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## Effects of Megestrol Acetate, A Progestin, on Female Rats

LENORE SOUTHAM

*Abstract.* Silastic (dimethylpolysiloxane) capsules containing megestrol acetate (6-methyl-17 $\alpha$ -acetoxyprogna-4,6-diene-3,20-dione) were implanted subcutaneously in mature female rats. The effects of megestrol on the ovary, on fertility, on body weight, on adrenal weight, and on physical activity were observed.

Megestrol acetate did not inhibit ovulation or fertility, and did not reduce ovarian weight; thus it did not have an anti-gonadotrophic effect at the dosages used. It affected vaginal cytology in a typical progestational fashion producing a constant diestrus or mixed cell smear.

Body weight increased during treatment and remained fairly constant after treatment stopped. Adrenal weight decreased during treatment and returned to normal after treatment stopped. These two effects may contribute to a decreased physical activity observed in some rats. Continuing obesity after treatment stopped may account for the failure of some rats to regain normal activity. Obesity may also be a factor in the inhibition of mating behavior observed in some of the animals.

Progesterone is a steroid hormone produced by the corpus luteum. It normally functions to stimulate the uterine epithelium to secrete in anticipation of implantation of a fertilized ovum and is responsible for the constant diestrus vaginal cytology which is characteristic of pregnancy. It tends to inhibit ovulation by acting as an anti-gonadotrophin and may inhibit ACTH release or action when administered exogenously (1).

Synthetic progestins exhibit some of the same properties as progesterone, but not necessarily all of them nor to the same degree. Some synthetic progestins, for example, may induce adrenal atrophy while others have no apparent effect (1).

The following is a study of the effects of megestrol acetate (6-methyl-17 $\alpha$ -acetoxyprogna-4,6-diene-3,20-dione), a synthetic progestin, on mature female rats. It was initiated to study the anti-fertility properties of the drug and the effects of long term hormone therapy by means of slow release silastic (dimethylpolysiloxane) capsules implanted subcutaneously. These capsules release the hormone at a constant rate as long as any hormone remains (2). They presumably, therefore, offer a method of administration which is constant rather than periodic as are most other methods.

### METHODS

Silastic capsules (32 mm. long, 0.132" I.D., 0.183" O.D.) containing 5 mg. megestrol acetate suspended in 0.2 ml. sterile Upjohn suspending media 100 were implanted subcutaneously in the dorsal region of mature female rats. These capsules release approximately 70  $\mu$ g

of hormone per 24 hours per capsule in vitro (Kincl, unpublished data). The rats were divided into three experimental and one control group of 15 animals each. Group I animals received one capsule, Group II animals received two capsules, and Group III animals received four capsules implanted at two separate sites. The control group, Group IV, received one capsule per animal of suspending media only.

The capsules were removed from five animals in each group 10 weeks after implantation. All surgery was performed using ether anesthesia. Food and water were supplied ad libidum. Vaginal smears were taken daily for two weeks during treatment and for three weeks after treatment stopped. Smearing was started about three weeks after implantation of the capsules to minimize the effect of stress on the animals. Body weights were recorded at the start of treatment and periodically throughout the experiment.

Males and females from each group were placed together in a ratio of three to two for three to seven days on Day 42 and again on Day 66 after implantation. Daily smears for sperm were taken and females showing sperm was autopsied after 10 days.

The general physical activity was observed and the four groups were compared qualitatively during and after treatment.

The females were autopsied either after mating, during megestrol treatment, or after cessation of treatment. Body, adrenal, and ovarian weights, and the number of corpora lutea, were recorded in mated rats. The capsules were recovered and checked visually for the presence of the medication. It was visible in all cases and the availability of megestrol acetate was, therefore, assumed to be constant.

### RESULTS AND DISCUSSION

Results are summarized in Tables 1 and 2 and in Figure 1.

Table 1  
Cycling Pattern During and After Treatment

Type of Cycle	After Treatment				During Treatment			
	I	II	III	IV	I	II	III	IV
4-5 days .....	—	—	—	15	5	2	4	5
Irregular .....	9	6	—	—	—	2	1	—
Not cycling .....	6	9	15	—	—	1	—	—

Table 1: Megestrol acetate affected the cycling pattern in all experimental groups in proportion to the dosage. The controls, Group IV, exhibited a normal 4- to 5-day cycling pattern.

Ovulation occurred in all rats during treatment as indicated by the presence of corpora lutea in the ovaries of all rats. Ovarian weights were within the normal range. Normal fertility was indicated by comparable numbers of uterine implantation sites in the mated females from each group. These indicate that the ovary was not materially affected by megestrol treatment at the dosages used.

Table 2  
Autopsy Data

Group No.	Mean Body Weight (gms.)		Mean Organ Weight (mgs.)		Uterine Implantation Sites
	Initial	Final	Adrenals	Ovaries	
I	267	T 347	65.1	86.6	13.4
		P 368	77.4	89.0	
II	271	T 365	62.6	82.2	12.2
		P 363	75.5	84.2	
III	276	T 400	66.1	86.9	10.0
		P 388	80.1	80.7	
IV (Control)	273	T 340	79.7	104.9	12.5
		P 360	86.5	74.2	

Table 2: T: Data on rats autopsied during treatment. P: Data on rats autopsied after cessation of treatment. Standard error was calculated for all weights and for the number of uterine implantation sites. All weights and the number of uterine implantation sites were within one standard error except for the T final body weights of Groups II and III, the P final body weight of Group III, and the T adrenal weights of Groups I-III which were within two standard errors of the control weights.

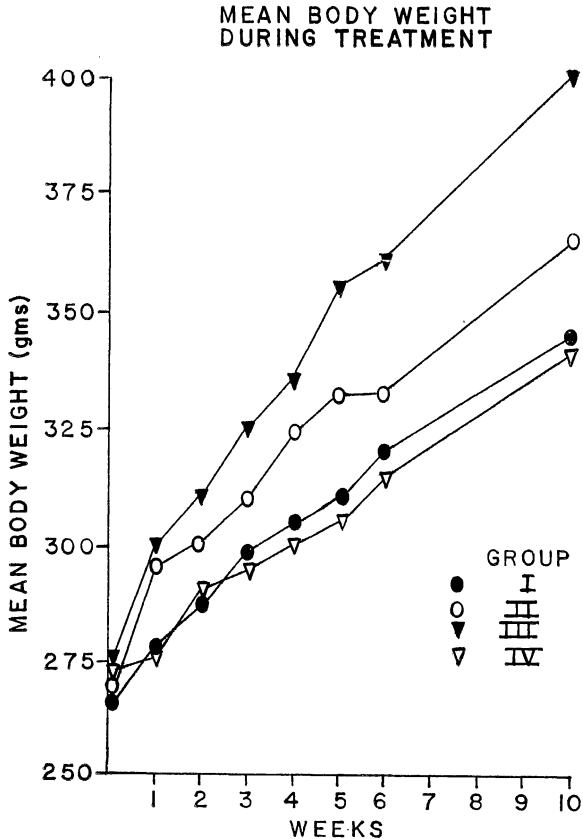


Figure 1. The mean body weight gain is proportional to the dosage of megestrol acetate.

The vaginal cytology, which normally exhibits a four- to five-day cyclical pattern, was affected in all treated groups and was normal in the controls. The degree of effect was roughly proportional to the dosage of the drug. No cyclical change was apparent in any of the Group III animals or in a large proportion of the Group I and II animals. Some of the Group I and II animals exhibited irregular cycling characterized by mixed-cell vaginal smears. The irregular cycling is probably due to concurrent effects of endogenous and exogenous hormones, while no apparent cycling is probably due to complete masking of the endogenous hormonal effects by the exogenous hormone.

Vaginal cytology is ordinarily a reliable index of the ovarian cycle and the ovarian cycle is controlled by pituitary gonadotrophins. The release of gonadotrophins is controlled largely by the response of the hypothalamus to steroid hormone feedback from the ovaries. Exogenous hormones may influence the vaginal cytology directly or via a pituitary-ovarian pathway. In the present study, the effect was apparently local since the ovaries did not appear to be influenced.

The vaginal cycling pattern returned to normal in most rats after treatment was stopped. The failure of a few animals to return to the normal cycling pattern may have been due to causes other than the treatment. In any case, the number of animals involved is too small to establish a positive correlation.

Megestrol treatment resulted in increased body weight in animals in Groups II and III. The gain was proportional to the dosage. The variation in amount of gain from animal to animal within a given group, illustrated by a larger standard error in the calculated weight of treated groups, may be due to location of the capsule in regions with differing vascularity. A low vascular supply might reduce the rate of absorption of exogenous hormone. Another factor might be the formation of fibroblast tissue around the capsules. This would reduce the rate of diffusion of hormone from the capsule. The animals did not lose weight after the capsules were removed, but neither did they continue to gain.

Adrenal weight decreased slightly during treatment indicating possible adrenal suppression. This effect was reversible. The adrenals returned to normal weight after the progestin capsules were removed.

Megestrol acetate treatment resulted in a decrease in apparent physical activity, especially in Group III. Most of the rats resumed normal activity after cessation of treatment. The decreased adrenal weight and decreased physical activity during treatment and the return to normal adrenal weight and physical activity after treatment suggests that the reduced activity may be due to decreased adrenal function. Another possible factor is obesity. The reduced activity remaining in some animals after treatment is probably a function of continuing obesity.

Inhibition of mating behavior in some animals may be related to obesity since in all cases animals which failed to mate were heavier than those which mated.

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