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THE SEPARATE RELEASE OF OXYTOCIN AND ANTIDIURETIC HORMONE

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The pressor activity of posterior pituitary extract was reported by Oliver & Schäfer in 1895, its oxytocic activity by Dale in 1906, and its antidiuretic activity by von Konschegg & Schuster in 1915. Molitor & Pick (1924, 1926) affirmed that its antidiuretic activity was caused more effectively by injecting it intrathecally rather than intravenously, Cushing (1933) that pituitary basophilism caused hypertension, and Anselmino & Hoffmann (1931), that ultrafiltrates from the blood of eclamptic women contained what they claimed to be excessive amounts of posterior pituitary substance.

Theobald (1934*a*, *b*) found that minimal inhibition of the diuretic response of the dog to 250 ml., of man to 1 l. and of pregnant women near term to 500 ml. of water was effected by the intravenous injection of the antidiuretic hormone (ADH) normally associated in the commercial preparation used with from 0·0005 to 0·01 of an oxytocin unit. Impressed by the fact that such consistent antidiuretic effects were caused by a commercial preparation standardized for its oxytocic content, he conjectured (Theobald, 1936*a*) that menstruation, ovulation, pregnancy and parturition were controlled by a centre or centres in the hypothalamus probably situated in 'two cell masses, named the paraventricularis and the supraopticus'. He thought that labour might be instituted and delivery effected by an amount of oxytocin in the blood of the same order as that of ADH which caused antidiuresis, and calculated that it would be necessary to deliver intravenously from 1 to 5 m-u./min of a commercial preparation of oxytocin.

A wide range of stimuli can cause simultaneous release of both oxytocin and ADH, and it is generally held that the former is invariably secreted in greater amounts than the latter, the reported ratios varying from 4:1 to 100:1; but there is no accepted evidence of their separate release (Haterius & Ferguson, 1938; Haterius, 1940; Ferguson 1941; Harris, 1947, 1948; Peeters & Coussens, 1950; Cross, 1951; Kalliala & Karvonen, 1951; Andersson, 1951; Kalliala, Karvonen & Leppänen, 1952; Abrahams & Pickford, 1954).

The exquisite sensitivity of the human myometrium to oxytocin which must be attained before labour can occur (Theobald, 1958) makes it reasonable to conclude that uterine activity provoked in the non-pregnant state by large amounts of this hormone may be no more physiological than the rise in blood pressure caused by pharmacological amounts of ADH. It follows that theoretically the best time to determine whether oxytocin can be released independently of ADH is during the relatively short period when the myometrium is peculiarly sensitive to oxytocin. Investigations during or immediately before labour, however, are worthless for several reasons, and particularly because on the one hand uterine contractions are provoked as easily by ADH as by oxytocin, and on the other the anxiety, pain, and work associated with parturition can in and of themselves cause ADH release. Fortunately the early puerperium is an eminently suitable time for this purpose. Suckling is indubitably a physiological act and the myometrium retains a high, albeit decreasing, sensitivity to oxytocin during the first week of the puerperium.

The purpose of this paper is to report clinical investigations devised to determine whether both oxytocin and ADH can be released separately and independently by the neurohypophysis. The evidence adduced is dependent on the prior determination of a concentration of oxytocin in the blood which institutes labour and effects delivery in man.

METHODS

All the uterine tracings shown were made with Smyth's guard-ring tokodynamometer. Those in Figs. 1 and 2, and the lower ones in Fig. 3 were from the abdominal wall, whereas the others were from a balloon, holding about 6 ml. of water, which was introduced into the uterus at least an hour before the investigation was started. It was held in position by strapping the connecting tube to a volsellum attached to the anterior lip of the cervix. Tracings of uterine activity were obtained for at least 1 hr before any test was commenced. On two occasions the introduction of the balloon was associated with frequent uterine contractions which persisted for several hours and made any experiment impossible. The intravenous infusion of adrenaline 10μg/min failed to stop these contractions but the intravenous infusion of Pitressin (vasopressin; Parke, Davis) 4 m-u./min did (Fig. 5*B*). ADH appeared to decrease the sensitivity of the myometrium to oxytocin, as also did the infusion of hypertonic NaCl (Fig. 4).

On a few occasions a second balloon was introduced into the rectum or lower sigmoid colon. It may be stated here that neither suckling nor the intravenous infusion of physiological amounts of either oxytocin or Pitressin appeared to disturb the rhythm of the relatively rapid peristaltic movements, but insufficient observations were made to justify any conclusions.

Water diuresis. The subject was encouraged to drink freely before the test. A rubber catheter (Foley's) was inserted into the bladder either before or at the same time that the balloon was introduced into the uterus. The catheter was held in place by a small rubber bag distended with water which was kept as close to the internal urethral orifice as possible. The hydrating dose was 500 ml. of water and the bladder was emptied immediately after it was given. The urine was collected every 5 min. The end of the catheter dangled into

a kidney dish which was kept close to the subject's thigh, and was kept open until the exact time of collection. The catheter was temporarily clamped while the urine was being measured. So soon as the kidney dish was replaced the clamp was removed. Each quarter of an hour the subject drank the same quantity of water that she had voided as urine during the preceding 15 min. This was found to be the most satisfactory method for use in the wards.

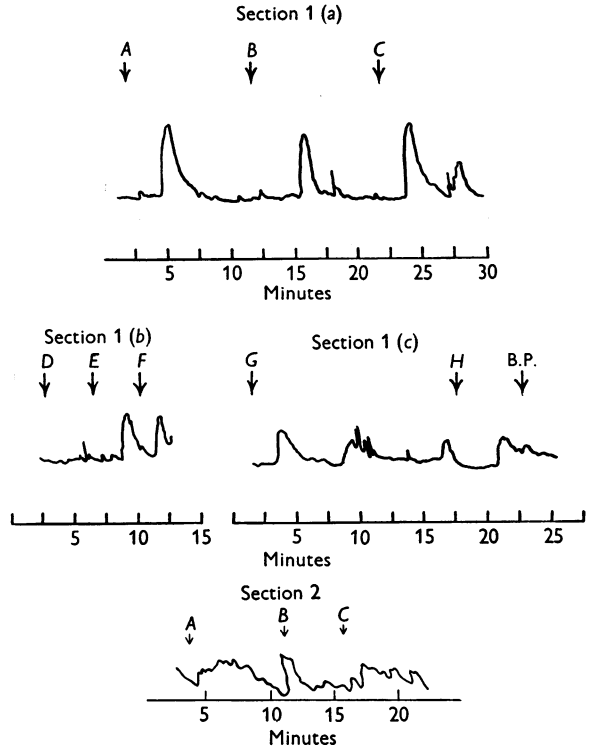

Fig. 1. Varying sensitivity of human uterus to Syntocinon, Pitocin and Pitressin. Tracing from fundus of uterus, time intervals 2½ min. Section 1(*a*), at term; at *A* and *B*, 10 m-u. Syntocinon, and at *C*, 20 m-u. Pitressin was injected intravenously. Section 1(*b*) 2 hr later; at *D*, 10 m-u. and at *E* and *F*, 100 m-u. Syntocinon was injected intravenously. Section 1(*c*) 1 hr later; at *G*, 1000 m-u. and at *H*, 2000 m-u. Pitressin was injected intravenously. B.P. = B.P. 110/80 mm Hg. Section 2, at 30 weeks; at *A* and *B*, 1000 m-u. Pitocin, and at *C*, 5000 m-u. Pitocin was injected intravenously.

The Drip. A standard 'giving' set, containing 540 ml. of 5% glucose in distilled water, was used; it connected to a small vein in the wrist by means of a No. 2 hypodermic needle. Oxytocin and other substances being investigated were either added to the bottle or injected into the rubber tubing close to the needle in the vein while the drip was temporarily stopped. When a fresh concentration, or a new substance, was added to the bottle, the rubber tubing of the giving set was disconnected from the needle, and about 20 ml. of the fluid allowed to escape and clear the dead spaces before it was again connected. Although the rate of flow could be kept fairly constant at either 16 drops (1 ml.) or 32 drops (2 ml.) a minute there was inevitably some variation in it. The required dilutions were made by using small

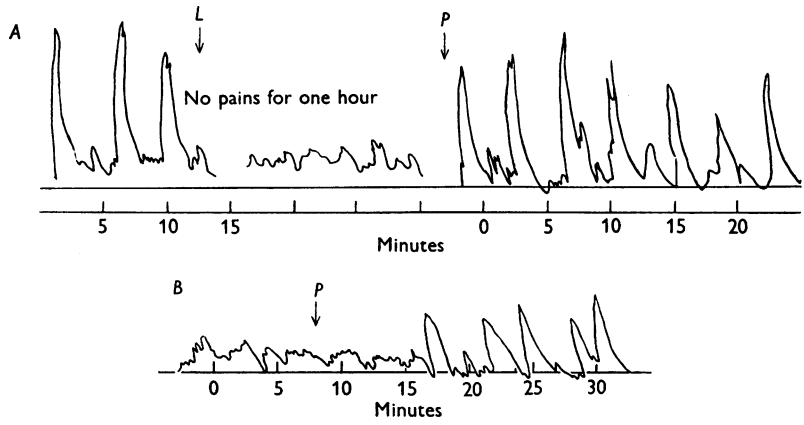

Fig. 2. Effect of Pitocin on uterus whose contractions had been inhibited (*A*) or had stopped spontaneously (*B*). Tracings from fundus of uterus, time intervals 5 min. (*A*) Primigravida, who had had incoordinate, ineffective, painful contractions for 2 days without sleep. Her cervix was two fingers dilated. At *L* her iliohypogastric and ilio-inguinal nerves were infiltrated with Xylocaine. Uterine contractions subsequently stopped. An hour later, at *P*, a drip delivering Pitocin 0·2 m-u./min was started and the subsequent uterine contractions were effective. *B*. Primigravida, aet. 17, laboured satisfactorily until her cervix became three-quarters dilated and then went out of labour for several hours. At *P* a drip delivering Pitocin 0·25 m-u./min was started and spontaneous delivery occurred 3 hr later.

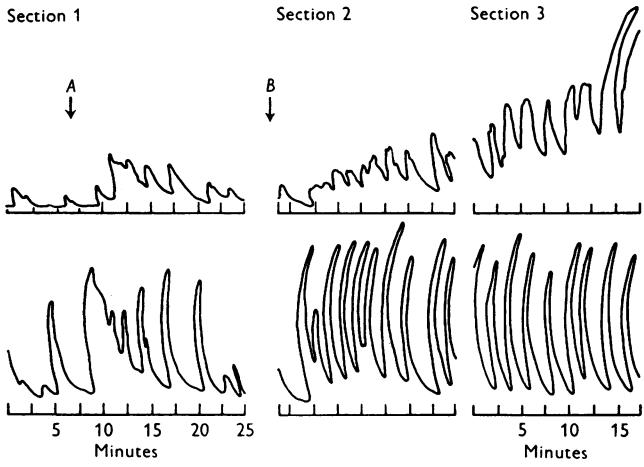

Fig. 3. Pitressin in the induction of labour. The subject was a gravida-5, aet. 35, at term. Amniotomy was performed at 10.00 hr, when a 5% glucose drip was started. The upper tracings were obtained indirectly from the lower uterine segment, and the lower simultaneously from the fundus; time intervals 2½ min. Section 1; at *A*, 100 m-u. Pitressin was injected intravenously. Section 2; at *B*, a drip delivering Pitressin 2 m-u./min was started. Section 3; 1 hr later, showing increase in tone, particularly of lower segment.

screw-top bottles containing 9 and 9·5 ml. of sterile 5% glucose solution, accurately measured in the pharmacy. By using a tuberculin syringe it was easy to make the required dilutions in the ward. In the early experiments the drip was set up when the catheter was inserted, but it made suckling difficult. More recently it was not started until the baby had been finally removed from the ward.

The baby. The original practice was to bring in the baby when the urine output had become stabilized, and put him to the breast forthwith. During recent months the baby was brought in and given to the mother to fondle for some time before suckling was commenced. The possible effects of emotion on water diuresis were thereby lessened. The baby was weighed immediately before and after being put to each breast.

Anaesthetizing the nipple. It was found that the injection of some 15 ml. of 1% Xylocaine (lignocaine; Duncan Flockhart) (without adrenaline) into the areola caused complete anaesthesia of the nipple to touch or prick, but on only two occasions was the mother unable to feel traction on the nipple during suckling. The use of a No. 19 hypodermic needle made this procedure all but painless. Anaesthesia of the nipple did not last more than 30 min. The only disadvantage noted was that the nipple became less erectile and in consequence more difficult for the infant to grasp.

Pitocin (Parke, Davis) and Syntocinon (Sandoz) were the two commercial preparations of oxytocin which were used. The latter was more convenient as 2 u. are put up in 2 ml. of water. Pitressin was the commercial preparation of ADH which was used.

RESULTS

Part I. The effects of injected drugs

Clinical evidence

It was reported by Theobald, Graham, Campbell, Gange & Driscoll (1948) that, after amniotomy, a 5% glucose drip (in distilled water) delivering from 1 to 5 m-u. oxytocin per minute usually sufficed to cause the onset of labour and to make ineffective uterine contractions effective. This concentration of oxytocin in the drip is still being used at Bradford (Theobald, Kelsey & Muirhead, 1956).

During the years 1957 and 1958 inclusive 5579 patients were delivered in this hospital and amniotomy was performed in 1479 or 27% of them, with the intent of inducing labour. If the women had not started labour by the following morning an oxytocin drip was usually started.

Of the 1431 women who were 38 weeks or more pregnant, 1162 or 81% went into labour after amniotomy and a purgative, without requiring an oxytocin drip. The total number of women given a drip for the purpose of inducing labour was 295 and of these only 34 or 11·5% required more than 5 m-u. of oxytocin per minute, while the infusion of between 1 and 2·5 m-u./min sufficed in 98 or 33% of this group. (Of the 1479 women in whom labour was induced only 34 required a drip delivering more than 5 m-u. of oxytocin per minute.)

The very fact that some women required an oxytocin drip suggested failure of the myometrium to achieve its maximum sensitivity to oxytocin. This view is supported by the fact that the oxytocin drip occasionally

failed to start labour for several days. In one patient the intravenous infusion of 2·5 m-u. of oxytocin a minute on the sixth day after amniotomy caused rapid dilation of the cervix and spontaneous delivery, notwithstanding the failure of stronger concentrations to have any effect on previous days (Theobald *et al.* 1956). It is usually true (Nixon & Smyth, 1957) that the uterus ready to undertake parturition will contract when from 10 to 30 m-u. of oxytocin is injected intravenously. It is also true that the sensitivity of the human myometrium at term to both oxytocin and ADH varies considerably from hour to hour. Sensitivity tests were carried out on a gravida-2, aet. 38, with intact membranes, at term. The tracings were from the abdominal wall and the injections were made into the rubber tube of a glucose drip and near to the needle. Figure 1 (sect. 1) shows tracings obtained during the course of a morning, the conditions remaining unaltered. In section 1*a* are shown the contractions caused by the intravenous injection of 10 m-u. Syntocinon and 20 m-u. ADH. Two hours later (sect. 1*b*) the injection of 100 m-u. Syntocinon had less effect than the original 10 m-u. and an hour later still (sect. 1*c*) the contractions caused by the injection of 2 u. Pitressin were less than those caused by 20 m-u. Pitressin earlier in the morning. This represents a hundredfold decrease in sensitivity within 3 hr.

A change in the opposite direction is shown in Fig. 1 (sect. 2). A young primigravida, aet. 17, some 30 weeks pregnant, was found to have an anencephalic foetus. At the points indicated by the arrows, 1 u., 1 u., and 5 u. Syntocinon, respectively, were injected intravenously, without causing a single uterine contraction or any subjective sensation. The next morning amniotomy was done and an oxytocin drip delivering 5 m-u./min was started. She was delivered naturally a few hours later. This represents a thousandfold increase in the sensitivity of the myometrium to oxytocin within the space of less than 20 hr.

It has been shown that 81 % of women went into labour within 20 hr of amniotomy, and that the intravenous infusion of from 1 to 2·5 m-u. a minute of oxytocin sufficed to put over a quarter of the remaining refractory patients into labour. It therefore appeared reasonable to assume that the physiological concentration of oxytocin which normally suffices to cause the onset of labour and effect delivery could not be more and might well be less. The only means that seemed open to determine this point were to discover the minimum amount of oxytocin necessary to restart labour, (*a*) after it had been deliberately stopped, and (*b*) after it had stopped spontaneously (secondary uterine inertia).

Stopping early labour. It was found possible to stop the uterine contractions of early labour for a considerable time by infiltrating the iliohypogastric and ilio-inguinal nerves with a local anaesthetic. The technique

was originally devised to abolish the pain associated with the first stage of labour (Theobald, 1936*b*, 1941), and for the purpose of this communication it is immaterial whether uterine contractions were stopped by the adrenaline added to the local anaesthetic, by the abolition of pain, or by a combination of both factors. Either 0·5 mg or 1 mg of adrenaline was added to 100 ml. of a 0·5 % solution of Xylocaine and 20 ml. of this solution was used on either side to infiltrate the iliohypogastric and ilio-inguinal nerves as they passed in close proximity to the anterior superior iliac spines. A further 30 ml. of the solution was used in some cases to infiltrate the pudendal nerves.

A primigravida, aet. 30, 10 days post-mature, was admitted after she had been in labour at home for 2 days without any sleep. Her cervix was only two fingers dilated. She was very tired and the incoordinate, ineffective uterine contractions were exceedingly painful. At point *L* in Fig. 2*A*, the iliohypogastric and ilio-inguinal nerves were infiltrated with Xylocaine. Uterine contractions ceased for an hour and the patient fell asleep. They restarted almost immediately after the glucose drip was changed to one delivering Pitocin 0·2 m-u./min (point *P*), which was continued until the placenta was delivered. The relief of pain and sleep lasted for 5 hr, and a female infant weighing 8½ lb. (3·9 kg) was delivered naturally 9 hr after the Xylocaine was injected. On every occasion that the uterine contractions of early labour were so stopped they could be started again by the intravenous infusion of from 0·2 to 0·5 m-u. oxytocin a minute.

Secondary uterine inertia. It sometimes happens that women start labour, proceed to almost full dilation of the cervix and then cease to have any uterine contractions for several hours. One such patient, a primigravida, aet. 17, proceeded satisfactorily until her cervix was three-quarters dilated and then went out of labour for several hours (Fig. 2*B*). The head was satisfactorily engaged and there was no cephalo-pelvic disproportion. A drip delivering Pitocin 0·25 m-u./min. was started at *P*, and was maintained until the patient delivered herself 3 hr later.

ADH and labour

ADH would appear to be as efficient as oxytocin in starting labour and effecting delivery. It was decided to induce labour in a gravida-5, aet. 35, and amniotomy was performed at about 16.00 hr (Fig. 3). A glucose drip was started at 16.30 hr, and an hour later at *A* (sect. 1) 100 m-u. of Pitressin was injected intravenously and caused a prolonged contraction. At 18.00 hr at *B* (sect. 2) a drip delivering 2 m-u./min Pitressin was begun, and sections 2 and 3 show the resulting increase in tone, and in the frequency and height of contractions of the lower uterine segment, and of the frequency and height of contractions of the fundus, recorded shortly

before delivery. This patient gave birth naturally to an infant weighing 7 lb. 9 oz. (3·4 kg) within 4 hr of amniotomy and 2 hr after the start of the Pitressin drip. A note was made that at no time did the Pitressin drip cause either pallor or any significant rise in the blood pressure.

Part II. The effects of suckling

The effects of suckling on the other breast

Very small amounts of oxytocin cause the mammary myoepithelium to contract and to express milk from the alveoli and ducts. Unless milk is present in the alveoli in reasonable quantities it cannot be expressed and it is important to choose suitable subjects, to wait until lactation is established, and not to conduct tests shortly after the breasts have been emptied or if the mother's fluid intake has been restricted. Nor should tests be carried out before the first feed in the morning because a free secretion of milk, unrelieved by suckling during the night, often results in retention overflow. Nearly all the tests to be reported were done just before the feed at 14.00 hr, and between the 4th and the 8th day of the puerperium.

During the week following the establishment of lactation suckling from one breast invariably caused escape of milk from the other nipple in all subjects. This effect could be matched, within from $1\frac{1}{2}$ to 3 min, by a single intravenous injection of from 5 to 10 m-u. oxytocin or its intravenous infusion at the rate of from 0·2 to 1 m-u./min. On no occasion was the let-down of milk noted to be effected by the intravenous injection of ADH, but this problem was not actively pursued.

Uterine activity. During the first 10 days of the puerperium suckling caused uterine contractions to occur within 3 min (Fig. 4) of its commencement, in each of approximately twenty patients who were investigated. This effect was matched by a single intravenous injection of 10 m-u. of a commercial preparation of oxytocin or its intravenous infusion at the rate of from 0·5 to 1 m-u./min. Similar uterine activity was caused by comparable injections of Pitressin, but this hormone when given in the non-pregnant state seemed to produce tachyphylaxis and to lessen the subsequent effect of oxytocin (Figs. 4 (sect. 1), and 5 (2)).

Water diuresis. Water diuresis curves obtained from some twenty women between the 4th and the 8th day of the puerperium confirmed previous observations that suckling was frequently associated with antidiuresis. The longer the infant was kept on the breast the more likely was antidiuresis to occur. Figure 6 shows that the effect could be matched by a single intravenous injection of less that 0·5 m-u. Pitressin. On other occasions 0·2 m-u. Pitressin sufficed. The effect could not be attributed to

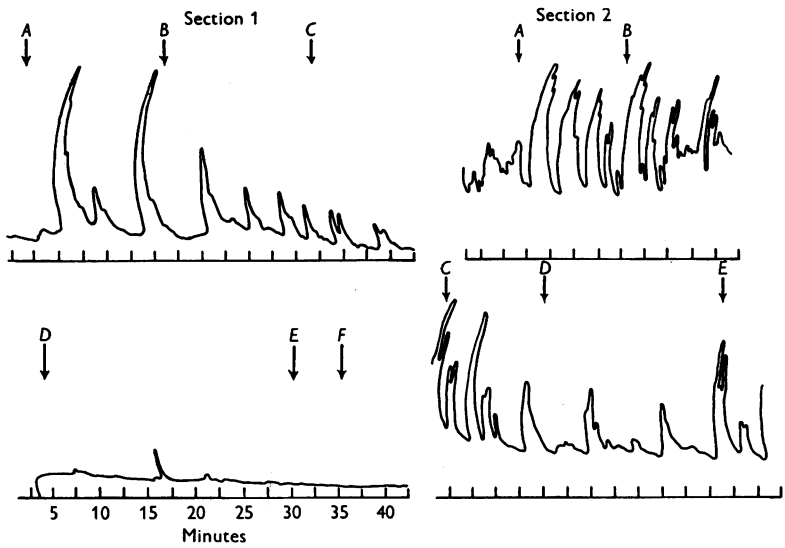

Fig. 4. Effects on the uterus caused by suckling, and by the infusion of hypertonic NaCl; records from balloon in uterus. Time intervals 2½ min. Section 1 (upper); at *A* baby was put to the right breast, at *B* to the left, and at *C* was taken from the room: (lower) at *D*, 35 min later, the tracing was readjusted and the intravenous infusion of 200 ml. of 5 % NaCl ended. At *E*, 10 m-u., and at *F*, 100 m-u. Syntocinon was injected intravenously without causing any uterine activity. The 'kick' in the tracing between *D* and *E* was an artifact. Section 2 (upper); from *A* to *B* baby was at the left breast (anaesthetic nipple) and the uterus became markedly hypertonic. Some 40 min later, between *C* and *D* (lower tracing), 100 ml. of 7·5 % NaCl was infused intravenously; this caused antidiuresis (Fig. 8) and marked decrease in uterine activity; at *E*, 5 m-u. Syntocinon was injected intravenously.

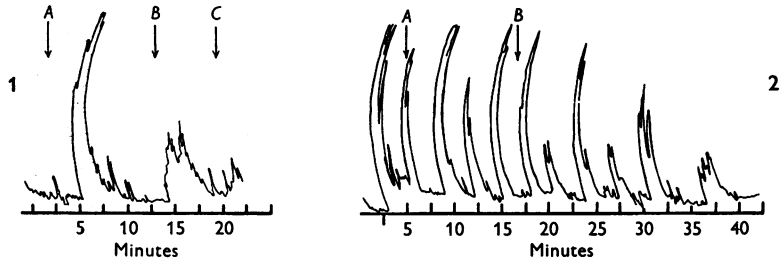

Fig. 5. Effects on uterus caused by suckling, by the breast pump and by the intravenous infusion of Pitocin and Pitressin; tracings from balloon in uterus; time intervals 2½ min. (1) At *A* baby was put to the breast: the electric breast pump, applied to the opposite breast, was switched on at *B* (shortly after the baby had been removed from the breast) and off at *C*. (2) At *A*, immediately after the baby had been removed from the breast, a drip delivering Pitocin 0·4 m-u./min was started and was changed at *B* to one delivering Pitressin 0·4 m-u./min.

oxytocin, for the intravenous infusion of 4 m-u. Syntocinon a minute did not cause antidiuresis (Fig. 7). Moreover, the marked antidiuresis caused by the intravenous infusion of Syntocinon 16 m-u./min for 25 min was short-lived. The two crucial observations were (1) that the onset of antidiuresis, when it did occur, was often delayed for 10–15 min after suckling commenced (Fig. 6), and (2) that in some subjects no antidiuresis occurred (Figs. 8, 9).

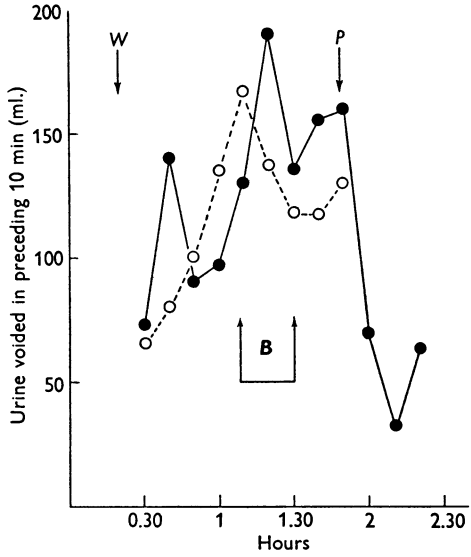

Fig. 6. Effect of suckling and of Pitressin on urine flow. Both curves from the same subject; interrupted line, 5th day, full line 8th day of puerperium. Hydrating dose of water given at *W*. The baby was at the breasts for the period between the two arrows labelled *B*. At *P* 0·5 m-u. Pitressin injected on 8th day.

Anaesthetizing the nipple in no way interfered with oxytocin release, for milk flowed from the other nipple and uterine activity occurred within 3 min of the commencement of suckling (Fig. 4, sect. 2). On the other hand antidiuresis did not occur when the mother experienced no sensation at all while her baby was at the breast (Fig. 8*L*). Conversely, the urine output fell to 2 ml. in 5 min (very much lower than on any other occasion) in a subject with painful nipples after the anaesthetic action had passed off and before suckling had ceased.

The intravenous infusion of hypertonic NaCl. The intravenous infusion of NaCl solution, either 200 ml. of 5% or 100 ml. of 7·5% (w/v), sufficed to inhibit water diuresis to approximately the same degree as a single intravenous injection of from 0·5 to 1 m-u. Pitressin. Figure 4 (sect. 1 *A*, *B*) shows the uterine activity associated with suckling in a gravida-3, aet. 26, on the 6th day of the puerperium. Some 25 min after the baby was

removed from the breast 200 ml. of 5% NaCl was given intravenously within 12 min and caused the 10-min urine output to fall from 164 to 17 ml. The myometrium subsequently became insensitive to oxytocin and it was necessary to inject 1 u. Syntocinon in order to provoke a single contraction, after which the sensitivity of the myometrium to oxytocin returned to its former level. Over-activity of the uterus of a gravida-3, aet. 26, on the 5th day of the puerperium is shown in Fig. 4 (sect. 2). Frequent and strong uterine contractions, which persisted for 40 min,

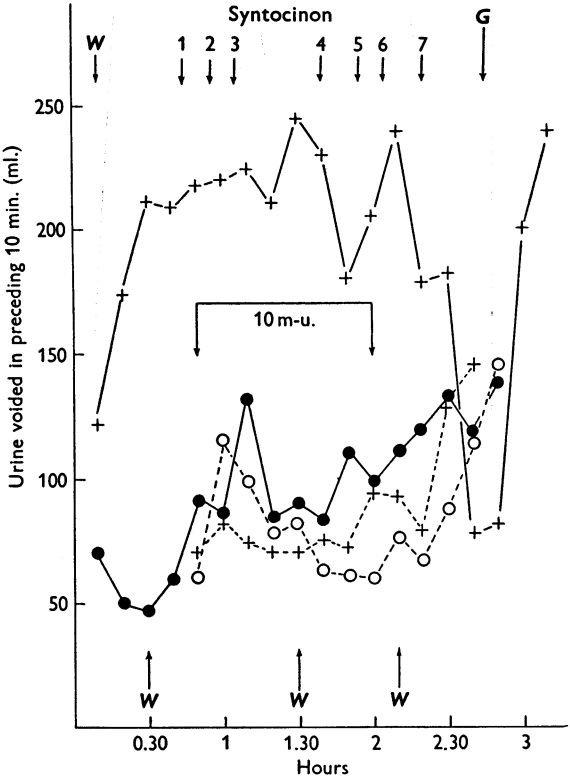

Fig. 7. The effect of Syntocinon on water diuresis during the puerperium and in the non-pregnant state. The topmost curve was obtained during the puerperium. A 5% glucose drip was started and at *W* the hydrating dose of water was given. At points 1, 2, 3, 4, 5, 6, and 7, Syntocinon 0·2, 0·5, 1, 2·5, 4, 6, and 16 m-u./min was successively infused intravenously; at *G*, the original glucose drip was restarted. The three lower curves were obtained simultaneously from non-pregnant women. Glucose drips were started on each of them, and 500 ml. water was given by mouth at each of the lower points marked *W*. An intravenous infusion delivering 10 m-u. Syntocinon a minute was given for 70 min between arrows labelled '10 m-u.' The original glucose drip was then resumed. The intravenous infusion of less than 5 m-u. Syntocinon a minute had little effect on water diuresis, but more than that amount lowered the urinary output.

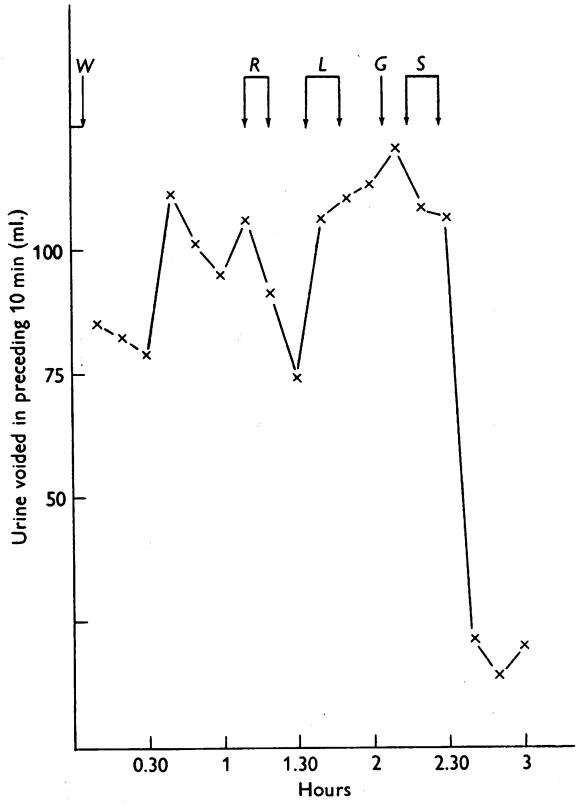

Fig. 8. Effect of suckling from an anaesthetized nipple (the left one). Hydrating dose of water given at *W*. Suckling from right breast (*R*) associated with antidiuresis. Suckling from left breast (*L*) associated with marked uterine activity (see Fig. 4, section 2). A glucose drip was started at *G*; 100 ml. of 7·5 % NaCl was infused intravenously between the arrows marked *S* and caused antidiuresis and lessening of uterine activity.

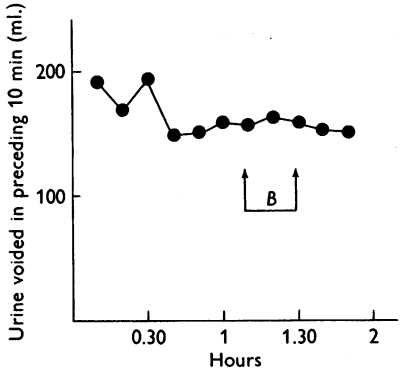

Fig. 9. Suckling without antidiuresis. The baby was at the breast during the period between the arrows, labelled *B*.

were provoked by suckling, although the mother felt nothing because the nipple was completely anaesthetic. The intravenous infusion of 100 ml. of 7·5 % NaCl caused a marked decrease in uterine activity and a sharp fall in the 10-min urine output (Fig. 8). The myometrium returned to its former exceedingly over-active state following an intravenous injection of 5 m-u. Syntocinon (Fig. 4, sect. 2*E*).

On no occasion did the intravenous infusion of hypertonic NaCl cause either flow of milk from the nipple or increased uterine activity.

DISCUSSION

It has been shown that the sensitivity of the human myometrium at term to both oxytocin and ADH may vary greatly in either direction within the space of a few hours, and that its sensitivity to the former may be increased a thousandfold within 20 hr merely by performing amniotomy and administering a purgative. That this change is causally related to the operation is proved by the fact that the medical induction of labour proved so unsuccessful in spite of the fact that quinine and oleum ricini were given and that 5 u. of posterior pituitary extract was injected intramuscularly every half hour until 30 u. had been given. Evidence has been given which suggests that no woman goes spontaneously into labour until her myometrium achieves a sensitivity which responds to the intravenous infusion of from 0·2 to 0·5 m-u. a minute of a commercial preparation of oxytocin. Further, if a woman has a miscarriage or goes into premature labour her myometrium is responsive to a physiological oxytocin drip.

The changes which occur in the sensitivity of the myometrium to oxytocin, ADH and ergot have been recognized for over a quarter of a century (Knaus, 1926; Robson, 1933; Moir, 1944) but the exquisite sensitivity attained before labour ensues has only been appreciated since the advent of the oxytocin drip. It must nevertheless be stated that Caldeyro-Barcia and his co-workers (Caldeyro-Barcia, Alvarez & Poseiro, 1955; Caldeyro-Barcia & Poseiro, 1959) maintain that the maximum sensitivity of the human myometrium to oxytocin is reached between the 30th and 36th weeks of pregnancy, and that the onset of labour is due to the increased release of oxytocin from the neurohypophysis of the order of from 4 to 8 m-u./min. The difference in our respective views may be more apparent than real, for most of the important papers which Caldeyro-Barcia and his colleagues have published have been concerned with uterine behaviour during pregnancy and before the onset of labour. Others have suggested that this change in sensitivity is apparent rather than real, and is due to the enzyme oxytocinase. The incubation of serum from blood withdrawn from women at any time after the 12th week until

the birth of the child inactivates added oxytocin and ADH (von Fekete, 1930; Werle, Hevelke & Buthmann, 1941; Woodbury, Ahlquist, Abreu, Torpin & Watson, 1946; Page, 1946; Hawker, 1955; Dicker & Tyler, 1956; Dicker & Whyley, 1959).

It is difficult to assign any significance to the increased amounts of histaminase, oxytocinase and vasopressinase found in the blood during pregnancy in man. Water diuresis, for example, is inhibited as readily throughout pregnancy as in the non-pregnant state by the intravenous injection of physiological amounts of Pitressin (Theobald, 1934*a*, 1956), notwithstanding the fact that all observers are agreed that the enzyme which inactivates ADH is present in the blood throughout the second and third trimesters of pregnancy. It is the change in the sensitivity of the myometrium to oxytocin rather than an alteration in the amount of circulating oxytocinase which determines the onset of labour, for it would otherwise be difficult to understand how oxytocinase could destroy 5 u. Pitocin injected intravenously so rapidly as to prevent it from causing a single contraction.

Oxytocin is destroyed rapidly, for uterine contractions caused by the oxytocin drip cease soon after the drip is stopped unless true labour has started. The concept that oxytocin must be liberated at frequent intervals during the course of labour is supported by the observation that in both rats and dogs the stores of this substance in the neurohypophysis are depleted at the time of delivery (Dicker & Tyler, 1953*a*, *b*; Fromageot, 1956; Acher & Fromageot, 1957).

The fact that ADH may be as effective as oxytocin in causing the onset of labour and delivery is surprising and must be regarded as a remarkable provision of nature, for when given in the non-pregnant state it produces tachyphylaxis (Figs. 4, 5 (2) and appears to lessen the subsequent response of the myometrium to oxytocin. The terminal stages of labour are most commonly associated with marked antidiuresis, which is in part attributable to the associated anxiety, pain and work, and in part to the fact that at that time the woman usually neither desires fluid nor is able to absorb much from the intestines. (Theobald, unpublished observations.) Delivery would be hindered, if not prevented, were it not for the above recorded alteration in the response of the myometrium to ADH.

The evidence so far discussed would be compatible with the view that oxytocin and ADH are invariably liberated together and in equal amounts, but such a conclusion is not supported by the investigations described in Part 2.

Verney (1946, 1947) postulated that the release of antidiuretic hormone is physiologically determined by the osmotic pressure of the arterial blood, and over the years he and his colleagues have all but established that

these osmoreceptors are situated in the supraoptic nucleus (Jewell & Verney, 1957). It is not, however, probable that release of ADH, provoked by attempts at lumbar puncture or by cauterizing the cervix with $AgNO_3$ (Theobald, 1934*b*, 1956, p. 358) or by a just-resented electrical stimulation of the lumbar muscles (Verney, 1947), is mediated by osmoreceptors. Neither would it appear probable, notwithstanding the possibility of a teleological association between lactation and antidiuresis, that the osmoreceptors are normally concerned with the release of oxytocin.

It is for these reasons that the observations of Andersson (1951) and of Abrahams & Pickford (1954) are important. The former found that the intracarotid injection of hypertonic NaCl caused milk ejection in goats, and the latter that either the intracarotid or the intravenous injection of hypertonic NaCl into conscious dogs caused increased uterine activity which was coterminous with the antidiuresis, and concluded that stimulation of the hypothalamic osmoreceptors by hypertonic NaCl caused the release of from 15 to 20 times more oxytocin than of ADH.

It has been reported above that the intravenous infusion of hypertonic saline during the early days of the puerperium caused neither increased activity of the uterus nor let-down of milk. The difference between these results and those reported by Abrahams & Pickford (1954) might be due either to species difference or to the pharmacological amounts of oxytocin necessary to stimulate the non-pregnant uterus.

The two most significant facts, however, are (*a*) that suckling can occur apart from antidiuresis, and (*b*) that the onset of the inhibition of urine flow may be delayed for 15 min after the commencement of suckling. Kalliala & Karvonen (1951) found that in some of their lactating women suckling was never associated with antidiuresis and one of the explanations they offered was that oxytocin could be released independently of ADH. Cross (1951) noticed the same fact in rabbits and suggested that whereas stimulation of the teats was sufficient to evoke release of the milk-ejection hormone, passage of milk out of the mamma was necessary to cause release of ADH. This explanation would not apply to lactating women, for removal of milk is far more efficiently done by an electric pump than by a new-born babe, but it causes relatively little increase in uterine activity, rarely causes escape of milk from the opposite nipple and has not caused antidiuresis on any observed occasion (Fig. 5 (1)).

If suckling can cause uterine activity without antidiuresis it is reasonable to postulate that oxytocin can be released independently of ADH, unless it can be shown that the renal tubules are at that time relatively insensitive to the latter hormone. On the many occasions that this point was tested during the puerperium it was found that a single intravenous injection of from 0·1 to 0·5 m-u. Pitressin caused a much greater fall in urine output

than was caused by suckling. It is clear from Fig. 8 that suckling from the right breast caused a fall in the urine output, whereas suckling from the left, during which the mother experienced no sensation, did not, although it was associated with marked uterine activity (Fig. 4, sect. 2). That the sensitivity of the renal tubules remained unaffected is shown by the fact that the subsequent intravenous infusion of 100 ml. of 7·5 % NaCl caused antidiuresis. Suckling unassociated with antidiuresis is shown in Fig. 9, and possibly in Fig. 6, and in the latter it is seen that an intravenous injection of 0·5 m-u. Pitressin caused a marked fall in urine output.

It is of course possible to argue that on the above and on other similar occasions a subthreshold amount of ADH was released, but as this may occur at all hours of the day and night there seems no valid reason to associate it with oxytocin release. Indeed the delay in the onset of antidiuresis on some occasions provides complementary and almost equally strong evidence of the independent release of oxytocin. All observers are agreed that it is released within 3 min of the start of suckling, and if ADH were released concomitantly antidiuresis should begin to occur shortly after the effects of the oxytocin are noted. But this is not always the case.

Cross (1951) reported that in rabbits the maximal oliguria occurred half an hour after suckling, and Kalliala & Karvonen (1951) stated that in lactating women antidiuresis 'seemed to consist in a drop in the urine excretion curve between 15 and 30 minutes after the beginning of the feeding'. In the above reported experiments the same time lag was noted on a number of occasions and was the more significant as the urine output was invariably measured every 5 min, although the 10-min output has been recorded.

It is evident that ADH release during suckling is not always synchronous with oxytocin release, which is prompt and invariable, neither does it always occur. This suggests that separate pathways from the nipple may be involved in their respective releases. Complete anaesthesia of the nipple does not interfere with oxytocin release, the stimulus for which may be an alteration of tension in the alveoli and ducts. The complete absence of sensation during suckling would appear to lessen the chance of antidiuresis occurring, but many more tests would have to be made before this point could be settled (Fig. 8). The converse is more easily established, for pain caused by suckling a sore nipple caused a much more marked fall in urine output than had occurred on any other occasion or has since been noted, although it must be regarded as probable that the antidiuresis on this occasion included an adrenaline-like element.

Seeing that antidiuresis is frequently but not always associated with suckling, that when it does occur it may only be after a significant time lag, that the renal tubules are as sensitive to ADH during the early days

of the puerperium as at any other time, that the intravenous infusion of hypertonic saline solution causes antidiuresis but neither increased uterine activity nor let-down of milk, and that an occasional woman may pass through labour without any diminution of urine output, it is clear (under strictly physiological conditions) that either hormone may be released without any evidence of release of the other. It therefore seems reasonable to conclude from a functional point of view that the separate release of both oxytocin and ADH occurs and to conjecture that separate pathways from the nipple may be involved in their respective releases.

SUMMARY

1. The concentration of oxytocin in the blood which suffices to initiate labour and effect delivery corresponds with that provided by the intravenous infusion of between 0·2 and 0·5 m-u. of either Pitocin or Syntocinon a minute.

2. The sensitivity of the human myometrium at term to oxytocin varies widely in either direction in the space of a few hours, and at 30 weeks may be increased a thousandfold within 20 hr by performing amniotomy and giving a purgative. The exquisite sensitivity to oxytocin which the myometrium must attain before labour can occur lasts but a few hours.

3. ADH, which in the non-pregnant state produces tachyphylaxis and lessens the subsequent response of the myometrium to oxytocin, is almost equally efficient as oxytocin in starting labour and effecting delivery.

4. Suckling is frequently associated with antidiuresis, but not always, and there may be a pronounced time lag between the start of suckling and the onset of antidiuresis; antidiuresis is less likely to occur if all sensation from the nipple is blocked.

5. The intravenous infusion of hypertonic NaCl causes antidiuresis but neither increased uterine activity nor let-down of milk.

6. It is concluded that oxytocin and ADH can be released independently of each other and that it is possible that impulses from the nipple which cause their respective release may travel along different pathways.

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