Living with the Past: Evolution, Development, and Patterns of Disease

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Epidemiological observations have led to the hypothesis that the risk of developing some chronic noncommunicable diseases in adulthood is influenced not only by genetic and adult life-style factors but also by environmental factors acting in early life. Research in evolutionary biology, developmental biology, and animal and human physiology provides support for this idea and suggests that environmental processes influencing the propensity to disease in adulthood operate during the periconceptual, fetal, and infant phases of life. This "developmental origins of health and disease" concept may have important biological, medical, and socioeconomic implications.

It has been proposed that the risk of suffering chronic diseases depends in part on environmental influences acting early in life (*1*). The "developmental origins of health and disease" model arose largely from retrospective epidemiological studies of human populations (*1*–*3*). The relative size and importance of such developmental and nongenetic effects have been disputed (*4*, *5*). We review the clinical and experimental data and the mechanisms involved, and evaluate the wider implications arising from this concept.

Epidemiological and Clinical Studies

Retrospective epidemiological analysis of causal factors in a disease process spanning most of a lifetime is challenging because concurrent risk factors carry greater weight and it is difficult to identify or attribute risk to distant, early-life factors. In addition, direct study of the potential impact of development on later disease outcomes is difficult because of the need for unbiased cohorts with both perinatal data and health outcomes documented well into middle age. Thus, most studies have used surrogate (i.e., indirect or proxy) measures of disease risk, such as systolic blood pressure or fasting insulin/glucose ratios. Although the definition of the health/disease boundary is inevitably arbitrary, where clinical cardiovascular or metabolic disease is the measured outcome, the effect of early environmental influences is clear (Fig. 1).

There are now many epidemiological studies (*1*–*3*) relating impaired fetal growth (deduced from birth weight or body proportions) to an increased incidence of cardiovascular disease or type 2 diabetes mellitus (T2D) or their precursors: dyslipidemia, impaired glucose tolerance, or vascular endothelial dysfunction. Disease risk is higher in those born smaller who become relatively obese as adolescents or adults (*1*). Interpretation of these studies has led to debate about the magnitude of the effect (*4*), although the only published estimate based upon a long-term Finnish cohort (*3*) suggests it to be substantial. Prospective clinical studies on children born small also provide support for the concept (*6*, *7*).

In evaluating the relative role of genetic and environmental factors, it is useful to note that birth size has only a small genetic component and primarily reflects the quality of the intrauterine environment. The observed relationship between disease risk and birth size does not imply a causal role of being born small but reflects the sensitivity of fetal growth to adverse intrauterine influences. It is considered that it is the effect of environmental influences acting during early development that is the causal trigger. Indeed, studies reviewed below indicate that adverse developmental influences can affect disease risk without birth size being affected. The term "maternal constraint" encapsulates those environmental factors that influence birth size even in healthy pregnancies, such as maternal size, age, parity, and multiple pregnancy, and various mechanisms limiting nutrient supply to the fetus (*8*). Firstborn offspring show a higher incidence of low birth weight and increased obesity in childhood and adolescence than their subsequent siblings (*9*). Although nutrition has received the most focus (*10*–*12*), other early-environmental factors such as infection, season of birth (*13*, *14*), and smoking (*15*) may have long-term effects.

There is now evidence for such developmental influences in an increasingly wide range of chronic diseases—osteoporosis (*16*), polycystic ovarian syndrome (*17*), mood disorders (*18*), and psychoses (*19*). Much more research is needed in these areas to establish the extent of the phenomenon unequivocally. Perhaps finding markers of early gene-environment interactions will allow definitive clinical data to be obtained.

Studies of famine indicate that the longer-term effects on offspring may depend on the duration and timing of undernutrition and can be independent of birth size (*20*, *21*). Further, there is increasing evidence that fetal development can be affected by nutritional variation within the normal range of western diets (*22*), and unbalanced dieting by mothers in early pregnancy is common. In addition to the embryonic and fetal periods, the postnatal environment and the infant phase may also play a role. For example, both cognitive function (*23*) and insulin secretion (*24*) in childhood are influenced by the type of feeding in

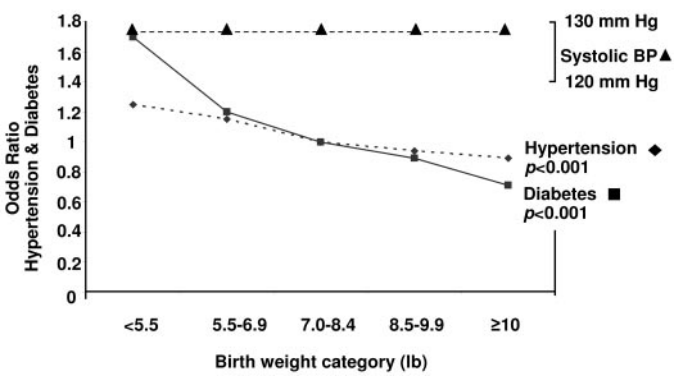

Fig. 1. Data from 22,846 men older than 40 years of age showing strong relationships between birth size and the relative risk of developing clinically significant hypertension or diabetes mellitus but no relationship with systolic blood pressure. These data demonstrate the importance of studying outcomes rather than surrogate measures of disease. Data are derived from G. C. Curhan *et al.* (*2*).

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the premature neonate, who is subjected to higher fat intakes than are experienced in utero. Rapid weight gain and growth in infancy or childhood may be a further compounding factor, even when birth size is relatively normal (*25*–*27*).

Experimental Studies

Experimental evidence that the prenatal or perinatal environment can influence adult postnatal physiology is available in several mammalian species (*12*, *28*). These studies demonstrate that manipulation of the periconceptual (*29*), embryonic, fetal, or neonatal (*30*) environment can lead to altered postnatal cardiovascular and/or metabolic function. Although the environmental triggering cues are not yet fully understood, most manipulations have been dietary and include maternal pan-undernutrition (*10*, *31*), low-protein diet (*11*), or high-fat (*30*, *32*) diet. Furthermore, in the normal nonmanipulated pig (*33*) and guinea pig (*31*), inverse relationships between birth size and later insulin sensitivity, and blood pressure are reported. Maternal glucocorticoid administration produces effects similar to those produced by undernutrition (*34*, *35*). Undernutrition may suppress placental 11-β-hydroxysteroid dehydrogenase type 2, which inactivates cortisol and exposes the fetus to excess maternal steroid; however, induction of long-term effects can occur well before the placenta is formed and independently of changes in glucocorticoid levels.

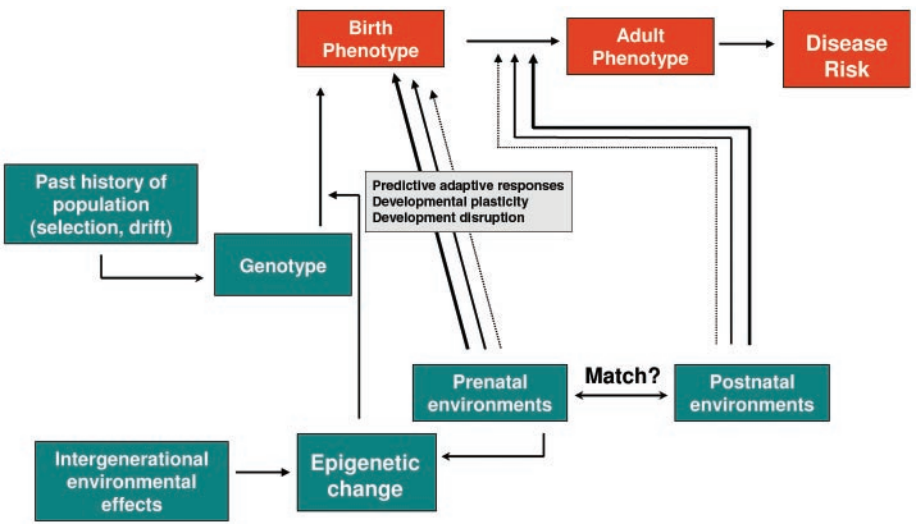

Fig. 2. A general model of how intergenerational, genetic and environmental, and prenatal and postnatal factors interact to create a pathway to altered disease risk in adulthood. If the prenatal and postnatal environments match, the physiological settings achieved through the processes of developmental plasticity will leave the organism well prepared for the postnatal environment. Conversely, a mismatch between the prenatal and postnatal environment may be pathogenic.

Environmental Effects via Developmental Plasticity

"Developmental plasticity" provides organisms with the ability to change structure and function in response to environmental cues; these responses usually operate during critical time windows and then become irreversible. Such plasticity permits a range of phenotypes to develop from a single genotype in response to environmental cues. In *Daphnia*, helmet formation (a defensive, morphological change) is dependent on the early environment and risk of predation (*36*). In the locust, *Locusta migratoria*, the wing shape and metabolic pathways are determined in the larval stage by pheromone signals indicating population density (*37*). In the axolotl, early environmental conditions determine whether the mature form will be purely aquatic or amphibious (*38*). Developmental plasticity sets the template on which continued postnatal homeostatic and homeorhetic [maintaining a time-dependent process, e.g., growth trajectory (*39*)] adaptation can occur.

There are several mechanisms by which environmental cues can influence the developmental program (Fig. 2). First, they can exert effects prior to implantation and affect gene expression, particularly by inducing epigenetic changes in the DNA. In the agouti mouse mutant, maternal dietary folate supplementation at conception alters the expression of the imprinted *agouti* gene by altering the capacity for methylation (*40*). In pregnant rats, giving an additional source of dietary methyl groups prevents vascular defects in the offspring, even if the diet is protein deficient overall. Prolonged in vitro culture of the ovine embryo affects later expression of the imprinted insulin-like growth factor–2 (IGF-2) system (*41*). Nonimprinted genes can also undergo epigenetic change in response to the environment—the choice of exon usage in the glucocorticoid receptor gene is altered both by prenatal glucocorticoids and neonatal behavioral manipulation owing to changes in histone acetylation and DNA methylation in a transcriptional factor binding site (*42*). These changes persist throughout life as manifested in altered hypothalamic-pituitary-adrenal (HPA) axis activity. Intriguingly, the effects could be reversed by a histone deacetylase inhibitor, suggesting potential reversibility. This finding may have broader implications.

Second, tissue differentiation may be altered. Prolonged in vitro culture of the rodent or ruminant embryo affects the allocation of blastocyst stem cells to inner cell mass or trophectoderm lineages (*29*). This influences the relative growth trajectories of the placenta and fetus, thus affecting fetal development in late gestation. Organ-specific effects are also reported. Fetal pancreatic islet cell differentiation is affected by maternal nutritional manipulation, leading to altered developmental apoptosis and expression of transcriptional regulators of the *Pdx* and *Pax* gene families (*43*). Differential expansion of periportal and perivenous hepatocyte cell clones is reported after maternal nutritional or hormonal manipulation and may lead to altered hepatic glucose and lipid metabolism (*44*). Maternal dietary (*45*) or glucocorticoid manipulation (*46*) in the rat reduces the number of renal glomeruli in the offspring. This "trade-off," although it conserves resources in the short term, may induce later glomerular hyperfiltration to maintain fluid and electrolyte homeostasis, and declining renal function with age leads to progressive hypertension. Indeed, this concept of trade-offs between prenatal growth/development and postnatal growth/function may explain the compounding role of rapid postnatal growth in generating additional disease risk (*26*, *27*).

Lastly, changes may be induced in homeostatic control mechanisms. Defects in both insulin secretion, as well as in insulin postreceptor action (*47*) and glucose transporter function in muscle, may predispose the individual to T2D. Vascular endothelial function is altered following maternal dietary manipulation (*48*), and this tissue is involved in controlling blood flow, clotting, inflammation, growth, and metabolism. Intrauterine environmental induction of changes in central nervous cardiovascular control (*49*) is also reported.

These various prenatal changes may alter the offspring's response to the postnatal environment. In rat pups subjected to prenatal undernutrition, exposure to a postnatal high-fat diet has much greater effects on the development of obesity and hyperleptinemia than in pups born to mothers with a normal dietary intake, but then fed a high-fat diet postnatally (*10*). Likewise, pigs exposed in utero to a high-fat diet have a different tolerance to high-fat diets postnatally (*50*).

Types of Response to the Early Environment

Some responses of the embryo or fetus to its environment may, however, be developmentally disruptive with no adaptive value—examples are responses to environmental teratogens. However, the fetus has many homeostatic and homeorhetic mechanisms that confer immediate survival advantage—e.g., alterations in regional blood flows and organ growth when nutrient or oxygen supply is reduced—even if there may be subsequent postnatal costs. A further class of response, termed a predictive adaptive response (PAR) (*28*, *51*), has been identified that appears primarily to have future adaptive value. For example, the coat of meadow vole offspring is thicker if offspring are born at a time of decreasing day length than if they are born in spring, even though the perinatal thermal environments are similar (*52*). It is proposed that PARs allow the developing organism to use developmentally plastic processes to set its postnatal physiological phenotype to one that it predicts will give it an optimal chance of survival to reproduce when an adult.

The responses to an environmental exposure in one generation may extend over several generations and are well recognized in comparative biology as "maternal effects." Their possible role in the developmental origins of disease has been recently reviewed (*53*). For example, birth size is reduced in the offspring of women who themselves were fetuses during transient famine (*54*), and effects on blood pressure, endothelial function, and insulin sensitivity are passed to F_2 offspring of undernourished pregnant rats (*55*). This might reflect either transgenerational passage of environmentally induced epigenetic change, as suggested by studies in the agouti mouse (*40*), or an effect on the reproductive tract of the F_1 generation, as suggested from clinical studies of girls with intrauterine growth retardation (*56*).

An Evolutionary Perspective

There have been several models proposed to explain the changing demography of "life-style" diseases such as T2D. The "thrifty genotype" concept (*57*) proposed that populations have been selected for alleles favoring insulin resistance. Such "thrifty genes" confer advantage in a poor food/high energy expenditure environment by reducing glucose uptake and limiting body growth. When individuals of this genotype encounter an environment of plentiful food/low energy expenditure, they are at risk of developing T2D and the metabolic syndrome (*58*). So although selection for these genes enabled our ancestors to survive as hunter-gatherers, they put modern humans at greater risk of disease, especially as our longevity increases. Because insulin is a fetal growth factor, selection for such genes might also induce lower birth weight (*5*). For example, mutation in the glucokinase gene produces reduced fetal growth and later insulin resistance independently (*59*).

But purely genetic models cannot explain the reported effects of human famine during gestation (*21*) or the experimental animal studies. The alternate "thrifty phenotype" model (*60*) posits that the fetus becomes growth retarded in response to adverse environmental conditions in utero, and the associated adaptations induce a phenotype better suited to a deprived postnatal food/energy environment. However, this model does not easily account for the graded effects on disease risk seen across the normal birth weight range (*1*, *2*), or the way in which the disparity between the prenatal and postnatal environment determines the level of risk.

Recent work stresses that both genetic and environmental factors must be involved. Studies of a polymorphism in the PPARγ2 gene (which codes for a transcription factor affecting gene expression involved in the control of insulin sensitivity) associated with increased risk of T2D show that the polymorphism is only associated with a higher risk of T2D if birth weight is reduced (*61*). Clearly, the relationship between birth size and disease risk cannot be explained by independent effects on insulin sensitivity and fetal growth. Another example is polymorphisms of the vitamin D receptor, the effect of which is that the risk of osteoporosis is influenced by birth size (*16*).

These various models lead to a more general synthesis (*28*, *51*) (Fig. 3). Developmental responses to environmental stimuli may be either disruptive or adaptive. The former have no evolutionary significance. For the latter, the advantage need not be immediate, but may arise from a PAR made in expectation of the future environment. Such PARs are made during the phase of developmental plasticity to optimize the phenotype for the probable environment of the mature organism, and epigenetic change is likely to be the mechanistic basis (*51*). Where there is a match between the predicted and actual mature environment, these PARs are appropriate and assist survival. Conversely, inappropriate predictions increase the risk of disease. Modeling suggests that such lagged responses aid the survival of a species (*62*).

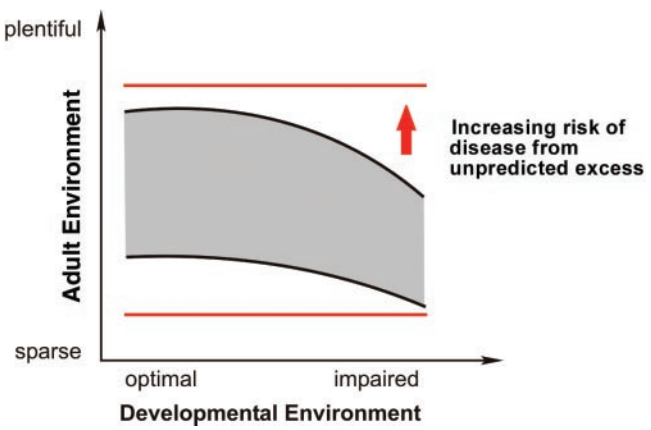

Fig. 3. The red lines show the upper and lower limits of the environmental range (for example, nutrition) to which the mature organism could be exposed. The PARs model proposes that the developing organism growing optimally (left side) adjusts its physiology to be appropriate for its predicted mature environmental range (shaded area). If the early environment is impaired (toward right side), then the range of environments for which the organism is adapted by PARs will not match the mature environment. This mismatch means that the organism is likely to have a physiology inappropriate for the environment in which it is now living (space between the shade area and upper red line). In modern humans, such a mismatch leads to a risk of disease. This scenario is common in the developing world where fetal growth is often constrained by small maternal size, maternal disease, and poor nutrition and where postnatal food availability is increasing. Because the upper limit of the nutritional environment is rising globally, the risk of disease due to mismatch increases even for individuals who had normal early development.

Longevity was short in ancestral hominids, and thus little negative selection pressure has operated to limit the adverse consequences of a strategy now manifest in modern humans as disease in middle age. However, recent studies charting demographic trends in longevity (*63*) show that such effects are of increasing importance. It appears that evolution has preserved genes encoding mechanisms that allow the organism to mount PARs. A key element of this model is that it focuses on the relative environmental state between the plastic and mature phases. Therefore, because of intrauterine constraint, even when fetal growth falls within the normal range, being born into an enriched postnatal environment can create a mismatch. This model, thus, encompasses both the evidence focusing on embryonic/fetal cues (*1*, *21*, *29*) and infant/childhood cues (*24*, *26*). The importance of the relative nature of the environments in the plastic versus mature phase is demonstrated by the observation that in mice, merely giving adequate postnatal nutrition reduces longevity in prenatally deprived offspring (*64*).

Relevance to Patterns of Disease

The intrauterine environment cannot change dramatically between generations (*51*). But in many societies, high-calorie food is now plentiful and the energy expenditure has become reduced. Thus, the potential for dispar-

ity between pre- and postnatal environments is increasing. In some developing societies, the postnatal food-energy environment has dramatically changed even within a generation, but fetal growth is still markedly constrained; this may explain the rapid increase in the incidence of T2D seen in such populations (*25*).

The experimental and prospective clinical studies add weight to the epidemiological data and suggest that early development does have significant echoes in disease risk throughout life. There is a growing awareness of the potential for epigenetic change to play a role in disease generation. A key issue is the relative importance of early-life events in informing interventional strategies during human development versus those instituted in adult life. If appetite, food choice, and exercise propensity are partially induced during early development as in experimental animals (*30*, *65*), then postnatal life-style interventions may be less effective than hoped. It seems that increasing awareness of the need to promote the health and nutrition of females of reproductive age is one important element for the prevention of chronic disease in future generations across the globe.

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Inflammatory Exposure and Historical Changes in Human Life-Spans

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Most explanations of the increase in life expectancy at older ages over history emphasize the importance of medical and public health factors of a particular historical period. We propose that the reduction in lifetime exposure to infectious diseases and other sources of inflammation—a cohort mechanism—has also made an important contribution to the historical decline in old-age mortality. Analysis of birth cohorts across the life-span since 1751 in Sweden reveals strong associations between early-age mortality and subsequent mortality in the same cohorts. We propose that a "cohort morbidity phenotype" represents inflammatory processes that persist from early age into adult life.

A long-term decline in mortality, beginning before 1800 in some countries in Northern Europe, has resulted in a 50% increase in adult life expectancy (*1*, *2*). Childhood mortality has decreased by 90%, and this has been attributed mainly to a decreased incidence of infectious disease (*2*–*4*). After 1850, older-age mortality declined, with greater improvement in recent decades (*1*, *5*). Most explanations of the long-term decline in mortality have focused on improvements in sanitation, nutrition, income, and medicine. We develop the specific hypothesis that decreased inflammation during early life has led directly to a decrease in morbidity and mortality resulting from chronic conditions in old age.

Our argument is supported by recent research linking an individual's exposure to past infection to levels of chronic inflammation and to increased risk of heart attack, stroke, and cancer. For example, the risk of heart attack and stroke is correlated with serum levels of inflammatory (acute phase) proteins such as C-reactive protein (CRP) (*6*–*8*). Within individuals, CRP levels are

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