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## VOLUME XCIV, FASCICULE IV

## AUGMENTOR EFFECT OF HYPOPHYSIS-EXTRACT AND ADRENAL-EXTRACT (CORTINE) ON THE PREPUTIAL GLANDS OF RATS

BY

R. KOOIJ

With statistical analysis by ANN M. J. A. VERBEEK

(Arch. int. Pharmacodyn.)

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FROM THE PHARMACO-THERAPEUTIC LABORATORY OF THE UNIVERSITY  
OF AMSTERDAM. HEAD : AT THE TIME PROF. DR E. LAQUEUR

## AUGMENTOR EFFECT OF HYPOPHYSIS-EXTRACT AND ADRENAL-EXTRACT (CORTINE) ON THE PREPUTIAL GLANDS OF RATS

BY

R. KOOIJ

With statistical analysis by ANN M. J. A. VERBEEK <sup>(1)</sup>

*(Received for publication 7-3-53).*

In 1933 FREUD and OESTREICHER (1) studied the effects of a combination of a pituitary with an adrenal extract on normal immature male rats. Despite the limited number of their observations, they found indications that cortine enhanced the hypertrophic action of the pituitary extract on the preputial glands.

During 1933-34 these investigations were carried further by the author but the results were, for various reasons, not published at the time. However, since the problem is still a relevant one, it was decided nevertheless to publish the findings now.

The experiments were conducted on normal immature and mature male and female rats, and also on adrenalectomized and castrated male and female rats. The animals were treated for periods varying between 7 and 9 days. Table I shows the results of these experiments.

The average of the relative weights (prep. gland wt./body wt.) of the preputial glands of all the animals used suggested the following :

1. cortine alone causes no increase in the weight of the preputial gland.
2. a pituitary extract does bring about an increase in weight of the gland.
3. when cortine is injected simultaneously with the pituitary extract, it enhances the aforementioned action produced by the pituitary extract alone (augmenting effect).

<sup>(1)</sup> Statistical Department, Mathematisch Centrum, Amsterdam. Head : Prof. Dr D. v. DANTZIG, Chief statistical consultation : Prof. Dr. J. HEMELRIJK.

TABLE I

Group	Condition rat	Sex	Number of animals per group	Mean value pr. gl. weight/body weight				Amount of hypophysis-extract	Amount of cortine	Weights rats gr.
				Controls	Hypophysis-extract	Hypophysis-extract and cortine	Cortine			
II	normal	male	3	0,42	0,73	0,85	0,63	7 × 0,1 ml. 150 mgr./ml.	7 × 0,5 ml.	62-145
IV	normal	female	3	0,65	0,53	0,83	0,50	9 × 0,1 ml. 150 mgr./ml.	9 × 0,5 ml. S 242	105-145
VII	normal	female	6	0,30	0,62	0,82	0,37	8 × 0,2 ml. 200 mgr./ml.	8 × 0,75 ml. S 242	40-61
III	adrenal-ectomized	male	3	0,66	0,76	0,96	0,58	7 × 0,1 ml. 150 mgr./ml.	7 × 0,5 ml. S 242	65-143
V	adrenal-ectomized	female	3	0,39	0,55	0,59	0,50	9 × 0,1 ml. 150 mgr./ml.	9 × 0,5 ml. S 242	86-130
IX	castrated	female	6	0,32	0,42	0,69	0,21	8 × 0,2 ml. 200 mgr./ml.	8 × 0,5 ml. S 251	34-52
X	castrated	female	8	0,17	0,32	0,36	0,26	8 × 0,2 ml. 200 mgr./ml.	8 × 0,5 ml. S 251	35-54
XI	castrated	male	5	0,16	0,23	0,26	0,17	8 × 0,2 ml. 200 mgr./ml.	8 × 0,5 ml. S 251	49-70
XIII	castrated	male	8	0,36	0,41	0,49	0,30	8 × 0,2 ml. 200 mgr./ml.	8 × 0,5 ml. S 251	30-59
Total Weighted mean			45	0,34	0,47	0,60	0,34			

These results were further subjected to a statistical analysis.

It had first to be decided whether any clear relationship existed between body weight and the weight of the preputial gland. In Fig. 1 the final body weight of each control animal was plotted against the weight of the preputial gland. A clear correlation is shown, in that the preputial gland increases in weight with the body weight. However, the observations are derived from a very inhomogeneous group of animals.

### CONTROLS

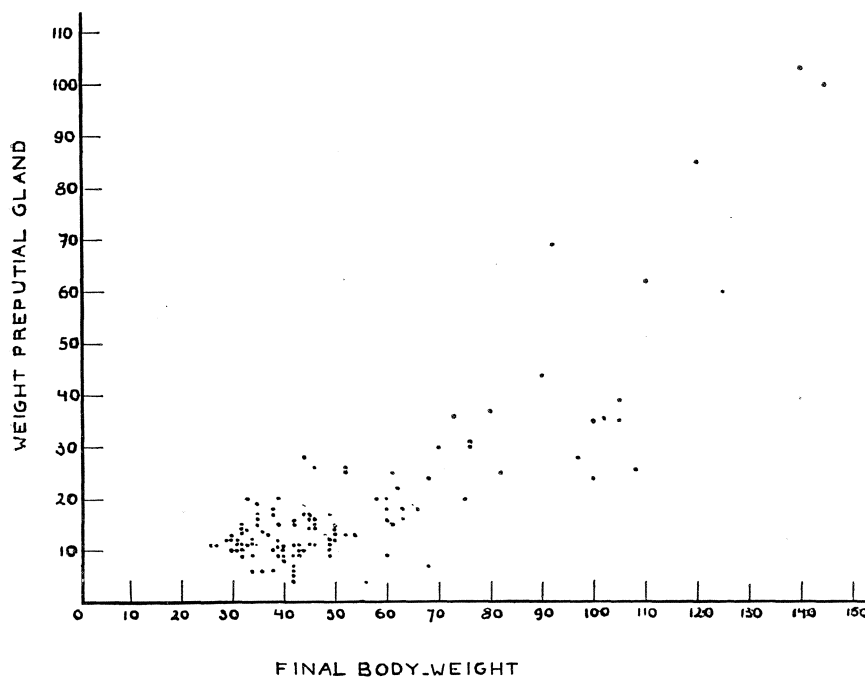


FIG. 1

Some of the subgroups do not show this correlation clearly at all. A further investigation of the groups separately would be necessary, to elucidate the matter, but the number of observations do not allow such an analysis. The correlation can not be neglected of course.

Especially when endeavouring to decide if a particular substance causes an increase in size of the preputial gland, it is essential that the groups of animals to be compared should agree sufficiently with one another as regards body weight.

The groups of animals were very small (3-8 rats). Combination of

the different groups was hardly justified, granting the divergences in physical constitution (normal, castrated, adrenalectomized), age and sex, and also the fact that they had undergone different types of treatment. Even a combination of the two groups of castrated immature male animals was not warranted, since the body-weight and the weight of the preputial gland were different for these two groups (even significantly so, according to WILCOXON'S test ; 2, 3) : the same applies to some of the groups of the castrated female animals.

In order to eliminate these differences from the statistical analysis without prejudice to the result, the analysis was applied to each of the small groups separately, and subsequently these were combined. This was carried out as follows : the value  $U$  of WILCOXON'S test was first calculated for each group individually. Next, the sum  $U'$  of all the  $U$ -values thus obtained was calculated ( $U' = \sum U$ ), the expectation of  $U'$  being the sum of the expectations ( $E U' = \sum E U$ ) and the variance being equal to the sum of the variances ( $\sigma_{U'}^2 = \sum \sigma_U^2$ ). The normal approximation for the distribution of  $U'$  under the hypothesis tested may then be used, large and small values of  $U'$  being critical values (two-sided test).

The factor of body weight was eliminated as far as possible by dividing the larger groups into 2 or 3 subgroups, containing the smallest possible divergences in body weight, and in so doing we tried to create subgroups to be compared containing about the same number of animals. Among the smaller groups, where such a subdivision was impossible (3 animals), only those groups were selected in which the factor of weight would definitely not have tended to work towards the expected experimental result. Where necessary and justifiable, i.e. if a deceptive conclusion might result from some especially heavy or light animal in a group, this animal was eliminated.

## RESULTS

A comparison of the group of cortine-treated animals with the controls revealed no evidence of an influence of cortine on the weight of the preputial glands. The tail-probability calculated by the above technique was  $P = 0,87$ .

By comparing the animals treated with pituitary-extract and the controls, a tail-probability of  $P < 10^{-6}$  was found, from which it must be deduced that pituitary-extract increases the weight of the preputial glands.

Comparison of the animals treated with pituitary-extract and also with cortine with the controls revealed again that a decided increase in the weight of the preputial glands had taken place ( $P < 10^{-6}$ ).

Comparing of the animals treated with pituitary extract with those which had also received cortine, a tail-probability of  $P = 0,006$  was found, whereby the weight of the preputial gland was shown to be higher in those animals to which both substances had been administered than in those which had only received the pituitary extract.

Since there was a possibility that the increase in weight of the preputial glands might have been due to the presence of growth hormone in the pituitary extract, this matter had also to be investigated.

For this purpose, the increase in body weight of the animals treated with pituitary extract from the beginning to the end of the experimental period was compared with the increase in weight over the same period of the control animals treated with saline solution, and the results were calculated in the way described above. A tail-probability of  $P = 0,28$  was thus obtained.

Comparing the increase in weight of the animals treated with pituitary extract and cortine with the controls, the tail-probability was  $P = 0,37$ . In this last instance the increases in weight of the control animals were in general somewhat higher than those of the treated animals.

Consequently, there was no evidence from the experimental data that the increase in weight of the preputial glands resulted from the action of growth hormone in the pituitary extract.

#### CONCLUSIONS

1. There is no evidence that the weight of the preputial glands of the rat can be influenced by the administration of cortine alone.
2. Hypophyseal extract, under the same experimental conditions, produces an increase in weight of the preputial glands.
3. If cortine is given to rats, in the way described, simultaneously with the administration of the pituitary extract, the cortine tends to enhance the action of the pituitary extract mentioned in "2" above.
4. In the material examined there were no grounds for supposing that the increase of weight of the preputial gland following the administration of pituitary extract was due to the presence of growth hormone in the extract.

## COMMENT

The above conclusions are only valid in general, and by no means indicate that each particular group (normal, adrenalectomized, castrated, male and female) reacted in the same way. In particular the groups of animals were too small to warrant reliable conclusions on the augmenting effect in each group separately.

Finally, to determine whether the augmentor effect could not possibly be brought about by extracts of other organs, a series of experiments was conducted in which a pituitary extract together with a liver extract as well as the pituitary and liver extracts individually were given to groups of normal and castrated immature male and female rats. In each instance a control series was treated with saline solution. The liver extract, which was prepared in the same way as the adrenal extract used above (method of Swingle and Pfiffner), apparently contained a small amount of oestrone. However, there was no indication in the experimental material that the liver extract augmented the action of the pituitary extract ( $P = 0,52$ ). The liver extract alone failed to exert any perceptible action on the preputial glands ( $P = 0,10$ ).

In a few preliminary tests the administration of cortine and pregnyl seemed not to produce any augmenting effect on the preputial glands in normal and adrenalectomized immature male rats.

Following the investigation on the preputial glands, some preliminary studies were made of the effects upon the uterine mucosa, by measuring the protoplasmic margin in relation to nuclear size (ocular micrometer and oil immersion). There were indications that the pituitary extract exerted a hypertrophic action on the uterine epithelium of normal female rats. The same effect, in approximately the same degree, was also seen in castrated females, showing that it was not mediated by the ovaries. There was no suggestion of an augmenting action of a combination of pituitary extract and cortine on the uterine mucous membrane. However, the number of observations was too small to establish this with certainty.

In castrated male rats the pituitary extract failed to show any effect on the epithelium of the seminal vesicles as on their weight.

No studies were carried out on the seminal vesicles in respect of an augmentor effect of pituitary extract and cortine.

No oestrone could be demonstrated in the cortine preparation (level  $1/5$  M.U. per ml.).



The pituitary extracts used were mostly aqueous, but on some occasions an ammoniacal extract was used.

From other experiments it appeared that these extracts also possessed a gonadotropic action (according to EVANS), thyrotropic action (also in castrates, FREUD c.s. (1), and also an adrenotropic action.

In conducting these experiments it was not known whether the pituitary extract used also contained the growth hormone. From our results this possibility appears to be remote.

The cortine preparation was made according to the method of Swingle and Pfiffner (1 ml. = extract of 50 gm. suprarenal). The preparation was active in promoting recuperation from muscular exhaustion [treadmill test KOOIJ, (4), EVERSE and DE FREMERY, (5)] and it could prolong the life of adrenalectomized rats.

In the literature several reports have appeared concerning an enhancing hypertrophic action of certain hormones when administered in combination with pituitary extract on the preputial glands of the rat. FREUD (6) found this to be the case with androgenic and oestrogenic substances given with a pituitary extract. Experiments using the pituitary extract alone were not performed. NOBLE and COLLIP (7) described: "an augmentation of the effect of pituitary corticotropic extracts by the simultaneous injection of other extracts of the pituitary, especially by a dilute saline suspension of the whole gland in the preputial glands of normal female rats. According to the authors the augmented stimulation of the preputial glands was mainly an indirect one through the adrenal or ovaries depending on the extract.

Recently SELYE and CLARKE (8) reported an augmenting action of the effect of a pituitary extract on the preputial glands produced by certain "testoids" (e.g.  $\Delta^5$ -pregnenolone) in normal, hypophysectomized and castrated female rats. In this last publication Selye describes an augmenting effect of growth hormone and cortine on the preputial glands of normal female rats.

There appeared to be no indication of the possibility in our material that the augmentor effect of pituitary extract ought to be attributed to the growth hormone.

#### SUMMARY

An augmentor effect of hypophysis-extract and adrenal-extract (cortine) was shown on the weight of the preputial gland in rats.

There were no grounds for supposing that the hypophysis-extract contained an active amount of growth hormone.

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