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Effects of Gonadotrophic Hormones on Lactation.*†

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The inhibiting effect of steroids on lactation is mediated through the ovaries[1,2,3] and is probably due to the hormonal secretions of the large corpora lutea formed under the influence of the steroids.[4] Since the ovaries are normally stimulated by gonadotrophins of pituitary or chorionic origin, we decided to investigate the effect of these hormones in lactating rats.

It has been reported that gonadotrophins from pregnancy urine inhibit lactation in the mouse and rat; the effective daily dose varies from 10 R.U. to 125 R.U.[5,6,7] Later studies showed, however, that more purified chorionic hormone possesses only a slight inhibitory effect, even when injected at the dose level of 100-500 R.U.;[8,9] its effectiveness can be increased by estrogens.[10] The report that pregnancy urine extracts were active in castrate animals[6] could not be confirmed.[9,11]

Pregnant mare serum has a marked inhibitory influence on lactation and results in the death of the young.[9]

Anterior pituitary extract, although active in adrenalectomized rats treated with cortin[12] has no effect in normal rats.[9] Inhibition of lactation has been obtained in combining such extracts with chorionic gonadotrophins.[13]

The present work was undertaken in order to study the effects of these hormones under the same conditions used previously for the steroids and to see whether some correlations could be established between the ovarian changes elicited by gonadotrophins and the degree of inhibition of lactation.

Forty-one albino rats weighing 250-300 g originating from the same colony and fed exclusively on purina fox chow were used. The number of young in the litters was reduced or brought up to 6 within 24-36 hours of parturition, time at which the treatment was initiated. The mothers were divided into 6 groups treated as follows: Group I, no treatment; Group II, lyophilized beef anterior pituitary preparation (L.A.P.) at the daily dose of 40 mg; Group III, chorionic gonadotrophin (A.P.L.) at the daily dose of 150 I.U.; Group IV, A.P.L. at the daily dose of 150 I.U. during the first 6 days, 300 I.U. from the 6th to the 13th day, and 450 I.U. from the 13th to the 16th day; Group V, pregnant mare serum (P.M.S.) at the dose of 300 I.U.; Group VI, P.M.S. at the dose of 600 I.U. All these preparations in a dry form were suspended or dissolved in a

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TABLE I.
Average Figures on the Growth Rate of Litters and Percentage of Survivals Following Treatment of Mothers.

Groups	Treatment	No. of litters	Initial body wt	Avg body wt on day			% of litters surviving on day		
				5th	10th	16th	5th	10th	16th
1	0	12	6.8	10.6	17.3	26.2	96	96	92
2	L.A.P. 40 mg/day	7	7	12.5	17.5	24.3	97	97	97
3	A.P.L. 150 I.U./day	6	7	10.9	15.8	19.7	100	100	100
4	A.P.L. 150-450 I.U./day	6	7.7	11.7	18.4	21.8	100	100	100
5	P.M.S. 300 I.U./day	5	6.3	11.2	14.8	15.	92	92	18
6	P.M.S. 600 I.U./day	5	6.2	9.6	14.5	13.2	100	71	37

physiologic saline solution; the daily dose was administered in 2 subcutaneous injections. The criteria of efficiency of lactation were provided by the growth curve of sucklings and also by the number of deaths among the young. The mothers were sacrificed on the 17th day, or before, whenever all the young from the same litter died. At autopsy, organs were removed, placed in fixative fluid, then weighed and examined histologically.

L.A.P. had no influence on the growth or the mortality of the young, in spite of a certain degree of toxicity as evidenced by the local reactions near the points of injection. A.P.L. exhibited some inhibitory effect; although the mortality was nil in Groups III and IV, the growth was somewhat retarded, as can be seen from Table I. This effect on growth was more evident from the daily average weight of litters; it reached a maximum around the 14th day, then plateaued or even decreased. P.M.S., the most active preparation, influenced the growth and the mortality of young; the degree of inhibition, however, did not differ significantly whether a dose of 300 or 600 I.U. was administered.

On microscopic examination, only the mammary glands of Group II did not differ from those of Group I (controls). The lumina of ducts and acini were dilated and filled with homogeneous secretion; there was an almost complete disappearance of inter- and intralobular connective tissue.

Mammary glands of Groups V and VI presented a marked variation from the normal controls. There was a marked regression of the glandular tissue. The acini were fairly indistinct and their lumina were filled with a vacuolar material. The acinar cells, which were cuboidal in type with large nuclei, showed no activity. The lobular masses were separated from each other by connective tissue. These glands were not secreting and presented signs of involution.

The picture of mammary glands of Groups III and IV was intermediary between that of controls and that of P.M.S.-treated rats. The acini were not distended by milk and the cells were low cuboidal in type but still secreting. The lobular masses were more distinct due to a decreased activity of the glandular tissue.

As expected, ovaries of all experimental groups were markedly stimulated. The ovarian weights for Groups II to VI were 138, 207, 257, 439 and 263 mg respectively to compare with 56 mg for the controls. On histologic examination the ovaries of Group II were found to contain numerous but small corpora lutea which gave to the organ a mulberry appearance. Those of Groups III to VI were more intensely luteinized; with P.M.S. the corpora lutea were larger than with A.P.L. and in many instances large vesicular or hemorrhagic follicles were observed. Since corpora lutea of the pregnancy type which are associated with inhibition of lactation can be identified by the size of the individual cells, we decided to draw a representative cell of the corpora lutea from each group. From Fig. 1 it can be seen that only the luteal cells of rats treated with P.M.S. presented an hypertrophy similar to that of normal pregnancy.

Although the experimental conditions of our studies and the criteria of activity were somewhat different from those used by others, the results are identical: P.M.S is the most active inhibitor of lactation, then comes

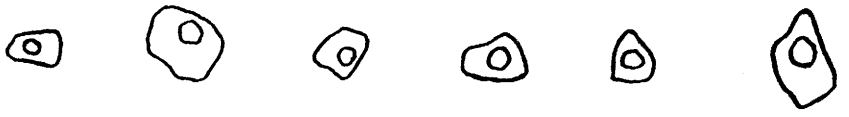

FIG. 1.

Camera lucida drawings of corpora lutea cells. (a) During lactation; (b) during pregnancy; (c) during lactation and A.P.L.; (d) during lactation and L.A.P.; (e) during lactation and Prolactin; (f) during lactation and P.M.S.

A.P.L., while the gonadotrophins of pituitary origin are without effect. It is interesting to note that all the hormonal preparations, especially P.M.S. and A.P.L., produced an intense luteinization of the ovaries; however, only P.M.S. was able to cause the formation of pregnancy corpora lutea. It can therefore be assumed that these large corpora lutea release hormonal substances either different from those secreted by the corpora lutea of lactation or in a different ratio. We tried to see whether the luteotrophic hormone, prolactin, would exaggerate the stimulation of the normally existing corpora lutea. We injected on the day following parturition for a period of 10 days a daily dose of 100 I.U. of prolactin. The growth of the young was normal if not better; the ovaries were slightly heavier (67 mg) than normal and the corpora lutea were well developed but not hypertrophied, as can be seen from Fig. 1. This is in accordance with another observation.[14]

If the small morphologic differences between the A.P.L.- and P.M.S.-treated rats are really associated with different hormonal secretions, the examination of the receptor organs should provide more information regarding the nature and even the level of the hormones in circulation. The vaginae in the 4 groups were mucified, indicating the presence of progesterone. The uteri presented, however, some interesting differences. In the case of the A.P.L.-treated rats the epithelium of the cuboidal type had an hillocky appearance. The stroma was dense, poorly developed and slightly edematous; the cells were darkly stained and fusiform. Glands were present. The general aspect was not much different from that seen in untreated controls although in the latter case this organ was not enlarged. In the P.M.S.-treated rats, the uterine epithelium was tall, not degenerating and presented also many folds. The stroma was well developed and edematous with glands; the cells were large and vesicular with a tendency to being transformed into fusiform cells.

When these observations are compared with those of Atkinson and Hooker,[15] who used the modifications of the endometrium to estimate the level of estrogens and progesterone, it is suggested that in the A.P.L.-treated rats there is a low level of estrogens and progesterone, while on the other hand in the P.M.S.-treated rats there is a high level of estrogens and progesterone. If that be the case, it should be possible to inhibit lactation in ovariectomized lactating rats by giving estrogens and progesterone in a certain ratio; experiments are already in progress to prove that point.

Summary. The influence on lactation of various gonadotrophins of pituitary and chorionic origin has been studied in lactating rats. P.M.S. had a strong inhibitory effect resulting in the death of most of the young; A.P.L. had a slight effect on the growth curve of the young, while an anterior pituitary preparation was inactive. From histologic studies of ovary, vagina and uterus it is suggested that the activity of P.M.S. is due to a high level of estrogens and progesterone.

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