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REVIEW ARTICLE

MECHANISMS OF DISEASE

Effect of In Utero and Early-Life Conditions on Adult Health and Disease

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A LONG LATENCY PERIOD BETWEEN AN ENVIRONMENTAL TRIGGER AND the onset of subsequent disease is widely recognized in the etiology of certain cancers, yet this phenomenon is not generally considered in the etiology of other conditions such as cardiovascular disease, metabolic disease, or osteoporosis. However, many lines of evidence, including epidemiologic data and data from extensive clinical and experimental studies, indicate that early life events play a powerful role in influencing later susceptibility to certain chronic diseases. An increased understanding of developmental plasticity (defined as the ability of an organism to develop in various ways, depending on the particular environment or setting) provides a conceptual basis for these observations.¹

Developmental plasticity requires stable modulation of gene expression, and this appears to be mediated, at least in part, by epigenetic processes such as DNA methylation and histone modification. Thus, both the genome and the epigenome interactively influence the mature phenotype and determine sensitivity to later environmental factors and the subsequent risk of disease. In this review, we synthesize evidence from several disciplines to support the contention that environmental factors acting during development should be accorded greater weight in models of disease causation.

EPIDEMIOLOGIC AND CLINICAL OBSERVATIONS

The epidemiologic observations that smaller size or relative thinness at birth and during infancy is associated with increased rates of coronary heart disease, stroke, type 2 diabetes mellitus, adiposity, the metabolic syndrome, and osteoporosis in adult life²⁻⁶ have been extensively replicated. Perinatal events appear to exert effects that are independent of environmental risk factors in adults^{7,8} or may be amplified by other risk factors.⁹ Slow growth in utero may be associated with increased allocation of nutrients to adipose tissue during development and may then result in accelerated weight gain during childhood,^{10,11} which may contribute to a relatively greater risk of coronary heart disease, hypertension, and type 2 diabetes mellitus. There is a continuous relation between birth weight and future risk — not just for extreme weights but also for normal weights.¹² Prematurity itself, independent of size for gestational age, has been associated with insulin resistance and glucose intolerance in prepubertal children¹³ that may track into young adulthood and may be accompanied by elevated blood pressure.¹⁴

In mammalian development, the mother transduces environmental information such as nutritional status to her embryo or fetus through the placenta or to her

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infant through lactation. Fetal growth is generally matched to the mother's body size (rather than to genetic potential) through what is termed maternal constraint.^{15,16} Maternal constraint may be mediated, in part, by the limiting effects of placental size in utero or perfusion on fetal nutrition, but imprinted genes, particularly those linked to the expression of growth factors, may also play a role in the allocation of nutritional resources.¹⁷ Maternal constraint is increased with short maternal stature, young or old maternal age, first pregnancy, or multiple pregnancy; in addition, the effects of unbalanced maternal diet or excessive maternal thinness or fatness influence fetal nutrition in the absence of other disease. Beyond these mechanisms, fetal development may be further impaired by poor placental function or maternal disease, each of which can influence several points along the pathway from the mother's intake of food to the delivery of nutrients to growing fetal tissues.¹⁸

The developmental-origins hypothesis proposes that an altered long-term risk of disease is initially induced through adaptive responses that the fetus or infant makes to cues from the mother about her health or physical state. Fetal or perinatal responses may include changes in metabolism, hormone production, and tissue sensitivity to hormones that may affect the relative development of various organs, leading to persistent alterations in physiologic and metabolic homeostatic set points. Thus, the association between reduced fetal growth rate, small body size at birth, and a later risk of disease may be interpreted as reflecting the long-term consequences of fetal adaptive responses. However, reduced overall fetal body growth is seen not as causing the long-term consequences but rather as constituting a marker of a coordinated fetal response to a limiting intrauterine environment, resulting in changes in tissue and organ development that are not necessarily evident at birth but that result in perturbed responses later in life.¹⁹

The effects of subsequent environmental exposures during infancy, childhood, and adult life may be influenced by these past exposures and may condition the later risk of disease. For example, there are hints from a cross-sectional study that insulin resistance develops at a lower body-mass index in British children of South

Asian ancestry than in British children of European ancestry,²⁰ perhaps reflecting the lower birth weight of the South Asian children, which is the result of different statures and nutritional states of the mothers.

When undernutrition during early development is followed by improved nutrition later in development, whether during late gestation or the early postnatal period, many mammals retain some capacity to compensate, by increasing their growth rate. Life-history theory predicts that such compensatory changes will carry costs — for example, a reduced life span as a result of diversion of resources from repair capacity to growth.²¹ This may explain why rapid childhood growth, especially in people who were born small or were thin in infancy, appears to have deleterious effects on later health.^{10,11}

Although it has been proposed that the associations between fetal and infant growth and later adult disease represent the multiple (pleiotropic) effects of genes transmitted from mother to child,²² maternally mediated environmental modulation of gene expression in offspring may be more important than purely heritable genetic risk. Studies of osteoporosis provide one example. Currently identified genetic markers explain only a small proportion of the variation in individual bone mass and risk of fracture,²³ as exemplified by the relatively weak associations between, on the one hand, single-nucleotide polymorphisms in the genes for the vitamin D receptor, type 1 collagen, or growth hormone and, on the other hand, adult bone density or bone loss. In a study of a small cohort of elderly subjects,²⁴ no significant association was found between either birth weight or vitamin D receptor genotype and bone mineral density; however, the relationship between lumbar spine bone mineral density and vitamin D receptor genotype varied according to birth weight (Fig. 1). These data hint that genetic influences on vitamin D response, and therefore on adult bone mineral density, might be modified by undernutrition in utero. The results of studies involving twins appear to support these observations: in a cohort study of female twins (4008 subjects), there was significant residual intrapair concordance between birth weight and bone mass, even between monozygous twins, suggesting that a larger proportion

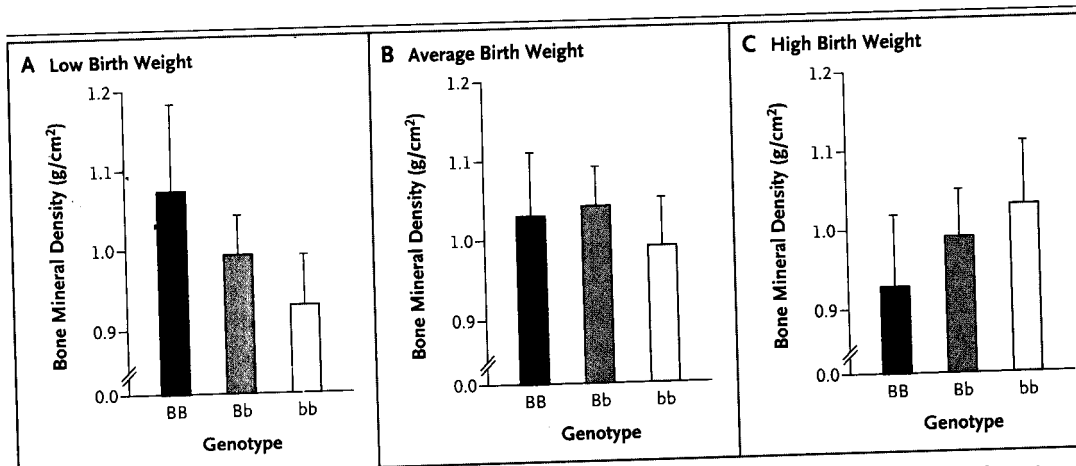


Figure 1. Birth Weight and the Relationship between Lumbar-Spine Bone Mineral Density and Vitamin D Receptor Genotype in Elderly Men and Women.

Among persons in the lowest third of the birth-weight distribution, spine bone mineral density was significantly higher among persons of genotype BB than among persons of the Bb or bb genotype ($P=0.01$) after adjustment for age, sex, and current weight. In contrast, in the highest third of the birth-weight distribution, spine bone mineral density was reduced among persons of genotype BB as compared with persons of the Bb or bb genotype ($P=0.04$). A significant interaction was found between vitamin D receptor genotype and birth weight as determinants of bone mineral density ($P=0.02$). Adapted from Dennison et al.²⁴

of variation in birth weight and bone mass in the population may result from the intrauterine environment than from genomic inheritance.²⁵

Much attention has been focused on fetal undernutrition as a facilitator of predisposition to later disease, but there is evidence that excessive energy supply to the fetus or infant also has adverse consequences. Maternal hyperglycemia, for example, may lead to fetal hyperinsulinemia and fat deposition, and substantial data suggest that the offspring of obese women or women with diabetes are at greater risk for developing metabolic disorders themselves, even during childhood.^{26,27} Thus, the relation between prenatal nutrition and later metabolic disease is likely to be U-shaped, with increased risk at both ends of the birth-weight curve. Infants who are fed formula have a higher energy intake and, in general, greater early gain in body weight than breast-fed infants, and they appear to have a greater risk of obesity in later life,²⁸ findings that suggest further complexity of the long-term effects of prenatal and early-life nutrition. In addition, epidemiologic studies have drawn other associations between higher birth weights and greater risk in adults of other conditions, such as breast cancer.²⁹

PHYSIOLOGICAL, CELLULAR, AND MOLECULAR BASES OF DEVELOPMENTAL PLASTICITY

INTEGRATED RESPONSES

The biologic basis for invoking developmental plasticity as an influence on the risk of disease derives from numerous studies in animals in which dietary, endocrine, or physical challenges at various times from conception until weaning induce persistent changes in cardiovascular and metabolic function in the offspring. The most commonly used animal models involve a prenatal nutrient imbalance, which can be induced by a global reduction in overall maternal food intake³⁰ or by protein restriction in an isocaloric diet,³¹ or glucocorticoid exposure (without any change in diet).³²

Embryos of pregnant rats fed a low-protein diet during the preimplantation period (0 to 4.25 days) show altered development in multiple organ systems, and if the gestation was permitted to reach term, the offspring had reduced birth weights, relatively increased postnatal growth, or adult-onset hypertension.³³ This outcome may reflect a direct effect on the environment of the fertilized ovum, since other rodent studies have

shown that *in vitro* culture from the two-cell stage to the blastocyst followed by embryo transfer, or even transfer at the blastocyst stage without previous culture, may result in elevated blood pressure in adult offspring.³⁴ The periconceptional period is clearly one of particular sensitivity, since even specific nutrient deficiencies (of B₁₂, folate, or methionine) at this stage can have effects on later metabolism and blood pressure in sheep³⁵; imbalance in maternal B₁₂ and folate status during pregnancy has recently been reported to contribute to childhood insulin resistance in humans.³⁶

The administration of glucocorticoids to the pregnant rat at specific points during gestation has been reported to cause hypertension³⁷ and insulin resistance³⁸ in the offspring in later life, as well as alterations in gene expression in the developing brain of the offspring and increased sensitivity to postnatal stress.³⁹ In the rat, maternal undernutrition during pregnancy may result in offspring that later show central obesity and reduced skeletal-muscle mass, altered insulin sensitivity, altered hepatic metabolism, reduced numbers of nephrons, hypertension, and altered endothelial function, together with altered appetite regulation, level of activity, and neuroendocrine control.^{30,31,40,41} Postnatal stress, in the form of reduced grooming and licking by the mother, has been shown to induce neurodevelopmental changes in rat pups that lead to excessive behavioral and hypothalamic-pituitary axis responses to stress later in life; such variations in maternal behavior appear to have effects on glucocorticoid-receptor gene expression in the hippocampus of the offspring.⁴² As in humans, however, the effects of early cues are complex. For example, in the offspring of rats, increases in blood pressure induced by a maternal low-protein diet are influenced by sex,^{33,43} estrogen level,⁴⁴ and the particular composition of the diet⁴⁵ and are subject to postnatal environmental factors.^{46,47}

There are several reported similarities, such as induction of hypertension and altered insulin sensitivity, between the effects of maternal nutritional challenges and glucocorticoid challenges on the offspring, findings that suggest common mechanisms. One hypothesis is that unbalanced maternal nutrition might lead to increased fetal cortisol levels or might alter the expression of the glucocorticoid receptor,^{48,49} influencing growth

and maturation of fetal organs. Such alterations might cause preterm delivery and might also affect the long-term function of many organs.⁵⁰ However, an elevated fetal cortisol level is unlikely to account for all the effects produced in animal models by manipulation of the intrauterine milieu, especially those induced by imbalanced periconceptional nutrition.⁵¹

EXPERIMENTAL DATA RELEVANT TO HUMAN DISEASE

There are critical periods in the differentiation and maturation of the tissues and cells involved in organogenesis throughout gestation and early postnatal life. We illustrate this concept using the examples of the kidney, heart, and pancreas, since their functional units are formed prenatally in the human fetus. The subject of environmental perturbations, organogenesis, and perinatal effects is extensively reviewed elsewhere.^{19,52}

In the kidney, maternal dietary imbalance may lead to developmentally induced deviations from the optimal ratio of body mass to nephron number. A relative deficiency in the number of nephrons is thought to create an increased risk of inadequate renal function and hypertension in later life^{31,53} and, ultimately, a predisposition to renal failure and a potentially reduced life span.⁵⁴ The severity of the hypertension in rodent models appears to depend on sex, with males having higher risk.⁴³ The molecular mechanisms are incompletely understood. In the rat, the intrarenal renin-angiotensin system appears to be critical for normal nephrogenesis and may be altered by maternal dietary imbalance, both during the neonatal stage⁵⁵ and at later time points.⁵⁶ Other studies have implicated reduced activity of the antiapoptotic homeobox gene product paired box 2 (Pax-2) in reduced number of nephrons^{57,58} or have suggested that hypertension in later life caused by maternal dietary imbalance results from up-regulated sodium transport in the distal nephron, possibly triggered by increased oxidative stress.⁵⁹

Nutritional stress in pregnant rats reduces the growth of the endocrine pancreas during organogenesis and increases beta-cell apoptosis,⁶⁰ leading to hyperglycemia and impaired insulin secretion when the offspring become adults. Glucocorticoids may be involved in inducing phenotypic changes and have been shown to inhibit the transcription factor pancreatic and duodenal homeobox 1 (Pdx-1) in beta-cell precursors, which

may affect the resultant number of beta cells.⁶¹ In the adult male rat offspring of mothers on a protein-restricted diet, low birth weight is associated with reduced expression of components of the insulin signal-transduction pathway in skeletal muscle (including the protein kinase C zeta isoform, the p85 regulatory subunit of phosphoinositide-3 kinase, and the insulin-sensitive glucose transporter type 4 [GLUT4]).⁶² Similar abnormalities have been reported in infants of low birth weight,⁶² and together with the developmentally induced reduction in skeletal muscle mass,³ these abnormalities might contribute to later insulin resistance.

In the rat model of nutritional imbalance, the offspring of rats fed an imbalanced diet during pregnancy later had elevated blood pressure, reduced nephron number, and increased responses to salt loading⁵⁵ as well as reduced vasodilator function in the systemic arteries.⁴⁰ Rat pups subjected to hypoxic conditions during gestation appear to have fewer but larger cardiomyocytes than pups exposed to normal oxygen levels and are more susceptible to infarction during periods of ischemia and reperfusion as adults.⁶³ Increased blood pressure in fetal sheep stimulates cardiomyocytes to leave the cell cycle prematurely and hypertrophy,⁶⁴ which may affect cardiac function in adult life. Cardiac hypertrophy is also evident in lambs born to ewes undernourished during early gestation.⁶⁵ Chronic fetal anemia alters the developing coronary vascular tree in the near-term sheep fetus, and the remodeled coronary tree persists into adulthood.⁶⁶ In one study, carotid intima-media thickness at 9 years of age in 216 children of European ancestry whose mothers had energy intake in the lowest quartile during early or late pregnancy was higher than that of children whose mothers had intake in the highest quartile, a finding that implies that maternal nutrition within an unexceptional range during pregnancy can affect the subsequent risk of atherogenesis in the offspring.⁶⁷

EPIGENETIC MECHANISMS

There is growing evidence that epigenetic mechanisms are responsible for tissue-specific gene expression during differentiation and that these mechanisms underlie the processes of developmental plasticity. Examples of epigenetic mechanisms include coordinated changes in the methylation of cytidine-guanosine (CpG) nucleotides

in the promoter regions of specific genes, changes in chromatin structure through histone acetylation and methylation, and post-transcriptional control by microRNA (Fig. 2).⁶⁸ Epigenetic modifications are gene-specific and cell-type-specific, and since only a small set of enzymes is involved in making these modifications, it is likely that this specificity is directed by interactions between DNA and small RNA molecules. Widespread epigenetic reprogramming occurs after fertilization to ensure totipotency of the developing embryo, although methylation patterns associated with imprinting are maintained.⁶⁹ Developmentally induced epigenetic modifications of DNA are generally stable during the mitotic cell divisions that continue throughout a lifetime.

Challenges during pregnancy or early neonatal life in experimental models of programming result in changes in promoter methylation and thus directly or indirectly affect gene expression in pathways associated with a range of physiologic processes. For example, in the rat, altered promoter methylation and gene expression have been shown for the hepatic glucocorticoid receptor and the peroxisome proliferator-activated receptor α (PPAR- α),^{49,70} influencing carbohydrate and lipid metabolism (Fig. 3).⁷¹ Similar epigenetic changes have been observed in p53 in the kidney⁷² and the angiotensin II type 1b receptor in the adrenal gland,⁷³ influencing renal apoptosis and pressor responses, respectively, and in the hypothalamic glucocorticoid receptor,⁴² influencing stress responses. The phenotypic effects of epigenetic modifications during development may not manifest until later in life, especially if they affect genes modulating responses to later environmental challenges, such as a high-fat diet. The extent of the developmental window for the induction of epigenetic change in key systems is not known, but it appears to extend from the periconceptual period³⁵ into postnatal life.⁴² There is also evidence from studies in twins for changes in the human epigenome related to age and the environment.⁷⁴ Many of the genes affected by epigenetic change do not appear to be classically imprinted (expressed according to the parental origin of the allele), although some imprinted genes may show altered expression after perturbations during early development, such as if blastocyst culture *in vitro* is prolonged.⁷⁵

The effects of maternal nutrition and behavior clearly target the promoter regions of specific

