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Developmental Origins of Adult Function and Health: Evolutionary Hypotheses

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Abstract

Many biological systems have critical periods that overlap with the age of maternal provisioning via placenta or lactation. As such, they serve as conduits for phenotypic information transfer between generations and link maternal experience with offspring biology and disease outcomes. This review critically evaluates proposals for an adaptive function of these responses in humans. Although most models assume an adult function for the metabolic responses to nutritional stress, these specific traits have more likely been tailored for effects during fetal life and infancy. Other biological functions are under stronger evolutionary selection later in life and thus are better candidates for predictive plasticity. Given the long human life cycle and environmental changes that are unpredictable on decadal timescales, plastic responses that evolved to confer benefits in adolescence or adulthood likely rely on cues that integrate matrilineal experiences prior to gestation. We conclude with strategies for testing the timescale and adaptive significance of developmental responses to early environments.

INTRODUCTION

Developmental plasticity: the ability of a gene to generate a range of possible phenotypes (body and behavior) contingent on environmental experience

Programming: an environmentally induced, durable biological change in the structure or function of a tissue, organ, or biological system

DOHaD: developmental origins of health and disease

CVD: cardiovascular disease

Induction: synonymous with programming

Anthropology has traditionally studied developmental plasticity as a contributor to human variation (Boas 1912) and as a mode of adaptation to environmental change (Lasker 1969, Frisancho 1993). There has recently been a resurgence of interest in developmental plasticity as research has demonstrated that nutritional, hormonal, and other aspects of the prenatal and infant environments have effects on physiology and metabolism that persist into adult life (Barker 1994). Such examples of biological programming can involve modified growth of organs and tissues and are increasingly being linked to durable epigenetic changes that modify patterns of gene expression (Waterland & Michels 2007).

The multidisciplinary enterprise that studies the developmental origins of health and disease (DOHaD) is illuminating long-standing questions of interest to anthropologists, including the origins of the high rates of diabetes among specific Native American groups (Benyshek et al. 2001), the rise of chronic diseases in the context of rapid cultural and nutritional transition (Adair & Prentice 2004), and the biology of race as manifested in the disproportionate burden of cardiovascular disease (CVD) among U.S. blacks compared with U.S. whites (Kuzawa & Sweet 2009). In addition to these health-related applications, research is increasingly addressing the role of these intergenerational processes in organismal adaptation (Wells 2003, Bateson et al. 2004, Kuzawa & Pike 2005). Most proposals assume that resources transferred from mother to offspring serve as cues of local ecology, which offspring use to adjust biological settings and developmental trajectory in anticipation of future environments. Because most developmental responses occur during fetal life and infancy, they are responses to maternal phenotype and thus can be viewed as a form of nongenomic information transfer between generations. These evolutionary models propose a process of transgenerational epigenetic adaptation that links the environmental experiences of mothers with phenotypic variation, adaptation, and disease risk in their offspring.

This review is organized in two sections. First, we selectively review evidence that early environmental stimuli, such as nutrition, growth, and stress, have persistent effects on biological systems. A comprehensive review of the empirical work is beyond our intent, and the reader is directed to the many excellent resources devoted to this topic (McMillen & Robinson 2005, Gluckman & Hanson 2006, Goldberg 2008). These summaries serve as background for the second section of the article, which reviews the functions and evolutionary origins that have been proposed to explain these findings. We first focus narrowly on the most heavily cited ideas relating to metabolic risk factors for CVD. We then suggest orienting future work in this rapidly expanding field around the goal of developing testable hypotheses aimed at clarifying the source and timescale of ecological information conveyed to offspring via maternal cues and characterizing the mechanisms that underlie offspring phenotypic change.

EVIDENCE FOR THE INFLUENCE OF EARLY ENVIRONMENTS ON ADULT BIOLOGY AND HEALTH

Early human cohort studies revealed relationships between deprivation during childhood and subsequent adult mortality rates (Kermack et al. 1934, Forsdahl 1977). These findings are now known to trace to the effects of prenatal and infant nutrition and stress on developmental plasticity (Barker 1994), a process described as developmental programming (Lucas 1991) or induction (Bateson 2001). The same suite of disease risk factors that relate to fetal growth or prenatal nutrition in humans are induced by dietary manipulation of animal models (Langley-Evans 1999, McMillen & Robinson 2005). The alterations induced involve changes in the growth, structure, and function of tissues, organs, or systems and are increasingly being linked to epigenetic changes that influence cellular gene expression (Waterland & Michels 2007).

In humans, these relationships are often studied using proxies of the prenatal environment, such as birth weight. Birth weight relates inversely to adult CVD risk, including blood pressure (Barker 2006), cholesterol (Kuzawa & Adair 2003), insulin resistance, and Type 2 diabetes, and a tendency to deposit fat in the central, metabolically active fat depot (Harder et al. 2007, Whincup et al. 2008). Maternal diet and nutritional status during pregnancy also predict risk for these conditions in offspring (Adair 2001, Brennan et al. 2006). Rapid postnatal growth, especially when expressed as catch-up growth following fetal growth restriction, may exacerbate the physiological changes that lead to CVD and adult metabolic disease (Lucas et al. 1999, Metcalfe & Monaghan 2001, Cameron 2007). The relevant research initially focused on populations in Britain, Europe, and the United States (Barker et al. 1989). However, these processes are increasingly recognized as contributing to chronic disease emergence in populations experiencing rapid economic and nutritional transition (Benyshek et al. 2001, Adair & Prentice 2004).

As an extension of the original focus on fetal nutrition, the role of breastfeeding in biological programming is now a focus of DOHaD research (Schack-Nielsen et al. 2004; Owen et al. 2006, 2008). Many of the adult metabolic states documented in lower-birth-weight individuals, including central obesity (Grummer-Strawn & Mei 2004, Harder et al. 2007), Type 2 diabetes (Owen et al. 2006), high cholesterol (Owen et al. 2008), and elevated blood pressure (Lawlor et al. 2005, Martin et al. 2005), are less common in individuals who were breastfed as infants. Formula feeding promotes increased weight gain, which could contribute to these adult health differences (Adair 2008). In addition, human and animal work has helped elucidate the role of specific nutrients as influences on future metabolic functioning. Dietary manipulation of newborn rat pups suggests that high carbohydrate exposure at this age decreases insulin and leptin sensitivity in adulthood (Srinivasan et al. 2006) and may increase risk of CVD, diabetes, obesity, and hyperlipidemia (Mitrani et al. 2007).

Although most work continues to focus on disease outcomes, studies are investigating the developmental origins of a wide range of traits with functional and life-history consequences (Kuzawa & Pike 2005). For instance, there is evidence for long-term effects of birth outcomes on gonadal hormone production in females and males (Jasienska et al. 2006, Nunez-de la Mora & Bentley 2008) and on future reproductive effort as reflected in offspring birth weight (Morton 2006). Different components of immune function relate to early environments (McDade 2005), as do somatic and life-history traits such as lean mass and body composition (Baker et al. 2009), stress physiology (Belsky 2008), maturational timing (Adair 2001, Chisholm & Coall 2008), and life span (Doblhammer & Vaupel 2001). Thus a wide and expanding suite of functional traits are now known to be modified by early environments, in addition to the metabolic and other adult diseases that are most extensively discussed in the literature.

Critical period: a limited time in early development when environmental stimuli can durably influence a trait or biological outcome

THE ROLE OF CRITICAL PERIODS IN THE TRANSGENERATIONAL TRANSFER OF PHENOTYPIC INFORMATION

Some of the plastic phenotypic variation induced in response to early environments reflects incomplete buffering of development and thus requires no adaptive explanation (Lummaa 2003, Jones 2005, Chisholm & Coall 2008). For example, during periods of rapid growth, growth-restricting deficits can have large impacts on the final size, structure, and function of tissues or organs (Widdowson & McCance 1975), such as the nephron-deficient kidneys that are believed to predispose lower-birth-weight individuals to developing hypertension and renal failure (Lampl et al. 2002, Luyckx & Brenner 2005).

Lingering effects of early environments can also trace to critical periods during which

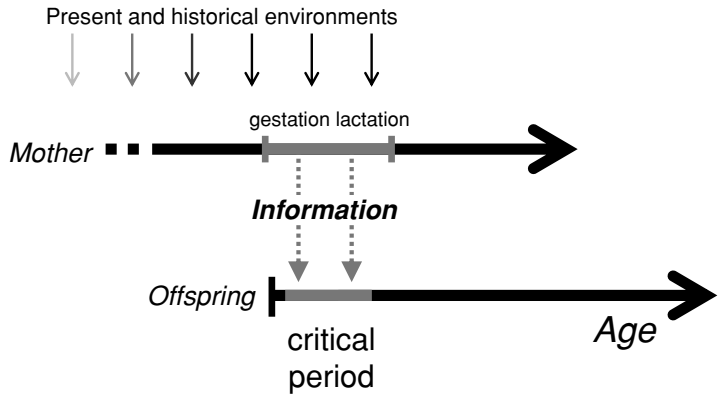

Figure 1

The timing of a critical period determines the capacity for transfer of phenotypic information between generations. Maternal phenotype comes to embody a record of a mother's cumulative environmental experiences, and this information is transferred via nutrients, hormones, and other cues.

developing systems permanently modify their settings in response to environmental experience (Bornstein 1989). Many systems, such as hormonal axes, have critical periods when settings are dependent on and respond to social and biological cues (Worthman 1999). For a developing biological system, a critical period effect can reflect changes in cell number, selection-driven changes in cell type (e.g., in neurons and lymphocytes), and epigenetic changes in cellular gene expression that are heritable by daughter cells (Waterland & Garza 1999). That many critical periods overlap with the timing of direct maternal provisioning via the placenta and lactation means that these periods are windows of opportunity for the transfer of phenotypic information from one generation to the next (**Figure 1**). Maternal phenotype is expressed via nutrients, growth factors, metabolites, hormones, and immune factors that reflect the mother's cumulative experience of the local environment (Emanuel 1986, Drake & Walker 2004, Wells 2007b).

Investigators have provided numerous examples of developmental systems that modify functional settings in response to cues reflecting the mother's social and physical environment. Breast milk contains the body fat–derived hormone leptin, which is present in milk in proportion to maternal levels (Houseknecht et al. 1997) and is absorbed into the neonatal circulation (Miralles et al. 2006). In rats, perinatal administration of leptin has been shown to reverse the metabolic phenotype established during a stressful gestation (Vickers et al. 2005), as does an oral dose prior to weaning (Palou & Pico 2009). Because the leptin content of milk may be related to maternal leptin levels (and thus, her body fat), it could convey information about her energy stores and thus her recent energy balance.

The hypothalamic-pituitary-testicular (HPT) axis that regulates testosterone (T) production experiences a critical period that spans two phases of dependency, the first during early gestation and the second during the months following birth. Both overlap with, and are sensitive to, maternal resource transfer (Worthman 1999). During the postnatal period, pituitary secretion of luteinizing hormone (LH) surges, leading to a temporary rise in T to near adult levels. By roughly 6 months of age, this activity is complete and the testes remain largely dormant until puberty. Although the function of this postnatal surge in HPT activity remains obscure, it likely provides opportunities for signals or experiences to influence system settings. Because stress may influence HPT activity, social factors may be important. For instance, Worthman (1987) speculates that the Kikuyu time ritual circumcision (and resulting stress) to coincide with this critical period, thus modifying HPT settings. In addition, the timing of this critical period during the first weeks after birth—likely coinciding with exclusive breastfeeding during much of human evolutionary history—suggests a capacity for cues transferred via breast milk to influence system settings. In rats, nutrient restriction during lactation has led to lower adult T in male offspring (Zambrano et al. 2005). This area is ripe for innovative research (e.g. Thompson & Lampl 2007).

The timing of the critical period for somatic growth also suggests an important role for cues transferred via placenta and breast milk. Unlike growth in childhood and adolescence, growth during fetal life and infancy is insulin dependent

HPT: hypothalamic-pituitary-testicular axis

T: testosterone

LH: luteinizing hormone

and thus driven by the composition and quantity of nutrients transferred across the placenta or in breast milk (Gluckman & Pinal 2003). This period of sensitivity accounts for the predominant impact of fetal, infant, and early childhood nutritional stress on adult stature in populations faced with chronic poverty and high pathogen burden (Martorell et al. 1995). The overlap of this period with direct maternal provisioning helps ensure that growth is buffered and, in contexts free from poverty and widespread childhood infections, could allow growth trajectory to be calibrated to a woman's provisioning capacity, itself reflecting the phenotypic embodiment of her cumulative nutritional experience (Wells 2003, Kuzawa 2005).

The diversity of maternal cues that have long-term effects on multiple systems in offspring suggests that many critical periods may be timed to allow signal transfer between generations. Indeed, many biological systems have a need to learn through experience, and their sensitivity to maternal phenotype hints at an ability to benefit from the mother's embodied experiential history. When a maternal cue is correlated with local conditions, this in theory allows a form of adaptive plasticity to evolve in which biological settings are established in anticipation of future environments (Mousseau & Fox 1998). Indeed, this has been the assumption of most evolutionary models of fetal plasticity in the DOHaD literature (e.g., Bateson et al. 2004), and we turn to these next.

THE THRIFTY PHENOTYPE AND FORECAST MODELS OF METABOLIC ADAPTATION

Because most DOHaD work has addressed outcomes related to CVD, the majority of speculations about the evolutionary origins of fetal and infant plasticity have focused on the cardiovascular risk factors induced by nutritional stress. Here we provide an overview of the most popular and widely cited of these ideas, and we suggest some ways in which evolutionary theory can be used to evaluate them (see also Wells 2007a).

As discussed above, individuals born small who gain excess weight as older children or adults are at elevated risk for developing metabolic risk factors for CVD. On the basis of these findings, Hales & Barker (1992) argued that the fetal response to prenatal undernutrition induces a "thrifty phenotype" characterized by insulin resistance, a shift in circulation to protect the brain ("brain sparing"), and a nutrient-conserving reduction in organ growth. They argued that these adjustments enhance immediate fetal survival but subsequently increase the risk of developing diabetes and CVD in the event that the individual later experiences nutritional excess and weight gain. This model, offered as a competing hypothesis to Neel's (1962) thrifty genotype model, proposed that high rates of diabetes among some populations might trace to stressful intrauterine environments rather than to susceptibility alleles.

As an extension of the thrifty phenotype model, Bateson (2001) suggested that fetal adjustments to prenatal nutrition are not merely designed to improve immediate survival, but also are initiated in anticipation of nutritional conditions during childhood (see also Worthman 1999, Kuzawa 2001):

> The condition of the mother in late pregnancy may be taken to provide a forecast about the state of the environment in which the child will grow. This then determines the pattern of growth and the metabolic pathways of the child. If the mother's forecast was wrong, the consequences for the child can be dire. The hypothesis is that the undernourished mother gives birth to a child who is small in size and is adapted to a thrifty environment. Conversely a well-nourished mother gives birth to a large baby who is adapted to an affluent environment. (Bateson 2001, p. 933)

According to this model, the metabolic responses of a nutritionally stressed fetus are at least in part geared toward improving survival during the postnatal period, but they also elevate risk for adult metabolic diseases in the

event of excess postnatal nutrition and weight gain.

As an amendment to this proposal, Gluckman & Hanson (2004) hypothesized that, using prenatal cues, the fetus "adjusts its physiology to be appropriate for its predicted mature environmental range" (p. 1735). They suggested that a prenatally stressed individual will have a metabolism geared to cope with a nutritionally poor adult environment and would thus be poorly suited to a nutritionally rich adult environment. The resultant mismatch between expected and experienced adult environmental conditions elevates risk for diseases such as CVD. In this popular version of the forecast model, fetal metabolic responses to undernutrition are presumed to have evolved to confer benefits primarily during adulthood.

EVOLUTIONARY PRINCIPLES APPLIED TO THE THRIFTY PHENOTYPE AND FORECAST MODELS

Each of the models described above offers an explanation for a range of biological and medical observations, and as such these models have intuitive appeal. However, because they assign evolutionary origins to plasticity in metabolism, they should be evaluated on the basis of their consistency with the expectations and assumptions of evolutionary theory. We suggest the following three observations as a constructive starting point.

Selection Against Late-Life Metabolic Disease Is Minimal

First, by proposing that diabetes and CVD reflect a mismatch between expected and actual adult environments, the adult-focused version of the forecast model implies that natural selection has shaped plasticity in metabolism to avoid these late-life conditions. However, for natural selection to shape a trait into an adaptation, the trait must be variable, have a heritable component, and modify genetic fitness via effects on survival or reproduction (Lewontin 1974). Diabetes and CVD are usually asymptomatic until postreproductive life and were likely rare prior to historically recent nutritional and economic transitions (Popkin 2004). Thus, there has been minimal selection for a capacity to adjust developmental biology to avoid such diseases because they likely had negligible impacts on genetic fitness (Williams 1966, Jones 2005, Kuzawa 2005, Worthman & Kuzara 2005, Rickard & Lummaa 2007, Wells 2007b, Chisholm & Coall 2008).

Parturition and Weaning Are Developmental Bottlenecks and Focal Points of Selection on Metabolism

Second, in contrast to the invisibility of late-life metabolic diseases to natural selection, many of the metabolic changes induced by nutritional stress could influence survival earlier in the life cycle. As Hales & Barker (1992) emphasized, the human fetus has a large, glucose-hungry brain, which must be protected during periods of shortage. The early postnatal period is similarly stressful from a metabolic perspective (Kuzawa 1998). The brain requires an uninterrupted flow of energy corresponding to roughly half of resting metabolism during much of human infancy and childhood (Holliday 1986). The challenge of meeting these needs is compounded by the nutritional and infectious disease stress of weaning, when infants may be cut off from provisioning and forced to rely on endogenous energy stores. Perhaps reflecting these selection pressures, the highly encephalized human is born with more body fat than any mammal for which data are available, and it devotes most growth expenditure to fat deposition in the months prior to weaning (Kuzawa 1998). The metabolic adjustments associated with the thrifty phenotype could improve survival during this difficult period. For instance, insulin resistance reduces peripheral glucose uptake, thus sparing glucose for the noninsulin-dependent uptake of the brain, whereas preferential deposition of visceral fat, which is innervated by sympathetic nerve fibers, allows rapid mobilization of stored fats during stress (Kuzawa 2009).

The original forecast model proposed that the thrifty phenotype was induced to match expectations to childhood nutrition rather than conditions in adulthood (Bateson 2001). From a similar but distinct perspective, Wells (2003, 2007b) has argued that thrifty adaptations are induced to match the level of likely provisioning after weaning, as reflected in the mother's life course and pregnancy nutritional exposures. These arguments assume that the primary benefit of fetal metabolic adaptations, and by implication the selection pressure that has favored their evolution, occurs after the mortality bottleneck of weaning. Yet childhood is the age of lowest mortality in the human life cycle and is characterized by very low nutritional mortality and thus minimal selection on metabolism (Kuzawa 1998). Therefore, we believe it more likely that these responses evolved to confer benefits prenatally or during infancy.

A glucose-sparing, insulin-resistant state is potentially beneficial to a nutritionally stressed fetus or neonate faced with the challenge of buffering the insulin-independent glucose uptake of a large brain (Hales & Barker 1992). These adjustments would also elevate risk for developing diabetes and CVD, especially in the event of metabolic disruption due to excess weight gain. Thus adult disease need not trace to a mismatch between anticipated and experienced adult environments; it is more likely a pleiotropic side effect of an adjustment in metabolic priorities adopted to improve fetal or infant survival (Kuzawa 2005, Rickard & Lummaa 2007).

Signal Fidelity (Predictive Ability) Decays with Time

Third, reliable predictions of environmental conditions in the distant future are not necessarily available to a human fetus or neonate. Many species do have access to early-life cues that are predictive of future conditions, and individuals of these species use this information to modify their life histories (see Bateson et al. 2004, Gluckman & Hanson 2004). However, many of these species share with humans few similarities in life history or ecology and thus provide limited insight into how maternal-offspring signaling might operate in our species (Kuzawa 2008).

Take the example of the vole, which is often cited as a mammalian precedent for predictive plasticity. Fetuses of some vole species living in highly seasonal environments monitor maternal melatonin (reflecting day length) and chemical by-products of grass ingestion as a way to calibrate maturational timing to the summer birth season (Berger & Negus 1992, Horton 2005). This process has been described as forward-looking prediction because it adjusts life-history scheduling to match a future, changed environmental state (Kuzawa 2008). The vole is capable of forward-looking prediction because it is short lived, and the ecological variation it faces is cyclical and tightly correlated with maternal endocrine and metabolic cues that cross the placenta. The seasonal cycle that determines the optimal strategy for the individual vole involves biological entrainment to a stable (and thus highly predictable) planetary orbital process, and as such, the fidelity of the prediction does not fade once it is established. Most of the species cited as examples of predictive developmental plasticity are analogous to the vole or have life spans short enough that cues experienced early in the life cycle are good indicators of conditions later in life.

Human populations face ecological variability that operates on multiple timescales, from millennial to decadal to seasonal (Potts 1998), and which is at least partly stochastic (unpredictable) rather than cyclical or regular (for more see Kuzawa 2005, 2008). The predictive ability, or fidelity, of early-life cues will thus decay with time through the human life cycle. It may be that cue fidelity need not be high for some prediction to be useful (Gluckman et al. 2005). Even so, because humans are not forward-looking predictors like the vole, early life cues will be more tightly coupled with conditions in early life than in a distant, adult future. As discussed below, Kuzawa (2005) has hypothesized that maternal phenotype could provide integrated information that records a mother's lifelong cumulative experiences and

Stochastic: change with a random component, a trend that cannot be predicted

might have long-term predictive value, even in stochastic environments. However, even with such a (hypothetical) stabilizing influence, signal fidelity will still decay with time, and evolution will have had more opportunities to harness early life cues to set short-term strategy.

In summary, strong selection related to metabolic stress during the mortality bottlenecks of gestation and weaning, combined with the time-dependent decay in signal fidelity, implies that metabolic plasticity and the traits associated with the thrifty phenotype have the greatest opportunity to influence Darwinian fitness early in life. To the extent that they are adaptive, metabolic responses to early nutritional stress should by default be assumed to have immediate or short-term benefits rather than benefits primarily in adulthood (Kuzawa 2005; 2008; Rickard & Lummaa 2007; Wells 2007b; Chisholm & Coall 2008). Hales & Barker (1992) originally emphasized that fetal responses to nutritional stress benefit immediate survival. In our view, this remains the most plausible scenario of selection on the key plastic metabolic traits related to CVD risk (the thrifty phenotype), perhaps with an extension of similar benefits to infancy and weaning.

Whereas the above discussion applies to metabolic traits, which are the most widely studied plastic phenotypes in the DOHaD literature, other biological systems experience strong selection pressure during different parts of the life cycle. For example, adult size, maturational timing, reproduction, and neuroendocrine systems that manage social interactions are under stronger selection during adolescence or adulthood than in early life. Phenotypes such as these are better candidates for having evolved to calibrate function in anticipation of adolescent or adult needs.

ON THE TIMESCALES OF MATERNAL PHENOTYPIC MEMORY

For a system to evolve such a capacity to set long-term strategy in a predictive fashion, the fetus or infant must have, as a minimal requirement, a reliable predictor of future conditions (DeWitt et al. 1998). The human generation time is several decades in length, and ecological change on this timescale is stochastic, implying that future changes are unpredictable. Some maternal cues appear to convey ecological information that has been integrated or averaged over some time period preceding gestation and, therefore, represents a better guess of average conditions likely to be experienced by offspring in the long term (Kuzawa 2005, 2008). For instance, offspring birth weight varies across women, tends to be heavier in better-nourished populations, and yet is refractory to supplementation (Morton 2006). Similarly, certain breast milk components, such as fat content and energy density, vary across women and populations in different ecological settings but are generally only poorly responsive to supplementation (Prentice 1991, Villalpando & del Prado 1999).

Some evidence indicates that this slow responsiveness of transgenerational nutritional cues reflects a lingering effect of a woman's nutritional history on nutrient transfer to offspring (Wells 2003, Kuzawa 2005). For instance, human and nonhuman primate evidence shows that a female's gestational nutritional experiences as a fetus—and thus the grandmother's nutritional history—influence her own intrauterine nutritional investment in offspring (Ounsted et al. 1986, Price et al. 1999). The resulting integration of long-term matrilineal experience, reflecting offspring responses to maternal signals of past environments, has been labeled "transgenerational phenotypic inertia" and may allow for cues that average information over decades or generations (Kuzawa 2005). Belsky (2008) has recently proposed an extension of this idea to the hypothalamic-pituitary-adrenal axis, which regulates production of the stress hormone cortisol (see also Chisholm & Coall 2008).

Building from the inertia concept, we hypothesize that offspring phenotypes that are calibrated for future function (e.g., reproduction) will be more strongly predicted by long-term maternal or matrilineal experience than by

acute maternal experiences during pregnancy (**Figure 2**). The longer the window of matrilineal averaging, the less responsive the resulting cue will be to transient environmental change, and the more useful the cue will be further into the future (**Figure 3**). As a corollary, cues that are acutely responsive to transient maternal experience during pregnancy are poor candidates for calibrating phenotype to anticipated future ecology. Candidate signals for a mother's longer-term environmental experience include nutrient, metabolic, or endocrine resources that (*a*) are transferred from mother to offspring in utero or via lactation; (*b*) induce phenotypic changes (e.g., in metabolic or endocrine settings) in offspring; (*c*) vary across women or populations living in different ecologies, suggesting environmental sensitivity; and despite this, (*d*) are minimally responsive to current, transient maternal experience (e.g., supplementation or acute stress during pregnancy or lactation). Together, these qualities define a system that is sensitive to chronic rather than acute environmental change and that therefore potentially transfers a more stable environmental signal to offspring.

Although there is evidence that maternal cues can be calibrated over long time scales, other examples suggest that offspring phenotype is potentially responsive to short-term ecological variability experienced by the mother during gestation. For instance, maternal illness during pregnancy has been found to predict offspring birth outcome (Heinke & Kuzawa 2008) and adult health and function (Almond 2006), suggesting that resource transfer to the fetus and some long-term biological settings may be responsive to transient maternal experiences during gestation. Similarly, in the Gambia, individuals born in the wet season have reduced adult life expectancy (Moore et al. 1997), and season of birth has been shown to predict life span in other populations (e.g., Doblhammer & Vaupel 2001).

Unlike the short-lived vole, it is difficult to imagine how a human would benefit by adopting different adult biological strategies contingent on season of birth. Thus, such findings

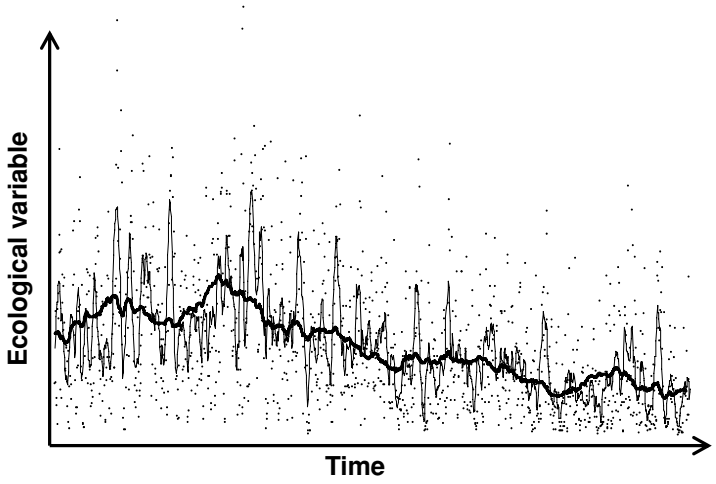

Figure 2

The value of averaging as a way to identify a trend in a noisy signal, in this case representing availability of a hypothetical ecological resource. The two lines are running averages calculated across 10 time units (*thin line*) and 100 time units (*dark line*). As the window of averaging increases, an underlying long-term trend is uncovered. Transgenerational influences of maternal and grandmaternal nutritional history on fetal nutrition may help achieve a similar feat.

suggest several possible interpretations (see also Ellison & Jasienska 2007). These responses may indeed be adaptive because, as outlined earlier, there are bottlenecks of nutritional mortality in early life. To the extent that short-term cues induce adjustments in metabolic or other biological settings that allow for survival of these early challenges, their long-term effects could be tolerated as side effects. A second possibility is that acute ecological stress during gestation may permanently modify offspring biology as a result of incomplete buffering. For instance, many of the above examples involved infections rather than simple nutritional stress, and perhaps immune activation reprioritizes maternal resource allocation in a fashion that negatively impacts fetal growth.

Because both developmental impairment and short-term signaling would manifest as a response to transient conditions during gestation or lactation, they are difficult to differentiate on the basis of the inducing cue. Fortunately, certain criteria are useful for helping differentiate impairment from adaptive function. We consider this problem next.

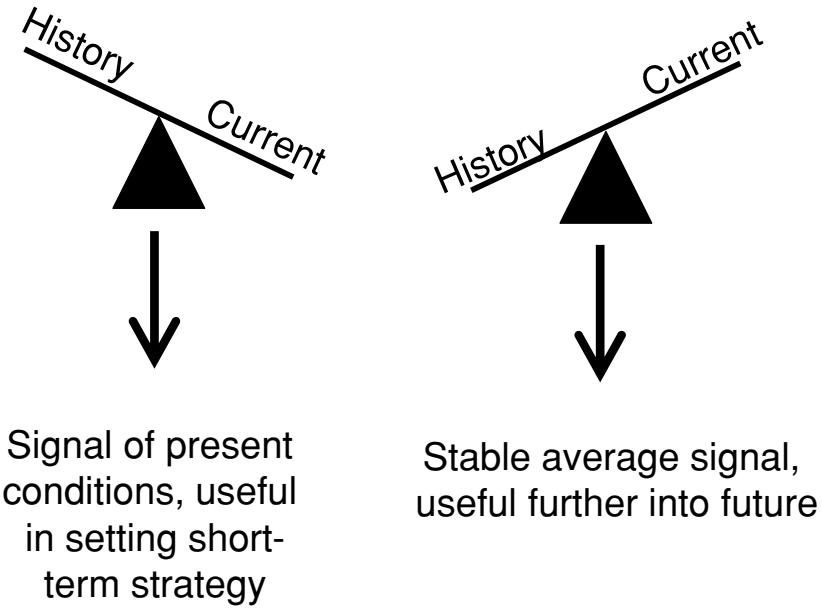

Figure 3

The balance of current versus historical influences on a maternal cue provides insights into its likely stability as a basis for predicting conditions into the future. Cues that respond to ecology but are refractory to transient experience during pregnancy or lactation convey information about average recent conditions and thus may be of use as a basis for calibrating long-term strategy. Cues that are sensitive to immediate experience during gestation or lactation will have poor long-term predictive ability and are therefore poor candidates for long-term signals.

EVALUATING THE REGULATORY BASIS OF OFFSPRING PHENOTYPIC CHANGE

Any proposal for an adaptive function for an induced phenotype, regardless of the presumed age of benefit, should strive to rule out the simpler interpretation of growth impairment (Gluckman et al. 2005, Worthman & Kuzara 2005, Bogin et al. 2007, Schell & Magnus 2007). Many of the outcomes predicted by early environmental conditions include physiologic, metabolic, or endocrine systems that are regulated by central (e.g., CNS) and peripheral components (e.g., an endocrine organ) linked through negative feedback. Endocrine systems regulate growth but also life history and resource allocation more generally and are thus a key coordinator of plasticity (Bribiescas & Ellison 2008). Studies investigating developmental programming of such systems should, where feasible, document not only the downstream phenotypic effect but also the regulatory changes that underlie it because this will help clarify whether the change reflects developmental impairment or a regulatory adjustment in system settings (see Worthman 1999, Ellison & Jasienska 2007).

For illustration, once again consider the HPT axis that regulates production of T and downstream somatic and behavioral expenditures related to male life history. Low adult T in relation to low birth weight could reflect a change in central set points or a reduced sensitivity of the testes to LH (for more see Worthman 1999). Low T despite elevated LH would suggest impairment in testicular responsiveness to LH, whereas parallel reductions in both T and LH would suggest that the decline in T production is centrally mediated (**Figure 4**). The latter finding would not prove

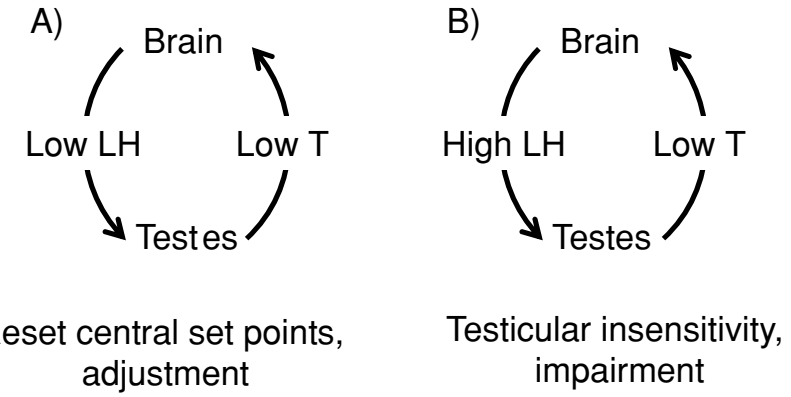

Figure 4

Two possible causes for a hypothetical reduction in testosterone (T) levels found in relation to a measure of early-life nutritional stress. T is produced by the testes in response to luteinizing hormone (LH) of pituitary origin. If T and LH are both low (*a*), then the reduction in T is centrally mediated by the brain. In this instance, the central set points that set the target production of the system (the equivalent of the temperature to which a thermostat is set) have been adjusted, and the reduction in T is not a simple result of growth impairment or developmental damage to the testes due to e.g., nutritional stress. If, however, low T is found despite high LH (*b*), then the testes are underproducing T despite high levels of LH, indicating reduced testicular sensitivity to LH. Of the two scenarios, the latter is more likely due to impaired growth or development of the peripheral organ.

that the adjustment is adaptive, but it would suggest that it is not simply a stress-induced developmental impairment of the peripheral tissue or organ.

Endocrine systems mediate trade-offs between competing functions in a context- or use-dependent fashion (Finch & Rose 1995). When evaluating effects on such systems, evidence for a change in trade-off priorities is also evidence for regulatory adjustment rather than impairment (see Ellison & Jasienska 2007). As one example, Jasienska et al. (2006) found that Polish women born as thin or fat babies were both capable of producing high estradiol as adults, but the women born thin suppressed steroid production at lower levels of physical activity. Evidence that an adult influence on a system is moderated by an early life cue suggests a change in regulatory threshold, making global impairment to the peripheral organ a less likely explanation.

The above data suggest that adaptive plasticity will induce adjustments in central set points of affected systems. Function will not be globally impaired but will be regulated with different priorities or thresholds, which can be evaluated statistically by testing for significant interactions between early life cues and concurrent factors (e.g., diet, activity, stress) that are known to modulate system behavior.

CONCLUSION

Forensic scientists have long appreciated that the phenotype embodies a record of past experience. The ability of researchers with limited snapshots of biology, such as a single blood sample, to identify the effects of early-life experiences on adult health attests to this historical record. The direct biological connection between the mother and offspring during gestation and lactation similarly provides opportunities for offspring developmental biology to harness and use this information. For instance, an individual's chronic stress may become physically embodied in the set points and activities of the stress hormone axis, which modifies production of the hormone cortisol; cortisol may then cross the placenta to influence the development of this same hormonal axis

in offspring (Worthman & Kuzara 2005). As discussed above, leptin indexes recent energy balance as reflected in body fat stores and may then transfer energetic information to offspring via breast milk. In a world without widespread obesity and metabolic dysregulation, insulin, which can cross the placenta, might reflect the nutritional sufficiency of the mother. And indeed, evidence indicates that the quantity of nutrients transferred in utero may itself reflect a woman's prior experience of nutrition, tracing back to her early formative years.

An adult phenotype is thus a storehouse of useful information about the social and physical environment. Because it interfaces directly with maternal physiology, the fetus, and later the neonate, has real-time access to this information. One recognized impediment to the evolution of adaptive plasticity is the cost of evolving and maintaining the appropriate systems of detection and response (DeWitt et al. 1998). With respect to information transferred between generations, the offspring already has the appropriate receptors and metabolic pathways in place to recognize many of these cues, which should lower these sensory costs (Kuzawa et al. 2008). A key question then is whether maternal cues are sufficiently reliable as predictors of future conditions to have allowed natural selection to shape appropriate adaptive responses to them (DeWitt et al. 1998).

To date, most work proposing such a function for fetal and infant plasticity has been inspired by findings related to the adult disease impacts of responses to early nutritional stress. As we and others have discussed, an approach grounded in adult disease–based definitions of organismal match are relevant to understanding impacts on longevity rather than on genetic success and, thus, are less than ideal as lenses into the evolutionary forces that would have shaped these responses. Opportunities for selection on the thrifty phenotype, and the potential for past cues to accurately predict current demands on these traits, are potentially high in fetal life, infancy, and early childhood and comparably low in adulthood. This fact does not make these findings uninteresting; they are critical to understanding the health impacts of early environments, and perhaps future work will investigate any functional role of these responses during the early-life nutritional bottlenecks that likely exert strong selective pressure on them. As we have argued, systems that are under stronger selection during adolescence or adulthood, compared with early life, are better candidates for the evolution of long-term adaptive anticipatory plasticity. We are excited by the possibility and implications of predictive adaptation, and for all the reasons outlined here, we feel that it remains a viable and testable hypothesis for many systems.

All models of predictive adaptation require that the fetus or infant has access to a reliable cue. We have argued that, for a human faced with unpredictable trends in ecological change, the historical time depth of a transgenerational signal will determine how stable the prediction is and, thus, how far into the future it will retain its fidelity. Evaluating the time depth and information content of cues requires information on maternal experience prior to pregnancy, ideally collected at different ages of her prereproductive life. Creative use of historical records (e.g., Clarkin 2008) or other retrospective measures, such as leg length (Lawlor et al. 2003), fingerprint patterns (Kahn et al. 2008), and epigenetic markings in different cell lines (Waterland and Michels 2007), show promise as proxies for reconstructing maternal experiential history. We anticipate other innovative strategies to help bring the study of maternal history to developmental programming research. Such a historical approach, coupled with a focus on documenting the regulatory bases of phenotypic inductions, will clarify the possible adaptive significance of findings and help to rule out simpler interpretations such as developmental impairment (Ellison & Jasienska 2007).

The study of fetal and infant developmental plasticity is making important contributions to two central questions in anthropology: why we get sick and how we adapt. We are excited to see what discoveries future research will yield, and we hope that the ideas raised in this short review will help inspire some of this work.

SUMMARY POINTS

1. The study of developmental plasticity has a long history in anthropology and has been reinvigorated by the literature documenting effects of early environments that persist into adulthood and even to the next generation.
2. Many biological systems have critical periods during which environmental exposures can permanently change their functions. Many of these periods overlap with direct maternal provisioning via placenta or lactation and respond to maternal nutrients and hormones that reflect a woman's experience in the local environment.
3. Most evolutionary interpretations of this literature assume that the fetus sets its postnatal strategy in response to these cues.
4. Although the most widely cited evolutionary ideas propose an adult function for metabolic programming, a function for thrifty metabolic responses in fetal life or infancy is more likely.
5. Other systems are under stronger selection later in life, and these are better candidates for having evolved a capacity to adjust function in anticipation of future needs.
6. Because humans inhabit environments that change in ways that are not predictable, long-term predictive adaptation must rely on historical averaging. There is mixed evidence to support this proposition.

FUTURE ISSUES

1. A focus on reconstructing the historical information encoded in maternal cues will be key to understanding any long-term adaptive function of changes induced in offspring.
2. Studies of the regulatory basis of offspring phenotypic change can help clarify whether the response reflects a change in regulatory set points or simple developmental impairment.
3. Moving forward, the field will benefit by prioritizing hypothesis testing.

DISCLOSURE STATEMENT

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