AMERICAN JOURNAL OF HUMAN BIOLOGY 17:5–21 (2005)

Wiley-Liss Plenary Symposium

Fetal Origins of Developmental Plasticity: Are Fetal Cues Reliable Predictors of Future Nutritional Environments?

CHRISTOPHER W. KUZAWA*
Department of Anthropology, Northwestern University, Evanston, Illinois 60208

ABSTRACT Evidence that fetal nutrition triggers permanent adjustments in a wide range of systems and health outcomes is stimulating interest in the evolutionary significance of these responses. This review evaluates the postnatal adaptive significance of fetal developmental plasticity from the perspective of life history theory and evolutionary models of energy partitioning. Birthweight is positively related to multiple metabolically costly postnatal functions, suggesting that the fetus has the capacity to distribute the burden of energy insufficiency when faced with a nutritionally challenging environment. Lowering total requirements may reduce the risk of negative energy balance, which disproportionately impacts functions that are not essential for survival but that are crucial for reproductive success. The long-term benefit of these metabolic adjustments is contingent upon the fetus having access to a cue that is predictive of its future nutritional environment, a problem complicated in a long-lived species by short-term ecologic fluctuations like seasonality. Evidence is reviewed suggesting that the flow of nutrients reaching the fetus provides an integrated signal of nutrition as experienced by recent matrilineal ancestors, which effectively limits the responsiveness to short-term ecologic fluctuations during any given pregnancy. This capacity for fetal nutrition to minimize the growth response to transient ecologic fluctuations is defined here as intergenerational "phenotypic inertia," and is hypothesized to allow the fetus to cut through the "noise" of seasonal or other stochastic influences to read the "signal" of longer-term ecologic trends. As a mode of adaptation, phenotypic inertia may help the organism cope with ecologic trends too gradual to be tracked by conventional developmental plasticity, but too rapid to be tracked by natural selection. From an applied perspective, if a trait like fetal growth is designed to minimize the effects of short-term fluctuations by integrating information across generations, public health interventions may be most effective if focused not on the individual but on the matriline. Am. J. Hum. Biol. 17:5–21, 2005.

There is now considerable evidence that the characteristics of the prenatal environment trigger, or "program," developmental changes in the endocrine, organ, and physiologic characteristics of the fetus that persist after birth to elevate risk of cardiovascular disease and its precursors, including hypertension, diabetes, and high cholesterol (Barker, 1994; Adair et al., 2001; Kuzawa and Adair, 2003; Eriksson et al., 2004). Many of the relationships observed in humans have been replicated in experiments using animal models, suggesting that the associations reflect a causal role of prenatal stimuli such as nutrients and hormones (Kind et al., 1999; Seckl, 2001). More recently, the list of postnatal traits shown to be influenced by the prenatal environment has expanded to include such important functions as immunity, reproductive function, muscle mass, and growth rate and tempo (Table 1). These traits have clear implications for survival and reproduction, and thus raise important questions about the evolutionary significance of these responses (Lummaa, 2003).

In the original formulation of the fetal origins hypothesis, the effects of fetal undernutrition on adult diseases such as diabetes were viewed as by-products of fetal adjustments initiated to boost survival of pregnancy (Barker et al., 1989). Hales and Barker (1992) later published the "thrifty phenotype" hypothesis, which proposes that adjustment of fetal growth rate might set nutritional expectations and thereby condition the organism's response to nutrition

*Correspondence to: Christopher W. Kuzawa, Department of Anthropology, Northwestern University, Evanston, IL 60208. E-mail: kuzawa@northwestern.edu

Received 7 September 2004; Accepted 1 October 2004

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ajhb.20091

TABLE 1. Postnatal traits that relate to prenatal nutrition or size at birth

Outcome	Association	Animal	Human
Somatic growth			
Postnatal growth	LBW → slow	Engelbregt et al., 2004	Strauss and Dietz, 1997; dos Santos Silva et al., 2004
Maturational timing	LBW → early	—	Koziel and Jankowska, 2002
	LBW → late	Dellemare-van de waal et al., 2002; Coe and Shirtcliff, 2004	Lienhardt et al., 2002
Adult size	LBW → short	Engelbregt et al., 2004	Li et al., 2003
Lean mass, muscle	LBW → reduced	Bedi et al., 1982	Li et al., 2003
Cancer	LBW → reduced	—	Mellemkjaer et al., 2003; Paltiel et al., 2004
Reproduction			
Hormone production	LBW → reduced	Da Silva et al., 2001	Ibanez et al., 2000; Cicognani et al., 2002
Fecundity	LBW → reduced	Engelbregt et al., 2002	Ibanez et al., 2000
Age at menopause	LBW → earlier	—	Cresswell et al., 1997
Immune function			
Cell-mediated immunity	LBW → reduced	Chandra, 1975	McDade et al., 2001a
Infectious mortality	LBW → increased	—	Moore et al., 1997
Metabolism and cardiovascular function			
Insulin resistance	LBW → increased	Kind et al., 2003	Newsome et al., 2003
Blood pressure	LBW → increased	Kind et al., 2002	Adair et al., 2001
Cholesterol	LBW → increased	Kind et al., 1999	Kuzawa and Adair 2003

later in life. Bateson et al. (2004:420) summarize this perspective in a recent review in *Nature*, in which they hypothesize that "... human development may involve induction of particular patterns of development by cues that prepare the developing individuals for the type of environment in which he or she is likely to live." They outline a model in which the health consequences of adult nutrition are contingent upon the level of nutritional expectations conditioned in response to fetal nutrition. This scenario is proposed to explain the finding, for instance, that individuals born small but who are overweight as adults have high rates of type II diabetes, hypertension, and cardiovascular disease.

The hypothesis that the organism might adjust its future nutritional expectations in utero is intuitively appealing and is supported by similar examples from other species (Mousseau and Fox, 1998; Bateson et al., 2004; Gluckman and Hanson, 2004). However, the plausibility of this hypothesis rests on the untested assumption that the fetus has access to a reliable cue of future nutritional conditions. Hypotheses such as the thrifty phenotype presume a cue with long-term predictive value, for only in a system capable of accurately predicting the future when the ecology is *stable* might significant *change* from this predicted environment lead to adult conditions like type II diabetes, which take decades to develop. And humans are not only long-lived, but tend to inhabit environments marked by seasonal and stochastic fluctuations in ecologic productivity, which will tend to limit the predictive value of the current ecology during any given pregnancy. Without a reliable intrauterine cue of future nutrition, there is no basis for a scenario of long-term adaptive fine-tuning, nor the adult disease consequences proposed to result from a "mismatch" between the environment predicted in utero and the actual environment experienced in postnatal life.

This review explores two questions that are critical for evaluating the hypothesis that fetal adjustments to the prenatal environment have long-term adaptive value. First, if adjusting growth in utero has payoffs that extend after birth, what are the costs and benefits that inform this decision? A brief review of life history theory and evolutionary models of energy partitioning highlight the possible benefits of such a strategy, while providing insights into the pattern of phenotypic outcomes that it might be expected to generate. Second, does prenatal nutrition have value as a signal of future nutritional environments? A review

of paleoclimate data, research on pregnancy energetics, and studies of intergenerational effects on birthweight suggest a novel hypothesis for the role of fetal nutrition as a long-term ecologic cue.

LIFE HISTORY PERSPECTIVE ON THE ADAPTIVE SIGNIFICANCE OF GROWTH RATE

Benefits of fast growth

Current theoretical perspectives on the adaptive significance of fetal programming emphasize the benefits of reducing nutritional requirements by initiating a lower growth trajectory in utero (Hales and Barker, 1992; Bateson et al., 2004). The branch of evolutionary biology called life history theory (LHT) places energy allocation and growth at the center of the organism's adaptive strategy, and thus provides a useful framework to evaluate the costs and benefits of fetal developmental responses to intrauterine nutrition (see also Jones, this issue). LHT builds from the assumption that the organism has a baseline level of maintenance expenditure required to sustain minimal functionality (Gadgil and Bossert, 1970; Stearns, 1992). Energy available above and beyond this minimal requirement, described as "productivity," may be allocated to growth, energy storage, and physical activity during the growing years (see Fig. 1). Life history models assume that the organism devotes a fixed fraction of its total metabolic budget to growth, which is reflected in the fact that growth rate (not unlike basal metabolic rate) scales to body size across species (e.g., Harvey et al., 1987). After cessation of growth at reproductive maturity, the resources previously devoted to supporting growth are then shunted into supporting reproduction.

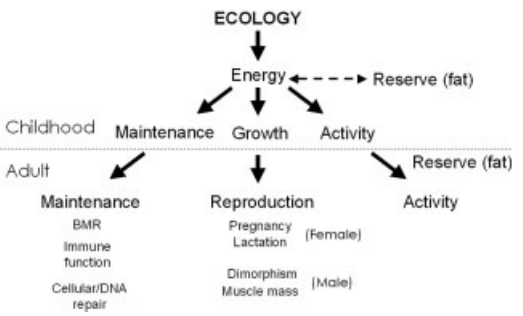

Fig. 1. The allocation rule: managing a finite energy budget. The organism is assumed to have a baseline level of metabolic expenditure required to sustain minimal functionality. Energy available above this minimal level, called "productivity," may classically be allocated to growth, reproduction, or energy storage. The figure further separates expenditure on physical activity to improve applicability to issues in human biology and health. Growth expenditure is used to support reproductive expenditures in adulthood, which take distinct forms in males and females.

Because any unit of energy (i.e., a molecule of ATP) may only be used once, an organism's decision to allocate energy to a function limits the resources available for allocation elsewhere, which leads unavoidably to functional trade-offs. In a determinant growing species like humans (who cease growing at reproductive maturity), the decision of when to switch from investing energy in growth to investing in reproduction is a classic example of such an adaptive trade-off, and may be particularly relevant for understanding the logic of fetal developmental adjustments. Because energy is finite, the organism is faced with deciding whether to initiate reproduction now, or to delay reproduction to build a bigger body with the capacity to give birth to bigger and more resilient offspring later (see Hill and Kaplan, 1999).

While the reproductive benefits of large adult size are well documented, there are risks associated with delaying maturity in order to grow large, as there is some chance of dying on any given day (Williams, 1966). At the age when the mortality risk associated with delaying maturity outweighs the reproductive benefits of growing larger, the organism is predicted to cease growth and shunt growth expenditure into supporting reproduction. These assumptions about the costs and benefits of delaying maturity have been used to successfully predict the timing of reproductive maturity both between species (Charnov, 1993), and within species due to developmental plasticity (Stearns and Koella, 1986; Hill and Hurtado, 1996). In the case of developmental plasticity in humans, a fast growth rate implies that the organism will be able to reach a larger adult size in less time, and thus enjoy positive effects on the ability to invest in reproduction, increasing offspring size and improving offspring survival.

Thus, from the perspective of LHT and the allocation rule, growth has adaptive significance through multiple pathways. First, growth rate is the outward manifestation of productivity, and thus serves as a proxy

measure of the metabolic fraction that the organism will be able to invest in offspring and other "nonessential" expenditures as an adult. And second, because delaying maturity in order to grow is risky, the rate of growth determines how large an adult body the organism can "afford" to build for any given level of prereproductive mortality risk. From this perspective, the fetal decision to adopt a lower growth trajectory is fateful, as it commits the organism to lower productivity and smaller adult size, with cascading negative effects on multiple fitness components (see also Jones, this issue).

Benefits of slow growth

Although shorter individuals suffer from a range of compromised functional and reproductive outcomes, including reduced size and survival of offspring (Martorell, 1989), they also have reduced total energy requirements (Fig. 2), which may provide advantages to genetic fitness when nutrition is restricted (see Arendt, 1997; Frisancho et al., 1973). For instance, Garrow and Pike (1967) review evidence that individuals with a higher genetic growth potential are more susceptible to severe malnutrition, consistent with the perspective that a high growth rate, per se, carries costs to survival in restrictive nutritional environments.

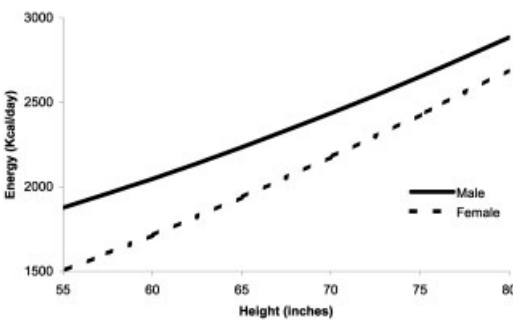

Fig. 2. Relationship between standing height and daily energy intake necessary for a 25-year-old male and female to sustain basal metabolism and light physical activity. Expenditure at a level slightly above minimal needs was calculated using the FAO/WHO/UN (1985) formulae, in which "light activity" = 1.4 × BMR, and BMR = 15.4 × (weight in kg) – 27 × (height in m) + 717 for males, and = 13.3 × (weight in kg) – 334 × (height in m) + 35 for females. The weight necessary to generate a body mass index in the middle of the healthy normal range (22.0 kg/m^2) was calculated for a range of standing heights and these heights and weights were used to calculate height-specific BMR.

The deleterious consequences of "falling short" on energy intake are well documented, and provide insights into the potential risks incurred when aiming for a high growth trajectory and large body size. When expenditure exceeds intake, allocation is adjusted to buffer critical functions such as brain metabolism at the expense of functions of less importance to immediate survival, with growth and reproduction hardest hit (Cahill, 1976; Wade and Schneider, 1992). Growth is slowed or may cease, with consequences that are contingent on the timing, duration, and severity of the imbalance (McCance and Widdowson, 1974). If a growth-restricting stressor is not chronic, or the nutritional imbalance rectified, the body may accelerate the pace of growth to reestablish the organism's original size and growth trajectory (Prader et al., 1963). While helping recover lost ground, relying heavily on such canalizing mechanisms may carry significant costs, including an increased risk of developing chronic disease and perhaps by increasing the rate of senescence (see Cameron and Demerath, 2002). Once growth has ceased and the organism is reproductively viable, protracted negative energy balance continues to have negative effects on genetic fitness by suppressing gonadal steroid production and ovulation (Ellison et al., 1993).

Thus, although the body is equipped to *survive* periods of negative energy balance, the metabolic adjustments that characterize this state run counter to the organism's teleological goals of growing into a mature adult, or once an adult, of reproducing. While this perspective is hardly new (reviewed in Frisancho et al., 1973; see also Janson and Van Schaik, 1993), the principle of life history allocation helps clarify the potential benefits of downregulating energy needs in a limiting environment (Fig. 3). Although a smaller organism has lower productivity, and thus a smaller pool of energetic resources to invest across functions, including reproduction, the potential benefit of this strategy is that the pattern of functional "deficit" is *balanced* across systems. Presumably all expenditures will be downregulated roughly equally in such an individual, and the resultant reduction in absolute requirements should minimize periods of negative energy balance when "nonessential" functions—growth and reproduction—are disproportionately compromised.

The pattern of relationships linking birthweight with the adult phenotype, as listed in

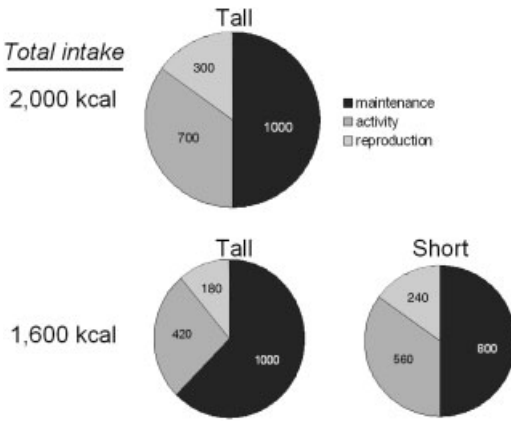

Fig. 3. Hypothetical effect of stature on the pattern of energy allocation during periods of adequate (2,000 kcal) and suboptimal (1,600 kcal) energy intake. During lean times, the tall individual has high metabolic overhead, which exacerbates energetic trade-offs with nonessential functions like reproduction. At the same level of reduced intake, the shorter individual has a balanced reduction in all expenditures, and the negative effect on reproduction is minimized.

Table 1, are consistent with this concept of distributed metabolic adjustment. Higher birthweight predicts taller and heavier adult size (Alberman et al., 1991; Li et al., 2003), but is also a positive predictor of a wide range of functions and traits, including immune function (see McDade, this issue), gonadal steroid production (Cicognani et al., 2002), lean body mass (Li et al., 2003), and adipose tissue deposition (Li et al., 2003). All of these traits are costly to build and maintain, and their positive association with birthweight is evidence for a fetal capacity to increase or decrease allocation in a distributed fashion, in parallel across systems.

Summary: Walking the metabolic tightrope

Thus, the fetus walks a metabolic tightrope, as it faces the challenge of setting its growth trajectory high enough to reap the fitness benefits of high productivity and growth rate, but not so high as to overshoot what available resources can support, and thereby increase the frequency or severity of negative energy balance. To minimize the postnatal consequences of negative energy balance in a nutrient-poor environment, this trajectory must be initiated *in advance* (e.g., Garrow and Pike, 1967). For only then is the burden of lower nutritional intake distributed evenly across systems, rather than disproportionately impacting growth and reproduction—the two functions (after survival itself) that are most central to the organism's adaptive strategy. The pattern of functions that positively associate with birthweight is consistent with this concept, and suggests that the fetus has a capacity to downregulate future expenditure in response to poor intrauterine nutrition. But is it reasonable to expect that the fetus might be able to do this in a *predictive* fashion?

ARE RELIABLE CUES OF FUTURE NUTRITION AVAILABLE TO THE FETUS?

Ecologic and climatic variability: Signal or noise?

The plausibility of the hypothesis that the fetus fine-tunes its developing physiology based on future nutritional expectations rests on several untested assumptions. Adaptive phenotypic plasticity requires that the developing organism have an ability to detect a predictive signal against a background of random or irrelevant noise (Levins, 1968; Getty, 1996). This problem seems particularly daunting for the fetus of a long-lived species aiming to calibrate its future nutritional requirements. Droughts and seasonal cycles of ecological productivity were likely commonplace for most if not all preindustrial populations (Foley, 1993), and these short-term ecologic dynamics reduce the value of current nutrition as a signal of average or future nutritional conditions. If a fetus happens to be in utero during the relative abundance of the harvest, would it improve its fitness by adjusting its future growth and productivity, and thus level of nutritional requirements, to expect abundance? Because the abundance is transient, such a capacity to "fine-tune" expectations would likely exacerbate susceptibility to negative energy balance, as outlined above.

Even if the current ecology provides little information about the typical future ecology in a long-lived species, it is likely that the fine-scale "noise" of the seasons and other transient events was superimposed on gradual, long-term trends in what might be described as the "baseline" ecology. Paleoclimate data for sub-Saharan Africa suggest an increase in climatic variability at various stages of the Pleistocene. These fluctuations appear as abrupt shifts between

ecologic extremes when viewed on a geologic time scale, but would have been experienced by our hominine ancestors as shifts in local ecology that play out over many generations (Potts, 1996a). Potts (1996b, 1998) hypothesizes that it was this increased climatic variability and the recurrence of ecologic extremes, rather than directional selection from relatively stable ecologies, that provided the evolutionary stimulus for key hominine innovations, including the generalist strategy of flexible capacities that are the hallmark of genus *Homo*.

From the perspective of the developmental biology of our hominine ancestors, this ecologic variability might have favored a capacity to adjust nutritional requirements to track these more gradual trends. If the fetus could filter out the "noise" of short-term fluctuations, allowing it to assay something like an "average" ecology, this information could be useful. It could allow it to adjust its level of nutritional expectations to track longer-term ecologic trends, thus potentially helping optimize its solution to the tightrope problem outlined above. While this seems a physiologically improbable feat, there are intriguing hints that such a "crystal ball" may in fact be available to the human fetus.

Fetal nutrition is an unreliable signal of the current nutritional ecology

Nutrients or related intrauterine factors only have signaling value for the fetus to the extent that they correlate with the local nutritional ecology. And while the strength of this correlation between the intrauterine environment and the external ecology is difficult to evaluate, the sensitivity of fetal growth to nutrition implies that the "information content" of fetal nutrition may be probed, in a rough fashion, by examining the maternal or ecologic predictors of birthweight. The nutrients delivered across the placenta stimulate fetal production of insulin and IGF-II, which are the key determinants of fetal growth rate (Gluckman, 1997; Lang et al., 2003). This makes birthweight a reasonable, if imperfect (Kuzawa and Adair, 2004), proxy for fetal nutrition.

While maternal nutrition and nutritional status prior to and during pregnancy are clearly linked with birthweight (Institute of Medicine, 1990), the maternal body has a sophisticated repertoire of metabolic responses that help maintain the intrauterine nutritional environment within relatively narrow limits. These homeostatic processes take many forms, and begin before conception. Ovulation itself is sensitive to maternal energetics, which limits initiation of pregnancy to periods when nutritional status is likely adequate to support it (Ellison, 2001). Once pregnant, a mother faced with restricted energy intake may buffer fetal growth by mobilizing fat stores, increasing the efficiency of certain metabolic processes, and by reducing physical activity (reviewed in Dufour and Sauther, 2002). The effectiveness of these buffering capacities is well documented. In a classic series of comparative studies of pregnancy energetics, the total energy cost of supporting a pregnancy was found to vary remarkably across populations, from a high of 125,000 kcal in well-nourished Swedish women, to a low of –7,000 kcal in unsupplemented Gambian women (reviewed in Prentice and Goldberg, 2000). Despite this variation in the energy intake necessary to sustain pregnancy, expenditure on growth of the fetoplacental unit itself varied less, with average birthweights differing by roughly 0.5 kg across these energetic extremes.

Teleologically, it makes sense that the maternal body would have the capacity to protect fetal nutrition when intake is compromised (Prentice and Goldberg, 2000). However, it is notable that maternal buffering works both ways: *increasing* maternal dietary intake typically also has relatively modest *positive* effects on fetal growth and birthweight. With notable exceptions (e.g., Ceesay et al., 1997), macronutrient supplementation trials among women in populations from developing nations typically result in relatively small improvements in birthweight. For instance, each 10,000 kcal provided to pregnant Guatemalan women yielded a change in birthweight of roughly 29 grams (Lechtig et al., 1978). In a systematic review of 13 studies (primarily in developing nations), balanced protein/energy supplementation of pregnant mothers resulted in a nonsignificant weighted-average increase in birthweight of 25.4 grams, or a little less than 1 ounce (Kramer, 2000), with some studies finding greater effects of maternal nutritional supplements on the birthweight of male offspring (e.g., Mora et al., 1979; Adair and Pollitt, 1985).

Even a small shift in the birthweight distribution may significantly improve birth

outcomes and perinatal survival in poorly nourished populations (Institute of Medicine, 1990). However, the modest differences in birthweight across populations varying dramatically in energy intake, combined with the relative refractoriness of birthweight to supplementation, imply that, from the perspective of the fetus, the nutrients delivered across the placenta are at best a fuzzy indicator of what the mother is *currently* consuming. This raises the important question of what factors, if not the mother's current intake, determine the strength of the intrauterine nutritional signal. Broadening the temporal frame beyond the current pregnancy provides important clues.

Intrauterine nutrition provides an integrated signal of chronic nutritional history of the matriline

Intergenerational studies that track birthweight records across multiple generations find that the mother's own birthweight is among the strongest predictors of her offspring's birthweight (Ounsted et al., 1986; Klebanoff and Yip, 1987; Emmanuel et al., 1992; Sanderson et al., 1995; Hypponen et al., 2004; reviewed by Ramakrishnan et al., 1999). This relationship is strengthened when the mother's gestational age at birth is controlled, suggesting that it is her fetal growth sufficiency, rather than variation in birth size tracing to the duration of gestation, that is important (Alberman et al., 1992). One possible interpretation of this finding is that women who were born small end up small as adults and thus give birth to smaller offspring as a function of the physical constraints of their reduced size. However, the relationship between a mother's birthweight and the birthweight of offspring is not diminished appreciably after adjusting for her adult size (Ramakrishnan et al., 1999). In some populations the mother's *adult size* is no longer significantly related to offspring birthweight once the effect of her birth size is held constant in multivariate analyses (Hypponen et al., 2004). Thus, while maternal size in adulthood is an important predictor of offspring birthweight, this relationship does not account for the intergenerational correlation between maternal and offspring birthweight.

While a shared genetic influence on maternal and offspring fetal growth may not be ruled out in such observational studies, a similar intergenerational effect of birth size has been observed in humans exposed to the quasi-experimental condition of famine (Stein and Lumey, 2000). Among women whose mothers experienced the Dutch Hunger Winter while pregnant, the trimester of exposure was found to influence birth size, with effects that carried over to influence the birth size of their own offspring (Stein and Lumey, 2000). Similarly, Price et al. (1999, 2000) document a gradual, intergenerational secular trend in birthweight in a troop of wild macaques that experienced an abrupt improvement in nutrition after being taken into captivity. In this troop, the secular trend in birthweight had not stabilized after five generations in captivity and there was an intergenerational component to the trend, with maternal birthweight predicting birthweight of female offspring. In contrast, the birthweights of males, which were larger prior to captivity, did not increase across successive generations in captivity. This suggests that the effect of maternal constraint on offspring size—reflected in smaller birth size at the onset of captivity—may have been limited to female offspring (Price et al., 1999), a finding consistent with observations in some human populations (e.g., Ounsted et al., 1986; Emanuel et al., 2004).

These findings have been taken as support for the hypothesis, now 35 years old, that the nutritional experiences of the mother when she was a fetus condition the intrauterine nutritional environment that she provides her own offspring, with effects stronger through the female line (Ounsted and Ounsted, 1968). And while this intergenerational effect is best documented for prenatal nutrition, several recent studies suggest that what a mother ate as a child also influences offspring growth. In a British cohort originally measured in 1937–39, a woman's size at 7 years of age was found to be a stronger predictor of offspring birthweight than was her adult height (Martin et al., 2004). The component of childhood height that predicted offspring birthweight was leg length, which is a sensitive marker of early life nutrition (Scrimshaw and B'Ehar, 1965). Although not focused on birthweight as an outcome, more direct evidence for an intergenerational influence of childhood nutrition comes from the INCAP supplementation trial in Guatemala (Stein et al., 2003, 2004). In this study, *offspring* of women who received a high-quality

nutritional supplement during childhood grew faster during the first 36 months of life. While the mechanisms remain to be established, these studies suggest that a female's nutritional experiences after birth continue to condition the nutritional environment that she will provide her own offspring, with measurable effects on both prenatal and postnatal growth in the next generation.

INTERGENERATIONAL PHENOTYPIC INERTIA: A NEW HYPOTHESIS FOR THE NONGENETIC TRANSMISSION OF NUTRITIONAL INFORMATION

The sensitivity of fetal and childhood growth in the *present* generation to the nutrition and growth experienced by the *prior* generation has broad theoretical implications. First, it suggests that the tendency for some mothers to give birth to growth-restricted newborns has an intergenerational component (Ounsted and Ounsted, 1968). Offspring fetal growth is not solely contingent upon a mother's current intake, which may change from pregnancy to pregnancy, but is also influenced by a constitutional factor that traces to her chronic nutritional history—including her nutrition in utero and during childhood. And second, because the uterine nutritional environment that the mother provides her offspring is in part a reflection of the nutritional environment that she received as a fetus, the fetal growth of the current generation is thereby linked with the nutritional experiences of the *grandmother*, and so on. In the macaque example, females of the precaptive troop had lower average birthweights than after captivity, and this constraint on fetal growth was still "washing out" after five generations of improved nutrition in captivity (Price and Coe, 1999; Price et al., 2000).

The phenotypic consequences of this intergenerational process intuitively make sense: growth rate increases in response to a sustained improvement in nutritional sufficiency experienced across successive generations (Price et al., 1999). However, while the capacity for intergenerational change in fetal nutrition and growth is impressive, from the perspective of the organism's adaptive strategy, the key "feature" of this response is arguably the *slow pace* with which it takes place. Intergenerational influences on fetal nutrition and growth may act as a form of what may be called *intergenerational phenotypic inertia*, in the sense that the growth response of the fetus to abrupt ecologic change is tempered by the collective nutritional experiences of recent matrilineal ancestors. Because the fetal nutritional signal reflects the mother's chronic nutrition tracing back to her own uterine environment, and thereby to prior generations of the matriline, this may allow the fetus to "see" an average nutritional environment as sampled over decades and even generations. In theory, this is the sort of signal detection capacity that the fetus of a long-lived species might be able to use—one capable of filtering out the white noise of transient nutritional changes to detect the current position within more gradual, sustained, and thus more adaptively relevant trends in the background ecology (Fig. 4). This is potentially an elegant solution to the adaptive problem of tracking environmental change, without falling into the trap of responding to seasonal or other short-term fluctuations that may happen to be in play during gestation.

Given the paucity of intergenerational studies that include measures of adult functional outcomes, additional research will be necessary to establish the long-term functional and developmental effects of this gradual process of change. Birthweight may increase with nutritional improvement (Fogel, 1986; Chen, 1990; Hop, 2003; Fok et al., 2003; but see Cole, 2000), and the finding of positive relationships between size at birth and such traits as adult size, muscle mass, immune function, adipose tissue deposition, and gonadal function in human populations (listed in Table 1), as discussed earlier, suggests that gradual

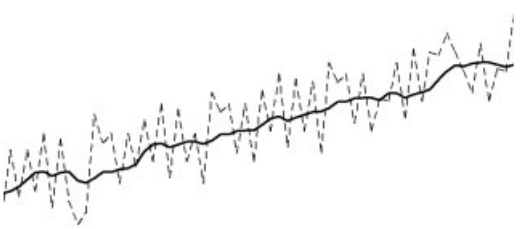

Fig. 4. Schematic illustration of the hypothesized capacity of intergenerational phenotypic "inertia" to reveal the "signal" of gradual long-term nutritional trends (dark solid line) by filtering out the "noise" from transient short-term ecologic fluctuations (dashed line). Maternal buffering mechanisms and intergenerational influences on fetal nutrition may allow the fetus to "see" the signal of the more gradual background trend in nutrition.

intergenerational adjustments in fetal nutrition are likely to be associated with distributed increases in allocation across multiple postnatal functions in addition to, or perhaps independent of, postnatal size.

Although data are sparse, evidence from longitudinal intergenerational studies support this concept in humans. In several populations the secular trend in adult size was found to be predictable on the basis of fetal growth (Kuh and Wadsworth, 1989; Alberman et al., 1991; but see Cole, 2000). For instance, in the 1958 British birth cohort study, there were intergenerational effects on birthweight, and a secular trend in adult stature, with male offspring gaining 3 cm over fathers, and female offspring gaining 1 cm over mothers. The magnitude of an offspring's stature increase over their same-sex parent was positively related to their rate of fetal growth, as indicated by size for gestational age (Alberman et al., 1991). Recent longitudinal analyses in the Guatemalan INCAP study show that much of the adult stunting in this population is either present at birth or predictable on the basis of birth length, with birth size positively related to adult stature, adipose tissue deposition, and lean body mass (Li et al., 2003). While the magnitude of phenotypic change is likely to be modest in any single generation, even minor intergenerational adjustments in traits such as these could cumulatively lead to significant change in function, and nutritional requirements, across many generations.

DISCUSSION

From the perspective of life history theory, the fetus faced with the decision of setting its growth trajectory is forced to walk a metabolic tight rope, as it must weigh the considerable reproductive and functional benefits of high productivity against the metabolic risk associated with higher total energy requirements. If a fetus has access to a cue that predicts postnatal nutritional conditions, it could use this information to adjust its trajectory accordingly (Bateson et al., 2004; Gluckman and Hanson, 2004). The finding that birthweight is positively related to expenditure across a range of important functions, as highlighted in Table 1, suggests that total requirements are being modulated by the fetus by up- or downregulating expenditure in a balanced fashion across systems. Thus, from this perspective, the well-documented reduced function of these systems in low birthweight individuals relative to individuals well-nourished in utero is not so much "impairment" as a preemptive strategy to avoid negative energy balance, which if not avoided, disproportionately impacts growth and reproduction.

Phenotypic inertia as a mode of human adaptability

While it remains to be determined if the fetus has access to reliable predictive information in utero, this review has proposed one form that such a cue might plausibly take. By stabilizing certain environmentally induced features of the phenotype across multiple generations, aspects of metabolism or physiology characterized by a pattern of intergenerational phenotypic inertia may allow the fetus to predict the future by seeing the past, as integrated by the soma of the matriline. Developmentally plastic traits that change only gradually across generations are good candidates for predictive cues, because they potentially filter the noise of short-term fluctuations, thereby allowing the fetus to see the signal of any underlying pattern of sustained and thus more adaptively relevant change.

The potential benefits of this strategy would naturally seem to be greatest when conditions, although changing over the long term, are relatively stable for multiple generations at a time. If matrilineal ancestors equilibrated their requirements to match the conditions of a relatively stable ecology, the inertia of intergenerational effects will limit the phenotypic response of offspring to an unusually good or bad year, or to particularly favorable or demanding conditions during pregnancy. The example of the macaque troop illustrates this well, as the collective intergenerational experience of the precaptive generations took five or more generations to wash out after an abrupt improvement in nutrition. However, the five generations of wash-out also illustrate the limitations of this strategy, as it will force the phenotype to lag when changes are rapid and sustained—in this case, maintaining the growth of offspring at a less-optimal level calibrated to the lower intake of past generations.

Despite this lag, intergenerational inertia is still likely to provide significant advantages over the more protracted phenotypic lag resulting from natural selection operating on

gene frequencies. In this sense, intergenerational phenotypic inertia may have a unique role to play within the organism's repertoire of adaptive strategies. It is well known that organisms have a suite of mechanisms that track environmental fluctuations occurring on different temporal scales, including change in gene frequencies via natural selection, nonreversible adjustments made to the growing body via developmental plasticity, and reversible physiologic processes that manage minute-to-minute and day-to-day fluctuations via homeostasis (Lasker, 1969). While inertial effects are clear examples of nongenetic phenotypic variation, they have properties that distinguish them from previously documented examples of developmental plasticity. Developmental plasticity classically includes permanent modifications to the phenotype triggered by environmental exposures experienced by the organism during its own growth and development (Lasker, 1969; Bogin, 1999). Traits influenced by intergenerational inertia, in contrast, allow nongenetic information acquired in the past, as accumulated in the soma across multiple generations of the matriline, to be conveyed to the soma of the current generation. From this perspective, what makes fetal developmental plasticity and the process of intergenerational inertia qualitatively different from conventional plasticity is not the developmental *timing* of the response, but the *time depth* of the information to which the developing body is responding.

Recent theoretical work highlights the potential advantage of an environmentally induced phenotype that is transmissible across generations. Using mathematical simulations, Jablonka et al. (1995) model the conditions under which three different organismal strategies would be favored—genetic (no environmental effect), plastic (no effect of prior generation's induced phenotype on trait expression in offspring), and what they call "carry over" effects, which are similar to plasticity but are transmitted to a variable number of future generations after being induced. While plasticity is favored in a predictable environment (e.g., seasonality), they find that carry-over effects provide advantages in situations that are unpredictable, leading them to suggest that they might "... fill the gap between the ontogenetic or physiological adaptations that underlie individual plasticity, and the classical genetic changes associated with long-term evolutionary adaptations. They may underlie the frequently observed rapid adaptation that takes place within a few generations of a change in environment" (p. 138).

Mode	Time scale	Process
Genetic	**Slow**	Natural selection
Intergenerational		**Phenotypic inertia**
Plasticity		Development
Physiologic	**Fast**	Homeostasis

Fig. 5. Intergenerational phenotypic inertia as a fourth mode of human adaptability. Fetal developmental plasticity with an inertial component may allow gradual, intergenerational response to ecologic change that occurs on a timescale intermediate to the slow change facilitated by natural selection operating on gene frequencies, and the more rapid adaptation facilitated by developmental plasticity within a single lifetime. While conventional developmental plasticity is a real-time response to the environment of rearing, phenotypic inertia responds to environmental information integrated across prior generations and transduced through the soma of the matriline.

From this perspective, the phenomenon of inertia that stabilizes the intrauterine nutritional signal across generations may allow the fetus to cope with ecologic trends that transcend multiple generations, and thus exceed the tracking capacity of developmental plasticity, but that are too rapid to be tracked by the more gradual changes in gene frequencies achieved via natural selection. If inertial effects like the intergenerational transmission of birthweight are indeed adaptive, they are thus likely to occupy a position intermediate to natural selection and developmental plasticity in the temporal hierarchy of human adaptability (Fig. 5).

Timing of benefit

The developmental age at which these responses could provide adaptive benefits to the organism remains to be established. In theory, the adaptive component of any response triggered by a predictive prenatal cue will tend to decline in old age, reflecting both the age-related decline in selection and the decoupling of the predicted environment from the actual lived environment. Selection on metabolic capacities is likely high during infancy (see Jones, this issue), when the burden of weaning and a relatively large and metabolically demanding brain render the infant prone to malnutrition (Kuzawa,

1998). Nutrition-related mortality has left its imprint on the pattern of energy allocation during the perinatal period, for instance, in the form of a metabolism heavily biased in favor of allocating energy to adipose stores (Kuzawa, 1998) and in support of a robust developmental cascade of immune defenses (see McDade, this issue). Any postnatal adaptive effect of fetal plasticity is likely weighted in favor of boosting survival during this period of elevated metabolic risk, which might be likened to an "ontogenetic bottleneck" through which any childhood or adult manifestations of the response must first pass. It is unlikely, for instance, that a downstream effect that boosts reproduction at the cost of infant survival would be stabilized into the developmental reaction norm (Fisher, 1930).

While selection is strong early in life, a downstream adaptive role for fetal responses during childhood or adulthood is also plausible. For one, if the intrauterine signal is predictive of future ecologic conditions, adjustments in nutritional requirements that are beneficial early in life may continue to have benefits late in life, which would minimize any antagonistic competition between trait expression during these two periods. Second, a more thorough evaluation of selection operating on fetal developmental plasticity would take kin effects into account (Lee, 2003), such as represented by the sizeable cumulative parental investment of energy, time, and knowledge in older offspring relative to infants (Hill and Kaplan, 1999), maternal–fetal genomic conflict during pregnancy that tempers maternal investment in any current fetus or infant (Haig, 1993; Wells, 2003), the boost to inclusive fitness gained by provisioning offspring after menopause (Hawkes, 2003; Lahdenpera et al., 2004), or the downstream effects of traits such as growth rate or reproductive effort on the size and survival of offspring (Allal et al., 2004). Each of these examples of kin selection will tend to increase the reproductive value of the post-infant period. Finally, examples from other species provide evidence for metabolic adjustments triggered by intergenerational undernutrition that specifically benefit reproduction. For instance, rats exposed to chronic intergenerational undernutrition give birth to more offspring per litter than pregnant rats undernourished for a single generation (Galler and Zartarian, 1981), as would be expected if reproductive effort was protected across successive generations of undernutrition by distributing the burden of nutritional deficit in a more balanced fashion across functions (see Fig. 3).

Possible mechanisms of intergenerational inertia in fetal nutrition and growth

Heritable modifications in the chromatin marking system, such as DNA methylation, have received most attention as potential pathways for nongenetic intergenerational inheritance, and could be involved in intergenerational effects on fetal nutrition and growth (Jablonka and Lamb, 1995; Waterland and Jirtle, 2004; Weaver et al., 2004). Patterns of DNA methylation may be modified by environmental exposures, are potentially passed on to offspring, and are often differentially expressed according to their parent of origin (Haig, 1993; Waterland and Jirtle, 2004). The contribution of such epigenetic mechanisms to the matrilineal influence on fetal nutrition and growth, as reviewed here, remains to be determined. However, it may be relevant that a cluster of maternally and paternally imprinted genes have recently been proposed to play counteracting roles in the regulation of fetal demand and placental supply (Reik et al., 2003). By influencing the flow of nutrients across the placenta, imprinting of these or similar genes by parental experiences, such as nutrition, could modify the flow of nutritional information to offspring. Although speculative, information about past environments might also be conveyed directly to the fetal soma, transferred via the maternal capacity to supply nutrients or other metabolites to an offspring developmental program designed to respond to and capture this information as the body grows (see below).

Adaptation or phylogenetic constraint?

The finding that many organisms have the capacity to reset their growth rate and nutritional requirements early in life has been taken as evidence that human developmental responses to prenatal nutrition may also have an adaptive component (Bateson et al., 2004; Gluckman and Hanson, 2004). While the plausibility of this hypothesis is supported by this review, there are other possible interpretations of this pattern that

require evaluation. For instance, a trait may also be widespread because it is a vestige from a common ancestor. If a pathway is highly integrated into the developmental infrastructure of an organism's basic body plan (bauplan), it may be difficult or costly to remove, and may therefore survive in modern lineages despite a lack of current utility (Gould and Lewontin, 1979). Most if not all developmental responses triggered by the fetus are likely to have both adaptive and vestigial elements, and disentangling the relative importance of these alternate explanations is far from straightforward.

It is notable, for instance, that the intergenerational effect on birthweight is not limited to species with long lifespans, making clear that this capacity did not *originally* evolve to help the human fetus face the unique nutritional and ecologic challenges discussed in this review. However, as in the example of the stress hormone axis, which has been coopted to serve homologous developmental functions in taxa as distantly related as amphibians and mammals (see Crespi and Denver, this issue), the regulation of the intrauterine nutritional signal itself, or the fetal response to it, could be modified to better suit the selective pressures faced by species varying in lifespan or inhabiting ecologies with different temporal dynamics. For instance, the phenotypic "penetrance" of intergenerational inertia, as reflected in the strength of the induced component of the phenotypic correlation across generations, or the number of generations required for an induced phenotype to "wash out," might be modifiable, allowing some level of fine-tuning to different temporal selection pressures. The downstream effects of the fetal response, both in terms of the systems influenced and the magnitude of the effect, could also be modified to match a species' metabolic and adaptive priorities.

The cascade of fetal responses to prenatal nutrition or growth appear to vary as a result of one's genotype, suggesting that the fetal response to prenatal stimuli is potentially amenable to this type of adaptive fine-tuning. Breeding experiments demonstrate significant effects of the uterine environment on the postnatal growth trajectory of offspring that vary by genotype of the fetus (Cowley et al., 1989). In humans, the relationship between birthweight and future glucose metabolism (Eriksson et al., 2003), blood pressure (IJzerman et al., 2003), and bone mineral density (Dennison et al., 2001) are all contingent upon polymorphic genes. These studies are important because they demonstrate that the fetal response to the prenatal environment is not a predictable outcome governed by simple physical laws, but rather, comprises a suite of contingent responses that are potentially modifiable by polymorphic genes. If the effects of these variants influence survival or reproduction, the best fit variants will be better-represented in future generations, leading to adaptive fine-tuning of the pathways themselves (Lewontin, 1970). Through such fine-tuning, the plasticity of the fetal developmental program may have evolved a capacity to directly incorporate somatic information from the mother, as reflected in the quantity or pattern of nutrients or hormones. Additional research on the genetic architecture of fetal responses, combined with a focus on identifying homologous pathways in other taxa, will go a long way towards clarifying the adaptive significance and mechanisms of fetal developmental plasticity in humans.

Public health implications

While these theoretical questions are important in their own right, clarifying the evolutionary significance of these pathways is likely to yield novel insights into their contribution to health and disease (Bateson et al., 2004). Many of the long-term health effects of small birth size—such as high blood pressure and diabetes—are exacerbated when followed by postnatal catch-up growth (Cameron and Demerath, 2002). This suggests that fetal nutrition and nutritional conditions experienced after birth may interact to influence adult health (Bateson et al., 2004). Given that catch-up growth is often a compensatory response to prior negative energy balance and growth restriction, the accuracy with which a fetus sets its level of nutritional demand could have implications for adult health by influencing the likelihood of experiencing negative energy balance during the period of prenatal, infant, or childhood growth. All else being equal, an individual with a higher growth trajectory should be more prone to energy shortfall during ecologic or developmental stages of high metabolic risk. From this perspective, the deleterious health consequences of small birth size might be reduced among individuals, particularly females, born to lineages with long histories of intergenerational undernutrition (Kuzawa, 2004). Their lower

growth trajectories might protect them against supply–demand imbalance in utero, thereby reducing the risk of late gestation growth restriction and obviating the need for postnatal catch-up growth. This hypothesis could be tested in an intergenerational study of a population experiencing abrupt change in nutritional sufficiency, in which the effects of inertia on fetal growth should be most evident.

Evidence was reviewed that the constraint of intergenerational undernutrition has less of an effect on the growth of male fetuses (Ounsted et al., 1986; Price et al., 1999), who also appear to have a stronger positive growth response to maternal nutritional supplementation during pregnancy (Mora et al., 1979; Adair and Pollit, 1985). The health implications of this sex difference in prenatal buffering have scarcely been explored, but could be important. For one, features of the adult male phenotype that are sensitive to early nutrition, such as muscle mass or gonadal function, may be more strongly influenced by factors experienced by the mother during pregnancy, including stochastic processes or transient events like seasonality or droughts—or by corollary, nutritional supplementation or other interventions. Sex differences in the effects of maternal constraint on fetal growth may indicate that fetal demand for nutrients is poorly calibrated to the level of maternal supply in the male fetus (Kuzawa, 2004), which might explain the stronger association between birthweight or maternal nutritional status during pregnancy and postnatal cardiovascular disease risk factors documented in some populations (reviewed in Kuzawa and Adair, 2003).

Perhaps the most intriguing public health questions are raised by the concept of phenotypic inertia itself. While this review has focused on nutrition and fetal growth, other traits, including maternal blood pressure, diabetes, and stress reactivity during pregnancy, also appear to be transmitted intergenerationally through epigenetic pathways, as recently reviewed elsewhere (Dabelea and Pettitt, 2001; Drake and Walker, 2004; Hypponen, 2004; Weaver et al., 2004). Each of these examples illustrate the capacity of the phenotype to be influenced by environmental conditions experienced by recent ancestors. It is possible, perhaps likely, that some of these tendencies for the phenotype to replicate across generations reflect little more than a developmental fluke that only expresses under conditions, such as gestational diabetes, that are uncommon in nature. Alternatively, we may be seeing the glimmerings of an infrastructure allowing certain features of the phenotype to be the beneficiary, albeit subtle, of environmental information integrated and accumulated within somatic lineages. While many questions remain to be clarified, the applied implications of this hypothesis are potentially broad. Most notably, if a system is *designed* to develop with the benefit of ecologic information integrated across multiple generations, short-term treatments in any single generation may reap limited long-term benefits. For such conditions, the most effective focus for intervention may not be the individual but the matriline.

SUMMARY

Several lines of evidence support the hypothesis that fetal responses to prenatal nutrition could help it adjust its level of postnatal nutritional expectations to match the local nutritional ecology. First, birthweight is positively related to a wide range of metabolically costly postnatal traits, suggesting that the fetus has the capacity to distribute the burden of reduced energy availability across multiple functions as nutritional sufficiency declines. By lowering total requirements, the organism may reduce its risk of experiencing negative energy balance, which disproportionately impacts functions—growth and reproduction—that are not essential for survival, but are crucial components of its adaptive strategy.

The long-term advantage of these adjustments is contingent on the fetus having access to information that is predictive of its future nutritional environment, a problem complicated by short-term ecologic fluctuations tracing to factors like seasonality. A review of the literature on the predictors of birthweight suggests that the stream of nutrients reaching the fetus, especially the female fetus, conveys information in the form of an integrated signal reflecting recent nutritional environments experienced by matrilineal ancestors. This has the effect of limiting changes in growth rate in response to short-term ecologic fluctuations, and thus may allow the fetus to cut through the ecologic "noise" of seasonal or other stochastic

influences to read the "signal" of any longer-term nutritional trends in the local ecology.

The capacity for fetal nutrition to minimize the growth response to short-term ecologic fluctuations is defined here as "intergenerational phenotypic inertia," which is hypothesized to allow the organism to cope with ecologic trends that are too gradual to be tracked by developmental plasticity, but too rapid to be tracked by natural selection operating on gene frequencies. The concept of phenotypic inertia has implications that extend beyond the study of human adaptation. Most notably, if traits like fetal growth are designed to develop in a fashion that minimizes the response to short-term ecologic fluctuations by integrating information across multiple generations, the most effective unit for public health intervention may not be the individual but the matriline.

ACKNOWLEDGMENTS

Emma Adam, Thomas McDade, Ivy Pike, and Elizabeth A. Quinn provided helpful comments on a previous draft of this article.

LITERATURE CITED

Adair L, Pollitt E. 1985. Outcome of maternal nutritional supplementation: a comprehensive review of the Bacon Chow study. Am J Clin Nutr 41:948–978.

Adair LS, Kuzawa CW, Borja J. 2001. Maternal energy stores and diet composition during pregnancy program adolescent blood pressure. Circulation 104: 1034–1039.

Alberman E, Filakti H, Williams S, Evans S, Emanuel I. 1991. Early influences on the secular change in adult height between the parents and children of the 1958 birth cohort. Ann Hum Biol 18:127–136.

Alberman E, Emanuel I, Filakti H, Evans SJ. 1992. The contrasting effects of parental birthweight and gestational age on the birthweight of offspring. Paediatr Perinat Epidemiol 6:134–144.

Allal N, Sear R, Prentice AM, Mace R. 2004. An evolutionary model of stature, age at first birth and reproductive success in Gambian women. Proc R Soc Lond B Biol Sci 271:465–470.

Arendt J. 1997. Adaptive intrinsic growth rates: an integration across taxa. Q Rev Biol 72:149–177.

Barker D. 1994. Mothers, babies, and disease in later life. London: BMJ Publishing.

Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. 1989. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. Br Med J 298:564–567.

Bateson P, Barker D, Clutton-Brock T, Deb D, D'Udine B, Foley RA, Gluckman P, Godfrey K, Kirkwood T, Lahr MM, et al. 2004. Developmental plasticity and human health. Nature 430:419–421.

Bedi KS, Birzgalis AR, Mahon M, Smart JL, Wareham AC. 1982. Early life undernutrition in rats. 1. Quantitative histology of skeletal muscles from underfed young and refed adult animals. Br J Nutr 47: 417–431.

Bogin B. 1999. Patterns of human growth. Cambridge, UK: Cambridge University Press.

Cahill G. 1976. Starvation in man. Clin Endocrin Metabol 5:397–415.

Cameron N, Demerath EW. 2002. Critical periods in human growth and their relationship to diseases of aging. Am J Phys Anthropol Suppl 35:159–184.

Ceesay SM, Prentice AM, Cole TJ, Foord F, Weaver LT, Poskitt EM, Whitehead RG. 1997. Effects on birthweight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. Br Med J 315:786–790.

Chandra RK. 1975. Antibody formation in first and second generation offspring of nutritionally deprived rats. Science 190:289–290.

Charnov E. 1993. Life history invariants: some explorations of symmetry in evolutionary ecology. Oxford: Oxford University Press.

Chen ST. 1990. Secular trend of growth in Malaysian children. J Singapore Paediatr Soc 32:102–107.

Cicognani A, Alessandroni R, Pasini A, Pirazzoli P, Cassio A, Barbieri E, Cacciari E. 2002. Low birth weight for gestational age and subsequent male gonadal function. J Pediatr 141:376–379.

Coe CL, Shirtcliff EA. 2004. Growth trajectory evident at birth affects age of first delivery in female monkeys. Pediatr Res 55:914–920.

Cole TJ. 2000. Secular trends in growth. Proc Nutr Soc 59:317–324.

Cresswell JL, Egger P, Fall CH, Osmond C, Fraser RB, Barker DJ. 1997. Is the age of menopause determined in-utero? Early Hum Dev 49:143–148.

Crowley D, Pomp D, Atchley W, Eisen E, Hawkins-Brown D. 1989. The impact of maternal uterine genotype on postnatal growth and adult body size in mice. Genetics 122:193–203.

Da Silva P, Aitken RP, Rhind SM, Racey PA, Wallace JM. 2001. Influence of placentally mediated fetal growth restriction on the onset of puberty in male and female lambs. Reproduction 122:375–383.

Dabelea D, Pettitt DJ. 2001. Intrauterine diabetic environment confers risks for type 2 diabetes mellitus and obesity in the offspring, in addition to genetic susceptibility. J Pediatr Endocrinol Metab 14:1085–1091.

Delemarre-van de Waal HA, van Coeverden SC, Engelbregt MT. 2002. Factors affecting onset of puberty. Horm Res 57(Suppl 2):15–18.

Dennison EM, Arden NK, Keen RW, Syddall H, Day IN, Spector TD, Cooper C. 2001. Birthweight, vitamin D receptor genotype and the programming of osteoporosis. Paediatr Perinat Epidemiol 15:211–219.

dos Santos Silva I, De Stavola BL, Hardy RJ, Kuh DJ, McCormack VA, Wadsworth ME. 2004. Is the association of birthweight with premenopausal breast cancer risk mediated through childhood growth? Br J Cancer 91:519–524.

Drake AJ, Walker BR. 2004. The intergenerational effects of fetal programming: non-genomic mechanisms for the inheritance of low birthweight and cardiovascular risk. J Endocrinol 180:1–16.

Dufour DL, Sauther ML. 2002. Comparative and evolutionary dimensions of the energetics of human pregnancy and lactation. Am J Hum Biol 14:584–602.

Ellison P. 2001. On fertile ground. A natural history of human reproduction. Cambridge, MA: Harvard University Press.

Ellison PT, Panter-Brick C, Lipson SF, O'Rourke MT. 1993. The ecological context of human ovarian function. Hum Reprod 8:2248–2258.

Emanuel I, Filakti H, Alberman E, Evans SJ. 1992. Intergenerational studies of human birthweight from the 1958 birth cohort. II. Do parents who were twins have babies as heavy as those born to singletons? Br J Obstet Gynaecol 99:836–840.

Emanuel I, Kimpo C, Moceri V. 2004. The association of maternal growth and socio-economic measures with infant birthweight in four ethnic groups. Int J Epidemiol Advance access published online on July 15, 2004, doi: 10.1093/ije/dyh269.

Engelbregt MJ, van Weissenbruch MM, Popp-Snijders C, Delemarre-van de Waal HA. 2002. Delayed first cycle in intrauterine growth-retarded and postnatally undernourished female rats: follicular growth and ovulation after stimulation with pregnant mare serum gonadotropin at first cycle. J Endocrinol 173:297–304.

Engelbregt MJ, van Weissenbruch MM, Lips P, van Lingen A, Roos JC, Delemarre-van de Waal HA. 2004. Body composition and bone measurements in intra-uterine growth retarded and early postnatally undernourished male and female rats at the age of 6 months: comparison with puberty. Bone 34:180–186.

Eriksson J, Lindi V, Uusitupa M, Forsen T, Laakso M, Osmond C, Barker D. 2003. The effects of the Pro12Ala polymorphism of the PPARgamma-2 gene on lipid metabolism interact with body size at birth. Clin Genet 64:366–370.

Eriksson M, Wallander MA, Krakau I, Wedel H, Svardsudd K. 2004. Birthweight and cardiovascular risk factors in a cohort followed until 80 years of age: the study of men born in 1913. J Intern Med 255: 236–246.

FAO/WHO/UNU. 1985. Report of joint expert consultation. Energy and protein requirements. WHO Technical Report Series No. 724. Geneva: WHO.

Fisher R. 1930. The genetical theory of natural selection. Oxford: Oxford University Press.

Fogel R. 1986. Physical growth as a measure of economic well-being of populations: the eighteenth and nineteenth centuries. In: Falkner F, Tanner J, editors. Human growth. A comprehensive treatise. New York: Plenum. p 263–281.

Fok TF, So HK, Wong E, Ng PC, Chang A, Lau J, Chow CB, Lee WH. 2003. Updated gestational age specific birthweight, crown-heel length, and head circumference of Chinese newborns. Arch Dis Child Fetal Neonatal Ed 88:F229–236.

Foley R. 1993. The influence of seasonality on hominid evolution. In: Ulijaszek S, Strickland S, editors. Seasonality and human ecology. Cambridge, UK: Cambridge University Press. p 17–37.

Frisancho A, Sanchez J, Pallardel D, Yanez L. 1973. Adaptive significance of small body size under poor socio-economic conditions in southern Peru. Am J Phys Anthropol 39:255–261.

Gadgil M, Bossert W. 1970. Life historical consequences of natural selection. Am Nat 104:1–24.

Galler JR, Zartarian G. 1981. Reproductive performance in rats with different histories of malnutrition. Br J Nutr 45:251–255.

Garrow JS, Pike MC. 1967. The long-term prognosis of severe infantile malnutrition. Lancet 1:1–4.

Getty T. 1996. The maintenance of phenotypic plasticity as a signal detection problem. Am Nat 148:378–385.

Gluckman PD. 1997. Endocrine and nutritional regulation of prenatal growth. Acta Paediatr Suppl 423: 153–157; discussion 158.

Gluckman PD, Hanson MA. 2004. Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. Pediatr Res 56:311–317.

Gould S, Lewontin R. 1979. The spandrels of San Marco and the Panglossian paradigm: a critique of the adaptationist programme. Proc R Soc Lond B 205:581–598.

Haig D. 1993. Genetic conflicts in human pregnancy. Q Rev Biol 68:495–532.

Hales C, Barker D. 1992. Type 2 (non-insulin dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 35:595–601.

Harvey P, Martin R, Clutton-Brock T. 1987. Life histories in comparative perspective. In: Smuts B, Cheney D, Seyfarth R, Wrangham R, editors. Primate societies. Chicago: University of Chicago Press. p 181–196.

Hawkes K. 2003. Grandmothers and the evolution of human longevity. Am J Hum Biol 15:380–400.

Hill K, Hurtado A. 1996. Ache life history: the ecology and demography of a foraging people. New York: Aldine De Gruyter.

Hill K, Kaplan H. 1999. Life history traits in humans: theory and empirical studies. Annu Rev Anthropol 28:397–430.

Hop le T. 2003. Secular trend in size at birth of Vietnamese newborns during the last 2 decades (1980–2000). Asia Pac J Clin Nutr 12:266–270.

Hypponen E. 2004. Paternal diabetes and offspring birthweight. Biomed Pharmacother 58:72.

Hypponen E, Power C, Smith GD. 2004. Parental growth at different life stages and offspring birthweight: an intergenerational cohort study. Paediatr Perinat Epidemiol 18:168–177.

Ibanez L, Potau N, de Zegher F. 2000. Ovarian hyporesponsiveness to follicle stimulating hormone in adolescent girls born small for gestational age. J Clin Endocrinol Metab 85:2624–2626.

IJzerman R, Stehouwer C, Geus Ed, Weissenbruch Mv, Waal HD-vd, Boomsma D. 2003. Low birthweight is associated with increased sympathetic activity: dependence on genetic factors. Circulation 108:566–571.

Institute of Medicine. 1990. Nutrition during pregnancy. Part I. Weight gain. Washington, DC: National Academy Press.

Jablonka E, Lamb M. 1995. Epigenetic inheritance and evolution. The Lamarckian dimension. Oxford: Oxford University Press.

Jablonka E, Oborny B, Molnar I, Kisdi E, Hofbauer J, Czaran T. 1995. The adaptive advantage of phenotypic memory in changing environments. Philos Trans R Soc Lond B Biol Sci 350:133–141.

Janson C, Schaik CV. 1993. Ecological risk aversion in juvenile primates: slow and steady wins the race. In: Pereira M, Fairbanks L, editors. Juvenile primates: life history, development, and behavior. New York: Oxford University Press. p 57–74.

Kind KL, Clifton PM, Katsman AI, Tsiounis M, Robinson JS, Owens JA. 1999. Restricted fetal growth and the response to dietary cholesterol in the guinea pig. Am J Physiol 277:R1675–1682.

Kind KL, Simonetta G, Clifton PM, Robinson JS, Owens JA. 2002. Effect of maternal feed restriction on blood pressure in the adult guinea pig. Exp Physiol 87: 469–477.

Kind KL, Clifton PM, Grant PA, Owens PC, Sohlstrom A, Roberts CT, Robinson JS, Owens JA. 2003. Effect of maternal feed restriction during pregnancy on glucose tolerance in the adult guinea pig. Am J Physiol Regul Integr Comp Physiol 284:R140–152.

Klebanoff MA, Yip R. 1987. Influence of maternal birth weight on rate of fetal growth and duration of gestation. J Pediatr 111:287–292.

Koziel S, Jankowska EA. 2002. Effect of low versus normal birthweight on menarche in 14-year-old Polish girls. J Paediatr Child Health 38:268–271.

Kramer MS. 2000. Balanced protein/energy supplementation in pregnancy. Cochrane Database Syst Rev(@):CD000032.
Kuh D, Wadsworth M. 1989. Parental height: childhood environment and subsequent adult height in a national birth cohort. Int J Epidemiol 18:663–668.
Kuzawa CW. 1998. Adipose tissue in human infancy and childhood: an evolutionary perspective. Yrbk Phys Anthropol 27:177–209.
Kuzawa CW. 2004. Modeling fetal adaptation to nutrient restriction: testing the fetal origins hypothesis with a supply-demand model. J Nutr 134:194–200.
Kuzawa CW, Adair LS. 2003. Lipid profiles in adolescent Filipinos: relation to birth weight and maternal energy status during pregnancy. Am J Clin Nutr 77:960–966.
Kuzawa CW, Adair LS. 2004. A supply-demand model of fetal energy sufficiency predicts lipid profiles in male but not female Filipino adolescents. Eur J Clin Nutr 58:438–448.
Lahdenpera M, Lummaa V, Helle S, Tremblay M, Russell AF. 2004. Fitness benefits of prolonged post-reproductive lifespan in women. Nature 428: 178–181.
Lang U, Baker RS, Braems G, Zygmunt M, Kunzel W, Clark KE. 2003. Uterine blood flow—a determinant of fetal growth. Eur J Obstet Gynecol Reprod Biol 110 Suppl 1:S55–61.
Lasker G. 1969. Human biological adaptability: the ecological approach in physical anthropology. Science 166:1480–1486.
Lechtig A, Martorell R, Delgado H, Yarbrough C, Klein RE. 1978. Food supplementation during pregnancy, maternal anthropometry and birthweight in a Guatemalan rural population. J Trop Pediatr Environ Child Health 24:217–222.
Lee RD. 2003. Rethinking the evolutionary theory of aging: transfers, not births, shape senescence in social species. Proc Natl Acad Sci USA 100:9637–9642.
Levins R. 1968. Evolution in changing environments. Princeton, NJ: Princeton University Press.
Lewontin R. 1970. The units of selection. Annu Rev Ecol System 1:1–18.
Li H, Stein AD, Barnhart HX, Ramakrishnan U, Martorell R. 2003. Associations between prenatal and postnatal growth and adult body size and composition. Am J Clin Nutr 77:1498–1505.
Lienhardt A, Carel JC, Preux PM, Coutant R, Chaussain JL. 2002. Amplitude of pubertal growth in short stature children with intrauterine growth retardation. Horm Res 57(Suppl 2):88–94.
Lummaa V. 2003. Early developmental conditions and reproductive success in humans: downstream effects of prenatal famine, birthweight, and timing of birth. Am J Hum Biol 15:370–379.
Martin RM, Smith GD, Frankel S, Gunnell D. 2004. Parents' growth in childhood and the birthweight of their offspring. Epidemiology 15:308–316.
Martorell R. 1989. Body size, adaptation and function. Hum Organ 48:15–20.
McCance RA, Widdowson EM. 1974. The determinants of growth and form. Proc R Soc Lond B Biol Sci 185: 1–17.
McDade TW, Beck MA, Kuzawa C, Adair LS. 2001. Prenatal undernutrition, postnatal environments, and antibody response to vaccination in adolescence. Am J Clin Nutr 74:543–548.
Mellemkjaer L, Olsen ML, Sorensen HT, Thulstrup AM, Olsen J, Olsen JH. 2003. Birthweight and risk of early-onset breast cancer (Denmark). Cancer Causes Control 14:61–64.
Moore SE, Cole TJ, Poskitt EM, Sonko BJ, Whitehead RG, McGregor IA, Prentice AM. 1997. Season of birth predicts mortality in rural Gambia. Nature 388:434.
Mora J, deParedes B, Wagner M, deNavarro L, Suescun J, Christiansen N, Herrera M. 1979. Nutritional supplementation and the outcome of pregnancy. I. Birth weight. Am J Clin Nutr 32:455–462.
Mousseau T, Fox C. 1998. Maternal effects as adaptations. New York: Oxford University Press.
Newsome CA, Shiell AW, Fall CH, Phillips DI, Shier R, Law CM. 2003. Is birthweight related to later glucose and insulin metabolism? A systematic review. Diabet Med 20:339–348.
Ounsted M, Ounsted C. 1968. Rate of intra-uterine growth. Nature 220:599–600.
Ounsted M, Scott A, Ounsted C. 1986. Transmission through the female line of a mechanism constraining human fetal growth. Ann Hum Biol 13:143–151.
Paltiel O, Harlap S, Deutsch L, Knaanie A, Massalha S, Tiram E, Barchana M, Friedlander Y. 2004. Birth weight and other risk factors for acute leukemia in the Jerusalem Perinatal Study cohort. Cancer Epidemiol Biomarkers Prev 13:1057–1064.
Potts R. 1996a. Humanity's descent. The consequences of ecological instability. New York: William Morrow.
Potts R. 1996b. Evolution and climate variability. Science 273:922.
Potts R. 1998. Environmental hypotheses of hominin evolution. Am J Phys Anthropol Suppl 27:93–136.
Prader A, Tanner JM, von HG. 1963. Catch-up growth following illness or starvation. An example of developmental canalization in man. J Pediatr 62:646–659.
Prentice AM, Goldberg GR. 2000. Energy adaptations in human pregnancy: limits and long-term consequences. Am J Clin Nutr 71:1226S–1232S.
Price KC, Coe CL. 2000. Maternal constraint on fetal growth patterns in the rhesus monkey (*Macaca mulatta)*: the intergenerational link between mothers and daughters. Hum Reprod 15:452–457.
Price KC, Hyde JS, Coe CL. 1999. Matrilineal transmission of birthweight in the rhesus monkey (Macaca mulatta) across several generations. Obstet Gynecol 94:128–134.
Ramakrishnan U, Martorell R, Schroeder DG, Flores R. 1999. Role of intergenerational effects on linear growth. J Nutr 129:544S–549S.
Reik W, Constancia M, Fowden A, Anderson N, Dean W, Ferguson-Smith A, Tycko B, Sibley C. 2003. Regulation of supply and demand for maternal nutrients in mammals by imprinted genes. J Physiol 547:35–44.
Sanderson M, Emanuel I, Holt VL. 1995. The intergenerational relationship between mother's birthweight, infant birthweight and infant mortality in black and white mothers. Paediatr Perinat Epidemiol 9:391–405.
Scrimshaw NS, B'Ehar M. 1965. Malnutrition in underdeveloped countries. N Engl J Med 272:193–198.
Seckl JR. 2001. Glucocorticoid programming of the fetus; adult phenotypes and molecular mechanisms. Mol Cell Endocrinol 185:61–71.
Stearns SC. 1992. The evolution of life histories. Oxford: Oxford University Press.
Stearns S, Koella J. 1986. The evolution of phenotypic plasticity in life-history traits: predictions of reaction norms for age and size at maturity. Q Rev Biol 40:893–913.
Stein AD, Lumey LH. 2000. The relationship between maternal and offspring birth weights after maternal prenatal famine exposure: the Dutch Famine Birth Cohort Study. Hum Biol 72:641–654.
Stein AD, Barnhart HX, Hickey M, Ramakrishnan U, Schroeder DG, Martorell R. 2003. Prospective study of protein-energy supplementation early in life and of

growth in the subsequent generation in Guatemala. Am J Clin Nutr 78:162–167.
Stein AD, Barnhart HX, Wang M, Hoshen MB, Ologoudou K, Ramakrishnan U, Grajeda R, Ramirez-Zea M, Martorell R. 2004. Comparison of linear growth patterns in the first three years of life across two generations in Guatemala. Pediatrics 113:e270–275.
Strauss RS, Dietz WH. 1997. Effects of intrauterine growth retardation in premature infants on early childhood growth. J Pediatr 130:95–102.
Wade GN, Schneider JE. 1992. Metabolic fuels and reproduction in female mammals. Neurosci Biobehav Rev 16:235–272.
Waterland RA, Jirtle RL. 2004. Early nutrition, epigenetic changes at transposons and imprinted genes, and enhanced susceptibility to adult chronic diseases. Nutrition 20:63–68.
Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. 2004. Epigenetic programming by maternal behavior. Nat Neurosci 7:847–854.
Wells JC. 2003. The thrifty phenotype hypothesis: thrifty offspring or thrifty mother? J Theor Biol 221: 143–161.
Williams GC. 1966. Adaptation and natural selection. Princeton, NJ: Princeton University Press.