

# PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

## REACTION OF THE PITUITARY-ADRENAL SYSTEM OF IRRADIATED RATS TO REPEATED STRESS

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It has been shown experimentally that under the influence of ionizing radiation changes develop in the pituitary-adrenal system which are similar in their general features to those arising in response to the action of other unfavorable factors on the organism. For instance, the fall in the concentrations of ascorbic acid and cholesterol in the adrenals and their hypertrophy, the changes in the level of the corticosteroids in the blood and in the concentration of ACTH in the pituitary, the decrease in the weight of the thymus, the changes in the peripheral blood, and so on, observed after irradiation are also present when other harmful agents (cold, toxic substances, trauma, etc.) act on the organism [6].

The problem of the effect of supplementary unfavorable factors on the pituitary-adrenal system during the period of acute radiation sickness has been inadequately discussed in the literature.

The present paper describes the results of an experimental study of the reaction of the pituitary and the adrenal cortex of irradiated animals to the repeated action of unfavorable conditions (unilateral adrenalectomy and irradiation with x-rays).

### METHOD

Investigations were conducted on two groups of male albino rats weighing 160-220 g. Some experiments were performed on intact rats (76 animals) and others on rats irradiated with a lethal dose of x-rays (85 rats). Irradiation was carried out in standard conditions: RUM-11 apparatus, voltage 180 kV, current 15 mA, filters 0.5 mm Cu and 1 mm Al, distance 35 cm, dose rate 28 R/min. The total dose of irradiation was 800 R. The animals took part in the experiments on the 5th-8th day after irradiation (at the climax of acute radiation sickness). Altogether three series of experiments were carried out. In series I the effect of unilateral adrenalectomy was studied on the system of the pituitary and adrenal cortex of control and irradiated animals (5 days after irradiation). The animal was anesthetized with ether, the left adrenal was removed, and 1 h later, the right adrenal was also removed. The adrenals were freed from the surrounding connective tissue, weighed on torsion scales with an accuracy of 0.1 mg, and the concentration of ascorbic acid in the glands was determined by the method of Roe and Kuether [5] as modified by Geschwind [4]. In the experiments on series II the reaction of the pituitary and the adrenal cortex of control and experimental rats was determined to the repeated action of a lethal dose of ionizing radiation. One hour after the first irradiation of the control rats and the second irradiation of rats previously irradiated, the left adrenal was removed from both groups of animals and its content of ascorbic acid was determined. In the experiments of series III, the reaction of the pituitary-adrenal system of intact rats and rats on the 5th day of radiation sickness to the prolonged absence of one adrenal was studied. On the 5th day of irradiation the rats were anesthetized with ether and the left adrenal was removed, and on the 7th day the right adrenal was also removed. The criterion of the reaction was the weight of the right adrenal.

TABLE 1. Effect of Unilateral Adrenalectomy on the Concentration of Ascorbic Acid in the Adrenals and on their Weight in Normal and Irradiated Rats

Growth of rats	Experimental conditions	Weight of rat (in g)		Wt. of adrenals (in mg)		Conc. of ascorbic acid in adrenals (in mg%)		Weight of thymus (in mg)
		before irradiation	5th day after irradiation	left	right	left	right	
Control 1st, Normal	Left and right adrenals removed in 1 stage	189	200	15,1 ± 0,4 (26)	14,6 ± 0,8 (9)	365 ± 11 (26)	354 ± 23 (9)	349 ± 25
	The same	190	170	$P > 0,5$ 20,7 ± 1,0 (27) 20,2 ± 1,9 (6)		$P > 0,5$ 378 ± 8 (26) 360 ± 19 (6)		81 ± 5 (26)
Experiment 3rd, Normal	Right adrenal removed 1 h after left	170	180	$P > 0,5$ 14,6 ± 0,6 (14) 14,0 ± 0,5 (14)		$P < 0,5$ 412 ± 17 (13) 312 ± 18 (13)		—
	The same	185	160	$P > 0,5$ 21,4 ± 1,4 (15) 19,5 ± 1,1 (15)		$P < 0,001$ 352 ± 8 (14) 276 ± 9 (14)		66 ± 10 (14)
				$P < 0,25$		$P < 0,001$		

Note. Here and in Tables 2 and 3, the number of experiments is given in parentheses.

TABLE 2. Effect of Repeated Irradiation with X-Rays on Concentration of Ascorbic Acid in the Adrenals of Irradiated Rats

Group of rats	Experimental conditions	Wt. of rat (g)		Weight of left adrenal (in mg)	Conc. of ascorbic acid in left adrenal (in mg%)	Difference
		before irradiation	5th day after irradiation			
1st, Normal	Control	182	—	$14,8 \pm 0,8$	$382 \pm 14$ (10)	-54
2nd, Normal	1 h after irradiation	184	—	$14,7 \pm 0,8$	$328 \pm 16$ (8)	
3rd, irradiated (on 5th-8th day after irradiation)	Control	194	161	$20,3 \pm 1,5$	$391 \pm 9$ (12)	-69
4th, irradiated (on 5th-8th day after irradiation)	1 h after repeated irradiation	184	161	$21,3 \pm 1,4$	$322 \pm 12$ (14)	

In all the animals the body weight, the weight of the thymus, and the number of leucocytes in the peripheral blood were determined and recorded.

## RESULTS

The irradiated rats developed acute radiation sickness, leading to death of 20-50% of the animals on the 5th-8th day of irradiation. During this period the weight of the adrenals increased appreciably, while the weight of the thymus and the body weight decreased. The leucocyte count in the peripheral blood also fell, and the animals developed severe clinical manifestations of the critical stage of acute radiation sickness (diarrhea in some animals, shagginess of the hair, and so on). The content of ascorbic acid in the adrenals of the irradiated animals at this period was much higher than normal. However, the concentration of ascorbic acid expressed per 100 g adrenal tissue was almost the same as in the intact rats. The results of the experiments of series I are given in Table 1. In the 1st and 2nd groups of experiments of this series both adrenals were taken from the animals in one stage under ether anesthesia. In these conditions the concentration of ascorbic acid in the two adrenals of the normal and irradiated rats was almost identical. The difference in the ascorbic acid concentration between the left and right adrenals of the irradiated rats, and also of the normal rats, was not statistically significant.

Investigations have shown [2, 3] that the surgical removal of one adrenal in rats is a stimulus to the liberation of ACTH from the pituitary, leading to a fall in the ascorbic acid level in the remaining adrenal. In the present experiments, removal of the left adrenal led after 1 h to a sharp decrease in the concentration of ascorbic acid in the right adrenal of both intact and irradiated rats (Table 1, Groups 3 and 4). These results show that the pituitary-adrenal system of the irradiated rats reacts to acute surgical intervention in the same way as in intact rats.

One hour after the end of irradiation of normal rats with a lethal dose of x-rays, the ascorbic acid level in the adrenals of the animals falls. This fact was confirmed by the present experiments (Table 2, Groups 1, 2). It was found that on the 5th day of radiation sickness, rats responded to repeated irradiation with a lethal dose of x-rays by a similar reaction (Table 2, Groups 3, 4). Consequently, on the 5th day after irradiation, the pituitary-adrenal system of the animals preserved its ability to react to this acute stimulus by lowering the ascorbic acid content in the adrenals.

The author has previously shown [2] that unilateral removal of the adrenal in intact rats leads to hypertrophy of the remaining gland, which is well marked after 24-72 h. This reaction is absent in hypophysectomized rats, thus demonstrating that ACTH, liberated from the pituitary, is concerned in the development of the compensatory hypertrophy of the adrenal. In the present experiments an attempt was made to ascertain whether compensatory hypertrophy of the adrenal can develop in irradiated rats. The results given in Table 3 show that compensatory hypertrophy of the adrenal did develop in these animals in the course of 48 h. The right adrenal of the irradiated rats (in the absence of the left) hypertrophied to a greater degree than the right adrenal of the normal animals (in the

TABLE 3. Development of Compensatory Hypertrophy of the Adrenal in Response to Unilateral Adrenalectomy in Normal and Irradiated Rats

Group of rats	Experimental conditions	Weight of rat (in g)		Wt. of adrenals (in mg)		Diff. between wt. of left and right adrenals (in mg)
		before irradiation	5th day after irradiation	left	right	
1st, Normal	Right adrenal removed 48 h after left	—	181	15,6±0,8 (18)	17,4±0,9 (18)	+1,8
2nd, Irradiated (5th day after irradiation)		195	157	21,9±1,3 (17)	29,5±2,1 (17)	+7,6

same conditions). On the assumption that the weight of the right adrenal was equal to the weight of the left (the right adrenal always weighs slightly less than the left), even in this case the mean increase in the weight of the right adrenal in the irradiated rats was 7.6 mg, and in the intact rats 1.8 mg. The more marked degree of compensatory hypertrophy in the irradiated rats may evidently be explained by the greatly increased liberation of ACTH from the pituitary as a result of the combined action of the two unfavorable factors: radiation sickness and removal of the left adrenal.

The decrease in the ascorbic acid content of the adrenal cortex observed in these experiments in the irradiated animal in response to surgical removal of the second adrenal, and also in response to the repeated action of ionizing radiation, must be assumed to be the result of the liberation of ACTH from the pituitary. In the author's previous investigations [1, 2] it was found that in hypophysectomized animals the level of the ascorbic acid concentration in the adrenals did not fall in response to the removal of one adrenal or to the action of ionizing radiation. The presence of this reaction in the irradiated animals demonstrates that the reaction of the pituitary and of the adrenal cortex of the irradiated rats to the repeated action of extremely strong stimuli was essentially unchanged. Consequently, in the irradiated animals, at this period of radiation sickness, the development of "cross resistance" to the action of surgical trauma or of "resistance" to the repeated action of radiation did not develop.

Judging by the weight of the adrenals and their high content of ascorbic acid, and also by the reaction of the adrenal to endogenous ACTH, there are likewise no grounds for postulating the development of a "phase of exhaustion" of the adrenal cortex at this period of radiation sickness, despite the fact that some of the irradiated animals were in a terminal state during the investigation.

Hence, during the action of lethal doses of ionizing radiation, no evidence could be found of the successive alternation of the phases described by Selye in the reaction of the pituitary-adrenal system. The results of the present investigation indicate that in the period of development of acute radiation sickness caused by lethal doses of x-rays the process of liberation of ACTH from the pituitary in response to the action of an unfavorable factor is not disturbed, and the reaction of the adrenal cortex to endogenous ACTH is also preserved.

#### SUMMARY

The response of the hypophyseal-adrenal system of irradiated rats to a repeated action of unfavorable factors was studied.

Excision of the left adrenal led to an ascorbic acid in the right adrenal both in intact and irradiated rats. Repeated irradiation of rats at the height of radiation sickness caused the same reduction of the ascorbic acid depletion in the adrenals as primary irradiation. Irradiated rats, just as the normal ones, developed compensatory hypertrophy of the remaining gland in response to excision of its counterpart.

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