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Failure of Estradiol Inactivation Products to Inhibit Pituitary Gonadotrophic Content and Secretion.

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It has been postulated that the level of pituitary gonadotrophins in the blood is regulated principally by the degree of activity of the ovaries, functioning ovaries inactivating gonadotrophins, and non-functioning ovaries permitting gonadotrophins to accumulate in the circulation.[1] This hypothesis was based on observations of female rats with ovaries autotransplanted to the spleen. By this means, ovarian secretion was directed through the portal vein directly to the liver, where the estrogenic substances were inactivated sufficiently to prevent their detection in the systemic circulation. As in castrates, it was noted that vaginal cell atrophy, uterine atrophy and thymic hypertrophy occurred; however, pituitary gonadotrophic content did not rise, as in castrates, but remained at normal levels. This refuted the concept that normal levels of estrogen maintain normal pituitary gonadotrophic content, and suggested instead that pituitary gonadotrophic content is the resultant of the activity of functional ovaries upon circulating gonadotrophins.

An alternate explanation for the lack of rise of pituitary gonadotrophins is the possible influence of estrogen inactivation products upon the hypophysis. In animals with their ovaries transplanted to the spleen, degradation products of the estrogens which have passed through the liver, although lacking estrogenic activity, might conceivably depress the hypophysis.

Smith[2] found that Westerfeld's lactone, an inactivation product of estrone, increased pituitary content of gonadotrophins. Segaloff[3] has found that bisdehydrodoisynolic acid, a degradation product of estrogens, is more active when administered intrasplenically than when injected subcutaneously. Since some inactivation products of estrogens do have effects on pituitary gonadotrophic content, it seemed possible that they might be the principal controlling factor. This possibility is the subject of the present investigation.

Only estrone and estradiol have been recovered from ovarian tissue. As estrone is changed to estradiol in the process of its inactivation by the liver,[4] α-estradiol was chosen as the estrogen for this study.

Materials and methods. Adult virgin female rats of the Sprague-Dawley strain weighing 200-250 g were castrated, and on the same day α-estradiol pellets weighing 1.1 to 10.8 mg were implanted in their spleens. One group of rats received pellets subcutaneously, and another group was included as intact controls. Operated rats with pellets implanted in the spleen which spontaneously developed vascular adhesions from the spleen to the systemic circulation served as additional controls.

From 33 to 40 days after the pellets were implanted, the donor rats were killed by decapitation. Pituitary gonadotrophin content was measured by suspending each anterior pituitary gland in 6.0 cc of saline by repeatedly drawing into and expelling from a syringe, then by injecting into one 24-day-old Sprague-Dawley female rat, 1.0 cc twice daily for three days. The assay rats were killed 24 hours after the last injection. Results are tabulated in Table I.

Discussion. The control of pituitary gonadotrophic secretion could conceivably be

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1 Jungck, E. C., Heller, C. G., and Nelson, W. O., PROC. SOC. EXP. BIOL. AND MED., 1947, **65**, 148.

2 Smith, O. W., PROC. SOC. EXP. BIOL. AND MED., 1945, **59**, 242.

3 Segaloff, A., *Fed. Proc.*, 1947, **6**, 399.

4 Heller, C. G., *Endocrin.*, 1940, **26**, 619.

TABLE I.

Donor rats							Recipient rats			
				α-estradiol pellets		At autopsy*		Uterus		
	No. of rats	Vaginal smears: Before operation	Vaginal smears: After operation	Avg wt when implanted, mg	Avg absorbed, μg/day	Appearance of uterus	Thymic wt, mg	With fluid, mg	Without fluid, mg	Ovarian wt, mg	No. of rats
Intact controls	3	cycling	cycling	—	—	normal	183	185	111	20	31
Castrate controls	11	,,	atrophic	—	—	atrophic	241	95	95	103	11†
α-estradiol pellet in spleen, no adhesions	16	,,	,,	5.4 (1.1-10.2)	21.9 (5.4-47.5)	,,	293	115	115	78	16
Same with adhesions	6	,,	estrus	5.3 (2.3-10.8)	19.7 (8.8-32.5)	estrus	83	54	54	25	6
α-estradiol pellet SQ	3	,,	,,	6.2 (4.3-9.7)	74.0 (39.4-119.0)	,,	38	34	34	16	3
						Uninjected recipient rats		36	36	13	63

* Autopsy 33-40 days after implantation of pellets.
† These values are in keeping with previous observations made on the same strain of rats.

due to estrogen inactivation products from the liver. Thus, when an animal is castrated, there are no estrogen inactivation products and the pituitary is permitted to increase markedly in gonadotrophic content. When the ovaries are present in the spleen, the pituitary gonadotrophic content would continue to be controlled by the estrogen inactivation products, thus accounting for the normal gonadotrophin levels found in these animals.

To test this hypothesis, pellets of α-estradiol were implanted into the spleens of mature female rats castrated the same day. The relationships in the experimental rats are diagrammed in Fig. 1. An α-estradiol pellet (at 1 in the figure) was implanted in the spleen. The estradiol was carried directly to the liver (at 2) and inactivated, so no active estradiol reached the general systemic circulation. (This was confirmed by the castration response elicited — hypertrophied thymus, atrophic uterus and atrophic vaginal smear.) Inactivation products of estradiol arrived in the circulation and were free to act on hypophyseal gonadotrophic content and secretion (at 3).

If the principal controlling factor of pituitary gonadotrophic content is estrogen inactivation products, then castrated female rats having pellets of α-estradiol in their spleens should have normal pituitary gonadotrophin content. If the main controlling mechanism is inactivation of gonadotrophins by the ovaries, as postulated, then the presence of estradiol pellets in the spleen should have little effect in maintaining normal pituitary gonadotrophic potency of castrated female rats.

The pituitaries of normal unoperated female rats contained sufficient gonadotrophin to stimulate recipient ovarian weights from 13 mg to 20 mg. Castrate control rat pituitaries stimulated recipient ovarian weight from 13 mg to 103 mg. The animals with α-estradiol pellets in the spleen (and no adhesions) had sufficient gonadotrophin in their pituitaries to stimulate recipient ovarian weight from 13 mg to 78 mg, which is in the castrate range. The average daily absorption of α-estradiol was 21.9 μg, several times the

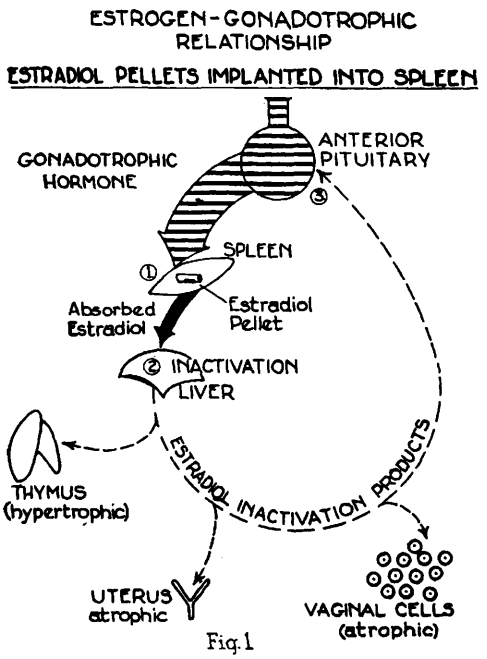

Fig. 1

dose necessary to maintain constant estrus in the intact animal. This large dose of α-estradiol was completely inactivated, as demonstrated by the atrophic uteri and vaginal smears, and the large thymus. Therefore, many times the physiological amount of inactivation products were present in the circulation. However, the pituitary gonadotrophic content rose to castrate levels.

The castrated rats with pellets implanted in the spleen which developed vascular adhesions from the spleen to the systemic circulation absorbed essentially the same amount of α-estradiol daily as the rats without adhesions (19.7 μg vs. 21.9 μg). The rats with estradiol pellets implanted subcutaneously absorbed 74.0 μg daily. In both the adhesion group and in the rats with pellets implanted subcutaneously, constant estrus was observed along with atrophy of the thymus and suppression of pituitary gonadotrophic content. These changes are noted only with unphysiologically large doses of estrogen,[1] thus indicating that larger than normal amounts of estrogen were being absorbed.

Conclusions. 1. The inactivation products of α-estradiol produced by passage of estradiol through the liver do not exert a significant inhibiting influence on anterior pituitary gonadotrophic secretion.

2. The absence of this effect supports the thesis that pituitary gonadotrophic content and secretion are controlled principally by ovarian inactivation of circulating gonadotrophins.

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Effect of Adrenal Cortical Extract on Recovery from Severe Pneumococcic Infection in Mice.*

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Many observations suggest that the increased adrenal cortical secretion during stress provides an increase in nonspecific resistance.[1] In patients or animals moribund from infections, it was thought that administration of large doses of adrenal cortical extract might temporarily increase resistance and thus gain time for antibacterial agents such as penicillin to effect recovery. To test this possibility two similar experiments were performed.

Methods. Albino Swiss mice were inoculated intraperitoneally with large numbers of Type I pneumococci. After a certain percentage of the inoculated mice had died, the survivors were placed at random into 3 dif-

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[1] Selye, H., *J. Clin. Endocrinol.*, 1946, **6**, 117.