

Principal Substrates of Fetal Metabolism

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I. INTRODUCTION

The requirements of a growing organism such as the mammalian fetus include both the fuels of energy transformation and the building materials for the production of new tissue. In this review we attempt to summarize present knowledge about the quantity and types of substrates that the fetus and some of the fetal organs use as major sources of energy and as major sources of carbon and nitrogen used for new tissue growth.

The fetus makes contact with the maternal organism via the placenta. In some species (e.g., rabbit) the modality of contact is complex, for it is made via two types of placentas that are perfused by two separate fetal circulations, the chorioallantoic and the vitelline (31). However, in most species the umbilical circulation is the only avenue by which the fetal body acquires substrates from the placenta and the maternal environment. For the sake of precision, note that even in these species some molecules can reach the fetus via another route: namely, molecules may enter the amniotic cavity via the uterine mucosa and be taken up by the fetus either through the skin or by swallowing. There is no evidence that this route is of any quantitative importance in comparison with the umbilical route. Therefore in this review the expressions "umbilical uptake of substrate" and "fetal

uptake of substrate" are used as synonyms, with both expressions meaning "uptake of substrates by the fetus via the umbilical circulation."

One can define in the fetus a "steady state" as one in which concentrations of solutes in blood and other body fluids are reasonably constant despite the fact the organism as a whole is growing and increasing its total body stores of most compounds. In such a steady state, substrates taken up by the fetus via the umbilical circulation do not accumulate in the fetal extracellular fluid but enter the fetal tissues, where they are utilized in a variety of ways, i.e., oxidized, stored, incorporated into new tissue, etc. Therefore, in the steady state, umbilical uptake and fetal utilization of substrate are equivalent, provided that by "fetal utilization of substrate" it is meant "fetal utilization of *exogenous* substrate." This qualification is essential when discussing substances that can be produced by the fetus. For example, consider glucose metabolism in a fetus capable of gluconeogenesis. The total rate of fetal glucose utilization, as determined by measuring the turnover rate of labeled tracer, would be greater than the rate of umbilical uptake, for it would include the utilization of glucose both endogenously produced and exogenously supplied.

In recent years, the study of fetal metabolism has advanced rapidly due to the availability of new biochemical and physiologic techniques. Several aspects of these advances have been reviewed (20, 67, 72, 78, 158, 161).

II. OXIDATIVE METABOLISM

A. Oxygen Consumption

The first attempt to measure fetal oxygen consumption was by Cohnstein and Zuntz in 1884 (41). Since then, there have been several measurements of this important aspect of fetal metabolism (3, 15, 16, 25, 29, 36, 39, 47, 56, 57, 95, 117, 119, 126, 142, 160, 196). Most measurements have been based on either of two methodological principles. According to the Fick principle, fetal oxygen uptake is equal to the product of umbilical blood flow times the difference in oxygen content between mixed umbilical venous and arterial blood. The Bohr principle (29) assumes that fetal oxygen uptake is the difference in maternal oxygen consumption before and during occlusion of the umbilical cord. Because of its sound theoretical basis and applicability to substances other than oxygen, the Fick principle has been used more extensively; however, its use requires the simultaneous sampling of umbilical arterial and venous blood and a method for measuring umbilical blood flow. Therefore, it entails fetal surgery and the risk of acquiring data that are not representative of normal in utero conditions. In order to minimize the effect that surgical stress and fetal exteriorization may have on fetal metabolism, in 1958 Barron and co-workers (28, 118) began the development of a fetal preparation in which arterial and venous umbilical blood could be drawn from the nonanesthetized, unstressed animal. Several versions of this preparation are currently in use for studies of fetal physiology.

Oxygen consumption rates measured by means of the Fick principle in the fetal lamb in utero have varied between 6 and 8.5 ml/min per kg body wt. The average fetal O_2 uptake measured in this species by means of the Bohr principle (39) was 9.4 ml/min per kg (Table 1). It is not clear how much of this variability is the result of methodological errors. For example, the assumption inherent in the Bohr principle (i.e., that the abrupt occlusion of the umbilical cord is not associated with rapid changes of oxygen consumption of the placenta and the maternal organism) may not be entirely valid. On the other hand, it is conceivable that incomplete recovery from surgery depresses the metabolic rate of some acutely or chronically catheterized fetuses. An indirect source of information about the oxygen consumption of fetal lambs is represented by studies of uterine oxygen uptake. The results of three sets of measurements of the oxygen consumption of the ovine gravid uterus are summarized in Table 2. The agreement is satisfactory in view of the fact that each estimate was obtained by means of substantially different methods. In the first of the two series of measurements by Abrams et al. (2), the Bohr principle was applied to the whole uterus: i.e., maternal oxygen consumption was measured before and immediately after interrupting the uterine circulation. In the second set of measurements, uterine oxygen uptake was calculated according to the Fick principle as the product of arteriovenous difference of oxygen across the uterine circulation times the uterine blood flow per kilogram of tissue. The latter was estimated by means of the diffusion-equilibrium technique of Huckabee et al. (90), using antipyrine as the test molecule. The measurements of uterine oxygen consumption

TABLE 1. *Comparison of mean oxygen consumptions of fetal lambs in utero*

Fetal Age Range, days	Fetal O_2 Uptake, ml STP \cdot min ⁻¹ \cdot kg ⁻¹	Ref.
81-136	6.9	119
106-139	8.5	117
100-146	8.5	47
125-146	6.0	95
70-145*	9.4†	39

* Estimated from fetal weight data. † Measured by application of the Bohr principle.

TABLE 2. *Oxygen consumption of gravid uterus in sheep*

Method	O_2 Consumption, ml/min per kg	Ref.
Bohr principle	9.2	2
Fick principle	9.2	2
Fick principle	8.1	125

by Morriss et al. (125) were also based on the Fick principle, but in this case uterine blood flow was measured by means of the microsphere technique. Several lines of evidence, which have been summarized in a paper by Raye et al. (139), indicate that in late gestation the fetal lamb consumes approximately 75% of total uterine oxygen uptake. This information, and the knowledge that the term fetus is approximately 80% of the mass of the gravid uterus (amniotic and allantoic fluids excluded), permits one to calculate from the data in Table 1 that mean fetal oxygen consumption is approximately 8 ml of oxygen/kg body wt per min.

In comparison with the data in sheep, measurements of fetal oxygen consumption in other species are much scantier (Table 3). The oxygen consumption of fetal goats appears to be the same as in fetal lambs (117), which is not surprising in view of the closeness of these two species. Bohr (29) applied his principle in 1900 in order to measure the oxygen uptake of fetal guinea pigs and obtained a mean consumption equal to 8.5 ml STP of oxygen/min per kg. In recent years, umbilical oxygen uptakes have been measured by means of the Fick principle in the cow (159), mare (160), and rhesus monkey (25). The mean uptakes in milliliters STP per minute per fetal body weight were 6.8 in the cow, 7.4 in the mare, and 7.0 in the rhesus monkey. There are no reliable measurements of oxygen consumption in the human fetus. Presumably, the Bohr principle could be applied safely by measuring maternal oxygen consumption at the time of cesarean section, but no such studies have been performed. Of interest in this context are the observations by Sandiford and Wheeler (147), who measured the basal metabolic rate of a pregnant woman repeatedly during pregnancy and postpartum. The data show an abrupt decrease of mean oxygen consumption from 243 ml STP min⁻¹ in the week preceding parturition to 205 ml min⁻¹ in the following week. The baby weighed 3.6 kg at birth. It can be inferred from such data that the whole conceptus (baby plus placenta and fetal membranes) weighed approximately 4.5 kg and consumed oxygen at the rate of 8.4 ml min⁻¹ per kg of tissue. An attempt to measure the oxygen consumption of the pregnant

TABLE 3. *Oxygen consumption rates of adults and fetuses in species of different size*

Animal	O ₂ Consumption, ml/min · kg body wt		Ref.
	Adult*	Fetus	
Horse	2.0	7.0	160
Cattle	2.2	7.4	159
Sheep	4.0	6-9.4	Table 1
Rhesus monkey	7.0	7.0	25
Guinea pig	9.7	8.5	29

* Values calculated according to equation 2.

human uterus by means of the Fick principle was made in 1955 by Romney et al. (142). According to this study, the mean oxygen consumption of the human fetus is approximately 5 ml STP min⁻¹ per kg body wt.

Caution must be exerted in comparing measurements of fetal oxygen utilization in different species, because of substantial differences in methodology and the physiological state of the preparations. Nevertheless, it is interesting to note the similarity of fetal oxygen uptakes per kilogram body weight reported in species that differ widely in size, from guinea pig to cattle. If this similarity were confirmed by further studies, it would have important implications in the comparative physiology of mammalian reproduction. In extrauterine life, the basal oxygen consumption is inversely related to body weight (107). Therefore, in species of small size the oxygen requirements per unit weight of fetus would be relatively small compared with oxygen uptake per unit weight of maternal tissue (Table 3). In addition, there would be a drastic increase in the rate of oxidative metabolism of the newborn in the transition from intra- to extrauterine life. By contrast, in large mammals the fetal tissues would be a site of comparatively high oxygen utilization within the maternal organism, and there would not be any major increase of oxygen consumption of the newborn at birth. If fetal oxygen consumption per unit body weight is constant across mammalian species it would help explain the allometric relationship between weight of the offspring and maternal weight. In a study of 15 simian primates (111), it was found that

$$F \approx 0.13M^{0.7} \quad (1)$$

where F and M are the neonatal and pregestational maternal weights in kilograms, respectively. Equation 1 is a quantitative expression of the observation that the offspring/mother weight ratio is relatively smaller the larger the species (189). The oxygen consumption (ml STP/min) of the mother prior to conception ($M_{V_{O_2}}$) is related to her weight in kilograms (M) as follows (107):

$$M_{V_{O_2}} \approx 10M^{0.75} \quad (2)$$

According to the data reviewed in this section, fetal oxygen consumption ($F_{V_{O_2}}$) may be related to fetal body weight (F) by the equation:

$$F_{V_{O_2}} \approx 8F \quad (3)$$

where $F_{V_{O_2}}$ is in milliliters STP per minute and fetal weight is in kilograms. If we assume that selective pressure favors a relatively constant relationship of fetal-to-maternal host oxygen consumption, or approximately:

$$\frac{F_{V_{O_2}}}{M_{V_{O_2}}} = 0.15 \quad (4)$$

the combination of *equations 2, 3, and 4* yields:

$$F \approx 0.2M^{0.75} \quad (5)$$

The good agreement between *equations 1 and 5* suggests that the weight of the term fetus (or the litter in polytocous species) may be limited by the necessity that fetal oxygen demands be a small proportion of maternal oxygen uptake. By virtue of the fact that maternal basal metabolic rate and related physiological variables such as cardiac output are quite high, the small adult mammal could accommodate a relatively bigger fetal mass than the larger species.

B. Carbon Dioxide Production

James et al. (95) measured the fetal CO_2 production rate in a chronic sheep preparation by applying the Fick principle to the umbilical excretion of CO_2 . The mean rate of CO_2 excretion ($5.65 \pm 0.17 \text{ ml} \cdot \text{min} \cdot \text{kg}^{-1}$) was comparable to the rate of O_2 consumption ($5.99 \pm 0.15 \text{ ml} \cdot \text{min} \cdot \text{kg}^{-1}$), giving a mean fetal respiratory quotient (RQ) of 0.94. In the adult, nongrowing organism it is possible to calculate from measurements of RQ and nitrogen excretion the proportion in which carbohydrates and fat are oxidized by calculating the so-called "N-free RQ" (107). With the umbilical excretion rate of urea (79) used to calculate the N-free RQ of the fetal lamb, a fetal N-free RQ virtually equal to 1 is obtained, suggesting the inference that the ovine fetus catabolizes negligible amounts of fat. However, in a rapidly growing organism this inference is unreliable because of the large discrepancy between carbon uptake and excretion. It has been estimated (20) that, in the ovine fetus growing at a normal rate, a total of 7.8 g of carbon/day per kg of fetal weight cross the placenta into the fetal circulation and that of these only 4.6 g are returned to the mother in the form of CO_2 and urea. Therefore, the evidence about types of substrates utilized by the fetus needs to be based on information more direct than RQ measurements.

III. FETAL CALORIC REQUIREMENTS

The flow of metabolic substrates from placenta to fetus serves two requirements: 1) maintenance of fetal oxidative metabolism and 2) formation of new tissue. It is possible to make a quantitative comparison of these two aspects of fetal metabolism by expressing both in calories per unit time, as illustrated by the following example. The consumption of 1 liter of oxygen is equivalent to the production of 4.7–5.0 kcal, depending on the types of substrates oxidized (107). Since the fetal lamb appears to oxidize a mixture of carbohydrates and amino acids (see below), the caloric equivalent of oxygen in the ovine fetus is approximately 4.9 kcal/liter. Hence, the daily caloric requirement of oxidative metabolism in a fetus that consumes 8 ml O_2 STP

$\text{min}^{-1} \text{ kg}^{-1}$ is $\sim 56 \text{ kcal} \cdot \text{day}^{-1} \cdot \text{kg}^{-1}$. Rattray et al. (138) have measured the caloric value of the fetal carcass in sheep by means of a bomb calorimeter. In addition, they have estimated fetal growth rate. Their results show that at 130 days of gestation the lamb fetus has a caloric value equal to 0.895 kcal/g and gains weight at the mean rate of $36 \text{ g} \cdot \text{day}^{-1} \cdot \text{kg}^{-1}$. It follows that the fetal lamb near term accumulates approximately $32 \text{ kcal} \cdot \text{day}^{-1} \cdot \text{kg}^{-1}$ in the form of new tissue. The analysis of the biochemical steps of growth (89, 120) leads to the conclusion that a negligible amount of the heat liberated by the fetal carcass in the bomb calorimeter represents energy formerly derived from oxidative metabolism (110). Such a conclusion has two important implications. First, it implies that virtually all the energy used to fuel fetal oxygen consumption is ultimately dissipated as heat. In agreement with this implication, Abrams et al. (1) have shown that there is a measurable transfer of heat from fetus to mother via the umbilical circulation of the ovine fetus and that the amount transferred is equal, within the limits of experimental error, to the caloric requirements of fetal oxygen consumption. The second implication is that the total caloric requirements of the fetus are equal to the sum of the caloric equivalent of oxygen consumption plus the caloric equivalent of tissue growth. In the above numerical example, the caloric requirements of the 130-day-old fetal lamb are $56 + 32$ or $88 \text{ kcal} \cdot \text{day}^{-1} \cdot \text{kg}^{-1}$. This calculation is only approximate, however. It has not yet been feasible to measure rates of growth and oxygen consumption in the same fetus. Furthermore, the unexplained variability in measurements of fetal oxygen uptake among and within different laboratories creates some uncertainty about the most appropriate average rate of oxygen consumption that should be attributed to a normally growing fetal lamb in the last month of gestation. Nevertheless, oxidative metabolism clearly is the major component of the total energy requirements of the ovine fetus near term. In order to extrapolate this knowledge to other fetuses it is important to realize that there are wide interspecies variabilities in fetal growth rates. If growth is expressed as a daily percent increment of fetal weight, the sheep fetus grows slower than the fetus of a smaller mammal, but approximately 3 times as fast as the human fetus at comparable stages of gestation (91). If one accepts the assumption that fetal oxygen consumption per unit body mass is virtually constant, one is led to the conclusion that in late gestation the relative rates of fetal catabolic and anabolic energy expenditure (i.e., oxygen consumption vs. growth rate) are quite different among species. In man the percentage of the total fetal caloric requirements represented by catabolism would be especially large because the human fetus grows disproportionately slowly in comparison with fetuses of mammals of similar size.

IV. CARBOHYDRATES

A. *Glucose*

A discussion of fetal carbohydrate requirements must begin with a

review of the role of glucose, since for many years exogenous glucose was considered the sole major substrate of fetal oxidative metabolism. This opinion was based on the inconclusive evidence that the fetal respiratory quotient is approximately 1, that the fetus and fetal tissues *in vitro* can metabolize glucose rapidly, and that a comparable rate of utilization of any other substrate had not been observed (175).

In assessing the role of glucose in fetal oxidative metabolism, it is important that the umbilical uptake of glucose be compared with fetal oxygen consumption. This comparison was first carried out by Tsoulos et al. (175), using a chronic fetal sheep preparation. They measured simultaneously the venoarterial concentration differences of whole-blood glucose (Δ glucose) and O_2 (ΔO_2) across the umbilical circulation and calculated a fetal glucose/ O_2 quotient, defined as:

$$\text{glucose}/O_2 \text{ quotient} = \frac{6 \times \Delta \text{ glucose (mM)}}{\Delta O_2 \text{ (mM)}}$$

The above quotient should be 1 or greater if exogenous glucose is the sole fuel of fetal oxidative metabolism. To the contrary, the mean glucose/ O_2 quotient measured by Tsoulos et al. was 0.49 in fed sheep and fell to 0.17 during maternal fasting. In a more recent study (152) the mean fetal glucose/ O_2 quotient in well-fed animals was 0.64 (95% confidence limits of the quotient 0.54–0.74). The difference in glucose/ O_2 quotients between the two studies of the animals in the fed state may reflect differences in nutritional state despite apparent free access to feed. With the onset of fasting, the quotient decreased rapidly in the first 2 days to a lower level that remained constant from the 2nd to the 8th day. The steady fasting level of the quotient was 0.30 (95% confidence limits between 0.25 and 0.35). The decrease in umbilical glucose/ O_2 quotient during fasting is due to a decreased umbilical uptake of glucose, as demonstrated by Boyd et al. (30). In their study, the glucose uptake of fetal lambs decreased from 18.0 to 9.7 mg/min with fasting, whereas the O_2 uptake decreased much less, from 26.7 to 22.8 ml STP/min. The mechanisms by which fetal utilization of exogenous glucose decreases with fasting have not been fully elucidated, but the available evidence suggests the following explanation. During fasting, the maternal level of plasma glucose decreases. Since glucose crosses the placenta by “facilitated diffusion” (187), this decrease in maternal glucose concentration causes a decrease in the rate of placental transfer of glucose (95). The reduced umbilical glucose uptake is not adequate to meet normal fetal glucose requirements and hence the fetus becomes hypoglycemic. The development of fetal hypoglycemia during maternal fasting induces the fetus to alter its metabolism and to require less exogenous glucose. There are several studies that suggest that this metabolic adjustment is hormonally mediated. First, the plasma concentration of fetal insulin decreases significantly during fasting (18). Second, the infusion of insulin into the fetal lamb increases the umbilical uptake of glucose, demonstrating that fetal utilization of exogenous glucose is insulin dependent (42, 162).

This information clearly establishes that glucose uptake, although an important component of fetal metabolism, is inadequate to account for the total oxygen consumption of the ovine fetus or to meet the carbon requirements of new tissue accretion. Of physiological interest is the finding that fetal glucose utilization, measured either in absolute terms or relative to oxygen uptake, is a function of the nutritional state of the mother. When the maternal level of plasma glucose is normal, the "fetal diet" contains a relatively large amount of glucose, capable of sustaining 50–70% of fetal oxidative metabolism and representing approximately 20% of the total fetal caloric requirement. With fasting, the supply of glucose to the fetus is reduced to approximately half the normal value.

Similar measurements of umbilical glucose/ O_2 quotients have been made in other mammalian species, including the cow, the horse, and man. Unfortunately, no such measurements are available in the smaller mammals, a group in which many studies of developmental enzymology and of the impact of maternal nutritional state on fetal growth have been made. Comline and Silver have reported umbilical glucose/ O_2 quotients in unstressed chronic animal preparations in the cow and the horse. The mean umbilical glucose/ O_2 quotients were 0.57 for the fetal calf (45) and 0.68 for the fetal horse (160). Although the 95% confidence limits of these quotients are not given, the variability of the umbilical glucose and O_2 uptakes makes it unlikely that these values differ significantly from those of the fetal lamb. The data in man (124) must be regarded as a rather crude estimate, since an average glucose/ O_2 quotient of 0.81 was obtained by means of single arterial and venous samples across the doubly clamped umbilical cord of the infant at the time of delivery by elective cesarean section. Not surprisingly perhaps, given the conditions of the study, there was far more variability in the umbilical glucose/ O_2 quotients of man than in the animal studies. Nevertheless, in at least four mammals the quantity of glucose entering the umbilical circulation from the placenta clearly is inadequate to meet even the caloric requirements represented by the oxygen consumption of the fetus. It is not known whether this would apply to the smaller mammals. Girard et al. (74) have reported that in the newborn rat the aerobic metabolism of glucose can account for the total oxygen consumption. Whether this is true in fetal life is not known.

B. Lactate

Lactate is a carbohydrate that recently has been found to be supplied by the placenta to the fetus in relatively large amounts and thus plays a role as a substrate of fetal metabolism. Burd et al. (34) have demonstrated a significant venoarterial difference of whole blood lactate concentration across the umbilical circulation of the fetal lamb. This finding has since been confirmed by Char and Creasy (38). The stoichiometric comparison of lactate and oxygen uptake shows that approximately 25% of fetal oxygen consumption could be accounted for if all the lactate were converted to CO_2 and water.

Therefore, the contribution of exogenous lactate to fetal metabolism, expressed either as O_2 equivalents or as a source of carbon, is approximately one-half to one-third that of glucose. The lactate delivered to the ovine fetus via the umbilical circulation is produced by the placenta (34). High rates of lactate production under aerobic conditions have been described for the rat (114) and human (179) placentas in vitro. Since there is a high glucose entry rate from the maternal circulation into the pregnant uterus, it is likely, although not yet established, that placental lactate is derived from maternal glucose. Similarly, Comline and Silver (45) have shown an appreciable umbilical uptake of lactate in the fetal calf. The high rate of lactate production under aerobic conditions by the placentas of five different mammalian species suggests an important role for lactate in fetal metabolism. The fate of lactate in the fetus is unknown. Presumably, it is used either directly as fuel for energy metabolism by various fetal organs or is used in gluconeogenesis.

The demonstration that the fetus as a whole is a consumer rather than a producer of lactate is interesting in light of the traditional view that anaerobic metabolism is an important component of fetal metabolism. In reality, a number of different observations tend to contradict this viewpoint. First, acid-base balance studies of the ovine, calf, horse, and human fetuses clearly show that the fetus is not in a state of chronic metabolic acidosis (43, 44, 143). When oxygen is increased in fetal blood above normal levels by the administration of 100% oxygen to the mother, there is no consistent increase of fetal oxygen consumption, suggesting that under normal conditions all aerobic requirements of the fetus are being met (22). Finally, although whole-blood lactate concentration in a chronic fetal sheep preparation is approximately twice that in the mother, the lactate/pyruvate ratios are similar in the maternal and fetal arterial blood, suggesting that there is no large "excess lactate" production by the normal fetus (34). Nevertheless, one cannot exclude at present that some fetal tissues (e.g., skeletal muscle) rely in part on anaerobic metabolism even under normal circumstances, their " O_2 debt" being paid by other fetal organs (e.g., the liver). Thus, the lactate turnover rate in the fetus may be much higher than the rate of consumption of exogenous lactate. Recently Warnes et al. (183) have shown that lactate is rapidly labeled after $[U-^{14}C]$ glucose is injected as a bolus into the circulation of the fetal lamb. In their study, radioactivities were expressed as "normalized specific radioactivities" and given in units of disintegrations per minute per milligram atom of carbon. Expressed in these units, the kinetics of lactate and glucose disappearance were approximately equal. Their experimental design consisted of a single bolus injection of the radioisotope into either the fetal femoral or umbilical venous circulations and did not permit a distinction between rates of utilization of carbohydrate within the fetus from placental utilization and diffusion into the mother. The study supports the concept that lactate is utilized rapidly by the fetus, although it is not yet clear whether it is used entirely for fuel.

C. Other Carbohydrates

Among the carbohydrates that may be a potential source of carbon and energy for the fetus, fructose has received particular attention since in some species—e.g., sheep, goats, cows, and pigs—it is the principal carbohydrate of fetal blood, being present at a concentration 3–4 times higher than glucose (137, 159, 175). In the sheep (175), pig (137), cow (159), and horse (159) no significant umbilical uptake of fructose could be demonstrated when pregnant animals were studied in the fed state. Furthermore, the injection of [^{14}C]fructose into the fetal lamb does not lead to the appearance of significant amounts of radioactivity in either glucose or lactate, and the rate of plasma clearance of fructose is extremely low (5, 154, 183). In liver slices from fetal, newborn, and adult sheep, there is little incorporation of [^{14}C]fructose into glycogen (14). In rats, [^{14}C]fructose incorporation into glycogen is present in the 19- and 21-day fetus, but increases markedly in the first few days of postnatal life. This sequence is also shown for changes in hexokinase activity in rat liver (13) and in the postnatal guinea pig and rabbit (181). These observations imply that fructose of placental origin is not an important substrate of fetal energy metabolism under normal conditions. However, it has been shown that fructose concentration in ovine fetal blood falls with maternal starvation (18). Thus in some species fructose appears to be a form of fetal carbohydrate storage that may be called on during fasting. The quantitative importance of this type of storage has not been investigated.

In contrast to fructose, galactose incorporation into fetal liver glycogen can be demonstrated easily in several mammalian species. In some ways this is surprising because galactose concentrations in the fetal circulation are quite low, increasing after birth in those mammals whose breast milk contains a high concentration of lactose. A large hepatic uptake of galactose during the neonatal period in those species would be appropriate hepatic adaptation to the postnatal diet. Perhaps the uptake of galactose by fetal liver should be regarded as a preparative adaptation in anticipation of parturition. The incorporation of [^{14}C]galactose into liver slices in the sheep is highest in the fetus and decreases during postnatal life (14). Incorporation is much higher with galactose than with either fructose or glucose. In rats, [^{14}C]galactose uptake by liver slices and $^{14}\text{CO}_2$ production from galactose are higher in the fetus than in the young or the adult (153). The hepatic uptake of galactose is associated with an increase in net glycogen synthesis (168). More recently, Sparks et al. (167) have shown that galactose uptake by the perfused fetal liver of the rhesus monkey is very large and associated with net glycogen synthesis. In contrast, glucose uptake by the perfused fetal liver could not be demonstrated. Thus in a number of mammals the rapid uptake of [^{14}C]galactose by fetal liver and incorporation of ^{14}C into liver glycogen have been demonstrated, but it has been more difficult to demonstrate significant hepatic uptake of glucose by fetal liver.

Myoinositol is another carbohydrate whose role in fetal metabolism

remains an enigma. It is present in high concentration in several fetal tissues, including brain, heart, and skeletal muscle (21). Inositol concentration is higher in fetal than in maternal blood. Whether inositol is transported to the fetus via the placenta or synthesized within the fetal body is not known.

D. Fetal Glucose Balance

It is useful to conclude this section on fetal carbohydrate metabolism by reviewing the major pathways of glucose supplied to the fetus and of glucose utilization by the fetus. Figure 1 presents in diagrammatic fashion the major pathways we need consider. Glucose utilization may occur by three paths: 1) glucose may be used as fuel by certain fetal organs (see sect. VII); 2) glucose may be utilized through conversion to other compounds such as nonessential amino acids that would then be used for protein synthesis and new tissue growth; and 3) glucose can be stored as glycogen in various fetal organs, principally in the liver.

The glucose utilization rate of the fetus is not known. However, in one study of the arteriovenous differences of glucose and oxygen across the hindlimb of the ovine fetus, the glucose/O₂ quotient was approximately 1 (122). If fetal tissues such as skeletal muscles, bones, and skin do indeed consume large quantities of glucose, the glucose requirement by these tissues may exceed umbilical glucose uptake. As further data are obtained for the rate of glucose utilization by individual fetal organs, it may be possible to establish whether gluconeogenesis occurs in fetal life by a comparative balance sheet. If the umbilical glucose uptake is less than the rate of glucose utilization, then the discrepancy must be met by glucose synthesis within the fetus. After birth portal venous uptake of glucose from the diet substitutes for umbilical glucose uptake from the placenta. Although the placenta has a high rate of glucose utilization, these needs are met under normal fed-state conditions by uptake of glucose by the placenta from the uterine circulation, and there is always a net delivery of glucose by the placenta to the umbilical circulation.

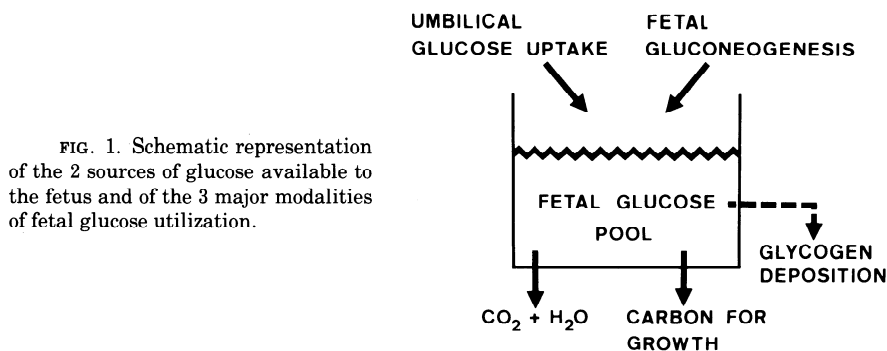


FIG. 1. Schematic representation of the 2 sources of glucose available to the fetus and of the 3 major modalities of fetal glucose utilization.

As pointed out earlier, it is unlikely that glycogen deposition in fetal liver occurs from hepatic glucose uptake. In all mammals thus far investigated fetal liver has shown little or no glucokinase activity. For this reason, the glucose that comes to the fetus from the placenta probably bypasses the liver and is delivered to other fetal organs.

Confusion arises when one attempts to evaluate whether appreciable gluconeogenesis occurs during fetal life. There are two general categories of studies that bear on this question. One group of studies is based on assays of enzymatic activity for those enzymes involved in glycolysis and gluconeogenesis. The second group is physiologic and is aimed at determinations of glucose turnover rates after infusions of radioactively labeled glucose.

Until recently, the data obtained from fetal liver, studied both in terms of various enzyme activities and in terms of *in vitro* incubation with glucose precursors, appeared to support the interpretation that in all mammalian fetuses gluconeogenesis did not occur to any significant degree prior to delivery. More recently, this hypothesis has been seriously challenged.

Let us consider an enzyme that is presumed to be one of the rate-limiting enzymes in the control of gluconeogenesis, phosphoenolpyruvate carboxykinase (PEPCK). This enzyme is found in both the mitochondrial and cytosol fractions of the liver in rabbit (8), sheep (184), man (81), and guinea pig (8, 9, 141, 166). Mitochondrial PEPCK activity is constant throughout fetal life. In the rat and the pig, PEPCK activity is almost entirely confined to the cytosol fraction. It is in this latter compartment that PEPCK activity changes markedly, beginning in late fetal life in sheep, man, and guinea pig or predominantly postnatally in the rat (8, 11, 131) and pig (172). The 25-fold change in cytosol activity in liver tissues of 2-day-old newborn rats compared with that of term rat fetuses has been interpreted as evidence that gluconeogenesis increases markedly after birth. However, in recent *in vitro* studies with fetal and adult liver tissue of the cow, Prior and Scott (134) were able to demonstrate gluconeogenesis by fetal liver as early as 88 days of gestation (term = approximately 280 days) and the rates of gluconeogenesis from a variety of precursors were comparable in adult and fetal liver. These comparable rates of gluconeogenesis were found despite striking differences in the levels of PEPCK activity. Cytoplasmic PEPCK activity was only 6% of that in maternal liver, whereas mitochondrial activity was 2 times higher in fetal compared with maternal liver. The relationship between gluconeogenesis from lactate and gestational age was expressed as a quadratic, with the rate highest at approximately 170 days and decreasing later in gestation. The reasons for this decrease in the rate of gluconeogenesis of fetal liver tissue near term are not clear. Similarly, Arinze (9) was able to demonstrate gluconeogenesis in fetal guinea pig liver *in vitro*. In the fetal guinea pig, PEPCK activity is high in the mitochondrial fraction and low in the cytosol fraction (8, 9, 166).

The changes in enzyme activities occurring during gestation in one ungulate, the fetus of the cow (134), are very similar to those described for the fetal lamb (184). In the lamb fetus, as in the cow fetus, there are

substantial levels of activity for all the enzymes required for gluconeogenesis. In addition, cytosol PEPCK activity, which is very low in the early fetus, increases throughout gestation. Despite the fact that all the appropriate enzymes for gluconeogenesis are present, Warnes et al. (183) were unable to demonstrate appreciable glucose synthesis from [^{14}C]lactate in chronically catheterized lamb fetuses. The approach used in these studies consisted of a single intravenous injection of radioactively labeled lactate or glucose for the calculation of turnover rates. The glucose turnover rate calculated from their data was considerably higher than the umbilical uptake of glucose measured directly (95), presumably reflecting the fact that umbilical venous blood samples were not obtained, and thus the glucose turnover rate included the uptake of [^{14}C]glucose by the placenta. The rate of lactate synthesis from [^{14}C]glucose calculated in the studies of Warnes et al., coupled with the apparent lack of gluconeogenesis, poses several problems of interpretation. Almost all the glucose utilization appears to be directed toward lactate synthesis yet, as pointed out earlier, the lamb fetus has a high rate of CO_2 production, of which only approximately 20% could be accounted for by the catabolism of amino acids. It is not clear how these differences can be reconciled.

Perhaps some of the confusion regarding the capability of the fetus for gluconeogenesis stems from the effect of stress or the level of maternal nutrition on the fetus. It is difficult to assess what are comparable biologic states when comparing studies in fetal and neonatal metabolism. Kervran et al. (104) demonstrated a striking effect of environmental temperature on glucose-induced insulin responsiveness in the newborn rat. A recent study by Girard et al. (75) has demonstrated that even in the rat fetus, where no capability for gluconeogenesis had been assumed on the basis of little mitochondrial and extremely low cytosol PEPCK activity, fetal gluconeogenesis could be induced by maternal starvation. These investigators infused labeled glucose into the mother and observed that the ratio of the specific activity in the maternal plasma to that in the fetal plasma changed from 1.0 with the mother in the fed state to 1.56 when the mother was fasted. Although the ratio of 1 in the fed state supports the hypothesis that little if any gluconeogenesis occurs in the rat fetus normally, the finding of a ratio higher than 1 in starvation indicates dilution of the labeled glucose by glucose formed within the fetal compartment. Earlier, Kirby and Hahn (106) had shown that enzyme activity could be induced in the liver of human fetuses early in gestation. The liver tissue cultured *in vitro* showed an increase in PEPCK activity when dibutyl cyclic AMP or oleic acid plus carnitine was added to the medium. Activity was also increased 10-fold in the fetal liver tissue obtained from a fetus whose mother had been receiving prednisolone. Numerous studies have demonstrated that PEPCK activity can be induced in a variety of ways in fetal and neonatal liver of the rat (73, 192, 193). The *in vivo* study by Girard et al. (75) on the rat and the *in vitro* studies support the hypothesis that, regardless of its normal rate, fetal gluconeogenesis can be increased markedly by various forms of maternal stress including starvation.

In summary, glucose is transported across the placenta in large amounts, although in all mammals studied by means of chronic preparations free of stress the umbilical uptake has been less than that necessary to meet the fuel requirements of the fetus. Probably, the glucose transported by the umbilical circulation bypasses the liver and is delivered to other organs. Lactate and amino acids (see sect. v), particularly glutamine and the neutral amino acids, are delivered from the placenta to the fetus, presumably to be taken up by the liver and other fetal organs. The extent to which these compounds are used directly as fuel or for gluconeogenesis is not established.

V. AMINO ACIDS

The list of amino acids that the fetus must receive from the mother includes all the essential amino acids plus those amino acids that the fetus is not capable of synthesizing in adequate amounts. According to the biochemical evidence, an example of the latter would be cysteine in the human and rhesus monkey fetus (67, 69, 171). In these species the fetal liver has virtually no active cystathionase, which is part of the pathway of transulfuration of methionine to cysteine, and it has been proposed that cysteine is a "fetal essential amino acid" (171). A similar claim has been made for tyrosine (101) and histidine (165). Biochemical evidence that fetal tissues are capable of synthesizing a given amino acid does not prove that transfer of that amino acid from mother to fetus does not occur or is unnecessary, for the synthesizing ability and/or availability of precursors may not be adequate to satisfy the requirements of growth and catabolism. Therefore it is important to examine the physiologic evidence about fetal uptake and requirements for each amino acid.

The concentration of most free amino acids, including some of the essentials, is higher in fetal than in maternal plasma (48, 66, 71, 102, 112, 155, 195). The higher concentration of essential amino acids in the recipient circulation suggests a process of active transport. This suggestion has been corroborated by observations on the placental transfer of nonmetabolizable amino acids, by experiments on artificially perfused placentas, and the comparison of D- and L-amino acid transfer from mother to fetus (53, 64, 68, 87, 103, 113, 128, 129, 140, 150, 164, 182). Fragments of human placenta incubated *in vitro* in a medium containing neutral amino acids concentrate them within the intracellular fluid (62). Therefore the transfer of amino acids from mother to fetus probably is a complex process involving, as an intermediate step, their active transport from the maternal plasma to the intracellular fluid of the trophoblast. An interesting aspect of the amino acid uptake by placental fragments *in utero* is the "preincubation phenomenon." If placental tissue is incubated *in utero* for some hours in an amino acid-free medium, its ability to concentrate amino acids is greatly enhanced (53, 163). The phenomenon is confined to amino acids transported by the A system of Christensen (62) and is a manifestation of increased \dot{V}_{\max} without appreciable change in K_m . A facilitation of amino acid transfer after preincubation in amino acid-free medium has been described for several embryonic and fetal

tissues (82). Although the physiologic implications of the preincubation phenomenon are obscure, it suggests that the acquisition of certain amino acids by the fetus could be regulated by altering the characteristics of the placental transport system.

Despite the evidence indicating that several amino acids are actively transported from mother to fetus, it should be emphasized that the placenta does not transport to the fetus each of the amino acids incorporated into fetal proteins. Lemons et al. (110) have measured the venoarterial concentration differences of 22 amino acids across the umbilical circulation of fetal lambs in the last third of gestation. The results of these measurements are presented in Figure 2. It is clear from this study that neutral and basic amino acids are transported from the ovine placenta into fetal blood, whereas the acidic amino acids glutamate, aspartate, and taurine are not. In fact, glutamic acid is delivered by the fetal lamb to the placenta in relatively large amounts, estimated to be 5 mmol/day per kg of fetus (110). Stegink et al. (169) have shown that when L-[3,4-¹⁴C]glutamate is infused into either the fetal or maternal circulations of the rhesus monkey there is virtually no transfer of the labeled compound across the placenta. In a second study they have shown this to be true also for aspartate (170). Using a preparation of the human placenta perfused in vitro, Schneider et al. (149) have demonstrated a significant placental uptake of glutamate from the fluid perfusing the fetal side of the placenta instead of a net transfer of glutamate from the maternal to the fetal side. Studies of the placental transfer of glutamine, glutamate, and aspartate in the rat have shown that there is little if any transfer of glutamate and aspartate and a rapid transfer of glutamine (59, 182). Among the free amino acids contained in the human placenta, the acidic amino acids glutamate, aspartate, and taurine are present in the highest concentrations (130). Therefore, the transfer rate of amino acids from placenta to fetus bears no simple relationship to their concentration in the trophoblast.

The amino acids that the placenta delivers to the umbilical circulation are used by the fetus in part to build new tissue and in part as fuels for catabolic processes. By measuring the amount of nitrogen present in the fetal carcass at different ages it has been estimated that the fetal lamb stores approximately 0.65 g of nitrogen/kg per day in the form of new tissue growth (20). Theoretically, it should be possible to infer the magnitude of amino acid catabolism in the fetal lamb by comparing this figure with the net umbilical uptake of amino acids. In the study by Lemons et al. (110) the estimated amino acid uptake was 1.5 g of nitrogen/kg per day, suggesting that the fetal lamb catabolizes a large fraction of its amino acid uptake. However, the measurement of venoarterial differences of some amino acids across the umbilical circulation is subject to large analytical errors. Therefore it has not yet been possible to make a precise measurement of the net umbilical uptake of amino acids in any species. More direct evidence about the existence and magnitude of fetal catabolism of amino acids comes from measurements of fetal urea excretion via the placenta.

The concentration of urea in fetal plasma is greater than in maternal

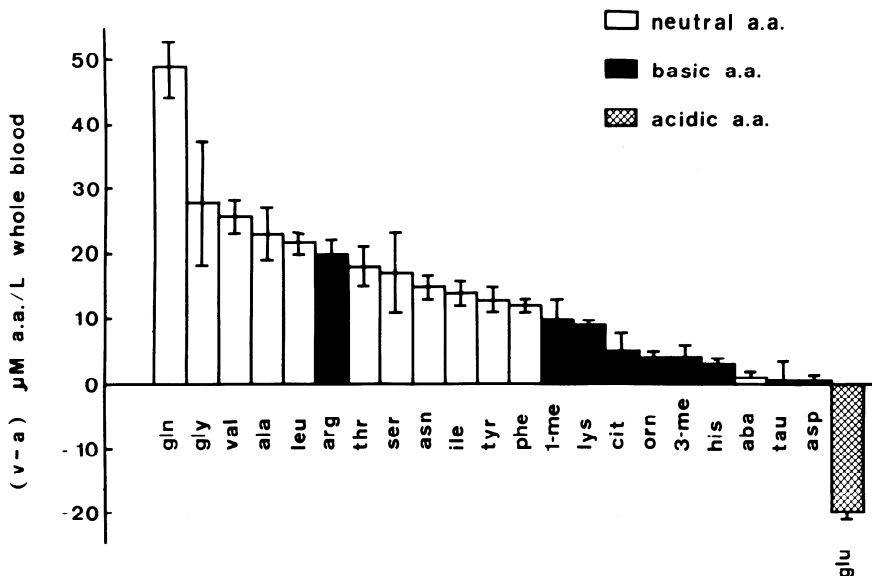


FIG. 2. Mean umbilical venoarterial concentration differences \pm SE in the ovine fetus are depicted in order of decreasing value. There is a large uptake of neutral and basic amino acids by the fetus from the placenta. Acidic amino acids taurine and aspartate show either no net flux or a flux in the direction of fetus to placenta (glutamate). [From Lemons et al. (110).]

plasma. The concentration difference is approximately 3.4 mg/dl plasma water in sheep (79) and approximately 2.5 mg/dl plasma water in man (80). This concentration difference indicates that both the ovine and human fetus are producing urea and excreting it through the placenta. Unfortunately, measurements of fetal urea excretion by application of the Fick principle are impractical because the arteriovenous difference of urea across the umbilical circulation is less than 1% of the urea concentration in fetal blood. Fetal urea excretion rate has been calculated in sheep (79) from measurements of placental urea clearance by means of [^{14}C]urea and of the concentration differences of urea between fetal and maternal arterial plasma, according to the equation:

$$\text{transplacental excretion rate} = \text{clearance} \times \text{concentration difference}$$

The urea excretion rate thus calculated had a mean value of 0.54 mg/min per kg of fetus (79). This is a high rate of urea excretion, regardless of whether one uses as a reference point the urea excretion rate of the adult or the oxygen requirements of the fetus. The urea excretion rate in fetal sheep is approximately fourfold the adult rate. If one assumes that fetal urea is derived from the catabolism of a protein of "average composition," the O_2 needed to sustain the observed rate of urea production would be approximately 1.6 ml STP/min per kg or approximately 20% of fetal oxygen consumption.

There are at least suggestive data supporting the hypothesis that a high urea production rate in late fetal life is not confined to sheep. Liver slices from human fetuses of an early gestational age are capable of producing urea (136). The placental urea clearance has been measured in the rhesus monkey (19) and has a mean value similar to that of the ovine placenta, i.e., 15 ml/min per kg of fetus. With this clearance value used to represent the primate placenta and the concentration difference of urea between fetus and mother in humans, the placental urea excretion rate of the human fetus has been estimated to be approximately 0.38 mg/min per kg (80). As in the sheep, this is a higher rate of excretion than in the adult (approx. 0.25 mg/min per kg). If indeed the human fetus produces relatively large amounts of urea during the last part of gestation, a striking change would occur at birth in the rate of amino acid catabolism. Barlow and McCance (17) published data showing urea excretion rates as low as 0.027 mg/min per kg for newborn infants born at term. More recently, Jones et al. (99) measured urea excretion rates of normal term babies that were considerably higher, probably reflecting different approaches to hydration and feeding of infants over the past 20 years. Nevertheless, even their mean value of urea excretion, 0.09 mg/min per kg, is much lower than that estimated for the fetus. A low nitrogen excretion rate in the neonate is not confined to man. We have been unable to find data for the lamb, but White and Miller (186) reported urinary nitrogen concentrations of approximately 4.7 mg/ml of urine in 3-day-old newborn rats, which increased to 11.3 mg/ml in the 19-day-old rat. This change occurs at a time when urinary flow rate is also increasing with age, leading to a marked increase in nitrogen excretion after the immediate neonatal period.

VI. FREE FATTY ACIDS AND KETOACIDS

All mammalian fetuses studied thus far have the capability of synthesizing lipids (10, 12, 63, 77, 93, 97, 132, 144, 180) but differ markedly with respect to the amount and origin of the fat stored before birth. According to a comparative study by Widdowson (188) fat constitutes 16% of birth weight in man, 10% in the guinea pig, but only 1.1% in the pig and rat. In the ovine fetus at term, fat is $2.1 \pm 0.04\%$ of body weight (138). There are also large discrepancies in rates of fat deposition. For example, although sheep and rabbits are born with approximately the same amount of lipid as a percentage of body weight, the 28-day rabbit fetus stores fat at a rate per unit body weight approximately 10 times higher than in the fetal lamb at term.

The origin of fetal lipids can be either from placental transfer of free fatty acids and glycerol or from *de novo* synthesis of nonessential fatty acids and glycerol within the fetus. There is an obligatory requirement for the placental transfer and umbilical uptake of essential fatty acids in all mammalian fetuses. The experimental evidence demonstrates rather striking interspecies differences, best exemplified by comparing the ovine and bovine fetuses with the rabbit and guinea pig fetuses.

In well-fed pregnant ewes, the concentration of long-chain free fatty acid (FFA), β -hydroxybutyrate, and acetoacetate in fetal blood is quite low. There is no appreciable net uptake of these substances by the fetus via the umbilical circulation (94, 123, 152). During fasting, the concentration of FFA and ketoacids in maternal blood increases severalfold, but their concentration in fetal blood remains low and the fetal uptake remains undetectable (152). The injection of [^{14}C]palmitate in the ewe has shown that the sheep placenta is poorly permeable to this molecule (178). The analysis of lipids in maternal and fetal blood tissues has revealed that the ovine fetus has only trace amounts of the essential linoleic and linolenic acids (108, 157). Similarly, in another ruminant, the cow, there is no detectable umbilical uptake of FFA; FFA levels are very low in fetal plasma and have no correlation with maternal plasma FFA concentrations (159, 161).

Before a significant umbilical uptake of lactate was demonstrated for the fetal lamb, it was clear from a comparison of carbon requirements of the fetus to the umbilical uptake of amino acids and glucose that some major carbon source was missing in the nutritional profile of the fetus. At that time, Cahill in an editorial (35) speculated that, in ruminants, short-chain fatty acids such as acetate and propionate might be important in fetal nutrition. This speculation was based on the fact that these fatty acids are used extensively by the adult ruminant. However, in acute (135) and chronic experiments (37) in sheep, small umbilical venous-arterial differences for acetate, the principal short-chain FFA, were found. Furthermore, these differences were not consistently positive, unlike those of major substrates. In chronic studies carried out on the bovine fetus in late gestation, Comline and Silver (45) noted a significant umbilical uptake of acetate whose magnitude was dependent on the maternal arterial concentration. Thus it is possible that, under certain physiologic conditions, acetate makes an appreciable contribution to the energy needs of the bovine fetus.

The rabbit and guinea pig placentas can transfer appreciable quantities of fatty acids from mother to fetus in the last part of pregnancy. The essential linoleic and linolenic acids are present in the guinea pig fetus in relatively large amounts (86, 148). Labeled palmitate crosses the rabbit placenta in either direction readily (61, 177). Both labeled palmitic and linoleic acids are transferred rapidly from maternal to fetal blood in the guinea pig (86). Large venoarterial differences of FFA have been measured across the umbilical circulation of anesthetized rabbits, especially in association with abnormally high concentrations of FFA in maternal blood (61). During fasting, the FFA concentration in the plasma of fetal rabbits (60) and guinea pigs (86) increases substantially. Paradoxically, a 48-h maternal fast in the pregnant rabbit near term causes an increase of the fat stored in the fetus to approximately twice the control values (60). Presumably, this phenomenon is a consequence of the high concentration of FFA in maternal plasma induced by fasting, which promotes an increased transfer of FFA to the fetus. Observations in rats (6, 51, 92, 100, 151), humans (52, 146, 173), and the rhesus monkey (133)

indicate that the placenta of these species also allows the transfer of both essential and nonessential FFA and ketoacids into the umbilical circulation and that part of the lipids stored in the fetus are of maternal origin. In the horse, fetal plasma FFA concentrations follow the maternal FFA concentrations over a wide range ($r = 0.88$, $P < 0.01$) (161). It is not clear, however, that a net transfer of large quantities of FFA occurs from the mare to her fetus, since Silver and Comline (159, 160) were unable to demonstrate a statistically significant umbilical venoarterial difference of FFA in chronically catheterized mares. There have been studies in which umbilical cord arteriovenous differences for FFA and glycerol were measured in man at the time of delivery (146). The conclusions by the authors were that FFA are not a major carbon source for the human fetus. However, the available information does not permit a reliable estimate of the contribution of maternal FFA to fat storage in the human fetus prior to labor, nor do we know how it varies under different conditions such as fasting. The hypothesis has been proposed that the increased adiposity in infants of diabetic mothers is due to increased availability to the fetus of FFA of maternal origin (174).

Whether FFA and ketoacids delivered to the fetus via the umbilical circulation are an important substrate of fetal oxidative metabolism in some species is open to question. The evidence in sheep and cows strongly supports the conclusion that a negligible fraction of the total caloric intake of the fetus is in the form of FFA and ketoacids, both in the fed and fasting states. A different situation could prevail in those animals in which the placenta permits the rapid transfer of FFA and ketoacids from mother to fetus. Against this hypothesis, Popjak (132) observed no apparent degradation of stored lipids in the fetal rabbit and concluded that fetal fat is not used as a major energy source until after birth. On the other hand, the capability for metabolic degradation of FFA and ketoacids by fetal tissues has been demonstrated *in vitro* (4, 23, 144, 145, 194).

The growth of the fetal brain may depend on the supply of long-chain polyunsaturated fatty acids derived from essential fatty acids (i.e., linoleic and linolenic acid). Thus brain growth could be affected by either a limitation in the supply of the precursor essential fatty acids transported across the placenta or by decreased synthesis. The composition of brain phosphoglycerides in terms of the pattern of long-chain polyunsaturated fatty acids is quite constant among species that differ widely in food sources and in fat composition in the body as a whole. Crawford et al. (46) studied the conversion of [^{14}C]linoleic and [^{14}C]linolenic acids to longer chain polyunsaturated fatty acids in man and in the guinea pig by oral administration of the labeled compounds to the mother. They found a stepwise increase in the proportion of radioactivity in the long-chain polyunsaturated fatty acids from maternal liver to placenta, to fetal liver, and to fetal brain in the guinea pig and from maternal plasma, to umbilical cord plasma, to fetal liver, and to fetal brain in man. These data suggest an important role for the placenta and fetal tissues in the synthesis of these compounds essential to brain growth.

VII. METABOLISM OF INDIVIDUAL ORGANS

A. Heart

The principal substrates used by the adult heart are free fatty acids, accounting for well over half its oxygen consumption (27). There have been only a few studies of the substrates used by the developing heart. Foà et al. (65) pointed out some of the developmental changes that occur in cardiac muscle when they showed that in the early life of the chick embryo there is no demonstrable effect of insulin on glucose uptake, whereas later such an effect could be demonstrated. Breuer et al. (32) measured arteriovenous differences of glucose, lactate, and oxygen across the coronary circulation of newborn and adult dogs. They found that in puppies 7–10 days of age, glucose could account for all the metabolic requirements of the heart. The glucose/O₂ quotient calculated from their data on puppies 7–10 days old was approximately 1.1. At 13–21 days the combined glucose plus lactate/O₂ quotient was 1.04. This fell to 0.3 in the adult dog hearts. Free fatty acid uptake by the heart could not be demonstrated in puppies, but only in the adult dog (33). A relatively small rate of FFA oxidation has been demonstrated by *in vitro* studies of newborn rat (190) and fetal bovine (185) heart, compared with the rate of FFA utilization by adult heart. This low rate of FFA utilization may be due to a low carnitine concentration *in vivo* as much as to differences in enzyme activities between adult and neonatal hearts (190). If the concept that cardiac metabolism starts out primarily glucose dependent and then switches to be primarily FFA dependent sometime during postnatal development holds true generally, it could help explain some of the physiologic properties of the fetal and neonatal heart. There have been reports in the pediatric literature (7, 191) suggesting that hypoglycemia leads to heart failure in newborn infants.

Fetal and neonatal hearts are relatively resistant to hypoxia. One hypothesis offered for this resistance is that the fetal myocardium accumulates glycogen in high concentration (55). The increased glycogen stores would then permit a longer period of anaerobic metabolism to meet the energy needs of the heart. The pattern of glycogen deposition during gestation varies among mammals. In the rabbit (88) glycogen concentration increases until approximately the 26th day of gestation. There is then a precipitous fall in glycogen concentration during the last 3 days of gestation that continues during the 1st wk of postnatal life. The pattern of a falling glycogen concentration in late fetal life has also been found in the sheep, guinea pig, and rhesus monkey. In other mammals such as the pig, myocardial glycogen concentration is remarkably constant throughout gestation (137). An *in vitro* study by Hoerter (88) has clearly established the importance of glycogen in providing energy to the heart when there is no glucose in the medium. The tension developed by the fetal heart under conditions of normoxia and hypoglycemia changes during gestation in a

manner paralleling the changes in glycogen concentration. Gennser (70) has demonstrated that the reduction in cardiac contractility brought on by hypoxia could be counteracted by increasing the concentration of glucose in the medium. This appears to be true for both neonatal and adult hearts, thus indicating the general importance of glucose as a substrate of the hypoxic heart. The *in vitro* studies of the effects of hypoxia on cardiac metabolism of glucose in the fetus and newborn have not been carried out in the presence of insulin. Morgan et al. (121) have shown in the adult heart that the effects of insulin and hypoxia on cardiac glucose uptake are cumulative, with a maximum glucose uptake in the presence of insulin and hypoxia. Developmental changes in cardiac response to insulin (65) and glucagon (189) have been shown. This difference in hormonal response might further accentuate developmental differences in the metabolic response of the heart to hypoxia.

In some mammals the switch to more dependence on nonglucose carbon sources may occur during fetal life. Glucose uptake by the fetal heart *in vitro* decreases during gestation in the rat (40). Beatty et al. (24) have shown in the rhesus monkey that the percentage of CO₂ derived from glucose decreases in fetal cardiac tissue during gestation.

B. Brain

Studies of brain slices *in vitro* have led some investigators to conclude that anaerobic metabolism represents a normal, major source of energy for the fetal brain (26, 54, 116). This conclusion is based on the observation of a high rate of lactate production by the slices. However, studies in chronic, unanesthetized fetal sheep preparations do not support this conclusion. There is no appreciable release of lactate by the brain of fetal lambs (98). Fetal cerebral O₂ consumption, measured as the product of cerebral blood flow times the difference of oxygen content between samples of carotid and sagittal sinus blood, is approximately 180 $\mu\text{mol/min}$ per 100 g (115), which is much higher than the rate of oxidative metabolism per unit weight of the whole fetus. Glucose is the major metabolic fuel of the ovine fetal brain. In fetal sheep the cerebral glucose/O₂ quotient is virtually 1 (0.98 with 95% confidence limits between 0.92 and 1.03) and there is no demonstrable cerebral uptake of ketoacids (98). The cerebral consumption of ketoacids in fetal sheep during fasting has not been measured, but it is doubtful that it could be substantial, since the concentration of ketone bodies in fetal blood is small and does not increase appreciably when the ewe is fasting (152).

There is no direct information other than in sheep about cerebral metabolism of the unanesthetized fetus *in utero*. However, a comparison with neonatal and adult data suggests that high rates of cerebral oxygen and glucose utilization are a general phenomenon irrespective of size and stage of development. The cerebral O₂ consumption of newborn rats, who have a brain weight of about 1.3 g, has been reported to be 143 $\mu\text{mol/100 g per min}$ (50), which is within the range of values reported for the 1000-fold larger adult human brain. Another similarity among brains of different species and

stages of development is the high rate of glucose utilization, which is approximately equivalent to the combined demands of O_2 utilization and lactate production in the neonatal brain of man (156), sheep (176), and rats (50) and in the adult brain of man (105) and sheep (98). It is interesting that cerebral glucose consumption should be high even in ruminants, which absorb the bulk of the carbon from the diet in the form of short-chain fatty acids. This may help explain the observation that glucose turnover rate in mammals is linearly related to the $3/4$ power of body weight (12), since brain weight follows a similar allometric relation (83).

A significant cerebral uptake of ketoacids has been described in adult man during prolonged fasting (127) and in the newborn of rat (50) and man (156). Although in each case the ketoacid uptake was related to the arterial concentration, the uptake by the neonatal brain was higher than uptake by the adult brain at comparable levels of plasma ketoacids. It is generally assumed that the neonatal uptake of ketoacids represents an adaptation to the high fat content of milk. There are discrepancies in the literature concerning the magnitude of the rate of ketoacid utilization by the neonatal brain. In newborn, anesthetized human infants, ketoacid uptake was the equivalent of 10–15% of cerebral O_2 consumption (156). In newborn rats, values ranging from 15 to 75% O_2 equivalents have been reported (85). Note also that the role of ketoacids in the metabolism of the neonatal brain is not necessarily that of a metabolic fuel. Devivo et al. (58) have reported that β -hydroxybutyrate is used by the neonatal brain of rats for the synthesis of amino acids, specifically glutamate, aspartate, and γ -aminobutyric acid (GABA). Whether this would be true in the fasting state is not known.

Given the importance of ketoacids as substrates of cerebral metabolism in the newborn, it is possible that they play an important role in the fetal cerebral metabolism of some species, perhaps as an alternate source of carbon whenever the supply of glucose is reduced. If this is the case, it would be interesting to know whether alternate substrates play a similar role in those species in which ketoacid levels are not elevated in fetal blood.

VIII. SUMMARY

Fetal oxygen consumptions ranging from 6 to 9 ml STP \cdot min⁻¹ \cdot kg⁻¹ have been measured in fetuses of different species. Fetuses of small mammals apparently do not have a higher rate of O_2 consumption per unit weight than fetuses of large mammals, in contrast to the behavior of the standard metabolic rate in adult animals. In man and larger mammals, the supply of calories needed to sustain fetal growth is small in comparison with that needed to sustain fetal oxygen consumption. In the ovine fetus the principal exogenous substrates of oxidative metabolism are glucose, lactate, and amino acids. The supply of glucose to the fetus decreases during maternal fasting and requires a reorientation of fetal metabolism toward an increased amino acid degradation. There is contradictory evidence in the literature concerning the rate of fetal gluconeogenesis and its regulation. The placenta supplies

neutral and basic amino acids to the fetus. In sheep, the acidic amino acids glutamate and aspartate are produced within the fetus and there is excretion of glutamate from fetus to placenta. There is also evidence that in man and other species the placenta does not supply acidic amino acids to the fetus in the amount needed for growth and catabolism. All mammalian fetuses studied thus far are capable of synthesizing lipids but differ markedly in the amount and origin of the fat stored before birth and the permeability of the placenta to fatty acids. Fetuses are also capable of oxidation of FFA and ketoacids but it is not clear whether these substances are an important source of energy in those species whose placenta is permeable to fatty acids. According to indirect evidence, the fetal heart consumes predominantly glucose under aerobic conditions. This is in contrast to the adult heart, for which FFA is the principal substrate. The fetal cerebral oxygen and glucose utilization rates per unit brain weight are comparable with those observed in adult mammals.

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