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Protecting Effects Specifically from Low Doses of Ionizing Radiation to Mammalian Cells Challenge the Concept of Linearity.

L.E. Feinendegen[1], V.P. Bond[2], C.A. Sondhaus[3], K.I. Altman[4]

[1]Medical Department, Brookhaven National Laboratory, Upton, NY
[2]Research Faculty, Washington State University, Richland, WA
[3]Department of Radiology and Radiation Control Office, University of Arizona, Tucson, AZ
[4]Until his death in January 1998,
Department of Biochemistry and Biophysics, University of Rochester Medical Center, Rochester, NY

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Abstract

Ionizing radiation is known to potentially interfere with cellular functions at all levels. Cell death and late effects such as malignant tumors may result. These stem from permanent damage to cellular DNA, which may lead to malignant transformation of the affected cells. Most such studies have used relatively high values of an absorbed dose, D, above about 0.3 Gy. After acute exposures of humans to between 0.3 and 2 Gy, the risk of cancer in the exposed individuals seems proportional to tissue D. For the purpose of radiation protection, this proportionality is assumed to extend down to zero D. This assumption defines the linear-no-threshold, LNT, hypothesis.

In addition to DNA damage, altered intracellular signaling results from acute exposure to cell doses below about 0.3 Gy, and involves radiation-induced reactive oxygen species, ROS. In consequence, different mechanisms of protection against DNA lesions may be induced and last from hours to weeks in different cell types. Damage to DNA is continuously and endogenously produced mainly by ROS generated in a normal oxidative metabolism. This DNA damage quantitatively exceeds by several orders of magnitude that caused by low-dose irradiation. Thus, the protective responses following acute low-dose irradiation may be presumed to mainly prevent and reduce endogenously caused DNA damage.

Protective responses are physiological and ubiquitous, albeit differently expressed in various cell types and species. Only in few cases has the induction of such responses been studied that occur after acute low-dose irradiation. Their incidence has been described to be nonlinear, increasing initially with D, beginning to decrease with D when D exceeds about 0.1-0.2 Gy, and eventually disappearing at higher D.

Accordingly, the model described here uses two dose-effect functions, one linear for causing and a nonlinear one for reducing DNA damage in the irradiated cells and tissues. The resulting net dose-risk function strongly suggests that the incidence of cancer against dose in the irradiated tissues is much less likely to be linear than to exhibit a threshold, or even to fall below the spontaneous incidence, when D to cells is below about 0.2 Gy. This relationship also suggests that alternative definitions of the relative effectiveness for a given type of radiation may be applicable at the cell level.

DISCLAIMER

Introduction

Ionizing radiation influences tissues by triggering responses in its constituent cells. At high values of absorbed dose D, cell death is the main cause of the tissue damage that results in acute radiation sickness (Bond V.P. et al. 1965). At lower values of D, various cellular metabolic responses, especially those involving DNA, determine tissue effects which may develop eventually into diseases such as cancer. All these responses can be taken as resulting mainly from energy deposition events in cells. Moreover, recent reports suggest that irradiated extracellular matrix of the tissues should also be considered as a source of products that may interact with cells (Boudreau et al. 1996; Roskelley et al. 1995). In any case, tissue response derives from cellular responses to discrete energy deposition events within that tissue. The frequency and quality of such events can be estimated from quantitative microdosimetric measurements (ICRU 1983; Feinendegen et al. 1994).

This report examines the origin of tissue effects that may follow from different cellular responses to low-dose irradiation, using published data. Two principal categories of cellular responses are considered. One response category relates to the probability of radiation-induced DNA damage. The other category consists of low-dose induced changes in intracellular signaling that induce mechanisms of DNA damage control different from those operating at high levels of exposure. Modeled in this way, tissue is treated as a complex adaptive system. The interaction of the various cellular responses results in a net tissue dose-effect relation that is likely to deviate from linearity in the low-dose region. This suggests that the LNT hypothesis should be reexamined.

The aim of this paper is to demonstrate that by use of microdosimetric concepts, the energy deposited in cell mass can be related to the occurrence of cellular responses, both damaging and defensive. By defining both dose and effect on the cellular level, the relative risk from low doses of radiation can be assessed more fundamentally than is presently the case. This approach also outlines a conceptual framework for further development and experimental testing so that assessment of risks from DNA damage may be improved. A prime example is cancer in tissues exposed to low and very low doses of ionizing radiation, where epidemiological studies alone are inadequate because of statistical limitations. Moreover, new questions arise regarding the meaning of the relative effectiveness of different types of ionizing radiation in cells.

To properly develop the chosen approach, the dose to the cell

mass is explained first in regard to acute and protracted exposure. Then, the various types of responses of irradiated cells are shortly reviewed including those after high and low dose irradiation also with reference to the DNA damage sustained from a normal cellular metabolism. In consequence, the probability of the various cellular responses is defined and summarily used to express tissue risk such as cancer. This leads to a discussion of the meaning of relative risk from exposures to ionizing radiation of different qualities.

Absorbed Dose in Tissue and its Cells

The absorption of penetrating ionizing radiation in matter results in the deposition of discrete amounts of energy from particle tracks that arise stochastically throughout the exposed matter (ICRU 1983). Compared to external irradiation, the situation may be different for exposure to internally deposited radionuclides that emit short-range particles. When such discrete sources are heterogeneously distributed within tissues, energy depositions from particle tracks are accordingly heterogeneous. However, in either case and depending on the type of radiation, these tracks exhibit a characteristic distribution in regard to their energy and their corresponding linear energy transfer (LET). For any exposure, the energy deposited by a single track in a defined mass of microscopic spherical dimensions, micromass, is an event with magnitude conventionally described by the term specific energy, z_1, the mean value of which is denoted by $\bar{z}_1$; this may be calculated, based either on the frequency of the events or on the distribution of z_1 per unit absorbed dose produced by a given spectrum of events (ICRU 1983). Particle tracks may occur both in cells and extracellular matrix of the exposed tissue. These tracks either fully or partially traverse the cells and equivalent masses of extracellular matrix.

The structure and function of a tissue are determined by its living cells. These respond wholly to physiological or pathological interventions. Malignant tumors are assumed to stem from single cells (Alberts et al. 1989) and the fraction of potentially carcinogenic cells, such as stem cells, in a given adult tissue is assumed to be constant.

The cell nucleus contains most of the genome of the cell, except mitochondrial DNA, and has thus been assumed to be the gross sensitive volume, GSV, for a given tissue (Bond et al. 1966, Cronkite et al. 1971, NCRP 1979, Feinendegen et al. 1985). However, cells react in their entirety to physiological or pathological interventions by way of cellular signaling.

Therefore, the present approach assumes an equivalent mammalian cell volume of spherical shape, whose average mass is approximately 1 ng, to represent the GSV (Feinendegen et al. 1994). For consistency, the same is also taken to apply to the extracellular matrix of the exposed tissue. This simplifies the relationship between the number of cells with a defined response and the incidence of energy deposition events in the exposed GSVs. The averaging of the tissue GSV over all cell types follows the practice used in calculations for radiation protection.

In this presentation, the corresponding $\bar{z}_1$ for cells and equivalent masses of extracellular matrix being the GSV is calculated on the basis of the frequency distribution of the individual values of z_1. The single energy deposition event in the GSV is called a hit, and the incidence of such hits is denoted by N_H. The value of z_1 as defined by the mass of the GSV has been called the hit size, cell dose, or microdose, and $\bar{z}_1$ denotes its mean value. The present paper uses the term microdose with the cell-dose being the sum of microdoses.

The probability of a GSV being affected, i.e., hit, by a particle track depends on the magnitude of the absorbed dose to the exposed tissue (D) (ICRU 1980, 1983), as well as the type of radiation. For a given D generated by particle tracks mainly of the "crosser" type (ICRU 1983), the probability of a GSV being hit is inversely related to the mean value of the LET of that radiation. The ratio of the number of hits of all sizes, N_H, to the number of exposed GSVs, N_e, multiplied by $\bar{z}_1$, is equal to D. As long as N_H and N_e refer to the same GSV, the ratio N_H/N_e is independent of the anatomical definition of the GSV, be it the biological entity cell, the equivalent mass of matrix, or both. Therefore:

$$D = \bar{z}_1 \cdot N_H/N_e. \qquad (1)$$

The values of $\bar{z}_1$ and N_H/N_e for four different types of radiation and for the spherical GSV being 1 ng, at a dose D of 0.01 Gy, are listed in Table 1 (Bond et al. 1995, Feinendegen et al. 1995).

Since $\bar{z}_1$ remains constant for a given type of radiation, only N_H/N_e increases in proportion to D. At low values of D, single GSVs experience only single hits or none at all, i.e., the ratio N_H/N_e is much lower than 1 (ICRU 1983, Booz et al. 1988). With increasing values of D, all GSVs eventually experience multiple hits, i.e., the ratio N_H/N_e becomes increasingly larger than 1.

Table 1

(At D = $\bar{z}_1 \cdot N_H/N_e$ = 0.01 Gy)

	$\bar{z}_1$ (Gy)	N_H/N_e
Cs-137 γ-rays	0.0004	28.57
250 kVp x-rays	0.0009	11.63
10 MeV protons	0.006	1.63
4 MeV α-particles	0.35	0.028

Dose Rate in Tissues Means Repetitive Doses to Cells

According to equation 1, during exposure to a defined radiation field the dose rate D per unit time t is:

$$D/t = \bar{z}_1 \cdot (N_H/N_e) \cdot (1/t)$$

or

$$D/t = \bar{z}_1 / (t \cdot N_e/N_H). \qquad (2)$$

The denominator $(t \cdot N_e/N_H)$ expresses the average time interval between two consecutive hits per exposed GSV (Feinendegen et al. 1988). This time interval gives the time available for the GSV to express its acute biochemical responses without any effects from a later hit. Here, only such acute or protracted exposures are considered, where $(t \cdot N_e/N_H)$ is sufficiently long for acute responses and repair to be caused only by instantaneous hits.

DNA Damage from Normal Metabolism

DNA damage in mammalian tissues has a steady state. It may come from erroneous base-pairing during DNA replication, from thermal instability, environmental toxins, but appears to be mainly caused by endogenous oxidant by-products of normal metabolism, i.e., by reactive oxygen species (ROS). Tens of thousands oxidative DNA adducts have been reported to be present in mammalian cells at anyone time (Ames et al. 1995; Beckman et al. 1997; Helbrock et al. 1998), of which in human cells more than ten thousand adducts turn over per day (Helbrock et al. 1998). Many of the DNA adducts are repaired with halftimes ranging from about 9 to 60 minutes (Jaruga et al. 1996). Even if some radiation-induced DNA damage is qualitatively distinct (Ward

1988), its difference to endogenous DNA damage is presently little understood. Nevertheless, the incidence of endogenous DNA damage in every cell per day is probably several orders of magnitude higher than comparable DNA damage caused by normal background radiation bringing per day just 1 microdose event in only about 1 out of 300 cells (Feinendegen et al. 1995; Pollycove et al. 1997).

A correlation appears to exist between the extent of endogenously caused DNA damage and the incidence of cancer or degenerative diseases (Cleaver 1968; Wei et al. 1993; Lohman et al. 1995; Ames et al. 1995). In normal human individuals, endogenously produced DNA damage is largely controlled by elaborate defense and repair mechanisms, that also operate after irradiation (Alberts et al. 1989; Wallace 1988; Wei et al. 1993; Lohman et al. 1995; Jaruga et al. 1996; for recent review: Rad.Res.Soc. 1998). The probability of a spontaneous malignant transformation throughout the life span of a blood-forming stem cell causing lethal leukemia in the exposed individual is in the order of only 10^{-11} (Feinendegen et al. 1995).

Responses of Cells at High Doses

Radiation effects in cells and tissues are usually described following high-dose exposure and often related to their application in radiation-therapy (for recent review: Rad.Res.Soc. 1998). High-dose exposure is known to affect cellular function at practically all levels, causes DNA damage and may lead to cell death, depending on the cell's sensitivity to radiation. Also, genomic or chromosomal instability has been described following such exposures and may persist for several cell generations. Surviving cells have a relatively high probability of acquiring gene mutations, with the consequence of malignant transformation and cancer. Such studies involve both high doses of low LET radiation and low doses of high LET radiation. As discussed above (see Table 1), both modes of exposure deliver relatively high doses to individual cells, either in single hits from high-LET radiation, or multiple, virtually simultaneous hits from low-LET radiation. DNA damage is also reported to occur in non-hit cells due to signal substances and clastogenic factors released by hit cells (Nagasawa et al. 1992; Emerit et al. 1995).

Depending on the exposure, the type and extent of DNA damage, repair mechanisms are known to operate, partially or fully restoring cellular structure and function (Alberts et al. 1989). These mechanisms are still not fully understood (see abstracts: Rad.Res.Soc. 1998). They determine the degree of radiation

sensitivity of a given cell, and un- or misrepaired DNA damage may decide the cellular fate.

Since Muller's discovery of mutation induction by x-rays (Muller 1927), the frequency of various types of DNA damage from ionizing radiation has been shown in innumerable studies to rise with absorbed dose, in single cell systems as well as in multicellular tissues (NRCP 1997). Similarly, after acute exposures to doses between about 0.3 and 2 Gy of both low and high LET radiation, the risk of cancer in exposed humans appears to be proportional to dose (UNSCEAR 1994). For the purpose of radiation protection, this proportionality is extended down to zero dose in accord with the linear-no-threshold hypothesis of radiation action on cellular DNA (ICRP 1990). This hypothesis assumes that a constant fraction of DNA damage remains un- or misrepaired, down to the smallest doses. As a consequence, a linear relationship is assumed to exist between even the lowest levels of absorbed dose and the incidence of cancer in the exposed tissue.

Responses of Cells at Low Doses

Acute exposure to low and high doses of ionizing radiation often affects exposed cells and tissues in a qualitatively similar manner. However, respective studies have usually employed such absorbed tissue doses that cause cell-doses well above about 0.3 Gy (see abstracts: Rad.Res.Soc. 1998). The measurement of DNA damage from cell-doses lower than about 0.3 Gy is increasingly confounded by the fraction of endogenously produced DNA damage mentioned above. Indeed, the probability of a malignant transformation of a potentially carcinogenic stem cell causing a tumor in humans, per microdose from low LET radiation is exceedingly small, in the order of 10^{-14} (Feinendegen et al. 1991).

On the other hand, cell-doses of less than 0.2 Gy of low LET radiation, even in the range of a single microdose, have been readily observed in mammalian cells to slowly induce acute and reversible changes in metabolism and function (Zamboglou et al. 1981; Sugahara et al. 1992; UNSCEAR 1994; Academie des Sciences 1995). In single cell microorganisms, very low doses stimulated growth (Planel 1965). The low dose responses have been regarded as physiological reactions of cells to background radiation (Planel 1965; Feinendegen et al. 1983) and were then shown to potentially adapt and protect cells against renewed irradiation (Olivieri et al. 1984).

Adaptive responses are understood to be such cellular reactions

which, for some period of time, tend to prevent both causation and accumulation of damage from renewed exposure to the same or a similarly operating toxic agent. If induced by low-dose irradiation, these reactions appear to involve cellular oxygen stress and the radical detoxification system. Oxidative stress responses are likely ubiquitous but differently expressed in various cell types and species. Responses to low doses of low LET radiation become understood only recently.

Adaptive responses following low-dose irradiation are here exemplified in four categories:

1) Damage prevention by stimulated detoxification of reactive oxygen species (ROS):

Acute whole body γ-irradiation of mice with doses even below 0.01 Gy caused an acute and temporary inhibition of the enzyme thymidine kinase in bone marrow cells. This response developed with a delay, reached a maximum at four hours and then disappeared by about 10 hours after irradiation (Zamboglou et al. 1981; Feinendegen et al. 1984). The observation of the effect depended crucially on an optimal pH and ionic composition of the medium in which the cells after irradiation in vivo were harvested prior to the assays. The enzyme inhibition was accompanied by a synchronously increased concentration of reduced glutathione expressing a radiation-stimulated detoxification of ROS (Feinendegen et al. 1987, 1988, Hohn-El-Karim et al. 1990). Indeed, the increase of glutathione concentration in the cells caused inhibition of the enzyme (Feinendegen et al. 1995) and increased the fraction of cells in S-phase, probably indicative of a retarded DNA synthesis (Coslar 1997). This also correlated with a temporary full protection of the enzyme against repeated irradiation with the same dose when this was given 4 hours after the first (Feinendegen et al. 1988). The effectiveness of protection of the enzyme against increasing doses of renewed irradiation declined when the second dose rose above about 0.1-0.2 Gy and fully disappeared above 0.5 Gy (Feinendegen et al. 1995). - When the mice were immobilized and exposed to a static magnetic field of 1.4 T, at a body temperature of 27°C for 30 minutes immediately following irradiation, the enzyme activity remained normal and radiation resistance did not develop (Feinendegen et al. 1987). Moreover, with the mice being on a vitamin E deficient diet, the concentration of reduced glutathione was increased and thymidine kinase activity in the bone marrow cells was reduced to the minimum level seen after low dose irradiation (Feinendegen et al. 1987); this also indicates the response of the observed radical detoxification system against metabolic challenges.

This set of data indicates that low-dose, but not high-dose, irradiation induced an alteration in intracellular signaling and causes a temporary inhibition of a vitally important enzyme for DNA synthesis, as a consequence of a temporarily increased ROS detoxification which in turn leads to a cellular protection against ROS. Similar results have been reported from various laboratories (Misonoh et al. 1992; Yamaoka et al. 1992). Because of the important role of ROS in causing DNA damage, the observed radiation-induced enhancement of ROS detoxification with its consequent cellular protection presumably also protects the DNA against metabolically produced ROS.

2) Damage repair expressed by prevention of chromosomal aberrations or mutations:

Acute low-dose exposure of human lymphocytes in vitro to low LET radiation induced chromosomal aberrations first to decline significantly before a dose dependent increase was seen above 0.05 Gy (Pohl-Rueling et al 1983). Indeed, an acute dose of as little as 0.005 Gy has been reported to condition human lymphocytes in vitro to exhibit fewer chromosomal aberrations upon renewed exposure to high doses, called challenging doses, compared to controls (Olivieri et al. 1984, Shadley et al. 1987, Wolff et al. 1988, Shadley et al. 1989; Wolff 1996). This protective response showed a maximum 4 hours and lasted over a period of more than two days following acute low-dose irradiation, and was also effective upon challenging exposure to various chemical mutagens (Wolff et al. 1988). The protective effect varied with the cell's position in the cell cycle at the time of the conditioning irradiation and is probably mediated through the induction of DNA repair (Shadley et al. 1992; Ikushima et al. 1996). Lymphocytes from different individuals showed various degrees of the response or none at all (Bosi et al. 1989). This protective response in human lymphocytes was not seen at very low dose rates, or when the conditioning dose exceeded 0.2 Gy (Shadley et al. 1987; Wolff 1996), or when the challenging dose was 4 Gy instead of 2 Gy (Shadley et al. 1992).

Working with human lymphoblastoid cells, a conditioning dose of 0,02 Gy of low LET radiation reduced the frequency of HPRT-mutations by 70% compared to the frequency observed after a high dose of 4 Gy without conditioning preirradiation (Rigaud et al. 1993). This effect may be due to the induction of error free DNA repair, by low-dose irradiation. Indeed, low-dose irradiation stimulated DNA repair regarding the removal of thymine-glycol in DNA caused by high-dose irradiation at 4 hours after low-dose exposure, in a human lung cancer cell line (Le et al. 1998). This conforms to the observation of a significant reduction of the

spontaneously high rate of transformation in a C3H cell line in culture, 24 hours after very low doses of low LET radiation (Azzam et al. 1996). Low-dose radiation effects on cell cycle checkpoints are considered to support or even facilitate the action of various repair mechanisms (Boothman et al. 1996; Tubiana 1996).

3) Damage removal by induction of apoptosis:

Programmed cell death, i.e., apoptosis, is presently a major topic of experimental cell research also with respect to radiation effects (see abstracts: Rad.Res.Soc. 1998). Apoptosis may be also induced by radiation probably via ROS. It eliminates potentially detrimental damage of DNA in the exposed cell population by replacement with normal cells (Kondo 1993). Indeed, the induction of apoptosis appears to favor cells with damaged DNA over normal cells. With respect to human lymphocytes, the incidence of apoptosis in vitro rose until day four after exposure to low LET radiation, and appeared to be linear with dose between about 0.1 and 2 Gy with a slope of 0.08 per 0.1 Gy (Menz 1996). On the other hand, at 24 hours after exposure of mouse thymocytes the incidence of apoptosis was significantly reduced at doses below about 0.2 Gy and only rose with higher doses, in a seemingly linear response (Shu-Zheng et al. 1996). Whether such a dose response relationship applies to other cells undergoing apoptosis is not known. Contrary to the data from mouse thymocytes, in various tissue culture cells showing radioresistance at high doses, low doses always induced a high rate of cell killing; this particular radiosensitivity to low-doses reached its maximum at about 0.2-0.3 Gy, to decline thereafter and fully disappear at 1.0 Gy (Joiner et al. 1996).

4) Damage removal by stimulated immune response:

Cells of the immune system in rodents were found to respond by stimulating the production of T-cells during fractionated γ-irradiation with 0.01 - 0.04 Gy per day for a total of 20 days (Makinodan 1992). These dose rates allow on average about 1 - 4 microdose events per cell per hour. The maximum response to acute whole-body γ-irradiation was at doses between 0.1 and 0.3 Gy. This response improved surveillance of immunogenic cells over periods of weeks, and eliminated cancer cells (Anderson et al. 1992; Makinodan 1992).

Cell responses at low versus high cell-doses

The common denominator of these low-dose effect data appears to

be a cellular reaction that is confined to low cell-doses with a maximum at about 0.2 Gy and that temporarily induces mechanisms of protection against causation and accumulation of damage, mainly against that from endogenous sources. This reaction also triggers a temporary increase of protection against DNA damage from high cell-doses when these are given several hours after low-dose exposure. This temporary protection is not initiated at high doses. It is justified to suggest a causal relationship between a radiation induced signaling from oxygen stress and such various system responses that are confined to low cell-doses (Laval 1988).

Indeed, the protective responses so far known to be induced by low but not by high cell doses appear to belong to a DNA damage control system that differs from the cellular DNA repair responses that are usually, but not exclusively, observed after high cell-doses of either low or high LET radiation (Kleczkowska et al. 1996). The latter responses may be regarded as more robust, belonging to a higher order cascade of reactions to acute DNA damage than the more subtle adaptive responses which apparently collapse or are consumed, as damaging events in cells increase. Also, the stress responses restricted to low cell-doses temporarily condition the expression of DNA repair systems when again challenged several hours later at high cell-doses. Moreover, repair mechanisms usually seen after high cell-doses eventually lose effectiveness with increasing doses and jeopardy to cellular integrity (Academie des Sciences 1995).

Probability of Cellular Responses

1) Malignant transformation

In this discussion, the probability per average microdose event, or hit, for malignant transformation of a potentially carcinogenic cell leading to a lethal tumor is assigned the term p_{ind}. It can only be estimated from effects seen at high doses. For example, acute high-dose exposure induces human leukemia proportionally to dose; at this high dose, p_{ind} is estimated to be approximately 10^{-14} per average hit from low LET radiation in human hemopoietic stem cells (Feinendegen 1991, 1995). This value has been obtained using the number of hemopoietic stem cells in humans and the risk coefficient of leukemia in the case of the atom bomb survivors, and converting tissue dose to microdoses. This p_{ind} is a net probability including the consideration of protective mechanisms operating at high doses. Interestingly, p_{ind} for cell transformation in tissue culture is about 10^{-5} and thus many orders of magnitude higher than for cells in tissue (Hall et

al. 1985). Cellular sensitivity and defense mechanisms in culture are obviously different from those in tissue.

In this presentation, p_{ind}, as defined above, is taken to be an average constant per microdose event per GSV, i.e., per N_H/N_e at low-dose exposure to low LET radiation. If an enhancement of p_{ind} were to result from an increase in N_H/N_e, for instance by way of genomic instability, the probability of enhancement per N_H/N_e would then be p_{enh}. If it occurs, p_{enh} may be independent of N_H/N_e but likely larger than p_{ind}, and the product $p_{ind}p_{enh}$ may confer linearity. However, the effect of p_{enh} in tissues may be negligible in the single hit range from low doses of low LET radiation.

The probability of spontaneous malignant transformation, p_{spo}, in the human hemopoietic stem cell with a lethal outcome is approximately 10^{-11} during the cell's life span (Feinendegen et al. 1995). This value has been estimated from the average incidence of spontaneously occurring leukemia in industrialized countries and the number of hemopoietic stem cells in humans.

2) DNA damage protection

For reasons discussed above, the various types of protective mechanisms against DNA damage must have evolved in cells and tissues to operate mainly against endogenous DNA damage. The contribution of the various types of mechanisms to an overall physiological DNA damage control capability is not known. Since at least some of them are obviously stimulated by low-dose irradiation, they need to be considered in risk assessment. In order to put these various mechanisms into perspective for further studies, their incidence after irradiation is estimated here in terms of a cumulative probability of protection per average hit, p_{prot} (Feinendegen et al. 1995, 1996a).

In contrast to p_{ind}, the individual components of p_{prot} are easily measurable in various cell systems at low doses, as described above. The value of p_{prot} at low doses must, therefore, be much larger than p_{ind}. Also, in contrast to p_{ind} in different cell systems, p_{prot} becomes an inverse function of dose when it exceeds about 0.1 to 0.2 Gy of low LET radiation. To account for this dependency, the cumulative probability of protection is here denoted by $p_{prot}(D)$.

3) Connecting the various probabilities of cell responses

In order to numerically connect the various p-values for DNA

damage induction and damage control, they need to apply to the same cell system and their averages need adjustment. This requirement arises from the differences in the duration of the detrimental and protective responses in the exposed tissue. A radiation-induced malignant transformation in a single cell may eventually cause a tumor to develop, but only over a period of perhaps several decades and in a series of subsequent steps. In contrast, most observed radiation-induced protective effects are singular events that operate over a relatively short period of time. Therefore, in order to offset one radiation-induced malignant transformation and its subsequent tumor development in the exposed tissue, either a single, potentially carcinogenic cell and its progeny must experience a protective response repeatedly and often, or an accordingly large number of cells at risk in the exposed tissue must all at once be temporarily protected, i.e., prevented from transmitting DNA damage to their viable progeny.

An Approach to Estimating Cancer Risk from Cellular Responses

In earlier papers, it was proposed that the risk of cancer from low doses of ionizing radiation could be assessed by combining the probabilities with which cells in the exposed tissue respond in various ways, directly or indirectly, to hits (Feinendegen 1991, Feinendegen et al. 1995, 1996a). It was postulated that the risk of cancer formation (R) in an irradiated tissue is proportional to the ratio of the number of transformed cells, N_q, in that tissue to the number of exposed GSVs, N_e. Moreover, by substituting D using equation (1) ($D = \bar{z}_1 \cdot N_H/N_e$) and multiplying each side by N_e, the conventionally used macroscopic dose-risk function for organs and tissues following low dose or dose rate exposure:

$$R = \alpha \cdot D \qquad (3)$$

becomes, on the cell level:

$$N_q / N_H = \alpha \cdot \bar{z}_1 . \qquad (4)$$

Thus, the conventionally used dose-risk function is transformed on the cellular level into a hit-number-effectiveness function (Bond et al. 1995).

While $\bar{z}_1$ is a constant for a given radiation quality and thus determined physically, the proportionality constant α expresses the biological response of the irradiated system. On the cell level, however, α is a composite of the previously defined

probabilities for cells in the exposed tissue:

p_{spo} = spontaneous malignant transformation,

p_{ind} = radiation-induced malignant transformation per average hit,

p_{enh} = enhancement of p_{ind} per average hit,

$p_{prot}(D)$ = protection against accumulation of damage to DNA in tissue, i.e., against p_{spo}, p_{ind}, p_{enh}, per average hit.

Regardless of the mechanisms involved, all the p-values are likely to vary with the species, cell type, and microdose when applicable.

The cumulative probability of DNA damage leading to cancer induction per average hit can be written as:

$$N_q/N_H = [p_{ind} + p_{ind}p_{enh} - p_{prot}(D)\,p_{spo} - p_{prot}(D)\,p_{ind} - p_{prot}(D)\,p_{ind}p_{enh}]. \quad (5)$$

Combining equations (3), (4) and (5) and solving for R:

$$R = [p_{ind}\ (1 + p_{enh}) - p_{prot}(D)\,(p_{spo} + p_{ind} + p_{ind}p_{enh})]\,(D/\bar{z}_1). \quad (6)$$

From the above, the term $\alpha = N_q/(N_H \cdot \bar{z}_1)$, equation (4), does not appear to be constant with changing D, since:

- $p_{prot}(D)$ has been shown in various cell systems to become an inverse function of D when D exceeds about 0.1 to 0.2 Gy of low LET radiation,
- the values of p_{ind} and p_{spo} appear to be independent of D over a wide range of D,
- p_{ind} and the product of p_{enh} and p_{ind} are taken to be comparatively small.

As discussed above, suppose that p_{ind} for hemopoietic stem cells is about 10^{-14} for human leukemia and the corresponding p_{spo} is about 10^{-11}, and that p_{enh} is taken to be zero at low D of low LET radiation. For $p_{prot}(D)$ about 10^{-3}, the value of the positive term $p_{ind}\ (1 + p_{enh})$ in equation (6) would then remain offset over a certain range of low D by the negative term $p_{prot}(D)\,(p_{spo} + p_{ind} + p_{ind}p_{enh})$ in this equation. If such were the case, a threshold for R would appear to exist, or with p_{prot} larger than 10^{-3}, R would

even become negative. Indeed, as discussed above, components of $p_{prot}(D)$ representing potential reduction of carcinogenesis have been readily measured at low D in various cell systems, while p_{ind} is not easily measurable. Without statistically significant changes in N_q after exposure of mammalian populations to low LET radiation below 0.2 Gy, it is impossible to determine whether detrimental or beneficial effects occur. However, several epidemiological and experimental data rather support the existence of a threshold or even beneficial (hormetic) effects at low-dose low LET radiation (UNSCEAR 1994; Azzam et al. 1996).

Figure 1 summarizes the model. The dashed line shows the increase of cancer (M) above background due to radiation if there were no protective mechanisms. The background line (Bkgd) shows the spontaneous cancer incidence, most of which is due to DNA damage resulting from normal cellular metabolism. The light solid line indicates the effect of the damage control response, which is mainly on the background cancer incidence. The heavy solid line shows the combined effects of cancer induction and prevention, the net dose-risk function. The shaded region represents the possible reduction of a cancer incidence due to protective effects which have been termed "radiation hormesis." The "threshold" shown for observable radiation-induced cancer, 0.2 Gy, complies with epidemiological data.

Concerning the term α for high LET radiation, the relatively high values of z_1 may be ineffective with regard to $p_{prot}(D)$ in the hit cells. However, p_{ind}, $p_{ind}p_{enh}$ and p_{spo} may be offset by $p_{prot}(D)$, if protective mechanisms are initiated in non-hit cells by intercellular signal substances and specific clastogenic factors stemming from irradiated cells. Such intercellular stimuli must be considered to affect non-hit cells in both ways, inducing damage and signaling for protection in terms of adaptive responses. It needs to be seen to what degree adaptive responses are initiated in multicellular systems exposed to very low D of high LET radiation.

The Meaning of Relative Risk Based on Cell-Dose Effects

The risk of damage from high LET radiation is usually expressed in relation to that from low LET radiation, with the latter serving as reference. It was shown above that the term α in the dose-risk function does not appear constant at low D of low LET radiation. Thus, relative risk as an expression of multiple cellular responses is here reexamined by using the approaches and terms developed in the previous paragraphs. In the following sections alternative expressions of relative risk are examined

for two different radiation qualities: a) per unit absorbed dose; b) per hit; and c) per unit microdose in the cell.

1) RBE as determined in tissue

The relative biological effectiveness (RBE) of two types of radiation is conventionally defined as the absorbed dose of low LET radiation required to produce a given level of a specified biological effect R, divided by the dose of a higher LET radiation producing an equal level of the same effect, i.e., RBE = D_L/D_H for $R_L = R_H$ (ICRU 1979). In the dose range where effect is linear with dose, the RBE is also defined as the ratio of α's, which from equation (3) is the ratio of R/D values for the two radiations. However, it has been shown here that the term α is a composite of several cellular response probabilities and hence quite probably not a constant but changes its value differently with D in the low-dose region. The RBE is therefore applicable only at each value of D with its corresponding value of R; that is, RBE= R_H/R_L for $D_L=D_H$. Accordingly, equation (6) for R_H and R_L yields:

$$\mathrm{RBE} = \frac{[p_{ind}\ (1 + p_{enh}) - p_{prot}(D)\,(p_{spo} + p_{ind} + p_{ind}p_{enh})]_{(H)}\,(D/\bar{z}_{1\,(H)})}{[p_{ind}\ (1 + p_{enh}) - p_{prot}(D)\,(p_{spo} + p_{ind} + p_{ind}p_{enh})]_{(L)}\,(D/\bar{z}_{1})_{(L)}} \quad . \qquad (7)$$

Letting: $\Sigma p_i = [p_{ind}\ (1 + p_{enh}) - p_{prot}(D)\,(p_{spo} + p_{ind} + p_{ind}p_{enh})]$,

then, according to equation (7):

$$\mathrm{RBE} = \frac{\Sigma p_{i(H)}\,(D/\bar{z}_1)_{(H)}}{\Sigma p_{i(L)}\,(D/z_1)_{(L)}} \qquad (8)$$

or using equation (1):

$$\mathrm{RBE} = (\Sigma p_{i(H)}/\Sigma p_{i(L)}) \cdot (N_{H(H)}/N_{H(L)}), \qquad (9)$$

where the ratio $N_{H(H)}/N_{H(L)}$ is taken at equal values of D. This again shows that the RBE does not express the relative biological effectiveness at equal D on the cellular level.

2) The Relative Hit Effectiveness

One may also compare the relative effectiveness per hit,

irrespective of their mean values $\bar{z}_1$, for two types of radiation. From equation (5) this quantity is just the ratio of cumulative probabilities for each radiation to cause N_q responses per N_H hits:

$$RHE = \Sigma p_{i(H)} / \Sigma p_{i(L)} \qquad (10)$$

Solving equation (9) for expressing the RHE:

$$RHE = RBE \cdot (N_{H(L)} / N_{H(H)}) \qquad (11)$$

For the same D, $N_{H(L)}$ is larger than $N_{H(H)}$, as shown in Table 1. Thus, the RHE is larger than the RBE. In the case of high energy neutron radiation, for example, the ratio $(N_{H(L)}/N_{H(H)})$ may exceed an order of magnitude (Feinendegen et al. 1985, 1996). The ratio of RHE to RBE for high energy neutrons is accordingly high. - As an example, mutations in the plant Tradescantia were measured at very low doses of 0.43 MeV neutrons versus 250 kVp x-rays; an RBE of 48 was observed (Sparrow et al. 1972). The RHE based on the corresponding $\bar{z}_1$ values is about 800 (Sondhaus et al. 1990).

3) The Relative Local Effectiveness

Since individual cellular responses determine risk to tissues, the cellular responses per unit microdose at equal values of D appear crucial. The ratio of $N_q/\bar{z}_1$ at equal values of D from two types of radiation has been called the relative local effectiveness, RLE (Feinendegen et al. 1985, 1996):

$$RLE = \frac{(N_q / (\bar{z}_1 \cdot D))_{(H)}}{(N_q / (z_1 \cdot D))_{(L)}} \qquad (12)$$

or according to equation (5), with equal D, and by rearrangement:

$$RLE = \frac{(\Sigma p_i \cdot N_H)_{(H)}}{(\Sigma p_i \cdot N_H)_{(L)}} \cdot \frac{\bar{z}_{1(L)}}{\bar{z}_{1(H)}}$$

The values of $\bar{z}_1$ and N_H/N_e per unit D are reciprocally related to each other (equation 1). Thus the ratio $\bar{z}_{1(L)}/\bar{z}_{1(H)}$ can be replaced by the ratio $N_{H(H)}/N_{H(L)}$. Then, according to equation (10):

$$RLE = RHE \cdot N_{H(H)}^2 / N_{H(L)}^2 \qquad (13)$$

and according to equation (9):

$$RLE = RBE \cdot N_{H(H)} / N_{H(L)} \qquad (14)$$

At the same D, $N_{H(H)}$ is smaller than $N_{H(L)}$, as shown in Table 1. Thus, the RLE is smaller than the RBE. In the case of high energy neutron radiation, for example, the ratio $N_{H(H)}/N_{H(L)}$ may fall below one tenth (Feinendegen et al. 1985, 1996); thus, the ratio of RLE to RBE for high energy neutrons is accordingly low. For the Tradescantia example cited above, the RLE is between 2 and 3.

In contrast to RBE then, the RLE defines at a given D the ratio of the effectiveness of two types of radiation per unit microdose in causing a defined cellular response such as a malignant transformation.

It may serve to clarify these concepts by summarizing the preceding example, as follows.

Since, in the case of Tradescantia mutation, every neutron-caused event of a microdose (hit) is about 800 times more effective than an x-ray photon-caused event, there will be about 800 times as many responses, N_q, to neutron events as there will be for the same number of photon events. The RHE is about 800.

But each neutron event of a microdose deposits on average 15 to 20 times more cellular microdose than an x-ray event does, so there will be 15 to 20 times fewer neutron events than x-ray events per unit tissue dose D. Thus only about 800/17, or 48 times as many responses N_q will occur per unit D of neutrons as will occur per unit D of x-rays. The RBE is about 48.

With respect to the RLE, 48 times as many responses N_q occur per average unit microdose from neutron events in the target cells as occur per average unit microdose of x-ray events there (but in 15 to 20 times fewer target cells per unit D); also, each neutron event deposits 15 to 20 times more microdose than an x-ray event; thus, on average each unit amount of microdose deposited by a neutron event is 48/20 to 48/15, i.e., about 2 to 3 times more effective than the same unit of microdose deposited by x-ray photons at equal values of D. The RLE is between 2 and 3.

Conclusion

The approach outlined in this presentation, however incomplete, suggests that the linear-no-threshold hypothesis needs to be reexamined. More generally, the presented model offers a conceptual framework for investigating the probability of late effects in terms of the different cellular responses occurring at low doses, where epidemiological analyses are severely limited by

the need for large populations.

Finally, since the risk of cell damage from exposure to ionizing radiation can be viewed as an expression of multiple cellular responses in the irradiated tissues, alternative ways are examined for expressing the relative risk of different radiations: a) per unit absorbed tissue dose, the conventional RBE; b) per average hit, the relative hit effectiveness, RHE; and c) per unit of microdose in the hit cells per unit tissue dose, relative local effectiveness, RLE. At the cell level, the RLE appears biologically more relevant than the RBE that is used at the tissue level for radiological protection.

Figure Legend

Figure 1. Schematic diagram showing the combined effects of low dose irradiation in causing and protecting against cancer (see text for details).

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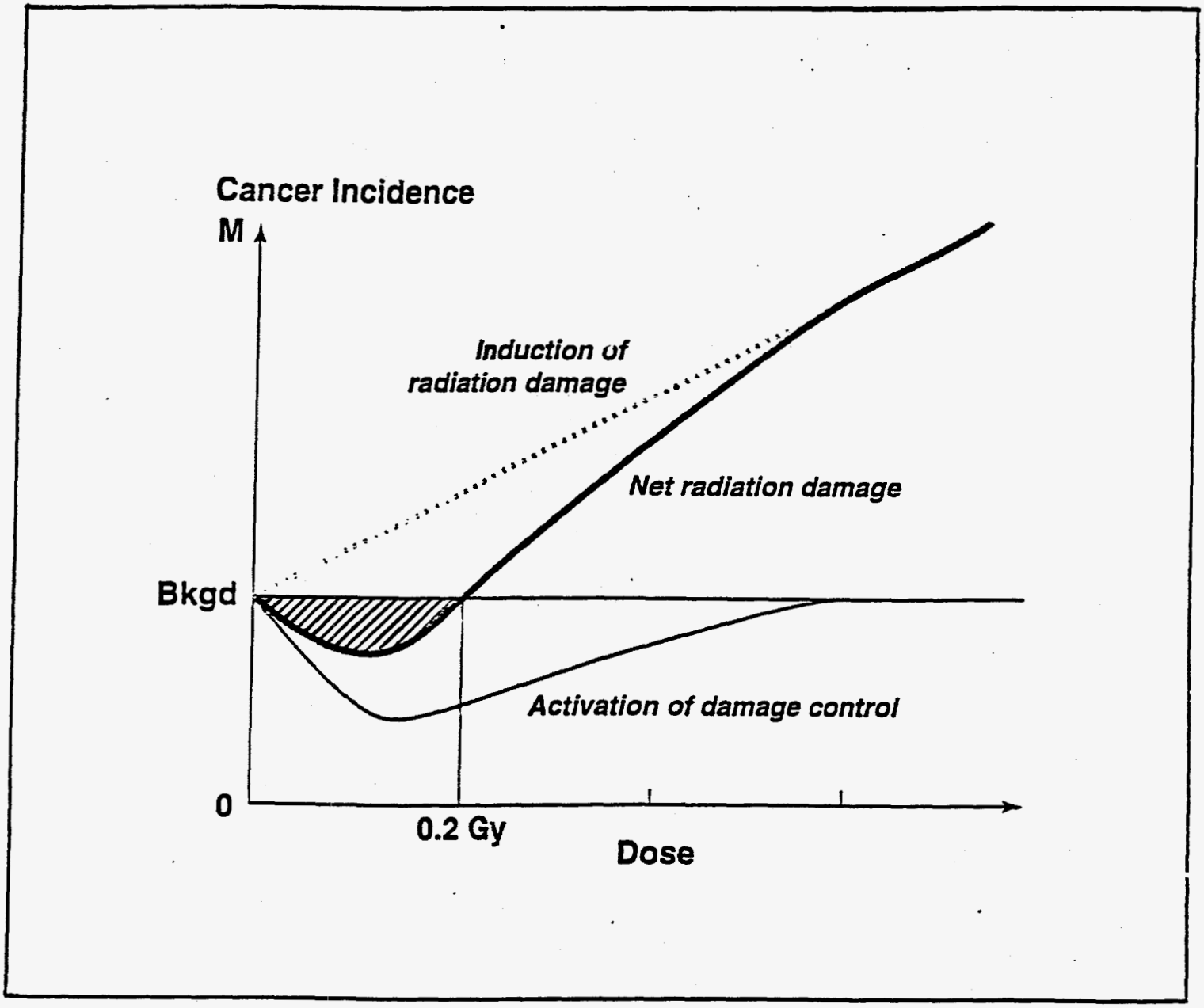
Cancer Incidence
M
Induction of
radiation damage
Net radiation damage
Bkgd
Activation of damage control
0
0.2 Gy
Dose

Fig. 1