CHAPTER 19

Evolution, developmental plasticity, and metabolic disease

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Introduction: diseases of excess or deficiency?

Cardiovascular disease (CVD) is now the leading cause of death worldwide (Mackay *et al*. 2004). Given their modern appearance as major public health scourges, cardiovascular diseases and related metabolic disorders had long been viewed as 'lifestyle' diseases caused primarily by the growing problems of adult overnutrition and weight gain. Then, beginning in the late 1980s, evidence started to accumulate that individuals born small also have higher rates of cardiovascular mortality as adults (Barker *et al*. 1989). Because fetal growth is largely determined by nutrient delivery across the placenta, this suggested that the risk of adult metabolic diseases might also be increased by undernutrition experienced prior to birth. Initial skepticism about these findings faded as similar results were described in other populations. Extensive animal studies now support findings from human populations and show that unbalanced or restricted maternal or fetal nutrition during pregnancy initiate a similar suite of physiological, metabolic, and morphological changes in adult offspring. These findings suggest that the classic 'diseases of excess' may also be characterized as 'diseases of deficiency' depending on the age at which the nutritional imbalance occurs.

This new developmental approach to the epidemiology of chronic degenerative disease (the 'developmental origins of health and disease,' or DOHaD for short) poses an interesting challenge to classic evolutionary explanations for the rise of these conditions. In its brief history, the field of evolutionary medicine has developed the elegant principle that a beneficial genetic adaptation to one environment can lead to disease when environments change rapidly, as has occurred with recent rapid cultural change (Neel 1962; Eaton and Konner 1985). Considered in an evolutionary light, today's populations are more likely to become obese not because the gene pool has changed, but because we now inhabit environments markedly different from those that our ancestors confronted. Previously, we had to move on foot to gather food that was widely dispersed. Now, as we consume more but expend less, our scarcity-adapted genome is confronted with the novelty of chronic, positive energy balance, leading to weight gain and its attendant health problems. Thus a genome well-adapted to one environment—the energetically balanced lifestyle of our ancestors—can lead to disease and premature death when placed in the nutritional ecologies of contemporary human societies (see also Chapter 20).

This concept of gene-environment 'mismatch' is a useful starting point for explaining why chronic overnutrition can lead to diseases like obesity, diabetes, and CVD. But why should *undernutrition*, when encountered earlier in the life cycle, lead to a similar constellation of adult ailments? Such outcomes could merely be the unavoidable, detrimental effects of an insult that disrupts the normal pattern of embryonic or fetal development (see Gluckman and Hanson 2005), such as the

well-known examples of embryopathy, congenital heart disease, and hypospadias. Although straightforward damage may contribute to the long-term effects of severe fetal undernutrition, it is difficult to see how it could explain the common pattern of outcomes seen across the normal range of birthweight or in response to normal variability in intrauterine nutritional sufficiency in both model organisms and humans. As discussed below, the responses induced by undernutrition early in life are not limited to pathologic outcomes. They include changes in the regulation of endocrine systems, central and peripheral changes in energy metabolism, and modifications in growth rate and maturational timing. A simple model of developmental insult might explain the attenuated growth or function of a specific organ or anatomical structure, but it is far less likely to explain this broad, consistent, and integrated response.

In this chapter we pose an alternative explanation for these findings. It is well established that developmental plasticity, defined as the potential for a single genome to create a range of phenotypes in different environmental circumstances, can serve as a powerful mode of biological adaptation, allowing organisms to adjust their 'hard-wired' biological settings in a single lifetime, much more rapidly than could be achieved by the slow process of natural selection operating on gene frequencies (Stearns and Koella 1986; West-Eberhard 2003; Bateson *et al*. 2004). At least some of the biological changes triggered by prenatal stimuli may be components of such a capacity for adaptive developmental plasticity in which the fetus anticipates its postnatal environment from nutritional and endocrine cues conveyed across the placenta (Gluckman and Hanson 2005). A capacity for tuning developmental biology to anticipate postnatal conditions could enhance genetic fitness by allowing the organism to adjust its adaptive priorities, such as its body size, nutrient requirements, and tendency to store excess energy in protective stores of body fat. When the actual environment does not match the predicted one, this same capacity for flexibility can elevate risk for disease.

First, a brief overview of the extensive literature documenting the role played by early environments in determining risks of later chronic degenerative diseases in both animal models and humans is given. Then a model of how the underlying biological responses might be integrated into a broader strategy aimed at adjusting the body's adaptive settings is proposed. Most of the biological changes that increase risk for future disease involve adjustments in the handling, metabolism, and allocation of energy within the body. These patterns provide insights into the likely function of these responses, and thus the selective pressures that may have shaped them. Having considered this functional perspective, we conclude by discussing the conditions under which a capacity to adjust metabolic settings in response to prenatal cues could lead to disease in humans. Collectively, these findings expand the classic model of evolutionary medicine by showing that there are not two, but three major sets of factors—genes, environments, *and* developmental history—that interact across the life cycle and even across generations to determine biological state and disease risk (Fig. 19.1). In this way, we build on the tremendous progress in this area in the past decade to extend the corresponding chapter in the first edition of this book (Barker 1999).

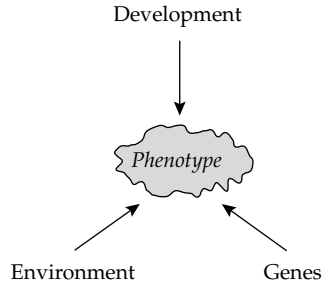

Figure 19.1 Expanding the classic model of cardiovascular epidemiology to account for developmental processes.

The developmental origins of health and disease (DOHaD) paradigm

Origin

Almost half a century ago, Neel (1962) focused attention on an evolutionary explanation for the rising prevalence of obesity and diabetes by proposing that a 'thrifty genotype' of alleles that were adaptive under the 'feast and famine' conditions

faced by our foraging hominin ancestors is now deleterious in a modern environment of nutritional excess. Despite our knowledge of the human genome, such 'thrifty genes' remain elusive, and CVD epidemiology is moving beyond simple genetic models of disease susceptibility to accommodate newer evidence for the importance of the early developmental environment.

Some of the first evidence that the environment early in the life cycle influences later susceptibility to chronic degenerative diseases came from studies of historical cohorts in Scandinavia. Using records from Norway, Forsdahl (1977) found that the rate of CVD was higher in cohorts that had experienced higher rates of infant mortality, which he interpreted as a marker of poverty and therefore of undernutrition. This interpretation was later supported by the work of Barker and colleagues (1989; 1994), who published a series of studies documenting inverse relationships between birthweight and adult outcomes such as hypertension, type II diabetes mellitus, and CVD. This work led to the key finding that individuals born small but who went on to gain weight by adulthood were at highest risk for metabolic disease, suggesting that the combination of fetal undernutrition followed by subsequent improvement in nutrition was particularly harmful. Building from this finding, and as an explicit reference to Neel's prior concept of the thrifty genotype, Hales and Barker (1992) posited the 'thrifty phenotype' hypothesis that the fetus faced with a compromised prenatal nutritional environment is forced to adjust organ growth to buffer the brain *in utero* but at the cost of increased risk for diabetes when that individual is faced with more abundant nutrition after birth. By framing the problem as one of fetal adaptation, this construct provided the foundation for a subsequent synthesis of evolutionary and developmental biology, life-history theory, and fetal medicine.

Evidence from epidemiology

Since the first observations of a relationship between birthweight and later disease risk, there has been a wealth of epidemiological studies linking measures of early nutrition and stress with a variety of clinical and physiological outcomes later in life. The initial observations on historical cohorts from Britain have now been extended by more recent studies in, for example, Finland, India (Yajnik 2004), and the Philippines (Kuzawa and Adair 2003); for an extended review see Godfrey (2006). Moreover, data from the much-studied survivors of the Dutch Hunger Winter of 1944–5, a well-defined period of maternal undernutrition and stress, broadly support the epidemiological observations (Painter *et al*. 2005). Epidemiological studies underpinning the DOHaD phenomena highlight several key points, as follows.

The outcomes shown to be affected by the human developmental environment include frank disease (CVD, type II diabetes, obesity, metabolic syndrome, osteoporosis, mood disorders, and cancers) and its underlying markers or precursors (cardiovascular function, hypertension, endothelial dysfunction, dyslipidemia, insulin resistance, and hormone levels) as well as factors reflecting growth and morphology (body size, muscle mass, neuron and nephron number), neurological and psychological development, and reproductive strategy (age of puberty, reproductive hormone levels and fecundity) (see Kuzawa 2005). In general, the epidemiological correlations are stronger for disease (e.g., heart disease) than for surrogate markers (e.g., blood pressure), which has been a source of controversy in the field. Although birthweight itself was initially seen as part of the causal pathway, it is now clear that this is an indirect indicator of environmental factors that modify physiology, metabolism, and the early developmental trajectory.

The most commonly used marker in these epidemiological studies has been birth size—usually weight, although thinness at birth, judged from the combination of weight and length or from studies of body composition, has been found to be a more sensitive marker in some studies (Godfrey 2006). While individuals of lower birthweight have poorer long-term health prospects, there is a continuous relationship between birthweight and later outcomes across the full range of birth sizes (Barker 1994), making clear that pathologically low birthweight is not an obligatory part of the pathway to later disease. Although some have suggested that the pleiotropic effects of certain genes, for instance those modulating insulin's effects on

both fetal growth and later diabetes risk, could explain some of the associations between birth size and adult disease (Hattersley and Tooke 1999), this perspective is not supported by experimental work on nutritional restriction in animal models. Yet, the increased disease risk conferred by polymorphisms in several genes involved in metabolic regulation is dependent on birthweight, suggesting an interaction with intrauterine nutrition or related factors. For example, susceptibility to later insulin resistance in people born small is modified by polymorphisms in the PPARγ2 receptor involved in adipocyte differentiation and metabolic signaling (Eriksson *et al*. 2002).

Although the first studies tended to focus on intrauterine conditions, as reflected in the initial labeling of the field as 'fetal origins of disease,' it has become apparent that critical windows of sensitivity to environmental cues begin prior to conception and extend to at least mid-childhood. Maternal diet and body composition both before and after conception affect various outcomes in the child (Morton 2006). Studies of children born after *in vitro* fertilization provide further evidence for periconceptional influences and also show that the effects of prenatal conditions are not unidirectional, since girls born after such procedures are taller and have greater insulin sensitivity (lowering CVD risk) than normally conceived controls (Miles *et al*. 2005). Postnatal nutrition can also have repercussions in later life, in some cases by modifying the effects of prenatal nutrition. The nature of infant feeding, for example breast milk versus formula, can affect later cognitive performance, insulin resistance, or obesity (Morley and Lucas 1997; Stettler *et al*. 2005), providing strong evidence for plasticity in the establishment of physiologic and metabolic settings during early postnatal life.

It is unlikely that the effects of prenatal undernutrition and postnatal overnutrition are independent, as postnatal growth patterns, presumably a reflection of nutrient availability, modify the effects of the intrauterine environment as indicated by birthweight. For example, slow growth in the first few months after birth increases the risk of diabetes in children of above-average birthweight, whereas children who are born small and later develop diabetes or insulin resistance are more likely to have experienced an earlier childhood adiposity rebound and to put on weight faster in late childhood (Eriksson *et al*. 2003). In other domains, birth size and adult nutrition interact to determine cholesterol levels (Robinson *et al*. 2006) and the timing of menarche (Adair 2001).

Finally, environmental exposures in early life can have transgenerational effects by which one generation's environmental experiences influence outcomes in their grandchildren. In a historical cohort from northern Sweden, diabetes mortality increased in men if their paternal grandfather was exposed to abundant nutrition during his prepubertal growth period, an effect later extended to paternal grandmother/granddaughter pairs and shown to be transmitted in a gender-specific fashion (Pembrey *et al*. 2006).

Experimental evidence

These epidemiological observations are matched by experimental studies addressing the DOHaD phenomenon in a range of mammalian species varying in size, growth rate, and life span. Most such studies have focused on models immediately applicable to human disease, such as those relating altered nutrition or stress in pregnancy (or its proximal effector glucocorticoid levels) to later outcomes such as blood pressure, fat deposition, or insulin resistance, although other phenotypic attributes such as behavior, body temperature, fluid balance, and longevity have also been studied. This area has been reviewed in detail (McMillen and Robinson 2005; Gluckman and Hanson 2006), and here some of the key findings will be summarized.

First, the experimental models reproduce the main features of the human epidemiological studies (see contributions in Gluckman and Hanson 2006). Various manipulations of nutritional and endocrine status around the time of conception, at various periods of pregnancy, or in the neonatal period result in a similar phenotype characterized by a trend to visceral obesity, insulin resistance, hypertension, and endothelial dysfunction. These outcomes are induced by a prenatal low-protein or high-fat diet, maternal global undernutrition, and maternal glucocorticoid exposure at differing times in gestation in sheep, rats, mice, and guinea

pigs. In another parallel with the epidemiology, low birthweight may be, but is not necessarily, part of the phenotype observed.

Secondly, the phenotype induced after an early nutritional insult involves parallel changes in different systems reminiscent of what is seen in humans born small. In the rat model of maternal undernutrition, the adult offspring show both centrally-mediated alterations in behavior (hyperphagia and lethargy) and peripheral changes in traits such as skeletal muscle insulin sensitivity and obesity (Vickers *et al*. 2000) as well as alterations in endothelial function, learning capacity, and mood.

Thirdly, in another parallel with the human studies, the effects of prenatal manipulations such as undernutrition can be modified by postnatal nutrition or other interventions, resulting in either exacerbation (Vickers *et al*. 2000) or amelioration (Vickers *et al*. 2000; Jimenez-Chillaron *et al*. 2006) of the induced phenotype, indicating a window of plasticity that extends beyond the intrauterine period.

The animal models have revealed some of the underlying mechanisms, which include modifications in physiologic, metabolic, morphologic, and epigenetic state. The few studies that have compared animal and human data have, encouragingly, pointed to similar pathways. For example, the proximate mechanisms underlying peripheral insulin resistance include reduced expression of specific insulin signaling proteins in skeletal muscle, which is observed both in low-birthweight humans and in the offspring of rats fed a low-protein diet (Fernandez-Twinn and Ozanne 2006).

Other studies explain the similar effects of nutritional challenge and various forms of stress. Maternal protein malnutrition and low birthweight are associated with reduced activity of 11β-hydroxysteroid dehydrogenase type II in the placenta. Because this steroid-metabolizing enzyme usually protects the fetus from maternal glucocorticoids, this exposes the fetus to higher levels of stress hormones (Bertram *et al*. 2001). Conversely, maternal administration of glucocorticoids affects intermediary metabolism and reduces the activity of placental glucose transporters (Hahn *et al*. 1999), providing a mechanism for the reduced fetal growth observed in situations of high maternal stress burden. These findings suggest why multiple forms of stress are experienced as similar exposures and induce similar responses in the developing fetus.

Epigenetic mechanisms

Epigenetic changes in gene expression are central to many induced developmental changes, and research in this area is currently brisk. The term *epigenetics* is increasingly being reserved for processes that establish and maintain distinct patterns of cellular gene expression that are mitotically heritable without changing the underlying DNA sequence. Such processes underlie a wide range of biological phenomena, including tissue differentiation during development, silencing of transposable elements, genomic imprinting, and X chromosome inactivation. The molecular basis for gene silencing by epigenetic processes has become clearer in recent years. Methylation of CpG islands in promoter regions generally results in reduced transcriptional activity, whereas chemical modification (particularly methylation, acetylation, and phosphorylation) of the histone proteins that package DNA controls the tightness of the chromatin framework, regulating access of transcription factors to DNA. Such epigenetic 'marking' is stable but potentially reversible, and is placed and cleared by a limited suite of DNA-binding proteins and DNA-modifying enzymes (Klose and Bird 2006; Nightingale *et al*. 2006). More recently, the epigenetic activity of small RNAs and microRNAs has become apparent; these non-coding molecules appear to act at multiple levels by regulating chromatin structure, directing the placement of other epigenetic marks, and modulating gene expression by pre- and post-transcriptional mechanisms (Krützfeldt and Stoffel 2006).

Most epigenetic marks on DNA are cleared after fertilization to ensure the totipotency of the zygote, with reprogramming as tissue differentiation proceeds; nevertheless, imprinted genes and certain retrotransposon sequences retain their marking and such instances of stability may contribute to observations of intergenerational epigenetic inheritance in animal models (Chong and Whitelaw 2004) and humans (Pembrey *et al*. 2006). Recent evidence

suggests that microRNAs may also mediate epigenetic inheritance (Rassoulzadegan *et al*. 2006). The growing recognition of such non-Mendelian processes adds considerably to the concept that phenotypic 'memory' can be transmitted over at least one or two generations; such parental effects are well recognized in plants and invertebrates, but their significance for human biology is only now coming to light.

Although epigenetic changes are integral to development and tissue differentiation, it is now clear that environmental factors can affect epigenetic marks and downstream patterns of gene expression, providing a mechanism for the lasting imprint of many early life exposures. Recent experimental studies have demonstrated how epigenetic markings in offspring are sensitive to maternal diet (Lillycrop *et al*. 2005) or behavior (Weaver *et al*. 2004). For example, in rats subjected to maternal protein restriction during gestation, reciprocal postnatal changes occur in the offspring in gene promoter methylation and expression of the peroxisome proliferator-activated receptor α (PPARα) and glucocorticoid receptor genes in the liver, associated with changed expression of downstream genes such as PEPCK and acyl-CoA oxidase (Lillycrop *et al*. 2005). Supplementation of the low-protein diet with folate prevented these changes, suggesting the importance of methyl group provision. Although the epigenetic basis remains under investigation, phenotypes induced by prenatal undernutrition or stress hormone exposure may be transmitted to both matrilineal and patrilineal offspring and grand-offspring, influencing risk for outcomes like the metabolic syndrome and diabetes (Drake *et al*. 2005; Benyshek *et al*. 2006). The capacity for the environment to modify epigenetic patterns of gene expression helps explain the continuity of environmental effects on biology from early life into adulthood, and at times across generations.

An integrated response to developmental cues

The complexity of the epigenetic changes that underlie early nutritional programming, and the similarity in the cluster of responses induced by a range of stressful prenatal stimuli, raise the important question of whether these responses evolved to provide the organism with a capacity to modify metabolic settings and what the advantage of this capacity might be at different stages of development. If we reassess the empirical work reviewed above with respect to the functional impacts of the responses, there is evidence for an integrated strategy in which postnatal nutritional requirements are reduced and glucose is spared for the most critical functions. Collectively, this may boost the body's capacity to cope with and prepare for challenge or threat.

Reduced body size and lean mass

Individuals born small are often shorter and have reduced muscle mass (sarcopenia) as adults. This reduction in insulin-sensitive tissue contributes to peripheral insulin resistance and suggests reduction in expenditure on body growth and alterations in metabolism to reduce overall nutritional requirements, which would improve survival in a nutritionally constrained environment. Experimental work has demonstrated some of the mechanisms that allow prenatal nutrition to modify the somatic priorities and postnatal growth trajectory of the developing body. For example, increased maternal nutritional intake during the first half of gestation in domestic pigs acts through effects on insulin-like growth factors to increase the number of secondary muscle fibers and the post-weaning growth rate in offspring, while reduced maternal nutrition has the opposite effect (Dwyer and Strickland 1994).

Muscle becomes insulin-resistant

In addition to a reduced number of muscle cells and reduced muscle mass, the muscle cells present are also less sensitive to insulin (Fernandez-Twinn and Ozanne 2006). The development of insulin resistance in muscle is a central component of the metabolic syndrome associated with obesity, and is a precursor for the development of non-insulin-dependent (type II) diabetes mellitus. In addition to this pathophysiologic role, insulin resistance has functional significance for the organism through its effects on energy substrate use. Most tissues

require insulin to acquire glucose from the circulation, and skeletal muscle is the largest insulin-sensitive tissue in the body. When muscle becomes insulin-resistant, this effectively shunts glucose to more vital insulin-independent organs like the brain and, perhaps, the fetoplacental unit during pregnancy (see also Chapter 6). Modifying muscle insulin sensitivity is an important mechanism of resource partitioning, and in this light insulin resistance can be viewed as a conservative strategy of glucose allocation.

There are multiple mechanisms underlying insulin resistance in individuals born small: they include modifications in insulin-mediated glucose uptake and glycogen synthesis, reduced mitochondrial number, and post-receptor changes in insulin action (Fernandez-Twinn and Ozanne 2006). The multiple targets for modified insulin action in response to prenatal undernutrition suggest a coordinated strategy rather than impairment. Importantly, insulin resistance is *not* present at birth, but is only expressed in the subsequent months or years, and particularly in association with rapid fat gain (Ibáñez *et al*. 2006). These points will be returned to later.

Fat deposition is enhanced in highly labile visceral depots

Epidemiologic and experimental studies consistently show that prenatally undernourished animals deposit fat preferentially in central or visceral depots, which have well-known adverse effects on metabolic status and disease risk. Unlike fat in peripheral depots, central fat is highly innervated with neuroendocrine-sympathetic fibers, allowing the rapid mobilization and release of free fatty acids (FFA) into the circulation. These FFAs provide energy for muscle and for gluconeogenesis but also influence the organism's strategy of energy use by inducing peripheral insulin resistance, thus amplifying the altered substrate partitioning discussed earlier. In addition, children born small-for-gestational age have adipocytes that release more FFA in response to sympathetic stimulation (Boiko *et al*. 2005). Thus, individuals faced with prenatal undernutrition not only *deposit* more fat in central depots, but also have an enhanced capacity to *mobilize* these energy stores when faced with a stressful challenge.

Stress responses and reactivity are accentuated

The physiologic response to stress, as mediated by the hypothalamic–pituitary–adrenal (HPA) axis or the sympathetic nervous system, is also accentuated in animals undernourished or exposed to stress hormones prior to birth. These systems modulate both the deposition (glucocorticoids) and the mobilization (sympathetic responses) of visceral fat, and also have systemic effects on energy use and metabolism, influencing traits like blood pressure and heart rate. They are critical to the organism's capacity to maintain homeostasis in the face of challenges such as danger, physical exertion, or the vagaries of dietary intake.

A developmental and evolutionary synthesis

Prenatally undernourished organisms are thus born with a set of metabolic biases that influence their developmental trajectory, physiology, and metabolism across the lifecourse. These changes are central to the adult disease consequences of fetal nutritional stress, but from a functional perspective they favor fat deposition in the more labile central depots, accentuate the capacity to mobilize these depots, and repartition glucose allocation away from the insulin-sensitive periphery to insulin-independent tissues, particularly the brain. These adjustments involve complex alterations at multiple levels of biological organization in both central and peripheral tissues, including epigenetic control of gene expression, modification of hormone sensitivity by changes in receptor density and post-receptor pathways, and adjustment of patterns of cell division in response to nutritional and endocrine cues.

Although evidence for 'design' is a weak basis for evaluating adaptation (Stearns and Ebert 2001), the distributed nature of these responses, their apparent functional integration, and the molecular and epigenetic complexity underlying them make it unlikely that they represent simple organ or tissue

damage. At the same time, however, it remains unclear how these changes are coordinated, what sequence they follow during development, and how or why they tend to co-occur. One possibility is that a small set of early developmental changes have cascading effects on related systems by triggering a compensatory process of phenotypic accommodation (West-Eberhard 2003). For example, any increase in vascular resistance will be associated with changes in the size and structure of the heart as its pattern of growth and development compensates for the added functional loading. In this way, a single primary adjustment could account for multiple correlated changes in the phenotype. By analogy, one or several of the changes in metabolic settings described above could be primary and have cascading effects on other metabolic traits.

Recent animal work has shown that simple hormonal cues can reverse many of the changes induced by prenatal nutritional stress, arguing against phenotypic accommodation as an explanation for their co-occurrence. The induction of all of the components of the phenotype associated with maternal undernutrition and postnatal high-fat feeding (obesity, insulin resistance, elevated leptin levels, hyperphagia and reduced activity) can be completely reversed by a simple hormonal manipulation—leptin administration—soon after birth (Vickers *et al*. 2005). This reversal is accompanied by correlated changes in epigenetic marking and expression of several key genes (Vickers *et al*. unpublished). Because leptin is an adipose-derived hormone that signals energy status, one interpretation of this finding is that exogenous leptin misleads the undernourished neonate into developing as if it were well-nourished, thus reversing the scarcity-anticipating adjustments initiated during fetal life. These findings suggest the presence of a small set of genes that are responsive to prenatal nutrition and that have pleiotropic effects on a range of interrelated metabolic characteristics. The ability to modify the entire suite of adjustments with a single cue is reminiscent of a polyphenism, a context-dependent switch in developmental form found in many species with an evolved capacity for adaptive developmental plasticity (West-Eberhard 2003).

Anticipating the future from maternal cues: predictive developmental plasticity

Why is such an integrated suite of changes triggered by poor early nutrition or stress? If there is indeed a design to these responses, what is their purpose and at what age are they meant to be expressed? The changes initiated by prenatal cues could be functional at more than one developmental stage (for an expanded discussion see Gluckman *et al*. 2005). Some adjustments triggered in response to prenatal stress, such as the premature termination of a difficult pregnancy or the redirection of blood flow to protect the brain, clearly accrue their benefit immediately. Indeed, early DOHaD proposals, such as the thrifty phenotype hypothesis (Hales and Barker 1992), assumed that the bulk of the benefit was experienced during gestation.

Some components of the fetal response to intrauterine stress may not have immediate benefits but instead be made in anticipation of postnatal conditions. Such adaptive anticipatory adjustments have been described as 'predictive adaptive responses' (Gluckman and Hanson 2005). Such long-term adaptive adjustment has been criticized and defended on a variety of theoretical and empirical bases (e.g., Wells 2003; Kuzawa 2005; Gluckman *et al*. 2007). There are many examples of mammalian taxa that convey predictive information to offspring *in utero*, providing a precedent to consider the operation of similar processes in humans (for examples see Gluckman and Hanson 2005). Many of these are shorter-lived species, however, and the extrapolation of these findings to long-lived species has been questioned (Kuzawa 2005). In addition, Wells (2003) proposed that the postnatal nutritional environment that the newborn experiences is constructed by the mother in service of her own goal of balancing reproductive investment across present and future offspring. In this scenario, the suite of metabolically thrifty adjustments made *in utero* is a fetal strategy for enhancing postnatal survival against the backdrop of less than optimal (from the offspring's perspective) maternal provisioning.

What is clear is that many of the metabolic changes induced by prenatal nutritional stress appear after birth, thus pointing to a predominantly postnatal function. Some of the more important changes in

biology triggered in response to prenatal stress are only expressed postnatally, and in some instances take months or years to emerge. This is seen clearly for insulin resistance, which is central to the induced metabolic phenotype and is an important factor in its pathological consequences in adults. Clinical studies show that individuals born small are more insulin sensitive at birth and do not develop insulin resistance until later in childhood, particularly in association with weight gain (Ibáñez *et al*. 2006). Recent work in rats suggests that the initial insulin sensitivity after prenatal stress reflects increased insulin sensitivity in adipose tissue, which, when coupled with insulin resistance in muscle, promotes rapid deposition of fat (Cettour-Rose *et al*. 2005). Thus, organisms born under stressful conditions enter the world with a set of tissue-specific metabolic biases that favor accrual of fat, which is preferentially deposited in rapidly mobilizable central depots. If the constellation of adjustments in metabolic partitioning represents a functional complex, as argued above, it must serve this function at or after the age when the central components of the complex—insulin resistance and enhanced fat depots—are established. Such modifications of energy partitioning and metabolism could provide an advantage for an organism entering a world of marginal or less predictable nutrition.

Weaning represents an important developmental bottleneck that could have particular relevance for understanding anticipatory metabolic adjustments in mammals. Nutritional stress has its greatest impact on human mortality during infancy and early childhood, and the pre-reproductive timing of this mortality peak means that selection for metabolic traits that improve survival—whether genetic or induced through plasticity—will be strongly favored. The brain is a particularly important determinant of this metabolic stress in humans because cerebral metabolism accounts for greater than 50% of energy use throughout human infancy and early childhood (see Kuzawa 1998). The requirement to devote a large fraction of the body's energy budget to the brain reduces flexibility in metabolic expenditure at this age, and the period of peak brain metabolism largely overlaps with the heightened infectious disease and nutritional stress that often accompany weaning. The metabolic risk imposed by this convergence of high demand and disruption in supply may explain the unique human tendency to begin deposition of sizeable body fat reserves prior to birth (Kuzawa 1998, see also Chapter 6). By the same reasoning, the constellation of traits induced by prenatal undernutrition—the tendency to deposit visceral fat late in gestation and postnatally, the enhanced ability to mobilize this energy reserve when faced with stress, and the emergence of an insulin-resistant, glucose-sparing phenotype—might help the infant or young child faced with the challenge of protecting a vulnerable and metabolically costly brain during this period of metabolic stress.

There are other examples of prenatal phenotypic induction that, although less important for adult metabolic disease, nonetheless have their greatest effects on the adult phenotype. Direct metabolic investment by the mother in reproduction, as reflected in birth size and growth rate of her offspring, is contingent on the nutritional conditions that she herself experienced during the prenatal and early postnatal periods (see Kuzawa 2005; Morton 2006). Thus, in higher nutrition environments, mothers invest more to support offspring growth, and this strategy is initiated in part in response to nutritional cues that she received *in utero* as a fetus. In males, adult production of testosterone, which stimulates the growth and maintenance of sexually selected traits such as muscle mass, is increased by favorable early nutrition (Cicognani *et al*. 2002), thus increasing investment in a costly trait related to reproductive strategy as environmental conditions improve. As with the metabolic syndrome, the modification in adult testicular function involves changes in peripheral hormone sensitivity coupled with a shift in central set points, suggesting complex regulatory adjustments rather than simple impairment. Similarly, in females, being born thin may increase the well-known sensitivity of ovarian steroid production to energetic stress in adulthood (Jasienska *et al*. 2006). In these examples of adjusting reproductive expenditure in response to prenatal signals, any benefits of the prenatal induction are delayed until adulthood.

When the benefit of an early developmental response is experienced later in life, the consequences for the organism will depend critically on the fidelity of the forecast. For a strategy of adaptive

plasticity to evolve, the fitness benefits of being able to adjust biological settings must outweigh the costs of maintaining the necessary sensor and effector mechanisms. Mathematical modeling suggests that such responses could evolve even when the reliability of the prediction is not particularly high, so long as the cost of plasticity is low (Sultan and Spencer 2002). For intrauterine nutrition as a predictive cue, the cost of plasticity is likely to be quite low, because the cue (nutrition) and the capacity to sense and respond to it (e.g., metabolic and growth response to substrate) are already integral to fetal development. Thus, barriers to the evolution of predictive responses based upon sensing and responding to the flow of nutrients may be minimal. In addition, several factors buffer fetal nutrition from short-term fluctuations in maternal intake and thus increase its reliability as a predictive cue (Wells 2003; Kuzawa 2005). The sensitivity of ovulation to energy status helps ensure that pregnancies are only initiated during favorable nutritional circumstances (Ellison 1990), while during gestation, the mother's body modulates appetite, expenditure, and fat mobilization to stabilize delivery of nutrients to the fetus. Fetal nutrition is also correlated with measures of the mother's prior nutritional experiences earlier in her own development (Ramakrishnan *et al*. 1999; McCarron *et al*. 2004), suggesting that fetal nutrition may convey an integrated or running average, and thus more reliable, measure of the mother's nutritional experiences (see Kuzawa 2005).

Medical and public health implications

The capacity to track a maternal signal of recent nutritional history could, however, lead to 'mismatch' and heightened risk of disease under

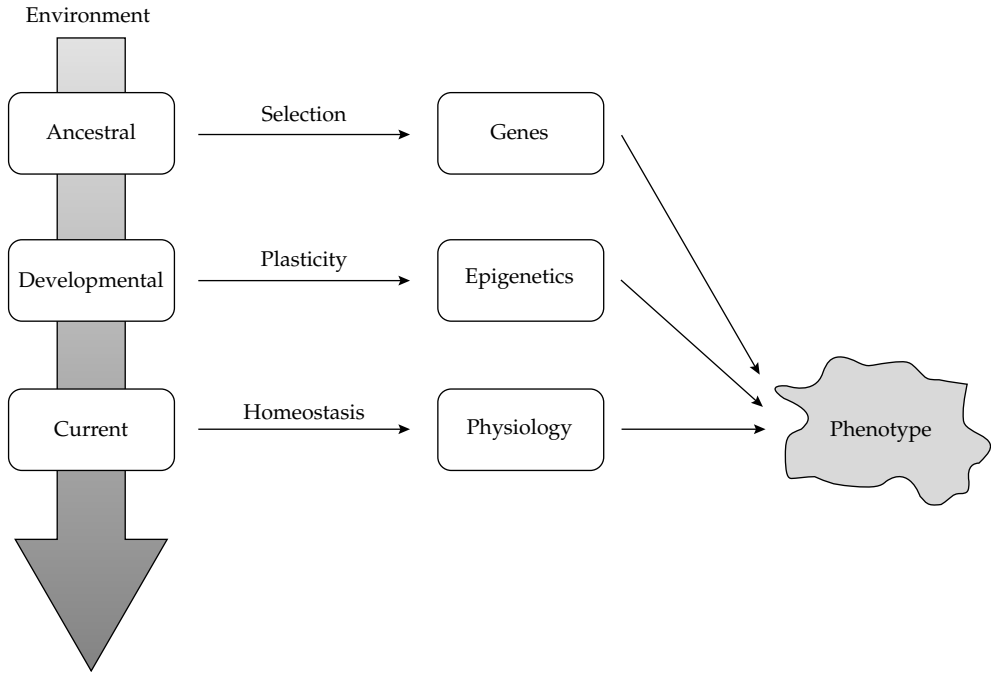

Figure 19.2 Biological basis and mechanisms of adaptation to environmental variability on different temporal scales. An individual's genome is the product of past natural selection (and other processes) operating in ancestral environments. Developmental adaptation occurs in response to early life environments, and may also have an intergenerational component. Reversible homeostatic mechanisms are capable of coping with short-term environmental changes, but have operating ranges constrained by the more stable developmental and genetic settings. A mismatch between the current environment and an organism's biological settings may occur as environmental change outstrips the pace that natural selection and developmental plasticity can accommodate.

conditions of rapid change, or those which mimic change (Fig. 19.2). Adaptation to the local environment during development can lead to metabolic or physiologic mismatch if the environment changes rapidly within a single generation—as occurs in many developing societies experiencing the 'nutrition transition' to higher dietary intake and reduced energy expenditure (Popkin 2004).

The finding that CVD risk is highest among individuals who were born small but later put on weight is consistent with the hypothesis of developmental mismatch, as it suggests that improved nutrition between birth and adulthood can exacerbate the effects of a compromised fetal environment (Oken and Gillman 2003). The epidemic of type II diabetes on the Indian subcontinent, predicted to result in nearly 80 million people with diabetes in India alone by 2030 (WHO 2006), may be a consequence of severe maternal constraint arising from generations of poor nutrition followed by nutritional excess later in life (Yajnik 2004). Developmental mismatch could also help explain why stunting—a measure of early life undernutrition—is a risk factor for obesity in some populations experiencing rapid nutritional transition (Popkin *et al*. 1996; Florencio *et al*. 2003). Poor gestational nutrition is *not* associated with elevated CVD risk in populations that remain marginally nourished in adulthood (Moore *et al*. 2001), also supporting the model. Populations shifting rapidly from low to higher nutritional status would be expected to experience a period of transition marked by high CVD risk, followed by a gradual intergenerational recalibration to the new and richer nutritional plane (Gluckman and Hanson 2005; Prentice and Moore 2005). It has been argued that this gradual recalibration could help explain the recent decline in CVD risk in developed populations that experienced high rates of CVD earlier in the twentieth century (Barker 1994).

Poverty can also cause mismatch, and this can have an important influence on disease patterns. The linkage between socioeconomic status and adult obesity may be explained by relatively high rates of early life undernutrition and growth stunting in lower income groups, related to factors like childhood diarrhea and respiratory tract infections. As these infectious causes of nutritional stress wane with age, this could lead to undernutrition followed by relative overnutrition later in life in the absence of economic or societal change during an individual's lifetime (e.g., Garrett and Ruel 2005).

The framework presented does not apply to all examples of metabolic disease caused by early developmental effects. The intergenerational consequences of maternal diabetes provide a prominent example with important public health implications. Maternal hyperglycemia leads to high fetal glucose and insulin levels, which encourage fat deposition. When these individuals are subsequently exposed to excess nutrition in later life, they are more likely to become obese and insulin-resistant themselves and to develop diabetes. This is a developmental pathway to obesity and metabolic derangement distinct from the role of prenatal stress discussed earlier (Kuzawa *et al*. 2007). The offspring of such diabetic pregnancies appear not to show the integrated pattern of response that characterizes induction by prenatal undernutrition or stress. This pathway shares more features with teratogenesis, or developmental disruption, than with fetal adaptation to a normal range of nutritional variation. Because frank gestational diabetes followed by infant survival is a new phenomenon, there is no need to invoke an evolutionary explanation for the novel phenotype that it produces.

Policy implications

Specific interventions arising from the DOHaD paradigm are some years away. However, there are stronger reasons than ever to ensure that women of reproductive age are healthy, consume a balanced diet, and are protected from stress during pregnancy. Restricting nutritional intake or stressing a pregnant rat induces in offspring all the long-term consequences of the metabolic syndrome, and this same constellation of conditions is predicted by small birth size in humans. Components of this syndrome are also more prevalent in people whose mothers were nutritionally stressed by an externally imposed famine during the Second World War. In addition, being exposed *in utero* to the stress of the September 11th attacks on New York City has been shown to have persistent effects on the stress hormone system (Yehuda *et al*. 2005).

Thus, the available evidence is sufficient to suggest that a focus on the health of mothers will have benefits for the next generation that transcend the widely acknowledged improvements in perinatal outcome and infant survival.

The intergenerational nature of some of these effects also has broad policy implications. Interventions targeting maternal health are likely to have benefits that extend beyond the current generation and that accumulate slowly over subsequent generations—the most potent strategies will therefore require sustained follow-up and intervention. The modest effects reported from nutrient supplementation trials during pregnancy attest to the fact that a single-generation solution is suboptimal for a trait with an intergenerational component. Given the now substantial evidence for the effects of early life nutritional experience on adult health, it is believed that intergenerational approaches will ultimately open up new strategies to help stem the global rise of metabolic disease. But the difficulties inherent in obtaining clinical evidence for, and long-term political commitment to, such approaches should not be underestimated.

Summary

1. A rapidly growing body of research demonstrates that an adverse early environment changes the developing organism's metabolism, physiology, and organ structure in a way that increases future risk of a variety of adult metabolic disorders, including the metabolic syndrome, diabetes, and cardiovascular disease.

2. Early environmental cues initiate what appear to be functionally coherent adjustments in the body's metabolic and physiologic priorities, with the end result being altered energy partitioning and modification of nutritional requirements.

3. Insofar as maternal nutritional and endocrine cues are reasonable predictors of future environmental conditions, adjustment of developmental and metabolic priorities in response to these cues could provide a mechanism for adjusting more rapidly to local environmental changes than is possible via natural selection operating on the genome.

4. As human nutritional and lifestyle change accelerates, individuals faced with scarcity early in life are now increasingly confronted with abundance later in life. There is now much evidence that a mismatch between the early developmental environment and the environment experienced later in life is an important contributor to patterns of human morbidity and mortality.

5. These findings underscore the need to expand current models of cardiovascular epidemiology from consideration of genes and environment alone to a triad of genes, environment, and developmental history.

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