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Fuel metabolism in the mammalian fetus

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Summary. The mammalian fetus receives energy fuels from its mother through the placenta. The placental transfer of substrates depends upon the placental permeability to the substrate and upon the difference of concentration of the substrate in maternal and fetal blood. The fetus uses the substrates for 3 purposes : synthesis of new tissues (growth), oxidative metabolism and building of energy stores. Since the O_2 consumption per Kg of body weight is relatively constant among the different species, the partitioning of substrates in anabolic and catabolic pathways is related to the rate of fetal growth. Glucose and lactate account for a large part of the oxidative needs of the fetus, but amino acids catabolism plays also an important role. During maternal starvation, ketone bodies can be used as oxidative substrates by the fetus of monogastrics. The fetus has a low capacity to oxidize free fatty acids, even in species in which the placental transfer of these substrates occurs rapidly. Free fatty acids are used as precursors of complex lipids or are stored in fetal adipose tissues or liver. Several recent observations suggest that gluconeogenesis could occur in the fetus of ruminants, and thus could allow the transformation of lactate and amino acids into glucose before utilization by individual tissues of the fetus (brain, skeletal muscle, heart).

The hormones secreted by the fetus has been shown to play an important role in inducing the storage of glycogen in fetal liver (glucocorticoids and a pituitary hormone) and the accumulation of triglycerides in fetal adipose tissue (insulin).

During pregnancy, a new structure : the conceptus (fetus and placenta) develops in the mother and is ultimately expelled after a finite and predictable length. The effects of conceptus upon maternal metabolism in pregnancy have been reviewed recently (Freinkel *et al.*, 1971, 1972, 1974 ; Knopp, 1978) and the principal results will be summarized briefly.

Adaptation of maternal fuel metabolism to fetal growth.

During gestation, the increased food intake by the pregnant mother contributes to a steady weight gain. This weight gain has 2 main components which accumulate at different times in gestation. During the first and second part of gestation the mother accumulates fat stores (Beaton *et al.*, 1954 ; Hytten and Leicht, 1971) and during the last part of gestation, the maternal weight gain consists of the increased weight of the

conceptus. Pregnancy represents an anabolic process (weight gain, protein anabolism) and the mother has always a positive caloric balance, unless she is deprived of adequate food intake. However, there is a shift in maternal fat metabolism during pregnancy ; fat storage occurs during the first and second part of pregnancy and these fat stores are then mobilized in the last part of gestation. This phase of fat catabolism can be explained by the appearance of maternal insulin resistance in late gestation. This insulin resistance has been attributed to the secretion in increasing amounts of contra-insulin hormones by the placenta : chorionic somatomammotrophin and progesterone.

There is a decrease in maternal glucose utilization which coincides with the increasing insulin resistance. The increased fat oxidation in maternal tissues in late gestation spares maternal glucose for fetal utilization. Since maternal fat catabolism occurs exactly at the time when the fetus is rapidly growing it is considered an important maternal adaptation for fetal growth (Knopp *et al.*, 1973).

Placental transfer of substrates.

The fetus makes contact with the maternal organism via the placenta. In most species, the umbilical circulation is the only way by which the fetus receives substrates from its mother. The placental transfer of substrates depends upon several factors : i) the blood flow across uterine and umbilical circulations, ii) the concentration of substrates in maternal blood or the gradient of substrates between maternal and fetal blood, iii) the permeability of the placenta to different substrates.

In all the species studied so far, the placental (uterine and umbilical) blood flow rises markedly towards the end of the gestation, as a result of an increased maternal and fetal cardiac output and of a decreased vascular resistance. The level of different substrates in maternal blood, the permeability of the placenta to various substrates, and the difference of concentration of these substrates in maternal and fetal blood vary considerably with the species considered (table 1). This is particularly striking when

TABLE 1

Maternal and fetal circulating substrates (m moles/liter) in various species in late gestation

Species		Glucose	F. F. A.	Glycerol	Ketones	Amino-acids	Lactate
Man	mother ...	5.5	0.2	0.11	0.5	1.7	1.3
	fetus.....	4.5	0.1	0.04	0.2	3.3	2.5
Monkey	mother ...	4.5	0.6	—	2.0	2.0	—
	fetus.....	3.6	0.3	—	6.0	6.0	—
Rabbit	mother ...	5.0	1.1	0.15	0.17	2.3	—
	fetus.....	3.0	0.9	0.09	0.17	6.0	—
Rat	mother ...	5.0	0.23	0.09	0.1	3.0	2.0
	fetus.....	3.7	0.16	0.04	0.1	9.0	6.0
Sheep	mother ...	3.0	0.3	0.04	0.7	4.0	0.9
	fetus.....	1.0	0.04	0.03	0.1	9.2	2.0
Cow	mother ...	3.5	0.6	—	—	—	1.0
	fetus.....	1.5	0.2	—	—	—	2.0
Horse	mother ...	5.0	0.8	—	—	—	1.0
	fetus.....	3.0	0.4	—	—	—	2.0

ruminants and monogastric are compared. However, one should be cautious in interpreting this to an increased substrate flow for all substrates in the non-ruminant fetuses, since maternal to fetal concentration differences for some substrates (e. g. glucose) increase when placental permeability to these substrates decreases. Therefore, it is not certain that any difference in the substrate flow to the fetus exists among the different species for these substrates.

1) *Glucose and glucose-derived substrates.*

In all the species studied, the fetal blood glucose levels are lower than the maternal levels, but they are directly correlated with the maternal levels over a wide range of concentrations (Battaglia and Meschia, 1973 ; Shelley, 1973 ; Silver, 1976). However, the absolute value of maternal blood glucose concentration and the maternal to fetal gradient of glucose vary according to the species considered. In well fed monogastric mammals, the maternal blood glucose concentration is in the range of 4.5 to 5.5 m mol/l (i. e. 0.8 to 1.0 g/l) and the fetal blood glucose levels are 20 p. 100 lower than those of their mother. In well fed ruminants, the maternal glycemia is lower than in monogastrics ; 2.2 to 2.7 m mol/l (i. e. 0.3 to 0.5 g/l) and the fetal glycemia is only 20 to 30 p. 100 that of the mother. Nevertheless, a steady flow of glucose from the mother crosses the placenta in the direction of the concentration gradient by a process of facilitated diffusion. Recently, it has been reported that the placental transfer of glucose was a function of the concentration difference of glucose between maternal and fetal blood (Battaglia and Meschia, 1973) and the level of insulin in fetal plasma (Rabain and Picon, 1974 ; Simmons *et al.*, 1978). The mechanisms by which fetal hyperinsulinemia leads to increased placental glucose transfer has not been clearly established. Insulin might increase umbilical glucose uptake simply by increasing fetal glucose utilization, thus decreasing fetal blood glucose and enlarging the glucose gradient across the placenta. Insulin might have also a direct effect on placental glucose transport since specific insulin receptors have been found on the placental membrane in different species (Haour and Bertrand, 1974 ; Marshall *et al.*, 1974 ; Posner, 1975).

In most of the species studied, fetal lactate concentration is 2 or 3 fold higher than maternal lactate concentration (table 1). Initially, it was thought that it was the result of the anaerobic metabolism of glucose by fetal tissues. However, recent studies in the sheep and in the cow have shown that the quantity of lactate entering the fetal circulation could be equal to approximately 30 to 50 p. 100 of the glucose removed by the placenta (Burd *et al.*, 1975 ; Char and Creasy, 1976a ; Silver, 1976). High rates of lactate production by the placenta, *under aerobic conditions in vitro*, have also been found in rat and man. The rate of placental lactate production is closely related to the rate of glucose utilization by the placenta.

In several species (sheep, goat, cow, pig and horse) a part of glucose (10 p. 100) taken up by the placenta is converted into fructose which is transferred to the fetus. Fructose is present in very high concentration in the blood of the fetus of those species but is absent from maternal blood, since it is not passed back to the mother. When the mother is in the fed state, there is no evidence for utilization of fructose by the fetus. However, during maternal starvation, a small but significant utilization by the sheep

fetus has been shown (Schreiner *et al.*, 1978). This suggests that fructose may be a carbohydrate store, as glycogen, which could be used in situation of emergency by the fetus.

2) *Amino acids.*

The level of amino acids is 2 to 3 fold higher in the fetal blood than in the maternal blood (table 1). The amino acids are concentrated by the placenta and released to the fetus against a concentration gradient, by an active transport mechanism (review in Young and Hill, 1973). In the sheep (Lemons *et al.*, 1976) fetal uptake of glutamine, branched chain amino-acids, arginine, phenylalanine and tyrosine is in excess of estimated growth requirements, suggesting that they are used for other purposes than protein synthesis. In the rat, fetal uptake of glutamine has also been found to be much higher than for other amino-acids (Yamamoto *et al.*, 1974). This will be discussed later.

3) *Free fatty acids.*

In most species (man, monkey, sheep, cow, mare and rat) the concentration of free fatty acids (FFA) and triglycerides is higher in maternal than in fetal plasma (table 1). In rabbit and guinea pig, the level of FFA and triglycerides in fetal plasma is equal to that of the mother near term. Experiments using labelled palmitate have demonstrated that FFA can cross the placenta from the maternal to the fetal circulation in several species (rabbit, guinea pig, monkey, and to a lesser extent rat and sheep). However, the magnitude of this transfer is small when maternal plasma FFA is not raised over normal values. It is generally accepted that triglycerides (chylomicrons and very low density lipoproteins) cannot cross directly the placenta. Nevertheless, a lipoprotein lipase, an enzyme capable of hydrolyzing triglycerides into FFA and glycerol, has been found in human, rabbit and rat placenta (Mallov and Alousi, 1965 ; Elphick and Hull, 1977b). This suggests that placenta does have the capacity to extract fatty acids from circulating triglycerides and to transfer them to the fetus, after hydrolysis by the lipoprotein lipase. Short chain fatty acids such as acetate, butyrate and propionate, are produced in large amounts during digestion in adult ruminants. Nevertheless, the placental transfer of short chain fatty acids is poor. In the sheep, small umbilical uptake of acetate is found (Char and Creasy, 1976b). In the cow and guinea-pig a significant umbilical uptake of acetate has been shown, and it is dependant upon maternal acetate concentration (Silver, 1976 ; Jones, 1976a).

4) *Ketone bodies.*

Ketone bodies are readily transferred from the mother to the fetus in human and rat (Sabata *et al.*, 1968 ; Scow *et al.*, 1958), and there is a close correlation between maternal and fetal blood levels. By contrast, the ewe placenta is poorly permeable to ketone bodies (see Schreiner *et al.*, 1978).

5) *Glycerol.*

Glycerol transfer across the placenta of the rat and rabbit has been demonstrated recently (Gilbert, 1977). In the human and sheep, glycerol doesn't cross the placenta rapidly (Sabata *et al.*, 1968 ; Schreiner *et al.*, 1978).

Utilization of substrates by the fetus.

The flow of substrates from the mother to the fetus serves to several requirements : 1) formation of new tissues i. e. growth, 2) oxidative metabolism, 3) synthesis of energy stores. A quantitative comparison of the caloric requirements for oxidative metabolism and for growth has been made recently in the fetal lamb near the term (130-140 days of gestation) by Battaglia and Meschia (1978). They have estimated that $42 \text{ kcal} \cdot \text{day}^{-1} \cdot \text{kg}^{-1}$ were required for oxidative metabolism and $31 \text{ kcal} \cdot \text{day}^{-1} \cdot \text{kg}^{-1}$ for formation of new tissues (table 2). Although fetal oxygen consumption per kilo body weight is relatively constant (5-8 ml/min/kg) despite large differences in fetal size at term (see Battaglia and Meschia, 1978), the total caloric requirements of the fetus and its partitioning between growth and oxidative metabolism will be different among different species. This results essentially from the wide interspecies difference in the rate of fetal growth and in the composition of the tissues added. If growth is expressed as a daily percent increase in fetal weight, the sheep fetus grows slower than the fetuses of small mammals (rat, rabbit, guinea-pig) but 3 times faster than the human fetus at comparable stages of gestation. A comparison between fetal sheep and human fetus (table 2) illustrates the lower accretion rate in new tissues in human fetus. One should be cautious in interpreting the estimated value for the caloric requirements for oxidative metabolism since oxygen consumption of the human fetus have been collected under conditions of acute stress (during delivery or at cesarean section).

TABLE 2

Caloric requirements of the sheep and human fetuses near the term

	Fetal sheep *	Human fetus **
Oxygen consumption (ml/min/kg body wt)	8	5
Caloric requirement for oxidative metabolism (kcal/day/kg body wt)	56	36
Fetal growth rate (g/day/kg body wt)	36	12
Caloric requirement for growth (kcal/day/kg body wt)	32	11

The consumption of 1 l of oxygen is equivalent to the production of 4.9 kcal when the fetus oxidizes a mixture of carbohydrate and amino-acids. — Caloric value of fetal carcass estimated as being 0.9 kcal/g body wt.

* Values measured in fetal sheep between 120 and 140 days of gestation. See Battaglia and Meschia (1973, 1978).

** Values calculated by Adam and Felig (1978).

1) Utilization of substrates for the formation of new tissues.

Carcass analysis at different stages of gestation and measurement of umbilical uptake of substrates and of urea and CO_2 passed back to the mother have enabled estimates to be made of the carbon and nitrogen balance in the fetal lamb near the

term (Battaglia and Meschia, 1978). The umbilical uptake of carbon is 7.8 g/day/kg fetal weight ; 3.2 g/day/kg are accumulated in the fetal carcass and 4.6 g/day/kg are passed back to the mother in the form of CO₂ (4.4 g/day/kg) or urea (0.2 g/day/kg). The umbilical uptake of nitrogen is 1 g/day/kg fetal weight ; 0.65 g/day/kg returned to the mother in the form of urea. The origin of carbon taken up by the fetal sheep has also been determined by these authors : amino acids supply 3.9 g/day/kg ; glucose 1.8 g/day/kg ; lactate 1.4 g/day/kg and other substrates, in part acetate, account for the remainder i. e. 0.7 g/day/kg (table 4). The same approach has been applied more recently by Adam and Felig (1978) to estimate the uptake and accretion of carbon

TABLE 3

Carbon and nitrogen balance in the sheep and human fetuses during the last part of gestation

	Sheep fetus *	Human fetus **
Umbilical uptake of carbon (g/day/kg fetal wt)	7.8	6.7
Accretion	3.2	3.1
Excretion { CO ₂	4.4	3.5
{ C of urea	0.2	0.1
	4.6	3.6
Umbilical uptake of nitrogen (g/day/kg fetal wt)	1	0.5
Accretion	0.65	0.3
Excretion (urea)	0.35	0.2

* Values measured in fetal sheep between 120 and 140 days of gestation. See Battaglia and Meschia (1973) and Lemons *et al.* (1976).

** Values calculated by Adam and Felig (1978). Accretion rates of carbohydrate, fat and nitrogen in human fetus are from Widdowson (1968).

TABLE 4

Carbon sources in sheep and human fetuses near the term

Substrate	Carbon (g/day/kg fetal weight)	
	Fetal sheep *	Human fetus **
Glucose	1.8	4.5
Lactate	1.4	?
Amino acids	3.9	?
Free fatty acids	?	0.2
Ketone bodies	0	0.2
Acetate	0.7	—
Unknown	—	2.8
Total	7.8	6.7

* Values measured in fetal sheep between 120 and 140 days of gestation. See Battaglia and Meschia (1973, 1978) ; Burd *et al.* (1975) ; Char and Creasy (1976b).

** Values calculated by Adam and Felig (1978) using an umbilical blood flow of 100 inl/m/kg and the umbilical venous-arterial differences of substrate concentrations during delivery.

and nitrogen by the human fetus between 30 and 40 weeks of gestation. Their estimations are shown in table 3. However, such calculations may be quite misleading based not upon direct measurements as in fetal sheep, but from extensive extrapolation : e. g. CO_2 excretion rates in the newborn (Jonxis *et al.*, 1967), placental urea excretion rates (Gresham *et al.*, 1971) and umbilical venous arterial differences of substrates measured in acute stress conditions (during labor or at cesarean section). The principal difference in the two species, bears upon a higher utilization of carbohydrates and fat-derived substrates, and a lower oxidation of amino acids in the human fetus than in the sheep fetus. The comparison between umbilical uptake and accumulation of each amino acid in the fetal carcass in the sheep fetus shows that for most of the amino acids, the umbilical uptake is far in excess of the needs for fetal body proteins (Lemons *et al.*, 1976). By contrast, there is no net transfer of glutamate and aspartate from the placenta to the fetus. As these 2 amino acids are major constituents of body proteins, they are formed in the fetus by deamination of glutamine of from other unknown sources. These recent data show that the role of the fetus in amino acid metabolism is not limited to assembling amino acids into proteins but also to synthesize some of them (glutamate and aspartate) and to use amino acids for energy metabolism.

The influence of fetal hormones, and particularly insulin, in the regulation of fetal growth has been reviewed recently (Girard *et al.*, 1976 ; Jost, 1977), and will not be considered again here.

2) Fetal oxidative metabolism.

Although the fetus requires little energy for movement, digestion, respiration and temperature regulation, its oxidative metabolism is very high. Fetal oxygen consumption per kilo body weight is relatively constant (7-8 ml/min/kg) in sheep, goat, cow, mare, monkey and guinea pig, despite wide differences in fetal size as originally described by Battaglia and Meschia (1978). This is in contrast with the situation found in postnatal life where basal O_2 consumption is inversely related to body weight (adult cow and horse : 2 ml/min/kg versus 10 ml/min/kg in adult guinea pig). Contrary to the generally received opinion, that anaerobic metabolism is an important component of fetal metabolism, several recent studies have clearly shown that fetal metabolism is fully aerobic under physiological conditions. Studies of acide-base balance in sheep, calf, horse and human fetuses, have shown that the fetus is not in a state of chronic metabolic acidosis. Despite the fetal blood has a low pO_2 , the oxygen affinity of fetal blood ensures adequate oxygen supply to the tissues of the fetus. Furthermore, when pO_2 is increased in fetal blood by the administration of 100 p. 100 oxygen to the mother, there is no increase in fetal oxygen consumption. Finally, although blood lactate level are much higher in the fetus than in its mother, the fetus as a whole, is a consumer rather than a producer of lactate.

Most of our quantitative informations about fetal oxidative metabolism have been obtained in the fetus of ruminants ; sheep and cow, and to a very limited extent in the horse (Battaglia and Meschia, 1973, 1978 ; Silver, 1976). The reason is that they are the only species in which it has been possible so far, to withdraw simultaneously arterial and venous umbilical blood from non anesthetized, unstressed and chronically catheterized animals. The simultaneous measurement of the venous arterial concen-

tration differences of blood substrates and oxygen, and the calculation of the quotient : substrate/oxygen, allow to draw a metabolic balance sheet for the fetus (see Battaglia and Meschia, 1978 for the details of calculations).

A) Oxidative metabolism in the ruminant fetus.

The results obtained in the fetal lamb near the term (130-140 days of gestation) are shown in table 5. In the fetus of *well fed mother*, glucose accounts for only 50 p. 100 of total oxygen uptake, lactate for 25 p. 100, amino acids for 20 p. 100, glycerol and ketone bodies for less than 1 to 2 p. 100 (Battaglia and Meschia, 1973, 1978). According to Char and Creasy (1976b), acetate could account for about 5 p. 100 of total oxygen uptake in the fetal lamb of the same age. There is not measurable umbilical uptake of long chain fatty acids in the sheep. When the pregnant ewe is starved for 3 to 7 days near the term (Schreiner *et al.*, 1978), a marked change in the metabolic balance of fetal sheep is observed (table 5). Glucose accounts for only 30 p. 100 of total oxygen uptake, lactate 15 p. 100 and amino acid 60 p. 100. Despite a marked rise in plasma FFA, blood glycerol and ketones bodies in the mother, these substrates don't contribute importantly to fetal oxidative metabolism, since the ewe placenta is not readily permeable to these substrates (see above section on placental transfer).

TABLE 5
*Metabolic balance in fetal sheep **

Substrate	p. 100 of O ₂ uptake	
	Fed mother	Fasted mother
Glucose	50	30
Lactate	25	15
Amino acids	20	60
Glycerol	1	1
Ketones	0.5	0.5
Acetate	5	—
FFA	unmeasurable	unmeasurable

* Values measured by Battaglia and Meschia (1973, 1978) and Schreiner *et al.* (1978).

TABLE 6
Metabolic balance in fetus of different species

Substrate	p. 100 of O ₂ Uptake			
	Sheep *	Calf *	Horse *	Human **
Glucose	50	60	70	80
Lactate	25	40	—	—
Amino acids	20	10	—	7
Acetate	5	10	—	—

* Values measured in unstressed chronically catheterized fetuses.

** Values measured in stressed fetuses during delivery or at cesarean section.

In the cow, the results have been obtained only in the fetus of well fed mother, near the term (250-270 days of gestation). It has been shown (table 6) that glucose and lactate account for a larger part of fetal oxidative metabolism and that amino acids play a less important role as a fuel than in the fetal lamb (Silver, 1976). Unfortunately the extrapolation of the data obtained in the sheep and the cow is rendered difficult, if not impossible, because of several important particularities to ruminants : 1) a low blood glucose level and an active gluconeogenesis in the *fed state* in the pregnant mother, 2) a very low permeability of the placenta to FFA and ketone bodies, 3) a low brain/body ratio (0.2 p. 100), so that the glucose consumption by maternal brain doesn't represent a serious metabolic problem for ruminants, 4) the inability of ruminants brain to use ketone bodies as fuels (Lindsay and Setchell, 1976).

B) Oxidative metabolism in the fetus of non ruminant species.

In well fed horse near the term (280-310 days of gestation), glucose accounts for 70 p. 100 of total oxygen uptake (table 6), but there is no data available at the present time for other metabolites (Silver, 1976). In the human, some measurements of difference in the concentration of glucose, urea and CO_2 in arterial and venous blood at the time of delivery by cesarean section, indicate a lower amino acid catabolism and a higher glucose utilization than in the fetal sheep or cow (table 6). Unfortunately, no similar data are available for other species such as rat, rabbit or guinea pig in which most of our biochemical knowledge has been obtained.

In the species in which the placenta permits the rapid transfer of FFA and ketone bodies, these substrates could be very important for fetal oxidative metabolism, particularly when they are present in large amounts in maternal circulation (starvation, high fat diet). In human, guinea pig and rabbit, there is a positive umbilical uptake of FFA. Nevertheless, FFA taken up by fetal tissues are mainly incorporated into lipids and only a small proportion undergoes oxidation (Roux and Yoshioka, 1970 for a review). So, FFA are not a major energy source for fetal tissues.

In most of the mammalian species, ketone bodies are rapidly transferred to the fetus across the placenta. The enzymes necessary for ketone body utilization are present in the brain and several other tissues of rat and human fetuses (Williamson, 1975 ; Bailey and Lockwood, 1973). As pregnant rats and women develop a marked ketonemia during a short term starvation (Freinkel *et al.*, 1972 ; Felig, 1973), the utilization of ketone bodies as an alternative fuel in the placenta and various fetal tissues (Shambaugh *et al.*, 1977a, b) could play an important role in sparing glucose, thus avoiding the appearance of maternal hypoglycemia. Because this type of adaptation doesn't occur in fetal sheep, it may explain why toxemic hypoglycemia appears in ewes with a twin pregnancy, when they are deprived of food during a short period of time, since they must continue to supply a large amount of glucose to the twin conceptus.

C) Does gluconeogenesis occur in the fetus ?

In all the mammalian species studied by means of chronic preparations, the umbilical uptake of glucose is less than required to meet the oxidative needs of the fetus. By contrast, studies on the relative ratio of uptake of glucose and oxygen by the brain and the hindlimb in the fetal lambs have shown that glucose uptake is sufficient

to supply all the energy needs of these organs (Morris *et al.*, 1973 ; Jones *et al.*, 1975). The heart of the newborn dog used only glucose as oxidative fuel (Breuer *et al.*, 1967) when adult heart used FFA as principal oxidative substrate. Recently, three studies have attempted to measure glucose turnover rates in the fetal sheep, using either bolus injection or constant infusion techniques for the delivery of ^{14}C or ^3H glucose into the fetus (Warnes *et al.*, 1977a ; Prior and Christenson, 1977 ; Hodgson and Mellor, 1977). The values reported (7.4, 7.6 and 8.4 mg.min $^{-1}$.kg $^{-1}$) are approximately twice the umbilical uptake of glucose (Battaglia and Meschia, 1973, 1978). If these values did in fact represent true rate of fetal glucose metabolism, the data would strongly support the existence of an active gluconeogenesis in fetal sheep.

In the sheep and cow, all the enzymes required for gluconeogenesis are present with a substantial activity in the liver of fetus near the term (Prior and Scott, 1977 ; Warnes *et al.*, 1977b). However, Warnes *et al.* (1977b) were unable to demonstrate glucose synthesis from ^{14}C lactate in chronically catheterized sheep fetuses. These investigations suggest that the relative hypoxia of the fetus is responsible for the inactivity of the gluconeogenic pathway *in utero* and that gluconeogenesis appears within few minutes after birth in relation with the oxygenation of the newborn. This explanation is difficult to accept since several data, cited above, show that fetal metabolism is *aerobic*. Moreover, fetal liver is one of the first organ receiving oxygenated blood from the placenta. Other investigators, using the same preparation, have reported that fetal sheep was capable to perform gluconeogenesis from ^{14}C alanine (Prior and Christenson, 1977), at a relatively low rate (0.3 mg/min/kg body wt) when compared with glucose turnover rate (7-9 mg/min/kg). The discrepancy between these two studies result from differences in the experimental procedures used (single injection of labelled compound or infusion), the site of injection and sampling and the difference in maternal stress during the experiments. Further experiments are needed to know if gluconeogenesis is really fonctionnal *in utero* in the sheep fetus.

In the guinea pig (Jones and Ashton, 1976a ; Raghunathan and Arinze, 1977) and the rabbit (Callikan and Girard, 1978), all the enzymes of gluconeogenesis are well developed in fetal liver at term, and the fetal guinea pig *in utero* is capable to convert labelled lactate, pyruvate and alanine to glucose (Jones, 1976). By contrast, gluconeogenesis is absent from fetal rat liver because phosphoenol pyruvate carboxykinase (PEPCK) is lacking (Hanson *et al.*, 1975). It has been possible to induce prematurely the appearance of fetal liver PEPCK by maternal starvation (Girard *et al.*, 1977a), by prolongation of the gestation (Pearce *et al.*, 1974 ; Portha *et al.*, 1978) or by phloridzin injection to the mother (Freund, Geloso and Girard, unpublished data). In all these situations, PEPCK induction resulted from an increased secretion of glucagon and a lowered release of insulin by fetal pancreas (review in Girard *et al.*, 1977b). Nevertheless it remains to demonstrate that full development of hepatic gluconeogenic enzymes in the fetus results in a premature appearance of a fonctionnal gluconeogenesis *in utero* (see Girard *et al.*, 1977b, for a discussion on this special point).

3) Synthesis of energy stores.

Two types of energy stores can be accumulated during fetal life : glycogen and triglycerides. They will be considered successively.

A) Glycogen stores.

In all the species studied, the mammalian fetus accumulates glycogen in many tissues at the end of the gestation (review by Shelley, 1961). A particular attention has been given to liver glycogen synthesis in the fetus, since this energy store is particularly important for glucose homeostasis in the newborn (Girard *et al.*, 1975). It has been clearly established that liver glycogen storage in the fetus is dependent upon an hormonal control (Jost and Picon, 1970). Deprivation of the rat fetus of corticosteroids (by fetal decapitation, which impairs fetal adrenal function, and by maternal adrenalectomy), prevents glycogen deposition in fetal liver. Cortisol injection in decapitated fetuses restores liver glycogen storage. Recent experiments in the sheep (Barnes *et al.*, 1978) have shown that hypophysectomy or adrenalectomy of the fetus markedly reduces fetal liver glycogen content and that infusion of cortisol in adrenalectomized or hypophysectomized fetuses, allows a normal glycogen deposition in the liver.

In the rabbit, fetal decapitation alone prevents glycogen storage in the liver of the fetus. Injection of corticosteroids *alone* doesn't allow to induce liver glycogen storage. Addition of growth hormone, prolactin or a rat placental extract is necessary to restore liver glycogen deposition. So, glycogen storage in fetal liver is under a dual hormonal control involving fetal corticosteroids and a pituitary like factor present only in fetal hypophysis in the rabbit but also released by the placenta in the rat and in the sheep.

B) Lipid stores.

The problem of fat deposition in fetal life is not well understood. The amount of fat laid down in the fetus varies considerably depending upon the species considered (table 7). A significant storage of fat occurs in the fetus of 3 species : human, guinea pig and rabbit. It is not dependent on maturity at birth, since the rabbit which is born with eyes still closed and very immature, has a relatively high body fat content, while the pig, the sheep and the foal which are so much mature and run about soon after birth, have a very low body fat content. From a metabolic point of view, fatty acids are the most important lipids, and they are stored as triglycerides in 3 different tissues in the fetus : liver, brown adipose tissue (BAT) and white adipose tissue (WAT).

TABLE 7

Lipid stores in the term fetuses of several species

Body fat (g/100 g body weight)	
Man	16
Guinea pig	10
Rabbit	6
Sheep	3
Calf	3
Foal	2
Cat	2
Monkey	2
Pig	1
Rat	1

In the rabbit and guinea pig fetuses, most of the triglycerides stores are located in BAT (50 p. 100 of body fat content) and liver (16 p. 100 of body fat content), while WAT contains little fat (8 p. 100 of body fat content). The human fetus is unusual since he has also a well developed WAT at birth and this particularity renders him not so dependent as other newborn mammals on the early establishment of milk feeding for its survival. WAT and BAT differ markedly in their physiological functions. WAT is involved in energy homeostasis. Fatty acids produced during triglycerides breakdown are transported via the blood to other tissues where they are oxidized. The function of BAT is quite different since it plays an important role in non-shivering thermogenesis. When BAT triglycerides are broken down, fatty acids are oxidized locally to produced heat to maintain body thermal neutrality (see Hull, 1974, for a review). The origin of lipids stored in the fetus has been the matter of controversy during the last 20 years. Theoretically, fetal lipids may have 2 origins: 1) transfer of free fatty acid from the mother to the fetus through the placenta, 2) De novo synthesis of fatty acid by fetal tissues from different substrates provided by the mother (glucose, lactate, acetate). In the 3 species in which lipid accumulation occurs during fetal life, it has been shown that free fatty acids (FFA) cross readily the placenta. Recent studies in guinea pigs and rabbits in late pregnancy suggest that maternal FFA contribute significantly to the triglyceride stores of fetal liver and adipose tissues (Bohmer *et al.*, 1972 ; Bohmer and Havel, 1975 ; Edson *et al.*, 1975 ; Jones, 1976a). Furthermore, recent experiments have shown that liver, BAT and WAT of fetal rabbits and guinea pigs have a high ability to take up and esterify ^{14}C -palmitate *in vivo* (Bohmer and Havel, 1975 ; Biezenski, 1976; Elphick and Hull, 1977, Hudson *et al.*, 1977). The same observation has been done *in vitro* with tissues from the human fetus (Roux and Yoshioka, 1970). It has been suggested that FFA entering fetal circulation are first incorporated into liver triglycerides before transport to extra hepatic tissues as lipoproteins (Bohmer and Havel, 1975 ; Hudson *et al.*, 1977).

The liver and adipose tissues of fetal rabbit and guinea pig have a high rate of lipogenesis from various substrates ($^3\text{H}_2\text{O}$, glucose, acetate and pyruvate) both *in vitro* (Jones, 1973, 1976a ; Iliffe *et al.*, 1973 ; Patel and Hanson, 1974 ; Jones and Ashton, 1976) and *in vivo* (Popjak, 1954 ; Jones and Firmin, 1976).

Several attempts have been made to estimate the relative contribution of maternal fatty acid transfer versus de novo fatty acid synthesis in the fetus, for the accumulation of fetal fat stores. Starvation of the pregnant does near the term is associated with an increase in triglyceride in liver and adipose tissue of the fetus (Shelley and Thalme, 1970 ; Edson *et al.*, 1975). As maternal starvation produces a decrease in fatty acid synthesis in fetal tissues (Fain and Scow, 1966) and since less glucose and more FFA cross the placenta from the mother to the fetus, it is suggested that fetal liver and adipose tissue triglycerides are derived from maternal FFA (Edson *et al.*, 1975). One other situation in which fetal adipose tissue stores are increased is the infant born to diabetic mother (Fee and Weil, 1963). Initially, it was proposed that fetal adiposity resulted from the excessive amounts of glucose which cross the placenta and result in an increase in fetal plasma insulin and an increase in fatty acid synthesis in fetal tissues (Pedersen, 1977). Recently this hypothesis has been challenged, and it has been proposed that an accelerated transfer of FFA to the fetus, due to raised plasma FFA levels in diabetic mothers, could also been an explanation of fetal adiposity (Szabo and Szabo, 1974).

In this latter hypothesis, fetal hyperinsulinism will enhance the esterification of circulating fatty acids in adipose tissue. At the present time, no experimental proofs have been given to support or reject one of these 2 theories. One possible reason is that human fetus is unusual in having a well developed WAT, which becomes hypertrophied in diabetic pregnancy. Unfortunately, all the experimental studies on the effect of diabetic pregnancy have been performed in species in which the fetus doesn't have any WAT until after birth (rat, monkey). It is clear that the study of diabetic pregnancy in rabbit or guinea pig will be a more rationale approach to the problem of adiposity of the fetus of diabetic mother.

Other hormones than insulin seem also involved in fetal fat storage near the term in the rabbit. Fetal decapitation or thyroidectomy produce an increased fetal body fat in the rabbit and thyroxine injection in decapitated or thyroidectomized fetuses prevents fat accumulation (Jost and Picon, 1958 ; Picon and Jost, 1963). This shows that thyroid hormones influence (under pituitary control) fat storage in fetal rabbit, by a mechanism (placental transfer of fatty acids, lipolysis in the fetus) still unknown.

Conclusions.

This review on fetal metabolism has shown that our basal knowledges have considerably evolved during the last ten years. Nevertheless, most our quantitative informations have been obtained in the ruminant fetus and unfortunately, these important data cannot be extrapolated to other species due to important metabolic particularities to this group of mammals. Quantitative data in the fetus of non ruminant species are needed to estimate the relative contribution of glucose and of other substrates in fetal oxidative metabolism. One other field of fetal development which needs further researchs is the mechanisms by which nutrition and hormonal environment in the mother (diabetes, over and undernutrition in calories or proteins) can modify fetal growth, fetal organ differentiation and fetal fat storage.

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Résumé. Le fœtus reçoit ses nutriments énergétiques de sa mère à travers le placenta. Le transfert transplacentaire des substrats dépend de la perméabilité placentaire au substrat et de la différence de concentration du substrat entre le sang fœtal et le sang maternel. Le fœtus utilise les substrats à trois fins : la synthèse de nouveaux tissus (croissance), le métabolisme oxydatif et la constitution de réserves énergétiques. Puisque la consommation d'O₂ par kg/poids est relativement constante d'une espèce à l'autre, la répartition des substrats entre les voies anaboliques et cataboliques dépend du taux de croissance fœtal. Le glucose et le lactate couvrent la majorité des besoins « oxydatifs » du fœtus, mais le catabolisme des amino acides y contribue aussi d'une manière importante. En cas de jeûne maternel, les corps cétoniques peuvent aussi être utilisés comme substrats oxydatifs par le fœtus des monogastriques. Le fœtus ne peut que faiblement oxyder les acides gras libres, même chez les espèces où existe un transfert rapide de ces substrats. Les acides gras libres sont

utilisés comme précurseurs de lipides complexes ou sont mis en réserve dans le tissu gras fœtal ou le foie. Plusieurs observations récentes suggèrent que le fœtus des ruminants peut effectuer une gluconéogenèse, ce qui lui permet de transformer le lactate et les amino acides en glucose avant leur utilisation par les différents tissus du fœtus (cerveau, muscles squelettiques, cœur).

Les hormones sécrétées par le fœtus jouent un rôle important dans le stockage du glycogène dans le foie fœtal (glucocorticoïdes et hormones hypophysaires) ainsi que dans l'accumulation des triglycérides dans le tissu adipeux du fœtus (insuline).

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