Determinants of Growth in Utero

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In a logical approach to the subject of determinants of growth in utero, genetic influences should be considered separately, since they are fixed at the time of conception and immutable. Then the fetus, the placenta, and the mother should be taken in that order, because it is helpful to review first how the fetus exerts control over its own development, assuming a normal and stable intrauterine environment. The placenta is central to the theme not only because it is the eye of the needle through which nutrient must pass from mother to fetus but also because placental hormone production influences fetal growth directly and also indirectly by altering maternal metabolic patterns. Maternal influences on fetal growth are in one sense peripheral but in another the most important, since they may be amenable to direct intervention by clinicians wishing to optimize intrauterine growth to minimize perinatal mortality and morbidity.

GENETICS

Normal fetal growth and development are the result of a precisely organized sequence of gene activation and suppression under the control of a biological clock. This is poorly understood (1). Chromosomal abnormalities that give rise to recognizable syndromes such as Turner’s syndrome (45,XO) or Down’s syndrome (trisomy 21) characteristically produce small babies. This is thought to be the result of a reduced rate of cell division (2), and in the case of Turner’s syndrome intrauterine blighting has lifelong consequences since birth weight is the most powerful single predictor of adult height (3).

Multiple gene loci contribute to the birth weight of the normal fetus. Models have been developed that partition the contribution of genetic and environmental factors in determining birth weight (Table 1) (4). Variation in birth weight can be roughly partitioned: one-third to genetic factors, one-third to recognizable environmental factors, and one-third unknown. Of the 38% that is genetic, the maternal genotype (20%) is more important than the fetal genotype (15%), and the paternal contribution is solely via the fetal genotype.
TABLE 1. Partitioning of birth weight variation

<table>
<thead>
<tr>
<th>Genetic</th>
<th></th>
<th>Environmental</th>
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<tbody>
<tr>
<td>Maternal genotype</td>
<td>20%</td>
<td>General maternal environment</td>
<td>18%</td>
</tr>
<tr>
<td>Fetal genotype</td>
<td>16%</td>
<td>Immediate maternal environment</td>
<td>6%</td>
</tr>
<tr>
<td>Fetal sex</td>
<td>2%</td>
<td>Maternal age and parity</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>62%</td>
</tr>
</tbody>
</table>

*Derived from Polani (4).

THE FETUS

The human fetus undergoes the equivalent of some 42 successive mitotic divisions in pregnancy in progressing from a fertilized ovum to a term infant, with only five more divisions being necessary to achieve adult size (5). Maximal growth velocity in length occurs at approximately 20 weeks of gestation, and in weight at 34 weeks. This reflects developmental changes in growth by cell number and size: in the first trimester growth is by increase in cell number, in the second there is a stable rate of cellular division accompanied by an increase in cell size, and in the third trimester growth in cell number slows, and that in cell size accelerates (6).

Adipocyte lipid becomes an important contributor to body weight in the last trimester. It is worth remembering that the first 1.5 kg of the 3.0 kg that a term infant weighs takes two-thirds of pregnancy to develop. In the first 1.5 kg there is about 50 g fat, whereas the second 1.5 kg acquired in the last 12 weeks of gestation includes 500 g fat (7). Lipid accumulation by the fetus in the third trimester, which is largely controlled by glucose-sensitive insulin secretion, is the most important single contributor to a term infant being overweight or underweight (8).

If fetal growth is compromised in the first trimester, the end result is usually abortion; in the second trimester, growth retardation results in shortness and underweight that are largely irreversible, whereas growth failure originating in the third trimester produces a long skinny baby who can catch up postnatally if nutrition is optimal.

Adequate cellular delivery of nutrient is an overriding condition for normal intrauterine growth. Nutrient oversupply is not known to influence growth before 28 weeks but may modulate weight gain in the third trimester by stimulating pancreatic B cell ontogeny and insulin secretion (9). Our understanding of the contribution of insulin, other hormones, and peptide growth factors to the control of fetal growth has advanced dramatically in recent years with an important shift from a
traditional concept of endocrine growth control to one in which endocrine hormones interact with peptide growth factors that function in a paracrine or autocrine manner.

The placenta is impermeable to peptide hormones, and the peptides involved in fetal growth control originate in the fetus or the fetal side of the placenta. The balance of evidence indicates that growth hormone (GH) plays little part in human fetal growth (10). Thyroid hormones are important in both neuronal development and osseous maturation but are not essential for tissue development overall (11). Candidates for a central part in the overall control of intrauterine cellular growth are insulin, placental lactogen, and the logically acting tissue growth factors. All growth factors induce a positive pleiotypic response in the target tissue, which includes glucose and amino acid uptake and DNA, RNA, and protein synthesis, and all are mitogens. Some, such as the somatomedins (insulin-like growth factors), epidermal growth factor, and nerve growth factor, induce differentiation of the target tissue, whereas others such as the transforming growth factors and fibroblast growth factor do not. A combination of growth factors is required to stimulate a cell to replicate (Fig. 1) (12).

FIG. 1. Sequence of events and their endocrine control leading to cell replication in BALB/c-3T3 fibroblasts. Cells growth-arrested in G₀ are made to enter G₁, where they progress to DNA synthesis in S phase. This is followed by preparation for G₂ and the process of mitosis (M). The sequential addition of competence and progression factors are required for the full cycle of events, and both are contained in platelet-rich human plasma. Platelet-poor plasma has only progression activity but will result in DNA synthesis if added following transient exposure of the cells to the competence factors platelet-derived growth factor (PDGF) or fibroblast growth factor (FGF). Platelet-poor plasma from GH-deficient subjects, which lacks somatomedins, allows progression over the initial part of G₁ only, but full G₁ progression is restored if such plasma is followed by exposure to somatomedin C (SM-C), multiplication-stimulating activity (MSA), or supraphysiological concentrations of insulin. The need for SM-deficient platelet-poor plasma in early G₁ is obviated by exposure of the cells to epidermal growth factor (EGF). These cells can therefore be induced to traverse the cycle of proliferation in serum-free medium by sequential exposure to PDGF or FGF, EGF, and a SM or insulin. (Adapted from Van Wyk et al., ref. 12).
In man more is known about the somatomedins than about other growth factors. There are two predominant classes of somatomedin: insulin-like growth factor I (IGF I), otherwise known as somatomedin C (SM-C), and IGF II. The analogous peptide to IGF II in the rat is called multiplication-stimulating activity (MSA). The IGFs are so called because they have structural and functional similarities with insulin and proinsulin. This has led to the concept that they are all members of a family of insulin-like molecules, more distant relatives in which are relaxin and nerve growth factor (13). This relationship helps explain the limited biological cross reactivity, insulin being a weak growth factor for fibroblasts and the IGFs enhancing glucose oxidation in isolated adipocytes (14). Insulin may therefore have a dual role in fetal growth, on the one hand behaving like the somatomedins and stimulating mitosis and on the other acting as a classical hormone controlling carbohydrate and lipid metabolism in the third trimester with important implications for term body weight.

The concentration of IGF I in human cord blood is one-half or less of that present in the normal adult (15) despite the rapid rate of fetal growth, but cord IGF I levels do correlate with both fetal age and body weight, whereas those of IGF II do not. The IGF II levels in cord blood are the same as or slightly lower than those in the adult. But it is naive to seek a biological link between cord IGF levels in fetal growth for a number of reasons. The total IGF concentration in the blood does not reflect the IGF free to react with receptor, since most IGF is bound to a carrier protein. In the adult and in neonates of 30 weeks or more gestation, this has a molecular weight of approximately 150,000, whereas in infants under 27 weeks of gestation it is approximately 40 kilodaltons in size (16). The ontogeny of binding protein form and affinity may control the amount of IGF available to the tissues.

The action of IGF and other growth factors depends as much on the ontogeny of receptors as on the messenger peptide. The apparent paradox of rapid fetal growth in the face of low circulating levels of IGF could be resolved if fetal tissues were more sensitive than postnatal tissues to the action of IGF. Most human fetal tissues possess receptors for both IGF I and IGF II, though the liver is said to have IGF II receptors only (17). Circulating monocytes from cord blood have a greater IGF I binding capacity than those in the adult circulation (18).

A major difference between pre- and postnatal life is that in the adult IGFs are synthesized mainly in the liver and are transported via the circulation to act in an endocrine fashion on cartilage growth plates, whereas in the fetus most if not all tissues synthesize IGFs, which are released to act locally in a paracrine or autocrine fashion (19). Some IGF I has been recovered from all tissues tested from human fetuses 9 to 19 weeks of gestation (Table 2) (20). Lung and intestine had the highest concentration, and liver the lowest. Complementary evidence of human fetal tissue IGF has been obtained by immunohistochemistry (21). The circulation therefore probably represents a sump receiving IGF overflow from all the tissues, and there seems to be little of biological import to be gained from analyzing blood IGF concentrations.
TABLE 2. Mean (± SEM) insulin-like growth factor 1 in human fetal tissues*

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Mean ± SEM</th>
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<tbody>
<tr>
<td>Lung</td>
<td>166 ± 35</td>
</tr>
<tr>
<td>Intestine</td>
<td>160 ± 20</td>
</tr>
<tr>
<td>Kidney</td>
<td>132 ± 18</td>
</tr>
<tr>
<td>Skin</td>
<td>127 ± 10</td>
</tr>
<tr>
<td>Pancreas</td>
<td>101 ± 12</td>
</tr>
<tr>
<td>Muscle</td>
<td>99 ± 7</td>
</tr>
<tr>
<td>Thymus</td>
<td>98 ± 25</td>
</tr>
<tr>
<td>Brain</td>
<td>82 ± 11</td>
</tr>
<tr>
<td>Heart</td>
<td>79 ± 10</td>
</tr>
<tr>
<td>Adrenal</td>
<td>76 ± 10</td>
</tr>
<tr>
<td>Liver</td>
<td>67 ± 16</td>
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</tbody>
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*All results are expressed in milliunits per gram. Between five and 26 determinations were made on tissues from fetuses of 9 to 19 weeks of gestational age. Mean plasma concentration: 270 ± 20 mU/ml. From D'Ercole et al. (20).

The control of fetal growth factor synthesis and release is clearly fundamental to an understanding of fetal growth control overall. What follows is of necessity speculative, since the evidence from which generalizations are made is based on \textit{in vitro} experiments on cellular growth and replication. A circular but plausible argument has been advanced that links delivery of nutrient to the fetal cell, fetal insulin secretion, and the synthesis of IGFs (8). If either of the first two variables is increased or decreased, a predictable change occurs in the others. The trio of nutrient, insulin, and IGF should now be enlarged to a quartet by the addition of human placental lactogen (HPL), a peptide secreted by placental trophoblasts that has amino acid sequence homology with both GH and prolactin. Ovine HPL is released into both fetal and maternal circulations. From 80 to 100 days, the level is higher in the fetus, but by term at 145 days, the maternal level has risen and the fetal level fallen to give a maternofetal ratio approximately 10 (22). A conventional view is that HPL influences fetal growth indirectly by acting as an insulin antagonist in the mother, stimulating the mobilization of metabolites, and increasing nutrient delivery to the fetus (23). There is indirect evidence that HPL also stimulates maternal IGF synthesis and release. Normal women have elevated IGF I levels in late pregnancy, and these fall following parturition (24). A GH-deficient woman was shown to have normal circulating levels of IGF I and II at 35 weeks of gestation, which fell rapidly postpartum in parallel with the disappearance of circulating HPL (25). Recent work suggests that HPL may also have a direct action on IGF synthesis and release in the fetal compartment.

Adams et al. (26) were the first to show that fetal rat fibroblasts release MSA in response to ovine PL but not to GH. Postnatally, rat fibroblasts were responsive to both hormones. We have shown that HPL is capable of stimulating amino acid
uptake and thymidine incorporation by human fetal fibroblasts and myoblasts (27) and that this can be inhibited but not abolished by IGF I antibody. We have also shown that HPL, but not GH, stimulates human fetal fibroblasts and myoblasts to release IGF I into the culture medium in a dose-dependent manner (28). In contrast, both HPL and GH simulate DNA synthesis and IGF I release by isolated human fetal hepatocytes (29). A possible direct link between HPL and insulin has been suggested by the observation that insulin stimulates HPL release from isolated cultured trophoblasts in a dose-dependent manner (30).

These findings can be woven into a working hypothesis that fetal cellular growth is dependent first on delivery of nutrient (e.g., glucose, amino acids, and fatty acids). The uptake of nutrient by the fetal cell is stimulated by insulin. Fetal insulin secretion is stimulated by amino acids up to 28 weeks of gestation and by amino acids and glucose thereafter (9). Cellular anabolism progresses to replication under the influence of growth factors. Growth factor synthesis and release are stimulated not only by intracellular events such as the delivery of fuel, which is augmented by insulin, but also by HPL, which may be acting on many fetal tissues in a manner analogous to GH acting on the hepatocyte postnally. Finally, there is a long loop in which insulin reinforces the anabolic process by stimulating HPL secretion.

THE PLACENTA

The influence of the placenta on fetal growth is twofold. First, there is a mechanistic role involving the transfer of nutrients and oxygen to the fetus and the removal of waste products. In this must be considered not only placental macro- and microanatomy but fetal and maternal blood flows, which are themselves controlled elsewhere. Then there are the metabolic and endocrine aspects of placental function, which include most importantly HPL production and steroid hormone metabolism.

The placenta grows faster than the fetus and reaches maximum weight at about 33 weeks of gestation, though surface area and vascularity continue to develop thereafter (31). Although there is a positive relationship between placental and fetal weights, this is unlikely to be linear as term approaches. In theory, if a fetoplacental weight ratio is assumed at which fetal growth is optimal, an increase of placental weight does not augment growth, which in these circumstances is under endogenous fetal control, but a reduction in placental weight can become rate limiting. In undergrowth there is interaction between fetus and placenta, as the majority of placental weight is fetal in origin, and there is some evidence that fetal abnormality can inhibit placental growth. In anencephaly placental weight is reduced (32).

Morphological abnormalities such as a bilobate or reniform placenta or a placenta with an accessory lobe do not appear to influence fetal development, but abnormalities of the umbilical cord do. Reduced birth weight is commonly associated with velamentous insertion of the cord or battledore placenta and also with a
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single umbilical artery, which is, however, often a clinical marker of other abnormal fetal morphology. Microscopic changes in the placenta are often associated with fetal growth retardation. There may be intervillous thromboses, placental infarction, and degeneration of the syncytiotrophoblast in preeclamptic toxemia (33). Placental pathology of this kind may arise from maternal disease such as hypertension or habits such as smoking and drug abuse.

The principal determinants of fetal placental perfusion are cardiac output and the distribution of blood in the fetal circulation. The fetal placenta has a low vascular resistance and receives about half the cardiac output. The umbilical arterial wall is muscular and is not thought to be innervated outside the abdomen but is sensitive to circulating vasoactive peptides. Important umbilical artery vasoconstrictors include angiotensin, vasopressin, bradykinins, serotonin, adrenergic agonists, and the prostaglandins. Angiotensin II may exert a tonic vasoconstrictor action, since saralasin, an angiotension II antagonist, has been shown to decrease ovine umbilicoplacental vascular resistance (34) when injected intravenously into the fetus. A corollary is that increased renin–angiotensin secretion in maternal hypertension might cause reduced umbilical flow and thereby fetal growth retardation (35).

Umbilical blood flow is highly dependent on fetal heart rate since there is little variation in stroke volume. Flow increases with body size but not proportionately, since in late gestation a greater fraction perfuses fetal organs. Hypoxemia causes a redistribution of blood flow between fetal organs but little alteration in umbilical vascular resistance. In early gestation hypoxemia causes fetal tachycardia and increased umbilical blood flow, whereas later on there is bradycardia coupled with increased arterial pressure, which helps to preserve umbilical flow (36). Morphine and other central nervous system depressants cause fetal bradycardia. The resulting fall in umbilical blood flow may partly explain the intrauterine growth retardation seen in the offspring of drug abusers.

Placental gaseous exchange is by passive diffusion. The major physiological determinants of oxygen delivery to the fetus are maternal and fetal blood flow and the relative affinities of fetal and maternal hemoglobin for oxygen. If placental surface area is reduced or the diffusion distance increased by thickening of the placental membrane, reduction in the overall oxygen diffusion capacity may restrict fetal growth. This can occur as a result of placental infarction or intervillous fibrin deposition.

A variety of transport mechanisms exists for nutrient delivery across the placenta. Glucose crosses the placenta by facilitated diffusion, and the major determinant of fetal glucose supply is maternal blood glucose concentration with lesser contributions from maternal blood flow and placental size. Maternal glucose was thought to be quantitatively the most important contributor to fetal energy supply. Recent evidence, reviewed by Battaglia and Hay (37), indicates that not only is the placenta an important consumer of maternal glucose but also that lactate produced from placental glucose metabolism passes largely into the fetal circulation. Maternal lipid also contributes to the fetal energy supply (38). The relative amounts of glycerol, free fatty acids, and ketone bodies crossing to the fetus at
different stages of human pregnancy are unknown, but it seems likely that some of the lipid stores of the newborn infant are derived directly from the mother, since they reflect the fatty acid pattern of the maternal diet (39).

Placental amino acid transport is active, carrier mediated, and largely uphill (40). The pattern of amino acids in the maternal circulation varies with gestation and with pregnancy-related illness such as preeclamptic toxemia. The relationship between the maternal aminogram and fetal development deserves further study in view of the observations that the total plasma free amino acids during the third trimester are positively correlated with birth weight (41) and that the maternal amino acid profile is related to fetal malnutrition as early as 25 weeks of gestation (42). Maternal hyperaminoacidemia, specifically hyperphenylalaninemia, may also damage fetal development (43).

The complicated way in which HPL influences fetal growth has been dealt with in the section on the fetus. The other important contribution of the placenta involves the secretion and metabolism of steroid hormones. In pregnancy, maternal cardiac output increases. This is in part because of an increase of maternal blood volume, which in turn is the result of an increase in plasma volume and erythrocyte mass. It has been argued that maternal placental perfusion is proportional to the increase in blood volume (44), and therefore factors controlling the latter play an important if indirect part in the control of fetal growth. Pregnenolone synthesized in the placenta is converted to dehydroepiandrosterone sulfate by the fetal adrenal, and this in turn is metabolized to estradiol-17α and estrone by the placenta. These steroids pass into the maternal circulation, where they stimulate the renin–angiotensin system, causing retention of fluid and expansion of the maternal vascular compartment. Maternal erythropoiesis in pregnancy is stimulated by HPL (45).

THE MOTHER

Maternal influences on fetal growth can be subdivided for practical convenience into those that are unalterable, such as maternal age, parity, and genotype, and those that reflect maternal life pattern. The latter include socioeconomic factors and disease and are very important since they are potentially manipulable in order to optimize fetal growth. Of all the influences on variation in birth weight (Table 1), the unalterable maternal contribution accounts for more than 28% (maternal genotype 20%, maternal age and parity 8%, plus an unknown proportion of maternal environment). The alterable maternal contribution could account for up to 54% (general maternal environment 18%, immediate maternal environment 6%, plus an unknown 30%) but is probably less than this.

The best-known examples of immutable maternal influences on fetal growth are uterine shape and size. In the crossing of Shire horses and Shetland ponies, the birth weight of the foals reflected maternal uterine size, those born to Shetland dams being much smaller than those born to Shire dams (46). The possible contribution of dwarf genotype in this kind of experiment was excluded in later experiments in which fertilized eggs were transplanted from dwarf pigs into normal-size
sows or vice versa. Genotypically normal piglets growing in dwarf sows were about half the expected size at birth, whereas dwarf piglets implanted in normal sows were twice as big as expected (47). A similar if less dramatic illustration of this phenomenon can be seen in man when birth weight is compared between different ethnic groups or examined as a function of maternal height. In man adult uterine size may be influenced by factors affecting postnatal growth; a plausible hypothesis is that infantile malnutrition compromises uterine growth, leading to suboptimal intrauterine development of the next generation and the vertical transmission of small stature (48).

Uterine size is important to fetal growth because the uterus is the site where the placenta interfaces the fetus and mother. Anything that adversely influences implantation and placental growth will reduce fetal development. This is part of the explanation for the progressive reduction in birth weight with increasing birth number in man. Anatomical abnormalities such as a bicornuate uterus are commonly associated with impaired prenatal growth, as is abnormal placental implantation; lower-segment implantation is associated with a reduction in birth weight of about 200 g (49).

The maternal influences on fetal growth that are amenable to intervention all act on the delivery of nutrient and oxygen to the fetus. The mechanism may be by alteration of the concentration in the maternal circulation or of placental perfusion and transfer. The adverse effect of low maternal socioeconomic status can be considered first, since there is a clear-cut relationship with low birth weight (50). But detailed analysis shows that the disadvantage can be explained in terms of specific factors such as nutrition, smoking, and disease associated with low socioeconomic status and that, in Western society at least, lower social class per se has no significant effect in its own right (51). Social class or socioeconomic grouping is a useful form of categorization for program planning to improve prenatal growth but is of limited value in scientific analysis.

Fetal caloric requirements in man are 95 kcal/kg per day, of which 40 are committed to growth and 55 are oxidized (52). This is accounted for by the small gross overall cost of pregnancy to the mother, 100 kcal/day, who nevertheless experiences profound metabolic and body tissue changes in preparation for parturition (53). Despite this relatively high optimal plane of maternal nutrition, underfeeding has a relatively small effect on fetal growth (54). Starvation, as experienced in Holland in 1944–1945, led to a fall in birth weight only when maternal intake was less than 1,500 calories/day in the third trimester (55). Of more contemporary relevance is the observation that food supplementation during pregnancy led to an increase in birth weight in a poor Guatemalan community (56).

It is a moot point whether maternal alcohol ingestion should be considered as nutrition or as a drug. A sustained high alcohol intake is now accepted as the specific cause of a clinical syndrome of fetal underdevelopment in which there are craniofacial, limb, and cardiac anomalies and psychomotor retardation (57). Less deviant patterns of drinking in pregnancy have also been alleged to reduce birth weight independently of any effect on maternal caloric intake (58). Ethanol and its metabolite acetaldehyde may inhibit growth by a direct toxic action on fetal
cellular mitosis or indirectly by inhibiting placental hormone synthesis (59) or causing fetal hypoperfusion and acidosis (60). Other drugs that the mother may take of her own volition include those characteristic of drug abuse, such as opiates, and those readily available for symptom relief, such as aspirin. Maternal drug abuse retards fetal growth. There is a 50% incidence of low birth weight in the offspring of women taking heroin, though whether this a direct effect or secondary to maternal malnutrition and other related factors is not clear (61).

There is an extensive literature on drugs used therapeutically during pregnancy (62), since in every instance the prescriber must consider possible side effects on the fetus. Many drugs are known to inhibit fetal growth and development and are avoided; these include all kinds of cytotoxic and immunosuppressive agents. Examples of drugs more likely to be used are salicylates and glucocorticoids. The daily ingestion of aspirin during pregnancy is associated with an increased stillbirth rate and reduction in birth weight (63). The effect may be mediated by inhibition of prostaglandin synthesis, resulting in uterine vasoconstriction (64). Glucocorticoids when used in pregnancy are usually required in pharmacological doses. In animals this is teratogenic; in man there is no clear-cut evidence of teratogenicity, but there is a reduction in birth weight (65). Whether the fetal growth retardation results from the steroid or from the maternal disease for which it was prescribed is unresolved.

Drugs that alter nutrient delivery to the fetus deliberately or fortuitously are particularly relevant to this review. These can be illustrated by the β-sympathomimetics and β-blockers, both of which cross the placenta freely. The β-mimetics are commonly used to suppress premature uterine contractions and may be administered for periods ranging from hours to weeks. Brettes et al. (66) reported improved fetal growth of small-for-dates infants whose mothers were treated with ritodrine and claimed that this was because of increased uterine blood flow and improved fetal nutrition, an interpretation that has subsequently been queried (67). Ritodrine is said to induce maternal carbohydrate intolerance, but when glucose tolerance of mother and baby was tested in control and ritodrine-treated pregnancies, no significant difference was found (68). An alternative explanation is that lipid metabolism may be altered. Isoxuprine, another β-mimetic, caused a large rise in plasma free fatty acids and insulin when given to newborn rabbit pups (69). It is possible that the fetal growth-promoting effect claimed for β-mimetics may result from stimulation of lipolysis and increased transplacental passage of lipid constituents, a mechanism already proposed for infants of diabetic mothers (70). Propranolol is the most commonly employed β-blocker and may be used in pregnancy for the treatment of hypertension, cardiac arrhythmias, or thyroid disease. Chronic fetal exposure to propranolol results in reduced body and placental weight (71). A suggested explanation is reduced uterine blood flow because of a fall in maternal cardiac output and increased uterine muscle tone coupled with reduced blood flows in the fetus (72). To this must be added a metabolic action; propranolol blocks cold-induced thermogenesis and may inhibit mobilization of nutrient from mother to fetus.
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Although nicotine is a drug, smoking is sufficiently prevalent and preventable to merit consideration separate from toxic drug actions in the fetus. Fetal growth retardation is directly proportional to the number of cigarettes smoked by the mother; 20 a day brings the birth weight down by 200 g. This is not related to associated malnutrition (73). Placental weight may be increased, and there is a characteristic placental pathology—obliterative endarteritis, villous cytotrophoblastic hyperplasia, and necrosis of the decidua basalis—all of which are compatible with hypoperfusion (74). These adverse effects are caused by both nicotine and carbon monoxide. High concentrations of nicotine in the circulation can increase uterine vascular resistance and decrease blood flow, leading to fetal hypoxia and hypercapnia (75). Nicotine has also been shown to depress human placental amino acid transfer in vitro (76). Inhaled carbon monoxide leads to tissue hypoxia by the formation of carboxyhemoglobin in both mother and fetus. Carbon monoxide also binds to cytochrome and therapy may impair active placental transport of nutrients.

Maternal disease influences fetal development by altering placental perfusion or by producing placental transfer of abnormal molecules. Impaired delivery of oxygen to the placenta occurs in maternal cyanotic heart disease or chronic debilitating lung disease. Maternal pregnancy-associated hypertension is often associated with poor intrauterine growth. This may be related to thromboses in the placental microvasculature or to associated renal involvement (77). A corollary is that factors increasing uterine blood flow, such as bed rest, stimulate fetal growth (78). Maternal undernutrition severe enough to affect fetal development is certainly an illness, but one that has been more appropriately considered in the context of socioeconomic factors. Maternal metabolic disorders characterized by excess circulating concentrations of one or more metabolites might be expected to affect fetal growth, the most often cited example being phenylketonuria (43). There are a group of conditions that have in common immunoglobulin overproduction. The placenta is permeable to IgG, and fetal tissue damage results from the transplacental passage of immunoglobulin in systemic lupus erythematosus (79). The baby born thyrotoxic as a result of the passage of long-acting thyroid stimulator (LATS) is often small and may have experienced thyrotoxicosis in utero (80).

Maternal infections have a spectrum of harmful effects on the fetus. Malaria inhibits fetal growth principally by impairing placental blood flow (81). Any serious maternal illness, especially an infectious one, in the first trimester usually results in abortion. Serious systemic bacterial infection, particularly gram-negative septicemia, at any stage of pregnancy may kill the fetus, whereas viral or protozoal infections such as rubella, cytomegalovirus, or toxoplasmosis all cause fetal tissue damage and growth retardation along with specific pathology characteristic of the infecting agent (82).

The only environmental factor with an unequivocal effect on human fetal development is altitude. Infants born at 15,000 ft have a mean birth weight 16% lower than do infants born at 500 ft (83). Fetal growth retardation in these circumstances results from decreased oxygen delivery.
ACKNOWLEDGMENTS

Any review is of necessity derivative, and this one has drawn particularly on the comprehensive account of the regulation of fetal growth by Gluckman and Liggins (84). I am grateful to Dr. D.J. Hill for helpful discussion.

REFERENCES

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**DISCUSSION**

*Dr. Tomkins:* Could I ask you to expand on why it is that socioeconomic status affects birth weight? As I understand it, there are many factors. The one that I would be particularly interested to hear about is the interaction with activity, which did not appear in your analysis. The reason I ask is that when we look at birth weight in relation to poor socioeconomic status, the women who are the poorest are often working the hardest, e.g., in agriculture or cleaning factories in Scotland, even though they are not malnourished by body mass index or fat stores. I wonder if you have any information, experimental or otherwise, on the effect of activity on placental blood flow, on hormone release, or anything like that?

*Dr. Milner:* That is a very good point that I have omitted to emphasize and is a corollary of what is accepted in current clinical practice. If maternal placental perfusion is jeopardized for whatever reason, whether because of maternal essential hypertension or preeclamptic toxemia, the surest way of improving it is maternal rest. That is totally compatible with what you are saying; i.e., the more active a pregnant woman has to be, certainly through the second and third trimesters, the more this could have an adverse effect on fetal nutrition as a result of a reduction in maternal placental perfusion.

*Dr. Tomkins:* David Saunders in Zimbabwe (personal communication) describes what they call "maternity villages" where mothers come at least for the last month of pregnancy and where everything is done for them. I don’t know how widespread this is in developing countries, but it is certainly not my experience in West Africa, where women have to keep going until delivery.

*Dr. Rappaport:* My understanding is that maternal rest at the end of pregnancy, at least in European countries, results in a decreased incidence of prematurity but not of intrauterine growth retardation (IUGR) and that the number of small-for-date children has decreased much less than the number of premature babies. In developing countries there are probably
many other factors that could affect the fetal growth. Has anybody tried to differentiate prematurity and IUGR, and their causes, in developing countries?

Dr. Milner: I believe that one of the problems commonly experienced is difficulty in being confident about gestational age.

Dr. Keller: In WHO we recently reviewed the literature on low birth weight. It seems that very little is actually known about the possible effect of maternal physical work on birth weight and on the development of the fetus. That hypothesis is very interesting because it would be a more plausible explanation for the very high rate of small-for-date babies, mostly in developing countries, than the hypothesis of a deficient calorie supply to the mother, which is the usual one.

Dr. Milner: That goes along with a mild but chronic intrauterine growth retardation; once you have got that as a piece of pathophysiology, then you are going to have a different kind of conceptus, and the implications for postnatal catch-up are adverse, whereas if the problem begins from, say, 28 weeks onwards, you may end with a baby that still weighs only 2.2 kg but with very good implications for postnatal catch-up, assuming that the extrauterine environment is favorable.

Dr. Waterlow: You used the phrase, "maternal placental perfusion." I have never been able to understand the idea that the fetus, during the third trimester of pregnancy, could not get enough nutrients from the mother. I tried to calculate from what we know of fetal oxygen consumption and fetal protein turnover rates what proportion of the nutrients that are circulating through the placental blood are actually taken up by the fetus. If I remember correctly, for amino acids, glucose, and even oxygen, it might come to something of the order of 10% of the supply. I find it very difficult to understand how a mother, for example, one who might have a slightly low blood amino acid concentration, would still not have a plentiful supply if only 10% had to be taken up? Do you have any comments on the arithmetic of the situation?

Dr. Milner: In the maternal-fetal transfer across the placenta of the three classes of nutrients, protein, fat, and carbohydrate, each differs from the other. Glucose crosses by facilitated diffusion. Amino acids cross by active transfer, where the fetal concentrations are always higher than the maternal and the fetomaternal differential increases towards term. Fatty acid transfer is now accepted to be more important in total fetal caloric accretion than was previously thought to be the case, specifically in respect to different classes of essential fatty acids. If the molecules can actually get to the maternofetal interface at the hemochorial junction, the fetus can pick up the molecule from the maternal side. The block to adequate delivery of nutrients to the fetus, in so far as the concept is acceptable, is in perfusion failure on the maternal side of the placenta.

Dr. Gopalan: What do you think of maternal anemia? Anemia is one of the most common conditions in developing countries. In particular, I would like your comment on the claims that folic acid supplementation to the mother brings about an increase in birth weight. If supplements have to be given, what would be the supplement? What would be the optimal time for the introduction of these supplements?

Dr. Milner: Your question makes it perfectly clear to everybody why I took refuge in simple concepts. When we turn back to real life, we know from the onset that your question, which is a very straightforward and legitimate one to ask, is nonetheless very difficult to answer because maternal anemia does not exist in isolation. So, to what extent anemia is responsible, and to what extent coexistence of adverse influences is responsible, I do not know.

Dr. Gopalan: Do you believe that iron supplementation could be an answer to the problem of low birth weight?
Dr. Milner: I am very pleased you introduced the word "believe." I do not know of evidence in support of that specific statement. There is increased maternal erythropoiesis to keep up with the increase in the maternal circulating blood volume. So although the hemoglobin concentration falls, the total circulating red cell mass increases. With respect to folate and other vitamin supplements, the question is also very complicated.

Dr. Valyasevi: We have some data on iron deficiency anemia and on the effects of iron supplements in about 300 pregnant mothers with moderate iron deficiency anemia (hemoglobin concentration around 8 g/dl). We could not demonstrate any difference in birth weight between the unsupplemented and the supplemented group with a hemoglobin level of about 12 g/dl.

Dr. Milner: When one thinks of the oxygen-binding capacity of fetal hemoglobin versus maternal hemoglobin, I would be surprised if maternal anemia, be it iron deficiency or a macrocytic anemia, is an important variable in determining fetal cellular development.

Dr. Kraisid: You said that fetal growth can be divided into three trimesters characterized by an increase in cell numbers and size. You used muscle tissue as an example. Can the same be applied to other organs such as bone and brain?

Dr. Milner: Information is available on liver, heart, lung, and skeletal muscle. It is not available on brain, but Dobbing and Sands (1) have information on the brain in which neuronal and neuroglial tissue follow different patterns of cellular growth. I do not know of analogous information pertaining to prenatal skeletal growth in man.

Dr. Kraisid: In your opinion, what would be the critical period for supplementation in terms of all nutrient supplementation? Should we supplement poor pregnant women during the first, second, or third trimester?

Dr. Milner: If I had a very limited amount of food to give as supplementation, I would be more concerned that it went in trimesters 1 and 2 and less concerned about trimester 3.

Dr. Guesry: I think it is very difficult to give a clear answer to this very important question. For example, if you want to reduce the incidence of neural tube defects, it seems that the vitamin supplements need to be given even before conception.

Dr. Davies: You said that intrauterine size possibly holds a key position. A recent study from Sweden (2) has shown that the "terminal flattening" (slowing down of fetal growth in the last few weeks of gestation) is now much less than previously. I wonder whether you can fit this in with your hypothesis of small uterine size having a constraining effect on growth: that the reason for the high incidence of small-for-date babies in women who themselves have been malnourished may simply be that the uterus is too small to allow optimum growth expression. The opposite would apply to the Scandinavian women who have enjoyed excellent nutrition throughout their lives.

Dr. Milner: There is a circularity in this argument, and it is almost seductive in its plausibility; on the other hand, it does not have to be wrong. The statement that you make does not surprise me. The point that I find interesting is that it would take a number of generations to get a secular trend, which could appear partly prenatally as well as postnatally.

Dr. Nabarro: In countries where there is a pronounced seasonal variation in infections and in the availability of nutrients, and where there probably are 3 or 4 months that are considered to be totally adverse by the local population, the timing of conception and birth would appear to be of extreme importance in determining the potential for linear growth. There is a need to examine cohorts of children born in different seasons to study their linear growth rates and to relate these to the season of birth.

Dr. Guesry: Do we have any information on this from the Dutch famine in 1944–1945? It seems that starvation during the last trimester had the most severe effect.

Dr. Milner: I accept that starvation experienced in the last trimester would have a dra-
matic effect on body weight, and that 500 g of fat would just not appear, but those babies would not be permanently disadvantaged, whereas the ones who experience the same starvation during the first trimester and who are not aborted—and of course fertility goes down—are the ones who might have lifelong disadvantages.

**Dr. Colombo**: Could you comment on the effect of alcohol? I think it is a bigger problem than usually thought, at least in Chile. Could the amount of alcohol necessary to affect fetal growth be less than what is usually said?

**Dr. Milner**: Social drinking as opposed to alcoholism is quite sufficient to have an adverse effect on cellular development in utero, and this, as is also the case with smoking, is not related to a reduction in total caloric intake, which is being compensated for by ethanol intake.

**Dr. Martorell**: Another possible environmental factor is smoke, cooking smoke. One of the first things the very poor, who live in single-room huts, do when they have money is build a separate kitchen. The effect of cooking smoke on intruterine growth has never really been studied seriously.

**Dr. Milner**: That is an excellent example of what I had to end up thinking about. In our vast area of ignorance, there are possibly all sorts of other factors that could have an adverse effect on growth throughout pregnancy. I was thinking of some of the herbal medicines that are taken because they are reputed to be beneficial for pregnancy, but some of them plainly are not.

**REFERENCES**