10031

Action of Oestrin and Progesterone on the Anterior Pituitary.

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The reciprocal relationship between the gonads and the anterior pituitary has been the subject of investigation from several angles. Not the least interesting of these is the study of the action of the gonad hormones on the hypophysis, from the point of view of prevention of castration changes and from that of producing cytological changes and macroscopic enlargement in normal and castrate animals. The action of oestrin in this respect has been well established, both as regards the repair of castration changes (Hohlweg and Dohrn,[1] Haterius and Nelson[2]) and production of hypertrophy (Hohlweg,[3] Nelson,[4] Wolfe[5]). The position with regard to the luteal hormone is less clear. Hohlweg and Dohrn[6] report that while 5 to 6 rat units of oestrin daily were necessary to prevent the castration changes in the pituitary of adult female rats, only one rat unit daily was necessary if 0.2 rabbit units luteal hormone were given simultaneously. In 1935, however, Hohlweg, working with crystalline progesterone, reported failure to prevent castration changes in the pituitaries of immature and adult female mice, while Clauberg and Breipohl,[7] using an impure progesterone alone, obtained inhibition of the castration changes in the pituitaries of adult female rats with 7.5 rabbit units daily. While the results of Clauberg and Breipohl might be explained on the grounds of contamination of the sample of luteal hormone with oestrin or androsterone, the earlier experiment of Hohlweg and Dohrn could be explained only on the grounds of a synergism between oestrin and progesterone. The following experiments were made to obtain evidence for or against the synergistic effect and at the same time to obtain data on the effect of progesterone alone.

Two series of experiments were made, differing only in the oestrogen used and the duration of treatment. In each case, 4 groups

1 Hohlweg, W., and Dohrn, M., *Klin. Wchnschr.*, 1932, **11**, 233.
2 Haterius, H. O., and Nelson, W. O., *J. Exp. Zool.*, 1932, **61**, 175.
3 Hohlweg, W., *Klin. Wchnschr.*, 1934, **13**, 92.
4 Nelson, W. O., *Endocrinol.*, 1934, **18**, 33.
5 Wolfe, J. M., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 757.
6 Hohlweg, W., and Dohrn, M., *Wien. Arch. inn. Med.*, 1931, **21**, 337.
7 Clauberg, C., and Breipohl, W., *Klin. Wchnschr.*, 1935, **14**, 119.

of 10 3-month-old virgin female rats were taken, and ovariectomized to avoid interference with the results by gonad hormones from the animal's own ovaries. On the day following castration, treatment with solutions in oil of the crystalline hormones was begun. Group A in both series received 500γ progesterone in 0.25 cc of oil daily; group B in the first series, 300γ ketohydroxyoestrin and in the second series, 100γ dihydroxyoestrin in the same volume of oil daily; group C, the same dosage of progesterone and of the oestrin appropriate to the series; while group D remained untreated as controls. After 10 days' treatment in the case of the first series, and 14 days in the second, the rats were killed and the pituitaries removed and weighed. Histological sections of the pituitaries of the animals in series 2 were stained by a modification of Mallory's aniline-blue orange G method and examined for castration changes.

The weights of the pituitaries are given in Table I.

TABLE I.
Pituitary Weight (mg).

Castrate Females	Series I Ketohydroxyoestrin		Series II Dihydroxyoestrin		Histology Castration Cells
	Avg	Range	Avg	Range	
Untreated controls	9.8	6 -12	9.5	7-12	+
Progesterone-treated	11.4	8.5-14	10.3	8-13	—
Oestrin-treated	14.9	9 -26	15.7	10-18	—
Oestrin + progesterone-treated	18.1	11 -23	18.7	15-25	—

It can be seen that significant differences exist among the 4 groups. The pituitaries of the untreated castrates do not show the enlargement characteristic of castration which is not usually well developed until after the 14th day from operation, and this factor does not therefore enter into the consideration of the results. The progesterone-treated animals show a slight increase of pituitary weight, which may be significant as the dose of 500γ progesterone is not high in comparison with the dosage of oestrin necessary to produce hypertrophy. The pituitaries of the oestrin-treated animals are markedly increased in weight though the average value of 14.9 mg in Series I is raised by 1 mg on account of the isolated occurrence in the group of a pituitary weighing 26 mg. The remaining values in the group lie between 9 and 17.5 mg, giving an average of 13.8 mg. The weights of the pituitaries of the oestrin plus progesterone-treated group are clearly higher than those of the other groups, presenting good evidence for the existence of the postulated synergism.

The histological findings are summarized in the last column of the table. Well marked castration changes were seen in the untreated controls and similar changes were also noted in the pituitaries of another group, not described, killed 7 days after castration. These changes were absent from the 3 other groups. It appears from this result that progesterone, even in this moderate dosage, has a definite inhibitory effect on the castration changes in the pituitary, and its action is continued over a period in which the departure from normal would have been quite distinct.

The physiological significance of these actions of progesterone is not at present obvious. It may be noted, also, that progesterone is evidently not an essential factor in the production of pituitary hypertrophy. The enlargement can be set up in castrate animals by oestrin alone, and can be continued for a long period in absence of the ovaries, as is shown by the following experiment.

Each of 24 3-month-old female rats was given 100γ of dihydroxyoestrin daily in 0.25 cc oil, the dose being increased to 150γ at the end of 14 days. Vaginal smears were made daily. On the 7th day of treatment, the rats were ovariectomized, when the ovaries were found to have large active corpora lutea. It was noted, confirming the observation of Selye, Collip and Thomson,[8] that the vaginal smears did not become cornified until 5 to 8 days after the operation. Six rats were killed on the 14th, 21st, 28th, and 35th days of treatment. It was found that the pituitary weights continued to increase with the oestrin treatment. The averages of the successive groups killed were: 14.3 mg, 17.4 mg, 23.5 mg, and 26.3 mg. In spite of these findings, the possibility of progesterone being an important factor in the gonad-hypophyseal relationship cannot be neglected, and further work on this problem is in progress.

Summary. It has been shown that 500γ progesterone daily will prevent castration changes in the hypophysis of 3-month-old female rats, and that the same dosage will enhance the action of oestrin in causing macroscopic enlargement of the pituitary.

[8] Selye, H., Collip, J. B., and Thomson, D. L., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1377.