Health Hazards of Radiation Exposure in the Context of Brain Imaging Research: Special Consideration for Children

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This review provides information on health and biological effects of low-dose radiation to help institutional review boards and investigators make educated assessments of the risks of low-level radiation exposure involved in research, particularly in children. **Methods:** Studies of low-level radiation exposure with large sample sizes and long follow-up were reviewed. To help interpret the studies, we clarified the measures and measurement strategies of radiation exposure and of health risks. The few large studies of risks of low-level radiation in children have failed to detect an increased incidence of cancer. Most studies of low-level radiation involve adults. **Results:** The risk of increased rates of cancer after low-level radiation exposure is not supported by population studies of health hazards from exposure to background radiation, radon in homes, radiation in the workplace or radiotherapy. Compared to the frequency of daily spontaneous genetic mutations, the biological effect of low-level radiation at the cellular level seems extremely low. Furthermore, the potentiation of cellular repair mechanisms by low-level radiation may result in a protective effect from subsequent high-level radiation. Studies approved by institutional review boards in the U.S. that involve the exposure of healthy normal children to ionizing radiation were reviewed. **Conclusion:** Health risks from low-level radiation could not be detected above the "noise" of adverse events of everyday life. In addition, no data were found that demonstrated higher risks with younger age at low-level radiation exposure.

Key Words: biological risks; ionizing radiation; linear no-threshold model; health hazards; radiation exposure

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The purpose of this article is to provide information on the health risks and biological effects of low-dose radiation to help institutional review boards and investigators make educated assessments of the risks of low-level radiation exposure involved in research (minimal risk, minor increase over minimal risk or greater than minimal risk, as defined by the U.S. Department of Health and Human Services [DHHS]). Special attention is given to children and adolescents, whose participation in research requires the most scrupulous evaluation of risks.

The need for objective up-to-date information is particularly well illustrated in a debate on the level of risk assigned to pediatric research involving radiation published in the journal *Institutional Review Board* (*1,2*). Information from the developing organism is essential for an understanding of normal maturational processes. Abnormal development can be characterized only in relation to normal development. Studies of normal healthy children are critical to the advancement of knowledge and to the development of new therapeutic interventions. Although the risk:benefit ratio of research in healthy children will not be considered in this article, it is important to recognize that healthy normal children may also benefit from participating in research. For example, acquisition of knowledge leading to better medical care and health status can directly affect healthy normal children who are relatives of individuals (e.g., siblings or parents) suffering from the disorders under study. These normal healthy children may gain improved quality of life as well as knowledge potentially useful for their own children.

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THE PROBLEM IN CONTEXT

The major mission of institutional review boards is to decide to what level of risk a research protocol exposes its participants. The involvement of children most often requires the risks to be minimal or just above minimal. As defined by the DHHS in 46.102(i), "minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (*3*). Several organizations are involved in issues of radiation safety. They are listed in Table 1. Various units of measure are used to quantify ionizing radiation (Table 2). To facilitate comparisons among studies, we will express measurements in rem (roentgen equivalents in man) whenever possible. Health hazards of ionizing radiation result from unrepaired alterations of cellular DNA materials leading to genetic mutations. As a reference, an average of 240,000 genetic mutations occur spontaneously every day in the human body. Exposure to 1 rem adds about 100 more genetic mutations (*4*).

An understanding of the strategies used to assess health hazards is essential to avoid biased interpretations. Table 3 lists the definitions of commonly used measures of risks. Risks can be estimated as rates of incidence of cancer or death or loss of life expectancy in days. These indices can be compared to various hazards encountered in daily life. For example, of the life expectancy of the average American, approximately 207 days are lost from motor-vehicle accidents, 95 days from accidents in the home, 74 days from job-related accidents and 40 days from accidents at jobs with radiation exposure (*5*). An increased incidence of leukemia is a sensitive indicator of radiation effect at high levels, partly because of its low spontaneous incidence and its short latent period after exposure and partly because of the presumed high radiosensitivity of the bone marrow. The breast also has a relatively high radiosensitivity, and the incidence rate of breast cancer in women has been used extensively to measure radiation risks. Another way to express the health risk of radiation from medical research is to compare it with risks of radiation from other familiar sources such as natural background radiation (average in the U.S.: 0.3

TABLE 1
Acronyms for Professional Organizations and Committees Contributing to Radiation Control

Acronym	Description
AEC	Atomic Energy Commission. Founded in 1945, it was replaced by the Energy Research and Development Administration (ERDA) in 1974.
BEIR	Committee on the Biological Effects of Ionizing Radiations, National Research Council (previously called BEAR).
DOE	U.S. Department of Energy.
ERDA	Energy Research and Development Administration. It was later broken into the Nuclear Regulatory Protection (NRC) and the Department of Energy (DOE).
FDA*	U.S. Food and Drug Administration. It is a federal agency responsible for approving the use of new drugs and new devices.
ICRP	International Commission on Radiation Protection (international counterpart of the NCRP).
ICRU	International Commission on Radiation Units and Measurements. It was started in 1925; its principal function is to recommend standards for quantities and units of radiation and radioactivity and procedures for clinical radiology and radiobiology.
MIRD	Medical International Radiation Dose Committee of the Society of Nuclear Medicine (SNM). It provides the methodology for internal dose calculations. Computerized version of the programs to calculate doses include MIRDOSE and DOSCAL.
NCRP	National Council on Radiation Protection and Measurement (originally known as the American X-ray and Radium Protection Committee, founded in 1929). It is sponsored by the National Academy of Sciences. It has no legal standing but is the standard of acceptable practice in the legal courts. Its recommendations serve as a basis for regulations but are not regulations themselves.
ORNL/TM 8381/V1-7	This Oak Ridge National Laboratory publication provides data for each age-specific and gender-specific body habitus.
NRC	U.S. Nuclear Regulatory Commission. It is a federal agency responsible for regulating the nuclear power industry and deciding issues involving environmental radiation. Naturally occurring and accelerator-produced radionuclides were exempted from NRC jurisdiction and left for the individual states to control and regulate.
SNM	Society of Nuclear Medicine.
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation.

*There are no specific governmental regulations for dose of *external* radiation, but there are limitations for administered activity and clinical applications of radioactive materials, described in package inserts approved by the FDA. These FDA limitations are not legally binding.

rem/yr [National Council on Radiation Protection and Measurement (NCRP)]; range: 0.1–2 rem/yr) (*6*). Finally, chromosome analysis of blood cells, either irradiated or from individuals exposed to radiation, measures the frequency of chromosomal aberrations. Although helpful, this measure cannot be used as a direct assessment of risks because the level at which the number of chromosomal aberrations becomes clinically significant is not known.

The distinction between low-level and high-level radiation is critical in the evaluation of biological consequences of exposure to ionizing radiation. Although controversial, three assumptions are currently guiding radiation protection standards and prac-

TABLE 2
Units for Use with Radiation and Radioactivity

Quantity	Old unit	New unit	Equivalence
Activity	Curie (Ci) (3.7×10^{10} dps)	Becquerel (Bq) (1 dps)	1 Ci = 3.7×10^{10} Bq
Exposure	Roentgen (2.58×10^{-4} C/kg)	Coulomb/kg (C/kg)	1 R = 2.58×10^{-4} C/kg
Absorbed dose	rad (100 erg/gm)	Gray (Gy) (1 J/kg)	1 Gy = 100 rad
Effective dose equivalent	rem	Sievert (Sv)	1 Sv = 100 rem

dps = desintegrations per second; effective dose equivalent = the weighted sum of doses to individual organs where the weighing factors are based upon estimates of relative risk of stochastic (probable) effects from irradiation of the different tissues. This measure, introduced by International Commission on Radiation Protection Publication 26, approximates inhomogeneous irradiation of the human body to a comparable whole-body radiation to permit the comparison of the relative risks from various radiation exposures (e.g., occupational radiation, exposure from medical procedures). Its use is not uniformly accepted.

TABLE 3
Definitions of Measures of Risks

Term	Definition
Absolute risk (AR)	Excess number of cases attributed to irradiation, usually expressed as the numerical difference of risk between the irradiated and nonirradiated populations; for example, excess number of cancers, per unit of time, in the exposed population, for a unit of dose.
Excess absolute risk (EAR)	The absolute difference between the instantaneous incidence or mortality rates between two groups of people; for example, those exposed and those unexposed.
Excess relative risk (ERR)	Relative risk minus one. The amount of risk over or under unity.
Relative risk (RR)	Ratio between the number of cases in the irradiated population to the number of cases expected in the unexposed population. It is usually expressed as a multiple of the natural risk.
Mortality ratio or incidence ratio (MR)	Observed number of deaths divided by the expected number of deaths. Significance of the difference between observed and expected given by tests such as the Mansel-Haenszel summary chi-square.
Standardized mortality ratio (SMR)	A ratio that indicates the percent increase or decrease in mortalities due to certain causes. It is the ratio of the number of deaths observed in the study population to the number of deaths that would be expected if it had the same age-, sex- and calendar-period-specific mortality rates as the standard population, which is often the relevant national population. A value equal to 1.00 is the incidence in the general population, whereas <1.00 would convey a decrease in mortality and >1.00 would convey an increase in mortality. For example, an SMR of 1.10 would indicate a 10% mortality increase compared to the general population.
Standardized incidence ratio (SIR)	Similar to the SMR, except that SIR involves incidence rates rather than mortality rates.
Unity	The value of 1.00 when referring to relative risks, absolute risks, standard incidence ratios and/or standard mortality ratios. This value represents the incidence in the general population.
Person-years	A unit of measurement combining persons and time, used as denominator in instantaneous incidence and mortality rate. It is the sum of individual years that the persons in the study population have been at risk of developing or dying from the condition of interest.
Person-rem	Unit that measures collective population dose. It is calculated by multiplying the number of persons exposed times their *average* individual dose in rem; 10,000 person-rem is the collective dose received by 10,000 persons exposed to an average individual dose of 1 rem. It is also the dose received by 100,000 persons each exposed to an average individual dose of 0.1 rem.

tices: (a) any radiation dose can produce adverse effects such as cancer or genetic damage; (b) the severity of adverse effects is directly proportional to the radiation dose received; and (c) children are more radiosensitive than adults. The first two premises led to the formulation of the theoretical linear no-threshold model to describe the dose-response relationship between radiation exposure and health hazards. This model is one of three possible types (Fig. 1): The linear no-threshold model posits that health risks increase linearly with higher doses of radiation and that the effects of radiation are unfavorable at all doses above zero. The threshold model presumes that adverse effects start at one point above zero and that below this point no adverse effects occur. Finally, in the hormetic model, adverse effects start at one point above zero, and below that

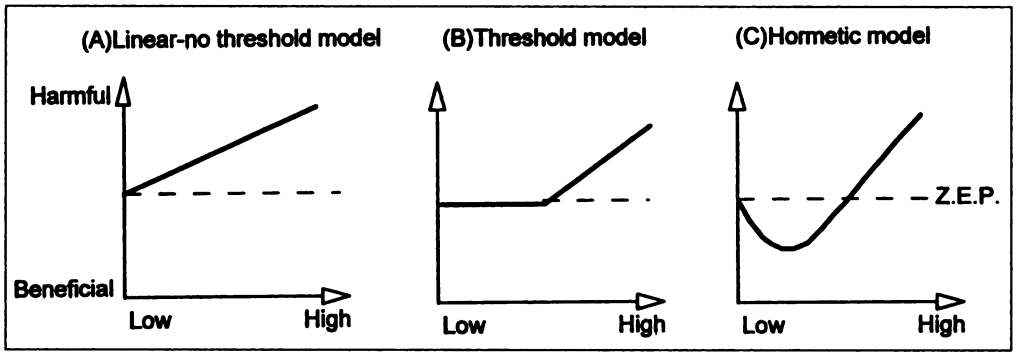

FIGURE 1. Models of the dose-effect relationship of ionized radiation exposure. x-axis = dose level of radiation exposure; y axis = magnitude of health hazards; A = linear no-threshold model, in which the effects of radiation are negative at all doses above zero; B = threshold model, in which adverse effects start at some point above zero; C = hormetic model in which positive effects occur at low doses; Z.E.P. = zero equivalent point at which radiation has no overall effect. [Adapted with permission from Van Wyngaarden Pauwels. *Eur J Nucl Med* 1995;22:481.]

point beneficial effects occur. To date, studies trying to verify the linear no-threshold model have found that, whereas radiogenic adverse effects are well demonstrated at high-level doses, they become contested at low-level doses (*7,8*). The linear no-threshold model fails to take into account cellular repair mechanisms that protect genetic material against low-level radiation (*9*). Consequently, extrapolation of risks from high-level radiation to those of low-level radiation can be misleading.

Radiation exposure in clinical research not involving therapeutic trials is exclusively low level, and studies presented here will be mostly those assessing risks of low-level radiation. Studies of populations exposed to high-level radiation, such as those of atomic bomb survivors, will not be reviewed. Doses lower than 10 rem are generally considered low-level radiation (intermediate doses range from 10 to 250 rem; high doses exceed 250 rem). Nuclear medicine procedures, with the exception of some cancer treatments, are by-and-large low level. The Food and Drug Administration limits the use of radioactive research drugs in human volunteers to the following: for participants under 18 yr—0.3 rem to the whole body, blood-forming organs, lens of the eye and gonads from a single administration and 0.5 rem annually and 0.5 rem to other organs from a single administration and 1.5 rem annually; for participants 18 or more yr—3.0 rem to the whole body, blood-forming organs, lens of the eye and gonads from a single administration and 5.0 rem annually and 5.0 rem to other organs from a single administration and 15.0 rem annually.

Several reports have claimed to evidence significant risk from relatively low levels of radiation. These reports have been largely discredited because of environmental or statistical artifacts, inadequate control population, small sample sizes and uncontrolled level of radiation exposure. They have nonetheless attracted much attention because of their appearance in prestigious journals, even though most of them were published as letters to the editor not subjected to peer review or as press releases. These outlier reports will not be discussed in this review. Most studies of low-level radiation involve adults. Extrapolations from findings in adults to populations of children may be acceptable if no detectable increase in sensitivity to low-dose ionizing radiation can be found at younger ages. This proposition is reviewed first.

POTENTIAL HEALTH HAZARDS FROM LOW- AND MODERATE-LEVEL RADIATION IN CHILDREN

Lundell and Holm (*10*) conducted a 39-yr retrospective study of the rate of mortality from leukemia after irradiation in infancy for skin hemangioma. From 1920 to 1959, 14,624 infants under the age of 16 mo (mean age: 6 mo) received radiotherapy. The average weighted bone marrow dose was 13 rem (range: <1–460 rem). Leukemias were identified through the Swedish Cause of Death Registry, the Swedish Cancer Registry and/or death certificates. A total of 20 deaths from leukemia were recorded, and 17 deaths were expected. For all leukemias, the relative risk was 1.0 for a dose of 1 μrem, 0.9 for a dose between 1 and 10 rem and 1.7 for a dose above 10 rem. No increase in incidence of leukemia was observed after low-level radiation exposure in infancy.

Similar findings were reported after radiation exposure in both infancy and childhood. After the Chernobyl incident in 1986, two studies from Finland (*11*) and Sweden (*12*) evaluated the incidence of childhood leukemia. In Finland, incidence rates of leukemia were calculated for 1 million children, ages 0–14 yr, who had been exposed to a range of radiation between 0.011 and 0.097 rem over the first 2 yr after the Chernobyl accident. Cancer incidence after the accident was not higher than before the accident and was not associated with dose of radiation exposure (*11*). The Swedish study involved 888 children, age 0–15 yr, diagnosed with acute leukemia out of a population of 1.6 million children. The level of radiation exposure ranged from less than 10 kBq/m^2 to 200 kBq/m^2. No significant increase in leukemia was found with increased radiation exposure (*12*).

For radiation doses higher than low level (average doses of 10–6000 rem), studies have found a relationship between exposure to ionizing radiation and thyroid tumors (*13–16*). However, for diagnostic doses of ^{131}I (*17*) and low-dose radiation fallout in southwestern Utah (*18*), no increased incidence of thyroid tumors has been found.

The only large study to report an increased incidence of thyroid cancers after radiation exposure in childhood is from Israel. The incidence of thyroid tumors after scalp irradiation of children with tinea capitis was calculated retrospectively for about 11,000 participants exposed to radiation before age 15 and 16,000 controls followed from 1950 to 1972 (*16*). Mean age at radiation exposure was 7.1 yr (range: 1–15 yr). Dose of exposure to the thyroid gland was estimated to average 9.3 rem with a range of 4.5–50.0 rem. These doses were estimates from post hoc measurements of representative exposures assumed to be analogous to the original exposures. Incidence of thyroid cancer was significantly higher in participants exposed to radiation compared to controls (14.5 excess thyroid cancer/100,000 person-years). Within this low-to-moderate radiation dose, findings indicated a higher risk with younger age for thyroid cancer, particularly in children younger than 5 yr at the time of exposure. The generalization of this conclusion to the risk from low-level radiation is problematic given the high proportion of children exposed to moderate-level radiation and the lack of true measure of the radiation exposure.

In conclusion, no studies have detected an excess of cancers after low-level radiation exposure in children above 5 yr old at the time of exposure. Studies of radiation exposure in infancy have not detected increased incidence of leukemia within 39 yr of the exposure. Because of the limited number of studies in children, studies of radiation exposure in adulthood are reviewed.

STUDIES OF POTENTIAL HEALTH HAZARDS FROM LOW-LEVEL RADIATION

Three types of widespread low-level radiation exposure have been exploited to determine health hazards: out-of-home background radiation (average intensity in the U.S.: 0.092 rem/yr; average range: 0.020 rem/yr–1.0 rem/yr), radon in homes (0 pCi/liter–60 pCi/liter, equivalent to 0.18 rem/yr–10.8 rem/yr) and medical/occupational exposure (average range: 0.001 × 10^{-3} rem/yr–15.0 rem/yr). Only those studies of low-level radiation (except for few studies of risks of radiotherapy) with large sample sizes and long follow-up are reviewed.

Radiation Background

The High Background Radiation Research Group in China (*19*) tested 73,000 participants, of which 90.6% had lived in the same region for six generations or more. The average dose for participants in the high-background radiation area was 0.231 rem/yr, and in the control area it was 0.096 rem/yr. Two cytogenetic studies analyzed lymphocyte chromosomal aberrations from blood samples at two different times in two different samples of 95 and 106 inhabitants from the high-background area compared to 95 and 104 inhabitants from the control area. In both studies, no significant differences of chromatid and chromosomal aberrations were found between the participants

of the high-background area and those of the control area. In fact, the frequency rates of hereditary diseases and congenital deformities were lower, although not significantly so, in the high-background group (n = 3504; rate = 13.70 per 1000) than in the control group (n = 3170; rate = 14.51 per 1000). Similar findings were found for spontaneous abortion rates, frequency of malignancy and growth and development of children. The authors concluded that either the sample size in this study was not large enough to detect differences or the dose-effect curve has a zero slope at these levels of radiation exposure.

Amsel et al. (*20*) compared the cancer death rates in about 825,000 inhabitants from low-altitude areas (<1,000 feet, low-background radiation) to 350,000 inhabitants from high-altitude areas (>3000 ft, high-background radiation) after controlling for urbanization, industrialization and ethnicity. Surprisingly, the most significant difference was a higher death rate from specific cancers (melanomas, cancers of the mouth and tongue, esophagus, larynx and lung) and from all combined cancers in low-altitude regions (low-background radiation) compared to high-altitude regions (high-background radiation). Death rates from cancers of the large intestine, rectum and pancreas were elevated in low-altitude areas only in isolated groups. Death rates from cancers of the ovary, kidney, eye, cervix, uterus, prostate and testis showed no differences between regions (*20*). This study suggests that at low levels of exposure, incidence rates of cancer do not follow a positive dose-risk relationship. Whereas industrialization, urbanization and ethnic distribution were held constant, the lack of control for smoking and diet represents a possible limitation in the interpretation of these findings.

A study by Frigerio and Stowe (*21*) compared cancer rates at different levels of background radiation within the U.S. The authors divided the U.S. into four groups: A = the 7 states with background radiation higher than 0.165 rem/yr; B = the 14 states with background radiation higher than 0.140 rem/yr; C = the 14 states with the lowest backgrounds; and D = the 50 states as a whole. The results showed a general decrease in malignancies as background radiation increased (*21*). Correlation analyses of background and rate with about 40 possible confounding factors (geographical, demographic, physical and socioeconomic domains) were performed, and none were significant. Furthermore, the age-specific rates of malignant mortality among the young (0–9 yr old and 10–19 yr old) of Groups A and B (high-background radiation) were lower than those of Groups C and D. These findings do not support low-level radiation as a significant environmental hazard and do not indicate higher vulnerability of children to radiation at low doses.

Radon in Homes

Radon is an inert noble gas whose decay products emit alpha rays. Studies of radon effects offer a unique opportunity to test carcinogenic effects of radiation because of the wide range of radon concentrations in conjunction with large exposed populations. Exposure to radon has been implicated in lung cancer (*22*) and has been reported to account for about 10,000 deaths from lung cancer per year in the U.S. (*23,24*). However, these estimates were extrapolated from data of miners exposed to a high concentration of radon and were calculated using the theoretical linear no-threshold model, which is controversial at low-dose levels. Indoor radon accounts for nearly half of radiation exposures in the general population (*25*). Exposure to radon gas is quantified by computing time-weighted exposures to radon concentration in air, in picocuries per liter (pCi/liter). For clarity, these measures will be converted to rem. According to National Council on Radiation Protection and Measurement Publication 93, 1 pCi/liter of radon in the home, assuming 75% occupancy and 50% equilibrium factor between radon and radon products, is equivalent to whole-body exposure of about 0.18 rem/yr.

A large study by Cohen and Colditz (*26*) was unable to support the relationship between radon exposure and lung cancer predicted by the Committee on the Biological Effects of Ionizing Radiation (BEIR) version of the linear no-threshold model (BEIR-IV). In fact, findings showed a strong tendency for a negative correlation between lung cancer rates corrected for smoking prevalence and radon exposure level in homes from 1730 counties (*7,26*). This finding would be consistent with the hormetic dose-response model that posits the occurrence of beneficial effects at low-level radiation exposure (Fig. 1).

Blot et al. (*27*) conducted a case-control study of rates of lung cancer as a function of indoor radon level in the houses of 308 women newly diagnosed with lung cancer and 356 randomly selected women. Participants were from Shenyang, People's Republic of China, an industrial city with the world's highest rates of lung cancer in women. The median radon level was about 0.414 rem/yr (range: 0.018–9.927 rem/yr). The U.S. Environmental Protection Agency recommends a threshold of 0.720 rem/yr (4 pCi/liter) for acceptable radon levels in homes. When controlled for age, education, smoking status and indoor air pollution, no correlation was found between radon levels and lung cancer.

Studies that reported a positive correlation between radon levels and cancer rate (*28–31*) had severe methodological limitations, including relatively small sample sizes and use of estimates of radon levels instead of actual measurements. For example, a study by Schoenberg et al. (*28*) observed a positive correlation between radon and cancer rate, but only six cases and two controls were exposed to radon levels ≥0.720 rem/yr in contrast to 86 cases and 107 controls in the Blot et al. study (*27*). Small case-control studies in Sweden showed positive associations between risk of lung cancer and living in houses whose structures were *estimated* to have high radon levels (*22,32*). In another example, Pershagen et al. (*29*) measured radon levels in houses of 1281 cases and 2576 controls selected from 109 municipalities in Sweden and found a positive association between radon exposure and lung cancer. This study may have suffered from a selection bias because both lung cancer rates and average radon levels were known before the selection of municipalities, cases and controls were made.

In conclusion, well-controlled large studies of long-term effects of exposures to radon, at doses congruent with low-level radiation, consistently indicate no association with incidence rate of lung cancer.

Medical Exposure

The risks associated with medical ionizing radiation (i.e., radiotherapy, also referred to as radionuclide therapy) may be overestimated because they comprise health risks from both radiation exposure and the primary medical condition. Radiation exposure in the studies discussed later exceeds, for the most part, the low-level dose threshold (10 rem).

Saenger et al. (*33*) studied 33,888 patients treated for hyperthyroidism from 26 medical centers. Four treatment groups were compared: 18,379 were given ^{131}I radioiodine, 10,731 underwent surgery, 3311 were treated with a combination of the two and 1467 were treated with drugs only. Radioiodine treatment resulted in an average exposure dose of 10 rem to the bone marrow, within a range of 7–15 rem. More

than half of the radiation dose was received over a week. The frequency of leukemia did not differ between the groups (*33*). At follow-up 3 yr later, rates of leukemia were unchanged (*34*).

A similar Swedish follow-up study reports on 10,552 patients (age range: 13–74 yr; mean: 57 yr) up to 15 yr after ^{131}I radioiodine treatment. Radiation treatment was delivered over 4 wk at doses ranging between 6000 rem and 10,000 rem to the thyroid and between 10 rem and 25 rem to other organs. The overall cancer risk at 10 or more years of follow-up was only slightly above the risk expected in the general population (*35*). There was no dose-response relationship, except for cancer of the stomach (the stomach received on average 25 rem, the second highest radiation dose after the thyroid) (*35*). The incidence of leukemia was not increased. This finding was in contrast to relatively higher rates of leukemia extrapolated from risks at high-level radiation effects (atomic bomb survivors). The authors concluded that their findings, drawn from over 10,000 patients with hyperthyroidism treated with ^{131}I, did not support the premise that relatively low-dose radiation exposure is associated with detectable elevated rates of cancer in humans.

Incidence of leukemia was assessed in 46,998 participants (age range: 1–75 yr; mean: 47 yr) exposed to radiation from ^{131}I to the thyroid for diagnostic and treatment purposes. Compared to the general population, incidence rates of overall leukemias, chronic lymphocytic leukemia and nonchronic lymphocytic leukemia were not elevated at 21-yr follow-up (*36*). Radiation exposure to the bone marrow was estimated at 1.4 rem. Risk was not higher among the young (<40 yr) nor in the high-risk period of 2–9 yr after exposure.

In summary, when large samples were followed, researchers found that exposure to radiation treatment at relatively low-dose levels did not increase the incidence rate of leukemia.

Occupational Exposure

Radiation exposure in the workplace is strictly regulated by the U.S. Nuclear Regulatory Commission (NRC) and by Agreement States for source, byproduct and special nuclear material. These safety regulations are based on the linear no-threshold model. The following NRC limits are required in the U.S. (NRC Standard in Revised 10 CFR 20): Occupational exposure of adults is limited to 50 rem/yr to any organ or tissue (except the eye), 15 rem/yr to the lens of the eye and 50 rem/yr to the skin or 5 rem/yr total effective dose equivalent. The occupational exposure of minors (<18 yr) is one tenth of these limits. In occupational studies, age-specific death rates for all causes and for cancer are often reported lower in the working population than in the general population. This finding is called colloquially "the healthy worker effect." In addition, estimates of radiation risk in some worker studies may be spuriously inflated because of additional risk from other sources such as chemicals.

Doody et al. (*37*) conducted the largest study to date evaluating the risk of radiation exposure among female radiologic technologists. All women had been certified by the American Registry of Radiologic Technologists between 1926 and 1980. Of 69,510 women, 528 valid cases of breast cancer were reported. The cases and controls were matched by year of birth, year of certification and length of follow-up. No significant association was found between breast cancer and the performance of radiotherapy procedures. In addition, the number of years working with radiation did not influence incidence of breast cancer. Unfortunately, measurements of individual radiation doses were not available.

In the United Kingdom, data from 95,217 participants were compiled in a cohort study to determine the risk of mortality from cancer associated with occupational radiation exposure in the nuclear industry between January 1976 and December 1988 (*38*). The mean lifetime dose per person was about 3.36 rem. Sixty-two percent of the participants had a lifetime exposure lower than 1.0 rem, and 9% had exposures greater than 10.0 rem. The only significantly increased cancer death rate was that of thyroid cancer (nine deaths). Incidences of all malignant neoplasms, pulmonary cancers, skin cancers other than melanomas and central nervous system cancers were significantly lower. Mortality from the remaining types of cancer was not significantly affected by histories of radiation exposure. Overall, rates of mortality (from all causes and from most specific cancers) were found lower in radiation workers than in the general population of England and Wales. The authors speculated that the higher incidence of thyroid cancers might have been a chance finding given the large number of statistical tests.

Report of combined data on 35,933 workers at Department of Energy facilities (Hanford Site, Hanford, WA; Oak Ridge National Laboratory (ORNL), Oak Ridge, TN; and Rocky Flats Nuclear Weapons Plant, Golden, CO), with a follow-up of 27–37 yr, found no association between chronic exposure to low-dose radiation (range: 0–50 rem) and mortality from all cancers or from leukemia (*39*). Myeloma was the only cancer of 11 specific types of cancer studied whose incidence was correlated with radiation exposure. This correlation resulted from three deaths with doses exceeding 5 rem in workers from Hanford only. Based on the assumption of equal multiple myeloma rates in the three sites, the expected deaths were 2.4, 0.52 and 0.12 in Hanford Site, ORNL and Rocky Flats Nuclear Weapons Plant, respectively. Whereas the failure to observe a multiple myeloma correlation in ORNL and Rocky Flats could have been due to small sample size, a causal relationship is difficult to conclude for the correlation in the Hanford workers (*39*).

A cohort of 736 white women employed in the radium dial-painting industry before 1930 were examined for incidence and death rates of breast cancer according to four possible risk factors: radium intake dose (internal alpha-emitting radionuclides), duration of employment, age at first exposure (10–39 yr) and parity (*40*). This sample included the participants with available measures of body radium content from a cohort of 1180 women. Follow-up time extended over 50 yr after initial exposure. Varying amounts of ^{226}Ra and ^{228}Ra were ingested because of inadequate safety practices. The mortality ratio for the total group was 1.24, not significantly different from unity. By doses, the mortality ratio was 4.8 for radium intake >50 μCi and 0.64 for radium intake <50 μCi. Taken at a constant rate for 1 yr, 50 μCi corresponds to a dose 25 times the current maximum permissible amount of 0.1 μCi of ^{226}Ra for radiation exposure. Mortality ratios for women employed before age 19 yr and after age 19 yr did not differ significantly from each other nor from the expected ratios. Similarly, mortality ratios for women employed for less than 50 wk and for longer than 50 wk did not differ significantly from each other nor from the expected ratios. Mortality ratio was 0.85 for women who had at least one live birth and 2.0 for women who never had a viable birth. Whereas neither of these ratios were significant at $p < 0.05$, they were consistent with values observed by other investigators.

These studies of risks from occupational radiation exposure failed to detect significant higher risks of cancer after exposure to low-level radiation.

Conclusion

This short review of health hazards from low-level radiation exposure does not support the applicability to low-radiation

doses of the linear no-threshold model for the dose-response relationship. To date, no large studies (with robust statistical power) have shown health risks from low-level radiation exposure. Furthermore, there is a suggestion that low-level radiation may have a protective effect.

CELLULAR EFFECTS OF LOW-LEVEL RADIATION

As mentioned in the introduction of this article, estimates of biological hazards from low-level radiation should take into account the protective effects of cellular repair mechanisms. These DNA repair mechanisms are very active during normal metabolism because of the large number of spontaneous DNA mutations. In a basal physiological condition, about 10,000 measurable genetic modification events occur per hour in each cell body due to endogeneous causes (*4*). A maximum of 100 measurable DNA alterations occur per rad (1 rad = 1 rem in low linear energy transfer radiation), which corresponds to 1% spontaneous DNA events. For specific alterations, the incidence rate of DNA damage is the following: single-strand breaks, 4.4×10^7 per year and 10 per rem; depurination or base lesion, 1.4×10^7 per year and 9.5 per rem; total events, 7×10^7 per year and 20 per rem. These mutations are repaired by cellular mechanisms that restore the breaks. It is likely that the biological impact of low-level radiation affects both the number of mutations and the cellular repair mechanisms. Several studies have addressed this issue.

The strategy used to evaluate potential protective effects of low-dose radiation was an assessment, in vitro at the cellular level, of the effect of pre-exposure to low-level radiation dose on the amount of damage induced subsequently by high-level exposure. This protective effect is thought to be mediated by the stimulation of chromosomal repair mechanisms through the synthesis of new proteins.

Hypotheses proposed to explain the mechanism of action of the protective effect of low-dose radiation include the following: activation of the immune system through the increase of human cytokine receptors; synthesis of new proteins through the activation of gene expression, possibly from damaged DNA and nucleoproteins; and formation of reduction products of oxygen.

A study conducted by Olivieri et al. (*41*) incorporated into human peripheral lymphocytes either nonradioactive thymidine or radioactive [^{3}H]thymidine. Continuous low-dose radiation exposure from [^{3}H]thymidine has been shown to cause chromatid aberrations reminiscent of x-ray effects. On the second to third day of culture, the cells were exposed to high-dose x-rays (150 rem). Chromosomal analysis was conducted from 3 to 11 hr after the high-dose exposure. The number of chromosomal aberrations after x-ray radiation was not elevated by the additional low-dose continuous radiation exposure from [^{3}H]thymidine; it was even lower compared to the effect of x-rays alone.

Shadley and Dai (*42*) examined lymphocytes from five human volunteers. Lymphocytes were exposed to various regimens of ionizing radiation and were distributed into six groups: (a) no radiation, (b) 5 rem, (c) 400 rem, (d) 200 rem, (e) 5 rem followed 6 hr later by 400 rem and (f) 5 rem followed 6 hr later by 200 rem. Cytogenic (chromosomal aberrations including dicentrics, rings and deletions) and survival analyses (number of replications, cell survival) were performed 7–10 days after irradiation. The 5 + 200 group showed fewer DNA aberrations in the lymphocytes of all five donors, statistically significant in the lymphocytes of only one donor. The 5 + 400 group showed a statistically significant reduction of aberrations in all five donors. Results of the survival analysis were less clear.

In a similar in vitro study of human lymphocytes, Sanderson and Morley (*43*) reported a reduction of the mutagenic effect of a challenging radiation dose (150 and 300 rem) but no changes in its lethal effect after pre-exposure to low-dose radiation (0.10 rem). Carcinogenecity, which results from the rate of DNA mutations, is not expected to be affected by the lethal effect of radiation. Human lymphocytes were incubated for 6 hr with and without [^{3}H]thymidine at 0.001–1.0 mCi/ml (total dose of 1.0 mCi/ml is equivalent to 0.10 rem). They were then irradiated with x-rays at 150 or 300 rem. Mutagenesis and survival were assayed 8–10 days after radiation exposure (*43*). The [^{3}H]thymidine alone did not affect the rate of mutation, whereas x-ray radiation alone significantly affected the mutation rate. Incubation with [^{3}H]thymidine at doses of 0.01 and 0.10 rem (0.1 and 1.0 mCi/ml) markedly diminished the mutagenic effect of both 150 and 300 rem of x-rays.

Kelsey et al. (*44*) exposed a group of human lymphocytes to 1 rem x-ray radiation 16 hr before an additional exposure to a 300-rem dose. The number of mutations at the hypoxanthine guanine phosphoribosyl transferase locus was measured 6–8 days after exposure to the high-dose radiation. The HPRT gene was studied because a large spectrum of mutations can be detected in this gene. The number of mutations was 70% lower in the pre-exposed group (4.5×10^6) than in the not pre-exposed group (15.5×10^6).

The analysis of the molecular nature of mutants (point mutations to complete deletions) from "adapted" cells (i.e., cells pre-exposed to low-dose radiation) was used to clarify the processes of premutagenic events induced by pre-exposure (*45*). Pre-exposure of human lymphoblastoid cells to 2.0 rem of gamma rays diminished the frequency of HPRT mutants after high-dose radiation exposure at 100–400 rem. Cell survival was not affected. Partial deletion was significantly lower in adapted compared to nonadapted cells after high-dose radiation. The pre-exposure dose may have acted preferentially against premutational lesions leading to deletions.

Shadley and Wolff (*46*) conducted two experiments in which human lymphocytes were pre-exposed to low-level x-ray radiation 14–16 hr before exposure to a challenging 150-rem x-ray dose. In a first experiment, the effects of adding 3-aminobenzamide (3AB) after the high-dose exposure were tested. The compound 3AB inhibits the enzyme poly(ADP-ribose) polymerase, which may play a role in repair mechanisms. Without 3AB, the number of chromatid and isochromatid breaks was decreased by nearly half in the pre-exposed cells. The addition of 3AB blocked the adaptive response (*46*). In a second experiment, effects of several doses of pre-exposure radiation (1, 5, 10, 20, 30, 40 and 50 rem) were compared. A significant decrease in the number of chromatid and isochromatid breaks was found at levels of pre-exposure doses < 20 rem (*46*).

Farooqi and Kesavan (*47*) studied bone marrow cells in mice, rather than lymphocytes in humans. Fewer chromosomal aberrations were produced when whole-body exposure to 100 rem of gamma rays was preceded by 2.5- or 5-rem x-ray exposure. Two groups of five mice, each group receiving 100 rem at various time intervals (2, 7.5, 13, 18.5 and 24 hr) after the conditioning low-dose irradiation, were tested (*47*). Pre-exposure to 2.5 rem had a protective effect at all time intervals between the conditioning and the challenging radiation doses; pre-exposure to 5 rem produced a protective effect only at the 2-hr and 7.5-hr time intervals. These results supported the hypothesis that low-level x-ray radiation can stimulate cellular repair mechanisms that reduce DNA breaks.

Finally, embryonic mortality (percentage of eggs from which no larvae hatch) of *Drosophila melanogaster* was examined in

TABLE 4
Institutional Review Board Approved Studies of Normal Healthy Children Exposed to Ionizing Radiation

Author	Age	n	Procedure	Dose
Gilsanz et al., 1991 (*49*)	2–20 yr	150	Quantitative computed tomography	100 mrem
Mora et al., 1994 (*53*)	4–20 yr	96	Quantitative computed tomography	100 mrem
Namgung et al., 1992 (*50*)	<3 days	55	Single-beam photon absorptiometry	6–60 mrem
Pittard et al., 1990 (*51*)	24 hr–16 wk	31	Photon absorptiometry	30–300 mrem
Pittard et al., 1992 (*52*)	24 hr–16 wk	20	Photon absorptiometry	Not mentioned
Pritchett et al., 1992 (*54*)	7 yr–skeletal maturity	244	Teleroentgenography	212 mrem
Zametkin et al., 1993 (*55*); Ernst et al., 1994 (*56*)	12–17 yr	30	^{18}F-fluorodeoxyglucose PET	500 mrem to the bladder; 60 mrem to whole body
Ernst et al., 1996 (*57*)	12–17 yr	10	^{18}F-fluorodopa PET	670 mrem to the bladder; 41 mrem to whole body
Kowatch et al., in progress	7–18 yr	30	^{99m}Tc Ceretec SPECT	For 40 kg body weight, 42 mrem to whole body; 416 mrem to the kidney
Chugani et al., in progress	8–18 yr	5	^{11}C-alpha-methyltryptophan PET	For 56.8 kg body weight, 58.5 mrem to whole body, 495 mrem to the kidney For 33.2 kg body weight, 69.0 mrem to whole body, 495 mrem to the kidney

germ cells, which differ in repair capacity as a function of cellular maturity (mature oocytes are radiosensitive, and immature oocytes are radioresistant) (*48*). Three different strains of *Drosophila melanogaster* were used: one repair-proficient *yw* strain and two repair-deficient *mus-302* and *mei-41* strains. A 2-rem dose of x-ray radiation preceded 200-rem x-ray radiation at different time intervals. Embryonic mortality in all stages and strains was lower when 2-rem preceded 200-rem irradiation, suggesting that the adaptive response could be induced both in the highly sensitive mature oocytes and in the repair-deficient strains. In both cases, the adaptive response may have removed repair-blocking factors.

Low-level radiation may enhance the repair processes in two possible ways. In one, the genes that are activated by low-level radiation stimulate or inhibit the production of some enzymes or proteins. The number of these proteins can delay cell mitosis, thus allowing more time for the repair processes to work effectively. In the other, radical detoxification is mediated by the increase of the levels of mobilizing enzymes that remove toxic radicals. This effect leaves more scavengers available to inactivate radicals produced by later radiation.

These repair processes may not only offset the excess of DNA damage produced by low-dose radiation but also protect the cells against further ionizing radiation. Their role in the biological effects of ionizing radiation may also be influenced by age.

STUDIES APPROVED IN THE U.S. INVOLVING RADIATION EXPOSURE TO CHILDREN

Several studies have been approved in the U.S. that involve the exposure of healthy normal children to ionizing radiation (*49–57*). These studies are listed in Table 4. Levels of exposure range from 0.018 rem to 0.67 rem for the critical organ exposure. The age range of healthy children enrolled in these studies cover infancy, childhood and adolescence.

The Institutional Review Board for Clinical Investigation at the Endocrine and Metabolism Clinic at Children's Hospital in Los Angeles approved a study in which 150 normal girls between 2 and 20 yr of age were exposed to 0.10-rem radiation over a 10-min period (*49*). Exposure was directed at a 10-mm-thick section of the vertebral body. The purpose of the study was to compare bone development between African-American and Caucasian girls. The results showed much greater bone density in the African-American than in the Caucasian girls, only in the last two stages of puberty. This finding has contributed to the understanding of osteoporosis in women.

The Institutional Review Board of the University of Cincinnati Medical Center approved a study assessing differences in newborn bone mineral content. Fifty-five healthy newborns, <3 days old, underwent a minimum of three scans by a single-beam photon absorptiometer (*50*). The dose, not mentioned by the authors, is estimated to be between 0.006 and 0.060 rem. Findings indicated a 12% lower bone mineral content in summer-born versus winter-born infants.

The Human Research Committee of the University of South Carolina approved two studies of photon absorptiometry in infants (*51,52*). The first involved 12 premature and 19 normal newborns at 2 days, 8 wk and 16 wk of age, who were exposed to an estimated radiation dose of 0.030–0.30 rem. Each newborn underwent five scans with a photon absorptiometric system that evaluated bone mineral content and bone width. The rate of bone mineralization among the premature neonates was found to be more rapid than the rate previously reported in similar infants who required more extensive medical support. The second study (*52*) involved 20 low birth weight infants. Bone mineral content was determined by photon absorptiometry at birth, 8 wk and 16 wk. The dose of radiation exposure was not provided. Bone mineral content was compared to serum osteocalcin (Gla) and skeletal alkaline phosphatase (SAP) concentrations to determine whether Gla and/or SAP concentrations were reliable predictors of changes in bone mineral content of very low birth weight infants. Gla and SAP concentrations were found unrelated to bone mineral content.

The Institutional Review Board for Clinical Investigation at the Endocrine Clinic at the Children's Hospital in Los Angeles approved a study of cortical and cancellous bone density in 96 normal Caucasian girls from the ages of 4 to 20 yr (*53*). Using quantitative CT methodology, each girl received a radiation dose of 0.10 rem localized to a 10-mm-thick section of the vertebral bodies. The results suggested that the regulation of bone density differed as a function of type of bone (cortical versus cancellous).

The Department of Orthopedic Surgery of the University of Washington in Seattle approved a study of longitudinal growth and growth-plate activity in the lower extremity in 244 normal children (123 boys and 121 girls; 6–17 yr old) (*54*). Roentgen-

ograms were made biannually between 1935 and 1967. This study provided reliable standards of longitudinal bone growth for middle-class children of European descent.

The Human Subjects Protection Committee of the National Institute of Mental Health and the National Institutes of Health Radiation Safety Committee reviewed and approved two large studies of PET that assessed neurodevelopmental disorders of childhood (*55–57*). In the first study, which included a control group of about 30 normal healthy adolescents (12–17 yr of age), the dose of radiation exposure was 0.060 rem to the whole body and 0.50 rem to the bladder. The bladder is the organ that receives the largest amount of radiation because radioactive molecules are excreted in the urine. In the second study, which included a separate control group of 10 normal healthy adolescents (12–17 yr of age), the dose of radiation exposure was 0.67 rem to the bladder and 0.041 rem to total body. These normal adolescents were siblings of patients with the disorders under scrutiny. The first study evidenced an influence of age and sex on brain abnormalities associated with attention-deficit hyperactivity disorder (*55,56*). The second study demonstrated a major deficit in dopaminergic function in Lesch-Nyhan disease, a rare but devastating neurodevelopmental disorder (*57*).

Kowatch et al. (study in progress) received approval from the Institutional Review Board of the University of Texas at Dallas to conduct a SPECT study comparing cerebral blood flow between normal and depressed children (7–17 yr old). To date, 30 normal healthy children have been studied. Radiation dose was based on body weight. For 40-kg body weight, which is approximately the average weight for 12-yr-old children, radiation exposure was 0.042 rem to the whole body and 0.42 rem to the kidney.

Chugani et al. (in preparation) received approval from the Institutional Review Board at Wayne State University, Michigan, to study normal healthy children, siblings of autistic children (≥8 yr old), using PET and alpha-methyltryptophan. To date, five normal siblings have completed the study. Radiation exposure for 56.8-kg body weight (average weight for a 15 yr old) was 0.058 rem to whole body and 0.495 rem to the critical organ (kidney), and exposure for 33.2-kg body weight (average weight for a 10 yr old) was 0.069 rem to whole body and 0.495 rem to the kidney.

CONCLUSION

Health risks from low-level radiation could not be detected above the "noise" of adverse events of everyday life. This conclusion is based on studies of health hazards after exposures to background radiation, radon in homes, medical procedures and occupational radiation in large population samples. In addition, no data were found that demonstrated higher risks with younger age at low-level radiation doses. With respect to radiation exposure in adults, a recent position statement by the Health Physics Society (*8*) recommended "against quantitative estimation of health risk below an individual dose of 5.0 rem in one year, or a lifetime dose of 10.0 rem in addition to background radiation." The report also states that "Below 10.0 rem (which includes occupational and environmental exposures), risks of health effects are either too small to be observed or are nonexistent." We hope that this review will help institutional review boards and investigators assign levels of health risk from low-dose ionizing radiation.

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