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Comparative Studies of Gonad-Stimulating Hormones.* II. Influence of Length of Period of Administration of Certain Extracts.

C. F. FLUHMANN.

From the Department of Obstetrics and Gynecology, Stanford University School of Medicine.

The importance of the "time factor" in studying the responses elicited in immature rats by gonad-stimulating hormones has been previously mentioned.[1, 2] A significant difference in the effects produced by a pregnancy blood extract from those by a sheep anterior pituitary extract has been noted when the *same total dose* of each preparation is administered over various periods of time.

The method of preparing the extracts has been described.[1, 2, 3] The injections were begun in rats 20 to 23 days of age, and the extracts were made up in various dilutions so that each animal received the required total dose when 0.25 cc. was administered twice daily for the duration of the experiment. A total of over 200 rats was used in studying the various aspects of this problem.

In one series, 23 animals were given 2.5 cc. of a blood extract equivalent to 5.75 cc. of a mixture of several specimens obtained from pregnant women. Five rats injected for 5 days showed an average increase over controls of 200% in ovarian weight and 309% in uterine weight (ave. body weight 34 gm., ovaries .036 gm., uterus .136 gm.). When the same dose was given to 5 rats in 10 days, the average increase in ovarian weight was 450% and in uterine weight 565% (ave. body weight 48 gm., ovaries .066 gm., uterus .199 gm.). In 15 days the ovaries of 5 rats gave an average increase of 387% in weight and the uteri of 570 % (ave. body weight 47 gm., ovaries .058 gm., uterus .207 gm.). The same total dose was given in 20 days to 8 rats, which showed an average gain in ovarian weight of 525% and in uterine weight of 615% (ave. body weight 56 gm., ovaries .083 gm., uterus .240 gm.).

In another series, 23 rats received a total dose of 2.5 cc. of an acid

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1 Fluhmann, C. F., PROC. SOC. EXP. BIOL. AND MED., 1932, **30**, 149.

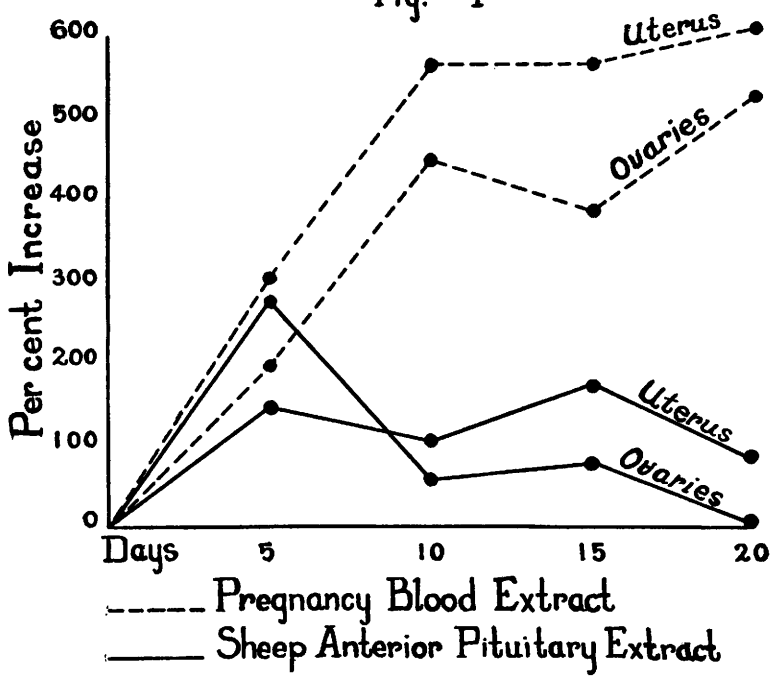
2 Fluhmann, C. F., PROC. SOC. EXP. BIOL. AND MED., 1933, **30**, 881.

3 Fluhmann, C. F., *Endocrinology*, in press.

extract of sheep anterior lobe made up so that 1.0 cc. of extract was equivalent to 500 mg. of the dried pituitary powder. The injection of this dose to 6 rats resulted in 5 days in an average increase in ovarian weight of 280% and in uterine weight of 152% (ave. body weight 32 gm., ovaries .048 gm., uterus .078 gm.). In 10 days, the average increase in weight of the ovaries of 5 rats was only 60% and of the uterus 111% (ave. body weight 35 gm., ovaries .019 gm., uterus .072 gm.). In 15 days, 6 rats gave an average increase in ovarian weight of 100% and in uterine weight of 175% (ave. body weight 41 gm., ovaries .022 gm., uterus .075 gm.). When the same total dose was given over a 20-day period to 6 rats, no increase in ovarian weight over uninjected controls was observed and the average increase in uterine weight was only 85% (ave. body weight 47 gm., ovaries .012 gm., uterus .055 gm.).

It is thus seen that in the case of the pregnancy blood extract there is a tendency to produce greater increases in ovarian and uterine weight as the period of administration is prolonged (Fig. 1). In a series of experiments comparing the results of 5 and 10-day periods of injection, it was found that this phenomenon is also characteristic of untreated human pregnancy blood serum, Antuitrin-S (Parke,

Fig. 1



Davis and Company), Collip's A-P-L extract of human placenta (Eli Lilly and Company), and Follutein (E. R. Squibb and Sons).

On the other hand, with sheep anterior pituitary extracts there is a marked diminution in the effect on ovarian weight when the period of administration is prolonged, and this finding also applies to acid extracts made from human hypophyseal tissue. An exception must be made for some instances when doses of anterior lobe extracts are employed which produce more than 1000% increase in ovarian weight in 5 days, as a greater response may then be obtained in 10 days. It would seem that in this case the ovaries are unable to respond completely to the excessive stimulus in the short period of 5 days.

Summary. The administration of a known total dose of an ovary-stimulating pregnancy blood extract over periods of 10, 15, or 20 days produced a much greater increase in ovarian and uterine weights of immature rats than when the same total dose was given in 5 days. The opposite result was obtained with acid extracts of sheep anterior pituitary glands, as the injection of a known dose in 5 days produced a greater increase in ovarian weight than when the administration of the same total dose was spread out over periods of 10, 15, or 20 days.