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Effect of Anterior Pituitary-Like Hormone on Lactation in the Albino Rat.

F. E. CONNON.* (Introduced by Bennet M. Allen.)

From the Department of Zoology, University of California at Los Angeles.

Experimental development of the mammary gland by administration of anterior pituitary-like hormone of pregnancy urine (A.P.L.) has been reported by several investigators. Bradbury[1] observed that the mammary glands of the mouse could be stimulated to develop by A.P.L. treatment, but only in those animals in which the uterus and ovaries were present. Selye, Collip, and Thomson[2] extended these findings to include the albino rat, and noted that increased development of the mammary glands paralleled an increase in the weight of the ovaries of A.P.L.-treated animals. No milk secretion occurred except after removal of the intensely luteinized ovaries, and then only in those animals in which the pituitary was intact.

In addition to a stimulative effect on the mammary gland, A.P.L. has been shown to inhibit milk secretion in normal lactating mice by Enzmann and Pincus,[3] and in normal and ovariectomized lactating mice by De Jongh.[4] Selye, Collip, and Thomson[5] administered A.P.L. and pig pituitary extract on the 3rd or 4th day after initiation of milk secretion in rats and observed an immediate inhibitory effect on lactation, which they suggest is exerted through the hypophysis rather than directly on the mammary glands. The mammary glands showed signs of secretion, but there was apparently lessened activity, since the suckling young of treated animals received little nourishment, lost weight, and eventually died.

The present work was undertaken to determine the effect of A.P.L. alone on lactation in the albino rat. Fifty-three lactating female animals of the Wistar strain and their litters were employed. Insofar as possible, litter-mate mothers were used and distributed among 3 groups: (1) normal untreated controls, (2) physiological saline-injected controls, and (3) Antuitrin S†-treated experimental

* The writer is grateful to Dr. Bennet M. Allen for helpful suggestions and criticisms throughout the course of this work.

1 Bradbury, J. T., PROC. SOC. EXP. BIOL. AND MED., 1932, **30**, 212.

2 Selye, H., Collip, J. B., and Thomson, D. L., *ibid.*, 1933, **30**, 588.

3 Enzmann, E. V., and Pincus G., *Am. J. Physiol.*, 1933, **103**, 30.

4 De Jongh, S. E., *Acta Brev. Neerl.*, 1933, **3**, 88.

5 Selye, H., Collip, J. B., and Thomson, D. L., *Endocrinology*, 1934, **18**, 237.

† I am indebted to Dr. O. Kamm of Parke-Davis & Co. for a generous supply of Antuitrin S which was used in this experiment.

animals. A standard number of 6 young per litter was maintained throughout by interchanging, when necessary, animals born on the same day. Intraperitoneal injection of the hormone was begun on the day of delivery of the young, since preliminary experiments had shown that there was little or no inhibitory effect on lactation in animals in which treatment was instituted several days after birth of litters. A.P.L. administration was continued from 3 to 5 days, the average daily injection being from 80 to 125 R.U. and the total amount given from 210 to 500 R.U. Injected controls were given physiological saline in volumes corresponding to the amounts of A.P.L. given, and over a period of time of 3 to 5 days. In preliminary work, 5 lactating animals were given from 20 to 50 R.U. per day, beginning on the day of delivery, and continuing for 3 to 5 days. No effect on lactation was noticed. The minimum effective daily injection was found to be about 80 R.U. Criteria for judging the inhibitory effect of the hormone were: (1) routine daily weighing of young and comparison of weight gains of control and experimental litters, (2) histological examination of mammary glands of the mothers in whole mounts and in sections as well as expression of milk through the nipples or cut edges of the glands after excision, and (3) examination of the stomach contents of the young animals. Mothers of control litters were sacrificed on the 21st day after delivery and those of experimental litters sacrificed on the 21st day or after death of the last young animal. Several mammary glands from each mother were fixed, and the ovaries and other endocrine organs removed for study.

In the 24 cases where large doses of A.P.L. were given the young exhibited smaller daily weight gains than the controls, and in only 8 instances did some of the young of hormone treated mothers survive to 21 days. The total number of 6 young survived for the 3-week period in only 2 of the experimental litters. In every case, young of such litters died within a few days after the mother was sacrificed, whereas the young of control animals were capable of surviving after weaning in all cases. The average weight of the surviving young of experimental mothers on the 21st day was from 7.8 to 16.3 gm. as compared with the control average weight at 21 days of 23.2 gm. In the remaining 16 experimental litters, all young were dead from 2 to 16 days after birth, and averaged from 2.6 to 8.3 gm. at death or shortly before. In numerous instances, the young weighed less at death than the average of 5.2 gm. recorded at birth. The stomachs of the young animals were examined at autopsy. Those of animals from experimental litters were devoid

of milk or contained only small amounts, while those of controls contained considerable milk in all individuals studied. The young of A.P.L. treated mothers continued to suckle until too weak to do so. The young of control litters survived the full period of 21 days, and after weaning, with the exception of 6 deaths in a total of 144 animals.

Microscopic examination of the mammary glands of the control mothers revealed full proliferation of all elements. Alveolar cells were vacuolated and exhibited evidence of active secretion. The alveoli were distended with milk. The nipples were fully developed and milk could be expressed from them and from the cut edges of glands excised for fixation. The mammary elements of the A.P.L.-treated animals were involuted in varying degrees, from complete breakdown of alveoli and terminal ducts to nearly full development of secretory structures. In the latter cases, secretion was dense and viscid and could not be expressed from the nipples which exhibited varying degrees of regression. Alveolar cells, when present in the more fully developed glands, where somewhat vacuolated and apparently secreting, but evidently not in normal fashion since the alveoli were not distended with milk. In general, the histological picture resembled that found in the normal involuting mammary gland and approximated to some extent the conditions described by Levenstein[6] in adrenalectomized lactating rats. Several mammary glands from each animal were studied to minimize the possibility of involution due to failure of the young to suckle. In each case, the glands from a single animal presented the same histological picture.

The ovaries of the experimental animals averaged 303.7 mg./kg. body weight as compared with 171.3 mg./kg. for the controls. Since there was some overlapping between the control and experimental ovary weights, the statistical significance of the data may be questioned. Histological study revealed intense luteinization in the ovaries of the A.P.L.-treated animals, this probably accounting for the increased weight. The high degree of luteinization suggested that the hormones of the corpus luteum possibly are involved in the inhibitory mechanism. However, this suggestion is not in accord with the observation of De Jongh,[4] who reported that A.P.L. inhibited lactation in ovariectomized mice. Also, a recent paper by Anselmino and Hoffmann[7] indicates that purified progesterone does not exert an inhibitory action on milk secretion, but they suggest that some other corpus luteum hormone may be concerned. It is pos-

[6] Levenstein, I., *Anat. Rec.*, 1937, **67**, 477.

[7] Anselmino, K. J., and Hoffmann, F., *Zentralbl. f. Gynäk.*, 1936, **60**, 501.

sible that increased oestrone production accompanies the observable ovarian stimulation after A.P.L. treatment. Further work is required on this problem, and experiments are being undertaken in an attempt to clarify the situation.

Conclusions. While the mechanism of the inhibitory action of A.P.L. on lactation is not clear at present, it may be concluded that administration of large amounts of this hormone is effective in bringing about partial or complete cessation of milk secretion in the albino rat. The effect is measurable by routine weighing of the young and by histological examination of the mammary glands of the mothers. The results of this work confirm previous observations in which mice were employed as experimental animals.

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Excretion of Some Purgative Salts of Magnesium.

RICHARD J. WEBER. (Introduced by W. C. Hess.)

From the Department of Biology, Georgetown University, Washington, D. C.

There are few experimental studies recorded of the effect of ingestion of purgative salts of magnesium on the level of urinary and fecal magnesium. Hay[1] found that one normal man excreted through the kidneys in 23½ hours, 3.5% of the magnesium taken in a 20 gm. dose of magnesium sulphate. Yvon[2] found an increase of less than 5.0% in 24 hours in the urinary magnesium output after the ingestion of a similar dose of the same salt. Hirschfelder and Serles[3] reported that 7 normal men excreted from 40 to 44% (average 42.6%) of the magnesium taken in a single ordinary purgative dose of Epsom salt within 24 hours after ingestion. Haldane[4] recovered only 8% of the magnesium ingested in a 25 gm. dose of magnesium chloride.

Wry[5] recovered in one hour from the feces of a normal man 9.52 gm. or about 78% of the magnesium taken in a 12.25 gm. dose of magnesium sulphate; from the feces of another he recovered in one

1 Hay, M., *J. Anat. and Physiol.*, 1882-83, **17**, 222.

2 Yvon, M. P., *Arch. de Physiol., Normale et Path.*, 1898, **5**, 304.

3 Hirschfelder, A. D., and Serles, E. R., *J. Clin. Invest.*, 1932, **11**, 841; *J. Biol. Chem.*, March, 1934.

4 Haldane, J. B. S., *Biochem. J.*, 1925, **19**, 249.

5 Wry, H., *Arch. für Verdauungs-Krankheiten*, 1909, **15**, 210.