

17178. Some Reactions of the Rat to Treatment with Progesterone and Estrone in Late Pregnancy.*

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Following the observation that extract of corpora lutea¹ prolonged pregnancy in the rat, reports on the effects of estrogens²⁻⁴ and progesterone^{4,5} on parturition in the rat have appeared. These reports have not included observations on the behavior of the treated animals at the normal time for delivery. Because pregnancy was allowed to continue the viability of the young at the normal time for delivery was not determined. The purpose of the present study is to observe viability of the young and labor in rats treated daily during late pregnancy with estrone, progesterone or a combination of estrone and progesterone.

Methods. In the strain of rats (Anheuser-Busch) used in these experiments the young were normally delivered in the night following the 21st day of pregnancy or in the morning of the 22nd day. The day that sperms were observed in the vaginal smear was counted as the first day of pregnancy. The hormone injection was continued daily from the time of the first injection. The young were removed in the afternoon of the 22nd day by hysterectomy in animals that had not delivered spontaneously. The passage of blood from the vagina was regarded as evidence of uterine bleeding. Confirmatory evidence of uterine bleeding was obtained when the young were removed.

Results. A summary of the results ob-

tained is shown in Table I. Although uterine bleeding occurred in the 3 animals given 1 mg of progesterone, attempts to deliver the young were seen in only 1. The other 2 rats were quiescent and contraction of abdominal muscles observed prior to parturition in normal animals was not seen. At the time of removal 20% of the young were dead. No labor attitudes or uterine bleeding occurred in 4 animals given 2.5 mg of progesterone and these animals remained quiet and showed no evidence of efforts to deliver the young. Only 3% of the young were dead at the time of removal.

The well-known tendency of estrogen to terminate pregnancy led us to attempt to bring about spontaneous delivery of young in late pregnancy. The data in Table I indicate that administration of estrone in late pregnancy may either prevent parturition or accelerate delivery. It was found that daily injection of 25 γ of estrone started on the 19th or 20th day of pregnancy caused prolonged labor but failure to deliver the young by the end of the 22nd day. One animal given 100 γ of estrone on the 20th day delivered young 1 day premature less than 20 hours after the injection. In 4 animals treated with 25 γ of estrone about 24 hours before time for delivery parturition seemed to be accelerated rather than prevented; about 12 to 18 hours after the first injection the animals became extremely active and delivered the young promptly. A point of particular interest is the sharp contrast in behavior of the estrone-treated animals as compared with the ones given progesterone. Those estrone-treated animals requiring removal of the young showed vigorous and prolonged efforts to deliver spontaneously. In the rats treated with estrone 40% of the young were dead on the 22nd day of pregnancy.

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¹ Nelson, W. O., Pfüfner, J. J., and Haterius, H. O., *Am. J. Physiol.*, 1930, **91**, 690.

² Hain, A. M., *Quart. J. Exp. Physiol.*, 1935, **25**, 131.

³ D'Amour, F. E., and Dumont, C., *Quart. J. Exp. Physiol.*, 1937, **26**, 215.

⁴ Boe, F., *Acta path. et Microbiol. Scandinav.*, suppl. 36, 1938.

⁵ Imaz, F. A. U., *Prensa Méd. Argent.*, 1943, **30**, 2309.

TABLE I.
Effects of Progesterone and Estrone in Late Pregnancy in the Rat.

Rat No.	Treatment daily*	Day begun	Delivery	Fetuses	Remarks
31	1 mg P†	19	Removed§	5 living, 4 dead	No labor. Uterine bleeding
32	1 mg P	19	"	11 "	" " " "
35	1 mg P	19	"	4 " 1 "	Labor. Uterine bleeding
42	2.5 mg P	19	"	10 "	No labor. No uterine bleeding
44	2.5 mg P	19	"	9 "	" " " "
45	2.5 mg P	19	"	7 "	" " " "
46	2.5 mg P	19	"	9 " 1 "	" " " "
50	200 γ E‡	19	Autopsy	8 "	Died 24th day after prolonged labor
51	25 γ E	19	Removed	2 " 5 "	Labor. Uterine bleeding
55	100 γ E	20	Spontaneous	11 "	1 day premature
56	25 γ E	20	Removed	1 " 6 "	Labor. Uterine bleeding
63	25 γ E	21	Spontaneous	3 " 3 "	22nd day of pregnancy
64	25 γ E	21	"	7 "	" " " "
65	25 γ E	21	"	7 "	" " " "
66	25 γ E	21	"	11 "	" " " "
71	25 γ E	18	"	4 " 5 "	Parturition delayed 1 day. Prolonged labor
81	100 γ E + 1 mg P	19	Removed	7 " 2 "	No labor. Uterine bleeding
82	100 γ E + 1 mg P	20	"	8 "	" " " "
92	25 γ E + 2.5 mg P	20	"	10 "	No labor. No uterine bleeding
93	25 γ E + 2.5 mg P	20	"	8 "	" " " "
1-5	None	—	Spontaneous	43 " 2 "	22nd day of pregnancy

* Except in rat No. 71, which received single injection.

† P = Progesterone.

‡ E = Estrone.

§ In all animals except Nos. 50 and 71, the young were delivered by hysterectomy toward end of 22nd day of pregnancy, if young were not delivered spontaneously.

The rats injected simultaneously with estrone and progesterone showed no effort to deliver the young and remained relatively inactive. It is possible, however, that labor may have occurred in some of the animals during the night when the animals were not under observation. Uterine bleeding was seen only in the 2 animals given large amounts of estrone. Only 6% of the young were dead.

Discussion. In only 2 studies of which we are aware has the daily injection of crystalline progesterone been continued in the rat beyond the normal term of pregnancy. Pregnancy was prolonged by daily injection of 1 mg of progesterone started the 18th day of pregnancy⁴ and by 0.5 mg daily started on the 16th day.⁵ The observation⁶ that 2 Corner-Allen Rb. U. (2 mg) of progesterone are required to maintain pregnancy in the ovariectomized rat suggested to us that the dosages of this hormone used in the above

studies on parturition may not completely prevent labor. In the rabbit, for example, it has been shown that 1 mg of progesterone maintains pregnancy after removal of the ovaries⁷ while 1.5 mg is required to prolong pregnancy significantly.⁸ Our results show that 2.5 mg of progesterone daily are required to prevent uterine bleeding when injections are begun on the 19th day of pregnancy.

It has been shown⁴ that 600 γ and 300 γ of estrone benzoate given daily from the 16th to the 22nd day of pregnancy in the rat kills most of the young and delays delivery. Similar results² were obtained in the rat with daily injection of 125 γ to 500 γ of estrogens begun late in pregnancy. Heckel and Allen⁹

⁷ Allen, W. M., and Corner, G. W., *Proc. Soc. Exp. Biol. and Med.*, 1930, **27**, 403.

⁸ Heckel, G. P., and Allen, W. M., *Am. J. Physiol.*, 1937, **119**, 330.

⁹ Heckel, G. P., and Allen, W. M., *Endocrinology*, 1939, **24**, 137.

⁶ Rothschild, I., and Meyer, R. K., *Proc. Soc. Exp. Biol. and Med.*, 1940, **44**, 402.

found that during daily injection of estrone in pregnant rabbits beginning on the 29th day 400 I.U. killed the young but did not significantly delay parturition and 1000 I.U. prevented delivery; delivery occurred normally on the 32nd day in this strain of rabbits. The prevention of parturition in the rabbit was regarded as due primarily to prolongation of the functional state of corpora lutea. The prolongation of pregnancy in the hypophysectomized rabbit¹⁰ and in the rat¹¹ by treatment with estrogens was similarly interpreted. Our findings that estrone injection started on the 19th day of pregnancy in the rat brought about vigorous but ineffective efforts to deliver young while progesterone treatment started on the same day induced quiescence, suggest that estrone plays a role in the prevention of parturition in the rat other than by way of its action on the corpora lutea. Because estrone apparently increases the frequency and intensity of contraction of abdominal muscle, it is suggested that failure to deliver the young is due to obstruction of the birth canal possibly as a result of failure of relaxation in the region of the cervix. In the rat wide abdominal incision during parturition practically stops transport and expulsion of the fetuses and closure of the incision restores both processes.³ This observation, which was interpreted as evidence that contractions of the diaphragm and ab-

dominal muscles provide the primary force for delivery of young, supports our view that failure of expulsion in estrone-treated rats showing vigorous labor is due to failure of uterine relaxation.

Our observation that progesterone injection started simultaneously with estrone treatment on the 19th or 20th day of pregnancy prevents labor, uterine bleeding and death of young suggests that the death of fetuses induced by estrone may be due, at least in part, to intense but ineffective labor.

Summary. Progesterone (2.5 mg daily) beginning on the 19th day of pregnancy in intact rats prevents labor, uterine bleeding and parturition. Estrone (25 γ) started on the 19th or 20th day induces uterine bleeding, vigorous but ineffective labor and death of fetuses. Estrone (100 γ) begun on the 20th day in 1 animal brought about delivery of young 1 day premature. Spontaneous delivery occurred in 4 rats given 25 γ of estrone about 24 hours before time for delivery. Progesterone (2.5 mg) given simultaneously with estrone (25 γ) beginning on the 20th day has the same effect as progesterone alone, preventing the above effects of estrone alone. It is suggested that estrone plays a role in the prevention of parturition in the rat other than by way of its action on the corpora lutea.

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17179. Urinary Excretion of Phosphate Following the Injection of Sodium p-Aminohippurate.

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In the course of recent studies of osmotic diuresis in man,¹ the rate of urinary excretion

of phosphate was found to be increased following the injection of sodium p-aminohippurate. Although PAH has been found to

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¹ Rapoport, S., West, C. D., and Brodsky, W. A., *Am. J. Physiol.*, in press.