ARMY MEDICAL RESEARCH LABORATORY

FORT KNOX, KENTUCKY

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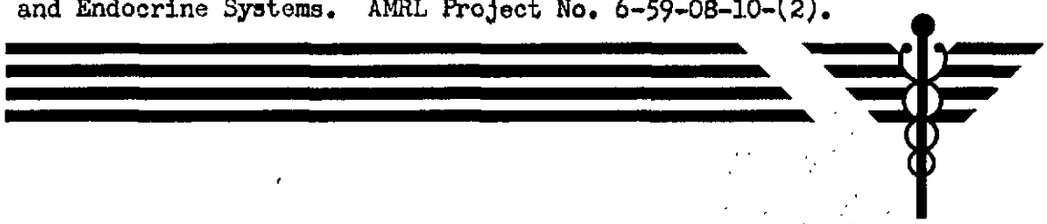
28 September 1951

THYROID RESPONSE TO TOTAL BODY X-IRRADIATION*

*Subproject under Effect of Total Body Irradiation on the Various Enzyme and Endocrine Systems. AMRL Project No. 6-59-08-10-(2).



MEDICAL RESEARCH AND DEVELOPMENT BOARD
OFFICE OF THE SURGEON GENERAL
DEPARTMENT OF THE ARMY

Report No. 66

THYROID RESPONSE TO TOTAL BODY X-IRRADIATION*

by

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Army Medical Research Laboratory
Fort Knox, Kentucky
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ABSTRACT

THYROID RESPONSE TO TOTAL BODY X-IRRADIATION

OBJECT

To evaluate thyroid response in rats following a potentially lethal dose of total body x-irradiation, by determining thyroid content of, and the conversion of injected radioactive iodine (I^{131}) and the total and protein-bound I^{131} in the blood serum.

RESULTS AND CONCLUSIONS

The changes in thyroid and serum I^{131} content (inorganic and organic) of rats, after total body x-irradiation at 1000 r, indicate a stimulation of thyroid activity by 2 hours after irradiation. This increased activity is apparent until one day after irradiation, from which time until the sixth day there is a progressive decrease in activity. These changes in functional activity of the thyroid are probably due to systemic damage caused by the radiation and are mediated through the hypophysis. The initial increased thyrotropin release from the hypophysis is followed by a shift of pituitary function towards increased adrenocorticotropin elaboration at the expense of thyrotropin production.

RECOMMENDATIONS

Response of the thyroid to total body x-irradiation of dosage lower than 1000 r should be studied. Effect of pitressin administration, given prior to irradiation, on the thyroid response to total body x-irradiation should also be investigated.

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THYROID RESPONSE TO TOTAL BODY X-IRRADIATION

I. INTRODUCTION

During the past several years there have been many investigations into the effects of x-irradiation on various mammalian organs. In the case of the thyroid gland, however, practically all of the studies undertaken have dealt with direct irradiation of the gland (1, 2) by use of local x-irradiation or massive doses of radioactive iodine. These studies have shown that in the rat local radiation of the thyroid produces essentially no change in morphology or function of that gland until the dosage reaches 3000-6000 r, a dose which is several times the magnitude of a lethal dose of total-body x-irradiation.

In a brief abstract, Evans et al. (3), reported an increased uptake of I^{131} by the thyroid as well as "increased activity" in the blood of rats three days after 500-1000 r total body x-irradiation. However, the reported data are rather incomplete and do not allow any definite conclusions as to the state of functional activity of the thyroid after total body x-irradiation.

It was the purpose of the present investigation to determine the content of radioactive iodine (I^{131}), both the total and organic, in the thyroid gland as well as the total and protein-bound I^{131} content of blood of rats at various time intervals after a potentially lethal dose (1000 r) of x-radiation. It was felt that such data might indicate possible changes in thyroid activity during the post-radiation period and thus present a possible aid in the interpretation of the physiological aberrations following lethal radiation.

II. EXPERIMENTAL

A. Methods

Male rats of the Sprague-Dawley strain (weighing 190-250 grams) were used. They were maintained on Purina laboratory chow and tap water until 24 hours before sacrifice, at which time they were deprived of food but allowed water ad lib. At this time each rat was injected intraperitoneally with 1.0 ml of a standardized radioactive iodine solution containing approximately 5 microcuries of carrier-free radioactive iodine (I^{131})* made up to volume with Krebs-Henseleit buffer of pH 7.4 (4).

The rats were irradiated, 2 at a time, in a well-ventilated lucite chamber. The radiation was performed with a 250 Kv Kelly-Koett x-ray unit, the factors being: 200 Kv, 6 ma., ½ mm copper and 1 mm aluminum filters,

* The radioactive iodine (I^{131}) used in this investigation was supplied by the Oak Ridge National Laboratories on allocation from the Isotopes Division, U. S. Atomic Energy Commission.

target distance 29 cm. This set-up gave a dosage of 40 roentgens per minute as measured in air with a Victoreen thimble chamber.* Each rat received 1000 r (25.0 min.) which was found to be approximately an LD/100 (8 days), with the maximal mortality occurring between the third and fifth day.

The animals were sacrificed by exsanguination via cardiac puncture at "zero", 2 hours, 1 day, 2 days, 3 days, 4 days and 6 days after irradiation. Very light nembutal or ether anesthesia was used. The thyroid gland was rapidly removed, weighed, and placed in hot 2N NaOH for hydrolysis. Pituitary and adrenal glands were removed and weighed at the same time.

The thyroid glands were processed and analyzed for their total and organic bound radioiodine and the blood serum analyzed for its total and protein-bound (PBI) radioiodine contents according to the procedure described elsewhere (5). Control groups were run with each set of irradiated animals. Groups of 8-24 experimental animals were used for each time period.

All values for radioiodine content were calculated as per cent of the injected dose. The values for experimental animals are expressed as percentage deviation from control values. These results are given in Table 1 and Figure 1 with the number of rats used in each group.

TABLE 1

THYROID GLAND AND BLOOD SERUM CONTENT OF I^{131} IN % OF INJECTED DOSE - GIVEN AS % VARIATION FROM NORMAL CONTROL VALUES

Time after irradiation	No. of rats used	Thyroid Gland		Blood Serum	
		Total	Organic	Total	PBI
"Zero"	12	0	+1	-7	-4
2 hours	12	-6	+10	-13	+32
1 day	12	0	-2	+63	+42
2 days	24	-21	-24	-57	-67
3 days	24	-29	-27	-32	-68
4 days	17	-66	-68	-25	-73
6 days	8	-54	-46	+71	-92

* The authors wish to express their appreciation to the Radiobiology Branch of this laboratory for assistance in the irradiation procedure.

B. Results

The data in Table 1 are presented graphically in Figure 1. It can be seen that as early as 2 hours after irradiation, there is a drop in total gland I^{131} content but a rise in the organic component (with a resulting rise in the organic/total ratio), accompanied by a similar picture in the serum total and PBI fractions. By 24 hours the gland content is back to normal while there is a rise of 40-60% in both the serum total and PBI^{131}. Between the first and fourth day after irradiation the gland content, showing a remarkably constant organic/total ratio, drops steadily to 68% below control values. By the sixth day there is a slight rise, but the gland content is still about 50% below normal. The serum I^{131} content, both total and PBI, drops from 50% above to 60% below control values between the first and second day after irradiation. From the second to the sixth post-irradiation day, the total serum I^{131} content rises steadily to 71% above control values while the serum PBI^{131} falls progressively to 92% below normal.

III. DISCUSSION

Since it has been shown (1, 2) that local radiation of the thyroid produces no noticeable change in morphology or function of that endocrine organ until the dosage reaches 3000-6000 r, the response of the thyroid gland to 1000 r total body x-irradiation is, probably, brought about by some systemic disturbance, which may be mediated through the hypophysis.

The increase in serum PBI^{131} and decrease in total I^{131} gland content as early as 2 hours and as late as one day after irradiation, probably, indicates stimulation of the thyroid. The slope of the curve as well as the time of response is quite similar to that following a single injection of thyrotropic hormone (5). This thyroid response agrees well with the finding of Kirschner et al. (6) that there is an elevation of oxygen consumption of 35% occurring in rats within 24 hours after total body irradiation of 809-972 r.

From the second until the sixth post-irradiation day, both the gland and serum I^{131} criteria responses are indicative of decreased thyroid activity, giving a picture similar to that observed in hypophysectomized animals (7, 8).

In an investigation of the adrenal response to total body x-irradiation of comparable magnitude to that used in the present studies, Patt et al. (9) found that there is an initial stimulation of the adrenal (3 to 6 hours after irradiation), followed by an apparent return to normal until after the second post-irradiation day. Thenceforth until death there appears to be a steady increase of adrenal size and function. These authors point out the similarity of the early adrenal response to that observed following an injection of the adrenocorticotropic hormone. Adrenal weights taken in the present studies (Table 2) are quite similar to those reported by Patt.

TABLE 2

ADRENAL WEIGHTS OF RATS SUBJECTED TO 1000 r TOTAL BODY X-IRRADIATION

Time after irradiation	Control	"Zero"	2 hrs.	1 day	2 days	3 days	4 days
Adrenal weight (mg/100 g body wt.)	12.3	12.9	14.3	12.5	14.8	22.0	25.6

Soffer and associates (10) have reported that administration of adrenocorticotropin results in a decreased content of injected I^{131} in the thyroid, suggesting that adrenocroticotropin inhibits the pituitary secretion of thyrotropin.

A comparison of the results presented, with those of the adrenal studies described above, is illustrated in Figure 2 These findings may be interpreted as follows: Systemic disturbance, due to total body x-irradiation, causes an initial increased elaboration of thyrotropic and adrenocorticotropic principles from the anterior pituitary, followed by a continuous increased demand for adrenal cortical hormones which can only be met by increased pituitary release of ACTH at the expense of thyrotropin production.

It is known that the food intake of irradiated animals is less than normal and it has been reported that inanition will cause a shift of pituitary function towards increased ACTH elaboration at the expense of thyrotropin production (11, 12). However, thyroid studies done in this laboratory on starved normal rats (Table 3) show a serum picture similar in slope to that of Figure 1, but much smaller in magnitude and not apparent until the third day after the beginning of complete starvation. There is no alteration in thyroid I^{131} content by the fourth day. The partial inanition caused by radiation would seem, then, to account for only part of the observed changes.

TABLE 3

THYROID GLAND AND SERUM PBI CONTENT OF I^{131} IN % OF THE INJECTED DOSE - GIVEN AS % VARIATION FROM NORMAL CONTROL VALUES

Days of Starvation	1	2	3	4	6
Thyroid Gland	-3	-6	-10	-4	--
Serum PBI	-2	0	-20	-22	-38

IV. CONCLUSIONS

The changes in thyroid and serum I^{131} content (inorganic and organic) of rats, after total body x-irradiation at 1000 r, indicate a stimulation of thyroid activity within 2 hours after irradiation. This increased activity is apparent for 24 hours after irradiation, after which time, until the sixth

day, there is a progressive decrease in activity. These alterations in functional activity of the thyroid may be due to systemic changes caused by the radiation and are probably mediated through the hypophysis, the initial increased thyrotropin release from the hypophysis being followed by a shift of pituitary function towards increased adrenocorticotropin elaboration at the expense of thyrotropin production.

V. RECOMMENDATIONS

Response of the thyroid to total body x-irradiation of dosage lower than 1000 r should be studied. Effect of pitressin, given prior to irradiation, on the thyroid response to total body x-irradiation should also be investigated.

VI. BIBIOGRAPHY

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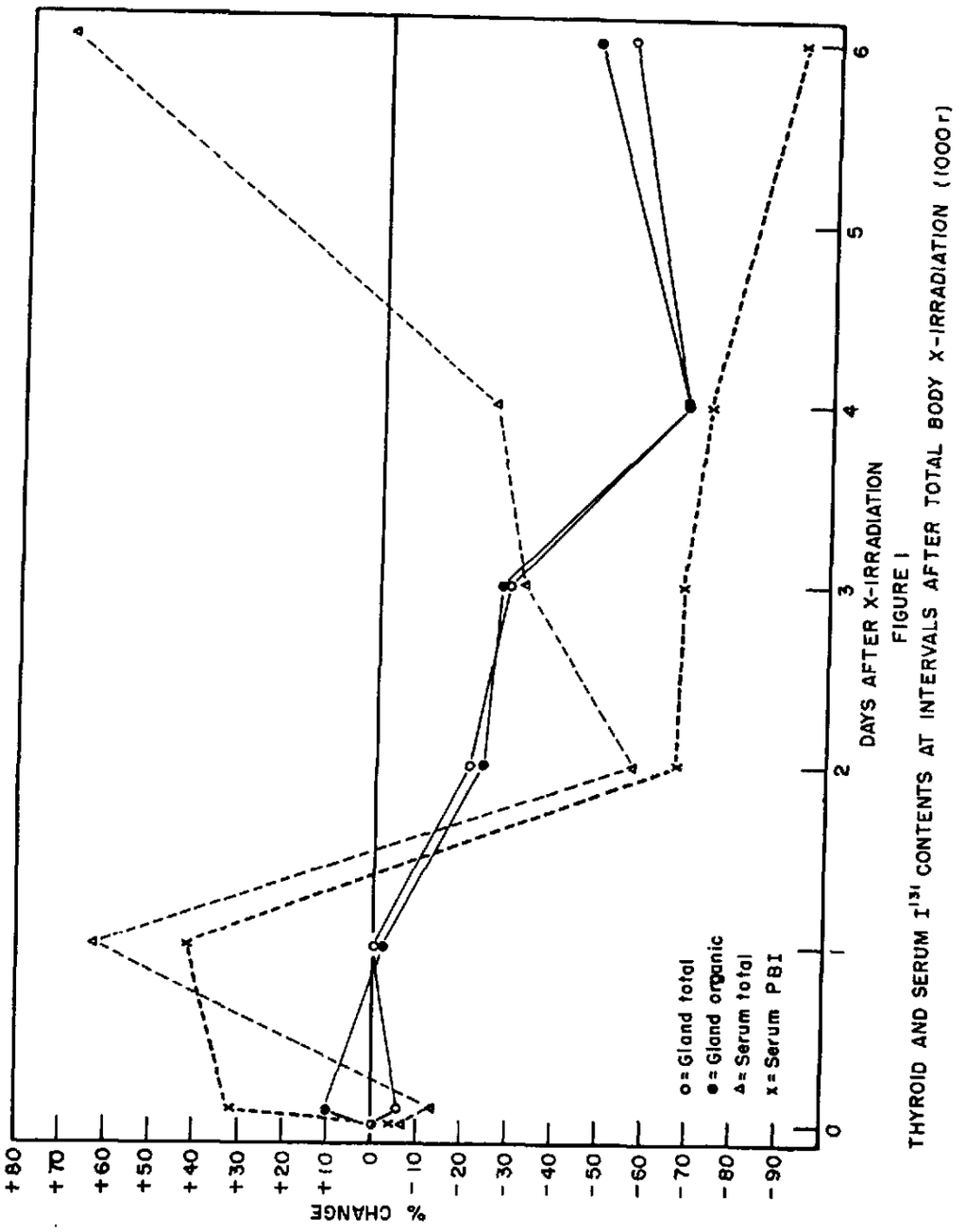

FIGURE I

THYROID AND SERUM I^{131} CONTENTS AT INTERVALS AFTER TOTAL BODY X-IRRADIATION (1000r)

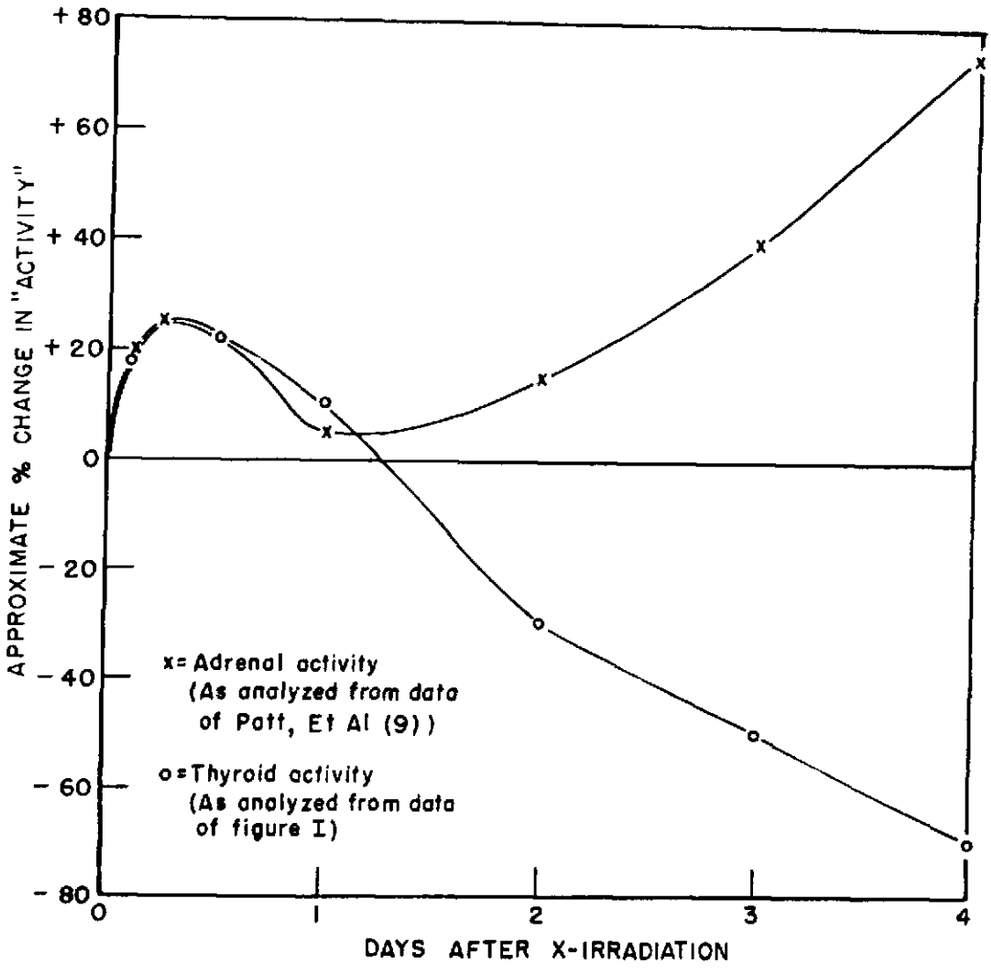

FIGURE 2

THYROID AND ADRENAL ACTIVITIES AT INTERVALS AFTER TOTAL BODY X-IRRADIATION (1000r)