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● *Animal Effects*

A REVIEW OF CERTAIN LOW-LEVEL IONIZING RADIATION STUDIES IN MICE AND GUINEA PIGS

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Abstract—**Starting in the early 1940s, Egon Lorenz and collaborators at the National Cancer Institute began an extended study of chronic low-level ionizing radiation effects in what was then the tolerance range for man. Observations on life span, body weight and radiation carcinogenesis, among others, were made in mice, guinea pigs and rabbits. At the then-permissible exposure level, 0.1 R** per 8-h day until natural death, experimental mice and guinea pigs had a slightly greater mean life span compared to control animals. In addition, there was marked weight gain during the growth phase in both species. Increased tumor incidence was also observed at the 0.1-R level in mice. The primary hypothesis for increased median life span has been rebound regenerative hyperplasia during the early part of the exposure; in the presence of continuing injury, there is physiological enhancement of defense mechanisms against intercurrent infection. The body weight gain has not been explained.**

INTRODUCTION

EGON Lorenz was one of the founders of contemporary radiation biology. In addition to his studies of low-level ionizing radiation effects in mice and guinea pigs, reviewed in part here, he made major contributions to treatment of acute lethal, whole-body irradiation and radiation carcinogenesis (Ka55; Co71).

The archival report that contains the results of these radiation studies in the tolerance range, at that time 0.1 R per day, appeared in the first six chapters in the book *Biological Effects of External X and Gamma Radiation* (Zi54). Lorenz and his collaborators examined life span, breeding behavior, body weight, hematology, carcinogenesis and other pathological processes at the exposure level of 0.11 R per 8-hr day from about 2 mo of age until natural death. Higher exposures of 1.1 R, 2.2 R, 4.4 R and 8.8 R were studied as well. Various other publications by Lorenz and his colleagues are also of interest in the overall evaluation of this monumental study started early in 1941 (Lo46; Lo47; Ja47; Es48; Ja49; Lo50; Lo51a; Lo51b; Fu54; Lo55a; Lo55b; Va72). Even into the 1980s, publications about these experiments continued to appear in the National Cancer Institute's Registry of Experimental Cancers (Ho79; Ho80; Ho81; Ho82).

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** After considerable thought and consultation, it seemed best to use the radiation units in Dr. Lorenz's publications rather than switch to the contemporary SI-derived units.

MEAN SURVIVAL TIME

LAF1 mice approximately 2 mo of age with appropriate controls were exposed to 0.11 R per 8-hr day until natural death (Zi54). Table 1 shows that the experimental group had a slightly longer mean survival time by nearly 2 mo compared to the control group. This difference was not statistically significant. A repeat of this experiment was then performed with a much larger number of LAF1 mice (Lo55a). The results, given in Table 2, again show longer mean survival time in the exposed group compared to the control. The difference in males was significant at the .01 level. The control group, unfortunately, in this experiment (Lo55a) had to be replaced 1 yr into the study because the original group developed dermatitis.

Hybrid guinea pigs exposed under similar conditions to this low level of γ radiation also had a mean survival slightly greater than the control, as shown in Table 3 (Zi54).

This unexpected effect of slightly increased median, but not total, life span in lightly irradiated laboratory animals compared to controls has been noted a number of times. T. D. Luckey (Lu82) has collected the relevant literature. It is interesting that small, single, acute exposure as well as low daily exposures are implicated, although this exposure-rate parameter needs further attention.

When Lorenz and his collaborators first observed this effect, now often designated radiation hormesis (Lu80), they were puzzled by it. In 1947 Lorenz *et al.* (Lo47) commented that ". . . the decreased initial slope

Table 1. Survival time in normal (i.e. non-irradiated) and lightly irradiated mice

DAILY DOSE R	NO. OF ANIMALS	MEAN SURVIVAL* DAYS	MEAN ACCUMULATED DOSE, R
0	59	703 ± 23	0
0.11	45	761 ± 26	110

*After beginning of exposure

of the curve for the animals of the 0.11 r group may be attributed to biological variations or may indicate a general stimulation effect of an obscure mechanism of the radiation. However, the death rate increases later and the slope of this curve increases over that of the control curve, indicating that the destructive action of the radiation is cumulative, even for such small doses as 0.11 r given in eight hours per day." Lorenz *et al.* (Lo47) further commented that the "initial stimulating effect" was also noted with body weight gain and tumor induction.

In 1950 Lorenz (Lo50) discussed the life span effect again in terms of human permissible exposure. At that time, he thought the size of the animal groups had been too small to be meaningfully interpreted. The archival paper of 1954 (Zi54) gives the same opinion as in 1947 but adds a suggested mechanism. "The initial decreased death rate of the 0.11 r group may suggest an initial 'beneficial' effect but is probably due to biological variation since the number of animals was small. Statistically it is not significant. Even if such a beneficial effect exists, i.e. some mechanism overcompensating for low-grade destructive effects by simulating 'stimulation,' it will be present only in the beginning of the exposure. Invariably the death rate is accelerated, thus indicating the destructive action of irradiation."

This interpretation gives the first speculation about mechanism in suggesting overcompensation for low-grade injury. In more general terms, the Lorenz *et al.* speculation can be rephrased to interpret higher ionizing radiation exposure as a situation where repair or compensation processes cannot keep up with continuing injury processes in radiosensitive tissues. At some lower level, repair processes and continuing injury could be in balance. At still lower levels of exposure, repair processes could rebound, over-shoot or out-distance continuing minimal injury in very radiosensitive tissues such as bone marrow and the small intestine. This regenerative hyperplasia, rebound repair or over-shoot in bone marrow and lymphatic tissues, could then create a larger mass of tissues devoted to defense mechanisms against intercurrent lethal infections. These infections are hypothesized to cause death in a few young animals in control groups but not in the "better defended" experimental ones. For a single, low radiation exposure of 20 R, the spleen weight was increased (over control values) 60 days later in mice, according to Grahn's studies (Gr54).

This kind of theoretical explanation for the "hormetic" effect on life span was considered by Lorenz *et al.* in 1955 (Lo55) in a repeat of the earlier low-level exposure in mice. For kidney infection in mice, the difference in experimental and control groups was not significant.

George Sacher (Sa56), reviewing the mean life-lengthening effect, commented that ". . . this effect is due to an as yet unexplained action of small repeated

Table 2. Survival time in normal (i.e. non-irradiated) and lightly irradiated mice

DAILY DOSE R	NO. OF ANIMALS	MEAN SURVIVAL* DAYS
0	110 (males)	683.5 ± 14.3
0	116 (females)	802.9 ± 16.1
0.11	111 (males)	783.1 ± 14.0
0.11	120 (females)	820.3 ± 17.6

*From birth

Table 3. Survival time in normal (i.e. non-irradiated) and lightly irradiated guinea pigs

DAILY DOSE R	NO. OF ANIMALS	MEAN SURVIVAL* DAYS	MEAN ACCUMULATED DOSE, R
0	24	1372 ± 95	0
0.11	17	1457 ± 129	180

*After beginning of exposure

dosages, which leads to a decreased rate of mortality from infectious disease. We have confirmed the existence of this effect and have it under further study at present." Sacher and Trucco (Sa62) made the interesting observation that variance was reduced by irradiation. "In mice the variance between replications within treatment groups is only about half as great in groups given 5 R/day as in controls." Two major papers by Sacher and his colleagues appeared in 1964 and 1965 (Sa64; Le65). Also of interest, for puzzlement over the paradoxical hormetic effect, is their study of γ-ray exposure of guinea pigs (Ru66). This work essentially confirmed the Lorenz result.

Although there is observational information about the reduction in deaths from infection in lightly irradiated animals† documentation is lacking. It was thought evidence might be found for death from major inflammatory processes by restudying the autopsy slides of mice in the Lorenz experiments. So much focus was placed originally on cancer diagnosis at the autopsy that non-neoplastic pathology might be put aside.

Ninety-six cases were located from the approximately 500 mice in the two Lorenz studies at the Registry of Experimental Cancers at the National Cancer Institute. Sixty of the mice were from the 0.11-R exposure group and 36 from the controls. Ten of the controls (28%) had a severe inflammatory process at autopsy and eight of the experimental group (13%) did. This result is suggestive of less inflammatory disease in irradiated animals, but more need to be located and examined. Amyloidosis was equal in the two groups. Lesher *et al.* (Le57) found only an earlier peak incidence of amyloidosis in mice exposed to daily γ irradiation compared with controls.

INCREASED BODY WEIGHT

Equally interesting and referred to in the contemporary literature as a hormetic effect is the body weight gain in lightly irradiated laboratory animals (Lu80; Lu82). Figure 1 shows this observation in LAF1 male mice from the original Lorenz experiment (Zi54).

In 1947, Lorenz *et al.* (Lo47) commented that ". . . a stimulating effect is also indicated by changes in the weight of the animals. . . . It is most striking in the animals exposed to 1.1 r, in which the average weight increased by about 50% over that of the controls after approximately sixty-nine weeks of exposure. The weight increase is mainly due to accumulation of abdominal fat. . . . No explanation can be offered for this phenomenon." The increased weight was greater in males than in females. No explanation was found for this unusual observation in later reports (Zi54; Lo55a).

Totter has suggested that ". . . exposure to low level ionizing radiation . . . appears to mimic the effect of extra food" (To85a; To85b) because free radicals from metabolism or radiation could alter neuroendocrine set points that determine body weight. Obviously, metabolic and caloric balance, activity measurement, food intake and related investigations will be needed to better understand the increased body weight in low-level ionizing radiation in laboratory animals.

RADIATION CARCINOGENESIS

In Lorenz's experiments, there was an increase in neoplasia at the low-level exposure of 0.11 R. Ovarian, lung, mammary, and lymphatic tissue tumors were more frequent than in the control mice (Lo55a). This type of pathologic growth at a hormetic level of exposure was compatible with the linear hypothesis of radiation injury.

COMMENT

A review of these radiation experiments in the tolerance range performed in the 1940s and 1950s shows that the theoretical explanation of the hormetic effects has not significantly changed. The concept of rebound repair processes in critical radiosensitive tissues, giving a physiological advantage in defense against inflammatory disorders, is the first hypothesis. Cronkite *et al.* found that 1.25 rad administered every day to mice decreases the stem cell content of the bone marrow by the time 80 rad is accumulated (Cr83). Studies with lower exposure by nearly a factor of 10 were contemplated by his group, putting the exposure level in the tolerance range of the 1940s.

The weight gain in the exposed experimental animals was not explained at the time of the research and remains a puzzle. A theoretical concept has emerged with Totter's

† Personal communication (1985) with D. Grahn, Argonne National Laboratory, Argonne, IL 60439.

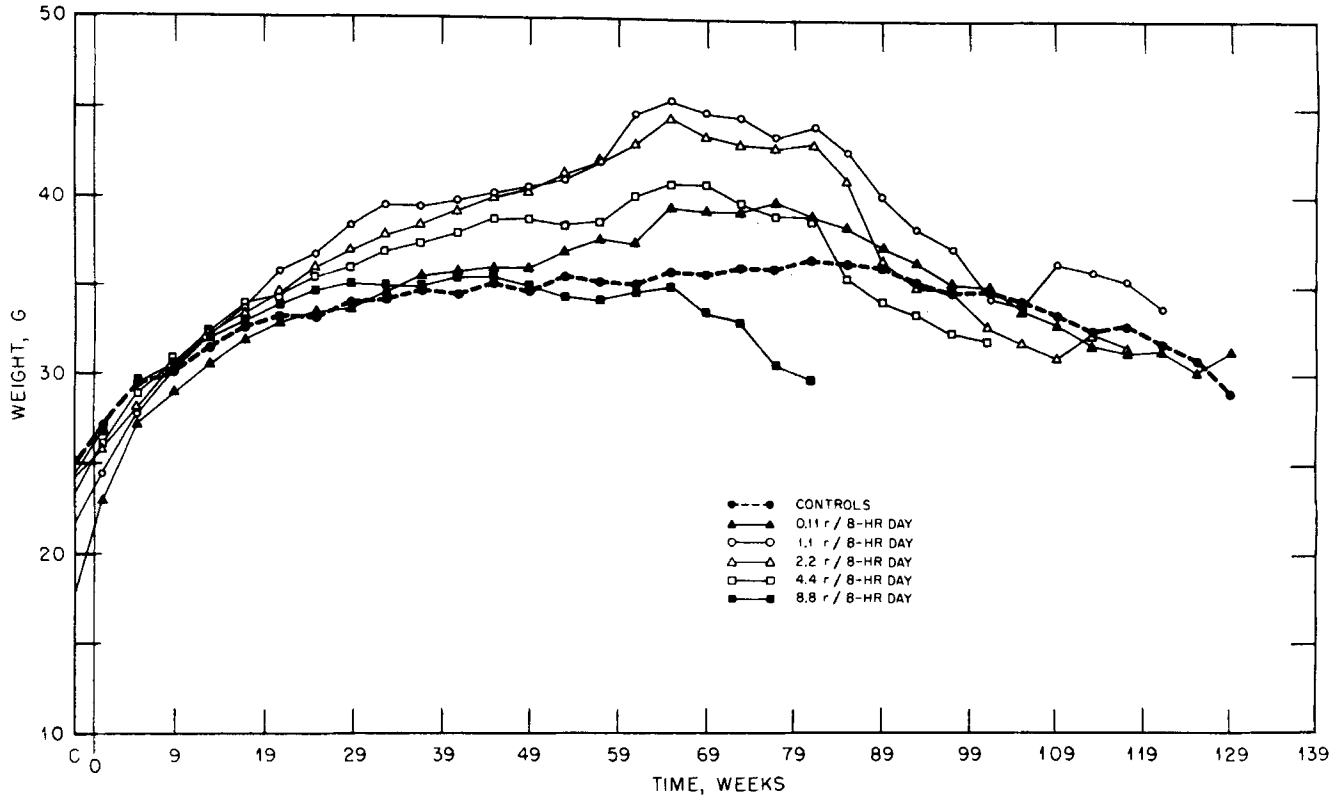

Fig. 1. Weight curves of male LAF1 Mice (adapted from Zi54).

work (To85a; To85b), and obvious extensions of the experiments looking at nutritional, metabolic and endocrine mechanisms can be proposed.

Of course, continued investigation of these hormetic effects in mice would be done with contemporary animal husbandry techniques and in pathogen-free animals. One hypothesis is that these median life span and possibly body weight changes of the hormetic type will not be found with use of state-of-the-art animal husbandry and mice free of parasites and the common mouse pathogens.‡

One still must consider, however, as Lorenz did in 1947 (Lo47), the possibility of "a general stimulation effect of an obscure mechanism of radiation," but keeping in mind, what George Sacher (Sa77) called a need for a "proper action."

‡ Personal communication (1985) with D. Grahn, Argonne National Laboratory, Argonne, IL 60439.

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