Adaptive Response in Patients Treated with ^{131}I

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The aim of this study was to investigate whether an adaptive response (defined as the induction of radiation tolerance after a small dose of radiation) could be observed in peripheral blood lymphocytes of patients treated with ^{131}I for thyroid disease. **Methods:** For each patient, blood samples were taken immediately before and 1 wk after ^{131}I administration. Each blood sample was divided into 3 fractions and the fractions were subsequently irradiated in vitro with 0, 0.5, and 1.0 Gy ^{60}Co γ-rays. After blood culture for 70 h, cells were harvested and stained with Romanowsky-Giemsa and micronuclei were counted in 1000 binucleated cells. The increase in micronuclei by the in vitro irradiation of the blood samples taken before and after therapy was compared. In this setup, an adaptive response is represented by a significant decrease of the in vitro induced micronucleus yield after therapy compared with that before therapy. The iodine therapy can be considered as an in vivo adaptation dose, after which the subsequent in vitro irradiation acts as a challenge dose. To investigate the reproducibility of the method, 2 subsequent blood samples of healthy volunteers were taken 7 d apart. Irradiation and cell culture were performed as described. **Results:** In 8 of 20 patients, a significant ($P = 0.0002$) decrease was found in the in vitro induced micronucleus yield in the blood sample taken 1 wk after ^{131}I administration compared with that of the blood sample taken before therapy. No significant ($P > 0.1$) differences were observed between these 8 patients and the other patients when the number of micronuclei induced in vivo by the iodine treatment and the resulting equivalent total body dose were compared. None of the control subjects showed a significant change in micronucleus yield after in vitro irradiation between both blood samples taken 1 wk apart. **Conclusion:** The iodine treatment can act as an in vivo adaptation dose and can induce an adaptive response that is observed by a decrease of the cytogenetic damage in peripheral blood lymphocytes after in vitro irradiation as a challenge dose. A large interindividual difference was observed.

Key Words: adaptive response; ^{131}I therapy; thyrotoxicosis; thyroid carcinoma

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Ever since its first therapeutic application in 1942 by Hertz and Roberts (*1*), ^{131}I has played a major role in the treatment of thyrotoxic patients and patients suffering from differentiated thyroid carcinoma. The risk for late detrimental effects after ^{131}I therapy was studied by several investigators (*2–5*) and was estimated to be <1% over a lifetime. Indeed, to our knowledge, no statistically significant increase in leukemia or solid tumors has been reported (*2,3,6*). An additional explanation for the lack of epidemiologic evidence for late detrimental effects could be found in the existence of an in vivo adaptive response. This theory states that exposure to low levels of ionizing radiation (adaptation dose) can stimulate the DNA repair system in certain individuals, resulting in less genetic damage after subsequent high levels of ionizing radiation (challenge dose). This phenomenon has been termed "adaptive response" because it is similar to the induced repair described in *Escherichia coli* (*7*).

Much in vitro data confirm the existence of an adaptive response. Most of these studies consist of in vitro work on human cell cultures (*8*). In vitro pretreatment of lymphocytes with tritiated thymidine or with low doses of ionizing radiation makes these cells less susceptible to cytogenetic damage by subsequent high doses of ionizing radiation (*8–16*). Some evidence of an in vivo adaptive response exists for animals, usually mice (*17–19*).

The existence of an in vivo adaptive response in humans could explain why the incidence of cancer in some occupationally exposed populations is lower than expected, as suggested by the results of some epidemiologic studies recently reviewed by Pollycove (*20*) and Van Wijngaerden and Pauwels (*21*). However, only Barquinero et al. (*22*) presented experimental evidence for its existence in peripheral blood lymphocytes of occupationally exposed individuals. To our knowledge, no studies indicating the existence of an in vivo adaptive response after medical use of radiation have been published. Therefore, the aim of this study was to assess whether an adaptive response in vivo could be observed in peripheral blood lymphocytes of patients treated with ^{131}I for thyroid disease.

MATERIALS AND METHODS

Patients

This study included 20 patients (5 men, 15 women; mean age, 57 y; range, 25–76 y) treated with ^{131}I for thyroid disease. Seventeen of the patients were suffering from thyrotoxicosis and received a mean activity of 642 MBq (range, 259–1110 MBq). The 3 other patients were suffering from differentiated thyroid carcinoma and

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received 3700 MBq. As a control population, 7 healthy volunteers (1 man, 6 women; mean age, 39 y; range, 27–57 y) were also included.

All patients and volunteers gave their informed consent.

Blood Sample Collection and Irradiation

The first blood sample (heparinized) was taken immediately before administration of the ^{131}I therapeutic activity. This blood sample was divided into 3 fractions. One fraction served as a nonirradiated control. The 2 other fractions were irradiated in vitro at 37°C with doses of 0.5 and 1.0 Gy ^{60}Co γ-rays at a dose rate of 1.5 Gy/min. The second blood sample (heparinized) was taken 7 d after ^{131}I administration. This blood sample was also divided into 3 fractions and subsequently irradiated following the same protocol as that used for the first blood sample.

Micronucleus Assay

Whole blood cultures were incubated at 37°C for 70 h in a 5% CO_2 atmosphere. Culture medium consisted of RPMI medium with 2 mmol/L L-glutamine and N-[2-hydroxyethyl]piperazine-N'-[2-ethane sulfonic acid] buffer (GIBCO Laboratories, Grand Island, NY) supplemented with 15% fetal calf serum and antibiotics. Phytohemagglutinin (Difco, Detroit, MI) was used at a concentration of 40 μg/mL to stimulate cell division. According to the method of Fenech and Morley (*23*), cytochalasin B (3.5 μg/mL in dimethyl sulfoxide; Sigma Chemical Company, St. Louis, MO) was added 42 h after culture initiation to block cytokinesis. After an incubation period of 70 h, the cells were harvested, treated with a hypotonic solution of 0.075 mol/L KCl, and fixed with an 8:1 mixture of methanol:glacial acetic acid following the protocol of Vral et al. (*24*). Slides were stained with Romanowsky-Giemsa, and micronuclei were counted under a light microscope (magnification ×400) based on criteria summarized by Fenech (*25*).

Equivalent Total Body Dose Calculated from Cytokinesis-Blocked Micronucleus Assay

The equivalent total body dose (ETBD) is the ^{60}Co dose that would produce the same yield of micronuclei as the in vivo ^{131}I dose actually received. The micronucleus yield, obtained after in vitro irradiation, was plotted against the ^{60}Co dose and an individual linear-quadratic dose–response curve was derived by a least-squares fit to the data. On the basis of this individual in vitro dose–response, the ETBD after ^{131}I therapy was calculated from the number of micronuclei in the blood sample of the patient 1 wk after administration of the activity. For thyrotoxicosis patients, the ETBD was corrected for the dose (because of activity retained in the body after the second blood sample was taken) using the effective half-life determined from the pretherapy uptake curve.

Adaptive Response

To assess the existence of an adaptive response, the increase in micronucleus yield after in vitro irradiation of the blood samples taken before and after ^{131}I therapy was compared. An adaptive response exists when the increase in micronucleus yield in vitro is significantly less in the blood sample taken after therapy than the increase in the blood sample taken before therapy.

MIRD Total Body Dose

For all thyrotoxicosis patients, the pretherapy uptake curve yielded both the maximal percentage uptake and the effective half-life of the ^{131}I in the thyroid. Using this information, the total body dose for each patient, following the MIRD protocol, was calculated by applying the MIRDOSE 3 code (Oak Ridge Associated Universities, Oak Ridge, TN) with the thyroid as the only source organ.

Statistical Analysis

Differences between the increase in micronuclei after in vitro irradiation were compared before and after therapy using 95% confidence limits and the Poisson distribution. Differences from the mean were assessed by 2-tailed unpaired Wilcoxon tests using Medcalc (Medcalc Software, Mariakerke, Belgium).

RESULTS

An overview of the results is given in Table 1.

The increase in micronuclei after in vitro irradiation (1.0 Gy ^{60}Co γ-rays) of the blood sample taken before and 1 wk after ^{131}I administration is shown in Figure 1. For the control subjects, the same variable determined for 2 subsequent weeks is presented. No significant differences ($P > 0.1$) were found between the increase in micronucleus yield after irradiation of the first and the second blood samples for the control subjects (Fig. 1). For the patient group as a whole, a significant decrease ($P = 0.470$) in micronucleus yield after in vitro irradiation with 1.0 Gy ^{60}Co γ-rays was observed after therapy compared with the yield before therapy. However, this decrease was attributed solely to highly significant reduction ($P = 0.0002$) in the indicated patient subgroup, whereas no significant difference was observed in the other patients ($P > 0.1$). The results of the 0.5 Gy in vitro irradiation are comparable with the results of the 1.0-Gy samples, but the margin of error is larger. None of the patients showed a significant increase in micronucleus yield after irradiation in the second blood sample compared with the yield in the first blood sample.

The mean dose–response curves after in vitro irradiation with ^{60}Co γ-rays before and after ^{131}I therapy are shown in Figure 2. For the control subjects (Fig. 2A), the dose–response curves for the first and the second blood samples were not significantly different. The dose–response curves for the blood samples taken before and after therapy (Fig. 2B) also were not significantly different for the patient subgroup that did not show a significant difference in the in vitro induced micronucleus yield before and after therapy. For the other patients (Fig. 2C), the mean micronucleus increase after in vitro irradiation of the blood sample taken after therapy decreased significantly ($P = 0.0002$) compared with the blood sample taken before therapy. For in vitro irradiation with 0.5 Gy, mean values of 52 and 26 micronuclei were found before and after therapy, respectively, whereas mean values of 150 and 78 micronuclei before and after therapy, respectively, were found after in vitro irradiation with 1.0 Gy. When the dose–response curves from Figures 2B and C were compared with the dose–response curves of the control population (Fig. 2A), the curves in Figure 2B were similar whereas the curve before therapy (Fig. 2C) was higher and became normalized after therapy.

For 17 of 20 patients (81%), a statistically significant ($P = 0.0164$) increase in micronuclei was observed after therapy. The mean increase in micronuclei after ^{131}I therapy

TABLE 1
Overview of Results Obtained in Study

Subject no.	Diagnosis	Sex	Age (y)	Adm. activity (MBq)	MIRD (Gy)	ETBD (Gy)	Incr. MN therapy (Gy)	Incr. MN before 0.5 Gy	Incr. MN before 1.0 Gy	Incr. MN after 0.5 Gy	Incr. MN after 1.0 Gy
1	C	F	27	0		0.00		26	109	26	94
2	C	F	27	0		0.00		34	124	29	100
3	C	F	39	0		0.00		24	91	23	93
4	C	F	40	0		0.00		25	84	24	71
5	C	M	57	0		0.00		31	90	25	85
6	C	F	35	0		0.00		27	92	32	81
7	C	F	48	0		0.00		28	127	21	106
8	TT	F	65	555	0.35	0.00	0	30	104	25	120
9	TT	F	50	592	0.14	0.25	9	27	119	37	100
10	TT	F	69	666	0.21	0.52	16	24	76	30	84
11	TT	F	51	740	0.21	0.31	13	29	62	17	53
12	TT	F	62	813	0.19	0.42	37	61	131	34	84
13	TT	F	25	259	0.17	0.54	9	14	59	18	78
14	TT	F	50	370	0.29	0.31	14	30	60	25	78
15	TT	F	71	481	0.35	0.57	10	36	97	31	105
16	TT	F	61	555	0.54	0.15	12	55	116	27	55
17	TT	M	51	555	0.40	0.43	9	22	87	20	90
18	TT	F	71	555	0.35	0.56	38	51	164	22	45
19	TT	M	42	703	0.31	0.13	6	47	139	21	86
20	TT	F	51	740	0.55	0.03	2	60	129	41	133
21	TT	M	43	740	0.21	0.19	15	55	108	18	104
22	TT	F	70	740	0.26	0.46	43	53	153	3	48
23	TT	F	74	740	0.23	0.48	24	42	150	12	109
24	TT	F	68	1110	0.28	0.96	121	66	219	74	126
25	TCA	M	76	3700		0.20	16	40	71	12	94
26	TCA	M	41	3700		0.42	34	44	124	11	69
27	TCA	F	40	3700		0.70	35	14	83	14	64

Adm. activity = administered activity; MIRD = total body dose calculated by MIRDOSE 3 (Oak Ridge Associated Universities, Oak Ridge, TN); ETBD = equivalent total body dose calculated by micronucleus assay; Incr. MN therapy = increase in micronuclei after ^{131}I therapy; Incr. MN before 0.5 Gy = increase in micronuclei after irradiation with 0.5 Gy before therapy; Incr. MN before 1.0 Gy = increase in micronuclei after irradiation with 1.0 Gy before therapy; Incr. MN after 0.5 Gy = increase in micronuclei after irradiation with 0.5 Gy after therapy; Incr. MN after 1.0 Gy = increase in micronuclei after irradiation with 1.0 Gy after therapy; C = control; TT = thyrotoxicosis; TCA = thyroid carcinoma.

observed in this study was 23 micronuclei (range, 0–121 micronuclei). There were no significant differences in the mean increase in micronuclei after ^{131}I therapy between thyrotoxicosis patients (mean, 23 micronuclei; range, 0–121 micronuclei) and thyroid carcinoma patients (mean, 29 micronuclei; range, 16–34 micronuclei). By fitting the micronucleus yield 1 wk after therapy to the dose–response curve after in vitro irradiation before therapy, the ETBD of each patient could be determined. The mean ETBD observed in this study was 0.37 Gy (range, 0.00–0.96 Gy). On the basis of these results, no significant difference in ETBD values could be observed between thyrotoxicosis patients and thyroid carcinoma patients. For the thyrotoxicosis patients, the MIRD total body dose was determined from the pretherapy uptake curve. These data are included in Table 1. A mean total body dose of 0.30 Gy (range, 0.14–0.55 Gy) was obtained, whereas the micronucleus assay yielded a comparable mean ETBD of 0.37 Gy (range, 0.00–0.96 Gy) for the thyrotoxicosis patient group.

The mean increase in micronucleus yield associated with ^{131}I therapy seemed to be higher in the patient group that showed a significant difference in the micronucleus increase after in vitro irradiation before and after therapy (mean, 39 micronuclei; range, 6–121 micronuclei) than in the patient group that did not show this difference (mean, 12 micronuclei; range, 0–35 micronuclei). Also, the mean ETBD tended to be higher in the first patient subgroup: 0.45 Gy (range, 0.13–0.96 Gy) and 0.34 Gy (range, 0.00–0.70 Gy), respectively, using the micronucleus yields and 0.31 Gy (range, 0.19–0.54 Gy) and 0.28 Gy (range, 0.14–0.55 Gy), respectively, using the pretherapy uptake curve for thyrotoxicosis patients. However, the differences did not reach statistical significance ($P > 0.1$). The mean administered activities in both subgroups, 1115 MBq (range, 555–3700 MBq) and 1092 MBq (range, 259–3700 MBq), respectively, also were not significantly different ($P > 0.1$).

DISCUSSION

The results of this study show that exposure to low doses of ionizing radiation during medical treatment (adaptation dose) makes human peripheral blood lymphocytes less

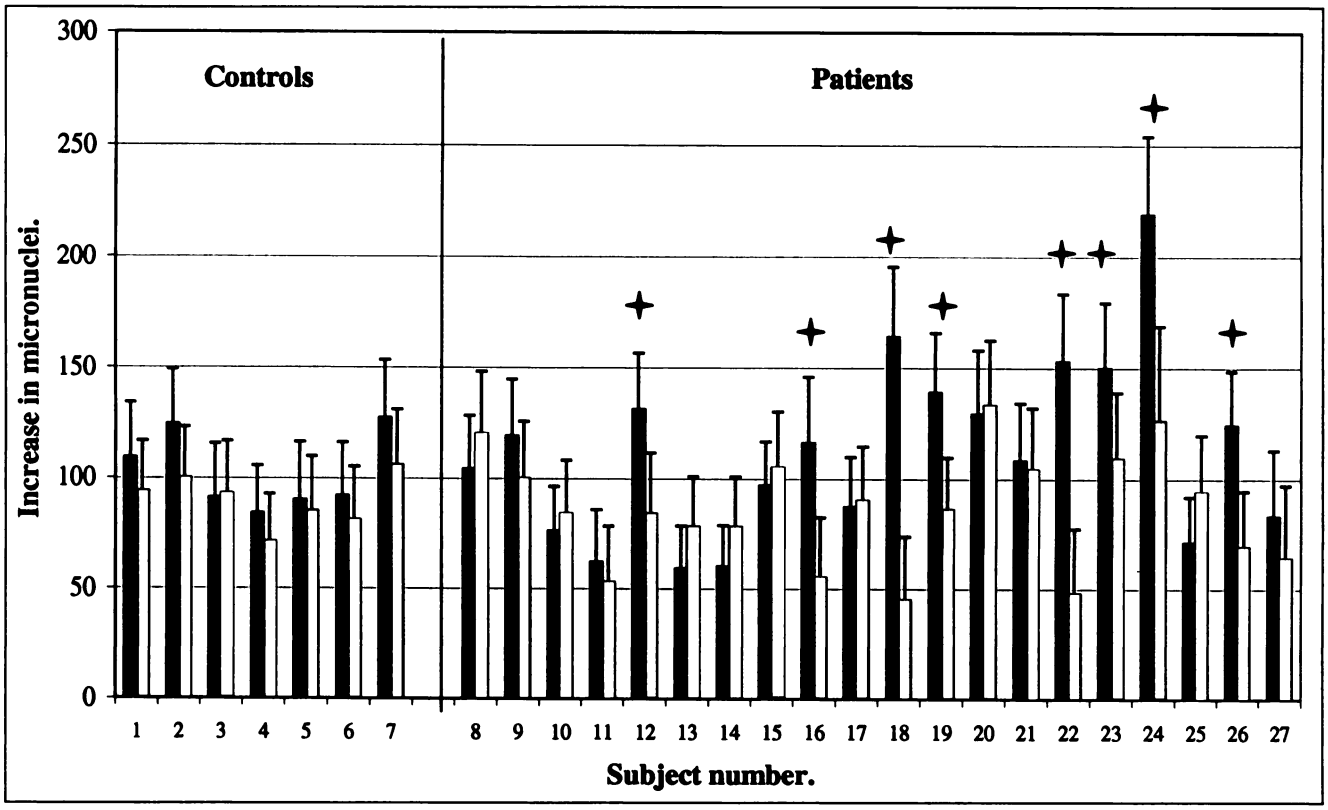

FIGURE 1. Overview of increase in micronuclei after in vitro irradiation (1.0 Gy ^{60}Co γ-rays) of blood samples taken before and after ^{131}I therapy. For controls, 2 blood samples taken 1 wk apart were irradiated. Error bars represent 95% confidence limits. Increase in micronuclei before therapy (■), increase in micronuclei after therapy (□), and patients who show adaptive response (+) are indicated.

susceptible to cytogenetic damage for subsequent in vitro irradiation at higher doses (challenge dose). The reproducibility of the data for the control population further shows that the observed differences cannot be attributed to cell culture or technical effects. Therefore, the observation can be interpreted as an adaptive response phenomenon. Barquinero et al. (*22*), using a similar experimental setup, reported the existence of an adaptive response in vivo after occupational exposure to ionizing radiation. In their study, a 2-Gy ^{60}Co dose was used as the challenge dose. Cytogenetic damage was scored as dicentrics, acentrics, and chromosome breaks. The occupationally exposed individuals showed a significantly lower amount of chromosomal damage after in vitro irradiation than did the nonexposed individuals.

Determination of the mechanism behind the adaptive response is beyond the scope of this study. This mechanism has been studied in vitro by many investigators (*10–14*). The currently accepted model of the mechanism of adaptive response is the signaling loop model, first described by Weichselbaum et al. (*26*) in 1991. The assumption has been made that on treatment with a DNA-damaging agent, an alarm signal is generated in the nucleus. Activation of a set of genes follows, which leads to de novo protein synthesis. Some of these proteins are involved in repair of the damage inflicted by the challenge dose; hence, a lower biologic effect of the dose is observed than that in nonadapted cells.

However, instead of an increased DNA repair rate, the fidelity of repair seems to be changed, leading to a different proportion of damage seen at the chromosomal level. The lowered mutation frequency in adapted cells also points to this possibility (*27*). Thus, adaptive response may involve primarily a qualitative change in damage repair or processing (*28*). Only a few centigrays are needed to produce an adaptive response in human lymphocytes (*29*). In this study, the mean ETBD in the patient subgroup that showed an adaptive response was only 0.45 Gy.

The observation that only 8 of 20 patients showed an adaptive response after receiving ^{131}I therapy clearly shows interindividual variability. This variability was also observed in the in vivo study by Barquinero et al. (*22*) and in previous in vitro studies (*30–33*). Both the pretherapy in vitro irradiation and the in vivo exposure by ^{131}I therapy led to a somewhat higher increase in micronuclei in the patient group that showed an adaptive response than that in the other patient group. The in vitro dose–response curve for the patients showing an adaptive response seemed to normalize after ^{131}I therapy (adaptation dose). Although the results did not reach statistical significance, the adaptive response in this study seems to be evident, especially in radiosensitive individuals.

For the 8 patients who showed an adaptive response, an in vivo exposure to ionizing radiation (challenge dose) after the ^{131}I therapy (adaptation dose) would probably lead to less genetic damage. The duration of the adaptive response in

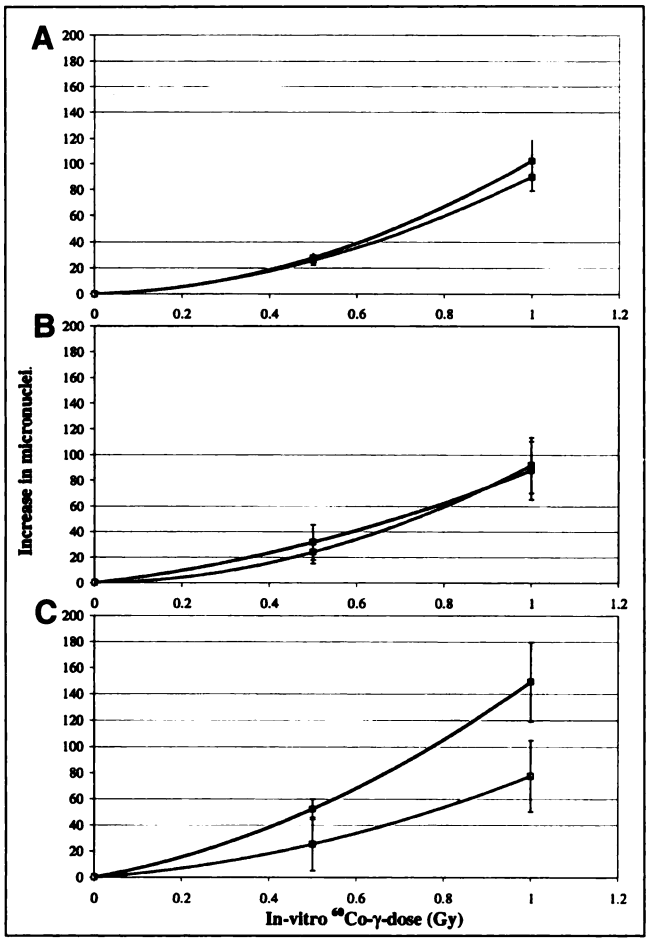

FIGURE 2. Mean dose–response curves after in vitro irradiation (0.5 and 1.0 Gy ^{60}Co γ-rays) of first (■) and second (□) blood samples. Error bars represent SD within population. (A) Healthy volunteers (control population). (B) Patients who did not show adaptive response. (C) Patients who show adaptive response.

vivo is currently unknown. According to Shadley et al. (*34*), the duration is relatively long lasting (at least 3 cell cycles in human lymphocytes) in vitro.

Although we know that radiation can be harmful, an inordinate fear of the least amount of radiation exists today in some groups (*29*). Instead, a fact-based scientific approach to evaluate the detrimental effects of low levels of radiation should be adopted. The results of this study support the point of view of an increasing number of investigators (*8–22,26–30,32,33*) that some consideration should be given to the importance of biologic defense mechanisms that could be stimulated by low levels of radiation. However, the results of this study do not mean that exposure to low levels of ionizing radiation by itself is beneficial. In exposed populations, higher levels of chromosome aberrations are found compared with those found in nonexposed populations (*35–40*).

CONCLUSION

These results show that, although the iodine treatment can act as an adaptation dose and can induce an in vivo adaptive response, interindividual variability exists. In the evaluation of the detrimental effects of exposure to radiation, some consideration should be given to the importance of biologic defense mechanisms. The results of this study do not suggest that exposure to ionizing radiation by itself is beneficial because the level of chromosomal damage is increased after the iodine treatment.

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