Antifibromatogenic Effects Produced by the Intermittent Action of Progesterone*†

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Abdominal fibroids and other toxic reactions induced by estrogens can be prevented by the simultaneous administration of progesterone; production of progesterone or other antifibromatogenic steroids might then tentatively be interpreted as a means of a bodily autodefense (1). But secretion of progesterone in the ovary is an intermittent phenomenon; so the question arises whether abdominal fibroids due to a prolonged administration of fibromatogenic quantities of estrogens can be prevented also by an *intermittent* action of progesterone as was the case with the *continuous* one in our former experiments.

Tablets of estradiol dipropionate were implanted subcutaneously into castrated female guinea pigs; tablets of progesterone also were implanted into these animals 10 days later but withdrawn after another 10 days, to be afterwards implanted again, and so forth (see Fig. 1). The progesterone tablets were prepared from a mixture containing 40 per cent of progesterone and 60 per cent of cholesterol; they weighed 63 to 128 mgm. They were 5 mm. in diameter and several mm. in thickness; repeated withdrawal without breakage was facilitated by their volume, form, and consistency.

The fibromatogenic effect was classified according to the rules explained in a former paper (2), and was compared with that obtained in a group of animals in which tablets of estradiol dipropionate alone were implanted.

As may be seen from Table I all animals with estradiol dipropionate alone, acting for 103 to 108 days or less, had abdominal fibroids with an average fibrous tumorous effect (F.T.E.) of 7.2. There were large uterine, apical, mesenteric, and splenic tumors. Seven out of 12 animals surpassed the average F.T.E. On the contrary, there was in the estradiol-progesterone group (50 days of simultaneous action of estradiol and progesterone, and 53 to 56 days of estradiol alone) not a single animal that would have reached the average of the estradiol group. The number of animals with tumors of classes 2 and 3 (about 3 to 6 mm. in diameter or more) dropped greatly. The average F.T.E. in the estradiol-progesterone group was only 2.5. The significant difference between the two groups was more than 5.

The preventive effect of the discontinuous action of progesterone became manifest also with respect to the uterus. As seen from the table the uterine weight in the estradiol-progesterone group was considerably smaller than in the estradiol group.

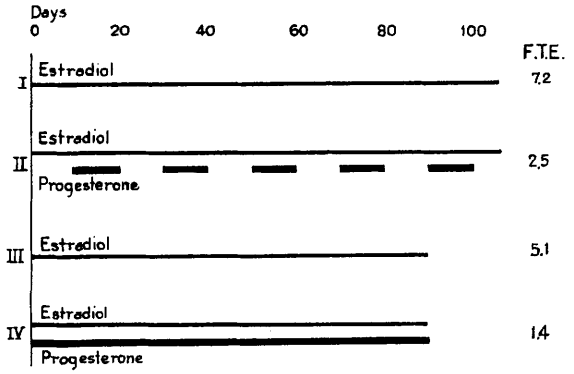

FIG. 1.—Comparative results with discontinuous (I-II) and continuous (III-IV) action of progesterone against estradiol. In the continuous progesterone group quantities of the steroid were absorbed that were near the antifibromatogenic threshold; in the discontinuous group quantities several times greater were used. Prevention of abdominal fibroids was effective in both cases, but was less complete with the discontinuous action. This might have been partly due to the greater duration of the experiments in the discontinuous group.

F.T.E.—average fibrous tumoral effect of the respective group.

The results above leave no doubt that abdominal fibroids induced by estrogen can be prevented by the intermittent action of progesterone, as by its continuous action, but the prevention was less complete. For the sake of comparison we may refer to a group of 14 animals that were under the simultaneous and continuous action of estradiol and small quantities of progesterone for 90 days (3; see Table II, Group Ib;

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also Fig. 1 of the present paper). The quantities of progesterone absorbed daily during the discontinuous progesterone periods (50 days) were 2 to 3 times greater than the quantities absorbed daily in the continuous progesterone group during 90 days in the tancously implanted tablets of estradiol can be prevented by progesterone, even when the antifibromatogenic steroid is allowed to act only intermittently.

These findings support the concept that the rhythmic secretion of progesterone in the ovary is a means of

TABLE I

Upper part: Castrated female guinea pigs under continuous action of estradiol dipropionate during 103 to 108 days. Lower part: Discontinuous interaction of progesterone—10 days free of progesterone, and 10 days with progesterone, etc.

No.	Estradiol absorbed daily * during 103 to 108 days, μgm.	Progesterone absorbed daily during 50 days, μgm.	Weight of uterus, gm.	Fibrous tumorous effect (F.T.E.), Total units †	Class of tumors ‡			
					Uterine	Apical	Dig. tract and abd. wall	Spleen
14	31	0	7.0	**2.5**	0.5pm.	1	0.5f.	0.5s.
8N	42	0	3.0	**2.5**	0	2	0.5u.bl.	0
2N	38 §	0	4.0	**5.0**	0	3	0	2
13	40	0	4.8	**6.5**	0.5pm.	3	3ms.	0
18	36	0	4.0	**6.5**	0	3	3ms.	0.5fs.
42N	27 ‖	0	5.6	**8.0**	2pm.	2	2ms.	2
10N	—	0	12.0	**8.0**	2ss., pm.	1	3ms., d.	2
17	39	0	4.3	**8.5**	2ss., pm.	3	3ms.	0.5f.
11	34	0	—	**9.0**	2pm.	3	3ms., pr.	1
12	42 *	0	8.2	**9.5**	3pm.	3	3ms.	0.5s.
15	41	0	—	**9.5**	3pm., ss.	3	3ms., d.	0.5s.
16	34	0	—	**11.0**	3pm.	3	3ms., d.	2
8	46	29	4.9	**1.0**	0	0	0.5f.	0.5f.
2	33	25	2.5	**1.0**	0	0	0.5f.	0.5fs.
10	40	56	2.5	**1.5**	0	0	0.5f.	1
11N	51	—	4.7	**1.5**	1ss.	0	0	0.5s.
5	39	46	2.5	**2.0**	0.5ss.	0	0.5fs.	0.5f.
4	40	32	2.2	**2.5**	0	2	0.5f.	0
3	40	39	4.1	**2.5**	0	0.5f.	1fs.	1fs.
9	42	29	3.7	**3.0**	0	2	0.5fs.	0.5f.
1	44	25	4.2	**3.0**	0	2	0.5f.	0.5fs.
6	48	36	5.5	**4.5**	1ss.	2	1s.	0.5s.
7	56	67	3.5	**5.0**	2pm.	0.5fs.	2d.	0.5fs.

* Free estradiol; the weight of estradiol dipropionate divided by 1.41.
† The F.T.E. is the sum of the figures of the following four columns.
‡ For the system of classification see (2).
§ 74 days only ‖ 90 days only.
Abbreviations: f = fibrous strands; s = accumulation of small tumorous nodules ("tumorous seed"); fs. = fibrous strands and "seed" together present; pm. = parametric tumors; ss. = subserous tumors of the uterus; ms. = mesenteric tumors; pr. = tumors of the peritoneum: d. = tumors of the diaphragm; u.bl. = tumor of the urinary bladder.

earlier experiments of Lipschütz and others. This gives evidence that the less complete prevention in the discontinuous group was not due to unfavorable quantitative conditions. It might have been due partly to the greater duration of the experiments in the discontinuous progesterone group. But one may also tentatively suggest that the antifibromatogenic effect depends also upon the time of the progesterone action in relation to the time of the fibromatogenic action of the estrogen.

SUMMARY

Uterine and other abdominal fibroids induced in the female guinea pig by the prolonged action of subcutaneously implanted tablets of estradiol can be prevented by progesterone, even when the antifibromatogenic steroid is allowed to act only intermittently.

These findings support the concept that the rhythmic secretion of progesterone in the ovary is a means of bodily autodefense against the toxic and tumor-producing actions of estrogens.

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