The Linear, No-threshold Hypothesis Linking Health Effects to Tissue Absorbed Dose Appears Principally Inapplicable at Low Doses.

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Introduction: The probability of detrimental effects (R), such as cancer induction in irradiated multicellular tissue, from low-dose exposure to ionizing radiation is conventionally related to absorbed dose (D)¹⁷ to tissue by the proportionality constant α for a given type of radiation:

\[ R = \alpha \cdot D. \]  

(1)

This expression formalizes the linear no-threshold hypothesis stating that radiation exposure may be harmful at all dose levels. The present paper challenges the validity of this hypothesis by examining tissue responses as an integral consequence of multiple and various cell responses especially at low dose levels.

Description of the actual work: According to microdosimetry (18), tissue absorbed dose D is equal to the product of \( \bar{z}_i \) and \( N_h/N_e \), with \( \bar{z}_i \) denoting the frequency-averaged specific energy deposited in a defined mass of microscopic dimension such as a cell (hit-size or cell dose), and \( N_h/N_e \) being the number of hits of any size within the number of exposed cells of that mass.
The mass of the average cell in mammalian tissue is taken to be 1 ng. Cell doses derive from single energy deposition events, hits, that are caused by discrete ionizing subatomic particles traversing, or being confined to, cells. The value of $z_1$ is a constant for a given type of radiation. The conventional dose-risk-function, $R = \alpha \cdot D$, is then transformed into the cellular hit-number-effectiveness-function:

$$N_q = \alpha \cdot z_1 \cdot N_H,$$

with $N_q$ being the number of malignant tumors in the exposed cells $N_e$.

Much data are available on single cell responses to hits from ionizing radiation both from own work and that of others. Estimates of the probabilities of various cellular responses and of their individual changes with $N_H$, are used to describe the term $\alpha$ as the sum of these probabilities with positive and negative terms.

Results: Malignant tumors have been observed to arise from single cells. Within the dose range where observable incidences of detriment such as malignant transformation of cells are proportional to the value of tissue absorbed dose, individual
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hits are assumed to act independently of each other in causing
detriment in the exposed cells. In case of a supra-linear
response, individual hits are assumed to have the probability of
enhancing the capability of single hits to cause the development
of a malignant tumor.

However, within complex multicellular tissue, hit cells also
respond acutely and temporarily by a variety of biochemical
reactions that potentially confer protection against the
accumulation of DNA damage in tissue. This is irrespective of the
cause of that damage. Since DNA damage has been related to the
development of cancer \(4, 31\), protection against DNA damage in
tissue is assumed to also operate against the development of
cancer.

The protective or adaptive cellular responses to low doses \(7, 21, 24\)
are likely triggered by a sudden change in the intracellular
concentration of free radical molecules produced by hits on cells
\(8, 10\). These responses appear temporarily over various periods of
time ranging from hours to days, and include the following
categories: 1. stimulation of the cellular radical detoxification
system with prevention of attacks by radicals on cellular
constituent molecules \(8, 10, 16\); 2. stimulation of cellular
mechanisms that reduce DNA-damage possibly through repair \(24, 25, 26, 
32\); 3. induction of programmed cell death, called apoptosis \(19\); 4.
induction of the immune system recognizing and eliminating cells
that carry malignant transformation. Each of these adaptive responses appears to have its own probability. They all act towards preventing and/or reducing lasting DNA damage in the exposed tissue. Clastogenic factors must also be considered to initiate adaptive responses. The probability of protection against action of radicals and of reduction of DNA damage per hit has been shown in various cell systems to decrease with tissue doses extending above 0.1 Gy and is seen in one system (mouse bone marrow) to have a maximum at a tissue dose of between 0.1 and 0.2 Gy of low LET radiation.

Thus, individual cells when exposed to ionizing radiation are taken to have different probabilities of a malignant transformation with the consequence of cancer:

\[ P_{\text{spo}} = \text{spontaneous malignant transformation}, \]
\[ P_{\text{ind}} = \text{radiation induced malignant transformation per average hit}, \]
\[ P_{\text{enh}} = \text{enhancement of } P_{\text{ind}} \text{ per average hit}, \]
\[ P_{\text{prot}} = \text{protection against DNA damage in surviving cells per average hit}, \]
The probability of cancer induction per hit can then be written as:

$$N_q/N_H = \left[ P_{ind} + P_{ind}P_{enh} - P_{prot}P_{spo} - P_{prot}P_{ind} \right]$$  \hspace{1cm} (4)

With $$N_q/N_H = \alpha \cdot \bar{z}_i$$ (see equation 3)

$$\alpha = \left[ P_{ind} (1 + p_{enh}) - P_{prot} (P_{spo} + P_{ind}) \right] (1/\bar{z}_j).$$  \hspace{1cm} (5)

For low-LET radiation, $$p_{enh}$$ is taken to be zero. Since the negative term in $$\alpha$$, $$P_{prot} (P_{spo} + P_{ind})$$, but not the positive term $$P_{ind} (1 + P_{enh})$$, is shown to be potentially an inverse function of $$N_H$$ at low doses of low-LET radiation, $$\alpha$$ can not be accepted being principally constant at low doses of low-LET radiation.\textsuperscript{12, 14, 15}

With $$P_{ind}$$ for hemopoietic stem cells being about $$10^{-14}$$ for human leukemia\textsuperscript{12}, with $$p_{enh}$$ being considered zero for low-LET radiation, and with $$P_{spo}$$ for the same cell type having been estimated to be about $$10^{-11}$$\textsuperscript{14}, the value of the negative term of $$P_{prot} (P_{spo} + P_{ind})$$ in $$\alpha$$ would become equal to $$P_{ind} (1 + p_{enh})$$ if $$P_{prot}$$ is $$10^{-3}$$ at low-level exposure to low-LET radiation. In this case, there would be a threshold for $$R$$ developing with increasing $$D$$. In fact, many epidemiological and experimental data\textsuperscript{20, 21, 30} support the existence of a threshold or even beneficial, hormetic, effects at low doses from low-LET radiation.
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