Sex Difference in the Effect of Progesterone on Body Weight of Mice. (18167)

J. J. TRENTIN.* (Introduced by W. U. Gardner.)
From the Department of Anatomy, Yale University, School of Medicine, New Haven.

In a number of species the female is normally smaller than the male. In the rat ovariectomy results in an increased body weight, to a level approaching that of the male. In the male, however, castration early in life results in no change or in a reduced body weight as compared to non-castrate controls(1-4). The effect of ovariectomy on body weight has been attributed to an elimination of the inhibiting effect of estrogen on body weight(4). The growth inhibiting effect of estrogen in a number of species has long been known. More recently progesterone has been reported to increase the body weight of rats(4-6).

During the course of an experiment designed to determine the effect of long continued progesterone administration on mammary tumor incidence of mice, a sex difference was observed in the effect of progesterone on body weight.

Methods. The mice used were first generation male and female AC_2 hybrids (C_3H ♀ x A ♂) and male AB_2 hybrids (CBA ♀ x A ♂). The female AC_2 mice were maintained as virgins and divided into two littermate controlled groups of 60 mice each, of ages ranging from 2 to 5 months at the start of treatment. One group received a 14 ± 1 mg pellet of progesterone subcutaneously every 28 days until death or sacrifice when death seemed imminent. The other group received no treatment. The considerably fewer animals in the progesterone treated group after 15 months of treatment (Table I) is the result of an earlier appearance of mammary tumors in this group. Weights of tumor bearing animals were not recorded. The male mice of each of the two stocks were divided into 8 groups, 4 intact and 4 castrated groups, each subdivided as follows: (a) untreated controls, (b) estrogen treated, (c) progesterone treated, (d) estrogen and progesterone treated. Estrogen treatment consisted of a 6 to 8 mg subcutaneous pellet composed of 25% diethylstilbestrol and 75% cholesterol. Such pellets are generally effective throughout the lifetime of a mouse. Progesterone treatment was the same as for the females. Castration was performed 1 to 3 days prior to the start of the experiment. The age of the mice used ranged from 1 to 5½ months at the start as indicated in Tables I to III. The oldest male mice at the time the experiment was set up were used as untreated controls in order to have the treated males as young as possible at the initiation of treatment. The reduction in number of mice in the estrogen treated groups with the passage of time is the result of mammary tumor development, and of the various other harmful effects of estrogen (bladder distension, hydronephrosis, scrotal hernia, etc.) All mice received Purina Fox Chow and water *ad libitum*.

Because the experiment was not designed with body weight changes in mind, the original body weights of the various groups were not obtained at the time treatment was started. Since the females were littermate controlled, it can safely be assumed that the initial body weights of the two groups were very similar. Among the males, the intact and castrated mice in each group were littermate controlled. Among the three classes of hormone treated males, the ages of the mice used were uniformly distributed within the age ranges indicated in Tables II and III. Differences un-

* Fellow of the Jane Coffin Childs Memorial Fund for Medical Research. This investigation has been aided by a grant from The Jane Coffin Childs Memorial Fund for Medical Research.

1. Stotsenburg, J. M., *Anat. Rec.*, 1909, v3, 233.
2. Bogart, R., Sperling, G., Barnes, L. L., and Asdell, S. A., *Am. J. Physiol.*, 1940, v128, 355.
3. Tang, Y. Z., *Anat. Rec.*, 1941, v80, 13.
4. Bogart, R., Lasley, J. F., and Mayer, D. T., *Endocrinology*, 1944, v35, 173.
5. Selye, H., *Canad. Med. Assn. J.*, 1940, v42, 113.
6. Gallardo, J. B. S., *Revista Soc. Argent. Biol.*, 1940, v16, 118.

TABLE I. Body Weights of Progesterone Treated Intact Virgin Female Mice (AC_2) and Their Untreated Littermate Controls.

	Age at start (mo.)	No. at start	Duration of treatment: 5 mo. Body wt (g)	5 mo. Age (mo.)	5 mo. No.	7 mo. Body wt (g)	7 mo. Age (mo.)	7 mo. No.	15½ mo. Body wt (g)	15½ mo. Age (mo.)	15½ mo. No.
Untreated controls	2-5	60	28.2	7–12	59	28.9	9–14	59	32.9	17–20	51
Progesterone treated	2-5	60	34.5	7–12	58	35.6	9–14	56	39.9	17–20	19

TABLE II. Body Weights of AC_2 Male Mice Receiving Estrogen and Progesterone Treatment, Alone and in Combination.

		Age at start (mo.)	No. at start	Duration of treatment: 7 mo. Body wt (g)	7 mo. Age (mo.)	7 mo. No.	15½ mo. Body wt (g)	15½ mo. Age (mo.)	15½ mo. No.
Untreated controls	Intact	4½–5	14	38.6	11½–12	14	38.2	20–20½	14
	Castrated	4½–5	13	40.0	11½–12	13	40.6	20–20½	13
Progesterone treated	Intact	1½–4½	16	38.5	8½–11½	16	39.0	17–20	15
	Castrated	1½–4½	17	38.3	8½–11½	17	37.1	17–20	17
Estrogen + Progesterone treated	Intact	1–5	15	33.7	8–12	15	36.8	16½–20½	4
	Castrated	1–5	15	31.9	8–12	15	33.1	16½–20½	8
Estrogen treated	Intact	1–5	16	28.9	8–12	12	33.6	16½–20½	2
	Castrated	1–5	16	28.4	8–12	14	27.4	16½–20½	2

TABLE III. Body Weights of AB_2 Male Mice Receiving Estrogen and Progesterone Treatment, Alone and in Combination.

		Age at start (mo.)	No. at start	Duration of treatment: 8 mo. Body wt (g)	8 mo. Age (mo.)	8 mo. No.	16½ mo. Body wt (g)	16½ mo. Age (mo.)	16½ mo. No.
Untreated controls	Intact	5½	13	39.1	13½	13	40.6	22	13
	Castrated	5½	12	39.1	13½	11	37.7	22	10
Progesterone treated	Intact	4–5	13	38.1	12–13	13	37.5	20½–21½	13
	Castrated	4–5	14	37.4	12–13	14	37.6	20½–21½	11
Estrogen + Progesterone treated	Intact	4–5	12	34.1	12–13	9	35.7	20½–21½	5
	Castrated	4–5	13	32.9	12–13	12	31.9	20½–21½	3
Estrogen treated	Intact	4–4½	18	30.8	12–12½	16	37.2	20½–21	4
	Castrated	4–4½	18	30.0	12–12½	17	31.9	20½–21	7

doubtedly existed between the original weights of the older untreated males and the younger treated males, particularly in the AC_2 mice. This difference, however, is minimized by the long-term nature of the experiment, such that one is dealing eventually with maximum body weights attainable on each regime. Since the mice are F_1 hybrids of inbred strains their growth potential should be highly comparable.

Results. Several months after treatment was started, it became visibly apparent that the progesterone treated virgin females had attained a considerably larger body size than their untreated littermates. At the first weighing, after 5 months of treatment, the progesterone treated females averaged 6.3 grams (22%) heavier than their littermate controls. This prompted the recording of weights among the male mice also, with the surprising finding of no increase in body

weight of the progesterone treated males over the controls, after as long as 16½ months of treatment (Tables II and III). A protective action of progesterone against the body weight suppressing effect of estrogen is, however, apparent in all but the 16½ month weights of the AB_2 males. The lack of effect among the reduced numbers of AB_2 mice at this time may be the result of (a) selective mortality of the mice more susceptible to the harmful effects of estrogen, (b) bladder distension with urine retention in the surviving estrogen treated mice.

Discussion. The difference in the effect of progesterone on body weight of the male and female mouse suggests that the action of progesterone on body weight is not a direct anabolic effect, but rather an indirect effect dependent upon some mechanism present or possible in the female mouse but not in the male mouse. In this regard it is interesting to speculate that the mechanism of action of progesterone on body weight of the female mouse may be to a large extent identical with that of ovariectomy. Progesterone is known to suppress FSH secretion, rendering the ovary non-cyclic and reducing estrogen secretion (7-9). The suppression of the secretion of growth inhibiting estrogen may be largely responsible for the greater growth of the progesterone treated intact female. To this may be added the above mentioned effect of progesterone in partially protecting the animal against the growth inhibiting action of any estrogen that may be secreted. Vaginal smears taken on the control and progesterone treated females confirmed the effectiveness of progesterone in suppressing ovarian activity and/or over-riding the effect of estrogen on the vagina under the conditions of this experiment. Vaginal smears taken 5 and 15 months after initiation of treatment showed no positives among the progesterone treated females (260 smears) while simultaneous smears (263) among the controls averaged 23% positive. Opposed to such an interpretation of the mechanism of action of progesterone on body weight is the possibility that in the rat progesterone may increase the body weight of males or ovariectomized females. The data in this regard, however, are conflicting and inconclusive. In groups of 6 rats receiving 2 mg of progesterone daily for 3 weeks, both the males and females gained more than their respective controls. The effect was greater in the females than in the males(5). In groups of 6 rats receiving 10 mg of progesterone daily for 10 days, young castrated progesterone-treated males gained the same as their controls, while old castrated progesterone treated males gained less than their controls(10). In groups of 2 rats receiving 5 mg of progesterone daily for 9 weeks the treated rats, both male and female, gained more than their controls. However, the extent of the difference was not statistically significant(6). In ovariectomized female rats receiving .05 mg of progesterone daily for 3 months, three large treated rats gained more than their untreated controls while 4 young treated rats gained the same as their controls(4). The need for further observations on possible differences in the action of progesterone on the body weight of the male versus the female and of the intact versus the ovariectomized female is indicated.

Summary. Virgin female mice receiving long term progesterone treatment attained an appreciably greater body weight than their untreated littermate controls. Male mice, both intact and castrate, receiving the same progesterone treatment failed to attain a greater body weight than their untreated controls. Progesterone exerted a protective action against the body weight suppressing effect of estrogen.

7. Selye, H., Browne, J. S. L., and Collip, J. B., PROC. SOC. EXP. BIOL. AND MED., 1936, v34, 472.

8. Burrows, H., *J. Endocrinol.*, 1939, v1, 417.

9. Biddulph, C., Meyer, R. K., and Gumbreck, L. G., *Endocrinology*, 1940, v26, 280.

10. Selye, H., and Albert, S., *J. Pharm. Exp. Ther.*, 1942, v76, 137.

Received September 6, 1950. P.S.E.B.M., 1950, v75.