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X Irradiation of the Hypophysectomized Rat

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In a previous communication we reported that X radiation, in common with other types of stress, appeared to result in an increased demand for the adrenal-cortical hormone (*3*). In general, the pattern of the adrenal response to irradiation in the lethal range consisted of a reduction in adrenal cholesterol initially, a normal or elevated cholesterol concentration associated with adrenal hypertrophy in the intermediate period, and a second marked fall in adrenal cholesterol terminally. Subsequent studies revealed that the initial reduction in adrenal cholesterol observed 3 hrs after X irradiation could be prevented by suitable administration of adrenal-cortical extract (*9*). This substantiates the findings of Sayers and Sayers (*5*), who found that the previous administration of cortical hormone prevented the rather similar fall in adrenal ascorbic acid seen in rats stressed by exposure to cold. The intermediate and terminal adrenal responses to irradiation, however, were not modified by the daily administration of cortical extract in an amount sufficient to prevent the initial cholesterol change, nor was the survival of irradiated rats altered by such treatment (*9*). Even when the dose of extract was increased 5-fold, the usual adrenal changes were observed 4 days after irradiation (*4*).

It is generally agreed that the early depletion in adrenal lipids and ascorbic acid seen after a variety of stressing stimuli, as well as the subsequent adrenal hypertrophy, are mediated through the pituitary adrenotropic hormone (*1, 2, 7, 10*). Since the possibility exists that the adrenal glands may play a role in mediating or modifying some of the changes observed after irradiation, it seemed of interest to determine whether hypophysectomy would prevent the adrenal response to X radiation and to note whether survival and some of the typical changes in organ weights would be altered under these conditions.

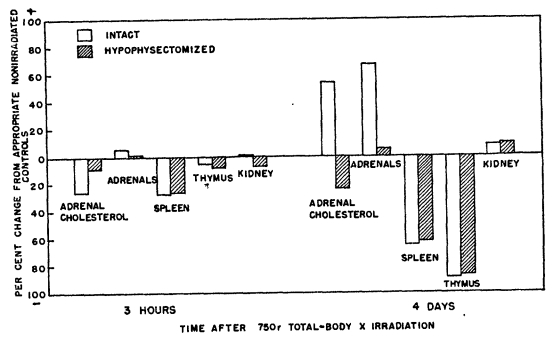

FIG. 1. Per cent change in adrenal cholesterol and organ weights in intact and hypophysectomized rats after 750 r. (Cholesterol and organ weights expressed as per cent of body weight in calculating per cent change. Minimum of 10 rats in each group.)

TABLE 1

ADRENAL CHOLESTEROL AND ORGAN WEIGHTS IN INTACT AND HYPOPHYSECTOMIZED RATS AFTER 750 r

Group	Sacrifice time: After hypophysectomy	Sacrifice time: After X-ray	No. of rats	Body wt. (gm)	Adrenal cholesterol (mg/100 mg of adrenal)	Adrenal cholesterol (mg/100 gm of body wt.)	Adrenal wt. (mg/100 gm of body wt.)	Spleen wt. (mg/100 gm of body wt.)	Thymus wt. (mg/100 gm of body wt.)	Kidney wt. (mg/100 gm of body wt.)
Intact										
Nonirradiated	.....	.....	14	278.5	1.90 ± 0.18*	0.25 ± 0.03	12.8 ± 0.4	301 ± 11	184 ± 6	346 ± 6
Irradiated	.....	3 hrs	10	268.9	1.37 ± 0.12	0.18 ± 0.02	13.5 ± 0.5	221 ± 8	174 ± 10	351 ± 5
"	.....	4 days	10	220.0	1.77 ± 0.24	0.38 ± 0.04	21.4 ± 0.9	104 ± 8	20 ± 1	374 ± 9
Hypophysectomized										
Nonirradiated	7 days	.....	10	194.3	4.11 ± 0.41	0.41 ± 0.05	9.8 ± 0.8	267 ± 10	190 ± 12	310 ± 7
Irradiated	7	3 hrs	10	204.4	3.74 ± 0.19	0.37 ± 0.08	9.9 ± 0.5	198 ± 9	174 ± 9	289 ± 9
Nonirradiated	11	.....	10	188.8	3.18 ± 0.36	0.30 ± 0.03	9.4 ± 0.3	215 ± 8	179 ± 9	290 ± 7
Irradiated	11	4 days	12	168.4	2.39 ± 0.28	0.23 ± 0.03	9.8 ± 0.4	81 ± 4	24 ± 1	317 ± 9
Nonirradiated	14	.....	5	199.9	2.36 ± 0.76	0.20 ± 0.07	8.4 ± 0.6	217 ± 8	168 ± 14	273 ± 7

* Indicates mean and standard error.

Sixty white male rats (Sprague-Dawley) weighing 200–300 gm each received total-body X radiation in a single exposure (750 r; 200 kv; dose rate, 18 r/min). Thirty of the rats were hypophysectomized one week prior to irradiation. The animals were exposed in groups of 10, each exposure group containing equal numbers of intact and hypophysectomized rats. All rats including the normal and hypophysectomized nonirradiated controls were fed bread and milk, Fox Checkers, and water *ad libitum*. Animals were sacrificed with Nembutal (IP) 3 hrs and 4 days after irradiation, and the adrenals, spleen, thymus,

and left kidney were removed, dissected free of fat, and weighed on a torsion balance. Total adrenal cholesterol was determined on paired adrenals from single animals by the Schoenheimer-Sperry method as modified by Sperry (*8*). Appropriate nonirradiated controls were sacrificed along with the irradiated rats. The completeness of hypophysectomy was checked at sacrifice.

The per cent changes in organ weights and in adrenal cholesterol after total-body X radiation of intact and hypophysectomized rats are indicated in Fig. 1. In calculating the per cent change for both groups of rats, comparison was made with the appropriate nonirradiated controls sacrificed at the same time. A summary of the data is presented in Table 1.

It will be noted that the adrenal response to X irradiation was prevented by hypophysectomy. The small changes seen in adrenal cholesterol and adrenal weight at 3 hrs and 4 days were not statistically significant. Furthermore, the terminal adrenal changes which are observed in intact animals were not seen in two hypophysectomized irradiated rats sacrificed in a moribund condition. Statistically significant changes identical with those reported previously were observed in the unoperated irradiated animals.[1]

Pituitary ablation did not alter the degree or time course of the splenic and thymic involution resulting from X irradiation. Kidney, which was weighed as a control, did not change appreciably in either group after irradiation. The small increase noted in kidney weight calculated on the basis of body weight may be accounted for by the observed decrease in body weight.

Hypophysectomy appeared to potentiate X-ray toxicity. Forty-five per cent of 20 hypophysectomized irradiated rats died 3–4 days after the exposure, whereas none of the intact irradiated animals succumbed at this time. Deaths in the latter group began at 6 days, and there was only a 30% mortality by 16 days after the irradiation. There were no deaths in the nonirradiated hypophysectomized group.

Atrophy of the adrenals was evident in the hypophysectomized group at the time of irradiation, 7 days after the operation (22% decrease in adrenal weight calculated on the basis of body weight). At this time the concentration of cholesterol in the gland was increased above that observed in the intact rat. However, the total cholesterol content of the adrenals was almost equivalent in both groups. Adrenal weight was decreased still further and the cholesterol concentration was reduced in the animals sacrificed 11 and 15 days after the operation. Rather similar changes in adrenal cholesterol in hypophysectomized rats have been described by Sayers, *et al.* (*6*), and Tyslowitz has reported a gradual fall in adrenal ascorbic acid after removal of the pituitary (*11*).

[1] It should be pointed out that the concentration of cholesterol in the adrenals of the intact nonirradiated rats was low in comparison with the many determinations made by us previously on other shipments of rats. We cannot account for this. The control rats were sacrificed at different intervals during the course of the experiment, and no gross evidence of disease was found.

There is evidence which suggests that the response of the adrenal cortex to the pituitary tropic hormone is dependent upon a certain level of activity of the cortical cells and diminishes with time after hypophysectomy (*6*). It remains to be determined, therefore, whether the adrenal cortex in the 7-day hypophysectomized rat does not respond to X radiation because it is generally less sensitive, owing to the removal of pituitary influence, or because its stimulation after irradiation is mediated solely by the adrenotropic hormone. In order to evaluate this point we plan to study the adrenal response in animals irradiated 2–3 days after hypophysectomy, before appreciable glandular atrophy and decreased sensitivity are evident. Nevertheless, we may conclude from the present experiments that hypophysectomy performed one week prior to irradiation prevents the intermediate and terminal as well as the initial adrenal changes resulting from exposure to X-rays. Under these conditions, the extent of the splenic and thymic involution is not altered, although toxicity appears to be enhanced.

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The Inhalation of Norisodrine Sulfate Dust

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There have been many favorable reports on the use of Norisodrine Sulfate as a bronchodilator. This drug has been known in the European literature as Aleudrin and has been chemically identified as 1-(3′,4′-dihydroxyphenyl)-2-isopropylaminoethanol. Its chief clinical use has been in the symptomatic treatment of asthmatic conditions. A considerable number of animal and human experiments have been carried out in relation to the properties of this drug. There is general agreement in the literature that (1) it is more effective than epinephrine in overcoming bronchiospasm induced experimentally; (2) it may cause vasodilation with a consequent fall in blood pressure; (3) it may cause an increase in the