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Reaction of Anterior Pituitaries of Mature Female Rats to Injections of Large Amounts of Oestrin.*

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We have found[1] that injections of extracts of pregnancy urine markedly increased the weight of the ovaries and the pituitaries of female rats. The ovaries contained many large corpora lutea and both partially luteinized and unluteinized follicles. The vaginae were usually mucified at autopsy. The anterior pituitaries exhibited marked loss of granules from practically all basophiles and a decrease in their relative percentage. Many eosinophiles were swollen and showed loss of granules; they were reduced in percentage. The degree of change in the eosinophiles was proportional to the increase in weight of ovaries and pituitaries. Oestrin stimulates the production of a luteinizing hormone by the anterior hypophysis[2, 3] and injection of oestrin into mature female rats results in the formation of large corpora lutea comparable to those of pregnancy.[4, 5] This paper is concerned with the anterior pituitaries of 30 mature female rats which received daily injections of 200 rat units of oestrin† for 12 days and in whose ovaries intense luteinization had been induced. Serial sections of the pituitaries were cut and cell counts made on representative sections. Previous studies on the anterior pituitaries of 143 normal female rats served as controls for these studies. The data on both groups are arranged in a frequency distribution table and analyzed statistically (Table I).

The pituitaries of the injected rats were greatly increased in weight (previously reported by Hohlweg[4]); the mean was 20.1 mg., the range from 12 to 27 mg. The mean pituitary weight of 143 normal cyclic females was 10.5 mg. (Table I). Marked morphologic changes were found in the anterior pituitaries; most outstanding of these was the complete loss of granules from all the baso-

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1 Wolfe, J. M., *et al.*, *Anat. Rec.*, 1934, **60**, 357.

2 Hisaw, F. L., *et al.*, *Anat. Rec.*, 1934, **60** (sup.), 53.

3 Lane, E. C., *Am. J. Phys.*, 1935, **110**, 681.

4 Hohlweg, W., *Klin. Woch.*, 1934, **13**, 93.

5 Wolfe, J. M., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 757.

† Progynon-B was used; a portion of this material was furnished gratuitously by the Schering Corporation, Bloomfield, N. J.

TABLE I.

Summary of quantitative data on control and experiment groups. Class intervals, means (M), and standard deviations (SD) are given in percentage.

Class Interval	Frequency		Mean—Standard Deviation	
	Control	Experimental	Control	Experimental
Eosinophiles:				
15.-19.9		3		
20.-24.9	4	17		
25.-29.9	14	10	M 34.2	M 23.6
30.-34.9	66		SD 4.3	SD 3.1
35.-39.9	49		Cells per section—304	Cells per section—308
40.-44.9	9			
45.-49.9	1			
Basophiles:				
0.- 1.9		27	M 4.1	M 1.2
2.- 3.9	55	3	SD 1.3	SD 1.9
4.- 5.9	74		Cells per section—38	Cells per section—14
6.- 7.9	14			
Chromophobes:				
45.-49.9	1			
50.-54.9	4			
55.-59.9	41		M 61.7	M 75.2
60.-64.9	69		SD 4.4	SD 3.4
65.-69.9	28	1	Cells per section—554	Cells per section—983
70.-74.9		12		
75.-79.9		14		
80.-84.9		3		
Mean Pituitary Weight	10.8 mg.	20.1 mg.	Total Cells Counted per Section 896	1305
Mitoses per section	1.6	36.6	—	—

philes. The non-granular basophiles remaining in the gland were considerably enlarged. We have followed the same procedure in making all cell counts.[6] The quantitative data indicate that, in the injected rats, both the relative percentage and the total numbers of the basophiles were reduced below the normal (Table I). Less conspicuous changes were found in the eosinophiles. Many were swollen and exhibited loss of granules. The negative image of the Golgi apparatus of these cells was often enlarged. The relative percentage of the eosinophiles was reduced more or less in proportion to the degree to which the pituitary was increased in weight (Table I). Although the relative percentage of the eosinophiles was reduced, our quantitative data indicate that the total number of these cells counted in the pituitaries of the injected rats was no lower than that found in the glands of normal rats. This condition was due to the large number of mitoses in the chromophobes which increased their absolute number as well as their relative percentage. However, many mitoses were also found in the eosinophiles, which most probably kept the absolute number of these cells near the

[6] Wolfe, J. M., *et al.*, *Amer. J. Anat.*, 1934, **55**, 363.

normal in spite of the fact that many were losing their granular material and gave rise to chromophobes.

The chromophobes were greatly increased in relative percentage and in the numbers counted (Table I). Mitoses were abundant (approximately 4 to 5 times as many as occurred in the eosinophiles). Many of these cells were greatly swollen. In some the cytoplasm stained light blue or was almost colorless; in such cells the cytoplasm was often fragmentary. In others of the enlarged chromophobes the cytoplasm was more dense and stained a deeper blue. Other chromophobes were smaller and had a dense blue cytoplasm. In both the large and small chromophobes the negative image of the Golgi apparatus was often increased in size. Often small yellowish masses were found in the region of the Golgi apparatus.

In the glands which were markedly increased in size, the vascularity was also increased; the capillaries in many regions were extremely dilated and greatly emphasized the cord-like arrangement of the anterior lobe cells. The increased size of the pituitary was due to several factors, among which was the increased vascularity, the swollen condition of many of the cells, and the increased number of the cells. Vaginal smears were made daily throughout the experimental period. The smears were usually completely cornified for the first 4 or 5 days, but with 2 exceptions the cornified epithelium failed to persist throughout the entire injection period. At autopsy the vaginal epithelium of 16 rats was mucified; that of the others was stratified and in 2 instances also cornified. These findings suggest that the direct effect of the oestrin on the vagina was partially nullified by the hormone of the corpus luteum produced in the animal's own body. This is in agreement with the recent work of Allen and Meyer.[7]

The weight and morphologic reactions of the anterior pituitaries of mature female rats to pregnancy urine extracts and to oestrin were strikingly similar. In both, the pituitaries were greatly increased in weight. Considering the groups as a whole, morphologic changes were more marked and constant in the rats receiving oestrin. Changes in the eosinophiles were identical in both instances: swelling of the cells, loss of granules, and reduction in relative percentage. This strongly suggests that the oestrin produced in the body of the rats which received pregnancy urine extract was responsible for the changes in the eosinophiles. In previous papers con-

[7] Allen, W. M., and Meyer, R. K., Abstract 4202, Wistar Institute Bibliographic Service.

cerned with the cyclic morphologic changes in the anterior lobe, we have reported that the eosinophiles exhibited loss of granules only when active corpora lutea were present in the ovaries. The findings reported here are similar and probably indicate that the changes found in the eosinophiles during the lutein phase of the normal oestral cycle were due to the action of oestrin. Although oestrin stimulates the luteinizing hormone and at the same time induces granular loss from the eosinophiles, there is at present insufficient evidence to make any definite statement concerning the significance of this finding. Severinghaus[8] has also reported changes in the eosinophiles of the mature female receiving extracts of pregnancy urine, and Nelson[9] found degranulated eosinophiles in rats following injections of oestrin.

The basophiles of rats receiving oestrin and of those receiving extracts of pregnancy urine were similar in appearance. This was especially striking in the anterior lobes of immature rats receiving extracts of pregnancy urine or oestrin. In both instances many large clear blue non-granular basophiles were found. Whether the fundamental factor acting on the basophiles in the rats receiving extracts of pregnancy urine was oestrin is at present not known. However, it is interesting to note that extracts of pregnancy urine do not have any action on the anterior lobes of castrated female rats, while oestrin is capable of direct action on the anterior pituitary. Furthermore, since extracts of pregnancy urine are capable of inducing the formation of oestrin in the ovary of the hypophysectomized female rat, the fact is suggested that oestrin is the effective agent in inducing the above basophilic changes in the anterior lobes of intact female rats receiving extracts of pregnancy urine.

[8] Severinghaus, A. E., *Anat. Rec.*, 1934, **60**, 43.

[9] Nelson, W. O., PROC. SOC. EXP. BIOL. AND MED., 1934, **32**, 452.