

# Radiation Hormesis

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"Radiation hormesis" is the name given to the putative stimulatory effects of low level ionizing radiation (generally in the range of 1–50 cGy of low-LET radiation). Based on historical and pharmacologic principles reminiscent of some of the major tenets of homeopathy, most of these effects are now generally ascribed to protective feedback systems that, upon exposure to low concentrations of toxins, proceed to stimulate metabolic detoxification and repair networks. The activation of these networks may then result in net beneficial effects on the cell, organism or species. Discussions of possible stimulatory effects of low levels of ionizing radiation have recently become entangled with the separate but related question of whether a threshold dose level exists on the radiotoxicologic dose-response curve. This review summarizes some of the relevant historical and scientific data bearing on the question of radiation hormesis. We find the data in support of most of the hormesis postulates intriguing but inconclusive.

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Is all nuclear radiation harmful? When this question was posed by Hugh Henry (1) in 1961, the debate was already over half a century old. Radiation hormesis (Greek, "rapid motion" from *hormaein*, "to excite") is a branch of a larger area of toxicologic inquiry that traces its roots back to the principles of medicinal homeopathy and the Arndt-Schultz conjecture: substances that inhibit biological processes at high levels may be expected to stimulate them at lower levels (2). In the field of ionizing radiation research, the concept of hormesis is often taken to imply some element of physiologic benefit from low-LET radiation in the range of 1–50 cGy total absorbed dose. Data sets offered in support of the hormesis hypothesis run the gamut from biochemical to organismal to evolutionary, and lack of consistency in the experimental endpoints used to quantitate hormesis has contributed greatly to the lack of consensus surrounding discussions of the topic (3).

The question of whether one can define a safe or

beneficial level of exposure to ionizing radiation has major economic and epidemiological implications (4). Increasing disenchantment with the dependence on fossil fuel energy and recent advances in nuclear reactor technology are forcing a reassessment of the risk/benefit equation for nuclear energy (5,6). In addition, it is now apparent that the major source of radiation exposure in our society comes not from man-made sources but from the inhalation of natural radon-222 and its decay daughters (7). The costs of effective radon abatement would be extraordinarily high and even partisans have difficulty rallying support for the costly elimination of this natural radioactive gas (8). Thus, the traditional assumptions that (a) essentially all exposure to ionizing radiation is measurably detrimental and that (b) the health effects of low level exposure may be directly inferred from linearly scaled deleterious high level effects, are both multi-billion dollar propositions that bear careful consideration (9).

## HISTORICAL ROOTS OF RADIATION HORMESIS

The elucidation of the principles of radioactive decay and ionizing radiation by such pioneers as Becquerel, Roentgen and the Curies captured the imagination of the public. Early investigations into the physiologic effects of ionizing radiation produced claims of dramatic responses in patients suffering from many types of skin diseases and malignancies. Weart (10) has traced the popular conceptions and portrayals of ionizing radiation as they changed from the early, positive impressions to the later, distinctly negative toxic associations. At the turn of the century, radioactivity was portrayed as a vital force capable of producing profound feats of rejuvenation. Even within the medical literature, advertisements and testimonials to "quack" radioactive devices and nostrums abounded. The oral and parenteral use of microgram quantities of radium-226 and radium-228 as treatments for various metabolic diseases such as diabetes, hypertension, infertility and impotence was referred to as "mild radium therapy," a title meant to distinguish this branch of radiation medicine from the high dose destructive treatments of the oncologists (11). Mild radium therapy was considered an accepted medical subspecialty at the interface of radiology and en-

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doocrinology, and thousands of patients were treated annually in the years 1910–1925.

The widespread use of radium compounds in the production of luminous paints for watch dials and other instrument display panels led to the recognition that chronic ingestion of microgram amounts of such bone-seeking isotopes led to osteoradionecrosis and osteosarcomas in significant numbers of factory workers exposed to these compounds (12). By the early 1930s, radium exposure was a well-recognized occupational illness (13), though the public's perception of radium and ionizing radiation remained very positive. The death of the Pittsburgh millionaire industrialist Eben M. Byers, an internationally known sportsman and playboy who for several years had been taking a radioactive over-the-counter rejuvenator called RADITHOR (14), finally succeeded in drawing public attention to the problem of radium control and resulted in strict radium control laws throughout the U. S. and Europe (11). This highly publicized incident sounded the death knell for the mild radium therapy movement though the public continued to regard nuclear technology as basically positive.

With the development of the atomic bomb and the consequent public realization of the potential for large-scale radioactive contamination, the perception of nuclear energy as a powerful but essentially benign technology began to change (10). Serious scientific inquiries into potential new uses of ionizing radiation in agriculture and biology slowed or stopped, and attention was refocused on the occult somatic and genetic effects of ionizing radiation exposure (15). These investigations brought nearly unanimous agreement from radiation researchers concerning the potentially serious detrimental effects of cumulative absorbed radiation doses of 1 Gy or more of low-LET radiation, with correspondingly lower toxic thresholds for high-LET sources. Data on the health effects of low-level ionizing radiation (LLIR) were much more equivocal, and the late biologic consequences of low-LET exposures in the range of 1–50 cGy were generally inferred from large epidemiologic data sets such as those acquired from study of atomic bomb survivors (16,17), nuclear industry workers (18, 19), and medically exposed patient cohorts (20). In the absence of specific evidence that a threshold existed for radiation damage, it was deemed prudent to assume that any measurable dose of ionizing radiation was potentially dangerous. This safety provision has led to divisive and acrimonious disputes between those radiation workers who favor a strict no-threshold linear or linear quadratic dose-effect toxicity curve, and those who argue that in the absence of definitive data the lower end of the dose-effect curve should be left undefined (21–26). Most current estimates of the health impact of populational exposures to LLIR continue to use a “risk per person per rem” extrapolation which

tacitly assumes that proportionally scaled high level exposures will accurately reflect the epidemiologic consequences of LLIR (27,28).

This is the heart of the modern radiation hormesis controversy. Hormeticists argue that these scaled epidemiologic extrapolations are invalid and that the majority of the available experimental data on LLIR do *not* support a significantly adverse health effect; rather much of the data suggest some theoretical and experimental “benefits” accruing from such exposures. This review will briefly outline some of the major lines of argument and experimental data in the ongoing hormesis controversy.

## THE SPECTRUM OF CLAIMS IN RADIATION HORMESIS

Many polemical discussions of radiation hormesis appear to have their roots in disagreements over terminology (29). As the word was initially used, “hormesis” was a pharmacologic term implying a paradoxical stimulatory effect at low concentrations of any substance found to be inhibitory at high concentrations (2). This definition was meant to be independent of assay, endpoint, and health implications. As the medical, industrial, and military uses of nuclear energy and radioactive materials have become more highly politicized, much of the radiation hormesis controversy has shifted to disagreements over the positive or negative implications of the putative “stimulatory” effects of LLIR for the ecosystem or for the population as a whole. Thus, some hormesis investigators claim that the evidence supports certain narrowly defined stimulatory effects of radiation without implying that such stimulatory effects are necessarily beneficial (26) or that the existence of such hormetic effects would exclude concurrent detrimental effects within the same dose range. Other, more extreme hormeticists argue that LLIR is not only beneficial but may be absolutely essential for life (30). The hormesis controversy is not one argument but many, and even the hormeticist camp is bitterly divided over the medical implications of their conjectures.

It is thus useful to divide the hormesis controversy into the evidence for and against specific claims that have been advanced within the hormesis rubric. The majority of the hormesis data can be broken down into nine separate but interrelated claims that run the gamut from narrow biochemical observations to cellular phenomenology to epidemiologic oncology (Table 1).

For the purposes of this analysis, we will review these claims separately, concentrating on the data obtained over the last three decades. It should be understood that not all hormesis proponents would agree with all of the above claims, and that most hormetic arguments are assumed to apply only to low-LET forms of radiation (74).

**TABLE 1**  
**Proposed Hormetic Effects of Low-Level Ionizing Radiation**

Biochemical	Cellular	Organismal
Stimulates unscheduled DNA repair	Stimulates immune response (humoral and cellular)	Selectively inactivates inhibitory or senescent parts of organisms
Induces free radical detoxification and repair systems	Functions as a vital life force that may even be essential requirement Functions as a general metabolic catalyst and fertility enhancer	Decreases cancer risk in chronically exposed populations Extends average life-span in lightly exposed populations Produces evolutionarily favorable selection pressure that benefits species as a whole

### **Ionizing Radiation Stimulates Unscheduled DNA Repair**

Because this claim is one of the most narrowly defined, it is also one of the most easily supportable of the hormesis postulates. Wolff has shown evidence that lymphocytes seem able to mount an adaptive response to the challenge of LLIR. Cells allowed to proliferate in the presence of 0.01–0.10  $\mu\text{Ci/ml}$   $^3\text{H-TdR}$  (and thus “primed” with the low-energy tritium emissions) appeared to become less sensitive to chromatid damage by subsequent 150 cGy doses of X-rays (31). This effect has been attributed to the stimulation of a damage-inducible repair system analogous to the “SOS” UV-inducible system found in prokaryotes (26,32). The process takes ~4–6 hr to induce, persists for several cell generations, and is blocked by the protein synthesis inhibitor cycloheximide. Gel electrophoresis studies using two-dimensional separations show new protein signals apparently induced by radiation exposure. The function and significance of these radiation-inducible gene products are not yet established.

Wolff and his colleagues are careful to point out that these data are at present only laboratory phenomena and their physiologic significance (if any) are not clear. However, the existence of any reproducible well-defined biochemical system induced in response to ionizing radiation (perhaps in response to the free radicals produced during this process) represents an important conceptual starting point for any claim of a damage-inducible feedback loop through which hormetic effects might be achieved. Whether the transitory increase in the steady state concentration of free-radicals that might be expected to occur after LLIR is enough to activate such a damage-inducible system is entirely conjectural (33).

### **Low-Level Ionizing Radiation Induces Free Radical Detoxification and Repair Systems**

Data in support of this contention have been derived from several sources, notably Feinendegan and his collaborators (34). These workers have investigated the

effect of LLIR and the radiation-related increase in intracellular free radical concentration on thymidine kinase activity, an indicator of DNA synthesis. They found that thymidine kinase activity was temporarily inhibited in murine bone marrow cells exposed to as little as several of cGy of cesium-137 gamma irradiation. This suppression reached its peak in 5 hr after which activity gradually recovered to normal levels within the next 24 hr. Biochemical maneuvers designed to increase intracellular free radical concentrations also reproduced this suppressive effect. Inhibition of the thymidine kinase activity was thought to be accompanied by an increase in the concentration of the free radical scavenger glutathione.

Feinendegan interpreted these and related data as evidence for a cellular control mechanism that functions to temporarily inhibit DNA synthesis in order to allow repair of lesions induced by free radical attack. By temporarily inhibiting critical intracellular processes and by triggering production of free radical scavengers in response to LLIR, this feedback mechanism would theoretically confer some degree of protection against the deleterious effects of future exposures to ionizing radiation (35) and other free radical challenges.

The interpretation of this set of experiments is complex. Critics have pointed out that the transient increase in intracellular free radical concentration after several cGy of low-LET radiation would be barely detectable above the background level and would, thus, be a poor trigger mechanism for an important homeostatic feedback loop (33). However, evidence is now accumulating that free radicals are involved in many detrimental cellular processes including chronic diseases and senescence (36) and the putative hormetic radiation impact on this feedback loop may be a consequence of a serendipitous utilization of a defense mechanism that evolved in response to entirely different organismal insults.

### **Ionizing Radiation as an Immunostimulant**

Although high dose ionizing radiation has long been known as an immunosuppressant, some data suggest

that LLIR actually may be immunostimulatory. In 1909, Russ reported that mice treated with radiation appeared to have acquired some level of resistance against bacterial disease (37), and Luckey collected several dozen references supporting this contention in his exhaustive review (30). Most of these studies are poorly designed and statistically unimpressive, though the data in aggregate are difficult to dismiss out of hand.

Murphy and Morton performed early studies on the effect of radiation on the growth rate of mouse tumors (38). They excised spontaneously occurring murine tumors, irradiated the mouse with an undefined “stimulating” dose of X-rays from a Coolidge Tube, then regrafted the tumors into the groins of the irradiated animals. Of 29 non-irradiated animals, 28 showed tumor regrowth. In contrast, tumor failed to recur in 26 of 52 irradiated mice. The tumors themselves showed no effect when irradiated with the same dose of X-rays. No data are presented to control for the effects of handling, treatment-related inflammation, etc. Evaluation of the white blood cell counts in the irradiated animals seemed to demonstrate a biphasic response—an initial period of leukopenia and immunosuppression followed by myeloid and lymphoid recovery with consequent reappearance of immunologic competence at supranormal levels.

Metcalf attempted to give a physiologic explanation for this recovery overshoot phenomenon by evaluating the effect of several Gy of total-body irradiation (TBI) on lymphocyte counts in C57BL/6 mice (39). Not only did he confirm a significant lymphocytosis in the recovering animals, he also found elevated levels of thymic lymphocyte growth factors in the post-radiation period. Finally, Liu et al. (40) showed that the reactivity of thymocytes to interleukin-1 and the magnitude of the “plaque-forming assay” (a gross measure of the level

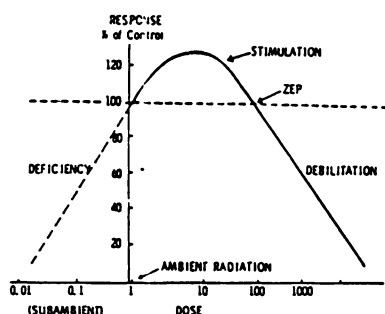
of antibody production) were both significantly enhanced by single or continuous exposure to 2.5–7.5 Gy of gamma radiation.

The implication in all of this work is that LLIR may produce a beneficial overshoot in the potency of the immune system during its recovery from radiation exposure (41). This overshoot may initially take the form of increased expression of certain hematopoietic cell growth factors which then induce rapid recovery of immunocompetence in the irradiated animals. These data are not inconsistent with the recent studies on the recovery of the immune system in bone marrow transplant patients undergoing TBI (42). These TBI patients often shown a supraphysiologic surge in “natural killer” (NK) cells during the period of recovery, and it is possible that these cells might have some anti-neoplastic potential. Whether radiation doses in the 1–50 cGy range are sufficient to trigger this response is not clear.

### Is Ionizing Radiation a Vital Life Force?

This postulate probably embodies the most controversial premise in the hormesis field. The core of this hypothesis is the assertion that LLIR is a basic biophysical phenomenon that has been present since the emergence of life and the beginning of evolution. Such a proto-stimulus, the argument goes, may well have initiated physiologic processes that have become so internalized in the cell life cycle that the deprivation of LLIR would be subtly detrimental to the organism. Thus, Hickey (4) speaks of a “hormetic deficiency” implying that life forms deprived of ionizing radiation will show deleterious effects.

Luckey has published a hypothetical “complete dose response curve” for ionizing radiation embodying this conjecture (30) (Fig. 1). The curve suggests that optimal organismal proliferation takes place in the presence of some baseline amount of ionizing radiation and that doses substantially above or below this optimal radiation level result in suboptimal growth. Data in support of this dose-response relation are mainly derived from protozoan studies attempting to quantitate amoeba proliferation under conditions in which the organisms are either exposed to LLIR or deprived of >95% of the usual background dose of ionizing radiation by careful shielding and growth media screening. The data suggested an ~40% decrease in cell number after eight days of such radiation privation (43). This inhibition could be reversed by the addition to the shielded amoeba colonies of radioactive thorium in concentrations meant to mimic natural background radiation levels. Luckey defined a number of potential facets of the “radiation deficiency syndrome” (30)—low growth rates, slow development, decreased fecundity, poor health, slow metabolism, and decreased lifespan—while acknowledging that evidence for many of these phenomena are fragmentary.



**FIGURE 1**  
Luckey's hypothetical “complete” dose response curve for chronic irradiation of organisms. The curve is meant to indicate qualitative patterns of change in response to different doses of ionizing radiation. Units are not specified and would depend on the experimental system. The “zero equivalent point” (ZEP) indicates a dose that elicits a response indistinguishable from controls. The projection to the left of the ordinate is based upon exposure to protozoa. (Reprinted with permission from *Health Physics* 1982;43:771–778.

These postulates and experiments are intriguing but have been greeted by skepticism over experimental methodology. In addition, the relevance of such single-cell organismal requirements to the metabolic needs of more highly evolved multicellular organisms is not clear. In a sense, the hypothesis that some baseline level of ionizing radiation is necessary for life has become the litmus test identifying the "true" hormeticists, as distinguished from those individuals who view background levels of ionizing radiation as biophysical phenomenon whose presence or absence is largely irrelevant to most physiologic processes.

### **Ionizing Radiation as a Metabolic Catalyst and Fertility Enhancer**

The belief that LLIR is a general metabolic catalyst was one of the underlying tenets of the mild radium therapy movement in the early decades of the century (11). This belief was originally based on a large body of circumstantial evidence concerning the salutary effects of mineral water from radon-rich natural springs found in many of the European spa centers. Experimental observations on the impact of low level radium exposure on the rate of membrane ruffling and metabolism of human leucocytes and bacteria seemed to confirm this effect. The German physiologist George Wendt reported that vitamin-deprived rats could be temporarily rejuvenated by exposure to radium or high-frequency electromagnetic radiation (44) and that many cell types responded to such stimuli by "radiotaxis," or purposeful movement toward the radiation source.

Luckey collected ~40 references suggesting that vertebrate growth and fecundity could be stimulated by LLIR (30). Some of these data are derived from acute exposure experiments and some from chronic, fractionated exposures on the order of 1 cGy per day or less. Despite the counter-intuitive nature of this claim, some investigators seem to have gone to great pains to control for all the obvious confounding factors such as animal handling time, environment, etc., and continued to claim a small but significant stimulatory effect. An apparently increased rate of fertility associated with LLIR is extensively documented with various strains of insects and rodents, and the effect has been reported both after external irradiation and after injection of radiopharmaceuticals.

Clinical data documenting such observations are sparse. Kaplan followed 644 women treated with 50–100 cGy (ovarian dose) of 200 KvP X-rays for infertility, reporting that approximately half went on to conceive (45). A plausible mechanism for this observation was reported by Meyer (46,47), who claimed that prenatal radiation kills some oocytes but stimulates the development of the remaining cells, producing a net

fertility increase. Higher, more cytotoxic doses of radiation negate this beneficial effect.

Though the "biopositive" effects of radiation on fertility are still occasionally discussed (primarily in Eastern European journals) in reference to the radon spas, Broda has criticized these data as inadequate and misleading (48). On balance, the data marshalled in support of the claim that radiation acts as a nonspecific biophysical catalyst in higher organisms seem unconvincing.

### **Ionizing Radiation Can Selectively Inactivate Senescent or Inhibitory Structures in Plants and Higher Organisms**

This claim is really a mechanistic outgrowth of the last conjecture. The underlying premise of this claim involves the putative existence within higher organisms of specific "inhibitory" centers whose natural role is to conserve the organism's resources and prevent it from outgrowing available nutritional resources. If these inhibitory centers are selectively destroyed by radiation, the organism may undergo a temporary increase in growth or fecundity.

This explanation has been invoked most compellingly as an explanation for the widely reported effect of LLIR on plant growth and fruiting patterns. Miller and Miller have reviewed the data on this subject (49) and find that most modern studies show a small (<10%) increase in such parameters as branches, flowers, linear growth, and fruit yields after exposure to LLIR. Some of the older data in the field may be suspect inasmuch as horticulture approaches involving LLIR treatment rather than crossbreeding of genetically determined crop traits were widely promoted in the Soviet Lysenkoist literature. In addition, the effect seems quite difficult to reproduce, though some investigators with many years of experience apparently could demonstrate the effect at will. The phenomenon apparently requires a precise relationship between the radiation dose, timing, nutritional status and species of the irradiated plant and it is doubtful that the small magnitude of the response would allow practical agricultural exploitation (75). It is intriguing to note, however, the recent reports of Soviet physicians concerning the lush floral overgrowth now taking place near Chernobyl.

Conceptually, this growth effect has been attributed to the selective destruction of the plant's apical meristem tissues, a part of the organism that appears to exercise control over lateral growth and fruition (49). The "pinching off" of the terminal meristem tissues has long been used by gardeners who wish to create fuller plants and more widely distributed fruiting and flowering patterns in axial-dominant plants (a process that has given rise to the expression "green thumb"), and it is not unreasonable to suppose that LLIR or pharma-

cologic interventions might reproduce this effect under certain circumstances.

Kondo extends this concept of selective radiation-mediated destruction of inhibitory tissues to higher organisms, proposing that the undifferentiated primordial cells may be the most sensitive to radiation effects because their response to LLIR involves a kind of "altruistic cell suicide" (50). This theory involves the observation that certain cells undergo programmed cell death (apoptosis) in response to LLIR (51). Kondo suggests that this behavior results in a proliferation of healthy pluripotent stem cells to replace those destroyed by the radiation. The hormetic effect is produced when the cellular proliferation more than compensates for those cells damaged by the radiation.

Kondo (50) attempts to distinguish this "altruistic cell death" from the "simple radiation death" discussed by Miller (49) in reference to the plant meristem tissues. Kondo believes that the meristem tissue destruction results in a disinhibition of tissues, while the altruistic cell death phenomenon relies on repopulation to produce the hormetic effect. In both cases, however, the driving principle is the selective destruction of one cell population in order to produce a proliferative effect on the organism as a whole.

#### **Low-Level Ionizing Radiation Decreases Cancer Risk**

No aspect of radiation toxicity has received more attention than the relationship between radiation exposure and the subsequent risk of malignancy. It seems clear that radiation exposures at the level of 1 Gy or more increase the relative risk of acute leukemia and other malignancies by factors of 2–5 or more (17). The effect of cumulative radiation doses of less than 25 cGy are less clear, and some have claimed that the error bars on the relative risk analyses at this low dose are broad enough that they do not exclude a negligible or even an inverse relationship between radiation exposure and subsequent risk of carcinogenesis (52).

The most extensive data set bearing on this issue is the information collected by the Radiation Effects Research Foundation (RERF) on the atomic bomb survivors. The latest estimates of relative risk of developing malignant neoplasms reflect the recent changes in radiation dosimetry for the explosions (17). For a group of 41,719 total subjects with an average shielded Kerma dose of 30 cGy, the latest estimates conclude that about half of all leukemic deaths and ~8% of the non-leukemic cancer deaths were related to the radiation exposure. These data obviously reflect a range of individual exposures, making exact dose-response extrapolations difficult at these low doses. At an exposure level of 1 Gy, the estimated relative risk of leukemia is approximately 5, while the relative risk of non-leukemic cancer is approximately 1.5. With 45 yr of follow-up,

the hazard function for leukemia appears to have peaked for this cohort, while the risk of solid tumors is continuing to rise.

The Biological Effects of Ionizing Radiation (BEIR) study group represents the most important U. S. panel of expert opinion on the subject of radiation toxicity and carcinogenesis. Based in part on the RERF data, the BEIR V report (53) suggests that risks of radiation carcinogenesis may be 3–4 times greater than previously believed. This increase is due in part to the realization that previous neutron flux estimates for the Nagasaki bomb were too high, and in part to the panel's skepticism concerning the possibility of a threshold for radiation carcinogenesis and the sparing effects of low dose rate exposures. Though their report makes extensive use of the RERF data, it admits that the confidence bars on the relative risk estimates are too broad to provide unambiguous information on whether radiation in the range of <25 cGy significantly increases (or decreases) cancer risk. In addition, the atomic bomb data set represents the effects of acute exposure to gamma (and in the case of Hiroshima, neutron) irradiation and is consequently not an ideal model for the sort of chronic, fractionated LLIR that has been proposed as the optimal hormetic regimen (77).

Because large epidemiologic data sets such as the atomic bomb data clearly demonstrate radiation carcinogenesis at high absorbed doses, the heart of the hormesis controversy with respect to cancer induction is the issue of a threshold on the dose response curve. It is beyond the scope of this review to reiterate the masses of data bearing on this question. However, the BEIR V report, unlike some of its predecessors, has come down squarely on the side of a no-threshold interpretation of the data, at least for the purposes of calculating cancer risks for an exposed population (65). The authors of the report make clear the oversimplified nature of such an analysis, but critics have argued that the way in which the report is presented will overemphasize the relevance of the data to the general population (77).

The hormetic argument that LLIR may actually decrease cancer risk is based primarily on environmental and occupational exposure data. The High Background Radiation Research Group has investigated thyroid nodularity and cancer rates in the Guangdong Province in China, an area with a natural radiation level ~3 times normal (54). For the years 1975–1978, the high background area had a cancer mortality rate of 36.53 per 10<sup>5</sup> person-years, compared to 52.85 per 10<sup>5</sup> person-years for the control area (4). In the U.S., the states with the three highest mean radon levels (Colorado, North Dakota, and Iowa) show a lung cancer death rate of 41 per 10<sup>5</sup>, as compared to a rate of 66 per 10<sup>5</sup> in the 3 lowest radon level states (Delaware, Louisiana, and California) (55). Recent analyses of cancer mortality data for workers at the Hanford, Oak

Ridge, and Rocky Flats nuclear weapons facilities also fail to show a statistically significant increased cancer risk for workers exposed to cumulative radiation doses on the order of 10 cGy (19).

These data and analyses are all controversial, and many have argued that the data are seriously limited by problems with cancer case records, population and ambient radiation figures, limited study timespans, and confounding variables such as smoking and lifestyle differences. Nevertheless, it seems clear that, whatever the effects of LLIR at doses less than 25 cGy, their epidemiologic consequences are generally not great enough to be statistically detectable against the great force of cancer mortality currently observed in industrialized societies (56). The animal data (30) offered in support of the hormesis "cancer protection" theory may be a reflection of small numbers and the publication bias toward interesting or desired results, but they certainly appear to be inadequate to prove the point. Conceptually, one might imagine that if LLIR were able to induce some sort of free-radical protection mechanism then the mutagenic risks of minute doses might be more than counterbalanced by the feedback protection (34). At present, however, this theory appears unsubstantiated (57).

With the recent report of 7–8-fold increases in the rate of leukemia and lymphoma in children of heavily exposed Sellafield nuclear workers, the potential genetic consequences of LLIR are being re-evaluated (58). This report is still very controversial and appears to contradict the accepted notion (derived primarily from the atomic bomb data) that LLIR has very little effect on the unexposed F1 generation of exposed individuals (59). As a consequence of the Sellafield report, major epidemiologic data sets are now being reinvestigated, and it seems clear that the question of the carcinogenic risks of fractionated, low-LET ionizing radiation has not yet been answered. All available evidence concerning radiation in the range of 1–25 cGy, however, points to an increase (or decrease) in relative cancer risk too close to negligible to allow direct detection in a cancer-prone society (60). For purposes of safety, however, the radiation protection community has adopted a conservative approach that assumes that the upper level estimates of carcinogenesis risk after LLIR exposure must be taken as the standard (61,20).

#### **Low-Level Ionizing Radiation Extends Average Lifespans**

Free radicals are thought by many to play an important role in aging and senescence (36) and one might, therefore, conjecture that a feedback mechanism triggered by LLIR that functioned to either reduce intracellular free radical levels or that eliminated free-radical damaged cells might result in increased longevity. Luckey's review of this subject (30) includes several dozen

references in which many organisms (primarily insects and rodents) appear to have increased average lifespans (often by as much as 20%) after exposure to LLIR. Because this effect was driven primarily by a decreased incidence of early deaths rather than an increased median lifespan, he and others have concluded that this effect may be related to the increased immunologic protection against disease (as discussed above). Once again, most of the primary vertebrate data bearing on this question were acquired in poorly controlled studies with relatively small numbers of animals and many potentially confounding variables.

Several sets of epidemiologic data have been analyzed for their relevance to the question of ionizing radiation and its impact on longevity. In 1956, Warren found that lifespans for radiologists were 5 yr shorter than those for physicians as a whole (62). However, correcting for age, Seltzer et al. used the same data to show that radiologists lived on average 2.5% longer than the average age-matched physician (63). Other attempts to study the subject have been similarly inconclusive.

Recent attempts to evaluate the process of senescence at the cellular level have implicated the repression of growth genes such as *c-fos* and the reciprocal activation of antiproliferative genes such as *Rb1* (64). One might, therefore, invoke radiation mutagenesis as either a cause or an inhibitor of the fundamental process of genetic aging, though there are few direct data to support either claim. Once again, it appears that the lack of independent reproducible differences in lifespan between high natural background and low natural background locations tends to rule out a very significant positive or negative effect of LLIR.

#### **Ionizing Radiation as an Evolutionary Drive**

The hypothesis that LLIR produces a net positive populational effect by catalyzing evolutionary changes in species is supported by very little direct evidence. Indeed, the Sellafield data notwithstanding, one of the most intriguing aspects of clinical radiation late effects studies has been the virtual absence of anticipated hereditary changes in children of exposed individuals. These data are in accord with the findings of Kaplan (65) who reported no genetic effects in children and grandchildren of women irradiated for infertility.

In contrast, Russel et al. found that rodents exposed to LLIR do show increases in mutation frequency (66). Wolff has argued that since most nonspontaneous mutations are not beneficial, any evidence for heritable radiation effects should be construed as potentially dangerous (26). Thus, while it is conceivable that LLIR did play a role in spontaneous evolution from single-celled to higher organisms, it is unlikely that any further benefits might accrue from continuing exposure of humans, and this line of argument appears to be of only



theoretical importance since humans appear relatively insensitive to the genetic effects of radiation (60).

## CONCLUSIONS

In reviewing the data on the health effects of LLIR, one is struck by the paucity of convincing data and by the lack of expert consensus concerning the health implications of what data are available. On balance, it appears that the large populational data sets such as the RERF data and the radon data do *not* support the existence of a discernible hormetic effect in the range of 1–25 cGy total absorbed dose, but neither do they argue strongly in favor of clear cut deleterious effects of the magnitude generally assumed from a linear dose-response model (77). Obviously, one must distinguish between the lack of evidence for a toxic effect and the presence of evidence for a beneficial effect (only the latter would constitute true hormesis); but the available data do suggest that at least some physiological processes are sensitive enough to LLIR to make a radiation-triggered “SOS repair” process feasible. Many of the hormesis conjectures share a common conceptual framework: a LLIR-induced feedback loop that originally evolved to help in radiation (or other free-radical inducer) detoxification, and that under some circumstances overshoots the set point to produce net beneficial effects on the cell or organism. This sort of system has clearly been demonstrated using other types of toxins (73).

At present, society has placed the burden of proof squarely on those who argue that the regulations concerning ionizing radiation should be reduced and brought more into line with other epidemiologic risks of the same demonstrated order of magnitude. Although some have argued that current levels of concern for LLIR are excessive and phobic (55), new data continue to appear that argue that the perceived risks may be accurate reflections of the dangers posed (67). Many processes that result in LLIR exposure also bear the concurrent potential for a disastrous high level radioactive release (68). Although this potential is clearly a separate issue, the risk of such a high level catastrophe plays an obvious role in the formulation of public policy on the issue of LLIR.

The health effects and carcinogenic risks of chemical mutagens and various types of non-ionizing radiation are currently being re-evaluated (69,70). Perhaps this would be an opportune time to reconsider the entire question of LLIR, and to develop a set of unified criteria for the assessment of risk for various proposed health threats including ionizing radiation, natural and artificial chemical carcinogens, and electromagnetic fields. The subject of radiation toxicology appears at present too politicized to allow a dispassionate risk analysis (71), and if a hormetic effect exists for ionizing radia-

tion it may be more readily accepted within the context of a broad-based inquiry into the physiologic responses to low levels of various classes of toxins (72,73). Until such time that the health risks are authoritatively re-evaluated, it seems reasonable to continue to be wary of the health risks of low-level ionizing radiation (76).

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