Ann. Rev. Nutr. 1983. 3:97–124

THE PLACENTA IN NUTRITION

Hamish N. Munro

USDA Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts 02111

Sydne J. Pilistine and Michael E. Fant

Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

CONTENTS

INTRODUCTION

The function of the placenta of the mammal is to ensure optimal nutrition at all stages of fetal development. This involves transmission of nutrients, gases, and

water to the fetus, excretion of waste products of fetal metabolism into the maternal bloodstream, and the adaptation of maternal metabolism to different stages of pregnancy by means of hormones. This review will focus on these roles of the placenta as a vehicle for fetal nutrient delivery and on the impact of maternal nutritional status on the capacity of the placenta to perform these functions.

Studies on placental function are complicated by the wide variety of placental structure in different species (152). To understand transport of maternal nutrients into the chorio-allantoic placenta, it is important to know whether the placental villi are in direct contact with the maternal blood, or whether in order to reach the villi the nutrients must pass through a layer(s) of maternal uterine cells with their own transport mechanisms and receptors. In this respect, it is a justifiable simplification to divide placentas into two types. The sheep, cow, pig, and horse have *epithelio-chorial* or *syndesmochorial* placentas, in which uterine epithelium, connective tissue and blood-vessel endothelium separate the maternal blood from the placental absorbing surface. On the other hand, most rodent placentas and those of higher primates including man are of the *hemochorial* type in which invasion and destruction of endometrium at the placental site is more or less complete, resulting in direct contact between the chorionic villi and a circulating pool of maternal blood.

The human placenta attains its mature architectural features during the first trimester of pregnancy. The chorionic villus, the unit of function, consists of a central loose core of connective tissue containing the fetal capillaries; the core is ensheathed by the two layers of the trophoblast, namely the outer syncytiotrophoblast and the inner cytotrophoblast. The cells of the latter layer become fewer as the placenta matures. The syncytiotrophoblast consists of a syncytium without cell boundaries containing numerous nuclei and an abundant rough endoplasmic reticulum consistent with its function of secreting hormonal and nonhormonal proteins into the maternal bloodstream. The maternal surface is folded into numerous microvilli, thus greatly increasing the area for absorption of nutrients. Such villi are called the *enteroid* type because of their similarity in structure and absorbing function to intestinal mucosal cells (115). In some villi, thin epithelial cells without microvilli replace the enteroid syncytium. This *epithelioid* type is believed to function in fluid transport. Finally, the cytotrophoblast consists of discrete cells and a cytoplasm with an abundance of free ribosomes, indicating that these cells do not secrete protein. The components of the mature human placenta have been quantitated by morphometry (101), including a computer-assisted videoscanning technique to measure tissue dimensions (100). Much of the mass of the placenta consists of structural supporting tissues. Although the trophoblast is metabolically the most active tissue, it represents only 13% of the placenta.

NUTRIENT TRANSPORT BY PLACENTA

Mechanisms by which nutrients enter and cross the placenta can be classified as passive diffusion, facilitated diffusion, active transport, and solvent drag (82). An increasing number of nutrients have been found to have specific receptors on the villus surface that facilitate nutrient uptake. In addition to these, adequate utero-placental blood flow is an important determinant in nutrient availability to the fetus. Finally, some nutrients may gain access to the fetus through the contact of the fetal trophoblast with the decidua of the uterus other than the placental site.

Maternal Blood Flow and the Transport of Gases and Water

Blood flow to the uteroplacental unit increases extensively during pregnancy. In the pregnant sheep, blood flow changes from 30 ml/min at 40 days to 1500 ml/min at term (156). At term, uteroplacental blood flow of the pregnant woman accounts for 20–25% of her cardiac output (112). In a detailed review of the role of blood flow in gas exchange, Longo (112) concludes that rates of maternal and fetal flow can be major determinants in the exchange of substances across the placenta. Increasing the flow of maternal blood can raise oxygen tension in fetal capillary blood and improve oxygen exchange, the relationship to blood flow being curvilinear (199).

Not all the oxygen entering the placenta is transferred to the fetus (Figure 1). Data for sheep in late pregnancy show that half is used for uterine and placental metabolic processes (121). Studies with inhibitors of respiratory enzymes (70) show that placental utilization of the oxygen depends on respiration in that organ, whereas oxygen transfer to the fetus occurs by simple diffusion. The observation (24) that drugs inactivating the cytochrome P-450 system reduce oxygen and carbon monoxide transport across sheep placenta seems to conflict with a diffusion mechanism, unless the intact uterine wall of the sheep syndesmochorial placenta actively secretes these gases in contrast to the hemochorial human placenta, where there is direct contact of the placental villi with the maternal blood. Longo and colleagues (63) did not find evidence for involvement of cytochrome P-450 in carbon monoxide transport across guinea-pig placenta. The placental transport of CO_2 generated by the fetus has been examined by Longo et al (113) in pregnant sheep using an inhibitor of fetal carbonic anhydrase to show that this enzyme is not a limiting factor in the conversion of H_2CO_3 to molecular CO_2. The major species crossing the placenta to the maternal side was molecular CO_2, the contribution of HCO_3^- and H_2CO_3 being negligible.

Finally, Power & Dale (149) discuss theories of placental transport of water, small amounts of which accumulate in the growing fetus to ensure adequate

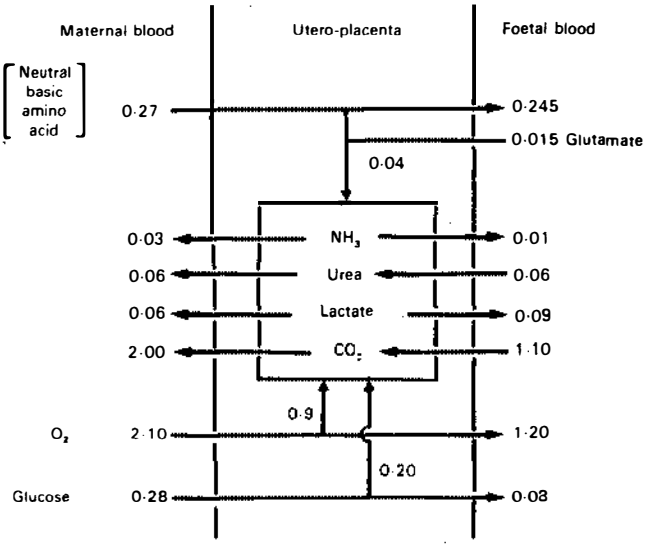

Figure 1 A block diagram describing some of the measured fluxes of substrates into and out of the uteroplacental unit of sheep during the latter 20% of gestation (amino acid fluxes in nitrogen meq/min; all other fluxes in mmol/min). Relevant information for nitrogen exchange is shown in the upper part of the diagram and that for carbohydrate and oxygen exchange in the lower half of the diagram. [from (10)]

expansion of fluid spaces. To account for this Faber (53) proposed a *hydrostatic* hypothesis, Longo & Power (114) developed the *bicarbonate-osmotic control* hypothesis, and Power & Dale (149) consider that uneven flow of maternal blood sets up a situation favoring fetal acquisition of water by the pumping effects of local increases in osmotic pressure. These hypotheses demand more data for validation.

Glucose

In 1952 Widdas (194) published a paper entitled: "Inability of diffusion to account for placental glucose transfer in the sheep and consideration of the kinetics of a possible carrier transfer." Three decades later, this prediction remains fully justified. Using vesicles made from the microvillous membrane of the human placental syncytiotrophoblast, Johnson & Smith (90) have shown that transportation occurs through facilitated diffusion with a K_m six times higher than maternal blood glucose level, implying that uptake of glucose will benefit by increased maternal blood glucose concentrations, a prediction confirmed by direct experimentation (30). Transport into the vesicles is specific for glucose-like molecules and is sensitive to inhibitors of glucose transport in other systems, but is not coupled to sodium transport. Despite the presence of abundant insulin receptors on the microvilli of human placentas (132, 148,

192), transportation of glucose into the vesicles is insensitive to addition of insulin to the medium (90), and so is amino acid transport (167). This is not surprising, since insulin stimulates sugar uptake by recruiting new glucose receptors from the interior of the cell (175), which is absent from microvillous preparations. By infusion of insulin into the uterine artery of the pregnant sheep, Morriss and colleagues (34) provided suggestive data of increased transfer of glucose from mother to fetus, but F. C. Battaglia (personal communication) could not confirm this action of insulin. It would be desirable to study this on a hemochorial placentation species in which the villi come in direct contact with maternal blood.

The requirement of the fetoplacental unit for glucose can represent as much as 70% of the glucose metabolism of the pregnant sheep (34), much of it used by the placenta. The remainder goes to the fetus where only 46% of the fetal energy requirements are met by glucose, with 25% from catabolism of amino acids and 20% from lactate, a small fraction also coming from alanine (34). Gluconeogenic enzymes in the liver of the fetal sheep allow these last two substrates to generate additional glucose (151), though Hay et al (77) report that this only occurs when fetal hypoglycemia is induced by maternal fasting. The fate of glucose taken up by the uteroplacental unit of the fetal sheep near the end of pregnancy has been quantitated by Battaglia, Meschia, and their colleagues (10, 77, 121, 164), who measured arteriovenous differences across the fetoplacental unit and the fetus itself. A large amount of the incoming glucose is used by the placenta (10), only one third of the glucose taken up by the placenta being transferred as such to the fetus (Figure 1). Within the uteroplacental unit, part of the glucose is converted to lactate and some is oxidized to yield CO_2. The release of lactate to both fetal and maternal circulations (Figure 1) can account for up to 37% of ovine placental glucose utilization, the remainder being oxidized to meet the energy needs of the placenta (121). Lactate passing into the maternal circulation is presumably made into glucose again by the well-known gluconeogenesis pathway in the maternal liver. Lactate exported to the fetus is used as an energy source (10, 166). Similar placental distribution data for glucose uptake and lactate release have been reported for pregnant cows (58). Glucose utilization and lactate release have also been confirmed using human placental fragments in vitro (84).

Amino Acids

The concentrations of free amino acids in fetal blood are higher than in the maternal blood of various mammalian species, leading to the concept of active or facilitated transport of L-amino acids across the placenta (195). This capacity of the placenta to abstract amino acids from the maternal circulation has been documented for the guinea pig (83, 153, 206,) man (142, 207, 207a), sheep (123), and cow (57).

Microvillous vesicles prepared from human placenta concentrate the nonmetabolizable model amino acid aminoisobutyric acid (AIB) from the medium, the transport process being sensitive to the sodium gradient across the membrane and being accelerated by prior amino acid depletion of the tissue (158). These similarities to amino acid transport in other tissues are confirmed by examining different classes of neutral amino acid transport system (52). Using specific inhibitors, transport into the vesicles was found, like that of intact mammalian cells, to have system A (alanine-preferring, which includes AIB and requires energy), system L (leucine-preferring and operated by exchange of amino acids across the membrane) and the ASC system (cysteine-preferring). Perfusion studies on human placentas show that active transport from maternal to fetal circulation occurs only for L-isomers of amino acids (161). The concentrations of many free amino acids in the trophoblast are higher than in the maternal or fetal blood. As in the case of other tissues of the mammal (80), a few nonessential amino acids (glutamic and aspartic acids, glycine and alanine) are found in considerably higher concentration in the placenta than in fetal or maternal plasma (206, 207, 207a) owing to their facile intracellular synthesis from general intermediates in metabolism.

Quantitation of amino acid transport has been reported. Ferrell & Ford (57) measured maternal blood flow and uptake of glucose and amino acids by the gravid bovine uterus. Total uptake of glucose and α-amino nitrogen both increased about 30-fold between one and six months of pregnancy, then plateaued. When calculated per kg gravid uterus, uptake increased two-fold between three and five months and then declined again, while urea output showed the same pattern of change, probably dependent on the large changes in blood flow during gestation. The role of placenta and fetus in utilizing these substrates has been quantitated by Battaglia & Meschia (10) for the sheep and by Ferrell et al (58) for the cow. In the case of pregnant sheep studies (Figure 1), almost all the amino acids taken up by the placenta were passed on to the fetus, whereas in the gravid cow 90 percent were retained in the utero-placental tissues which were considered to be the major source of urea excreted into the maternal circulation. In contrast, Battaglia & Meschia find that all urea entering the maternal circulation can be accounted for by fetal production (Figure 1). No mechanism for formation of urea by placenta has been demonstrated. Finally, Meschia, Battaglia, et al (121) estimate that 14% of the amino nitrogen entering the uteroplacenta of the sheep is returned to the maternal and fetal circulation as ammonia (Figure 1). Similarly, human placental fragments showed in vitro release of ammonia that increased when glutamine but not glutamate was added to the medium (84).

Battaglia & Meschia (10) have compared the daily fetal accretion of individual amino acids as tissue protein by the fetal lamb with uptake of these amino acids from the placenta into the fetal circulation. Neutral amino acids

enter the fetal circulation at much higher levels than are needed for tissue protein synthesis, whereas supplies of the basic amino acids lysine and histidine approximate their rates of accretion in fetal tissue protein. The behavior of some individual amino acids differs from these patterns. First, only neutral and basic amino acids are taken up, entry of glutamic and aspartic acids across the placenta being minimal (10, 45, 121, 161, 169). In contrast, glutamate can enter the placenta from the fetal side and can als
(14). In the case of the pregnant sheep (107) and the human (78), this results in a net uptake of glutamate by placenta, whereas in the guinea pig (14) a net outflow of glutamate from placenta returns to the fetal circulation.

Although very little glutamate taken up by the fetal aspect of the placenta is directly amidated to glutamine (14), glutamine is extensively taken up from maternal blood by the gravid sheep uterus (123) and cow uterus (57). In the nonpregnant mammal, glutamine and alanine represent inter-organ carriers for amino-nitrogen and carbon (127). Much of the glutamine and alanine entering the peripheral circulation is released by muscle. Alanine is taken up by the liver for gluconeogenesis and urea formation, whereas about half the glutamine released from muscle undergoes transamination to alanine in the intestinal mucosa, the remainder passing directly to the liver. The later stages of pregnancy thus provide a significant new sink for utilization of glutamine. Uptake of alanine by the pregnant uterus may account for the reduced plasma levels of this amino acid in fasting pregnant women as compared to fasting nonpregnant women (55).

Taurine is also actively transported into the fetal plasma of the monkey (168), an observation that is significant in view of the suggested need of the neonate for taurine (173). Some studies have been made on the uptake of amino acids across the placenta when the maternal plasma levels are excessively high. Since phenylketonuric mothers with high plasma levels of phenylalanine can give birth to retarded children, placental permeability to raised phenylalanine levels has been studied in the pregnant rat (111). This confirms that the fetus is vulnerable to high levels of phenylalanine in maternal blood, and also to maternal plasma levels of tryptophan (189). Finally, the human and the sheep placentas both show dipeptidase activity (33).

Lipids

Placental transfer of fatty acids from mother to fetus appears to differ in various species. The maternal diet has to be the source of the large amounts of essential fatty acids in the fetal lipids of guinea pigs (139) and rabbits (48), while their absence from sheep fetal adipose tissue (50) confirms data (104) that labeled fatty acids do not cross the sheep placenta. Conceivably, the intact uterine mucosa and wall of the syndesmochorial placenta of the sheep may not allow direct access of albumin-bound free fatty acids from the maternal blood to the

placental villi. Even for the hemochorial human placenta, uptake of fatty acids is affected by the albumin content of the maternal plasma (37). Free fatty acids cross the human placenta unselectively (15, 49) and essential fatty acids of maternal origin are found in the fetal tissues (198).

Transport of fatty acids across the term placenta of the rat has been examined in some detail (85, 86). The rat placenta has little capacity to synthesize fatty acids from acetate (85), but takes up considerable amounts of free fatty acids from the maternal plasma. Some of this is transported to the fetus (86), while the remainder is retained in the placenta mainly as fatty acids bound to intracellular protein, with some being esterified to form placental phospholipids and triglycerides. Most of the protein-bound fatty acids are available for transfer to the fetal circulation, where they bind to fetal albumin for transport to the tissues. Studies of the fate of ^{14}C-labeled *cis*-fatty acids (oleic and linoleic acids) and the corresponding *trans* acids (elaidic and linoelaidic acids) injected into rat maternal plasma showed that both types entered the placenta (125).

The cholesterol used by the placenta for steroid hormone synthesis comes from the maternal plasma (79). The trophoblast of human placenta carries high-affinity receptors for the cholesterol-rich low-density lipoproteins in the maternal plasma (202). The cholesterol enters by endocytosis and is stored as cholesteryl esters at a rate regulated by the level of progesterone synthesized from free cholesterol, thus coupling placental steroid synthesis with an adequate supply of free cholesterol. Administration of isotopically labeled cholesterol to rabbits or subhuman primates (145) and to pregnant women (109) shows that the fetus receives some cholesterol from maternal sources. The developing brain has a considerable requirement for cholesterol and has been shown in the rat to synthesize this sterol continuously throughout pregnancy (146). It is thus uncertain whether the acquisition of maternal cholesterol serves any important function for the fetus other than providing substrate for steroid hormone biosynthesis in the placenta. Finally, free choline is present in high concentration in the placenta and is taken up from maternal plasma, where it is much lower in concentration (191), by a sodium-independent facilitated diffusion mechanism (M. E. Fant, unpublished data).

Vitamins

An early review by Hagerman & Villee (73) found that all the water-soluble vitamins traverse the placenta. The presence of ascorbic acid in the placenta in highest concentration in the chorionic villi has been known for many years (74). The same authors observed a fall in ascorbic acid concentration as the placenta matures. Both ascorbic acid and dehydroascorbic acid are taken up from maternal blood by the placenta at similar rates, but the product transferred to the fetus is only ascorbic acid (172). At plasma concentrations within the

normal range, ascorbic acid is transported against a concentration-gradient by a saturable, energy-requiring active transport system (172).

Among the B-vitamins, total riboflavin is higher in concentration in the fetal tissues than in the maternal blood, whereas fetal FAD levels are lower (116). Since the placenta has the capacity to degrade FAD and FMN to free riboflavin, it probably converts incoming flavin nucleotides to free riboflavin before entry into the fetal circulation. Under conditions of marginal vitamin B_6 intake, the human placenta appears to maintain normal B_6 levels although the concentration in the fetal blood falls (6). Surprisingly, administration of vitamin B_6 to women with low maternal blood levels of the vitamin raised the placental concentration but failed to elevate fetal levels. Receptors for folic acid have been reported in human villi (3). The placenta exhibits dihydrofolate reductase activity (89), which may imply that it can produce methyltetrahydrofolate for the fetus. Pregnant women with low blood folate levels also exhibit depressed placental and fetal plasma folate concentrations, which respond to oral folate administration (6). Finally, vitamin B_{12} is taken up by the placenta through binding to a specific glycoprotein receptor (133). In maternal serum, vitamin B_{12} is transported bound to transcobalamins I and II. The latter transport protein accepts vitamin B_{12} absorbed from the gut and transfers it to the peripheral tissues; similar receptors on the placenta can also bind transcobalamin II and accept vitamin B_{12}. In addition, the placenta influences vitamin B_{12} metabolism indirectly through an increase in secretion of intrinsic factor by the stomach during pregnancy, an effect caused by placental lactogen (155).

In the case of vitamin A, only retinol bound to its specific carrier protein in maternal blood is taken up by the rat placenta (176). Although the rat fetus begins to make retinol-binding protein around day 16 of pregnancy (duration 21 days), the process of placental uptake of vitamin A begins earlier at mid-gestation and appears *not* to depend on placental receptors for retinol-binding protein found in other vitamin A–requiring tissues. Instead, the retinol-binding protein appears to enter the placenta where it acts as a transport mechanism into the fetal circulation. The rat fetus is partly protected against insufficient maternal intake, severe vitamin A depletion of the dam causing only a modest effect on vitamin A levels in the pups (177). During pregnancy, the maternal plasma vitamin E levels rise to four times the nonpregnant level, but fetal plasma does not show this elevated concentration (120, 186). Uptake of vitamin K and its transport to the fetus can be inferred from the observation (42) that vitamin K administration to pregnant women taking anticonvulsive drugs prevents the low fetal plasma prothrombin levels and hemorrhages associated with use of such drugs. Finally, in human placenta, Friedmann et al (59) describe a vitamin K–dependent microsomal system that can carboxylate glutamic acid residues in proteins.

Vitamin D and Calcium Transport

The total maternal plasma levels of vitamin D and its hydroxylated metabolites remain unchanged during pregnancy (17). However, because the vitamin D binding protein (DBP) in maternal plasma increases during pregnancy, free vitamin D concentration decreases (71). In the rat, vitamin D_3 and 25-hydroxy-vitamin D_3 are transported across the placenta (72, 135); in the case of the human, a correlation between vitamin D levels in maternal and fetal blood suggests similar transport (170). However, because fetal DBP is lower than maternal DBP, more free vitamin D circulates in fetal plasma (71).

An important observation is that, during pregnancy, the level of the active metabolite 1,25-dihydroxy-vitamin D increases in the maternal plasma of the rat (7) and of the human (170). Nephrectomy of the pregnant rat causes only a small reduction in plasma levels of 1,25-dihydroxy-D, whereas this metabolite is completely suppressed in nephrectomized nonpregnant rats (66). The source of the persisting 1,25-metabolite in nephrectomized pregnant rats is not the fetal kidney (66). Instead, 1-hydroxylation occurs in both rat (178) and human (190) placenta, where it may play a role in inducing a calcium transport protein. Recently, it has been shown that 25-hydroxy vitamin D_3 can also be hydroxylated by the rat yolk sac endodermal cells to give the 1,25-dihydroxy metabolite (36) and that the same tissue contains a vitamin D-dependent calcium-binding protein (61). This means that areas of the conceptus wrappings other than the chorioallantoic placenta *may* make a significant contribution to fetal nutrition.

For both man and the rat, levels of calcium in fetal plasma are higher than in maternal plasma (7, 118, 144). Studies on calcium transport across the placenta show it to be bidirectional in the rat, rabbit, and monkey, but in the sheep it operates only from mother to fetus (18). Uptake of calcium is intrinsic to the placenta, since it continues after the fetus is removed (182). Vesicles prepared from the microvilli of human placenta have been shown to take up calcium ions actively (193) by a mechanism involving Ca^{2+}–ATPase (163). A role of vitamin D in calcium transport is suggested by the presence of receptors for the vitamin in rat (31) and human (143) placental cytosol, and by the occurrence in mouse placenta of a calcium-binding protein (CaBP) that increases six-fold in concentration in the last trimester (21) and is similar to the vitamin D–inducible CaBP of the intestinal mucosa (118). As is the case with the intestinal CaBP, parathyroidectomy reduces the abundance of this protein in rat placenta (61) while administered 1,25-dihydroxy-D restores the amount of CaBP. However, although intestinal and placental CaBPs both become less abundant in animals fed high levels of calcium in the diet, their responses to other manipulations of the calcium and vitamin D status of the mother are not always similar (20).

Other Major Minerals

The placenta contains an active transport mechanism for magnesium (40), so that fetal plasma maintains higher magnesium concentrations than maternal plasma, whereas the concentration of magnesium in the rat placenta decreases (69). When the pregnant rat is fed a magnesium-deficient diet, the maternal tissues and the placenta show little reduction in magnesium content, whereas maternal and fetal plasma levels undergo considerable reductions (40). In magnesium deficiency, the calcium contents of the placenta and of the fetal plasma rise considerably, indicating competition between magnesium and calcium for placental transport.

Phosphate ions are also actively transported across the human placenta (46). In the course of pregnancy, maternal serum phosphate levels increase, while fetal serum levels fall (144, 196), a phenomenon attributed to rapid removal for bone formation in the third trimester (87).

In the pregnant rat, maternal plasma concentrations of potassium remain constant throughout pregnancy, while placental and fetal tissue concentrations decrease slightly (69). When the pregnant rat is depleted of potassium, maternal plasma potassium can be severely reduced (hypokalemia) without a reduction in placental or fetal plasma levels (39). In contrast to this protection of the fetus against potassium deficiency, induction of high potassium levels in the blood of the pregnant rat (hyperkalemia) causes high potassium concentrations in fetal plasma, indicating free uptake of excess potassium by the placenta.

In contrast to the preceding elements, there appears to be no active transport mechanism in the placenta for sodium and chloride ions (38). Consequently, maternal hyponatremia results in a proportional reduction in fetal plasma sodium levels (39). As gestation progresses in the rat, there is a reduction in sodium concentration in the placenta and fetal tissues (116).

Iron

Like other minerals, iron deposition in the fetus accelerates sharply towards term (197), a finding confirmed by the increasing avidity with which the developing placenta of the rabbit takes up ^{59}Fe-labeled salts (16). Since the levels of iron bound to transferrin are higher in fetal blood than in maternal blood, transport by the rat placenta thus occurs against a concentration gradient (23). The determinant role of the placenta in iron transfer to the fetus is confirmed by the demonstration that removal of rat fetuses does not reduce iron uptake by the placenta (117). Analogously, the increased absorption of iron by the intestine of the pregnant rat still occurs following fetectomy (9). The uptake of iron by hemochorial placentas (rat, rabbit) involves its transfer from transferrin in maternal blood to receptors on the placental surface, followed by release of the iron into the placental cells, the apotransferrin being returned to the

maternal blood for reutilization (122). This recycling is confirmed by the absence of rat maternal transferrin in rat fetal blood (8). Within the placental villi, the iron binds to transferrin in the fetal circulation. Transferrin receptors that cross-react with antibody to reticulocyte transferrin receptors have been identified in human placenta (51, 162, 187). Finally, the iron-storage protein ferritin has been purified from human placenta (19). Although Brown (19) suggests that placental ferritin is an obligatory acceptor of the incoming iron, ferritin functions in other tissues as a store for *excess* iron (128).

Iron transport from mother to fetus presents some interesting variations in the pig, whose placenta is of the epitheliochorial type in which maternal uterine epithelium is not invaded, and there is thus no opportunity for maternal transferrin to bind to the placental villi. Instead, the uterine mucosa of the pregnant pig secretes an iron-carrying protein, uteroferrin (22, 29), which is smaller than transferrin and accepts only one atom of iron. During pregnancy, uteroferrin is induced in the uterine mucosa by progesterone and is secreted into the space between mucosa and placental villi. It either crosses the placenta directly and enters the allantoic sac surrounding the fetus and amnion, or is taken up by fetal blood vessels in the placenta, which direct the uteroferrin to the fetal liver, excess passing to the kidney for excretion into the allantoic sac. Within the allantoic sac, the iron of uteroferrin is donated to transferrin, which carries it into the fetal circulation while the apouteroferrin is removed by proteolysis. At mid-pregnancy about 1 g of uteroferrin is secreted daily by the pig uterus, and the allantoic sacs of the ten or so fetuses together contain about 1.3 g of uteroferrin carrying 2 mg of iron. Thus uteroferrin is an intermediate in iron transfer from mother to fetus, while the accumulation in the allantois may represent a reserve store. The uterus of the horse also secretes uteroferrin (210).

Other Trace Elements

The fetoplacental unit of the mouse can take up administered zinc rapidly from maternal blood, the major part being retained in the placenta (13). The zinc-chelating protein metallothionein is present in fetal liver and in placenta, where it can be induced by giving additional zinc to pregnant rats (26). The role of placental metallothionein in the zinc nutriture of the fetus is unknown. Dietary zinc diminishes lead absorption from the intestine and in this way protects the fetus against intoxication with lead, which passes freely across the placenta (44). Cadmium, another toxic metal in the environment, causes destruction of the mouse placenta, an effect that can be prevented by prior oral administration of zinc (2) or selenium (138), probably by diminishing cadmium absorption from the intestine. Finally, there is some preliminary evidence (147) that various forms of chromium are absorbed across the rat placenta, the extent of absorption increasing with the stage of pregnancy.

THE FETOPLACENTAL UNIT AND MATERNAL METABOLISM

Hormone Secretion by the Placenta

The human placenta synthesizes two types of hormone, peptide and steroid (27). In the case of man and other primates, early in pregnancy the placenta secretes a peptide hormone, chorionic gonadotropin, into the maternal circulation. This represses pituitary secretion of luteinizing hormone, the regulator of corpus luteum activity in the ovary, while at the same time it directly stimulates the corpus luteum to make progesterone. From the 7th week of human pregnancy, chorionic gonadotropin in conjunction with a second peptide hormone, placental lactogen, promotes increasing placental production of progesterone from maternal cholesterol. Part of this placental progesterone passes into the maternal circulation to supplement progesterone made in the corpus luteum, the remainder being exported to the fetus, which uses this steroid to form androstanedione and dehydroepiandrosterone, products that are then returned to the placenta to undergo chemical modification to estradiol and estriol. Thus early human pregnancy is marked by high blood levels of chorionic gonadotropin, along with a sharp rise in progesterone output, whereas the maternal blood in later pregnancy shows much lower levels of chorionic gonadotropin but increasing levels of estrogens and progesterone.

Although placentas of nonprimate mammals appear not to synthesize chorionic gonadotropin, mammalian species in general secrete a placental lactogenic hormone into the maternal circulation during the second half of pregnancy (93). This hormone serves three functions: First, in conjunction with chorionic gonadotropin, it stimulates the corpus luteum to secrete progesterone in later pregnancy; second, it promotes growth of the mammary gland in preparation for lactation; finally, it probably participates in making glucose and amino acids available from the maternal tissues via the placenta to the growing fetus (27). The early secretion of chorionic gonadotropin and the later secretion of placental lactogen are programmed by changes in the placental abundance of messenger RNA for each hormone as pregnancy progresses (28).

Other peptide hormones have been identified or claimed as products of placental synthesis (27, 126). Like chorionic gonadotropin and placental lactogen, they are analogs of the corresponding pituitary or hypothalamic hormones. Earlier evidence for ACTH secretion has been confirmed by isolating a large precursor containing the sequence of this hormone from placenta (98); placental ACTH may explain much of the rise in plasma cortisol levels in later pregnancy. The placenta also secretes prolactin (65), but the presence of a chorionic follicle-stimulating hormone, a thyroid-stimulating hormone, and two hypothalamic releasing factors, remains controversial (27). For the purposes of this review, we shall explore the actions on maternal metabolism of the

placental steroid hormones, chorionic gonadotropin, placental lactogen, and ACTH, and relate these changes to availability of nutrients to the fetus during pregnancy.

Effects of Placental Hormones on Maternal Metabolism

Maternal metabolism undergoes adaptive changes throughout pregnancy to ensure the nutrient supply to the fetus at all stages of its growth (for review see 92, 95). These changes are mediated by alterations in maternal hormonal balance, in which insulin probably plays a central role. Pregnancy causes growth of the rat pancreas (32) and increases secretion of insulin in the rat (67) and human (99). Despite some conflicting evidence (95), these changes appear to occur in response to the increased estrogen and progesterone concentrations in maternal blood, since they can be simulated by administering these hormones to nonpregnant rats (32, 41), and both hormones augment the insulin response to glucose administration (4, 5, 32). Human placental lactogen also stimulates insulin formation by the rat (119) and the human (91), increases the response of insulin to administered glucose (12), but perversely antagonizes the effect of progesterone on insulin release by monkeys fed glucose (11). Reports on glucagon secretion at different stages of pregnancy are contradictory, but the insulin/glucagon ratio generally increases (95).

In the postabsorptive state, pregnant women have decreased plasma levels of glucose (95), probably owing to a combination of factors: increased placental uptake; decreased hepatic gluconeogenesis due to diversion to placenta of precursor alanine, the plasma concentration of which falls (55); finally, elevated basal insulin output (56), which may explain the increased liver glycogen synthesis and decreased glucagon-dependent glycogenolysis observed in the fasting pregnant rat (179, 188). In the fed state, there is normal tolerance for carbohydrate in early pregnancy (110), whereas in the second half of gestation the woman becomes progressively less tolerant of glucose administered orally or intravenously (25, 204), and sensitivity to insulin is blunted (58a). As noted earlier, the second half of pregnancy is also marked by increased plasma levels of cortisol, estrogens, progesterone, and placental lactogen. The role of each hormone is unclear. In nonpregnant rats, elevated cortisol levels impair glucose tolerance by antagonizing insulin action (141). Although progesterone administration leads to increased insulin release, it causes a decrease in carbohydrate tolerance (174) and may thus be a factor in insulin-resistance in pregnancy. Although human placental lactogen stimulates insulin output by the pancreas of the nonpregnant rat (160), and increases glycogen deposition in muscle (154), it slightly diminishes the tolerance of nonpregnant humans for glucose (12).

Increased conversion of glucose to triglyceride in adipose tissue is characteristic of pregnancy (96), and the free fatty acid content of blood increases up to

the third trimester and then declines (95). Fat deposition is regulated by all the major hormonal changes occurring in pregnancy. The increased insulin levels both stimulate lipogenesis and reduce lipolysis. Increased conversion of glucose to fat also follows administration to nonpregnant animals of estrogens (64), progesterone (81), and human placental lactogen (60, 103). In concert, these hormonal changes make accumulation of body fat an inevitable feature during much of the course of pregnancy. In early pregnancy, synthesis exceeds breakdown, whereas in late pregnancy lipolysis predominates even in both fed (92) and fasted (96) states, the released fatty acids and glycerol providing the mother with an alternative fuel to glucose and amino acids, which are important as fetal nutrients. Placental lactogen increases lipolysis in rats (181) and in humans (200). The insulin resistance of later pregnancy probably also contributes to lipolysis.

The impact of pregnancy on maternal protein and amino acid metabolism is still incompletely understood. During late pregnancy, plasma amino acid levels are low in the postabsorptive state and show smaller increases after mixed protein-carbohydrate meals (47), the latter owing to increased tissue deposition of amino acids from the higher insulin level in pregnancy (95). Naismith (131) has proposed a biphasic pattern in which protein metabolism is anabolic for the first two thirds of pregnancy and catabolic for the remainder of gestation. During the first phase, the rat shows a positive nitrogen balance and protein accumulates, probably in muscle; this store is used during the second (catabolic) phase to provide amino acids for the fetus. Although his experiments on rats show an increase in carcass protein on day 12 of pregnancy followed by a loss at the time of delivery (130), Zartarian et al (209) did not observe this biphasic pattern when they measured three hind limb muscles of rats at day 12 and day 21 of pregnancy. At day 12, these muscles contained the same amount of protein as did the muscles of nonpregnant females, whereas at day 21 they were significantly depleted, especially for a group fed a diet low in protein. This confirms the thesis of Naismith that increased fetal demands for amino acids during the last part of pregnancy can be provided by muscle losses. In our view, the loss of muscle protein in late pregnancy is likely to be due to progressively increasing insulin resistance. According to Naismith (131), the raised progesterone level in the maternal blood may depress catabolism of amino acids by the liver, thus diverting the supply of amino acids from muscle to the fetus instead of catabolism.

In summary, the maternal body undergoes changes during pregnancy, which we must assume optimize the availability of nutrients to the fetus. In early pregnancy, maternal fat deposition from glucose is favored by the elevated plasma insulin, whereas in late pregnancy resistance to insulin and the action of placental lactogen encourage lipolysis so that the stored fat is made available for maternal energy and, in some species, for fetal energy. A similar accumula-

tion of muscle protein in early pregnancy followed by utilization of the store in late pregnancy has been suggested as a mechanism for providing increased amounts of amino acids during the rapid fetal growth period just before birth. This latter phase may be another expression of insulin resistance in which the stimulant action of insulin on muscle protein synthesis is diminished. Opposition to the action of insulin may thus be the central mechanism in making fatty acids and amino acids available from maternal tissues in the second half of pregnancy.

MATERNAL NUTRITION AND THE PLACENTA

Maternal Nutrition and Placental Structure

The effects of malnutrition on placental structure and function have been frequently reported in both human populations and animal models. The studies on malnourished women are frequently confounded by multiple nutrient deficiencies, poor hygiene and depressed socioeconomic conditions. Placentas delivered by women in the lower socioeconomic strata of Third World countries often weigh less than those in developed countries (41, 101, 105, 106, 129, 208). Morphometric measurements on placentas of Guatemalan women showed that they weighed 14% less than placentas from Boston women (101). This masked larger deficits in trophoblastic mass (25%) and in the surface areas of the villi (20%) and of the fetal capillaries of the villi (31%), thus prejudicing nutrient absorption. Similarly, among women in India known to be on inadequate food intakes, placental volume and surface area were decreased (129). In the Dutch famine of World War II, those women who conceived prior to the famine and delivered their children during it had smaller placentas than did women who became pregnant during the famine and gave birth after it was over (171), implying that placental development is more sensitive to caloric malnutrition during the second half of pregnancy. Pregnant women with iron-deficiency anemia were found in one study in India (165) to have smaller placentas with fewer cotyledons, whereas in another such study (1) also in India, the placentas of anemic women were heavier than normal. In neither study were other nutritional deficiencies excluded.

Animal studies provide information about defined nutrient deficiencies. Feeding of a diet low in protein to pregnant rats causes a decrease in placental weight and in total protein and RNA content (203) provided that the deficiency of protein is severe enough (209). In protein-depleted pregnant rats, Hastings-Roberts & Zeman (76) also observed smaller placentas containing less RNA and DNA, whereas van Marthens & Shimomaye (184) found no reduction in total DNA content although weight and protein content were reduced, especially when the protein-deficient diet was fed during the second half of pregnancy. Deprivation of arginine in the diet of the pregnant rat also results in reduced

placental weight, protein and RNA content, but not DNA content (138a). Pregnant guinea pigs showed a reduction in placental weight on either an energy-deficient or a protein-deficient diet, the latter causing a larger deficit (208). Vitamin A deficiency in the rat causes morphological changes attributed to lack of cell differentiation (134). Substitution of 20% alcohol for the drinking water of the pregnant rat did not affect placental weight but reduced its protein and RNA content (203). Thus a variety of nutritional factors can impair the capacity of the placenta to achieve full functional capacity.

The cellular events involved in these deficits will now be examined. The placenta is an organ in a state of growth and development for most of its existence and consequently follows the sequence, common to many tissues, of hyperplasia (increase in cell number) followed by hyperplasia with some hypertrophy (increase in cell size) and finally only hypertrophy (126). Thus the placenta of the rat, which has a 21-day period of gestation, undergoes its most rapid growth during the third week, but DNA content does not increase beyond day 17 of pregnancy. In the human, the DNA content of the placenta ceases to increase later, about the 36th week. Consequently, the cell population of the placenta is vulnerable to stunted growth if malnutrition occurs during the long period of hyperplasia in both species. Indeed the placentas of malnourished women show a reduced DNA content (157) with little or no change in cell size (protein/DNA ratio) (102). Studies on rats receiving protein-deficient diets are contradictory, some investigators (76) finding that DNA content is reduced, others (184) that it may even exceed that of controls on an adequate diet. Though variation was large, the placentas of poor women in Guatemala tended to show a reduction in total RNA per placenta, and had a significant reduction in polyribosomes on which proteins are synthesized (102). In the case of pregnant rats on a protein-deficient diet or receiving ethanol, total placental RNA and ribosomal RNA were extensively reduced, and the actively synthesizing polysomal fraction was lower for rats on the protein-free diet (203). These findings are compatible with reduced capacity for protein synthesis by the placentas of malnourished humans or animals.

Maternal Nutrition and Placental Hormones

It is apparent that a diminished capacity for protein synthesis by the placentas of protein-deficient rats could affect output of placental peptide hormones. Indeed, severe protein deficiency in the second half of pregnancy reduced dramatically the placental lactogen content of the rat placenta and of the maternal serum (203). These changes paralleled the reduction in ribosome content of the placenta, thus confirming the relationship to protein synthesis potential. A similar picture was observed in ethanol-fed rats. Recently we (S. J. Pilistine, H. N. Munro, A. C. Moses, unpublished data) have extended these findings by showing that receptors for placental lactogen on the liver of the

pregnant rat are also reduced by protein deficiency, and that the serum levels of somatomedin and its carrier proteins made in the liver are depressed, effects that are reversed by administering placental lactogen to the protein-deficient rats. Since somatomedin receptors on the placenta increase with advancing pregnancy (43), a feedback loop for lactogen secretion may exist, analogous to the feedback loop between somatomedin and pituitary growth hormone.

Human studies of the effect of nutritional status on placental lactogen are fragmentary. Indian women with anemia had higher serum levels of the lactogen, but also larger placentas (1). Although the serum placental lactogen levels of pregnant rats are depressed by an overnight fast (S. J. Pilistine, H. N. Munro, unpublished data), this does not occur overnight in pregnant women (159). Glucose given orally (140) or slowly by vein (150) also has no effect on the placental lactogen levels of human maternal blood. On the other hand, a 3-day (183) or 4-day (94) fast raises the placental lactogen levels of pregnant women awaiting abortion, which is probably evidence of a physiological response rather than of malnutrition. However, the placental lactogen levels in the serum of monkeys remain normal on a diet low in protein (136).

Placental steroid hormone output is also affected by malnutrition. A group of Indian women of low socioeconomic status showed a reduced urinary excretion of estrogens (88) and progesterone (157). The pregnant rat on a protein-deficient diet shows lowered plasma progesterone levels by the end of the first trimester, whereas, in contrast to the human, plasma estrogen levels are unaffected (97). Finally, although chorionic gonadotropin regulates steroid hormone production by the placenta, there does not appear to be published evidence of the effects of malnutrition on its secretion, which could be the primary reason for the low steroid output by the placentas of malnourished women.

Maternal Nutrition and Nutrient Availability to the Placenta

The delivery of nutrients to the placenta can vary with blood supply. Rosso (157) has studied uptake of the model amino acid aminoisobutyric acid and glucose by fetuses of control rats and protein-restricted rats following injection of ^{14}C-aminoisobutyric acid or ^{3}H-glucose. In both cases, there was reduced transfer to the fetus; on the other hand, in vitro uptake of aminoisobutyric acid by placental slices failed to show a difference due to previous diet. Rosso finds that malnourished rats fail to undergo the expansion in cardiac output and placental blood flow found in normally nourished mothers, which may explain the in vivo difference in nutrient uptake. Young (205) confirms the influence of blood flow on uptake of glucose and amino acids across the guinea-pig placenta, the effect being maximal for branched-chain and basic amino acids.

The significance of blood flow is confirmed by other evidence. Winick (201) has shown that ligation of one of the two arteries of the rat uterus reduces blood

supply differentially to fetuses close to as compared with remote from the ligature, as evidenced by the greatest reduction in fetoplacental size near to the ligature. It also reduces the normal increase in placental DNA during the phase of placental hyperplasia, thus mimicking the placental response to malnutrition. The RNA content of the placentas affected by ligation apparently was also reduced, related to an increase in placental ribonuclease activity (185). Several other investigators emphasize the importance of blood flow in both placental development and nutrient supply. Ferrell & Ford (57) have demonstrated a parallelism between maternal blood flow and uptake of glucose and amino acids by the gravid bovine uterus. In support of this interpretation, placental blood flow diminished and uterine uptake of oxygen, glucose, essential amino acids, and glutamine were reduced when pregnant sheep were fasted for several days (124). An interesting link of a specific nutrient to placental blood flow has been reported for zinc. The increased perinatal mortality of zinc-deficient rat pups has been attributed to increased placental formation of prostaglandins which may contribute to the reduced uteroplacental blood flow demonstrated in the deficient rats (35).

Other Maternal Factors Affecting Nutrient Supply

Placental function and capacity to transport nutrients can be affected by maternal constitutional and environmental factors. Exercise diminished the size and carbon monoxide diffusing capacity of the guinea-pig placenta (131A). Exposure of wool-clipped pregnant sheep to a cold environment for two hours raised the levels of glucose, glycerol, and free fatty acids in maternal blood, whereas in fetal blood only glucose rose (180). This is compatible with the characteristics of placental transport of glucose (30, 90) and the lack of fatty acid transfer across the sheep placenta (104). In the same study of cold stress in sheep (180), corticosteroid levels were elevated in maternal plasma but not fetal plasma. Fant and colleagues (54, 75) have shown that human placental membrane vesicles take up glucocorticoids by a saturable process, followed by inactivation through conversion of C-11 hydroxyl groups to the inactive ketones by the 11-β-ol-dehydrogenase of placenta (108). The raised plasma corticosteroid levels in pregnancy may, nevertheless, have some physiological action on the placenta. Women with poor weight gain in pregnancy release more placental alkaline phosphatase into their bloodstream, and this has been attributed to increased maternal corticosteroid action on the placenta (137).

CONCLUSIONS

Study of placental function reflects the major interest in the nutritional needs of the fetus. The present review deals first with transport of nutrients where detail regarding mechanisms involved is continuously undergoing expansion. The

changes in maternal metabolism during pregnancy are complex, and it is still not certain how these ensure an optimal nutrient supply for the fetus. In addition, maternal malnutrition has effects on placental function that are only beginning to be understood, and that even demonstrate new hypotheses of action, notably through reduction in placental blood supply. Finally, it is important to recognize that the considerable variations in mammalian placentation make it hazardous to transfer conclusions from subhuman species to man. In particular, direct access of blood to the placental surface of hemochorial placentas must provide them with some different absorption opportunities from those of the epitheliochorial and syndesmochorial placentas in which the blood supply is separated from the fetal placenta by layers of cells. Examples of these differences are illustrated by iron uptake across the epitheliochorial placentas of the pig and horse, by the lack of fatty acid uptake by the syndesmochorial sheep placenta, and also by the impeded uptake of sodium and chloride across the ovine placenta (38). In addition, the synthesis of a vitamin D dependent calcium binding protein by the rat yolk sac indicates that nonplacental tissues surrounding the embryo may also serve to pass nutrients to the fetus. Finally, this review does not deal systematically with the continuing adaptation of the placenta to the changing needs of the growing fetus. For example, Widdowson (197) calculated that the major deposition of iron, zinc and copper in the fetus occurs in the last month of pregnancy, suggesting accelerated placental transport at this time. Future studies of placental function should aim to quantitate such adaptation of transport.

Literature Cited

1. Agboola, A. 1978. The effect of low haematocrit on serum human placental lactogen values. *Brit. J. Obstet. Gynecol.* 85:758–60
2. Ahokas, R. A., Dilts, P. V., LaHaye, E. B. 1980. Cadmium-induced fetal growth retardation: protective effect of excess dietary zinc. *Am. J. Obstet. Gynecol.* 136:216–21
3. Antony, A. C., Utley, C., Van Horne, K. C., Kolhouse, J. F. 1981. Isolation and characterization of a folate receptor from human placenta. *J. Biol. Chem.* 256: 9684–92
4. Ashby, J. P., Shirling, D., Baird, J. D. 1978. Effect of progesterone on insulin secretion in the rat. *J. Endocrinol.* 76: 479–86
5. Bailey, C. J., Matty, A. J. 1972. Glucose tolerance and plasma insulin of the rat in relation to the oestrous cycle and sex hormones. *Horm. Metab. Res.* 4:266–70
6. Baker, H., Frank, O., DeAngelis, B., Feingold, S., Kaminetzky, H. A. 1981. Role of placenta in maternal-fetal vitamin transfer in humans. *Am. J. Obstet. Gynecol.* 141:792–96
7. Baksi, S. N., Kenny, A. D. 1978. Does estradiol stimulate *in vivo* production of 1,25-dihydroxyvitamin D_3 in the rat? *Life Sci.* 22:787–92
8. Bardos, P., Luthier, B., Avenet, J. M., DeRusse, J., Muh, J. P., Soutoul, J. H., Weill, J. D. 1976. Variations des concentrations de certaines glycoproteines au niveau du sang maternel, foetal, et du liquide amniotique lors de la grossesse. *Clin. Chem. Acta* 66:353–63
9. Batey, R. G., Gallagher, N. D. 1977. Role of the placenta in intestinal absorption of iron in pregnant rats. *Gastroenterology* 72:255–59
10. Battaglia, F. C., Meschia, G. 1981. Foetal and placental metabolisms; their interrelationships and impact upon maternal metabolism. *Proc. Nutr. Soc.* 40:99–113
11. Beck, P. 1970. Reversal of progesterone-

enhanced insulin production by human chorionic somatomammotropin. *Endocrinology* 87:311–15
12. Beck, P., Daughaday, W. H. 1967. Human placental lactogen: studies of its acute metabolic effects and disposition in normal man. *J. Clin. Invest.* 46:103–11
13. Bergman, B., Soremark, R. 1968. Autoradiographic studies on the distribution of zinc-65 in mice. *J. Nutr.* 94:6-12
14. Bloxam, D. L., Tyler, C. F., Young, M. 1981. Foetal glutamate as a possible precursor of placental glutamine in the guinea pig. *Biochem. J.* 198:397–401
15. Booth, C., Elphick, M. C., Hendrickse, W., Hull, D. 1981. Investigation of [^{14}C]linoleic acid conversion into [^{14}C]arachidonic acid and placental transfer of linoleic and palmitic acids across the perfused human placenta. *J. Devel. Physiol.* 3:177–89
16. Bothwell, T. H., Pribilla, W. F., Mebust, W., Finch, C. A. 1958. Iron metabolism in the pregnant rabbit: iron transport across the placenta. *Am. J. Physiol.* 193:615–22
17. Boullion, R., Van Assche, F. A., Van Baelen, H., Heynes, W., DeMoor, P. 1981. Influence of the vitamin D-binding protein on the serum concentration of 1,25-dihydroxyvitamin D_3. Significance of the free 1,25-dihydroxyvitamin D_3 concentration. *J. Clin. Invest.* 67:589–96
18. Braithwaite, G. D., Glascock, R. F., Riazuddin, S. H. 1972. Studies on the transfer of calcium across the ovine placenta and incorporation into the foetal skeleton. *Br. J. Nutr.* 27:417–24
19. Brown, P. J., Johnson, P. M., Ogbimi, A. O., Tappin, J. A. 1979. Characterization and localization of human placental ferritin. *Biochem. J.* 182:763–69
20. Bruns, M. E. H., Wallshein, V., Bruns, D. E. 1982. Regulation of calcium-binding protein in mouse placenta and intestine. *Am. J. Physiol.* 242:E47–52
21. Bruns, M. E. H., Vollmer, S., Wallshein, V., Bruns, D. E. 1981. Vitamin D-dependent calcium binding protein: immunochemical studies and synthesis by placental tissue in vitro. *J. Biol. Chem.* 256:4649–53
22. Buhi, W. C., Ducsay, C. A., Bazer, F. W., Roberts, R. M. 1982. Iron transfer between the purple phosphatase uteroferrin and transferrin and its possible role in iron metabolism of the fetal pig. *J. Biol. Chem.* 257:1712–23
23. Burman, D. 1974. Iron Metabolism in Infancy and Childhood. In *Iron in Biochemistry and Medicine,* ed. A. Jacobs, M. Worwood, I:543–62. NY: Academic
24. Burns, B., Gurtner, G. H. 1973. A specific carrier for oxygen and carbon monoxide in the lung and placenta. *Drug Metab. Dis.* 1:347–77
25. Burt, R. L., Leake, N. H., Rhyne, A. L. 1969. Glucose tolerance during pregnancy and the puerperium. A modification with observations on serum immunoreactive insulin. *Obstet. Gynecol.* 33:634–41
26. Charles-Shannon, V. L., Sasser, L. B., Burbank, D. K., Kelman, B. J. 1981. The influence of zinc on the ontogeny of hepatic metallothionein in the fetal rat. *Proc. Soc. Exp. Biol. Med.* 168:56–61
27. Chatterjee, M., Munro, H. N. 1977. Structure and biosynthesis of human placental peptide hormones. *Vitam. Horm.* 35:149–208
28. Chatterjee, M., Baliga, B. S., Munro, H. N. 1976. Synthesis of human placental lactogen and human chorionic gonadotropin by polyribosomes and messenger RNA's from early and full-term placentas. *J. Biol. Chem.* 251:2945–51
29. Chen, T. T., Bazer, F. W., Gebhardt, B., Roberts, R. M. 1975. Uterine secretion in mammals: synthesis and placental transport of a purple acid phosphatase in pigs. *Biol. Reprod.* 13:304–13
30. Chinard, F. P., Danesino, V., Hartmann, W. L., Huggett, A. St. G., Paul, W., Reynolds, S. R. M. 1956. The transmission of hexoses across the placenta in the human and the rhesus monkey. *J. Physiol.* 132:289–303
31. Christakos, S., Norman, A. W. 1980. Specific receptors/binding proteins for 1,25(OH)$_2$-vitamin D_3 in rat and human placenta. *Fed. Proc.* 39:560 (Abstr.)
32. Costrini, N. V., Kalkhoff, R. K. 1971. Relative effects of pregnancy, estradiol, and progesterone on plasma insulin and pancreatic islet insulin secretion. *J. Clin. Invest.* 50:992–99
33. Crandell, S. S., Adcock, E. W., Morriss, F. H. 1981. Hydrolysis of dipeptides by human and ovine placentas. *Pediatr. Res.* 15:357–61
34. Crandell, S. S., Palma, P. A., Morriss, F. H. 1982. Effect of maternal serum insulin on umbilical extraction of glucose and lactate in fed and fasted sheep. *Am. J. Obstet. Gynecol.* 142:219–24
35. Cunnane, S. C., Majid, E., Senior, J., Mills, C. F. 1982. Perinatal mortality in zinc deficient rats is associated with significantly reduced utero-placental blood flow. *Proc. Nutr. Soc.* 41:69A (Abstr.)
36. Danan, J. L., Delorme, A. C., Mathieu, H. 1982. Presence of 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 24-hydroxylase in vitamin D target cells of

rat yolk sac. *J. Biol. Chem.* 257: 10715–21
37. Dancis, J., Jansen, V., Levitz, M. 1976. Transfer across perfused human placenta. IV. Effect of protein-binding on free fatty acids. *Pediatr. Res.* 10:5–10
38. Dancis, J., Kammerman, S., Jansen, V., Schneider, H., Levitz, M. 1981. Transfer of urea, sodium, and chloride across the perfused human placenta. *Am. J. Obstet. Gynecol.* 141:677–81
39. Dancis, J., Springer, D. 1970. Fetal homeostasis in maternal malnutrition: potassium and sodium deficiency in rats. *Pediatr. Res.* 4:345–51
40. Dancis, J., Springer, D., Coughlan, S. A. 1971. Fetal homeostasis in maternal malnutrition. II. Magnesium deprivation. *Pediatr. Res.* 5:131–36
41. Dayton, D. H., Filer, L. J., Canosa, C. 1969. Cellular changes in the placentas of undernourished mothers in Guatemala. *Fed. Proc.* 28:488 (Abstr.)
42. Deblay, M. F., Vert, P., Andre, M., Marchal, F. 1982. Transplacental vitamin K prevents haemorrhagic disease of infant of epileptic mother. *Lancet* 1:1247
43. D'Ercole, A. J., Foushee, D. B., Underwood, L. E. 1976. Somatomedin-C receptor and levels in porcine fetal and human serum. *J. Clin. Endocrinol. Metab.* 43:1069–77
44. Dilts, P. V., Ahokas, R. A. 1979. Effects of dietary lead and zinc on pregnancy. *Am. J. Obstet. Gynecol.* 135:940–46
45. Eaton, B. M., Yudilevich, D. L. 1981. Uptake and asymmetric efflux of amino acids at maternal and fetal sides of placenta. *Am. J. Physiol.* 241:C106–12
46. Economou-Mavrou, C., McCance, R. A. 1958. Calcium, magnesium and phosphorus in foetal tissues. *Biochem. J.* 68:573–80
47. Elliott, J. A. 1975. The effect of pregnancy on the control of lipolysis in fat cells isolated from human adipose tissue. *Eur. J. Clin. Invest.* 5:159–63
48. Elphick, M. C., Edson, J. L., Lawler, J. R., Hull, D. 1978. Source of fetal-stored lipids during maternal starvation in rabbits. *Biol. Neonate* 34:146–49
49. Elphick, M. C., Hull, D., Sanders, R. R. 1976. Concentrations of free fatty acids in maternal and umbilical cord blood during elective caesarean section. *Br. J. Obstet. Gynaecol.* 83:539–44
50. Elphick, M. C., Hull, D., Broughton-Pipkin, F. 1979. The transfer of fatty acids across the sheep placenta. *J. Devel. Physiol.* 1:31–45
51. Ens, C. A., Sussman, H. H. 1981. Physical characterization of the transferrin receptor in human placentae. *J. Biol. Chem.* 256:9820–23
52. Enders, R. H., Judd, R. M., Donohue, T. M., Smith, C. H. 1976. Placental amino acid uptake. III. Transport systems for neutral amino acids. Am. J. Physiol. 230:706–10
53. Faber, J. J. 1972. Regulation of fetal placental blood flow. In *Respiratory Gas Exchange and Blood Flow in the Placenta,* ed. L. D. Longo, H. Bartels, pp. 157–72. Washington, DC: DHEW Publ. No. (NIH)73–361
54. Fant, M. E., Harbison, R. D., Harrison, R. W. 1979. Glucocorticoid uptake into human placental membrane vesicles. *J. Biol. Chem.* 254:6218–21
55. Felig, P. 1975. Amino acid metabolism in man. *Ann. Rev. Biochem.* 44:933–54
56. Felig, P., Lynch, V. 1970. Starvation in human pregnancy: hypoglycemia, hypoinsulinemia and hyperketonemia. *Science* 170:990–92
57. Ferrell, C. L., Ford, S. P. 1980. Blood flow, steroid secretion and nutrient uptake of the gravid bovine uterus. *J. Anim. Sci.* 50:1113–21
58. Ferrell, C. L., Ford, S. P., Prior, R. L., Christenson, R. K. 1983. Blood flow, steroid secretion and nutrient uptake of the gravid bovine uterus and fetus. *J. Anim. Sci.* In press
58a. Freinkel, N. 1980. Banting lecture 1980; of pregnancy and progeny. *Diabetes* 29:1023
59. Friedman, D. A., Hauschka, P. V., Shia, M. A., Wallace, J. K. 1979. Characteristics of the vitamin K-dependent carboxylating system in human placenta. *Biochem. Biophys. Acta* 583:261–65
60. Friesen, H. G. 1965. Purification of a placental factor with immunological and chemical similarity to human growth hormone. *Endocrinology* 76:369–81
61. Garrel, J. M., Delorme, A. C., Marche, P., Nguyen, T., Garabedian, M. 1981. Vitamin D_3 metabolite injections to thyroparathyroidectomized pregnant rats: effects on calcium binding proteins of maternal duodenum and of fetoplacental unit. *Endocrinology* 109:284–89
62. Deleted in proof
63. Gilbert, R. D., Cummings, L. A., Juchau, M. R., Longo, L. D. 1979. Placental diffusing capacity and fetal development in exercising or hypoxic guinea pigs. *J. Appl. Physiol.* 46: 828–34
64. Gilmour, K. E., McKerns, K. W. 1966. Insulin and estrogen regulation of lipid synthesis in adipose tissue. *Biochem. Biophys. Acta* 116:220–28

65. Golander, A., Hurley, T. Barrett, J., Hizi, A., Handwerger, S. 1978. Prolactin synthesis by human chorion-decidual tissue: a possible source of prolactin in the amniotic fluid. *Science* 202: 311–13
66. Gray, T. K., Lester, G. E., Lorenc, R. S. 1979. Evidence for extra-renal 1-alpha-hydroxylation of 25-hydroxyvitamin D_3 in pregnancy. *Science* 204:1311–13
67. Green, I. C., Howell, S. L., Montagne, W., Taylor, K. W. 1973. Regulation of insulin release from isolated islets of Langerhans of the rat in pregnancy. The role of adenosine 3':5'-cyclic monophosphate. *Biochem. J.* 134:481–87
68. Deleted in proof
69. Greizerstein, H. B., Abel. E. L. 1979. Electrolyte composition of fetuses, placentas, and maternal plasma during the last trimester of gestation in the rat. *Biol. Neonate* 36:251–54
70. Guiet-Bara, A. 1980. Human placental oxygen transfer and consumption. Dissociation by cooling or use of respiratory enzyme inhibitors. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 10:83–98
71. Haddad, J. G., Walgate, J. 1976. Radioimmunoassay of the binding protein for vitamin D and its metabolites in human serum; concentration in normal subjects and patients with disorders of mineral homeostasis. *J. Clin. Invest.* 58: 1217–22
72. Haddad, J. G., Boisseau, V., Avioli, L. V. 1971. Placental transfer of vitamin D_3 and 25-hydroxycholecalciferol in the rat. *J. Lab. Clin. Med.* 77:908–15
73. Hagerman, D. D., Villee, C. A. 1960. Transport functions of the placenta. *Physiol. Rev.* 40:313–30
74. Hamil, B. M., Monks, B., Moyer, E. Z., Kaucher, M., Williams, H. H. 1947. Vitamin C in the blood and urine of the newborn and in the cord and maternal blood. *Am. J. Dis. Children* 74:417–33
75. Harrison, R. W., Yeakley, J. M., Fant, M. E. 1980. Glucocorticoid binding to solubilized components of human placental trophoblast membranes. *Life Sci.* 26:2173–77
76. Hastings-Roberts, M. M., Zeman, F. J. 1977. Effects of protein deficiency, pair-feeding or diet supplementation on maternal, fetal and placental growth in rats. *J. Nutr.* 97:973–82
77. Hay, W. W., Sparks, J. W., Quissell, B. J., Battaglia, F. C., Meschia, G. 1981. Simultaneous measurements of umbilical uptake, fetal utilization rate, and fetal turnover rate of glucose. *Am. J. Physiol.* 240:E662–68
78. Hayashi, S., Sanada, K., Sagawa, N., Yamada, N., Kido, K. 1978. Umbilical vein-artery differences of plasma amino acids in the last trimester of human pregnancy. *Biol. Neonate* 34:11–18
79. Hellig, H., Gattereau, D., Lefebvre, Y., Bolte, E. 1970. Steroid production from plasma cholesterol I. Conversion of plasma cholesterol to placental progesterone in humans. *J. Clin. Endocrinol. Metab.* 30:624–31
80. Herbert, J. D., Coulson, R. A., Hernandez, T. 1966. Free amino acids in the caiman and rat. *Comp. Biochem. Physiol.* 17:583–98
81. Hervey, E., Hervey, G. R. 1967. The effects of progesterone on body weight and composition in the rat. *J. Endocrinol.* 37:361–84
82. Hill, E. P., Longo, L. D. 1980. Dynamics of maternal-fetal nutrient transfer. *Fed. Proc.* 39:239–44
83. Hill, P. M. M., Young, M. 1973. Net placental transfer of free amino acids against varying concentrations. *J. Physiol.* 235:409–22
84. Holzman, I. R., Philipps, A. F., Battaglia, F. C. 1979. Glucose metabolism, lactate, and ammonia production by the human placenta in vitro. *Pediatr. Res.* 13:117–20
85. Hummel, L., Zimmermann, T., Schirrmeister, W., Wagner, H. 1976. Synthesis, turnover and compartment analysis of the free fatty acids in the placenta of rats. *Arch. Biol. Med. Germ.* 35: 1311–16
86. Hummel, L., Schirrmeister, W., Zimmermann, T., Wagner, H. 1974. Studies on the lipid metabolism using ^{14}C-1-palmitate in fetal rats. *Biol. Neonate* 24:298-305
87. Hytten, F. E., Leitch, I. 1971. *The Physiology of Human Pregnancy*. Oxford: Blackwell, p. 379. 2nd ed.
88. Iyengar, L. 1968. Urinary estrogen excretion in undernourished pregnant Indian women. *Am. J. Obstet. Gynecol.* 102: 834–38
89. Jarabak, J., Bachur, N. R. 1971. A soluble dihydrofolate reductase from human placenta: purification and properties. *Arch. Biochem. Biophys.* 142:417–25
90. Johnson, L. W., Smith, C. H. 1980. Monosaccharide transport across microvillous membrane of human placenta. *Am. J. Physiol.* 238:C160–68
91. Kalkhoff, R. K., Kim, H. J. 1979. Effects of pregnancy on insulin and glucagon secretion by perifused rat pancreatic islets. *Endocrinology* 102:623–31

92. Kalkhoff, R. K., Kissebah, A. J., Kim, H. J. 1978. Carbohydrate and lipid metabolism during normal pregnancy: relationship to gestational hormone action. *Semin. Perinatol.* 2:291–307
93. Kelly, P. A., Tsushima, T., Shiu, R. P. C., Friesen, H. G. 1975. Lactogenic and growth-hormone like activities in pregnancy determined by radioreceptor assays. *Endocrinology* 99:765–74
94. Kim, Y. J., Felig, P. 1972. Maternal and amniotic fluid substrate levels during calorie deprivation in human pregnancy. *Metabolism* 21:507–12
95. Kitzmiller, J. L. 1980. The endocrine pancrease and maternal metabolism. In *Maternal-Fetal Endocrinology,* ed. D. Tulchinsky, K. L. Ryan, pp. 58–83. Philadelphia: W. B. Saunders
96. Knopp, R. H., Saudek, C. D., Arky, R. A., O'Sullivan, J. B. 1973. Two phases of adipose tissue metabolism in pregnancy: maternal adaptations for fetal growth. *Endocrinology* 92:984–88
97. Köhler, E., Wojnorowicz, F., Borner, K. 1975. Effects of a protein-free diet on amino acids and sex hormones of rats during the early postimplantation stages of pregnancy. *J. Reprod. Fertil.* 42:9–21
98. Krieger, D. 1982. The placenta as a source of brain and pituitary hormones. *Biol. Reprod.* 26:55-73
99. Kühl, C. 1975. Glucose metabolism during and after pregnancy in normal and gestational diabetic women. *Acta Endocrinol.* 79:709–19
100. Laga, E. M., Munro, H. N. 1972. Computer-assisted quantitative videoscanning technique for measuring cross-sectional areas and dimensions of tissue components. *Med. Biol. Engin.* 10:473–82
101. Laga, E. M., Driscoll, S. G., Munro, H. N. 1972. Comparison of placentas from two socioeconomic groups. I. Morphometry. *Pediatrics* 50:24–33
102. Laga, E. M., Driscoll, S. G., Munro, H. N. 1972. Comparison of placentas from two socioeconomic groups. II. Biochemical characteristics. *Pediatrics* 50: 33–39
103. Leake, N. H., Burt, R. L. 1969. Effect of human placental lactogen and pregnancy on glucose uptake in rat adipose tissue. *Am. J. Obstet. Gynecol.* 103:39–43
104. Leat, W. M. F., Harrison, F. A. 1980. Glucose metabolism during and after pregnancy in normal and gestational diabetic women. I. Influence of normal pregnancy on serum glucose and insulin concentration during basal fasting conditions and after a challenge with glucose. *J. Devel. Physiol.* 2:257–74
105. Lechtig, A., Delgado, H., Martorell, M., Yarbrough, C., Klein, R. E. 1979. Maternofetal nutrition. In *Nutrition and Growth,* ed. D. B. Jelliffe, E. F. P. Jelliffe, pp. 79–127. NY: Plenum
106. Lechtig, A. C., Yarbrough. C., Delgado, H., Martorell, M., Klein, R. E., Behar, M. 1975. Effect of moderate malnutrition on the placenta. *Am. J. Obstet. Gynecol.* 123:191–201
107. Lemons, J. A., Adcock, E. W., Jones, M. D., Naughton, M. A., Meschia, G., Battaglia, F. C. 1976. Umbilical uptake of amino acids in the unstressed fetal lamb. *J. Clin. Invest.* 58:1428–34
108. Levitz, M., Jansen, V., Dancis, J. 1978. The transfer and metabolism of corticosteroids in the perfused human placenta. *Am. J. Obstet. Gynecol.* 132:363–64
109. Lin, D. S., Pitkin, R. M., Connor, W. E. 1977. Placental transfer of cholesterol into the human fetus. *J. Obstet. Gynecol.* 128:735–39
110. Lind, T., Billewicz, W. Z., Brown, G. A. 1973. A serial study of changes occurring in the oval glucose tolerance test during pregnancy. *J. Obstet. Gynaecol. Brit. Comm.* 80:1033–39
111. Lines, D. R., Waisman, H. A. 1971. Placental transport of phenylalanine in the rat: maternal and fetal metabolism. *Proc. Soc. Exp. Biol. Med.* 136:790–93
112. Longo, L. D. 1981. The interrelations of maternal-fetal transfer and placental blood flow. *Placenta* (Suppl. 2): 45–64
113. Longo, L. D., Delivoria-Papadopoulos, M., Forster, R. E. 1974. Placental CO_2 transfer after fetal carbonic anhydrase inhibition. *Am. J. Physiol.* 226: 703–10
114. Longo, L. D., Power, G. G. 1973. Long-term regulation of fetal cardiac output. *Gynecol. Invest.* 4:277–87
115. Ludwig, K. S. 1972. The morphological structure of the placenta in relation to its exchange function. See Ref. 53, pp. 13–21
116. Lust, J. E., Hagerman, D. D., Villee, C. A. 1953. The transport of riboflavin by human placenta. *J. Clin. Invest.* 33: 38–40
117. Mansour, M. M., Schubert, A. R., Glasser, S. R. 1972. Mechanism of placental iron transfer in the rat. *Am. J. Physiol.* 222:1628–33
118. Marche, P., Delorme, A., Cuisinier-Gleizes, P. 1978. Intestinal and placental calcium-binding proteins in vitamin D-deprived or supplemented rats. *Life Sci.* 23:2555–62
119. Martin, J. M., Friesen, H. G. 1969. Effect of human placental lactogen on the

isolated islets of Langerhans in vitro. *Endocrinology* 84:619–21
120. Martinez, F. E., Goncalves, A. L., Jorge, S. M., Desai, I. D. 1981. Vitamin E in placental blood and its interrelationship to maternal and newborn levels of vitamin E. *J. Pediatr.* 99:298–300
121. Meschia, G., Battaglia, F. C., Hay, W. W., Sparks, J. W. 1980. Utilization of substrates by the ovine placenta in vivo. *Fed. Proc.* 39:245–49.
122. Morgan, E. H. 1974. Transferrin and transferrin iron. See Ref. 23, pp. 29–71.
123. Morriss, F. H., Adcock, E. W., Paxson, C. L., Greeley, W. J. 1979. Uterine uptake of amino acids throughout gestation in the unstressed ewe. *Am. J. Obstet. Gynecol.* 135:601–8
124. Morriss, F. H., Rosenfeld, C. R., Crandell, S. S., Adcock, E. W. 1980. Effects of fasting on uterine blood flow and substrate uptake in sheep. *J. Nutr.* 110: 2433–43
125. Moore, C. E., Dhopeshwarkar, G. A. 1981. Placental transport of trans fatty acids in the rat. *J. Lipid Res.* 15:1023–28
126. Munro, H. N. 1980. Placental protein and peptide hormone synthesis: impact of maternal nutrition. *Fed. Proc.* 39:255–60
127. Munro, H. N. 1982. Interaction of liver and muscle in the regulation of metabolism in response to nutritional and other factors. In: *The Liver, Biology and Pathobiology,* ed. I. M. Arias et al, pp. 677–91. NY: Raven
128. Munro, H. N., Linder, M. C. 1978. Ferritin: structure, biosynthesis and role in iron metabolism. *Physiol. Rev.* 58: 317–96
129. Murthy, L. S., Agarwal, K. N., Khanna, S. 1976. Placental morphometric and morphologic alterations in maternal undernutrition. *Am. J. Obstet. Gynecol.* 124:641–46
130. Naismith, D. J. 1969. The foetus as a parasite. *Proc. Nutr. Soc.* 28:25–31
131. Naismith, D. J. 1973. Adaptations in the metabolism of protein during pregnancy and their nutritional implications. *Nutr. Rep. Int.* 7:383–90
131a. Nelson, P. S., Gilbert, R. D., Longo, L. D. 1983. Fetal growth and placental diffusing capacity in guinea pigs following long-term maternal exercise. *J. Devel. Physiol.* In press
132. Nelson, D. M., Smith, R. H., Jarrett, L. 1978. Nonuniform distribution and grouping of insulin receptors on the surface of human placental syncytiotrophoblast. *Diabetes* 27:530–38
133. Nexø, E., Hollenberg, M. D. 1980. Characterization of the particulate and soluble acceptor for transcobalamin II from human placenta and rabbit liver. *Biochem. Biophys. Acta* 628:190–200
134. Noback, C. R., Takahashi, Y. I. 1978. Micromorphology of the placenta of rats reared on marginal vitamin-A-deficient diet. *Acta Anat.* 102:195–202
135. Noff, D., Edelstein, S. 1978. Vitamin D and its hydroxylated metabolites in the rat. Placental and lacteal transport, subsequent metabolic pathways and tissue distribution. *Horm. Res.* 9:292–300
136. Novy, M. J., Aubert, M. L., Kaplan, S. L., Grumbach, M. M. 1981. Regulation of placental growth and chorionic somatotropin in the rhesus monkey: effects of protein deprivation, fetal anencephaly, and placental vessel ligation. *Am. J. Obstet. Gynecol.* 140:552–62
137. Oesterling, M. J., Cox, S. E., Carrington, E. R. 1977. Placental phosphatase of maternal serum: relationship to pregravid weight, prenatal weight gain, and infant birth weight in normal human pregnancies. *Am. J. Clin. Nutr.* 30:182–90
138. Parizek, J. 1964. Vascular changes at sites of oestrogen biosynthesis produced by parenteral injection of cadmium salts: the destruction of placenta by cadmium salts. *J. Reprod. Fertil.* 7:263–65
138a. Pau, M. Y., Milner, J. A. 1981. Arginine deficiency during gestation and lactation in the rat. *J. Nutr.* 111:184–193
139. Pavey, D. E., Widdowson, E. M. 1975. Influence of dietary fat intake of the mother on composition of body fat of newborn guinea-pigs. *Proc. Nutr. Soc.* 34:107A (Abstr.)
140. Pavlou, C., Chard, T., Landon, J., Letchworth, A. T. 1973. Circulating levels of human placental lactogen in late pregnancy: the effect of glucose loading, smoking and exercise. *Eur. J. Obstet. Gynec. Reprod. Biol.* 3:45–49
141. Peterson, R. E., Imperato-McGinley, J. 1976. Cortisol metabolism in the perinatal period. In *Diabetes and Other Endocrine Disorders During Pregnancy and in the Newborn,* ed. M. I. New, R. H. Fiser, Jr., pp. 141–72. NY: Liss
142. Philips, A. F., Holzman, I. R., Teng, C., Battaglia, F. C. 1978. Tissue concentrations of free amino acids in term human placentas. *Am. J. Obstet. Gynecol.* 131: 881–87
143. Pike, J. W., Gooze, L. L., Haussler, M. R. 1980. Biochemical evidence for 1,25-dihydroxy-vitamin D receptor macromolecules in parathyroid, pancreatic, pituitary and placental tissues. *Life Sci.* 26:407–14

144. Pitkin, R. M. 1975. Calcium metabolism in pregnancy: a review. *Am. J. Obstet. Gynecol.* 121:724–37
145. Pitkin, R. M., Connor, W. E., Lin, D. S. 1972. Cholesterol metabolism and placental transfer in pregnant rhesus monkeys. *J. Clin. Invest.* 51:2584–92
146. Plotz, E. J., Kabara, J. J., David. M. E., LeRoy, G. V., Gould, R. G. 1968. Studies on the synthesis of cholesterol in the brain of the human fetus. *Am. J. Obstet. Gynecol.* 101:534–38
147. Polansky, M. M., Anderson, R. 1980. Role of inorganic chromium in placental transport. *Fed. Proc.* 39:903 (Abstr.)
148. Potau, N., Riudor, E., Ballabriga, A. 1981. Insulin receptors in human placenta in relation to fetal weight and gestational age. *Pediatr. Res.* 15:798–802
149. Power, G. G., Dale, P. S. 1981. Placental water transfer with uneven blood flows. *Placenta* (Suppl. 2):215–28
150. Prieto, J. C., Cifuentes, I., Serrano-Rios, M. 1976. hCS regulation during pregnancy. *Obstet. Gynecol.* 48:297–301
151. Prior, R. L. 1982. Gluconeogenesis in the ruminant fetus: evaluation of conflicting evidence from radiotracer and other experimental techniques. *Fed. Proc.* 41: 117–22
152. Ramsey, E. M. 1975. *The Placenta of Laboratory Animals and Man,* pp. 55–58. NY: Holt, Rinehart & Winston.
153. Reynolds, M. L., Young, M. 1971. The transfer of free alpha-amino nitrogen across the placental membrane in the guinea-pig. *J. Physiol.* 214:583–97
154. Riggi, S. J., Boshart, C. R., Bell, P. H., Ringler, I. 1966. Some effects of purified placental protein (human) on lipid and carbohydrate metabolism. *Endocrinology* 79:709–15
155. Robertson, J. A., Gallagher, N. D. 1979. Effect of placental lactogen on the number of intrinsic factor receptors in the pregnant mouse. *Gastroenterology* 77: 511–17
156. Rosenfeld, C. R., Morriss, F. A., Makowski, E. L., Meschia, G., Battaglia, F. C. 1974. Circulatory changes in the reproductive tissues of ewes during pregnancy. *Gynecol. Invest.* 5:252–68
157. Rosso, P. 1980. Placental growth, development, and function in relation to maternal nutrition. *Fed. Proc.* 39: 250–54
158. Ruzycki, S. M., Kelley, L. M., Smith, C. H. 1978. Placental amino acid uptake. IV. Transport by microvillous membrane vesicles. *Am. J. Physiol.* 234:C27–36
159. Samaan, N., Yen, S. C. C., Friesen, H. G., Pearson, O. H. 1966. Serum placental lactogen levels during pregnancy and in trophoblastic disease. *J. Clin. Endocrinol.* 26:1303–8
160. Samaan, N., Yen, S. C. C., Gonzales, D., Pearson, O. H. 1968. Metabolic effects of placental lactogen (HPL) in man. *J. Clin. Endocrinol. Metab.* 28: 485–91
161. Schneider, H., Mohlen, K. H., Dancis, J. 1979. Transfer of amino acids across the in vitro perfused human placenta. *Pediatr. Res.* 13:236–40
162. Seligman, P. A., Schleicher, R. B., Allen, R. H. 1979. Isolation and characterization of the transferrin receptor from human placenta. *J. Biol. Chem.* 254: 9943–46
163. Shami, Y., Messer, H. H., Copp, D. H. 1975. Calcium uptake by placental plasma membrane vesicles. *Biochem. Biophys. Acta* 401:256–64
164. Simmons, M. A., Battaglia, F. C., Meschia, G. 1979. Placental transfer of glucose. *J. Devel. Physiol.* 1:227–43
165. Singla, P. N., Chand, S., Khanna, S., Agarwal, K. N. 1978. Effect of maternal anaemia on the placenta and the newborn infant. *Acta Paediatr. Scand.* 67: 645–48
166. Sparks, J. W., Hay, W. W., Bonds, D., Meschia, G., Battaglia, F. C. 1982. Simultaneous measurements of lactate turnover rate and umbilical lactate uptake in the fetal lamb. *J. Clin. Invest.* 70: 179–92
167. Steel, R. B., Mosley, J. D., Smith, C. H. 1979. Insulin and placenta: degradation and stabilization, binding to microvillus membrane receptors, and amino acid uptake. *Am. J. Obstet. Gynecol.* 135: 522–29
168. Stegink, L. D., Reynolds, W. A., Pitkin, R. M., Cruickshank, D. P. 1981. Placental transfer of taurine in the rhesus monkey. *Am. J. Clin. Nutr.* 34:2685–92
169. Stegink, L. D., Pitkin, R. M., Reynolds, W. A., Filer, L. J., Boaz, D. P., Brummel, M. C. 1975. Placental transfer of glutamate and its metabolites in the primate. *Am. J. Obstet. Gynecol.* 122: 70–78
170. Steichen, J. J., Tsang, R. C., Gratton, T. L., Hamstra, A., DeLuca, H. F. 1980. Vitamin D homeostasis in the perinatal period: 1,25-dihydroxyvitamin D in maternal, cord, and neonatal blood. *N. Engl. J. Med.* 302:315–19
171. Stein, Z., Susser, M., Saenger, G., Marolla, F. 1975. In *Famine and Human Development: The Dutch Hunger Winter*

of 1944–1945, Ch. 10, pp. 87–118.NY: Oxford Univ. Press
172. Streeter, M. L., Rosso, P. 1981. Transport mechanisms for ascorbic acid in the human placenta. *Am. J. Clin. Nutr.* 34: 1706–11
173. Sturman, J. A., Rassin, D. K., Gaull, G. E. 1976. Taurine in development: is it essential in the neonate? *Pediatr. Res.* 10:415 (Abstr.)
174. Sutter, B. C., Sutter-Dub, M. T., Leclercq, R., Jacquot, R. 1973. Inhibition of insulin action by progesterone in the rat. *Diabetologia* 9:92 (Abstr.)
175. Suzuki, K., Kono, T. 1980. Evidence that insulin causes translocation of glucose transport activity to the plasma membrane from an intracellular storage site. *Proc. Natl. Acad. Sci. USA* 77: 2542–46
176. Takahashi, Y. I., Smith, J. E., Goodman, D. S. 1977. Vitamin A and retinol-binding protein metabolism during fetal development in the rat. *Am. J. Physiol.* 233:E263–72
177. Takahashi, Y. I., Smith, J. E., Winick, M., Goodman, D. S. 1975. Vitamin A deficiency and fetal growth and development in the rat. *J. Nutr.* 105:1299–1310
178. Tanaka, Y., Halloran, B., Schnoes, H. K., Deluca, H. F. 1979. In vitro production of 1,25-dihydroxyvitamin D_3 by rat placental tissue. *Proc. Natl. Acad. Sci. USA* 76:5033–35
179. Thomas, J. A. 1963. Modification of glucagon-induced hyperglycemia by various steroidal agents. *Metabolism* 12:207–12
180. Thompson, G. E., Bassett, J. M., Samson, D. E., Slee, J. 1982. The effects of cold exposure of pregnant sheep on foetal plasma nutrients, hormones and birth weight. *Br. J. Nutr.* 48:59–64
181. Turtle, J. R., Kipnis, D. M. 1967. The lipolytic action of human placental lactogen on isolated fat cells. *Biochem. Biophys. Acta* 144:583–93
182. Twardock, A. R., Austin, M. K. 1970. Calcium transfer in perfused guinea pig placenta. *Am. J. Physiol.* 219:540–45
183. Tyson, J. E., Austin, K. L., Farinholt, J. W. 1971. Prolonged nutritional deprivation in pregnancy: changes in human chorionic somatomammotropin and growth hormone secretion. *Am. J. Obstet. Gynecol.* 109:1080–82
184. Van Marthens, E., Shimomaye, S. Y. 1978. In-utero fetal and placental development following maternal protein repletion in rats. *J. Nutr.* 108:959–66
185. Velasco, E. G., Brasel, J. A., Sigulem, D. M., Rosso, P., Winick, M. 1973. Effects of vascular insufficiency on placental ribonuclease activity in the rat. *J. Nutr.* 103:213–17
186. Vobecky, J. S., Vobecky, J., Shapcott, D., Blanchard, R., Lafond, R., Cloutier, D., Munan, L. 1974. Serum alpha-tocopherol in pregnancies with normal or pathological outcomes. *Can. J. Physiol. Pharmacol.* 52:384–88
187. Wada, H. G., Hass, P. E., Sussman, H. H. 1979. Transferrin receptor in human placental brush border membranes. *J. Biol. Chem.* 254:2629–35
188. Walaas, O. 1952. Effect of oestrogens on the glycogen content of the rat liver. *Acta Endocrinol.* 10:193–200
189. Wapnir, R. A., Dierks-Ventling, C. 1971. Placental transfer of amino acids in the rat II. Aromatic amino acids. *Biol. Neonate* 17:373–80
190. Weisman, Y., Harrel, A., Edelstein, S., David, M., Spirer, Z., Golander, A. 1979. 1,25-dihydroxyvitamin D_3 and 24,25-dihydroxyvitamin D_3 in vitro synthesis by human decidua and placenta. *Nature* 281:317–19
191. Welsch, F. 1976. Studies on accumulation and metabolic fate of [N-Me^3H]choline in human term placenta fragments. *Biochem. Pharmacol.* 25: 1021–30
192. Whitsett, J. A., Lessard, J. L. 1978. Characteristics of the microvillus brush border of human placenta: insulin receptor localization in brush border membranes. *Endocrinology* 103:1458–68
193. Whitsett, J. A., Tsang, R. C. 1980. Calcium uptake and binding by membrane fractions of human placenta: ATP-dependent calcium accumulation. *Pediatr. Res.* 14:769–75
194. Widdas, W. F. 1952. Inability of diffusion to account for placental glucose transfer in the sheep and consideration of the kinetics of a possible carrier transfer. *J. Physiol.* 118:23–29
195. Widdas, W. F. 1961. Transport mechanisms in the foetus. *Brit. Med. Bull.* 17:107–11
196. Widdowson, E. M. 1968. Growth and composition of the fetus and newborn. In *Biology of Gestation: The Fetus and Neonate*, ed. N. S. Assali, 2:1–49. NY: Academic
197. Widdowson, E. M., Dauncey, M. J., Shaw, J. C. L. 1974. Trace elements in foetal and early postnatal development. *Proc. Nutr. Soc.* 33:275–84
198. Widdowson, E. M., Dauncey, M. J., Gairdner, D. M. T., Jonxis, J. H. P., Pelikan-Filipkova, M. 1975. Body fat of British and Dutch infants. *Br. Med. J.* 1:653–55

199. Wilkening, R. B., Anderson, S., Martensson, L., Meschia, G. 1982. Placental transfer as a function of uterine blood flow. *Am. J. Physiol.* 242:H429–36
200. Williams, C., Coltart, T. M. 1978. Adipose tissue metabolism in pregnancy: the lipolytic effect of human placental lactogen. *Br. J. Obstet. Gynecol.* 85:43–46
201. Winick, M., Brasel, J. A., Rosso, P. 1972. Nutrition and cell growth. In *Current Concepts in Nutrition*, Vol. 1, *Nutrition and Development*, ed. M. Winick, pp. 49–97. NY: Wiley
202. Winkel, C. A., Macdonald, P. C., Hemsell, P. G., Simpson, E. R. 1981. Regulation of cholesterol metabolism by human trophoblastic cells in primary culture. *Endocrinology* 10:1084–90
203. Wunderlich, S. M., Baliga, B. S., Munro, H. N. 1979. Rat placental protein synthesis and peptide hormone secretion in relation to malnutrition from protein deficiency or alcohol administration. *J. Nutr.* 109:1534–41
204. Yen, S. S., Tsai, C. C., Vela, P. 1971. Gestational diabetogenesis: quantitative analysis of glucose-insulin interrelationship between normal pregnancy and pregnancy with gestational diabetes. *Am. J. Obstet. Gynecol.* 111:792–800
205. Young, M. 1979. Transfer of amino acids. In *Placental Transfer*, ed. G. B. P. Chamberlain, A. W. Wilkinson, pp. 142–58. London: Pitman
206. Young, M. 1981. Placental factors and fetal nutrition. *Am. J. Clin. Nutr.* 34: 738–43
207. Young, M. 1981. Amino acid uptake by the fetus. *Placenta* (Suppl. 1):125–38
207a. Young, M. 1981. Placental amino acid transfer and metabolism. *Placenta* 1: (Suppl. 1):177–84
208. Young, M., Widdowson, E. M. 1975. The influence of diets deficient in energy, or in protein, on conceptus weight, and the placental transfer of a non-metabolizable amino acid in the guinea pig. *Biol. Neonate* 27:184–91
209. Zartarian, G. N., Galler, J. R., Munro, H. N. 1980. Marginal protein deficiency in pregnant rats. I. Changes in maternal body composition. *J. Nutr.* 110:1291–97
210. Zavy, M. T., Bazer, F. W., Sharp, D. C., Wilcox, C. J. 1979. Uterine luminal proteins in the cycling mare. *Biol. Reprod.* 20:689–98