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Ineffectiveness of Pitocin on the Sheep Gravid Uterus: The Role of Pitocinase.* (27023)

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Continuous slow infusion of a low concentration of oxytocin is highly effective in stimulating rhythmic contractility of the human uterus(1,2). With faster infusion, the uterus remains contracted. The effect of intravenous infusion on the uterus of other animals has not been tested although Assali *et al.*(3) have done so in a study on uterine blood flow in sheep. The present study was undertaken to compare the response of the myometrium of the ewe with that of the human to obtain a controlled means of stressing the fetus if the uteri of the 2 species behave similarly.

In pregnant women, rhythmic contractions of the gravid uterus can be induced in an otherwise virtually quiescent uterus. Strength and frequency vary progressively, within limits, with amount of pitocin infused(2). Sensitivity of the uterus increases as pregnancy advances. To obtain comparable outputs of contractility *(force, in mm Hg, X frequency of contraction per unit of time)*, Caldeyro-Barcia and Poseiro (2) found that Syntocinon dosage requirement decreased with increase in time of pregnancy.

We decided to investigate the sensitivity of the gravid sheep uterus in an exactly similar manner. Six pregnant ewes in the last half of gestation (circa 150 days) were used. Four ewes were lightly anesthetized with diallylethylbarbituric acid and urethane (Dial), 0.2 ml per kg of body weight, given intravenously. Two ewes were prepared under local anesthesia (Procaine) only.

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The ewe was placed on her side and part of the uterus delivered through a midline abdominal incision. Intrauterine pressure was recorded by a polyethylene catheter admitted to the amniotic sac and connected to a pressure transducer. At the same time, umbilical artery and vein pressures were recorded by small catheters admitted through branches of these vessels, as the membranes were maintained intact and the uterus closed after the operation. The fetus was *in utero*, in its normal habitat (4). In addition, maternal respiration was recorded from an intrapleural trocar and carotid arterial pressure by a catheter in that artery; the trocar and catheter were connected to Statham pressure transducers. Records were obtained on an ink-writing Offner recorder.

Syntocinon, synthetic pitocin, was infused into the jugular vein of the ewe by a continuous infusion pump (Harvard). Dilutions and rates of infusion were carefully controlled. After an initial 20-30 minute recording period, infusion was commenced, always starting at the lowest infusion rate. The starting rate was either 0.76 or 1.9 mμ Syntocinon per min. After 20 min the rate of infusion was doubled. This was repeated successively until 191-1928 mμ per min was being infused.

In no case was rhythmic uterine contractility observed prior to, or during, infusion of pitocin. An increase in tonus (intrauterine pressure) occurred. It will be seen that the onset of increased tonus commences with dose levels of 0.76 and 19.1 mμ of Syntocin per min (Fig. 1). The lowest thresholds (0.76 and 1.9 mμ per

TABLE I. Summary of Myometrial Response in the Ewe to Pitocin

Stage of Pregnancy (by fetal Kg wt)	Threshold of uterus to Pitocin (mμ/min)	Maximum tonus Developed (mm Hg)	Change in tonus over initial level (mm Hg)	Infusion rate of Syntocinon at max. tonus level (mμ/min)
0.6 (twins)	.76	10	10	10
1.25 "	1.9	10	10	382
3.0 (singlet)	7.6	(12)	(8)	(191)
3.75 "	7.6	15	14	191
3.75 (twins)	7.6	12	6	764
5.25 (singlet)	19.1	10	8	191

Figures in parentheses are below maximum level which was not determined.

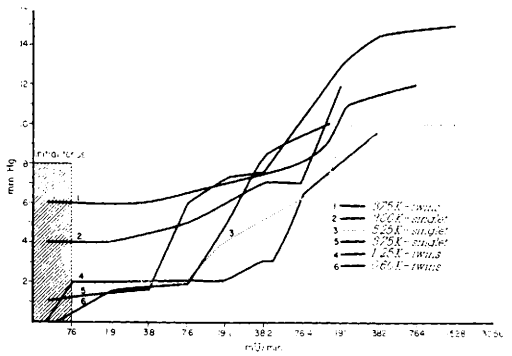

FIG. 1. Effect of pitocin on uterine tonus. Abscissa, amount of continuous infusion of pitocin per minute. Ordinate, pressure in mm Hg as recorded in the amniotic cavity.

min) are in the cases of the smallest fetuses (0.6 and 1.25 kg) in the middle trimester of pregnancy. The highest threshold (19.1 mμ per min) was in the case of the largest fetus (5.25 kg). The 3.0-3.75 fetuses were intermediate; the threshold for onset of increased tonus was 7.6 mμ per min.

Maximum tonus was only about 10-15 mm Hg, a fraction of the force developed by a mildly stimulated human uterus (40-60 mm Hg,3). The actual rise above the initial non-stimulated tonus was less (6-14 mm Hg), compared to the human (30-50 mm Hg). The infusion rate at the point of maximum tonus was very high (170-764 mμ per min) (Table 1).

No relation exists between rate of tonus increase or the magnitude of it and the initial, resting tonus, stage of pregnancy (i.e. fetal size) and the order of onset of increase of tonus with fetal size. There is no correlation between the half-way point of tonus increase and any of the foregoing factors. The data suggest that if initial tonus is high, the slope of the increase in tonus is low and conversely, that if initial tonus is low, the slope and height attained are high.

In short, the gravid myometrium of the ewe is relatively insensitive to infused pitocin, and it fails to exhibit the rhythmic contractility which the human shows under any reasonable dose of pitocin. The doses used span by many times the effective dose range used by Caldeyro-Barcia and Poseiro(2). Two post partum uteri and one non-gravid uterus of the ewe yielded results exactly comparable to the gravid uteri, as described.

Exploring for a basis for the difference between the ewe and the human, one is struck by a known but unappreciated fact. The human placenta is a source of the enzyme, pitocinase (5), and the blood levels of this substance reach a maximum at term when the human uterus is most sensitive to pitocin(6). On the contrary, the sheep is devoid of measurable blood pitocinase since only species having a hemochorial placenta elaborate this enzyme (7). We suggest that pitocin acts efficiently on the myometrium only in conjunction with the enzymatic splitting action of pitocinase. This interpretation accounts for the virtual non-reactivity of the uterus to pitocin in the ewe and the reactivity of the uterus observed in women. Moreover, it gives point to the otherwise unaccountable rise of a pitocin-inactivating substance at the time when, in women, pitocin is most effective.

Summary. Infusion of Syntocinon into pregnant ewes increased tonus but never induced rhythmic contraction of the gravid uterus. The infusion rates spanned a range of 0.76 to 1928 mμ per min. This is many times the effective infusion rate that elicits rhythmic uterine contractility in the human. Since sheep blood contains no pitocinase whereas that of the human

does, it is suggested that pitocin is effective in the presence of pitocinase.

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A Comparison of Some Properties of Polyoma Virus and Pneumonia Virus of Mice.* (27024)

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Polyoma virus (PY) and pneumonia virus of mice (PVM) are not related to each other serologically(1), but because of their similarity in size and their semi-ubiquitous presence in a latent form in mice, the possibility was considered that they belong to the same or related groups of viruses. Since sensitivity to ether serves to distinguish groups of viruses(2, 3), and since it is known that PY is ether resistant(4), the reaction of PVM towards ether was investigated. Ability of the 2 viruses to grow in tissue culture, and their *in vivo* effects on mouse lung were also compared.

Materials and Methods. Three strains of PY were used in these experiments. Strain LID-1 (5) was kindly provided by Dr. R. J. Huebner. Strain Lp or large plaque virus was derived by Dr. R. Dulbecco by single plaque isolation from a stock originally provided by Dr. W.P. Rowe(6,7). Sp or small plaque virus was isolated from transformed hamster embryo cells after exposure to Lp virus(7). Both Lp and Sp viruses were kindly provided by Dr. R. Dulbecco. The stocks of the various strains of polyoma assayed on secondary mouse embryo layers, according to the procedure of Dulbecco and Freeman(8), contained approximately the same number of plaque forming units, about $1x10^8$ PFU/ml.

A single stock of PVM was used. This had been prepared by Dr. F.L. Horsfall, Jr. in 1953 and had been stored at $-60°C$ since that time.

Standard procedures were used for intranasal infection of mice(9) and for preparation and infection of tissue cultures. Ether treatment was done according to the procedure of Andrewes and Horstmann(2).

Lung specimens were fixed in 10% formalin and stained with hematoxylin-eosin.

Results. Results of experiments on ether sensitivity of PVM are recorded in Table 1.

TABLE I. Ether Inactivation of Pneumonia Virus of Mice.

	Mouse ID50 per ml.	
Exp. No.	Control	Ether treated‡
1	7.5×10^4	No lesions at 10^{-2} dilution
2	5.8×10^4	idem. 10^{-1}
3	6.5×10^5	<7.0

‡ Virus was exposed to 20% ethyl ether for 18 hrs at 4°C.

Virus infectivity was measured by the ability to produce gross lesions in the lungs of weanling mice(9). The per cent of mice with lesions was plotted vs. dilution on probit paper and ID_{50}/ml was estimated graphically. In all experiments the virus appeared to be highly sen-

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