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THE COMPOSITION OF FOETAL AND MATERNAL BLOOD DURING PARTURITION IN THE EWE

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SUMMARY

1. Changes in the composition of foetal and maternal blood have been followed during the last 5–10 days of gestation and throughout parturition in the conscious sheep.

2. Catheters were placed in the foetal inferior vena cava through a tarsal vein and in a maternal uterine vein in ten ewes under sodium pentobarbitone anaesthesia. In four of the foetuses blood pressure and heart rates were recorded before and during parturition from an arterial catheter.

3. Foetal blood gas tensions, pH and PCV remained stable during the latter part of gestation and throughout labour until 15 min before delivery, when P_{O_2} and pH fell while PCV and P_{CO_2} rose in about 50 % of the foetuses examined.

4. Metabolite levels were also relatively stable at the end of gestation. Plasma glucose in both maternal and foetal blood rose during the hour before birth, while foetal plasma lactate was elevated as early as 4 hr before birth and was unrelated to any maternal changes. Foetal fructose levels were maintained until after delivery.

5. Rises in foetal blood pressure before birth were associated with uterine contractions. Foetal heart rate changes during labour varied in different individuals. The heart rate either fell gradually before birth or there was little change until a sudden drop at delivery.

6. The most striking changes in the lamb occurred at, or a few minutes after, birth; pH and P_{O_2} fell, P_{CO_2} and PCV rose, and bradycardia at delivery was succeeded by prolonged tachycardia. There were marked increases in plasma glucose and lactic acid at this time.

7. P_{O_2} rose rapidly once respiration was established, while pH and P_{CO_2} levels were restored within $\frac{1}{2}$–1 hr. Plasma FFA levels rose rapidly in the lambs 10–30 min after birth and remained high, while plasma glucose, lactate and fructose concentrations declined slowly in the 1–2 hr after birth, although suckling raised the plasma glucose levels. Consider-

able individual variation in the metabolite levels was found in both ewes and lambs.

8. In the majority of ewes delivery was associated with an abrupt maternal hyperglycaemia, with a much smaller rise in lactate and virtually no change in maternal blood gases or pH.

9. These findings are discussed in relation to existing information on new-born lambs and the human infant during birth.

INTRODUCTION

From evidence based primarily on acute experiments on animals and on cord blood studies in man, it has been assumed until comparatively recently that the foetus becomes anoxic during parturition, especially during the late second stage and delivery (James, 1960; see review by Dawkins, 1966). In the past decade some doubt has been cast on this assumption, particularly since the introduction of the technique for blood sampling from the human foetal scalp (Saling, 1962). Its widespread application has indicated that in the human foetus at least, anoxia and acidosis in normal labour is comparatively rare (Bretscher & Saling, 1967; Gare, Shime, Paul & Hoskins, 1969) and that the major changes occur during delivery and after birth (Koch & Wendel 1968). However, scalp samples can only be obtained after presentation of the head and rupture of the foetal membranes; the values obtained, therefore, are not necessarily representative of normal conditions *in utero* during late gestation.

Observations on the sheep with indwelling foetal and maternal catheters (Meschia, Cotter, Breathnach & Barron, 1965; Comline & Silver, 1970) have shown that, contrary to earlier beliefs, blood gas tensions, pH, O_2 capacity and other components of foetal blood remain relatively stable in this species during the last third of gestation, at a time of rapid foetal growth and increased oxygen consumption. Comparable data to those on the human foetus during parturition are not, however, available for the sheep, nor indeed for any other species. In the present experiments we have examined the changes in the composition of the foetal blood by means of sequential samples taken during the last part of gestation and throughout normal parturition in ewes with indwelling foetal and maternal catheters.

METHODS

The techniques used in these experiments were based on those described previously (Comline & Silver, 1970) but were modified to increase the stability of the catheters during movements of the foetus before and at parturition and to reduce the incidence of infection.

Animals. Welsh ewes (30–40 kg) of known gestational age were used; the housing, feeding and pre-operative treatment of the ewes were the same as in the earlier experiments.

Anaesthesia. All operations were carried out under sodium pentobarbitone anaesthesia as described previously.

Operative procedures. Vinyl catheters (Bolab Inc. Reading, Mass., U.S.A.) (0·97 mm o.d.) were used for all intravenous catheters in both the ewe and foetus and polytetrafluoroethylene (PTFE) catheters (Beckton, Dickinson & Co., Rutherford, N.J., U.S.A.) (0·86 mm o.d.) for arterial catheters in the foetus.

The hind limb of the foetus could be readily identified in the pregnant horn after a mid line incision in the abdominal wall with the ewe on her back. A catheter was first inserted into the middle uterine vein through a small tributary at the tip of the pregnant horn. After an incision through the uterine wall the foetal foot was extruded within the membranes so that the chorion and amnion could be secured separately before the hind limb was withdrawn for the insertion of the catheters. With this procedure the two membranes could be closed separately at the end of the operation.

Foetal catheters were placed in the vena cava above the level of the diaphragm through the lateral tarsal vein (7–10 in.) and in the aorta through the plantar branch of the saphenous artery (6–8 in.). Direct inspection at post mortem and radiological examination in the conscious animal showed that the tip of the venous catheter might move about 2 in. on flexion of the limb. Both arterial and venous catheters were tied to the skin of the limb to retain them during parturition. About 24 in. of catheter was then pushed into the amnion and the membranes closed with silk ligatures. The catheters were secured to the peritoneal surface of the uterus and were then taken subcutaneously to the dorsal region of the flank, exteriorized through a stab wound and kept in a plastic bag sewn to the skin of the ewe.

Aseptic precautions. Previous experience had shown that infection of the foetus was not a major problem compared with the difficulties found in keeping umbilical catheters patent; in these first experiments 60% of the animals had catheters patent for 4 or more days (Comline & Silver, 1970). With the use of foetal limb catheters, which rarely became blocked or pulled out, 70% of the foetuses were born alive in a later series of thirty animals. Foetal deaths were generally due to mild or severe infection and coliform organisms were isolated from the majority of these foetuses. In addition to the aseptic precautions described previously the following more stringent procedures were therefore adopted for the treatment of animals and withdrawal of samples.

(i) All animals received 600,000 i.u. procaine penicillin with 500,000 i.u. streptomycin, I.M. (Distavone, Dista Products Ltd) 1 day before, and for at least 6–10 days after, the operation or until parturition.

(ii) Catheter storage: all catheters were sealed with small artery forceps and tapered clock pins and were wrapped in swabs soaked in chlorhexidine gluconate solution (1/1000 (v/v) dilution of 20% (w/v) chlorhexidine gluconate (Hibitane, I.C.I.)).

(iii) Sampling: face masks and disposable plastic gloves were worn and the catheter bag surrounded by a sterile cloth. Sterile disposable syringes were used throughout the experiments and shortened syringe needles and clock pins were autoclaved in sealed packets made from autoclavable nylon film (Portland Plastic Ltd).

(iv) Heparin solutions: solid heparin and pyrogen free 0·9% NaCl (w/v) were sterilized by radiation in separate sealed bottles (5 ml.) and were stored before use in hibitane solution. Solutions of heparin with concentrations of either 1000 i.u./ml.

for maternal catheters or 100 i.u./ml. for foetal catheters were made up immediately before use; any residue was discarded and fresh solutions used for each period of sampling.

When these procedures were followed meticulously, the incidence of infection was greatly reduced and over 90% live births at term were achieved.

Blood samples. Daily samples from the ewe and foetus were taken between 9 and 10 a.m. When the onset of parturition was suspected samples were taken more frequently and foetal arterial blood pressure recorded continuously. After maternal abdominal contractions had started samples were taken at 30–15 min intervals until delivery. A foetal sample was taken at birth and at 5 min intervals afterwards for 15 min and then at $\frac{1}{2}$, 1, $1\frac{1}{2}$, 2, $2\frac{1}{2}$, $3\frac{1}{2}$ and 4–5 hr. Not all animals could be sampled as frequently during parturition or for as long after birth, particularly in those ewes in which labour was more rapid than expected or when it begun at times when insufficient assistance was available for the normal routine to be carried out. In two foetuses blood could not be withdrawn on the day of parturition due to a shift in the position of the catheters, probably associated with movement of the foetus. Since samples were available for the preceding days from these animals, and both lambs were sampled from the moment of birth, the data from these two are included in the present series.

Before parturition, maternal samples were usually taken immediately after the foetal samples, although in five animals sampling from the ewe was less frequent. The uterine venous catheter sometimes became blocked during the course of parturition; when this occurred subsequent samples were taken from the jugular vein. Maternal samples were generally taken after birth at 5, 15, and 30 min and at 1 and 2 hr.

The lambs were weighed soon after birth and then returned to the ewe but were not allowed to suckle for 1–2 hr. Five lambs were kept unsuckled for periods of 3–5 hr. In those lambs in which the hind-limb catheter remained *in situ* after delivery it was closed after sampling with a tapered clock pin and bound to the limb with Sellotape: it could then be used for sampling for a week or more after birth.

Measurements. The techniques used for the estimation of blood gas tensions, pH, PCV and the components of the plasma, with the exception of the free fatty acids (FFA), have all been described previously (Comline & Silver, 1970). All estimations of glucose, fructose, lactic acid and FFA were carried out on plasma which was separated as soon as possible after the measurement of pH, P_{CO_2} and P_{O_2} (on standard Radiometer (Copenhagen) Equipment) and PCV (on an Adams Autocrit centrifuge). The FFA were estimated by the titrimetric method of Dole (1956), modified to remove lactic acid and phospholipids (Trout, Estes & Friedberg, 1960) which was adapted for use with an autoanalyser (D. E. Faulkner & R. S. Burns, unpublished observations).

Blood pressure was recorded with a strain gauge pressure transducer connected to a pen recorder. Routine daily measurements were made with the transducer placed at the level of the foetal heart. During parturition the transducer was kept in the catheter bag to avoid damage during movement of the ewe, and the records were corrected to compensate for differences in position.

RESULTS

Resting values during late gestation

The effect of the process of parturition on the foetus and new-born lamb was investigated in ten ewes; eight of the ewes had foetal and maternal catheters implanted 18–5 days before lambing and the other two 3 days and 1 day before parturition occurred. Daily blood samples were taken for a routine pH and PCV check, but since some of the animals formed part of another experimental programme, full analyses of foetal and maternal blood gas levels, plasma hexose, FFA and lactic acid concentrations were made only when sufficient blood was available. Table 1 gives the mean values obtained from samples taken from the uterine vein and the foetal inferior vena cava at 9, 5 and 1 day before parturition. The results confirm the relative stability of these preparations during the last stages of gestation.

Foetal arterial blood samples were also taken in those animals with an indwelling catheter in the lower aorta. Blood gas and metabolite levels in these samples did not differ significantly from those found in the foetal venous blood, provided the tip of the venous catheter lay near the level of the diaphragm. It was always apparent when this catheter had been pulled back into the lower vena cava, since P_{O_2} levels dropped to 18–20 mm Hg and pH to 7·31–7·33.

The foetal arterial catheter was used to record blood pressure and heart rate at intervals during the last 9–10 days of gestation as well as during parturition. Mean values for five animals are given in Table 2. Two of these animals which were additional to the present series, lambed at night and did not yield any data during parturition.

Changes found during parturition

In the sheep delivery can be extremely rapid and the clinical signs are not always easily recognized. Distension of the udder generally occurred 12–24 hr before delivery, although in some individuals this was evident 2–3 days earlier. The ewe frequently refused her ration of concentrates 12–2 hr before lambing and 1–2 hr before delivery she could be seen scraping the bedding, licking her lips and behaving in a restless manner.

The mean age at which parturition occurred was 143 days and all but one (137 days) lambed between 141 and 147 days gestation. The mean weight of the lambs was $3{\cdot}1 \pm 0{\cdot}1$ kg which is within the normal range for this breed at full term. Seven out of the ten foetuses were normally presented and were delivered unassisted. In the remaining three ewes some manual assistance was given because of malposition of the forelimbs (two foetuses) and a breech presentation (one foetus).

TABLE 1. Mean resting values (± S.E.) in foetal and maternal blood during late gestation

Samples from	No. of days before parturition	n	Blood: pH	Blood: P_{CO_2} (mm Hg)	Blood: P_{O_2} (mm Hg)	Blood: PCV (%)	Plasma: Glucose (mg/100 ml.)	Plasma: Lactic acid (mg/100 ml.)	Plasma: Fructose (mg/100 ml.)	n	Plasma: FFA (m-equiv/l.)
Foetal vein	9	5	7·39 ± 0·02	49·0 ± 2·5	25·4 ± 1·5	31·4 ± 0·9	13·3 ± 1·8	16·7 ± 1·5	74·3 ± 7·2		0·15 ± 0·03
	5	7	7·39 ± 0·02	47·3 ± 2·6	25·8 ± 1·2	32·8 ± 1·7	12·7 ± 1·2	16·8 ± 1·3	77·8 ± 8·1		0·15 ± 0·02
	1	8	7·38 ± 0·01	49·0 ± 2·0	25·0 ± 1·5	33·8 ± 1·8	15·0 ± 2·3	19·1 ± 1·6	67·7 ± 5·8		0·13 ± 0·03
Uterine vein	9	5	7·45 ± 0·02	*	52·3 ± 1·7	28·6 ± 0·9	57·6 ± 7·3	11·2 ± 2·0	—	4	0·8 ± 0·2
	5	7	7·45 ± 0·01	*	52·2 ± 1·2	28·0 ± 1·0	58·0 ± 4·6	9·8 ± 1·8	—	4	0·8 ± 0·4
	1	7	7·45 ± 0·01	*	53·8 ± 2·1	28·4 ± 0·9	68·0 ± 8·1	9·6 ± 1·4	—	4	1·0 ± 0·4

* Mean values for uterine vein P_{CO_2} not available. Occasional measurements made; values did not differ from the level of 37·9 ± 1·1 found previously (Comline & Silver, 1970).

TABLE 2. Mean arterial blood pressure (B.P.) and heart rate (H.R.) in five foetal lambs during late gestation

No. of days before parturition	Mean B.P. ± S.E. (mm Hg)	Mean H.R. ± S.E. (beats/min)
9	48 ± 4	150 ± 7
5	58 ± 2	146 ± 5
3	63 ± 3	143 ± 6
1	60 ± 2	147 ± 7

In the majority of animals sampling from both ewe and foetus was started 1–3 hr before parturition and continued throughout the process until 3–5 hr after birth, but in four animals sampling was begun either at birth or ¼ hr before delivery and continued thereafter. Further details of the timing of samples and their subsequent treatment are given in the Methods section.

Foetal blood pressure and heart rate

Irregular changes in blood pressure were frequently seen in several animals 24–48 hr before parturition but it was not known whether such changes were associated with uterine movements in any way. The first indication of definite uterine contractions, in those animals with foetal arterial catheters, was the appearance of regular rises in foetal arterial blood pressure. In the ewe with a breech presentation these fluctuations in foetal blood pressure were observed at 1–2 min intervals, 8–9 hr before manual delivery of the foetus, although there was no evidence of any maternal abdominal effort until much later.

In three animals blood pressure recordings were made throughout the latter part of labour and during delivery; recordings were continued in two of the new-born lambs. Mean arterial pressure in these foetuses was 55–75 mm Hg at 1 hr and 65–75 mm Hg at 10 min before delivery. Rises in blood pressure of ¼–½ min duration were seen in all three 1–2 hr before birth (Fig. 1*a*); in one foetus these were accompanied by considerable bradycardia. Preliminary observations on intra-amniotic pressure during parturition have now shown that uterine contractions, which begin 10–12 hr before delivery, are generally associated with increases in foetal blood pressure of similar magnitude. Abdominal contractions generally started ¾–½ hr before delivery and they increased in strength and frequency as parturition became imminent. These were always associated with very large, rapid fluctuations in foetal blood pressure which were superimposed on the slower waves (Fig. 1*b* and *c*); some bradycardia generally occurred under these conditions. These very sharp increases in pressure appeared to be the direct effect of the 'bearing down' efforts of the ewe.

The changes in heart rate before and during parturition are shown in Fig. 2. Although a fall was observed in all foetuses, the time at which this occurred varied in the different individuals. In the breech (▲), bradycardia was evident 3–4 hr before delivery and 1–2 hr before the onset of the second stage; in this animal further cardiac slowing was associated with the frequent uterine contractions. In two other animals (○, ×), foetal heart rate remained relatively high and within the range found during late gestation until just before or at delivery, when a marked drop occurred. There was little or no change in heart rate during uterine or

abdominal contractions in these animals and their blood gas and pH levels remained stable until delivery. An intermediate picture was seen in the fourth animal (●), in which the heart rate was within the normal foetal range at 1 hr but declined steadily 40 min from birth, arterial P_{O_2} also fell during this period; in addition marked bradycardia occurred in this foetus during each uterine contraction. Foetal bradycardia associated with uterine contractions is frequently seen during labour in the human (Goodlin, 1971).

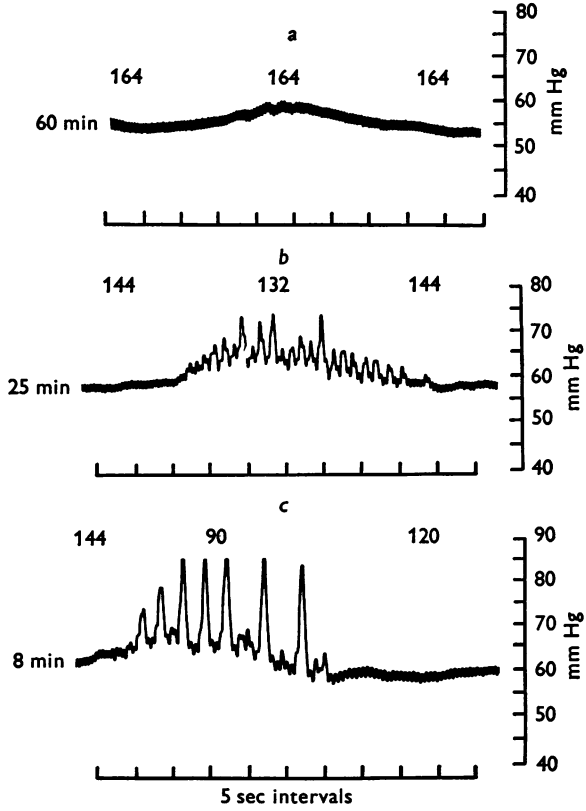

Fig. 1. Changes in foetal arterial blood pressure during labour, (*a*) during a uterine contraction, (*b*) and (*c*) during uterine and abdominal contractions. Heart rates (beats/min) are given above each record, and time before delivery on the left.

In the two new-born lambs there was an immediate rise in heart rate as soon as respiration became established and the very high rates, double those in the foetus, were maintained for some time. Mean arterial blood pressure in the new-born was not, however, markedly different from that in the foetus.

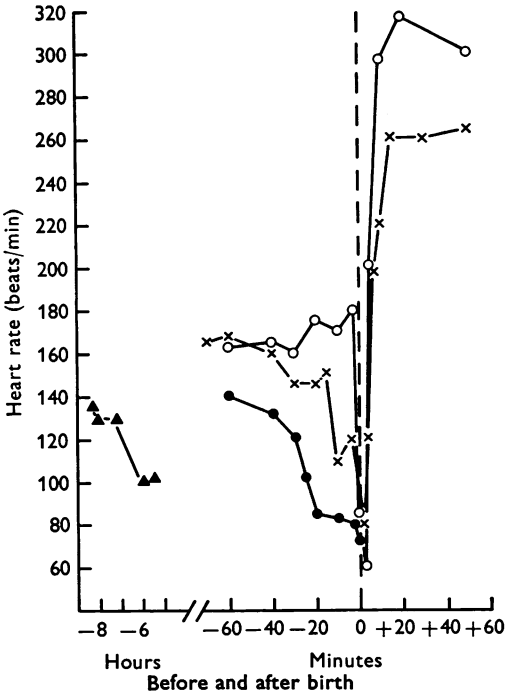

Fig. 2. Changes in heart rate in foetal and new-born lambs before and after parturition. Each symbol represents a single animal. Heart rates were measured during intervals between uterine contractions, when foetal blood pressure was stable.

P_{O_2}, P_{CO_2} pH and PCV levels

Fig. 3 summarizes the mean changes observed in the lambs during the process of parturition. The larger S.E.S of values obtained near delivery compared with those found earlier or on previous days indicate the greater variation encountered at this time. Nevertheless, the results show that in general the condition of the foetal lamb *in utero* remains relatively unchanged with respect to blood gas levels, pH and PCV, until about 15 min before delivery, and that the major changes occur immediately after birth.

In some animals alterations in P_{O_2} and pH were not detected before lambing, the PCV rise was small and an intense but short-lived drop in pH occurred immediately after birth; a typical example is given in Fig. 4*a*. In other animals a fall in pH and P_{O_2} and a rise in PCV began at least 15 min before delivery; P_{O_2} levels were restored rapidly once respiration started but pH rose more slowly after birth (Fig. 4*b*).

Foetal arterial P_{O_2} was measured in three animals and the levels were similar to those found in foetal venous blood from the upper inferior vena

cava (Fig. 3). At birth, after the first two or three breaths, arterial P_{O_2} changed only marginally, but by 2 min it had risen to 34 mm Hg and at 5 min the value was 65 mm Hg. The subsequent fall to a level of about 50–55 mm Hg was associated with a rise in pH and fall in P_{CO_2}.

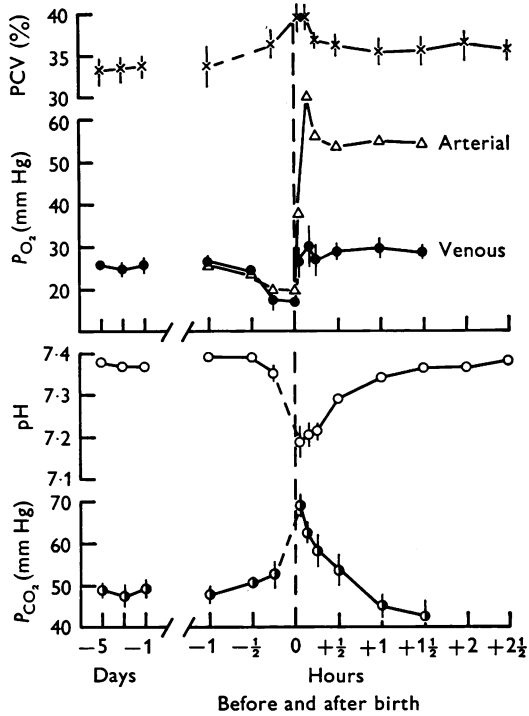

Fig. 3. Mean changes in PCV (×), venous P_{O_2} (●), pH (○) and P_{CO_2} (◑) in ten lambs before and after parturition. S.E.S of means, when greater than the diameter of the symbols, are shown as vertical lines. △, mean arterial P_{O_2} in three lambs (S.E.S not calculated for these, nor for all mean values at 30 min before parturition when $n = 3$).

While the changes in foetal blood pH and P_{CO_2} at birth were statistically significant, the transient rise in PCV was not. This was due to the widely differing basal PCV levels in the individual foetuses. When the changes were calculated on a percentage basis, taking the average PCV between 1–5 days previously as 100% for each individual, the mean rise immediately after birth to $118 \pm 1{\cdot}8$% was highly significant ($P < 0{\cdot}01$). Even the change from $98 \pm 2{\cdot}5$% at 1 hr before birth to $111 \pm 0{\cdot}6$% at 15 min before delivery was statistically significant ($P < 0{\cdot}05$).

Samples of maternal blood from the uterine or jugular vein were taken throughout parturition although not as frequently as those from the foetus. Little obvious change in either P_{CO_2}, pH or PCV levels occurred

during or after labour. In the ewe blood pH is normally high and P_{CO_2} low (Comline & Silver, 1970) and there was no evidence of any further alkalosis during delivery. After birth uterine venous samples could not always be obtained, but in those animals in which the vessel remained patent there was a definite increase in P_{O_2}. Before parturition uterine venous P_{O_2} was 50–55 mm Hg and this rose to about 80 mm Hg immediately after birth; 1–2 hr later the level had declined to 70 mm Hg.

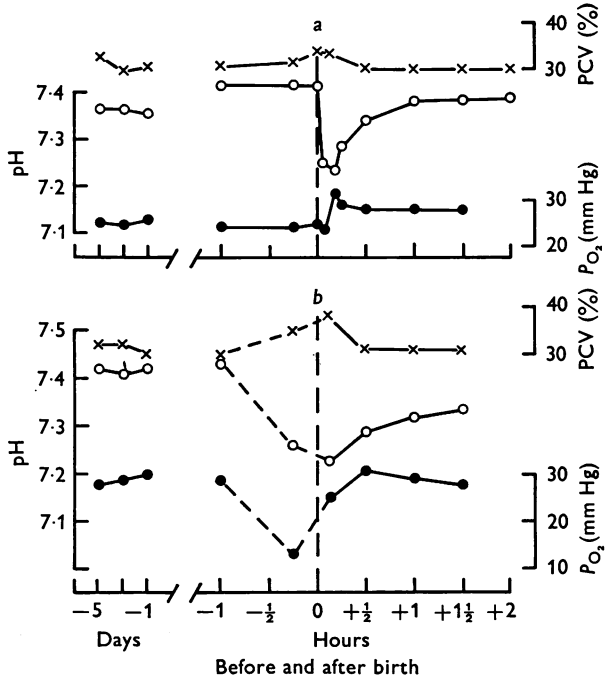

Fig. 4. Changes in PCV (×), pH (○) and venous P_{O_2} (●) in two lambs (*a* and *b*) before and after parturition, to show individual variation.

Plasma lactic acid concentration

While part of the pH change in the foetal blood at birth could be associated with the rise in P_{CO_2}, this was not sufficient to explain the fall of 0·15–0·2 pH units which occurred immediately after birth. However, plasma lactate concentrations increased in all lambs at this time; mean values are given in Fig. 5 together with the pH data from Fig. 3. Although the greatest rise in lactic acid occurred 5–10 min after birth, there was also a significant increase in the hour preceding birth; the levels were almost double those found 24–72 hr previously. In two animals samples were obtained at 4–8 hr before parturition. In one foetus some rise in lactic acid had occurred at 4 hr; in the other (breech), in which frequent uterine

contractions were present at 8 hr, plasma lactate was normal at 8 and 7 hr but had more than doubled by 4 hr before manual delivery.

Maternal plasma lactate levels during labour were higher ($P < 0{\cdot}05$) than those of the preceding day but the rise was much smaller than that in the foetus. There was little relation between individual foetal and maternal values in the hour before birth which presumably reflects the relative impermeability of the sheep placenta to lactate. In the human, foetal and

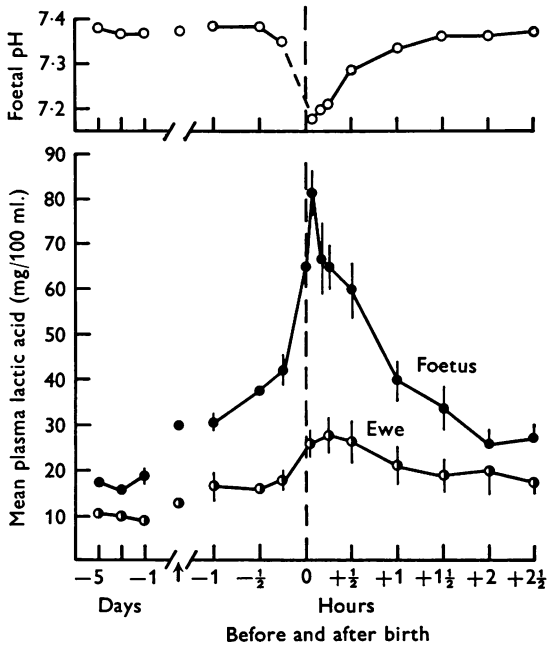

Fig. 5. Mean changes in plasma lactic acid concentration in maternal (◑) and foetal (●) blood before and after parturition in ten ewes; pH data for foetus and new-born (○) from Fig. 2 shown above. S.E.s for each group are indicated as in Fig. 2. ↑ mean for two animals at 4 hr.

maternal changes are more closely related, foetal levels are only slightly higher than those of the mother, and lactate appears to pass fairly freely across the placenta (Derom, 1964).

The extent of the changes in the new-born lambs varied between moderate and severe lactic acidaemia. This is shown in Fig. 6 in which data from two individuals are given. These observations also indicate that there was a close relationship between the post-natal drop in pH and the maximum rise in lactic acid. The plasma lactate concentration fell slowly after birth in all animals (Fig. 5), whereas pH levels were restored more rapidly. The critical lactic acid concentration which was associated with

a definite fall in foetal or neonatal blood pH appeared to be 35–40 mg/100 ml.

A significant and fairly prolonged rise in maternal plasma lactic acid levels occurred immediately after delivery, but the changes were not as great as those in the foetus and were overshadowed by the maternal hyperglycaemia.

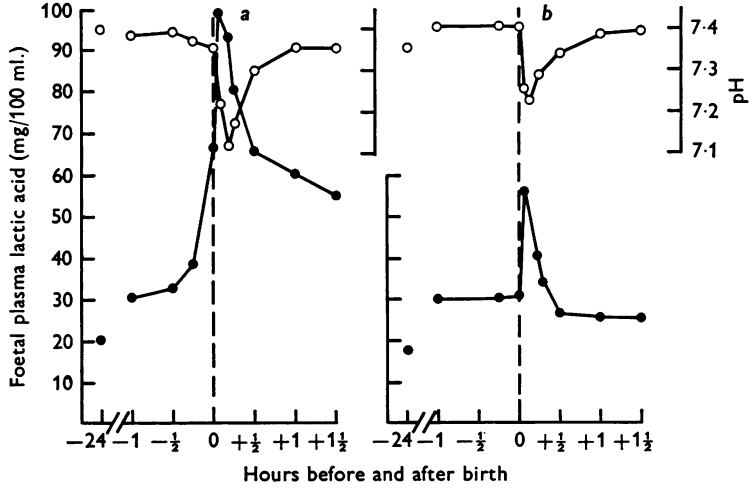

Fig. 6. Changes in pH (○) and plasma lactic acid (●) in two lambs (*a* and *b*) before and after parturition to shown individual variation.

Plasma glucose levels

The mean values found before and after parturition are summarized in Fig. 7. Like the plasma lactate levels, the greatest changes in both ewes and lambs occurred immediately after birth. In the foetus the slight increases in plasma glucose at 1 hr and 30 min before delivery were not significantly higher than the mean values found 24 hr previously. However, the rise at 15 min before birth was statistically significant ($P < 0{\cdot}05$) and was associated with a similar increase in maternal plasma glucose. The further rise in plasma glucose in the new-born lambs in the first 15 min after birth was presumably due to endogenous release since the maternal source of glucose was no longer available. If the lambs were not suckled their glucose levels then fell to near foetal values.

Wide individual variation was encountered in this series of ewes and lambs; this is illustrated in Fig. 8 in which the results from three animals are given. In two of the ewes moderate or severe hyperglycaemia occurred at birth but there was little change during labour (Fig. 8*a*); the degree of hyperglycaemia in the corresponding lambs was not very great. In the

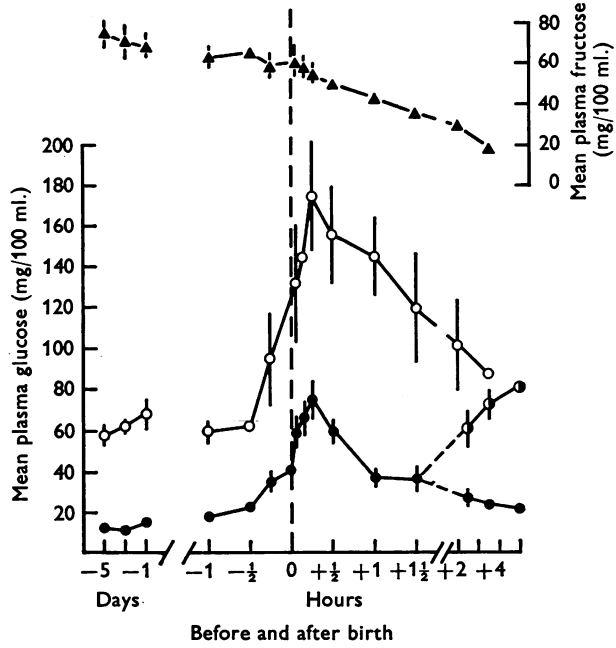

Fig. 7. Mean changes in maternal (○) and foetal (●) plasma glucose and foetal plasma fructose (▲) concentration before and after parturition. ◑, mean plasma glucose levels in four lambs allowed to suckle 1½–2 hr after birth. S.E.s for each group are shown where they exceed the diameter of the symbols except in the groups at $-\frac{1}{2}$ and $+4\frac{1}{2}$ hr when $n = 3$.

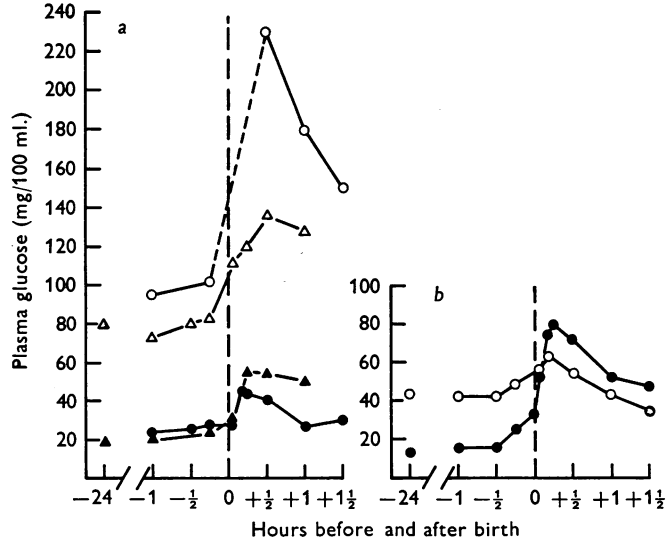

Fig. 8. Changes in maternal (△, ○) and foetal (▲, ●) plasma glucose levels before and after parturition in three animals: two shown in *a* and one in *b*.

third sheep (Fig. 8*b*) which had a low resting plasma glucose, there was only a small maternal rise which began before birth and was accompanied by a corresponding increase in foetal levels. At birth, hyperglycaemia in the lamb was rapid in onset, reached a peak of 80 mg/100 ml. and was more prolonged, whereas that in the mother was slight and short-lived.

In the majority of foetuses plasma fructose levels were high until parturition (Fig. 7). Although the levels found on the day of birth appeared to be lower than those on previous days, the differences were not statistically significant. Fructose levels always fell steadily after birth.

Plasma FFA levels

One of the most consistent findings in the present series of observations on foetal lambs was the low plasma FFA concentration in all foetuses irrespective of gestational age or maternal level. The range of values found lay between 0·05 and 0·2 m-equiv/l. and this was not exceeded up to the time of parturition (Fig. 9). In fact there was little change in FFA levels until 10 min after birth, but thereafter the rise was extremely rapid, the maximum increase occurring between 15 and 30 min of birth. The levels then remained high for the rest of the period under investigation.

In the ewes the FFA levels were extremely variable and a similar situation was found in a number of non-pregnant animals. In general the lowest plasma FFA concentrations were found in the quietest animals. Because of this variability and the fact that maternal levels bore no relation to those in the foetus, routine analyses on maternal plasma were discontinued. Values found during parturition in four animals were somewhat more consistent than those found earlier (Fig. 9). High levels were found 1 hr before delivery and these were maintained until just after birth; thereafter, there was a gradual fall.

Effects of catecholamine infusions on the foetus

In three animals the effects of the I.V. infusion of adrenaline or noradrenaline into the foetus were examined during the last week of gestation. Changes in foetal blood pressure, heart rate, plasma glucose, lactic acid and FFA were measured. The catecholamine level infused in two animals was 5 μg/min for 5 min (*ca.* 2 μg/kg.min). In the third animal a longer infusion period (30 min) was adopted and the rate of infusion after an initial priming dose of 10 μg was 2·5 μg/min for 10 min and 1·25 μg/min for 20 min (i.e. 1·0 and 0·5 μg/kg.min respectively). These levels were selected as being of the same order as the endogenous discharge from both adrenal glands during asphyxia (Comline, Silver & Silver, 1965).

In all three animals a rise in mean arterial pressure of about 20 mm Hg occurred during both adrenaline and noradrenaline infusions. The initial

rise in blood pressure was accompanied by slowing of the heart from resting rates of 140–160/min to 108–120/min. The bradycardia continued for 3–5 min; thereafter the heart rate increased to 180–200/min while the blood pressure fell 5–10 mm Hg. The tachycardia continued for ½–1 hr after both short and long infusions had ceased, whereas the mean arterial pressure returned to resting levels immediately.

In contrast to the cardiovascular changes, noradrenaline infusions had little or no effect on plasma glucose, lactic acid or FFA levels in the foetus, whereas both 5 and 30 min infusions of adrenaline produced measurable

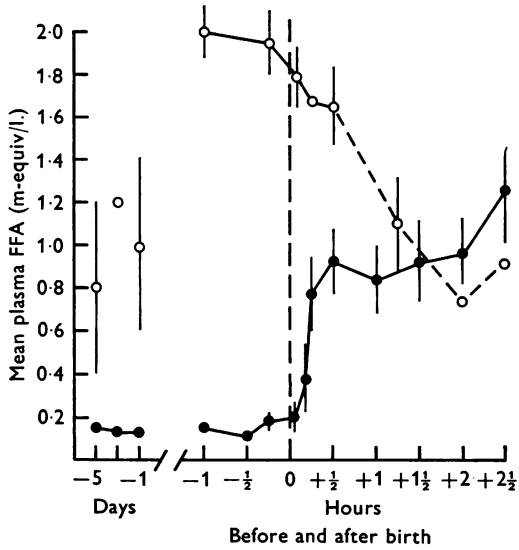

Fig. 9. Mean changes in plasma FFA concentration in four ewes (○) and ten foetuses (●) before and after parturition. S.E.s not calculated for maternal groups at −3 days, +¼ hr, 2 hr and 2½ hr, since $n = 3$. S.E.s for all other mean values are indicated as in Fig. 2.

changes in all three parameters (Fig. 10). Sharp rises in plasma glucose and lactic acid of 6–12 mg/100 ml. were seen after the short infusions of adrenaline; during and after the 30 min infusion a prolonged rise in lactic acid occurred which was accompanied by a rise in glucose of somewhat shorter duration. The changes in FFA after 5 min adrenaline were equivocal since base line levels, which varied between 0·05 and 0·15 m-equiv/l. in the different foetuses, were difficult to measure accurately. There was, however, an obvious increase of 0·15–0·2 m-equiv/l. during and after the 30 min infusion of adrenaline; but no change in FFA with a similar infusion of noradrenaline.

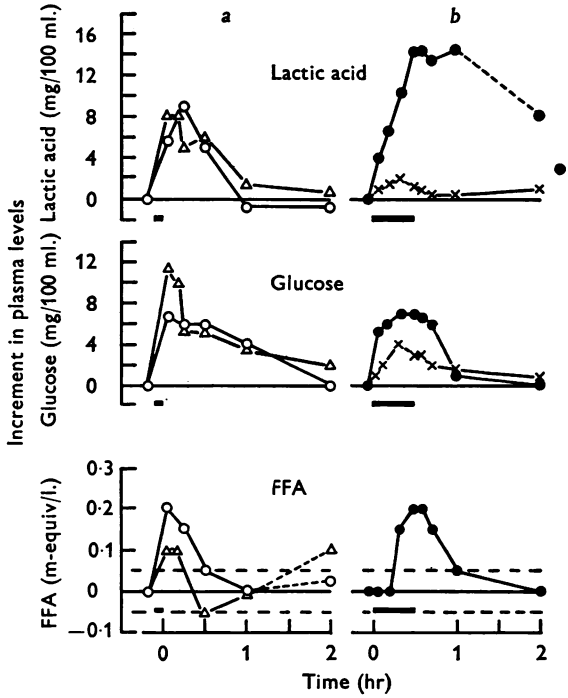

Fig. 10. The effect of catecholamine infusions on the changes in foetal plasma lactic acid, glucose and FFA. All values are given as increments from the resting levels at time = 0. Dashed lines, range of resting plasma FFA; *a*, 5 min adrenaline infusion (■) in two foetuses △, ○; *b*, 30 min infusion (▬) of adrenaline (●) or noradrenaline (×) in one foetus tested at 7 and 3 days before birth (no change in FFA after 30 min noradrenaline). Details of catecholamine levels infused are given in the text.

DISCUSSION

Changes in the foetus and new-born

The virtual absence of any change in the foetal blood gas or pH levels until, at the most, 15 min before delivery is perhaps the most surprising feature of this study of parturition. Indeed, in more than half the animals the blood gas levels remained unchanged until birth and in all cases the lowest pH and P_{O_2} were found shortly after delivery. The relatively stable conditions of the foetal blood previously reported during the latter part of gestation (Meschia *et al.* 1965; Comline & Silver, 1970) are therefore maintained, and the needs of the rapidly growing foetus continue to be met until the very end of gestation. The only comparable results in other species are those obtained from human scalp samples but for obvious reasons these observations are limited to a comparatively restricted

period. However, the present results indicate that values obtained early in labour are probably representative of conditions in the foetus during late gestation.

The first signs of uterine contractions in the sheep occur 10–12 hr before delivery (Hindson, Schofield, Turner & Wolff, 1965) and these increase in force from about 5 mm Hg to 20–30 mm Hg during the course of labour. Preliminary studies with intra-amniotic balloons have now shown that uterine contractions are generally, though not always, reflected in changes in foetal arterial blood pressure of similar magnitude (R. S. Comline & M. Silver, unpublished observations). Very large rapid fluctuations in foetal blood pressure were only associated with the onset of abdominal straining; these were sometimes accompanied by bradycardia. Throughout this period, however, the placental exchange was sufficient to maintain normal foetal blood gas values; the rapid drop of pH and the asphyxia which follow rupture of the cord emphasize this point.

The factors responsible for the maintenance of placental exchange were not examined specifically in the present experiments. Unfortunately, the relatively slow collection of blood through the catheters precluded any measurement of possible short-term fluctuations of P_{O_2} associated with the uterine or abdominal contractions, similar to those recorded with P_{O_2} electrodes from the human foetal scalp (Walker, Philips, Powe & Wood, 1968; Kunke, Heidenreich, Erdmann & Christ, 1972) and from the umbilical artery of the sheep foetus during oxytocin-induced contractions (Goodwin & Paul, 1966). The variations in P_{O_2} appeared to be small, but even a relatively large decrease in umbilical venous P_{O_2} would be damped on the arterial side of the foetal circulation. Nevertheless, the possibility exists that the foetal aortic chemoreceptors may be stimulated intermittently under these conditions to produce a peripheral sympathetic vasoconstriction (Dawes, Duncan, Lewis, Merlet, Owen-Thomas & Reeves, 1969) which would result in the redistribution of the foetal circulation and enhance placental perfusion and exchange.

Thus the foetus during labour, with its unexpanded lungs and possible periods of decreased P_{O_2} bears a strong resemblance to the adult during apnoeic asphyxia where aortic chemoreceptor discharge causes bradycardia and peripheral vasoconstriction (Angell James & Daly, 1969). The variable foetal bradycardia and rise in foetal plasma lactate which preceded all other changes in the foetal blood before birth would be consistent with this view.

Widespread stimulation of the sympathetic system during and after birth has been postulated for many years on the basis of experiments on Caesarean delivered lambs (Barcroft, 1938; Van Duyne, Parker, Havel & Holm, 1960; Comline & Silver, 1961) and observations on the human

infant at birth (Roux, Romney & Hausinger, 1967). The present observations of a rapid increase in heart rate, the 15–20 % rise in PCV and the large increase in plasma lactate, FFA and glucose, which occurred within 15 min of delivery, all support this assumption. Since asphyxia and acidosis coincide with increased sensory stimulation from the external environment a general sympathetic discharge might be expected at this time. Many of the effects, however, can be explained as specific responses to stimuli which occur at birth.

After birth, the fall in P_{O_2} and rise in P_{CO_2} will provide a short period of increased stimulation to the arterial chemoreceptors. When breathing starts, however, their primary cardiovascular effects of bradycardia and vasoconstriction will be over-ridden by the afferent stimuli from the expanded lungs (Angell James & Daly, 1969) resulting in the characteristic tachycardia of the new-born lamb. These changes will probably be enhanced by the subsequent rise in P_{O_2} which would decrease the chemoreceptor drive and increase the response to lung inflation. Furthermore, the large rise in the lactate concentration after birth may at least in part be attributed to the change from peripheral muscular vasoconstriction to the vasodilation which follows pulmonary expansion (Daly & Robinson, 1968). In fact, the results of the present experiments are in agreement with the comparison made by Scholander (1959) and James (1960) between the reactions of the foetus at birth and those of the diving mammal during and after a dive.

The rise in FFA after birth may also be a further example of a specific sympathetic response to a new stimulus after birth. The rate of the rise and the final concentration of FFA attained in the present experiments are similar to those reported in new-born lambs (Van Duyne, Parker, Holm, Hirai & Gallager, 1965; Alexander & Mills, 1968) and infants (Roux *et al.* 1967). Their release may be due to cold and other external stimuli; in particular cooling by evaporation seems to be a very potent stimulus (Alexander & Mills, 1968). In the present experiments the newly born lambs were neither cooled nor kept in a thermoneutral environment and the FFA changes observed lay between those reported by Alexander & Mills for these two environmental extremes.

The comparative insensitivity of the FFA mobilizing mechanism in the foetus to both small (present experiments) and large (Dawkins, 1964) doses of adrenaline and the lack of any effect of noradrenaline is perhaps surprising, since similar doses in the new-born can evoke pronounced rises provided the initial resting levels are low (Alexander & Mills, 1968). It is possible that the low P_{O_2} of the foetus limits the rate of release of FFA from fat depots so that FFA mobilization can occur only when P_{O_2} levels rise after birth. Hypoxia is known to depress the activity of brown fat in

the new-born (Heim & Hull, 1966) although little is known of its effect on the white fat depots, the alternative source of the free fatty acids in the plasma. On the other hand, measurements of plasma concentrations alone do not give any information about FFA turnover and since there may be a high rate of local FFA metabolism in brown fat (Dawkins & Hull, 1964) the absence of any rise in plasma levels in the foetus may merely mean that they are not liberated into the circulation.

On present evidence it is difficult to assess the role of the adrenal medulla during parturition. While many of the reactions may be due to peripheral sympathetic nerve activity, some discharge from the adrenal medulla may also occur. Thus the increase in foetal plasma glucose just before birth was sometimes greater than that predicted from the corresponding maternal levels, and part of the rise in foetal plasma lactate during labour might well be due to circulating adrenaline. The results obtained with infusions of adrenaline into the foetus support this view. However, the changes before parturition were, in general, relatively small and did not occur in all foetuses. Adrenal medullary discharge before birth may therefore be an emergency mechanism which is only stimulated fully during abnormal conditions (Comline *et al.* 1965), whereas at delivery and in the new-born, catecholamine release seems more likely in view of the brief asphyxia at birth and the high lactate and glucose levels in the plasma.

All the results of the present experiments indicate that during normal parturition placental exchange is maintained in a remarkable manner and that the most critical period is after delivery and severance of the umbilical cord. Thereafter, the new-born lamb is dependent on mechanisms, such as the efficient inflation of the lungs and reflex responses, all of which mature during the last part of foetal life, but which may depend upon a higher P_{O_2} and increased sensory input for their full activation.

Maternal changes

The pronounced hyperglycaemia was by far the most striking change found in the ewe during parturition. Its extent and duration varied in different animals, but it was always associated with the terminal stages of labour and especially with the actual delivery of the lambs. Disturbance or handling of the ewe is unlikely to have been a major contributory factor, particularly as high plasma glucose levels were found in the two ewes which had not been sampled until immediately after parturition. A more likely cause is the discharge of adrenaline from the adrenal medulla stimulated during the distension caused by expulsion of the foetus and possibly by traction on the umbilical cord transmitted to the uterus. The abrupt onset of the hyperglycaemia certainly resembles that produced by adrenaline in the pregnant ewe (Setchell & McClymont, 1955).

By comparison, the increase in maternal plasma lactate was small at birth; it was only one third of that seen in the lamb. The changes in plasma glucose and lactic acid in the ewe and foetus at parturition may well illustrate the difference between the effects of adrenaline in the adult and in the foetus and neonate. In the adult adrenaline may produce hyperglycaemia with only a small rise in lactate, while in the foetus, new-born and also the young lamb (Alexander, Mills & Scott, 1968) it results in a rise in plasma lactate which is greater or at least equal to that of glucose.

The high maternal plasma FFA levels observed during the last hour of labour were a further indication of a sympathetic discharge at this time. However, since resting levels in the maternal plasma varied widely it is difficult to assess the extent and significance of this type of sympathetic activity during labour.

In contrast to the metabolic changes, the blood gas and pH levels remained remarkably stable in the ewes throughout parturition, whether they were restless, quiet or straining. Blood P_{CO_2} in the sheep is always low and pH relatively high (Comline & Silver, 1970) and, unlike the human (Low, Boston & Cervenko, 1970) there was no evidence for respiratory alkalosis during parturition. The sudden rise in uterine venous P_{O_2} immediately after birth presumably reflects the loss of the foetus and the consequent alteration in O_2 exchange in the uterus.

Technique

The results from the present experiments indicate the value of catheters inserted into the vessels of the foetal limbs for sequential sampling from individual foetuses over long periods. The position of the hind limb in the pregnant horn of the uterus of the sheep allows the insertion of catheters with the minimum of trauma to either the placenta or the foetus. Thus in the present series of ten foetuses, no abrupt preparturient falls in foetal plasma fructose were found, such as those frequently observed before birth or abortion of foetuses with umbilical catheters (Comline & Silver, 1970). This emphasizes the likelihood of impairment of at least part of the placental circulation when umbilical catheters are present, whereas the great advantage of those in the limb vessels is their stability, particularly at the end of gestation and during birth. In our experience, infection, though comparatively rare, appeared to be the only limiting factor in experiments of this type. Passive immunity from infusions of maternal plasma into the foetus may provide a partial solution to the problem (Liggins, Grieves, Kendall & Knox, 1972) but successful preparations still largely depend on the precautions taken to reduce the incidence of non-specific infections.

All experiments which require the insertion of foetal catheters are open to the criticism that the manoeuvre may alter the normal course of gestation. Certainly, parturition is sometimes slightly early by 2–3 days in preparations of this type but it is not easy to give a clear and unequivocal reason from the evidence at present available. Many factors may be involved, such as the nutrition of the ewe or environmental conditions, but a more likely explanation may lie in the foetus itself. The foetal hypothalamic system becomes increasingly sensitive to various stimuli near the end of gestation (Nathanielsz, Comline, Silver & Paisey, 1972). In the present experiments the now familiar pattern of a rising foetal plasma cortisol level 1–2 days before birth, followed by a fall in the first 48 hr post partum was found, irrespective of the duration of gestation (Bassett & Thorburn, 1969; Comline, Nathanielsz, Paisey & Silver, 1970). It is possible that repeated sampling near the end of gestation may, in spite of stringent aseptic precautions, introduce a stimulus, such as a slight infection, which triggers the unstable hypothalamus. However, in the present experiments, the development of the lambs as assessed by criteria such as weight, wool growth and activity after birth, appeared to be essentially normal and there is no reason to suppose that the changes described here are not representative of normal conditions during parturition in the sheep.

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