BNL-65902

CONF-9804105--

Low Doses of Ionizing Radiation to Mammalian Cells May Rather Control than Cause DNA Damage.

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

This research was supported in part by the United States Department of Energy under contract No. DE-AC02-98CH10886

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 that caused by low-dose irradiation by several orders of magnitude. 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 one nonlinear 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. These data, however incomplete, support a reexamination of the validity of the LET hypothesis.

Introduction

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 metabolic changes that induce mechanisms of DNA damage mitigation, which do not operate 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.

DISCLAIMER

This paper aims at demonstrating tissue effects as an expression of cellular responses, both damaging and defensive, in relation to the energy deposited in cell mass, by use of microdosimetric concepts. 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.

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.

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). For any exposure, the energy deposited by a single track in a defined spherical mass of microscopic dimension, here called micromass, is an event with magnitude conventionally described by the term specific energy, z_1, the mean value of which is denoted by $\bar{z}_1$. The relevant micromass is here taken to be 1 ng and represents one average cell volume of spherical shape (Feinendegen et al. 1994). The cell must be viewed as a living whole with its structural and functional components interacting through signaling networks cooperating in cascades of complexity. The averaging of the tissue micromass over all cell types follows the practice used in calculations for radiation protection. The single energy deposition event in the micromass is called a hit, and the incidence of such hits is denoted by N_H. The value of z_1 as defined by the micromass 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. The cell-dose is made up of microdoses.

The ratio of the number of hits of all sizes, N_H, to the number of exposed micromasses, N_e, multiplied by the microdose $\bar{z}_1$, is equal to D:

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

Since $\bar{z}_1$ remains constant for a given type of radiation, only N_H/N_e increases in proportion to D. Per unit D from different types of radiation, $\bar{z}_1$ and N_H/N_e are inversely related to each other.

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 micromass (Feinendegen et al. 1988). This time interval gives the time available for the cell 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. 1998).

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; see abstracts: Rad.Res.Soc. 1998). For the present discussion, the probability of a spontaneous malignant transformation arising from endogenous DNA damage throughout the life span of a potentially carcinogenic stem cell causing a tumor in the exposed individual is here denoted by p_{spo}. This value is in the order of 10^{-11} (Feinendegen et al. 1995).

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. Relevant studies have usually employed 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. Indeed, the probability of a malignant transformation of a potentially carcinogenic stem cell causing a tumor in humans, p_{ind}, 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 have been readily observed in mammalian cells to slowly induce acute and reversible changes in metabolism and function (Sugahara et al. 1992; UNSCEAR 1994; Academie des Sciences 1995). An early report showed that even single microdoses to mouse bone marrow cells *in vivo* cause a delayed and temporary reduction in the rate of incorporation of the thymidine analog 5-iodo-2-deoxyuridine into DNA (Zamboglou et al. 1981). In single cell microorganisms in a growth medium, background radiation proved to stimulate growth (Planel 1965, 1992). 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 have so far been identified only in some cells and tissues.

Low-dose induced temporary stimulation of detoxification of ROS protects cellular constituents (Feinendegen et al. 1984, 1987, 1988; Laval 1988; Hohn-El-Karim et al. 1990); this expresses prevention of damage. Repair of DNA appears to be involved in the low-dose induced reduction of chromosomal aberrations (Olivieri et al. 1984; Wolff et al. 1988; Wolff 1996; Ikushima et al. 1996), of somatic mutations (Rigaud et al. 1993) and of cell transformation (Azzam et al. 1996). Low-dose induced DNA repair was indeed demonstrated with an ultrasensitive assay for *in vivo* DNA damage that occurs both endogenously and after irradiation (Le et al. 1998). The various mechanisms of protection may be directly or indirectly linked with the control of cell cycle check points (Boothman et al. 1996; Tubiana 1996). Low-dose induced elimination of damage from tissues may operate through apoptosis (Kondo 1993; Shu-Zheng et al. 1996), cell killing (Joiner et al. 1996), and stimulation of immune competence (Makinodan 1992; Anderson et al. 1992). The proven effect of intercellular communication in causing DNA damage (Nagasawa et al. 1992; Emerit et al. 1995) suggests that adaptive responses may even be initiated by extracellular factors as well.

The case of ROS detoxification

An quantitative relation between dose and degree of adaptive response has been developed

regarding the radiation-induced detoxification of ROS and the coupled reaction of thymidinekinase in murine bone marrow cells after acute exposure of the whole body to low LET radiation giving cell-doses even below 0.01 Gy. This response developed slowly with a delay of some 30 minutes, reached a maximum at 4 hours and then disappeared by about 10 hours after irradiation (Zamboglou et al. 1981; Feinendegen et al. 1984). The concentration of reduced glutathione increased in synchrony with the time course of enzyme inhibition; vice versa, an increase in cellular free glutathione caused enzyme inhibition (Feinendegen et al. 1987, 1988, 1995; Hohn-El-Karim et al. 1990).

Thus, low-dose irradiation induces an alteration in intracellular signaling causing a temporary inhibition of at least one vitally important enzyme for DNA synthesis, as a consequence of a temporarily increased ROS detoxification. Similar results in rodents, involving superoxide-dismutase (SOD) as well and checking for the degree of membrane oxidation, have been reported from various laboratories (Misonoh et al. 1992; Yamaoka et al. 1992).

Cell protection at low doses disappearing at high doses

When the low-dose irradiated mice were 4 hours later again challenged with the same dose, the initially inhibited thymidinekinase in bone marrow cells rapidly converted to normal activity (Feinendegen et al. 1988).The effectiveness of this reversion of enzyme inhibition by a renewed low-dose irradiation declined when the second dose rose above about 0.1 to 0.2 Gy and fully disappeared above 0.5 Gy (Feinendegen et al. 1995). This inverse dose response function describes an initial activation and then a suppression of the ROS detoxification system and expresses a kinetic component of cellular oxygen stress response.

An inverse dose-response function also appeared in human lymphocytes. Chromosomal aberrations in human lymphocytes in vitro first declined significantly after single acute low doses of low LET radiation before a dose dependent increase was seen above 0.05 Gy (Pohl-Rueling et al 1983). Moreover, acute low LET irradiation at doses below but not above about 0.2 Gy conditioned human lymphocytes in vitro to become protected against high-dose induced chromosomal aberrations; this protective effect lasted from 4 to about 60 hours after conditioning low-dose irradiation (Wolff et al. 1988; Shadley et al. 1987, 1989, 1992; Wolff 1996). Another example of an inverse dose response function was reported for apoptosis in mouse thymocytes; at 24 hours after exposure, the incidence of apoptosis was significantly reduced at doses below about 0.2 Gy and only rose with higher doses in a seemingly linear fashion (Shu-Zheng et al. 1996). Various immune responses in rodents showed first a rise with low doses and a decline with doses exceeding about 0.2 Gy (Anderson et al. 1992; Makinodan 1992). An inverse dose response function also applies to the data reported for various radioresistant cell lines; they showed an increased sensitivity to being killed only at low doses with a maximum at about 0.2-0.3 Gy after which radioresistance took over (Joiner et al. 1996). Also, the expression of the c-jun gene in tissue culture cells responded to low but not high LET radiation in the low-dose range (Woloschack et al. 1992). It is justified to suggest that the various system responses that are confined to low cell-doses are related to radiation-induced signaling at least partly involving

oxygen stress (Laval 1988).

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 DNA damage that arises mainly from endogenous sources. This reaction also triggers a temporary protection against DNA damage that is caused by high cell-doses when these are given several hours after low-dose exposure. High doses do not initiate this temporary protection.

Indeed, the protective responses so far known to be induced by low but not to operate after high doses of radiation appear to belong to a DNA damage control system that differs from the cellular DNA repair responses usually 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, stress responses restricted to low doses apparently condition the expression of repair genes when challenged at high doses. Repair mechanisms usually seen after high doses lose effectiveness with increasing doses that eventually fully jeopardize 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 with consideration of protective mechanisms that operate 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.

The value of p_{ind}, as defined above, is taken to be an average constant per microdose event, 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 genetic instability, the probability of enhancement per N_H/N_e would then be p_{enh}. It is not known wether p_{enh} occurs a at cell-doses below about 0.2 Gy. It may be independent of N_H/N_e but likely larger than p_{ind}, and the product $p_{ind}p_{enh}$ may be a constant at low doses. However, *in vivo* genetic instability causes an increased rate of somatic mutations in the descendent cell population. These mutated cells are likely to initiate tissue responses leading to their elimination. Otherwise, background radiation hitting on

average each cell in the body once per year alone would eventually produce mutated cells outnumbering normally functioning cells. Indeed, genetic instability may be considered as a kind of adaptive response of a last resort preventing damaged cells from accumulating in tissues. The value of p_{enh} is here taken to be neglibly small at low doses.

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 population'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, 1996).

In contrast to the extremely low value of p_{ind}, the individual components of the cumulative probability of protection, p_{prot}, can be easily measured *in vivo* and in vitro in various mammalian cell systems at low doses, as described above. This probability, therefore, appears to be much larger than p_{ind}. Also, in contrast to p_{ind}, the value of p_{prot} has been shown to decline with N_H, when D exceeds about 0.1 to 0.2 Gy of low LET radiation. To account for this dependency, p_{prot} is here denoted by $p_{prot}(D)$.

3) Connecting the various probabilities of cell responses

Regardless of the mechanisms involved the p-values appear variable with the species, cell type, and microdose. In order to connect p_{ind} and p_{prot} with each other, both need to relate to the same radiation quality and be applied to the same cells. Also, the fraction of potentially carcinogenic stem cells in a tissue is taken to be constant. Thirdly, because of p_{prot} being transient one malignant transformation and its subsequent tumor development in the exposed tissue may be offset either by having a potentially carcinogenic stem cell and its progeny experience a protective response repeatedly and often, or by letting a large number of such cells in the exposed tissue be protected simultaneously.

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 expressed as the cumulative probabilities of various cellular responses to microdose events (Feinendegen 1991, Feinendegen et al. 1995, 1996). It can be postulated that the risk of cancer (R) in an irradiated tissue is proportional to the ratio of the number of malignantly transformed cells, N_q, in that tissue to the number of exposed micromasses, N_e.

Taking the conventionally used macroscopic dose-risk function for organs and tissues following low dose or dose rate exposure is

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

and substituting for R the ratio N_q / N_e and for D using equation (1) ($D = \bar{z}_1 \cdot N_H/N_e$) and multiplying each side by N_e the following equation

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

gives the transformation of the conventionally used dose-risk function 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 various probabilities affecting cells in the exposed tissue, as defined above:

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}, and p_{enh}, per average hit.

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

$$N_q = [p_{ind} + p_{ind}p_{enh} - p_{prot}(D)p_{spo} - p_{prot}(D)p_{ind} - p_{prot}(D)p_{ind}p_{enh}] \cdot N_H \qquad (5)$$

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

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

From the above, the value of $\alpha = N_q/(N_H \cdot \bar{z}_1)$, equation (4), can not remain constant with changing D in all reported situations in which the value of $p_{prot}(D)$ declines with increasing D while p_{ind} remains constant.

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 (Sugahara et al. 1992; UNSCEAR 1994; Academie des Sciences 1995).

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 various epidemiological data.

Concerning the term α for high LET radiation, the relatively high values of $\bar{z}_1$ 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.

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.

Figure Legend

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

Acknowledgments: The authors express their appreciation to Dr. Marvin Frazier from the Office of Health and Environmental Research of the U.S. Department of Energy, Washington, D.C., and Dr. John R. Cameron, University of Wisconsin, Madison, WI, for their valuable discussions and editorial help.

References

Academie des Sciences, Institut de France
Problems associated with the effects of low doses of ionizing radiations.
Rapport de l'Academie des Sciences, No.38; Lavoisier, TecDoc, Paris, London, New York, 1995

Alberts B., Bray D., Lewis J., Raff M., Roberts K., Watson J.D. Eds.
Molecular Biology of the Cell
Garland Pub., New York, New York, 1989

Ames B.N., Gold L.S., Willet W.C.
The causes and prevention of cancer.
Proc.Natl.Acad.Sci.USA 92: 5258-5265 (1995)

Anderson R.E.
Effects of low-dose radiation on the immune response
in: Biological effects of low level exposures to chemicals and radiation. Ed. E.J. Calabrese.
Lewis Pub. Inc., Chelsea, Michigan, 1992, 95-112

Azzam E.I., de Toledo S.M., Raaphorst G.P., Mitchel R.E.J.
Low-dose ionizing radiation decreases the frequency of neoplastic transformation to a level below the spontaneous rate in C3H 10T1/2 cells.
Radiation Res. 146: 369-373 (1996)

Beckman K.D., Ames B.N.
Oxidative decay of DNA
J.Biol.Chem. 272: 19633-19636 (1997)

Bond V.P., Benary V., Sondhaus C.A., Feinendegen L.E.
The meaning of linear dose-response relations, made evident by use of absorbed dose to the cell.
Health Phys. 68: 786-792 (1995)

Boothman D.A., Meyers M., Odegaard E., Wang M.
Altered G_1 checkpoint control determines adaptive survival responses to ionizing radiation.
Mutation Res. 358: 143-153 (1996)

Cleaver J.
Defective repair replication of DNA in Xeroderma Pigmentosum.
Nature (London) 218: 652-656 (1968)

Emerit I., Oganesian N., Sarkisian T., Arutyunyan R., Pogosian A., Asrian K., Levy A., Cernjavski L.
Clastogenic factors in the plasma of Chernobyl accident recovery workers: Anticlastogenic effect of Gingko biloba extract.
Radiation Res. 144: 198-205 (1995)

Feinendegen L.E., Muehlensiepen H., Lindberg C., Marx J., Porschen,W., Booz J.
Acute effect of very low dose in mouse bone marrow cells: a physiological response to background radiation?
in: Biological Effects of Low Level Radiation, IAEA Vienna, 1983, 459-471

Feinendegen L.E., Muehlensiepen H., Lindberg C., Marx J., Porschen W., Booz J.
Acute and temporary inhibition of thymidine kinase in mouse bone marrow cells after low-dose exposure.
Int.J.Radiat.Biol. 45: 205-215 (1984)

Feinendegen L.E., Muehlensiepen H., Bond V.P., Sondhaus C.A.
Intracellular stimulation of biochemical control mechanisms by low-dose low-LET irradiation.
Health Phys. 52: 663-669 (1987)

Feinendegen L.E., Bond V.P., Booz J., Muehlensiepen H.
Biochemical and cellular mechanisms of low-dose effects.
Int.J.Radiat.Biol. 53: 23-37 (1988)

Feinendegen L.E.
Radiation risk of tissue late effect, a net consequence of probabilities of various cellular responses.
Europ.J.Nucl.Med. 18: 740-751 (1991)

Feinendegen L.E., Bond V.P., Booz J.
The quantification of physical events within tissue at low levels of exposure to ionizing radiation.
ICRU-News 2: 9-13 (1994)

Feinendegen L.E., Loken M., Booz J., Muehlensiepen H., Sondhaus C.A., Bond V.P.
Cellular mechanisms of protection and repair induced by radiation exposure and their consequences for cell system responses.
Stem Cells 13(1): 7-20 (1995)

Feinendegen L.E., Bond, V.P., Sondhaus C.A., Muehlensiepen H.
Radiation effects induced by low doses in complex tissue and their relation to cellular adaptive responses.
Mutation Res. 358: 199-205 (1996)

Hall E.J., Hei T.K.
Oncogenic transformation in vitro by radiation of varying LET.
Radiat.Protect.Dosimetry 13: 149-151 (1985)

Helbock H.J., Beckman K.B., Shigenaga M.K., Walter P.B., Woodall A.A., Yeo H.C., Ames B.N.
DNA oxidation matters: The HPLC-electrochemical detection assay of 8-oxo-deoxyguanosine and 8-oxo-guanine.
Proc.Natl.Acad.Sci.USA 96: 288-293 (1998)

Hohn-El-Karim K., Muehlensiepen H., Altman K.I., Feinendegen L.E. Modification of effects of radiation on thymidine kinase.
Intern.J.Radiat.Biol. 58: 97-110 (1990)

ICRU (International Commission on Radiation Units and Measurements).
Microdosimetry.
ICRU, Bethesda, MD, USA, Report 36 (1983)

Ikushima T., Aritomi H., Morisita J.
Radioadaptive response: Efficient repair of radiation-induced DNA damage in adapted cells.
Mutation Res. 358: 193-198 (1996)

Jaruga P, Dizdaroglu M.
Repair of products of oxidative DNA base damage in human cells.
Nucleic Acid Res. 24: 1389-1394 (1996)

Joiner M.C., Lambin P., Malaise E.P., Robson T., Arrand J.E., Skov K.A., Marples B.
Hypersensitivity to very-low single radiation doses: Its relationship to the adaptive response and induced radioresistance.
Mutation Res. 358: 171-183 (1996)

Kleczkowska H., Althaus F.R.
The role of poly(ADP-ribosyl)ation in the adaptive response.
Mutation Res. 358: 215-221 (1996)

Kondo S.
Health Effects of Low Level Radiation.
Kinki Univ.Press, Osaka, Japan; Medical Physics Publishing, Madison, WI, 1993.

Laval F.
Pretreatment with oxygen species increases the resistance of mammalian cells to hydrogen peroxide and γ-rays.
Mutation Res. 201: 73-79 (1988)

Le X.C., Xing J.Z., Lee J., Leadon S.A., Weinfeld M.
Inducible repair of thymine glycol detected by an ultrasensitive assay for DNA damage.
Science 280: 1066-1069 (1998)

Lohman P.H.M., Cox R., Chadwick K.H.
Role of molecular biology in radiation biology.
Int.J.Radiat.Biol. 68: 331-340 (1995)

Makinodan T.
Cellular and subcellular alteration in immune cells induced by chronic, intermittent exposure *in vivo* to very low dose of ionizing radiation (ldr) and its ammeliorating effects on progression of autoimmune disease and mammary tumor growth.
In: Low-Dose Irradiation and Biological Defense Mechanisms.
Ed.: Sugahara T., Sagan L.A., Aoyama T.; Exerpta Medica; Amsterdam, London, New York, Tokyo, 1992, 233-237

Misonoh J., Yoshida M., Okumura Y., Kodama S., Ishii K.
Effects of low-dose irradiation of x-rays on IUDR incorporation into mouse tissues.
In: Low-Dose Irradiation and Biological Defense Mechanisms.
Ed.: Sugahara T., Sagan L.A., Aoyama T.; Exerpta Medica; Amsterdam, London, New York, Tokyo, 1992, 233-237

Nagasawa H., Little J.B.
Induction of sister chromatid exchanges by extremely low doses of alpha-particles.
Cancer Res. 52: 6394-6396 (1992)

Olivieri G., Bodycote J., Wolff S.
Adaptive response of human lymphocytes to low concentrations of radioactive thymidine.
Science 223: 594-597 (1984)

Planel H., Soleilhavoup J.P., Tixador R.
Recherches sur l'action des radiations ionisantes naturelles sur la croissance d'etres unicellulaires.
C.R.Acad.Sciences 260: 3770-3773 (1965)

Planel H., Caratero C., Croute F., Conter A.
Investigations on the biological effects of very low doses of ionizing radiations.
In: Low-Dose Irradiation and Biological Defense Mechanisms.
Ed.: Sugahara T., Sagan L.A., Aoyama T.; Exerpta Medica; Amsterdam, London, New York, Tokyo, 1992, 13-20

Pohl-Rueling J., Fischer P., Haas O.
Effect of low-dose acute x-irradiation on the frequencies of chromosomal aberrations in human peripheral lymphocytes *in vitro*.
Mutation Res. 110: 71-82 (1983)

Pollycove M., Feinendegen L.E.
The relationship between spontaneous and background radiation incuded DNA damage
in preparation, 1998

Radiation Research Society (USA)
Program abstracts, forty-sixth annual meeting in Louisville, Kentucky.
Rad.Res.Soc., Oak Brook, IL 60523, USA, 1998

Rigaud O., Papadopoulo D., Moustacchi E.
Decreased deletion mutation in radioadapted human lymphoblasts.
Radiat.Res. 133: 94-101 (1993)

Shadley J.D., Wolff S.
Very low doses of X-rays can induce human lymphocytes to become less susceptible to ionizing radiation.
Mutagenesis 2: 95-96 (1987)

Shadley J.D., Afzal V., Wolff S.
Characterization of the adaptive response to ionizing radiation induced by low doses of X-rays to human lymphocytes.
Radiation Res. 111: 511-517 (1987)

Shadley J.D., Wienke, J.K.
Induction of the adaptive response by X-rays is dependent on radiation intensity.
Int.J.Radiat.Biol. 56: 107-118 (1989)

Shadley J.D., Dai G.
Cytogenetic and survival adaptive responses in G_1 phase human lymphocytes.
Mutation Res. 265: 273-281 (1992)

Shu-Zheng L., Yin-Chun Z., Ying M., Xu S., Jian-Xiang L.
Thymocyte apoptosis in response to low-dose radiation.
Mutation Res. 358: 185-191 (1996)

Suganara T., Sagan L.A., Aoyama T., Eds.
Low Dose Irradiation and Biological Defense Mechanisms.
Proceedings of the International Conference on Low Dose Irradiation and Biological Defense Mechanisms,
held in Kyoto, Japan, 12-16- July, 1992.
Excerpta Medica, Amsterdam, London, New York, Tokyo, 1992.

Tubiana M.
Effets cancerogenes des faibles doses du rayonnement ionisant.
Radioprotection 31: 155-191 (1996)

UNSCEAR.
Sources and Effects of Ionizing Radiation.
United Nations, New York, N.Y., 1994

Wallace S.S.
AP-endonucleases and DNA-glycosylases that recognize oxidative DNA damage.
Environ.Mol.Mutagen. 12: 431-477 (1988)

Ward J.F.
DNA damage produced by ionizing radiation in mammalian cells: Identities, mechanisms of formation, and repairability.
Prog.Nucleic Acid Res.Mol.Biol. 35: 95-125 (1988)

Wei Q., Matanoski G.M., Farmer E.R., Hedayati M.A., Grossman L.
DNA repair and aging in basal cell carcinoma: A molecular epidemiologic study.
Proc.Natl.Acad.Sci.USA 90: 1614-1618 (1993)

Wolff S., Afzal V., Wienke J.K., Olivieri G., Michaeli A.
Human lymphocytes exposed to low doses of ionizing radiations become refractory to high doses of radiation as well as to chemical mutagens that induce double-strand breaks in DNA.
Int.J.Radiat.Biol. 53(1): 39-49 (1988)

Wolff S.
Aspects of the adaptive response to very low doses of radiation and other agents.
Mutation Res. 358: 135-142 (1996)

Woloschak G.E., Chang-Liu C.-M.
Effects of low-dose radiation on gene expression in Syrian hamster embryo cells: comparisons of Janus neutrons and gamma rays.
In: Low-Dose Irradiation and Biological Defense Mechanisms.
Ed.: Sugahara T., Sagan L.A., Aoyama T.; Exerpta Medica; Amsterdam, London, New York, Tokyo, 1992, 239-242

Yamaoka K., Edamatsu R., Mori A.
Effects of low dose x-ray irradiation on old rats - SOD activity, lipid peroxide level, and membrane fluidity
In: Low-Dose Irradiation and Biological Defense Mechanisms.
Ed.: Sugahara T., Sagan L.A., Aoyama T.; Exerpta Medica; Amsterdam, London, New York, Tokyo, 1992, 419-422

Zamboglou N., Porschen W., Muehlensiepen H., Booz J., Feinendegen L.E.
Low dose effect of ionizing radiation on incorporation of iodo-deoxyuridine into bone marrow cells.
Int.J.Radiat.Biol. 39: 83-93 (1981)

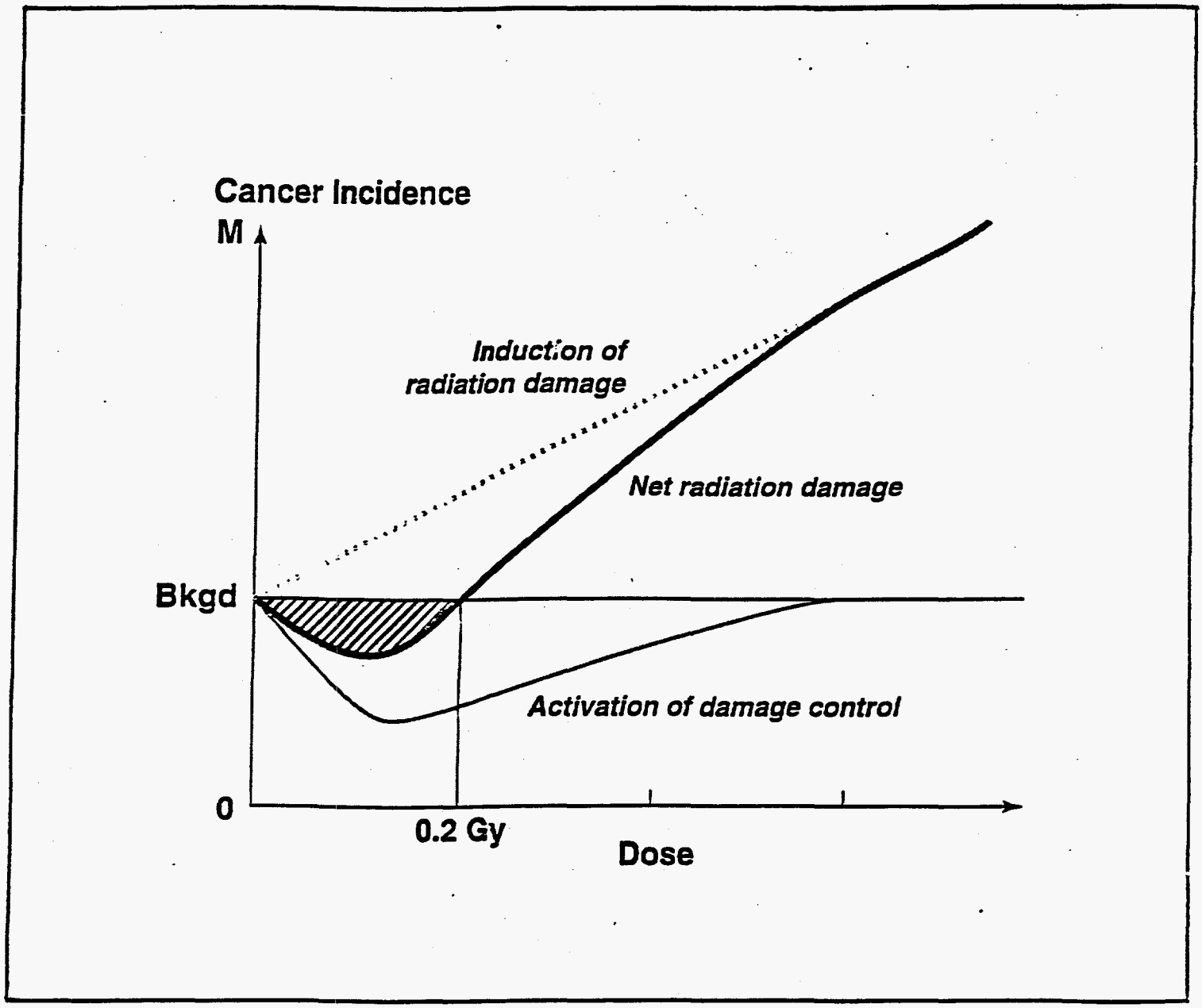
Cancer Incidence
M
Induction of
radiation damage
Net radiation damage
Bkgd
Activation of damage control
0
0.2 Gy
Dose

Fig. 1