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## Inhibitory Action of Testosterone Propionate on the Human Ovary.

S. H. GEIST, J. A. GAINES AND U. J. SALMON.

*From The Mount Sinai Hospital, New York City.*

In previous communications,<sup>1, 2, 3</sup> it has been shown that, by the administration of adequate amounts of testosterone propionate to cyclical women, menstruation can be suppressed and the secretory phase of the endometrium abolished, resulting in hypoplasia or atrophy of the endometrium. These effects of testosterone propionate were interpreted as indicating inhibition of ovulation (probably mediated through the hypophysis) with consequent suppression of estrogen and progesterone formation.

In animals, some workers have reported that synthetic androgens have a stimulating action upon the ovaries of rats<sup>4-8</sup> and mice.<sup>9</sup> Others have reported inhibition of ovulation in rabbits<sup>10</sup> and monkeys<sup>11</sup> and ovarian atrophy in rats.<sup>12, 13</sup>

In the study reported here, an attempt was made to determine what effect testosterone propionate has upon the ovaries of cyclical women and to correlate the ovarian response with the endometrial and vaginal changes.

Two regularly cyclical women, requiring exploratory laparotomy, were selected for this study. Endometrial biopsies were taken

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<sup>1</sup> Gaines, J. A., Salmon, U. J., and Geist, S. H., *Proc. Soc. Exp. Biol. and Med.*, 1938, **38**, 779.

<sup>2</sup> Geist, S. H., Salmon, U. J., and Gaines, J. A., *Endocrinology*, 1938, **23**, 784.

<sup>3</sup> Salmon, U. J., Geist, S. H., and Walter, R. I., *Am. J. Obs. and Gyn.*, 1939, **38**, 264.

<sup>4</sup> Korenchevsky, V., Dennison, M., and Hall, K., *Biochem. J.*, 1937, **31**, 780.

<sup>5</sup> Wolfe, J. M., and Hamilton, J. B., *Proc. Soc. Exp. Biol. and Med.*, 1937, **37**, 189.

<sup>6</sup> McKeown, T., and Zuckerman, S., *Proc. Roy. Soc., London, s.B.*, 1937, **124**, 362.

<sup>7</sup> Salmon, U. J., *Proc. Soc. Exp. Biol. and Med.*, 1938, **38**, 352.

<sup>8</sup> Nathanson, I. T., Franseen, C. C., and Sweeney, A. R., Jr., *Proc. Soc. Exp. Biol. and Med.*, 1938, **39**, 384.

<sup>9</sup> Starkey, W. F., and Leatham, J. H., *Proc. Soc. Exp. Biol. and Med.*, 1938, **39**, 218.

<sup>10</sup> Cotte, G., Martin, J. F., and Mankiewicz, E., *Gynecologie*, 1937, **36**, 561.

<sup>11</sup> Zuckerman, S., *Lancet*, 1937, **2**, 676.

<sup>12</sup> McEuen, C. S., Selye, H., and Collip, J. B., *Proc. Soc. Exp. Biol. and Med.*, 1937, **36**, 390.

<sup>13</sup> Mazer, M., and Mazer, C., *Endocrinology*, 1939, **24**, 175.

before and during the period of testosterone propionate administration, at intervals of 1 to 2 weeks. Vaginal smears were taken 3 times weekly. Testosterone propionate was administered for 31 and 15 days, respectively, the total amounts being 925 and 1,225 mg. The histologic findings of the ovaries were correlated with the endometrium and vaginal smears. A resumé of the protocols follows:

*Case I. Age 29. Gravida 1. Para 0.* Menses lasting 5 days occurred at regular intervals of 4 weeks. A preliminary endometrial biopsy, taken during the menstrual period, revealed the presence of secretory changes. It was assumed, therefore, that an ovulatory cycle had just been completed. Preliminary vaginal smears were of the normal physiologic type. Testosterone propionate\* injections were started 3 days pre-menstrually and continued, at 1 to 3 day intervals, until 925 mg had been administered over a period of 31 days. Menstruation failed to take place by the 34th day of the cycle, at which time operation was performed. At this time, the endometrium was reduced to a state of hypoplasia, while the vaginal smears revealed typical estrogen deficiency characteristics. The ovaries showed no gross evidence of a mature follicle or recent corpus luteum. Two longitudinal sections were made through the entire width of each ovary down to the hilus and the central wedges removed for histologic study. Microscopic examination revealed the presence of small, collapsed or cystic corpora lutea of previous cycles, but no maturing follicles or current corpus luteum.

*Case II. Age 47. Gravida 2. Para 2.* Menses had occurred quite regularly at 26 to 28 day intervals, lasting for 5 to 6 days. The patient entered the hospital because of lower abdominal pain related to uterine fibromyomata. An endometrial biopsy, taken pre-menstrually, revealed a typical secretory phase. Preliminary vaginal smears revealed a normal estrogen effect. During the first 16 days of the next cycle, 1,225 mg of testosterone propionate was administered. A supravaginal hysterectomy and bilateral salpingo-oophorectomy was performed on the 17th day. The endometrium showed moderate proliferation and a complete absence of secretory phenomena. The vaginal smear, at this time showed early signs of regression. Microscopic sections of the ovaries failed to reveal any signs of a recent corpus luteum or maturing follicle.

*Summary and Conclusions.* Two women with regular menstrual

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cycles were injected with testosterone propionate (925 and 1,225 mg), in order to determine whether ovulation could be inhibited. In one patient, the ovaries, examined on the 34th day of the cycle, showed no evidence of a recent corpus luteum or mature graafian follicle. In the second patient, examination of the ovaries, on the 17th day of the cycle, did not reveal any evidence of ovulation. In the latter case, while ovulation might have occurred after the 17th day, it was deemed unlikely in an individual with a regular 26 to 28 day cycle.

It appears from this study that testosterone propionate, if administered in adequate amounts to the cyclical human female, can inhibit full follicle maturation, ovulation and corpus luteum formation, associated with regressive changes in the endometrium and vaginal mucosa. The question arises as to whether the testosterone propionate acts directly upon the follicular apparatus or indirectly through inhibition of the gonadotropic activity of the pituitary. In view of the fact that testosterone has been shown to suppress the gonadotropic activity of the hypophysis in post-menopausal women<sup>14, 15</sup> and rats,<sup>16-18</sup> it is logical to conclude that the inhibitory effect of testosterone propionate upon the human ovary is mediated through the pituitary.

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### Effectiveness of Sulfanilamide upon Anaerobic Hemolytic Streptococci.

E. H. SPAULDING AND AMEDEO BONDI, JR.  
(Introduced by J. A. Kolmer.)

*From the Department of Bacteriology and Immunology, Temple University School of Medicine, Philadelphia, Pa.*

Previous work in this laboratory<sup>1</sup> has indicated that on primary isolation a significant proportion of hemolytic streptococci are incapable of developing upon the surface of aerobic, infusion blood-

<sup>14</sup> Salmon, U. J., *Proc. Soc. Exp. Biol. and Med.*, 1937, **37**, 488.

<sup>15</sup> Nathanson, I. T., and Towne, L. E., *Endocrinology*, 1939, **25**, 754.

<sup>16</sup> Nelson, W. O., and Gallagher, T. F., *Anat. Rec.*, 1935, **64**, 129.

<sup>17</sup> Wolfe, J. M., and Hamilton, J. B., *Endocrinology*, 1937, **21**, 603.

<sup>18</sup> Allanson, M., *Proc. Roy. Soc., London, s.B.*, 1937, **125**, 196.

<sup>1</sup> Spaulding, E. H., and Goode, W., *J. Lab. and Clin. Med.*, 1939, **25**, 305.