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State of Research and Perspective on Radiation Hormesis in Japan

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ABSTRACT
In 1982, Prof. Thomas D. Luckey of the University of Missouri published a paper in the journal of Health Physics describing radiation hormesis. Radiation hormesis research in Japan has been based on the rationale that if Luckey's claim were to be true, radiation management in Japan has been extremely erroneous.

After results were obtained from various experiments on the health effects of low doses of radiation supporting the hormesis hypothesis, a Round Robin collaborative testing program was initiated on about twenty research plans with more than ten universities in Japan. These activities are categorized as follows: A. Effects of free radicals produced by low dose radiation B. Molecular biological responses to low dose radiation C. Radiation effects on the neurotransmission system D. Stimulative effects of low dose radiation on the immune system E. Epidemiological studies

INTRODUCTION
In the review article "Physiological Benefits from Low Levels of Ionizing Radiation" in Health Physics (December, 1982), Luckey asserted the existence of "radiation hormesis". This resulted in the first International Symposium on Radiation Hormesis at Oakland in California, August 1985. Subsequently, interesting surveys and experiments on the effects of low dose radiation on mammals in Japan have expanded on the body of knowledge which in general have supported Luckey's claim that "low dose radiation is stimulating and essential for life!" The following article will describe various radiation hormesis research findings and the current "Round Robin Radiation Hormesis" research

program in Japan which represents a collaborative multiorganizational endeavor involving CRIEPI and various research organizations including various universities.

TOPICS OF RADIATION HORMESIS RESEARCH

Survey of A-bomb Survivors

The follow up data of people who received radiation from the Atomic Bomb show us an interesting feature especially in the low dose range. Figs. 1 and 2 show that about 8 cGy is the optimum dose for the suppression of leukemia through the survey of the people of Hiroshima and Nagasaki exposed to the radiation of the Atomic Bomb. The exposed groups are showing longer lives through the comparison of the death rate of each age between exposed group and non-exposed group (Fig. 3).

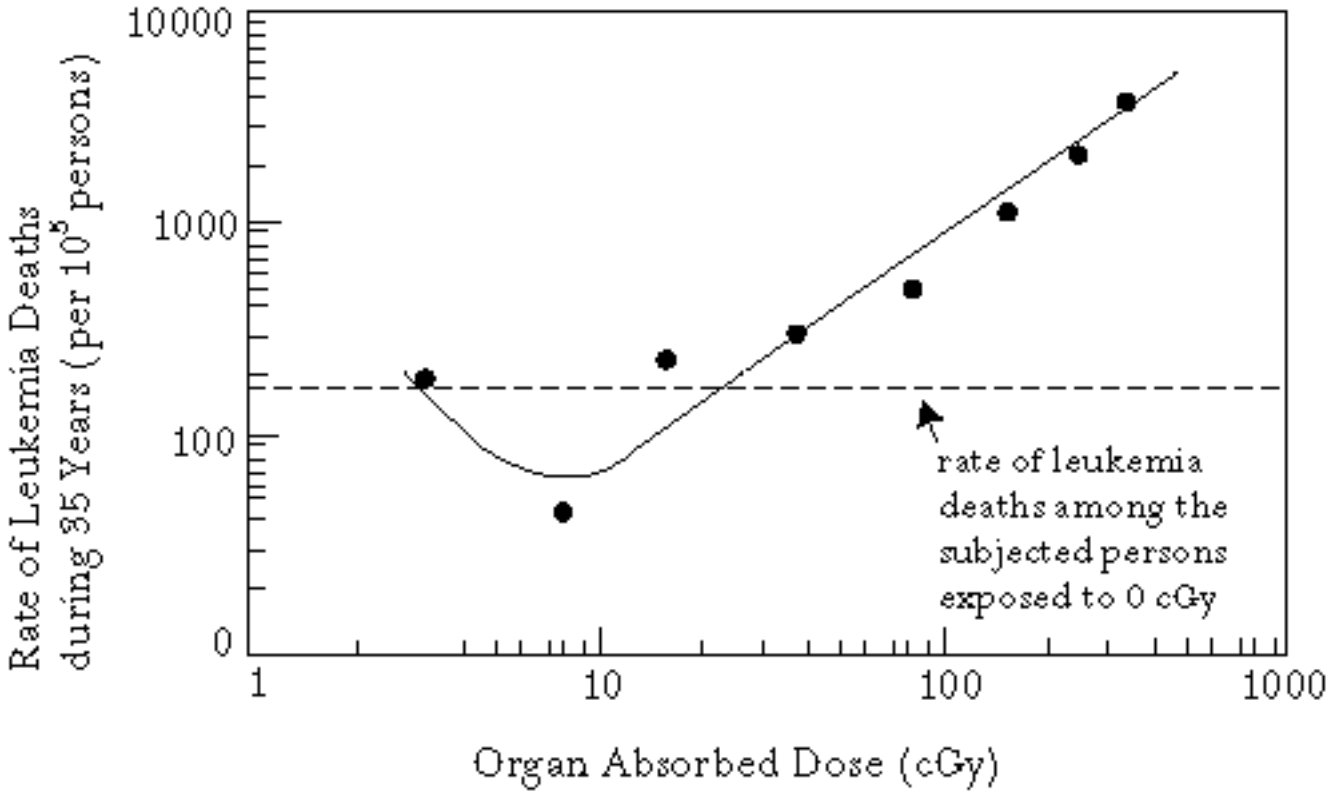


Figure 1 Dose-response relation of leukemia deaths among A-bomb survivors.

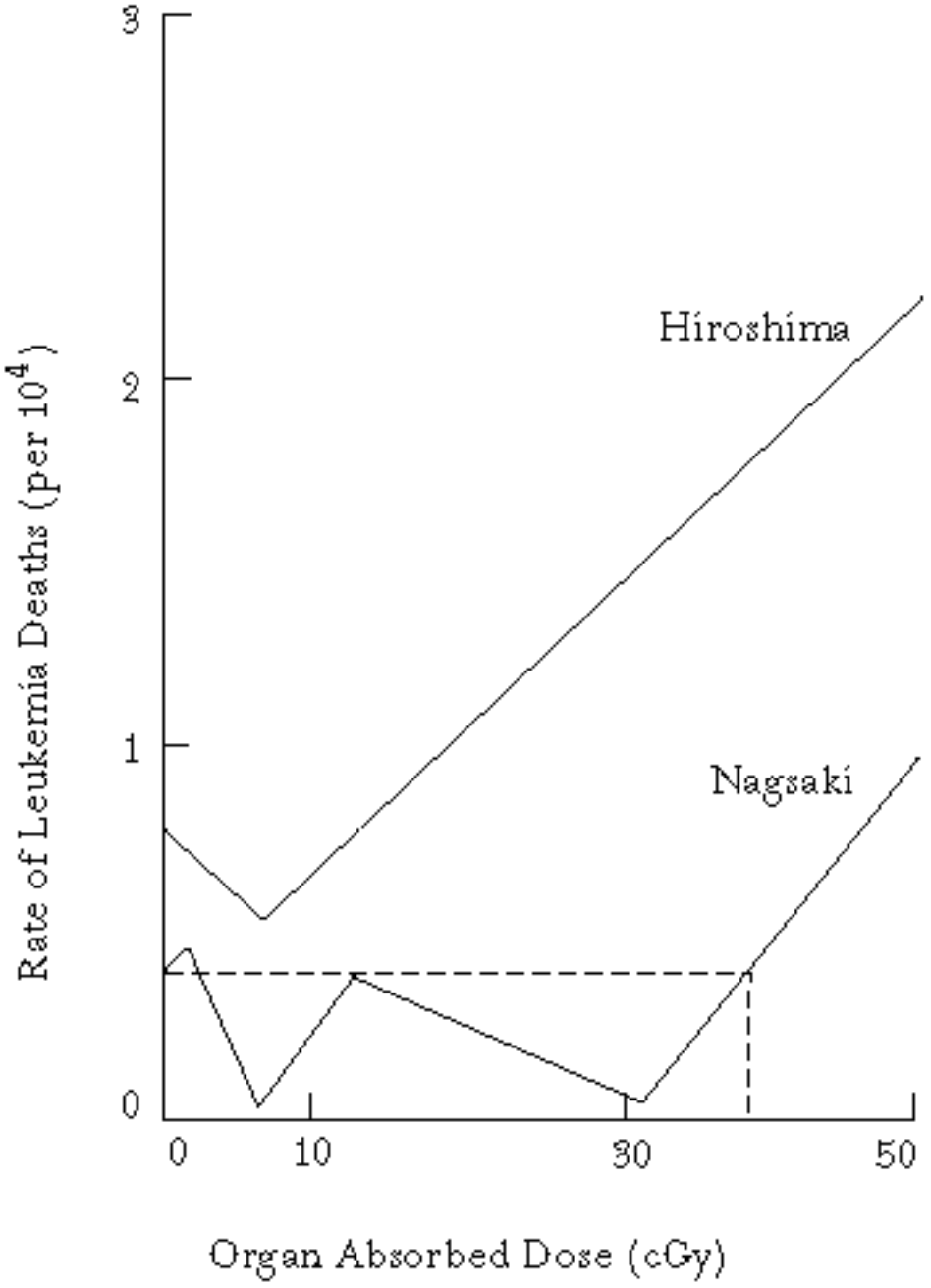


Figure 2 Threshold-like dose - - - - - - - - - estimated from dose-response relation curve of leukemia deaths among A-bomb survivors.

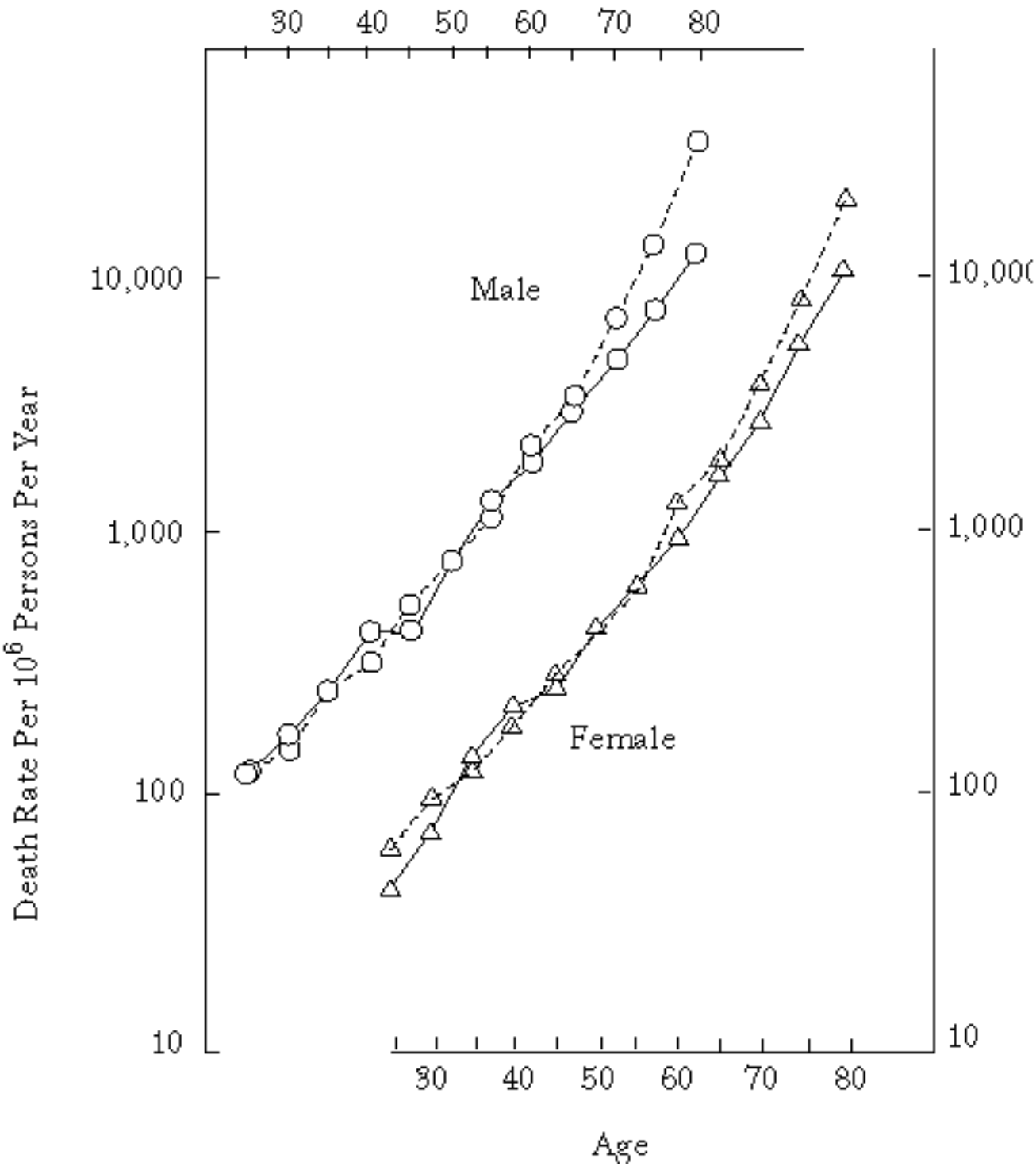


Figure 3 Higher death rate after 55 years old (dotted line) corresponds to the people who were not exposed to A. Bomb living in Nagasaki, Lower death rate after 55 years old (solid line) corresponds to A. Bomb survivors.

The Beneficial Effect of Misasa Spa

Professor Emeritus of Osaka University Dr. Kondo and Dr. Tanooka, former Chairman of Japan Radiation Research Society, conducted statistical comparisons of cancer of the people of Misasa villages (i.e. high radon levels in drinking water), adjacent villages and all Japan. The result was meaningful as shown in Fig. 4.

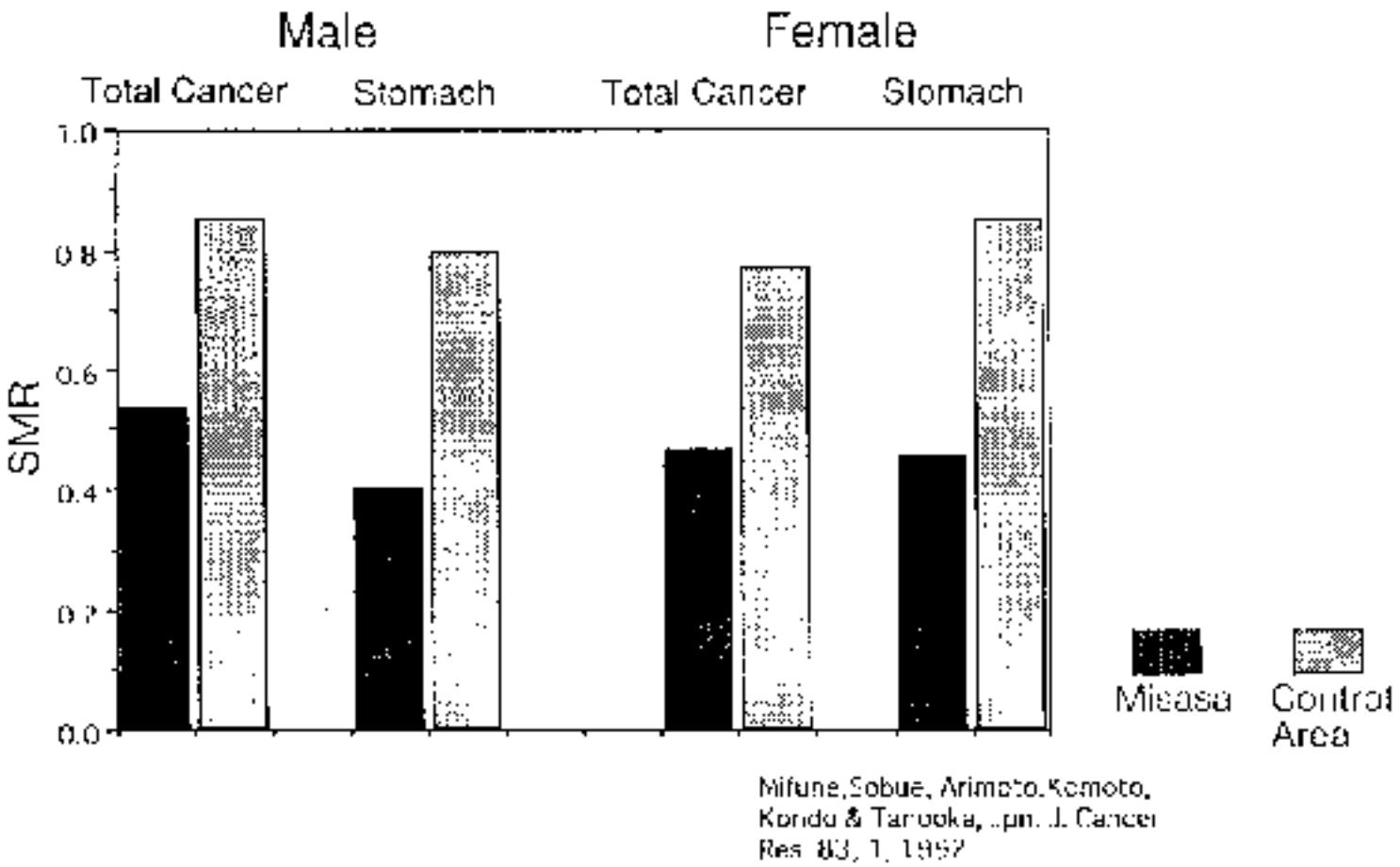


Figure 4 Comparison of standardized mortality ratio, Misasa/control area.

Medical Application: Treatment of Cancer

Professor Sakamoto is using radiation hormesis to cure and to suppress the reappearance of cancer in the hospital of Tohoku University. For example, he applied 10 cGy twice weekly for several weeks successfully against liver cancer and lymphatic tumors. He is successfully applying whole body or half body low level dose combined with local high dose irradiation to treat non-hodgkin's lymphoma. The low survival rate of 36% in patients with non-hodgkin's lymphoma after five years of the therapy improved to a 90% survival rate with a low dose treatment schema. Some

analytical results demonstrate an increase of the ratio of the helper T cells to suppressor T cells.

Suppression of Lung Cancer

Ishii of CRIEPI and Hosoi of Tohoku Univ. examined the suppression of metastasis by counting lung colonies of mice, (Fig. 5). Ishii also measured the activation of rat splenocytes, as shown in Fig. 6 by low dose radiation exposure.

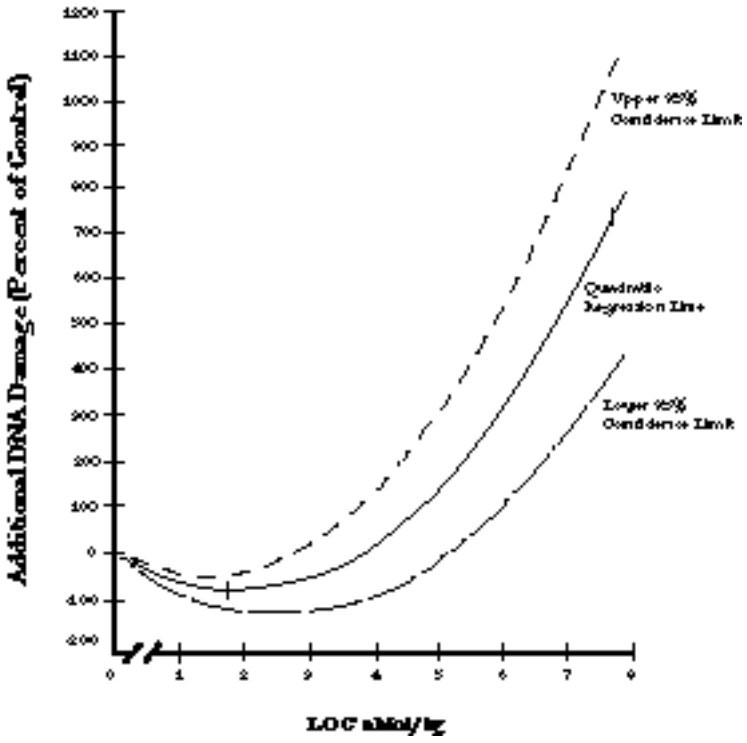


Figure 5 Inhibition of spontaneous metastasis to lung by whole body X-ray irradiation with 15 cGy and combined treatment. (15 cGy was irradiated 20 days after transplantation with murine squamous cell carcinoma).

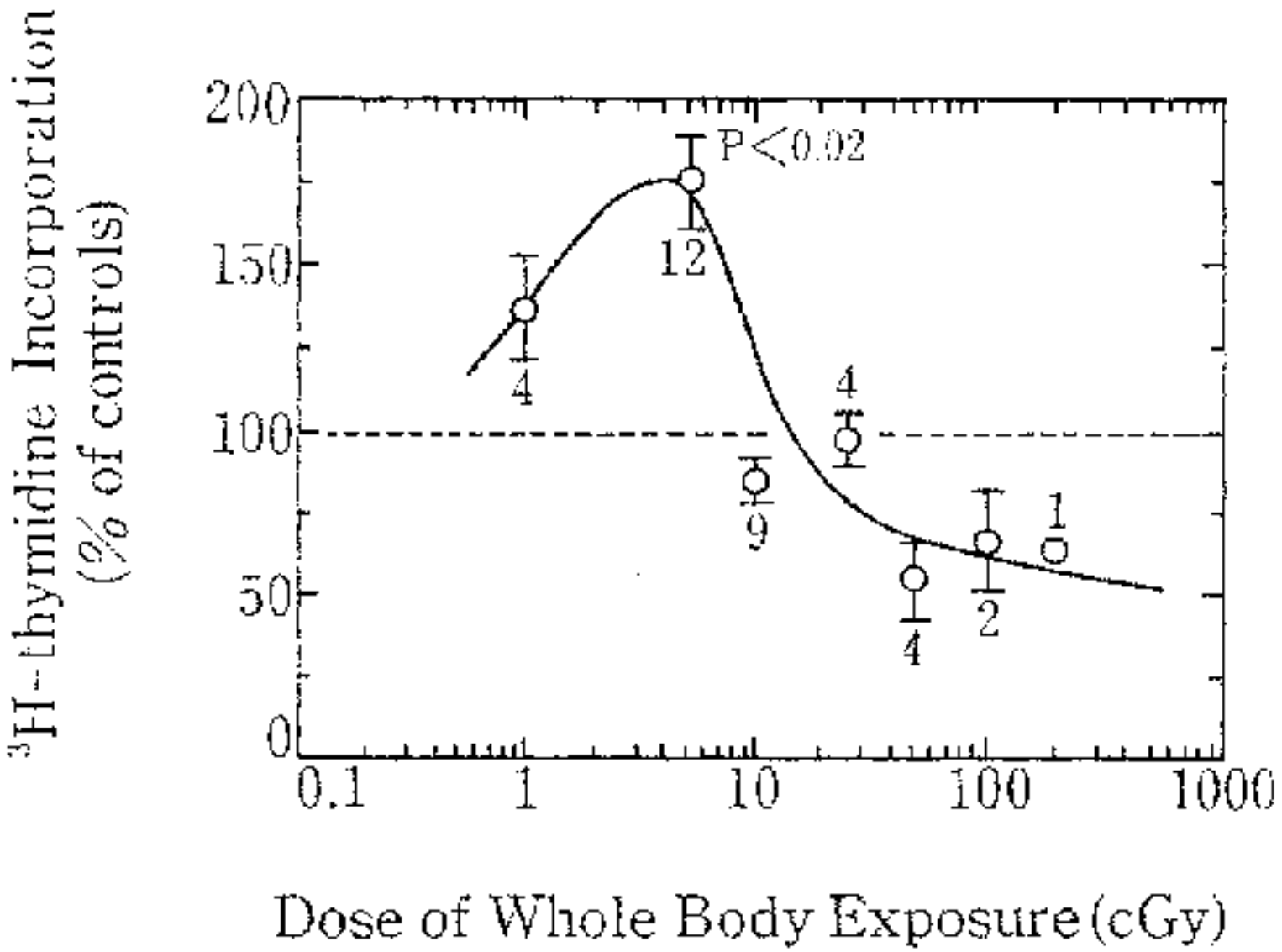
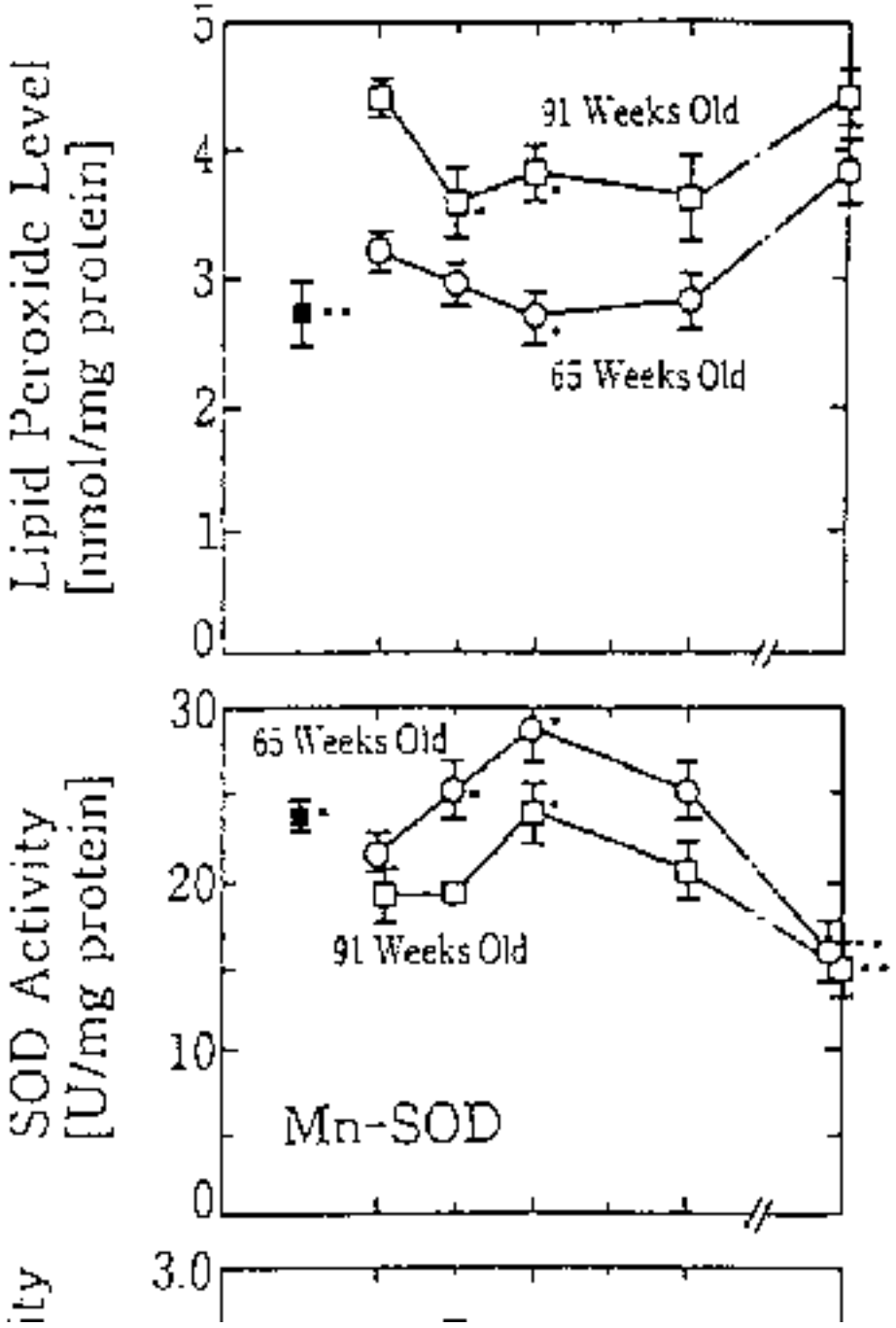


Figure 6 Effect of various doses of whole body X-ray irradiation on Con A-induced proliferative response of rat splenocytes. The splenocytes were obtained from rats at 4 hrs after X-ray irradiation.

Yamaoka of CRIEPI measured the properties of cell membranes and superoxide dismutase activities. Fig. 7 shows data from some of his experiments.



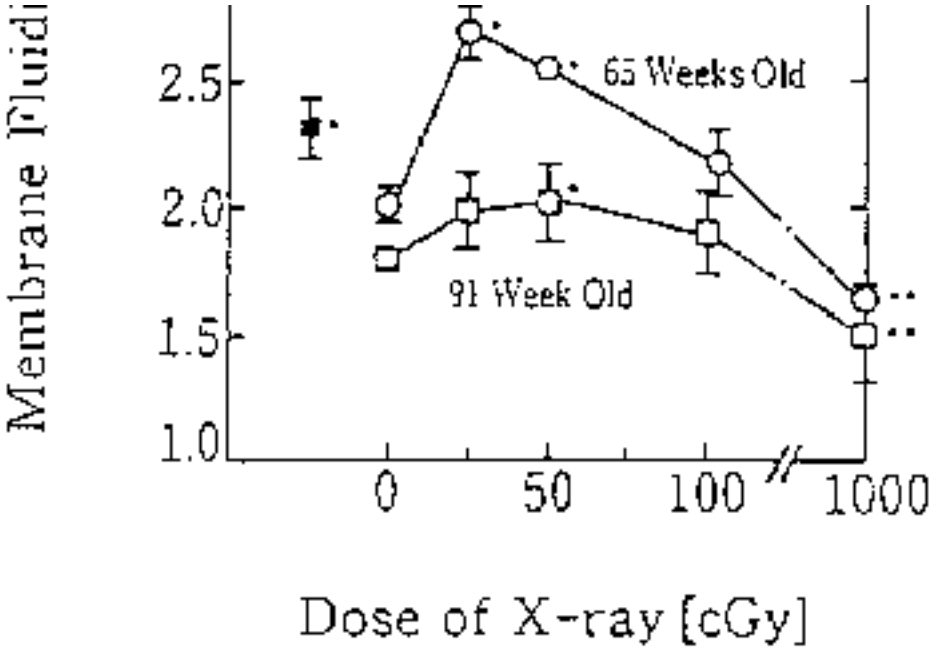


Figure 7 Dose and aging-dependent changes in lipid peroxide (TBARS) level, SOD activity and membrane fluidity (W/S ratio) of rat's brain cortex by X-ray irradiation.
Membrane fluidity was determined by spin-label method using ESR spectrometer. W/S means ratio of weak to strong bonds.
'n' shows the data from sham-irradiated 7 weeks old control.
Each value indicates the mean± S.E.M..
The number of rats per experimental point is 1015.
*P<0.05 and **P>0.01 vs sham-irradiated 65 or 91 weeks old control (t test).

Radiation Adaptation

Ikushima of Kyoto Univ. examined the radio-adaptive response as shown in Fig. 8. Chinese hamster V 79 Cells were incubated with 3H-Thymidine for 16 hrs (one cell cycle) and irradiated with a dose of 1 Gy of 60Co gamma-rays (0.4 Gy/min). The cells were fixed and assayed for the formation frequency of the micronucleus 6 hrs after

irradiation. Misonoo of CRIEPI estimated the optimum irradiation dose for radio-adaptation as shown in Fig. 9.

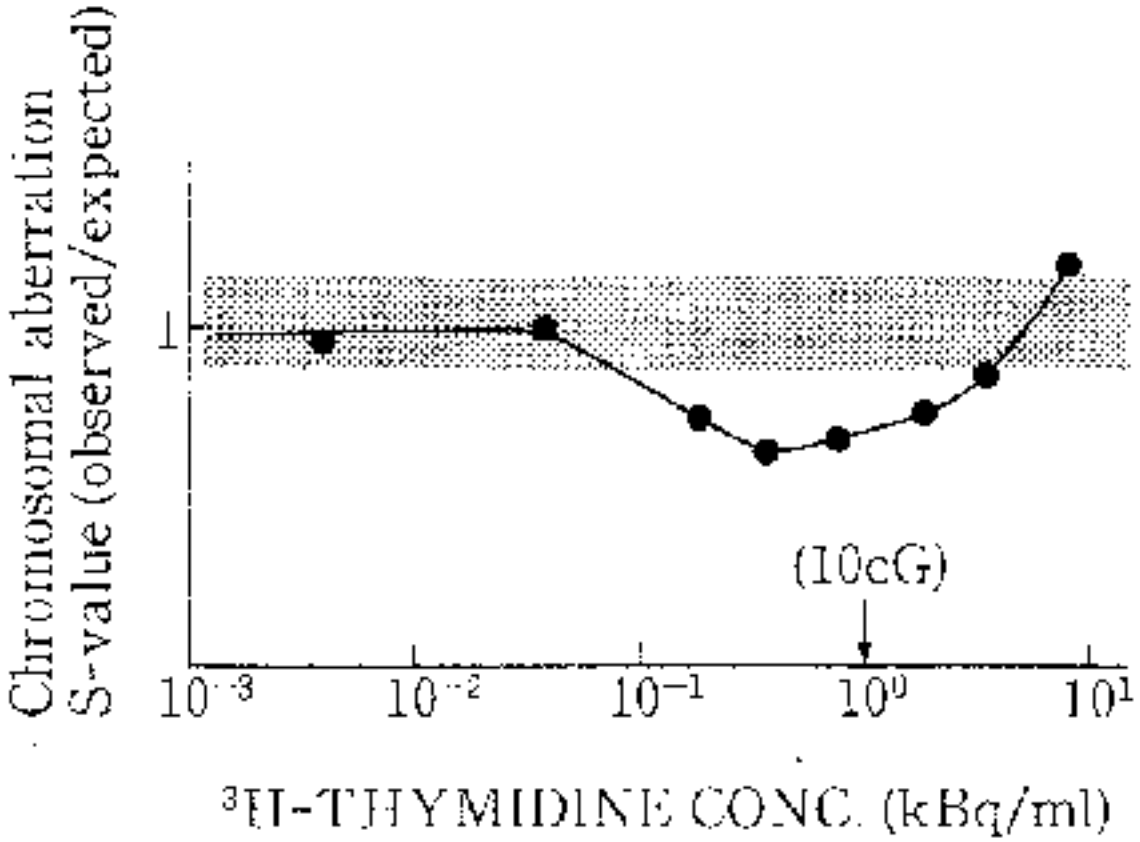


Figure 8 An optional dose range of low-level tritium for the micronuclei induction of radio-adaptive responses.

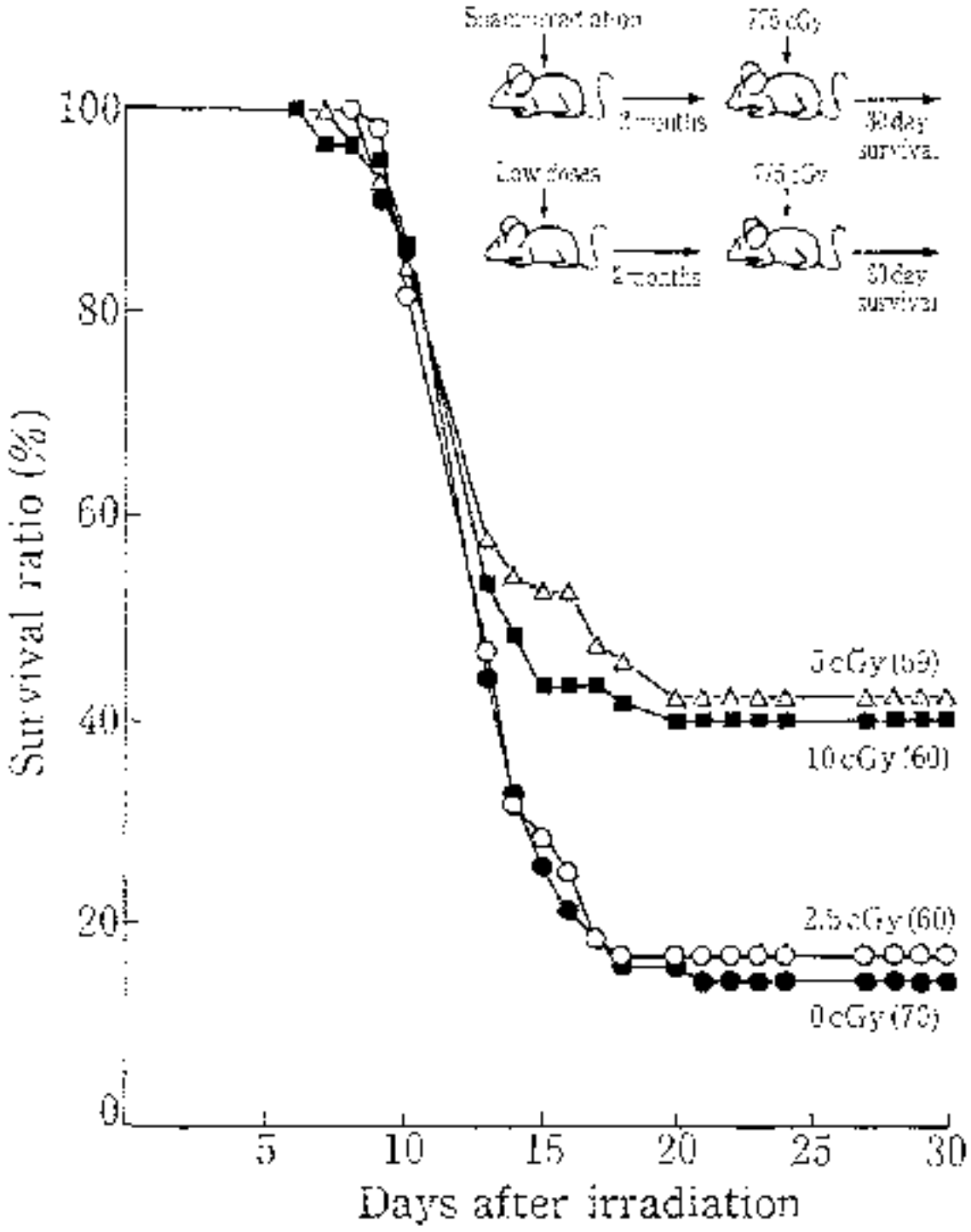


Figure Survival ratios of mice irradiated with low doses 2 months

before the second irradiation with 775 cGy of X-rays.

Zones of Hormesis

Yonezawa of University of Osaka prefecture confirmed two phases of radio-hormetic responses by using a priming dose and survival after a sublethal dose administration. He found that a low (i.e. priming) dose (i.e. hormetic dose) enhanced resistance to sublethal x-radiation given two months but not two weeks later, (Fig. 10). Opposite results were observed when the primary dose was substantially greater (Fig. 10).

Two types of acquired radioresistance after small doses of X-rays in Mice

Priming Dose of X-rays (cGy)	Radioresistance*	
	2 weeks interval	2 months interval
2.5		No
5-10	No	Yes
15		No
20	No	No (1.5 months)
30-50	Yes	No

* Increase in 30-day survival rate after sublethal X-irradiation

Figure 10 Preirradiation with 510 cGy resulted in the radioresistance 2 months later. The acquired radioresistance was also observed when the mice were exposed to 3050 cGy. In this case, the radioresistance appeared 2 weeks later. Preirradiation with the intermediate doses of 15-20 cGy did not result in any radioresistance.

Vitalization of Human Cells

Watanabe of Nagasaki Univ. compared the growth rate of human embryonic cells which had been exposed to a high

acute dose or to periodic multiple doses. Cells which received 7.5 cGy/week showed an hormetic response. Fig. 11 shows one of his experimental results.

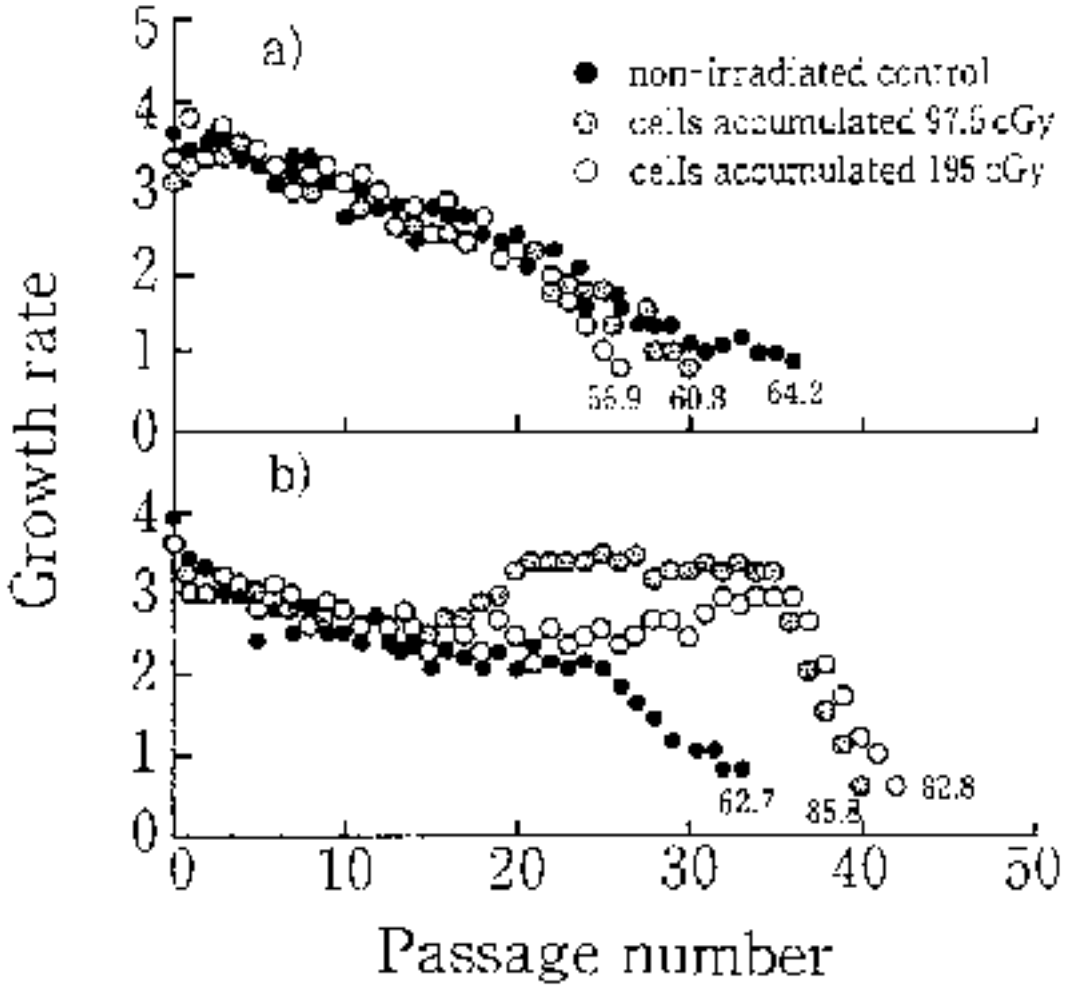


Figure 11 The growth rate at each passage in human embryonic fibroblasts (HE7) irradiated with single dose at passage 0(A) and multiple doses of 7.5 cGy of Cs137 gamma-rays (B).

An Effect on the Neurotransmitting System

Miyachi of Tohoku Univ. discovered an interesting behavior of mice when he initiated the first work of his hormesis research in CRIEPI. The 5 ~ 10 cGy whole body X-ray irradiation to the ICR mice which inevitably fight caused a drastic change of the behavior after seven days. Fig. 12 shows one of his tests results. Moderation of offensive behavior was observed with the isolated-resident versus isolated-intruder paradigm. Significant differences (p is less than 0.01) between control and irradiated groups are represented by the asterisk.

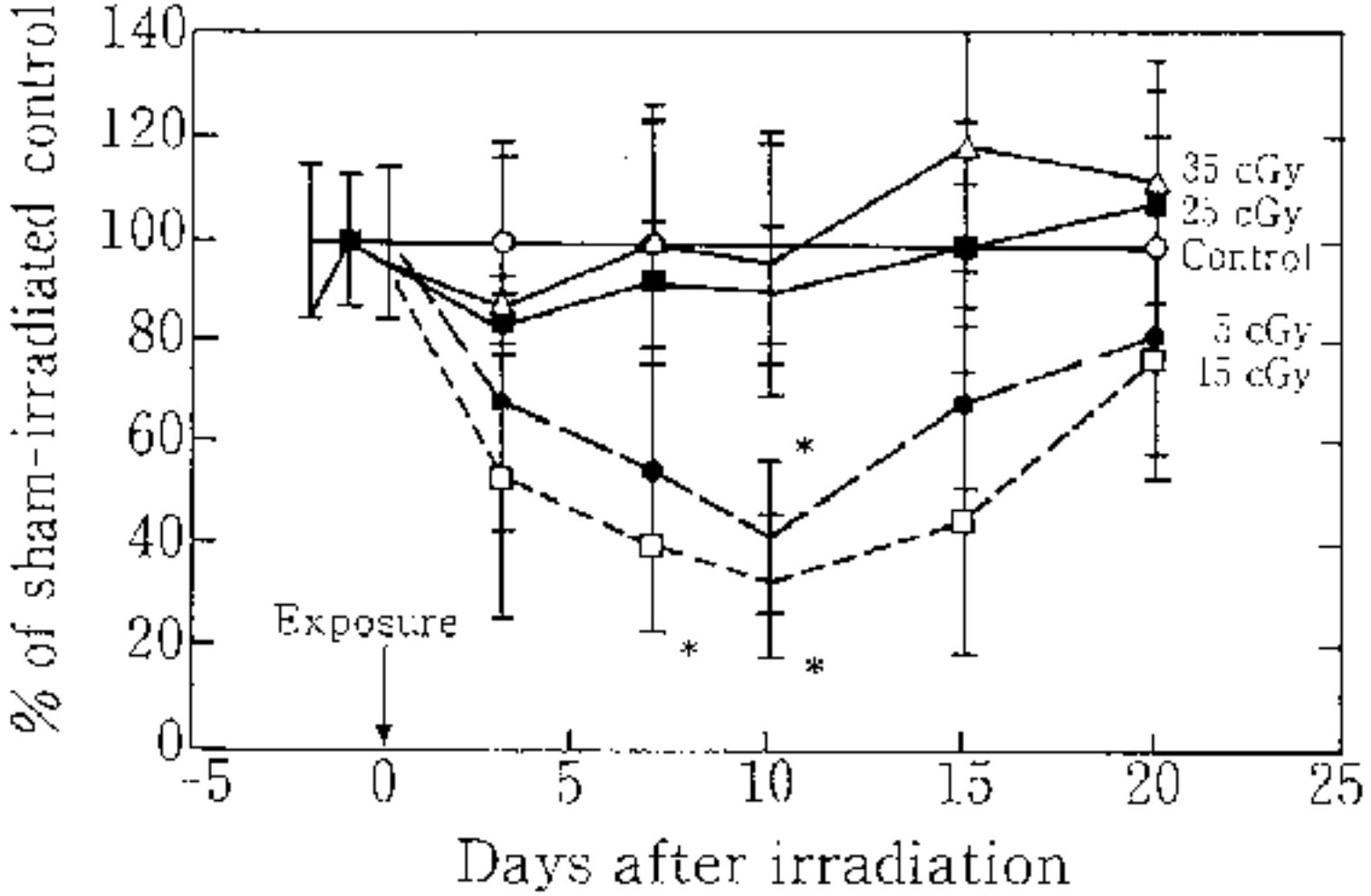


Figure Effect of low-dose X-rays on aggression displayed by isolated

 resident vs isolated intruder.

Thorotrast Study

Dr. Mori, former principal researcher of National Institute of Radiological Sciences, is directing epidemiological follow up studies on thorotrast patients in Japan. He has indicated no harmful lung effects are observed following a 10 year exposure to 2 Gy via an internal alpha-ray source.

Response of p53

Professor Onishi of Nara Medical College discovered a marked increase of stress protein production by p53 genes. Doses of 10 to 25 cGy were effective. Fig. 13 shows his experimental results.

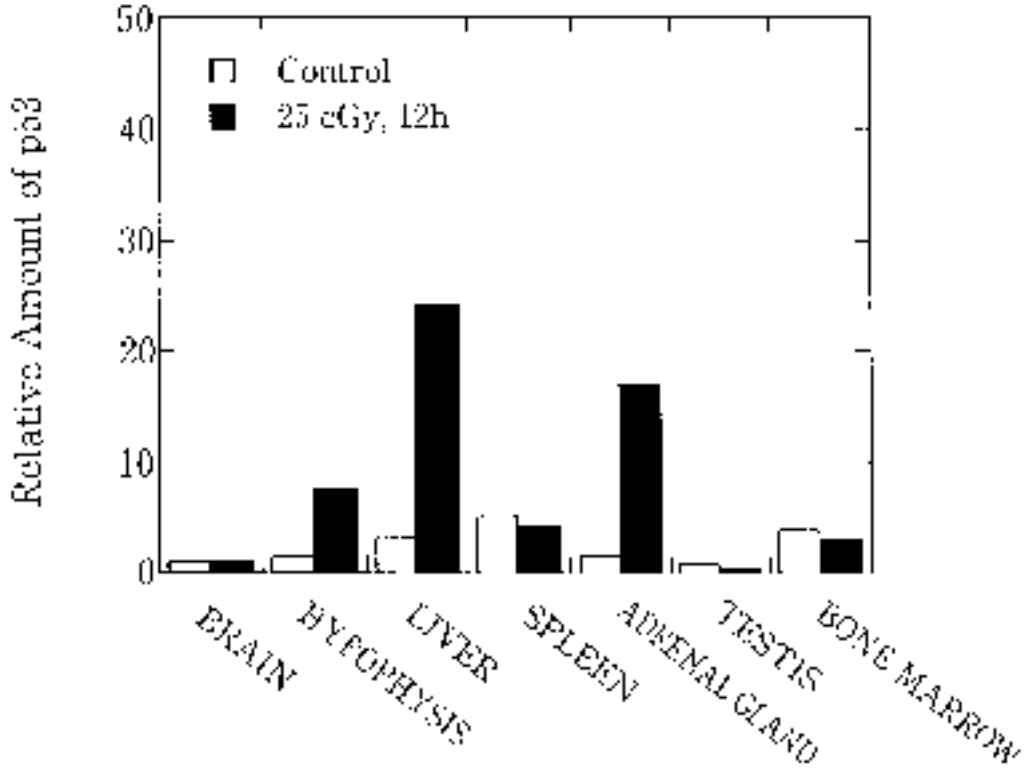


Figure 13 Accumulation of p53 in various organs by X-ray.

Importance of Low Dose Steady Irradiation
Prof. Nomura confirmed the importance of steady low dose irradiation for gene repairing activities, giving evidence that steady low dose administration is essential for obtaining beneficial health effects.

THE ROUND ROBIN TESTS PROGRAM

So-called Round Robin Tests Program (1993 - 1996) on Radiation Hormesis being carried out in Japan is as follows:

Studies on Special Biological Responses to Low-Dose Radiation

Anti-Carcinogenesis and Anti-Cancer Effects induced by Low-dose Radiation

Two different groups are working on anti-carcinogenesis effects induced by low-dose radiation (LDR): One is looking at the suppression of leukemogenesis through the augmentation of the immune system by LDR using AKR mice. The other is looking at the suppression of chemical carcinogen (Fe-NTA) induced tumor formation through enhanced SOD (Superoxide dismutase) activity by LDR.

Title & Researcher

1. Anti-Leukemogenesis Test (S. Sakamoto, Faculty of Medicine, Tohoku University)
2. SOD and Possible suppression of Fe-NTA induced Tumor (K. Utsumi, Institute of Medical Science, Center of Adult Diseases, Kurashiki)

Anti-Aging Effects

Two different groups are looking at the possibility of LDR induced increase in longevity of laboratory animals. Possible depressive effects of LDR on the aging process of the immune system and/or regulatory system of energy metabolism are tested using SAM (Senescence Accelerated Mouse) and/or other laboratory animals.

Title & Researcher

1. Possible Depressive Effect of Low-Dose on the Aging Process (Y. Okumura, Faculty of Medicine, Nagasaki University)
2. Low-Dose Radiation and Energy Metabolism Regulation (A. Mori, Faculty of Medicine, Okayama University)

Epidemiological Studies

One group is looking at the possibility of LDR induced increase in longevity of human populations using the data bases of the Atomic Bomb Survivors Health Survey.

Title & Researcher

1. Analysis of Data showing the Longevity Increasing Effect of Low-Dose using Data Base of A-Bomb Survivors Health Survey in Nagasaki (Y. Okumura, Faculty of Medicine, Nagasaki University)

Studies on Mechanisms underlying Low-Dose Effects

Activation of Basic Biological Functions

There are four different groups here: One is looking at organic radicals with long half lives produced by LDR, and their biological/molecular effects. The other is looking at the stimulative effects of fractionated LDR on the proliferation of cultured cells. Using human embryonic fibroblasts, total passages, transformation frequency, mutation frequency and other alterations of cells are examined in this study. The third group is looking at stem-cell activation through apoptosis induced by LDR. The effects of protracted irradiation with low dose rates are examined in intestinal crypts of mice. Using LacZ gene introduced transgenic Mutamouse, somatic cell mutation induced by LDR is being observed by another group. Mutation frequency and spectrum in the introduced LacZ gene are examined after acute and/or chronic LDR.

Title & Researcher

1. Identification of the Initial Radicals induced by Low-Dose (T. Miyazaki, Faculty of Engineering, Nagoya University)
2. Examination of the Inhibitory Effects of Low-Dose on Cell Aging and its Mechanism (M. Watanabe, Department of Pharmacy, Nagasaki University)
3. Stem-cell Activation by Low-Dose through Apoptosis Induction (K. Ijiri, Radioisotope Center, Tokyo University)
4. Specification of the Somatic Cell Mutation induced by Low-Dose using Mutamouse (T. Ono, Faculty of Medicine, Tohoku University)

Activation of Biological Defense Mechanisms

There are five different groups in this study: Two groups are looking at the acquired radioresistance in mice. When the radioresistance appears after conditioning irradiation, how long it lasts and the relation to the recovery of hematopoietic tissues are examined in preirradiated mice. Relationship between stressors, including LDR, and defense mechanisms is also examined in the mice pretreated with stressful stimuli, such as diet restriction, i.p. injection of heavy metals, skin-excision and LDR. Activation of defense mechanisms is also looked at in relation to the stimulation of stem-cell proliferation through apoptosis by LDR. Application of the Altruistic Cell Death Hypothesis to stem-cells in thymus and other hematopoietic tissues are examined in this study.

Depression of aggressive behavior observed in mice irradiated whole-body or partially on the head portion with low dose X-rays suggests the organisms can perceive the LDR through the central nervous system (CNS). One group is looking at the effects of LDR on the immune system, as well as behavior, because the defense mechanisms are closely connected with CNS function. Radicals generated by LDR are detoxified by a detoxification system which includes a group of enzymes, such as catalase, SOD and glutathione peroxidase. An hypothesis that LDR can induce expression of genes and a variety of gene products related to detoxification of radicals is also examined in relation to activation of molecular/ biochemical defense mechanisms.

Title & Researcher

1. Acquired Radioresistance in Low-Dose Irradiated Mice (M. Yonezawa, Research Center of Radioisotopes, Osaka Prefecture University)
2. Acquired Radioresistance and the Activated Defense Mechanisms (J. Matsubara, Faculty of Medicine, Tokyo University)
3. Examination of "Altruistic Cell Death Hypothesis" (Stimulation of Stem Cell Proliferation through Low-Dose Induced Apoptosis) (T. Yamada, School of Medicine, Toho University)
4. Action of Low-Dose to the Central Nervous System and Anti-stress Effects of Low-Dose Irradiation (T. Yamada, School of Medicine, Toho University)
5. Stress Protein and the Expression of Genes related to Active Oxygens (M. Inoue, Faculty of Medicine, Osaka City University)

Activation of Damage Recovery Mechanisms

Adaptive responses to radiation suggest that cells have intrinsic defense systems against circumstances that might cause irreversible damage. There are two groups: One group is looking at the activation of genes associated with DNA repair. In this study induced gene products and expression of genes related to DNA repair are examined using cultured CHO cells. The other group is looking at cellular changes in the adaptive response induced by LDR. Intercellular and intracellular signal transduction is examined in this study.

Title & Researcher

1. DNA Damage Repair Mechanisms (T. Ikushima, Research Reactor Center, Kyoto University)

2. Cellular Responses and Signal Transfer (M. Watanabe, Department of Pharmacy, Nagasaki University)

CLOSING

Formation of free electrons and free radicals by ionizing radiation creates many complex chemical reactions followed by significant biological responses. This article describes important research directions that will provide important mechanistic understandings of how cells and organisms adapt to environmental stimuli such as low dose radiation.

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Those University persons who are giving respectful advise and direction to the research are Dr. Luckey (Missouri), Dr. Kondo (Osaka), Dr. Sugawara (Kyoto), Dr. Sakamoto (Tohoku), Dr. Makinodan (UCLA), Dr. Okada (Tokyo), Dr. Sasaki (Kyoto), Dr. Yamada (Toho), Dr. Kubodera (Tokyo Science), Dr. Watanabe (Nagasaki), Dr. Tanooka (National Cancer Inst.), and Dr. Aoyama (Shiga Medical).

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Spontaneous DNA Damage and Its Significance for the "Negligible Dose" Controversy in Radiation Protection

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One of the crucial problems in radiation protection is the reality of the negligible dose or de minimus concept (1-4). This issue of a "practical zero" and its resolution is central to our understanding of the controversy concerning the existence of a "safe" dose in radiological health. However, for very low levels of environmental mutagens and carcinogens including low doses of low-LET radiations (less than 1 cGy or 1 rad), spontaneous or endogenous DNA damage may have an increasing impact on the biological consequences of the induced cellular response. It is this issue that is addressed in this communication.

The following discussion is intentionally limited to a comparison of low-LET radiation since its effects are due primarily to indirect damage in cellular DNA brought about by OH radicals. Indirect effects of low-LET radiation under aerobic conditions are reported to account for 50-85% of measured radiation damage in cells (5, 6). High-LET radiation, on the other hand, produces unique DNA damage (7) primarily by direct effects (5) which is less likely to be properly repaired (7).

Spontaneous or intrinsic modification of cellular DNA is ubiquitous in nature and likely to be a major cause of background mutations (8), cancer (9), and other diseases (10). The documentation of this intrinsic DNA decay has increased at a rapid pace in recent years and has not gone unnoticed by contemporary radiobiologists. Setlow (11)

and more recently Saul and Ames (12) summarized the findings of Lindahl and Karlstrom (13) and others (14) which suggest that approximately 10,000 measurable DNA modification events occur per hour in each mammalian cell due to intrinsic causes.

The current radiation literature will be interpreted to show that ~100 (or fewer) measurable DNA alterations occur per centigray of low-LET radiation per mammalian cell. Therefore every hour human and other mammalian cells undergo at least 50-100 times as much spontaneous or natural DNA damage as would result from exposure to 1 cGy of ionizing radiation. Since background radiation is usually less than 100-200 mrem (1-2 mSv)/y, it can be concluded, as discussed by Muller and Mott-Smith (15), that spontaneous DNA damage is due primarily to causes other than background radiation.

"Intrinsic" Or "Spontaneous" DNA Damage

DNA is not as structurally stable as once thought. On the contrary, there appears to be a natural background of chemical and physical lesions introduced into cellular DNA by thermal as well as oxidative insult. In addition, in the course of evolution, many cells have evolved biochemic mechanisms for repair or bypass of these lesions.

Some of the more common "natural" DNA changes include depurination, depyrimidination, deamination, single-strand breaks (SSBs), double-strand breaks (DSBs), base modification, and protein-DNA crosslinks. These are caused by thermodynamic decay processes as well as reactive molecules formed by metabolic processes leading to free radicals such as OH, peroxides, and reactive oxygen species.

Shapiro (14) has recently discussed and summarized the frequency at which various kinds of spontaneous DNA damage occur. Spontaneous DNA damage events per cell per hour are shown in Table I and were estimated from the data presented by Shapiro [Table 11(14)].

Table 1 Estimated Spontaneous DNA Degradation Events (Cell/h)a

Reaction	Single-strand DNA	Double-strand DNA
Depurination	4000	1000

Depyrimidination	200	50
Deamination of cytosine	4000	15
Chain break resulting from depurination	‹	1000
Direct chain break	‹	4000
a Calculated from Shapiro (14)		

For single-stranded DNA of mammalian cells at least, 8x103 damage events occur/cell/hr, whereas for double-stranded DNA there were ~6 x103 damage events per hour (Table I). While the ratio of single-stranded DNA to double-stranded DNA varies with phase of the cell cycle, it is reasonable to assume that double-stranded DNA is the usual configuration for most cellular DNA at any one time. From the data summarized in Table I it is not unreasonable to suggest that, at a minimum, the spontaneous DNA damage is of the order of 6-10 x 103 events/cell/h and to use 8 X 103 DNA damage events/cell/h as a reasonable average for the purpose of discussion. This allows a calculation of 1.9 x 105 spontaneous cellular DNA damaging events/cell/day or 7 x 107 per year in mammals including humans (Table II). The lifetime load of spontaneous DNA damage events per cell is then ~5 x 109 if an average life span of 75 years is allowed for humans.

DNA Damage Induced By Irradiation

Several recent reviews summarize the types and quantities of alteration of DNA in cells caused by exposure to low-LET radiation (16-18). The reader should refer to these for references to the original works from which the reviews were drawn.

The estimate of about 100 DNA events/cell/cGy used in this discussion is based on information contained in the reviews by Ward (16, 20) and assumes the molecular weight of the mammalian genomic DNA to be 6 X l012 Da, constituting about 1% of the cell weight.

Ward [Table II (16)] lists the amount of energy deposited in various DNA constituents/cell/Gy. From this table a total of 13.3 DNA events/cGy is calculated. His estimate of damaged DNA sites/cell/cGy is 10-100. I chose the 100-

lesion estimate to make as reasonable a conservative comparison with spontaneous DNA damage as possible (Table II). This number of damaged sites would include both direct and indirect DNA damage.

Table 2 DNA Damage Events per Mammalian Cell

	Spontaneous	**DNA damage**	**events**	
Character of event	**Per second**	**Per hour**	**Per year**	**DNA damage/cGy[a]**
Single-strand breaks	1.4	—5 x 103	—4.4 x 107	10
Double-strand breaks				0.4
Depurination and/or base lesions	0.8	—1.5 x 103 —1.25 x 103	—81.4 x 107 —1.1 x 107	9.5
Total events	2.2	—8.0 x 103	—7 x 107	—20
cGy equivalents (1 cGy = 100 events)[b]	0.022	8.0 x 101	7 x 105	

a From Ward (2()).
b Since other radiation-induced DNA damage such as DNA-protein crosslinking and base modifications (18) occur, 100 events/cGy is used as a "ballpark" value for ease of comparison with spontaneous events.

Spontaneous vs Induced Dna Modifications And Their Biological Consequences

Wallace has recently reviewed the nature of the DNA lesions caused by active oxidizing species produced both naturally and by low-LET radiation (17). Oxidizing radicals and especially OH radicals resulting from either cause produce similar types of DNA lesions (17 19). The enzymes involved in their repair are similar whether the DNA damage is produced spontaneously or by radiation. However, radiation is known to induce an error-prone repair system in bacterial cells and perhaps in mammalian cells as well (21, 22).

DNA glycosylases and endonucleases are involved in the repair of base damage. Other nucleases are available for sugar damage repair (17). Recognition of the damage site by the appropriate enzymes is dependent not on the initiating event but on the chemical nature of the end product. These end products appear to be similar whether induced by natural causes or radiation (17). It would seem reasonable to conclude that, due to common oxidizing radicals, many of the qualitative changes in DNA are quite similar for radiation-induced or spontaneous DNA damage.

The quantity and distribution of each class of lesion may, however, differ significantly. As indicated earlier there would appear to be relatively more DNA strand breaks than other lesions resulting from spontaneous causes as compared to radiation insult. A good portion of these may result from depurination (Table I) with production of 3' OH termini ("clean ends") as part of the repair process.

Many of the DNA strand breaks caused by low-LET radiation are incapable of serving as primer for DNA polymerase (23). However, endo- and exonucleases exist which can restore these blocking ends to clean ends and allow completion of the repair process (17).

A strong correlation exists between DNA DSBs and lethality in mammalian cells for low-LET radiation. While the quantity of DSBs produced by ionizing radiation is fairly well documented, this is not true for spontaneous DSB production in mammalian cells.

In spontaneous DNA decay, formation of a DSB is likely to be the result of single-strand events occurring in close proximity on each daughter strand and leading to cohesive ends which can be repaired easily by a ligation step.

A survey of the literature on the doubling dose for mutagenesis in eukaryotes exposed to low LET radiation indicates a range of 4 to 300 cGy and for carcinogenesis a range of 100 to 400 cGy. Using the "ballpark" value of approximately 100 DNA events/cell/cGy, this would represent a range of 400 to 40,000 induced DNA damage events per doubling dose. Using 100 cGy as the approximate doubling dose, a total of 1 x 104 DNA damage events would be required to induce mutations in numbers equal to that observed in nature. This is approximately the number of DNA events (8.0 x 103) produced spontaneously in each cell/h (Table II).

The Negligible Dose Controversy

The comparison of low-LET radiation-induced DNA damage with that which occurs spontaneously indicates (Table II) that a relatively large number of DNA damage events can occur spontaneously during the lifetime of mammalian and other cells.

Dose protraction over a period of weeks or months would lead to an increasing ratio of spontaneous DNA damage events to those caused by irradiation. By extrapolation from high doses and high dose rate as discussed by Ward (16, 20), 1 cGy delivered in 1 s would cause 40 50 times as many DNA damaging events per cell as that caused spontaneously during the same time span (Table II). However, 1 cGy delivered evenly over 1 year would cause (on average) less than 1 DNA damaging event per cell/day. This can be compared to ~2 x 105 natural events caused per cell/day.

From these numbers, it seems reasonable to suggest that there does exist a "negligible" dose in the range of our terrestrial background annual radiation dose of ~1 mSv (~10 DNA events/cell/year). This can be compared to the approximately 7 x 107 DNA events/cell/year produced by spontaneous causes.

Adler and Weinberg (24) have proposed that the standard deviation of the background irradiation (~0.2 mSv) be used as an acceptable additional dose due to human activities. This would lead to ~2 additional induced DNA damaging events/cell/year as compared to ~ 7 x 107 spontaneous DNA damage events. Considering the magnitude of the spontaneously induced DNA changes in each human cell, it is not unreasonable to predict that 0.2 mSv delivered over a year would have negligible biological consequences.

When temporal considerations are factored in, it becomes clear that spontaneous DNA damage in mammalian cells

may be many orders of magnitude greater than that caused by low and protracted radiation doses, especially in the terrestrial background range of 1-2 mSv (100-200 mrem) per year. It is important that further studies on the effects of both ionizing radiations and spontaneous events on DNA decay and repair be conducted to better understand the practical health consequences of low and protracted doses of radiation (2, 9, 25).

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