

● *Special Feature*

THE DOSE-RATE EFFECT REVISITED: RADIOBIOLOGICAL CONSIDERATIONS OF IMPORTANCE IN RADIOTHERAPY

ERIC J. HALL, D.Sc. AND DAVID J. BRENNER, Ph.D.

Center for Radiological Research, College of Physicians & Surgeons of Columbia University, New York, NY 10032

A wide range of dose-rates have been used in radiation biology and radiation therapy, extending from a few cGy per day to hundreds of Gy in a fraction of a second. The dose-rate range of importance in radiotherapy extends from about 0.1 Gy/hr to several Gy/min. In this range, the fraction of cells killed by a given dose decreases as the dose-rate is reduced, principally because of the repair of sub-lethal damage. In some cell lines, an inverse dose-rate effect is observed where, over a narrow range of dose-rates, the effectiveness of a given dose increases with decreasing dose-rate if cells move through the cycle and are arrested in G₂, which is a radiosensitive phase. In recent years data have accumulated for cells of human origin. About 40 data sets have been analyzed for values of the survival curve parameters and the rate of repair of sub-lethal damage. These data have been used to address three questions of relevance to radiotherapy. (1) The proposal to use pulsed rather than continuous irradiation in interstitial brachytherapy. (2) The equivalence of high dose-rate and low dose-rate intracavitary treatments for carcinoma of the cervix. (3) An analysis of equivalent doses for a range of dose-rates in interstitial implants.

Brachytherapy, Dose rate, Pulsed treatment.

INTRODUCTION

Dose-rates covering a wide range have been used in radiation biology and/or in radiotherapy, ranging from a fraction of a Gy per day to thousands of Gy in a small fraction of a second. The dose-rate spectrum is illustrated in Figure 1.

The extremes at either end, ultra-high dose-rate or very low dose-rate, have been studied experimentally in the laboratory to address basic mechanisms. Clinical radiotherapy is concerned largely with intermediate dose-rates: either high dose-rate for external beam radiotherapy, or low dose-rate for interstitial and intracavitary therapy.

We will first briefly review the extremes of the dose-rate spectrum, which define the boundary conditions for the range of dose-rates used in the clinic.

Ultra-high dose-rates

Ultra-high dose rates, where doses of thousands of cGy may be delivered in a small fraction of a second, have been produced by discharge machines and by electron linear accelerators. In a discharge machine, electrical energy stored in a condenser is instantaneously discharged to produce a pulse of electrons lasting 3 to 50 ns. Typically, a dose of 10 Gy may be delivered in 10 ns, which represents an instantaneous dose-rate of about 10¹¹ Gy/min. In the case of

an electron linear accelerator, the dose may be given in a single pulse lasting about 1 μs, but in fact the radiation is not delivered continuously throughout this pulse, but during several thousand short periods during the microsecond pulse. The instantaneous dose-rate may again approximate to 10¹¹ Gy/min. If both the dose and instantaneous dose-rate are sufficiently high, the rapid deposition of radiant energy consumes oxygen too quickly for diffusion to maintain an adequate level of oxygenation, and dose-response curves obtained are those characteristic of hypoxia. Dewey

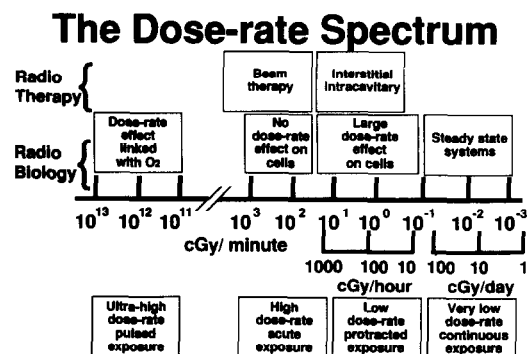


Fig. 1. The Spectrum of dose-rates used in radiation biology and radiation therapy.

Reprint requests to: Eric J. Hall, D.Sc.
 Based on research conducted under Grant No. CA24232 awarded to the Center for Radiological Research by the National

Cancer Institute DHEW.
 Accepted for publication 24 May 1991.

and Boag (7) first demonstrated an anoxic-like response of bacteria irradiated in 1% oxygen at ultra-high dose rates, and their results have been confirmed by Epp, Weiss, and Santomasso (9) and by Phillips and Worsnop (24). The state of knowledge concerning mammalian cells exposed to ultra-high dose-rates is less satisfactory than for bacteria, but there is no reason to believe that it would be dissimilar. At one time it was thought that ultra-high dose-rates could be exploited in radiotherapy as a means of killing cells that is independent of oxygen tension since at sufficiently high dose-rates even aerated cells exhibit an anoxic-like response. However, the total doses required to use up local oxygen are too high, and the instantaneous dose-rates enormous, so that interest in this development for the clinic did not materialize.

Very low dose-rates: Continuous exposure

The effects of very low dose-rates have been investigated by measuring the growth-rate of mammalian cells cultured *in vitro* and by observing the renewal tissues in small rodents. Nias and Lajtha (20) irradiated HeLa cells with β -rays from tritiated water at a dose-rate of 0.3 Gy/day and found that the growth rates in the irradiated samples were indistinguishable from controls, at least for 10 days.

Courtenay (6) showed that a suspension culture of mouse lymphoma cells, irradiated continuously at a dose-rate of 0.72 Gy/day, grew exponentially, although more slowly than normal, for a period of over 10 months. In a later paper, Lamerton and Courtenay (15) reported that cultures of these cells had survived continuous irradiation at 1.2 Gy/day for 2 years, during which time radioresistant mutants arose in the irradiated cultures.

A steady-state cell population can be maintained under continuous irradiation in a number of renewal tissues, as long as the death-rate per cell generation does not exceed the birth-rate. The dose-rate that can be tolerated varies with species and type of tissue concerned. The testis appears to be the most sensitive tissue studied; reproduction can be maintained in male rats and mice for 10 generations or more under continuous exposure at a dose-rate of 0.02 Gy/day (4, 29). At the other extreme, the small intestine in the rat has been shown to maintain cell division and a steady state cell population, albeit smaller than normal, under continuous exposure at dose-rates as high as 4 Gy/day (5, 26). The blood-forming tissues are intermediate between these two extremes. Lamerton *et al.* showed that red cell production in the rat can be maintained at close to normal levels for several months while being exposed to 0.5 Gy/day (15).

The factors that determine the response of renewal tissues to radiation include: (1) The inherent radiosensitivity of the stem cells involved; (2) The duration of the cell cycle; and (3) The ability of some tissues to adapt to a trauma such as continuous irradiation, especially the ability to shorten the cell cycle and speed up the production of new cells.

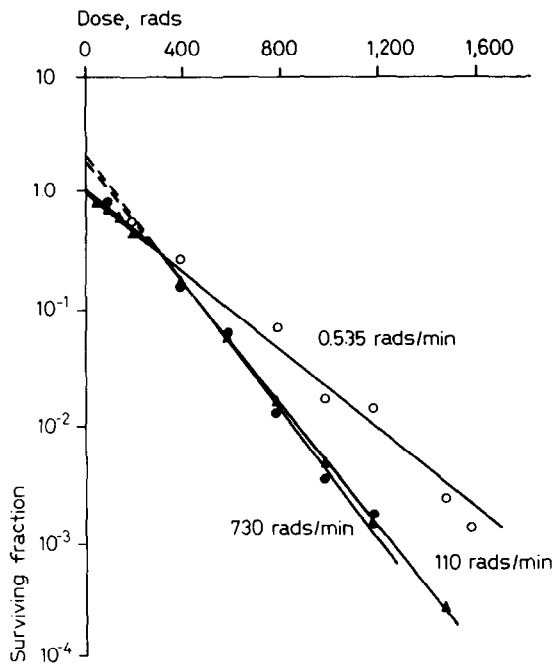
General considerations that apply to renewal tissues also apply to tumors. Provided that cell birth exceeds cell death, a tumor will also continue to grow under continuous irradiation at low dose-rate, even though the total absorbed dose may be large. This observation has implications for the very low dose-rates typical of permanent interstitial implants using radionuclides such as Iodine-125, which will be discussed later.

High and low dose rates relevant to radiotherapy

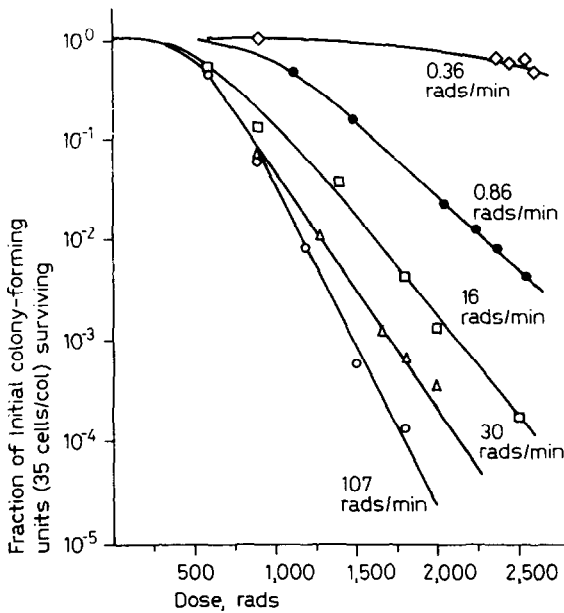
The most complete dose-rate data for the important dose-rate range between 0.1 Gy/hr and 10 Gy/min have been obtained for cells cultured *in vitro*. The earliest studies of this sort were performed by Hall and Bedford (11) using HeLa cells. In subsequent years, many radiobiological principles, including the demonstration of repair of sub-lethal damage, were established with cells of rodent origin, particularly Chinese hamster cells; dose-rate studies with these cells were performed by Bedford and Mitchell (1). The HeLa and hamster data are compared in Figure 2. Hamster cells tend to be characterized by a survival curve for acute doses of X rays that has a large initial shoulder, and there is a correspondingly large dose-rate effect. By contrast, the acute survival curve for HeLa cells has a modest shoulder and the magnitude of the dose-rate effect is likewise more modest. It appears to be generally true that a large shoulder in the acute response is associated with a substantial dose-rate effect, whereas a smaller shoulder is associated with a modest dose-rate effect. This is not surprising since the shoulder on the acute dose response curve reflects the accumulation of sub-lethal damage, and the dose-rate effect reflects the repair of sub-lethal damage.

As predicted by Lajtha and Oliver (14) and before that by Lea and Catcherside (16), when the dose-rate is progressively reduced, the slope of the survival curve becomes progressively shallower as a greater proportion of sub-lethal damage is repaired. A limiting slope is reached, reflecting complete repair of sub-lethal damage, which is an extension of the initial slope of the acute dose response curve. This has seldom been demonstrated experimentally because of the difficulty of preventing cell division. In perhaps the most elegant dose-rate study performed to date, Wells and Bedford (33) demonstrated this limiting slope in C₃H10T1/2 cells, which show good contact inhibition in plateau phase. In cells that are not prevented from dividing, there is a further dose-rate effect due to cell proliferation, as the dose-rate effect is further reduced and the exposure time encompasses several cell cycles, allowing cell birth to offset cell killing.

In some cell systems an *inverse* dose-rate effect has been demonstrated; for example, Mitchell *et al.* showed that reducing the dose-rate from 1.54 to 0.37 Gy/hour in HeLa cells results in more cell killing for a given absorbed dose (18). This is illustrated in Figure 3a. The explanation for this, illustrated in Figure 3b, is that a certain dose-rate range can exist which allows cells to move through the cy-



(a)

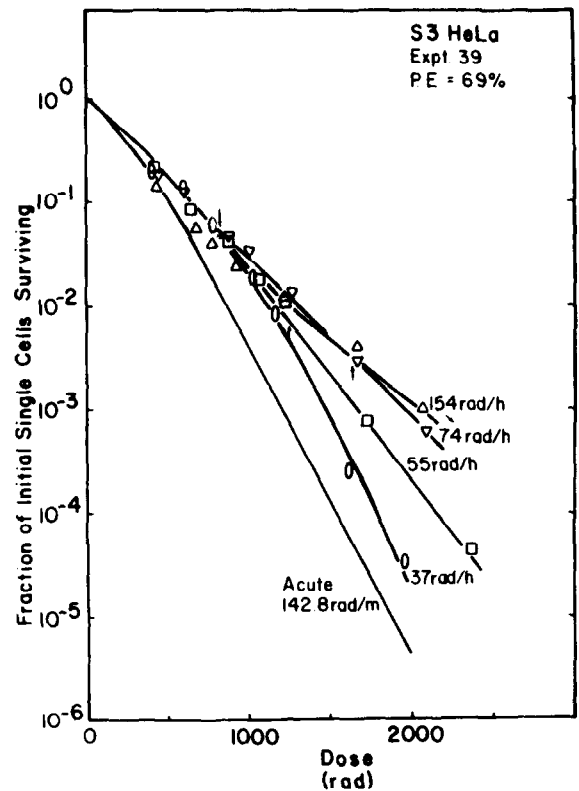


(b)

Fig. 2. (a) Dose-response curves for HeLa cells cultured *in vitro* and exposed to γ -rays from ^{60}Co or radium at various dose-rates (12). (b) Dose response curves for Chinese hamster cells (CHL-F line) grown *in vitro* and exposed to ^{60}Co γ -rays at various dose-rates (1).

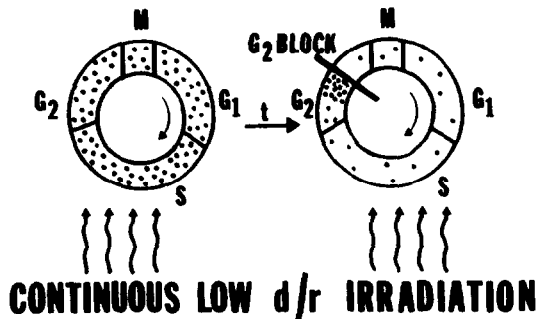
cle, but interposes a block in the phase of the cell cycle G_2 , which is relatively radiosensitive.

The overall picture of the dose-rate effect is illustrated in Figure 4. As the dose-rate is reduced from that characteristic of an acute exposure, the survival curve gets shallower and the shoulder disappears. A limiting slope is



(a)

MECHANISM OF THE INVERSE d/r EFFECT



(b)

Fig. 3. (a) Illustrating the inverse dose-rate effect. A range of dose rates can be found for HeLa cells such that *lowering* the dose rate leads to *more* cell killing. At 154 rad/hour cells are "frozen" in the various phases of the cycle and do not progress. As the dose rate is dropped to 54 or 37 rad/hour, cells progress to a block in G_2 , which is a radiosensitive phase of the cycle (18). (b) Explanation for the inverse dose-rate effect. A range of dose rates can be found, at least for HeLa cells, which allow cells to progress through the cycle to a block in late G_2 cells which are radiosensitive.

reached when complete sub-lethal damage repair occurs, but the dose-rate is still sufficient to "freeze" cells in their cycle and prevent progression. A further reduction in dose-rate allows cells to progress through the cell cycle, and accumulate in G_2 , which is a radiosensitive phase. This

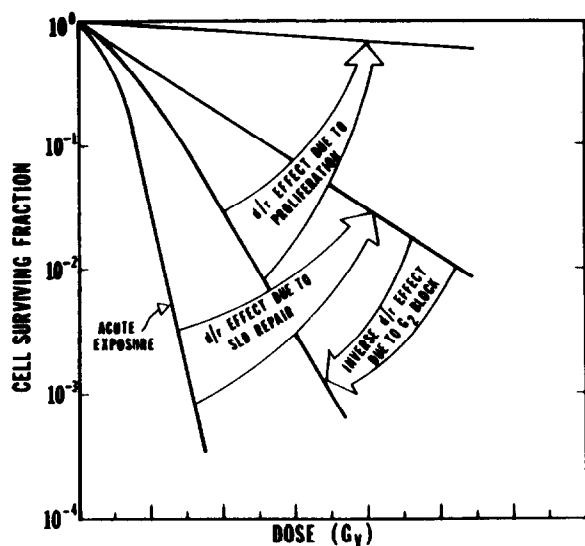


Fig. 4. Revised and updated illustration of the dose-rate effect caused by repair of sublethal damage, redistribution within the cycle, and cell proliferation. The dose-response curve for acute exposures is characterized by a broad initial shoulder. As the dose rate is reduced the survival curve becomes progressively shallower as more and more sublethal damage is repaired, but cells are "frozen" in their positions within the cycle and do not progress. As the dose rate is lowered further, and for a limited range of dose-rates, the survival curve steepens again as cells can progress through the cycle and pile up at a block in G_2 , which is a radiosensitive phase, but still cannot divide. A further lowering of dose rate allows cells to escape the G_2 block and divide; cell proliferation may then occur during the protracted exposure and the survival curve becomes shallower as cell birth due to mitosis offsets cell killing due to the irradiation (redrawn from an idea by Joel Bedford).

results in the inverse dose-rate effect. As the dose-rate is reduced still further, cells can escape the G_2 block to divide and then a dose-rate effect in the normal direction results from cell proliferation as cell birth offsets cell killing in a protracted exposure that encompasses several cell cycles.

In the past decade, developments in technique, and particularly the availability of more sophisticated tissue culture media and growth factors, have combined to make possible the culture of a variety of human cells of both normal and neoplastic origin. As a result, a considerable body of data for cells of human origin has become available, a consequence of which is the need to revise some radiobiological concepts based on older data obtained with hamster cells. This represents the major change in the field since our previous review of dose-rate in 1972 (10).

Figure 5a summarizes the results of a large number of experiments to determine sublethal damage repair (SLDR) in normal and tumor cells. For each cell line, a comparison was made of the response of cells to single and split doses, where an interval of 4 hr was allowed between split doses. We show in this figure only SLDR survival ratios obtained by dividing the split-dose surviving fraction (1% in this case) by the surviving fraction resulting from single-

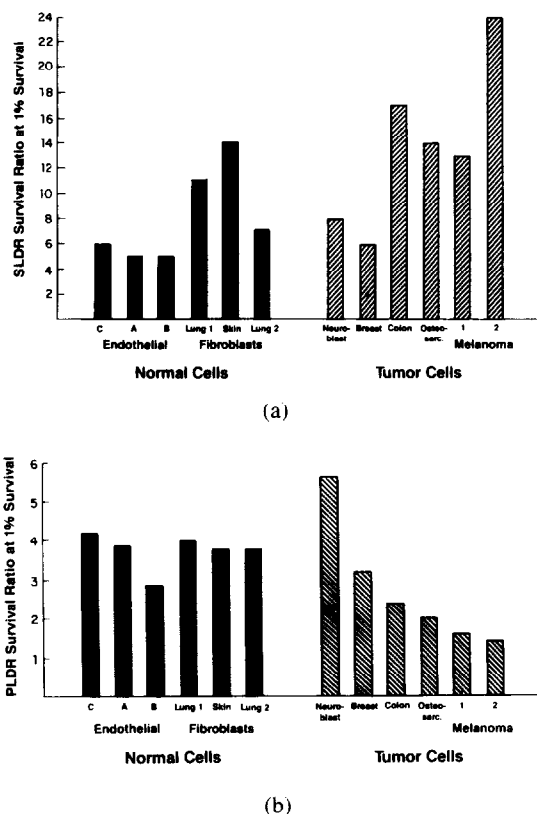


Fig. 5.(a) A comparison of sublethal damage repair (SLDR) for human cells of normal and tumor origin. The survival ratio is the ratio of the fraction of cells surviving when the radiation is delivered in two equal fractions separated by 4 hr to the fraction of cells surviving the same dose delivered in a single exposure. In each case, the calculation was performed at the level of 1% surviving fraction for the single dose. It is evident from these data that there is no consistent difference in the capabilities of normal and malignant cells to repair sublethal damage (13). (b) A comparison of potentially lethal damage repair (PLDR) for human cells of normal and malignant origin. Cells were irradiated in plateau phase and replated at low density to assay for colony formation either immediately after irradiation or after being held in plateau phase for 6 hr following irradiation. The PLDR survival ratio is the ratio of the fraction of cells surviving for delayed replating to the fraction of cells surviving for immediate replating. In each case the calculation was performed at the 1% survival level for immediate plating. It is evident from these data that cells of normal origin repair potentially lethal damage at least as well as cells from tumors (13).

dose exposure. The data indicate that there is considerable variation in the magnitude of sublethal damage repair for different cell lines. However, there is no consistent trend for tumor cells to differ in their ability to repair sublethal damage compared to the normal cells. There is, however, a good correlation between the extent of sublethal damage repair, as evident in split-dose experiments, and the size of the shoulder on the single-dose response curve. For example, the most resistant melanoma line shows the greatest degree of sublethal damage repair and also the largest shoulder on the single-dose response curve.

Figure 5b represents a summary of the *potentially* lethal damage repair experiments carried out with normal and tumor cells. In this case, cells in plateau phase were irradiated with graded doses of rays and then replated at low density to assay for colony formation, either immediately after exposure or after a delay of 6 hr with the cells held in plateau phase to allow the repair of potentially lethal damage. The data are expressed in terms of the PLDR survival ratio, defined to be the ratio between the fraction of cells surviving following delayed and immediate plating. The most striking feature of these data is that potentially lethal damage appears to be repaired at least as well in the normal cells, both endothelial cells and fibroblasts, as in most of the tumor cell lines. There is also no correlation between the extent of PLD repair and overall radiosensitivity of the cells. For example, melanoma 2 is the most resistant line and yet it repairs PLD less efficiently than, for example, breast carcinoma cells, which are the most sensitive.

There are important clinical implications to be drawn from the data concerning the repair of sub-lethal and potentially lethal damage repair. All of the fibroblasts and endothelial cell lines tested show at least as much repair of potentially lethal damage as any of the tumor cells. Consequently, the use of inhibitors of PLDR to increase the damage in tumors resulting from radiotherapy would appear to be questionable at present, until it has been clearly demonstrated that there is a differential between tumors and normal tissues, an unlikely scenario according to the present data. Finally, there is no apparent correlation between the extent of PLDR and the radioresponsiveness of a particular tumor type. This conclusion is in contrast to the suggestion of Weichselbaum and colleagues (32) that the extent of PLDR is a dominant factor in determining radiosensitivity. Indeed, if anything, there would appear to be a negative correlation, since the most resistant tumor cells (melanoma) show the smallest amount of potentially lethal damage repair. The extent of sub-lethal damage repair appears to be a better predictor of radiosensitivity than any measure of potentially lethal damage repair, since it has already been pointed out above that a good correlation exists between the extent of sub-lethal damage repair as evident in split-dose experiments and the size of the shoulder on the single dose response curve which largely determines survival at 2 Gy.

A substantial body of data now exists for the dose-rate effect in cells of human origin. About 40 data sets can be identified in the literature, which includes cells of normal and neoplastic origin. These data were summarized and analyzed using the linear-quadrant formalism by Brenner and Hall (3). The expression used to fit the data was

$$S = e^{-\alpha D - G\beta D^2} \quad (1)$$

where S is the fraction of cells surviving a dose D , α and β are constants, and G is a factor to allow for the dose-rate or fractionation pattern, as first proposed by Lea and Catcheside (16). G depends on the temporal pattern of the

dose delivery the half-time of repair of sub-lethal damage. The fitted curves (without experimental data) for acute and low dose-rate irradiation are shown in Figure 6. There is a considerable variation in the radiosensitivity of the different cell lines, particularly those derived from tumors. The low dose-rate curves fan out, showing an even greater range of radiosensitivities, reflecting different initial slopes and rates of repair of sub-lethal damage. More detailed data for one particular cell line (derived from an astrocytoma) are shown in Figure 7. The results are typical of those found for a number of human cell lines, namely a dose-rate effect between 1 Gy/min and 0.6 Gy/hr that is modest compared with that seen for Chinese hamster cells, with little further dose-rate effect below 0.6 Gy/hr or even a small inverse dose-rate effect over this range. The analysis of the 38 sets of data by Brenner and Hall (2) shows a range of values for α/β and $T_{1/2}$, the half time for repair of sub-lethal damage, that are shown as frequency distributions in Figure 8 and 9. These *in vitro* data for cells of human origin represent a body of information that can be used to address a variety of questions relating to early response to radiotherapy. We report here three such applications pertaining to current developments in brachytherapy.

Pulsed interstitial brachytherapy

A major revolution in brachytherapy during the last decade has been the introduction of afterloading devices, which allow more complex source distributions and also essentially eliminate the radiation exposure of nursing and technical staff. An interstitial implant usually involves the use of a large number of radioactive sources which are loaded into catheters previously implanted into the tumor. A typical prescribed dose rate would be about 0.5 Gy/hr for a total exposure time of about 60 hr. This would correspond to a boost treatment to be added to external beam therapy. Commercially-available afterloading devices are complex and expensive because they must house multiple channels and a large inventory of radioactive sources to

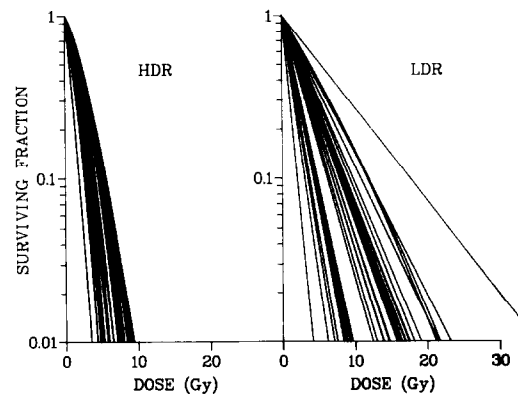


Fig. 6. Dose response curves for 38 human cell lines exposed to high dose-rate (HDR) and low dose-rate (LDR) radiation. The data sets are the same as those to which the frequency distributions in Figures 8 and 9 refer.

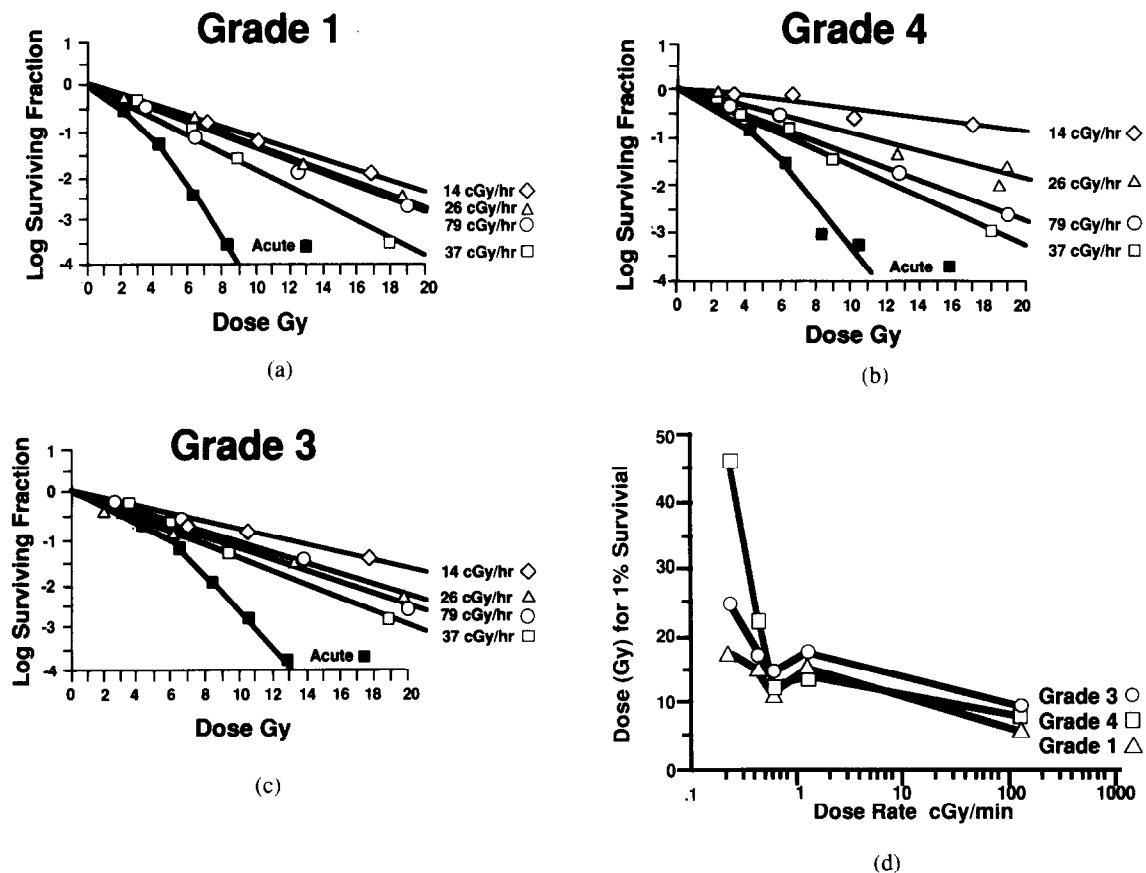


Fig. 7.(a,b,c) Survival curves for astrocytic tumor lines irradiated with Cesium 137 gamma rays at high dose rate (78 cGy/hr) and various low dose rates (14 cGy/hr to 79 cGy/hr). High dose rate data fit to linear quadratic model. Low dose rate data fit to linear model (28). (d) Dose to achieve 1% surviving fraction as a function of dose-rate for three human astrocytic tumor lines. There is a clear hint of an inverse dose-rate effect at about 1 cGy/min (28).

cope with a variety of small or large, single or multi-plane implants. Iridium-192 is the radionuclide of choice, so that source inventories must be replaced several times each year to allow for radioactive decay.

A possible strategy to simplify such machines would be the use of pulsed, rather than continuous, low dose-rate brachytherapy. An afterloading device based on this principle would consist of a *single* high-activity radioactive source that would step through the catheters making up an implant, with computer-controlled dwell times in each position reflecting the differential loading of activity required by the Parker-Paterson or Quimby rules. This single source could replace the complex inventory of sources required in current afterloaders for interstitial brachytherapy.

The three primary advantages to be gained by such a strategy would be: (1) Potentially better dose optimization because of the opportunity to control the computer-controlled dwell times; (2) A greatly simplified afterloading device, which may therefore be less costly to build and operate; and (3) A single radioactive source to be replaced at regular intervals, instead of a large inventory of sources; source replacement could also be less frequent leading to considerable cost saving.

Equation (1) was used by Brenner and Hall with the ra-

diobiological data for human cells summarized in Figures 8 and 9 to determine the combination of radiation pulse widths and frequencies that would be equivalent to continuous irradiation (2). Each of the 38 parameter sets [α , β , $T_{1/2}$] were used to calculate, for given values of the total dose and irradiation time, which combinations of the pulse width and pulse frequency would be predicted to yield cell survivals equivalent to a continuous protocol. One representative result is shown in Figure 10 for a particular human cell line. The representation in this figure is such that any combination of pulse width and pulse frequency that is within the enclosed shaded region will yield a cell survival functionally equivalent to that predicted for the continuous protocol.

The regions of interest are the upper boundaries of the shapes in Figure 10 because the longer the period between treatments, the more practical the protocol becomes. The maximum time between pulses is independent of the pulse width as long as the pulse width is significantly shorter than the time constant for sub-lethal damage repair. As the pulse width becomes longer, a longer period between pulses becomes acceptable. The results for all 38 cell lines are summarized in Figure 11. For a 10-min pulse, this figure shows the maximum time between pulses that would

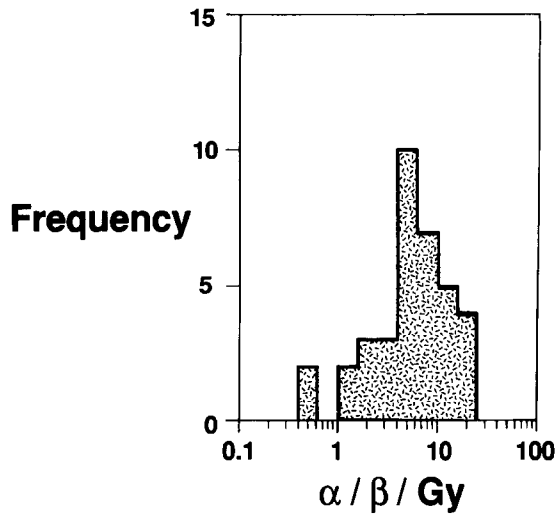


Fig. 8. Distribution of values of α/β , taken from the analysis of *in vitro* low dose-rate studies on 38 cell lines of human origin, some from our own laboratory and some from the literature (redrawn from (2)).

result in an acceptable equivalence to continuous low dose-rate. If it can be assumed that the survival curve characteristics, and more importantly the repair time characteristics, of the 38 cell lines of human origin are representative of those found in the target volume of human tumors *in vivo*, then a pulse width of several minutes, and a pulse interval of about 1 hour, would result in a close equivalence of cell killing by the pulsed irradiation scheme and a continuous low dose rate scheme of 30 Gy in 60 hr (0.5 Gy/hr). This

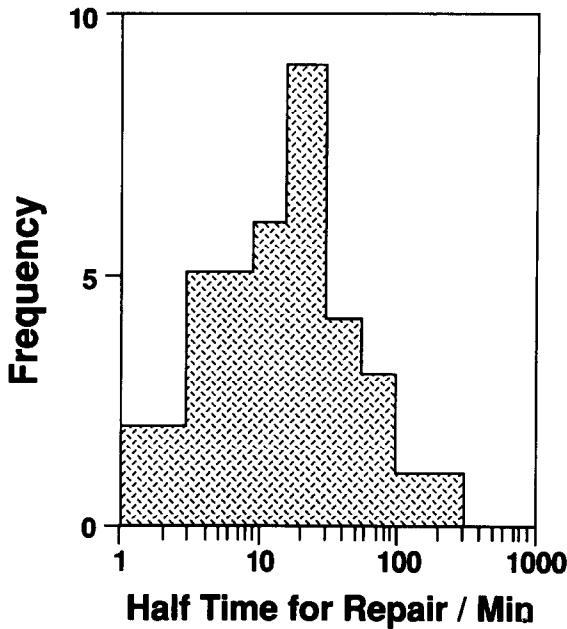


Fig. 9. Distribution of 38 values of the half time for sublethal damage repair, taken from the analysis of *in vitro* low dose-rate studies on 38 cell lines of human origin (redrawn from (2)).

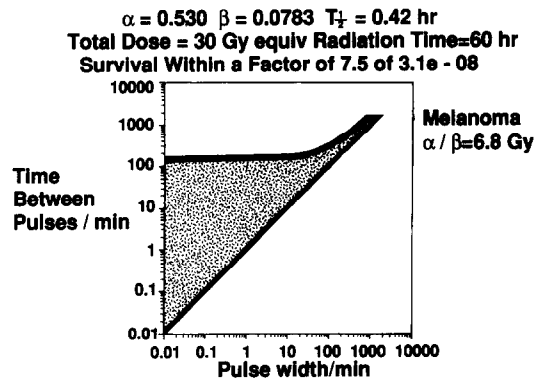


Fig. 10. Combination of pulse widths and periods between pulses that will yield an equivalent survival to a continuous low dose rate irradiation of 30 Gy in 60 hours. Any combination of pulse width and period within the marked boundary is predicted to yield equivalent cell killing. The figure shows representative data for one of the 38 cell lines analyzed (redrawn from (2)).

system would be very flexible since, as the iridium 192 source decays, the pulse width could be adjusted to compensate, keeping the average dose-rate and the overall time constant.

That this quantitative conclusion is not unreasonable may be seen on the following grounds. The pulsed and continuous protocols involved the same overall dose in the same overall time. In addition, the dose per hour is the same in both cases (0.5 Gy), but in the pulsed case it is delivered in 10 min of each hour, whereas in the continuous case it is spread out over the entire hour. A dose fraction as small as 0.5 Gy is on the initial part of the survival curve where single track (α) killing predominates, and there is unlikely to be a detectable difference in the fraction of cells killed if the dose is delivered in 60 min or 10 min.

We have also made corresponding calculations to predict the late effects for such pulsed regimens relative to

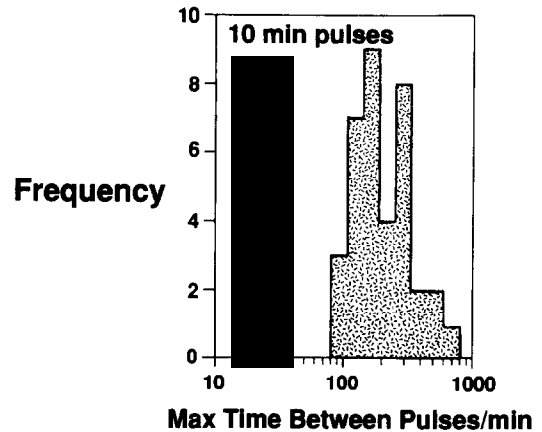


Fig. 11. Distribution of maximum times between 10-min pulses that would yield equivalent survival to a continuous low dose rate treatment of 30 Gy delivered in 60 hr (redrawn from (2)).

those for continuous irradiation. Based on data from three *in vivo* endpoints, hourly 10 min pulses might produce up to a 2% increase in late-effect probability, which is probably acceptable for the small volumes irradiated in interstitial brachytherapy.

The principle of pulsed brachytherapy is illustrated in Figure 12. A new generation of pulsed low dose rate after-loading devices is likely to come into use that will combine better dose optimization with increased simplicity. The development of such machines should allow the advantages of computer-controlled afterloaders for low dose rate brachytherapy to be more readily available to smaller clinics and hospitals in both developed and developing countries.

High dose-rate versus low dose-rate in the treatment of carcinoma of the cervix

Intracavitary brachytherapy at low dose rate (LDR), often with the addition of external beam radiotherapy, has been the treatment of choice for carcinoma of the cervix for over half a century. Initially, radium tubes were used, replaced in more recent years by cesium-137 or iridium-192 sources. A typical low-dose rate (LDR) regimen for cervical cancer involves two insertions, 1 to 3 weeks apart, to a total dose to point-A of 30 to 70 Gy (plus external whole-pelvic irradiation), or to a total of 75 to 80 Gy with no external treatment (19, 23, 30). The LDR treatment is usually delivered at about 0.5 to 1.0 Gy/hr.

High dose-rate (HDR) treatment for cervical carcinoma was introduced about 25 years ago, motivated by the practical advantages to the patient, who may undergo therapy on an outpatient basis. A number of different HDR fraction numbers, from 2 to 15, are currently in use. From the treatment standpoint, HDR units provide accurate and flexible dosimetry, as well as allowing more patients to be on treatment at a given time (21, 31).

The radiobiological data for cells of human origin, summarized earlier in this paper, may also be used to estimate the equivalence of HDR fractionated schemes to LDR pro-

ocols. Equation (1) can be used to calculate the total dose in the fractionated scheme that would give equivalent early effects to the LDR treatment. Figure 13 (a-b) shows, for various HDR fractionation schemes, the distribution of point-A HDR doses predicted (based on the 38 parameter sets of Figs. 8 and 9) to yield comparable acute effects to two fractions totalling 60 Gy, delivered at 0.5 Gy/hr. This latter is a typical LDR brachytherapy regimen used in conjunction with external irradiation. Figure 14 shows the corresponding means of these histograms, as a function of fraction number, and also presents a comparison with the regimens reported in the literature as having been used for such HDR clinical trials.

In an analysis such as this, HDR fractionation schemes down to two or even one fraction are included, but there may be compelling reasons, unrelated to dose-rate considerations, to exclude so few fractions. An obvious factor is the need to allow adequate reoxygenation of possible hypoxic tumor cells. Prudence may dictate a lower limit to the number of HDR fractions of about 5.

An overriding consideration in any discussion of changing dose-rate or fractionation schemes in radiotherapy is the impact of the change on the possibility of late-effects. Laboratory data and clinical experience over the last de-

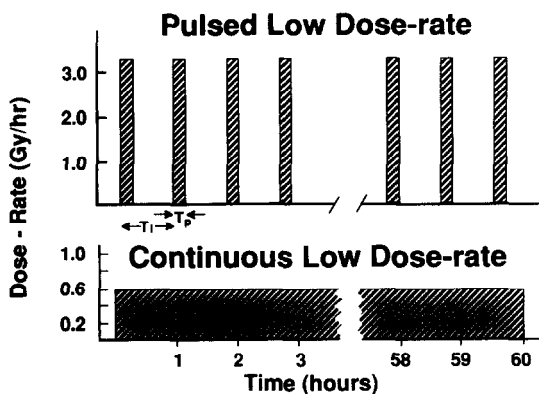
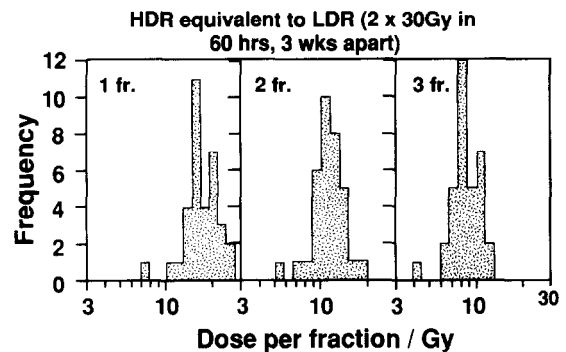
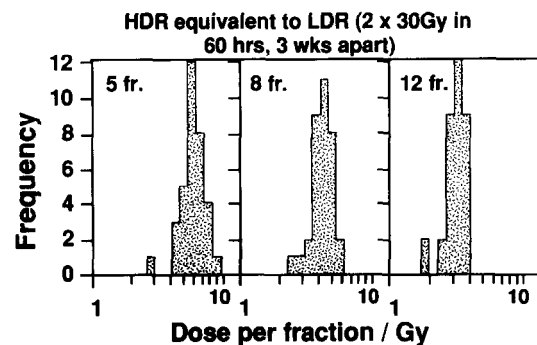


Fig. 12. Illustrating the concept of replacing continuous low dose-rate irradiation by a series of short pulses.



(a)



(b)

Fig. 13. Distributions of point-A HDR doses predicted (based on the 38 parameter sets) to yield comparable acute effects to two fractions totalling 60 Gy, delivered at 0.5 Gy/hr. (a) 1, 2, and 3 HDR fractions; (b) 5, 8, and 12 HDR fractions (redrawn from ref. 3).

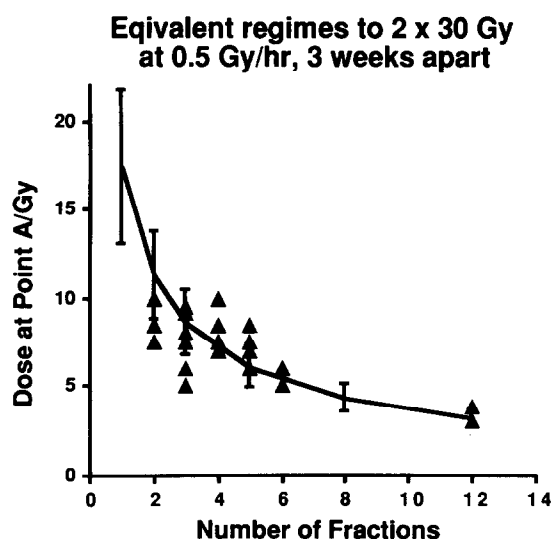


Fig. 14. Arithmetic means of the distributions shown in Fig. 13. The bars correspond to the standard deviations of the samples. The points represent HDR intracavitary brachytherapy regimens reported in the literature to have been used in clinical trials (re-drawn from (3)).

cade have shown that late responding tissues are more sensitive to changes of fractionation than early responding tissues (including tumors), which is consistent with the notion that the dose-response relationship is more "curvy" for late than for early responding tissues, corresponding to a smaller value of α/β (34, 35). It would be predicted on radiobiological grounds, and it is certainly observed in clinical practice, that if doses are matched for early effects, a protocol consisting of a few large fractions will result in *worse* late effects than a protocol consisting of many small fractions, or continuous low dose-rate. However, this is true *only* if the late responding tissues receive the same total dose as the early responding tissues for which the different fractionation patterns were matched. If, in fact, the normal tissues at risk for late effects receive a dose *lower* than that at which early effects are matched, then it does not follow inevitably that late effects will be worse for the protocol involving the few small fractions. It can be shown mathematically (3) that if the total doses in two protocols involving different fractionation patterns are matched for early effects, then late effects for the two protocols will be equal at a point distant from the treatment volume where the ratio of the local dose to the prescribed treatment dose is approximately:

$$\frac{\alpha/\beta \text{ (late)}}{\alpha/\beta \text{ (early)}}$$

For typical values of the parameters of the dose response curves for early and late responding tissues, this may be 1/3 to 1/2.

The principle derived above is based on sound radiobi-

Table 1. Percentage of point-A dose delivered to normal tissues at risk for late effects during intracavitary brachytherapy of the uterine cervix

Site	Percentage of Point-A dose	Reference
Rectum (anterior)	45 ± 12	Bidmead and Staffurth
	52	Joslin
	77 ± 29	Krishnan <i>et al.</i>
	56 ± 15	Martel (1990, personal communication)
Rectum (midpoint)	43 ± 15	Krishnan <i>et al.</i>
	35 ± 8	Martel
Rectum (posterior)	27 ± 11	Krishnan <i>et al.</i>
Bladder (posterior)	63 ± 24	Hunter <i>et al.</i>
	103 ± 41	Krishnan <i>et al.</i>
	80 ± 27	Martel
Bladder (midpoint)	57 ± 20	Krishnan <i>et al.</i>
	49 ± 15	Martel
Bladder (anterior)	35 ± 11	Krishnan <i>et al.</i>
Sigmoid	28 ± 7	Bidmead and Staffurth

Taken from Brenner and Hall (3). Details of references can be found in this paper.

ological principles. Whether it has any relevance to the treatment of carcinoma of the cervix by intracavitary brachytherapy is a more debatable point. The normal tissues most at risk for developing late effects as sequelae to treatment of carcinoma of the cervix are the rectum, bladder, and sigmoid. Table 1 shows results of measurements and estimates of doses to these organs, which fall in the range 1/3 to 1/2 of the point A prescribed dose. To the extent that this is correct, or at least representative, these data would lead one to predict that five HDR intracavitary fractions, chosen to match early LDR effects, would not produce noticeably worse late effects than LDR intracavitary treatments. On the other hand, it is clear that critical normal tissues may occasionally receive 75 to 100% of the point A dose, and then the HDR treatments may be at a serious disadvantage. One unresolved issue raised from inspection of Table 1 is whether the average or the maximum dose to the rectum/sigmoid is more relevant for the prediction of late effects.

A further important factor that will contribute to making HDR techniques acceptable is that applicators to retract normal tissues away from the intracavitary radioactive sources can be used for the short exposure times (a few minutes) characteristic of HDR, whereas they would not be tolerable for the protracted exposures (days) necessary for LDR techniques. While desirable in itself, this dose reduction will also improve the radiobiological considerations of late effects discussed above.

In conclusion, low dose-rate data for cells of human origin, combined with radiobiological theory, can provide guidance for the choosing of doses at HDR that may pro-

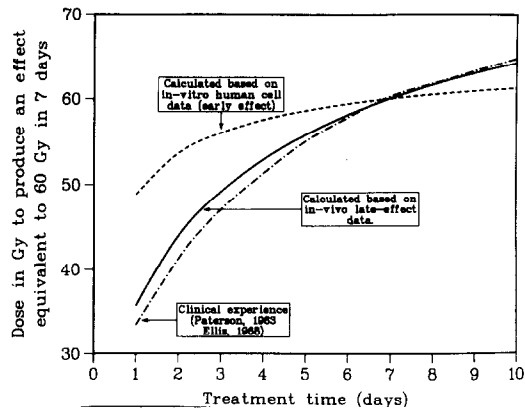


Fig. 15. Dose equivalent to 60 Gy in 7 days calculated in different ways. (a) Based on clinical experience of normal tissue tolerance (8, 22). (b) Calculated from α/β and $T_{1/2}$ values related to late effects. (c) Calculated from the average α/β and $T_{1/2}$ values for cells of human origin cultured *in vitro*—i.e., early effects.

duce equivalent early effects to LDR, and suggest situations in which late effects may not be worse for HDR treatments. It should be emphasised that dose prescriptions for the clinician must come ultimately from clinical trials, but *in vitro* data can provide a guide where clinical experience does not exist.

Correcting for overall time with interstitial implants

Interstitial implants, using radium needles in earlier days, but more recently almost exclusively using iridium-192 wires and seeds, cover the range of dose-rates where the variation of biological effect with dose-rate is substantial and important—at least for cells in culture where pre-

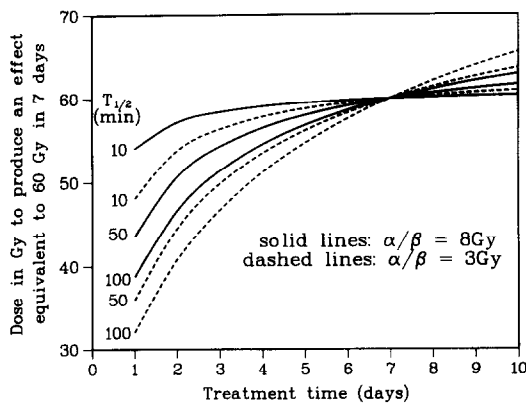


Fig. 16. Curves for the dose equivalent to 60 Gy in 7 days as a function of implant time, calculated for α/β values representative of typical early and late responding tissues (8 and 3 Gy, respectively), and corresponding to various half-times of repair of sublethal damage. The relation between equivalent dose and time is a consequence of the combination of α/β and $T_{1/2}$.

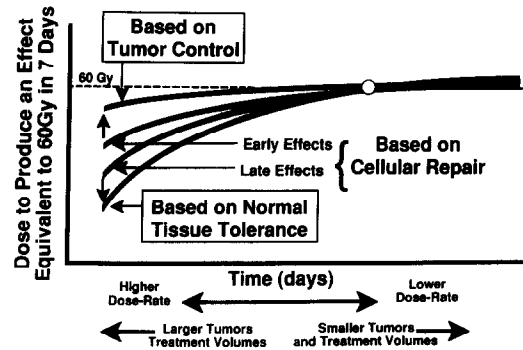


Fig. 17. Theoretical curves to illustrate how the relation between biologically equivalent dose and implant time can be biased by the fact that large tumors and implant volumes tend to be associated with higher dose-rates, and vice-versa. If dose is chosen to equalize tumor control, this tends to flatten the curve since larger tumors require larger doses. If the dose is chosen on the basis of normal tissue tolerance, this tends to steepen the curve since larger volumes tolerate smaller doses.

cise measurements are possible. In the case of interstitial implants in a clinical setting, it was pointed out by Paterson (22) that the limiting factor is the tissue tolerance, which should be fully used to maximize the possibility of tumor control. The maximum dose that can be delivered without unacceptable damage to surrounding normal tissue depends not only on the volume of tissue irradiated, but also on the dose-rate. In the past, when standard radium needles were used, distributed according to the Parker-Paterson or Quimby rules, the dose-rate at 0.5 cm outside an implant varied little from one case to the next (17, 27). The variability is much greater with iridium-192 wires since the linear activity may vary from batch to batch, and may be used over a period of time corresponding to at least one half-life of the radionuclide. Dose-rates may vary by a factor of 3 (25). It may be unrealistic, therefore, to use a fixed dose even for a given volume; rather, common sense would dictate that the dose should be varied according to the dose-rate (and therefore the overall time) employed. As discussed earlier, their corrections can be reliably calculated using Equation 1 and the data set of $[\alpha, \beta, T_{1/2}]$ described above.

In the 1960s, Paterson (22) deduced from practical experience a curve of biological equivalence, based on limiting late effects, for treatments given at different dose-rates. Regarding 60 Gy in 7 days as the standard tolerance dose, he proposed that a shorter time implant should have slightly less dose, and a longer time implant an augmented dose. This curve is reproduced in Figure 15. Ellis proposed a very similar scheme for use in clinical practice (8). The data upon which this curve was drawn were obtained from clinical experience and are attributed to T. A. Green (unpublished data, Ellis, F. 1968) (8). Also shown in Figure 15 are the corresponding curves calculated from the α/β and $T_{1/2}$ values for cells cultured *in vitro* and for late effects, referred to earlier in this paper. Figure 16 shows that

the relation between equivalent dose and implant time is a consequence of the combination of α/β and $T_{1/2}$.

A complication and confounding variable in the interpretation of clinical data relating dose to produce an equivalent effect to implant time (and therefore to dose-rate) is the fact that for interstitial implants the dose-rate tends to increase as the size of the implant increases. This is particularly true for implants using iridium-192 wires which are all of the same linear activity. The bias of larger tumors and larger treatment volumes associated with higher dose-rates, while smaller tumors and smaller treatment volumes are associated with lower dose-rates, was pointed out by Pierquin and colleagues (25). If tumor control is the endpoint used to deduce biological equivalence for various dose-rates, the fact that higher dose-rates tend to be associated with larger tumors tends to flatten the curve in Figure 15. This is inevitable since larger tumors require larger doses. This principle is illustrated in Figure 17. On the other hand, if normal tissue tolerance is the endpoint used to deduce biological equivalence for various dose-rates, the fact that higher dose-rates tend to be associated with larger volumes tends to exaggerate the slope of the curve in Fig-

ure 15. This results from the fact that the larger the volume irradiated, the smaller the tolerance dose. This principle is also illustrated in Figure 17.

These considerations may partly explain the longstanding disagreement between centers that follow the advice of Paterson (22) and Ellis (8) to vary the prescribed dose with dose-rate, compared with the Paris school which advocates that a standard invariant dose may be prescribed regardless of the implant time from 3 to 8 days (25). As pointed out earlier, the experience upon which the advice of Paterson (22) and Ellis (8) was based largely involved implants with radium needles of varying activity implanted according to the Parker Paterson rules. This results in a smaller variation of dose-rate with volume than the Paris technique (25), which uses iridium wires of uniform activity. These dose/volume considerations are, of course, in addition to the fact that, irrespective of volume, the curves in Figures 15 and 16 are flatter for early effects (the pertinent endpoint for the Paris school) than for late effects (on which Paterson drew his conclusions). This is simply a consequence of smaller α/β ratios for late effects compared to early effects.

REFERENCES

- Bedford, J. S.; Mitchell, J. B. Dose-rate effects in synchronous mammalian cells in culture. *Radiat. Res.* 54:316-327; 1973.
- Brenner, D. J.; Hall, E. J. Conditions for the equivalence of continuous to pulsed low dose-rate brachytherapy. *Int. J. Radiat. Oncol. Phys. Biol.* 20:181-190; 1991.
- Brenner, D. J.; Hall, E. J. Fractionated high dose-rate versus low dose-rate regimens for intracavitary brachytherapy of the cervix. 1. General considerations based on radiobiology. *Brit. J. Radiol.* 64:133-144; 1991.
- Brown, S. O. Effects of continuous low intensity radiation on successive generations of the albino rat. *Genetics* 50:1101-1113; 1964.
- Cairnie, A. B. Studies in the intestinal epithelium of rats; response to continuous irradiation. *Radiat. Res.* 32:240-246; 1967.
- Courtenay, V. D. The response to continuous irradiation of the mouse lymphoma L5178Y grown *in vitro*. *Int. J. Radiat. Biol.* 9:581-592; 1965.
- Dewey, D. L.; Boag, J. W. Modification of the oxygen effect when bacteria are given large doses of radiation. *Nature* 183:1450-1451; 1959.
- Ellis, F. Dose time fractionation in radiotherapy. In: Ebert, M., Howard, A., eds. *Current topics in radiation research*. Amsterdam: North-Holland Publishing Company; 1968: 359-397.
- Epp, E. R.; Weiss, H.; Santomaso, A. The oxygen effect in bacterial cells irradiated with high intensity pulsed electrons. *Radiat. Res.* 34:320-325; 1968.
- Hall, E. J. Radiation dose-rate; a factor of importance in radiobiology and radiotherapy. *Brit. J. Radiol.* 45:81-97; 1972.
- Hall, E. J.; Bedford, J. S. Dose-rate: its effect on the survival of HeLa cells irradiated with gamma-rays. *Radiat. Res.* 22:305-315; 1964.
- Hall, E. J.; Berry, R. J.; Bedford, J. S. Dose-rate effects in mammalian cells *in vitro* and *in vivo*. In: Brown, D. G., Cragle, R. G., Noonan, T. R., eds. *The Proceedings of a Symposium on Dose-Rate in Mammalian Radiation Biology*. United States Atomic Energy Commission; 1968: 15.1.
- Hall, E. J.; Marchese, M.; Hei, T. K.; Zaider, M. Radiation response characteristics of human cells *in vitro*. *Radiat. Res.* 114:415-424; 1988.
- Lajtha, L. G.; Oliver, R. Some radiobiological consideration in radiotherapy. *Br. J. Radiol.* 34:252-257; 1961.
- Lamerton, L. F.; Courtenay, V. D. The steady state under continuous irradiation. In: *Dose-rate in mammalian radiation biology*. United States Atomic Energy Commission, Division of Technical Information, Conference 680410; 1968: 3.1-3.12.
- Lea, D. E.; Catcheside, D. G. The mechanism of the induction by radiation of chromosome aberrations in *Tradescantia*. *J. Genet.* 44:216-245; 1942.
- Meredith, W. J., ed. *Radium dosage: the Manchester system*, 2nd edition. Baltimore: Williams & Wilkins; 1967: 42.
- Mitchell, J. B.; Bedford, J. S.; Bailey, S. M. Dose-rate effects in plateau-phase cultures of S3 HeLa and V79 cells. *Radiat. Res.* 79:520-536; 1979.
- Moss, W. T.; Cox, J. D. *Radiation oncology. Rationale, technique, results*. St. Louis: C.V. Mosby Company; 1989.
- Nias, A. H. W.; Lajtha, L. G. Continuous irradiation with tritiated water of mammalian cells in a mono-layer; 1964.
- O'Connell, D.; Howard, N.; Joslin, C. A. F.; Ramsey, N. W.; Liversage, W. E. A new remotely controlled unit for the treatment of uterine carcinoma. *The Lancet* 2:570-571; 1965.
- Patterson, R. *The treatment of malignant disease by radiotherapy*, 2nd edition. Baltimore: Williams and Wilkins; 1963.
- Perez, C. A.; Brady, L. W. *Principles and practice of radiation oncology*. Philadelphia: J. B. Lippincott Company; 1987.
- Phillips, T. L.; Worsnop, R. B. Oxygen depletion by ultra-high-dose-rate electrons in bacteria and mammalian cells (Abstract). *Radiat. Res.* 35:545; 1968.
- Pierquin, B.; Chassagne, D.; Baillet, F.; Paine, C. H. Clinical observations of the time factor in interstitial radiotherapy using iridium-192. *Clin. Radiol.* 24:506-509; 1973.

26. Quastler, H.; Bensted, J. P. M.; Lamerton, L. F.; Simpson, S. M. Adaptation to continuous irradiation; observations on the rat intestine. *Br. J. Radiol.* 32:501-512; 1959.
27. Quimby, E. H.; Castro, V. The calculation of dosage in interstitial radium therapy. *Am. J. Roentgenol.* 70:739; 1953.
28. Schultz, C. J.; Geard, C. R. Radioresponse of human astrocytic tumors across grade as a function of acute high dose rate and chronic irradiation. *Int. J. Radiat. Oncol. Biol. Phys.* 19:1397-1404; 1990.
29. Stadler, J.; Gowan, J. W. Proceedings of International Symposium on Effects of Ionizing Radiation on the Reproductive System (1962). Oxford: Pergamon Press; 1964: 111.
30. Stout, R.; Hunter, R. D. Clinical trials of changing dose-rate in intracavitary low dose-rate therapy. In: Mould, R. F., *Brachytherapy 2*, The Netherlands: Nucletron; 1989.
31. van't Hooft, E. The selectron HDR: philosophy and design. In: Mould, R. F., *Brachytherapy*, 1984. The Netherlands: Nucletron; 1985.
32. Weichselbaum, R. R.; Schmitt, A.; Little, J. B. Cellular repair factors influencing radiocurability of human malignant tumors. *Br. J. Cancer* 45:10-16; 1982.
33. Wells, R. L.; Bedford, J. S. Dose-rate effects in mammalian cells IV. Repairable and non-repairable damage in noncycling C3H/10T cells. *Radiat. Res.* 94:105-134; 1983.
34. Withers, H. R.; Thames, H. D.; Peters, L. J. Differences in the fractionation response of acute and late responding tissues. In: Karcher, K. H., Kogelnik, H. D., Reinartz, G., eds. *Progress in radio-oncology II*. New York: Raven Press; 1982: 287-296.
35. Withers, H. R. Biologic basis for altered fractionation schemes. *Cancer* 55:2086; 1985.