10516 P

Production of Antihormones by Prolonged Administration of Pituitary Extract. Effect on Anterior Hypophysis.

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A cytological study has been made of the hypophyses of 2 dogs and 2 sheep which had received prolonged injections of extracts of sheep-pituitary glands,* and of 2 dogs that had been injected with antihormone-serum. The striking physical changes in one of the dogs, namely, an atrophy of the thyroid, adrenals and gonads, a cessation of growth, and the development of obesity, have been reported elsewhere.[1]

The 2 dogs which were injected subcutaneously with the sheep-pituitary extract for 4 and 7 months respectively, developed antihormones which inactivated not only the injected pituitary extract, but also several of the hormones of their own hypophyses.

The 2 dogs which were injected daily with 10 cc of canine antihormone-serum showed signs of moderate inactivation of the gonads, thyroids and adrenals.

Twin ewes were injected with sheep-pituitary extract† daily for 6 months. Their genitalia and mammary glands continually showed signs of activation, and at autopsy their gonads and uteri were found to be stimulated. No gonadotropic antihormone developed. A half-sister of these ewes served as a control.

The hyophyses of the dogs injected with sheep-pituitary extract. The basophile cells show the most striking abnormalities consisting of: (1) a great increase in the size and number of the basophiles; (2) an excessive clumping and liquefaction of cytoplasmic granules; (3) the formation of many vacuoles of 3 different types: (a) clear round spaces containing a non-stainable substance or one removed by the technic employed; (b) scattered clear pale blue vacuoles which in some of the basophiles coalesced to become extensive vacuolar

* Prepared by a slight modification of a method by van Dyke and Wallen-Lawrence.

[1] Thompson, K. W., and Cushing, H., *Proc. Roy. Soc.*, B, 1934, **115**, 88.

† One ewe was injected with the van Dyke and Wallen-Lawrence extract, while the other was treated with an equal amount of an extract prepared from acetone-dried sheep hypophyses. This fact is important because of its relation to the matter of denaturation of the proteins in the extracts.

inclusions; (c) scattered deeply basophilic vacuoles which in some cells displaced the cytoplasm almost entirely.

In these widespread disturbances it is readily possible to demonstrate cells in which the vacuolation is identical to that of the typical castration cell, or again to that characteristic of total thyroidectomy. Still other cells show a combination of granular and liquefied areas which are indistinguishable from the hyalinization described by Crooke[2] as characteristic for the Cushing syndrome.

Certain acidophilic regions of the glands show small irregularly shrunken cells in varying stages of degranulation with pyknotic, deeply basophilic nuclei. Scattered among these are many chromophobic cells with exactly the same nuclear characteristics. These 2 cell types represent stages in an extensive reversion of acidophiles to chromophobes.

The hypophyses of the dogs injected with canine antihormone. These glands show 3 notable features: (1) a scarcity of the typical areas of chromophobe cells; (2) an almost total absence of normally granulated basophilic cells, many of the cells containing the hyaline material similar to that described by Crooke; and (3) marked hyperemia and edema.

In many of the basophile cells there is a large Golgi zone which together with an increase in mitochondria leads to the interpretation that these cells are active in the production and release of a secretory product. The predominance of these cells and the absence of chromophobes indicates an unusual force demanding maturity of basophiles. In other regions cells with the Crooke changes predominate.

There is without question an active degranulation of some basophilic cells into the edematous areas surrounding the capillaries or (in places) continuous with them.

The hypophyses of the injected ewes. The most striking change is a degranulation of the basophile cells in which mitochondria and Golgi apparatus are prominent. The acidophiles are increased in size, compactly granulated, and stain more brilliantly than do those of the control. Also there are areas with small acidophiles with pyknotic nuclei. These glands give cytological evidences in both the basophilic and acidophilic cells that the secretory activity is considerably increased over the normal.

The most important of the findings may be enumerated as follows: (1) The "Crooke changes" heretofore described only in the human pituitary gland have been experimentally produced in dogs, most prominently in the hypophyses of the dogs injected with the

2 Crooke, A. C., *J. Path. and Bact.*, 1935, **41**, 339.

canine antihormone. (2) The changes in basophiles characteristic of both castration and thyroidectomy were observed in the hypophyses of the long-time injected dogs. (3) The presence of basophilic granules in the perivascular spaces and in the capillaries has been observed.

It is possible that the following reactions occurred in sequence during the course of prolonged injections of the sheep-pituitary extract: (1) An initial activation of the endocrine glands subsidiary to the pituitary gland occurred. In the sheep this process continued for the entire 6 months of injections. (2) The increased secretion of the subsidiary glands in turn activated the hypophyseal function. (3) The foreign protein linked to the injected sheep-extract gradually produced in the dogs a tissue and humoral resistance (antihormones), which ultimately inactivated the injected sheep-extract as well as certain pituitary hormones of the injected animal itself. (4) Thus, the antihormones produced a state of physiological hypophysectomy, which caused subsequent atrophy of the subsidiary glands. (5) The atrophy of the thyroid and gonads (and adrenals?) produced the final changes in the hypophyses characteristic of gonadectomy and thyroidectomy (and adrenalectomy?).

The Crooke changes characteristically found in the Cushing syndrome, associated with a diminished function of the gonads and thyroids, are believed to be related in some way to the effects of the inactivation of the subsidiary endocrine glands by the antihormone in these animals.

10517

A Case of Delayed Ovulation After Estrin Administration in the Intact Monkey.*

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In the course of experiments designed to throw light on the hormonal basis of sex behavior a case of ovulation was encountered which was apparently delayed by the injection of estrin during the first part of the menstrual cycle. This occurred in monkey No. 634 which had been menstruating regularly (Sept. 22, Oct. 19, Nov. 19, Dec. 27, 1938, and Jan. 26, 1939). Ovulation, diagnosed by palpa-

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