

# EFFECT OF CORTICOSTEROIDS AND X-RAY IRRADIATION ON GROWTH OF TRANSPLANTABLE HARDING-PASSY MELANOMA

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In experiments on mice (C57BL × CBA) F<sub>1</sub>, hydrocortisone and prednisolone caused a significant delay (by 2-3 times) in growth of the tumor. With a combination of hydrocortisone and x-ray irradiation, no summation of the effects of these two factors was observed. Combined treatment with prednisolone and x-ray irradiation caused more marked inhibition of growth of the tumor than each of the agents separately, but complete summation of the effects was not observed.

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In a previous paper [1] results were described showing the inhibitory action of certain hormones, notably cortisone, on growth of a transplantable Harding-Passy melanoma. In this paper the action of hydrocortisone and prednisolone, both alone and in combination with x-ray irradiation, on the growth of this tumor is described.

## EXPERIMENTAL METHOD

Experiments were carried out on 258 male mice (C57BL × CBA) F<sub>1</sub> weighing 25-30 g. The tumor was inoculated subcutaneously into the mouse's flank by the method usually adopted in the Institute, a homogenized suspension of tumor tissue in a dilution of 1:3 being injected into each animal in a dose of 0.2 ml. Treatment of the animals began 17-18 days after inoculation, when the diameter of the tumor was 6-15 mm. The mice were chosen for the experiment in such a way that their distribution by size of the tumor nodules was the same in all groups. At the end of the experiment the animals were killed and the tumor nodules weighed. Differences between the mean weights were compared by Student's criterion for a pair of related variables.

In series I (experiments 1 and 2) the action of hydrocortisone alone was studied in various doses, administered as gelatin-coated capsules implanted subcutaneously into the animal's right or left flank. The capsules were prepared as described by Parkan [2] in the laboratory of Hormone Therapy. This method was chosen because it enabled the hormone to enter the blood stream more uniformly than when given by

TABLE 1. Effect of Hydrocortisone on Growth of Harding-Passy Melanoma

Experiment	Group	No. of animals	Procedure	Sessional dose of hormone (in µg/mouse)	Mean (M ± m) weight of tumor at end of treatment (in g)	Inhibition of tumor growth (in %)	P (relative to control)
1	1	14	Hydrocortisone	100	1.6 ± 0.20	23.9	< 0.01
	2	14	"	200	1.6 ± 0.20	23.9	< 0.01
	3	14	Control	—	2.1 ± 0.21		
2	1	20	Hydrocortisone	500	2.0 ± 0.41	63.7	< 0.001
	2	20	"	200	2.3 ± 0.46	58.2	< 0.001
	3	20	Control	—	5.5 ± 0.87		

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TABLE 2. Separate and Combined Action of Corticosteroids and X-Ray Irradiation on Growth of Harding-Passy Melanoma

Experiment	Group	No. of animals	Procedure	Sessional dose of hormone and total dose of x-ray irradiation	Mean ( $M \pm m$ ) weight of tumor at end of treatment (in g)	Inhibition of tumor growth (in %)	P (relative to control)	P (relative to groups 1 and 3)
3	1	10	Hydrocortisone	200 $\mu$ g	$0.53 \pm 0.22$	53.5	< 0.01	> 0.05
	2	10	Hydrocortisone	200 $\mu$ g	$0.40 \pm 0.14$	65.0	< 0.01	
	3	10	Hydrocortisone and x-ray irradiation	5 000 R				
	4	10	X-ray irradiation	5 000 R	$0.61 \pm 0.16$	46.5	< 0.05	
			Control	—	$1.14 \pm 0.33$			
4	1	15	Prednisolone	1 mg	$0.80 \pm 0.12$	53.0	< 0.01	< 0.01
	2	15	Prednisolone	1 mg	$0.30 \pm 0.03$	82.2	< 0.001	
	3	15	Prednisolone and x-ray irradiation	5 000 R				
	4	15	X-ray irradiation	5 000 R	$0.60 \pm 0.08$	64.8	< 0.001	
			Control	—	$1.7 \pm 0.18$			
5	1	14	Prednisolone	1 mg	$0.07 \pm 0.0$	65.0	< 0.001	< 0.01
	2	14	Prednisolone	1 mg	$0.16 \pm 0.02$	92.0	< 0.001	
	3	14	Prednisolone and x-ray irradiation	7 000 R				
	4	14	X-ray irradiation	7 000 R	$0.30 \pm 0.03$	85.0	< 0.001	
			Control	—	$2.00 \pm 0.36$			

daily injections. In experiment 1 hydrocortisone was injected in doses of 100 and 200  $\mu$ g/mouse/day. The period of observation was limited to 10 days. In experiment 2 larger doses of hormone were used—200 and 500  $\mu$ g/mouse/day. Observations continued for 12 days. Similar gelatin capsules, but not containing hormone, were implanted into control mice in both experiments. No toxic effect of the hormone was observed.

In series II (experiments 3, 4, and 5) the action of corticosteroids and x-ray irradiation was studied separately and in combination. The mice in these experiments were distributed among 4 groups: group 1 receiving only the hormone, group 2 the hormone together with x-ray irradiation, group 3 x-ray irradiation only, and group 4 the control. In experiment 3, hydrocortisone was used as the hormone, but since this experiment took place before experiments 1 and 2, a suspension of hormone in physiological saline was given to the animals by daily subcutaneous injections for 10 days in a dose of 200  $\mu$ g/mouse. In experiments 4 and 5 the suspension of prednisolone in starch mucilage was given in a dose of 1 mg/mouse/day by gastric tube. Control mice received physiological saline or starch mucilage, given in the same doses and by the same method as the hormone suspension.

Irradiation was carried out on the RUM-7 x-ray apparatus (voltage 30 kV, current 13 mA, skin-focus distance 75 mm). The animals were irradiated in fractional doses, for a period of 10 days in experiments 3 and 4, and for 14 days in experiment 5, with intervals of 48 h between sessions. The sessional dose of 1000 R and the total dose 5000 in experiments 3 and 4 and 7000 R in experiment 5.

#### EXPERIMENTAL RESULTS

Hydrocortisone in doses of 100 and 200  $\mu$ g/mouse/day inhibited growth of the tumor after 10 days by 23.9%. In the case of a more prolonged (14 days) administration of this hormone in a dose of 200  $\mu$ g/mouse per day, the inhibition effect was somewhat greater (58.2%). The effect of inhibition of tumor growth caused by hydrocortisone in a dose of 500  $\mu$ g/mouse/day did not differ significantly from the effect observed after

a dose of 200  $\mu\text{g}$ /mouse/day given for the same period of time (Table 1). Prednisolone also inhibited growth of the tumor by 53% over 10 days and by 65% over 14 days.

With the combined treatment with hydrocortisone and x-ray irradiation, no summation of the effects of these factors was found. Combined treatment with prednisolone and x-ray irradiation caused more marked inhibition of tumor growth than each of these agents separately, but complete summation of the effects was not observed (Table 2).

#### LITERATURE CITED

1. V. L. Grigor'yan, Byull. Éksperim. Biol. i Med., No. 2, 91 (1968).
2. M. S. Parkan', Value of the Formation of Tissue Depots of Gonadotropins for Increasing the Sensitivity of Some Diagnostic Methods in Oncology, Candidate Dissertation, Moscow (1967).