THE RESEARCH ON THE HEALTH EFFECTS OF LOW-LEVEL RADIATION IN JAPAN

Sadao Hattori
Central Research Institute of the Electric Power Industry, Japan

ABSTRACT

Professor Don Luckey identified the phenomenon of “radiation hormesis,” and he described it in a paper in the Health Physics Society Journal, in 1982. (He also authored two books on this subject.) CRIEPl initiated a research program on radiation hormesis following this publication to confirm, "Is it true or not?"

After nearly ten years of research activities on data surveys and animal tests with many universities, we are realizing the scientific truth of bio-positive effects caused by low-level radiation exposures.

The interesting bio-positive effects we found could be categorized in the following five groups:

- Rejuvenation of cells, such as increase of SOD and cell membrane permeability,
- Moderation of psychological stress through response of key enzymes,
- Suppression and therapy of adult diseases, e.g., diabetes and hypertension,
- Suppression of cancer through enhancement of immune systems, such as lymphocytes,
- Suppression of cancer and radio-adaptive response by activation of DNA repair and apoptosis.

INTRODUCTION

In a review article entitled, "Physiological Benefits from Low Levels of Ionizing Radiation," Professor T.D. Luckey, of the University of Missouri, described the phenomenon of “radiation hormesis” and provided 200 references (Luckey, 1982). His two books provided many more references (Luckey, 1980 & 1991).

This resulted in the first International Symposium on Radiation Hormesis in Oakland, California (in August 1985). CRIEPI consulted many specialists about Luckey's paper and studied many other papers, such as Lorenz 1954, Luckey 1980 and Liu et al 1985.

Radiation hormesis research in Japan has been based on the rationale that if Luckey's claim is true, then radiation management in Japan has been extremely inappropriate.

In the responses of many specialists to our initiation of the radiation hormesis research program, following Luckey's claim about low level radiation, I have to acknowledge, first of all, the great success of Professor Sakamoto. He had already been applying whole-body, low-dose irradiation for ten years before our radiation hormesis research started on the therapy to suppress the cancer reappearing after conventional treatment. He reported about his successful trials on real patients and showed an enhancement of their immune systems.

CRIEPI organized a Hormesis Research Steering Committee, composed of leading specialists in the field concerned, and began research in cooperation with a number of universities, as well as the National Cancer Research Institute and the National Institute of Radiological Sciences. After obtaining interesting results in

various experiments on the health effects of exposure to low doses of radiation, we proceeded on an expanded program which involved fourteen universities and two research institutes throughout Japan.

We are now carrying out experimental activities on the effects of low-dose radiation on mammals. After several years of research activities, we are recognizing Luckey's claim. Some basic surveys, including Hiroshima, Nagasaki and animal experiments in Japan, have brought us valuable information on the health effects of low-dose radiation. The following are some topical research information obtained across Japan (Hattori, 1994 &1995).

TOPICS OF LOW-DOSE RADIATION RESEARCH

Survey of A-bomb Survivors

Professor Okumura of Nagasaki University compiled the data from Hiroshima and Nagasaki, and revealed new scientific information. The follow-up data on the people who received radiation from the atomic bombs showed us an interesting feature, especially in the low dose region, less than 1 Gy. A certain optimum dose for the suppression of leukemia was discovered as a result of the survey of the people of Hiroshima and Nagasaki who were exposed to the radiation of the atomic bombs (Kondo, 1993).

The Beneficial Effect of the Misasa Spa (Figure 1)

Dr. Kondo, professor emeritus of Osaka University, and Dr. Tanooka, former chairman of the Japan Radiation Research Society, conducted statistical comparisons of the occurrence of cancer in the people who live in Misasa villages (where the radon level in drinking water is high) with its occurrence in people who live in the adjacent village and the average for Japan. The result was meaningful, especially on the suppression of total cancer (Mifune et al, 1992).

Medical Application: Treatment of Cancer (Table 1)

Professor Sakamoto used low-dose radiation to cure and to suppress the reappearance of cancer in the hospital of Tohoku University. For example, he applied a dose of 10 cGy, three times a week, for several weeks to liver cancer and to lymphatic tumor patients. He applied whole-body or half-body low-level doses, combined with local high-dose irradiation, to treat non-Hodgkin's Iymphoma. The low survival rate of the patients with non-Hodgkin's Iymphoma after five years of the local high-dose therapy improved to a higher survival rate with a low-dose whole-body treatment schema. Some analytical results demonstrate an increase of the ratio of the helper T cells to suppresser T cells.

Cell Rejuvenation (Figures 2, 3, 4)

Yamaoka of CRIEPI found cell rejuvenation on the permeability of cell membranes and the activities of superoxide dismutase (SOD) as a result of 25 cGy to 50 cGy of irradiation.

After a low dose of X-ray whole-body irradiation, the increase of SOD enzyme and the decrease of lipid-peroxide had been maintained for more than six weeks (Yamaoka,1991).

Stress Moderation

Professor Yamada and his assistant Miyachi found that the tendency of male mice to fight under stress changed (moderated) after ten days of one low dose (5 to 10 cGy) of irradiation.

Other confirmation tests on animals also showed a certain moderation of stress, or response of the central nervous system.

Adaptive Response (Figures 5 & 6 and Table 2)

Professor Ikushima of the Kyoto University of Education examined the radio-adaptive response. Professor Yonezawa of the University of Osaka prefecture confirmed two phases of radio-adaptive responses by using a priming dose and studying survival after administering a sublethal dose. He found that there are two windows of low-level priming doses to bring enhanced resistances to sublethal X-radiation, given two months after a 5 to 10 cGy whole-body dose, and two weeks after a 30 to 50 cGy dose also (Yonezawa et al, 1990).

Response of p53 (Figures 7 & 8)

Professor Onishi of Nara Medical University found a marked increase of P53 protein production by the p53 gene. Doses of 10 to 25 cGy were effective (Ohnishi et al, 1993).

P53 protein induced by the tumor suppression gene p53 brings important activities on DNA repair and apoptosis.

Importance of Low-Dose Steady Irradiation

Professor Nomura of Osaka University confirmed the importance of steady low-dose irradiation for the enhancement of gene-repairing activities, giving evidence that steady low-dose administration is essential for obtaining beneficial health effects.

CLOSING REMARKS

Formation of ions, free electrons and free radicals by ionizing radiation enhances and creates many comprehensive bio-chemical reactions, followed by significant biological responses.

Animal test results give us a certain scientific synopsis on the adaptive response to the low-dose effect on carcinogenesis and malignant tumors, suppression of cell aging and activation of biological defense mechanisms.

We have the impression that a certain low dose of radiation raises some vitalizations of basic biological functions. The recent progress of an analytical technique on the observation of DNA structural responses greatly contributes to the unbelievable success of our research on the adaptive responses to low-dose radiation.

We have to expand our research to describe the mechanism of beneficial effects of low-level radiation by animal tests including DNA repair, apoptosis, immune system, intercellular signal transduction, and various genes and enzymes response.

Furthermore, we had better extend our research to establish clear scientific data to support the beneficial effects of radon springs, such as inhibitory effects of various diseases of old age, including diabetes and neuralgia.

Analysis of the history of the evolution of living matter through billions of years shows us all kinds of environmental conditions were put in the extremity of positive utilization without exception in our physical processes, air, water, sunlight, temperature, salt and radiation. This pursuit of the extremity of the positive utilization of all kinds of environmental factors through the process of evolution is the life itself, in a sense. It is obvious that the natural radiation background on the earth was significantly higher in the distant past than it is in present times.

In this sense, the adaptive response is the fundamental characteristic of life. All kinds of damages caused by environmental influences, diseases, loss of power are to be overcome by enhancement of DNA repair and apoptosis activities. This is the way of the adaptive response.

ACKNOWLEDGMENT

I would like to acknowledge with appreciation the sincere advice and the direction for research activities given by Dr. T.D. Luckey, Dr. S. Kondo, Dr. T. Sugawara, Dr. K. Sakamoto, Dr. T. Yamada and Dr. H. Tanooka.

REFERENCES

Cohen, A.F. and Cohen, B.L. "Tests of the linearity assumption in dose-response relationship for radiation-induced cancer," *Health Phys.* **38**, p 53, 1980.

Hattori, S. "State of research and perspective on radiation hormesis in Japan," *International Journal of Occupational Medicine and Toxicology*, **3**, No.2., 1994.

Hattori, S. "State of research on radiation hormesis by CRIEPI," *Am. Nucl. Soc. Trans.* **73**, pp 40-42, 1995. See also BELLE Newsletter **3**, pp 1-7, 1995.

ICLB. *Proceedings of the International Conference on Low-Dose Irradiation and Biological Defense Mechanisms*, Kyoto, Japan, July 12-16, 1992, Sugahara, T., Sagan, L.A. and Aoyama, T., eds., Elsevier Science Publishers B.V., Amsterdam.

Kondo, S. 1993. *Health Effects of Low-Level Radiation,* Kinki University Press, Osaka, Japan and Medical Physics Publishing, Madison, Wisconsin.

Liu, S.Z., Li, X.Y., Xia, F.Q., Yu, H.Y., Qi, J., Wang, F.L. and Wang, S.K. "A restudy of immune functions of the inhabitants in a high background area in Guangdong," *Chin. J. Radiol. Med. Prot.* **5**, pp 124-127, 1985.

Liu, S.Z. "Multilevel mechanisms of stimulatory effects of low dose radiation in immunity," in *Low Dose Irradiation and Biological Defense Mechanisms*, Sugahara, T., Sagan, L. and Aoyoma, T., eds., Excerpta Medica, Amsterdam, Holland, pp 225-232, 1992.

Lorenz, E. 1954. *Biological Effects of External Gamma Radiation, Part I,* Zirkle, R.E. ed., McGraw-Hill, New York, p 24.

Luckey, T.D. 1980. *Hormesis with Ionizing Radiation*, CRC Press, Boca Raton, Florida.

Luckey, T.D. "Physiological benefits from low levels of ionizing radiation," *Health Phys.* **43**(6), pp 771-789, 1982.

Luckey, T.D. 1991. *Radiation Hormesis*, CRC Press, Boca Raton, Florida, p 239.

Mifune, M., Sobue, T., Arimoto, H., Komoto, Y., Kondo, S. and Tanooka, H. "Cancer mortality survey in a spa area (Misasa, Japan) with a high radon background," *Japan. J. Cancer Res.* **83**, pp 1-5, 1992.

Ohnishi, T., Matsumoto, H., Omatsu, T. and Nogami, M. "Increase of wpt53 pool size in specific organs of mice by low doses of X-rays," *J. Radiat. Res.* **34**, p 364, 1993.

Yamaoka, K., Edamatsu, R. and Mori, A. "lncreased SOD activities and decreased lipid-peroxide level in rat organs induced by low-dose X-irradiation," *Free Radical Biol. Med.* **11**(3), pp 299-306, 1991.

Yonezawa, M., Takeda, A. and Misonoh, J. "Acquired radioresistance after low-dose X-irradiation in mice," *J. Radiat. Res.* **31**, pp 256-262, 1990.

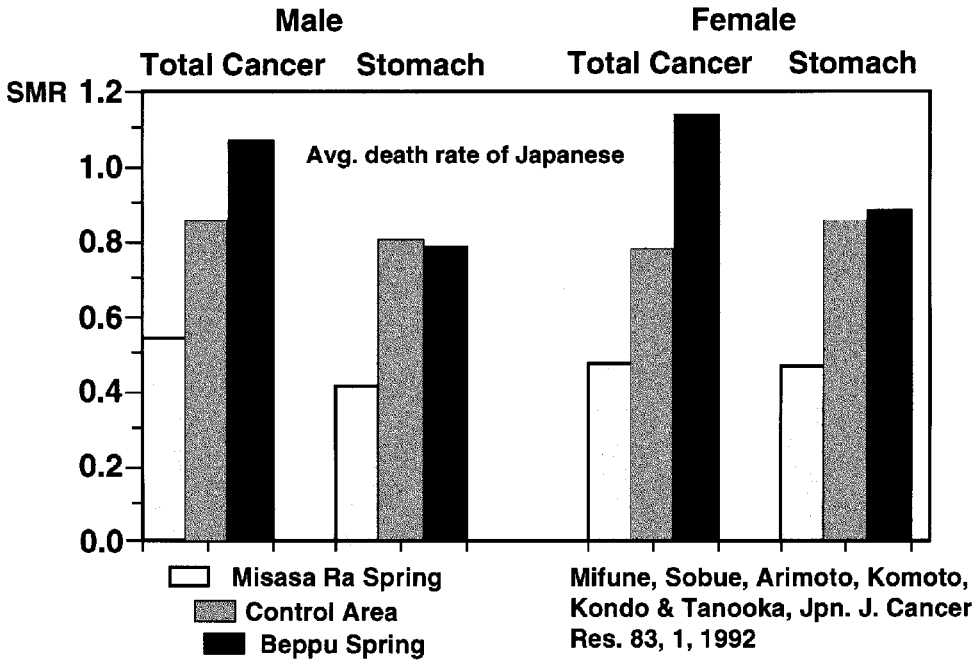


Figure 1 Comparison of standardized mortality ratio. Misasa/control area, lowest correspond to Misasa

Table 1 Results of T lymphocyte tests on the patients after low dose whole body irradiation (28 patients)

	increase	decrease	no change
Helper T cell	19 (68%)	4 (14%)	5 (18%)
Helper inducer T cell	18 (64%)	5 (18%)	5 (18%)
Activated helper T cell	21 (75%)	4 (14%)	3 (11%)
Suppressor T cell	3 (11%)	17 (61%)	8 (28%)
Radio Thelp./Tsupp.	2 (75%)	5 (18%)	2 (7%)

Prof. S. Sakamoto Tohoku University

Brain Cells

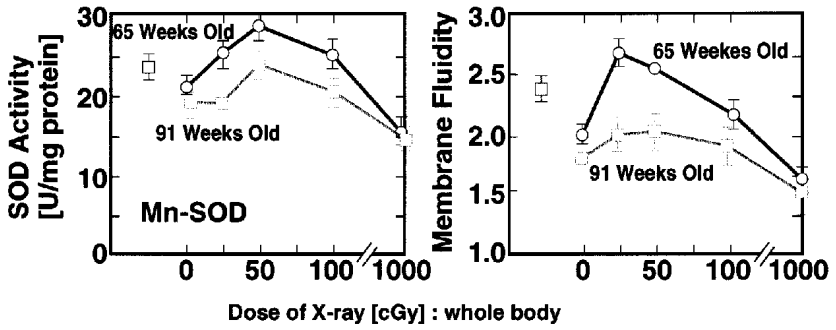


Fig.2 Dose and aging-dependent changes in SOD activity and membrane fluidity of rat's brain cortex by X-ray irradiation. (4 hrs after irradiation) Membrane fluidity was determined by spin-label method using ESR spectrometer. '□' shows the data from sham-irradiated 7 weeks old control. The number of rats per experimental point is 10-15 *p<0.05

K. Yamaoka (CRIEPI)

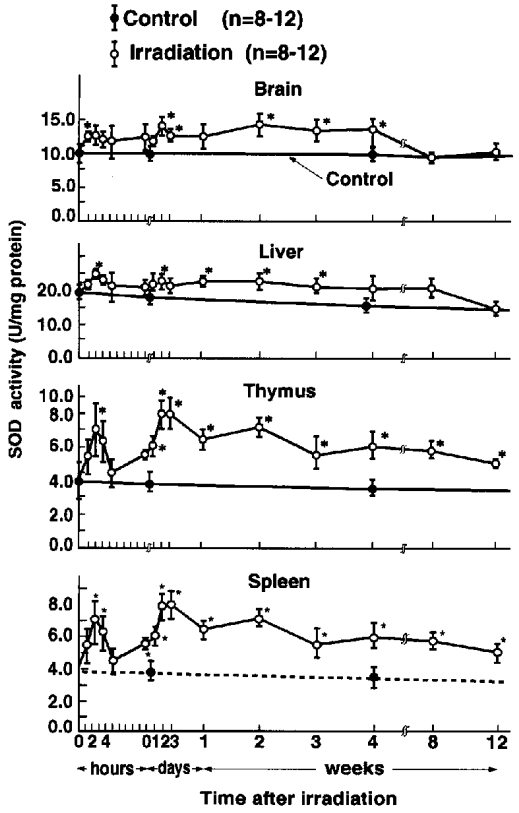


Fig.3 Time-dependent changes in SOD activity in organs of rats after X-irradiation at dose of 0.25 Gy.

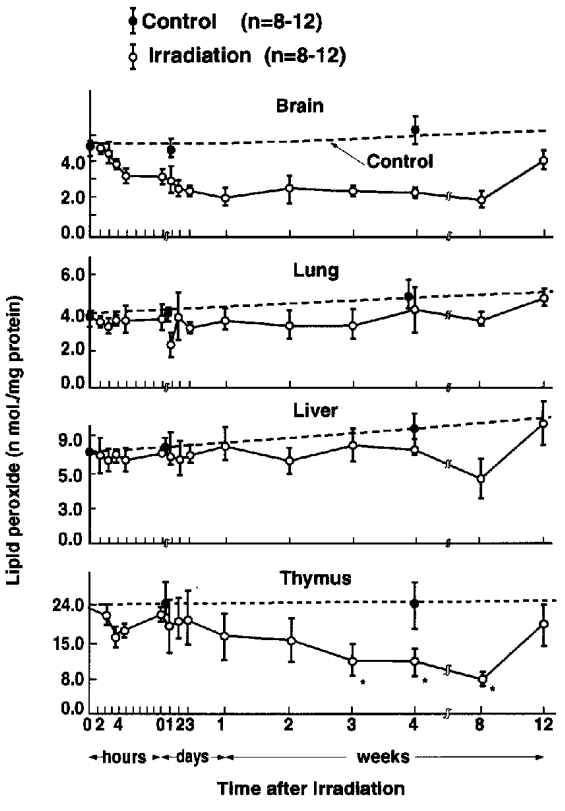
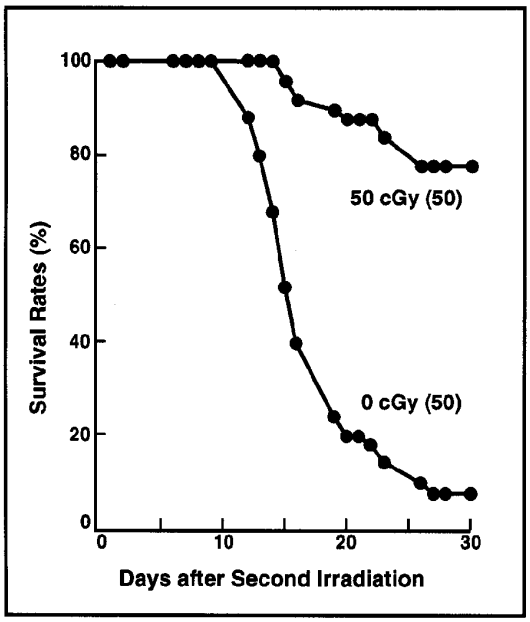
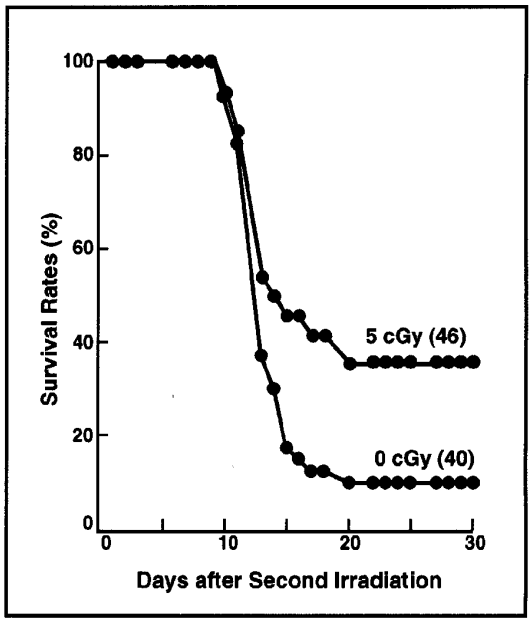


Fig.4 Time-dependent changes in Lipid peroxide level in organs of rats after X-irradiation at dose of 0.25 Gy.



Survival rates of C5781 mice irradiated with 50 cGy of X-rays 2 weeks before the second irradiation with 7.4 Gy. Numbers in parentheses represent the number of mice used.

Fig. 5



Survival rates of C5781 mice irradiated with 5 cGy of X-rays 2 weeks before the second irradiation with 8 Gy. Numbers in parentheses represent the number of mice used.

Fig. 6

[Two types of X-ray-induced radioresistance in mice]

Table 2

Priming does of X-rays (cGy)	Induction of radioresistance (7.75 G Survival) 2 weeks interval	2 months interval	Part needed to be preirradiated
2.5		NO	
5-10	NO	YES	Whole body (head + trunk)
15-20	NO	NO	
30-50	YES	NO	Trunk

(Yonezawa & Mosonoh, 1995)

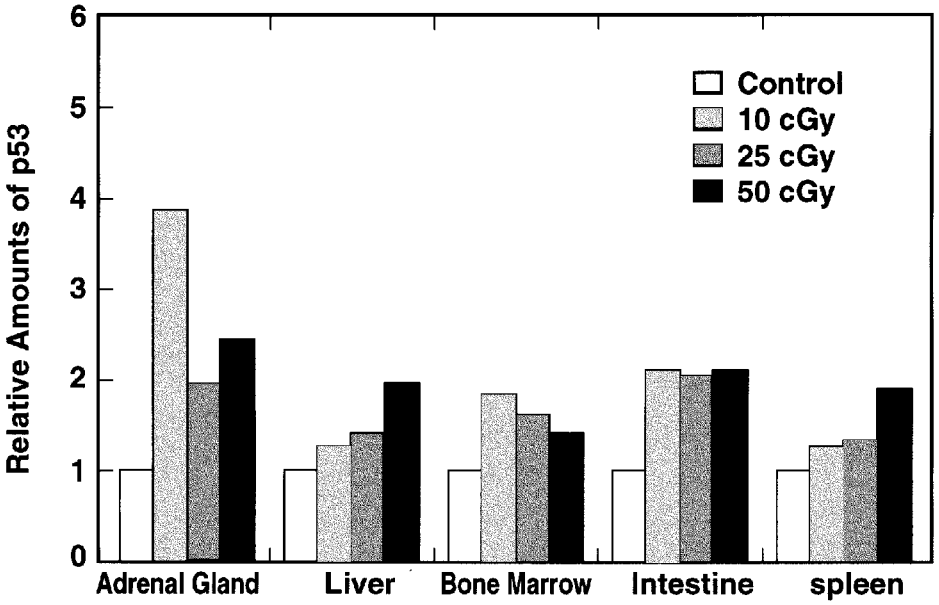


Fig. 7 Relative Amounts of p53 at 6 h after X-ray Irradiation in Various Organs of Rats

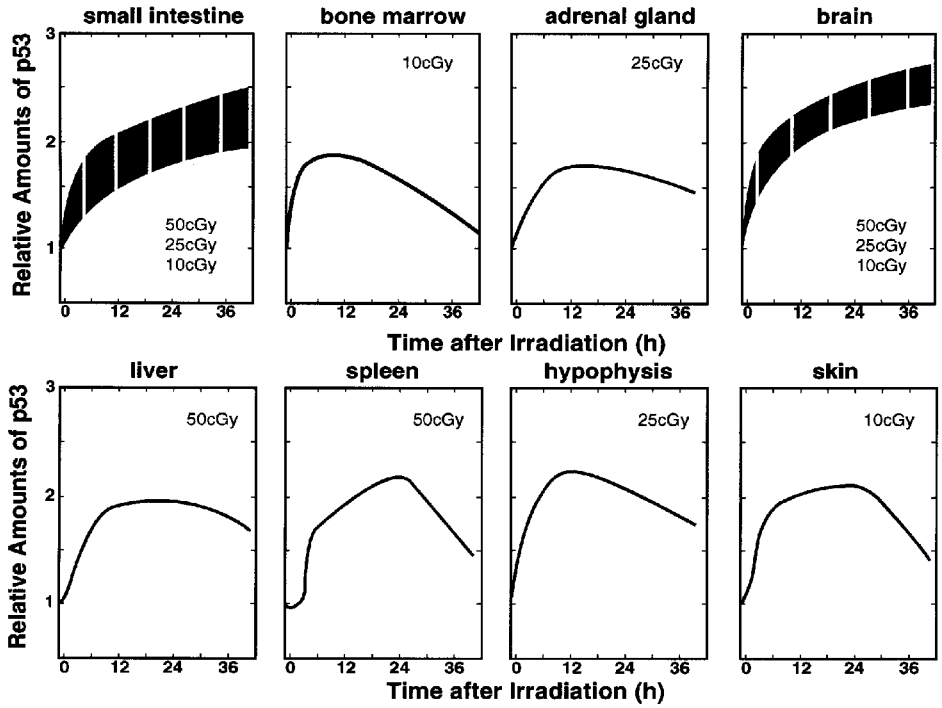


Fig.8 P53 Protein Accumulation in Organs of Rats After Low-dose X-rays Prof.Ohnishi,Nara Medical University