Commentary

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 10⁹ 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 10⁶ 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 10⁶ 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 x 10⁻³/cell/d including 10⁻⁴ DSB/cell/d (31). Enzymatic repair of these DSB leaves about 10⁻³ persistent DNA alterations that also are reduced by apoptosis and immune system removal 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 of cancer (Fig. 5).
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-

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,
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 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
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) 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 239Pu. 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).
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).

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.
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 10^6 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

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Lines from the SNM President

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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
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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 Newsl ine 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

Detector Responses of Organisms

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