

## Glucose partitioning in the pregnant ewe: effects of undernutrition and exercise

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Maternal whole-body glucose entry rate and uterine and umbilical net uptakes of glucose and oxygen were measured in single-pregnant ewes which were either well-fed throughout, or fed at 0.3–0.4 predicted energy requirement for 7–21 d during late pregnancy. All ewes were studied while standing at rest and then while walking on a treadmill at 0.7 m/s on a 10° slope for 60 min. Underfed ewes suffered significant decreases in live weight and had lower fetal, but not placental, weights at 140–144 d gestation. Undernutrition also caused large decreases in maternal glycaemia and glucose entry rate, which were associated with equally large decreases in uterine and umbilical net uptakes and O<sub>2</sub> quotients of glucose, and with a decrease in placental glucose transfer capacity. Exercise caused increases in maternal blood concentration, entry rate and uterine net uptake of glucose, the magnitudes of which were not significantly affected by plane of nutrition. Umbilical glucose uptake and placental glucose transfer capacity increased during exercise in underfed but not fed ewes. The fractional distribution of maternal glucose to the pregnant uterus, and of uterine glucose uptake to the fetus, were unaltered by undernutrition; during exercise, a disproportionately small fraction of the increased maternal glucose supply went to the uterus. The results confirm that the ovine conceptus responds to nutritional reduction in maternal glucose availability in a manner similar to non-uterine maternal tissues. Major reductions in glucose supply appear to override putative glucose-sparing mechanisms which may operate to favour the conceptus in better-nourished animals.

**Glucose: Pregnancy: Uterus: Fetus: Sheep**

It is well-established that the growing sheep conceptus makes substantial demands on the maternal glucose supply, especially in late pregnancy. At this time the gravid uterus may account for about 30–50% of whole-body glucose utilization in well-fed, monotocous ewes (Hay *et al.* 1983; Oddy *et al.* 1985). However, there is conflicting evidence on the degree to which uterine glucose consumption is responsive to changes in maternal supply. On the one hand, the findings of Oddy *et al.* (1985) appear to support the long-held notion (e.g. Barcroft, 1946) that when maternal glucose production is limited by undernutrition, the unmodified demands of the conceptus take priority over those of maternal tissues. On the other, studies by Hay *et al.* (1983, 1984*b*) strongly suggest that fetal and utero-placental uptake of maternal glucose is attenuated in proportion with the reduction of maternal supply during short-term starvation.

Therefore, in the present study we re-investigated the effects of undernutrition during late pregnancy on the partitioning of maternal glucose between the pregnant uterus and non-uterine maternal tissues and, within the uterus, between fetal and utero-placental tissues. In the same animals we also examined uterine and fetal responses to an acute perturbation of maternal glucose metabolism, achieved by treadmill exercise. Results confirm that the ovine conceptus is indeed responsive to nutritional reduction in maternal glucose supply,

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to a similar degree as non-pregnant maternal tissues. In exercising ewes, uterine net uptake of glucose increased in response to a substantial increase in maternal glucose flux. This was accompanied by a major increase in umbilical net uptake in underfed, but not in well-fed ewes.

#### MATERIALS AND METHODS

##### *Animals and management*

Twenty-two single-pregnant, multiparous Merino ewes, weighing 31–45 kg at surgery, were used. Time of mating was detected by colour marks left on ewes by rams fitted with coloured crayons (Sire-sine; Hortico, Melbourne, Victoria). Ewes were inspected daily and date of conception was taken as the first date of marking followed by subsequent failure to mate. Ewes were brought indoors at 80–100 d post-coitus (pc), housed in individual metabolism cages and accustomed to experimental surroundings and procedures, including walking on a moving-belt treadmill, for several weeks before the experiment.

*Feeding.* Ewes were given 800–1200 g lucerne (*Medicago sativa*) chaff (metabolizable energy (ME) content approximately 9 MJ/kg) per d, according to body-weight and stage of pregnancy, until surgery at 115–120 d pc. After they had re-attained presurgery feed intakes (usually 2–3 d post-surgery) they were randomly assigned to one of two nutritional treatments: eleven ewes were given 1000–1200 g lucerne chaff/d (fed group) and the remaining eleven were given 350 g lucerne chaff/d (underfed group), until they were slaughtered at 140–144 d pc. In both groups the daily ration was given in twelve equal portions at two-hourly intervals, with *ad lib.* access to water and a mineralized salt block (Cheetham Salt, Geelong, Victoria).

*Surgery.* Ewes at 115–120 d pc were fasted for 24 h before general anaesthesia was induced by intravenous injection of thiopentone sodium (Pentothal; Abbott Laboratories, Kurnell, Australia) and maintained with a halothane (Fluothane; ICI, Villawood, Australia)–oxygen mixture (3:97, v/v) given in closed-circuit through an endotracheal tube. The uterine vein draining the pregnant horn of the uterus and the common umbilical vein were catheterized as described by Meschia *et al.* (1969) and the fetal abdominal aorta as described by Chandler & Bell (1981). Catheters were also inserted into the fetal posterior vena cava via a lateral saphenous vein and into the maternal abdominal aorta via a medial saphenous artery. Post-operative care of ewes, including antibiotic treatment, and maintenance of catheter patency were as described previously (Chandler & Bell, 1981). On the day before an experiment, a catheter was placed in an external jugular vein of each ewe.

##### *Experimental procedure*

Experiments were performed on fed ewes at least 7 d after surgery, when they were at 123–137 d pc, and on underfed ewes at 10–22 d after surgery, when they had been underfed for 7–21 d, and were at 124–138 d pc. Where possible, two studies per animal were attempted, with an interval of at least 1 week between studies. Ewes were killed with an overdose of sodium pentobarbitone at 140–144 d pc to measure weights of the pregnant uterus, fetus and placenta.

On the day of study, experimental infusions were begun at least 45 min after the ewe had been placed on the stationary treadmill. D-[2-<sup>3</sup>H]glucose (nominal specific activity 15 Ci/mmol; Amersham, Bucks), dissolved in sterile isotonic saline (9 g sodium chloride/l), was given by primed continuous infusion into a maternal jugular vein (priming dose 80  $\mu$ Ci, followed by continuous infusion at 0.8  $\mu$ Ci/min). At the same time, infusion of antipyrine (20–30 mg/min, dissolved in sterile isotonic saline) into the fetal vena cava was commenced, for measurement of umbilical and uterine blood flows (see p. 451). Blood samples were simultaneously drawn from the maternal aorta and uterine vein (each 5 ml), fetal aorta and

common umbilical vein (each 1.2 ml) at about 90, 110, 130 and 150 min after infusions commenced, while the ewe stood at rest. Additional maternal and fetal arterial samples were taken at about 100, 120 and 140 min.

The ewe then commenced walking (0.7 m/s, 10° slope) and the previously described sampling routine was repeated after about 40, 50 and 60 min of exercise. Additional maternal and fetal arterial samples were taken after 5, 10, 15, 20 and 30 min of exercise.

Blood samples for measurement of O<sub>2</sub> content were sealed and stored anaerobically in glass syringes on ice before analysis within 1 h of sampling. Samples for analysis of glucose concentration and specific radioactivity (SRA) and of antipyrine were stored on ice in capped, heparinized syringes before being deproteinized with zinc sulphate–barium hydroxide (Somogyi, 1945); supernatant fractions were stored at –20°.

#### Measurements

Uterine and umbilical blood flows were measured by the transplacental steady-state diffusion technique (Meschia *et al.* 1967). Blood concentrations of antipyrine were measured by the method of Brodie *et al.* (1949), as modified by Chandler (1983). Blood haemoglobin (Hb) and oxyhaemoglobin saturation ( $S_{O_2}$ ) were measured in an automatic, direct reading photometer (OSM2; Radiometer A/S, Copenhagen, Denmark) calibrated with sheep's blood. Blood O<sub>2</sub> content (ml/l) was calculated as: Hb (g/l)  $\times$   $S_{O_2}$   $\times$  1.34. Blood glucose was analysed by the glucose oxidase (EC 1.1.1.34) method of Bergmeyer & Bernt (1974). Glucose SRA was determined after anion-exchange chromatography, freeze-drying to remove <sup>3</sup>H<sub>2</sub>O and reconstitution in 0.5 ml water; the procedures were essentially those of Hay *et al.* (1981) as slightly modified by Leury (1987). Samples derived from blood extracts and infusates for a given experiment were counted at the same time in a Packard Tricarb 460C liquid-scintillation system (Packard Instrument Co., IL, USA).

#### Calculations

Net fluxes of O<sub>2</sub> and glucose from the uterine circulation to the pregnant uterus were calculated as the product of uterine blood flow and maternal arterial–uterine venous concentration difference. Similarly, net fluxes from the placenta to the fetus were calculated as the product of umbilical blood flow and the umbilical venous–arterial concentration difference. Net utero-placental utilization of O<sub>2</sub> and glucose were calculated as the difference between the net uterine and net umbilical rates of exchange (Meschia *et al.* 1980). Placental glucose transfer capacity (ml/min) was calculated as the quotient of umbilical uptake and maternal arterial–fetal arterial concentration difference of glucose. This term should be distinguished from placental glucose transfer rate (i.e. umbilical uptake). It is equivalent to placental glucose clearance if the potential influence of placental glucose metabolism on net transfer is ignored.

Whole-body glucose entry rate was calculated by dividing the infusion rate of [<sup>3</sup>H]glucose (disintegrations/min (dpm) per min) by maternal blood glucose SRA after the latter was no longer time-dependent. In resting ewes, preliminary experiments showed that this plateau was achieved after about 60 min. Despite the short duration of exercise, a new plateau SRA was usually discernible after about 30 min. Thus, entry rates calculated by the above steady-state approach were not significantly different from those calculated using the non-steady state equation of de Bodo *et al.* (1963), as validated for estimation of glucose flux rate in exercising sheep (Brockman, 1984).

#### Statistics

Where more than one study was done per animal, the values were averaged before statistical analysis of treatment effects. The significance of the effects of exercise were

Table 1. *Maternal and fetal body-weights (kg) and placental weight (g)† in well-fed and underfed ewes‡*

(Values are means with their standard errors; no. of animals in parentheses)

	Gestational age (d)	Fed		Underfed		Effect of nutrition
		Mean	SE	Mean	SE	
Ewe	120	41.5	1.9 (9)	40.9	1.0 (11)	NS
Ewe	140-144	43.1	2.8 (7)	36.5	1.2 (8)	*
Fetus	140-144	3.83	0.14 (9)	3.22	0.22 (9)	*
Placenta	140-144	367	23 (8)	338	19 (8)	NS

NS, not significant.

\*  $P < 0.05$ .

† Aggregate weight of whole placentomes, dissected from fetal membranes and endometrium.

‡ For details of feeding regimen, see p. 450.

assessed by the paired  $t$  test with  $n - 1$  degrees of freedom, where  $n$  is the number of pairs. The effect of undernutrition on resting absolute values and on exercise-induced changes from resting values were assessed by the unpaired  $t$  test. Relations between variables were determined by least-squares linear-regression analysis.

## RESULTS

Numbers of observations shown in the Tables rarely match the number of sheep (eleven) used per treatment, mainly because we were unable to maintain patency of all catheters in all animals on all sampling days, and because more than one study was done on some animals.

### *Maternal, fetal and placental weights*

Mean live weight increased by about 2 kg in fed ewes during the period of study, but decreased by about 4 kg in the underfed group, so that the latter were significantly lighter than the former when slaughtered at 140-144 d ( $P < 0.05$ ) (Table 1). Mean fetal weight at this time was about 600 g (16%) less in underfed than in fed ewes ( $P < 0.05$ ), but placental weights were not significantly affected by maternal nutrition (Table 1).

### *Uterine and umbilical blood flows and $O_2$ exchanges*

In resting ewes, uterine blood flow tended to be lowered by underfeeding ( $P < 0.1$ ), whereas umbilical blood flow was unaffected by plane of nutrition (Table 2). During exercise, uterine blood flow decreased by 18 and 27% in fed and underfed ewes respectively (both  $P < 0.01$ ), but the absolute decrease (ml/min) in uterine flow was not affected by nutrition (Table 2). Exercise-induced changes in umbilical blood flow were smaller and less consistent.

Maternal and fetal arterial blood  $O_2$  concentrations were unaffected by maternal plane of nutrition (Table 3). Uterine  $O_2$  uptake was lower in underfed than in fed ewes ( $P < 0.05$ ; Table 3). This was entirely explained by a 60% reduction in utero-placental  $O_2$  consumption ( $P < 0.01$ ), since umbilical  $O_2$  uptake was unchanged by maternal plane of nutrition (Table 3).

Maternal arterial  $O_2$  concentration was significantly increased during exercise in fed ( $P < 0.001$ ) and underfed ( $P < 0.01$ ) ewes, while fetal arterial  $O_2$  concentration was decreased by 18% ( $P < 0.05$ ) and 23% ( $P < 0.01$ ) in fed and underfed groups respectively (Table 3). Uterine  $O_2$  uptake and its partition between the fetus and utero-placental tissues

Table 2. *Effects of undernutrition and exercise on uterine and umbilical blood flows in ewes†*

(Values are means with their standard errors; no. of studies and no. of sheep respectively in parentheses)

Blood flow (ml/min)	Fed				Underfed				Effect of nutrition	
	R		ΔE		R		ΔE		R	ΔE
	Mean	SE	Mean	SE	Mean	SE	Mean	SE		
Uterine	1506	122	-265**	57	1206	82	-329**	67	NS	NS
Umbilical	677	45	-59	29	719	65	-32	54	NS	NS

R, rest; ΔE, change with exercise; NS, not significant.

\*  $P < 0.05$ , \*\*  $P < 0.01$ .

† For details of feeding regimen and exercise, see pp. 450–451.

Table 3. *Effects of undernutrition and exercise on maternal and fetal arterial blood concentrations, and on uterine and umbilical exchanges of oxygen in ewes†*

(Values are means with their standard errors; no. of studies and no. of sheep respectively in parentheses)

	Fed				Underfed				Effect of nutrition	
	R		ΔE		R		ΔE		R	ΔE
	Mean	SE	Mean	SE	Mean	SE	Mean	SE		
Arterial O <sub>2</sub> concentration (ml/l)										
Maternal	107.0	3.6	+25.7***	4.9	103.3	4.4	+20.4**	5.2	NS	NS
Fetal	77.7	5.0	-13.6*	5.1	83.0	4.7	-19.4**	4.6	NS	NS
O <sub>2</sub> consumption (ml/min)										
Uterine	33.5	2.0	+4.2*	1.3	27.1	2.2	+4.0	3.6	*	NS
Umbilical	20.3	0.6	+1.6	1.0	20.5	1.5	+3.0	1.8	NS	NS
Uteroplacental	14.8	2.3	+1.7	2.4	6.0	1.6	+2.1	3.0	**	NS

R, rest; ΔE, change with exercise; NS, not significant.

\*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ .

† For details of feeding regimen and exercise, see pp. 450–451.

were largely unchanged by exercise, although a small, significant increase in uterine uptake was observed in fed ewes ( $P < 0.05$ ) (Table 3).

#### Glucose metabolism

*Maternal and uterine.* Undernutrition caused approximately 50% reductions in maternal blood concentration ( $P < 0.001$ ), whole-body entry rate ( $P < 0.001$ ) and uterine net uptake ( $P < 0.01$ ) of glucose, and a somewhat smaller (34%) decrease in uterine glucose:O<sub>2</sub> quotient ( $P < 0.05$ ) (Table 4). Exercise caused increases in maternal blood concentration (fed  $P < 0.1$ , underfed  $P < 0.001$ ), entry rate (fed  $P < 0.01$ , underfed  $P < 0.001$ ) and uterine

Table 4. *Effects of undernutrition and exercise on maternal arterial concentration, whole-body entry rate, and uterine net uptake and oxygen quotient of glucose in ewes†*

(Values are means with their standard errors; no. of studies and no. of sheep respectively in parentheses)

Glucose	Fed			Underfed			Effect of nutrition		
	R		ΔE	R		ΔE	R		ΔE
	Mean	SE		Mean	SE		Mean	SE	
Arterial concentration (mmol/l)	2.65	0.10	+0.64 (14, 11)	0.32	1.43	0.12	+0.96*** (14, 11)	0.17	NS
Entry rate (μmol/min)	528	20	+453*** (11, 9)	94	259	11	+333*** (12, 9)	44	NS
Uterine uptake (μmol/min)	249	27	+64* (12, 9)	26	130	13	+75** (13, 10)	17	NS
Uterine glucose: O <sub>2</sub> quotient‡	0.99	0.10	+0.18 (11, 9)	0.12	0.65	0.08	+0.20** (12, 9)	0.04	NS

R, rest; ΔE, change with exercise; NS, not significant.

\*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ .

† For details of feeding regimen and exercise, see pp. 450-451.

‡ Glucose uptake (μmol/min) × 6/O<sub>2</sub> uptake (μmol/min).

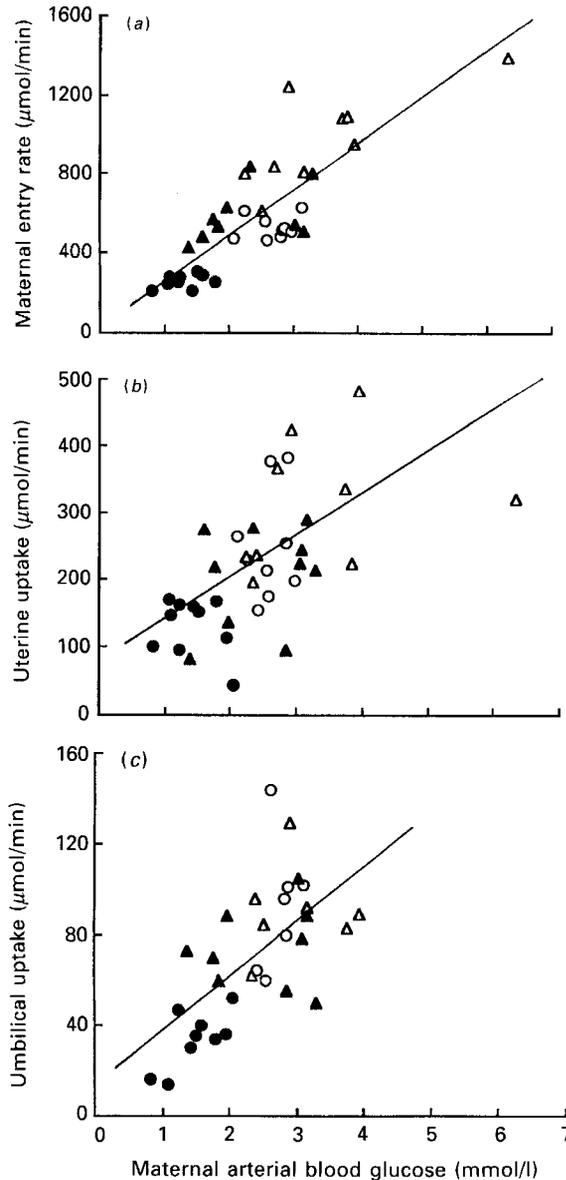


Fig. 1. Relations between maternal blood glucose concentration and (a) maternal glucose entry rate ( $y = 228x + 32$ ,  $r = 0.83$ ,  $n = 36$ ,  $P < 0.001$ ), (b) uterine net glucose uptake ( $y = 52x + 83$ ,  $r = 0.54$ ,  $n = 38$ ,  $P < 0.001$ ) and (c) umbilical net glucose uptake ( $y = 25.7x + 9.4$ ,  $r = 0.66$ ,  $n = 32$ ,  $P < 0.001$ ) in fed (○, △) and underfed (●, ▲) ewes at rest (○, ●) and during exercise (△, ▲). For details of feeding regimen and exercise, see pp. 450–451.

uptake of glucose (fed  $P < 0.05$ , underfed  $P < 0.01$ ), none of which was significantly affected by plane of nutrition. Mean increases in uterine glucose:O<sub>2</sub> quotient were significant in underfed ( $P < 0.01$ ) but not in fed ewes (Table 4).

When values from all treatments (fed, underfed, rest, exercise) were pooled, both maternal entry rate (Fig. 1(a)) and uterine net uptake of glucose (Fig. 1(b)) were significantly correlated with maternal arterial blood glucose concentration (both  $P < 0.001$ ).

Table 5. *Effects of undernutrition and exercise on fetal arterial concentration, umbilical net uptake and oxygen quotient, utero-placental utilization and placental transfer capacity of glucose in ewes†*

(Values are means with their standard errors; no. of studies and no. of sheep respectively in parentheses)

Glucose	Fed				Underfed				Effect of nutrition	
	R		ΔE		R		ΔE		R	ΔE
	Mean	SE	Mean	SE	Mean	SE	Mean	SE		
Arterial concentration (mmol/l)	0.70	0.04	+0.19*	0.07	0.28	0.04	+0.43**	0.09	***	*
Umbilical uptake (μmol/min)	92	11	-2	7	34	4	+42**	8	***	**
Umbilical glucose: O <sub>2</sub> quotient‡	0.57	0.04	-0.08	0.05	0.27	0.04	+0.13	0.07	***	*
Utero-placental utilization (μmol/min)	185	29	+52	44	89	18	+23	26	*	NS
Placental transfer capacity (ml/min)	45.7	5.5	+0.4	5.8	27.7	2.5	+17.9*	7.4	**	NS

R, rest; ΔE, change with exercise; NS, not significant.

\*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ .

† For details of feeding regimen and exercise, see pp. 450-451.

‡ Glucose uptake (μmol/min) × 6/O<sub>2</sub> uptake (μmol/min).

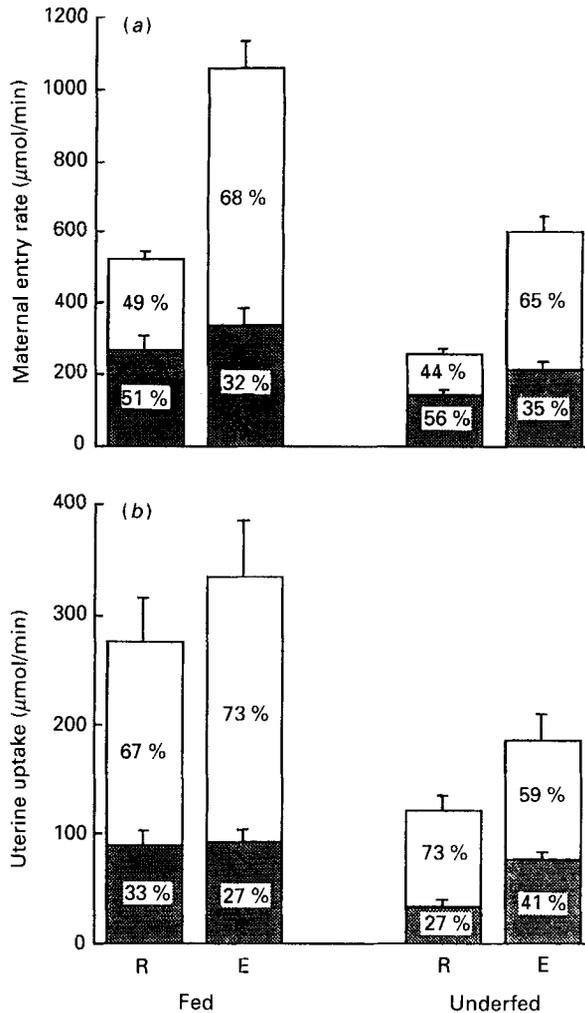


Fig. 2. Partition of (a) maternal glucose entry rate between pregnant uterus (■) and maternal non-uterine tissues (□), (b) uterine net uptake of glucose between the fetus (▨) and uteroplacental tissues (□) in fed and underfed ewes at rest (R) and during exercise (E). Values are means with standard errors represented by vertical bars.

*Fetal and uteroplacental.* Maternal underfeeding caused greater than 50% reductions in fetal glycaemia ( $P < 0.001$ ), umbilical net glucose uptake ( $P < 0.001$ ), umbilical glucose:  $O_2$  quotient ( $P < 0.001$ ) and utero-placental glucose utilization ( $P < 0.05$ ), and a 40% reduction in placental glucose transfer capacity ( $P < 0.01$ ) (Table 5). Exercise resulted in increased fetal blood glucose concentrations (fed  $P < 0.05$ , underfed  $P < 0.01$ ), which were significantly greater in underfed ewes ( $P < 0.05$ ). Umbilical glucose uptake was unaffected by exercise in fed ewes, but increased more than twofold ( $P < 0.01$ ) in underfed ewes (effect of nutrition  $P < 0.01$ ). Mean increases in utero-placental glucose utilization during exercise were variable and not statistically significant. Placental glucose transport capacity was unchanged in fed ewes but increased in underfed ewes ( $P < 0.05$ ) during exercise (Table 5).

Umbilical net uptake of glucose was significantly correlated with maternal arterial blood glucose concentration when values were pooled across treatments ( $P < 0.001$ ; Fig. 1(c)).

### *Glucose partitioning*

Simultaneous measurements of all variables of glucose metabolism were obtained in too few animals within each treatment group for these to be representative of overall treatment effects. Therefore, the partitioning of glucose between uterine and maternal non-uterine tissues is presented separately (Fig. 2(a)) from that within the uterus, between fetal and utero-placental tissues (Fig. 2(b)).

The fraction of maternal glucose entry rate accounted for by the pregnant uterus was not significantly affected by plane of nutrition (Fig. 2(a)), but was reduced by exercise to a similar degree in fed ( $P < 0.05$ ) and underfed ewes ( $P < 0.01$ ), despite significant absolute increases in uterine glucose uptake (Table 3). The fractional distribution of uterine glucose uptake between the fetus and utero-placental tissues was not significantly affected by maternal nutrition or exercise (Fig. 2(b)).

## DISCUSSION

### *Effects of undernutrition*

The severity of undernutrition imposed in the present study (0.3–0.4 recommended ME intake) was reflected by substantial loss of maternal live weight and development of hypoglycaemia during the treatment period of approximately 3 weeks. This was accompanied by a significant decline in fetal weight as previously observed in monotonous Merino ewes which were underfed during late pregnancy (Everitt, 1968; Alexander & Williams, 1971). It is likely that fetal growth retardation was mainly a direct consequence of inadequate maternal nutrient supply, since placental weight was little affected. Additional compromise of fetal nutrient supply through reduction in placental size appears to occur only after more prolonged undernutrition (see Mellor, 1983). Nevertheless, decreased weight-specific functional activity of the placenta is indicated by the decreased placental glucose transfer capacity, together with depressed utero-placental blood flow and  $O_2$  and glucose consumption in undernourished ewes (Chandler *et al.* 1985; present study).

Present values for glucose entry rate in resting, fed ewes, when adjusted for body-weight, were similar to those previously reported for well-fed, monotonous ewes in late pregnancy (Steel & Leng, 1973*a*; Baird *et al.* 1983; Wilson *et al.* 1983). The use of [2- $^3$ H]glucose as tracer provides a maximal estimate of the rate at which glucose enters the bloodstream, including the recycling of glucose-C through non-hexose intermediates (Judson & Leng, 1972). This was deemed an acceptable kinetic variable on which to base estimates of glucose partitioning, not least because in the present study values for uterine uptake of glucose were not corrected for the considerable efflux of lactate from the pregnant uterus (Burd *et al.* 1975; Faichney *et al.* 1981). The major decrease in glucose entry rate of underfed ewes was quantitatively similar to that observed in late-pregnant ewes which had been either starved for several days or moderately underfed through mid- and late pregnancy (Steel & Leng, 1973*a*). Bergman *et al.* (1970) showed that in starved, pregnant ewes this was almost entirely attributable to a reduced rate of hepatic glucose synthesis. Thus, any increase in the supply of endogenous glucogenic substrates, such as glycerol, falls far short of making up the deficit in dietary glucose precursors, especially propionate (Steel & Leng, 1973*b*), despite the substantial mobilization of body tissue reserves (Table 1).

Decreased maternal glucose supply and glycaemia in underfed ewes were associated with a similar relative reduction in uterine net uptake of glucose, such that the fractional distribution of glucose between the pregnant uterus and non-uterine maternal tissues was essentially unchanged. This and the direct relation between maternal arterial concentration and uterine uptake of glucose agree closely with the findings of Hay *et al.* (1983), who compared well-fed with acutely fasted ewes. In contrast, Oddy *et al.* (1985) concluded that uterine glucose uptake at 125 d pc was little affected by chronic undernutrition which

increased in severity throughout pregnancy, despite a 50% reduction in the rate of whole-body irreversible loss of glucose. It is possible, as suggested by these authors, that their chronically undernourished ewes adapted in a manner different to that of the acutely starved ewes of Hay *et al.* (1983). However, the present underfed ewes were studied, on average, after 14 d of treatment, which should have allowed time for significant metabolic adaptation. Also, there must be some uncertainty about the estimates of Oddy *et al.* (1985) for uterine glucose uptake, which depend on assumed values for uterine weight and do not take account of a likely treatment effect on conceptus growth. In particular, the suggestion that uterine glucose uptake accounts for 84% of glucose irreversible loss rate in underfed ewes more than 3 weeks before term (Oddy *et al.* 1985) seems untenably high, although it should be borne in mind that glucose irreversible loss rate is less than glucose entry rate (Steel & Leng, 1973*a*; Baird *et al.* 1983), as measured in the present study.

It appears, then, that in starved or severely undernourished late-pregnant ewes, glucose requirements for the conceptus do not necessarily take priority over those of maternal tissues. This need not conflict with the concept of glucose sparing in better-nourished animals, possibly regulated by homeorhetic modulation of insulin sensitivity or responsiveness in non-uterine maternal tissues (Bauman & Currie, 1980). However, pregnancy-induced insulin resistance appears to be quantitatively less significant in the sheep than in several non-ruminant species (Hay *et al.* 1988; Petterson *et al.* 1989). Thus, in underfed ewes the marked decline in maternal glucose availability may have overridden any advantage conferred on the pregnant uterus by its unresponsiveness to insulin relative to non-uterine peripheral tissues (Hay *et al.* 1984*a*).

The present study has corroborated previous findings that partitioning of the reduced uterine glucose uptake between fetus and utero-placental tissues is essentially unaltered by starvation or undernutrition (Hay *et al.* 1983; Chandler *et al.* 1985), and that over the range of values observed in well-fed and underfed ewes, umbilical net uptake of glucose is linearly related to maternal glycaemia (Crandell *et al.* 1983; Hay *et al.* 1984*b*). It has also shown, for the first time, that undernutrition reduces glucose transfer capacity in addition to glucose consumption of the placenta. Thus, the reduction in placental transport (umbilical uptake) of glucose in underfed ewes was greater than could be explained by a decreased maternal-fetal blood concentration gradient. This implies a decreased number or affinity, or both, of glucose transporters in placental cell membranes, which are believed to mediate glucose transport by the ovine placenta (Stacey *et al.* 1978), since the importance of placental perfusion in limiting placental glucose transfer is relatively small (Wilkening *et al.* 1985).

#### *Effects of exercise*

Exercise caused a dramatic increase in glucose entry rate in fed and underfed ewes, associated with an increase in maternal glycaemia which was consistently large in underfed ewes, but smaller and less consistent in fed animals. Similar increases in glucose entry rate (Judson *et al.* 1976; Brockman & Halvorson, 1982; Leury, 1987) and hepatic glucose production (Brockman, 1987) were observed in non-pregnant sheep exercising at comparable levels. These are most likely achieved initially by rapid stimulation of hepatic glycogenolysis via increased adrenergic activity and, possibly, pancreatic secretion of glucagon (Brockman & Halvorson, 1982), quickly followed by an increased rate of hepatic gluconeogenesis (Judson *et al.* 1976; Brockman, 1987). The latter would be favoured by the rapid and sustained increases in plasma concentrations of pancreatic glucagon and cortisol and unchanged plasma insulin as previously reported in fed, pregnant ewes during exercise (Bell *et al.* 1983).

The large exercise-induced increase in glucose entry rate of severely underfed ewes is remarkable in view of their very low resting rate of glucose synthesis (Table 4) and likely

depletion of hepatic glycogen stores (Ford, 1962). Much of this may have been sustained by increased gluconeogenesis from non-propionate glucose precursors such as lactate and glycerol, as observed in exercising, non-pregnant sheep fasted for only 24 h (Brockman, 1987).

A smaller fraction of the increased maternal glucose supply was distributed to the uterus during exercise. This is not surprising, given the greatly increased utilization of, and presumably predominant requirements for, glucose in exercising muscle (Bird *et al.* 1981; Pethick *et al.* 1987). Nevertheless, absolute increases in uterine uptake accounted for 14 and 23% of the increment in whole-body glucose entry rate in fed and underfed ewes respectively. These increases were achieved despite 15–30% decreases in uterine blood flow, and resulted in significant augmentation of umbilical glucose uptake in underfed but not fed ewes, as previously observed (Chandler *et al.* 1985). Umbilical glucose uptake is little affected by uterine blood flow within the normal physiological range (Wilkening *et al.* 1985). The failure of fetal glucose uptake to increase in fed ewes was more likely due to fetal capacity for glucose utilization being limited by hypoxic inhibition of fetal insulin secretion, despite the development of moderate fetal hyperglycaemia (Bell *et al.* 1983).

Maternal exercise not only substantially increased umbilical uptake but also significantly improved the umbilical glucose:O<sub>2</sub> quotient in underfed *v.* fed ewes, suggesting substitution of maternal glucose for the direct or indirect catabolism of other fetal substrates, particularly amino acids. Less than half the increase in umbilical uptake was attributable to the increased gradient between maternal and fetal arterial glucose concentrations. Thus, in underfed but not fed ewes, exercise apparently stimulated a rapid and substantial increase in placental glucose transfer capacity. We do not have a ready physiological explanation for this observation. The role of factors other than insulin in the acute regulation of glucose transporter location and activity in mammalian tissues is poorly understood (Simpson & Cushman, 1986), and glucose transport in the ovine placenta is relatively insensitive to insulin (Rankin *et al.* 1986).

In conclusion, it is clear that uterine and fetal uptake of maternal glucose is severely restricted by undernutrition in the resting ewe. However, the present study raises the intriguing possibility that as long as the ewe's body reserves can sustain an adequate glucogenic response to exercise, maternal activity may actually improve fetal nutrient supply and utilization in the undernourished state.

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