RADIATION RESEARCH 133, 365–369 (1993)

Mechanistic Considerations on the Dose-Rate/LET Dependence of Oncogenic Transformation by Ionizing Radiations

D. J. BRENNER, E. J. HALL, G. RANDERS-PEHRSON, AND R. C. MILLER

Center for Radiological Research, Columbia University, 630 West 168th Street, New York, New York 10032

BRENNER, D. J., HALL, E. J., RANDERS-PEHRSON, G., AND MILLER, R. C. Mechanistic Considerations on the Dose-Rate/LET Dependence of Oncogenic Transformation by Ionizing Radiations. *Radiat. Res.* 133, 365–369 (1993).

When exposure to densely ionizing radiation is protracted, the resulting biological effect is sometimes, but not always, enhanced for transformational end points, relative to acute exposure. A pattern has emerged as to the dependence of this effect on dose, dose rate, and radiation quality. Previous calculations indicated that the dose and dose-rate trends can be predicted by a model in which there is a period within the cell cycle of very high sensitivity to oncogenesis. Recent experiments indicate that the inverse dose-rate effect is significant over a very limited range of LETs—from about 30 to 130 keV/μm. We discuss such LET effects in the context of cell cycle-dependent models, and suggest that the effects are understandable on the basis of such models. In essence, the inverse dose-rate effect disappears at high LET because of a reduction in the number of cells being hit, and disappears at LETs below about 30 keV/μm because most of the dose is deposited at low specific energies, insufficient to produce the saturation effect which is central to the phenomenon. At even lower LETs, damage repair yields the familiar sparing associated with protraction of X- or γ-ray doses.

INTRODUCTION

It is well documented that, for carcinogenesis and life shortening, and for *in vitro* oncogenic transformation, protraction of a given dose of medium-LET radiation produces increased biological effects relative to single acute exposures. Reviews of relevant data are given in Refs. (*1–4*).

This "inverse dose-rate effect" is a response opposite to that at low LET, where low dose rate or fractionation produces a decrease in the biological damage observed. The effect also appears to be confined to certain radiobiological end points: for clonogenic survival, for example, the biological effectiveness at medium or high LET is virtually independent of protraction.

The quality and quantity of the published reports on the inverse dose-rate effect suggest that the effect is real. The data, however, suggest that the magnitude of the effect is a complex function of dose, dose rate, and radiation quality. Such complexity means that experimental results in this field are quite hard to interpret, except within the context of a theoretical framework.

In this work we single out the effects of radiation quality. Recent experiments with monoenergetic charged particles by Miller *et al.* [(*5*), and see Fig. 1] suggest that the effect is limited to an LET range from about 30 to 130 keV/μm. This conclusion has been reinforced by a comparison between two data sets on oncogenic transformation of C3H 10T1/2 cells by α particles from isotopic sources (*6, 7*): in the first, from Heiber *et al.* (*6*), 140 keV/μm α particles produced no inverse dose-rate effect; in the second, from Bettega *et al.* (*7*), 101 keV/μm α particles did produce a significant inverse dose-rate effect, at comparable doses.

That the significance of the inverse dose-rate effect is confined to a limited LET range was also suggested by the results of earlier experiments with photons [low average LET, Ref. (*8*)] and with 14-MeV neutrons [high average LET, Ref. (*9*)]; neither of these experiments showed a significant inverse dose-rate effect.

A model of the inverse dose-rate effect has been suggested (*1*) by Brenner and Hall based on a suggestion by Rossi and Kellerer (*10*). It produced results consistent with all the then-available experimental data in the C3H 10T1/2 *in vitro* oncogenic transformation system. We investigate here whether it produces results consistent with the observed LET dependence.

METHODS

The Biophysical Model

There is general agreement that the inverse dose-rate effect must in some way be related to a cell cycle phenomenon (*2, 10, 11*). Rossi and Kellerer (*10*) suggested a specific mechanism for the inverse dose-rate effect as a function of dose, dose rate, and radiation type. The basic approach was developed further by Brenner and Hall (*1*) and by Elkind (*11*); the hypothesis is that cells in part of their cycle are more sensitive to radiation (for transformation) than in the rest of the cycle. Then an acute medium-LET exposure of cycling cells will result in some fraction of the sensitive cells receiving large depositions of energy—greater than required for the effect. If the exposure is protracted, a larger proportion of sensitive cells will be exposed, but to smaller numbers of energy depositions, though still sufficient to produce the effect.

0033-7587/93 $5.00

As demonstrated by Brenner and Hall (*1, 3*), the model produces results that are consistent with all available data on enhancement of transformation in the C3H 10T1/2 cell system by protraction or fractionation at medium or high LET. Recently, the model has been subjected to more direct tests of its premises: Miller *et al.* (*5*) exposed C3H 10T1/2 cells to 40-keV/μm deuterons, both in plateau phase and while exponentially growing. No inverse dose-rate effect was seen with plateau-phase cells, but a significant effect was seen with cells that were exponentially growing. Hill *et al.* (*12*) exposed synchronized C3H 10T1/2 cells to neutrons, and preliminary observations indicate a significant variation in sensitivity to transformation through the cell cycle. Miller *et al.*[1] have also found a strong variation in transformation yield through the cell cycle for synchronized C3H 10T1/2 cells exposed to 6 MeV neutrons.

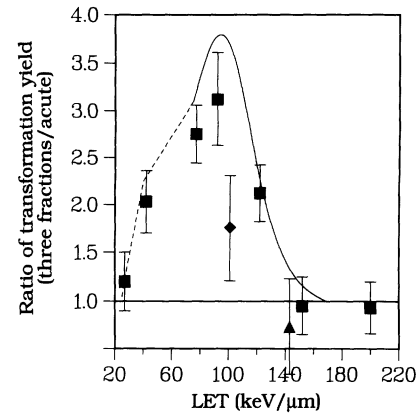

FIG. 1. Factors by which oncogenic transformation rates in C3H 10T1/2 cells produced by different radiations are increased when the dose is divided into three well-separated fractions. The squares are experimental results from Miller *et al.* (*5*); doses were 0.6 Gy (25 keV/μm), 0.3 Gy (50 keV/μm), and 0.2 Gy for the higher LETs. The diamond is data from Bettega *et al.* (*7*) (0.21 Gy; 101 keV/μm); the triangle is from Hieber *et al.* (*6*) (0.25 Gy; 0.05 Gy/h). The solid curve is the calculated result for doses of 0.2 Gy delivered in three well-separated fractions. The dashed curve shows calculated results at the same doses as the two lower-LET experimental data points.

Mathematical Formalism

The model of Rossi and Kellerer (*10*) is formulated in terms of the following components: P, the probability that a cell is hit at least once in a fraction; Q, the probability that a hit cell was in its "sensitive" phase; and K, the probability that a hit sensitive cell will show the effect.

The probability that a sensitive cell is not hit in a single fraction will be $(1 - PQ)$, and the probability that a sensitive cell is not hit in n well-separated fractions will be $(1 - PQ)^n$. Thus the yield of transformed sensitive cells will be

$$K[1 - (1 - PQ)^n], \tag{1}$$

and the total transformation yield, including a term for transformations produced through the rest of the cell cycle, will be

$$T = K[1 - (1 - PQ)^n] + \alpha D, \tag{2}$$

where α is the initial slope of the transformation yield per non-sensitive cell at risk. If the surviving fraction, S, of sensitive cells varies with protraction, we can simply take this into account by replacing PQ with PQS; similarly, if the surviving fraction, S_1, of all exposed cells varies with protraction, we may replace αD with $\alpha S_1 D$. Finally, if repair of the damage responsible for the transformation of cells outside the sensitive window is important (for example, after protraction of an X-ray dose), the αD term can be replaced with an $(\alpha D + \beta D^2)$ term, where β depends on protraction/repair. The possible significance of survival and damage-repair phenomena is discussed further in the Appendix.

For small values of PQ (or PQS), Eq. (2) can be written

$$T = nKPQ + \alpha D. \tag{3}$$

The quantity Q, the probability that a hit cell was in its sensitive phase, is simply the ratio of the total duration of the sensitive phase or phases, τ, to the total cell cycle time, s. Thus,

$$T = nKP\tau/s + \alpha D. \tag{4}$$

The quantity P, the probability that a cell is hit at least once in a fraction, is simply

$$P = 1 - \exp(-N), \tag{5}$$

where N is the mean number of energy deposits per fraction to which cells are exposed. Brenner and Hall (*1*) discuss the dependence of N on protraction, dose, and target size. The dependence of N, and the effect in general, on radiation quality is discussed in more detail below.

LET Effects

In terms of radiation quality, N is inversely proportional to the frequency-averaged lineal energy, y_F, or (approximately) to the average LET. This is because, for a given dose, as the LET increases, the mean number of energy depositions to which the sensitive cells are exposed decreases; thus P will decrease and the magnitude of the inverse dose-rate effect will diminish (Eq. 5). By the same logic, however, the formalism, as described by Eqs. (1–5), predicts a continuous increase in the inverse dose-rate effect with decreasing LET which, as shown in Fig. 1, is not observed.

A qualitative reason for the effect not increasing indefinitely with decreasing LET was suggested by Brenner and Hall (*1*). The basis of the effect is that the smaller numbers of energy depositions in sensitive cells in a protracted exposure may still be adequate to produce the effect; however, Brenner and Hall suggested (*1*) "to the extent that this latter postulate may not hold at low LET, the inverse dose-rate effect would not be expected to apply to such radiations." The implication here is that the LET dependence of the inverse dose-rate effect also enters through the parameter K, the probability that hit sensitive cells show the effect. In the formalisms of Rossi and Kellerer (*10*) and Brenner and Hall (*1*), K was simply assumed to be a constant, but a more realistic description would be

$$K = \int f(z;D)\epsilon(z)\mathrm{d}z, \tag{6}$$

where z is the specific energy deposited in the nucleus and $f(z;D)$ is the probability density function of the specific energy for a dose D. Equation (6) assumes only that the biological effect of one radiation type relative to another can be based on the (distribution of) energy depositions in the exposed cell nuclei. (Brenner and Hall (*1*) discuss evidence that the appropriate site size for the inverse dose-rate effect is the cellular nucleus.) The function $\epsilon(z)$ is a biological "weighting" function (*13–18*).

Equation (6) is more conveniently written as

[1] Private communication, R. C. Miller, April 1992.

$$K = \int zf(z;D)k(z)\mathrm{d}z, \tag{7}$$

where $k(z) = \varepsilon(z)/z$. In Rossi and Kellerer (*10*) and Brenner and Hall (*1*), there was an implicit assumption that

$$\begin{aligned} k(z) &= 0, && z < z_{\mathrm{crit}} \\ &= \text{constant}, && z \geqslant z_{\mathrm{crit}} \end{aligned} \tag{8}$$

and

$$f(z;D) = 0, \quad z > z_{\mathrm{crit}}, \text{ at low LET} \tag{9a}$$

$$f(z;D) = 0, \quad z < z_{\mathrm{crit}}, \text{ at high LET;} \tag{9b}$$

i.e., there is some threshold specific energy (z) value for inducing the effect (z_{crit}), and high-LET radiations deposit all their dose above z_{crit}, whereas low-LET radiations deposit dose only at specific energies below this value.

Although the step-function form of Eq. (8) for the biological response function is oversimplistic, biological response functions of this type do tend to rise sharply with increasing specific energy to some maximum value and then saturate (*13–18*). On the other hand, at low doses Eq. (9) is completely unrealistic because of the various stochastic factors dominating energy deposition in small sites (*19, 20*).

If sufficient experimental data were available, a model-free estimate of $k(z)$ could be unfolded from Eq. (7). Lacking such data, we will assume a reasonable functional form for $k(z)$, and investigate whether the model described here predicts trends consistent with the experimental results in Fig. 1.

RESULTS

We have calculated microdosimetric distributions to use in Eq. (7) based on Poisson distributions of numbers of tracks traversing the cell nucleus:

$$f(z;D) = \sum_{\nu=0}^{\infty} e^{-n} n^{\nu}/\nu!\, f_{\nu}(z), \tag{10}$$

where $f_{\nu}(z)$ is the distribution of z deposited in ν traversals [$f_0(z) = \delta(z)$], calculated by convolution [using an algorithm described in Ref. (*19*)] of the single-event distribution, $f_1(z)$. This latter was estimated by assuming (*20*) that the dominant contribution to the variance is the path-length distribution in a spherical nucleus of diameter d. Apart from a normalization factor

$$\begin{aligned} f_1(z) &= z, && z \leqslant 0.306\ \mathrm{LET}/d^2 \\ &= 0, && z > 0.306\ \mathrm{LET}/d^2 \end{aligned} \tag{11}$$

(z in Gy, LET in keV/μm, d in μm).

Based on such calculated microdosimetric spectra, we use Eqs. (4) and (7) to estimate the enhancement produced by three well-separated fractions:

$$\frac{3P_3K\tau/s + \alpha D}{P_1K\tau/s + \alpha D}. \tag{12}$$

Here K is estimated using Eq. (7) and, for a dose D (Gy),

$$P_n = 1 - \exp(-5Dd^2/\mathrm{LET}/n). \tag{13}$$

In calculating K using Eq. (7), instead of using a step function (Eq. 8) for the function $k(z)$ in Eq. (7), we have used a smooth exponential

$$k(z) = 1 - \exp(-z/z_{\mathrm{crit}}), \tag{14}$$

and have varied z_{crit} so that Eq. (12) gives the best fit to the experimental data in Fig. 1. All the parameters were kept the same as in Brenner and Hall (*1*), except K, the LET dependence of which was calculated from Eqs. (7) and (14) and multi-event $f(z,D)$ spectra.

It may be noted that we have not taken into account survival effects, or damage recovery effects, in calculating the enhancement using Eq. (12). These issues are discussed in more detail in the Appendix. As discussed there, at medium LETs, differential survival within the cell cycle might decrease the magnitude of the predicted enhancement. At low LET (for example, for X rays), damage repair produces a sparing effect with protraction (*8*), an effect predicted in this approach (see Eq. 12) when $K \Rightarrow 0$, and αD is replaced by $(\alpha D + \beta D^2)$, as discussed above.

The results, with an optimized value of z_{crit} of 0.54 Gy, are shown in Fig. 1 and suggest that the current approach does produce predictions which are consistent with the trend of the data. Thus, according to the biophysical model outlined here, the inverse dose-rate effect disappears at very high LET because of a reduction in the number of cells being hit, and disappears at LETs below about 30 keV/μm, because the majority of the dose is deposited at low values of specific energy, insufficient to produce the saturation phenomenon central to the effect. At even lower LETs, damage repair will produce the characteristic sparing associated with protraction of X- or γ-ray doses (*8*).

DISCUSSION

We have shown elsewhere that a model assuming a period of extra sensitivity within the cell cycle of about 1 h correctly predicts the observed trends of the inverse dose-rate effect in terms of dose and dose rate/fractionation. In this paper we show that observed LET effects above about 20 keV/μm can also be understood simply within such an approach. At even lower LETs (e.g., X rays), damage repair will produce a reversal of effects, i.e., a sparing of damage by protraction.

This consistency with experiment in no sense proves that

the biophysical model is correct. LET effects do, however, yield an additional constraint on any attempt to provide a plausible model of the inverse dose-rate effect. In conjunction with the experiments discussed in the Introduction, which directly address the model assumptions, the ability of this approach to predict LET effects lends additional credibility to the notion that the inverse dose-rate effect is produced by differential sensitivity through the cell cycle.

If it is the case that there is an inverse dose-rate effect in a limited LET range, this would limit the number of situations in which the effect is of practical significance in radiological protection.

One area in which the effect might still be significant is radon. Most exposures to radon-daughter α particles are at LETs in the range from 150 to 200 keV/μm (*21*). At low doses (i.e., in a domestic exposure), no dose-rate effect would be expected, as multiple traversals of single cell nuclei would be rare. At higher doses, however, the LET at which the effect disappears due to the absence of multiple traversals will be increased. Thus analysis (*22*) of the Colorado uranium miner data (the most extensive data base for radon risk estimation) may be complicated by inverse dose-rate effects (*23–25*), which could lead to an overestimation of risk factors for environmental exposures to radon daughters.

APPENDIX

Potential Significance of Cellular Survival and Damage Repair on the Inverse Dose-Rate Effect

In calculating the enhancement in oncogenesis produced by the inverse dose-rate effect at LETs above 30 keV/μm (Eq. 12), we have not calculated the effect of survival or "conventional" damage repair explicitly. We have, however, described how the formalism can describe these effects, which are particularly important at lower LETs, such as those of X and γ rays. In this Appendix, we discuss the potential influence of these phenomena.

We first discuss the possible significance of cellular survival. Assuming (a) the survival of exposed sensitive cells is not affected by protraction in this LET range and (b) survival is the same for cells both inside and outside the "sensitive window" for oncogenesis, the effect of survival on any dose-rate enhancement would simply be a constant multiplicative factor on all four of the terms in Eq. (12), and would cancel out. Assumption (a) is probably reasonable in the dose/LET range of interest here (0.2 to 0.6 Gy, 25 to 200 keV/μm), in that the effect of fractionation on survival becomes more important with increasing dose and decreasing LET (i.e., increasing curvature of the survival curve); we can estimate whether survival will be affected by fractionation by comparing the doses used with the value of α/β, which is the value, in the linear-quadratic model, at which the quadratic component (which is affected by protraction) becomes comparable in effect to the linear component (which is independent of protraction). Survival data for C3H 10T1/2 cells (*26*) yield α/β values of >2.5 Gy for all measured LETs (X rays to 120 keV/μm). In that we are here considering doses of 0.2 to 0.6 Gy, it is therefore reasonable to assume that fractionation of these doses will not affect survival in the LET range from 25 to 200 keV/μm.

Assumption (b), that survival will be the same for cells both inside and outside the sensitive window, is based on the observation that cellular survival varies with cell cycle in a much less pronounced way after high-LET exposure, compared with low LET (*27–29*). Even at high LET, however, the survival does vary through the cell cycle; until a sensitive window is identified within the cell cycle, we cannot begin to measure any survival differences; qualitatively, however, by preferentially reducing the first terms in both the numerator and denominator of Eq. (12), this effect would probably reduce the predicted magnitude of the inverse dose-rate effect.

The effect of damage repair on transformation yields is probably negligible at the doses and LETs under consideration here (i.e., above 20 keV/μm). For example, at 80 keV/μm, α/β for transformation induction of C3H 10T1/2 cells is $\sim$5 Gy (*26*), which is far larger than the doses under consideration here. Thus damage repair is unlikely to be the explanation for the reduction in the inverse dose-rate effect at LETs below $\sim$90 keV/μm.

A complete theory of dose-rate effects extending down to very sparsely ionizing radiations such as γ rays needs to consider damage repair. As discussed in connection with Eq. (2), this can naturally be accommodated into the current formalism by replacing the αD term in Eq. (2) or Eq. (12) with an $(\alpha D + \beta D^2)$ term, in which the β parameter depends on protraction/damage repair. Thus, for example, in Eq. (12), in comparing an acute γ-ray exposure with a higly fractionated one, $K \Rightarrow 0$, and the ratio of fractionated to acute rates would become

$$\frac{\alpha D}{\alpha D + \beta D^2}, \tag{12a}$$

i.e., $\beta \Rightarrow 0$ for the highly fractionated exposure, and $0 < \beta \leqslant 1$ for the acute exposure. Equation (12a) describes a repair-related sparing of effect due to fractionation.

ACKNOWLEDGMENTS

The advice of Drs. Stanley Curtis, Charles Geard, and Ray Sachs is gratefully acknowledged. This work was supported by Public Health Ser-

vice Grants OH-02931 (NIOSH) and CA-49062 (NCI), and by Grant DE-FG02-88ER60631 (DOE).

RECEIVED: January 14, 1992; ACCEPTED: October 13, 1992

REFERENCES

1. D. J. Brenner and E. J. Hall, The inverse dose rate effect for oncogenic transformation by neutrons and charged particles. A plausible interpretation consistent with published data. *Int. J. Radiat. Biol.* **58,** 745–758 (1990).
2. M. Charles, R. Cox, D. T. Goodhead, and A. Wilson, CEIR forum on the effects of high-LET radiation at low doses/dose rates. *Int. J. Radiat. Biol.* **58,** 859–885 (1990).
3. D. J. Brenner and E. J. Hall, Radiation-induced oncogenic transformation: The interplay between dose, dose protraction and radiation quality. *Adv. Radiat. Biol.* **16,** 167–179 (1992).
4. NCRP, *The Relative Biological Effectiveness of Radiations of Different Quality.* Report 104, National Council on Radiation Protection and Measurements, Bethesda, MD, 1990.
5. R. C. Miller, G. Randers-Pehrson, L. Hieber, S. A. Marino, M. Richards, and E. J. Hall, The inverse dose-rate effect for oncogenic transformation by charged particles is LET dependent. *Radiat. Res.* **133,** 259–263 (1993).
6. L. Hieber, G. Ponsel, H. Roos, S. Fenn, E. Fromke, and A. M. Kellerer, Absence of a dose-rate effect in the transformation of C3H 10T1/2 cells by α particles. *Int. J. Radiat. Biol.* **52,** 859–869 (1989).
7. D. Bettega, P. Calzolari, G. N. Chiorda, and L. Tallone-Lombardi, Transformation of C3H 10T1/2 cells with 4.3 MeV α particles at low doses: Effects of single and fractionated doses. *Radiat. Res.* **131,** 66–71 (1992).
8. C. K. Hill, A. Han, F. Buonaguro, and M. M. Elkind, Multifractionation of ^{60}Co gamma rays reduces neoplastic transformation *in vitro*. *Carcinogenesis* **5,** 193–197 (1984).
9. R. C. Miller, D. J. Brenner, C. R. Geard, K. Komatsu, S. A. Marino, and E. J. Hall, Oncogenic transformation by fractionated doses of neutrons. *Radiat. Res.* **114,** 589–598 (1988).
10. H. H. Rossi and A. M. Kellerer, The dose rate dependence of oncogenic transformation by neutrons may be due to variation of response during the cell cycle (letter). *Int. J. Radiat. Biol.* **50,** 353–361 (1986).
11. M. M. Elkind, Enhanced neoplastic transformation due to protracted exposures of fission neutrons: a biophysical model (letter). *Int. J. Radiat. Biol.* **59,** 1467–1475 (1991).
12. C. K. Hill, M. Renan, and E. Buess, In *Radiation Research, A Twentieth-Century Perspective* Vol. 1, (J. D. Chapman, W. C. Dewey, and G. F. Whitmore, Eds.), p. 344. Academic Press, San Diego, 1991. [Abstract]
13. ICRU, *The Quality Factor in Radiation Protection.* Report 40, International Commission on Radiation Units and Measurements, Bethesda, MD, 1986.
14. A. A. Edwards, D. C. Lloyd, and J. S. Prosser, The induction of chromosome aberrations in human lymphocytes by accelerated charged particles. *Radiat. Prot. Dosim.* **13,** 205–209 (1985).
15. M. Zaider and D. J. Brenner, On the microdosimetric definition of quality factors. *Radiat. Res.* **103,** 302–316 (1985).
16. M. Zaider and D. J. Brenner, Evaluation of a specific quality function for mutation induction in human fibroblasts. *Radiat. Prot. Dosim.* **15,** 79–82 (1986).
17. P. Pihet, H. G. Menzel, R. Schmidt, M. Beauduin, and A. Wambersie, Biological weighting function for RBE specification of neutron therapy beams. Intercomparison of 9 European cities. *Radiat. Prot. Dosim.* **31,** 437–442 (1990).
18. M. N. Varma and M. Zaider, A non-parametric, microdosimetric approach to the evaluation of the biological effects of low doses of ionizing radiation. In *Biophysical Modelling of Radiation Effects* (K. H. Chadwick, G. Moschini, and M. N. Varma, Eds.), pp. 145–153. Adam Hilger, Bristol, 1992.
19. A. M. Kellerer, Fundamentals of microdosimetry. In *The Dosimetry of Ionizing Radiation* (K. R. Kase, B. E. Bjarngard, and F. H. Attix, Eds.), Vol. 1, pp. 78–161. Academic Press, Orlando, 1985.
20. A. M. Kellerer and D. Chmelevsky, Criteria for the applicability of LET. *Radiat. Res.* **63,** 226–234 (1975).
21. D. J. Brenner, The microdosimetry of radon daughters and its significance. *Radiat. Prot. Dosim.* **31,** 399–403 (1990).
22. National Research Council, Committee on the Biological Effects of Ionizing Radiations, *Health Risks of Radon and Other Internally Deposited Alpha-Emitters* (BEIR IV). National Academy Press, Washington, DC, 1988.
23. S. C. Darby and R. Doll, Radiation and exposure rate. *Nature* **344,** 824 (1990).
24. R. W. Hornung and T. J. Meinhardt, Quantitative risk assessment of lung cancer in U.S. uranium miners. *Health Phys.* **52,** 417–430 (1987).
25. J. H. Lubin, Y. L. Qiao, P. R. Taylor, S. X. Yao, A. Schatzkin, B. L. Mao, J. Y. Rao, X. Z. Xuan, and J. Y. Li, Quantitative evaluation of the radon and lung cancer association in a case control study of Chinese tin miners. *Cancer Res.* **50,** 174–180 (1990).
26. T. K. Hei, K. Komatsu, E. J. Hall, and M. Zaider, Oncogenic transformation by charged particles of defined LET. *Carcinogenesis* **9,** 747–750 (1988).
27. W. K. Sinclair, Radiation survival in synchronous and asynchronous Chinese hamster cells *in vitro*. In *Biophysical Aspects of Radiation Quality: Proceedings of the Second IAEA Panel,* pp. 30–54. IAEA, Vienna, 1968.
28. H. R. Withers, K. Mason, B. O. Reid, N. Dubraysky, H. T. Barkley, B. W. Brown, and J. B. Smathers, Response of mouse intestine to neutrons and gamma rays in relation to dose fractionation and division cycle. *Cancer* **34,** 39–47 (1974).
29. E. J. Hall, Radiobiological measurements with 14-MeV neutrons. *Br. J. Radiol.* **42,** 805–813 (1969).