REVIEW ARTICLE

MECHANISMS OF DISEASE

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

Peter D. Gluckman, M.D., D.Sc., Mark A. Hanson, D.Phil., Cyrus Cooper, M.D., and Kent L. Thornburg, Ph.D.

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.

From the Liggins Institute, University of Auckland, and National Research Centre for Growth and Development, Auckland, New Zealand (P.D.G.); Institute of Developmental Sciences, University of Southampton (M.A.H.), and Medical Research Council Epidemiology Resource Centre, University of Southampton (C.C.) — both in Southampton, United Kingdom; and Heart Research Center, Oregon Health & Science University, Portland (K.L.T.). Address reprint requests to Dr. Gluckman at the Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand, or at pd.gluckman@auckland.ac.nz.

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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 life[2-6] 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 children[13] 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

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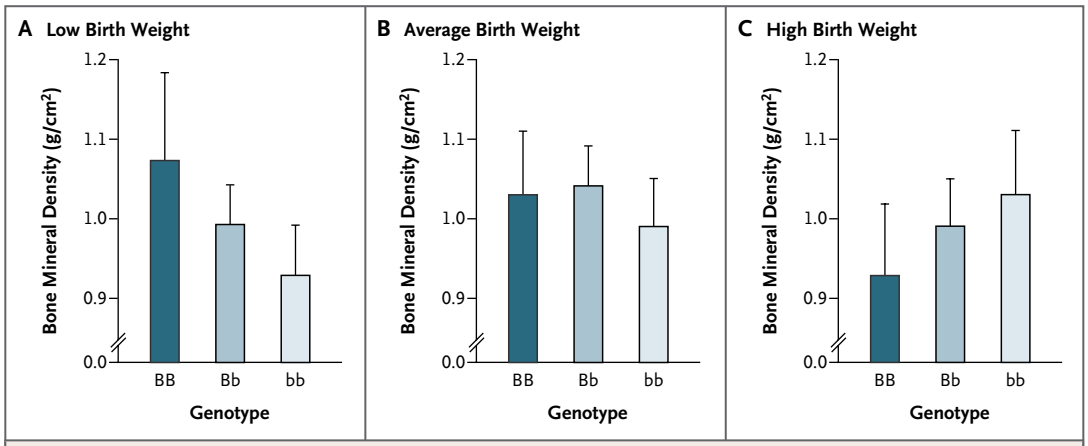

Figure 1. Birth Weight and the Relationship between Lumbar-Spine Bone Mineral Density and Vitamin D Receptor Genotype in Elderly Men and Women.

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 intake[30] 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

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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 B_{12}, folate, or methionine) at this stage can have effects on later metabolism and blood pressure in sheep[35]; imbalance in maternal B_{12} 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 hypertension[37] and insulin resistance[38] 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 diet[45] 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 stage[55] 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

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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 loading[55] 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 kidney[72] 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 periconceptional period[35] 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

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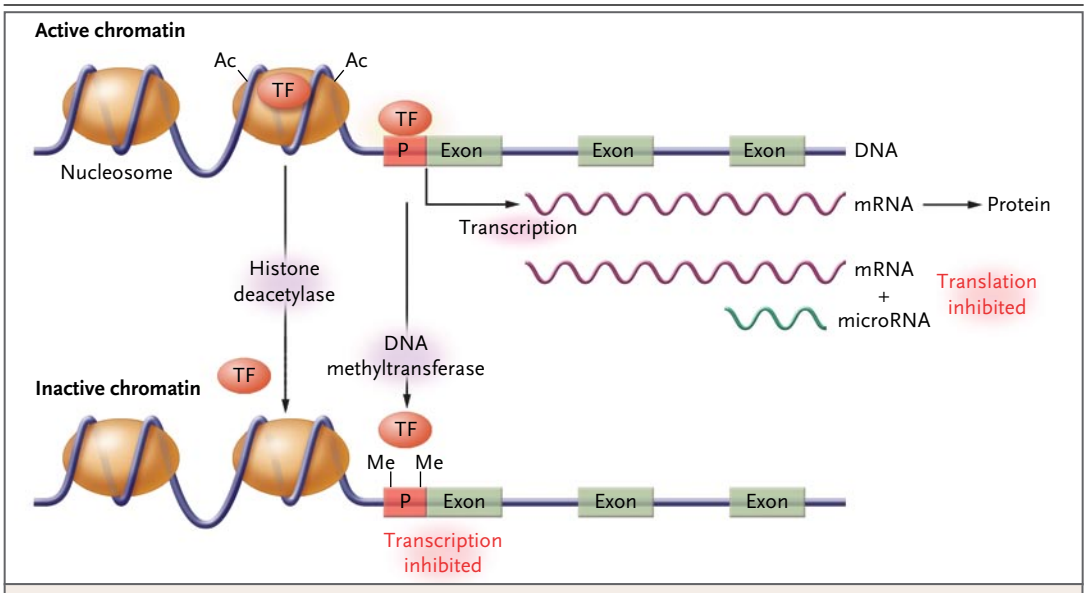

Figure 2. Regulation of Gene Expression through Epigenetic Processes.

Epigenetic modification of histones or of DNA itself controls access of transcription factors (TFs) to the DNA sequence, thereby modulating the rate of transcription to messenger RNA (mRNA). Transcriptionally active chromatin (top) characterized by the presence of acetyl groups (Ac) on specific lysine residues of core histones in the nucleosome, which decreases their binding to DNA and results in a more open chromatin structure that permits access of transcription factors. In addition, cytidine–guanosine (CpG) sequences in the promoter regions (P) of actively transcribed genes are generally unmethylated, allowing for the binding of transcription factors. Transcriptionally inactive chromatin (bottom) is characterized by histone deacetylation, promoter CpG methylation (as indicated by methyl groups [Me]), and decreased binding of transcription factors. (For simplicity, other histone modifications [such as methylation] and additional regulatory factors [such as methyl-CpG binding proteins] are not shown.) A further level of epigenetic control is provided by microRNA molecules (19 to 22 nucleotides in length), which bind to complementary sequences in the 3′ end of mRNA and reduce the rate of protein synthesis.

genes rather than being associated with global changes in DNA methylation. For example, in a rat model, protein undernutrition in mothers affects the expression and promoter methylation of PPAR-α in the liver but does not affect methylation of the related transcription factor PPAR-γ (a regulator of adipogenesis).[49] Additional studies of this model indicate that altered promoter methylation appears to result from reduced capacity of the specific DNA methyltransferase that maintains methylation patterns through cell division[70] and that the changes in gene expression and promoter methylation can be transmitted to the F_2 generation without further nutritional challenge to the F_1 generation.[76]

REVERSIBILITY

Recent laboratory studies have explored the reversibility of induced phenotypic effects and whether aberrant phenotypes induced in utero or during early development can be rescued. Corrective effects on phenotypic changes, gene expression, and associated methylation changes in PPAR-α have been reported after exogenous leptin administration to the neonatal offspring of undernourished rats (Fig. 4).[77,78] Other studies suggest that hyperleptinemia and hypertension may be reversed by dietary intervention with n–3 fatty acids[79] and that altered behavioral responses can be reversed by pharmacologic manipulation of epigenetic status.[80] Research exploring methods of restoring aberrant phenotypes to normal has led to promising speculation that, ultimately, susceptible people might be identified by means of screening for epigenetic markers during early life and that customized interventions might then be instituted.

DEVELOPMENTAL PLASTICITY AND LATER DISEASE

Responses to environmental cues during early human development appear to initiate a range of overlapping effects that are induced according to

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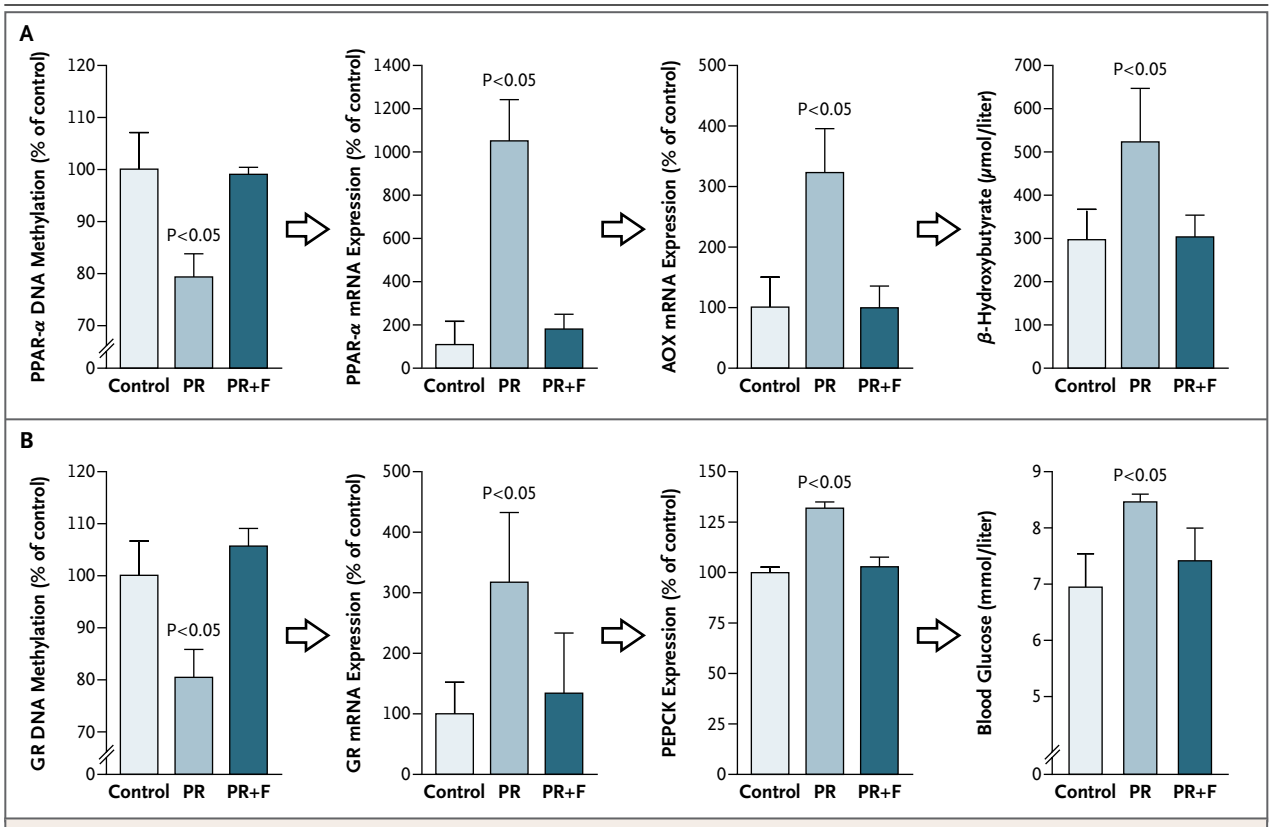

Figure 3. Metabolic Phenotype of Prenatally Undernourished Rats and Changes in Promoter Methylation and Gene Expression.
The offspring of rats fed a protein-restricted diet (PR) show reduced promoter methylation and increased messenger RNA (mRNA) expression of the transcription factor peroxisome proliferator-activated receptor α (PPAR-α) in the liver, as compared with control rats fed a normal diet (Panel A). Increased PPAR-α expression is associated with increased expression of the downstream enzyme acyl-CoA oxidase (AOX), a key enzyme in fatty acid β oxidation, and increased circulating concentrations of the ketone β-hydroxybutyrate. These effects were prevented by supplementation of the maternal diet with folate (PR+F). The offspring of rats in the PR group show reduced promoter methylation and increased mRNA expression of the glucocorticoid receptor (GR) in the liver, associated with increased expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK) and increased blood glucose levels (Panel B). Again, the effects are not seen in offspring of rats in the PR+F group. P values are shown for the comparison of the PR group with the control group; the P values for the comparison of the PR+F group with the control group indicated no significant difference. Data are means; T bars indicate SEs. Adapted from Lillycrop et al.[49,70] and Burdge et al.[71]

the nature, size, and timing of those cues.[1,81] One example is pathologic disruption (teratogenesis) by toxins or by extreme conditions such as poorly controlled maternal diabetes, which ultimately leads to cardiac abnormalities.[82] Another type of example is a nondisruptive yet substantial developmental challenge such as inadequate maternal nutrition, which can induce a range of phenotypes that have been called "thrifty,"[5] which means that the response of the developing fetus is a defense against an immediate challenge. The defensive fetal response usually involves a reduction in somatic growth, which may be specific to an organ or tissue, such as diminished skeletal muscle mass and restricted numbers of nephrons and neurons. Once such a challenged fetus has been born, it has to cope with the consequences of altered body composition, often through tradeoffs affecting other functions such as ultimate adult size or the timing of reproductive function.

An environmental cue that does not require an immediate defensive response, such as mild nutritional stress not substantially affecting birth weight, may nevertheless cause the developing organism to make phenotypic modifications that have a later fitness advantage in terms of tuning its physiology to better match aspects of the predicted adult environment. Such modifications have been termed predictive adaptive responses,[83] and striking examples have been reported in hu-

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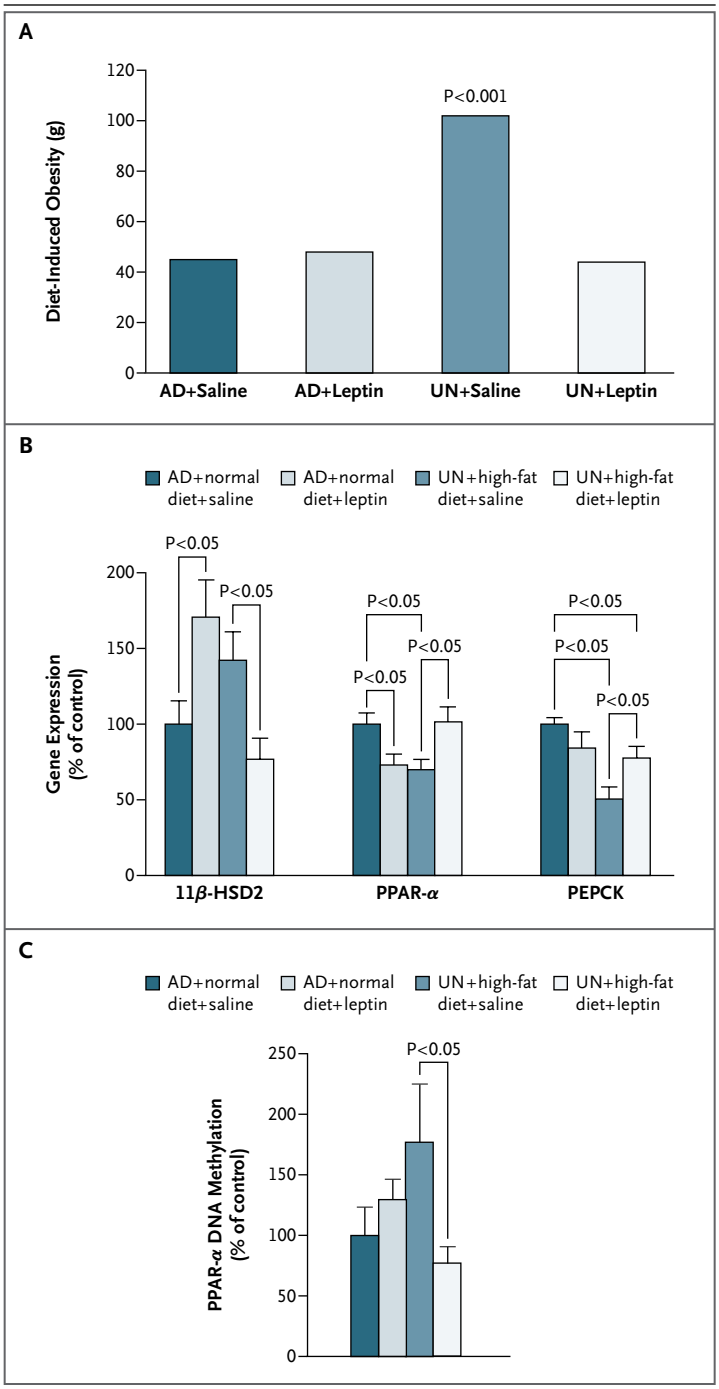

Figure 4. Effect of Neonatal Leptin Treatment on Metabolic Programming Caused by Maternal Undernutrition in the Rat.

Female rats were subjected in utero to maternal undernutrition (UN) or ad libitum feeding (AD), treated with saline or leptin between days 3 and 13 of life, and fed a normal diet or a high-fat diet after having been weaned. Panel A shows the diet-induced obesity (defined as the difference in total body weight between rats fed a high-fat diet and those fed a normal diet) at 170 days of age. Neonatal leptin treatment prevented the increased susceptibility to diet-induced obesity associated with a high-fat diet after maternal undernutrition. The P value is for the comparison of the UN group with the other three groups. The expression of hepatic genes (for 11β-hydroxysteroid dehydrogenase type 2 [11β-HSD2], peroxisome proliferator-activated receptor α [PPAR-α], and phosphoenolpyruvate carboxykinase [PEPCK]) (Panel B) and promoter methylation of the PPAR-α gene (Panel C) are shown for female rats at 170 days of age. The data in Panels B and C are means, with T bars indicating SEs, for eight rats per group. The control groups in Panels B and C consisted of female offspring in the AD group, treated with saline and fed a normal diet after weaning. Adapted from Vickers et al.[77] and Gluckman et al.[78]

mans (e.g., the early-life establishment of patterns of thermoregulation[84]) and other species. The adaptive advantage of such responses is determined by the probability that the choices made in early development are appropriate for the environment that the organism will experience during its maturation and reproductive life.[81] If the prediction is accurate, then the organism is matched to its subsequent environment and will cope adequately, ensuring positive selection for the mechanisms mediating such predictive responses. One example is a poor intrauterine environment inducing the reduced development of skeletal muscle and increased visceral fat deposition, a pattern that favors survival in a poor postnatal environment. This pattern has been observed in some South Asian babies, such as those in India.[85] But if the developmental choices made are not appropriate for the subsequent environment, the person may be more susceptible to later disease. For instance, sarcopenia and visceral obesity in a nutritionally rich postnatal environment that favors overconsumption are likely to promote further obesity, insulin resistance, and development of the metabolic syndrome (Fig. 5). The same "match–mismatch" theory can be applied to other systems, such as those affecting fluid balance[86] and the timing of puberty.[87]

HERITABLE ENVIRONMENTAL INFLUENCES

The developmental cue is not limited to the nutritional environment during the period of gestation; rather, the information passed to the fetus

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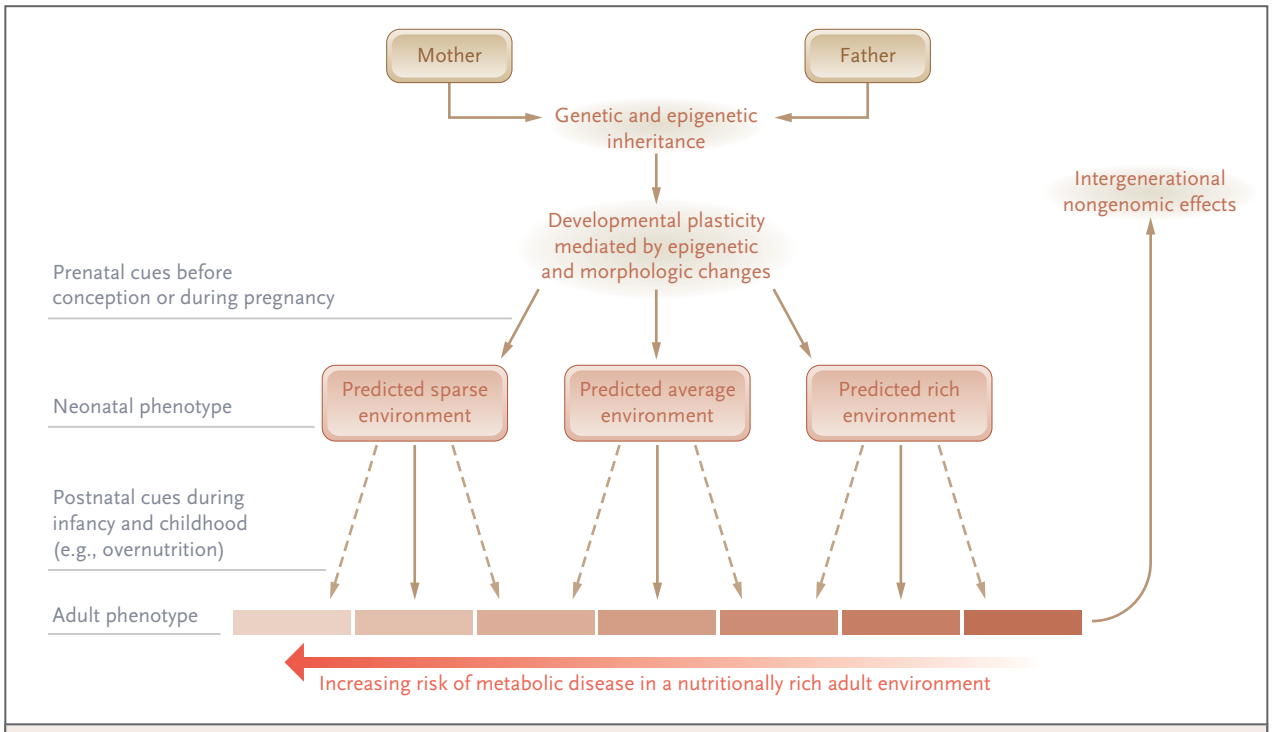

Figure 5. Environmental Cues during Development, Developmental Plasticity, and Determination of the Adult Phenotype.
Prenatal cues predicting a nutritionally sparse environment will cause a shift in the trajectory of structural and functional development toward a phenotype matched to that environment. Such a phenotype will have a reduced capacity to cope with a nutritionally rich environment later in life, increasing the risk of metabolic disease. Postnatal cues, such as childhood overnutrition leading to compensatory growth, could further shift the positioning of the adult phenotype, exacerbating the mismatch (dashed lines) between phenotype and environment. Although there is a continuous range of possible developmental trajectories and multiple sequential cues that act during development, for simplicity only two developmental cues (before and after birth) and three trajectories are shown.

or neonate from conception to weaning is a summation of maternal nutritional experience, integrating a lifetime of signals from the mother and perhaps even the grandmother.[88-90] Such intergenerational transfer of environmental information may confer an adaptive advantage, even if the environment changes between generations, as shown in modeling studies.[91] For example, in rat models, exposure during pregnancy to glucocorticoids[92] or a low-protein diet[76] results in altered expression of liver enzymes, elevated blood pressure, and endothelial dysfunction in the F_1 generation. These changes can be transmitted to the F_2 generation without further challenge to members of the F_1 generation during their lives. Limited clinical data are concordant with these experimental observations: epidemiologic studies have linked grandpaternal nutrition in one generation to the risk of diabetes in the F_2 generation.[93] The mechanism of intergenerational transfer is not clear, although it is known that postfertilization erasure of epigenetic marks such as DNA methylation and histone modification is incomplete for imprinted genes and similar processes may operate for some nonimprinted genes.[94] In addition, inheritance mediated by microRNA in the gametes, as recently shown in the mouse,[95] may act by altering post-transcriptional processing of factors affecting early embryonic development. Epigenetic changes induced in developing oocytes in the F_1 fetus would be lost after the F_2 generation, as shown experimentally.[92] Environmental influences during the F_0 pregnancy could also be transmitted nonepigenetically through the pregnancies of F_1 female offspring. These effects might involve the size[96] or vascular responses[97] of the reproductive tract, maternal behavior,[98] or body composition.[99] These considerations raise the possibility that familial clusters of metabolic disease may have an environmental and epigenetic basis, rather than a purely multigenic basis. In humans, there is a considerable contribution

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from familial and learned behaviors, such as eating patterns.[100]

MEDICAL AND PUBLIC HEALTH IMPLICATIONS

Observational and experimental evidence increasingly supports a relation between growth and development during fetal and infant life and health in later years. This relation has two major implications. First, it reinforces the growing awareness that investment in the health and education of young people in relation to their responsibilities during pregnancy and parenthood is of fundamental importance. Second, any rational approach to health care should embrace a life-course perspective. These considerations have been recognized by the World Health Organization in their consultations on diet, nutrition, and chronic disease[101] and on promoting optimal fetal development.[102] Thus, the outcome of a pregnancy must be considered in terms of maternal and neonatal health, the growth and cognitive development of the infant, its health as an adult, and even the health of subsequent generations.

Even in a developed nation, an imprudent diet before or during pregnancy may be common.[103] Interventions could involve correction of micronutrient and macronutrient imbalances in the mother before conception or at critical periods of early development[89] or, more broadly, could involve aspects of social structure, education, health information, nutrition, and behavior modification both before and after birth. Such complex interventions require novel thinking about trial design in a socially and culturally appropriate context.

CONCLUSIONS

The high incidence of metabolic disease in modern populations has been explained by selection for thrifty metabolism during evolution in an uncertain nutritional environment,[104] yet anthropologic evidence suggests that nutrition was not a primary challenge for preagricultural humans.[105] Molecular epidemiology has, to date, failed to define strong genetic determinants of the risk of developing metabolic disease.[106] Perhaps epigenetics will provide some explanations of how subtle early-life influences can produce long-term functional and structural changes. Furthermore, the concept of developmental plasticity could contribute an adaptive model that includes the effects of environmental factors during early development.[5,81]

Human demographics are changing, with smaller families and older mothers as well as more teenage pregnancies; these demographic changes are concurrent with dramatic shifts in nutritional and workload environments of many populations. Against this background, it is essential to learn how influences on early development will interact with the physiologic processes of developmental plasticity to determine patterns of noncommunicable chronic disease.

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