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Hormesis by Low Dose Radiation Effects: Low-Dose Cancer Risk Modeling Must Recognize Up-Regulation of Protection

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Abstract

Ionizing radiation primarily perturbs the basic molecular level proportional to dose, with potential damage propagation to higher levels: cells, tissues, organs, and whole body. There are three types of defenses against damage propagation. These operate deterministically and below a certain impact threshold there is no propagation. Physical static defenses precede metabolic-dynamic defenses acting immediately: scavenging of toxins;—molecular repair, especially of DNA;—removal of damaged cells either by apoptosis, necrosis, phagocytosis, cell differentiation-senescence, or by immune responses,—followed by replacement of lost elements. Another metabolic-dynamic defense arises delayed by up-regulating immediately operating defense mechanisms. Some of these adaptive protections may last beyond a year and all create temporary protection against renewed potentially toxic impacts also from nonradiogenic endogenous sources. Adaptive protections have a maximum after single tissue absorbed doses around 100–200 mSv and disappear with higher doses. Low dose-rates initiate maximum protection likely at lower cell doses delivered repetitively at certain time intervals. Adaptive protection preventing only about 2–3 % of endogenous lifetime cancer risk would fully balance a calculated-induced cancer risk at about 100 mSv, in agreement with epidemiological data and concordant with an hormetic effect. Low-dose-risk modeling must recognize up-regulation of protection.

This work represents the opinion of its authors. It should not be read as representing the position of the NIH, DHHS, nor the US Government.

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1 Introduction

Epidemiology so far fails to substantiate the claim of an increase in cancer incidence in humans following low-level exposure to ionizing radiation, below about 100 mGy or mSv.

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Rather a decrease in cancer risk has shown up repeatedly (Pollycove and Feinendegen 2001; Tubiana et al. 2005, 2009; Nair et al. 2009). Nevertheless, observed data are fitted using the linear-no-threshold (LNT) hypothesis (ICRP 1977). This hypothesis expresses proportionality between dose and risk, and is the basis for radiation protection regulation and most widely used. Despite contradicting epidemiological and experimental findings the LNT-hypothesis is also applied to predict cancer risks of low-dose irradiation (Brenner and Hall 2007). What was a good intention years ago to protect workers from overexposure to ionizing radiation has been turned to producing a widespread radiation phobia now.

The initial plausibility of the LNT-hypothesis derived from two assumptions: (1) immediate damages to the genetic material (DNA) from radiation absorption increase in proportion to the absorbed dose; (2) certain immediate DNA damage is amplified and propagates in organisms to cause the cancer incidence in an exposed population to rise in proportion to dose.

The second assumption is debatable for both epidemiological and experimental reasons. Regarding epidemiology, data show statistical constraints and require very large numbers of irradiated individuals to assess the carcinogenic risks of low doses (<100 mSv), such large numbers are not available at present. Thus, modeling of data with the LNT-hypothesis arrives at relative risks of cancer that are actually not observed (Heidenreich et al. 1997; Pollycove and Feinendegen 2001; Tanooka 2001, 2011; Preston et al. 2004, 2007; Cardis et al. 2007; Nair et al. 2009; Tubiana et al. 2009).

The LNT-hypothesis assumes its scientific justification because of the immediate linear dose–effect relationships at the molecular level of the DNA; it does not consider the complex nonlinear dynamics of oncogenesis in the body. Indeed, more recent data on low-dose effects in experiments with various biological systems from cells to animals increasingly show specific responses of physiological damage control systems limited to low doses at various levels of biological organization (Feinendegen et al. 2004; Tubiana et al. 2005, 2009; Mullenders et al. 2009), and also show a low-dose induced reduction of the incidences of neoplastic transformation in culture cells and overt malignancies in animals (Azzam et al. 1996; Mitchel et al. 2003, 2008; Elmore et al. 2009). Such responses have not been observed at, and also were not expected from, high-dose radiation exposures. In fact, new findings challenge the validity of the LNT-hypothesis, and now suggest that this hypothesis cannot be maintained (Tubiana et al. 2005, 2009; Feinendegen 2005; Feinendegen and Neumann 2005, 2007a, b, 2011; Feinendegen and Neumann 2005).

Currently, the discussion of the low-dose risk of cancer has become polarized on how to best incorporate new findings into practical application. A case in point is the serious disagreement between recent statements by the French Academy of Sciences (Tubiana et al. 2005) and the US National Academy of Sciences by way of its BEIR VII report (National Research Council 2006). The focus on the new radiobiological findings on low-dose related cancer risk leads to predict that also in humans after low-dose exposures clinical cancer develops as a consequence of the balance between cancer induction and cancer prevention by the cascade of the body's physiological defenses.

This chapter emphasizes both the proportional relationship between absorbed dose and DNA damage and the nonlinearly operating body's defense systems that block damage propagation from the molecular level to the whole organism. Research on cells, tissues, and animals indicate that there are at least three types of "defending" barriers to damage induction and propagation: a physical static one, and two metabolic-dynamic defenses. One of the latter two defenses responds soon after perturbation, while the other involves delayed up-regulations of defenses in terms of adaptive responses that appear with a delay of hours and last for various times up to more than 1 year after low-dose exposure. Adaptive protections can operate against both radiogenic and nonradiogenic DNA damage and its consequences. Accepting the observed experimental and epidemiological data at low doses, with their wide ranges of uncertainties, the resulting dual probability model embraces both low-dose induction of radiogenic damage and radiogenic adaptive protections. This model re-emphasizes not only the inconsistency of the LNT-hypothesis but also the high probability of beneficial, i.e., hormetic effects following low-dose irradiation (Calabrese and Baldwin 2003).

2 The Meaning of Absorbed Dose in the Low Dose Region

The term absorbed dose describes concentration and not the amount of the energy absorbed in the exposed mass such as an organ or the whole body (ICRU 1998). The unit of absorbed dose (D) is the gray: 1 Gy (100 rad) = 1 J/kg. This is equivalent to 6.24×10^{15} eV per g mass, or 6.24×10^{6} eV per ng mass. The unit of the equivalently effective dose from different radiation qualities is the sievert, Sv (ICRU 1998). At a sufficiently high value of absorbed dose from an external radiation field, absorbed dose in a large mass is identical to the absorbed dose in any small mass of the same exposed tissue; but, the total energies absorbed in these masses are not the same (ICRU 1983).

The above definition of absorbed dose poses problems when it comes to analyzing and understanding the effects both of low-dose exposure from external sources, (ICRU 1983, 2005) as well as from heterogenous exposure to incorporated radionuclides, for instance in nuclear medicine tests (ICRU 2002). In both instances, ionizing radiation

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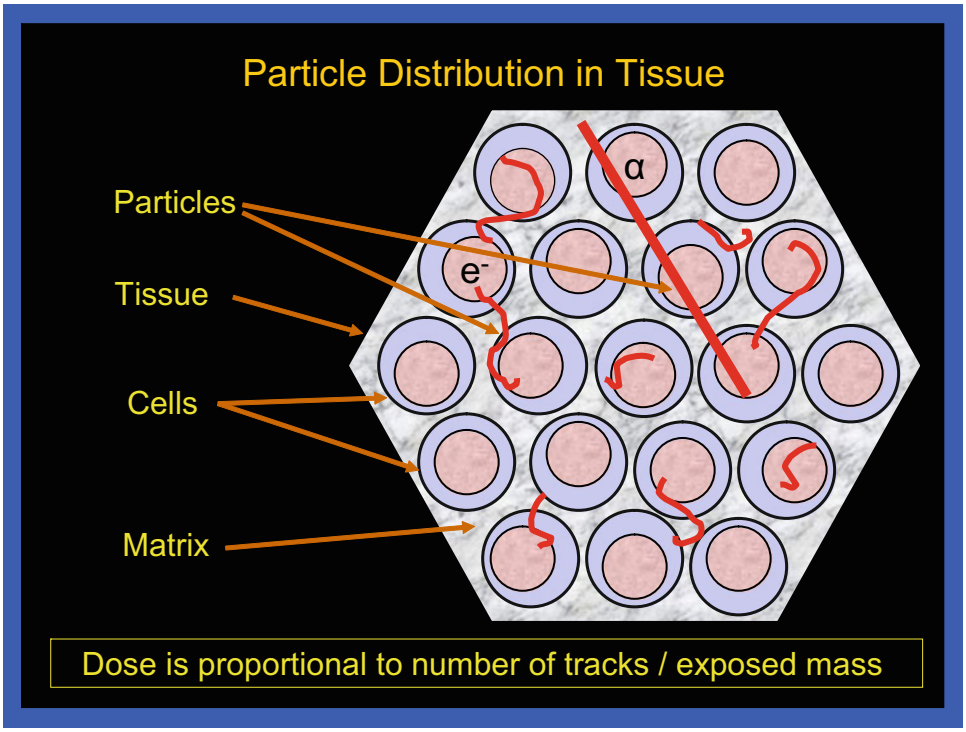

Fig. 1 Scheme of particle distribution in tissues. Shown are several electrons and an alpha particle. Clearly, total energy absorbed per unit mass, i.e., dose correlates with the number of particles in that mass

causes the deposition of energy from charged particle tracks that arise either through interaction of uncharged particles with charged particles, such as photons (X- or gamma rays) that can dislodge electrons from atomic orbitals, or through charged particles as they may be produced by accelerators or result directly from the decay of radionuclides (alpha-, beta-emission). The energy deposited by a single particle track in traversing a tissue micromass of 1 ng will be denoted in this chapter by the term "microdose", and the event delivering this microdose is referred to as a "microdose event" (ICRU 1983). The micromass of 1 ng generally is taken to correspond to the average mass of a mammalian cell in vivo.

Large absorbed doses D in the tissue create large numbers of microdose events per exposed micromass. The sum of energies delivered by multiple microdoses per given micromass is here denoted "cell-dose." As D in the body decreases, the number of microdose events per exposed micromass is reduced eventually below an average value of 1 per micromass. Then, the dose to each micromass becomes either zero or it will be the microdose from a single track traversing the micromass, and only some fractional number of micromasses experience a microdose event (see Fig. 1) (ICRU 1983).

The microdose values compose a spectrum according to charged particle energies from a given radiation quality. This spectrum may vary by a factor of up to ten or more, around the mean value. According to the radiation quality, the mean microdoses have defined values, as shown in Table 1 middle column. In case of exposure from incorporated radionulcides, the overlaying and more or less severe topographical heterogeneity of decays occurring localized in the tissue of interest makes dosimetry more difficult and has been dealt with extensively (ICRU 2002).

In the context of comparing man-made low-level exposures, for instance in diagnostic medicine, with exposure from natural sources of background radiation the following considerations may be helpful in risk assessment. As an example, the exposure of tissue to 100 kVp X-rays causes on average 1 electron track delivering about 6 keV per 1 ng mass—corresponding to the average cell mass—and the mean microdose is about 1 mGy (ICRU 1983). A body dose of 1 mGy from 100 kVp X-rays then means an average of about 1 microdose event in each ng mass of the exposed tissue. One mGy per year accordingly means that about 1 event per ng occurs per year, or each ng experiences on average one microdose of 1 mGy once about every 365 days.

Normal background radiation causes whole-body absorbed doses in the range of several mSv per year from different radiation sources and qualities, largely cosmic gamma rays with a relatively small contribution from alpha irradiation coming mainly from inhaled radon. Background radiation may vary considerably with altitude and geographic region, and may be more than 10-fold higher than the average value at sea level in the northern hemisphere. The above considerations imply that every ng or cell in the body experiences a microdose event several times a year.

Table 1 The energy absorbed per micromass, here of 1 ng, per particle traversal is formally called specific energy with the symbol z, and $\bar{z}_{F1}$ is the fluency-derived mean value of z (33). The table gives the value of $\bar{z}_{F1}$ and the approximate number of reactive oxygen species (ROS) produced by this value in the hit micromass

$\bar{z}_{F1}$ ($\bar{x}$ Microdose) in mGy (1 mGy = 6.24 keV / ng)

Cell doses are multiples of microdoses.

	mGy	*ROS / hit / ng*
^{60}Co γ-rays	~ 0.3	*~ 45*
^{137}Cs γ-rays	~ 0.4	*~ 60*
250 kVp x-rays	~ 0.9	*~ 135*
100 kVp x-rays	~ 1.0	*~ 150*
10 MeV protons	~ 6.0	*~ 900*
4 MeV α-particles	~ 350.0	*~ 52.5 x 10³*

More specifically, taking an adult body to have 7×10^{13} ng, and a year to have about 3.2×10^7 s, then, for the sake of easy calculation, an annual whole-body dose of 1 mGy from chronic exposure to X-rays causes per second around 2.2×10^6 ng to have 1 mGy-microdose event on average, and each of those events would have the potential of triggering secondary consequences.

Such calculations are easy also for other radiation qualities than 100 kVp X-rays. The mean microdose values are displayed for a few different types of radiation in Table 1. Thus, if the background radiation field would be equivalent to gamma rays from ^{137}Cs delivering about 0.4 mGy per microdose event, chronic exposure to an annual whole-body dose of 2 mGy would cause on average 1 microdose event five times a year in each ng in the body, or each ng would experience on average one event every 2.4 months.

The microdosimetry approach used here to describe energy deposition in exposed tissue helps to understand mechanistically what happens at low doses and dose-rates physically and biologically. This approach is consistent also with the International Commission on Radiation Units and Measurement (ICRU 2011).

3 Primary Biological Interactions

Each microdose event whether from external sources or from internally deposited radionuclides causes numerous atomic ionizations and excitations stochastically along the particle track depending on the type of radiation. Biological tissues consist by weight of ~75 % water. Hence, a correspondingly large fraction of ionizations induce hydrolysis resulting in reactive oxygen species (ROS); on average about 25 ROS are produced by hydrolysis for each keV absorbed in tissue, based on the expenditure of an average of 30 eV per ionization. The number of ROS per each mean microdose event from different radiation qualities is also listed in Table 1, right column. In general, ROS are both signaling molecules and can be toxic (Sen et al. 2000) depending on concentration. When produced by irradiation ROS attack largely at random all kinds of biochemical substrates in the immediate and in some distant molecular "neighborhood" of the site of their creation, and add to biochemical damage by direct ionizations.

The ROS induced by radiation are biochemically similar to those that are constantly and abundantly produced in different cellular compartments, mainly mitochondria, during normal oxidative metabolism. Mitochondria alone let leak out some 10^9 ROS into the cytosol per cell per day (Pollycove and Feinendegen 2003). One needs to consider the effects of both endogenous and radiogenic ROS alongside with direct effects, especially on DNA. The latter effects generally are more toxic but less frequent than the first.

4 Damage to DNA and its Repair

Biological responses to ionizing radiation, wherever they become observable either acute or delayed, appear to always originate because of changes in cellular molecules, especially the DNA. The immediate DNA damage includes inter-molecular cross links of various kinds, base changes, single-strand breaks (SSB), and the more serious double-strand breaks (DSB) (Hall and Giaccia 2005).

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It needs to be stressed that the radiation-induced immediate damages to DNA increase linearly with dose. The reason for this linearity is the dose-dependent number of microdose events produced, and each of them causes a given degree of damage according to their energy spectrum characteristic for a given type of radiation. Thus, as dose increases, the number of microdose events according to the given spectrum increases, and with them the number of individual damage sites caused by each one of the events. A dose effect curve for immediate DNA damage in tissue actually conforms to a linear "Impact-Number-Effectiveness Function" without threshold (Bond et al. 1995). This linear function is not identical in various cell types, and is lost as complex biological systems respond to low doses in various ways, as discussed below.

Within minutes after irradiation there is a plethora of DNA and chromatin modifications involved in DNA repair (Hall and Giaccia 2005). Immuno-histochemical methods now allow, for instance, the microscopic observation of DNA DSBs in individual cells (Rothkamm and Löbrich 2003; Sedelnikova et al. 2004; Neumaier et al. 2012). Well within 24 h, the fluorescent foci, supposedly indicative of DSBs, decrease to a lower number, closer to that of the background "spontaneous", i.e. pre-irradiation, number (Rothkamm and Löbrich 2003). By way of these techniques one has learned that experimentally nonirradiated cells, depending on type and age, contain on average from about 0.1 to numerous DSBs at steady state, a finding that was strongly disputed for years (Sedelnikova et al. 2004). This value corresponds well to the calculated probability of 0.1 for a DSB to occur per average cell in the human body per day from endogenous, nonradiogenic sources (Pollycove and Feinendegen 2003). In contrast, at background radiation level, the probability of a radiogenic DSB to occur per day was calculated to be on average only about 1 in 10,000 cells. In other words, the calculated quotient of nonradiogenic to radiogenic DSBs produced per day in the human cell average amounts to about 1,000.

The capacity of normal cells to repair damage to DNA and other cellular components is genetically determined and may vary individually. Today, more than 150 genes have been described to be involved in DNA repair at high and low doses (Franco et al. 2005; Feinendegen et al. 2007a, 2008). Some genes are active only in low-dose stress responses; others again are modulated only after high doses (Franco et al. 2005; Mullenders et al. 2009; Tubiana et al. 2009). This reproducible data alone already contradicts the justification of the LNT-hypothesis for assessing health detriment as function of low dose. Moreover, low-dose irradiated confluent cells in culture appear to stall DNA repair until cell proliferation begins again (Rothkamm and Löbrich 2003). Indeed, an immediate induction of DNA repair in proliferating culture cells is reported to be elevated at low doses of about 1 mGy of X- and gamma radiation (Day et al. 2006; Mullenders et al. 2009; Tubiana et al. 2009).

In general, then, immediate damages of DNA provoke ready attempts at structural and functional reconstitution at the cell level. Radiation-induced effects in tissues are determined eventually by the degree of remaining DNA- and cell damage.

5 Hierarchy Level Responses in Biological Systems

To fully appreciate the sequence of events to be reckoned with after irradiation, the body may be viewed as a composite of hierarchy levels of "protection" organization, as shown in Fig. 2.

Responses to the primary molecular perturbations and damages first involve the cells that have experienced one or more microdose events within a given period of time. The initially responding cells may transfer their perturbation or damage to neighboring nonirradiated cells causing so-called by-stander effects, which may be damaging and/or induce defenses (Mothersill and Seymour 2006). Similarly, energy deposition events in the intercellular matrix may affect nonirradiated cells (Barcellos-Hoff and Brooks 2001). These two damage categories are commonly referred to as nontargeted effects, in contrast, to targeted effects referring to the immediate damage in irradiated cells. If damage becomes lethal in many cells in a tissue, acute radiation effects may result in acute illness, the symptoms of which depend on the organ where cell death occurs. The degree of organ damage per unit dose largely depends on the response of the most sensitive organ–specific stem cells (Bond et al. 1966; Hall and Giaccia 2005; Fliedner et al. 2005). On the other hand, individual cells having escaped lethal radiation effects may still suffer malignant transformation and eventually cause cancer with metastases. The mechanisms of malignant transformation may include genomic instability induced in exposed cells and "handed down" to the cell's progeny over several cell generations (Kadhim et al. 2006; Dziegielewski et al. 2008; Morgan and Sowa 2009).

Whereas the incidence of immediate DNA damage rises linearly with dose, damages to DNA and cells from both by-stander and matrix effects, and from genomic instability apparently have different dose thresholds, probably below 150 mGy, and, at least for by-stander effects reach plateaus with increasing dose at about 300–500 mGy. Immediate plus secondary damages to DNA and cells, i.e., targeted and nontargeted radiation damages, all induce the body's defenses against such damaging events and against damage propagation to subsequent higher levels at tissues and the whole organism. The defense and protection systems also against nontargeted damage appear to add to the relatively

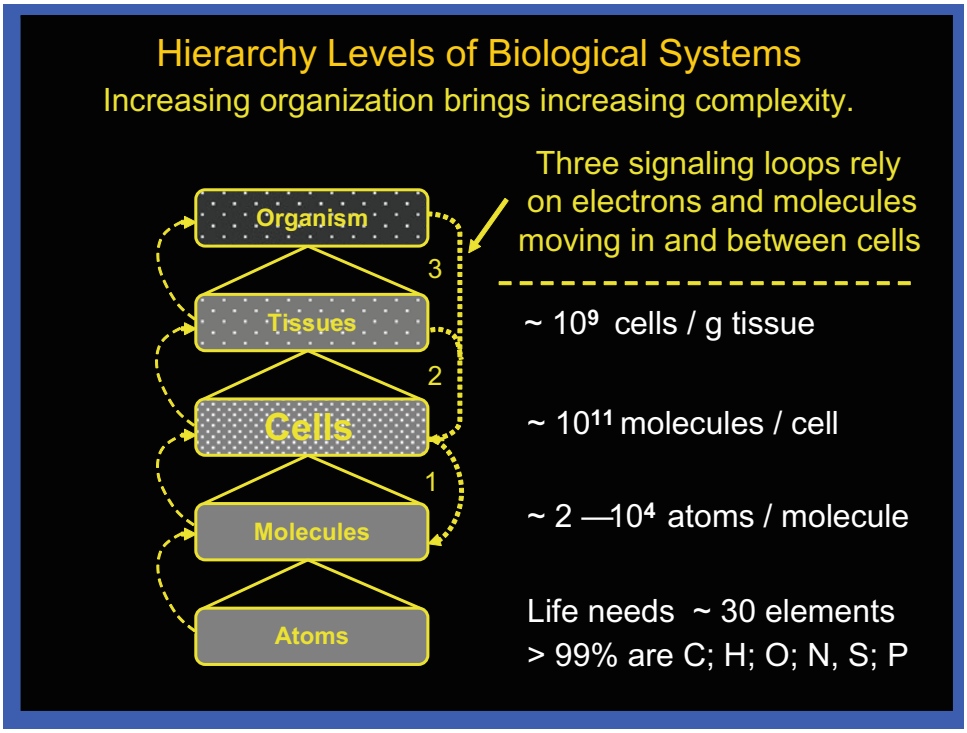

Fig. 2 The body may be viewed being organized in hierarchical levels with increasing complexity from bottom up. Intricate signaling within and between the various levels always involves cells. The three principal signaling loops assure functional integrity of the body in the face of abundant threats by toxic impacts from external and internal sources

low risk of radiogenic cell transformation, since epidemiology does not reveal cancer increase at doses below about 100 mGy (mSv).

6 Three Categories of Physiological Defenses of Complex Biological Systems

The extent of the targeted and nontargeted damage and its propagation in cells, tissues, and finally the whole-body depend on the type and degree of initial homeostatic perturbations and on the tolerance of homeostatic controls and defenses that operate at sequentially higher levels. Signaling loops coordinate controls within and between cells, between cells of different tissues and/or organs, and within the whole body, and all are subject to gene modulations (Guyton and Hall 2005). Therefore, certain defects in the involved genes may change individual susceptibility to radiation drastically.

One may, in general, discern three prototypes of defense: physical static ones, and two metabolic-dynamic ones, usually involving enzymes according to the individual's genome.

The physical static barriers prevent impacts from changing matter, from disrupting a material structure and consequently its function in a system. For instance, a certain impact size, i.e., force, is required to move a body such as a stone on a surface in a given direction—well known and described by physical laws. Similarly, a certain target specific impact is needed to injure the skin, or to kill a cell, or to break an inter-atomic bond in a molecule. Moreover, tissue damage only occurs if a minimum number of cells that are essential to structure and function have been removed from their structural and functional places in tissue. Obviously, there are thresholds for a force to overcome a physical static barrier before an effect can be registered at the impacted object. With increasing magnitude of the impact, the effect becomes larger or more severe and eventually reaches a maximum. The corresponding Impact-Size-Effectiveness Function that describes the relationship between impact size and severity of effect gives graphically a sigmoid shaped curve (Bond et al. 1995).

Metabolic defenses can operate practically instantly at all levels of organization in normal organisms against potentially life-threatening events, which are shown schematically in Fig. 3. An example of defense at the tissue level presents the protection by the skin against manifold different types of impacts. If injured, the normal skin promptly initiates protective responses leading, for instance, to wound healing through signal-induced cell death, cell necrosis, phagocytosis, cell proliferation, and differentiation. At the molecular level, DNA damages of various kinds, be the base alterations, strand breaks or intermolecular linkages, induce a large number of specific repair responses (Hall and Giaccia 2005).

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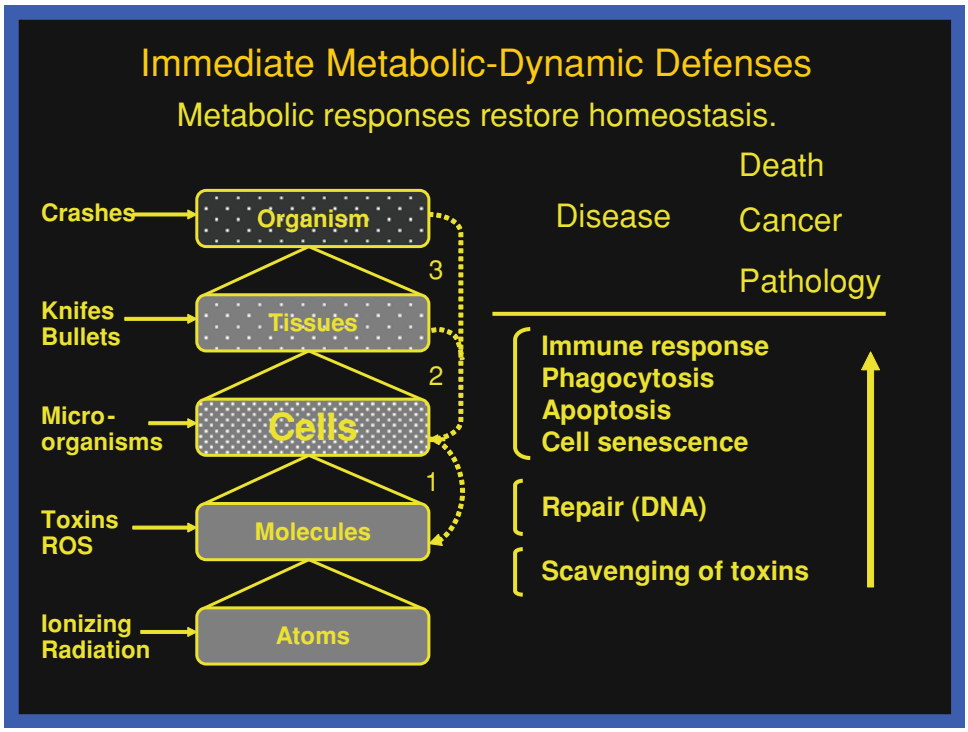

Fig. 3 Threats at the various organizational levels of the body are met by physical static and metabolic-dynamic defenses against damaging impact, damage creation and damage propagation. These defenses are successful if they restore homeostasis, from the molecular to the tissue-organ level. Only when the defense barriers are overcome, pathology develops with acute and late health effects, such as cancer. The individual defenses respond with individual probabilities

With a holistic view of systemic function at various levels one may distinguish the following prompt metabolic-dynamic defenses, as shown in Fig. 3. These may be put into three operational groups (Feinendegen et al. 1995, 1999, 2004, 2007a, b; Feinendegen and Neumann 2005):

a. defenses by scavenging mechanisms at the atomic-molecular level;
b. molecular repair, especially of DNA, with reconstitution of essential cell constituents, and functions;
c. removal of damaged cells by induced cell death, i.e., apoptosis, cell necrosis, and an immediate immune response in an immunized body, with phagocytosis of killed cells, or by cell proliferation toward senescence.

In this context it is important to adhere to careful definitions. Thus, repair of a skin wound involves removal of damaged cells and cell debris as well as cell proliferation and differentiation. Therefore, terms like defense, repair, and damage removal must be linked to the levels where the damage occurs. Repair, damage removal, and replacement of damaged and/or lost molecules and cells in the course of tissue reconstruction for maintenance of tissue function usually are subsequently intertwined events.

Like the physical static barriers metabolic-dynamic barriers do not operate at a level always proportional to the degree of perturbation. In fact, these mechanisms of protection appear to allow perturbation to a certain degree before they begin to act to restore homeostasis, and thus prevent propagation of damage to successively higher levels of organization. This means, an impact must be large enough to overcome a threshold depending on the organizational level before structure and/or function are perturbed sufficiently to threaten the next higher level. There are many common daily examples with this principle response pattern.

In general then, only when homeostatic perturbations overwhelm structural and functional barriers at successive levels, from chemicals to molecules, to cells, to tissue, etc., disease can develop.

The above summarized cascade of defenses also operates against local damage and damage propagation from ionizing radiation. Because, increasing doses of ionizing radiation with large numbers of microdose events in the exposed tissues eventually overwhelm barriers at all hierarchical levels, high doses in large target volumes may allow damage at basic levels to propagate with minimal or no inhibition, and thus to evolve into clinically evident disease. As a consequence, many, but definitely not all, dose–response functions expectedly tend to be linear at higher doses, but not so at low doses.

There is a second metabolic-dynamic type of barrier which becomes activated by low-degree perturbations at a given level of biological organization. This barrier type is commonly referred to as stress response. It expresses an adaptation of the exposed system to better withstand renewed exposure to a potentially damaging impact by an agent that may be identical to the initial agent or mimics this agent. A common experience of this type of adaptation is the development of callus in a chronically burdened skin, or immunization for protecting the

body against exposure to an infecting agent. Another example is properly conducted physical training to strengthen muscles and the cardiovascular system to improve physical endurance and/or athletic performance. A fourth example is properly dosed exposure to sunlight to induce tanning which will protect against a higher-degree exposure to sunlight by reducing the probability of sun burn, yet also may enhance the probability of skin tumors. Adaptive protections result from up-regulation of existing cascades of metabolic-dynamic barriers described above. In contrast to the promptly acting barriers; however, adaptive protections appear after a delay and increase to a maximum after one or repetitive stimulating impacts followed by a decline after the stimulus has disappeared. This decline is comparatively slow and may be observed for months to more than 1 year; some immunizations even protect for a lifetime.

Thus, low-dose irradiations, in contrast to high doses, can cause adaptive protections to function in cells, tissues, animals, and humans. There is a widespread misunderstanding of these low-dose induced adaptive protections only to act against renewed radiation and not to radiomimetic perturbations. Yet, radiation-induced adaptive protections operate also against the effects of other agents that may cause, for instance, DNA damage (Wolff et al. 1988), as referred to below.

7 Low-Dose Induced Adaptive Protections

Over the past three decades, experimental data in cultured cells and in animals have established that cells may respond very sensitively to low doses of low-LET type radiation by altering cell signaling (Zamboglou et al. 1981). This may lead with a delay of several hours after a single irradiation to the up-regulation of physiological defenses in terms of adaptive protection, discussed above (Feinendegen et al. 1999, 2004, 2007a, b; Mullenders et al. 2009; Tubiana et al. 2009). Up-regulation was quantified, for instance, regarding: scavenging of ROS that lasted for more than 10 h (Zamboglou et al. 1981; Feinendegen et al. 1984, 1995; Hohn-el-Karim et al. 1990); DNA repair lasting for several days (Olivieri et al. 1984; Wolff et al.1988); apoptosis to reach a maximum about 4 h after single exposure and to continue being elevated for more than 2 weeks following cessation of repetitive low-dose exposures (Kondo 1988; Fujita et al. 1998) and an increased immune response lasted for months and even more than 1 year with concomitant reduction, for instance, of metastases (James and Makinodan 1990; Tubiana et al. 2005, 2009). An integrated effect of adaptive protections shows in the degree of reduction of neoplastic transformations in cultured cells as well as primary cancer and metastases in animals following a single low-dose irradiation (Azzam et al. 1996; Feinendegen et al. 2004; Mitchel et. al. 2003, 2008; Elmore et al. 2009). In cultured cells a single low-dose, low-LET irradiation reduced neoplastic transformation to about 30 % of the transformation incidence in nonirradiated controls; and, a threshold for neoplastic transformation existed in such cells even after high cell doses from accelerated particles (Azzam et al. 1996; Elmore et al. 2009).

Like in the case of immediately protecting responses, adaptive protections do not necessarily develop proportionally to the degree of the perturbing event. Adaptive protections are related to dose in that they appear after single exposure at a low threshold of cell dose, increase to a dose around 100 mGy, then disappear as doses increase beyond 200 mGy of low-LET radiation and are hardly, or not at all, seen above about 500 mGy (Feinendegen et al. 1996, 1999, 2007a). An exception is apoptosis, in that its incidence apparently increases linearly over a certain dose region beyond single doses of 500 mGy, whereas at doses below about 100 mGy, there is evidence of apoptosis incidence to fall below the control level (Liu et al. 1996). In addition, unrepairable DNA damage obviously predisposes cells to induction of apoptosis more frequently than normal cells (Chandra et al. 2000). High-dose irradiation of mammals with alpha particles in vivo suggests induction of the body's immune responses via the activation of immune cells in the neighborhood of high-LET damaged single cells (Harder 2008).

Adaptive responses are well known, for instance, following so-called oxygen stress (Chandra et al. 2000; Finkel and Holbrook 2000; Sen et al. 2000). They may be similar to those that in part are associated with radiation-induced adaptive protection (Hohn-el-Karim et al. 1990; Feinendegen et al. 1995, 2000a, b; Feinendegen 2002). As referred to above, a normal average mammalian cell experiences a mitochondrial leak of about 10^9 ROS molecules per day, i.e. about 100 ROS molecules per millisecond, in the cytoplasm outside mitochondria, mainly from metabolic reactions; and additional small ROS bursts come from various responses to external cell signaling (Sen et al. 2000; Pollycove and Feinendegen 2003). An average microdose event, for instance produced by 100 kVp X-rays, creates about 150 ROS in the hit cell within a fraction of a millisecond. Both metabolic and radiation-induced ROS can trigger oxidative stress responses in terms of adaptive protections depending on concentrations, species, tissues, and cells (Finkel and Holbrook 2000; Feinendegen and Neumann 2005; Feinendegen 2002). In this context, normal background irradiation with its causing single microdose events per cell several times a year, as explained above, should be seen also as adjuvant for maintaining homeostasis (Feinendegen 2002), for instance by inducing apoptosis of predamaged cells (Chandra et al. 2000).

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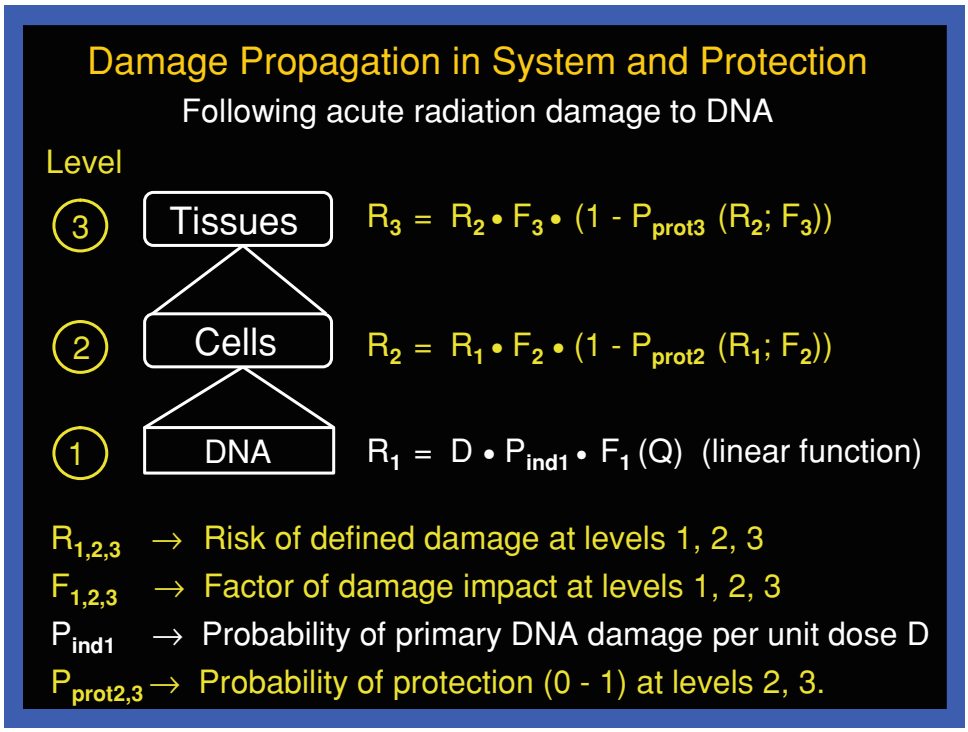

Fig. 4 Damage propagation to successive higher level of organization, from DNA, to cells, to tissue, and the effect of protection at the cell and tissue levels may be expressed schematically by a simple set of equations

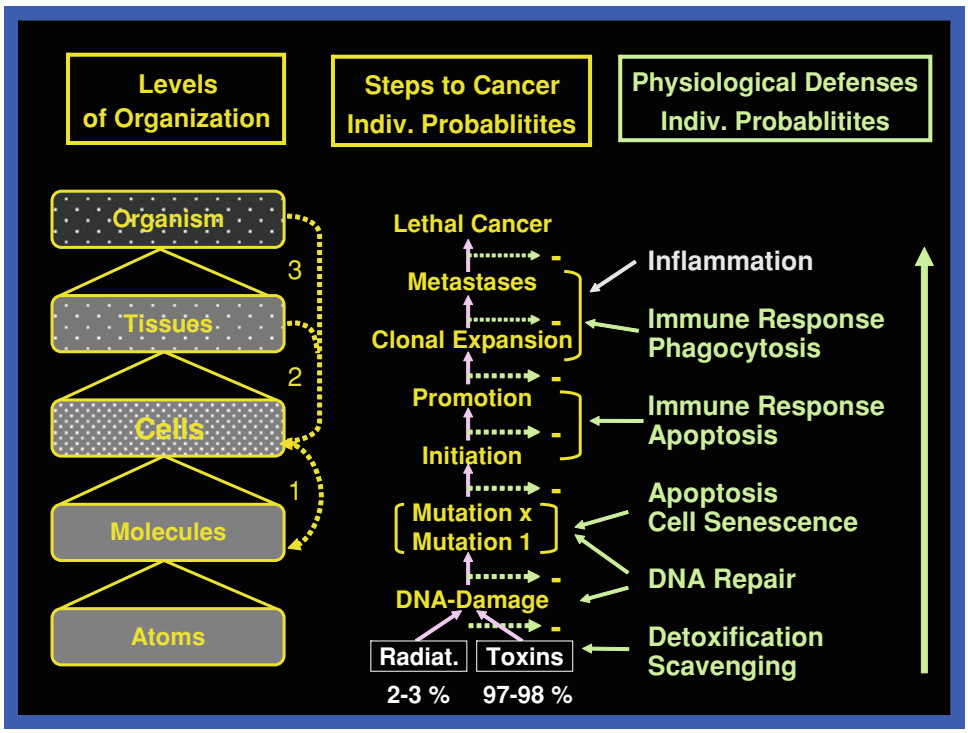

Fig. 5 The metabolic defenses also operate against the development of cancer. The various steps to clinical cancer have individual probabilities. About 1 in 10^9 cancer cells may escape defense barriers and cause clinical tumors and disseminated metastases. In industrialized countries, about 2–3 % of cancer incidence is being attributed to background radiation, as is calculated on the basis of the LNT-hypothesis (adapted from Feinendegen et al. 2007a, b)

To repeat, adaptive protections were assumed initially to be confined to DNA repair following renewed irradiation (Olivieri et al. 1984; Wolff et al. 1988). Yet, it has become clear that the delayed stimulated protections may not only involve all physiological defenses but also operate against nonradiogenic damage, such as damage from endogenous toxins, like ROS (Chandra et al. 2000; Feinendegen et al. 1995) and from chemical mutagens (Wolff et al. 1988). Cells rarely can afford the energy "costs" associated with creating a special response to a rare or unique perturbation. The broad effectiveness of adaptive protections at all levels of biological organization, against both radiogenic and

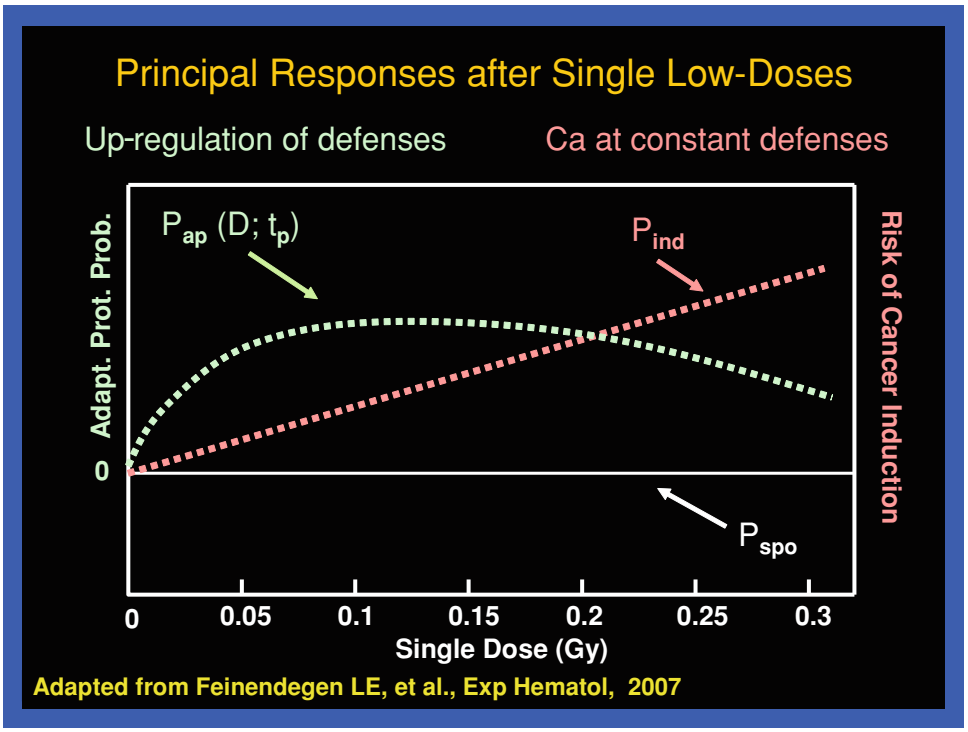

Fig. 6 Schematic representation of the dual responses to single low doses feeding into the "Dual-Probability-Model" in Fig. 7: **a** Low doses of ionizing radiation can up-regulate physiological defenses with delay and some last beyond a year. The up-regulated defenses are also called adaptive protections and depend on dose D and on he time t_p of their action: the probability of protection ranges from 0–1 and is P_{ap} (D; t_p). **b** The risk of radiation-induced cancer assumes constant defenses in the body at every dose D according to the LNT-hypothesis and is expressed here by the value of P_{ind} per unit dose. Note that also damage from by-stander effects and genomic instability challenges the body defenses including immediate and adaptive protections (adapted from Feinendegen et al. 2007a, b). This nontargeted damage and responses to it are omitted from this Figure, for reason of ease of presentation. Note that the scales of the two probabilities P_{ind} and P_{ap} (D; t_p) are independent of each other

nonradiogenic damage, expresses a hormetic response, and is crucial in estimating probabilities of late radiation effects such as cancer, as will be discussed in more detail below.

The effect of cascades of homeostatic responses against propagation of primary damage at the DNA level to successive higher levels of the cell's organization and tissues may be expressed by a set of equations shown schematically in Fig. 4.

8 Physiological Defenses Against Cancer

The various physiological barriers against damage and damage propagation sketched out above also operate in the course of oncogenesis, as illustrated in Fig. 5. Even if the protective mechanisms against cancer still are not fully understood, their effects are obvious. An illustrative example is the very low probability of a radiation-induced average DNA double-strand break in a potentially oncogenic blood-forming human tissue stem cell to bring about a lethal leukemia. This probability has been estimated to be close to 10^{-12} (Feinendegen et al. 1995). The claim that even a single DNA double-strand break, however grave, in a human stem cell may lead to cancer is scientifically unjustified.

Low-dose induced cancer is, nevertheless, assumed by many to increase proportionally with dose. This opinion hypothesizes that irrespective of dose a certain, however small, fraction of radiogenically transformed cells escapes all barriers and expands into clinical cancer (Brenner and Hall 2007). The probability of such a transformed cell to sneak through the defense systems may be estimated from experimental and epidemiological observations. Thus, the probability of neoplastic transformation in a cell in vitro is about 10^{-5} per low-LET microdose event (Hall and Giaccia 2005) and the probability of lethal leukemia per low-LET microdose event in a human hemopoietic stem cell in vivo is a about 10^{-14} (Feinendegen et al. 1995). Assuming that the in vitro probability also applies in vivo, the quotient $10^{-14}/10^{-5}$ is about 10^{-9} and expresses the probability of the affected cell to escape all in vivo defense mechanisms. The claim of constancy of the effectiveness of defense barriers in vivo irrespective of dose is contradicted by the induced adaptive protections following low doses but not high doses.

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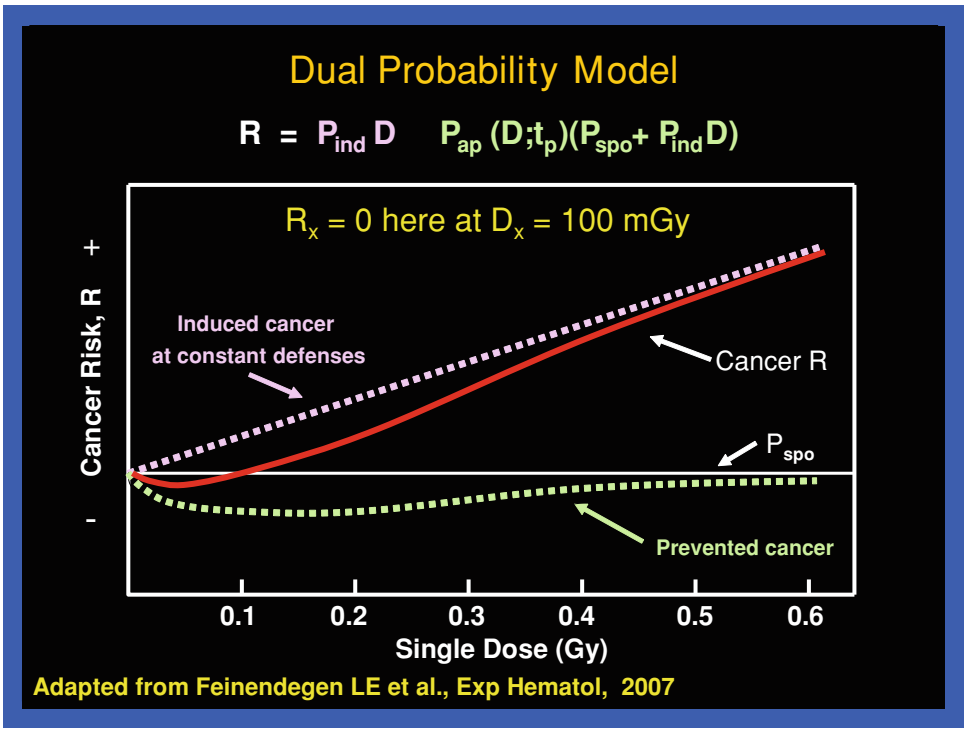

Fig. 7 This Figure illustrates the applicability of the "Dual-Probability-Model" for assessing low-dose cancer risk. Adaptive protections, as shown in Figs. 5 and 6, may also operate against nonradiogenic damage and thus reduce "spontaneous" cancer. The product of the probability of protection against spontaneous cancer, from 0 to 1, and the probability of spontaneous cancer gives the probability of cancer prevention The clinically observed cancer risk *R*, then, is the difference between the probabilities of radiation-induced cancer and of prevented cancer, given by the solid line. Assuming here a maximum value of P_{ap} (D, t_p) at 100–200 mGy, the reduction of cancer risk to and below the spontaneous risk appears as an obvious hormetic effect, despite the low values of P_{ap} (D, t_p), see Tables 2 and 3 (adapted from Feinendegen et al. 2007a, b). Note that, again, for reasons of ease of presentation nontargeted damage and responses to it are omitted from the figure

9 Damage and Protection in the "Dual-Probability-Model" of Cancer Risk

In the attempt to assess cancer risk from low-dose exposure realistically, both probabilities, of damage and of protection after low-dose irradiation, need to be taken into consideration. To do so coherently and effectively, one should try to choose a model into which all the phenomena that affect low dose responses can be accommodated. Instead of examining the various types of protections individually (Heidenreich and Hoogenweem 2001; Schöllnberger et al. 2005), an average degree of protection may be preferable for modeling (Feinendegen et al. 1995; Scott 2004; Leonard 2007), in which all mechanisms are incorporated and yield together a probability value between 0 and 1, i.e., between no and full protection against a risk of induction of a clinical cancer.

The model of choice here derives from an approach proposed in 1995 (Feinendegen et al. 1995). It rests on the dual effect of low doses in both causing damage and protection (Feinendegen et al. 1999, 2000, 2004, 2007a, b). Figure 6 shows as a function of dose the model inputs of the two opposing effects: (a) the risk of cancer per unit dose, denoted by P_{ind}, mainly according to the LNT-hypothesis; (b) the probability of protection against cancer as a function of D and time of effectivenesst_p, denoted by P_{ap} (D; t_p); with the base line showing the probability of lifetime "spontaneous" cancer incidence that is observed in industrialized countries, denoted by P_{spo}. Whereas the probability of protection according to experimental observations is given here to rise with increasing doses to a maximum at about 100–200 mGy and then to fall toward 0 as doses increase beyond 300 mGy, the cancer risk rises linearly with dose if existing defenses against cancer are constant irrespective of dose. The figure excludes for ease of presentation, on the one hand, the potential contribution of detrimental nontargeted damage (genomic instability and by-stander effects) at low doses and, on the other, the subsequent immediate and protective responses against such damage. Note that the scales for the two probabilities, P_{ind} and P_{ap} (D; t_p) are independent of each other.

In order to grasp the full consequence of low-dose induced adaptive protections one must recall that the probability of endogenous, nonradiogenic, i.e. spontaneous,

Table 2 Numerical values of the graph in Fig. 7 for a given set of assumptions made on the basis of experimental evidence, as explained in the text

Dose-Risk Function - Acute Exposure - Adult Person
assuming max. adaptive protection at D_x 100 - 200 mGy
measured R_x at 100 mGy = 0

D (mGy)	P_{ind} D ($\bullet 10^{-3}$)	P_{ap} (D; t_p) ($\bullet 10^{-2}$)	P_{ap} (D; t_p) P_{spo} ($\bullet 10^{-3}$)	R ($\bullet 10^{-3}$)
1	0.06	*0.4*	1.0	- 0.9
10	0.6	*1.0*	2.5	- 1.9
50	3	*2.0*	5	- 2
100	**6**	***2.4***	**6**	**0**
200	12	*2.4*	6	6
400	24	*1.0*	2.5	21.5
600	36	*0.2*	0.5	35.5

Table 3 Numerical values of protections covering lifetime risk of spontaneous cancer in industrialized countries, as they are expected at 100 mGy with different values of risk estimated from epidemiological observations in irradiated populations

Values of P_{ap} (D; t_p) at 100 mGy
With various R_x at D_x ~ 100 mGy
P_{ind} = 6 • 10^{-5} / mGy; and P_{spo} = 2.5 • 10^{-1}

R_x ($\bullet 10^{-3}$)	P_{ap} (D_x; t_p) ($\bullet 10^{-2}$)
6	0
4	0.8
2	1.6
0 →	2.4
-2	3.2
-4	4.0

cancer (P_{spo}) at any time outweighs the probability of cancer from average background radiation, probably by a factor of 30–50, if the LNT-hypothesis is applied (Pollycove and Feinendegen 2003), It is to be noted that, this probability quotient is much lower than the quotient of about 1,000 for DNA DSBs produced per day from endogenous sources to those from background radiation per average cell in an adult human. This quotient of about 1,000 only expresses quantities. Yet, with respect to qualities a large percentage of radiogenic DNA DSB are more complex, of the multi-damage type (Nikjoo et al. 1999), and thus probably cause more cellular damage than simple DSB from endogenous sources, perhaps by a factor of 20–30 (Pollycove and Feinendegen 2003).

Following a single low-dose irradiation one may, thus, rightly assume that the delayed and especially the long lasting adaptive protections operate mainly against endogenous damage and cancer development rather than cancer induced by irradiation (Feinendegen et al. 1995), as it is implied also by experimental evidence (Mitchel et al. 2003, 2008). The risk of cancer following a single low-dose exposure, therefore, would at every dose level be the difference between the calculated radiogenic cancer risk at constant defenses, and the prevented cancer risk being the sum of the probabilities of protection against radiogenic as well as spontaneous cancer risks. This approach gives the "Dual-Probability-Model" illustrated in Fig. 7.

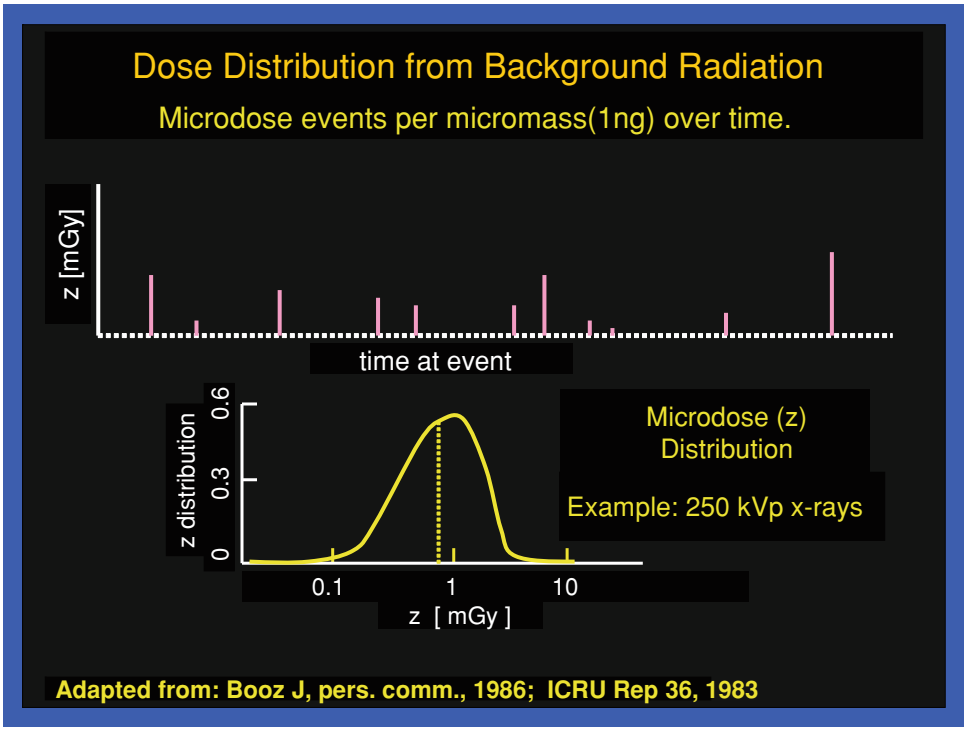

Fig. 8 Chronic irradiation conforms to repetitive irradiations of micromasses. Microdoses z occur per micromass over time stochastically with various values, *upper part*, according to their spectrum depending on radiation quality, *lower part* for 250 kVp X-rays

Thus, in accordance with previous reports (Feinendegen et al. 2007a, b, 2008).

R = clinically observed risk of cancer induced by a single dose D,

P_{ind} D = radiation-induced lethal cancer risk calculated with constant defenses in the system, based on the LNT-hypothesis, from a single dose D,

$P_{ap}(D; t_p)$ = probability of adaptive protection (0–1) as function of D and time of effectiveness t_p, with target to be defined,

P_{spo} = "spontaneous" lifetime cancer risk of the exposed individual, in industrialized countries, then taking the targets of protection to be both P_{spo} and P_{ind} D,

$$R = P_{ind}D - P_{ap}\left(D; t_p\right)\left(P_{spo} + P_{ind}\,D\right) \qquad (1)$$

This "Dual-Probability-Model" allows one to estimate the probability of adaptive protection, P_{ap} $(D; t_p)$, by assigning a value of R from epidemiological data, and for P_{ind} and P_{spo}, as follows:

$P_{ind} = 6 \times 10^{-5}$ induced lethal cancer risk/person/mGy, from atom bomb data according to the LNT-hypothesis (Preston et al. 2004, 2007),

$P_{spo} = 2.5 \times 10^{-1}$ "spontaneous" cancer risk/individual lifetime, in industrialized countries,

By taking into consideration that P_{ind} is comparatively negligibly small versus P_{spo}, the risk estimate, R_x, at a given dose D_x from epidemiological studies conforms to

$$R_x = P_{ind}\,D_x - P_{ap}\left(D_x; t_{p1}\right)P_{spo} \qquad (2)$$

Rearranging Eq. 2 to

$$P_{ap}\left(D_x; t_{p1}\right) = \left(P_{ind}\,D_x - R_x\right)/P_{spo} \qquad (3)$$

gives the probability of protection for a value of R_x at a given dose D_x with the protection target being the lifetime risk of cancer P_{spo}. For instance, letting the cancer risk R_x be zero at 100 mGy, as compatible with most epidemiological data, and inserting the above defined values of P_{spo}, and of P_{ind} for 100 mGy being approximately 6×10^{-3}, the value of P_{ap} $(D_x; t_{p1})$ becomes

$$P_{ap}\left(D_x; t_{p1}\right) = \left(6 \times 10^{-3} - 0\right)/2.5 \times 10^{-1} \qquad (4)$$

or

$$P_{ap}\left(D_x; t_{p1}\right) = 2.4 \times 10^{-2} \qquad (5)$$

In other words, a very small degree of adaptive protection covering about 2.4 % of a person lifetime cancer risk in industrialized countries would be sufficient to balance the assumed cancer risk at 100 mGy, based on the LNT-hypothesis.

In fact, the application of the dose effect curve for overall protection as seen in Fig. 6, together with the degree of protection in Eq. 5 to an epidemiologically estimated R value of 0 at 100 mGy, and assuming that the maximum adaptive protection here occurs at 100–200 mGy, yields a hormetic effect up to 100 mGy, as illustrated by the solid line in Fig. 7. The numerical values of the data in Fig. 7 are listed in Table 2.

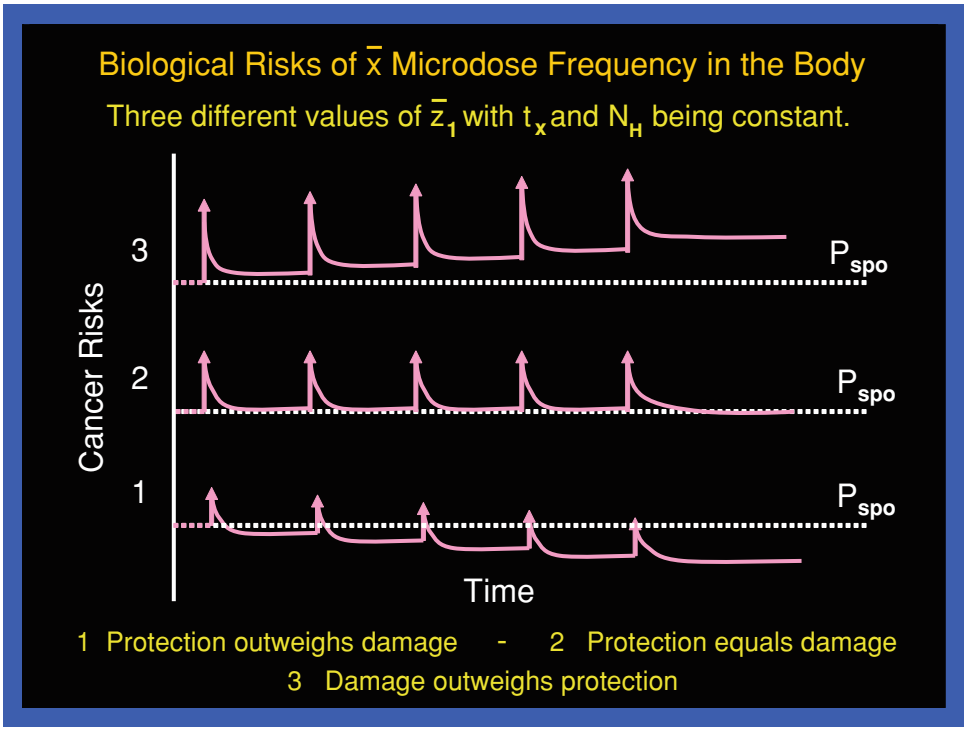

Fig. 9 The biological risk of chronic irradiation depends on the values of microdoses and the time interval between consecutive microdose events. Mean values for both may be used for assessing risk. The term "cancer risks" here expresses the probability of cancer induction by the hit cell at the time during exposure, with the added time intervals allowing for repair and protection. Shown schematically are three scenarios: (1) where protection outweighs damage; (2) where protection equals damage; (3) where damage outweighs protection

If the degree of protection at 100 mGy would cover more than 2.4 % of the lifetime cancer risk, the cancer risk after 100 mGy would fall below the control value, and show up as a hormetic effect at 100 mGy. Increasing P_{ind} by a factor of two to a value of 12×10^{-3}, for instance by a by-stander damage, the protection probability would attain 4.8 % with R_x being 0 at 100 mGy. Assuming, for instance, a by-stander damage at 50 mGy to increase P_{ind} by a factor of two, i.e., to 6×10^{-3}, with R_x measured at 50 mGy being 0, the protection probability would become again 2.4 % (see Eq. 4).

The above listed low-dose induced reductions in the R values, even if small, could add to the failure to observe any statistically significant increase in radiation-induced cancer risk at doses below about 100 mGy in epidemiological analyses of exposed cohorts of humans. In fact, these epidemiological data, taken as they are without modeling, indicate reduction of cancer risks at low doses more frequently than increases, with borderline statistical significance (Pollycove and Feinendegen 2001; Preston et al. 2004).

According to above Eq. 4, the values of P_{ap} ($D_{\mathbf{x}}$; t_{p1}) that would operate at different, epidemiologically estimated values of risk at 100 mGy are shown in Table 3. It is obvious that only less than 5 % of a person's lifetime risk of cancer need to be covered by low-dose induced adaptive protection in order to produce a hormetic effect in terms of a reduction of the risk of spontaneous cancer at 100 mGy. These predictions of adaptive protection probabilities are well in line with experimental data on protection effectiveness following single low-dose exposure.

10 Chronic Irradiation

The above model is applicable also to chronic or repetitive low-dose irradiation. During chronic irradiation, individual microdoses from a given quality of radiation occur in an exposed micromass at time intervals the mean length of which is determined by the dose rate. For a given dose rate of a defined radiation quality, there is a proportional relationship between the mean microdose value, as shown in Table 1, and the mean time interval between two consecutive microdose events. The higher the mean microdose the longer is the mean time interval between two consecutive microdose events at given dose rate. An example of stochastic distribution of events per micromass and appropriate time intervals between two consecutive events for 250 kVp X-rays is shown schematically in Fig. 8.

Radiation quality determines the range of the microdose values and their time intervals at given dose rates, and thus the probabilities of cellular reactions to the individual microdoses, in terms of damage, and protection. The time interval between two consecutive microdose events in a given cell or cell group then allows for the cellular responses to develop fully or not. Here, all types of responses need attention regarding the degree of damage and its propagation.

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To appreciate biological effects of dose rates or repetitive irradiations properly, it appears paramount to consider the following questions: what are the individual microdose values that may cause damage and induce prompt metabolic defenses and adaptive protections at a given time interval between consecutive events; and what are the values of the time intervals that allow for defined damage manifestation, and prompt and late responses to individual microdose events. The answers to these questions are very fragmentary, yet appear crucial in understanding results both of low dose-rate experiments (Vilenchik and Knudson 2000; Ishizaki et al. 2004) and of epidemiological investigations from cohorts of chronically exposed mammals and people with reduced rather than increased cancer incidences (Tanooka 2001, 2011; Mitchel et al. 2003, 2008; Cardis et al. 2007; Nair et al. 2009). A schematic display of possible consequences of different low dose-rate scenarios is in Fig. 9.

11 Conclusion

Current radiogenic cancer epidemiology reports cannot overcome their statistical constraints and these papers do not assure the validity of the LNT-hypothesis at low doses. In fact, the LNT-hypothesis is inconsistent with many experiments, both in the laboratory and in the human exposure realms.

Low doses may cause at the molecular level, especially in the DNA, targeted and nontargeted effects. These may propagate in succession to increasingly complex levels of biological organizations, from molecules to cells, to tissues, and the whole body. In this fashion, it seems opportune to distinguish between trigger and responses with the latter encompassing both increased perturbations, as well as defenses to restore homeostasis. There appear to be three principle types of defense barriers against damage and its propagation: physical static ones, and two metabolic-dynamic defenses. One of the latter type operates promptly and the other by way of delayed up-regulation of protection at successive levels of organization, i.e., by adaptive protections. These operate also against a multitude of constantly arising endogenous mutagenic toxins and their consequences. The actual observed cancer risk of low-dose irradiation, thus, appears to express the balance between cancer induction and cancer prevention by metabolic-dynamic defenses through prompt and adaptive protections. The consequences of these experimental findings are not contradicted by epidemiological data on radiation-induced cancer from low doses.

The type and extent of cell defenses are under genetic control. Thus, effects of low dose irradiation are expected to vary among individuals, and may even become predictable by individual gene-expression profiles. This information promises to have clinical applications, for instance, in treating cancer with low-dose irradiation.

Radiation biology has advanced to provide sufficient data that justify the rejection of the validity of the LNT-hypothesis also in concepts of collective dose or collective effective dose for predicting cancer risks of single, chronic, or repetitive low-level exposures.

It is hoped that an appropriate consensus conference eventually provides new guidance based on scientific evidence in order to arrive at optimal radiation risk estimates with their impact on radiation protection.

Frequently voiced arguments that the new low-dose experimental data are either irrelevant, or questionable, or irreproducible are not in line with scientific methodology.

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