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Masculinization of the Female Rat by Gonadotropic Extracts.

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The original purpose of this investigation was to repeat an experiment of Selye and Collip[1] in which continuous vaginal estrus was obtained in immature rats treated with an anterior pituitary-like extract. Injections were started on the sixth day of age and continued until the thirtieth day but the dose employed was not stated. As a preliminary test, 8 six-day-old female rats were treated daily with 1 R.U. of anterior pituitary-like substance (Antuitrin-S). Vaginal patency occurred from the seventeenth to the nineteenth day of age but continuous estrus was not demonstrated by daily vaginal smears. When the dose was increased to 2 R.U. of Antuitrin-S daily, vaginal patency occurred from the fourteenth to the twentieth day but only 2 of 17 rats had continuous estrous smears. Daily doses of 5 R.U. induced vaginal patency from the sixteenth to the twentieth day but only 2 of 7 rats had smears suggestive of continuous estrus. Ten rat units daily resulted in continuous estrus in 7 of 8 rats treated. In this group the smears were continuously estrous from the fifteenth and seventeenth days, when vaginal patency occurred, until the termination of the experiment on the thirtieth day. The present report is concerned with a masculinizing effect that became more apparent as the trial doses were increased.

The animals used in this study were female rats selected at 6 days of age and made up in groups of 8 to standardize litter size and facilitate treatment. To date 24 of these selected litters have been treated and several others have been utilized as controls. Daily injections of gonadotropic substances were given from the sixth until the thirtieth day of age.

Definite masculinization as evidenced by hypertrophy of the clitoris occurred in 6 of 8 litters which received 2 R.U. of Antuitrin-S daily or its equivalent of Antophysin or A.P.L. The hypertrophy of the clitoris was evident after 10 days and increased with further treatment. The prepuce developed so that it could be drawn back to expose the clitoris. At 30 days of age the preputial glands were at least twice as large as those of the controls and an abundance of waxy

[1] Selye, H., and Collip, J. B., PROC. SOC. EXP. BIOL. AND MED., 1933, **30**, 647.

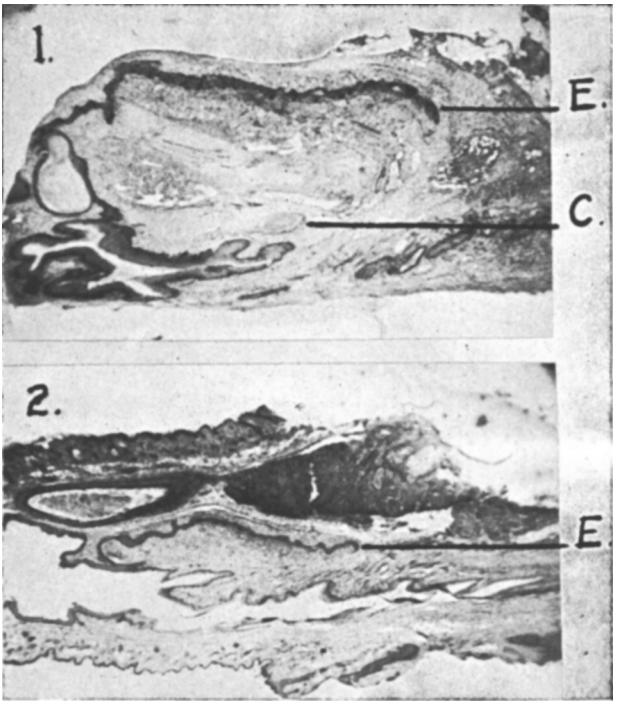

FIG. 1.
Median longitudinal section through the clitoris of a female rat 33 days of age treated with Antuitrin-S, 2 R.U. daily, from the 6th day of age. E. Epithelium of glans clitoridis. C. Cartilage.

FIG. 2.
Median longitudinal section through the clitoris and prepuce of a female rat 31 days of age, normal untreated control. E. Epithelium of glans clitoridis.

secretion was easily expressed. The glans clitoridis resembled a small glans penis and the horny spicules covering the glans were nearly as prominent as those in the male. The penile hypertrophy was limited to the glans and the cartilage anlage of the os priapi developed in the treated rats (Fig. 1). Ten R.U. of Antuitrin-S daily produced an even greater development of the clitoris.

To determine whether this masculinizing effect was peculiar to anterior pituitary-like preparations, 2 litters were treated with pregnant mare's serum (Gonadogen), 0.5 R.U. daily. The vaginæ were patent by the fourteenth day of age and the development of the clitoris and preputial glands was comparable to that of rats treated with 10 R.U. of Antuitrin-S. When 2 litters were treated with a pituitary extract (Prephysin), 5 R.U. daily, vaginal patency occurred from the sixteenth to the eighteenth day of age but there was no appreciable enlargement of the clitoris or preputial glands.

For comparison 2 litters were treated with estrone (Amniotin) and 2 with testosterone (Perandren). Ten international units of estrone were given on alternate days until the fourteenth day of age, when this dose was increased to 125 international units. Vaginal patency occurred on the sixteenth day and the vaginal smears remained consistently estrous during the period of treatment. There was no enlargement of the clitoris. Two litters were given 0.3 mg testosterone acetate on alternate days. The vaginæ were all patent by the fourteenth day of age but the smears were consistently diestrous. The development of the clitoris and preputial glands was greater in rats treated with testosterone than in those treated with Antuitrin-S or Gonadogen. The masculinization with testosterone was entirely comparable to that reported by Greene, Burrill and Ivy.[2]

Treatment with anterior pituitary-like extracts continued beyond 30 days of age did not cause any further increase in the size of the phallus. Cessation of treatment at 30 days was followed by some regression of the induced masculinization. The development of the clitoris and preputial glands was greatest in those rats in which the dosage was sufficient to induce continuous estrus. Apparently the infantile rat responds to gonadotropic treatment in a bisexual manner by producing effective amounts of both estrogenic and androgenic substances.

The results reported here are anticipated by Greene, Burrill and Ivy.[3] They may be comparable to those of Papanicolaou and Falk[4] and Guyenot and Naville-Trolliet[5] in which they induced masculinization of the female guinea pig by pregnancy urine and anterior pituitary extracts. The ovary was necessary to mediate the effect since pregnancy urine extract was not effective in ovariectomized guinea pigs. Domm[6] reported masculinization of the newly hatched chick by treatment with an anterior pituitary extract. The ovarian response in these young chicks was characterized by a marked hypertrophy of the medullary portion of the ovary and an absence of any follicular stimulation. It appeared that the medullary portion of the chick ovary was the probable source of androgenic hormone. A recent paper[3] suggests that the androgen produced by ovaries may be

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3 Greene, R. R., Burrill, M. W., and Ivy, A. C., *Endocrinology*, 1939, **24**, 351.

4 Papanicolaou, G. N., and Falk, E. A., PROC. SOC. EXP. BIOL. AND MED., 1934, **31**, 750.

5 Guyenot, E., and Naville-Trolliet, I., *Revue Suisse de Zoologie*, 1936, **43**, 415.

6 Domm, L. V., *Cold Spring Harbor Symposia on Quantitative Biology*, 1937, **5**, 241.

progesterone. In agreement with earlier reports there was no follicular maturation or luteinization in the earlier stages of treatment in our rats.

Summary. Gonadotropic extracts of human pregnancy urine or pregnant mare's serum cause masculinization of female rats if treatment is started at 6 days of age and continued until the thirtieth day. The hypertrophy of the clitoris, prepuce and preputial glands is quite comparable to that induced by a similar course of treatment with testosterone. A gonadotropic pituitary extract did not cause any masculinization.

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Absorption of Glucose from the Stomach of the Dog.

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It is surprising that on so simple a subject as the fate of glucose in the stomach the published opinion is not of one accord.[1-13] Verzar and McDougall[14] state that "there is practically no absorption of carbohydrates in the stomach."

London and Tschekunow[9] in experiments on dogs with gastric fistulæ concluded that glucose was not absorbed during approximately a one-hour period. McLeod and his associates[10] reported similar observations in the rat when the pylorus was ligated.

More recently Maddock, Trimble and Carey[11] reported data from experiments on dogs from which they concluded that there was no

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11 Maddock, S. J., Trimble, H. C., and Carey, B. W., *J. Biol. Chem.*, 1933, **103**, 285.

12 Maddock, S. J., *J. Lab. and Clin. Med.*, 1932, **17**, 369.

13 Shay, H., Gershon-Cohen, J., and Fels, S. S., *Ann. Int. Med.*, 1938, **11**, 1563.

14 Verzar, F., and McDougall, E. J., *Absorption from the Intestine*, Longmans, Green and Co., London, Eng., 1936.