canine antihormone. (2) The changes in basophiles characteristic of both castration and thyroidectomy were observed in the hypophyses of the long-time injected dogs. (3) The presence of basophilic granules in the perivascular spaces and in the capillaries has been observed.

It is possible that the following reactions occurred in sequence during the course of prolonged injections of the sheep-pituitary extract: (1) An initial activation of the endocrine glands subsidiary to the pituitary gland occurred. In the sheep this process continued for the entire 6 months of injections. (2) The increased secretion of the subsidiary glands in turn activated the hypophyseal function. (3) The foreign protein linked to the injected sheep-extract gradually produced in the dogs a tissue and humoral resistance (antihormones), which ultimately inactivated the injected sheep-extract as well as certain pituitary hormones of the injected animal itself. (4) Thus, the antihormones produced a state of physiological hypophysectomy, which caused subsequent atrophy of the subsidiary glands. (5) The atrophy of the thyroid and gonads (and adrenals?) produced the final changes in the hypophyses characteristic of gonadectomy and thyroidectomy (and adrenalectomy?).

The Crooke changes characteristically found in the Cushing syndrome, associated with a diminished function of the gonads and thyroids, are believed to be related in some way to the effects of the inactivation of the subsidiary endocrine glands by the antihormone in these animals.

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A Case of Delayed Ovulation After Estrin Administration in the Intact Monkey.*

JOSEPHINE BALL AND CARL G. HARTMAN.

From the Phipps Psychiatric Clinic, Johns Hopkins Medical School, and the Department of Embryology, Carnegie Institution of Washington, Baltimore.

In the course of experiments designed to throw light on the hormonal basis of sex behavior a case of ovulation was encountered which was apparently delayed by the injection of estrin during the first part of the menstrual cycle. This occurred in monkey No. 634 which had been menstruating regularly (Sept. 22, Oct. 19, Nov. 19, Dec. 27, 1938, and Jan. 26, 1939). Ovulation, diagnosed by palpa-

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tion, took place in each of these cycles; the exact date was not determined in the first cycle but in the last 3 cycles it occurred on days 11, 12 and 17, respectively.

Observations of the animal's sexual receptivity[1] had been started on November 23 and continued regularly 3 times a week until February 27, the date of laparotomy (Fig. 1). In spite of her apparently excellent physiological condition there had seemed to be none of the normal[1] tendency to increased sexual excitability in this animal at the time of ovulation. For this reason efforts were made to reproduce the normal picture by the administration of various hormones that have been found to produce or increase sex activity in castrates.

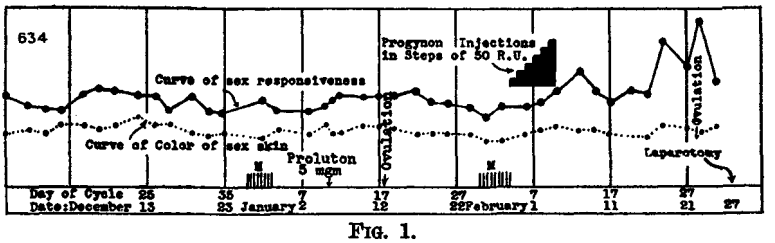

FIG. 1.

Progesterone (5 I.U. of Proluton Schering†) was given first, namely on January 5, day 10 of that cycle, without detectable effect on sex behavior, perhaps because the injection was made too long before ovulation took place.[2]

The following cycle estradiol benzoate (Progynon-B Schering) was tried in a dose that had produced in castrated female monkeys an increase in sexual responsiveness similar to that typically seen in normal animals at the time of ovulation.[3] This dose, as shown in Fig. 1, consisted of increasing daily injections for 6 successive days, starting on day 4 with 50 R.U. and augmenting the dose by 50 R.U. each day. This seemed to result in a slight increase in sex interest and in repression of ovulation. The left ovary had become slightly larger by day 14 but thereafter it remained stationary in size until day 27. As indicated in Fig. 1, the animal's sex interest was at this time rising slightly. As this was contrary to all previous experience with such tests at the end of the menstrual cycle, the ovarian changes were closely followed by palpation. Ovulation was diagnosed on day 29 (Feb. 23) and 4 days later observation at laparoto-

[1] Ball, J., and Hartman, C. G., *Am. J. Obst. and Gynecol.*, 1935, **29**, 117.

† We wish to thank the Schering Corporation for the Proluton and Progynon-B used in this experiment.

[2] Dempsey, E. W., Hertz, R., and Young, W. C., *Am. J. Physiol.*, 1936, **116**, 201.

[3] Ball, J., *Psychol. Bull.*, 1936, **33**, 811.

my confirmed this diagnosis. A fresh corpus luteum was found in the left ovary with a blood-red stigma 1 mm in diameter surrounded by an elliptical pink field 1.5 x 3 mm.

Of the 400 ovulations that have previously occurred in the Carnegie Rhesus colony, only 5 have taken place later than day 16. These 5 occurred on days 17, 19, 20, and 21 with a doubtful case on day 24. It seems, therefore, highly probable that the injection of estrin delayed ovulation in the present instance.

The rise of sex interest concomitant with the growth of the follicle and ovulation at the end of the cycle is not, however, to be attributed to the injections. This dose of estrin has been given repeatedly to some dozen castrates and the effect on sex behavior has always practically disappeared by the end of the week following the last injection. The increased sexual responsiveness probably occurred rather as a normal response to the animal's own hormones, this typical response having been inhibited earlier in the year by factors which, although unknown, seem, nevertheless, to have been operative in the whole group of 8 animals of which No. 634 was a member. Of the 6 other females in this group that were ovulating, 4 have shown improvement in sex responsiveness in February without reference to injected hormones; indeed, 2 of these have received no hormone treatment at any time throughout the year. It is evident that something was happening to the whole group which was improving their response to the mating situation.

Delay of ovulation does not regularly result from injection of estrogens during the early part of the cycle. Similar experiments have been made 3 times in another animal (No. 627), which was apparently in a similar physiological condition, without disturbing ovulation in the first and second cycles but completely inhibiting[4] it in the third cycle. In a third animal (No. 668), ovulation was inhibited (and sex behavior entirely uninfluenced) by the daily injection of 250 R.U. Progynon-B on days 8 to 12, increased to 500 R.U. on days 13 to 19 of the same cycle. However, the possibility of delayed ovulation suggested by the case here reported must be considered if estrin is to be used clinically to inhibit ovulation. It is also interesting to note this prompt recovery of the ovary from estrin inhibition.

The female under discussion was found to be menstruating on the morning of March 4, 9 days after ovulation.

Summary. Ovulation in a monkey was apparently delayed by administration of estrin in the first part of the menstrual cycle. Accompanying changes in sexual responsiveness are described.

[4] Corner, G. W., *Am. J. Physiol.*, 1935, **113**, 238.