K bedlivému pročtení:

Biological Effects From Low Doses and Dose Rates of Ionizing Radiation: Science in the Service of Protecting Humans, a Synopsis

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Forum Article

There is considerable controversy regarding risk of health detriment after low-level exposure to ionizing radiation. This stems in part from a sort of distance between radiation biologists, epidemiologists, and radiation protection professionals, as well as regulatory institutions. Also, there is a lack of overview of the relevant data and their origins regarding health risks at low doses of ionizing radiation. This feeds seriously into a somewhat hazy fear of ionizing radiation that besets large portions of the public. The current synopsis aims at presenting a holistic view in a concise yet comprehensive manner in order to help people understand the full extent of inputs into attempting to relate low-dose radiation exposure to health risk. It emerges again that different approaches must be found for optimal radiation protection replacing the use of the linear no-threshold (LNT) model.

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INTRODUCTION

THIS SYNOPSIS is an overview of the current state of knowledge regarding the biological effects of exposures to low levels of ionizing radiation. Risk of harm (cancer) from low doses is widely discussed by different social, political, and professional groups, including radiation protection institutions. The challenge is to comprehend the scientific facts and use them for optimal modeling of dose- and dose-rate-induced effects, irrespective of whether they are harmful or beneficial. Epidemiology alone is very limited in its ability to predict radiogenic risks at low doses, even on large numbers of exposed people. From the point of view of biology, the entire spectrum of its subspecialties must enter a holistic approach in order to link low-dose radiation to health risk. This synopsis aims at accomplishing this.

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Energy deposition by ionizing radiation

In biological tissue, ionizing radiation causes targeted and nontargeted (bystander) molecular damage through energy deposition along tracks of charged subatomic particles, creating topical packages of absorbed energy usually of microscopic dimensions (Feinendegen et al. 1985). These energy deposition events (i.e., particle hits) excite atoms or dislodge electrons from them (cause ionizations) and damage molecular structures. With about three-fourths of tissue mass being water, the majority of initial damage leads to breakdown products of water, mostly reactive oxygen species (ROS) and hydrogen peroxide (H_2O_2). These radiolysis products of water appear as bursts within 10^{-8} seconds per particle hit. The type of radiation (x ray, gamma, beta, or alpha) determines the characteristics of the tracks at different track energies. The number of tracks in a defined tissue mass relates to absorbed dose, and the number of tracks per unit of mass per unit of time relates to the dose rate (Feinendegen et al. 1985, 2004). The dose rate defines the average time interval between consecutive particle hits in a defined mass, such as that of a cell. A long time interval between hits may allow the cell to operate its mechanisms for damage control without interference from the next hit. Indeed, the amount of damage tends to be smaller, per unit of accumulated dose, when the dose rate is low than when it is high (Hall and Giaccia 2011).

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Responses to energy deposition events

Different kinds of radiation in tissue cause different types and distributions of particle hits and thus different types of primary molecular damage (Feinendegen et al. 1985 ; Hall and Giaccia 2011). If not immediately repaired or removed, primary damage evolves into persistent damage and/or causes different secondary cellular responses that vary with dose in a nonlinear fashion, as discussed below. More or less by chance, damage may express itself in cells as structural changes of different kinds in any molecule, such as those in subcellular building blocks. Dreaded are the serious changes in genetic material, the DNA, especially as double-strand breaks (DSBs), chromosomal aberrations, and genetic mutations of different kinds. Such changes after high-dose irradiation have been studied extensively (Hall and Giaccia 2011). After a low dose, changes in intra- and intercellular cell signaling of the stress-response type appear to dominate, as explained in the following sections.

Acute radiation sickness derives predominantly from the death of many cells, whereas diseases such as cancer arise later in life from cells that have acquired mutations and genomic instability and have become resistant to protective mechanisms in the body (Hall and Giaccia 2011 ; Vogelstein and Kinzler 2004).

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Radiation effects and similar effects from metabolism

The primary radiogenic damage may trigger secondary responses at the molecular, cellular, and tissue levels (Feinendegen et al. 1999, 2004, 2011 ; Hall and Giaccia 2011). In general, secondary responses may propagate and amplify damage but may also activate, as discussed further below, tissue-inherent protective mechanisms of damage prevention (scavenging of toxins), repair (including DNA repair), and damaged cell removal in various ways (such as by apoptosis and immune responses). These secondary responses operate in a nonlinear fashion with respect to dose. The ratio of damage manifestation to damage prevention and handling in irradiated tissues tends to be high at high doses and low at low doses (Feinendegen et al 2004, 2011 ; Szumiel 2012).

If only the physics of dose absorption was to be considered, the primary impact of radiation in the target tissue would conform to a linear dose-effect function. However, it is difficult to observe this at low doses because nonradiogenic (naturally occurring) molecular damage, mainly from metabolically produced ROS and H_2O_2 in aerobic organisms, occurs at a rate per day that is many orders of magnitude greater than the rate of such damage caused by low-level radiation (Pollycove and Feinendegen 2003 ; Feinendegen et al. 2012). More serious nonradiogenic damage (i.e., natural DNA damage, such as DSBs) happens about once in every 10 cells per day (Feinendegen et al. 2012). This rate per day is about the same as that of radiogenic DSBs induced by about 2.5 mGy of x rays per day, or about 900 mGy per year. If one assumes radiogenic DSBs to be 30 times more toxic than natural DSBs on average, the natural DSB production rate would have the same toxicity as an x-ray dose rate of about 30 mGy per year or about 0.1 mGy per day. However, there is no evidence of an elevated cancer incidence in people exposed to this level of radiation.

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Adaptive responses, under genetic control, protect against damage

The biological responses to the primary impacts of radiation are genetically determined and vary individually. Thus, some 5% of exposed people may exhibit increased radiosensitivity, and about 25% are reported to show intermediate radiosensitivity (Foray et al. 2013).

Following low doses, responses are induced both instantly and after delay at the different levels of the exposed body. The immediate responses can result in both propagation of damage as well as induction of repair and reconstitution of functional homeostasis (Hall and Giaccia 2011). Delayed responses are similar to stress responses as consequences of changed cellular signaling in and between cells (Sies et al. 2017 ; Sies and Feinendegen 2017). They appear in cells and tissues within hours after low-dose irradiation and can express up regulation of various physiological protections, as outlined above, in terms of damage prevention, repair, and removal (Feinendegen et al. 2011, 2012 ; Tang et al. 2017). This is accompanied by changes in gene expression (Yin et al. 2003). The delayed responses express system adaptation following sublethal system disturbances and are referred to as adaptive responses or adaptive protections (APs) (Wolff et al. 1988).

The degree of APs rises to a maximum at about 100 mGy, and they increasingly vanish as the radiation dose increases above about 200 mGy (Feinendegen 2016). APs may persist for hours to months and even for a lifetime, stimulating damage prevention, repair, and removal in the irradiated organism, regardless of the causal history of the damage, be it radiogenic or nonradiogenic (natural) (Feinendegen et al. 2004 ; Feinendegen 2016 ; Scott et al. 2004).

Some damage, such as cell transformation, may escape defenses and evolve into, for instance, cancer cells. However, the degree of protection by the immune system against cancer cells tends

to be relatively high after low doses and in young people. There is, without doubt, no proportionality between the expression of these mechanisms and the radiation dose.

Contrary to low-dose-induced damage, for instance to DNA, APs are experimentally observed readily and easily. This also follows from the fact that, at low x-ray doses, the ratio of radiogenic probabilities of a cell-signaling event, which here is considered a radiogenic burst of signaling substrates (per hit average), to a DNA DSB event (range of 10^{-2} per hit average) is about 100 (Feinendegen et al. 2012 ; Hall and Giaccia 2011). This ratio also speaks in favor of benefit far outweighing risk of detriment at low doses because stress-response signaling is viewed as the gatekeeper to survival, its stimulation thus being beneficial.

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Adaptive protection and epidemiology

The epidemiological data on risk versus dose at low doses are fed into models of various kinds (Feinendegen et al. 2004 ; Scott et al. 2007, 2009 ; Dobrzynski et al. 2016). The linear no-threshold (LNT) model is the current choice for radiation protection purposes, despite the fact that it has no scientific base of radiobiological data (Calabrese 2017 ; Szumiel 2012).

Epidemiology without modeling does not show significantly increased cancer incidence at doses below about 100 mGy. Rather a prevention of cancer may be seen (Cuttler and Welsh 2015). The limited power of significance is at least partly due to statistical constraints.

Low-dose-induced APs also occur in humans (Mortazavi et al. 2014 ; Tubiana et al. 2009), and this can explain observed benefits in people who were exposed to low-dose radiation. Indeed, calculations show that low-dose-induced prevention of only a few percent of the nonradiogenic (normal) lifetime cancer incidence could balance radiation-induced incidence, if it occurs at all. This balance would result in a dose threshold for cancer to appear. In the case where damage prevention in the exposed person is greater than damage causation, a hormetic effect ensues (Feinendegen et al. 2004 ; Szumiel 2012). Both thresholds and hormetic effects have appeared in epidemiological data (Feinendegen et al. 2011, 2012).

Prolonged life spans have been reported in rodents and also in humans after low-dose exposures. This was again apparent in dogs; there was evidence of a significant increase in life spans at a dose rate of about 50 mGy of gamma rays per year. There were thresholds of around 700 mGy per year for radiation-induced life-span shortening (Cuttler et al. 2017 ; Fliedner et al. 2012).

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Animal experimental data and effects in humans

Experimental data, mainly in animals and tissue culture cells, express a multitude of reactions and responses to low-level irradiation, as referred to above. The measurements at the various levels of biological organization use all currently available methods and technical advances in biological research.

The hierarchy of systems of elements is ubiquitous in all organisms and is qualitatively and quantitatively very similar in all mammals. Indeed, mechanisms of cell signaling and elemental responses to them at the various levels of biological organization appear alike in different mammalian species including humans, even when individual genetic differences are considered. The general compatibilities of responses, notwithstanding exceptions in animals and humans, are broadly and unquestionably obvious. Moreover, the dramatic advances in clinical medicine are largely a consequence of observations in animal experiments.

There appears to be no reason to make an exception when it comes to biological responses to low doses of ionizing radiation. Thus, if the LNT model is principally not validated at low doses in animal experiments, one may rightly question the justification for using the LNT model in humans to relate health detriment to low doses and low dose rates.

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CONCLUSION

The LNT model has not been validated at low doses. Its indiscriminate use to predict an increase in cancer risk following a low-dose exposure tends to cause more harm than it is intended to prevent. Although the International Commission on Radiological Protection judges (ICRP 2007) "that it is not appropriate for the purpose of public health planning, to calculate the hypothetical number of cases of cancer or heritable disease that may be associated with very small doses received by large numbers of people over very long periods of time," blanket radiation phobia with its manifold negative impacts on society, economy, medicine, and public health is one of the examples of derivative damage. Other models of the multiresponse type have been proposed to reflect biological reality much more accurately (Feinendegen et al. 2004 ; Scott et al. 2007, 2009 ; Dobrzynski et al. 2016). An alternative approach, especially for the purpose of radiation protection, is the acceptance of a threshold dose and a threshold dose rate below which a radiogenic health detriment cannot be comprehended. Threshold doses for radioprotection of acutely and chronically exposed workers and the general public have been entertained for decades and were based mainly on epidemiological data from human and animal cohorts, with their inherent constraints, as discussed above.

In view of the current abundance of radiobiological data on low-dose effects, it appears timely to suggest a renewed consensus conference that should establish dose and dose-rate limits for radiation protection, below which risk cannot be comprehended. These limits should be based on measured radiobiological and epidemiological data for different types of ionizing radiation. The removal of comprehendible risk from low-dose exposures also would remove the ethical concerns that impede many medical applications of low-dose radiation (Block et al. 2017).

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