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Review article

The effects of gamma rays on longevity

Edward J. Calabrese* & Linda A. Baldwin
Department of Environmental Health Sciences, Morrill Science Center, School of Public Health, University of Massachusetts, Amherst, MA 01003, USA; Author for correspondence (e-mail: edwardc@schoolph.umass.edu; fax: +1-413-545-4692)

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Abstract

A number of animal model studies have assessed the capacity of long-term whole body gamma rays to affect life span. The initial goal of such studies was to establish the equivalent of a no observed adverse effects level (NOAEL) that would provide a toxicological foundation for deriving an acceptable worker exposure standard. In the course of initial studies to establish such a 'tolerance threshold', data emerged suggesting that low dose rates/cumulative doses enhanced longevity in mice and guinea pigs of both sexes. Extensive large scale follow-up investigations with other mouse strains and rats revealed what appear to be inter-strain/species differences in response with some models providing strong evidence for a low dose increase in longevity. The subsequent positive studies in mouse models were generally well designed, well conducted and used extensive numbers of mice. In all experiments that displayed enhanced longevity the average life span was enhanced by 10–30% but not the maximum life span potential. The underlying mechanisms affecting the apparent enhancement in longevity are believed to result from the stimulation of hematopoietic and immune systems following an initial low level chronic injury to the bone marrow.

Introduction

Relatively soon after their discovery in the 1890s, the adverse effects of ionizing radiation upon the blood-forming tissue and the peripheral blood were discovered by the pioneering work of Heineke (1903). These findings were soon extended by other investigators across a broad spectrum of biological and clinical effects. The experimental findings were principally confined to animal experiments where lethal or near lethal doses of externally administered X-rays or gamma rays were administered to a part of the body or to the whole body via a single dose or in closely divided doses. According to Jacobson and Marks (1947), no deliberate studies with animal models or humans had been undertaken with chronic exposure to ionizing radiation within the so-called threshold or tolerance range over the ensuing four decades. Some reports were available from clinics and radium institutes concerning hematological effects of radiation (Goodfellow 1935; Mottram and Clarke 1920), but these reports provide estimated rather than accurately measured exposures. Information on the biological effects of radioisotope deposition was available from the radium-dial industry and the subsequent therapeutic and tracer studies of relatively short-lived isotopes such as P^{32} (Low-Beer et al. 1942), Sr^{89} (Hamilton 1942), I^{131} (Hamilton and Soley 1940), and Na^{24} (Hamilton and Stone 1937). As for the radium dial painters, initial doses were unknown with only the residual deposition being measurable (Martland 1929, 1931). The short-lived tracers used for therapeutic studies were not employed to assess the more general biological effects. Limited effects were reported with radium in rabbits (Rosenthal and Grace 1936) and rats (Dunlap et al. 1944).

The present paper assesses the effects of long-term exposure to gamma radiation on longevity in mammalian models. While data exist on other forms of ionizing radiation [i.e., fast neutrons (Evans 1948; Upton et al. 1970; Ullrich et al. 1976; Morin et al. 1986; Lafuma et al. 1987); X-rays (Hollcroft et al. 1955; Boche 1967; Ishii et al. 1996; Maisin et al. 1996)], the predominant form studied in whole-body lifetime studies has been gamma rays. The dominant role of gamma rays is due to the historical ease of technical incorporation into testing protocols especially during the early years of life span testing (i.e., 1941–1960), the high interest in this form of radiation in relationship to the atomic bomb where the majority of exposure would be gamma rays (Upton and Furth 1955), and the close energy level relationship of gamma and X-rays. In addition, by the early 1980s long-time experts in lifetime studies in radiation such as Grahn (1986) called for an end to such investigations with their replacement by more mechanistically oriented studies. These combined factors contributed to the fact that most lifetime studies with whole body radiation were conducted with gamma rays. In addition, the most commonly employed animal model, due principally to its smaller size, reduced cost and capacity for greater numbers, was the mouse. Consequently, this review will necessarily reflect the effects of gamma rays on the longevity of the mouse with recognition, as appropriate, to the complementary role of other less studied models, such as the rat and guinea pig.

Initial investigations

Since the data base concerning the biological effects of ionizing radiation in general and of certain radioactive materials was so superficial, the medical and biological division of the Plutonium Project of the US government was organized in 1941 to assess the fundamental and comparative action of radiations and radioactive materials and to apply such findings to worker and community health assessment. Within the context of the Plutonium Project the first formal and systematic attempt was made to assess the effects on animal models of whole body chronic exposures to externally originating radiation including gamma rays, X-rays, beta rays, and neutrons (Stone 1947).

Consistent with the above goal to assess chronic daily whole body exposures to external ionizing radiation, Lorenz et al. (1947) designed what Jacobson and Marks (1947) referred to as an exhaustive study to duplicate in animals the laboratory exposures that scientists and their co-workers may experience assuming an 8 h/day, 6 days per week scenario. In their investigation four strains of mice (Strain A, C3H, dba, and LAF_1), two strains of guinea pigs and one rabbit strain were selected. The LAF_1 strain was chosen based on its resistance to the common ‘mouse typhoid’ and pneumonia and its low spontaneous tumor incidence. The species and substrains were divided into 5 gamma ray (radium source) exposure dose groups (0.11, 1.1, 2.2, 4.4, and 8.8 r) for 8 h per day and other groups for 24 h/day, 6 days per week. The animals, which were followed until death, had blood samples routinely obtained throughout the study.

Lorenz et al. (1947) displayed the findings only for the LAF_1 mice and guinea pigs. While the data revealed a dose-dependent decrease in survival at the higher doses, the 0.11 r/8 h exposure group displayed a notably longer average survival than the controls (703 vs 763 days). This enhanced survival duration was interpreted as being either the result of chance or possibly a real effect attributable to a general stimulatory effect from obscure mechanisms. However, the authors noted that the average life span was enhanced in the low dose group, not the absolute life span. With respect to tumor incidence, the mice exposed to the 0.11 r/8 h treatment displayed a noticeably lower incidence of leukemia but a marked increase in ovarian tumors. Other tumors were not notably affected.

Based on the above findings the authors concluded that, “long-continued absorption of penetrating radiation is associated with damage even for doses of 0.11 r given in 8 h per day”. Despite this quoted conclusion, Lorenz et al. (1947) stated that “... it is of paramount importance that the present permissible dose of 0.1 r per day be maintained. However, due to the enhanced sensitivity of the mouse ovary to develop gamma ray induced ovarian tumors and the fact that ovarian tumors in mice are similar in type to those of humans, it is prudent to reduce the standard for women to 0.02 r or that the duration of exposure should be reduced to a few years”.

Despite the uncertain interpretation of the enhanced life span at the 0.11 r/8 h exposure dose in the original Lorenz et al. (1947) study, Lorenz et al. (1955) replicated the original low-dose enhancement of longevity. However, in the later study the irradiated males lived significantly longer than the controls while no such difference was evident in the females.

This gender difference was not observed in the original study.

These initial findings by Lorenz et al. (1947, 1955) were the crucial papers that provided the initial suggestion that low doses of gamma rays may enhance longevity. These findings were subsequently cited by advocates of an hormetic perspective such as Carlson et al. (1957), Carlson and Jacobson (1959), Sacher and Trucco (1962), and Sacher and Grahn (1964), and more recently by Luckey (1980, 1991), Congdon (1987), and Caratero et al. (1998). Such enhanced longevity was also noted by Upton (1957) who emphasized that the enhanced longevity only affected the median life span not the absolute longevity and that the incidence of ovarian tumors were significantly higher than in the controls.

Despite the tempered comments of Upton (1957) there was nevertheless a general consensus that the findings of Lorenz et al. (1947, 1955) suggested that low doses of gamma rays may enhance longevity. Given the pivotal role that the two studies of Lorenz et al. (1947, 1955) had in initiating interest in the radiation hormesis hypothesis, it is important to consider these investigations in greater detail. While the two papers of Lorenz et al. were published in the *Journal of the National Cancer Institute*, a more detailed report of the methodology and findings of the 1947 study was presented in a 1954 book edited by Zirkle. A comparison between the journal publication and the more detailed technical document of the same study revealed possible important discrepancies. These include aspects relating to (1) the control group, (2) the differential housing conditions of the low dose treatment group, (3) lack of precise replication, and (4) inconsistent control responses between studies.

(1) *Control group*

The study #1 (Lorenz et al., 1947) control group was comprised of 59 surviving male and female mice (from a total of 64 male and female mice). The control group was originally 32 male and female LAF_1 mice of equal numbers. An additional 32 mice (i.e., 16 males and 16 females) were added to the original 32 from two other groups of 16 male and female mice. These mice received a single dose of X-rays of either 13–14 r or 50–56 r at 2 months into the study. The data from all 64 mice were combined to make the controls. Since 5 mice were lost for various reasons the final number was reduced to 59. The authors justified the decision to combine untreated and single X-ray dosed mice into a combined control based on data indicating that the single exposure did not affect blood parameters nor life span.

The combining of the three groups (i.e., original 32 animal untreated control group plus the 2 single X-ray dosed groups) was not noted in the journal publication. No separate analysis was provided to support the combining of these three subgroups. It should be noted that even a single acute dose of 50 r over 4.5 h was reported to increase ovarian tumor incidence from a background of 10–15% to slightly over 70% (Lorenz et al. 1955). In fact, Lorenz et al. (1955) emphasized that the ovarian tumor response above some minimal gamma ray exposure is largely independent of dose in the LAF_1 female mice. A similar combining of gamma and X-ray treated subgroups occurred for each treatment group. In these cases each treatment group received their indicated chronic dose (0.11, 1.1, 2.2, 4.4, 8.8 r/8 h). However, at two months into the study 2 such groups of 16 male and female mice received a single acute dose of X-rays (i.e., 13–14 r or 50–55 r). These two 16 mouse subgroups (i.e., chronic gamma and acute X-rays) were combined with the original 16 mouse treatment group (i.e., chronic gamma rays) yielding a total of 32 mice. As in the control, this practice of combining treatment subgroups was never reported in the journal publication. However, it was alluded to in a 1950 report by Lorenz in a footnote to Table 1 (p. 177) where it said, “some animals of all groups received additional acute exposure of 12.5 r or 50 r, respectively”. Note this is different from the 13–14 r and 50–55 r actual exposure values reported in the latter paper (see Lorenz et al. 1954).

(2) *Housing conditions*

All LAF_1 mice, with the exception of the lowest dose group (0.11 r/8 h day group), were maintained in air-conditioned rooms with the room temperature maintained between 78 and 80 °F. However, the 0.11 r/8 h day group was the only group maintained in a room without air conditioning. The temperature rose during the summer months occasionally to 90 °F, with the average summer temperature between 80 and 84 °F. This differential maintenance condition was not reported in the journal paper nor was the potential impact of this differential maintenance ever assessed in the discussion.

Table 1. Comparison of study designs concerning the effects of gamma rays on life span.

Study	Strain	Gender	Number of doses	Dose range	Age (D)	Number of animals	When exposed	Number of mice per cage	Histology	Temperature	Control life span (days)	% life extension
Caratero (1998)	C57BL/6	Female	2	0.02 and 0.04 r/d	40–10	300/group	N/A	30	Y	20–22 °C	Not provided	20.7
Lorenz #1 (1947)	LAF_1	Both	5	0.11–8.8 r/8 h	52–80	45–60	N/A	N/A	Y	75–80 °F 0.11 r and higher in summer	703 combined male/female	8.2
Lorenz #2 (1955)	LAF_1	Both	1	0.11 r/8 h	30	110–120	N/A	N/A	Y	75–80 °F	683 male 802 female	14.4 (male)
Sacher and Grahn (1964)	LAF_1	Both	24	5–2500 r/8 h	100	90–183/group at lower doses females at higher doses	Night	3	N/A	75–80 °F	598 males 661 females	NA
Bustad et al. (1965)	C57BLX 101	Male	2	0.1 and 0.2 r/8 h	42	70 study replicated	Night	1	Y	28 °C	880–970	NA
Grahn (1970)	A/Jax BALB/c C57BL BCF_1	Both	9	0.3–5.6 r/8 h	100	BCF_1 168/group at low doses lower number at higher doses; other strains have 80/group at low doses	Night	3	Y	24 °C	710 males	7.1 (male) BCF_1
Upton et al. (1970)	RF/Un	Both	41	0.5, 1.0, 1.1, 5.1, 5.3, 1.4 (lowest six doses)	56–60	Control 586 treated 80–230	N/A/	8–10/cage	Y	75 °F	608 ± 7	NA
Storer et al. (1979)	RFM/Un	Female	1	1.0 r/d for 188 days	65–70	Control – 312 Treatment – 368	N/A/	8/cage	Y	Not reported	644 ± 8	NA
Spalding et al. (1982)	C57BL/6J	Male	5	0.2, 0.6, 1.8, 5.4, 16.2 r/d	Neonate 60, 180, 450	∼50/neonate, ∼25/other groups; >90 groups assessed	N/A	7–9/cage	Y	Not reported	870 ± 139	13–36

NA = not applicable.

(3) *Age at start of study*

In their 1954 publication Lorenz et al. reported that the age of mice at the start varied amongst the different groups with a low average of 52 days (0.11 r group) to a high average of 85 days (8.8 r group), with the control average of 70 days. The use of different ages across treatment and control groups, especially in a chronic study involving an agent with recognized age-dependent susceptibilities, is a highly questionable procedure. It also demonstrated that the animals were not randomly allocated to treatment groups. This inter-treatment variability was not noted in the original journal paper and cannot be discerned by the offered statement that the mice ranged in age from two to three months.

(4) *Lack of replication*

In the replication study of Lorenz et al. (1955) the 0.11 r/8 h day treated mice were noted as being one month of age when placed into the exposure room where they were exposed for the duration of life. As noted earlier, the 0.11 r/8 h day treatment group was 52 days old on average when the original study started.

(5) *Combining of male/female data*

The 1947 study of Lorenz et al. stated that since no sex differences were apparent the data on life span were combined. In the replication study (Lorenz et al. 1955), the initial control groups developed a dermatological infection, requiring the establishment of a new control approximately one year into the study. In this new control there was a profound gender difference in mean survival time [683.5 ± 14.5 (SE) days (males) vs 802.9 ± 6.1 (SE) (females)] of the control males and females. The fact that the females lived four months longer than the males on average in the second study ($P < 0.01$) while displaying no apparent differences in study #1 (Lorenz et al. 1947) was troubling but not addressed by the authors.

It is unknown why the journal papers did not address the above concerns with respect to control group integrity, housing conditions, and random allocation by age. It is also unknown why none of these standard experimental procedures, already well incorporated into testing protocol by the 1940s, were not noted in the above cited papers, even by those citing the 1955 reference. Regardless of the omissions, the principal point is that the original findings of Lorenz et al. (1947) which suggest that a low dose hormetic effect on life span be viewed with much less confidence than has been historically been attributed to it (see above references). The initial findings of Lorenz et al. (1947) should be viewed as suggestive of a future area of research rather than as documented support for the radiation hormetic hypothesis.

These findings of Lorenz et al. (1947, 1955) were supported via a statistical interpretation by Sacher and Grahn (1964) based on a ~5000 male and female mice (LAF_1) study with 24 treatment groups plus concurrent controls. In this study the mice received gamma rays from a cobalt 60-source with the dose ranging from 5 to 2500 r/8 h day. The data revealed a clear dose-dependent decrease in mean life span. However, the authors noted different linear dose response patterns in the male and female data. Based on these observations the authors derived two linear equations based on the dose (range #1, 5–24 r/day and range #2, 24–56 r/day) in order to predict the Y-intercept or control group value. In the case of the 24–56 r/day based model, the Y-intercept (control) was underestimated by 27 and 53 days for males and females, respectively. The opposite occurred for the 5–24 r/day group model where the life span estimates for the males and females overestimated the actual control values by 70 and 32 days, respectively. Sacher and Grahn (1964) stated that since the low dose linear model prediction for the control life span was some 30–70 days greater than observed, doses below 5 r/day were likely to reduce mortality, an observation consistent with the earlier findings of Lorenz et al. (1947, 1955).

Follow-up investigations

During this general time period Carlson and colleagues published three papers on the effects of gamma rays on longevity. The initial two papers indicated a low dose enhancement of life span in the male Sprague-Dawley rat (Carlson et al. 1957, 1959). As a result Carlson (Bustad et al. 1965) conducted a carefully designed investigation of the effects of gamma rays on male mice of the C57 BLX101 strain with 140 mice/group from 6 to 56 weeks of age and then permitted to live out the remainder of their lives. The life span in both treatment groups were marginally less than in the controls, not supporting the hypothesis of an enhancement of longevity.

Other relevant studies of that era were Grahn (1970), Upton et al. (1970), Storer et al. (1979) and

Spalding et al. (1978, 1982). Grahn (1970) compared the effects of gamma rays on male and female mice of four strains (A/Jax, BALB/c, C57BL/6, and BCF_1) with nine doses ranging from 0.3 to 56 r/day. This exposure began at 100 days of age with the irradiation continuing for life. The sample sizes for the BCF_1 strain were inversely related to dose with 160 mice/sex in the controls to 1.3 r/day dose groups, and 96 mice/sex for 2.6 r/day and 6 r/day groups. The other three strains had 80 mice/sex (or half that of the BCF_1 strain) in the controls and lower dose groups. Due to unanticipated problems data were not collected at 0.3 r/day for the C57BL/6 males and females. Only the BCF_1 treated mice, especially the male, displayed an enhanced longevity ($P < 0.05$) at the lowest dose. The Upton et al. (1970) and Storer et al. (1979) reports utilized the same strain of mice (i.e., RFM/Un) with a similar age at the start of the study. The Upton et al. (1970) study investigated a broad range of doses with the lowest being 0.5 r/day, while the lowest dose in the Storer et al. (1979) study was 1 r/day. Neither study supported the hormetic hypothesis.

The reports by Spalding et al. (1978, 1982) utilized C57BL/6J mice with five dose rates (0.7–56.7 r/day) and cumulative doses of 20, 60, 180, 540, 1120 r. This spectrum of dose rate-cumulative dose exposures were administered to neonates, 60-, 180-, and 450-day-old mice. This study yielded a large array of exposure responses by age at the start of exposure as a function of dose rate and cumulative dose. Given such an array of approximately 90 possible response comparisons, it is most useful to consider consistent trends rather than any particular individual subgroup response. What clearly emerges is that the lower dose groups of mice, when treatment started at two months of age, generally had their life spans significantly enhanced, while treatments starting at the other times were highly inconsistent in their responsiveness (Table 1).

Several other papers explored the concept of longevity in generational studies in mice (Gowen and Stadler 1964; Searle 1964; Spalding et al. 1964; Luning 1960). None of these studies is directly relevant to the issue of whether ionizing radiation (gamma and/or X-rays) affects longevity nor do these data present a direct comparison to the present studies. For example, Searle (1964) and Luning (1960) measured mortality from birth to weaning while the other studies assessed ancestral (i.e., earlier generations) dosing on reproduction, productivity, and longevity in subsequent generations.

Of the relevant studies, three (Lorenz et al. 1947, 1955; Sacher and Grahn 1964) used the LAF_1 mice, two use RFM/Un mice (Upton et al. 1970; Storer et al. 1979) and two used C57BL/6J mice (Grahn 1970; Spalding et al. 1978, 1982). With the exception of the Sacher and Grahn (1964) paper (i.e., 5 r/day) and the Storer et al. (1979) (1 r/day) study doses, the lowest doses in each study were $\leq$0.7 r/8 h. day. The age at the start of the study ranged from neonate to 450 days with most between 40–70 days. Sample sizes were substantial ranging from 45 to 183/group with two studies providing their own internal replications (Bustad et al. 1965; Spalding et al. 1982).

Positive results and/or interpretations in the mouse studies were provided by Lorenz et al. (1947, 1955), Sacher and Grahn (1964), Grahn (1970), and Spalding et al. (1978, 1982). However, while five studies provided positive findings/interpretation, each has unique features that need to be placed in perspective. As noted earlier, the Lorenz et al. (1947) study has important limitations as a result of combining of subgroups that were differentially treated and the maintaining of the low dose group in different environmental conditions than the controls and other groups. The Lorenz et al. (1955) study needed to replace the original control group one year after the start of the study. The research of Sacher and Grahn (1964) neglected to include exposure groups below 5 r/8 h day (i.e., the stimulatory zone of the Lorenz et al. studies). This study design limitation is even more curious since Sacher and Grahn (1964) used novel interpretations of biostatistical models to predict low dose enhanced longevity effects. Nonetheless, the data of Sacher and Grahn (1964), while extensive, shed no experimental light on the critical issue of low dose enhancement of longevity. The Grahn (1970) study reported enhanced longevity only in the BCF_1 mouse strain. However, this study had the greatest statistical power with sample size double that of other groups in the controls and low dose groups (160 vs 80 mice/group). Positive replication findings for low dose enhancement of longevity were reported in the rat strains of Carlson et al. (1957, 1959) and the guinea pig investigations of Lorenz et al. (1947) and Rust et al. (1966).

One particularly important limitation of all the above studies, with the exception of the Spalding et al. (1982) report, is that only one dose was in the apparent stimulatory zone. This markedly affects the ability to assess the nature of the stimulatory response. However, the nature of the dose spacing in conjunc-

tion with dose rate/cumulative dose of the Spalding et al. (1982) study yields a markedly improved exposure response matrix. In addition to the strength of the Spalding et al. design in the low dose area to better define the potential stimulatory (i.e., enhancement longevity responses), this study also included a dose rate treatment group with sufficiently high exposure to lead to a reduction in longevity by nearly 20%. The Lorenz et al. (1947) and Grahn (1970) experiments also cover the stimulatory and inhibitory range but each is limited to only single doses in the stimulatory zone. The inclusion of the entire dose-response spectrum (i.e., stimulatory and inhibitory responses) allows the defining of biological thresholds that are useful to the risk assessment process.

More recently, a report by Caratero et al. (1998) revealed that low doses of gamma rays (0.02 and 0.04 r/day) enhance the longevity of C57BL/6 females by 120 days (20–25%). Age at the start of exposure was not clearly stated but appears to be early adulthood (soon after mouse purchase, which was 3–4 weeks of age). The daily dose rate was 1/5 of Lorenz et al.'s lowest dose and 1/10 that of Grahn (1970). The key feature in this research was the adoption of the much lower doses than previous mouse studies. The basis of the doses selected was previous research by this group in the response of single cell organisms such as on the clonal life span of *Paramecium tetraurlia*.

In their study, Caratero et al. (1998) did not observe enhanced incidence of tumors in the treated or control mice. Thus, the enhanced life span was not due to treatment-induced reduction of tumor incidence. The enhanced longevity was again not due to an increase in the maximum life span but an increase in the median life span, an observation consistent with those of Lorenz et al. (1947, 1955), Grahn (1970) and Spalding et al. (1982).

Discussion

This review indicates that long-term whole body exposure to low dose rates/cumulative doses of gamma rays extends average life span but not absolute longevity in three strains of mice, one strain of rats and guinea pigs. The enhancement occurs in males and females of selected mouse strains and guinea pigs. The magnitude of the enhanced average life span ranged from 10–30% depending on the study. This increase in average life span is biologically quite remarkable since absolute longevity was not affected and parallels various past public health interventions in which average life span has been enhanced while having little impact on maximum life span potential.

While average longevity enhancement occurred in five biological models, it has been replicated in one mouse strain (LAF_1), as well as the rat and guinea pig models. The fact that a number of other well-conducted studies were negative (Sacher and Grahn 1964; Upton et al. 1970; Storer et al. 1979) does not invalidate nor directly challenge the findings of the positive studies principally because different animal models were used and doses higher than the stimulatory zone established by Lorenz et al. (1947, 1955) were employed. Nonetheless, the negative studies can establish reasonably likely boundaries for possible low dose stimulatory responses across model, age, gender, exposure rate/cumulative dose and experimental conditions.

While the collective findings remain to be more firmly established, the median longevity enhancement response can not be discounted due to its repeated observation from experiments with extensive sample sizes far exceeding National Toxicology Program (NTP) testing protocols and their conduct by multiple research teams over three generations of scientists with progressively advancing study protocols. The principal concerns associated with confidence in the positive findings are that most studies identified only one stimulatory dose and that the magnitude of the response is modest (10–30%), even if shown to be frequently statistically significant. Despite the extremely large sample sizes, the occurrence of a modest enhancement on longevity in a single dose raises the possibility of a chance response. The counter argument is that Spalding et al. (1982) and Caratero et al. (1998) reported low dose enhancement of longevity in multiple doses, thereby blunting to some extent this possible criticism.

The appreciation for the possibility that low doses of gamma rays enhance longevity has long been muted since the initial findings of Lorenz et al. (1947) also reported that ovarian tumor incidence was enhanced in the low dose group displaying the enhanced longevity. In fact, as noted earlier, this recognition of ovarian tumorigenesis in the LAF_1 mouse model led to the recommendation that the exposure standard to radiation for workers be reduced to accommodate the enhanced cancer risk.

The recommendation of Lorenz et al. (1947) was a critical decision based on limited data. Subsequent experimentation has called into question the extrapolative relevance of the female mouse data for humans since only relatively small doses of gamma rays can lead to sterility in the female mouse but not so in other species. In fact, this unique susceptibility of the female mouse to gamma irradiation-induced ovarian toxicity led to it being dropped as a model in the extensive Spalding et al. (1982) test. In addition, the use by Caratero et al. (1998) of the C57BL/6 mouse strain, a strain with a normally low incidence of spontaneous tumors, revealed a low dose enhancement of median longevity with no tumor increase in females. This recent report is of importance since it separated the low dose longevity-enhancement response from the tumor response which had dominated the earlier health assessments.

While the focus of the present assessment involves the effect of gamma rays on experimental mammalian models, low dose enhancement of longevity has been reported for gamma rays in an extensive experiment with fish involving over 600,000 alevin (Bonham and Donaldson 1966), for X-rays with mice (Hollcroft et al. 1955; Ishii et al. 1996; Maisin et al. 1991, 1996) and dogs (Boche 1967) and for radionuclides such as radium 226 with mice (Finkel 1959; Finkel et al. 1969; Loutit et al. 1976; Mays et al. 1976; Mays and Finkel 1980; Schoeters and Vanderborght 1986) as well as for other radionuclides in various rodent species (Finkel 1959).

Mechanism

The mechanism underlying the enhanced median longevity is unknown but was speculated by Lorenz et al. (1947, 1955) to involve the stimulation of hematopoetic and immune systems following an initial low level injury to the bone marrow. The enhanced immune response was speculated by Sacher (1977) and reasserted by Luckey (1991) as increasing survival in the mice by decreasing mid-life infection (Sacher 1955a, b, 1956). While not directly addressing the issue of prolonged average life span, a number of studies have revealed that ionizing radiation at lower doses may enhance while at higher doses inhibit various aspects of immune function (Glenn 1946a, b; Taliaferro et al. 1964; Taliaferro and Taliaferro 1969, 1970; Schmidtke and Dixon 1973; Anderson and Lefkovits 1979; Anderson et al. 1980, 1988; Anderson and Troup 1982; Anderson 1992) *in vitro* and *in vivo* in rodent models. Such biphasic dose responses on multiple immune functions suggests possible avenues for follow-up research that could be related to adaptive mechanisms affecting microbial infection. It should be noted that the above cited examples of either fast neutron or X-ray enhanced life span in mice (Hollcroft et al. 1955; Maisin et al. 1991, 1996; Ishii et al. 1996) resulted in a prolonged absolute life span in contrast to the average life span of the gamma ray studies. These consistent differences in the patterns of ionizing radiation enhanced longevity may reflect differences in the effects of the different types of radiation and/or differences in study design in which the fast neutron/X-ray studies were typically of a much more limited exposure duration. Consequently, the fact that ionizing radiation can enhance median and absolute longevity within different protocols suggests the involvement of diverse mechanisms.

While the initial intent of the Plutonium Project's health assessment research was to address the health concerns of workers in the nuclear industry, the findings of low dose enhancement of median longevity may have relevance to ongoing studies of the survivors of the atomic bomb blast where the principal exposures were to gamma rays. Studies by Mine et al. (1981, 1990), Stewart and Kneale (1984, 1988), and assessments by Kondo (1993) suggested an enhancement of life span of surviving men and women aged $\geq$35 year at the time of the explosion. These findings which relate age at the time of exposure to the ionizing radiation are consistent with the animal model studies displaying enhancement in average life span at low but reductions at high doses. Despite the similarities in apparent enhanced survival between the animal model studies discussed here and the atomic bomb survivors, caution must be expressed in drawing too close a linkage. The animal studies were designed to be chronic exposures to a single type of ionizing radiation as compared to the acute nature of the atomic blast, the more complex nature of the ionizing radiation, as well as other potentially important differences between those types of assessments. Nonetheless, sufficient commonalities exist with respect to the nature of the exposure and dose-response to warrant closer comparative evaluation.

Despite evidence that the median life span may be enhanced by low dose rate/cumulative doses of gamma radiation, this concept does not appear to have been

widely accepted within the radiation health literature. For example, the text by Turner (1995) notes that the earlier suggestion that low doses of gamma rays may enhance longevity was viewed as unconvincing due to questions raised about the adequacy of the controls. It is presumed that Turner (1995) is referring to the second LAF_1 mouse study by Lorenz et al. (1955). This conclusion represents a judgement based on an inadequate review of the literature and purpetuates an unbalanced assessment of the data. Furthermore, the hypothesis that low doses of gamma rays may enhance median longevity was also unfairly influenced by principal leaders in the radiation research community. This is exemplified by the paper of Failla and McClement (1957) modeling the life-shortening of chronic whole-body ionizing radiation, even at very low doses, based on the Lorenz et al. (1947) paper. Failla and McClement (1957) made the decision to exclude the low dose (0.11 r) data "because it is very close to the one for the controls". This decision to exclude the data indicating enhanced longevity at low doses ensured that the low dose linear modeling predictions for radiation-induced reduction in median life span would be realized. Such improper analyses (Failla and McClement 1957) and inadequate evaluations (Turner 1995) are not isolated attempts to marginalize the concept of hormesis but reflect an unfortunate and long standing trend that has permeated the field of both chemical and radiation hormesis (Calabrese and Baldwin 1999, 2000).

While the issue of whether ionizing gamma rays affect life span has long been dominated by the high end of the dose-response continuum and concern of decreased life span and cancer incidence, the existing animal data base is sufficiently robust to establish that the low dose response can not reliably be predicted from high dose exposure studies. Although concerns with preventing high dose exposures have rightly dominated past decades of radiation health, greater emphasis must be placed on understanding the entire radiation effect continuum including the low dose (i.e., hormetic) domain.

Conclusions

1. Multiple studies have assessed the influence of gamma rays on longevity in mice, rats, and guinea pigs.
2. Low dose enhancement of the median life span was reported in two experiments in LAF_1 mice, one experiment in BCF_1 mice, and one separate experiment with C57BL/6 male and female mice. Similar low dose enhancement was reported in replicated studies in male Sprague-Dawley rats and male and female guinea pigs.
3. Multiple experiments in other strains of mice, often at higher doses, did not demonstrate enhancement of longevity.
4. The enhancement of longevity by gamma radiation affected the median life span, not the absolute life span potential.
5. The collective findings support the hypothesis that low-dose, whole-body exposure to gamma rays enhanced longevity in a range of biological models under a defined set of experimental conditions.

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