linear regressions of the data obtained with exposures at high and low dose rates.

Variations on the Theme

For many years there have been sporadic reports of increased effectiveness at very low dose rates. The mechanism of such a phenomenon, if true for cancer (most of the reports are for genetic effects), is an enigma unless it represents one aspect of the complex dose response of the effects of radiation on DNA repair. It is not an observation that the devotees of hormesis have taken to heart!

Others have devoted some time to inverse dose-rate effects at somewhat higher doses seen in studies on cells *in vitro.* The same term has, unfortunately, been applied to findings with radon where lower exposure rates have resulted in a higher induction rate of lung cancer than with higher exposure rates. Since the exposures are to α particles, the term dose rate seems suspect. There are differences in protraction and dose rate. Although low-dose-rate exposures are protracted, there can be different biological factors at play. Consider the simple example that a protracted exposure may be less effective purely because with an exposure that is sufficiently protracted, the age-dependent reduction in susceptibility to induction of cancer may come into play. There are other ways that protraction can affect the behavior of initiated cells, such as through the effects on cytokines and their control. Time is not a simple matter when it comes to biology.

The role of radiation-induced genomic instability has been suggested as central to the induction of cancer by radiation. The suggestion is attractive because it is a possible explanation of how a single exposure to radiation could result in multiple mutations leading to cancer quite some time after the exposure. Most of the current data is for high doses and much of it for high-LET radiations. It will be very important to delineate the role of dose rate in the induction of genomic instability.

What is the Future for the DDREF?

The apparent linearity of the dose–response curve for total cancers as a function of dose in the atomic bomb survivors raised the question in some minds that perhaps there was not an effect of dose rate. There is no absolute evidence that a linear dose response up to high doses implies a lack of a dose-rate effect. Perhaps more pertinent is whether the apparent linearity says anything about the dose response of the initial event. It is on this question that Goodhead (*5*) has written recently. He points out that analysis of FISH-painted chromosomes indicates that chromosome exchanges can be induced by damage due to a single track to only one chromosome and that the response is linear. It is the complex aberrations that contribute the curvature to the responses. Goodhead believes that there is little justification for a DDREF greater than 1 and that the application of the linear-quadratic model to the interpretation of radiation carcinogenesis is, in other words, a snare and a delusion. It is not so easy to claim that dose rate, protraction and fractionation have no significant effect on the induction of cancer.

Since the greatest contribution to the uncertainty of the current estimates of risk of induction by low doses of radiation lies in the choice of the value of the DDREF (*6*), there is a compelling need to resolve the mysteries of time in relation to how cells, tissues and whole organisms react to radiation.

References

1. UNSCEAR, *Sources and Effects of Ionizing Radiation.* No. E77.1X.1, United Nations, New York, 1977.
2. ICRP, *1990 Recommendations of the International Commission on Radiological Protection.* ICRP Publication 60, *Annals of the ICRP*, Vol. 21, Pergamon Press, Elmsford, NY, 1991.
3. UNSCEAR, *Sources, Effects and Risks of Ionizing Radiation.* No. E.88.1X.7, United Nations, New York, 1988.
4. NCRP, *Influence of Dose and Its Distribution in Time on Dose-Response Relationships for Low LET-Radiation.* Report No. 60, National Council on Radiation Protection and Measurements, Bethesda, MD, 1980.
5. D. T. Goodhead, Clustered damage to DNA: Time to re-evaluate the paradigm of radiation protection. In *Radiation Research*, Vol. 2 *Proceedings of the Eleventh International Congress of Radiation Research* (M. Moriarty, C. Mothersill, C. Seymour, M. Edington, J. F. Ward and R. J. M. Fry, Eds.), pp. 342–347. Allen Press, Lawrence, KS, 2000.
6. NCRP, *Uncertainties in Fatal Cancer Risk Estimates used in Radiation Protection.* Report No. 126, National Council on Radiation Protection and Measurements, Bethesda, MD, 1997.

Protraction Effects in Radiation Studies: Basic Biophysics

D. J. Brenner

Center for Radiological Research, Columbia University, New York, New York

(with R. K. Sachs, University of California, Berkeley)

The dose rates relevant to radiation biophysics cover an enormous range. The exposures of the A-bomb survivors were effectively instantaneous, but environmental or occupational dose rates down to mGy/year are of interest. When a given dose is protracted, various processes can decrease, increase or leave unchanged the biological response. A protracted exposure can be either continuous or in a series of acute fractions; these alternatives may not differ too much if the number of fractions is large. We discuss dose protraction here mainly in terms of splitting a given acute dose D into two equal fractions $D/2$ separated by some interval, but the same trend putatively holds, details apart, for any other kind of dose protraction.

Protraction and the Acute Dose–Response Curve

With some limitations (see below), one can often consider the effect of protraction in a fairly model-independent way by considering the response to a fractionated exposure as the result of repeating the dose–response relationship for each fraction (*1*). Then, if the acute dose–response relationship has an upward curvature [as in the classic linear-quadratic (LQ) relationship], fractionation would be expected to decrease the response. A decrease of response with increasing dose protraction is often called a *direct* dose-rate effect. On the other hand, downward curvature in the acute dose–response relationship would imply that fractionation increases the response, giving an inverse dose-rate effect. If the acute dose–response relationship is more complex, fractionation could either decrease or increase the response, depending on the dose. On the other hand, a system whose dose–response relationship for acute irradiation is linear—even if linearity resulted from the cancellation of various curved dose–response relationships—would be expected to show little protraction effect.

The applicability of this rule—that the effect of fractionation approximates repeated applications of the same initial part of the dose–response curve—depends on how a cell population changes between dose fractions (or during continuous irradiation). The rule holds if there is restoration of radiosensitivity properties between fractions, so that the distribution of sensitivity within the cell population is the same just before the second fraction as it was before the first fraction. Restoration can occur through repair or other biological processes such as progression of cells in radioresistant parts of the cell cycle to sensitive parts and *vice versa.* But the rule does not hold if the first dose more or less permanently distorts the cell population structure, e.g. by removing most of a genetically different sensitive subpopulation. The rule can also fail if the first fraction initiates new biological processes, e.g. if induced resistance develops between fractions and persists until the time of the second fraction.

Where the fractionation rule can be tested (i.e. in the laboratory), it often does seem to hold, implying that low-dose response and the effects

of protraction are inextricably linked and, in some sense, represent the same phenomenon.

Dose–Response Relationships with Upward Curvature

Upwardly curving acute dose–response curves are indeed frequently associated with a direct dose-rate effect (review in ref. *2*). A classic mechanism leading to acute dose–response relationships with upward curvature is DNA double-strand break (DSB) repair. For example, for radiation-induced leukemia, the basic model is: (1) leukemias are caused by the induction of chromosomal translocations; (2) translocations in turn require the production of two DSBs; (3) if these two DSBs are produced in a fractionated exposure at different times, the first DSB could be repaired before the second is formed, in which case that DSB pair does not have the potential to make a translocation, as it would if both DSBs were formed at the same time in an acute exposure. This argument would not apply to translocations produced entirely by a single track of radiation, which is probably the dominant mode of translocation formation at very low doses (i.e. when the linear term dominates over the quadratic in the LQ equations), so the doses at which this DSB repair phenomenon tends to dominate are comparatively high.

Most dose–response relationships having (or appearing to have) a threshold can be considered in the present context. That is, protraction would be expected to decrease the response (assuming restoration occurs).

Dose–Response Relationships with Downward Curvature

While various explanations have been suggested for an initial downward curvature in the acute dose–response relationship at low doses (sometimes referred to as low-dose hypersensitivity), most interpretations involve saturation of damage to a radiosensitive subpopulation of cells. For example, for the end point of oncogenesis, some small subpopulation would be transformed, or stimulated to become less sensitive, even if only a fairly small dose is given. There appears to be some evidence that such a hypersensitive subpopulation may be affected by a damage signal, rather than directly by radiation—a manifestation of the so-called bystander effect. Such a small subpopulation could be genetically or epigenetically different, or it could be in a narrow window of the cell cycle, or perhaps it could be cells temporarily possessing some endogenous, repairable, non-radiative damage. The detailed models are different for these cases, but the resulting acute dose response is rather similar. Protraction could then increase response if the cell population structure is restored on time scales comparable to the protraction time.

Dose–Response Relationships with a Complex Shape

For X rays, there is evidence, at least *in vitro*, for a complex response: initial downward curvature at low doses, followed by a region of upward curvature (the classic LQ) at somewhat higher doses, followed perhaps by a high-dose plateau. Some *in vitro* oncogenic transformation studies using X rays show such a complex acute dose–response relationship leading to an inverse dose-rate effect at low doses (*3*), as would be expected on the arguments given above.

Linear Dose–Response Relationships

Almost all mechanistically based biophysical models predict a linear response with dose at very low doses, though the dose below which linearity occurs is a matter of much debate. As the acute dose is reduced to the point where this linearity dominates, one would not, in the picture outlined above, expect any dose-rate effects, whatever the mechanism. An example can be seen in the analysis of dose-rate effects from radon exposure. Here, at relatively high doses, there is clear evidence of an inverse dose-rate effect; the explanation probably relates to a subpopulation of very radiation-sensitive cells. However, as the radon exposure is reduced to the level where it is very rare for a single cell to be traversed by more than a single particle (and thus a linear dose–response relationship is expected), there are no dose-rate effects of any kind. This phenomenon was first predicted theoretically and then demonstrated epidemiologically—a nice example of synergy between radiation biology and radiation epidemiology.

Conclusions

Protracting acute exposures can increase, decrease or leave unchanged the biological response. Dose-rate effects can be intimately related to low-dose acute response, and in these situations each can give us clues to the other. Making the assumption that protraction leaves response unchanged could result in either overestimates or underestimates of risk, much as linear extrapolations from high to low doses could result in either overestimates or underestimates. Epidemiological studies and mechanistically based extrapolations probably offer the main hopes for improving low-dose or low-dose-rate risk estimates.

Acknowledgments

The late Dr. H. H. Rossi first elucidated many of the concepts discussed here. This research was supported by grants CA77285, CA24232, ES07361, CA86823 and DE-FG02-98ER62686.

References

1. H. H. Rossi, E. J. Hall and M. Zaider, The role of neutrons in transformation research: I. Theory. In *Neutron Carcinogenesis* (J. J. Broerse and G. B. Gerber, Eds.), pp. 371–380. Report EUR 8084, Commission of the European Communities, Luxembourg, 1982.
2. R. K. Sachs, P. Hahnfeldt and D. J. Brenner, The link between low-LET dose–response relations and the underlying kinetics of damage production/repair/misrepair. *Int. J. Radiat. Biol.* **72**, 351–374 (1997).
3. R. C. Miller, E. J. Hall and H. H. Rossi, Oncogenic transformation of mammalian cells *in vitro* with split doses of x rays. *Proc. Natl. Acad. Sci. USA* **76**, 5755–5758 (1979).
4. J. H. Lubin, J. D. Boice, Jr., C. Edling, R. W. Hornung, G. Howe, E. Kunz, R. A. Kusiak, H. I. Morrison, E. P. Radford and S. X. Yao, Radon-exposed underground miners and inverse dose-rate (protraction enhancement) effects. *Health Phys.* **69**, 494–500 (1995).

Protraction Effects in Radiation Studies: Epidemiology

Elaine Ron

Radiation Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Although a great deal is known about the carcinogenic effects of acute or high-dose-rate radiation exposure in humans, much less is known about the effects associated with low-dose-rate and fractionated exposures. As a result, risk estimates are based mainly on populations exposed to radiation delivered at high dose rates. However, protracted exposures over a period of time are more relevant for human experiences. To extrapolate from high to low dose rates, the term ''dose and dose-rate effectiveness factor'' (DDREF) was introduced by the International Commission on Radiation Protection (ICRP). The DDREF is a factor by which the biological effect caused by a specific dose changes at low compared to high dose rates. Currently the ICRP and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) suggest that compared with risks from acute or high-dose-rate exposure, risks from fractionated or low-dose-rate exposure should be reduced by a factor of 2 or 3, respectively (*1, 2*).

There is a fairly large body of literature on protraction effects from animal studies. In addition, experiments on cell transformation in culture, somatic cell mutations *in vitro*, and germ cell mutations *in vivo* have added to this literature. These studies have documented that the effects of dose vary depending on the level of protraction. Because findings from animal studies differ depending on species and strain, and cell transfor-