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Effects of Low Dose Radiation on Mammals[1]

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SUMMARY : Radiation has been applied widely to clinics, researches and industries nowadays. Irradiation by atomic bomb produced many victims in Hiroshima and Nagasaki. Radiation effects on animals and human belings have been reported extensively, especially at a dose range of high amount of radiation. As radiation effects at low dose have not been well studied, it is believed that even a small amount of radiation produces hazardous effects. However, it might not be true. Beneficial effects of a low dose of radiation are summarized here.

INTRODUCTION

Radiation is a useful too in clinics, researches and industries. However, it is hazardous when its large amount is exposed to human beings. It has been thought that even a small amount of radiation produces damages in proportion to its amount. However, we don't know how a low dose of radiaton affects human beings. The beneficial effects of low dose radiation on mammals are summarized here.

IMMUNE RESPONSE

The immune suppressive effects of radiation have been known when a large amount of radiation is exposed. However, radiation acts as immune augmentation when a small dose of radiation is exposed[1, 8]. In vitro response of spleen cells to sheep red blood cells after exposure to radiation is shown in **Fig. 1.**[1] The number of plaque-forming cells is indicated as a percentage of the control against radiation dose. Low doses of radiation, 0.25 to 0.5 Gy, showed augmented response. Above 0.75 Gy, the response was reduced less than control. This augmentation might be due to injury of highly radiosensitive suppressor T cells or their subpopulation. It can be said that the low dose of radiation results in an enhancement of the immune mechanism leading to increased antibody formation. When radiation exposure is performed with a low dose rate for a extended period of time, it become clear whether cell delation and radiation damage are accumulative, or whether homeostatic adaptation to radiation is generated. Radiation exposure to mice at a low dose rate was extended for a period of 25 days[6]. Proliferative response of spleen cells from irradiated mice was analyzed by phytohemagglutinin stimulation. The increase in ^{3}H-thymidine uptake is shown in **Fig. 2.** Radiation exposure with a dose to 0.8 Gy during a period of 20 days increased proliferative response of spleen cells. Stimulative effect

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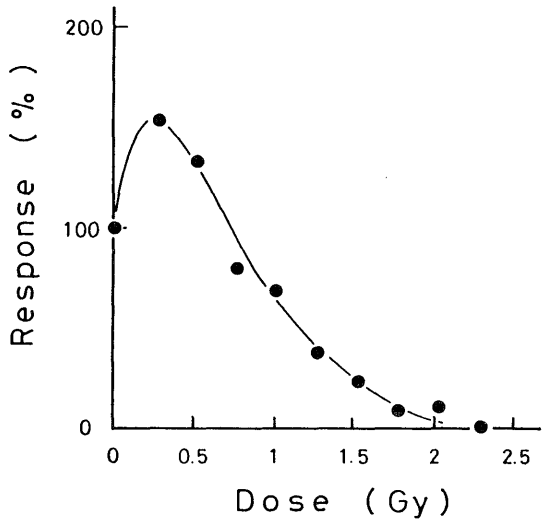

Fig. 1. In vitro response of spleen cells to sheep red blood cells after exposure to radiation[1].

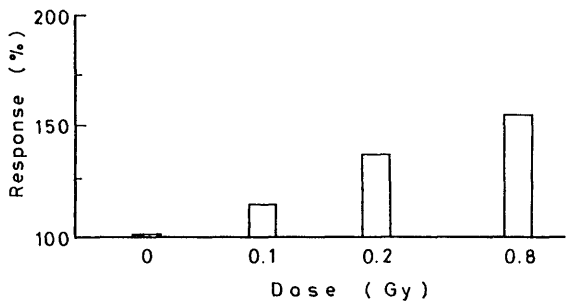

Fig. 2. The increase in ^{3}H-thymidine uptake to spleen cells after the exposure to radiation for a period of 20 days[6].

of radiation was seen in the short period exposure as well as the long period exposure.

TUMOR GROWTH

Irradiation with a low dose augments the immune function of animals and affects suppression of the grpwth of transplanted tumors[2]. A dose of 0.15 Gy was exposed to whole body of mice and 10^4 mitomycin-treated tumor cells were injected subcutaneously into mice. After 21 days, mice received 10^4 viable tumor cells. The tumor size after the inoculation of the viable tumor cells is shown in **Fig. 3.** A solid curve with closed circles is of control. Shaded bars are of mitomycin-treated cells. Open bars are

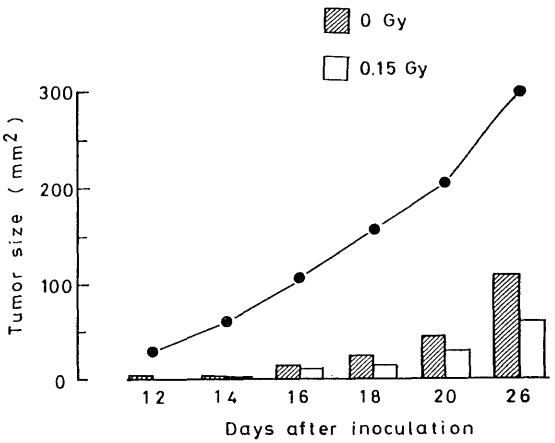

Fig. 3. Tumor growth after implantation of 10^4 cells[2]. Solid curve: control, shaded bars: injection of 10^4 mitomycin treated cells, open bars: injection of 10^4 mitomycin treated cells with whole body irradiation with a dose of 0.15 Gy.

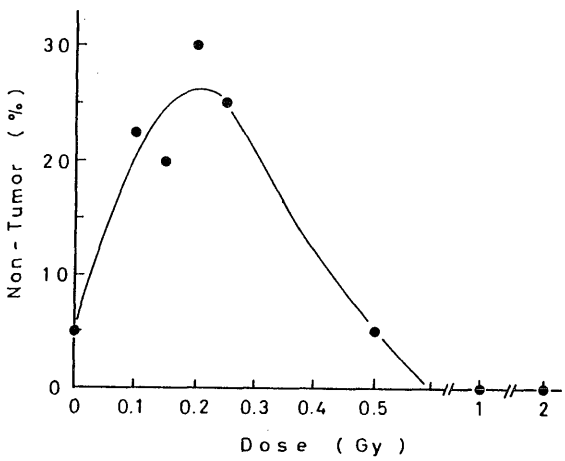

Fig. 4. The fraction of irradiated mice failed to develop tumors after inoculation of 10^4 tumor cells[3].

of mitomycin-treated cells with whole body irradiation. With 0.15 Gy. By the injection of mitomycin-treated cells, the tumor growth was inhibited, and the irradiation suppressed the tumor growth further. These effects might be caused by the immune augmentation.

The low dose irradiation suppressed the transplantability of tumors[3]. Radiation was exposed to mice just before the inoculation of 10^4 tumor cells. The exposure with low doses, from 0.1 Gy to 0.3 Gy, resulted that 20 % to 30 %

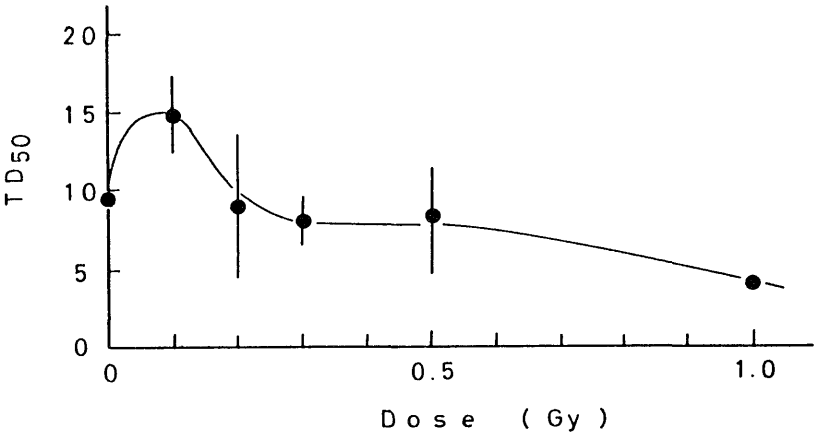

Fig. 5. Tumor dose 50, TD_{50}, of mice irradiated with a dose of 0.1 Gy[11].

of mice failed to develop tumors as seen in **Fig. 4.** This low dose augmentation is less pronounced in animals that have undergone splenectomy. Very radiosensitive suppressor T cells might be implicated in this phenomenon.

The tumor transplantability was assayed by tumor dose 50 %, or TD_{50}, which indicates the number of tumor cells forming a tumor in transplanted mice in 50 %[11]. The larger TD_{50} means the more difficulty of tumor formation. Irradiation with a dose of 0.1 Gy increased TD_{50} value than nonirradiated control (**Fig. 5**). This means that a low dose suppressed the transplantability of tumor cells in mice. The result is associated with the suppression of the tumor transplantation which is shown in the above study.

It was examined whether the low doe affected radiosensitivity or tumor cells growing in mice[11]. 10^4 tumor cells were transplanted into mice, and after 12 days of the transplantation, a dose of 0.1 Gy was exposed to the whole body of the tumor bearing mice. The radiosensitivity after 12 hours of irradiation is show in **Fig. 6.** Solid curve with solid circles in figure is of control, nonirradiation. The curve has a steep decreasing part of the surviving fraction at a low dose region, and a tail part at a high dose region. The steep part corresponds to the surviving fraction of aerobic cells in tumors, and the tail part dose to that of hypoxic cells. A dotted curve with open circles is of tumor bearing mice irradiated with the dose of 0.1 Gy. The initial

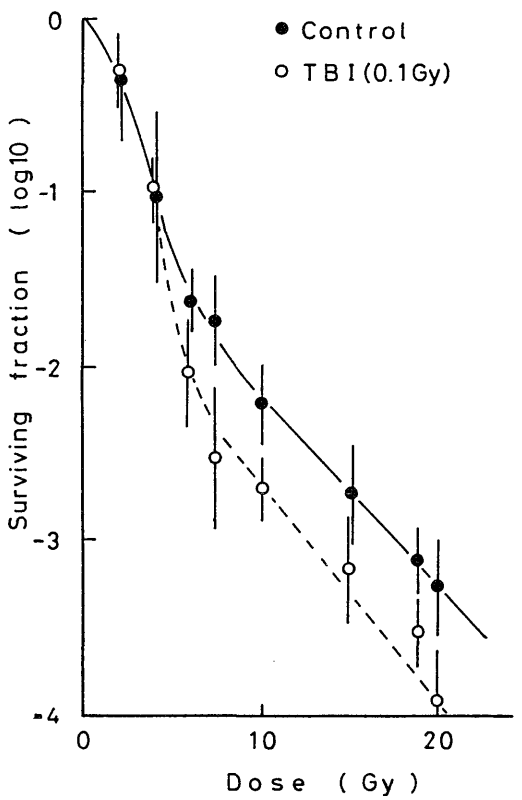

Fig. 6. Radiosensitivity of tumor cells in mice after the whole body irradiation with a dose of 0.1 Gy[11].

decreasing part was the same of the control. However, the tailing part of the surviving faction was lower than the control. This means irradiation changed immune function resulting

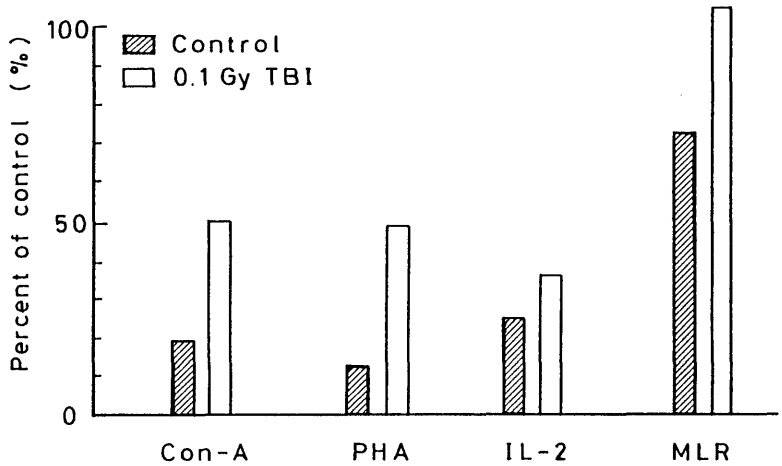

Fig. 7. The incorporation of ^{3}H-thymidine into spleen cells isolated from tumor bearing mice by the stimulation by mitogens[11]. Con-A: concanavalin-A, PHA: phytohemagglutinin, IL-2: interleukin 2, MLR: mixed lymphoid reaction

in as if the decrease in the fraction of hypoxic cells.

Irradiation with the dose of 0.1 Gy changed immune response assayed by the stimulation by mitogens[11]. **Fig. 7** shows the incorporation of ^{3}H-thymidine into spleen cells isolated from tumor bearing mice in the stimulation by concanavalin-A (Con-A), phytohemagglutinin (PHA), interleukin 2 (IL-2) and mixed lymphoid reaction (MLR). The percentage of the incorporation into spleen cells from nontumor bearing mice was indicated. Shaded bars are of tumor bearing mice without irradiation, and open bars are of tumor bearing mice for 0.1 Gy whole body irradiation. In any stimulation, irradiation with the dose 0.1 Gy augumented immune response.

SURVIVAL TIME

Mice were irradiated with a low dose rate, 0.14 mGy per hour, every days for 8 hours a day until mice died[9]. And the mean survival time was examined (**Table 1**). For male mice, the mean survival time was 684 days for control and 783 days for irradiated mice. The mean survival time was increased by 99 days by irradiation. However, for female mice, the mean survial time was 803 days for control and 820 days for irradiated mice, the difference was 17 days. This difference was not significant statistically. Male mice would be affected by the environmental conditions such as irradiation, although female mice would not.

Table 1. Mean Survival time of LAF_1 mice[9]

Sex	Control	Irradiated	Difference
	days	days	days
Male	684 ± 14	783 ± 14	99
Female	803 ± 16	820 ± 18	17

CHROMOSOME ABERRATION

Chromosome aberration of human lymphocytes was produced by the exposure with a dose of 1.5 Gy. The exposure with a low dose of 0.01 Gy before 1.5 Gy irradiation decreased the chromosome aberration[12]. **Fig. 8** shows the decrease of chromosome aberration with the interval between two doses, 0.01 Gy and 1.5 Gy. This decrease in the chromosome aberration might be adaptive response to irradiation. A low dose might change the structure of chromosome, and this change suppreassed the chromosome aberration induced by successive irradiation.

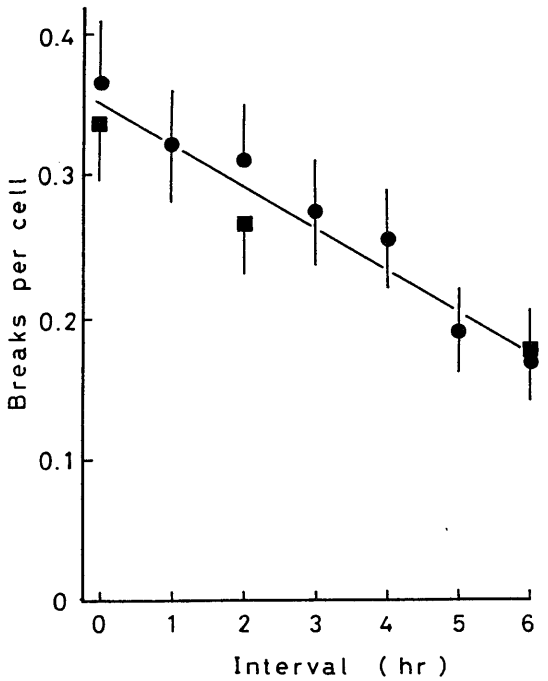

Fig. 8. The decrease of the chromosome aberration irradiation with a low dose[12]. The time interval between a dose of 0.01 Gy and a test dose of 1.5 Gy is indicated on abscissa.

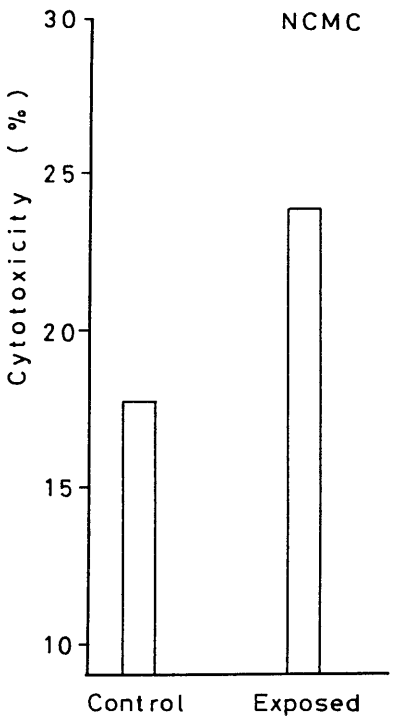

Fig. 9. Natural cell-mediated cytotoxicity of A-bomb survivors[4].

A-BOMB SURVIVORS

Cellular immune functions were analyzed among victims who survived the atomic bomb in Hiroshima and who lived in the United States of America[5] Radiation doses of the exposed group were from 0.01 Gy to 0.5 Gy. Lymphocytes were isolated from the peripheral blood of those individuals, and natural cell-mediated cytotoxicity (NCMC) was assessed and the results are shown in **Fig. 9.** The difference of cytotoxicity was significant statistiacly. Other immune function was analysed by mitogen responsr to phytohemagglutinin and to allogeneic lymphocytes and interferon production. Although the same trend of the increase was observed, the differences were not significant statistically. The same study has been performed on the atomic bomb survivors living in Hiroshima[4]. But the study did not confirm this difference. The different environmental conditions between the United States and Japan might have affected the immune function.

The rate of death from leukemia in atomic bomb survivors in Nagasaki and Hiroshima is shown in **Fig. 10**[7]. A solid curve is for Hiroshima, and a dotted curve is for Nagasaki. The death rate increases with dose for both cities, although the rate for Hiroshima was higher than that for Nagasaki. From this figure it is clear that there is a threshold dose before the rate increases with dose. Above the threshold dose, the increase in death rate is observed. Below the threahold the rate is nearly the same or smaller than control.

It is widely belived that cancer death is observed even at a low dose range in proportion to radiation dose. Howere, the threshold dose of cancer mortality analyzed for the atomic bomb surviors is observed as shown in **Table 2.** The threshold dose was observed in many cancer deaths. From the table, we can understand that thre is no increase in the incidence of cancer death by irradiation under the threshold dose in some cancer.

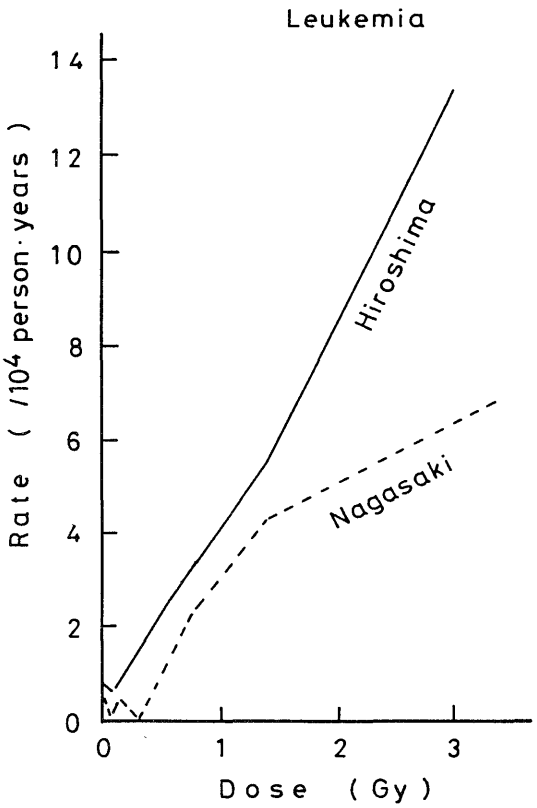

Fig. 10. The Rate of death of leukemia in A-bomb survivors in Nagasaki and Hiroshima[7].

Table 2. Threshold of Cancer Mortality[7]

Cancer	Nagasaki	Hiroshima
	Gy	Gy
Leukemia	0.36	0.12
Lung	0.28	ND
Breast	0.08	ND
Colon	0.54	0.31
Stomach	ND	0.12

ND: Not detected

The risk of death, or the ratio of death rate to that of control, for male survivors is shown in **Fig. 11**[10]. For total death, the risk was about unity for the dose range examined. The risk of cancer increased with dose. We confirmed that the irradiation causes cancer. However, the risk of noncancer disease decreased to 0.65 around 1 Gy of radiation dose, and this decrase was significant statistically. Radiation from atomic bombing decreased the mortality from noncancer disease at a low dose range. This beneficial effect of low dose radiation is called radiation hormesis.

In conclusion, it can be said that animal and human beings have systems to respond to the low dose radiation. One of main response is of immune system. And the stimulation by the low dose radiation resulted in the low martality

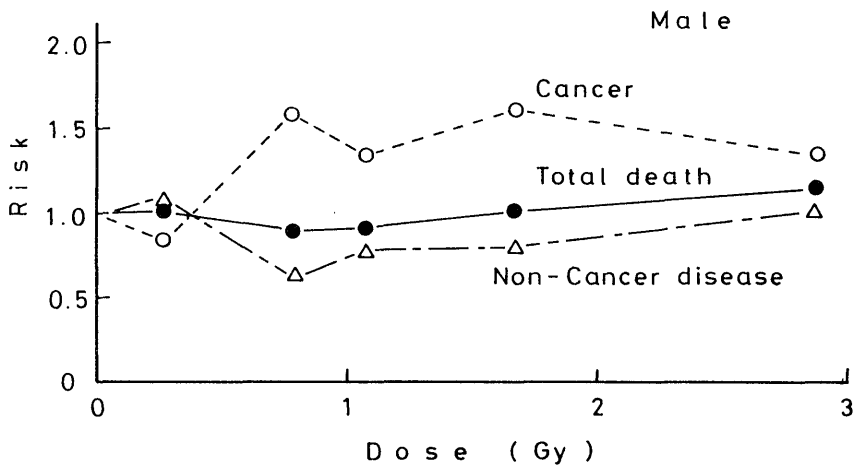

Fig. 11. The risk of death for male A-bomb survivors: total death, cancer and non-cancer diseases[10].

from noncancer disease for male survivors. The low dose of radiation is not necessarily harmful, but rather beneficial under certain conditions.

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