Written contribution to the debate

Molecular biology, epidemiology, and the demise of the linear no-threshold (LNT) hypothesis

Biologie moléculaire, épidémiologie et la fin de la relation linéaire sans seuil

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Abstract – The prime concern of radiation protection policy since 1959 has been protecting DNA from damage. The 1995 NCRP Report 121 on collective dose states that since no human data provides direct support for the linear no threshold hypothesis (LNT), and some studies provide quantitative data that, with statistical significance, contradict LNT, ultimately, 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. Current understanding of the basic molecular biologic mechanisms involved and recent data are examined before presenting several statistically significant epidemiologic studies that contradict the LNT hypothesis. Over eons of time a complex biosystem evolved to control the DNA alterations (oxidative adducts) produced by about 10^{10} free radicals/cell/d derived from 2–3 % of all metabolized oxygen. Antioxidant prevention, enzymatic repair of DNA damage, and removal of persistent DNA alterations by apoptosis, differentiation, necrosis, and the immune system, sequentially reduce DNA damage from about 10^6 DNA alterations/cell/d to about 1 mutation/cell/d. These mutations accumulate in stem cells during a lifetime with progressive DNA damage-control impairment associated with aging and malignant growth. A comparatively negligible number of mutations, an average of about 10^{-7} mutations/cell/d, is produced by low LET radiation background of 0.1 cGy/y. The remarkable efficiency of this biosystem is increased by the adaptive responses to low-dose ionizing radiation. Each of the sequential functions that prevent, repair, and remove DNA damage are adaptively stimulated by low-dose ionizing radiation in contrast to their impairment by high-dose radiation. The biologic effect of radiation is not determined by the number of mutations it creates, but by its effect on the biosystem that controls the relentless enormous burden of oxidative DNA damage. At low doses, radiation stimulates this biosystem with consequent significant decrease of metabolic mutations. Low-dose stimulation of the immune system may not only prevent cancer by increasing removal of premalignant or malignant cells with persistent DNA damage, but used in human radioimmunotherapy may also completely remove malignant tumors with metastases. The reduction of gene mutations in response to low-dose radiation provides a biological explanation of the statistically significant observations of mortality and cancer mortality risk decrements, and contradicts the biophysical concept of the basic mechanisms upon which, ultimately, the NCRPs confidence in the LNT hypothesis is based. (© Académie des sciences / Elsevier, Paris.)

1. Background

The main initial scientific evidence of human ionizing radiation effects came from epidemiological lifespan studies (LSS) of atomic bomb survivors in Hiroshima and Nagasaki. These early studies showed a roughly linear relationship between cancer mortality and high doses of very high-dose rate radiation. This was consistent with the knowledge that ionizing radiation can damage DNA and produce gene mutations in linear proportion to dose (*figure 1*). The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) then tentatively proposed the LNT hypothesis in 1958 [1]. It seemed prudent in 1959 for the International Commission on Radiation Protection (ICRP) [2] to adopt the LNT hypothesis that extrapolates linearly from effects observed at high doses to the same effects at low doses, even those approaching zero.

The National Council on Radiation Protection and Measurements NCRP Report 121 on Collective Dose [3] (11/30/95) summarizes the current status of LNT theory:

"...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 no threshold, 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.... [Cancer] 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 no threshold 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".

2. Antimutagenic DNA damage-control biosystem

This biophysical presumption, despite the lack of any human data, assumes that all radiation doses are harmful in linear proportion to dose and is used to calculate the number of cancer deaths in populations from exposure to minute fractions of background radiation. Many people have been informed and do believe that exposure to radiation in any dose causes cancer in our bodies and genetic changes in our children. Currently, a new understanding of the effects of radiation on organisms has developed from rapid advances in molecular biology over the past two decades. We now understand why low-level radiation is beneficial. These biological studies

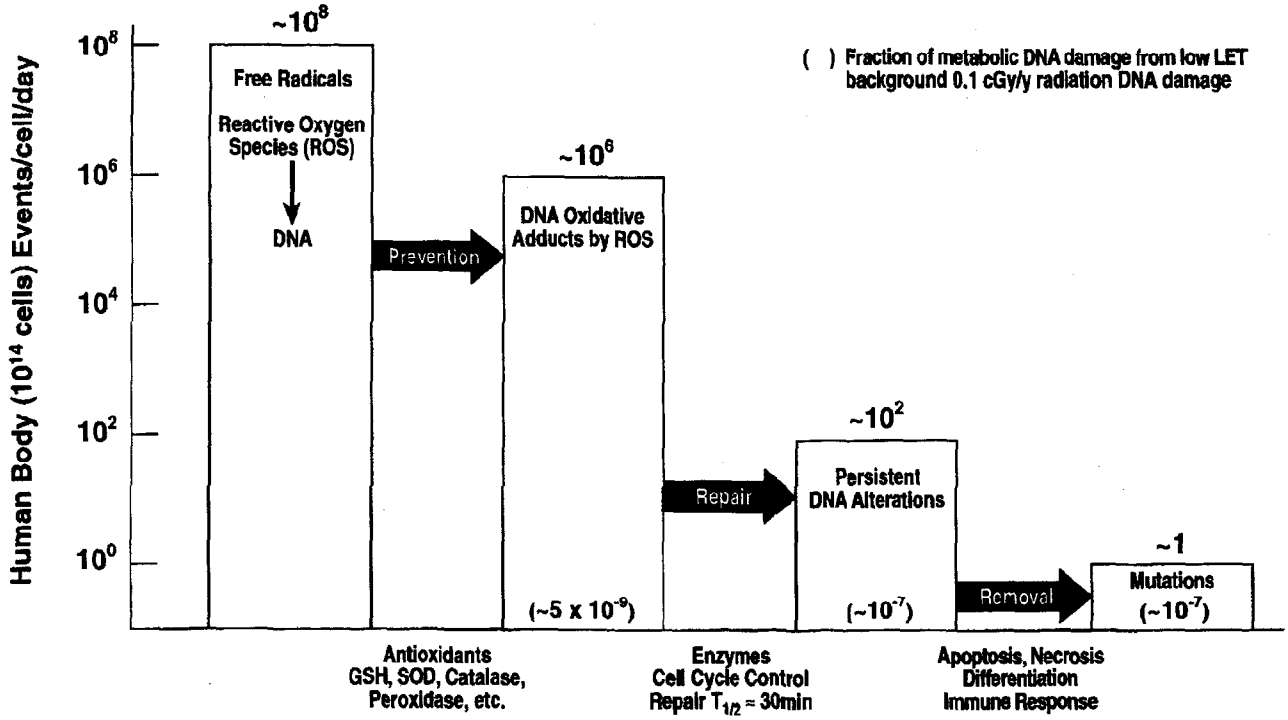

Figure 1. The antimutagenic DNA damage-control biosystem.
Estimates based on data in literature (Pollycove M., Feinendegen L.E.).

have confirmed that free radicals produced by the normal metabolism of oxygen generate a very high background of oxidative DNA damage in every cell every day. However, as Michael Bishop, Nobel Laureate discoverer of the oncogene, states [3], "A single mutation is not enough to cause cancer. In a lifetime, every single gene is likely to have undergone mutation on about 10^{10} separate occasions in any individual human being. The problem of cancer seems to be not why it occurs, but why it occurs so infrequently.

Evidently, the survival of mammals must depend on some form of double – or more than double – insurance in the mechanisms that protect us from being overrun by mutant clones of cells that have a selective advantage over our healthy normal cells: if a single mutation in some particular gene were enough to convert a typical healthy cell into a cancer cell, we would not be viable organisms."

Our survival depends upon the control of this enormous damage by a highly efficient antimutagenic biosystem that prevents, repairs, and removes almost all of these alterations of DNA (*figure 1*) [4].

DNA alterations which are not eliminated by this biosystem are residual mutations that gradually accumulate during a lifetime in stem cells which remain quiescent or may divide and replicate. This accumulation of residual mutations is associated with decreased biosystem efficiency, aging, and the associated development of cancer with the 3rd to 5th power of age [5–15]. Cancer is the cause of death in approximately 25 % of our population. In comparison, the rate of mutations produced by background ionizing radiation, also generated by free radicals of oxygen, is quantitatively negligible: 10 million times lower than the normal metabolic rate of oxidative damage (*figure 1*) [4].

Nevertheless, ionizing radiation has a very significant effect on our damage-control biosystem as a result of spatial and temporal differences in the distribution of the DNA alterations it produces [16, 17, 23]. High-dose radiation suppresses the activity of this biosystem with consequent increased metabolic mutations and cancer mortality. Low-dose radiation, on the other hand, stimulates increased biosystem activity that produces fewer persistent metabolic alterations and mutations with lower cancer mortality and increased longevity [16–21]. The efficiency of the DNA damage-control biosystem is increased by adaptive responses to low-dose radiation of DNA damage prevention, repair, and removal [22]. This is well documented in UNSCEAR 1994 [23]. Very recently Le et al. at the University of Alberta reported that 25 cGy accelerates enzymatic repair of oxidative DNA damage [24]. In vivo antioxidant and immune system responses of 133 and 140 %, respectively, to low-dose radiation are reported [18, 20].

A ten-fold increase of annual background radiation stimulates overall biosystem activity by approximately 20 %, producing a significant decrease in the metabolic rate of mutations and corresponding decreases of cancer mortality and mortality from all causes (*figure 2*).

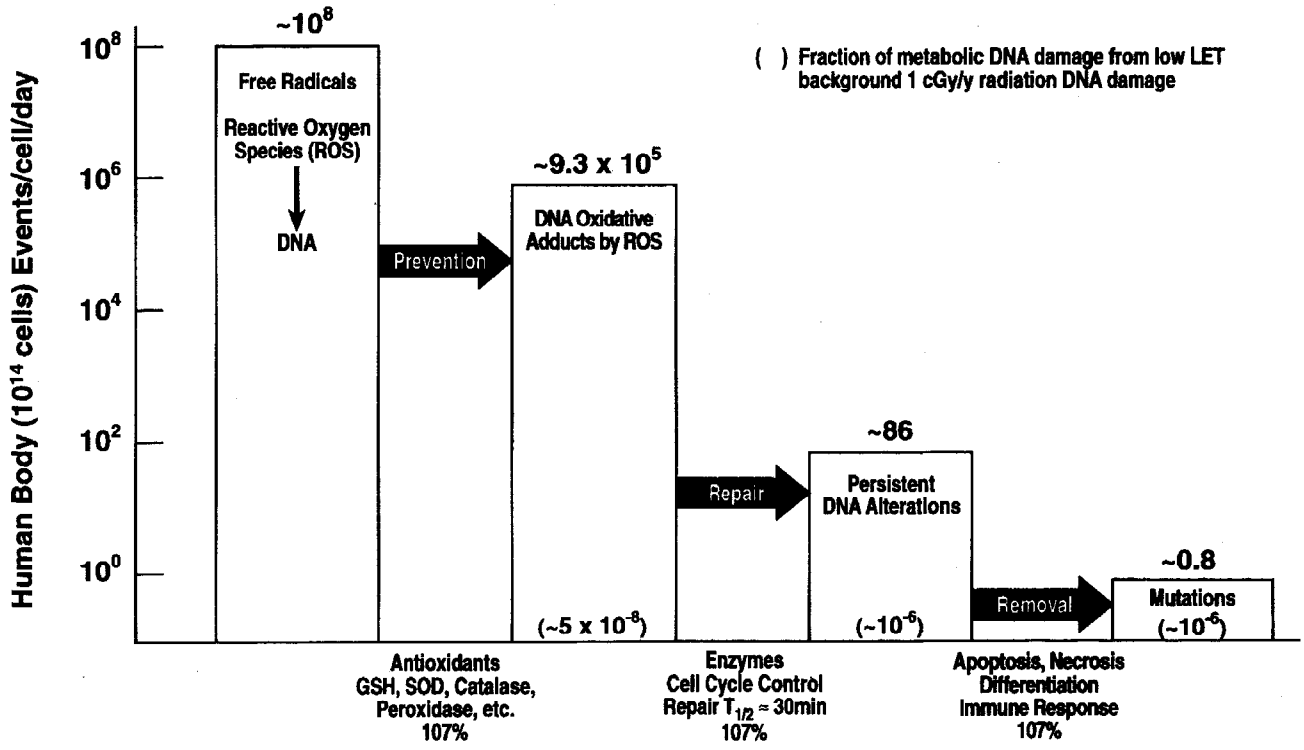

Figure 2. The antimutagenic DNA damage-control biosystem response to high background radiation = 120 %.
Estimates based on data in literature (Pollycove M., Feinendegen L.E.).

The predictions of this hormesis model have been confirmed by many observations that contradict the LNT model prediction of increased cancer mortality in proportion to the amount of low-dose radiation. For several decades increased longevity and decreased cancer mortality have been reported in all populations exposed to high background radiation. Established radiation protection authorities consider such observations to be spurious or inconclusive because of unreliable public health data or undetermined confounding factors such as pollution of air, water and food, smoking, income, education, medical care, population density, and other socioeconomic variables. Recently, however, several epidemiologic statistically significant ($P < 0.05$) well-controlled studies have demonstrated that exposure to low or intermediate levels of radiation are associated with positive health effects.

3. Epidemiologic studies

Dr Zbigniew Jaworowski, past chairman of UNSCEAR, in his current review of hormesis cites recent data showing hormetic effects in humans from the former Soviet Union [25]. After radiation exposure from a thermal explosion in 1957, 7 852 persons living in 22 villages in the Eastern Urals 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, 29 and 27 % lower in the 49.6, 12.00 and 4.0 cGy groups, respectively, than in the non-irradiated control population in the same region. In the 49.6 and 12.0 cGy groups the difference from the controls was statistically significant. Epidemiologic studies showing beneficial effects of low doses of radiation in atomic bomb survivors [26] and other populations were reviewed by Sohei Kondo, Professor of Radiation Biology, Atomic Energy Research Institute, Kinki University, Osaka, Japan [27]. Included are the apparently beneficial effects of low doses of external gamma rays on the lifespan of radium-dial painters and the significantly lower mortality from cancers at all sites of residents of Misasa, an urban area with radon spas, than residents of the suburbs of Misasa.

These beneficial effects are consistent with the findings of B.L. Cohen, Professor of Physics, University of Pittsburgh, that relate the incidence of lung cancer to radon exposure in nearly 90 % of the population of the United States [28]. The 1 601 counties selected for adequate permanence of residence provide extremely high-power statistical analysis. After applying the BEIR IV [29] correction for variations in smoking frequency, the study shows a very strong tendency for lung cancer mortality to decrease with increasing mean radon level in homes, in sharp contrast to the BEIR IV theoretical increased mortality derived by linear no threshold extrapolation of effects in uranium miners exposed to very high radon concentrations [29]. The discrepancy between theoretical and measured slopes is 20 standard deviations. Rigorous statistical analysis of 54 socioeconomic, seven physical, and multiple geographic variables as possible confounding factors, both single and in combination, demonstrates no significant decrease in the discrepancy. The multiple independent requirements that a possible unknown confounding factor must meet make its existence highly improbable. A reasonable explanation is that stimulated biological mechanisms more than compensate for the radiation 'insult' and are protective against cancer in a low-dose, low-dose-rate range.

The 13-year US Nuclear Shipyard Workers study of the health effects of low-dose radiation was performed by the Johns Hopkins Department of Epidemiology, School of Public Health and Hygiene, reported to the Department of Energy in 1991 [30] and reported in UNSCEAR 1994 [23]. Professor Arthur C. Upton, who concurrently chaired the NAS BEIR V Committee on 'Health Effects of Exposure to Low Levels of Ionizing Radiation [31]', chaired the Technical Advisory Panel that advised on the research and reviewed results.

The results of this study contradict the conclusions of the BEIR V report [31] that small amounts of radiation have risk – the LNT hypothesis. From the database of almost 700 000 shipyard workers, including about 108 000 nuclear workers, three closely matched study groups were selected, consisting of 28 542 nuclear workers with working lifetime doses ≤ 5 mSv (many received doses well in excess of 50 mSv), 10 462 nuclear workers with doses < 5 mSv and 33 352 non-nuclear workers. Deaths in each of the groups were classified as due to: all causes, leukemia, lymphatic and hematopoietic cancers, mesothelioma, and lung cancer. The results demonstrated a statistically significant decrease in the standardized mortality ratio for the two groups of nuclear workers for 'death from all causes' compared with the non-nuclear workers. For the ≤ 5 mSv group of nuclear workers, the highly significant risk decrement to 0.76, 16 standard deviations below 1.00, of the standard mortality ratio for death from all causes is inconsistent with the LNT hypothesis and does not appear to be explainable by the healthy worker effect. The non-nuclear workers and the nuclear workers were similarly selected for employment, were afforded the same health care thereafter, and performed the identical type of work, except for exposure to ^{60}Co gamma radiation, with a similar median age of entry into employment of about 34 years. This provides evidence with extremely high statistical power that low levels of ionizing radiation are associated with decreased risks.

The Canadian Breast Cancer Fluoroscopy Study [32] reports 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. The observed rates of mortality are related to breast radiation doses and presented only in tabular form. The authors compare linear and linear–quadratic dose–

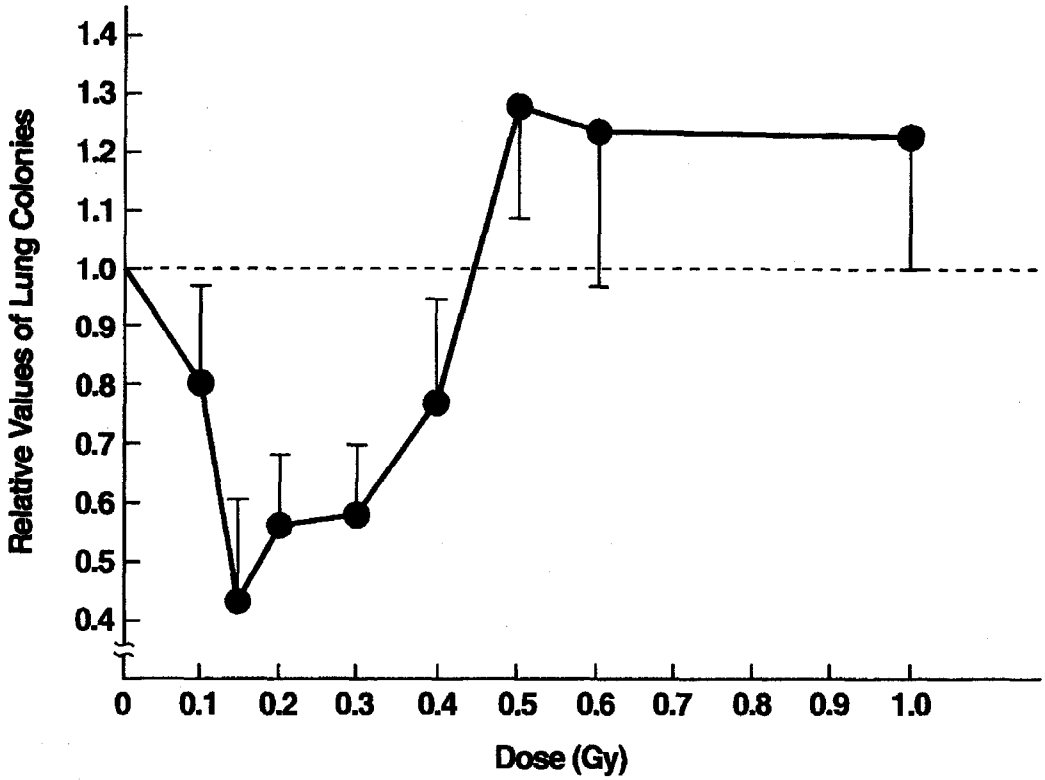

Figure 3. Spontaneous lung metastasis after total body irradiation (TBI) of mice.
TBI given 15 d after tumor cell transplantation into groin. Adapted from Sakamoto et al., J. Jpn. Soc. Radiol. Oncol. 9 (1997) 161–175.

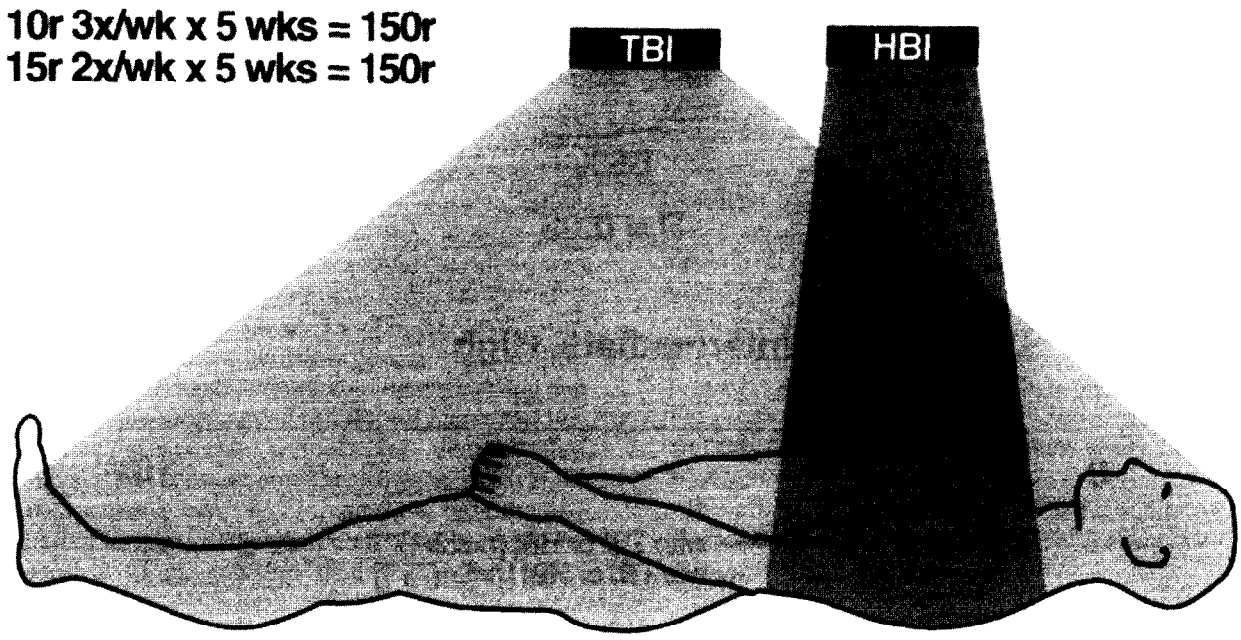

Figure 4. Treatment of patients with non-Hodgkins lymphoma with half (HBI) or total (TBI) body irradiation.
Adapted from Sakamoto et al., J. Jpn. Soc. Radiol. Oncol. 9 (1997) 161–175.

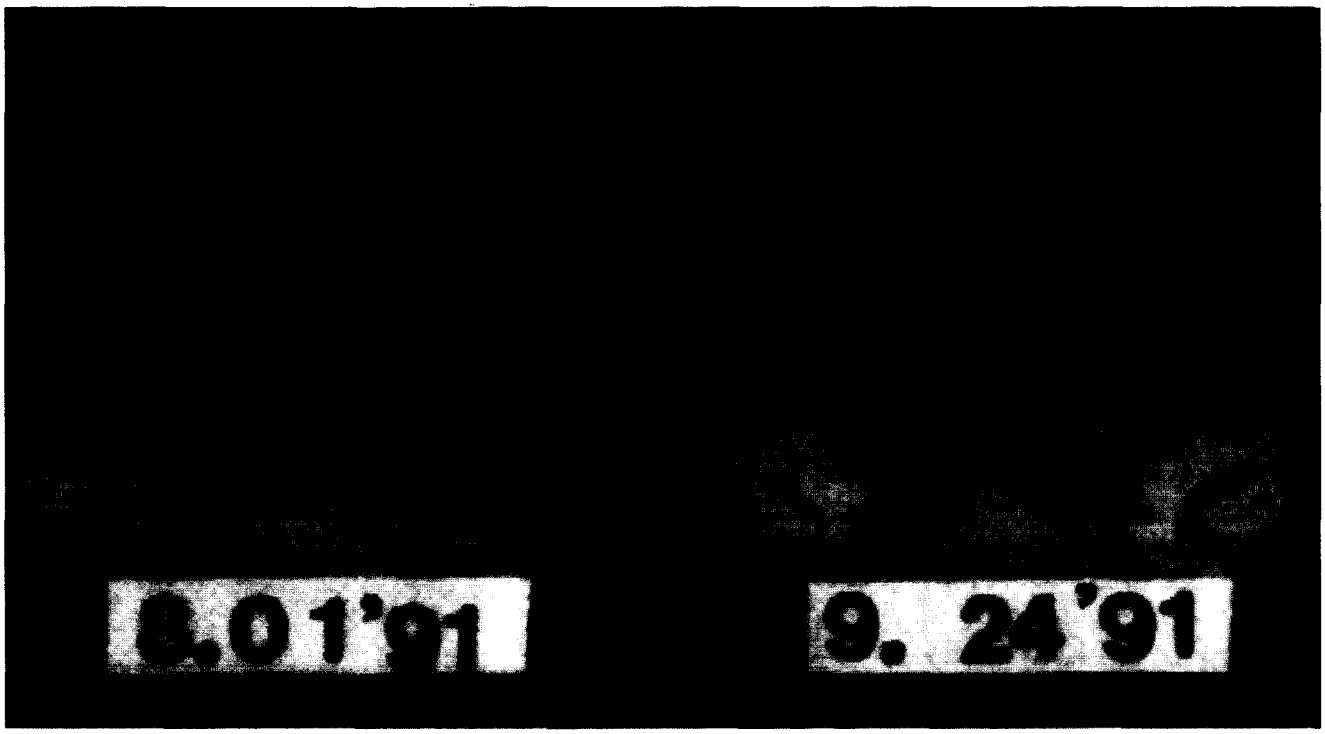

Figure 5. CT (computerized tomographic) scan of upper nasal cavity before and after half body irradiation (HBI). Nasal tumor, through completely outside HBI field, completely disappeared after low-dose HBI.

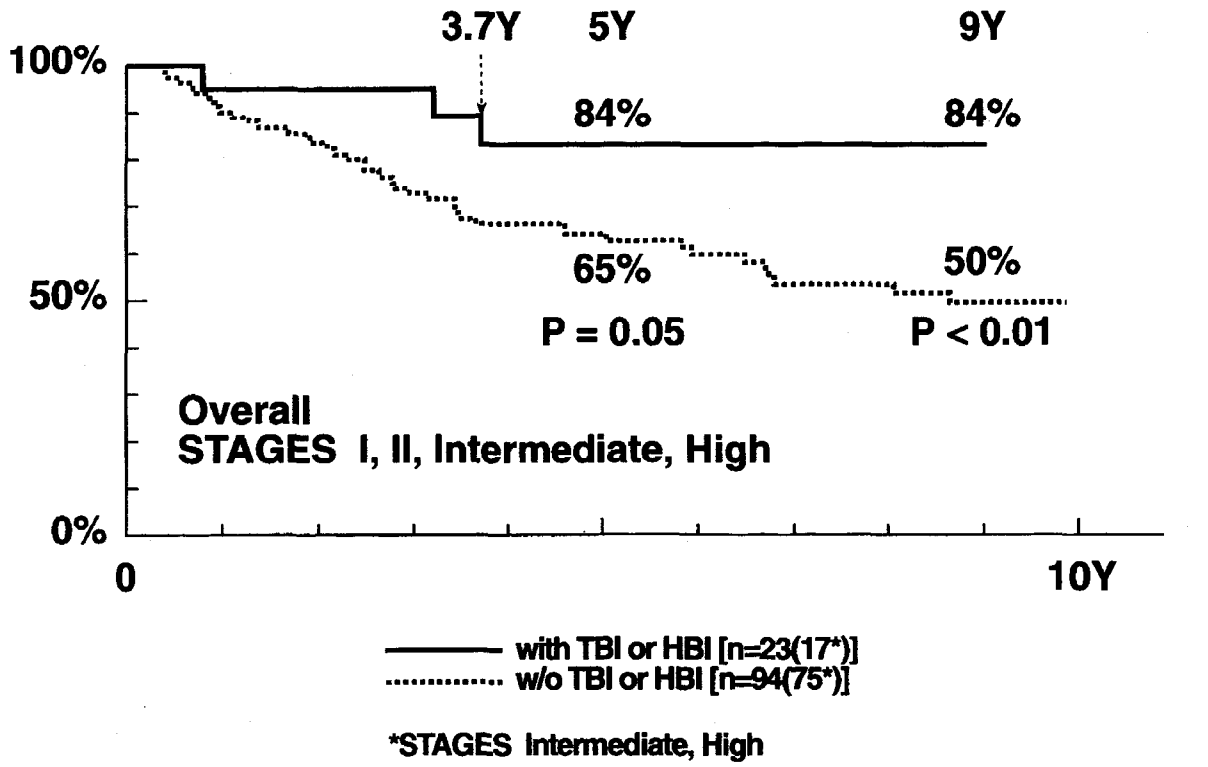

Figure 6. Survival of patients with non-Hodgkins lymphomas with or without low-dose half (HBI) or total (TBI) body irradiation. Adapted from Sakamoto et al., J. Jpn. Soc. Radiol. Oncol. 9 (1997) 161–175.

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 includes only non-significant data and excludes the data with the highest confidence limits, the authors predict the lifetime excess risk of death from breast cancer after a single exposure at age 30 to 1 cGy(1r) to be approximately 60 per million women or 900 per million women exposed to 15 cGy. The observed data, however, demonstrate with high statistical confidence, a reduction of the relative risk of death from breast cancer to 0.66 ($P = 0.05$) at 15 cGy and 0.85 ($P = 0.32$) at 25 cGy. The second author, in his 1996 revision of this study, removed this highly significant contradiction of the LNT hypothesis by lumping all low-dose data into a single 1–49 cGy category [33]. The study actually predicts that a dose of 15 cGy would prevent 7 000 deaths from breast cancer in these million women. Lauriston S. Taylor, past president of the NCRP, considered application of LNT hypothesis for calculations of collective dose as, "deeply immoral uses of our scientific knowledge" [34].

4. Radioimmunotherapy

Low-dose stimulation of the immune system may not only prevent cancer by increasing removal of premalignant or malignant cells with persistent DNA damage, but may also destroy gross cancer growths with metastases (*figure 3*) [35]. Discounted sporadic reports of human total body irradiation (TBI) treatment for cancer were made more than 20 years ago. However, for more than 30 years progressive confirmed immunologic research in mice receiving TBI has demonstrated the effectiveness of murine radioimmunotherapy of cancer. In 1997 Sakamotoet al. at Tohoku University, Sendai, Japan, reported successful treatment of non-Hodgkins lymphoma with total or half body low-dose radiation [35]. Half body irradiation (HBI) of the rib cage area (thorax from xyphoid process to suprasternal notch) was as effective as whole body irradiation (TBI). Fractionated doses of 10 cGy 3×/week or 15 cGy 2×/week were given for 5 weeks for a cumulative dose of 150 cGy (*figure 4*). In some patients tumors completely outside the HBI field disappeared after HBI alone (*figure 5*) [36]. Analysis of peripheral lymphocytes demonstrated immune system stimulation. The 10-year survival of patients receiving only local high-dose radiotherapy and chemotherapy is 50 % compared to 84 % for the 9-year survival of patients (no deaths after 3.7 years) receiving additional low-dose TBI or HBI. ($P < 0.05$, *figure 6*).

5. Conclusion

The biologic effect of radiation is not determined by the number of DNA mutations it creates, but by its effect on the antimutagenic biosystem that controls the relentless enormous burden of oxidative DNA damage. High-dose radiation impairs this antimutagenic biosystem with consequent significant increase of metabolic mutations and corresponding increased risk of cancer mortality. Low-dose radiation stimulates the DNA damage-control biosystem with consequent significant decrease of metabolic mutations (*figure 2*). This reduction of gene mutations in response to low-dose radiation provides a biological explanation of the statistically significant observations of decreased cancer mortality and mortality from all causes and contradicts the biophysical understanding of the basic mechanisms upon which, ultimately, confidence in the LNT hypothesis is based.

Nevertheless, since 1959 the LNT hypothesis has remained the basic principle of all radiation protection policy. This hypothesis is used to generate collective dose calculations of the number of deaths produced by background radiation. The increase of public fear through repeated statements of deaths caused by 'deadly' radiation has engendered an enormous increase in expenditures now required to 'protect' the public from all applications of nuclear technology: medical, research, energy, disposal, and cleanup remediation. These funds are allocated to appointed committees, the research they support, and to multiple environmental and regulatory agencies. The LNT hypothesis and multi-billion dollar radiation activities have now become a symbiotic self-sustaining powerful political and economic force.

Scientific understanding 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. Instead of adhering to non-scientific influences on radiation protection standards and practice [34] that impair health care, research, and other benefits of nuclear technology, and waste many billions of dollars annually for protection against hypothetical risks, these resources could be used productively for effective health measures and many other benefits to society.

This article represents the views of the author and not necessarily those of the US Nuclear Regulatory Commission.

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