)$$

where $\theta = \exp(-\lambda T)$; (b) for irradiation with n short fractions, each separated by a time T; then (*17*)

$$G = [2\theta/(1 - \theta)]\,[n - (1 - \theta^n)/(1 - \theta)]. \quad (5)$$

More complicated fractionation/protraction schemes have more complicated time factors, G, any of which can be calculated (*5*) from Eq. (3).

Saturable Repair Formalisms

Various saturable repair models have been considered (e.g. refs. *19–29*), all having in common the notion that the per-lesion repair rate decreases as the dose—and the production of initial damage—increases. In the following, we consider a representative model proposed by Kiefer (*23*). However, the results we derive hold for most models of this class, with one exception which we shall note.

Saturable repair models generally consider the production of "initial lesions", which can be repaired or can undergo misrepair to produce lethal lesions. We here denote the average numbers of initial and lethal lesions per cell at time t by $U(t)$ and $L(t)$, respectively. In the particular saturable repair formalism proposed by Kiefer (*23*), the average yield of these lesions is given by

$$\frac{dU}{dt} = \delta \dot{D} - \frac{\lambda_1 U}{1 + \varepsilon_1 U} - \frac{\lambda_2 U}{1 + \varepsilon_2 U}, \quad (6A)$$

$$\frac{dL}{dt} = \frac{\lambda_2 U}{1 + \varepsilon_2 U}, \quad (6B)$$

where the first term in Eq. (6A) corresponds to the production of initial lesions, the second to their repair and the third to the formation of lethal lesions from initial lesions. Here δ, λ_i and ε_i ($i = 1,2$) are adjustable parameters interpreted as follows: δ is the number of initial lesions produced per unit dose, and the terms involving $\varepsilon_1 U$ in Eq. (6A) correspond to saturable repair (technically, Michaelis-Menten) kinetics—as U gets large, the average repair rate per repairable lesion $[\lambda_1/(1 + \varepsilon_1 U)]$ decreases, corresponding to increasing overloading of the repair system. Similar comments apply to the misrepair term producing lethal lesions, i.e. involving λ_2 and ε_2.

When supplemented by initial conditions, the differential equations (6A and 6B) uniquely determine $U(t)$ and $L(t)$. It is assumed that the surviving fraction S is

$$S = \exp[-L(\infty)], \quad (6C)$$

where the use of $t = \infty$ reflects the assumption that survival is determined after repair and misrepair have run their full course. The use of the exponential, common to all these formalisms as well as to the LQ formalism, corresponds to the assumption that lethal lesions are Poisson-distributed from cell to cell, which is appropriate for low-LET radiation, though not at high LET (*9*, *35*).

RESULTS

Fractionation/Protraction in Saturable Repair Formalisms: Analytical Results

In this section we discuss how the LQ formalism, including the G factor describing the effects of fractionation/protraction (see Eqs. 2 and 3), approximates saturable repair formalisms at clinically relevant doses and dose rates.

In the case of the particular saturable repair formalism described above, we show in Appendix I that, for low doses or dose rates, this can be written in the form of the LQ equation, $S = \exp(-\alpha D - G\beta D^2)$, where G is the generalized Lea-Catcheside factor calculated from Eq. (3). Specifically, survival can be written in terms of the parameters of the saturable repair formalism as

$$S = \exp\{-[\lambda_2\delta/(\lambda_1 + \lambda_2)]D - G\,[\delta^2\,\lambda_1\,\lambda_2\,(\varepsilon_1 - \varepsilon_2)/2(\lambda_1 + \lambda_2)^2]D^2\}, \quad (7)$$

where G is calculated from Eq. (3) using the sum $\lambda = \lambda_1 + \lambda_2$. In other words, at appropriate doses and dose rates (which we now discuss), this saturable repair formalism reduces to the LQ formalism, with the same dependences on fractionation/protraction. For the special case of a single acute dose, this result was pointed out by Kiefer and Löbrich (*24*).

In Appendix I, approximate inequalities are derived for the doses and dose rates that are small enough that the LQ form of the saturable repair formalism, Eq. (7), is equivalent to the saturable repair equations (6A and 6B). For a single acute dose fraction, a dose condition is

$$D \ll \frac{\alpha}{\beta}\frac{3\lambda_1}{2\lambda_2}, \quad (8)$$

and for a continuous low-dose-rate exposure, a sufficient dose-rate condition is

$$\dot{D} \ll (\alpha/2\beta)\,\lambda_1. \quad (9)$$

In these inequalities, typically $\lambda_1 \gg \lambda_2$, so λ_1 is close to the observed repair rate, λ. Both inequalities involve the ratio α/β.

Fractionation/Protraction in Saturable Repair Formalisms: Numerical Results

In this section, we generate numerical estimates comparing the saturable repair formalism of Eqs. (6) with its

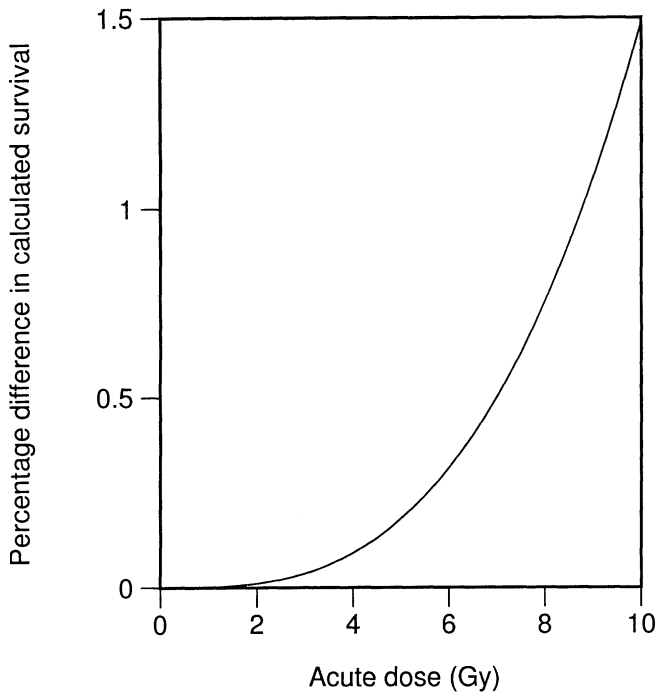

FIG. 1. Single acute dose fraction: percentage relative difference $[100(S_{SR} - S_{LQ})/S_{SR}]$ between survival calculated exactly using the saturable repair formalism (Eqs. 6A and 6B) and calculated using the corresponding LQ approximation (Eq. 7). The parameters used, based (see text) on those from Kiefer and Löbrich (*24*), are $\delta = 14.3\ Gy^{-1}$, $\varepsilon_1 = 0.016$, $\varepsilon_2 = 0$, $\lambda_1 = 1.983\ h^{-1}$, and $\lambda_1 + \lambda_2 = 2\ h^{-1}$. The corresponding equivalent LQ parameters (see Eq. A12) are $\alpha = 0.12\ Gy^{-1}$, $\alpha/\beta = 8.8$ Gy, and $T_{1/2} = 0.35$ h, which are appropriate for early-responding effects such as tumor control.

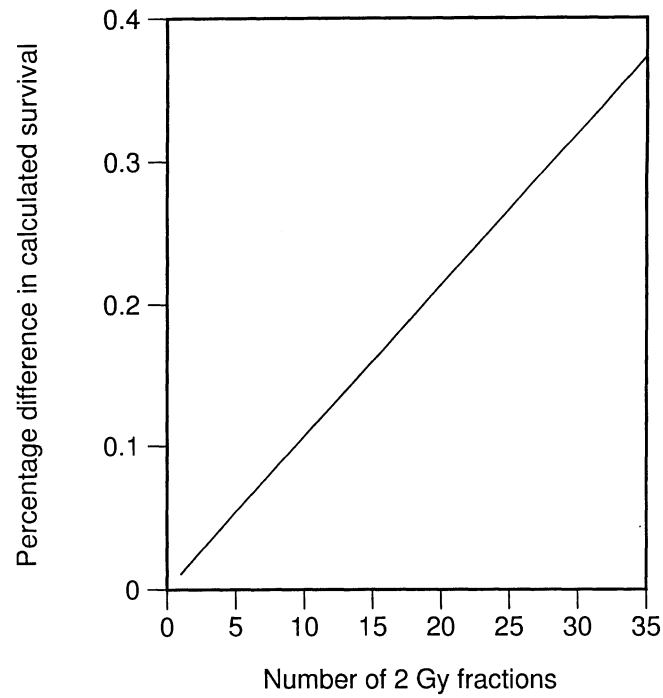

FIG. 2. Multiple daily 2-Gy fractions: percentage relative difference $[100(S_{SR} - S_{LQ})/S_{SR}]$ between survival as calculated exactly using the saturable repair formalism (Eqs. 6A and 6B) and using the corresponding LQ approximation (Eq. 7). Parameters of the formalisms as in Fig. 1.

LQ form (Eq. 7). We compare predictions of the effect of fractionation and protraction in terms of both comparisons of effect at a given dose and comparisons of dose to produce a given effect. To accomplish these comparisons, it is necessary to consider reasonable values for the parameter set $[\delta, \varepsilon_1, \varepsilon_2, \lambda_1, \lambda_2]$ describing the saturable repair formalism of Eqs. (6). We show in Figs. 1–3 some comparisons generated with the parameter set based on that described by Kiefer and Löbrich (*24*), who used the saturable repair formalism (Eqs. 6) to analyze data for survival of mammalian cells (*36*). Their parameter values were $\delta = 14.3\ Gy^{-1}$, $\varepsilon_1 = 0.016$, $\varepsilon_2 = 0$, and $[\lambda_1 + \lambda_2]/\lambda_2 = 119$. These parameters were supplemented with an overall repair constant $[\lambda_1 + \lambda_2]$ of $2\ h^{-1}$, corresponding to a repair half-time of about 21 min (*37*). Based on this parameter set, the equivalent LQ parameter set (i.e. the linear and quadratic dose coefficients in Eq. 7) are (see Eq. A12) $\alpha = 0.12\ Gy^{-1}$, $\beta = 0.0137\ Gy^{-2}$ ($\alpha/\beta = 8.8$ Gy), and $T_{1/2} = 0.35$ h—which are typical values for early-responding tissues (*37–39*).

For the special case of a single acute dose, Fig. 1 compares survival as calculated numerically with the saturable repair formalism (Eqs. 6) and with its LQ form (Eq. 7). Here the agreement is good up to large acute doses, as would be expected from Eq. (8) and the results of Kiefer and Löbrich (*24*).

For a fractionated regimen (in this case, daily 2-Gy fractions), Fig. 2 shows a comparison of survival as calculated numerically with the saturable repair formalism of Eqs. (6) and with its LQ form, Eq. (7). Over the clinically relevant dose range, the LQ form of the saturable repair formalism shows good agreement with the saturable repair model of Eqs. (6), with differences of less than 1% in calculated survival at relevant doses. The corresponding differences in calculated isoeffect doses are very small; for example, doses per fraction calculated to produce isoeffect after 30 fractions are 2 Gy (Eqs. 6) and 1.9993 Gy (Eq. 7). A difference in isoeffect doses that might be clinically significant is probably in the range of 1–3% or more (e.g. one dose fraction in a 35-fraction regimen), so this difference in isoeffect dose of less than 0.05% is insignificant.

Figure 3 compares isoeffect doses for the LQ and saturable repair formalisms calculated at different dose rates to produce the same effect as 35 Gy given at a low dose rate of 0.55 Gy/h (a common practical problem). For example, using the parameter set described above (which is typical for an early-responding end point such as tumor control), the saturable repair formalism predicts the isoeffect dose at 1.5 Gy/h to be 31.2 Gy, while the LQ form of the saturable repair formalism predicts 31.8 Gy.

We have performed similar calculations for a variety of reasonable parameter sets. In all cases, good agreement was found for comparisons of practical fractionated external-beam regimens. For protocols of relevance to brachytherapy, the parameters which most affect the agreement between the saturable repair formalism and its LQ form are the repair constant, λ (or, equivalently, the repair half-time, $T_{1/2}$), and

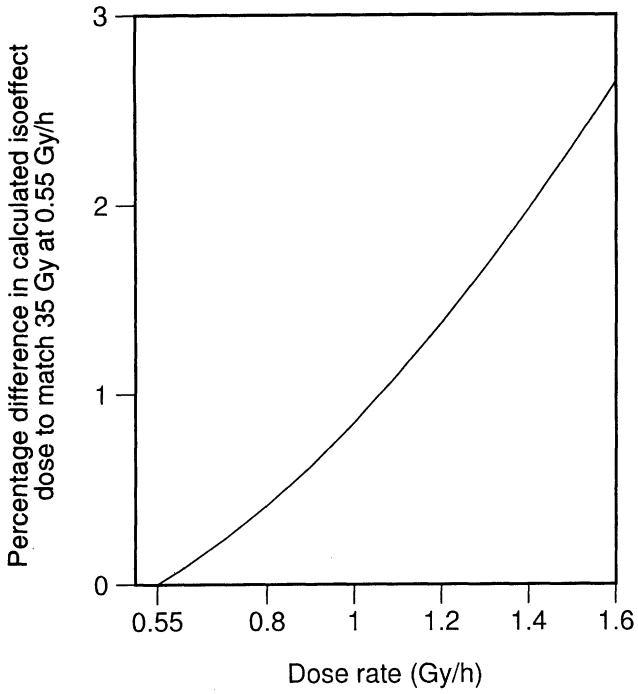

FIG. 3. Continuous low-dose-rate irradiation: isoeffect doses calculated to be equivalent to 35 Gy delivered at 0.55 Gy/h. Percentage relative difference $[100(D_{LQ} - D_{SR})/D_{LQ}]$ between isoeffect doses calculated exactly using the saturable repair formalism (Eqs. 6A and 6B) and calculated using the corresponding LQ approximation (Eq. 7). Parameters of the formalisms as in Fig. 1.

the α/β ratio. As would be expected from Eqs. (8) and (9), the agreement decreases with decreasing λ (increasing $T_{1/2}$) and with decreasing values of α/β. Consequently the agreement will decrease for late-responding tissues, which exhibit smaller α/β ratios (*6*, *38*), and possibly also longer repair times, $T_{1/2}$ [Brenner *et al.* (*40*), but see Fowler (*41*)]. As an example, if the parameter set used above is changed to one typical for late-responding tissue (α/β decreased from 8.8 to 3 Gy, and $T_{1/2}$ increased from 0.35 to 1 h), the difference in isoeffect brachytherapy dose between the saturable repair formalism and its LQ form (using the example in Fig. 3) increases from less than 2% to 4%. In an extreme situation where the α/β ratio is very small (<2 Gy) and the repair time is also very long (>3 h), Eq. (7) would not represent a good description of the saturable repair formalism (using our criterion of requiring isoeffect doses to differ by less than 1–3%) at dose rates relevant to brachytherapy—though the equivalence would still hold for fractionated external-beam regimens.

Other Saturable Repair Models

While we have investigated the practical equivalence of a particular saturable repair formalism to the LQ formalism (specifically including the time factor, G), formalisms describing other saturable repair models also show this equivalence. For example, for the saturable repair model described by Sontag (*29*), which is conceptually similar, though described by a slightly different formalism, a corresponding theorem on equivalence to the LQ formalism can be proved by similar manipulations. More generally, we show in Appendix II that the formalisms describing a very broad class of radiobiological reaction rate models, whether based on binary misrepair or saturable repair, all lead to the same generalized Lea-Catcheside time factor, G, for dose protraction.

An exception to this equivalence for fractionation/protraction concerns saturable repair models which relate survival to damage fixation at a time before repair and misrepair have run their full course (so that the limit $t \to \infty$ used above becomes inapplicable). Saturable repair models based on a finite damage fixation time include those of Calkins (*20*) and the "suicide enzyme" model suggested by Goodhead (*21*), in which repair proceeds after an acute exposure only for a finite time, after which unrepaired lesions become "fixed". To date, however, such finite-time damage-fixation models have not been quantified for protracted exposures because of the inherent ambiguity involved in specifying an appropriate fixation time for lesions during a prolonged exposure. Thus formalisms describing these finite-time damage-fixation models, in which perturbation calculations do not lead to an LQ formalism with the standard time factor, G, represent models whose application to protracted regimens is ambiguous.

The Underlying Basis for the Equivalence of Predictions of the LQ and Saturable Repair Formalisms

Having demonstrated that most saturable repair formalisms do show similar fractionation/protraction effects to the LQ formalism, at least at most clinically relevant doses and dose rates, we now discuss the underlying basis for this, *prima facie*, surprising result. We consider the special case of two acute dose fractions, D_1 and D_2, separated by a time T. Then, using the LQ formalism, Eqs. (2) and (3), the surviving fraction is (*1*)

$$S = \exp\left[-(\alpha D_1 + \alpha D_2 + \beta D_1^2 + \beta D_2^2 + 2\beta D_1 D_2 e^{-\lambda T})\right]. \quad (10)$$

In terms of the LQ model, the components of this equation can be understood as follows:

1. The two linear time-independent terms refer to production of lethal lesions by a single X or γ ray, from either the first (αD_1) or the second (αD_2) dose. The two quadratic terms refer to production of lethal lesions from pairs of DSBs produced by different X or γ rays from within either the first (βD_1^2) or second (βD_2^2) dose.
2. The time-dependent term $2\beta D_1 D_2 \exp(-\lambda T)$ in Eq. (10) refers to production of lethal lesions from pairs of DSBs, one of which is produced in the second dose fraction (DSB yield $\propto D_2$), and one of which is produced in the first fraction (at time T, remaining DSB yield $\propto D_1 \exp[-\lambda T]$); overall this produces the final $D_1 D_2 \exp(-\lambda T)$ term.

By contrast, in saturated repair models, pairs of DSBs or other "initial lesions" do not interact directly in a reaction

such as binary misrepair. However, there is an indirect interaction in the sense that repair of one DSB results in reduced repair capability for other DSBs. Under these circumstances the interpretation of Eq. (10) in a saturable repair model is:

1. The average number of lethal lesions made by the first dose is αD_1, plus an additional quadratic term βD_1^2; this latter dose synergism is due to competition for repair enzymes among DSBs made by the first dose. Similarly for the second dose, D_2.
2. The time-dependent term $2\beta D_1 D_2 \exp(-\lambda T)$ reflects competition for repair enzymes between DSBs produced by the first dose and those produced by the second. Among the DSBs made by the first dose, only a fraction, approximately $\exp(-\lambda T)$, is still present at the time of the second dose, due to repair, accounting for the last term in Eq. (10). [This estimate of the remaining DSB fraction is itself an approximation, since saturated repair does not give rise to strictly exponential decay. However, deviations of the remaining DSB fraction from $\exp(-\lambda T)$ are themselves approximately linear in dose. From Eq. (10) this implies that the corresponding correction to $-\ln(S)$ is cubic in dose, and is thus neglected in the LQ approximation to the saturable repair formalism].

DISCUSSION

The LQ formalism is by far the most commonly used tool to analyze radiation response data both *in vitro* and *in vivo*. There is nevertheless a persistent school of thought that the underlying assumptions of the model are not those responsible for the bulk of dose–response and dose-protraction relationships, with the suggestion that saturation of repair capability is more important. In this paper we have investigated the relationship between the formalisms describing these very different models for predicting time–dose relationships.

We emphasize again that the LQ formalism, as applied to time–dose relationships, does not merely represent a truncated power series in dose. Rather, its key feature here is a specific functional form for the Lea-Catcheside time factor (Eq. 3), which takes into account dose protraction or fractionation.

There is some intrinsic interest in the question of the relationship between binary misrepair and saturable repair models, in terms of designing critical experiments to distinguish between these two very different explanations of basic radiobiological effects (*42*). However, the most pressing application of this issue is in the field of radiotherapy: There is a clear need here for a reliable formalism that predicts isoeffect doses when the time course of the radiation exposure changes—for alternative fractionation schemes, for different dose rates in brachytherapy, or to correct for treatment interruptions. For this purpose, the most common current approach is use of the LQ formalism, which makes specific predictions as to the effects of changing the time course of the treatment, i.e. the fractionation or protraction. The LQ formalism involves only three parameters, and, in isoeffect calculations, only two. The small number of parameters is essential to its practicality, but does limit the capability of the formalism to describe a more complex and possibly more realistic model. Its widespread application in radiotherapy therefore does necessitate critical analysis and comparison with other possible formalisms that are practical in the sense of using limited numbers of parameters. In this paper, we have addressed the question of whether the particular form describing fractionation/protraction effects which is embedded in the LQ formalism is still valid for other practical radiobiological models.

We have shown that, remarkably, the formalisms describing many commonly considered mechanistically based models do reduce to the LQ formalism, *including the same time factor, G, describing time–dose relationships*. This equivalence is true (and perhaps not surprising) for models which involve binary misrepair and so are conceptually similar to the LQ model, but it also holds for models which embody an entirely different explanation of fractionation/protraction effects—saturation of cellular repair capacity. The fact that both binary misrepair and saturated repair formalisms lead, at low or intermediate doses, to the same (LQ) behavior for any type of dose fractionation/protraction explains in part the otherwise somewhat puzzling similarity (*21*, *43*) between the predicted consequences of the two mechanisms.

Numerically, we estimated virtual equivalence between the formalisms of LQ and most saturable repair models, in terms of calculating isoeffect doses relating to changes in fractionation in external-beam radiotherapy. This equivalence applies to both early- and late-responding end points. It also applies to early-responding tissues in brachytherapy; depending on the parameters, the equivalence for late-responding end points in brachytherapy would be less reliable.

It should be emphasized that there is considerable, albeit indirect, evidence that binary misrepair mechanisms do influence fractionation and protraction (*12*). There is much less evidence that saturable repair mechanisms are important at the doses and dose rates of relevance to radiotherapy, and several experiments have suggested that saturable repair may be of only minor importance (*44*), except possibly at very high doses (*30*). However, contributions to fractionation/protraction effects from saturable repair mechanisms have not been excluded (*21*), and so the fact that they would affect fractionation/protraction in largely the same ways as LQ mechanisms is of some significance.

Our results here may also have an impact on the issue of designing "critical experiments" (*42*) to distinguish between binary misrepair and saturable repair mechanisms. If the dose–effect and dose-protraction patterns predicted by both are the same, then efforts to distinguish between models on these bases (*29*) may not be feasible, and attempts may need to be redirected, perhaps toward identifying appropriate enzymatic processes.

We conclude that the use of the LQ formalism to predict dose–time relationships is a notably robust procedure, depending less than previously thought on knowledge of detailed biophysical mechanisms, since various conceptually different biophysical models lead, in a reasonable approximation, to the LQ relationship including the standard form of the generalized Lea-Catcheside time factor, G.

APPENDIX I

The LQ Equivalence of a Saturable Repair Formalism

We show in this Appendix how the LQ formalism, including the functional form of the generalized Lea-Catcheside time factor, G, describing the effects of dose protraction, arises as an approximation to the particular saturable repair formalism described in the text by Eqs. (6A) and (6B).

We assume that the yields of "initial" and "lethal" lesions as a function of time are $U(t)$ and $L(t)$, described by the differential equations (6A and 6B). These equations do not have simple explicit solutions for an arbitrary dose-rate function $\dot{D}(t)$. However, for small numbers of initial lesions, U, as would occur at clinically relevant doses, the denominators in Eqs. (6), such as $1 + \varepsilon_1 U$, are approximately 1; for denominators exactly 1 the equations *are* soluble. This behavior means that it is possible to generate a systematic approximation procedure by regarding ε_1 and ε_2 in Eqs. (6A) and (6B) as small parameters in the sense of nonsingular (i.e. "regular") perturbation theory (*45*). To generate an approximation whose inaccuracy is small to second order, first-order nonsingular perturbation theory can be used as follows.

The first step is to expand the functions for lesion numbers as the first two terms of a formal power series; i.e.,

$$U(t) = U_0(t) + \varepsilon U_1(t) + O(\varepsilon^2), \quad L(t) = L_0(t) + \varepsilon L_1(t) + O(\varepsilon^2), \quad \text{(A1)}$$

where ε is a formal perturbation parameter having the same order of smallness as ε_1 and ε_2. Next the expressions (A1) are substituted into the differential equations (6A and 6B), expanding these equations formally into a power series, and neglecting terms of order ε^2 (*45*). For example, the term $\lambda_1 U/(1 + \varepsilon_1 U)$ in Eq. (6A) has the approximation

$$\lambda_1 U/(1 + \varepsilon_1 U) = \lambda_1 U_0 + \varepsilon\lambda_1 U_1 - \varepsilon_1\lambda_1 U_0^2 + O(\varepsilon^2), \quad \text{(A2)}$$

where the first term on the right is zeroth order, i.e. is $O(\varepsilon^0)$, and the next two terms are first order, i.e. are $O(\varepsilon^1)$; the remainder is higher order and is treated as negligible. Terms of the same order are then grouped, to get separate differential equations for U_0, U_1, L_0 and L_1, which turn out to be explicitly soluble. After solving, the formal expansion parameter ε is set to unity. More details on the general procedure are given in standard texts (*45*). The procedure gives the differential equations for U corresponding to the expansion in Eq. (A2), namely

$$dU_0/dt = \delta\dot{D} - \lambda U_0, \quad dU_1/dt = -\lambda U_1 + \chi U_0^2, \quad \text{(A3)}$$

where $\lambda = \lambda_1 + \lambda_2$ and $\chi = \lambda_1\varepsilon_1 + \lambda_2\varepsilon_2$. The explicit solutions of Eqs. (A3) are (*46*)

$$U_0(t) = \delta\int_{-\infty}^{t} dt'\,\dot{D}(t')e^{-\lambda(t-t')}, \qquad U_1(t) = \chi\int_{-\infty}^{t} dt' U_0^2(t')e^{-\lambda(t-t')}. \quad \text{(A4)}$$

To compute the surviving fraction, $L(\infty)$ is needed (Eq. 6C). Expanding and integrating Eq. (A1) for $L(t)$ gives, for the first two terms $L_0(\infty) + L_1(\infty)$ in the perturbation series (i.e. neglecting terms of order ε^2),

$$L(\infty) = \lambda_2\int_{-\infty}^{\infty} dt[U_0(t) + U_1(t) - \varepsilon_2 U_0^2], \quad \text{(A5)}$$

where U_0 and U_1 are given explicitly by Eq. (A4). The integral in Eq. (A5) can be evaluated by using the following auxiliary formula. Suppose $g(t)$ is a smooth function which vanishes for t sufficiently negative, and suppose ν is a positive constant. Then integration by parts gives

$$\int_{-\infty}^{\infty} dt\, e^{-\nu t}\, g(t) = (1/\nu)\int_{-\infty}^{\infty} dt\, e^{-\nu t}(dg/dt). \quad \text{(A6)}$$

Applying this auxiliary formula, with $\nu = \lambda$ and $g = \int_{-\infty}^{t} dt'\,\dot{D}(t')\exp(\lambda t')$, to the first term on the right in Eq. (A5) gives

$$\int_{-\infty}^{\infty} dt\ U_0 = \delta\int_{-\infty}^{\infty} dt\ \dot{D}(t) = \delta D, \quad \text{(A7)}$$

where D is the total dose delivered during the entire irradiation regimen. Next, the auxiliary formula is applied with $\nu = \lambda$ and $g = \int_{-\infty}^{t} dt'\ U_0^2(t')\exp(\lambda t')$, to rewrite the second term on the right in Eq. (A5) as follows:

$$\int_{-\infty}^{\infty} dt\ U_1(t) = (\chi/\lambda)\int_{-\infty}^{\infty} dt\ U_0^2(t). \quad \text{(A8)}$$

Combining Eq. (A8) with the last term on the right in Eq. (A5) shows that the following quantity needs to be evaluated:

$$\lambda_1(\varepsilon_1 - \varepsilon_2)\int_{-\infty}^{\infty} dt\ U_0^2(t). \quad \text{(A9)}$$

Applying the auxiliary formula (A6) a third time, with $\nu = 2\lambda$ and with

$$g = \left[\int_{-\infty}^{t} dt'\,\dot{D}(t')\exp(\lambda t')\right]^2, \quad \text{(A10)}$$

gives

$$\int_{-\infty}^{\infty} dt\ U_0^2(t) = \frac{1}{\lambda}\int_{-\infty}^{\infty} dt\, e^{-\lambda t}\,\dot{D}(t)\int_{-\infty}^{t} dt'\, e^{\lambda t'}\,\dot{D}(t) = GD^2/2\lambda, \quad \text{(A11)}$$

where G is the generalized Lea-Catcheside time factor, Eq. (3).

Collecting results from Eqs. (6), (A5), (A7), (A8), (A10) and (A11), and comparing with Eq. (2), it is clear that for the saturable repair formalism of Eqs. (6A) and (6B), the zeroth and first orders of non-singular perturbation theory give the LQ formalism with the following parameter identifications:

$$\lambda = \lambda_1 + \lambda_2, \quad \alpha = \lambda_2\delta/\lambda, \quad \beta = \delta^2\lambda_2\lambda_1(\varepsilon_1 - \varepsilon_2)/2\lambda^2. \quad \text{(A12)}$$

It can be proved that the perturbation series, if carried to infinite order, would converge to the true solution. The underlying reason is that U is a non-negative function bounded from above by δD.

A partial check on these perturbation manipulations can be obtained by considering the solutions of Eqs. (6A) and (6B) for the special case of a single acute dose, where the exact solution and the corresponding LQ approximation have been discussed by Kiefer and Löbrich (*24*). In this special case,

$$L(\infty) = (\alpha + 2\beta\zeta^{-1})D - 2\beta\zeta^{-2}\ln(1 + \zeta D), \quad \text{where } \zeta = \delta(\lambda_2\varepsilon_1 - \lambda_1\varepsilon_2)/\lambda, \quad \text{(A13)}$$

where α and β are defined in Eq. (A12).

Expanding Eq. (A13) in a power series gives $L(\infty) = \alpha D + \beta D^2 - (2/3)\beta\zeta D^3 + \ldots$. In the special case of a single acute dose, the generalized Lea-Catcheside time factor obeys $G = 1$, so the first two terms of the power series expansion $[\alpha D + \beta D^2]$ are the appropriate LQ expression. This argument shows that the LQ approximation, in addition to requiring

that there be enough time for repair and misrepair to run their full course, is a low-dose approximation. The criterion of its validity in the special case of Eq. (A13) is that the cubic term in the dose be small, i.e., $\beta D^2 \gg 2\beta\zeta D^3/3$, equivalent to $D \ll 3/(2\zeta)$. A numerical criterion can be obtained by assuming that $\varepsilon_2 = 0$, which is often a good approximation (*29*). In this case, algebraic manipulations of the equations above show that the criterion of validity becomes

$$D \ll \frac{3}{2\zeta} = \frac{\alpha}{\beta}\frac{3\lambda_1}{2\lambda_2}. \tag{A14}$$

Typically, $\lambda_1 \gg \lambda_2$, so, in view of standard estimates for the α/β ratio (*38*, *39*), Eq. (A14) does not represent a very stringent limitation in practice. Adopting the parameter values discussed in the text, Eq. (A14) would always hold at clinically relevant doses.

For continuous low-dose-rate irradiation, we may likewise obtain a rough estimate of the constant dose rate, $\dot{D}$, below which the LQ approximation to the saturable repair formalism would be expected to be close to the exact saturable repair formalism. In the LQ approximation, the terms in the denominators of Eq. (6A) are nearly 1. Since $\varepsilon_2 \ll \varepsilon_1$ in all cases, the relevant criterion is $\varepsilon_1 U(t) \ll 1$ for all times t. At a constant low dose rate, the size of $U(t)$ is initially zero, gradually rising toward an equilibrium value during the irradiation (without ever quite attaining this equilibrium value) and then declining after irradiation is complete. Thus the equilibrium value, say U_e, is larger than any value that U attains at any time, so a sufficient criterion for the validity of the approximations is $\varepsilon_1 U_e \ll 1$. The equilibrium value, U_e, can be estimated by the standard technique (*45*) of setting $dU/dt = 0$; using the approximation that the denominators are 1, the equation for the equilibrium value becomes $\delta\dot{D} = \lambda U_e$. Combining results, a sufficient criterion for the LQ approximation to the saturable repair formalism to be reasonable is that $\dot{D} \ll \lambda/(\varepsilon_1\delta)$. For $\varepsilon_2 = 0$, this can be expressed in terms of the α/β ratio as

$$\dot{D} \ll (\alpha/2\beta)\lambda_1. \tag{A15}$$

Here λ_1 is typically close to the observed repair rate, i.e. $\lambda_1 \sim 0.25$–$2.5\ \mathrm{h}^{-1}$. For the parameter set considered in the Results section, we obtain $\dot{D} \ll 9$ Gy/h.

APPENDIX II

The LQ Equivalence of Formalisms Describing a Broad Class of Radiobiological Models

A generalization of the argument we have given is possible, covering the formalisms describing many radiobiological reaction rate models, including as special cases the saturable repair formalism of Eqs. (6A) and (6B), the RMR formalism (*14*) and the LPL formalism (*15*). As before, we assume that the yields of "initial" and "lethal" lesions as a function of time are $U(t)$ and $L(t)$, and that survival is given by the formula $S = \exp[-L(\infty)]$. Suppose the equations for U and L have the form

$$dU/dt = \delta\dot{D} - \lambda U - \varepsilon\kappa U^2 + O(\varepsilon^2), \tag{A16}$$

$$dL/dt = \psi\dot{D} + \chi U + \varepsilon\kappa^* U^2 + O(\varepsilon^2), \tag{A17}$$

where ε is a small parameter, but where δ, λ, κ, ψ, χ and κ^* are $O(\varepsilon^0)$, i.e. are not necessarily small. Then, neglecting terms of $O(\varepsilon^2)$, i.e. accurate to first order, the LQ expression for S holds; i.e.,

$$S = \exp(-\alpha D - G\beta D^2), \tag{A18}$$

where G is the generalized Lea-Catcheside time factor (Eq. 3) formed using λ, and

$$\alpha = \psi + \chi\delta/\lambda, \tag{A19}$$

$$\beta = \varepsilon\kappa^*\delta^2/2\lambda - \varepsilon\kappa\chi\delta^2/2\lambda^2. \tag{A20}$$

The proof of this result involves manipulations similar to those given in Appendix I.

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