Effect of Cortisol and Norethandrolone on Inflammation and Tumor Growth[1]

The anti-inflammatory activity of cortisol in rats usually parallels the loss of body, thymus, and adrenal weight[2–4]. Practically all these effects are antagonized by growth hormone and, to a certain extent, desoxycorticosterone and aldosterone[3,5,6]. On the other hand, certain anabolic androgens and more especially nortestosterone derivatives can selectively antagonize the body weight loss[7–9]. Hence, it seemed of interest to investigate this antagonism as regards inflammation and tumor growth. The present study deals with the effect of cortisol and norethandrolone upon the inflammatory reaction of croton oil induced granuloma pouches in intact and adrenalectomized rats, and upon the growth of a transplanted fibrosarcoma.

Materials and Methods: 136 female Sprague Dawley (Holtzman) rats, weighing between 100 and 115 g were maintained on Purina Fox Chow and tap water, except for adrenalectomized rats, which received 1% NaCl in their drinking fluid. Hormone treatment was started 3 days before induction of the granuloma pouches or implantation of the tumors. Bilateral adrenalectomies also preceded the production of the pouches by 3 days. Cortisol acetate (Pfizer) was administered at a dose of 1 mg, daily for the first 3 days and every second day thereafter. Norethandrolone (Searle) was given at a daily dose of 5 mg for the duration of the experiment; both steroids were injected subcutaneously as microcrystal suspensions in 0·2 ml of saline. The granuloma pouches were produced with croton oil according to the modified technique of ROBERT and NEZAMIS[10], with the difference that 1 ml of irritant was given at a concentration of 0·75%. A methylcholanthrene fibrosarcoma, recently induced in our laboratory, was used as transplantable tumor: 0·2 ml of a cellular suspension, obtained by grinding 1 g of fresh tumor tissue with 5 ml of physiologic saline, was injected underneath the dorsal skin of the rat. A neoplasm, free of necrotic tissue, was taken from a single donor, thus insuring a uniform growth in the receivers. The distribution of groups in each experiment is indicated in the Tables. The first experiment lasted 6 days after the production of the pouches, while the second experiment, on tumor growth, ended 9 days after implantation of the tumors. To assess the inflammatory reaction quantitatively, exudate from the pouches was measured into graduated cylinders at the time of autopsy. The thymus and adrenals, together with the tumors, were fixed into Susa solution for subsequent dissection, weighing, and histologic examination.

Results: *Effect of cortisol and norethandrolone on inflammation in intact and adrenalectomized rats* (Table I). As expected, cortisol decreased, while norethandrolone increased the rate of somatic growth and both hormones antagonized each other in this respect. The rate of exudation in the granuloma pouches did not follow the same pattern and there was no visible antagonism between the steroids;

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Table I: Effect of Cortisol and Norethandrolone on Inflammation in Intact and Adrenalectomized Rats

Treatment	Final Body Weight (g)[c]	Weight Gain (g)	Exudate (ml)	Thymus (mg)	Adrenals (mg)
Intact[a]	136 ± 1·8[d]	32 ± 1·4	10·4 ± 0·9	328 ± 10·4	36·6 ± 0·8
Intact Cortisol	112 ± 1·5	8 ± 1·9	1·8 ± 0·4	74 ± 7·5	20·9 ± 1·0
Intact Norethandrolone	150 ± 2·3	49 ± 2·2	6·7 ± 0·7	177 ± 7·8	33·3 ± 1·3
Intact Cortisol + Norethandrolone	131 ± 1·5	28 ± 2·1	0·9 ± 0·4	22 ± 1·5	23·5 ± 0·9
Adr-X[b]	128 ± 2·5	+13 ± 3·2	11·7 ± 1·0	373 ± 36·1	
Adr-X Cortisol	110 ± 2·4	− 7 ± 1·3	1·5 ± 0·5	59 ± 5·5	
Adr-X Norethandrolone	136 ± 4·5	+21 ± 5·0	8·3 ± 0·2	235 ± 31·6	
Adr-X Cortisol + Norethandrolone	127 ± 2·0	+13 ± 1·8	2·2 ± 0·5	23 ± 2·2	

[a] Groups of 10 rats each. [b] Groups of 14 rats each. [c] Calculated after removal of exudate. [d] Mean ± standard error.

Table II: Effect of Cortisol and Norethandrolone on Tumor Growth in Intact Rats

Treatment[a]	Final Body Weight (g)[b]	Weight Gain (g)	Tumor (mg)	Thymus (mg)	Adrenals (mg)
—	156 ± 2·1[c]	+41 ± 2·3	2770 ± 198	308 ± 12·7	43·8 ± 1·6
Cortisol	122 ± 1·7	+ 7 ± 2·0	1591 ± 177	71 ± 6·3	19·3 ± 0·5
Norethandrolone	190 ± 1·5	+75 ± 2·2	2658 ± 249	219 ± 14·7	37·9 ± 0·9
Cortisol + Norethandrolone	147 ± 2·4	+31 ± 2·5	1434 ± 199	27 ± 1·8	23·8 ± 1·1

[a] Groups of 10 rats each. [b] Calculated after removal of the tumor. [c] Mean ± standard error.

norethandrolone even significantly reduced the inflammatory reaction ($p < 0{\cdot}01$). As judged from the thymus weight, both steroids caused lympholysis, although norethandrolone had a much weaker effect than cortisol. The marked atrophy of the adrenal glands caused by cortisol was not significantly influenced by norethandrolone. On the contrary, the latter hormone given alone slightly diminished the adrenal weight, with a reduction in sudanophilia.

Adrenalectomy did not change the animals' response to norethandrolone, even as regards its anabolic property; the loss of body weight caused by cortisol, which is relatively higher after adrenalectomy, was effectively prevented by norethandrolone.

Effect of cortisol and norethandrolone upon the growth of a transplanted fibrosarcoma (Table II). The effects of both hormones on body and thymus weights obtained here are similar to those reported in the previous experiment. The higher gain in body weight is attributable to the longer period of treatment. Tumor weight revealed that the neoplastic growth responded to the steroid treatment exactly as did the inflammatory reaction.

Discussion: Analysis of our results reveals a remarkable degree of uniformity in the responsiveness of intact and adrenalectomized animals to treatment with cortisol and norethandrolone. The remarkable tolerance of adrenalectomized rats for norethandrolone was unexpected, since another anabolic hormone, the pituitary growth hormone, is very toxic in the absence of adrenals[11]; thus, the presence of that gland is not indispensable for the occurrence of tissue anabolism.

It is noteworthy that two somewhat metabolically opposed steroids exerted an additive effect upon the evolution of inflammation and cancer. This influence seems to be a direct one, at least in the case of inflammation, since it is also demonstrable in the absence of adrenals. Like other testoids[12], norethandrolone causes a weak, but direct, involution of the thymus. At the dosage used, the hormone also exhibited progestative properties, with definite hypertrophy of the preputial glands and external genitals; this effect was not prevented by cortisol treatment.

In the present study, the inhibitory action of cortisol upon the growth of the fibrosarcoma was highly significant ($p < 0{\cdot}01$). These results may not agree with other reports[13,14], but the effect of the corticosteroid upon the growth of transplantable tumors largely depends upon the origin of the neoplasm and the modality of treatment[15]. Here, the rate of the tumor growth singularly compares with the reaction of the connective tissue.

These observations may provide useful therapeutic applications, especially when anti-inflammatory corticosteroids are to be administered in high doses and for a prolonged period. In such instances, the conjoint treatment with norethandrolone may be indicated until the advent of a more specific anti-inflammatory steroid.

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Résumé

Le norethandrolone administré chez le rat intact ou surrénalectomisé se montre très efficace à prévenir la perte de poids causée par le cortisol. Cet antagonisme, toutefois, n'est pas démontrable en ce qui concerne l'effet anti-inflammatoire, la diminution de la croissance tumorale et l'atrophie du thymus et de la surrénale dus au cortisol. En outre, le norethandrolone présente à lui seul des propriétés anti-inflammatoires et thymolytiques, plus spécialement chez l'animal intact.

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The Action of 5-Hydroxy-DL-Tryptophan and 5-Hydroxy-Tryptamine on the Cortical Electrical Activity of the 'Midpontine Pretrigeminal Preparation'

In order to study the action of 5-hydroxy-tryptophan (5HTP) and 5-hydroxy-triptamine (5HT) on the central nervous system, we followed the EEG changes induced by these drugs on the midpontine pretrigeminal cat with or without midbrain hemisection. The drugs were injected into the carotid artery. Electro-cortical activity, arterial blood pressure, and carotid blood flow (Rein's Thermostromuhr) were simultaneously recorded.

The main results were as follows:

(1) The EEG pattern of the midpontine pretrigeminal preparation is characterized by the low voltage fast rhythms which are considered typical of the waking state[1]. 5HT (2–80 μg) slowly injected into the carotid artery – the controlateral artery being closed – never changed this pattern, neither modified, at least in some of our experiments, the carotid blood flow and the arterial blood pressure.

On the contrary, 5HTP (8–20 mg) injected in the same way, brought about high voltage slow EEG rhythms similar in every respect to those produced by thyopental. This pattern, which lasted more than 30 min, was reversible and was easily activated by olfactory and visual stimulations. In many instances, 5HTP, at doses active on the EEG, was ineffective on the carotid blood flow and the arterial pressure.

(2) 5HTP (8–20 mg) injected into the carotid artery – the controlateral artery being open – yielded a clear EEG asymmetry, the cerebral hemisphere on the side of the injection showing a degree of synchronization more pronounced than the one of the opposite hemisphere (Fig.). This means that the EEG effect of 5HTP (a) is most likely to start just at the first passage of the drug into the cerebral circulation, and (b) must be largely independent of extra-cerebral metabolic products of 5 HTP, which ought to impinge symmetrically upon the nervous structures. At lower dosage (4–8 mg), 5HTP produced a latent asymmetry which was revealed by small doses of thiopental (2–3 mg/kg i. v.) which produced a higher degree of synchronization over the hemisphere ipsilateral to the injection of 5HTP. Whatever the doses of 5HTP used, we never obtained, an EEG asymmetry opposite in sign to that described above.

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