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THE BEHAVIOUR OF THE CERVIX UTERI *IN VIVO*

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The most important work on the behaviour of the cervix uteri is that of Newton [1934, 1937], who found that the cervical muscle, examined *in vitro*, was insensitive to the oxytocic principle of the posterior lobe of the pituitary and also that there was evidence of reciprocal activity between the cervix and the horn of the uterus. Observations on the activity of the horn of the uterus in different species indicate that there may be wide discrepancies between the behaviour of excised tissues and the behaviour of the same tissues in the intact animal. In view of this difficulty and its importance in relation to the theory of parturition we thought it advisable to repeat the experiments on the cervix *in vivo*. By investigating three species, guinea-pig, rabbit and cat, we hoped to make our conclusions as general as possible, since species differences are so common in this field.

Method

The movements of the cervix were recorded by placing a small rubber balloon in the cervical canal. These movements are very small, and it was soon apparent that the usual methods of volume recording by tambours were too easily upset by environmental changes at the sensitivity required. A new optical device was therefore designed and has already been described [Adler, Bell & Knox, 1941]. This apparatus has the advantage of giving immediate records on smoked paper. In all cases the capacity of the balloon was 0·3 c.c., this being approximately the capacity of the prism. The balloon was tied on the end of a fine metal cannula which carried a moveable sleeve with a cup-shaped end. After separating the bladder and vagina by blunt dissection the undistended balloon was inserted through a mid-line incision in the vaginal wall into the cervical canal, and the cup-shaped end was stitched to the lip of the cervix (Fig. 1). The cannula was then pulled back through the sleeve until the balloon was just touching the cup. The balloon was now fixed in the cervical canal, and could not slip forward into the uterine horn. The balloon and cannula were filled and connected to the recording device by a waterfilled tube; the balloon was thus under a pressure of 7 cm. of water. At the end of each experiment the position of the balloon was checked by inspection or by fixing the uterus *in situ*

with formalin without disturbing the balloon. When the uterus was laid open the cervix was easily recognized because of the granular character of its lining membrane. The apparatus was calibrated at the end of each experiment by substituting a graduated pipette for the cervical balloon. A scale was drawn on the smoked paper corresponding to hundredths of a c.c. change in volume.

The cornual movements were recorded by the cannula described by Bell & Robson [1936] and records were made directly on the smoked drum; no photoelectric amplification was necessary. We are satisfied that contractions of the cornu did not affect the cervical record. The experimental evidence for this is given later under the heading of 'evidence for the separate identity of the cervix and cornu'.

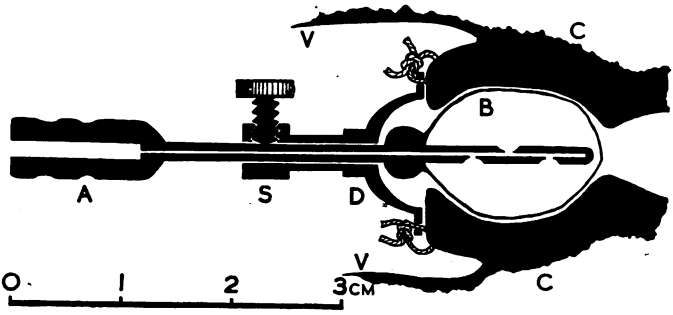

Fig. 1. Diagram of cannula and balloon in position in the cervical canal. *C*, cervix. *V*, vagina. *A*, cannula. *B*, balloon. *S*, sleeve. *D*, cup-shaped end of sleeve.

A small glass cannula with a rubber stopper was tied into the external jugular vein. All drugs were injected through this stopper by means of a hypodermic needle. The rigidity of the stopper prevented any alteration of volume on withdrawal of the needle, no blood was sucked into the cannula and clotting was avoided.

In certain of the experiments it was necessary to compare the effect of a quick injection with a continuous injection. A quick injection means that it was given in the usual way by means of a hypodermic syringe, the total time of injection being only a few seconds. A continuous injection, on the other hand, lasted in these experiments about 20 min. A block of wood on a lead screw driven by an electric motor through reduction gearing gradually pressed out the contents of a 10 c.c. syringe which was connected to the vein by a narrow rubber tube ending in a needle passed into the stopper of the non-clotting cannula.

Details of the pre-operative treatment of the animals will be found in the description of the results. Guinea-pigs were anaesthetized with chloralose given subcutaneously (7 mg./kg.), supplemented by ether when necessary. Rabbits and cats were anaesthetized with nembutal (50 mg./kg.) given sub-

cutaneously. In all experiments an attempt was made to estimate the threshold dose of oxytocin for both cornu and cervix, using a specially purified oxytocic hormone (purified pitocin), kindly supplied by Dr White of Parke Davis and Co. The other drugs used were adrenaline chloride (Parke Davis and Co.), acetylcholine (Pragmoline, May and Baker Ltd.), and vasopressin (Pitressin, stock sample, Parke Davis and Co.).

Results

The results of the experiments are summarized in Table 1. In the following description the word 'uterus' should be taken to include both cornu and cervix.

Guinea-pigs

Group I, non-pregnant. A fortnight after spaying, three animals were given 0·05 mg. oestrone in oil daily for 7 days; recording of uterine movements took place 3 days later. Three animals were given 1 mg. oestradiol dipropionate (kindly supplied by Mr Taylor of Ciba Ltd.) after spaying, the experiment being carried out a week later. Lastly, three intact animals were operated upon at oestrus; all showed large follicles in the ovaries.

Group II, non-pregnant guinea-pigs. Four animals received 0·05 mg. oestrone in oil for 7 days (as in group I); on each of the next 3 days they received 5 mg. of progesterone (Proluton, kindly supplied by Messrs Schering Ltd.). Records were made on the day after the last injection of progesterone. In addition, two intact animals were operated upon 7 days after the opening of the vagina (which occurs at oestrus), large corpora lutea being present.

Group III, pregnant guinea-pigs near term. These five animals were from 55 to 60 days pregnant. The age of the pregnancy was judged from the length of the foetuses [Bell, 1941].

Group IV, parturient guinea-pigs. Except in one case, these seven animals were operated on within 12 hr. of parturition. In one instance the experiment began within half an hour of delivery.

The spontaneous movements were in all cases measured at the beginning of the experiment before any drugs, except the anaesthetic, had been introduced into the circulation. The cervix showed spontaneous movements in twenty out of twenty-seven experiments; the amplitude depended more on the size of the cervix than on the hormonal condition of the animal. In those cases in which no cervical activity was noted early in the experiment it became evident later on. The frequency of the spontaneous contractions was higher in the cervix than in the cornu. As has been previously shown [Bell & Robson, 1936; Adler & Bell, 1943] there is very little difference between the behaviour of the cornual muscle in groups I and II; the threshold dose of pitocin in group III is much lower [Bell, 1941]. The cervix responded to injections of pitocin by contracting in all cases except two, in which the dosage may have been in-

TABLE 1. Summary of results

Group	No. in group	Average wt. g.	Extent and period of spontaneous movements: Cornu	Extent and period of spontaneous movements: Cervix	Threshold dose of pitocin in o.u.: Cornu	Threshold dose of pitocin in o.u.: Cervix	Effect of adrenaline: Cornu	Effect of adrenaline: Cervix	Effect of acetylcholine: Cornu	Effect of acetylcholine: Cervix	Effect of pitressin
I. Guinea-pigs treated with oestrin or those with ovarian follicles	9	473	2·8 cm. 6 min. 20 sec.	0·002 c.c. 2 min. 10 sec.	0·011 C (8) 0·1 N (1)	0·034 C (6) N (3)	N (5) R (3)	C (3) N (3) R (2)	N (3) C (1)	N (4)	—
II. Guinea-pigs treated with oestrin and progestin, or those with corpora lutea	6	427	2·4 cm. 1 min. 40 sec.	0·002 c.c. 1 min.	0·03 C (6)	0·06 C (2) 0·1 N (2) 0·005 N (2)	R (3) N (3)	N (4) C (1) R (1)	N (4) I (1)	N (5)	—
III. Pregnant guinea-pigs near term	5	588	1·7 cm. 5 min. 30 sec.	0·036 c.c. 6 min.	0·003 C (4)	0·011 C (4)	N (1) R (2) C (1)	N (2) R (1) C-R (1)	N (1)	N (1)	N (2)
IV. Parturient guinea-pigs	7	545	1·6 cm. 4 min. 40 sec.	0·019 c.c. 2 min. 40 sec.	0·018 C (4) 0·02 N (2)	0·015 C (6)	R (4) N (1)	C (2) I (1) R (1) N (1)	N (1)	N (1)	C of both (1)
V. Non-pregnant rabbits treated with oestradiol	3	2500	1·7 cm. 50 sec.	0·03 c.c. 2 min.	0·07 C (3)	1·0 C (1) 0·25 C (1) 0·5 R (1)	C (3)	C (1) C-R (2)	C (1)	C (1)	C (2) cornu N (2) cervix
VI. Pregnant rabbit	1	2600	1·5 cm. 1 min.	0·01 c.c. 1 min.	0·05 C (1)	0·05 N (1)	—	—	—	—	—
VII. Parturient rabbits	5	2250	3·8 cm. 1 min. 20 sec.	0·04 c.c. 40 sec.	0·017 C (5)	0·04 C (5)	C (2) C-R (1) I (1) R (1)	C-R (3) C (2)	C (2)	R (1) N (1)	C (2) cornu C (1) cervix N (1) cervix
VIII. Pregnant cat	1	7200	2·0 cm. 5 min.	0·01 c.c. 5 min.	0·1 C (1)	0·1 C (1)	R (1)	R (1)	—	—	—
IX. Parturient cats	2	2600	Nil	0·01 c.c. 30 sec.	0·02 C (2)	0·01 C (1) 0·3 C (1)	R (2)	C (1) C-R (1)	N (1)	N (1)	—

Abbreviations: C = contraction, R = relaxation, N = no effect, I = inhibition, C-R = contraction followed by relaxation. Numbers in brackets refer to number of cases, e.g. C (3) means a contraction obtained in three animals. o.u. = oxytocic units.

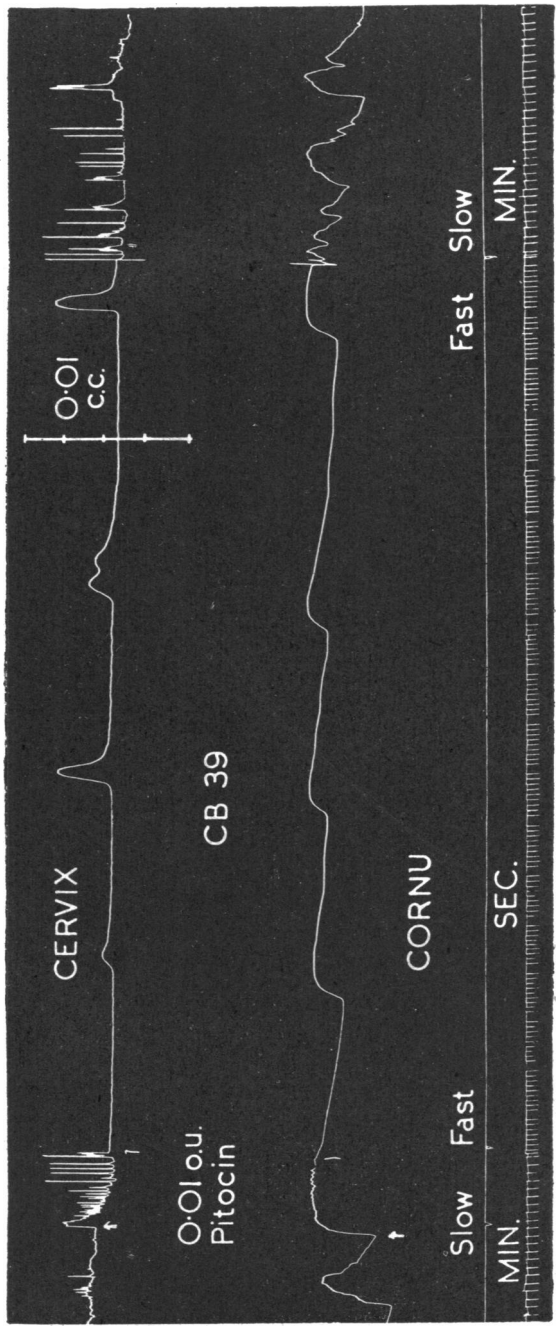

Fig. 2. CB 39. Guinea-pig, non-pregnant. Spayed and given 1 mg. oestradiol dipropionate. Tracing made one week later. Contraction of cornu and cervix after intravenous injection of 0·01 o.u. pitocin. Calibration scale in hundredths of a c.c. has been superimposed on the cervical tracing. In this and the subsequent tracings contraction is indicated by an upstroke.

adequate. The threshold dose required to produce a contraction of the cervix was about three or four times that required to produce a contraction of the cornu in the same animal. In addition, the cervical response to a given dose of pitocin was of very much shorter duration than that of the cornu; for example, in the case of CB 39 (Fig. 2), after the intravenous injection of 0·01 o.u. (oxytocic units) of pitocin, the rise of tone lasted for 3 min. in the case of the cervix, and for 20 min. in the case of the cornu. To explore this question further, continuous injections were given. Thus CB 53 was given 0·13 o.u. pitocin in 18 min.; the

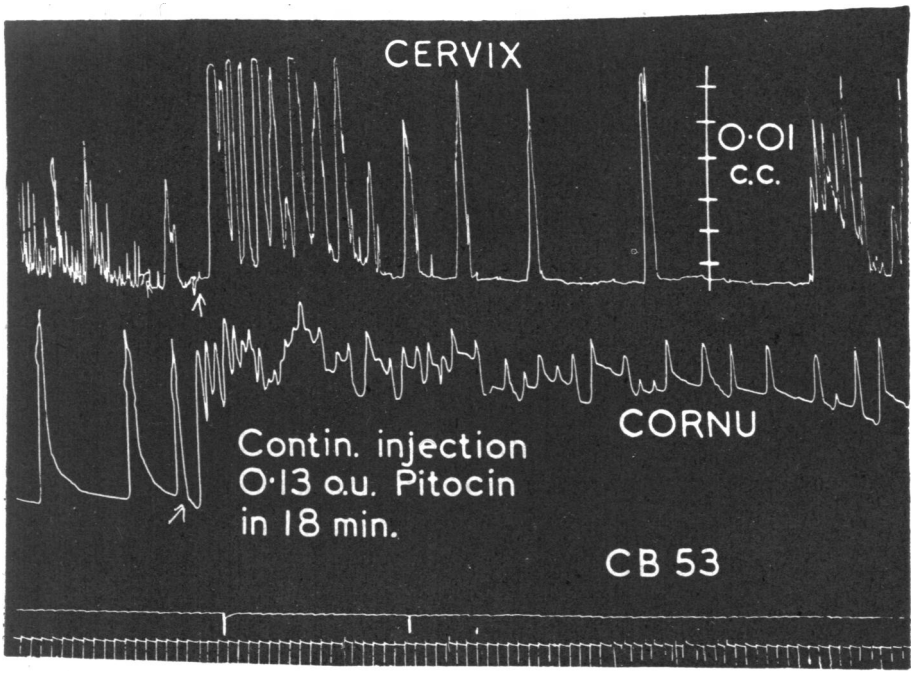

Fig. 3. CB 53. Guinea-pig, 5 hr. post-partum. Continuous injection of pitocin. Time tracing in minutes.

cornu showed increased activity for 1½ hr., whereas the effect on the cervix was over in about 18 min.; thereafter for about ¾ hr. the cervix was less active than before the injection (Fig. 3). A characteristic feature of many of the tracings, shown in both Figs. 2 and 3, was that after the short period of tonic contraction of the cervix following injection of pitocin there was for a time increased clonic activity, i.e. isolated contractions with intervening periods of complete relaxation. As shown in Fig. 3, while the cornu was still tonically contracted under the influence of pitocin, the intervals between the clonic contractions of the cervix steadily lengthened and were for a time much greater than before the injection of pitocin.

Rabbits

Group V, non-pregnant rabbits. These three animals were spayed and 5 days later were given 1 or 2 mg. oestradiol dipropionate; 1 week later the movements of the uterus were recorded.

Group VI, pregnant rabbit. From the length and weight of the foetuses [see table in Needham, 1931] this animal was approximately 27 days pregnant.

Group VII, parturient rabbits. These five animals were operated upon within 12 hr. of full-time parturition. In one case, one living foetus still remained within the uterine horn, two having been born shortly before the experiment.

The cervix and the cornu showed spontaneous movements in all nine cases, the largest amplitudes being shown by the parturient animals. The threshold dose of pitocin for the cervix was in all cases higher than that for the cornu, the range being from three to ten times. There was very little difference between the behaviour of the uteri in the three groups, except that the parturient animals were more reactive to oxytocin than the non-pregnant animals, in spite of the very large dose of oestrogenic material given to the latter.

Cats

Three non-pregnant cats were spayed and injected with large doses of oestrin, up to a total of 5 mg. of oestradiol dipropionate at intervals over 1 month. In all cases the cervix remained extremely narrow and rigid and did not permit the passage of the balloon.

Group VIII, pregnant cat. This animal was approximately 1 week prepartum judged by the length of the foetuses [see data in Windle & Griffin, 1931].

Group IX, parturient cats. Records were obtained from these two animals within 12 hr. of normal full-time delivery.

In this species it was again found that the cervix contracted after an injection of pitocin, was less reactive than the horn, and that the effect on it of a given dose was shorter.

Action of adrenaline

In guinea-pigs this drug, administered intravenously, usually produced a relaxation of the cornu, but was often without effect in the dosage used (usually not more than 50μg.); this is in agreement with Gunn & Gunn [1914]. Its effect on the cervix was extremely variable, contractions and relaxations being produced in approximately equal numbers. Newton found that the guinea-pig cervix *in vitro* was contracted by adrenaline. There were only five cases of reciprocal activity between the cervix and the cornu (Fig. 4). In the rabbit, on the other hand, the cervix always contracted after injection of adrenaline, although in some cases this was followed by a relaxation (Fig. 5); the effect on the cornu was usually a contraction [see also Langley, 1901; Dale,

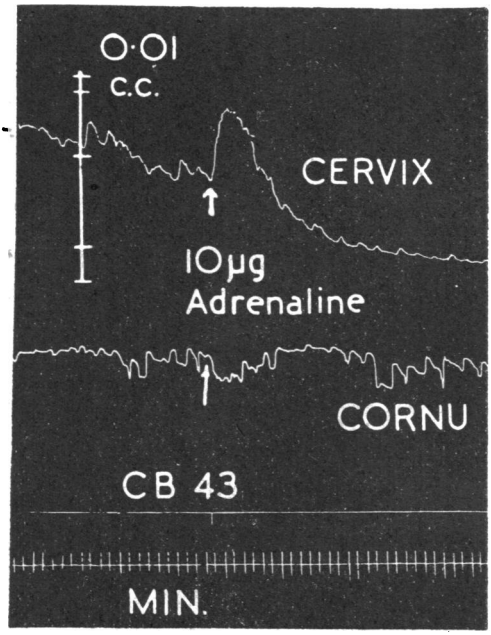

Fig. 4. CB 43. Guinea-pig at oestrus. Effect of intravenous injection of 10μg. adrenaline. The steady fall in the cervical tracing is due to a very slow leak in the recording system.

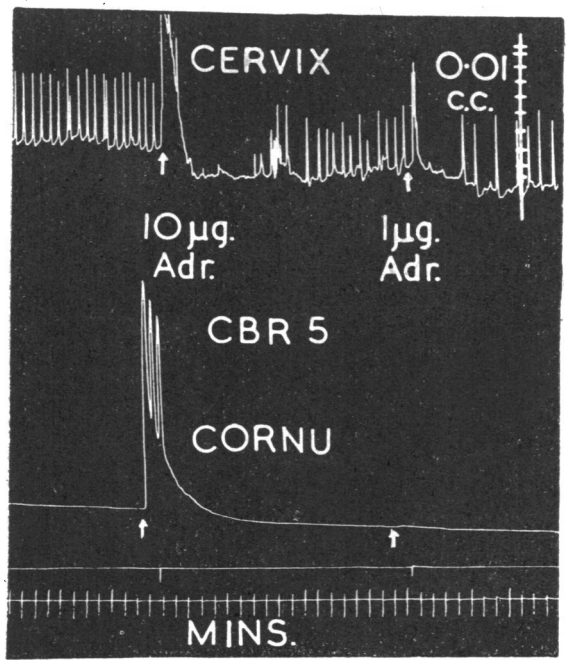

Fig. 5. CBR 5. Rabbit, 11 hr. post-partum. Effect of intravenous injection of 10μg. adrenaline.

1906]. There was thus no clear-cut instance of reciprocal activity in this species. The parturient cats both showed reciprocal activity to adrenaline, the horn relaxing [see also Dale, 1906] while the cervix contracted (Fig. 6). In a pregnant cat adrenaline relaxed both parts of the uterus; Dale [1906] and Cushny [1906] obtained a contraction of the horn. Kehrer [1907] found that

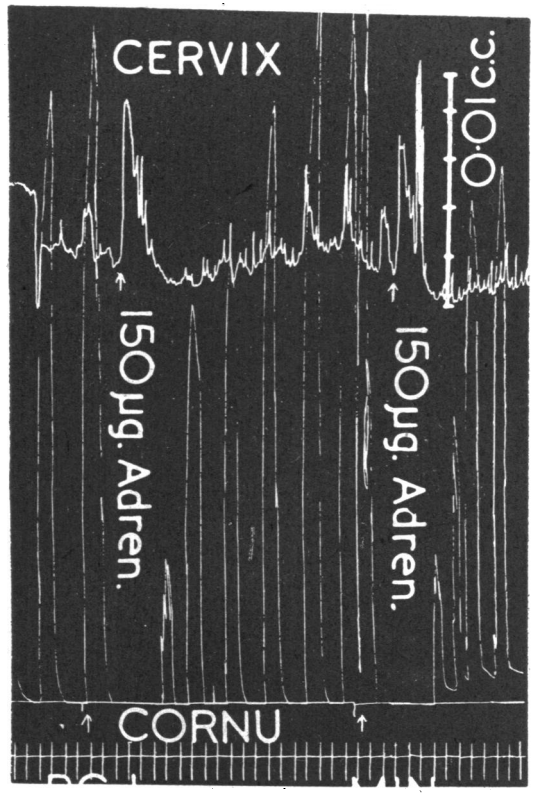

Fig. 6. PC 1. Cat. 7 hr. post-partum. Effect of injection of 150 μg. adrenaline intravenously. Time in min.

the pregnant cat cervix was contracted *in vitro* by adrenaline. In our three spayed cats treated with oestradiol, adrenaline caused a relaxation of the cornu; this is in agreement with the findings of Dale and Cushny in virgin cats.

Action of acetylcholine

Acetylcholine usually had no effect on the activity of the cervix or cornu. It ought to be stated, however, that this drug was administered towards the end of the experiments when the effects of pitocin and adrenaline had been investigated, and accordingly not much stress ought to be laid on the absence of effect.

Action of pitressin

The action of pitressin could be fully accounted for on the basis of its oxytocin content.

Discussion

There is no doubt now that the cervix uteri can be made to contract in the living animal under the influence of the oxytocic principle of the posterior lobe of the pituitary gland. This is in direct contrast to the results obtained by Newton [1934, 1937] who found that the cervix in the goat, rat and guinea-pig when examined *in vitro* was quite insensitive to oxytocin. The large molecule of oxytocin may penetrate the muscle cells of the cervix *in vitro* with difficulty, but it may obtain access more easily *via* the circulation. The small molecule of adrenaline can apparently reach the cervical muscle cells readily *in vitro*. The uterine muscle of the monkey [Bell, 1942] behaves similarly, being more reactive to oxytocin *in vivo* than *in vitro*; also *in vitro* it is easily stimulated by the small molecule of histamine. This is, however, not an invariable finding, the uterine muscle of the guinea-pig, for example, being more sensitive to oxytocin *in vitro* than *in vivo* [Bell & Robson, 1936; Bell, 1941].

On general principles it would seem wiser to build a theory of parturition on evidence obtained from experiments performed *in vivo*. The question then arises as to the position of the oxytocic principle of the posterior lobe as *the* oxytocic agent concerned in parturition. Newton says [1934]: 'If labour is due to the action of an oxytocic substance the advantages of insensitivity to such bodies on the part of the circular cervical muscle are obvious.' Again [1937]: 'The most severe, and at the same time the most easily demonstrable, type of inco-ordination would be a simultaneous contraction of the cervix and cornu of the uterus, and in the author's opinion this would, if brought about by the oxytocic principle, definitely settle all doubts on the score of its physiological activity.' The present work at first sight seems, therefore, to require that the oxytocin theory of parturition be discarded. There are, however, two mitigating features: first, the cervical threshold is higher than the cornual, and secondly, the effect of oxytocin on the cervix is relatively transient.

If we accept the possibility of a certain balance of strength between the cervical and cornual musculature we may fit the present findings into an oxytocic theory of parturition in the following way. In the latter part of pregnancy the uterine movements are of considerable amplitude; it may be that they are spontaneous or it may be that they are caused or augmented by oxytocin. The cervix may during this time remain unaffected. When the secretion of oxytocin increases and the first stage of labour begins the cervix will be stimulated and the constriction of the cervix, while the body is also showing active contractions, will aid in the development of the lower uterine segment, and perhaps also in the moulding of the foetal head. After a time, however,

the cervix will cease to be affected by the oxytocic principle and dilatation of the uterine os can then take place. In addition, the peculiar behaviour of the cervical musculature towards the oxytocic hormone may have the effect of preventing precipitate labour, and may be a good example of co-ordination rather than a severe type of inco-ordination as Newton would have it.

Cervical dystocia. It may be mentioned that true cervical dystocia is, apart from trauma or disease, an infrequent occurrence [Sackett, 1941], being usually encountered in elderly primigravidae with a history of constitutional deficiency and genital underdevelopment. If, as suggested above, the cervix plays something more than a mere mechanical role in parturition this association of cervical dystocia with symptoms of endocrine disturbance may be significant.

Preparation of the cervix for parturition. The cervix in the pregnant and parturient animals was always larger than in the non-pregnant animals, and was in addition somewhat oedematous. This hypertrophy may be due to the same causes, hormonal and mechanical, as those which stimulate the growth of the pregnant uterus. The guinea-pig results indicate that the increase in the size of the cervix, estimated directly and from the extent of the spontaneous movements, cannot be accounted for on the basis of the action of either or both of the ovarian hormones. The reactions of the pregnant and non-pregnant cervix to drugs show no clear-cut differences except perhaps that the threshold to pitocin is lower in the case of the pregnant guinea-pigs. In the case of the pregnant rabbits the cervix appeared to be more oedematous but was very little larger than in the spayed animals treated with large doses of oestradiol. The cervix of the parturient rabbits was much more reactive to oxytocin than that of the spayed animals, although the latter had been given very large doses of oestradiol; this statement applies also to the horn in these groups (V and VII). These findings make it doubtful if oestrogenic stimulation is the complete explanation of the high reactivity observed at parturition. This is in conflict with the usual description of the cause of the high reactivity at parturition in rabbits [Robson, 1933] which was founded on experiments *in vitro*. The cervix in groups V and VII was highly reactive to adrenaline (in some cases less than 1μg. was effective), but there was no distinction between the two groups. In the case of the cat there is no doubt whatever that intensive oestrin treatment by itself cannot account for the very great change from the small, very firm cervix of the non-pregnant condition to the large and oedematous cervix of parturition. The number of animals in groups VIII and IX is too small to allow any conclusions to be drawn from the actions of pitocin and adrenaline.

Reciprocal activity. Reciprocal activity between the cervix and cornu is not prominent in the present work. *In vitro*, the cervix of the goat and guinea-pig is contracted by adrenaline, while that of the rat is not affected, and it is only in the goat that a clear-cut case for reciprocal activity has been made out; in

the guinea-pig reciprocal activity is probably present during di-oestrus and early pregnancy, but not at oestrus [see Newton, 1934, 1937]. All the evidence from the three species we have investigated shows that reciprocal activity to adrenaline is by no means general, and the variability of the results makes it difficult to find any role for this substance in pregnancy or parturition.

Evidence for the separate identity of the cervix and cornu. Newton's experiments *in vitro* demonstrate that pharmacologically the cervix and cornu are quite different tissues. Our evidence obtained *in vivo* strongly suggests that these two parts of the uterus are also physiologically separate. *In vivo* the spontaneous activity of the body and the cervix of the uterus was not very dissimilar, as will be seen from the figures, but there were differences in detail in the contractions (e.g. fast portion of Fig. 2). Also cervical contractions were observed in the absence of cornual contractions and vice versa. Usually, however, when the cornu contracted the cervix contracted a few seconds later (fast portion of Fig. 2). The following series of stop-watch observations on successive spontaneous movements in a parturient rabbit (CBR 5) shows that there may be considerable variations in the interval between cornual and cervical contractions (+ means that the cervix is leading, and − means that the cornu is leading by the stated number of seconds): +2, +4, +2, −2, −7, −2, −6, −9, −11, −11, −11, −10, −7, −7, −3, −2, −6, −5, −6, −5, −11, −1, 0, 0, +2, +2, +3, 0, −7, −5, 0, −9, −10, −7, −16, −11, −18, −19. Moir [1934] found that in the puerperal human subject the cervical rhythm appeared to be independent of that of the fundus, but that there were a few tracings in which the two were plainly co-ordinated. When in addition to these observations we take into account the examples of reciprocal activity to adrenaline, and the differences in the responses of the cervix and cornu to pitocin, we must conclude that the cervix is not merely the end of the uterus but that it is a specially modified part of that organ with a physiological and pharmacological identity.

Summary

1. The movements of the smooth muscle of the cervix and cornu of the guinea-pig, rabbit and cat have been examined in the living animal in the non-pregnant, pregnant and parturient states. In the majority of cases the cervix showed spontaneous movements of small amplitude, but of greater frequency than those of the cornu.

2. The cervix in nearly all cases contracted after intravenous injection of purified oxytocin; the threshold dose was usually several times higher than that for the cornu, but the cervical response to a given dose of oxytocin was of much shorter duration than that of the cornu. These results are very different from those of Newton [1934, 1937] who found that the cervix *in vitro* was insensitive to oxytocin.

3. The action of adrenaline on the guinea-pig cervix was very variable. In the rabbit and in the parturient cats the cervix contracted; in a pregnant cat adrenaline relaxed the cervix.

4. The present findings may be readily fitted into an oxytocic theory of parturition. It is difficult to account for the condition of the cervix at parturition on the basis of oestrogenic stimulation. The cervix appears to be a specially modified part of the uterus with a physiological and pharmacological identity.

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