

Biologic Responses to Low Doses of Ionizing Radiation: Detriment Versus Hormesis

Part 2. Dose Responses of Organisms

The damage and signaling to cells and tissues with subsequent stimulatory responses induced by low doses of ionizing radiation were reviewed in Part 1 (*J Nucl Med.* 2001;42[7]:17N–27N). In the intact organism, these responses are expressions of complex adaptive systems that maintain homeostatic control essential for survival. The antimutagenic DNA damage-control system is the central component of this homeostatic control. The effect of ionizing radiation on this system and its consequences to the organism are the subjects of this review.

Antimutagenic System Control of Metabolic DNA Damage

Aging, mortality, and cancer mortality are generally accepted to be associated with stem cell accumulation of permanent alterations of DNA (“mutations”) (1–3). These alterations are principally the result of DNA interactions with reactive oxygen species (ROS) produced by free radicals. Over eons of time, a complex DNA damage-control system evolved in aerobic organisms to control the vast number of DNA alterations (oxidative adducts) produced by ROS, generated principally by leakage of free radicals from mitochondrial metabolism of oxygen (4). In humans, about 10^9 free radicals/cell/d are derived from about 0.25% of all metabolized oxygen. In a low background γ radiation area of 1 mGy/y, these are reduced by antioxidants and other intermediate reactions to about 10^6 DNA alterations/cell/d, including approximately 10^{-1} double-strand breaks (DSB), calculated from measurements of steady state alterations and their repair rates (5–7). A complex system of specific enzyme repair mechanisms, with an error rate of 10^{-4} (except for DSB repair error rate of about 10^{-1}), reduce these to about 10^{-2} persistent DNA alterations (8–15). These remaining alterations are subsequently removed with an error rate of nearly 10^{-2} by apoptosis (programmed self-destruction) and immune system surveillance, leaving about one mutation/cell/d (Fig. 1) (16–26).

The estimate of 10^6 endogenous DNA alterations/cell/d is conservative, because it is calculated from ROS DNA damage produced by oxygen metabolism without considering significant contributions from micronutrient deficiencies and environmental toxins (27–30). In comparison, 1 mGy/y background radiation produces two DNA alterations/cell/y, 5×10^{-3} /cell/d including 10^{-4} DSB/cell/d (31). Enzymatic repair of these DSB leaves about 10^{-5} persistent DNA alterations that also are reduced by apoptosis and immune system removal

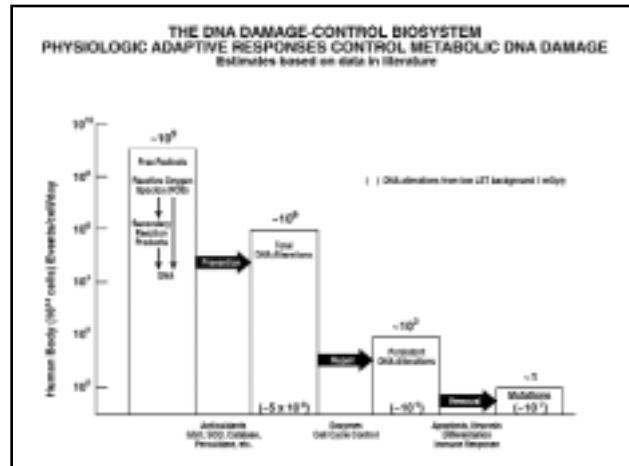


Figure 1. Antimutagenic DNA damage-control biosystem. Estimates based on data in literature.

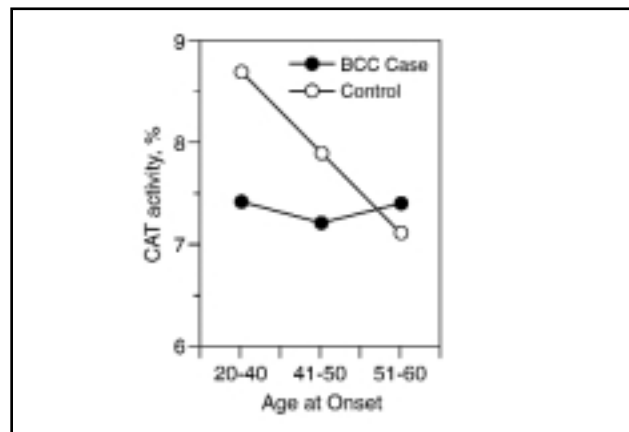


Figure 2. Chloramphenicol acetyl transferase (CAT) activity, a measure of cellular DNA repair capacity, progressively declines with age and correlates inversely with carcinoma. Rarely, young patients with genetic defective DNA repair capacity also develop basal cell cancer (BCC), which is common in the elderly. (Adapted with permission from (40).)

to about 10^{-7} radiation-induced mutations/cell/d (Fig. 1).

DNA alterations that are not eliminated by this biosystem are residual mutations that gradually accumulate during a lifetime in stem cells, at least 30,000 metabolic mutations/stem cell/70 y. This accumulation of residual mutations is associated with decreased DNA damage-control efficiency (Figs. 2 and 3), aging (Fig. 4), and the associated development

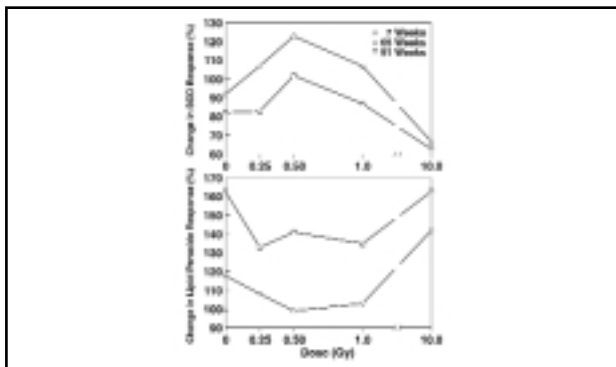


Figure 3. Antioxidant superoxide dismutase (SOD) and lipid peroxide response to age and radiation of rat brain cortex. (Adapted with permission from (44).)

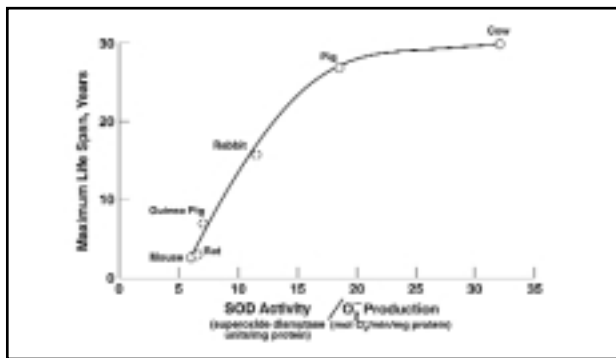


Figure 4. Antioxidant activity, oxygen radicals, and maximum life span. (Adapted with permission from (35).)

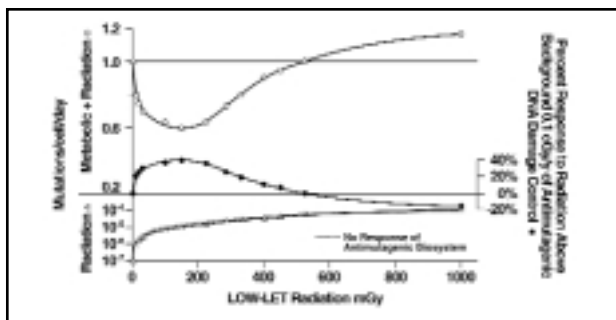


Figure 5. Response of antimutagenic DNA damage-control biosystem and mutations to low linear energy transfer (LET) ionizing radiation.

of cancer to the third to fifth powers of age (32–41). Cancer is the cause of death in approximately 25% of the U.S. population. Mutations produced by background ionizing radiation, also generated largely by oxygen free radicals, are quantitatively negligible.

Biphasic Response to Radiation of the Antimutagenic System

Nevertheless, ionizing radiation has a very significant effect on DNA damage control as a result of spatial and temporal differences in the DNA alterations it produces. High-dose, high-dose-rate radiation suppresses the activity of this bio-

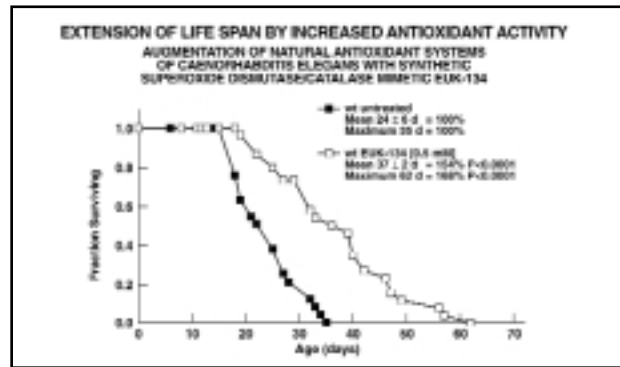


Figure 6. Survival of wild-type (wt) adult worms with and without synthetic superoxide dismutase/catalase mimetic EUK-134 in S medium during culture with *Escherichia coli* as a food source. Shortened 15-day mean survival of mutant *Caenorhabditis elegans* with increased free radical oxidants was increased to normal 25-day mean survival with 0.5 mmol EUK-134 in S medium culture. (Adapted with permission from (48).)

system, with consequent increased mutations and cancer mortality. Low-dose radiation (LDR), on the other hand, stimulates increased antimutagenic biosystem activity that decreases metabolic mutations (Fig. 5), thus lowering cancer mortality and increasing longevity (25,26,42–46). The efficiency of the DNA damage-control biosystem is increased by homeostatic adaptive responses of increased prevention, repair, and removal of DNA damage. This is well documented in the 1994 report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (47). Increased preventive antioxidant activity is associated with increased life span (Figs. 4 and 6), and its response to radiation is biphasic (Fig. 3) (35,44,48). Enzymatic repair of damaged DNA is tripled by exposure to 25 cGy (Fig. 7) (45). Response of immune system removal to radiation is biphasic (Fig. 8) (25,26). The biphasic reaction of antimutagenic adaptive responses to radiation predictably precludes a linear dose–response relation of radiation and health effects (49,50).

A tenfold increase of background radiation of 1–10 mGy/y stimulates overall DNA damage-control activity by about 20%, producing a corresponding decrease in the production of metabolic mutations and associated decreases of cancer mortality and mortality from all causes (Figs. 5 and 9) (45–52). Radiation hormesis provides the biological basis for statistically significant epidemiologic observations of LDR-induced decreased human mortality and cancer mortality.

Epidemiology

None of the epidemiologic surveys of populations with high background radiation in the United States, China, India, and Iran has observed increased mortality or cancer mortality compared with control populations with low background radiation (53–64). In 2001, the National Council for Radiation Protection Report 136 stated: “...it is important to note that the rates of cancer in most populations exposed to low-level radiation have not been found to be detectably increased,

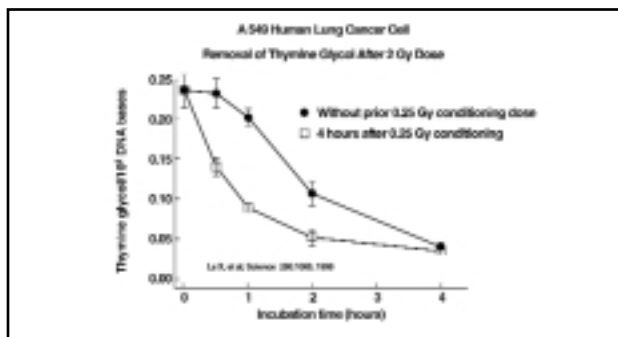


Figure 7. Low-dose induced DNA repair. (Adapted with permission from (45).)

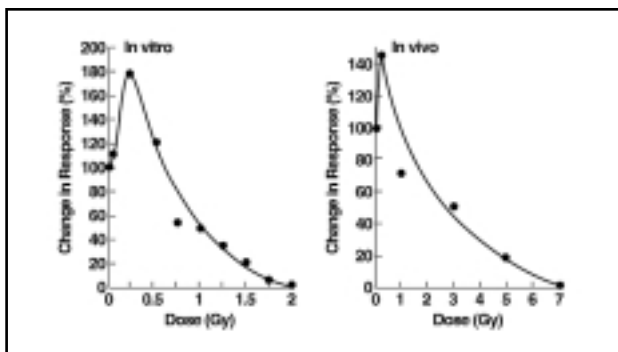


Figure 8. Immune system response to radiation. Mouse splenic cells primed with antigenic sheep red blood cells. (Adapted with permission from (26).)

and that in most cases the rates have appeared to be decreased” (65).

Chromosomal aberrations are formed during mitosis of damaged DNA. High-dose, high-dose-rate radiation of cultured human lymphocytes produces large numbers of chromosomal aberrations. These aberrations are decreased about 50% if enzymatic repair of DNA damage is increased by lymphocyte exposure to a conditioning dose of 10–100 mGy 4 hours before exposure to the high-dose, high-dose-rate challenge dose (66,67). Ghiassi-nejad et al. (68) recently measured lymphocyte chromosome aberrations after a dose of 1.5 Gy to lymphocytes of residents in high (H; 10 mGy/y) and normal (N; 1 mGy/y) background radiation areas (BRAs) of Ramsar, Iran. Lymphocytes of HBRA residents had 55% of the chromosomal aberrations of NBRA residents ($P < 0.001$) (Fig. 10) (68). These findings suggest that chronic LDR may not only reduce mortality from all causes and cancer mortality but may also be protective against accidental high-dose radiation (HDR).

During the past decade, decreased mortality and decreased cancer mortality in human populations exposed to LDR have been observed with high statistical power and with careful consideration of controls in large populations:

- Kostyuchenko and Kristina (69) reported cancer mortality in 7,852 Eastern Urals villagers after radiation exposure produced by the 1957 Mayak thermal explosion. Tumor-related mortality was 28% ($P < 0.05$), 39% ($P < 0.05$), and 27% lower

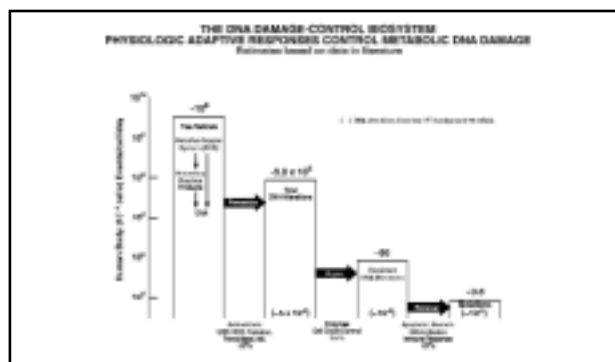


Figure 9. The antimutagenic DNA damage-control biosystem response to high background radiation = 120%. Estimates based on data in literature. GSH = glutathione reductase.

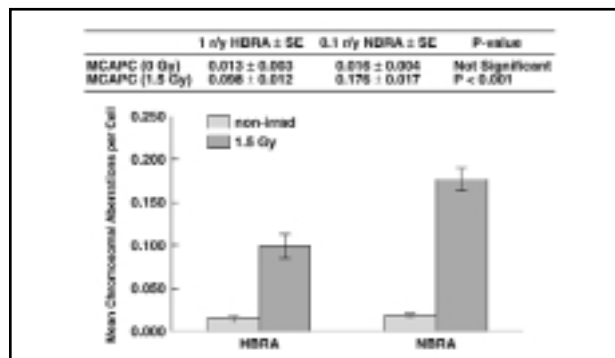


Figure 10. Mean chromosomal aberrations per cell (MCAPC) were measured in lymphocytes before and after exposure to 150 r. Lymphocytes were obtained from Ramsar, Iran, residents in a high background γ radiation area (HBRA) of about 10 mGy/y and residents in a normal background γ radiation area (NBRA) of about 1 mGy/y. The MCAPC results, based on analysis of about 200 cells/person and obtained during two sampling events, indicate a radioadaptive response to high background radiation levels. (From data reported in (68).)

in the 496, 120, and 40 mGy groups, respectively, than in unexposed villagers.

- In 1993, Kondo (20) reviewed the beneficial effects of LDR in atomic bomb survivors, radium dial painters, and residents of Misasa, Japan, an urban area with radon spas.

- The metaanalysis by Rossi and Zaider (70) of human relative risk (RR) of lung cancer after exposure to low linear energy transfer (LET) radiation indicated that “doses < 2 Gy do not appear to cause lung cancer but, in fact, indicate reduction of the natural incidence” (Fig. 11).

- Cohen (71) related lung cancer mortality to residential radon exposure in nearly 90% of the U.S. population. After correction for smoking, lung cancer mortality decreased with increasing mean residential radon levels, in sharp contrast (20 SD) to the Biological Effects of Ionizing Radiation (BEIR) IV study’s increasing mortality calculated by linear extrapolation of effects in uranium miners exposed to very high radon concentrations (Fig. 12).

- Miller et al. (72) in the Canadian Breast Fluoroscopy Study reported breast cancer mortality in 32,710 women examined

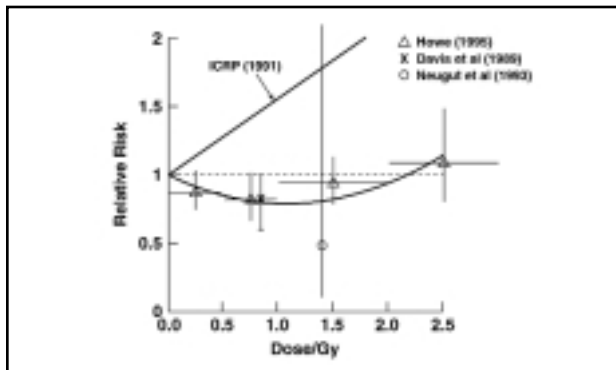


Figure 11. Relative risk of lung cancer after exposure to low linear energy transfer (LET) radiation. The data by Howe (89) are given together with horizontal bars that indicate the dose bins he used. The data point from Neugut (90) et al. represents the relative risk in the contralateral lung 10 years or more after diagnosis of breast cancer, shown as the average of the two doses reported. The 95% confidence intervals, indicated by vertical bars, were taken from the original publications, for the data point from Neugut et al. and the confidence interval was estimated. (Adapted with permission from (70).)

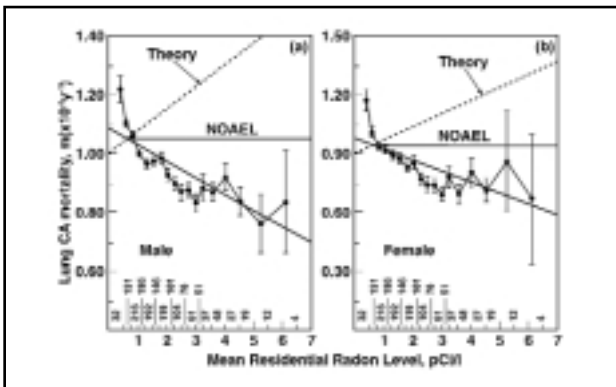


Figure 12. Lung cancer mortality rates corrected for smoking versus mean residential radon level for 1,601 U.S. counties. Data points shown are the mean of the number of counties within the range of radon concentrations shown on the base line. Error bars are SD of the mean. Theory lines (National Academy of Sciences Biological Effects of Ionizing Radiation [BEIR] Study IV and BEIR VI studies) are obtained by linear extrapolation of lung cancer mortality in uranium miners exposed to prolonged very high radon concentrations. NOAEL = no adverse effect level. (From data reported in (71).)

by multiple fluoroscopy between 1930 and 1952. Standardized mortality rates show breast cancer RR reduced to 0.66 ($P < 0.05$) at 150 mGy and 0.85 at 250 mGy (Fig. 13).

• Matanoski (73), UNSCEAR 1994 (47), and the U.S. Nuclear Shipyard Worker Study (NSWS) reported cancer mortality and mortality from all causes among almost 700,000 nuclear industry workers, including about 108,000 nuclear workers (NW). “The healthy worker effect” was excluded by including an internal control of 33,352 nonnuclear workers (NNW) scrupulously matched with 28,542 NW with lifetime doses >5 mSv. Standardized mortality ratios of death from “all causes” were 1.02 for NNW versus 0.76 for NW (a decrease of 16 SD)

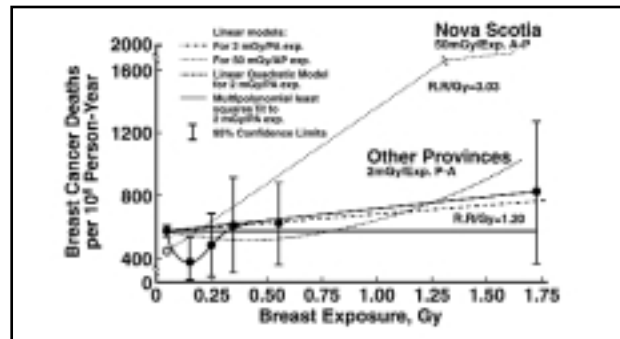


Figure 13. Canadian study of effects of breast fluoroscopy. (Adapted with permission from (72).)

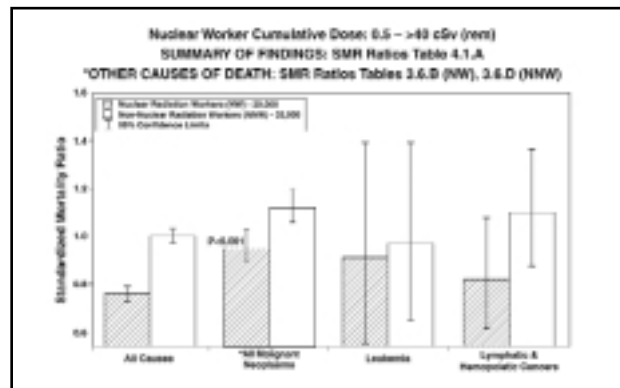


Figure 14. Standardized mortality ratios (SMRs) for selected causes of death among shipyard workers in the United States. (Adapted with permission from (73).)

and from “all malignant neoplasms” were 1.12 for NNW and 0.95 for NW ($P < 0.001$; a decrease >4 SD). This highly significant reduced mortality of NW from “all malignant neoplasms” (cancer) was omitted from the group’s summary of findings (Fig. 14).

• Cardis et al. (74), in the study of Cancer Mortality among Nuclear Industry Workers in Three Countries, reported cancer mortality among 95,673 nuclear industry workers. For all cancers, excluding leukemia, RR was 0.93. For “leukemia excluding chronic lymphocytic leukemia [CLL]” an RR of 2.18 with trend of 1.85 were reported, both figures invalidated by the statistical methods used: “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. For leukemia excluding CLL, the number of deaths was less than 30, P value presented was estimated using computer simulations based on 5,000 samples, rather than the normal approximation.”

• Tokarskaya et al. (75) reported cancer incidence induced in 500 Mayak NW after chronic inhalation of ^{239}Pu . Compared with internal controls, lung cancer incidence, corrected for smoking, at body burdens of 0.343 kBq, 1.18 kBq, and 4.2 kBq, was significantly reduced to 0.56, 0.59, and 0.83, respectively (Fig. 15). Decreased lung cancer incidence at low body burdens of plutonium was also reported by Voelz et al. (76), Tietjen (77), and Gilbert et al. (78).

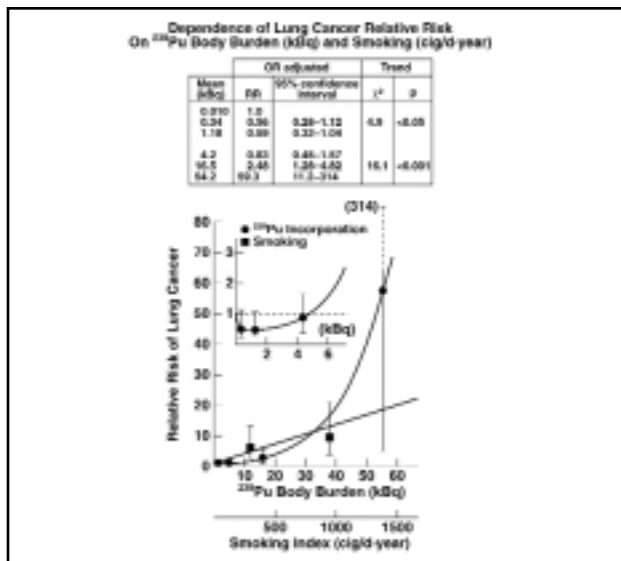


Figure 15. Relative risk of lung cancer and 95% confidence interval, depending on incorporation of ²³⁹Pu and smoking. (From data reported in (75).)

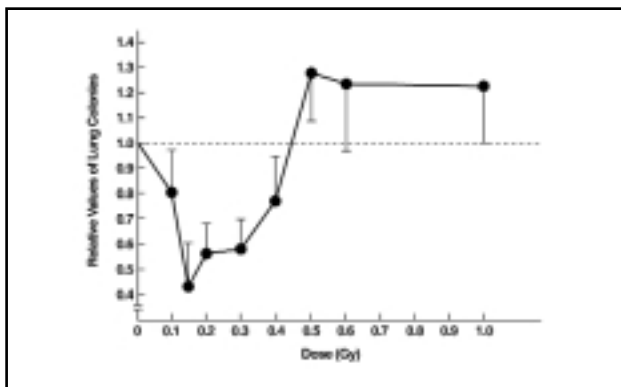


Figure 16. Spontaneous lung metastasis after total-body irradiation (TBI) of mice. TBI given 12 days after tumor cell transplantation into groin. (Adapted with permission from (23).)

These epidemiologic observations of decreased cancer mortality and increased longevity of public, occupational, and medical cohort populations exposed to increased LDR are consistent with the antimutagenic biosystem model prediction of radiation hormesis: a high background of 1.0 cGy/y decreases metabolic mutations occurring at a low background 0.1 cGy/y from approximately 1 to 0.8 mutations/cell/d, with corresponding decreases of mortality and cancer mortality (Fig. 9).

Immune System Prevention and Therapy of Cancer

Immune system destruction of cells with persistent DNA damage is an essential component of effective antimutagenic control of malignant cells and tumors. Low-dose stimulation of the immune system may not only prevent cancer by increased removal of premalignant or malignant cells but may also destroy gross cancer tumors with metastases. These findings have been reported in mice for almost 40 years, more recently in rats and humans (22–26, 79–84).

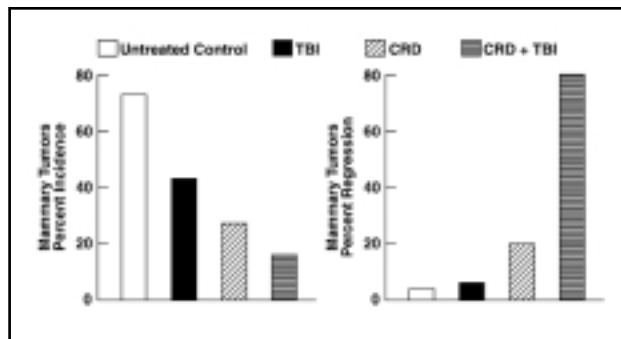


Figure 17. Eight-month-old, mammary-tumor-susceptible female C3H/He mice were first adjusted in a stepwise manner to chronically restricted diet (CRD; calorically 70% of ad libitum diet) over a period of 3 weeks. The mice were maintained on CRD until completion of the study. After their diet was adjusted, the mice were exposed to total-body irradiation (TBI) (0.04 Gy, 3 alternating d/wk for 4 weeks) and observed for 35 weeks. Tumor regression of the CRD + TBI group was rapid and large numbers of CD8+ T cells were found infiltrating the regressing tumors. These cells were not found in mice in the untreated control, low-dose radiation, or CRD groups. (Adapted with permission from (24).)

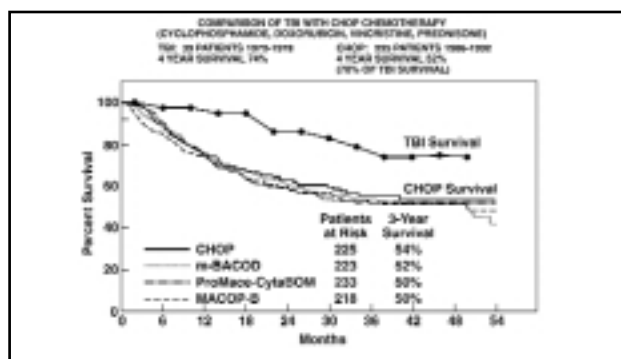


Figure 18. Low-dose fractionated total-body irradiation (TBI) in the treatment of advanced non-Hodgkin's lymphoma (NHL). The 150-cGy, 5-week course consisted of 15 cGy 2 times/wk or 10 cGy 3 times/wk. Complications included thrombocytopenia requiring temporary interruption of scheduled therapy in 40% of patients in both dose schedules. CHOP remains the best available chemotherapy treatment for patients with advanced-stage intermediate- and high-grade NHL (88). BACOD = low-dose methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone; MACOP-B = prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue; ProMACE-CytoBOM = methotrexate with leucovorin rescue, doxorubicin with cyclophosphamide, vincristine, prednisone, and bleomycin. (Adapted with permission from (80).)

The maximal immune response of mouse splenic cells to sheep red blood cells occurs after a single dose of 0.25 Gy (25 r) (Fig. 8) (25,26). Mice inoculated with subimmunogenic tumor antigen and exposed simultaneously to 0.15 Gy total-body irradiation (TBI) are immunized to the tumor (25). A dose of 0.15 Gy produces maximal immune suppression of tumor metastases to lung. Doses >0.50 Gy suppress immune system activity, with associated increased metastases to lung

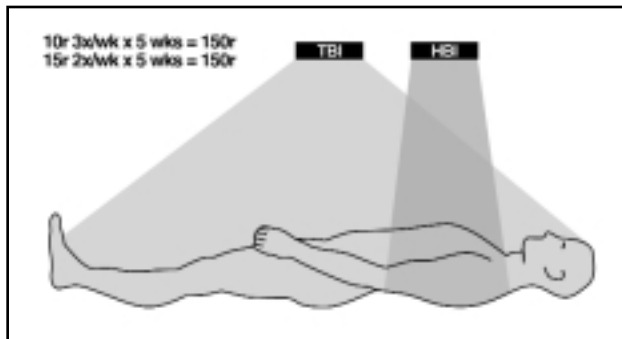


Figure 19. Total-body irradiation (TBI) and half-body irradiation (HBI) of patients with non-Hodgkin's lymphoma. (Adapted with permission from (23).)

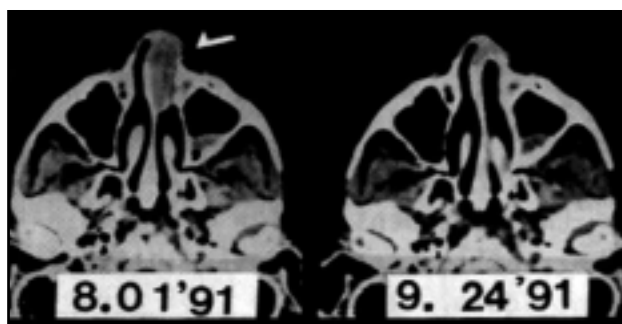


Figure 20. CT scan of upper nasal cavity before and after half-body irradiation (HBI). Intracranial nasal tumor, far above the HBI field, disappeared completely after low-dose HBI. (Adapted with permission from (81).)

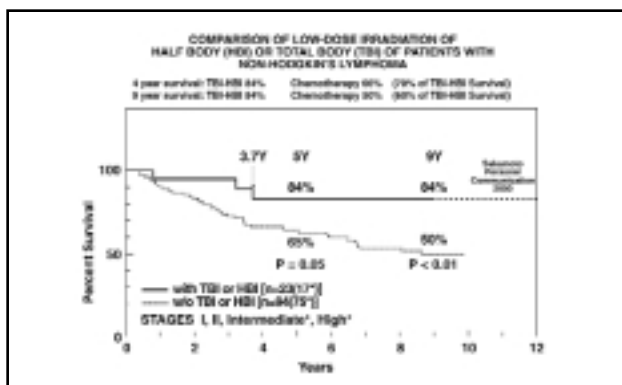


Figure 21. Patients in both groups (about 25% low-grade and 75% intermediate- and high-grade) received chemotherapy and localized tumor high-dose radiation. (Adapted with permission from (23).)

(Fig. 16) (23). Rats exposed to 0.20 Gy suppress metastases to lung and lymph nodes >70%, with >900% increased tumor tissue infiltration by lymphocytes (*J Nucl Med.* 2001 (6);42:24N) (Fig. 8) (22). Chronic TBI (LDR course of TBI fractions) of mice increases immune system response of splenic T-lymphocyte proliferation (26). TBI of mice on a chronically restricted diet (calorically 70% of ad libitum diet) prevents and removes spontaneous breast cancer tumors (Fig. 17) (24).

Low-Dose Radiation Immunotherapy of Cancer

Three clinical trials of patients with low-, intermediate-, and high-grade non-Hodgkin's lymphoma used similar protocols of fractionated 10- or 15-r doses, 30 r/wk for a 5-week total of 150 r. Two were conducted by Harvard University in 1976 and 1979 (Fig. 18) (79,80) and one by Tohoku University, Japan, with reports in 1992 and 1997 (Figs. 19–21) (23,81). Each study administered TBI to patients receiving chemotherapy and localized HDR with tumor grades matched to controls without TBI. The Harvard studies reported survival data for 4 years and the Tohoku study for 9 years after initiation of TBI.

At 4 years, the three studies showed 20% increased survival of TBI patients compared with those receiving cyclophosphamide, doxorubicin, vincristine, and prednisone and 30% increased survival compared with those receiving less effective earlier cyclophosphamide, vincristine, and prednisone (COP) chemotherapy. At 9 years, the 84% survival of TBI patients in Japan remained the same as at 3.7 years, whereas survival of control CHOP patients declined to 50%. The 13-year survival of these LDR patients, with TBI or half-body irradiation, remains 84% (K. Sakamoto, oral communication, May 2000).

Summary

The antimutagenic biosystem of prevention, repair, and removal of damaged DNA has evolved in response to relentless high levels of metabolic oxidative damage by free radicals, i.e., ROS. Mutations produced by metabolic oxidative DNA damage are about 10⁶ times greater than those produced by low LET background radiation of 1 mGy/y.

Acute subinhibitory LDR (≤250 mGy) stimulates all components of the antimutagenic system, reducing the cumulative mutation load observed in aging, disease, and cancer.

All statistically significant, adequately controlled epidemiologic studies of the public, medical cohorts, and occupational workers confirm low doses of radiation are associated with reduced mortality from all causes and decreased cancer mortality and may be protective against accidental HDR.

Low-dose body irradiation for cancer immunotherapy has been shown to be effective in rodents and humans. Clinical trials of LDR immunotherapy for patients with breast, prostate, colon, and ovarian cancers and lymphomas are needed.

Successful implementation of these trials would provide a long-sought major advance in cancer therapy. Public recognition of radiation hormesis would terminate radiation phobia. Ending the enormous expenditure of billions of dollars for needless protection from LDR would also furnish funds needed for health care and medical research that includes LDR immunotherapy of cancer and infectious disease (85–87) and development of effective, therapeutic radiopharmaceutical stimulation of the immune system.

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References

1. Kirkward TBL, Austad SN. Why do we age? *Nature* (London). 2000;408:233–238.
2. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of aging. *Nature* (London). 2000;408:239–247.
3. De Pinho RA. The age of cancer. *Nature* (London). 2000;408:248–254.
4. Beckman KB, Ames BN. Free radical theory of aging matures. *Physiol Rev*. 1998;78:547–581.
5. Pollycove M, Feinendegen LE. Quantification of human DNA alterations: intrinsic and radiation induced. *Department of Energy/National Institutes of Health Workshop: Cellular Responses to Low Doses of Ionizing Radiation*. April 27–30, 1999. Washington, DC: US Department of Energy; 2001.
6. Helbock HJ, Beckman KB, Shigenaga MK, et al. DNA oxidation matters: the HPLC-electrochemical detection assay of 8-oxo-deoxyguanosine and 8-oxo-guanine. *Proc Natl Acad Sci USA*. 1998;96:288–293.
7. Jaruga P, Dizdaroglu M. Repair of products of oxidative DNA base damage in human cells. *Nucleic Acid Res*. 1996;24:1389–1394.
8. Wood RD, Mitchell M, Sgouros J, Lindahl T. Human DNA repair genes. *Science*. 2001;291:1284–1289.
9. Eisen JA, Hanawalt PC. A phylogenomic study of DNA repair genes, proteins and processes. *Mutation Res*. 1999;435:171–213.
10. Wallace SS. Enzymatic processing of radiation-induced free radical damage in DNA. *Radiation Res*. 1998;150(suppl 5):60–79.
11. Lohman PHM, Cox R, Chadwick KH. Role of molecular biology in radiation biology. *Int J Radiat Biol*. 1995;68:331–340.
12. Hanawalt PC. DNA repair comes of age. *Mutat Res*. 1995;336:101–113.
13. Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD, eds. *Molecular Biology of the Cell*. 3rd ed. New York, NY: Garland Pub.; 1994.
14. Frakenberg-Schwager M. Induction, repair and biological relevance of radiation-induced DNA lesions in eukaryotic cells. *Radiat Environ Biophys*. 1990;29:273–292.
15. Freidberg EC, Walker GC, Siede W. *DNA Repair and Mutagenesis*. Washington, DC: American Society of Microbiology Press; 1995.
16. Chandra J, Samali A, Orrenius S. Triggering and modulation of apoptosis by oxidative stress. *Free Radical Biol Med*. 2000;29:323–333.
17. Kondo S. Evidence that there are threshold effects in risk of radiation. *J Nucl Sci Technol*. 1999;36:1–9.
18. Kondo S. *Health Effects of Low-Level Radiation*. Madison, WI: Medical Physics Publishing; 1993.
19. Potten CS. Extreme sensitivity of some intestinal crypt cells to X and γ irradiation. *Nature*. 1977;269:518–521.
20. Hashimoto S, Shirato H, Hosokawa M, et al. The suppression of metastases and the change in host immune response after low-dose total-body irradiation in tumor-bearing rats. *Radiat Res*. 1999;151:717–724.
21. Sakamoto K, Myogin M, Hosoi Y, et al. Fundamental and clinical studies on cancer control with total or upper half body irradiation. *J Jpn Soc Ther Radiol Oncol*. 1997;9:161–175.
22. Makinodan T. Cellular and subcellular alteration in immune cells induced by chronic, intermittent exposure in vivo to very low dose of ionizing radiation (LDR) and its ameliorating effects on progression of autoimmune disease and mammary tumor growth. In: Sugahara T, Sagan LA, Aoyama T, eds. *Low-Dose Irradiation and Biological Defense Mechanisms*. Amsterdam, The Netherlands: Elsevier Science Publishers; 1992:223–237.
23. Anderson RE. Effects of low-dose radiation on the immune response. In: Calabrese EJ, ed. *Biological Effects of Low Level Exposures to Chemicals and Radiation*. Chelsea, MI: Lewis Publishers; 1992:95–112.
24. Makinodan T, James SJ. T-cell potentiation by low-dose ionizing radiation: possible mechanisms. *Health Phys*. 1990;59:29–34.
25. Fenech M. Micronucleus frequency in human lymphocytes is related to plasma vitamin B12 and homocysteine. *Mutat Res*. 1999;428:299–304.
26. Ames BN. Micronutrients prevent cancer and delay aging. *Toxicol Lett*. 1998;102–103:5–18.
27. Fenech M, Aitken C, Rinaldi J. Folate, vitamin B12, homocysteine status and DNA damage in young Australian adults. *Carcinogenesis*. 1998;19:1163–1171.
28. Blount BC, Mack MM, Wehr CM, et al. Folate deficiency causes uracil misincorporation into human DNA and chromosome breakage: implications for cancer and neuronal damage. *Proc Natl Acad Sci USA*. 1997;94:3290–3295.

29. Ward JF. DNA damage produced by ionizing radiation in mammalian cells: identities, mechanisms of formation, and reparability. *Prog Nucleic Acid Res Mol Biol*. 1988;35:95–125.
30. Martin GM. Somatic mutagenesis and antimutagenesis in aging research. *Mutat Res*. 1996;350:35–41.
31. Morley AA. The somatic mutation theory of aging. *Mutat Res*. 1995;338:19–23.
32. Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. *Proc Natl Acad Sci USA*. 1993;90:7915–7922.
33. Sohal RS, Weindruch R. Oxidative stress, caloric restriction, and aging. *Science*. 1996;273:59–63.
34. Miller RA. The aging immune system: primer and prospectus. *Science*. 1996;273:70–74.
35. Ames BN, Gold LA, Willet WC. The causes and prevention of cancer. *Proc Natl Acad Sci USA*. 1995;92:5258–5265.
36. Ross DW. Biology of aging. *Arch Pathol Lab Med*. 1996;120:1148.
37. Lithgow GJ, Kirkwood TBL. Mechanisms and evolution of aging. *Science*. 1996;273:80.
38. Wei Q, Matanoski GM, Farmer ER, Hedayati MA, Grossman L. DNA repair and aging in basal cell carcinoma: a molecular epidemiology study. *Proc Natl Acad Sci USA*. 1993;90:1614–1618.
39. Varmus H, Weinberg RA. *Genes and the Biology of Cancer*. New York, NY: Scientific American Library; 1993:153.
40. Feinendegen LE, Loken MK, Booz J, Muhlensiepen H, Sondhaus CA, Bond VP. Cellular mechanisms of protection and repair induced by radiation exposure and their consequences for cell system responses. *Stem Cells*. 1995;13(suppl 1):7–20.
41. Feinendegen LE, Sondhaus CA, Bond VP, Muhlensiepen H. Radiation effects induced by low doses in complex tissue and their relation to cellular adaptive responses. *Mutat Res*. 1996;337:199–205.
42. Yamaoka K. Increased SOD activities and decreased lipid peroxide in rat organs induced by low X-irradiation. *Free Radical Biol Med*. 1991;11:3–7.
43. Le XC, Xing JZ, Lee J, Leadon SA, Weinfeld M. Inducible repair of thymine glycol detected by an ultra sensitive assay for DNA damage. *Science*. 1998;280:1066–1069.
44. Duke RD, Ojcius DM, Young JD-E. Cell suicide in health and disease. *Sci Am*. 1996;(12):80–87.
45. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and Effects of Ionizing Radiation. Annex B. Adaptive Responses to Radiation in Cells and Organisms. In: *UNSCEAR 1994 Report to the General Assembly, with Scientific Annexes*. New York, NY: United Nations; 1994:185–272.
46. Melov S, Ravenscroft J, Malik S, et al. Extension of life span with superoxide dismutase/catalase mimetics. *Science*. 2000;289:1567–1569.
47. Pollycove M, Feinendegen LE. Molecular biology, epidemiology, and the demise of the linear no-threshold (LNT) hypothesis. *Compt Rend Acad Sci Paris Life Sci*. 1999;322:197–204.
48. Pollycove M. Nonlinearity of radiation health effects. *Environ Health Perspect*. 1998;106:363–368.
49. Azzam EI, de Toledo SM, Raaphorst GP, Mitchel REJ. Low-dose ionizing radiation decreases the frequency of neoplastic transformation to a level below the spontaneous rate in C3H 10T1/2 cells. *Radiat Res*. 1996;146:369–373.
50. Redpath JL, Antoniono RJ. Introduction of an adaptive response against spontaneous neoplastic transformation in vitro by low-dose gamma radiation. *Radiat Res*. 1998;149:517–520.
51. Nair KMK, Nambi KSV, Amma NSSF, et al. Population study in the high natural background radiation area in Kerala, India. *Radiat Res*. 1999;152:S145–S148.
52. Cheriyan VD, Kurien CJ, Das B, et al. Genetic monitoring of the human population from high-level natural radiation areas of Kerala on the South West Coast of India. II. Incidence of numerical and structural chromosomal aberrations in the lymphocyte of newborns. *Radiat Res*. 1999;152:S154–S158.
53. Jaikrishnan G, Andrews VJ, Thampi MV, Koya PKM, Rajan VK, Chauhan PS. Genetic monitoring of the human population from high-level natural radiation area of Kerala on the South West Coast of India. I. Prevalence of congenital malformations in newborns. *Radiat Res*. 1999;152:S149–S153.
54. Kesavan PC. Indian research on high levels of natural radiation: pertinent observations for further studies. In: Wei L, Sugahara T, Tao Z, eds. *High Levels of Natural Radiation. Radiation Dose and Health Effects*. Amsterdam, The Netherlands: Elsevier; 1996:111–117.
55. Sohrabi M. Recent radiological studies of high level natural radiation areas of Ramsar. In: Sohrabi JUAM, Durrani SA, eds. *High Levels of Natural Radiation*. Ramsar, Iran: International Atomic Energy Agency; 1990:39–47.
56. Nambi KSV, Soman SD. Further observations on environmental radiation and cancer in India. *Health Phys*. 1990;59:339.
57. Nambi KSV, Soman SD. Environmental radiation and cancer in India. *Health Phys*. 1987;52:653.
58. Webster EW. The effects of low doses of ionizing radiation. *J Tenn Med Assoc*. 1983;76:499.
59. Zahi S, Lin X, Pan T, et al. Report of survey on mortality from malignant tumors in high background area of Guangdong. *Radiat Res* (Japan). 1982;22:48.
60. Cohen JJ. Natural background as an indicator of radiation induced cancer. In: *Proceedings of the Fifth International Radiation Protection Association Meeting*. Jerusalem, Israel: IRPA; 1980.
61. Frigerio NA, Stowe; RS. Carcinogenic and genetic hazard from background radiation. In: *Biological and Environmental Effects of Low Level Radiation*, vol. 2. Vienna, Austria: International Atomic Energy Association; 1976:385.
62. Craig L, Seidman H. Leukemia and lymphoma mortality in relation to cosmic radiation. *Blood*. 1961;17:319.

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Lines from the SNM President

(Continued from page 11N)

My intent was not to finalize a new name for our Society but, instead, to begin a dialogue within the Society on considering this important change. This proposal was presented to the members of the House of Delegates, the SNM–Technologist Section (SNM–TS) National Council, and the Board of Directors. I also spoke to many individuals. Some commented that nuclear medicine is not the same as molecular medicine, but most acknowledged that much of what we do is closely related to this evolving field and most agreed that it is time to consider a name change. None of these individuals, however, believed that he or she had the perfect new name.

The House of Delegates voted that, as a next step, we publicize a request for members of the Society to submit new names. I am asking, therefore, that interested members submit what you think would be the best new name for the Society. Any current member in good standing in the SNM or SNM–TS can participate. An announcement will also be mailed to all members. Please write or type your suggested name on a sheet of paper, along with your name, title, and return address, and send to:

Virginia Pappas
Society of Nuclear Medicine
1850 Samuel Morse Drive
Reston, VA 20190-5316

A summary of the submitted names will be prepared and presented first to the Board of Directors. The deadline for receipt of submitted names will be December 15, 2001. The Board of Directors will choose five finalists from the submissions. At the Mid-Winter meeting, these will then be submitted to the House of Delegates for consideration. According to SNM bylaws, no name change can take place until the name is formally proposed and approved as a bylaw change.

The member submitting the final approved new name will be reported in a future Newsline article and will receive additional recognition as approved by the House and Board of Directors. In the case of duplicate submissions, the submitted name with the earliest postmark will be the one recognized.

I look forward to your ideas and your input as we take this next step into the future of our Society. The year ahead promises to be challenging and rewarding both for the Society and for advancements in nuclear medicine in the United States and around the world.

—Alan Maurer, MD
President, SNM

Dose Responses of Organisms

(Continued from page 32N)

65. National Council on Radiation Protection and Measurements. *Evaluation of the Linear–Nonthreshold Model for Ionizing Radiation*. NCRP Report 136. Bethesda, MD: National Council on Radiation Protection and Measurements; 2001:6.
66. Wolff S, Afzal V, Wienke JK, Olivieri G, Michaeli A. Human lymphocytes exposed to low doses of ionizing radiations become refractory to high doses of radiation as well as to chemical mutagens that induce double-strand breaks in DNA. *Int J Radiat Biol*. 1988;53:39–49.
67. Shadley JD, Afzal V, Wolff S. Characterization of the adaptive response to ionizing radiation induced by low doses of x-rays to human lymphocytes. *Radiat Res*. 1987;111:511–517.
68. Ghiassi-nejad M, Mortazavi SMJ, Beitollahi M, et al. Very high background radiation areas of Ramsar, Iran: preliminary biological studies and possible implications. *Health Phys*. 2001:in press.
69. Kostyuchenko VA, Kristina LYu. Long-term irradiation effects in the population evacuated from the East-Urals radioactive trace area. *Sci Total Environ*. 1994;142:119–125.
70. Rossi HH, Zaider M. Radiogenic lung cancer: the effects of low doses of low linear energy transfer (LET) radiation. *Radiat Environ Biophys*. 1997;36:85–88.
71. Cohen BL. Test of the linear no-threshold theory of radiation carcinogenesis in the low dose, low dose rate region. *Health Phys*. 1995;68:157–174.
72. Miller AB, Howe GR, Sherman GJ, et al. Mortality from breast cancer after irradiation during fluoroscopic examination in patients being treated for tuberculosis. *N Engl J Med*. 1989;321:1285–1289.
73. Matanoski GM. *Health Effect of Low-Level Radiation in Shipyard Workers. Final Report*. Report No. DOE DE-AC02-79 EV10095. Washington, DC: U.S. Department of Energy; 1991.
74. Cardis E, Gilbert ES, Carpenter L, et al. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. *Radiat Res*. 1995;142:117–132.
75. Tokarskaya ZB, Okladnikova ND, Belyaeva ZD, Drozhko EG. Multifactorial analysis of lung cancer dose–response relationships for workers at the Mayak Nuclear Enterprise. *Health Phys*. 1997;73:899–905.
76. Voelz GL, Wilkinson CS, Acquavella JF. An update of epidemiologic studies of plutonium workers. *Health Phys*. 1983;44(suppl 1):493–503.
77. Tietjen GL. Plutonium and lung cancer. *Health Phys*. 1987;52:625–628.
78. Gilbert ES, Petersen GR, Buchanan JA. Mortality of workers at the Hanford site: 1945–1981. *Health Phys*. 1989;56:11–25.
79. Chaffey JT, Rosenthal DS, Moloney WC, Hellman S. Total body irradiation as treatment for lymphosarcoma. *Int J Radiat Oncol Biol Phys*. 1976;1:399–405.
80. Choi NC, Timothy AR, Kaufman SD, Carey RW, Aisenberg AC. Low dose fractionated whole body irradiation in the treatment of advanced non-Hodgkin's lymphoma. *Cancer*. 1979;43:1636–1642.
81. Takai Y, Yamada S, Nemoto K, et al. Anti-tumor effect of low dose total (or half) body irradiation and changes in the functional subset of peripheral blood lymphocytes in non-Hodgkin's lymphoma patients after TBI (HBI). In: Sugahara T, Sagan LA, Aoyama T, eds. *Low-Dose Irradiation and Biological Defense Mechanisms*. Amsterdam, The Netherlands: Elsevier Science Publishers; 1992:113–116.
82. Richaud PM, Soubeyran P, Eghbali H, et al. Place of low-dose total body irradiation in the treatment of localized follicular non-Hodgkin's lymphoma: results of a pilot study. *Int J Radiat Oncol Biol Phys*. 1998;40:387–390.
83. Safwat A. The immunology of low-dose total-body irradiation: more questions than answers. *Radiat Res*. 2000;153:599–604.
84. Safwat A. The role of low-dose total body irradiation in treatment of non-Hodgkins lymphoma: a new look at an old method. *Radiation Oncol*. 2000;56:1–8.
85. Shen R-N, Lu L, Kaiser HE, Broxmeyer HE. Murine AIDS cured by low dosage total body irradiation. In: Hohn KV, et al., eds. *Eicosanoids and Other Bioactive Lipids in Cancer Inflammation and Radiation Injury*. New York, NY: Plenum Press, New York, 1997.
86. Shen R-N, Lu L, Kaiser HE, Broxmeyer HE. Curative effect of split low dosage total-body irradiation on murine AIDS induced by Friend virus: the results and the possible mechanism. *In Vivo*. 1996;10:191–200.
87. del Regato JA. Trial of fractionated total-body irradiation in the treatment of patients with acquired immunodeficiency syndrome: a preliminary report. *Am J Clin Oncol*. 1989;12:365.
88. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med*. 1993;328:1002–1006.
89. Howe GR. Lung cancer mortality between 1950 and 1987. *Radiat Res*. 1995;142:295–304.
90. Neugut AI, Murray T, Santos J, et al. Increased risk of lung cancer after breast cancer radiation therapy in cigarette smokers. *Cancer*. 1994;71:3054–3057.