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ABSTRACT

The growth of the ventral and the dorsolateral prostate, the coagulating glands and the seminal vesicles was studied in cortisone-treated and non-treated castrated non-adrenalectomized and castrated adrenalectomized rats. The cortisone was administered in daily doses of 3 mg or 9 mg for a period of 15 days.

Combined castration and adrenalectomy resulted in a greater degree of atrophy of the ventral prostate than castration alone, thus indicating some maintenance effect of the adrenals on the ventral prostate. No differences in the other accessory reproductive organs were demonstrated when comparing non-treated castrated non-adrenalectomized with castrated adrenalectomized rats.

Both doses of cortisone stimulated the growth of the dorsolateral prostate, the coagulating glands and the seminal vesicles, but the larger dose resulted in a greater degree of stimulation. Only the larger dose of cortisone gave histological changes in the ventral prostate indicative of a slight stimulating effect. Catabolic or anti-anabolic effects of cortisone as registered by a decrease in body weight and weight of the levator ani muscle did not inhibit the growth stimulating effect of cortisone on the accessory reproductive organs.

Cortisone stimulated the growth of both the epithelium and the smooth muscle tissue of the glands. The effect on the different accessory reproductive organs after cortisone administration was contrary to previous studies, which demonstrated the stimulating effects of androgens in the rat, in that the ventral prostate was relatively unstimulated.

Possible mechanisms for the stimulation of the growth of the accessory
reproductive organs are discussed in the light of our present knowledge of cortisone metabolism and of the secretion in the cortisone-treated rats of hormones which have been found to modify the growth of the accessory reproductive organs.

Several experiments have been reported on the male accessory reproductive organs in castrated rats after cortisone administration. Moore (1953) found no definite effects on the weight or histology of the seminal vesicles or the ventral prostate after cortisone in daily doses of 5 mg for a period of 10 days. With lower doses of cortisone or shorter experimental periods than those used by Moore (1953), negative results according to the weight increase of the seminal vesicles (Courrier & Marois 1952; Eisenberg & Gordan 1954) and of the ventral prostate and the seminal vesicles (Hershberger et al. 1953) have been reported.

Following cortisone administration in daily doses of 3 mg for a period of 3 weeks to castrated rats as compared with untreated controls, Arvola (1961) found somewhat higher absolute mean weights (but without statistical verification) of the ventral prostate with attached lateral prostate, of the dorsal prostate, and of the coagulating glands. When he used relative organ weights (organ weight/body weight) he found significantly higher weights of the above mentioned parts of the prostate in the cortisone treated rats than in the controls. The possibility that the lower body weight after cortisone might result in higher relative organ weights was not analysed. The use of such ratios as relative organ weight has been criticized (Angervall & Carlström 1963). Using a quantitative histological method, Arvola (1961) found changes in the prostatic lobes after cortisone administration which he regarded as indicative of a stimulation. His experiments, however, included no systematic qualitative histological study of the prostatic lobes.

Experiments on the effects of cortisone on male accessory reproductive organs have also been performed on animals other than the rat. In castrated mice Kochakian (1944) did not find any effect on the weights of the seminal vesicles or prostate after implantation of cortisone pellets. Talalay et al. (1952) could not maintain the prostatic secretion of castrated dogs with cortisone in daily doses of 50 mg and from their results concluded that cortisone was not androgenic. Delost (1954) castrated field voles and observed atrophy of the dorsal and lateral prostate. But the ventral prostate, after a short period of regression, exhibited a marked secretory activity, which could be prevented by adrenalectomy. Administration of cortisone in total doses of 25 to 35 mg given during 10 to 21 days stimulated the epithelium of the ventral prostate in the castrated adrenalectomized field vole but had no effect on the dorsal and lateral prostate.

Thus hitherto performed animal experiments have not given conclusive evidence of an androgenic effect of cortisone except in the field vole, and
there are no known experiments reported on simultaneous quantitative and qualitative morphological studies of all the prostatic lobes and the seminal vesicles in castrated non-adrenalectomized, and castrated adrenalectomized rats. The present paper deals with a quantitative and qualitative morphological study of the growth of the ventral prostate, the dorsolateral prostate, the coagulating glands and the seminal vesicles in non-treated and cortisone-treated castrated non-adrenalectomized and castrated adrenalectomized rats.

MATERIAL AND METHODS

The investigation was performed on thirty-six rats of the Sprague-Dawley strain supplied by Anticimex AB, Stockholm.

The rats were castrated when weighing 44 ± 0.5 g (mean and standard error of the mean). The castration was performed by the transcrotal route, and the epididymis was removed together with the testis. Twenty rats were adrenalectomized 45 days after castration at a mean weight of 226 ± 3 g. Adrenalectomy, performed by the dorsal route, was done by careful free dissection of the adrenal gland and inspection of its capsule. The result was checked by examination of the operative field after the experiments had been terminated. All the operations were performed under ether anaesthesia. On the day of adrenalectomy the rats were divided into the following groups and were given injections during the last fifteen days of the experimental period. All rats were killed 60 days after castration.

G: Castrated non-adrenalectomized rats injected with 0.5 ml physiological saline twice daily – 5 rats
C-Co1: Castrated non-adrenalectomized rats injected with 1.5 mg cortisone acetate twice daily – 6 rats
C-Co2: Castrated non-adrenalectomized rats injected with 4.5 mg cortisone acetate twice daily – 5 rats
CA: Castrated adrenalectomized rats injected with 0.5 ml physiological saline twice daily – 7 rats
CA-Co1: Castrated adrenalectomized rats injected with 1.5 mg cortisone acetate twice daily – 8 rats
CA-Co2: Castrated adrenalectomized rats injected with 4.5 mg cortisone acetate twice daily – 5 rats

A commercial cortisone acetate preparation, Cortodrin® (Astra), 25 mg/ml was used. Cortisone acetate was given as subcutaneous injections in the lower part of the body at 8.30 a.m. and 3.30 p.m. Throughout the experiment all the rats ate ad libitum a special commercial rat diet supplied by Teknosan AB, Malmö, Sweden. The food consumption was estimated for the different groups in periods of up to four days, beginning a week before the treatment and continuing throughout the investigation. The rats were weighed before castration, and before the period of injections, as well as at autopsy. Adrenalectomized rats which were not given cortisone received physiological saline, other rats tap water ad libitum.

The urinary excretion of sugar was estimated by means of Tes-Tape (Lilly) during the last two days of the experiment. During the period when urinary glucose was estimated, the rats were transferred to separate cages specially adapted for urine collection. Some contamination of the urine with food was unavoidable.

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On the day of autopsy 0.05 ml of blood was taken from the vena jugularis of all rats while under ether anaesthesia. The blood glucose values were determined according to the glucose oxidase method (Teller 1956). For this a modified commercial reagent was used, supplied by Kabi Ltd., Stockholm, Sweden. There were no limitations in the food and drink supply during the period when urinary and blood glucose values were estimated. After the last blood samples had been taken, the rats were exsanguinated through a large cardiac incision while under ether anaesthesia. Rats were taken alternatively from the six groups. The adrenal glands, the thymus, the ventral prostate, the dorsolateral prostate, the coagulating glands, the seminal vesicles and the levator ani muscle were dissected free, while immersed in physiological saline, with the aid of a stereoscopic microscope. The organs were blotted and weighed on an analytical balance with an accuracy of 0.01 mg.

Student's t-test was used for testing differences between the means.

For histological examination the ventral prostate, the dorsolateral prostate, the coagulating glands and the seminal vesicles were fixed in Bouin's solution for two hours. After dehydration the organs were embedded in paraffin and cut into 5 µm thick sections which were stained according to Weigert-van Gieson or with PAS-staining (McManus 1948).

RESULTS

Food consumption, blood and urinary glucose (see Figs. 1 and 2)

After adrenalectomy the food consumption was markedly decreased during the first postoperative days, and increased thereafter, though throughout the experiment it was below that of castrated non-adrenalectomized rats. Cortisone administration resulted in a decrease in the food consumption. This was more

![Graph](Fig. 1)

Food consumption of castrated non-adrenalectomized rats.

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marked after the larger dose, both in castrated non-adrenalectomized and in castrated adrenalectomized rats.

Cortisone administration had no demonstrated tendency to change blood glucose values either in castrated non-adrenalectomized or in castrated adrenalectomized rats, with the exception of one castrated non-adrenalectomized rat which received the larger dose of cortisone. On the day of autopsy this rat had a blood glucose value of 330 mg/100 ml, as compared with the mean value of 109 ± 10 mg/100 ml for the other rats in the group. This rat also had 0.5% glucose in the urine samples while the other rats had negative results in urinary glucose tests.

**Weights of body and of levator ani muscle** (see Table 1)

The mean body weight increased for non-treated castrated non-adrenalectomized rats (group C) during the injection period (*P* < 0.025). The mean body weights decreased significantly during the injection period for all the rats given cortisone and this was most marked after the larger dose (groups C–Co₁ (*P* < 0.01), C–Co₂ (*P* < 0.005), CA–Co₁ and CA–Co₂ (*P* < 0.001)).

Cortisone administration in daily doses of 3 mg to castrated non-adrenalectomized rats (group C–Co₁) and castrated adrenalectomized rats (group CA–Co₁) significantly (*P* < 0.005 and *P* < 0.001 respectively) decreased the mean weights of the levator ani muscle as compared with those of non-treated controls (groups C and CA respectively). There was no significant difference between the mean weights of the levator ani muscle between rats given corti-
sone in daily doses of 3 mg or 9 mg, either for castrated non-adrenalectomized or for castrated adrenalectomized rats.

Weights of adrenal glands and thymus (see Table 1)

Castrated non-adrenalectomized rats given cortisone in daily doses of 3 mg and 9 mg (groups C–Co₁ and C–Co₂) respectively had similar adrenal mean weights. These mean weights were about 40 per cent of that of non-treated castrated non-adrenalectomized rats.

Cortisone administration in daily doses of 3 mg to castrated non-adrenalectomized and castrated adrenalectomized rats (groups C–Co₁ and CA–Co₁) decreased the mean thymus weights to about a twentieth of that of the comparable non-treated rats (groups C and CA). Cortisone administration in daily doses of 9 mg to castrated adrenalectomized rats gave a further small decrease in the thymus mean weight as compared with that of rats given cortisone in daily doses of 3 mg (P < 0.005).

Weights of ventral prostate, dorsolateral prostate, coagulating glands and seminal vesicles (see Table 1 and Figs. 3 and 4)

Castrated adrenalectomized rats (group CA) had a lower mean weight of the ventral prostate than castrated non-adrenalectomized rats (group C) P < 0.005. Mean weights of the dorsolateral prostate, the coagulating glands and the seminal vesicles were similar in castrated non-adrenalectomized rats (group C) and castrated adrenalectomized rats (group CA).

After the administration of cortisone in daily doses of 3 mg there was a small but significant (P < 0.05) decrease in the mean weight of the ventral prostate in castrated non-adrenalectomized rats (group C–Co₁) as compared with non-treated controls (group C). The mean weights of the dorsolateral prostate and the coagulating glands were increased as compared with the mean weights found in the control rats, both in castrated non-adrenalectomized and castrated adrenalectomized rats (groups C–Co₁ and CA–Co₁). However, these increases were only significant for castrated adrenalectomized rats (P for the dorsolateral prostate was < 0.025 and P for the coagulating glands < 0.005). The mean weights of the seminal vesicles were increased both in castrated non-adrenalectomized (P < 0.005) and in the castrated adrenalectomized rats (P < 0.001). After the administration of cortisone in daily doses of 9 mg the mean weight of the ventral prostate was increased in castrated adrenalectomized rats (group CA–Co₂) as compared with the control rats (group CA) P < 0.05. In the castrated non-adrenalectomized and castrated adrenalecto-
mized rats (groups C–Co₂ and CA–Co₂) the mean weights of the dorsolateral prostate (P < 0.001), the coagulating glands (P < 0.005 and P < 0.001 respectively) and the seminal vesicles (P < 0.01 and P < 0.001 respectively) were increased. The rat with signs of hyperglycaemia and glucosuria in group

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Table 1.

Mean body weights and mean weights of adrenal glands, thymus, ventral and dorsolateral prostate, coagulating glands, seminal vesicles and levator ani in castrated non-adrenalectomized and castrated adrenalectomized rats given cortisone in daily dosages of 3 mg and 9 mg and in castrated non-adrenalectomized and castrated adrenalectomized control rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number of rats</th>
<th>Body weight (g)</th>
<th>Adrenal glands (mg)</th>
<th>Thymus (mg)</th>
<th>Ventral prostate (mg)</th>
<th>Dorsolateral prostate (mg)</th>
<th>Coag. glands (mg)</th>
<th>Seminal vesicles (mg)</th>
<th>Levator ani (mg)</th>
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<tbody>
<tr>
<td>C</td>
<td>5</td>
<td>227 ± 6</td>
<td>274 ± 15</td>
<td>52.2 ± 2.7</td>
<td>710 ± 79</td>
<td>9.0 ± 0.2</td>
<td>6.9 ± 1.2</td>
<td>3.5 ± 0.5</td>
<td>7.8 ± 0.6</td>
</tr>
<tr>
<td>C–Co₁</td>
<td>6</td>
<td>227 ± 8</td>
<td>194 ± 7</td>
<td>20.4 ± 1.0</td>
<td>35 ± 2</td>
<td>8.0 ± 0.3</td>
<td>10.8 ± 1.9</td>
<td>4.3 ± 0.2</td>
<td>12.6 ± 1.1</td>
</tr>
<tr>
<td>C–Co₂</td>
<td>5</td>
<td>232 ± 8</td>
<td>177 ± 8</td>
<td>21.3 ± 0.7</td>
<td>33 ± 6</td>
<td>9.0 ± 0.6</td>
<td>24.5 ± 2.9</td>
<td>7.5 ± 0.8</td>
<td>27.7 ± 5.6</td>
</tr>
<tr>
<td>CA</td>
<td>7</td>
<td>228 ± 5</td>
<td>237 ± 6</td>
<td>–</td>
<td>874 ± 42</td>
<td>7.7 ± 0.3</td>
<td>7.9 ± 0.6</td>
<td>3.1 ± 0.3</td>
<td>7.5 ± 0.4</td>
</tr>
<tr>
<td>CA–Co₁</td>
<td>8</td>
<td>227 ± 5</td>
<td>173 ± 7</td>
<td>–</td>
<td>38 ± 2</td>
<td>7.3 ± 0.2</td>
<td>10.1 ± 0.6</td>
<td>4.4 ± 0.2</td>
<td>13.1 ± 0.5</td>
</tr>
<tr>
<td>CA–Co₂</td>
<td>5</td>
<td>222 ± 7</td>
<td>153 ± 9</td>
<td>–</td>
<td>24 ± 3</td>
<td>9.1 ± 0.6</td>
<td>18.1 ± 2.6</td>
<td>8.1 ± 0.8</td>
<td>34.6 ± 5.1</td>
</tr>
</tbody>
</table>

The figures given in Table 1 are mean weight ± standard error of mean.
Weights of the accessory reproductive organs of castrated non-adrenalectomized rats.

C–Co₂ had accessory reproductive organ weights similar to those of the other rats in the group.

There were no significant differences in the weights of the accessory reproductive organs between castrated non-adrenalectomized rats and castrated adrenalectomized rats after administration of cortisone in the two doses.

**Histological examination of the accessory reproductive organs**

**Ventral prostate:** Castrated non-adrenalectomized rats (group C) exhibited an immature appearance histologically (Fig. 5). The small acini had low epithelium without papillary formations. The cytoplasm was pale and no supranuclear clear zone was observed. This zone has been used to denote secretory activity of epithelial cells of the ventral prostate (Price 1936). In the acini there was no or slight, PAS-positive secretion. The small acini were surrounded by immature smooth muscle cells with small nuclei. The fibrous
Weights of the accessory reproductive organs of castrated adrenalectomized rats.

stroma was conspicuous and relatively abundant. The ventral prostate in the castrated adrenalectomized control rats (group CA) was even more undeveloped than in castrated control rats (Fig. 6).

The histological appearance of the ventral prostate in rats receiving daily doses of 3 mg cortisone (groups C–C0₁ and CA–C0₁) was similar to that of untreated controls (groups C and CA respectively). Rats given cortisone in daily doses of 9 mg (groups C–C0₂ and CA–C0₂) showed small signs of stimulation of the ventral prostate (Fig. 7), the acini were larger than in the control rats (groups C and CA) with cuboidal to columnar epithelium but no supranuclear clear zone was observed except in the epithelium of some peripheral acini in one castrated adrenalectomized rat. No papillary formations were demonstrated. In the acini there was no or slight, PAS-positive secretion. The smooth muscle layer around the acini was somewhat more developed than in the control rats. Thus the muscle cells had larger nuclei and more cytoplasm.
Fig. 5, 6 and 7.

5 Section of undeveloped ventral prostate from untreated, castrated non-adrenalectomized rat (group C). Weigert-van Gieson × 192.

6 Section of ventral prostate from untreated, castrated adrenalectomized rat (group CA). Immaturity is even more marked than in the castrated non-adrenalectomized rat. Weigert-van Gieson × 192.

7 Section from one of the most stimulated ventral prostate of a castrated adrenalectomized rat injected daily for fifteen days with 9 mg cortisone (group CA-Co2). Note the rather high epithelium. Weigert-van Gieson × 192.
**Dorsolateral prostate:** Castrated non-adrenalectomized and castrated adrenalectomized rats (groups C and CA) showed a similar immature picture. The dorsal part (Fig. 8) had small acini with cubical to low columnar epithelium. In the acini there was no or slight, PAS-positive secretion. The acini were surrounded by immature smooth muscle cells.

The acini of the lateral part (Fig. 10) were somewhat larger than in the dorsal part and showed cubical to low columnar epithelium. Moreover the acini in the lateral part were surrounded by undeveloped smooth muscle cells. However, the muscular layer was not as conspicuous as in the dorsal part.

Rats given cortisone in daily doses of 3 mg (groups C-CA and CA-CA) showed signs of stimulation (Fig. 9). The dorsal part had larger acini than in untreated control rats. The acini were surrounded by layers of smooth muscle cells which were better developed than in the groups C and CA. The epithelium was cubic to columnar with granulated cytoplasm and dark nuclei. The acini contained exfoliated cells and PAS-positive secretion. The lateral part (Fig. 11) had larger acini than in the control rats. The acini had some papillary formations, the cubic to columnar epithelium was granulated and there was PAS-negative secretion in the lumina. The smooth muscle cells surrounding the acini had larger nuclei and more cytoplasm than in non-treated control rats.

In rats given cortisone in daily doses of 9 mg (groups C-CA and CA-CA) the dorsal and lateral parts of the gland were even more developed and the secretion in the acini was more abundant than in the rats given daily doses of 3 mg cortisone.

**Coagulating glands:** Castrated non-adrenalectomized and castrated adrenalectomized rats (groups C and CA) showed a similar immature picture (Fig. 12). The small acini had either a suggestion of or no papillary formations. The epithelial cells were cubic to low columnar. In some acini there was scanty PAS-positive secretion. The acini were surrounded by concentrically arranged undeveloped smooth muscle cells.

Rats given cortisone in daily doses of 3 mg (groups C-CA and CA-CA) had somewhat larger acini with columnar granulated epithelium and some papillary formations. The lumina contained some PAS-positive secretion. The acini were surrounded by more fully developed smooth muscle layers than in the non-cortisone treated control rats.

Rats given cortisone in daily doses of 9 mg (groups C-CA and CA-CA) had still larger acini with columnar granulated epithelium with nuclei placed centrally in the cells (Fig. 13). The acini had several papillary formations and the lumina contained PAS-positive secretion. Around the acini there were well-developed muscular coats.

**Seminal vesicles:** Seminal vesicles of castrated non-adrenalectomized and castrated adrenalectomized rats (groups C and CA) had small lumina lined by cubical to low columnar pale epithelium. The muscular tissue out-
side the mucosa consisted of an outer longitudinal and an inner circular layer. The muscle cells were undeveloped and there was fibrous tissue between the muscle bundles (Fig. 14).

The seminal vesicles of rats given cortisone in daily doses of 3 mg (groups C–Co1 and CA–Co1) had larger lumina with folded epithelium. The epithelium
Section of undeveloped coagulating gland from untreated, castrated adrenalectomized rat (group CA). Weigert-van Gieson × 192.

was columnar and granulated. The granules were often surrounded by light halos as is seen in secretory functioning cells (Moore et al. 1930). The ovoid nuclei were basally positioned and the nucleoli were conspicuous. The lumina contained PAS-negative secretion. The muscular layers were well developed, the cells had larger nuclei and more cytoplasm than in non-treated control rats. Rats given cortisone in daily doses of 9 mg (groups C-Co2 and CA-Co2) exhibited marked signs of stimulation. There was marked folding of the epithelium which was high columnar and granulated. The granules were consistently surrounded by light halos. The lumina were large and contained an abundance of secretion (Fig. 15).

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Figs. 8, 9, 10 and 11.

8 Section of undeveloped dorsal part of dorsolateral prostate from untreated, castrated non-adrenalectomized rat (group C). Weigert-van Gieson × 192.

9 Section of dorsal part of dorsolateral prostate from a castrated non-adrenalectomized rat injected daily for fifteen days with 3 mg cortisone (group C-Co1). There is stimulation of the epithelium and of the smooth muscle tissue around the acini. McManus' PAS-staining × 192.

10 Section of lateral part of dorsolateral prostate from untreated, castrated adrenalectomized rat (group CA). There are undeveloped acini with no papillary formations. McManus' PAS-staining × 192.

11 Section of lateral part of dorsolateral prostate from a castrated adrenalectomized rat, injected daily for fifteen days with 3 mg cortisone (group CA-Co1). The epithelium is rather high and there are papillary formations. Weigert-van Gieson × 192.
Fig. 13.
Section of coagulating gland from a castrated adrenalectomized rat injected daily for fifteen days with 9 mg cortisone (group CA-Coa). There is marked stimulation of the epithelium and of the smooth muscle tissue around the acini.
Weigert-van Gieson × 192.

Fig. 14.
Section of undeveloped seminal vesicle from untreated, castrated non-adrenalectomized rat (group C). Weigert-van Gieson × 192.
Fig. 15.

Section of seminal vesicle from castrated adrenalectomized rat injected daily for fifteen days with 9 mg cortisone (group CA-Co2). Note the well developed muscular coat, the high granulated epithelium and the secretion in the lumen.

Weigert-van Gieson X 192.

DISCUSSION

In the present experiments combined castration and adrenalectomy resulted in no greater degree of atrophy of the dorsolateral prostate, the coagulating glands and the seminal vesicles than castration alone. Thus the adrenals do not seem to have any maintenance effect on these organs in the castrated rat. The ventral prostate, however, was still more immature after combined castration and adrenalectomy than after castration alone. It is known that the ventral prostate is more sensitive than the seminal vesicles to small quantities of most androgens (cf. Hershberger et al. 1953). The results may indicate that androgens sufficient to give some stimulation of the ventral prostate are secreted from the adrenals of castrated rats.

Cortisone in daily doses of 3 mg caused a small but significant weight decrease of the ventral prostate in castrated non-adrenalectomized rats as compared to non-treated control rats. Without histological differences no conclusion can be drawn from this finding. After cortisone in daily doses of 9 mg there were histological signs of stimulation of the ventral prostate both in the castrated non-adrenalectomized and in the castrated adrenalectomized rats. But there were no constant signs of secretory activity and the mean weights did
not exceed that of castrated non-adrenalectomized control rats. Thus cortisone in the larger dose had a weak growth stimulating effect on the ventral prostate.

Cortisone stimulated the growth of the dorsolateral prostate, the coagulating glands and the seminal vesicles of both castrated non-adrenalectomized and of castrated adrenalectomized rats. Lostroh & Li (1957) found that the administration of a daily dose of 0.050 mg ACTH containing 20–25 IU/mg during ten days was effective in stimulating the growth of the ventral prostate and the seminal vesicles in castrated hypophysectomized rats. That a daily dose of 0.065 mg had no effect was attributed to antianabolic or catabolic effects accompanying «the hypercorticoid condition». Catabolic or antianabolic effects after cortisone administration in the present investigation were evident as shown by the decrease of body weight and weight of the levator ani muscle. But in the present experiments these effects did not prevent the growth stimulating effect of cortisone on the accessory reproductive organs. Actually the growth of the accessory reproductive organs was most pronounced after the larger dose of cortisone.

Throughout the investigation it was found that whenever cortisone stimulated the growth of the accessory reproductive organs the epithelium as well as the muscular layers around the acini were better developed. It was impossible, however, to judge whether the growth of the fibrous stroma was also stimulated as it constitutes a much larger proportion of the unstimulated gland than of the stimulated gland. This, however, does not dispute the possibility that it may have increased in amount after cortisone administration. That the growth of the smooth muscle tissue was stimulated by cortisone is contrary to the opinion of Arvola (1961) who, after his histoquantitative studies, concluded that the stimulation by cortisone on the growth of the prostatic lobes of castrated rats was different from that of testosterone, as the amount of connective tissue and muscular tissue did not increase after cortisone administration. Furthermore, Delost (1953) found that cortisone could stimulate the growth of the epithelium of the ductus deferens in castrated adrenalectomized field vole whilst the muscular layer remained unaffected, whereas testosterone propionate caused thickening of the muscular layer. In this connection it is interesting that Franks & Barton (1960) found that epithelial cells of the mouse prostate in tissue culture reacted to androgens only if all the components grew and functioned as a unit, whilst those epithelial cells which grew at the border of the culture, isolated from other tissue components, showed no reaction.

Important differences have been observed between different androgens on the basis of their effect on the growth of the seminal vesicles and the ventral prostate in castrated rats. Thus, the administration of testosterone propionate results in a similar degree of growth stimulation in both organs, while androsterone and dehydroepiandrosterone have a more marked effect on the ventral prostate than on the seminal vesicles (Hershberger et al. 1953). That the
ventral prostate of the castrated rat is less responsive to cortisone than the dorsolateral prostate, the coagulating glands and the seminal vesicles is particularly noteworthy. **Saunders (1958)** found that the administration of oestrone to castrated rats resulted in similar effects on the weights of the ventral prostate and the seminal vesicles as was found after cortisone in the present investigation. The increase in the growth of the seminal vesicles after oestrone administration has been shown to be due to the increased growth of fibromuscular tissue rather than of secretory epithelium (*Korenchevsky & Dennison 1935*). In no experiment so far performed have oestrogens been found to induce secretory activity of the accessory reproductive organs of castrated male rats (cf. **Price & Williams-Ashman 1961**). On the other hand cortisone in the present investigation gave marked stimulation of growth and secretory activity in the seminal vesicles as well as in the dorsolateral prostate and the coagulating glands.

Most of the in vivo studies of cortisone metabolism have been concerned with human subjects. If cortisone acetate is administered to man, two to five per cent are excreted as 17-ketosteroids, mainly of the aetiocholane series (Gemzell et al. 1953). These compounds have not been reported to be androgenic (cf. **Dorfman & Shipley 1956**). The metabolism of cortisone to androstan derivatives has been indicated but the quantities isolated have been small as compared with the amount of aetiocholane derivatives found (cf. **Dorfman & Shipley 1956**). One of the androstan derivatives found, 11β-hydroxy-androsterone, has an androgenic effect about one quarter of that of androsterone as determined by a chick comb method (Miller et al. 1946). There is no known study about its effect on the accessory reproductive organs of male rats. Thus, no definite conclusion can be drawn as to whether cortisone per se or some of its metabolites were responsible for the effects on the accessory reproductive organs.

Some of the effects of cortisone may be secondary. **Houssay et al. (1954)** and **Yoshinaga et al. (1967)** found that cortisone gave rise to an increase in the number and size of pancreatic isulae in rat. In Chinese hamster cortisone administration has been found to markedly increase serum insulin levels (Campbell et al. 1966). From the result of a previous investigation it has been concluded that insulin deficiency was responsible for the smaller stimulating effect of testosterone propionate on the accessory reproductive organs of castrated male alloxan-diabetic rats as compared with non-diabetic rats (Angervall et al. 1967). It has also been found that insulin stimulates the growth of the accessory reproductive organs of castrated male rats in the presence of morphological signs of increased secretion of adrenal steroids (Tisell & Angervall 1969). Furthermore, evidence of an effect per se of insulin has been obtained by **Calame & Lostroh (1964)** who found that insulin could restore the histological picture and stimulate protein synthesis in the ventral
prostate of castrated male mice in vitro. Hence in the present experiments, an increased production of insulin has possibly contributed to the stimulated growth of the accessory reproductive organs.

There is some evidence that hypophyseal growth hormone and prolactin have a direct effect, not mediated through the testis, on the accessory reproductive organs of male rats. The growth promoting effect of testosterone on the accessory reproductive organs of castrated male rats is less marked after hypophysectomy (Grayhack et al. 1955; Van der Laan 1960). Hypophyseal growth hormone (Huggins et al. 1955; Lostroh 1962) and prolactin (Grayhack et al. 1955; Grayhack 1963) enhance the growth promoting effect of testosterone on the accessory reproductive organs in these rats. A synergism between hypophyseal growth hormone, prolactin and testosterone has also been demonstrated (Chase et al. 1957). Experiments have been reported on the effect of glucocorticoids on the secretion of hypophyseal growth hormone and prolactin in the rat. In experiments by Pecile & Müller (1966) cortisol decreased hypophyseal growth hormone release in rat after insulin induced hypoglycaemia, as shown by the tibia test in hypophysectomized rats. Furthermore, Birge et al. (1967) by an immunoassay technique found that cortisol decreased the release of hypophyseal growth hormone from the isolated rat adenohypophysis in vitro. From their results they also assumed that the synthesis of hypophyseal growth hormone was affected by the presence of cortisol in the incubation medium. Johnson & Meites (1955) found that cortisone administration to female rats increased prolactin levels in the pituitary gland and initiated mammary secretion. However, no conclusion can be drawn as to whether cortisone in the present experiment induced changes in the secretion of hypophyseal growth hormone and/or prolactin that could have influenced the growth of the accessory reproductive organs.

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REFERENCES


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Teller J. D.: Abstr. of Papers. 130th Meeting Amer. chem. Soc. (1956) p. 69 C.

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