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Mammary Gland Development in the Hypophysectomized Albino Rat.*

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Numerous investigations on mammary gland development in recent years have indicated that the ovarian hormones, estrone and progestin, are responsible for the growth of the glands. However, since increasing knowledge of the physiology of the pituitary gland seems to give it a central position in the endocrine system, investigators have become interested in determining whether or not the mammary glands could be experimentally developed in hypophysectomized animals.

Pencharz and Long[1] who hypophysectomized rats in late pregnancy (20th and 21st days) concluded that mammary development continued in the absence of the pituitary. However, at this stage of pregnancy growth is complete and lactation is being initiated. In fact, Selye, Collip and Thomson[2] observed that milk secretion always set in normally after parturition, but stops after a few hours, in rats hypophysectomized during the latter half of pregnancy. The mammary glands of rats hypophysectomized during the second half of pregnancy have been studied cytologically by Jeffers.[3] The epithelial cells were observed to resemble those of glands from normal pregnant animals. These studies appear to indicate that the development of the mammary gland which normally occurs during the second half of pregnancy can continue in the absence of the pituitary. However, lactation fails within a few hours after parturition. Selye, Collip and Thomson[4] found that the continued application of large doses of estrone in lactating

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1 Pencharz, R. I., and Long, J. A., *Am. J. Anat.*, 1933, **53**, 117.

2 Selye, H., Collip, J. B., and Thomson, D. L., Proc. Soc. Exp. Biol. and Med., 1933, **30**, 589.

3 Jeffers, K. R., *Am. J. Anat.*, 1935, **56**, 279.

4 Selye, H., Collip, J. B., and Thomson, D. L., Proc. Soc. Exp. Biol. and Med., 1935, **32**, 1377.

rats failed to lead to repair of the rapid involution of the mammary gland which takes place after hypophysectomy. They were of the opinion that the presence of the pituitary gland is necessary for the action of estrone upon the mammary glands.

Although the above studies indicate that the hypophysis plays no part in the development of the mammary glands during the second half of pregnancy, and that it may play some rôle in preventing the rapid involution of lactating glands, they bring us no closer to an understanding of the part played by the pituitary gland, if any in the growth of the mammary gland. Ruinen,[5] in injecting hypophysectomized male rats (90 to 120 gm. in weight) subcutaneously, twice daily for 14 days after operation, with 50 mouse units of crystalline menformon (keto-hydroxy-oestrin) in 0.1 cm. of oil, secured mammary development in 4 of these which was comparable with that which one usually sees in animals under the same menformon treatment with their hypophysis intact. Freud and De Jongh[6] treated a series of young castrated female rats the first two weeks with 100 International units of menformon per day. The animals were then hypophysectomized and during a following week they were treated with menformon and progestin. These investigators observed an extension of the alveolar system with side branchings along the ducts and concluded that the hypophysis of rats is not involved in the changes of the mammary glands produced by progestin. Asdell and Seidenstein[7] ovariectomized a series of rabbits and then kept them for 2 months to exhaust their supply of ovarian hormone. The animals were then hypophysectomized and the injections begun 2 months later. The rabbits were injected daily with 25 R. U. of progynon-B and 0.5 cc. of progestin (equal to about 4 rabbit units). The animals were injected for 15 days and then sacrificed. They state that the degree of development of the mammary glands was about the same in hypophysectomized animals as in those in which the hypophysis was not disturbed or was incompletely removed, and conclude that mammary gland development can occur in the absence of the hypophysis. Nelson[8] reported mammary development in 4 male hypophysectomized guinea pigs, treated with 40 R. U. of oestrone

[5] Ruinen, F. H., *Acta Brevia Neerl.*, 1932, **2**, 161.

[6] Freud, J., and De Jongh, S. E., *Acta Brevia Neerl.*, 1935, **5**, 47.

[7] Asdell, S. A., and Seidenstein, H. R., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 931.

[8] Nelson, W. O., PROC. SOC. EXP. BIOL. AND MED., 1935, **33**, 222.

daily, comparable to that observed in normal guinea pigs.[9] Lyons and Pencharz[10] secured nipple development in 4 hypophysectomized male guinea pigs which had been injected for 2 months with progynon-B, almost equal to that which they obtained in 6 normal male animals under similar treatment. However, there was only a limited growth of ducts and alveolar buds in the hypophysectomized animals in comparison to the functional alveolar development found in the injected intact males.

In order to further investigate whether or not the pituitary gland plays any rôle in bringing about the growth of the mammary gland when animals are under the influence of estrogenic substances, we have hypophysectomized a series of immature albino rats and subsequently treated them with varying amounts, 25 to 500 International units per day, of the benzoate of hydroxyestrin (Progynon-B§). Of the animals which were operated upon there were 5 females and 4 males which survived 15 days or longer and in which the pituitary gland had been completely removed as was revealed at autopsy. The results are summarized in Table I.

TABLE I.

Rat No.	Sex	Date of Birth	Date of Castration	Date of hypophysectomy	Date injections began	Dosage in I.U. per day	Days injected	Evidence of mammary gland growth
3	F	5-15	6-14	7-3	7-15	25	35	No
12	F	5-16	7-5	7-9	7-15	75	45	No
17	M	5-16	—	7-5	7-7	25	26	No
19	M	5-22	—	7-2	7-6	75	20	No
48	F	6-29	—	8-7	8-9	250	15	No
49	M	6-29	—	8-5	8-9	500	15	No
50	M	6-29	—	8-7	8-9	100	18	No
51	F	6-29	—	8-7	8-9	100	23	No
52	F	6-29	—	8-5	8-9	500	24	No

None of the mammary glands from these 9 hypophysectomized immature rats showed any evidence of growth. The duct system was limited and showed only few end-buds. In comparison with these mammary glands, the glands from control animals which had been castrated, subjected to similar treatment, but whose pituitary glands were intact and in animals whose pituitary glands were incompletely removed developed an extensive duct system with numerous end-buds. Even the mammary glands of 3 females

[9] Nelson, W. O., and Smelser, G. K., *Am. J. Physiol.*, 1933, **103**, 374.

[10] Lyons, W. R., and Pencharz, R. I., PROC. SOC. EXP. BIOL. AND MED., 1936, **33**, 589.

§ The Progynon-B used in this study was kindly supplied by Dr. E. Schwenk of the Schering Corporation.

whose ovaries were intact and in which injections were begun 2 to 4 days after hypophysectomy showed no mammary gland growth.

Conclusion: Progynon-B injected subcutaneously into 5 female and 4 male, immature, hypophysectomized albino rats in dosages varying from 25 to 500 International Units per day, produced no evidence of mammary gland growth.

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Action of Oestrin on the Vagina During Lactation.

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The injection of oestrin during lactation has resulted in contradictory opinions regarding the vaginal reaction. Previous experiments on the ovarian hormonal antagonism[1] have shown that the injection of 18, 10, 6, 4, and 2 rat units of oestrin, in oily solution, daily during the first 5 days of lactation always provoked typical oestrus as indicated by vaginal smears. Doses of less than one rat unit have demonstrated the existence of different thresholds of anti-luteinic action of oestrin, the vaginal reaction of oestrus being the first to appear.

Recently, Selye and co-workers have observed that doses of thirty micrograms of Oestrone, in oily solution, daily from the fifth to the tenth day of lactation have failed to provoke vaginal oestrus.[2, 3] They also reported that 100 or 500 micrograms of Oestrone, injected daily from the fourth to the fourteenth day, had no influence on the vaginal smear which remained typical of dioestrus. "The vaginal epithelium showed a high degree of mucification, a condition regularly seen in pregnancy but not in lactation." It seems difficult to accept this hypothesis of complete antagonism of corpora lutea to the vaginal reaction due to oestrin since a decidual reaction is not maintained under conditions of follicular dominance.

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* C. R. B. Educational Foundation Fellow.

1 Votquenne, M., *Compt. Rend. des Seances de la Soc. de Biol.*, 1934, **117**, 1121.

2 Selye, H., Harlow, C., and McKeown, T., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1253.

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