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Studies of the Relation of the Pituitary to Watermetabolism.

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Recent studies of Hoff and Wermer[1] reveal the presence of increased quantities of pituitary hormone in the cerebrospinal fluid after administration of diuretics. They explain their observation of increased liberation of antidiuretic substances from the posterior pituitary lobe, as an attempt on the part of the body to prevent excessive loss of water. In other words, it is a compensatory process.

The following studies were made to reveal whether there are demonstrable changes in the hypophysis after the administration of diuretics and whether such changes precede or follow the loss of water.

The experiments were made on guinea pigs of the same breed and weighing from about 250 to 600 gm. Only male animals were used. We used novasurol in a dilution of 1 to 25 of the commercial preparation. One cc. was given subcutaneously to each animal. We kept the guinea pigs without food after the injection. They were killed at intervals of 20 minutes, 40 minutes and 1, 2, 3, and 6 hours. Their hypophysis was removed, fixed in Zenker's solution and studied histologically.

We determined the loss of water by weighing the animals before and after administration of the diuretics. Weighing was chosen as our method in order to account also for loss of water by ways other than diuresis.

Normal guinea pigs kept without food lose 3.5% of their body weight as an average within 6 hours. In contradistinction to this, the animals which were given novasurol lost 5.2% of their weight within the experimental period of 6 hours. These figures tallied well with those obtained on a series of white mice. The average loss of weight in normal mice kept without food for 6 hours was 3.6% whereas mice after the administration of novasurol lost 4.8% weight in the same time.

In removing the hypophysis of the guinea pigs we noticed that 40 minutes after novasurol was given, there was already a distinct hyperemia of the anterior lobe as compared with the controls. This was corroborated by the histological findings which showed wide

[1] Hoff, H., and Wermer, *Arch. f. exp. Path. and Pharm.*, 1928, cxxxiii, 84-87.

sinuses filled with blood in between the trabecles of the pituitary cells.

We could not determine any changes in the structure of the posterior lobe but in the anterior lobe there were changes which seemed to differ according to the time which had elapsed between the injection of novasurol and the killing of the animal. These changes involved alteration of the size of the chromophil cells, the quantity of their granules, the relation of chromophil cells to chief cells, the relation of eosinophils and basophils and finally the appearance of vacuoles in the cell bodies. These changes were already noticeable to a certain extent after 20 minutes, they were well marked after 40 minutes and could be observed throughout the experimental period. The most important feature seems to us the decrease in the number of eosinophil cells with a marked increase of basophils. This change persisted after 6 hours at which time most of the other alterations were subsiding. There was not only a decrease in the number of eosinophils but also in the quantity of eosinophil substance. Many cells showed only a crescent shaped eccentric eosinophil seam, while the rest of the cell body did not contain any chromophil substance. In other cells there appeared a perinuclear area of an amphophil or distinctly basophil color reaction. The late stage of these changes is particularly characterized by the appearance of numerous vacuoles in both types of chromophil cells. Moreover there were occasional large cells present with chromophobe cytoplasm which may also contain vacuoles.

These changes are quite comparable to those seen in other glandular organs whose function has been stimulated. They apparently express increased activity, such as the discharge of glandular cell products. Therefore it seems that the injection of novasurol acts as a stimulant upon the cells of the anterior pituitary. This effect is noticeable at a time preceding the onset of the diuresis, at least if we take the accepted figures which show that diuresis follows 45 minutes after the injection of the diuretic and reaches its maximum in from 1½ to 2 hours. (Hoff and Wermer). According to our experiments, however, there was a noticeable loss of weight in 20 minutes. This was possibly due to defecation and urination following the psychic effects of handling the animals.

We have repeated the same experiments on another series of animals to which theobromin was given instead of novasurol. The results were quite similar, showing that such changes of the pituitary can be obtained by diuretic substances of very different chemical character.

Comparing our observations with those of Hoff and Wermer we are impressed by 2 apparently paradoxical facts. First, that diuresis is accompanied by changes in the anterior lobe, whereas Hoff and Wermer determined the appearance of antidiuretic substances from what seemed to be of posterior lobe origin. Second, that these changes precede or at least coincide with the onset of diuresis. This would contradict the explanation of Hoff and Wermer according to whom the pituitary discharges its hormone in order to check a further loss of water.

The rôle of pituitary activity in the production of diuresis permits of two different explanations. It is known since the first contributions of Magnus and Schaefer[2] that pituitary extracts occasionally produce diuresis instead of oliguria. Frank,[3] Oehme,[4] Fromherz,[5] Pentimalli[6] and others maintain that the effect of these extracts is biphasic, i. e. intravenous administrations of large amounts produce diuresis, while slow or subcutaneous infusion of small amounts yields oliguria. This reminds us of the biphasic reactions obtainable with adrenalin. Yet Cow[7] has demonstrated the appearance of a diuretic substance in the cerebrospinal fluid of animals, the pituitary of which had been stimulated by injection of duodenal extracts. Moreover, the observations of von Hann[8] from Goldzieher's laboratory have shown that in cases of diabetes insipidus due to lesions of the posterior lobe, polyuria ceases terminally if the lesion gradually encroaches upon and destroys the anterior lobe. This would suggest the production of a diuretic substance by the cells of the anterior lobe antagonistic in its effect to the product of the posterior lobe. The experiments presented here are in favor of this conception, yet further evidence seems necessary before the diuretic function of the anterior lobe can be recognized.

Our observations gain additional interest in view of the autopsy findings of Kraus,[9] Berblinger[10] and others who observed a considerable increase in the number of basophil cells in the pituitary in cases of hypertension and particularly of chronic renal disease.

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[2] Magnus and Schaefer, as quoted by Hoff and Wermer.

[3] Frank, E., *Klin. Wochensch.*, 1924, iii, 847, 895.

[4] Oehme, C. and M., *Deutsch. Arch. Klin. Med.*, 1918, cxxvii, 261.

[5] Fromherz, K., *Arch. f. exp. Path. and Pharm.*, 1923, c, 1.

[6] Pentimalli, F., *Sperimentale*, 1921, lxxv, 145.

[7] Cow, D., *J. Phys.*, 1914, xlix, 367, 441.

[8] von Hann, F., *Frankf. Z. f. Path.*, 1918, xxi, 337.

[9] Kraus, E. J., *Virch. Arch.*, 1923, ccxlvii, 421.

[10] Berblinger, W., *Virch. Arch.*, 1929, cclxxv, 230.