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Feature Article

Early Life Events and Their Consequences for Later Disease: A Life History and Evolutionary Perspective

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ABSTRACT Biomedical science has little considered the relevance of life history theory and evolutionary and ecological developmental biology to clinical medicine. However, the observations that early life influences can alter later disease risk—the "developmental origins of health and disease" (DOHaD) paradigm—have led to a recognition that these perspectives can inform our understanding of human biology. We propose that the DOHaD phenomenon can be considered as a subset of the broader processes of developmental plasticity by which organisms adapt to their environment during their life course. Such adaptive processes allow genotypic variation to be preserved through transient environmental changes. Cues for plasticity operate particularly during early development; they may affect a single organ or system, but generally they induce integrated adjustments in the mature phenotype, a process underpinned by epigenetic mechanisms and influenced by prediction of the mature environment. In mammals, an adverse intrauterine environment results in an integrated suite of responses, suggesting the involvement of a few key regulatory genes, that resets the developmental trajectory in expectation of poor postnatal conditions. Mismatch between the anticipated and the actual mature environment exposes the organism to risk of adverse consequences—the greater the mismatch, the greater the risk. For humans, prediction is inaccurate for many individuals because of changes in the postnatal environment toward energy-dense nutrition and low energy expenditure, contributing to the epidemic of chronic noncommunicable disease. This view of human disease from the perspectives of life history biology and evolutionary theory offers new approaches to prevention, diagnosis and intervention. Am. J. Hum. Biol. 19: 1–19, 2007.

There has been an increased focus on the possible role that early life events might play in the generation of later disease risk in humans. There is a considerable literature relating the nature of infant feeding to later health consequences (e.g., Lucas, 1991) and also relating birth size to later risk of disease (e.g., Syddall et al., 2005). These observations in turn arose from earlier studies linking the conditions of life in infancy to later disease risk and mortality (Barker and Osmond, 1986; Forsdahl, 1977), a link more recently confirmed by extensive epidemiological studies (reviewed by Godfrey, 2006).

Although the epidemiological associations are strong, a mechanistic understanding is essential in order to demonstrate that these associations are causal and in what way, and to identify the potential for intervention. Mechanistically and experimentally, there is an increasing body of knowledge showing that manipulation of the environment in the period extending from conception to infancy can be associated with permanent changes in physiology and/or structure. In turn, many of these changes are associated with permanent alterations in gene expression regulated by epigenetic factors such as DNA methylation and histone methylation/acetylation (Gluckman and Hanson, 2006a).

In this article, we place these clinical and experimental observations connecting early life

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events with later disease consequences, generally known as the "developmental origins of health and disease" (DOHaD) phenomenon, within a wider framework encompassing life history and evolutionary concepts. We suggest that the DOHaD phenomenon represents the most visible manifestation of the fundamental processes of developmental plasticity by which mammals adjust their life history strategy in response to environmental cues during early development.

DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

The origin of the DOHaD concept arose from epidemiological observations relating birth size to an altered risk of cardiovascular disease (Barker and Osmond, 1986) and type 2 diabetes (Hales et al., 1991). The earliest concepts directly linked failure of fetal growth to permanent changes in structure and function that predisposed to disease. Subsequently, it was suggested that these changes might also have adaptive value in a deprived (in nutritional terms) postnatal environment by making the individual permanently "thrifty," e.g. by being small and insulin resistant. This "thrifty phenotype" hypothesis (Hales and Barker, 2001) was placed in contradistinction to Neel's "thrifty genotype" hypothesis (Neel, 1962) in which he had proposed that the thrifty aspects of the contemporary individual arose from genes selected over a long time period during our ancestors' hunter–gatherer existence. The consequences were however similar—the adult organism would be well suited to an environment in which nutrient supplies were limited but would be more likely to be become unhealthy in a nutritionally rich environment.

It is now clear that small birth size is not an obligatory part of the pathway leading to increased disease risk—during development, many environmental factors (cues) can induce changes in physiology and anatomy with long-term consequences, and in humans, these may be manifested as altered disease risk, without necessarily inducing a major, or indeed any, change in birth size. This is partly evident from the graded relation between disease risk and birth size that occurs across the normal birthweight range (e.g., Barker, 1998). Moreover, it is now known that prematurity independent of growth retardation is also associated with long-term metabolic consequences (Hofman et al., 2004), and the offspring of women subjected to severe undernutrition in early pregnancy during the famine in the winter of 1944/1945 in the Netherlands did not have reduced birth weight but do have an increased risk of obesity (Painter et al., 2005).

A range of epidemiological studies in many populations now extends the disease risk profile to include coronary heart disease and stroke; insulin resistance and thus type 2 diabetes; altered endothelial function and increased risk of hypertension; central and peripheral propensity to obesity; altered body composition, including reduced bone mineral density which may lead to osteoporosis; and possible effects on cognitive and emotional function. There are several recent biomedically focused reviews of the DOHaD concept and the observations that support it (Gluckman and Hanson, 2006a), including those published recently in this journal (Kuzawa and Pike, 2005), so this review will focus on the broader interpretation and significance of this association.

There are limitations to both the classical thrifty genotypic and phenotypic models, although both have been important in the evolution of understanding in the field. We have built off these to consider further the potential adaptive basis of the DOHAD phenomenon and its relationship to the processes of developmental plasticity. The original thrifty genotype hypothesis posited that the high incidence of obesity and insulin resistance in western populations was a result of ancestral selection for marginal nutritional environments and that the expression of these thrifty genes resulted in a greater risk of obesity and insulin resistance in the presence of high energy intake and low energy expenditure. But famine in our hunter–gatherer ancestors may have been less common than supposed (Benyshek and Watson, 2006), the search for thrifty genes has been unproductive, and the ability to reproduce these phenomena by manipulation of experimental animals of uniform genetic background (reviewed in Gluckman et al., 2005b; McMillen and Robinson, 2005) and by short-term "natural experiments" such as the Dutch Hunger Winter (Painter et al., 2005) argues against a purely genetic explanation. Nonetheless, genetic variation will play a role in determining sensitivity to environmental stimuli, and the presence of such effects as reflected in the influence of specific polymorphisms within the epidemiological observations is well documented (Eriksson et al., 2002; Jordan et al., 2005; Kajantie et al., 2004; Kubaszek et al., 2004; Weedon et al., 2005). How genetic variation and environmental cues may interact to

match the phenotype predictively to the environment has recently been modeled (Leimar et al., 2006).

The thrifty phenotype model developed by Hales and Barker attempted to explain the epidemiological relationship between birth size and disease risk by proposing that the fetus adapts to maternal undernutrition by growth retardation, which leaves the adult better equipped to cope in a deprived rather than an enriched postnatal environment. This adaptive model suggests that the organism responds to immediate challenges by reducing growth, perhaps by mechanisms involving reduced insulin sensitivity, but must then cope postnatally with the consequences for the rest of its life. Although this model can explain a relationship between low birthweight and disease risk, it has limitations. As noted above, it cannot easily explain the continuous relationship between birth size and disease risk that occurs even in the upper part of the birthweight range. Nor can it explain how early life events can induce long-term physiological changes without changes in birth size. It cannot explain developmental induction in systems not involving nutrition—for example induction in the systems regulating behavior, body temperature, or fluid balance for which there is good experimental evidence (Gate et al., 1999; Ross et al., 2005; Vickers et al., 2003). Finally, it is inconsistent with recent clinical data suggesting that small-for-gestational-age individuals are born with enhanced insulin sensitivity and that insulin resistance appears later in life (Ibáñez et al., 2006; Mericq et al., 2005)—these observations imply that any adaptive advantage of reduced insulin sensitivity only becomes manifest after the neonatal period.

The word "thrifty" implies directionality inherent in the underlying mechanisms and this is not the case. Recent studies in infants born after in vitro fertilization show that they grow up thinner, taller, and with enhanced insulin sensitivity, demonstrating that early life events can adjust subsequent metabolic physiology in either direction (Cutfield, 2005). Moreover, large infants are also at risk of other later-life disease consequences, such as an increased risk of breast cancer (Dos Santos et al., 2004) probably mediated by higher estradiol levels (Jasienska et al., 2006). We have therefore suggested that the original observations relating birth size to cardiovascular and metabolic disease risk represent a special case of a much broader and generalizable phenomenon that allows the pattern of development to be modified in either direction as a result of developmental cues (Gluckman and Hanson, 2004b; Gluckman et al., 2005c,d).

CLASSES OF DEVELOPMENTAL RESPONSE AND THEIR ADAPTIVE VALUE

Environmental factors acting during the phase of developmental plasticity can either act to disrupt the normal program of development or to modulate it (Gluckman et al., 2005d). Developmental disruption may be overtly teratogenic, leading to gross structural malformation, or may be much more subtle. Clearly, such disruptive responses cannot be considered adaptive.

The processes of phenotypic plasticity permit a range of phenotypes to be expressed from one genotype—indeed, the concept of the "reaction norm" was developed to demonstrate and illustrate this potential range of phenotypes (Schlichting and Pigliucci, 1998). The presumption is that there is potential adaptive advantage for a particular phenotype in a specific environmental situation (Eshel and Matessi, 1998), although empirical proof of such enhanced fitness is a formidable challenge. However, as we have detailed elsewhere (Gluckman and Hanson, 2005), it is useful to distinguish adaptive responses to environmental cues that have their potential advantage in close temporal proximity to the cue from those where the cue operates in one phase but the potential advantage is manifested in a later phase of the life course.

Immediately adaptive responses

Traditionally, developmental plasticity has largely been viewed in terms of the immediately adaptive class of response. For example, the altered morphology of the tadpole in response to intraspecific competition can be seen as immediately advantageous although it may incur a cost later in life (Relyea and Hoverman, 2003). Premature metamorphosis in the spadefoot toad is another example of a response where the advantage is essentially immediate—linked to survival if the pond is evaporating—but which may have a fitness cost in reduced adult size later in life (Newman, 1992). Both these examples illustrate that the advantages of an immediate alteration in developmental pattern that ensures short-term survival must be traded off against potential disadvantages in a later environment, and such adaptive arguments are generally used

to explain the evolution of developmental plasticity.

Intrauterine growth retardation and mild prematurity in the human can both be seen as analogous immediately advantageous adaptations. The major nongenetic cause of intrauterine growth impairment is a reduced nutritional supply across the placenta to the fetus. This may arise because of maternal or placental disease or from excessive maternal constraint. The fetus responds to reduced nutrient supply by reducing its anabolic demand, in part by reducing plasma concentrations of insulin and of plasma and tissue concentrations of insulin-like growth factor (IGF)-1, which are the two best-documented fetal growth-promoting hormones (Gluckman, 1995). There is also a major redistribution of fetal blood flow to protect development of the critical organs, in particular the fetal brain, which can lead to a degree of asymmetrical growth retardation. This reduction in fetal growth is clearly necessary to allow fetal survival to birth. But being born small has consequences. The risk of neonatal death and morbidity is significantly higher (Spencer, 2003; Wilcox, 2001) and so are the risks of subsequent cognitive impairment and persistent growth failure (Gluckman and Harding, 1997; McCarton et al., 1996). Clearly, immediate survival has been achieved at the cost of the individual being at greater subsequent risk.

Prematurity provides a similar example. Premature birth can result from an infectious intrauterine environment in which the fetus is at greater risk. Some prematurity also appears to be induced by maternal behavior that might compromise the fetus, such as poor nutrition or smoking, or by maternal psychosocial stress. Premature induction of labor clearly involves a tradeoff between the risk of continued exposure to an abnormal intrauterine environment and that of being born at full-term but with the increased risk of postnatal morbidity and mortality (Pike, 2006). Preterm delivery as an immediately adaptive response may also benefit the mother's future reproductive fitness by limiting investment in a particular pregnancy (Pike, 2006).

Predictive adaptive responses

Conversely, there are a number of clear examples where the developing organism makes phenotypic responses during development to obtain an adaptive advantage, but where that adaptive advantage is delayed. We have termed these predictive adaptive responses (Gluckman et al., 2005c).

Adult desert locusts show polyphenism, existing as migratory or solitary forms in which metabolism, wing shape, behavior, and coloration differ. The "choice" of adult phenotype is determined in the larval stage in response to chemical cues from the mother, but the advantages and appropriateness of the choice are exhibited only after final metamorphosis (Applebaum and Heifetz, 1999). Clearly in this case the constraints of developmental pathways require the choice to be made at an early stage in development, and in polyphenic species such as the locust there are two distinct morphs, although intermediates may form. In the mountain vole, the decision about the tempo of growth and acquisition of sexual maturity is made in relation to the season of year—animals born early in the summer undergo rapid growth and breed early, whereas animals born late in the season grow slowly and overwinter as prepubertal animals of subadult size (Negus et al., 1992). In the meadow vole, coat thickness for life is determined before birth by maternal signals involving melatonin, related to whether day length is shortening or lengthening. The thermal environment before birth and in the nest is similar, so the advantage of the choice of coat thickness does not appear until some months later when summer or winter temperatures are encountered (Lee and Zucker, 1988; Lee et al., 1989). In each of these examples, a developmental pathway is chosen in expectation of a future environment and fitness is enhanced if the predicted environment is matched to the phenotype that has developed. It is easy to envisage the evolutionary pathway to the appearance of these predictive adaptive responses, since they involve some relatively predictable feature of the environment. Although these examples illustrate a dichotomy in the mature phenotype, we would anticipate that predictive adaptive responses can also be reflected over a continuous range of phenotypes.

Predictive adaptive responses can only be adaptive if the forecast is correct and will be maladaptive if it is not. The retention of mechanisms underpinning such phenotypic memory will be advantageous provided that the prediction is generally more often correct than incorrect, although this in turn depends on the relative fitness of each phenotype in the predicted and nonpredicted environments and on the rate of environmental change relative to generation time (Jablonka et al., 1995; Moran, 1992; Sultan and Spencer, 2002). Modeling shows

that these processes would be particularly valuable in allowing an organism to survive during a transient environmental shift (Gluckman et al., 2005c; Jablonka et al., 1995; Moran, 1992).

These different types of response—immediate or predictive, disruptive, or adaptive—to an environmental cue have been presented as discontinuous, but there will be overlap. Indeed, the same environmental cue may induce presumptively adaptive or disruptive responses depending on its magnitude. For example, maternal hyperglycemia may induce congenital heart defects, a disruptive response, or alterations in fetal growth with long-term consequences that may be adaptive. A developmental response to an endocrine disruptor may involve interactions between the hormone-like toxin and the normal processes of developmental plasticity (Heindel and Lawler, 2006), but although such interactions use physiological mechanisms they disrupt development and cannot be considered adaptive.

Evaluating whether a response is adaptive or disruptive may be difficult in a given experimental situation. For example, is the reduction in nephron number in sheep after maternal exposure to very high doses of glucocorticoids in early gestation (Wintour et al., 2003) a process where the steroid has disrupted the normal pattern of nephron differentiation, or is it part of some adaptive process mimicking a normal situation where the fetus responds to maternal glucocorticoids crossing the placenta under situations of maternal stress? Similarly, is the continuous relationship between maternal vitamin A intake and nephron number in the rat (Lelievre-Pegorier et al., 1998) a dose-dependent disruptive effect or does it have adaptive value? Equally, a fetal adaptive response may have both an immediate and a predictive component. The accelerated maturation of the fetus of a malnourished mother may induce premature delivery, which we can consider as providing advantage potentially benefiting both mother and fetus (Pike, 2006), but it may also be part of a predictive response allowing the organism to cope better in a later environment perceived to be threatening.

There are now several lines of evidence that support the predictive adaptive hypothesis. In rats subjected to maternal undernutrition during pregnancy, the offspring develop a perturbed metabolic phenotype showing obesity, hyperphagia, hyperinsulinemia, and reduced activity in open field testing, particularly if they are fed a high-fat diet after weaning (Vickers et al., 2000, 2003). In this case, the poor prenatal nutrition led to prediction of a poor postnatal environment, but in reality the postnatal environment was nutritionally rich. Recent data (Fig. 1) show how the prediction can be reversed provided that the modifying cue occurs during the phase of developmental plasticity. If prenatally undernourished rat pups are given leptin subcutaneously in the neonatal period they grow up, even on a high-fat diet, with a metabolic phenotype identical to that of rats born to a normally nourished mother (Vickers et al., 2005). It appears that the neonatal rat pup has been "tricked" into perceiving that it is fatter than it is, leptin being a hormone made by fat. Because this neonatal stimulus occurs within the window of developmental plasticity, at least for metabolic physiology, it is possible for the prenatal prediction to be changed from one of an adverse environment to one of an energy-rich environment, with the consequent alterations in physiology (Gluckman et al., 2006). At a mechanistic level this may involve the synaptogenic actions of leptin (Bouret et al., 2004) or its peripheral actions, for example on pancreatic cell apoptosis and proliferation (Islam et al., 2000; Shimabukuro et al., 1998).

Another consideration recently recognized is the importance of the interaction between the effect of the prenatal cues on the phenotype and its consequent effect on the response to the postnatal environment. For example, in rats the prenatal environment determines both peripheral and central sensitivity to high-energy nutritional intake imposed after weaning (Vickers et al., 2000). The effects of the induced phenotype can be exacerbated (Hales and Ozanne, 2003; Vickers et al., 2000) or ameliorated (Jimenez-Chillaron et al., 2006; Stoffers et al., 2003; Vickers et al., 2005; Wyrwoll et al., 2006) by postnatal interventions, indicating a window of physiological plasticity that extends beyond the intrauterine period. In this discussion, we have simplistically described only one developmental environment and only one mature environment, but it would be more realistic to envisage a cascade whereby a series of genotype-environment interactions during one stage in development determines the setting for interactions with the environment at the next stage, and so on.

There is increasing evidence that predictive adaptive responses are underpinned by epigenetic changes. These may be manifest as altered gene expression and consequent altered regulatory control or, given the importance of

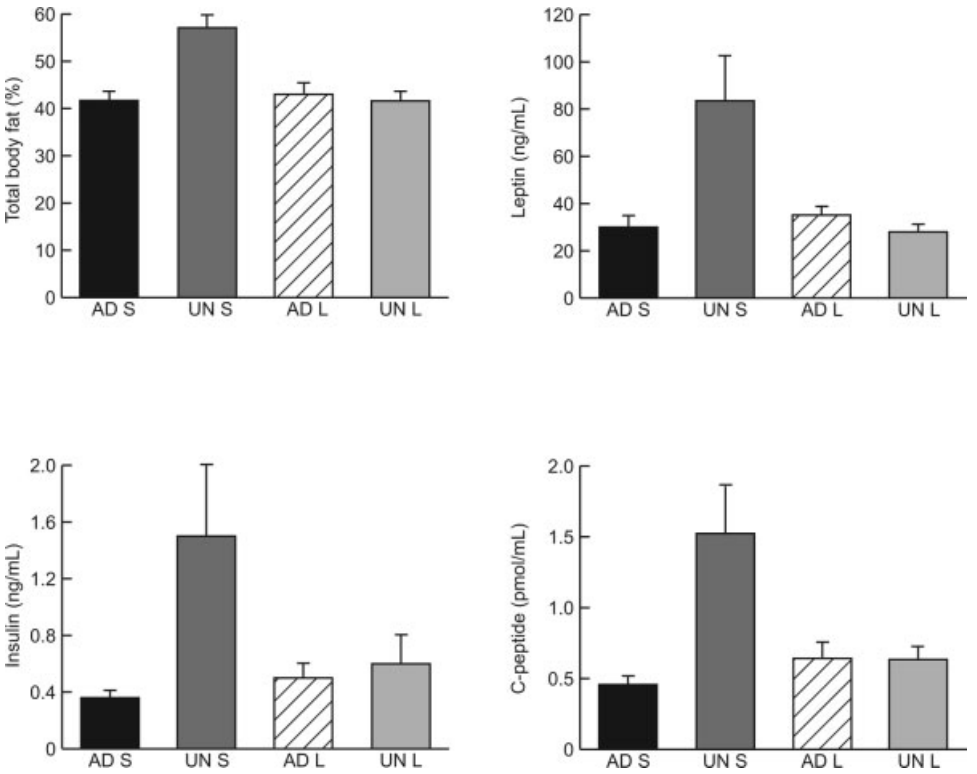

Fig. 1. Reversal of developmental induction by neonatal leptin treatment. Rat dams were fed *ad libitum* throughout pregnancy (AD) or undernourished throughout pregnancy (UN). Pups from UN mothers were cross-fostered to AD mothers after birth to standardize postnatal feeding, and all offspring were fed a high-fat diet after weaning. The neonates were treated with either saline (S) or recombinant rat leptin (L) on postnatal days 3–13. Total body fat and metabolic profile as reflected by fasting plasma leptin, insulin and C-peptide (a marker of pancreatic insulin secretion) concentrations were measured in adult females (postnatal day 170). Untreated prenatally undernourished animals (UN S) were obese, hyperinsulinemic and hyperleptinemic as adults compared with control animals (AD S); development of this "metabolic" phenotype was prevented by neonatal leptin treatment (UN L). Values are means ± SEM for eight animals per group (redrawn from data in Vickers et al., 2005).

epigenetic mechanisms to developmental biology, as organizational change and altered tissue development. There is a growing body of literature relating prenatal manipulation by hormonal or nutritional stimuli to methylation of DNA and changes in chromatin structure affecting the expression of genes underlying the altered phenotype. For example, maternal behavior in rats can be manipulated to leave the offspring as adults with altered stress responses and behavior. This is associated with alterations in the expression of the glucocorticoid receptor in the hippocampus, which in turn are caused by alterations in DNA methylation in a promoter sequence for the gene. The altered phenotype can be reversed by chemical manipulation of histone acetylation, one of the consequences of DNA methylation (Weaver et al., 2004). In another experimental model, the offspring of female rats exposed to a low-protein diet show changes in expression of several genes, including that for the glucocorticoid receptor, in the liver, heart, muscle, and fat (Bertram et al., 2001); such changes are associated with altered DNA methylation and can be reversed by folic acid supplementation during the period of maternal malnutrition (Lillycrop et al., 2005). We have preliminary evidence that the reversal of the effects of prenatal undernutrition by postnatal leptin treatment (Vickers et al., 2005) is accompanied by coordinated changes in expression and promoter methylation of key genes.

There is increasing interest in epigenetic transmission across generations (Chong and Whitelaw, 2004; Drake and Walker, 2004), although the mechanisms and their relevance

to reported transgenerational inheritance in humans (Kaati et al., 2002; Pembrey et al., 2006) are poorly understood. There is experimental evidence that developmental induction can be transmitted from the F_0 generation to the F_1 generation and beyond through the male and/or female lines after hormonal (Drake et al., 2005) or nutritional (Benyshek et al., 2006; Zambrano et al., 2005) cues. Alternatively, there are indirect means by which environmental influences can be reflected across two or more generations—for example, the uterine size of a female may be influenced by her experience as a fetus (Ibáñez et al., 2003) and this in turn may influence the size of her own progeny.

THE DOHaD PARADIGM—AN ADAPTIVE PERSPECTIVE

We have used the concept of predictive adaptive responses to explain the observations that led to the development of the DOHaD paradigm (Gluckman et al., 2005b). We have suggested that the developing organism senses its metabolic milieu and adjusts its physiological homeostatic setpoints according to the environment it forecasts will exist after birth. If the signals in the developmental phase suggest limited nutrient availability, then the organism will adjust its developmental trajectory such that the mature individual has a metabolic homeostasis better adapted for survival in a sparse environment. Any association between the outcome and birth size is thus an epiphenomenon of the relationship between nutrient availability and the induction of predictive adaptive responses. Such a model can explain the observed continuous associations between birth size and disease risk, how disease risk may be independent of changes in birth size, and how developmental induction can occur in other physiological systems.

An important feature of such a model is that the alterations in regulatory systems induced by the developmental cues may be subtle and not observable under basal conditions—they may affect the sensitivity of a physiological response underpinning a specific trait in the adult and thus make the organism more or less susceptible to disease in an extreme postnatal environment. Lifestyle disease in the human then occurs when the individual lives in an environment beyond their forecasted and induced physiological homeostatic range—we term this the "match-mismatch model." Where the organism's physiology is matched by developmental processes to the environment in which it lives in later life, its risk of disease is lower; when it is mismatched, its risk is higher (Fig. 2). Clearly, both immediate and predictive components may play a role in the final phenotype and there will be a degree of interaction between the two, particularly if the environmental cues are more extreme. For example, we have elsewhere suggested that predictive responses play a role in determining the role of prenatal nutrition in the timing of menarche, although this effect is modified by nutritional status in the peripubertal period (Gluckman and Hanson, 2006b).

Implicit in this discussion is the view that the DOHaD phenomenon is underpinned by physiological mechanisms that have evolved in mammals to provide adaptive advantage. There are several reasons, based on a large body of experimental evidence reviewed in detail elsewhere (Gluckman et al., 2005b), why we believe this to be so. First, it is very easy to demonstrate this phenomenon in a wide variety of mammalian species with diverse life history strategies, there being data from experimental manipulation in mice, rats, sheep, pigs, guinea pigs, and non-human primates and from epidemiological studies in humans. Second, relationships similar to the human epidemiological findings can be seen in animals even in the absence of maternal manipulation, suggesting a phenomenon that represents physiological plasticity rather than pathology. Third, a relatively similar phenotype can be induced by a variety of nutritional or hormonal manipulations acting either early or late in development—for example, a trend to obesity, insulin resistance, and endothelial dysfunction can be induced by high-fat diets, low-protein diets, maternal global undernutrition, and maternal glucocorticoid exposure at differing times in gestation in sheep, rats, mice, and guinea pigs. That these different cues converge on a common outcome reflecting an integrated response of the fetus to a perceived threatening postnatal environment suggests that the induced phenotype has value for the fitness of the offspring. Finally, our demonstration that the integrated phenotype induced by prenatal nutritional insult can be completely reversed by a simple postnatal endocrine manipulation (Fig. 1; Vickers et al., 2005) argues for a single mechanism underpinning a broad range of developmental effects.

Stearns and Ebert (2001) have usefully summarized criteria for distinguishing adaptive from nonadaptive processes. One such criterion defines "an adaptation as a change in a phe-

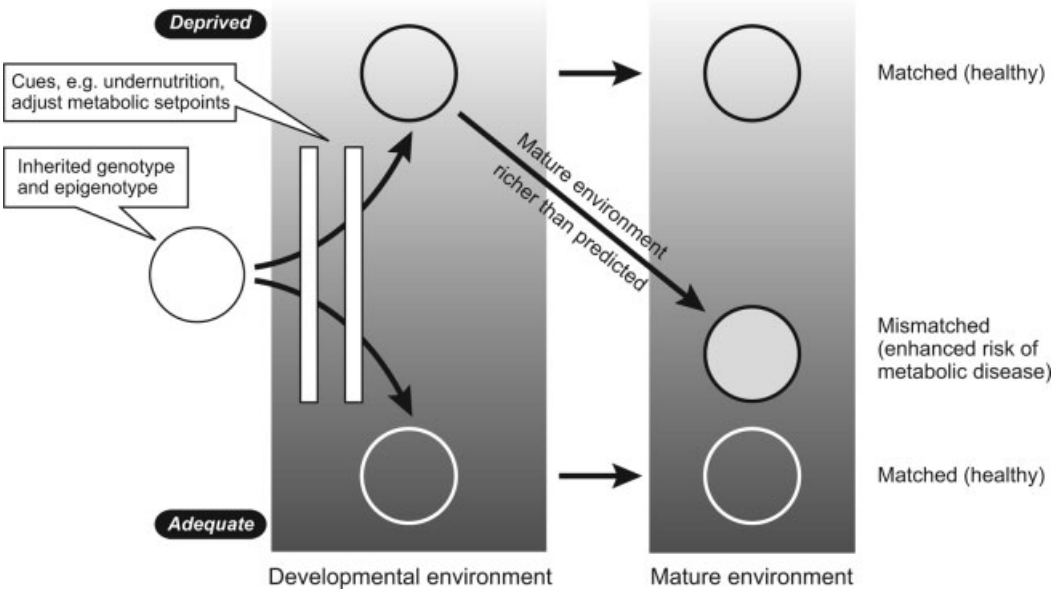

Fig. 2. The match–mismatch paradigm of metabolic disease. The developing organism senses maternally transmitted environmental cues, such as undernutrition, during prenatal and early postnatal life. Developmental plasticity in response to these cues modifies the default trajectory defined by the inherited fetal genome and epigenome according to whether the environment is perceived as adequate (dark background) or deprived (light background), resulting in adjustment of metabolic setpoints. If the eventual mature environment, whether adequate or deprived, matches the prediction then the risk of metabolic disease in later life is low. If there is a mismatch between the predicted and actual mature environments, particularly if the mature environment is richer than anticipated, then the risk of metabolic disease is enhanced.

notype that occurs in response to a specific environmental signal . . . resulting in improved growth, survival, or reproduction." We have linked prenatal nutritional insult to a defined change in phenotype; later in this review, we explain why we believe that this phenotype improves survival in a sparse postnatal environment.

To summarize, our model invokes established concepts from comparative biology to extend the thrifty hypotheses by proposing that the developing organism senses its environment throughout development and adjusts its physiology to be appropriate for the environment in which it predicts that it will live until and through reproductive age. These mechanisms constitute predictive adaptive responses that are influenced by the normal range of environments experienced by the organism's mother. The fetus may also make some immediately adaptive responses if they assist in surviving until birth, and these responses may be reflected in birth size. In this way, developmental plasticity tunes physiological homeostatic settings in ways that are much faster and potentially more sensitive to changing conditions than those achieved by classical genetic mechanisms alone. For any postnatal environment there will be a set of physiological settings associated with optimal fitness for that environment, and in the case of humans a risk of disease will exist when we live beyond the range of the expected environment.

THE FETAL ENVIRONMENT AND MATERNAL CONSTRAINT

The consequences of alterations in the developmental environment will depend on how the fetus perceives that environment and the accuracy of the forecasts it makes. The mammalian embryo and fetus has the particular challenge of interpreting the maternal–placental transduction of environmental information, a process that may not operate with complete fidelity.

Fetal nutrition is not the same as maternal dietary intake. The provision of fetal nutrients depends on the maternal nutritional environment, her energy expenditure, her behavior

and health, her metabolic and cardiovascular function, placental health and function, and fetal endocrine status. A further feature of mammalian development is that fetal growth is constrained by a number of factors. The term "maternal constraint" was introduced by Ounsted (1965) to describe nongenetic maternally determined environmental and physiological influences that limit fetal growth. The concept derived from the classical work of Walton and Hammond (1938) which showed that the size of the fetus was significantly affected by the size of the mother, as opposed to the fetal genotype. Later work has confirmed this to be the case in several monotocous mammalian species. Indeed, in human pregnancies originating from egg donation and surrogate motherhood, birth size is more tightly correlated with recipient stature than with donor stature (Brooks et al., 1995).

The mechanisms underlying maternal constraint are poorly understood. In some way, maternal size determines nutrient availability to the fetus. Whether the constraint mechanism lies in the uterine vasculature or in placental structure and function is not yet clear, but in general shorter mothers who have smaller pelvises have smaller babies. An alternative explanation might lie in parent–offspring conflict, a concept originated by Trivers (1974) and extended by Haig to include the observations that the genes for IGF-2 and the IGF-2 clearance receptor are imprinted in the mouse—IGF-2 being expressed in the fetus from the paternal allele and the receptor being expressed from the maternal allele in the placenta (Haig and Graham, 1991). The conflict argument suggests that the fetus drives fetal growth under paternal influences, while the mother attempts to limit fetal growth by clearing IGF-2 from the fetal circulation via the placenta. However, in humans the IGF-2 receptor is not imprinted, and in species that have a long gestation with a long fetal as opposed to embryonic phase IGF-1 and insulin are the primary determinants of fetal growth in late gestation and thus of birth size (Gluckman and Pinal, 2003). However, there are some limited data suggesting that the placenta might also clear IGF-1 (Gluckman and Pinal, 2003). Whatever the mechanism, nongenetic factors including maternal constraint have been estimated to contribute over 50% of the variance in birth size in humans (Morton, 1955; Ounsted and Ounsted, 1973).

Maternal constraint is of particular importance in human evolution. Maternal height and pelvic proportions are tightly correlated. As a result of the adoption of an upright posture, pelvic proportions were altered. Further, the large brain of our species meant that we had to adopt a secondarily altricial life course to ensure the head could exit the pelvic canal. Even so, whereas the chimpanzee head can readily exit the pelvis, the human head can only just exit the maternal pelvic canal and only then by some complex rotations (Trevathan, 1988). Thus, maternal constraint has been the key to limit fetal growth and allow our species to reproduce successfully.

The concept of maternal constraint has been extended to include other nongenomic and intrinsic physiological mechanisms that impact on birth size and developmental trajectory, although whether all rely on the same underlying mechanisms is not clear (Gluckman and Hanson, 2004a). Such effects are seen in primiparous women, who generally have smaller babies, in women of young maternal age, and in multiple pregnancies. There is no *a priori* reason why the mechanisms by which these different situations constrain fetal growth need be identical. Indeed, the reduced growth of twins is obviously a reflection of limits on the nutrient supply that can cross from mother to fetus. The constraint on fetal size in the first pregnancy is likely to be due to poorer perfusion of the uterine bed but can also be interpreted in life history terms as a mechanism by which a mother limits her investment in her first offspring, which generally would have happened at a young age, in expectation of subsequent pregnancies. Recent studies indeed show that the effect of parity on maternal constraint is an important influence on relationships between birth size and later outcomes: truncal obesity is greater in first-born children (Stettler et al., 2000) and the inverse relationship between blood pressure and birth size is stronger in first-borns (Hardy et al., 2004).

The reduced size of infants born to adolescent mothers appears to be due to continued diversion of nutrients to support maternal development (Wallace et al., 2004) and again can be argued in life history terms as a strategy to enhance maternal survival, both by protecting her nutritional status and because her pelvis does not reach maximal dimensions until some years after menarche. As women now delay their first pregnancy, at least in western societies, we are seeing a greater number of pregnancies at advanced maternal age—these babies are also of reduced birthweight (Gilbert et al., 1999).

Parenthetically, variation in birthweight might also be affected by subtle changes in

gestational length. There is experimental, and increasing clinical, evidence that mothers undernourished or stressed early in pregnancy may give birth after shorter gestational lengths (reviewed in Gluckman et al., 2005a). This is an alternative strategy that the fetus may use to respond to a threatening situation, and in experimental studies it is associated with accelerated activation of the hypothalamic–pituitary–adrenal (HPA) axis (Bloomfield et al., 2003).

The net effect of maternal constraint is generally to limit nutrient availability to the fetus. Thus one does not anticipate a linear relationship between birth size and maternal nutritional status. As fetal conditions improve, fetal growth increases asymptotically (at least in terms of lean body mass). There are exceptions—for example, the fetal overgrowth syndromes such as the Beckwith–Weidemann syndrome where both alleles of IGF-2 are expressed by the fetus instead of one being silenced by parental imprinting. In infants of diabetic mothers, the fetus is heavier due to increased fat mass secondary to the adipogenic effects of increased fetal insulin that is released in response to the increased transplacental glucose transfer (Schwartz and Teramo, 2000). There is a much smaller effect on lean body mass. Such infants are large, but have an abnormal body composition with increased adiposity and suffer pathological consequences. Historically, their poor survival might have excluded them from the normal pattern of human development. Thus, with the exception of gestational diabetes, fetal growth in virtually all human pregnancies is limited by maternal constraint, even when birth weight is within the normal range. This limits the environmental range that the fetus can detect and therefore predict. This in turn has the effect of limiting the range of nutritional environments to which the physiology of the organism can respond in postnatal life (Gluckman and Hanson, 2004b; Gluckman and Hanson, 2004c).

Analyses of fitness in wild populations (Charmantier and Garant, 2005) confirm that environmental factors play a greater role in phenotypic variation in populations under poor conditions than under good conditions. Such an observation is compatible with the relationships we have described. The asymptotic relationship seen under conditions when the fetus is exposed to a good environment will mean that trait variation in such fetuses is primarily a reflection of genetic variation. Conversely, when the fetus is making predictions based on a poor environment, the individual lies on a steeper part of the predicted/actual relationship curve (Fig. 3) and one would anticipate greater variation in the trait as an adult. The variation is enhanced further because of the various ways in which maternal nutritional information may be misinterpreted by the fetus, for example after maternal or placental disease, thus giving rise to a greater risk of inaccuracy in the prediction.

DEVELOPMENTAL MISMATCH AND PATTERNS OF DISEASE

In a population living in a stable environment, evolution will have matched physiology to that environment. But the developmental environment may vary and thus shift the positioning of the range of environments an individual can live in as an adult (discussed in DeWitt and Scheiner, 2004). One way in which this can occur is through predictive adaptation. If the prediction is correct then there will be a good match between the phenotype adopted and the environment in which the organism will later live, and resulting fitness will be high. If the prediction is poor, there will be a mismatch between the environment experienced and the phenotype induced. We have suggested that concepts of developmental mismatch can provide a useful perspective on the DOHaD phenomenon (Gluckman et al., 2005a).

Impaired fetal growth is an indirect reflection of an impaired fetal environment arising from excessive maternal constraint, the presence of a severe maternal environment, or maternal or placental disease. The fetus "sees" all these situations as reflecting impaired nutrition, predicts a deprived postnatal environment and adjusts its metabolic phenotype accordingly. But most of these situations lead to faulty predictions, because the postnatal environment is adequate. Thus, the individual will have some mismatch between its mature physiology and the environment it inhabits. The greater the mismatch, the greater is the risk of adult disease.

Such a paradigm can explain why populations undergoing rapid nutritional transition such as in India and China are witnessing a massive increase in the prevalence of metabolic and cardiovascular disease. Although the intrauterine environment can only change slowly across generations (Gluckman and Hanson, 2005), the postnatal environment can change very rapidly. Thus, a stunted mother will se-

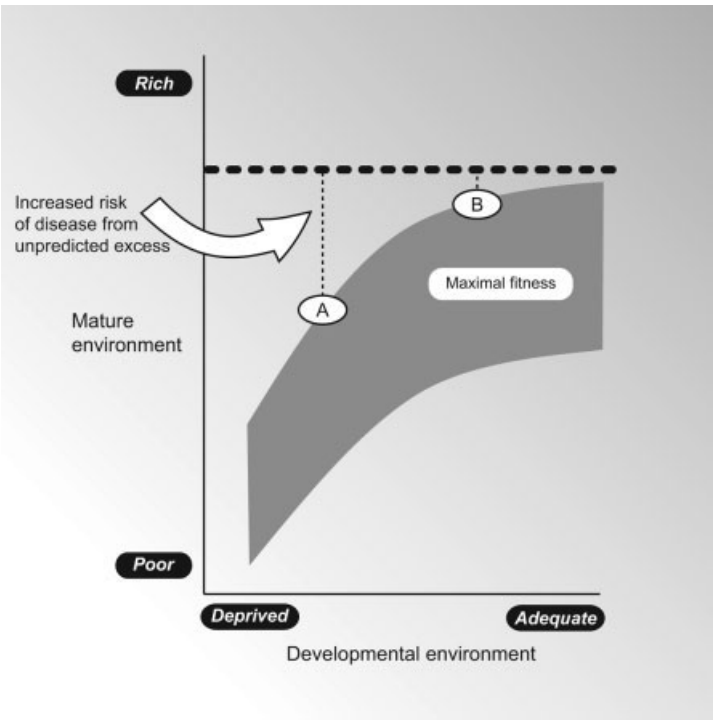

Fig. 3. Consequences of a mature environment outside the predicted range. The zone of maximal fitness resulting from the different developmental trajectories determined by environmental cues in early life is shaded. Note the nonlinearity of the relationship, arising from maternal constraint acting to limit the size of the fetus at delivery and setting the upper limit of the postnatal environment which the species can tolerate without the risk of metabolic disease even when maternal constraint is minimal (horizontal heavy broken line). Fetuses A and B are shown at the upper limits of their range of fitness. Fetus A has set its developmental trajectory in expectation of a relatively deprived environment. If the mature environment is richer than predicted, the risk of metabolic disease is increased. In contrast, fetus B has developed in expectation of an adequate environment, the extent of unpredicted excess is smaller, and a higher level of postnatal nutrition is needed for the risk of metabolic disease to be increased. As increasing affluence raises the richness of the mature environment and because of the limiting effect of maternal constraint, a greater proportion of even optimally nourished fetuses *in utero* are mismatched to their postnatal environment (modified from Gluckman and Hanson, 2005).

verely constrain the growth of her fetus and induce a metabolic phenotype appropriate for a nutritionally deprived environment, but the postnatal environment will not match those settings. Indeed, Figure 3 would suggest that development in a severely constrained setting reduces the upper limit of the range of postnatal environments that can be tolerated without risk of disease. Such a paradigm explains the increase in lifestyle disease that occurs when a population migrates rapidly from the less developed to the developed world, for example from Ethiopia to Israel (Cohen et al., 1988). One implication of such a model is that, even if there is optimal fetal growth, maternal constraint always limits the postnatal environment that the fetus can predict and prepare for. Thus, the issue is the relative change (mismatch) from developmental to adult environment, not whether the fetal environment is deprived or adequate, and the model is therefore relevant to the current obesity epidemic in the developed world.

PRENATAL AND POSTNATAL EFFECTS

Most of the discussion above has focused on the nutritional and energetic environment. This is inevitable, given that in life history terms energetics are a very important component of the environment and nutritional manipulation has been the major experimental system studied. However, the same model can apply to other dimensions of the environment,

in particular stress which in comparative terms may reflect both intraspecific competition and predator risk. There is ample data suggesting that glucocorticoid exposure *in utero* as a result of elevated maternal glucocorticoid levels can induce long-term changes in the glucocorticoid axis (O'Regan et al., 2001) that may have short-term adaptive value—for example, by tuning stress responses during the population cycle of the snowshoe hare (Boonstra et al., 1998). There is also increasing evidence that nutritional and hormonal cues intersect. In experimental animals, the phenotypes arising from maternal glucocorticoid exposure and from maternal nutritional manipulation are very similar (Bertram and Hanson, 2001). The enzyme 11β-hydroxysteroid dehydrogenase type 2 in the placenta normally inactivates maternal glucocorticoids to limit fetal exposure. Undernutrition reduces 11β-hydroxysteroid dehydrogenase type 2 activity in the rat (Bertram et al., 2001) and low birthweight is associated with reduced enzymatic activity in the human placenta (reviewed in Seckl and Meaney, 2004), suggesting a possible common mechanism. The glucocorticoid receptor in the brain and liver appears to be a target of epigenetic regulation by maternal factors (Lillycrop et al., 2005; Weaver et al., 2004). The same paradigm can also explain the induction of long-term change in other physiological systems, such as those regulating temperature (Diamond, 1991), thirst (El-Haddad et al., 2004) and reproduction (Cooper et al., 1996; Gluckman and Hanson, 2006b).

The initial cues may act at differing points in the window of plasticity. For each organ, there will be a time in development after which plasticity is clearly no longer possible. Equally, some cues may act very early in development—there is, for example, experimental evidence that changing the maternal environment in the pre-implantation period can have long-term effects on metabolic and cardiovascular function (Kwong et al., 2000). Similarly, in experimental in vitro fertilization, changing the culture conditions can induce long-term developmental changes (Walker et al., 1996; Young et al., 2001). Some may be disruptive in nature but others may be a reflection of evolved adaptive processes. In the agouti mouse, changing nutrient balance in the periconceptional period alters for life the methylation status of the mutant gene underlying the agouti phenotype (Cooney et al., 2002; Wolff et al., 1998), again suggesting that the periconceptional period is a stage in which epigenetic change can be induced. The limited human data suggests that nutritional status at conception also has important influences on both gestational length (Susser and Stein, 1994) and birth size (Neggers and Goldenberg, 2003; Villar and Rivera, 1998).

Conversely, there is both experimental (reviewed above) and clinical evidence to suggest that the postnatal period is also one in which longer-term effects can be induced or the effects of earlier cues can be modulated. In humans, there is much data suggesting that the nature of infant feeding has long-term metabolic, cardiovascular and cognitive effects (Lucas et al., 1998; Singhal et al., 2003; Singhal et al., 2004; Stettler et al., 2005). Parenthetically, the term "programming" was first adopted to describe such linkages and the same term has been used extensively in discussions of the fetal origins paradigm. We have avoided using it, as we and others see conceptual limitations in its use. It implies a hardwired process, whereas the effects observed are clearly much more flexible. In general, bottle-feeding appears to have relatively deleterious effects. Such studies have led some to conclude that enhanced infant growth itself induces long-term consequences (Singhal and Lucas, 2004). This may indeed be so, but it is difficult to separate out this effect from the earlier and inevitable constraint *in utero* which then sets the scene for such accelerated infant growth to occur. Other studies have suggested that, rather that rapid infant growth being the most significant factor, it is prolonged impaired infant growth followed by rapid growth in childhood (Bhargava et al., 2004; Eriksson et al., 2003). Although these different conclusions have led to some considerable debate as to the importance of different patterns of growth, one consistent theme emerges—that constrained fetal or infant growth followed by nutrition-enhanced infant or later childhood growth has metabolic consequences. Both patterns are compatible with the predictive model and the deleterious effect of nutritional mismatch suggested earlier. The issue of whether these two phases of perinatal development are independent or interdependent is more complex and requires further research.

DOHaD, EVOLUTION, AND LIFE HISTORY STRATEGY

There has been much recent progress in the field of ecological developmental biology as well as a greater integration of developmental biology into the evolutionary synthesis (Gilbert, 2001; West-Eberhard, 2003). Much of this

paper has suggested that the phenomena reflected in the experimental and clinical observations associated with the DOHaD paradigm are generalizable and related to basic processes of development.

We would suggest that the processes of developmental plasticity, in particular those having longer-term potential adaptive significance, have been central to the survival of mammalian species through variable environments. They would have been particularly important in a generalist species such as the human. Developmental plasticity acts to increase the potential for phenotypic variation, allowing a shift in the positioning of the individual's physiology within the reaction norm to optimize its phenotype for a particular environment and increase its fitness (survival and reproductive success). In this way, a greater proportion of individuals will survive a transient environmental shift and greater genotypic variation can be maintained (Gluckman and Hanson, 2005). The concept that an environmental stimulus can shift the organism into a different developmental pathway (in the case of the DOHaD paradigm, a pathway anticipating a sparse or threatening postnatal environment) was classically visualized by Waddington (1942, 1957) as "canalization" towards alternative end-states, with constraint on variation of a particular end-state pictured as the steepness of the local gradients of the epigenetic landscape. More recent usage of the term canalization, also termed "auto-regulation" by Schmalhausen (1949), has focused on the implied aspect of constraint of phenotypic variation against the effects of genetic or environmental perturbations (Debat and David, 2001). Although developmental plasticity and environmental canalization act in opposite directions on phenotypic variation, they both act to preserve genetic variation—the former by promoting variation of the phenotype in a changing environment, the latter by constraining variation of an evolved optimal phenotype in a stable environment. The classic experiments of Belyaev and his coworkers, who demonstrated that phenotypic variation could be exposed when an apparently homogeneous population of foxes was selected for one behavioral characteristic, tameness, are particularly relevant to our model of integrated responses in that such selection appeared to act on components of the HPA axis but resulted in the appearance of variation in a wide range of morphological, physiological, and behavioral traits (Trut, 1999).

Human development does not involve the generation of the distinct morphs described above for the desert locust, but it can nonetheless be envisaged in an analogous way. The human embryo, fetus and neonate senses its future nutritional status via signals from its mother and makes an integrated response to those signals. This response is manifest as a range of phenotypes later in life, with consequences dependent on the energy density of the environment in which the individual lives as an adult.

We propose that such plasticity is a result of well-integrated responses regulated by a limited number of key genes whose expression is affected by the developmental cue and which then regulate subsequent patterns of gene expression and tissue organization. Whether such regulation is positive (conceptually, "activation of plasticity") or negative (conceptually, "deactivation of canalization") remains to be determined. The existence of genes for plasticity is a subject of debate (DeWitt and Scheiner, 2004), whereas candidate canalization genes acting at the whole-organism level have been identified, for example HSP90 in *Drosophila* (Queitsch et al., 2002). However they are regulated, these integrated responses determine the subsequent phenotype and life course.

Life-history theory is based on consideration of the allocation of resources to somatic effort (growth and survival) and reproductive effort, with the assumption that selection operates to maximize reproductive fitness by determining the optimal allocation between somatic and reproductive investment. A corollary is that investment in post-reproductive longevity does not affect reproductive fitness and is not favored by selection. Our model suggests that if the fetus predicts an uncertain future, which may be reflected in being born smaller or prematurely, it will invest less in somatic effort, possibly by lower investment in maintenance and repair (Kirkwood, 2002), and hence those born smaller tend to die earlier (Kajantie et al., 2005). Associated with this there may be less investment in systems in which there is some redundancy, for example fewer nephrons (Hinchliffe et al., 1992; Langley-Evans et al., 2003) and fewer neurons in some regions of the brain (Mallard et al., 2000; Tolsa et al., 2004)—observations confirmed both experimentally and clinically. Because the fetus predicts a shorter life it will invest less in musculoskeletal growth, predisposing to sarcopenia and osteopenia, both features of the human born smaller (Sayer and Cooper, 2005). There is advantage when living

in a poor nutritional environment to laying down fat when possible and to having peripheral insulin resistance, both features well demonstrated in humans. In experimental animals, this potential advantage can be seen in hyperphagia (Vickers et al., 2000), altered appetite regulation (Plagemann et al., 2000) and a preference for a high-fat diet (Bellinger et al., 2004). Given the relationship between the nutritional and HPA axes, it would not be surprising that the HPA axis is altered under such conditions, as is reported in both humans (Phillips et al., 1998) and animals (Seckl and Meaney, 2004), and this change may also contribute to the obese phenotype.

Resource allocation to reproductive effort, reflected in age of maturity and fecundity, will also be affected by developmental cues. In humans, good nutrition in childhood leads to earlier puberty (Karlberg, 2002). Conversely, low birthweight leads to accelerated sexual maturation if postnatal energetics allow (Cooper et al., 1996; Gluckman and Hanson, 2006b; Ibáñez et al., 2000; Karlberg, 2002), although fecundity is lower in both females (Ibáñez et al., 2003) and males (Cicognani et al., 2002; Francois et al., 1997) of low birthweight; both these observations are in accordance with predictions of life history theory (Stearns and Koella, 1986). Lower testosterone levels in males may also represent a trade-off between reproductive and immune functions (Muehlenbein and Bribiescas, 2005). Furthermore, early maturation may itself involve a trade-off between offspring quantity and quality in the subsequent generation (Coall and Chisholm, 2003; Wallace et al., 2004), perpetuating a cycle of low birthweight.

Two extreme examples are illustrated in Figure 4—a fetus exposed to an optimal nutritional environment *in utero* and a fetus exposed to a less than optimal environment. Although the definitive life courses will inevitably be modified by subsequent environmental exposure, consideration of the developmental component alone in the context of the immediately adaptive and predictive responses made in the alternative environments allows us to understand the biology of those born smaller.

While we have focused on the extremes to make this point, we propose that there is a continuous range of human metabolic "morphs" representing a suite of integrated responses to the environmental cues received *in utero* or by the neonate which establish the setpoints of the metabolic and related systems. We suggest that these different developmental trajectories are set by altered expression, presumably regulated by epigenetic processes, of key regulatory genes. Although the specific nature of these processes remains to be determined, components of the HPA axis seem to be key candidates. Depending on the postnatal environment, such responses may manifest in an altered risk of disease.

Such an integrated suite of somatic and reproductive responses to early cues forecasting a sparse or threatening postnatal environment will have evolved to promote individual survival to reproductive age and avoid extinction of the lineage, and at a population level will preserve genetic variation. But in an enriched postnatal environment this mismatched developmental trajectory results in metabolic disease—mechanisms to ameliorate such disease would not have evolved since the adverse consequences occur predominantly in the post-reproductive period. In this way the predictions of the "match-mismatch" model are not dissimilar from those of antagonistic pleiotropy (Williams, 1957), which model suggests that alleles conferring fitness advantage early in life will be selected for even if they are deleterious later in life. The fundamental difference between the two models is that an adaptive mechanism involving phenotypic plasticity will allow reversibility at the individual (Vickers et al., 2005) level should environmental conditions improve (or be perceived to have improved).

It has been argued that although induction of "thriftiness" in the offspring has adaptive advantage, such advantage is predominantly for the mother, reducing the demand of the current pregnancy and lactation cycle and enhancing her future reproductive fitness (Wells, 2003). There are several reasons why we believe this to be a flawed argument. First, predictive responses cause an integrated change in the offspring's phenotype and subsequent life history across several dimensions rather than a reduction in birth size alone, an observation not readily explained by the maternal fitness hypothesis. Second, such reduction in birth size is not an obligatory part of the suite of alterations induced by an adverse prenatal environment. Third, we again point to data showing that one of the hallmarks of "thriftiness"—insulin resistance—does not appear until well after birth in small-for-gestational-age individuals (Ibáñez et al., 2006; Mericq et al., 2005), implying little immediate advantage for the mother.

Humans evolved in environments very different from those in which we now live. Analysis of paleoclimatic data (Potts, 1998) offers

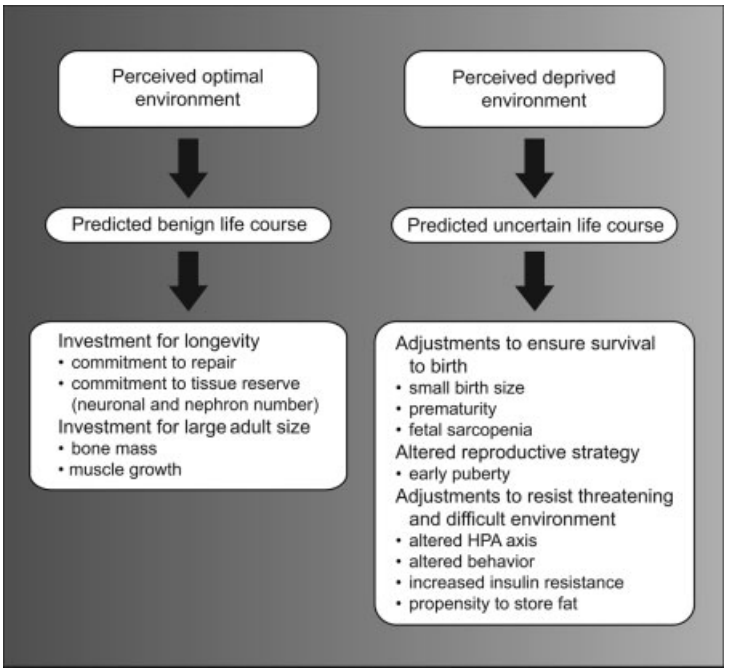

Fig. 4. Integrated life history responses to developmental cues. Two extreme examples of developmental trajectories are shown, one in response to a perceived adequate nutritional environment and the other in response to a perceived deprived environment.

support for the view that hominin evolution occurred in response to change over long (several generations) rather than short (seasonal or single-generation) time frames. In such a situation, "forecasting" (Bateson et al., 2004) of the environment would have been valuable, and the accuracy of the cue reaching the fetus may have been enhanced by "phenotypic inertia" integrating the signal across multiple generations to reduce the effects of short-term fluctuations (Kuzawa, 2005). It is probable that enriched environments were experienced only rarely and that selection favored the operation of maternal constraint and the continued operation of ancestral mechanisms of adaptive developmental plasticity because they matched the individual to the postnatal environment most of the time. Together with the relatively short life expectancy of Paleolithic and Neolithic humans (Austad, 1994), this meant that these processes were usually adaptive. However, in the enriched and rapidly changing nutritional environments of post-industrial society the risk of postnatal mismatch between the developmentally induced phenotype and the actual conditions experienced has increased dramatically. Lifestyle diseases reflect that we live in a manner and in an environment beyond the range we evolved to live within, a range that remains limited by maternal constraint. What clinicians observe as the DOHaD phenomenon is actually part of a fundamental process by which the organism adjusts its life course strategy in response to environmental influences acting early in development.

CONCLUSIONS

Attempts to explain the original observations of a relationship between birth size and later risk of heart disease and of the long-term impact of various infant feeding regimens have moved from consideration of specific situations to a much broader emphasis on how life history and evolutionary biology intersect with studies of human disease. Major research questions remain to be resolved: the genotypic determinants of environmental sensitivity during development, the identification of the key regulatory genes, the fundamental epigenetic processes involved in phenotypic plasticity, the basis of the adjustment and integration of the various

components of the life course strategy, and the complexities surrounding the role of the infant period in modifying earlier phenotypic choices. It is clear that life history biology offers much to inform our understanding of human chronic noncommunicable disease. It shifts the disease paradigm from one of external causation to one of the match or mismatch between the evolutionarily and developmentally defined constitution of the organism and the environment in which it finds itself. This bridges the gap between the traditional medical and anthropological models. The developmental component offers approaches to prevention and the expanding knowledge of epigenetics offers approaches to intervention.

At a pragmatic level, this perspective means that different strategies may be more appropriate for disease reduction in different populations (Gluckman et al., 2005b). Thus, in developed countries the focus must remain on postnatal interventions to limit energy intake and increase energy expenditure. In populations in developing countries a greater focus on the well being of the mother may be important to allow subsequent generations to maintain metabolic health during a socioeconomic transition to an environment of higher energy density. Important approaches in this setting include delaying first pregnancy until the mother is fully grown, say at least 4–5 yr after menarche, ensuring adequate nutritional status at conception, and focusing on maternal health and nutrition during pregnancy.

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