Nonlinearity of Radiation Health Effects

Myron Pollycove

U.S. Nuclear Regulatory Commission, Washington, DC

The prime concern of radiation protection policy since 1959 has been to protect DNA from damage. In 1994 the United Nations Scientific Community on the Effects of Atomic Radiation focused on biosystem response to radiation with its report *Adaptive Responses to Radiation of Cells and Organisms*. The 1995 National Council on Radiation Protection and Measurements report *Principles and Application of Collective Dose in Radiation Protection* states that because no human data provides direct support for the linear nonthreshold hypothesis (LNT), confidence in LNT is based on the biophysical concept that the passage of a single charged particle could cause damage to DNA that would result in cancer. Several statistically significant epidemiologic studies contradict the validity of this concept by showing risk decrements, i.e., hormesis, of cancer mortality and mortality from all causes in populations exposed to low-dose radiation. Unrepaired low-dose radiation damage to DNA is negligible compared to metabolic damage. The DNA damage-control biosystem is physiologically operative on both metabolic and radiation damage and effected predominantly by free radicals. The DNA damage-control biosystem is suppressed by high dose and stimulated by low-dose radiation. The hormetic effect of low-dose radiation may be explained by its increase of biosystem efficiency. Improved DNA damage control reduces persistent mis- or unrepaired DNA damage i.e., the number of mutations that accumulate during a lifetime. This progressive accumulation of gene mutations in stem cells is associated with decreasing DNA damage control, aging, and malignancy. Recognition of the positive health effects produced by adaptive responses to low-dose radiation would result in a realistic assessment of the environmental risk of radiation. — *Environ Health Perspect* 106(Suppl 1):363–368 (1998). *http://ehpnet1.niehs.nih.gov/1998/Suppl-1/363-368pollycove/abstract.html*

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The best scientific evidence of human radiation effects initially came from epidemiologic studies of atomic bomb survivors in Hiroshima and Nagasaki. Although no evidence of genetic effects has been found, these studies showed a roughly linear relationship between the induction of cancer and extremely high dose-rate single high doses of atomic bomb radiation. This was consistent with the knowledge that ionizing radiation can damage DNA in linear proportion to high-dose exposures and thus produce gene mutations known to be associated with cancer. In the absence of comparable low-dose effects it was prudent to propose tentatively the no-threshold hypothesis that extrapolates linearly from

effects observed at high doses to the same effects at very low doses. It was accepted in 1959 by the International Commission on Radiological Protection (*1*) then adopted by national radiation protection organizations to formulate regulations for the protection of occupationally exposed workers and the public (*2*).

The hypothesis that all radiation is harmful in linear proportion to the dose is the principle used for collective dose calculations of the number of deaths produced by any radiation, natural or generated, no matter how small. The National Council on Radiation Protection and Measurements (NCRP) Report 121, *Principles and Application of Collective Dose in Radiation*

Protection (*3*), summarizes the basis for adherence to linearity of radiation health effects:

Taken as a whole, the body of evidence from both laboratory animals and human studies allows a presumption of a linear no threshold response at low doses and low-dose rates, for both mutations and carcinogenesis. Therefore, from the point of view of the scientific bases of collective doses for radiation protection purposes, it is prudent to assume the effect per unit dose in the low-dose region following single acute exposures or low-dose fractions is a linear response. There are exceptions to this general rule of no threshold, including the induction of bone tumors in both laboratory animals and in some human studies due to incorporated radionuclides, where there is clearly evidence for an apparent threshold.

However, few experimental studies, and essentially no human data, can be said to prove or even to provide direct support for the concept of collective dose with its implicit uncertainties of nonthreshold linearity and dose-rate independence with respect to risk. The best that can be said is that most [sic] studies do not provide quantitative data that, with statistical significance, contradict the concept of collective dose.

Ultimately, confidence in the linear no threshold dose–response relationship at low doses is based on our understanding of the basic mechanisms involved. Genetic effects may result from a gene mutation, or a chromosome aberration. The activation of a dominant acting oncogene is frequently associated with leukemias and lymphomas, while the loss of suppressor genes appears to be more frequently associated with solid tumors. It is conceptually possible, but with a vanishing small probability, that any of these effects could result from the passage of a single charged particle, causing damage to DNA that could be expressed as a mutation or small deletion. It is a result of this type of reasoning that a linear nonthreshold dose–response relationship cannot be excluded. It is this presumption, based on biophysical concepts, which provides a basis for the use of collective dose in radiation protection activities (*3*).

The NCRP report (*3*) summarizes that although some studies "provide quantitative data that, with statistical significance, contradict the concept of collective

dose....Ultimately, confidence in the linear no threshold dose–response relationship at low doses [linear nonthreshold hypothesis (LNT)] is based on our understanding of the basic mechanisms involved." This paper will examine current understanding of the basic biologic mechanisms involved in the LNT and present some of the statistically significant epidemiologic data that contradicts the LNT. Recent biologic data will be examined; they also contradict "the presumption, based on biophysical concepts, which provides a basis for the use of collective dose in radiation protection activities (3)."

Increased longevity and decreased cancer death rates have been observed in populations exposed to high natural background radiation and reported for several decades. These observations contradict the LNT, the radiation paradigm that all radiation including that of natural background is harmful in linear proportion to the dose. Established radiation authorities consider such observations spurious or inconclusive because of unreliable public health data or undetermined confounding factors such as smoking, income, education, medical care, population density, pollution of air, water, and food, and other socioeconomic variables. Recently, however, the following statistically significant controlled epidemiologic studies (4–13) have demonstrated that exposure to low or intermediate levels of radiation are associated with positive health effects.

In his current review of hormesis (4) Z. Jaworowski, past chairman of the United Nations Scientific Community on the Effects of Atomic Radiation (UNSCEAR), cites recent data showing hormetic effects in humans from the former Soviet Union. After high radiation exposure from a thermal explosion in 1957, 7852 persons living in 22 villages in the Eastern Ural mountains were divided into three exposure groups averaging 49.6, 12.0, and 4.0 cGy and followed for 30 years. Tumor-related mortality was 28, 39, and 27% lower in the 49.6, 12.0, and 4.0 cGy groups, respectively, than in the nonirradiated control population in the same region. In the 49.6 and 12.0 cGy groups the difference from the controls was statistically significant (Figure 1). Epidemiologic studies showing beneficial effects of low doses of radiation in atomic bomb survivors and other populations were reviewed by S. Kondo (Figure 2) (5). Included in Kondo's review are the apparently beneficial effects of low doses of external γ-rays on the life span of radium-dial painters and the significantly

lower mortality from cancers at all sites of residents of Misasa, Japan an urban area with radon spas, than of residents of the suburbs of Misasa (Figure 3).

These beneficial effects are consistent with findings of B.L. Cohen (6), which relate the incidence of lung cancer to radon exposure in nearly 90% of the population of the United States. The 1601 counties selected for adequate permanence of residence provide a high-power statistical analysis. After applying the Committee on the Biological Effects of Ionizing Radiation (BEIR) IV 1988 report (7) correction for variations in smoking frequency, the

Cohen study (6) shows a strong tendency for lung cancer mortality to decrease with increasing mean radon level in homes. This finding is in sharp contrast to the BEIR IV theoretical increased mortality derived by linear nonthreshold extrapolation of effects in uranium miners exposed to high radon concentrations (7). The discrepancy between theoretical and measured slopes is 20 SD (Figure 4). Rigorous statistical analysis of 54 socioeconomic, 7 altitude and weather, and multiple geographic variables as possible confounding factors both singly and in combination demonstrates no significant decrease in the discrepancy. The
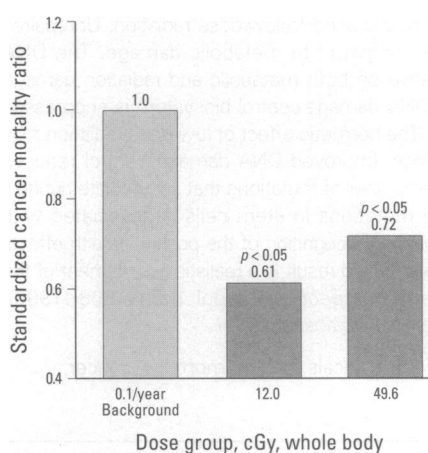

Figure 1. Standardized cancer mortality ratio in three exposure groups followed for 30 years after a thermal explosion. Adapted from Jaworowski (4).
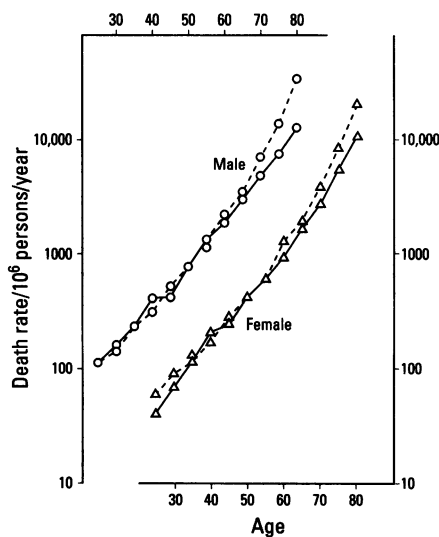
Figure 2. The higher death rate after 55 years old (dotted line) corresponds to the people living in Nagasaki who were not exposed to the atomic bomb. Lower death rate after 55 years old (solid line) corresponds to atomic bomb survivors. Adapted from Mine et al. (30).
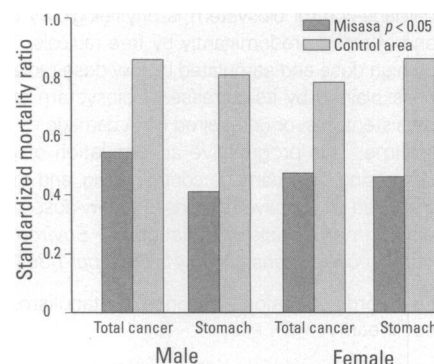
Figure 3. Standardized mortality ratios of populations continually exposed to high (Misasa radium springs) and low (control area) air concentrations of radon. Adapted from Kondo (5).
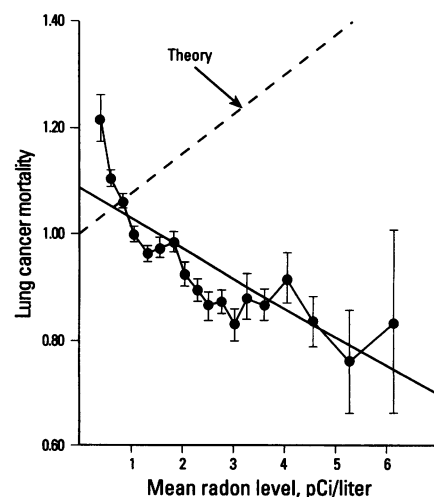
Figure 4. Lung cancer mortality rates corrected for smoking compared with mean home radon levels by U.S. county and comparison with BEIR IV linear model (7). Observed mortality risk is 1.00 at 1.7 pCi/liter, the average U.S. residential radon level. Adapted from Cohen (6).

multiple independent requirements that a possible unknown confounding factor must make its existence highly improbable. A reasonable explanation is that stimulated biologic mechanisms more than compensate for the radiation insult and are protective against cancer in a low-dose, low-dose-rate range.

The 13-year U.S. Nuclear Shipyard Workers Study (NSWS) of the health effects of low-dose radiation was performed by Matanoski (8) and reported in UNSCEAR 1994 (9). A.C. Upton, who concurrently chaired the National Academy of Sciences BEIR V Committee on *Health Effects of*

Exposure to Low Levels of Ionizing Radiation (10), chaired the technical advisory panel that advised on the research and reviewed results of the NSWS.

The results of the NSWS (9) contradict the conclusions of the BEIR V report (10) that small amounts of radiation have risk (the LNT). From the database of almost 700,000 shipyard workers, including about 108,000 nuclear workers, three study groups were selected: a) 28,542 nuclear workers with working lifetime doses ≥ 5 mSv (many of them received doses well in excess of 50 mSv); b) 10,462 nuclear workers with doses < 5 mSv; and (c) 33,352 nonnuclear

workers. Deaths in each of the groups were classified as attributable to leukemia, lymphatic and hematopoietic cancers, mesothelioma, lung cancer, or all causes. The results demonstrated a statistically significant decrease in the standardized mortality ratio (SMR) for the two groups of nuclear workers for death from all causes compared with the nonnuclear workers. For the ≥ 5 mSv group of nuclear workers, the highly significant risk decrease to 0.76 of the SMR for death from all causes, 16 SD below 1.00, is inconsistent with and not explained by the healthy worker effect (Figure 5) (9). The SMR of these nuclear workers for leukemia and lymphatic and hematopoietic cancers were also decreased, but not statistically significant. The nonnuclear and nuclear workers were similarly selected for employment, were afforded the same health care thereafter, performed the same type of work except for exposure to ^{60}Co γ-radiation, and had a similar median age of entry into employment of approximately 34 years. This provides high statistical evidence that low levels of ionizing radiation are associated with risk decrements.

Upton (11) considers the three-country low-dose radiation and cancer study of Cardis et al. (12) the best occupational study of nuclear workers (Figure 6). Cardis et al. (12) concluded "There was no evidence of an association between radiation dose and mortality from all causes or from all cancers. Mortality from leukemia, excluding chronic lymphocytic leukemia (CLL) ... was significantly associated with cumulative external radiation dose (one-sided p-value = 0.046: 119 deaths)." In reference to the statistical methods used, the authors stated: "As there was no reason to suspect that exposure to radiation would be associated with a decrease in risk of any specific type of cancer, one sided tests are presented throughout" (12). The authors' analysis of the 119 deaths from all leukemias except CLL excluded 86 deaths in dose categories 1, 3, 4, and 6, in which there were fewer deaths than expected. Trend analysis of the remaining 33 deaths in dose categories 2, 5, and 7 for estimated $p = 0.046$ was obtained "using computer simulations based on 5000 samples, rather than the normal approximation" (12) (Figure 6).

The Canadian breast cancer fluoroscopy study reported the observations of the mortality from breast cancer in a cohort of 31,710 women who had been examined by multiple fluoroscopy between 1930 and 1952 (13). The observed rates of mortality are related to breast radiation doses and
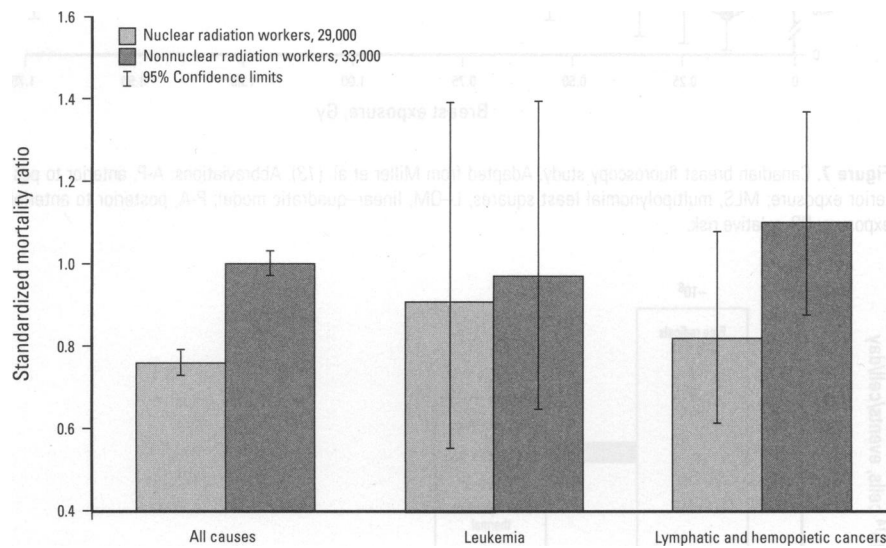
Figure 5. Standardized mortality ratios for selected causes of death among shipyard workers in the United States. Nuclear worker cumulative dose: 0.5 to > 40cSv (rem). Adapted from Matanoski (8).
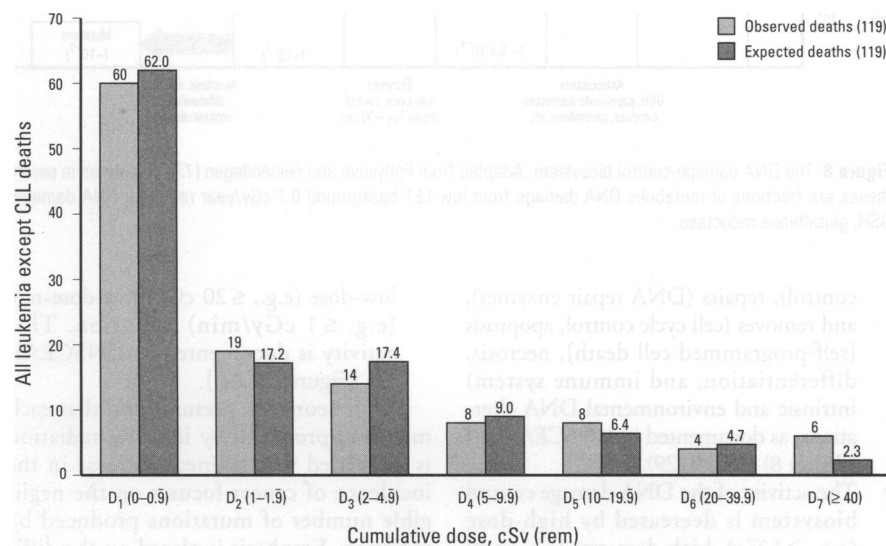
**Figure 6.** Cancer mortality among nuclear industry workers in three countries. Adapted from Cardis et al. (12). Data from D₁, D₃, D₄, and D₆ were excluded (86 of 119 deaths). Data from D₂, D₅, and D₇ were included (33 of 119 deaths).

presented only in tabular form. Miller et al. (*13*) compared linear and linear–quadratic dose–response models fit to the data and conclude "that the most appropriate form of dose–response relations is a simple linear one, with different slopes for Nova Scotia and the other provinces." On the basis of this linear model, which excludes the data with the highest confidence limits (Figure 7), the authors predicted the lifetime excess risk of death from breast cancer after a single exposure to 1 cGy (1 r) at age 30 to be approximately 60 per 1 million women or 900 per 1 million women exposed to 15 cGy. The observed data, however, demonstrate with high statistical confidence a reduction of the relative risk of breast cancer to 0.66 ($p = 0.05$) at 15 r and 0.85 ($p = 0.32$) at 25 r. The study predicted that a dose of 0.15 Gy would be associated with 7000 fewer deaths in these 1 million women. L.S. Taylor, past president of the NCRP, considered application of LNT for calculations of collective dose as "deeply immoral uses of our scientific heritage" (*14*).

During the past decade rapid advances in our knowledge of molecular biology and cell function have enabled us to understand why low-dose, low-dose-rate radiation is associated with positive health effects despite the carcinogenic effect of high-dose, high-dose-rate radiation. Our understanding is based on three cellular molecular biology observations:

- The high background of intrinsic potential mutations (DNA alterations, 10^6/cell/day) produced by reactive oxygen species (ROS): free radicals and reactive oxygen metabolites and thermal instability compared to 20 potential mutations produced predominantly by the free radicals generated by 1 cGy of low linear energy transfer (LET) radiation (*15–17*). In addition, because of fundamental limitations on the accuracy of DNA replication and repair, every class of genes is likely to undergo 400,000 mutations/day in each person (*18*). The comparatively rare mutations (persistent mis- or unrepaired DNA alterations) produced by low-LET low-dose radiation (averaging 10^{-7}/cell/day for 0.1 cGy/year background) are similar to the 1/cell/day intrinsic mutations occurring in an environment free of mutagens (Figure 8) (*17*).

- The presence of an active DNA damage control biosystem that, until declining with age, effectively prevents (antioxidant detoxification of ROS and cell cycle
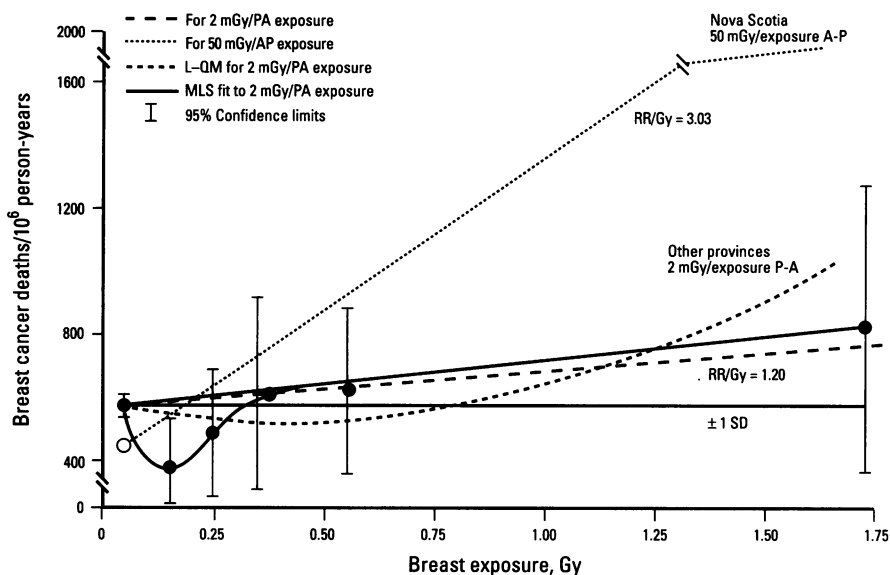
Figure 7. Canadian breast fluoroscopy study. Adapted from Miller et al. (*13*). Abbreviations: A-P, anterior to posterior exposure; MLS, multipolynomial least squares; L–QM, linear–quadratic model; P-A, posterior to anterior exposure; RR, relative risk.
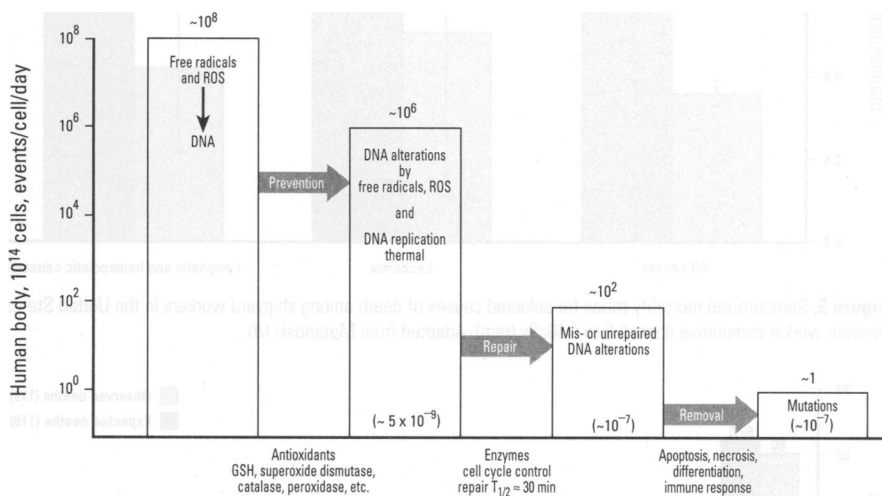

Figure 8. The DNA damage-control biosystem. Adapted from Pollycove and Feinendegen (*17*). Quantities in parentheses are fractions of metabolic DNA damage from low-LET background 0.1 cGy/year radiation DNA damage. GSH, glutathione reductase.

control), repairs (DNA repair enzymes), and removes (cell cycle control, apoptosis [self-programmed cell death], necrosis, differentiation, and immune system) intrinsic and environmental DNA alterations, as documented in UNSCEAR (*9*) (Figure 8) (*17,19–29*).

- The activity of the DNA damage control biosystem is decreased by high-dose (e.g., ≥ 1 Gy), high-dose-rate (e.g., ≥ 20 cGy/min) radiation, but adaptively responds with increased activity to

low-dose (e.g., ≤ 20 cGy) low-dose-rate (e.g. ≤ 1 cGy/min) radiation. This activity is documented in UNSCEAR (*9*) [Figure 9; (*22*)].
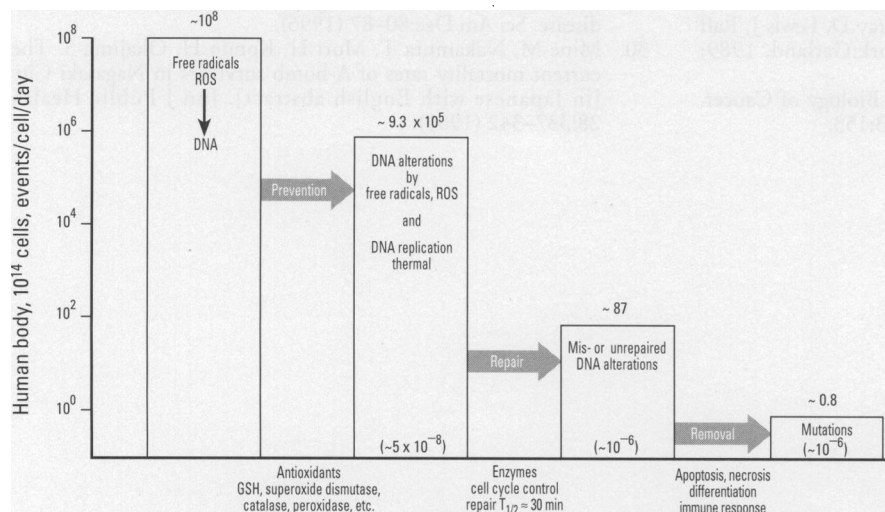
The theoretical presumption that each mutation produced by ionizing radiation is associated with a linear increase in the incidence of cancer focuses on the negligible number of mutations produced by radiation. Emphasis is placed on the difficulty of repairing relatively rare double strand breaks [0.4/cell/cGy low-LET
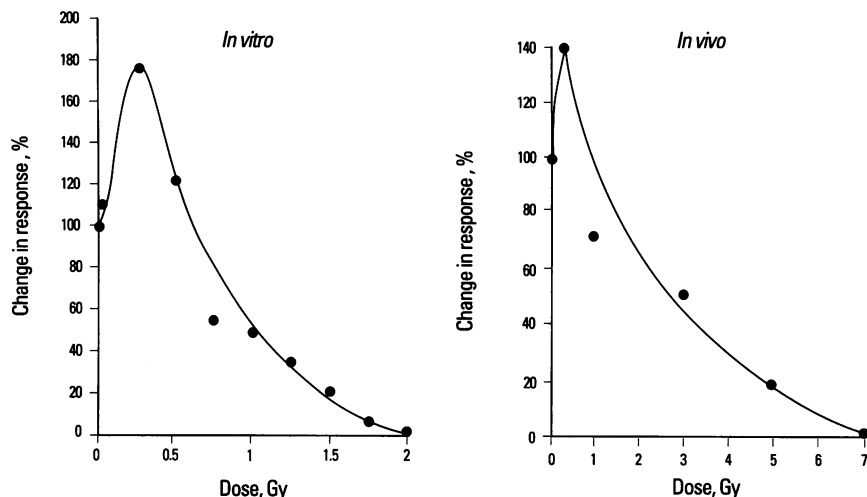
Figure 9. Immune system response to radiation. Mouse splenic cells primed with antigenic sheep red blood cells. Adapted from Makinodan and James (20).

Figure 10. The DNA damage-control biosystem response to high background radiation. Adapted from Pollycove and Feinendegen (15). Quantities in parentheses are fractions of metabolic DNA damage from low-LET background 1 cGy/year radiation DNA damage.

radiation (16)] and if unrepaired, ignoring their removal each day together with trillions of other intrinsic and environmental unrepaired DNA defects by the adaptive responses of the DNA damage-control biosystem. The high number of intrinsic mutations are disregarded, as are the adaptive responses to radiation that until diminished with age effectively prevent, repair, and remove both intrinsic and environmental DNA alterations. Contrary to the increased risks associated with their suppression by high-dose radiation, these adaptive responses are stimulated by low-dose radiation to function even more effectively and decrease the risks of mortality and cancer (Figures 9, 10) (9,17,22). "In a lifetime, every single gene is likely to have undergone mutation on about 10^{10} separate occasions in any individual human being"(18). These observations of fundamental biologic cellular functions contradict the theoretical presumption based on biophysical concepts and exclude an LNT dose–response relationship.

Recognition of the positive health effects produced by adaptive responses to low-level radiation would result in a realistic assessment of the environmental risk of radiation. There is no statistically significant human low-dose radiation data that supports the LNT hypothesis (1). Instead of adhering to nonscientific influences on radiation protection standards and practice (14) that impair health care and research and waste many billions of dollars annually for protection against hypothetical risks of low-level radiation exposure, this resource could be used productively for effective health measures and many other benefits.

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