Influences of Pre- and Postnatal Nutritional Exposures on Vascular/Endocrine Systems in Animals

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Human epidemiological and animal studies have revealed the long-term effects of malnutrition during gestation and early life on the health of the offspring. The aim of the current review is to survey the different means of achieving fetal malnutrition and its consequences, mainly in animals, and to identify key areas in which to direct future research. We address the impact of various models of a maternal protein-restricted diet and global maternal caloric restriction (either through the reduction of nutrient supply or through mechanic devices), the influence of maternal diabetes, and other maternal causes of fetal damage (maternal infections and toxic food components). More specifically, we enumerate data on how the different insults at different prenatal and early postnatal periods affect and program the development and the function of organs involved in diabetes, hypertension, and cardiovascular disease. Particular emphasis is given to the endocrine pancreas, but insulin-sensitive tissues, kidneys, and vasculature are also analyzed. Where available, the protective effects of maternal food supplementation for fetal organ development and function are discussed. Specific attention is paid to the amino acids profile, and the preventive role of taurine is discussed. Tentative indications about critical time windows for fetal development under different deleterious conditions are presented whenever possible. We also discuss future research and intervention. *Key words*: early malnutrition, endocrine pancreas, gestational diabetes, kidneys, taurine, vasculature. — *Environ Health Perspect* 108(suppl 3):563–568 (2000).
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Programming has been described as the process whereby a stimulus or an insult during a critical period of development has lasting or lifelong effects. Fetal growth is a complex dynamic process that depends on the continuous supply of nutrients from the mother. Supply from the mother could be altered by changes in maternal nutrition and/or placental function. The concept of early programming of degenerative diseases due to growth retardation *in utero* has developed during the last decade, prompted by the results of epidemiological studies in humans. These studies revealed associations between low birth weight or weight at 1 year of age and the subsequent development of type 2 diabetes, hypertension, ischemic heart disease, obesity, and insulin resistance (*1,2*). Indications of increased susceptibility to such conditions are often apparent in young adulthood (*3*) and even during infancy (*4*). The Thrifty Phenotype hypothesis (*5*) was proposed to explain the basis of such a relationship. This hypothesis suggests that a nutritionally deprived fetus adapts two strategies to ensure survival: first, it diverts nutrients to critical organs such as the brain at the expense of peripheral tissues such as muscle. Second, it is proposed that metabolic adaptations (programming) occur that maximize the short-term chances of survival under conditions of poor postnatal conditions.

The concept of early programming of adult diseases has been explored extensively in animal models. These animal models address, at least partially, the mechanism by which the memory of adverse nutritional and metabolic events early in life are stored and subsequently expressed later in life. It is possible that this is mediated by a reduction in cell number or by selective expansion of specific populations of cells. Indeed, both maternal protein (*6*) and global maternal food (*7*) restriction reduce β-cell mass of the offspring at birth. In the protein-restricted model, fetal insulin secretion is blunted (*8*) and the offspring are insulinopenic (*9*). When such female offspring themselves are pregnant, they cannot adapt to the increased insulin demand (*10*). Consequently, the development of the fetal pancreas in the second generation is also impaired (*11*). This opens the way for a possible vertical transmission of the deficit. Parallel studies in the offspring of protein-restricted dams have suggested that such early growth retardation is associated with changes in hepatic metabolism suggestive of the selective expansion of periportal as opposed to perivenous type cells (*12*).

In vitro studies also showed that gene expression may be modified permanently after exposure to specific nutrients (*13*).

Recent human and animal studies addressed the consequences of an imbalance between fetal and postnatal growth. Rat studies showed that growth restriction *in utero* followed by rapid postnatal catch-up growth is detrimental in terms of longevity (*14*). Epidemiological studies similarly revealed that individuals who were growth restricted *in utero* and undergo catch-up growth in childhood are at increased risk of cardiovascular disease.

We review the data from a number of animal models where fetal growth has been compromised by maternal malnutrition, surgical intervention, maternal diabetes, or maternal infection. These models have been used to elucidate the link between maternal health and the occurrence of diabetes, hypertension, and cardiovascular disease. We thus focus on effects on the endocrine pancreas, insulin-sensitive tissues, kidney, and blood vessel development and reactivity. The consequences of different degrees of malnutrition at different periods of development are present with the aim of identifying critical windows. However, the results are sometimes disparate and therefore the conclusions are tentative.

Fetal Malnutrition Jeopardizes the Development of Different Organs

Protein Restriction during Gestation and Lactation

Organ and tissue development. **Endocrine pancreas.** Maternal protein restriction (8 vs. 20% protein) in the presence of adequate calories during pregnancy leads to disturbances in the development of the endocrine pancreas of the rat progeny. Fetal and neonatal β-cell mass is lower and therefore pancreatic insulin content is reduced. Islet size is decreased because islet cell proliferation is diminished (*6*) and more β-cells are apoptotic (*15*). These β-cells have less of the surviving factor IGF-I and IGF-II than normal β-cells and the G_1 phase of their cell cycle is lengthened (*15*). In addition, the function of these fetal β-cells is affected, as demonstrated by a 50% reduction in insulin secretion in response to various secretagogues when compared to controls (*8*). Moreover, islet vascularization is also reduced (*6*).

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Some alterations acquired *in utero* are permanent; a 20% protein diet given postnatally is unable to restore fully a normal structure and function of the endocrine pancreas by adulthood (*10*). Low-protein female offspring suckled by a normal mother and weaned onto a control diet have a lower plasma insulin level. However, glucose levels appear comparable to controls when fasted and after an oral glucose challenge. At 3 months of age, islets from low-protein female offspring are larger; however, the pancreatic insulin content is decreased. This may suggest an increased proliferative rate but a reduced rate of neogenesis (resulting in fewer islets) during fetal development in the growth-restricted group (*10*). Thus, fetal life appears to be a critical time window for the function and structure of the endocrine pancreas. A more severe protein restriction (5%) given only during the last week of gestation in the rat (the period of the final development of the endocrine pancreas) also leads to lower pancreatic insulin content and lower β-cell mass at adulthood (*16*). However, in general, the stages most susceptible to protein restriction during gestation remain to be clearly determined.

The early postnatal period could also be sensitive to maternal malnutrition. Potentially important events in pancreatic islet ontogeny have been recognized in the neonatal rat. A wave of apoptosis occurs between 1 and 2 weeks of age in islets of neonatal rat fed a normal diet (*17*). This is compensated by differentiation and proliferation of β-cells, so β-cell mass is maintained. Although the wave of apoptosis occurs in low-protein progeny at the same period as that of the control pups, the rate of apoptosis was increased and β-cell proliferation decreased (*15*). This may explain the decrease in islet size and β-cell mass during the postnatal period in these growth-restricted offspring. The lasting consequences of malnutrition during this specific period have not been investigated, but when the low-protein diet is present during gestation and lactation, females as well as male adult offspring are insulinopenic (*11*).

Glucose tolerance. Insulin secretion of adult progeny of mothers whose protein intake was 8% instead of 20% during pregnancy is not normalized even when a normal diet is made available postnatally (*10*). During pregnancy such offspring are unable to increase their insulin level in response to the demands of pregnancy and are glucose intolerant (*10*). In young adult life, the offspring of rats fed 8% protein diet instead of 20% protein during pregnancy and lactation have a better glucose tolerance than control offspring (*18*). However, these offspring undergo a greater age-dependent loss of glucose tolerance compared to controls such that by 15 months of age these animals have a significantly worse glucose tolerance than controls (*9*). There are also data to suggest that this deterioration can be accelerated by the provision of a high-fat diet (*19*).

Insulin-sensitive tissues. Maternal low-protein diets (8 vs. 20%) have large effects on insulin-sensitive tissues in the offspring. Livers of low-protein offspring have changes in enzyme activities involved in glucose metabolism. A reduced glucokinase activity and an increased phosphenol-pyruvate carboxykinase activity were observed at weaning and in adulthood in offspring of dams fed a low-protein diet during gestation and lactation or during gestation alone (*12*). These changes appeared to be associated with an increased hepatic glucose output (*20*). In young adult life, low-protein offspring express more insulin receptors in liver (*21*), adipocytes (*18*), and skeletal muscle (*22*) compared to controls. A compensatory increase in whole-body insulin sensitivity is likely to explain the better glucose tolerance observed in young low-protein offspring, despite their impaired insulin secretion. Consistent with increased insulin sensitivity, an altered distribution of Glut 4 protein in muscle is apparent (the level is increased in the plasma membrane of muscle under fasting conditions). In young adulthood, adipocytes from low-protein offspring have increased basal and insulin-stimulated glucose uptake and a phosphatidyl inositol 3 kinase (*18*). The impact of moderate maternal protein restriction (8 vs. 20%) during pregnancy and lactation is also apparent when adipocytes of the pregnant offspring are tested for glucose uptake in response to various insulin concentrations. Protein restriction enhances the capacity for adipocytes to take up glucose at high concentrations but dampens the response to insulin at low physiological concentrations, which demonstrates the programming of the adipocytes the maternal diet (*23*).

Vasculature. Lifelong elevation of blood pressure is another consequence of protein undernutrition *in utero*. In rats, fetal exposure to a maternal low-protein (9 vs. 18%) diet was associated with abnormal fetal growth and later elevation of blood pressure. The placental enzyme 11β hydroxy-steroid-dehydrogenase activity was reduced when a low-protein diet was administrated during pregnancy (*24*). This was suggested to result in increased exposure of the fetus to maternal glucocorticoids with potential deleterious consequences for fetal organ development (*25*). Plasma angiotensin-converting enzyme activity was permanently elevated in such conditions (*26*). Another mechanism requiring further investigation is the modification of the hypothalamic–pituitary–adrenal (HPA) axis, which may also be responsible for alterations in the homeostatic mechanisms controlling blood pressure in adulthood.

Vascular structure of different organs during development was also disturbed in the offspring of dams fed a low-protein diet during gestation (8 vs. 20%). At birth, islet (*6*) as well as the cerebral cortex (*27*) had a lower blood vessel density. Long-lasting consequences of the maternal diet were evaluated in these two organs. The blood vessel density of the brain remained lower at adulthood even when a normal diet was given after birth. However, blood vessel density can be restored in rodent islets in adulthood when a 20% protein diet was provided at birth (*27*). Thus, the critical window for the vascularization of the brain seems to be fetal life, whereas that for the endocrine pancreas seems to be postnatal. Blood flow was normal in different organs (islets, exocrine pancreas, colon, kidney, and duodenum) from the progeny of a mother fed a low-protein diet during gestation but fed a normal diet after birth (*28*). It should be noted that, when the protein deprivation was maintained after birth, blood vessel density remained lower in the islets, the endocrine pancreas, the duodenum, the brain (*27*), and the retina (*29*). This is associated with functional vascular defects in the islets, the exocrine pancreas (*28*), and the retina (*29*). For islet vascularization, one could predict that the phase of remodeling of β-cell mass after birth, described previously (*17*), would create a critical time window during lactation. However, data concerning the impact of a low-protein diet on islet vascularization during this period alone are not yet available.

Kidneys. Kidney weights of neonates are reduced by a low-protein diet given to the pregnant mother in species such as rats and subhuman primates. In the latter, this is induced specifically by protein restriction and is not observed in cases of caloric constraint when protein intake remained adequate in the maternal diet (*30*). In rats, mature glomeruli were reduced in number and immature glomeruli increased in kidneys of low-birth-weight pups born from dams fed a 5% protein diet from day 8 of gestation (*31*).

There is a broad critical window for the effect of a maternal low-protein diet on the kidney—effects that are observed when the insult is maintained throughout gestation or in mid to late gestation alone. At term the total number of nephrons is reduced relative to controls in rats that were protein undernourished throughout gestation as well as between gestation days 8 and 14 or 15 and 22. These rats have a reduced (13%) nephron mass at 4 weeks postnatally and their blood pressure is raised 13 mmHg compared to control animals. Lower renal size and elevated blood pressure persist to 19 weeks of age, at which time glomerular filtration rate is normal. Kidney weight relative to body weight at

3 months of age was still reduced despite the introduction of a control diet postnatally (*32*).

In conclusion, the postnatal recuperation of the alterations in the endocrine pancreas, insulin-sensitive tissues, the vasculature, and the renal glomeruli is not assured in the offspring when a poor protein diet is given during pregnancy or during pregnancy and lactation even with a normal protein diet postnatally.

Hence, adequate protein intake is a crucial factor to be considered during pregnancy that affects fetal development. The fetal period is a critical time window for organs responsible for degenerative diseases in adulthood.

Amino acid metabolism. A deficient protein intake (8 vs. 20%) by the mother modifies the amino acid profile in maternal and fetal plasma as well as in the amniotic fluid, although it does not change the maternal and fetal glycemia and insulinemia. More specifically, alpha amino butyric acid, phosphoserine, leucine, isoleucine, taurine, and valine were reduced (*33*). Taurine, which has many intra- and extracellular functions, especially in the fetus, was the amino acid most affected (*33*). This might be due to the down-regulation of the placental transporter. Enzyme activities such as those of cystathionase and cysteine sulfinate decarboxylase responsible for the endogenous production of taurine are lower in pregnant than in nonpregnant females. With protein restriction, the activity of cysteine dioxygenase (cystathionase) decreases and cysteine sulfinate carboxylase increases (*34*). These adaptations of sulfur amino acid-producing enzymes to low-protein intake during gestation may affect the availability of taurine for the fetus and the neonate.

Taurine is abundant in several tissues (*35*) including the endocrine pancreas (*36*). In animal experiments, taurine deficiency during gestation and lactation is associated with growth failure, abnormal cerebellar development, neurological deficit, retinal degeneration, and cardiac damage (*35*). Taurine is also an insulin secretagogue for fetal β-cells, at least *in vitro* (*37*), but is unable to stimulate insulin secretion *in vitro* from β-cells from the fetuses of low-protein-fed dams (*38*). These β-cells are also poorly sensitive to other secretagogues. However, supplementation of taurine in the drinking water of low-protein-fed dams normalized their plasma taurine levels and those of their fetuses, resulting in normal secretion of insulin secretion from the fetal β-cells (*38*). It is thus clear that appropriate fetal plasma levels of taurine are essential for fetal β-cells to acquire a normal secretory function.

Other developing tissues such as the vasculature might also be sensitive to changing taurine availability. In adult rats, intravenous taurine administration modulates the content of other amino acids in several blood vessels such as the aorta (*39*). In young subhuman primates, low protein intake is also associated with changes in plasma sulfur amino acids levels and causes major early vascular damage. Furthermore, specific modification of the sulfur amino acid levels such as increased plasma homocysteine in adulthood have been correlated with chronic heart disease (*40*). Vascular changes encountered in congenital homocysteinuria have been attributed to the metabolic effects of elevated tissue concentrations of methionine, homocysteine, homocysteine, or to the metabolic consequences of decreased tissue concentrations of cystionine. Hence, individuals with a predisposition to vascular anomalies induced by protein malnutrition during intrauterine growth may possibly endure further vascular damage if adult concentrations of homocysteine or homocysteine derivatives are elevated or if taurine levels are low.

Pyridoxine-deficient monkeys develop arteriosclerotic lesions that could be explained by potentially elevated homocysteine concentrations initiating vascular damage. Pyridoxine is a cofactor both for cystathionine synthethase and cystathionase and is therefore responsible for the proper metabolism of homocysteine. Vitamin B12, folic acid, and vitamin B6 activate enzymes responsible for amino acid production and metabolism and have been used as a prophylactic measure in homocysteinemia associated cardiovascular disease (*41*). Similarly, supplementation folate during fetal development has been suggested to prevent neural tube defects (*42*).

Protein Restriction after Weaning

Endocrine pancreas. In rats, pups fed a low-protein diet (5 instead of 15%) from weaning for 3 weeks failed to gain weight, but growth resumed immediately when they were returned to a normal diet. However, this short nutritional insult had long-term effects on the structure and the function of the endocrine pancreas. At 6 weeks, β-cell mass and β-cell size of the low-protein pups were lower compared to control pups. β-Cell mass remained lower, which led to a diminished insulin reserve (*43*). This lower β-cell mass may predispose to glucose intolerance after an oral glucose challenge. In such conditions, insulin response is blunted and remains blunted at 12 weeks (*44*). When such islets are stimulated *in vitro* with glucose or arginine, insulin release is lower at 6 weeks as well as at 12 weeks (*45*). During malnutrition, the low-protein animals show increased insulin sensitivity in muscle and hepatocytes that diminished with age (*46*). Therefore, temporary protein restriction at a young age impairs pancreatic β-cell function and decreases peripheral sensitivity to insulin. These data indicate that protein deprivation during growth has permanent implications for health later in life.

Global Caloric Restriction during Gestation and Lactation

Endocrine pancreas. Global caloric deprivation during fetal life also has deleterious consequences for the development of the endocrine pancreas. A 50% reduction in caloric intake during the last week of gestation in rat leads to growth-retarded pups (*7*). At birth such offspring have lower β-cell mass and pancreatic insulin content due to a reduced rate of neogenesis, which is maintained even when a normal caloric diet is given after birth. Altered β-cell development also occurs when maternal food restriction (50% of *ad libitum* intake) is prolonged until the end of lactation and *ad libitum* feeding is introduced from weaning (*47*). This relatively late global food restriction in gestation decreases β-cell mass and has long-term effects on the evolutionary stages of the β-cell, with increased apoptosis and decreased neogenesis, whereas proliferation is not affected. This contrasts with observations in low-protein pups where β-cell proliferation was reduced *in vivo* (*6,15*). Subsequent renutrition after weaning is followed by an increased β-cell proliferation that is not sufficient to restore a normal β-cell mass (*48*). Adequate adaptation to pregnancy is not possible because β-cell mass does not expand and apoptosis is increased (*49*). The processes that global restriction may have initiated and the metabolic change occurring in the mother and fetus which might be responsible for structural alterations of the endocrine pancreas have not been fully analyzed.

Glucose tolerance. Such pancreatic alterations have consequences for glucose metabolism. In animals with a decreased β-cell mass at adulthood, additional demands such as pregnancy (*49*) or aging (*48*) lead to glucose intolerance.

Vascular system and the HPA. In sheep, global undernutrition in early pregnancy produces a reduction in the birth weight/placental weight ratio (*50*). In contrast, in early to mid gestation such an insult produces an increase in placental growth, whereas in late gestation it only reduces fetal growth (*51*).

Early undernutrition achieved by a 15% reduction of food intake of the mother during the first 70 days of gestation affects the development and responses of the HPA in late gestation. Both the pituitary response to an arginine vasopressin/corticotrophin-releasing hormone challenge and the adrenal cortical response to an adrenocorticotrophic hormone (ACTH) challenge are reduced (*52*). These fetuses have a lower basal plasma cortisol concentration, which may account for their lower arterial blood pressure (*53*).

Cardiovascular and HPA axis development are also influenced postnatally. Lambs born after periconceptual undernutrition have higher arterial blood pressures and an exaggerated arterial blood pressure response to an HPA axis challenge (*52*). Their ACTH and cortisol responses are also greater. Therefore there is a switch from a blunted response *in utero* to enhanced responses postnatally when undernutrition occurred early in gestation.

The effects of undernutrition in early gestation are also manifest at the level of local vasculature. The responses of small arteries, especially to endothelium-dependent vasodilator agonists, are altered in ewes and fetuses (*54*). Similar effects have also been reported in experimental diabetes and with a high-fat diet in the rat, although the mechanisms are unknown.

Growth retardation is also provoked by the removal of placental caruncles or single arterial uterine ligation in ewes or dams, respectively. The sheep fetuses have lower mean arterial blood pressure, higher heart rate, and altered response to an episode of acute hypoxia in late gestation (*55*). Fetal heart rate and the rise in arterial blood pressure are greater in carunclectomized fetuses, suggesting the acquisition of greater chemoreflex or endocrine responses.

Such hypoglycemic and hypoaxemic fetuses have higher levels of adrenaline and noradrenaline, suggesting greater sympathetic activity. Their higher levels of cortisol without increased ACTH and suppressed pituitary pro-opio-melanocortin expression also suggest a potential alteration of the HPA feedback, which may also affect maturation of organ systems and initiation of parturition (*56*).

Reports of the effects of maternal global dietary restriction in rats do not arrive at the same conclusion. It appears that the timing of the insult in gestation is critical, with insults that occur earlier having greater effects on cardiovascular development in the offspring. Also, when the reduction of the total intake was only 30% of the appropriate daily requirement throughout gestation, only male pups were smaller than controls. Nonetheless, they showed perturbed vascular development, particularly in arterial blood pressure and in the response of small vessels to vasodilator agonists (*54*). In contrast, when 50% food restriction occurs during the second half of pregnancy or during the second half of pregnancy and lactation, no significant differences in heart rate or systolic and diastolic blood pressure were detected in conscious female offspring (*57*). When isolated resistance artery function was assessed *in vitro*, small mesenteric arteries showed reduced endothelium-dependent relaxation to acetylcholine and bradykinin but enhanced sensitivity to exogenous nitric oxide. Therefore, subtle changes in vascular function were acquired early during development (*57*).

Interestingly, the growth of the spontaneously hypertensive rat (SHR) is reduced at days 16–20 but is normal at birth. Growth retardation is associated with a placenta larger than normal (*58*). Postnatally, the cardiovascular function was abnormal; the spontaneously hypertensive pups had larger hearts and kidneys. SHR blood pressures are permanently lowered when angiotensin conversion enzyme inhibitors are given during gestation or if the pups are nursed by normotensive dams for 2 weeks after birth. The milk of SHR differs from the milk of other strains in protein and electrolyte concentrations (*59*). The intrauterine environment of the SHR is different, with a high osmolarity and sodium concentration in the amniotic fluid. Maternal diabetes in SHR will further affect blood pressure in the offspring.

Most strikingly, taurine administration prenatally and postnatally to dams with spontaneous hypertension lowered the blood pressure in the offspring at least until 3 months of age (*60*). Taurine administration to suckling rats induced a greater reduction in blood pressure than in the group given taurine prenatally but not postnatally. Therefore, early dietary intake of sulfur-amino acids such as taurine delays and possibly prevents the onset of the hypertension as well as attenuates the development of both severe hypertension and atherosclerosis in SHR.

A critical window of exposure appears during gestation and lactation for blood pressure control and atherosclerotic damage, which may be linked with the metabolism of sulfur amino acids. Taurine has a specific preventive effect during fetal and early postnatal development.

Adipose tissue. Nutritional deficiencies during pre- and postnatal growth cause marked morphophysiological changes in the adipose tissue and its distribution. Under some circumstances these changes are irreversible. Dysfunctions in the neural control of adipocyte metabolism seem to lead to obesity, insulin resistance, and, subsequently, glucose intolerance. Early intrauterine global malnutrition modifies the adipocyte and the control of food intake in the offspring, which causes the offspring to become hyperphagic and obese (*61*). In both male and female offspring, hypertrophy of adipocytes and marked fat deposition occur with an hyperlipidic diet later in life. However, there are sex-specific differences. Males have an impaired weight gain and fat deposition associated with hormonal changes. Females feature a marked fat accumulation and diminished brown adipose tissue activity. Thus, the maternal diet may have long-term effects of the susceptibility of an individual to becoming obese.

Kidneys. In rats, unilateral uterine artery ligation leading to fetal caloric restriction and intrauterine growth retardation leads to smaller kidneys with a reduced number of glomeruli at birth. Altered development of the kidneys could not be restored postnatally (*62*).

Maternal Diabetes Permanently Alters the Development of the Different Organs in Offspring

Organ Development

Maternal diabetes affects fetal tissue development in humans (*63*) and experimental animals (*64,65*). It may induce congenital malformations. Epidemiological observations in humans have identified specific time windows for fetal organs having acquired a malformed structure because of increased blood sugar in the mother. These effects on organ structure occur before the 12th week of pregnancy. Congenital malformations may affect more specifically the vascular, genitourinary, and neurological systems, depending on the time of the insult. The causal mechanisms for congenital malformation are continuously explored and have been attributed to increased cellular oxidation and a lack of scavengers or vitamins such as vitamin A or vitamin B12. Maternal diabetes has been associated with both higher and lower birth weights of the offspring. Organ development is affected in both instances; heart, kidney, liver, adrenal, adipose tissue, and endocrine pancreas are the most affected. Besides high blood sugar, other metabolic disturbances occur in the diabetic mother, such as a modified amino acid profile (*66*) and lipid disturbances or catabolic effects related to poorly controlled diabetes (*64*). Both types of neonates (those with high or low birth weights) have an increased risk of diabetes at adulthood.

Endocrine pancreas. Macrosomic human neonates have an increased percentage of pancreatic endocrine tissue with β-cell hyperplasia and high vascularity (*67*). Similar alterations associated with an increase in degranulated β-cells are provoked by mild diabetes induced by streptozotocin in rats (*68*). The proliferative capacity of the islet cell was increased *in vivo*, and it remained elevated when cultured in a normal medium for 7 days (*65*). At adulthood, these pups became glucose intolerant, which was associated with insulin depletion in their islets of Langerhans. A decreased islet size and β-cell mass were also induced by severe maternal diabetes experimentally produced by streptozotocin. β-Cell proliferation rates *in vivo* and *in vitro* were decreased (*69*). These pups became insulin resistant and diabetic at adulthood (*70*). There are also effects of maternal streptozotocin-induced diabetes on the responses of small resistance arteries in pups (*71*).

Kidneys. The effect of maternal hyperglycemia on kidney development in the rat has recently been reported. Maternal hyperglycemia has been induced throughout gestation by one injection of streptozotocin or by infusing glucose from gestational days 12–16. In both experimental situations, kidney development was altered; the number of nephrons was lower than in offspring from a normal pregnancy. This may have serious consequences on renal function (*72*).

Amino Acid Metabolism

Total amino acid concentration was normal in mildly diabetic rats but was decreased in severely diabetic rats. It was also decreased in the fetal plasma regardless of the severity of the maternal diabetes (*66*). Moreover, the amino acid profile was altered in the feto-maternal unit. It is interesting to note that, as in the low-protein model, branched amino acids and taurine were most affected in the fetuses of mildly diabetic rats.

Other Adverse Early Life Exposures

Not only prenatal and early postnatal nutrition influence the risk of developing chronic degenerative diseases. Among the environmental influences imposed by the mother are the effect of nitrosamine intake during gestation on diabetes in male offspring, rubella infection during gestation on diabetes in HLA-predisposed progeny, and cytomegalic infection during pregnancy on early diabetes onset in descendants.

Epidemiological studies revealed a high prevalence of diabetes type 1 occurring in children or young adults who were followed up for complications of fetal rubella embryopathy syndrome (*73*). These cases seem to carry the same HLA-susceptibility genes (*74*). Similar observations have been made in relation to the cytomegalic virus, as well as coxsackie B4, which is transmitted from mother to fetus in many instances and which induces diabetes at a later stage (*75*). In the early 1980s, an epidemiological study from Iceland revealed a clustering of birth dates of type 1 insulin-dependent-diabetes children in October (*76*). The interpretation was that it was caused by the high intake of cured smoked mutton (containing a large amount of nitrosamine) very early in pregnancy, because around Christmas large amounts are consumed in Iceland. Experimental animal studies confirmed this maternal influence for developing diabetes later in life (*77*).

Changes in vitamin A supply to the fetus may prove responsible for most variations in nephrons, which are a major cause in inborn nephron deficit, either as a feature of intrauterine growth retardation or independently of growth retardation. The possibility that vitamin A status may also influence renal vascular development has also been suggested (*78*).

Conclusions

The intrauterine milieu is the first environment that the fertilized ovum encounters. Both epidemiological and experimental studies emphasize the impact of this first environment on fetal development. Experimental conditions in dams such as protein restriction, caloric reduction, diabetes, or even environmental toxicants emphasize their impact on the offspring and allow us to establish causal relationships between events early in life and later disease on the basis of metabolically induced mechanisms. Several tissues involved in the endocrine/vascular system are affected. Some of these changes, which result in a suboptimal maternal environment, only manifest themselves in adulthood. The incipient alterations leading to degenerative complications in the endocrine/vascular system may occur without changes in birth weight, which is a crude proxy for intrauterine events. Lifestyle, including postnatal nutrition, may influence the delay or the haste of appearance of health alterations in adulthood.

Several considerations have still to be made when the origin of adult diseases is to be related with early life events:

- Intergenerational effects have been observed and some mechanisms have been elucidated under conditions of maternal protein or caloric restriction and diabetes (*10,64*).
- Many factors may intervene in the fetal growth and size leading to a birth weight that is less than optimal. The fetal genotype, the maternal genotype, the mother's nutritional status during pregnancy, her metabolism and physiology, and the resultant hormonal and circulatory milieu all may have strong influences. Growth-arrest genes may also intervene in the early determination of fetal growth. They are highly sensitive to nutritional supply (*13*) and have a diverse range of function such as the control of cell–cell communication and the induction of apoptosis. Hence the environmental conditions imposed on the fetus by the mother may interact with the genetic influences on birth weight and presumably other functional changes in the neonate.

A specific deficiency in the mother, such as iodine, is associated with neonatal goiter and hypothyroidism could be averted by the single reinforcement of iodine in maternal food. Catabolic events such as infections will modify amino acid availability in the fetus, which will affect its growth. However, for all of the potential factors involved, there is a need to determine the specific mechanisms by which these affect fetal development. This may ultimately lead to the development of ways to modulate the early environment and to engage in primary prevention of chronic degenerative diseases.

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