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CELLULAR AND ORGANISM DOSE-RESPONSE: BIOPOSITIVE (HEALTH BENEFIT) EFFECTS

Myron Pollycove, M.D., NRC/UCSF and Ludwig E. Feinendegen, M.D., Julich/DOE/NIH

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ABSTRACT

The genes in every cell continuously undergo an immense amount of metabolic damage by reactive oxygen species (ROS) which is prevented, repaired, and removed by a complex antimutagenic system. Recent studies document low dose radiation stimulation of many cellular functions, including antioxidant prevention, enzymatic repair, and immunologic and apoptotic removal of DNA damage. This homeostatic system is stimulated by a ten, or even a hundredfold increase in background radiation. Enhanced prevention of gene mutations by the spatial and temporal differences of ionizing radiation ROS and metabolic ROS is associated with radiation hormesis: decreased mortality and decreased cancer mortality observed in populations exposed to low dose radiation. Therapeutic stimulation of the immune system by low dose body irradiation prevents and removes cancer metastases in mice, rats, and humans.

INTRODUCTION

The prime concern of radiation protection policy since 1959 has been protecting DNA from damage by reducing exposure to ionizing radiation "as low as reasonably achievable" (ALARA). This policy is based upon the linear nonthreshold hypothesis (LNT) that carcinogenic gene mutations are produced in linear proportion to the radiation dose, no matter how small, 1995 NCRP Report 121¹. 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 will be examined after presenting several statistically significant

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Myron Pollycove
U.S. Nuclear Regulatory Commission
11555 Rockville Pike, M/S O-16E15
Rockville, MD 20852
e-mail: mxp@nrc.gov
Tel: 301-415-1785, Fax: 301-415-2162

epidemiologic studies that contradict the LNT hypothesis. Over eons of time a complex biosystem evolved in aerobic organisms to control the DNA alterations (oxidative adducts) produced by about 10^9 free radicals/cell/d derived from about 0.2-0.3% of all metabolized oxygen. Antioxidant *prevention* of DNA alterations, enzymatic *repair* of DNA damage, and *removal* of persistent DNA alterations by the immune system and apoptosis, 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 implicated in 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 determined 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.* This reduction of gene mutations in response to low-dose radiation provides a *biological* explanation of the statistically significant observations of decreased human mortality and cancer mortality that contradict the *biophysical* concept upon which confidence in the LNT hypothesis is based.

EPIDEMIOLOGIC STUDIES

What are some of the statistically significant epidemiologic studies that demonstrate risk *decrements* (hormesis) as predicted by the adaptive responses to low-dose radiation of the DNA damage-control biosystem? For several decades increased longevity and decreased cancer mortality have been reported in populations exposed to high background radiation. Such observations have been considered spurious or inconclusive because of unreliable public health data or undetermined confounding factors such as pollution of air, water and food, smoking, and socioeconomic variables. Recently, however, several epidemiologic statistically significant controlled studies have demonstrated that exposure to low or intermediate levels of radiation are associated with positive health effects. Radiation hormesis is the stimulatory response to subtoxic radiation exposure.

Dr. Zbigniew Jaworowski, past chairman of UNSCEAR, in his review of radiation hormesis² cites recent data showing hormetic effects in humans from the former Soviet Union.³ After radiation exposure from a thermal explosion in 1957, 7852 persons living in 22 villages in the Eastern Urals were divided into three exposure groups and followed for 30 years. Tumor-related mortality was 28% $P < 0.05$, 39% $P < 0.05$, and 27% lower in the 49.6 cGy(r), 12.0 cGy, and 4.0 cGy groups, respectively, than in the nonirradiated control population in the same region (Figure 1). Epidemiologic studies showing beneficial effects of low doses of radiation in atomic bomb survivors (Figure 2) and other populations were reviewed by Sohei Kondo, Professor of Radiation Biology, Atomic Energy Research Institute, Kinki University, Osaka, Japan.⁴ Included are the apparently beneficial effects of low doses of external gamma rays on the life span 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 (Figure 3).

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.⁵ The 1601 counties selected for adequate permanence of residence provide extremely high-power statistical analysis. After applying the BEIR IV⁶ correction for variations in smoking frequency, the study shows that lung cancer mortality decreases with increasing mean radon level in homes, in sharp contrast to the BEIR IV theoretical increased mortality derived by linear extrapolation of effects in uranium miners exposed to very high radon concentrations. The discrepancy between theoretical and measured slopes is 20 standard deviations (Figure 4). 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. 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 thirteen-year 10 million dollar U.S. Nuclear Shipyard Workers Study (NSWS) 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 1991⁷ and reported in UNSCEAR 1994.⁸ Professor Arthur C. Upton, who concurrently chaired the NAS BEIR V Committee on "Health Effects of Exposure to Low Levels of Ionizing Radiation,"⁹ 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 report⁹ 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 (NW) with working lifetime doses ≥ 5 mSv (many received doses well in excess of 50 mSv), 10,462 NW with doses < 5 mSv and 33,352 non-nuclear workers (NNW). Deaths in each of the groups were classified as due to: all causes, all malignant neoplasms, leukemia, lymphatic and hematopoietic cancers, mesothelioma, and lung cancer. The results demonstrate statistically significant decreases of the standardized mortality ratios for NW > 0.5 mSv of death from "all causes", 0.76 vs. 1.02 for NNW, a decrease of 16 standard deviation (SD), and of death from "all malignant neoplasms", 0.95 vs. 1.12 for NNW, a decrease of > 4 SD $P < 0.001$ (Figure 5). This highly significant risk decrement for death from "all malignant neoplasms" is omitted from the NSWS Summary of Findings, the UNSCEAR 1994 report of the NSWS, and the DOE press release of this study. The NNW and NW were similarly selected for employment, both with a median age of entry of about 34 years, were afforded the same health care thereafter, and performed the identical type of work, except for exposure to ⁶⁰Co gamma radiation. The highly significant risk decrements for NW > 0.5 mSv exclude "the healthy worker effect" and contradict the LNT hypothesis. This DOE NSWS was never published. The study provides evidence with extremely high statistical power that low levels of ionizing radiation are associated with risk *decrements*, i.e., are hormetic. Radiation hormesis is the stimulatory response of the organism to subtoxic exposure to radiation.

The Canadian Breast Cancer Fluoroscopy Study¹⁰ 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 in tables with no graphs. The authors compare 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 fit that includes only non-significant data and excludes the data with the highest confidence limits (Figure 6), the authors predict the lifetime excess risk of death from breast cancer after a single exposure to 1 cGy(1r) at age 30 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 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.¹¹ This study actually predicts that a dose of 15 cGy would be associated with 7,000 *fewer* deaths in these million women. Lauriston S. Taylor, past president of the NCRP, considered application of LNT theory for calculations of collective dose as, "deeply immoral uses of our scientific heritage"¹².

BIOLOGY OF THE ANTIMUTAGENIC SYSTEM OF DNA DAMAGE CONTROL

During the past decade rapid advances in our knowledge of molecular biology, cell and body function explain why low-dose radiation is associated with positive health effects in contrast to the carcinogenic effect of high-dose radiation. Our understanding is based upon current, cellular molecular biology observations. Estimates are based on published data:

- Two to three tenths percent of all metabolized oxygen is leaked from mitochondria as free radicals, reactive oxygen species (ROS)¹³. Humans generate about 10^9 ROS/cell/d that produce about 10^6 DNA oxidative adducts/cell/d¹⁴. These adducts include an average of 10^{-1} double strand breaks/d¹⁵. In addition, a relatively small number of metabolic DNA alterations are produced by DNA replication¹⁶, deamination and

depurination, and thermal instability¹⁷. By comparison, 1 mGy (0.1 r) per year low LET background radiation produces 5×10^{-3} DNA oxidative adducts/cell/d that include an average of 1×10^{-4} double strand breaks/d¹⁸.

- Over eons of time, as multicellular animals developed and metabolized oxygen, a complex DNA damage-control system evolved (figure 7)¹⁹. Much of the damage corresponding to 10^9 ROS/cell/d is prevented by antioxidants. The resultant $\sim 10^6$ DNA oxidative adducts/cell/d are reduced by enzymatic repair to about 10^2 persistent DNA alterations/cell/d. The immune system, apoptosis, differentiation, and necrosis remove approximately 99% of these persistent alterations so that an average of ~ 1 mutation/cell/d, possibly up to 2-3 remain¹⁹. These accumulate in genes throughout life, decreasing DNA damage control and are implicated in aging and cancer^{17,20-33}. Cancer increases as the third to fifth power of age. This highly efficient antimutagenic biosystem prevents precocious aging and malignancy unless impaired by genetic defects, or damaged by high doses of radiation or other toxic agents.
- How does background radiation add to the metabolic accumulation of mutations? A much larger fraction of double strand breaks occurs in DNA oxidative adducts produced by radiation than in those produced by metabolism (2×10^{-2} vs 1×10^{-7}).^{15,18} Their repair is less accurate. Consequently, the persistent fraction of these double strand breaks is also much larger than that of other metabolic DNA oxidative adducts ($\sim 10^{-1}$ vs $\sim 10^{-4}$). Nevertheless, the number of metabolic DNA oxidative adducts ($\sim 10^6$ /cell/d) is so much greater than the number of oxidative adducts from low LET background of 0.1 cGy/y (5×10^{-3} /cell/d), that an average of only $\sim 10^{-7}$ radiation mutation/cell/d is added to ~ 1 metabolic mutation/cell/d (Figure 7).¹⁹

RESPONSE TO LOW-DOSE RADIATION

The activity of the antimutagenic DNA damage control biosystem is decreased by high-dose radiation, but adaptively responds with increased activity to low-dose radiation (e.g., ≤ 30 cGy) (Figures 8-10).^{21,22,25-28} Though the ROS produced by low-dose ionizing radiation are very few compared to those produced by oxygen metabolism, their microdosimetric spatial and temporal differences have significant biphasic effects upon antimutagenic cell function: stimulation at low doses and suppression at high doses.

The efficiency of this biosystem is increased by adaptive responses to low-dose ionizing radiation (Figures 8-10). This is well documented in UNSCEAR 1994:⁸

“There is substantial evidence that the number of radiation-induced chromosomal aberrations and mutations can be reduced by a small prior conditioning dose in proliferating mammalian cells *in vitro* and *in vivo*.

There is increasing evidence that cellular repair mechanisms are stimulated after radiation-induced damage... Whatever the mechanisms, they seem able to act not only on the lesions induced by ionizing radiation but also on at least a portion of the lesions induced by some other toxic agents.”

This statement applies not only to the mutations produced by radiation and other environmental toxic agents, but also to the enormous number of endogenous daily metabolic mutations. The operative effect of reducing *metabolic* mutations by stimulatory adaptive response of the DNA damage-control biosystem to low-dose radiation damage is the critical factor, not reduction of a relatively negligible number of mutations produced by low-dose radiation.

Assuming a 20% increased efficiency of biosystem control in response to a tenfold increase of annual background radiation from 0.1 cGy/y, to 1 cGy/y, radiation mutations would indeed increase from 1×10^{-7} /cell/d to 8×10^{-7} /cell/d but *metabolic* mutations would *decrease* from ~ 1 /cell/d to ~ 0.8 /cell/d (Figures 7, 11).¹⁹

UNSCEAR did not consider that the increase of radiation mutations by low-dose radiation is negligible compared to the operative effect of the adaptive response to low-dose radiation upon the high background of metabolic mutations. *The biologic effect of radiation is determined by its effect on the biosystem that controls the relentless enormous burden of oxidative DNA damage.* Acute high-dose radiation impairs this biosystem with consequent significant increase of radiation and metabolic mutations and corresponding risk increments. Low-dose radiation stimulates the DNA damage-control biosystem with consequent significant decrease of metabolic mutations and corresponding *risk decrements* (Figures 7-12),^{35,36} i.e., radiation hormesis.

RESPONSE OF THE IMMUNE SYSTEM TO RADIATION

Low dose total body irradiation (TBI) and chronic TBI (LDR) stimulate immune system prevention and removal of cancer metastases in mice, rats, and humans. This has been shown in mice for almost 40 years³⁷ and more recently in rats³⁸ and humans³⁹⁻⁴².

The maximal immune response of mouse splenic cells to sheep red blood cells, both *in vitro* and *in vivo*, occurs after a single dose of 0.25 Gy (25 r) (Figure 10)²⁷. Compared to the *in vitro* response, better homeostasis of the *in vivo* response is shown by both the smaller maximal response and a greater resistance to suppression by high dose radiation.

TBI with subimmunogenic tumor antigen induces tumor immunization (Figure 13)⁴³. Sham irradiated controls inoculated subcutaneously with 100 non-viable tumor cells did not suppress growth of 10,000 viable tumor cells inoculated subcutaneously 21 days later. However, TBI 15 r given simultaneously with 100 non-viable tumor cells induced marked suppression of tumor cell growth exceeding that induced by 100,000 non-viable tumor cells without TBI.

TBI stimulates immune suppression of tumor metastases to lung (Figure 14)⁴¹. Lung colonies counted 20 days after TBI given 12 days after tumor cell transplantation into axilla of mice, were decreased by TBI doses less than 50 r. 15 r induced the maximal decrease of 60%. High doses greater than 50 r suppressed the immune system with associated increased metastases to lung.

Metastases are also suppressed by TBI of tumor-bearing rats (Figure 15)³⁸. Metastases to lung and to mediastinal and axillary lymph nodes in TBI rats were reduced by more than 70% of those in both control and locally irradiated rats. Tumor tissue infiltration by lymphocytes in TBI rats was more than 900% of that in both control and locally irradiated rats.

Chronic TBI (multiple TBI fractions comprising a total course of low dose radiation [LDR]) increases immune system response of splenic T lymphocyte proliferation in mice (Figure 16)³⁹. Mice irradiated 5 days/week for 4 weeks with LDR courses of 10 r, 20 r, and 80 r showed proliferative responses of 115%, 140%, and 160%, respectively, relative to the unirradiated control group 100%.

LDR in mice on a chronically restricted diet (CRD: calorically 70% of ad libitum diet) prevents and removes spontaneous breast cancer tumors (Figure 17)³⁷. Eight month old, breast tumor susceptible female mice, after 3-week adjustment to CRD were exposed to a 4-week course of LDR 48 r and then observed for 35 weeks. While 73% of the control ad libitum diet mice and 27% of the CRD mice developed breast cancer, only 16% of the CRD+LDR mice developed breast cancer. Most impressive was the very rapid 80% tumor regression of the CRD+LDR mice compared to 20% and 4% regression in the CRD and control mice, respectively. Large numbers of cytotoxic T cells were observed infiltrating the regressing tumors of CRD+LDR mice, but not in CRD and control mice.

LOW DOSE RADIATION (LDR) IMMUNOTHERAPY OF CANCER

Two Harvard University clinical trials of LDR therapy of patients with non-Hodgkin's lymphoma were published in 1976 (Figure 18)³⁹ and 1979 (Figure 19)⁴⁰. The protocols were very similar. The Chaffey, et al.³⁹ (1976) trial used a LDR course of 150 r given in fractionated TBI doses of 15 r 2x/week for 5 weeks. The Choi, et al.⁴⁰ (1979) trial also used a course of 150 r given in fractionated TBI doses of either 15 r 2x/week or 10 r 3x/week for 5 weeks. In both studies transiently low platelets requiring temporary interruption of scheduled therapy occurred in 35-40% of patients, irrespective of 10 r or 15 r dose schedule. Both control and LDR patients received chemotherapy and localized tumor high dose irradiation. Histologic grades of tumors in LDR and control patients were matched. COP chemotherapy used in the 1976 trial was replaced in the 1979 trial by more effective CHOP chemotherapy.

Both studies present 4 year survival data. The 1976 study shows 70% 4 year survival in 25 LDR patients and 40% survival in 25 matched control patients treated with COP (Figure 18)³⁹. The 1979 study shows 4 year survival of 74% in 39 LDR patients and 52% survival in 225 matched control patients treated with CHOP (Figure 19)⁴⁰.

Sakamoto, et al. (1997) at Tohoku University, Sendai, Japan, published a review of their experimental studies in mice and a clinical trial of LDR in humans⁴¹. In mice 15 r TBI induced the maximal suppression of tumor metastases

(Figure 14)⁴¹. TBI given 6-12 hours before localized high dose tumor therapy increased effectiveness of tumor therapy. 15 r doses of TBI, upper half body irradiation (HBI), and localized splenic irradiation were equally effective in stimulating the mouse immune system.

This 1997 study of LDR therapy of patients with non-Hodgkin's lymphoma is similar to the 1979 study by Choi, et al. Both used a LDR course of 150 r with equally effective doses of either 15 r 2x/week or 10 r 3x/week for 5 weeks and CHOP chemotherapy. Choi, et al. used TBI while Sakamoto, et al. used either TBI or HBI (Figure 20) with equal effectiveness and without interruption of scheduled therapy because of low platelets.

Sakamoto, et al. present 9 year survival data of 23 LDR patients and 94 control patients with matched histologic tumor grades (Figure 21)⁴¹. Tumors outside the HBI field were shown to regress completely in response to LDR (Figure 22)⁴². The 9 year survival of LDR patients is 84% compared with 50% survival of control CHOP patients. Subsequently, the 12 year survival of LDR patients continues to be 84% (personal communication).

Comparisons of 4 year survival in the Harvard and Tohoku studies are consistent in showing about a 20% better survival of LDR patients compared with control CHOP patients. In the Japanese study, however, a moderate decrease of platelets did not require schedule interruption and the 4 year survival of both LDR and control CHOP patients is increased about 10% above those of the United States studies. This may be related to the well established benefits of lower caloric dietary intake (Figure 17)³⁷ and more exercise in the Japanese population. Though racial differences may be a factor, this has not been demonstrated in Japanese living in the United States. In general, the population of Japan is lean and physically active with a diet low in calories and fat, high in vegetables (particularly soy and seaweed products), with some fruit, little fish and very little meat. Sound nutrition and regular exercise stimulate the immune system. LDR therapy is more effective when administered to patients with better initial immune system activity.

SUMMARY

The reduction of gene mutations in response to low-dose radiation stimulation of the antimutagenic biosystem of antioxidant *prevention*, enzymatic *repair*, and immune system and apoptotic *removal* of metabolic ROS DNA damage, provides a *biological* explanation of the statistically significant observations of radiation hormesis: decreased cancer mortality and decreased mortality from all causes. Radiation hormesis contradicts the *biophysical* concept upon which confidence in the LNT hypothesis is based.

Recent research has led to recognition of the importance of the immune system in controlling cancer as well as infectious disease. LDR cancer immunotherapy has been shown to be effective in rodents and man with high statistical significance and repeated confirmation. Published results justify strong financial support of well designed clinical trials of LDR therapy in patients with breast, prostate, colon, ovarian cancer, and lymphomas. Clinical trials are also indicated to determine the efficacy of LDR immune stimulation in therapy of patients with early HIV disease and in potentiation of vaccines for HIV and other infectious diseases.

Successful implementation of these trials would provide a long sought major advance of cancer therapy and terminate radiation phobia. Ending the enormous expenditure of many billions of dollars for needless protection from low dose radiation would also furnish funds needed for health care that includes low dose radiation immunotherapy of cancer and infectious diseases.

REFERENCES

1. National Council on Radiation Protection and Measurements. Principles and Application of Collective Dose in Radiation Protection. NCRP Report No. 121. Bethesda, MD: NCRP, 1995;45.
2. Jawarowski Z. Beneficial radiation. Nukleonika 40:3-12 (1995).
3. Kostyuchenko VA, Krestina L Yu. Long-term irradiation effects in the population evacuated from the East-Urals radioactive trace area. The Sci. Total Environ. 142: 119-125 (1994).
4. Kondo S. Health Effects of Low-Level Radiation. Osaka, Japan: Kinki University Press Madison, WI: Medical Physics Publishing, 1993.

5. Cohen BL. Test of the linear no-threshold theory of radiation carcinogenesis in the low dose, low dose rate region. *Health Phys* 68:157-174 (1995).
6. National Academy of Sciences, Committee on Biological Effects of Ionizing Radiation. Health Risks of Radon and Other Internally Deposited Alpha Emitters (BEIR IV). Washington: National Academy Press, 1988.
7. Matanoski GM. Health effects of low-level radiation in shipyard workers final report. Report No. DOE DE-AC02-79 EV10095. Washington: US Department of Energy, 1991.
8. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and Effects of Ionizing Radiation; UNSCEAR 1994 Report to the General Assembly, with Scientific Annexes. New York, NY: United Nations, 1994; Annex B. Adaptive Responses to Radiation in Cells and Organisms: 185-272.
9. National Academy of Sciences, Committee on Biological Effects of Ionizing Radiation. Health Effects of Exposure to Low Levels of Ionizing Radiation (BEIR V). Washington: National Academy Press, 1990.
10. Miller AB, Howe GR, Sherman GJ, Lindsay JP, Yaffe MJ, Dinner PJ, Risch HA, Preston DL. Mortality from breast cancer after irradiation during fluoroscopic examination in patients being treated for tuberculosis. *N Engl J Med* 321:1285-1289 (1989).
11. Howe GR, McLaughlin J. Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with breast cancer mortality in the atomic bomb survivors study. *Radiat Res* 149: 694-707 (1996).
12. Taylor LS. Some non-scientific influences on radiation protection standards and practice. *Health Phys* 39: 851-874 (1980).
13. Beckman KD, Ames BN. The free radical theory of aging matures. *Physiol. Rev.* 78:547-581 (1998).
14. Pollycove M. Molecular biology, epidemiology, and the demise of the linear no-threshold (LNT) hypothesis. In *Proceeding of the International Symposium, International Centre for Low Dose Radiation Research*. Ottawa, Canada; 1999:83-110.
15. Pollycove M, Feinenden LE. Quantification of human DNA alterations. In *Proceedings of the DOE/NIH Workshop on Cellular Responses to Low Doses of Ionizing Radiation, April 1999, Washington, D.C.* In press; 2000.
16. Friedberg EC, Walker GC, Siede W. DNA Repair and Mutagenesis. ASM Press, Washington, D.C., 1995.
17. Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD Eds. *Molecular Biology of the Cell*, 3rd Ed. Garland Pub., New York, New York, 1994.
18. Ward JF. Radiation chemical methods of cell death. In Fielden EM, Fowler JF, Hendry JH, Scott D, eds, *Proceedings of the 8th International Congress of Radiation Research, Vol. II*. London, England; Taylor & Francis; 1987;162-168.
19. Pollycove M, Feinenden LE. Low-level radiation improvement of health and therapy of cancer. In *Proceedings of the 10th International Congress of the International Radiation Protection Association*. Hiroshima, Japan, May 2000, Hiroshima, Japan, In press; 2000.
20. Sohal RS, Weindruch R. Oxidative stress, caloric restriction, and aging. *Science* 273:59-63 (1996).
21. Feinenden 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* 13 (Suppl. 1): 7-20 (1995).
22. Feinenden LE, Sondhaus CA, Bond VP, Muhlensiepen H. Radiation effects induced by low doses in complex tissue and their relation to cellular adaptive responses. *Mutation Res.* 199-205 (1996).
23. Varmus H, Weinberg RA. *Genes and the Biology of Cancer*. New York, NY: Scientific American Library;1993:153.
24. Ames BN, Gold LS, Willet WC. The causes and prevention of cancer. *Proc Natl Acad Sci USA* 92:5258-5265 (1995).
25. Yamaoka K. Increased SOD activities and decreased lipid peroxide in rat organs induced by low X-irradiation. *Free Radical Biol Med* 11:3-7 (1991).

26. Le XC, Xing JZ, Lee J, Leadon SA, Weinfeld M. Inducible repair of thymine glycol detected by an ultrasensitive assay for DNA damage. *Science* 280: 1066-1069 (1998).
27. Makinodan T, James SJ. T cell potentiation by low dose ionizing radiation: possible mechanisms. *Health Phys* 59(1):29-34 (1990).
28. Anderson RE. Effects of low-dose radiation on the immune response, Chapt. 5. In *Biological Effects of Low Level Exposures: Dose-Response Relationships* (Calabrese EJ, ed). Chelsea, MI: Lewis Publishers, 1992; 95-112.
29. Lithgow GJ, Kirkwood TBL. Mechanisms and evolution of aging. *Science* 273:80 (1996).
30. 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* 90:1614-1618 (1993).
31. Miller RA. The aging immune system: primer and prospectus. *Science* 273:70-74 (1996).
32. Ross DW. Biology of aging. *Arch Pathol Lab Med* 120:1148 (1996).
33. Duke RC, Ojcius DM, Young JD-E. Cell suicide in health and disease. *Scientific American Dec*: 80-87 (1996).
34. Mine M, Nakamura T, Mori H, Kondo H, Okajima S. The current mortality rates of A-bomb survivors in Nagasaki City. *Jpn J Public Health* 28: 337-342 (1981). (In Japanese with English abstract).
35. Azzam El, 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* 146: 369-373(1996).
36. Melov S, Ravenscraft J, Malik S, et al. Extension of life-span with superoxide dismutase/catalase mimetics. *Science* 289: 1559(2000).
37. Makinodan, T., 1992, "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: *Low-Dose Irradiation and Biological Defense Mechanisms*. Ed.: Sugahara, T., Sagan, L.A., Aoyama, T., Excerpta Medica, Amsterdam, London, New York, Tokyo, 233-237.
38. Hashimoto, S., Shirato, H., Hosokawa, M., Nishioka, T., Kuramitsu, Y., Matushita, K., Kobayashi, M., and Miyasaka, K., 1999, "The Suppression of Metastases and the Change in Host Immune Response after Low-Dose Total-Body Irradiation in Tumor-Bearing Rats," *Radiat Res* 151:717-724.
39. Chaffey, J.T., Rosenthal, D.S., Moloney, W.D., and Hellman, S., 1976, "Total Body Irradiation as Treatment for Lymphosarcoma," *Int. J. Radiat Oncol. Biol. Phys.* 1:399-405.
40. Choi, N.C., Timothy, A.R. Kaufman, S.D., Carey, R.W., and Aisenbert, A.C., 1979, "Low Dose Fractionated Whole Body Irradiation in the Treatment of Advanced Non-Hodgkin's Lymphoma," *Cancer* 43:1636-1642.
41. Sakamoto, K., Myogin, M., Hosoi, Y., Nemoto, K., Takai, Y., Kakuto, Y., Yamada, S., and Watabe, M., 1997, "Fundamental and Clinical Studies on Cancer Control with Total or Upper Half Body Irradiation," *J Jpn Soc Ther Radiol Oncol* 9:161-175.
42. Takai, Y., Yamada, S., Nemoto, K., Ogawa, Y., Kakuto, Y., Hosoi, Y., and Sakamoto, K., 1992, "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: *Low-Dose Irradiation and Biological Defense Mechanisms* (Sugahara, T., Sagan, L.A., and Aoyama, T., eds). Amsterdam, the Netherlands: Elsevier Science Publishers, 1992:113-116.
43. Anderson RE, Tokoda S, Williams WL, Spellman CW, Low dose irradiation permits immunization of A/J mice with subimmunogenic numbers of SaI cells. *Brit. J. Cancer* 54:505-510 (1986).

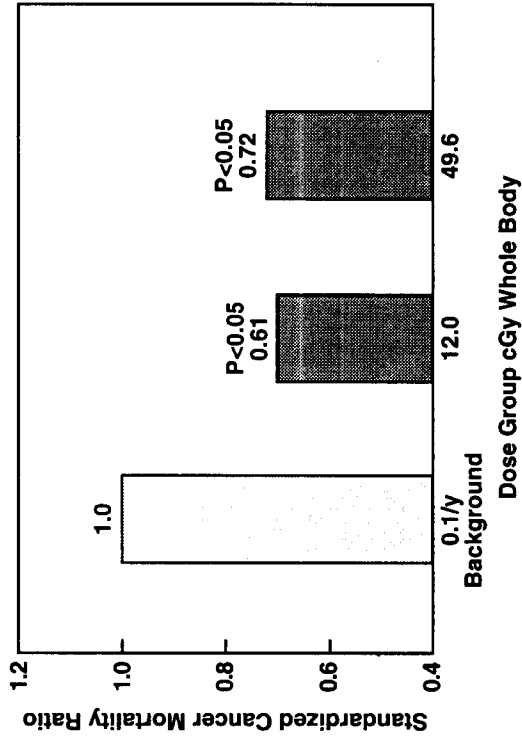


Figure 1. Standardized cancer mortality ratio in 3 exposure groups of Eastern Urals villagers followed for 30 years after a thermal explosion, September 1957 in the Mayak USSR reprocessing facility. Jaworowski Z (1995) Kostyuchenko VA, Krestina L, Yu. Long-term irradiation effects in the population evacuated from the East-Urals radioactive trace area. The Sci Total Environ 142:119-125 (1994)

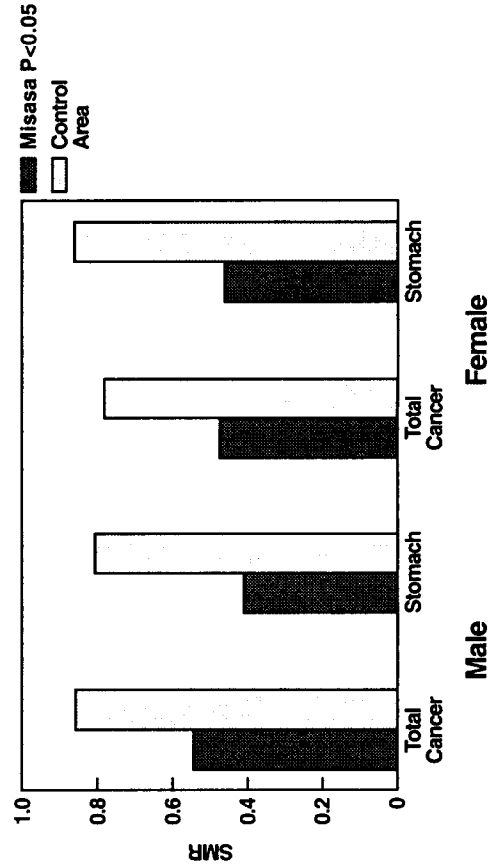


Figure 3. Standardized mortality ratios of populations continually exposed to high, Misasa radium springs, and low air concentrations of radon. Kondo S. 1993.

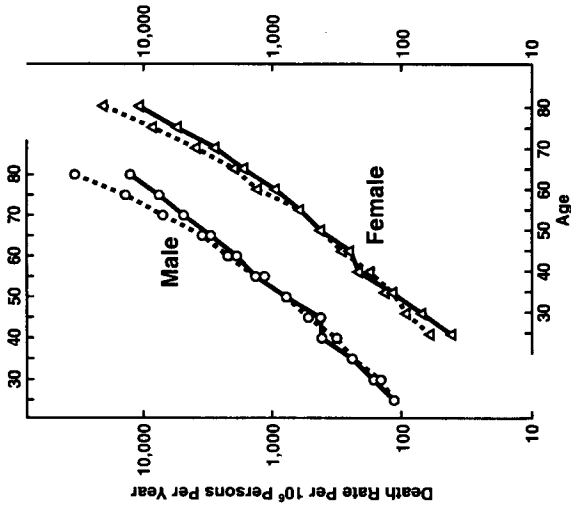


Figure 2. The higher death rate after 55 years old (dotted line) corresponds to the people living in Nagasaki, who were not exposed to A. Bomb. Lower death rate after 55 years old (solid line) corresponds to A. Bomb survivors. Milne M, et al. (1961)

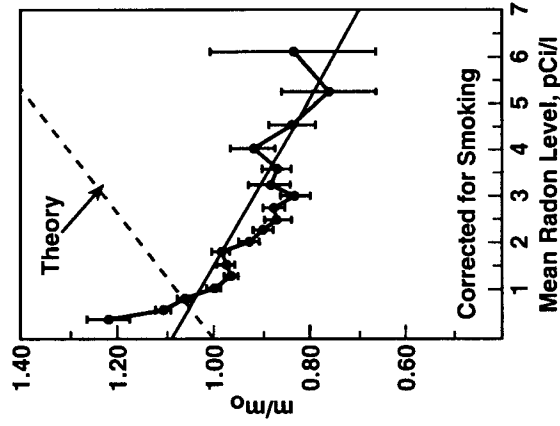


Figure 4. Lung cancer mortality rates compared with mean home radon levels by U.S. county and comparison with linear model by BEIR IV. m/m_0 = ratio of lung cancer mortality rate for residential radon levels to that at 0 level (theoretical), or to that of average residential level, 1.7 pCi/l. Cohen B. (1995)

Nuclear Worker Cumulative Dose: 0.5 - >40 cSv (rem)
SUMMARY OF FINDINGS: SMR Ratios Table 4.1.A
***OTHER CAUSES OF DEATH: SMR Ratios Tables 3.6.B (NW), 3.6.D (NNW)**

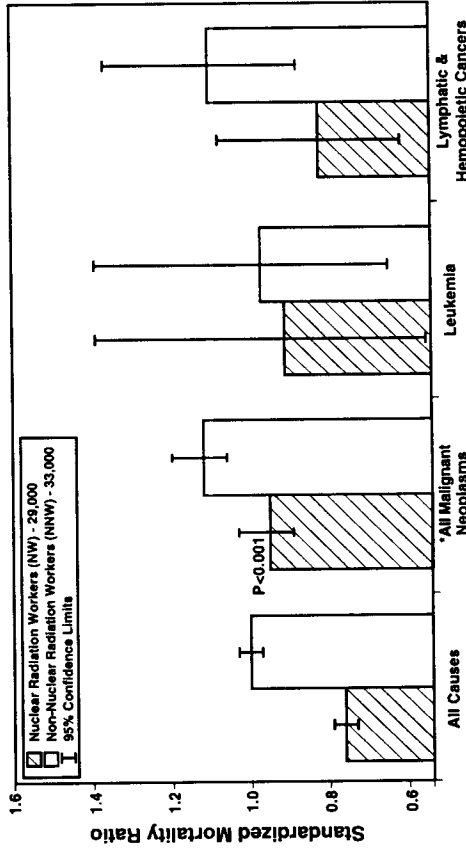


Figure 5. Standardized mortality ratios for selected causes of death among shipyard workers in the U.S. Matanoski GM. (1991)

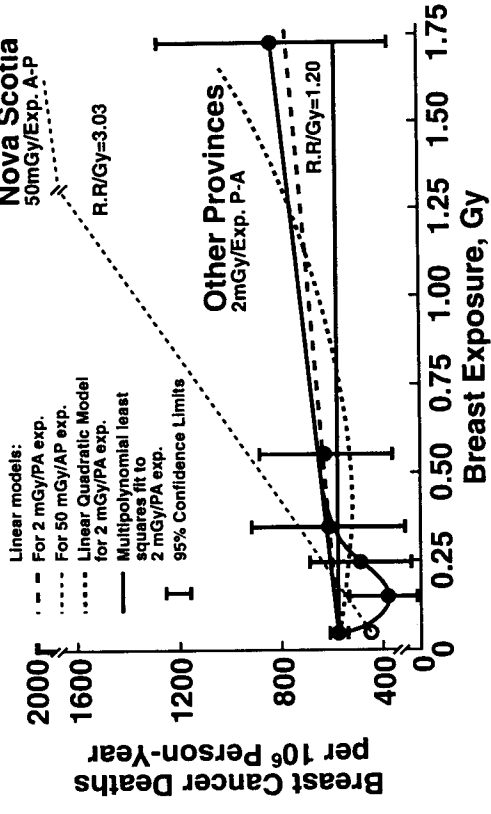


Figure 6. Canadian breast fluoroscopy study. Adapted from Miller AB, et al. (1989)

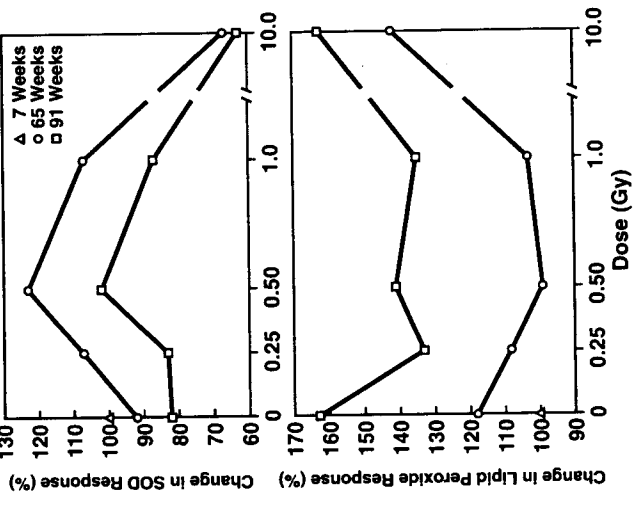


Figure 8. Antioxidant SOD and lipid peroxide response to age and radiation of rat brain cortex. Yamaoka K. (1991)

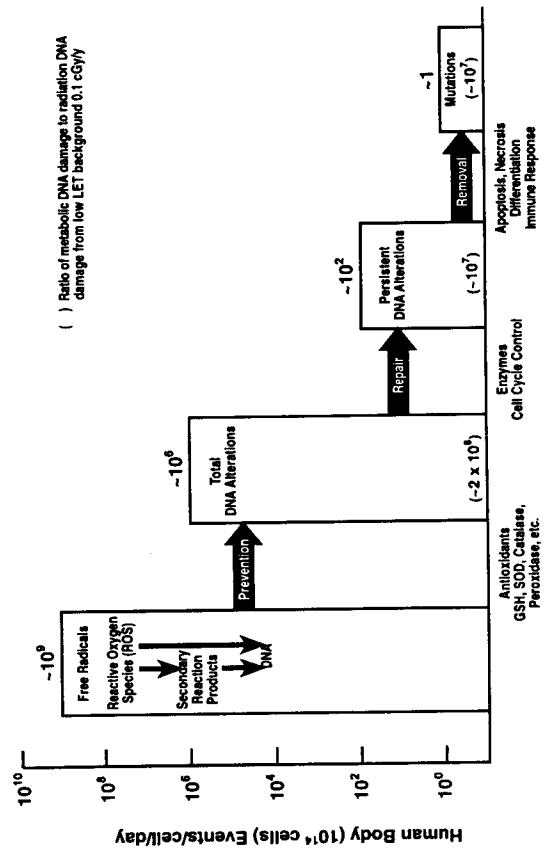


Figure 7. The antimutagenic DNA damage-control biosystem. Estimates based on data in literature. Polycova M and Feinendegen LE.

A 549 Human Lung Cancer Cell
Removal of Thymine Glycol After 2 Gy Dose

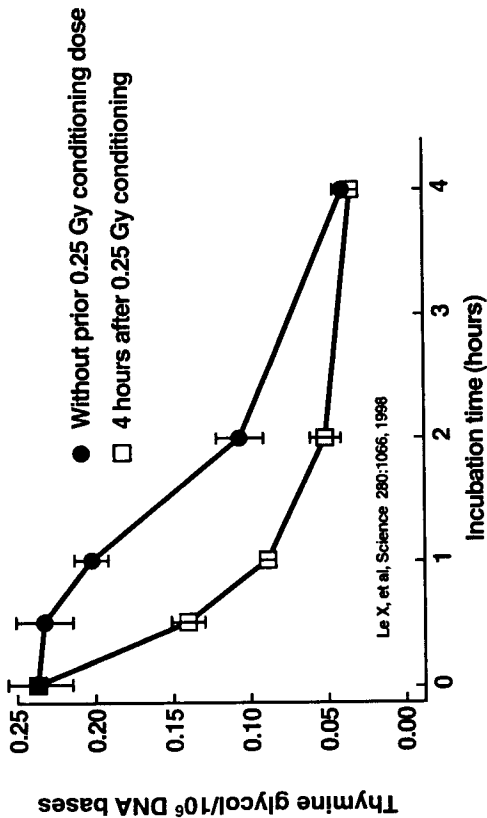


Figure 9. Low dose induced DNA repair. Le X, et al. Science 280:1066 (1998)

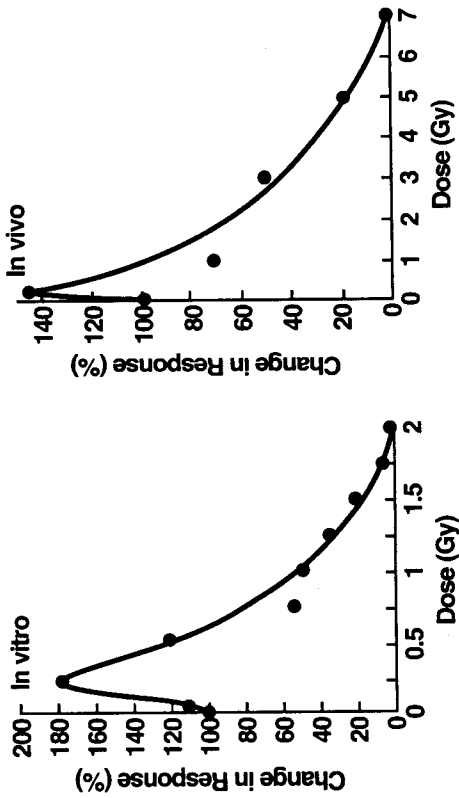


Figure 10. Immune system response to radiation. Mouse splenic cells primed with antigenic sheep red blood cells. Makinodan T and James S.J. (1990)

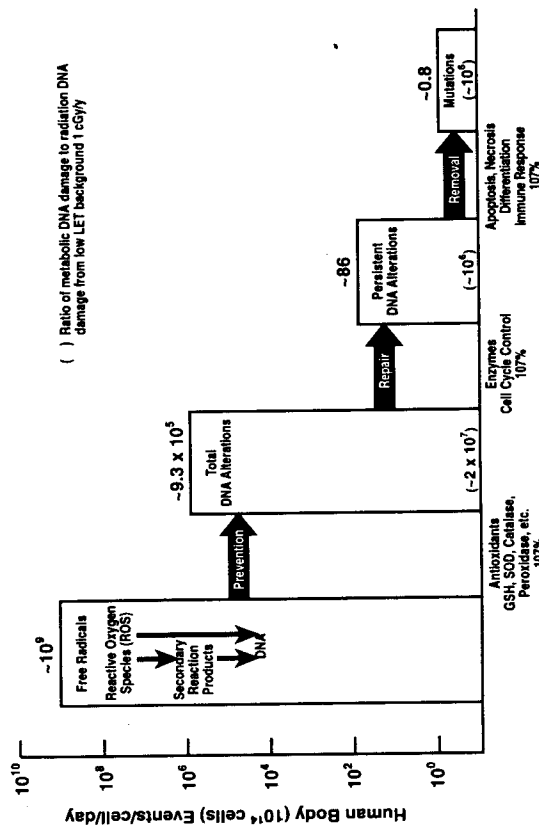


Figure 11. The antimutagenic DNA damage-control biosystem response to high background radiation = 120%. Estimates based on data in literature. Pollycove M and Feinendegen LE.

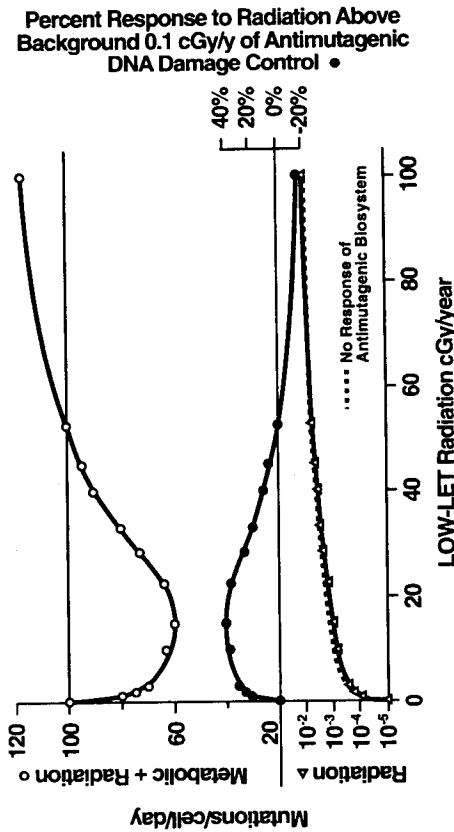


Figure 12. Response of antimutagenic DNA damage-control biosystem and mutations to low-LET ionizing radiation. Pollycove M and Feinendegen LE.

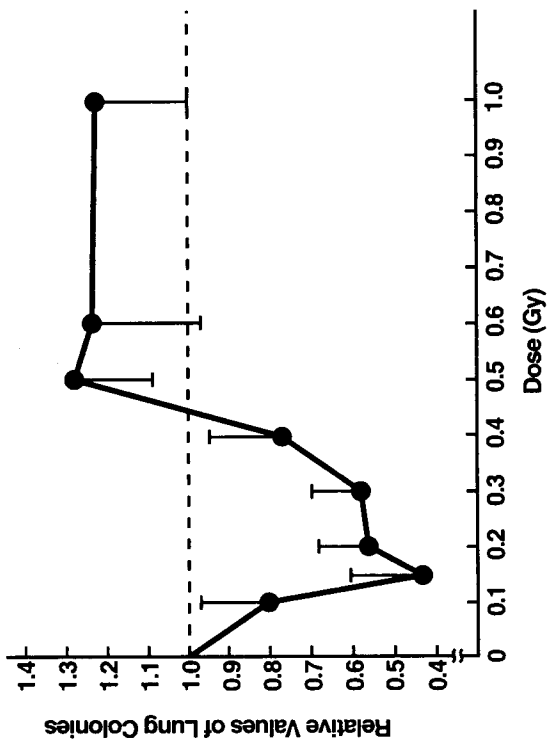


Figure 14. TBI given 12 days after tumor cell transplantation into axilla. Lung colonies counted 20 days after TBI. Low dose TBI ineffective with spleen blocked. Low dose splenic irradiation, half-body irradiation (HB) and TBI equally effective. Adapted from Sakamoto, et al. J Jpn Soc Ther Radiol Oncol 9:161-175, 1997

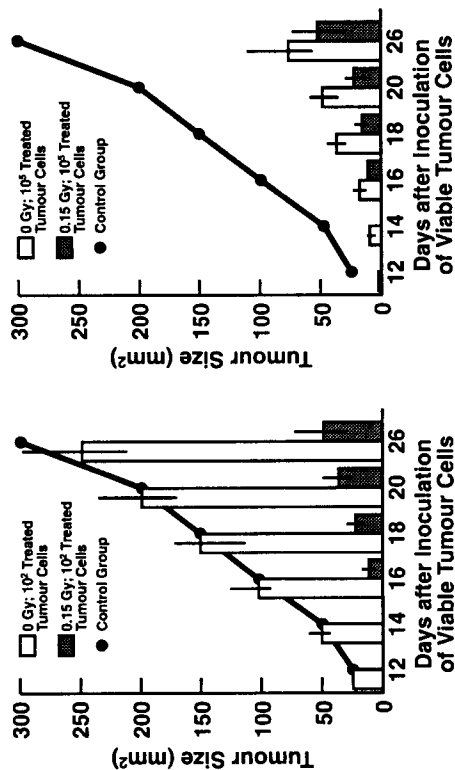


Figure 13. Effect of 0.15 Gy upon response of A/J mice to subimmunogenic and immunogenic numbers of non-viable mitomycin-treated fibrosarcoma (3a1) tumor cells. Groups of 60 mice were exposed to whole-body irradiation or sham-irradiated and inoculated subcutaneously with the indicated numbers of mitomycin-treated tumor cells. Twenty-one days later, all animals received 10⁵ untreated 3a1 cells and were followed for tumor size. A control group did not receive mitomycin-treated cells. Adapted from Anderson, et al (1988).

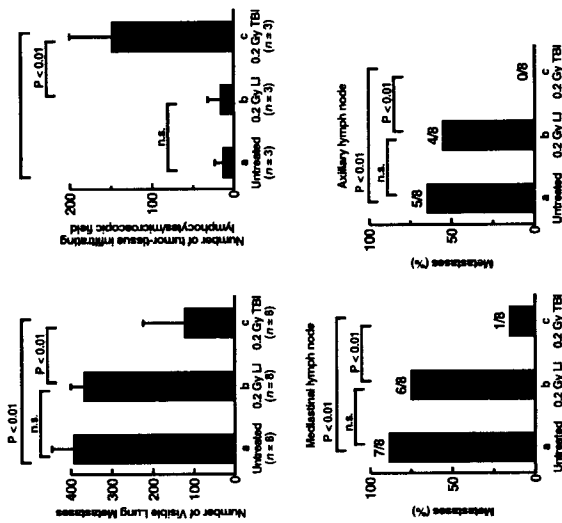


Figure 15. The number and incidence of metastases in lung and lymph nodes of mediastinum and axilla 50 days after intramuscular (leg) tumor implantation in rats, and the number of tumor infiltrating lymphocytes 21 days after implantation. Total body or localized tumor irradiation, with 0.2 Gy was given 14 days after implantation 5x10⁵ allogeneic hepatoma cells. Hashimoto et al. Radiation Res. 151:717-728 (1999).

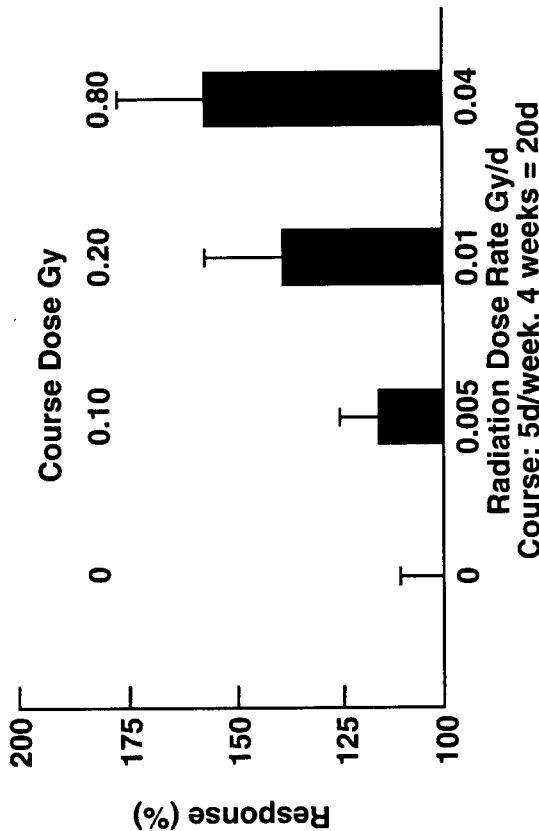


Figure 16. Dose-response analysis of splenic T cell proliferative response 3-5 d after the last radiation exposure of immunologically normal, long-lived C57B1/6J +/- mice. Results are expressed as the mean percent increase in ³H-thymidine uptake relative to 0 Gy control group as 100%. The vertical bars = 1 SEM. Makinodan and James (1990); adapted from James and Makinodan (1988).

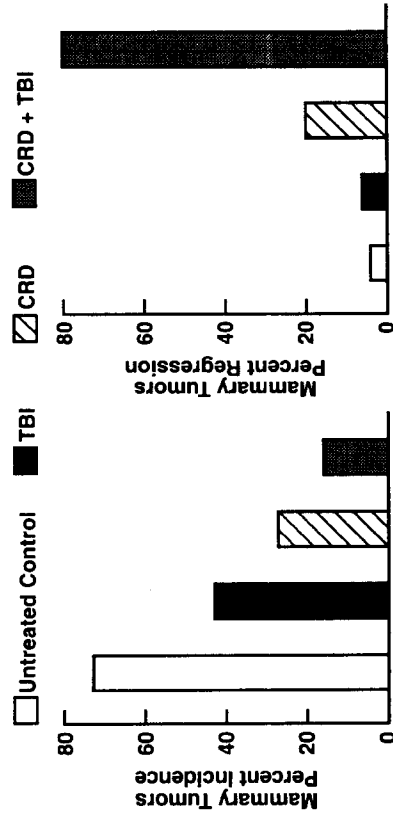


Figure 17. Eight month old, mammary tumor-susceptible, female C3H/He mice were first adjusted in a stepwise manner to chronically restricted diet (calorically 70% of ad libitum diet) (CRD) over a period of 3 weeks. The mice were maintained on CRD until completion of the study. After their diet was adjusted, the mice were exposed to TBI (0.04 Gy, 3 alternating days/week, 4 weeks) and were observed for 35 weeks. Tumor regression of the CRD + TBI group was very rapid and large numbers of CD8+ T cells were found infiltrating the regressing tumors, which were not seen in mice of the untreated control, LDR and CRD groups. Adapted from Makinodan (1992).

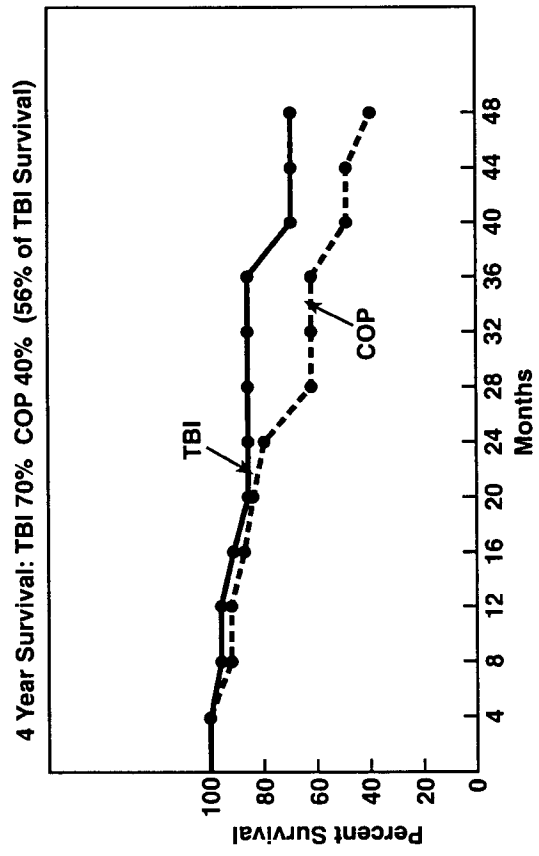


Figure 18. Comparison of TBI with COP Chemotherapy (Cytosoxan, Oncovin, Prednisone) in matched groups of 25 patients.

TBI: 39 PATIENTS 1972-1978
4 YEAR SURVIVAL 74%

CHOP: 225 PATIENTS 1986-1992
4 YEAR SURVIVAL 52%
(70% OF TBI SURVIVAL)

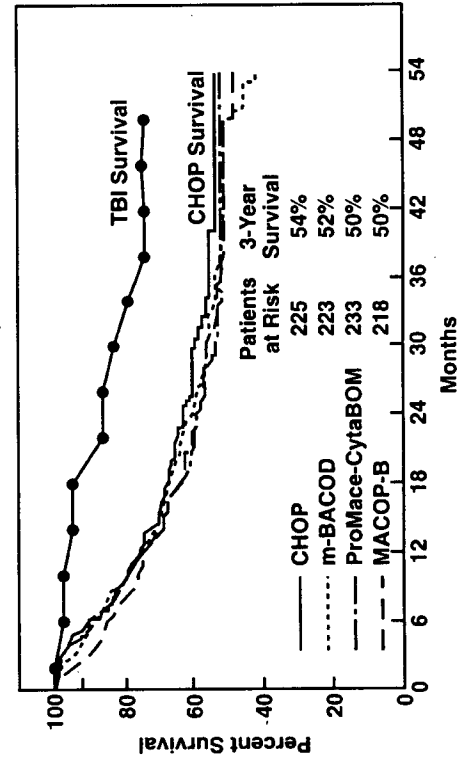


Figure 19. Comparison of TBI with CHOP Chemotherapy (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone). CHOP remains the best available chemotherapy treatment for patients with advanced-stage intermediate-grade or high-grade non-Hodgkin's lymphoma. N Engl J Med 1993;328:1002-6.

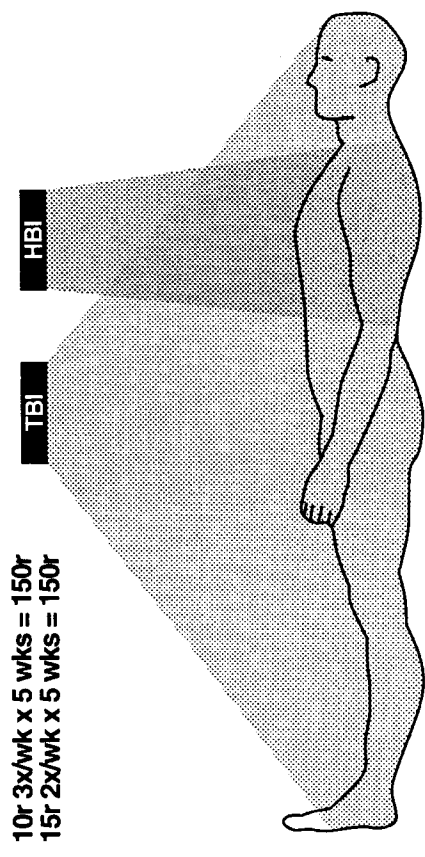


Figure 20. Treatment of patients with Non-Hodgkins Lymphoma with half (HBI) or total (TBI) body irradiation. Adapted from Sakamoto K, et al. J Jpn Soc Ther Radiol Oncol 9:161-175 (1997)

4 year survival: TBI-HBI 84% Chemotherapy 66% (79% of TBI-HBI Survival)
 9 year survival: TBI-HBI 84% Chemotherapy 50% (60% of TBI-HBI Survival)

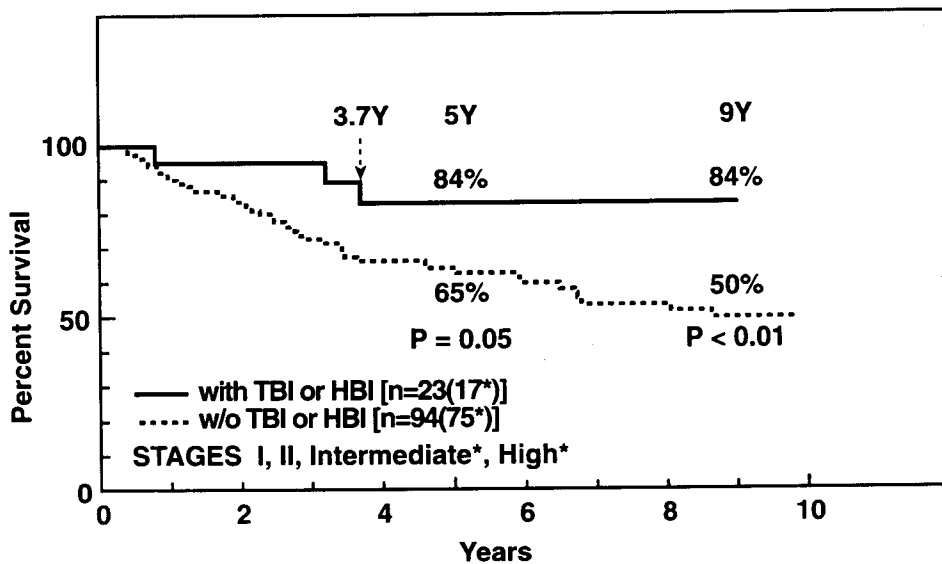


Figure 21. Comparison of low-dose irradiation of half body (HBI) or Total Body (TBI) of patients with Non-Hodgkin's Lymphoma. Patients in both groups received chemotherapy and localized tumor high-dose radiation. Adapted from Sakamoto et. al. J Jpn Soc Ther Radiol Oncol 9:161-175, 1997

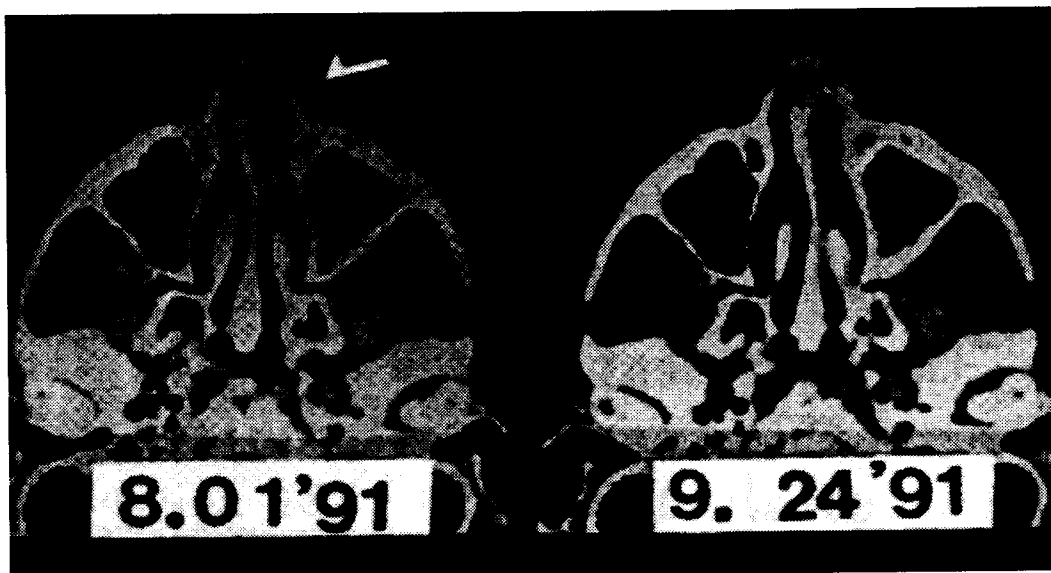


Figure 22. CT (computerized tomographic) scan of upper nasal cavity before and after half body irradiation (HBI). Nasal tumor, though outside HBI field, disappeared after low-dose HBI. Takai et al. In: Low Dose Irradiation and Biological Defense Mechanisms (Sugahara, Sagan, Aoyama, eds). Amsterdam, Elsevier Science Publishers, 1992:115-116.