

this explanation is a valid one in view of the absence of any observable hemorrhage in this region or within the ventricles. Only 8 animals were operated; all 8 showed the same qualitative symptoms, there being only a slight quantitative difference. If such symptoms were due to hemorrhagic involvement of the brain-stem, it would seem remarkable that such a similar group of symptoms could be produced in 8 consecutive animals, without any evidence whatever of other symptoms such as rigidity of a decerebrate type or impairment of the respiratory mechanism. Furthermore, the nature of the symptoms was a constant finding in all animals regardless of their period of survival, although quantitatively there was some diminution in later stages.

8907 C

Stimulation of Birth-mechanism in Experimentally Monotocous and Oophorectomized Rats.

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It was demonstrated recently¹ that ovarian ablation in the rat during the last third of pregnancy need not interrupt this condition, providing the litter being carried has been surgically reduced to one fetus and that the placentae of the fetuses removed have been allowed to remain intact. Under these circumstances, however, the animals fail to deliver and the young, to be obtained alive, must be recovered by operative procedure; retention *in utero* much beyond the normal time of parturition serves progressively to compromise their viability. It seems improbable that failure of birth is due to the manipulations involved since control animals, receiving similar treatment save for retention of one ovary, will litter at the usual time. In failure of the birth mechanism the rat appears to differ from other species reported to carry to term following upon oophorectomy; the guinea pig, for example, spayed during the latter half of pregnancy, frequently continues to term and to normal delivery;² substantially the same situation prevails for the mare³ and, as is well known, for the human being.⁴

¹ Haterius, H. O., *Am. J. Physiol.*, 1936, **114**, 399.

² Nelson, W. O., *Endocrinol.*, 1934, **18**, 33.

³ Hart, G. H., and Cole, H. H., *Am. J. Physiol.*, 1934, **109**, 320.

⁴ Ask-Upmark, M. E., *Acta obst. et gynec. Scand.*, 1926, **5**, 211.

The marked rigidity and contraction of the uterus in cases of uninterrupted pregnancy suggest either that it has become insensitive to, or that it lacks, the stimuli involved in the processes of labor. Since oestrin serves as a powerful, and in certain respects a specific, sensitizer of uterine tissue⁵ it seemed probable, in the absence of ovaries, that deficiency in this principle might be an underlying factor in failure of birth. The present communication is concerned with the results of attempts at testing this possibility.

Female rats, prepared by unilateral tubal resection, were mated; resulting pregnancies were carefully timed and at laparotomy upon the 12th-13th day all fetuses in the fertile horn in excess of one were removed, the placentae being left *in situ*; in addition one ovary was extirpated. Uniformly upon the 15th day the remaining ovary was ablated. As reported elsewhere rats so prepared will usually carry to term but will fail in delivery, although the young may be recovered through timely surgical intervention.

In preliminary work, following upon complete oophorectomy, single, rather large doses of oestrin (Amniotin*) were administered as the animals approached term. In 7 cases dosages of 500 R.U. on day 20 or 21 of gestation failed to evoke a response. In 5 instances 2 daily doses of 500 R.U. produced no effect, beyond the appearance of cornified smears, and dead, somewhat macerated fetuses were recovered surgically upon the 24th day. It appeared that the normal course of events might more readily be simulated by daily administration of smaller quantities (25 and 50 R.U.) beginning soon after oophorectomy. Results were negative, however, in 12 animals employed. It was only when the daily dosage, although comparatively small, was markedly increased from day to day that a response at all resembling parturition was elicited, and the present report deals with results obtained in 5 series treated in this manner.

Series A. Commencing upon the day following complete oophorectomy, oestrin was administered in 3 daily injections in an effort to replace so far as possible the presumptive oestrin loss occasioned by ovarian removal. The dosage was arbitrary, for lack of accurate data, in this series being progressively increased, *i. e.*, 16 R.U. on the 16th day, 24 on the 17th, 32 on the 18th, 40 on the 19th, 48 on the 20th—a total of 160 R.U. over a 5-day period. Treatment was suspended after the 20th day. Considerable variation in response was encountered, 4 animals aborting upon the 19th day, 3 upon the 20th, and 3 carrying to term but failing in delivery; one

⁵ Reynolds, S. R. M., *Am. J. Obst. and Gynec.*, 1935, **29**, 630.

* The writer is indebted to Dr. J. A. Morrell, of E. R. Squibb and Sons, for generous supplies of Amniotin.

fetus was recovered alive, but deformed and not viable, on the 24th day. The fetuses aborted either were eaten or were recovered dead; one aborted on the 20th day was alive but died shortly after delivery.

Series B. In the second group the original dosage was doubled (32, 48, 60, 80, 96 R.U. upon successive days of the 5-day period). These all aborted on the 19th and 20th days, the vaginal smears displaying cornified cells mixed with leucocytes and blood from the third day onward. Two dead fetuses were recovered, the remainder apparently having been eaten.

Series C. Attempts were made to give a dosage such that 50% of the animals would abort, allowing the remainder to carry to the 21st day. Fifteen animals in this group were given 24, 36, 48, 60, 72 R.U. on successive days, treatment being suspended after the 20th day. Five animals aborted on the 19th and 20th days, displaying cornified and bloody smears. Ten animals carried through and were sacrificed on the 23rd day. From these 4 viable young were recovered, 3 living but not viable, 2 dead; the uterus of the remaining animal had been recently emptied.

Series D. (Table I.) The same dosage was employed in this series with the exception, however, that treatment was continued beyond the 20th day, the non-responsive animals receiving 96 R.U. on the 21st day and 120 R.U. on the 22nd. Of 12 animals used, 4 aborted on days 19 and 20, 3 on the 21st, and 3 on the 22nd day. Two of the young recovered on the 22nd day were viable and were reared by foster mothers. The remaining two of this series failed

TABLE I.
Influence of Oestrin Administration in the Monotocous Oophorectomized Rat.

Rat	Days Injected	Total R.U. Injected	Results
D38	16-18	108	Aborted 19th day; fetus not recovered
D33	16-19	168	" 20th " " dead
D41	16-19	168	" 20th " " not recovered
D26	16-20	240	" 21st " " living, not viable
D39	16-20	240	" 21st " " " " "
D23	16-20	240	" 21st " " recovered, half eaten
D28	16-20	240	" 21st " " living, viable
D30	16-21	336	" 22nd " " " " "
D24	16-21	336	" 22nd " " recovered, half eaten
D29	16-21	336	" 22nd " " living, not viable
D43	16-22	456	Sacrificed 24th day; dead, macerated fetus
D27	16-22	456	" " " Uterus empty (large and hyperemic)
Control Animals—Not Injected.			
DX12			Sacrificed 24th day; fetus living, viable
DX13			" " " " deformed, not viable
DX14			" " " " living, viable
DX15			" " " " " "
DX16			" " " " " "

to deliver and upon autopsy on the 24th day the uterus of one was empty and that of the other contained a badly macerated fetus.

Series E. (Table II.) In this group of 15 animals, treatment was not instituted until the 18th day of pregnancy, *i. e.*, on the 3rd day after complete oophorectomy; dosages were given as in Series D and were continued when necessary until the 24th day. Four animals aborted on the 21st day, 6 on the 22nd, 2 on the 23rd. The remaining 3 failed to respond and upon sacrifice (26th day) 2 dead fetuses were recovered; the uterus of the third was empty. It is noteworthy that of the 21-day series 2 young were alive when aborted, 1 of which was viable; of the 22-ray animals, 3 were alive and viable.† In a sense, therefore, the abortion induced at or near the time of normal term simulated parturition, *i. e.*, in that live and viable young were delivered. The process of expulsion, when observed, seemed to differ in no way from that occurring during normal parturition.

TABLE II.
Influence of Delayed Oestrin Administration.

Rat	Days Injected	Total R.U. Injected	Results on Fetus
E47	18-20	108	Aborted 21st day; living, viable
E51	18-20	108	" 21st " partly eaten
E56	18-20	108	" 21st " not recovered
E46	18-20	108	" 21st " living, viable
E50	18-21	168	" 22nd " " "
E48	18-21	168	" 22nd " " "
E59	18-21	168	" 22nd " not recovered
E52	18-21	168	" 22nd " living, viable
E58	18-22	240	" 23rd " not recovered
E61	18-21	168	" 22nd " dead, deformed
E54	18-23	336	" 23rd " living, not viable
E60	18-23	336	" 23rd " not recovered
E45	18-23	336	Sacrificed 25th day; cystic growth in uterus
E73	18-23	336	" " " dead, macerated
E71	18-24	456	" " " very large, dead
Control Animals—Not Injected			
EX21			Sacrificed 24th day; living, viable
EX22			" " " " "
EX25			" " " " " (very large)
EX31			" " " dead, macerated
EX33			" " " living, badly deformed, non-viable
EX27			" " " " viable

All animals were sacrificed immediately after uterine evacuation, the oophorectomies verified and the uteri examined. The latter were

† The practical difficulties involved in being on hand for every abortion resulted in failure to recover fetuses in many instances. It seems probable that some, at least, of the fetuses missed were alive at the time of expulsion but were promptly eaten—a characteristic cannibalism frequently displayed by the experimental female.

markedly hyperemic, large and well-nourished, comparing rather favorably with those of normal full-term females, and showing a marked contrast to the rigid, contracted tissues of untreated oophorectomized females. It is apparent that oestrin exercises some function during pregnancy, in the rat, in maintenance of the uterus and in this respect perhaps operates synergistically with progesterin.

A positive response, when elicited, followed upon a continuous, and progressive increase in, oestrin dosage; abortion occurred during treatment and, with one exception, no response was evoked following withdrawal of oestrin administration. The marked variation in response, however, was striking. Thus, in Series A, 4 animals responded to a total of only 72 R.U., and 3 to 112; 3 failed to respond to a total of 160 R.U., however. In B, 5 responded to 140, 5 to 220, and in C, 3 responded to 108 and 2 to 168, whereas 10 animals failed to react to a total of 240 R.U. Variations in Series D and E are shown in the tables, where it will be seen that 4 animals failed to respond to 336 and to 456 R.U. The quantity required to produce an effect, apparently, is subject to marked individual variation, and the manner and the time of oestrin administration would appear to be of greater importance than the amount administered.

The foregoing observations suggest that oestrin in adequate, timely amounts appears to be definitely involved in preparation of the uterine structure for parturition; whether this consists in a sensitization to the action of some other agency or whether oestrin in itself initiates the birth mechanism remains to be determined.

8908 C

Lead Content of the Spinal Fluid with Special Reference to Multiple Sclerosis.

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Lead was suggested as an etiological factor in multiple sclerosis by Putnam.¹ Cone, *et al.*,² examined a series of 40 spinal fluids for

¹ Putnam, J. J., *Boston M. and S. J.*, 1883, **109**, 315; *J. Nerv. and Men. Dis.*, 1883, **10**, 446.

² Cone, W., Russel, C., Harwood, R. N., *Arch. Neurol. Psych.*, 1934, **31**, 236.