CHAPTER 18

The Developmental Origins of Adult Health

Intergenerational Inertia in Adaptation and Disease

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Lower weight babies end up as smaller adults with reduced muscle mass and changes in metabolism, making them more prone to developing diabetes and cardiovascular disease. In this chapter Kuzawa illustrates how a woman's nutritional status at conception can serve as an important cue for the developmental direction of the fetus. Perhaps even more interesting is that the early nutritional stress encountered by a fetus is useful for predicting the likely health status of the same individual much later in life. Kuzawa proposes a possible answer to one of the most important questions confronting initiatives aimed at improving global health: Why is it that "transitioning" populations have elevated cardiovascular disease when they experience much lower average intakes of fat, traditionally have low blood pressure, and experience much less populationwide obesity than is characteristic of industrialized nations?

EVOLUTIONARY MEDICINE AND THE RISE OF CARDIOVASCULAR DISEASES

More people die from heart attacks and stroke than from any other cause (MacKay et al., 2004). This global statistic is unsettling, but it is also rather remarkable considering that cardiovascular diseases (CVDs) were a minor contributor to human suffering and mortality until recent history. There are good reasons to suspect that our ancestors were not afflicted with CVDs during most of human evolution, and that several recent changes have contributed to their emergence as important health problems. The first and most straightforward is that many of us are now living longer than our ancestors likely did and, as a result, are more prone to chronic degenerative diseases that only afflict individuals

lucky enough to reach old age (Omran, 1971). The second includes the changes in lifestyle, behavior, and diet that have swept across the globe in recent generations to radically transform the environments that we confront in our daily lives. The classic biomedical model views CVD as the cumulative result of unhealthy lifestyle practices that interact with the specific genetic susceptibilities that we inherited from our parents at conception.

From an evolutionary perspective, the rapid emergence of chronic diseases like CVD has been explained as a result of the fact that cultural practices like diet may change at a pace that is far more rapid than can be accommodated by the gradual process of adaptive evolution operating on gene frequencies (Neel, 1962). With respect to human diet and energy balance, our ancestors subsisted for millions of years as small bands of highly active foragers who rarely had access to concentrated sources of carbohydrates, fats, or salt. As a species, our metabolism and the human body's "expectations" for nutrients were sculpted during this long era of high physical activity and balanced dietary intake, and there has been little opportunity for natural selection to modify our genetic constitution to match the changed realities of contemporary human ecologies. The resultant "mismatch" between our "Paleolithic" genome and our changing way of life is assumed to help explain conditions like obesity, diabetes, and hypertension, and, through these, the now global epidemic of CVD (Eaton & Konner, 1985).

Is a Gene–Environment Model Sufficient to Explain the Current Global CVD Epidemic?

Although this concept of gene–environment mismatch is intuitively appealing, there are reasons to question whether "genes" and "environments" are the only factors influencing the development of conditions like CVD, and thus, whether an amendment to the model might be due. This interpretation is supported by the aforementioned status of CVD as a cause of mortality. The current global CVD epidemic is occurring very rapidly in societies that were scarcely afflicted by it a mere generation or two ago (MacKay et al., 2004). Although it is expectable that disease patterns will shift as life expectancy improves and lifestyles change, there are differences in the disease experiences of these populations compared to the prior experiences of populations that went through a similar but more gradual transition in places like western Europe and the United States. Many currently transitioning populations have an elevated risk for CVD at lower levels of exposure to unhealthy lifestyle or environmental factors (Colin Bell et al., 2002). In the Philippines, for instance, adolescents have high levels of cholesterol in the absence of obesity or high intakes of dietary fat (Kuzawa et al., 2003), while the increase in blood pressure that accompanies weight gain is also more severe, leading to higher risk of hypertension at any given level of body mass index (Colin Bell et al., 2002; Deurenberg-Yap et al., 2002; Lear et al., 2003). A pattern of high CVD susceptibility and CVD risk factor clustering has been documented among such diverse groups as Brazilians (Sawaya et al., 1998), Venezuelans (Molero-Conejo et al., 2003), Native Americans (Benyshek et al., 2001), Australian Aboriginals (Gault et al., 1996), and Indians (Yajnik, 2004), to name only a few.

If CVD is a simple product of a mismatch between our evolved genome and our current lifestyle, how do we make sense of these heterogeneities in the global experience of disease change? One possibility is that these recently transitioning populations have

genes that make them respond more adversely to lifestyle change. Although this would be in keeping with the general framework of the gene–environment mismatch model, it seems quite unlikely that populations as unrelated as Indians, Filipinos, and Native Americans should share high frequencies of high-risk genes that are not shared by populations that experienced these transitions several generations prior. Similar patterns of high disease susceptibility in genetically unrelated populations point to the need for an alternate explanation for these differences in CVD risk.

Refining the Model: The Developmental Origins of Health and Disease (DOHaD)

Insights into this problem are coming from a rapidly growing new area of medical research. Starting in the late 1980s, David Barker and his colleagues at Southampton University in Britain published a series of papers showing that the risk of dying from CVD, or of suffering from conditions that precede CVD like hypertension or diabetes, is higher among individuals who were born small (Barker et al., 1989, 1994). Although earlier studies had found evidence for similar relationships between deprivation during childhood and subsequent adult mortality rates (Forsdahl 1977; Kermack et al., 1934), Barker and his colleagues were the first to link these associations to a biological marker—birth weight—that hinted at possible mechanisms to account for them. Building from the assumption that a baby born small had been a poorly nourished fetus, they proposed that these relationships were the byproduct of adjustments made by the fetus in responseto a compromised intrauterine nutritional environment. They reasoned that a fetus faced with undernutrition would be forced to adapt to this stress. It would slow its growth rate as a strategy to reduce nutritional requirements, but might also change its metabolism and physiology in such a way that would linger into adulthood to influence the risk of developing chronic disease. These permanent alterations to an organism's metabolism, physiology, or organ structure in response to early environments have been described as developmental "programming" (Lucas 1991), and more recently, "induction" (Bateson, 2001).

The hypothesis that adult risk for CVD could be programmed by prenatal nutrition was initially greeted with skepticism (Kramer & Joseph, 1996; Paneth et al., 1996). Most of the early studies documenting these relationships merely linked death records or adult health characteristics with birth weight data that had been recorded many decades earlier in birth records. This allowed an evaluation of relationships between birth weight and adult health or mortality, but largely ignored other aspects of lifestyle or environment that could influence the development of cardiovascular risk between birth and the onset of adult disease. This left open the possibility that birth weight was merely serving as a marker for other unmeasured factors that are known to influence CVD risk. For instance, small babies are born into lower income households, and perhaps birth weight was merely an indirect measure of class or socioeconomic status.

There have now been hundreds of human studies documenting similar relationships, many of which incorporate longitudinal data on a wider range of lifestyle and environmental influences that might confound associations with birth size. Small birth size relates to an elevated risk of developing hypertension (reviewed by Adair and Dahly, 2005), insulin resistance and diabetes (Eriksson et al., 2002; Yajnik, 2004), abnormal

cholesterol profiles (Kuzawa & Adair, 2003), an abdominal or visceral pattern of fat deposition (Oken & Gillman, 2003), and an elevated risk of suffering CVD and cardiovascular mortality (Leon et al., 1998). Although birth weight is an admittedly crude measure of intrauterine nutrition, animal model studies now number in the hundreds as well and show that restricting the nutritional intake of pregnant rats or sheep has similar adverse effects on blood pressure, insulin resistance, and cholesterol levels of adult offspring (reviewed by Langley-Evans et al., 2003; McMillen & Robinson, 2005; Seckl & Meaney, 2004).

Although programming of fetal biology has received most research attention, developmental responses continue to be important during infancy and childhood. For instance, small size in infancy is also associated with higher CVD risk in adulthood, while breastfed infants have lower rates of hypertension (Lawlor et al., 2005), obesity, and diabetes as adults (Arenz et al., 2004). There is also evidence that prenatal and postnatal exposures interact to influence adult health. Being born small but then experiencing rapid "catch-up" growth after birth, itself suggestive of an improvement in nutrition, predicts the same constellation of adult diseases (Adair & Cole, 2003; Ong, 2006). Small birth size is particularly deleterious among individuals who put on more weight or body fat later in life, which is associated with high CVD risk (Oken & Gillman, 2003). In Cebu City, the Philippines, individuals from higher income households eat more fat, have lower levels of physical activity, and have more body fat (Kuzawa et al., 2003). Although still relatively lean by U.S. standards, higher income adolescents in this population have higher

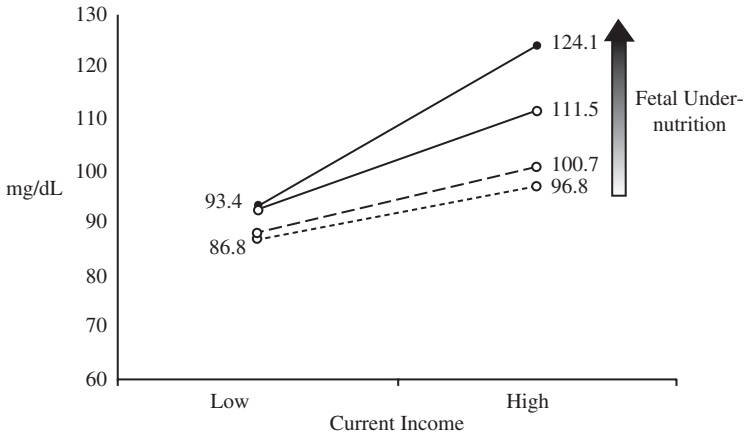

FIGURE 18-1 Low-density lipoprotein cholesterol by current household income among Cebu males, and stratified by different criteria of prenatal undernutrition (after Kuzawa, 2001). The lowest (dotted) line represents the entire male sample, while the second (dashed) line is limited to males with lower than average birth weights (<3 kg). The third and fourth lines use maternal characteristics to further restrict the lower-birth-weight subsample to individuals who likely ended up small as a result of fetal growth restriction. Line 3 (solid line, hollow dots) represents lower-birth-weight individuals born to taller-than-average mothers, while the top line (solid line, solid dots) further restricts this subgroup to the offspring of tall mothers with poor nutritional status, as indicated by triceps skinfold during pregnancy.

levels of low-density lipoprotein (LDL) cholesterol ("bad cholesterol"). What is intriguing is that the effect of living in a higher income household on LDL cholesterol differs among individuals who vary in fetal nutritional sufficiency (Figure 18-1). In these relatively lean adolescent Filipinos, the combination of fetal undernutrition followed by relative affluence after birth is associated with highest cholesterol levels (Kuzawa, 2001).

EVOLUTIONARY APPROACHES TO THE DOHaD LITERATURE

Although seemingly paradoxical, the finding that early life *undernutrition* may heighten the disease impact of *overnutrition* experienced later in the life cycle just might make sense if the fetus is calibrating its nutritional requirements on the basis of its prenatal experiences. Building from this idea, Hales and Barker (1992) proposed that adult risk of diabetes might trace to developmental adaptations made in response to prenatal undernutrition. They cited evidence that the nutritionally stressed fetus is forced to reduce the growth of nonessential organs like muscle or liver, while also inducing changes in insulin metabolism, in part to protect the large and glucose-demanding brain. According to their hypothesis, the resultant "thrifty phenotype" helps the fetus survive a difficult pregnancy, but later predisposes that individual to diabetes and CVD when faced with adequate or abundant postnatal nutrition and weight gain.

More recently, researchers have hypothesized that the adjustments made by the fetus may be designed to do more than merely help it survive gestation, but could also help improve its fit with the postnatal world (Bateson, 2001; Bateson et al., 2004; Gluckman & Hanson, 2005; Kuzawa, 2001, 2005; Wells, 2003). To the extent that prenatal exposures like nutrition or hormone levels are a response by the mother to the external ecology, these resources may act as cues, providing the fetus with opportunities to fine-tune its biology to better match the realities of the world that it will be born into. In one recent formalization of this idea, Gluckman and Hanson (2004a) propose that the adjustments made *in utero* are an example of a *predictive adaptive response* (PAR) "... made during the phase of developmental plasticity to optimize the phenotype for the probable environment of the mature organism" (p. 1735). According to these newer proposals, a rapid pace of environmental change within a single lifetime might lead to a new form of mismatch—not between our environment and our Paleolithic genome, but between *postnatal* environments and a biological imprint established in response to a *prenatal* cue signaling a marginal future nutritional ecology (Gluckman & Hanson, 2005; Wells, 2003). Like the biological equivalent of the linguistic accent that we learn as young children, this imprint could serve us well if we stay in place and the ecology remains stable, but might lead to a form of developmentally based mismatch, heightening risk for CVD, when individuals experience a brisk pace of nutritional or lifestyle change within their lifetimes.

If this model of developmental adaptation is correct, the pace and magnitude of recent change in nutrition or lifestyle may be an important influence on a population's pattern of disease risk, in addition to the more widely acknowledged role of genetic background and lifestyle. This might help explain the heterogeneity of disease risk observed across populations and between ethnic groups within nations. But just how plausible is this idea

of developmental prediction? Are there comparable examples from other species, and, if so, what similarities and differences are there between them and the types of responses that we see in humans? And perhaps most importantly, does the human fetus have access to an ecological cue of sufficient reliability to allow it to predict the nutritional ecology that it is likely to confront decades after birth?

In this chapter I review examples of predictive developmental plasticity in other species as a basis for critically evaluating the plausibility that a similar process is at work in humans. As will be discussed, some mammals have evolved elaborate strategies that allow true "forward-looking" prediction based upon intrauterine cues. Humans, in contrast, have few options but to rely upon a form of "backward-looking" prediction based upon a signal reflecting the past nutritional experiences of recent ancestors. This capacity to anchor nutritional expectations to past experiences allows the fetus to calibrate its developmental biology to typical local conditions, but can heighten risk for diseases related to metabolism, such as CVD, when the ecology changes rapidly within a single generation. A developmental approach to CVD reveals that the lingering biological imprint of the past is not limited to our "Paleolithic" genome. Instead, there are multiple potential causes of biological mismatch that trace to different mechanisms of inheritance, each designed to cope with ecological change operating on different temporal scales (Kuzawa et al., 2007).

PREDICTIVE DEVELOPMENTAL PLASTICITY

Predictive Developmental Plasticity: Lessons from Amphibians

Developmental plasticity refers to the ability of a gene or genome to produce a range of different phenotypes[1] in response to the environmental conditions that an individual experiences during development (West-Eberhard, 2003). Because plasticity is a process of altered development, it is generally not reversible and is often sensitive to conditions experienced early in the life cycle. The differences in behavior or biology of identical twins reared apart attest to the power of plasticity (Heller et al., 1993). Many European nations witnessed a decline in menarcheal age from around 17 to 13 years in little more than a century, which is far too rapid to be due to changes in the genetic composition of these populations (Tanner 1962). Instead, this secular trend may be traced to the effects of improvements in hygiene and nutritional status on plasticity in growth rate and maturational timing (Eveleth & Tanner 1990).

Although not all plasticity is beneficial to the organism, the animal kingdom is filled with examples of species that have evolved an adaptive capacity to modify development in response to ecological characteristics that vary across the species' home range or that vary from generation to generation (West-Eberhard, 2003). The western spadefoot toad (*Scaphiopus hammondii*) provides a particularly interesting and relevant example. The spadefoot inhabits dry grasslands in areas like eastern California. Given the aridity of its ecology, the adult spadefoot spends much of the year in damp underground burrows, only to emerge after a heavy downpour to lay its eggs in one of the newly formed pools. Although this is a safe strategy for an amphibian living in an arid ecology, the ponds are temporary and have an unpredictable life, making it impossible to know in advance the

amount of time available for the tadpoles to complete their growth. This lack of predictability does not leave the tadpole without recourse, because there are certain cues that are correlated with the pond's rate of drying, which the tadpole senses and uses to calibrate its pace of maturation. The spadefoot has evolved a remarkable capacity to shift the timing of metamorphosis from aquatic tadpole to terrestrial adult to match the life of its pond (Denver, 1999).

Research into the hormonal control of this developmental plasticity led to a finding that is as surprising as it is fascinating (reviewed in Crespi & Denver, 2005). A tadpole that senses that its pond is drying speeds up the timing of the developmental transition into the adult stage by producing a peptide called corticotropin-releasing factor (CRF). In amphibians, as in mammals, CRF (also called CRH) is a key regulatory molecule for the stress hormone system. This same peptide is produced by the fetuses of certain mammalian species, including humans, and it is believed to help initiate parturition early in the event of a difficult pregnancy (Challis et al., 2005). Thus, CRF and the stress hormone axis modulate the timing of key developmental transitions in response to ecological signals in these distantly related species, acting like a larval escape signal in each— in the case of the tadpole initiating early morphogenesis and exit from the pond, and in the human fetus speeding up the transition from intrauterine to extrauterine life (Denver, 1999).

What should we make of this odd parallel between the developmental biology of toads and humans? It is a fundamental principle of evolutionary biology that when a complex structure or trait is found in two species, it was very likely already present in their last common ancestor.[2] Considering the toad and human, our last common ancestor very likely had four legs and reproduced sexually. It was also bilaterally symmetrical, had two eyes, one mouth, and a gastrointestinal tract. Such patterns of "homology" are one basis for inferring that all living species share common ancestors if we go back far enough in evolutionary time. Research on developmental plasticity in the spadefoot helps extend the concept of homology to the hormonal architecture that regulates how bodies develop, including in this case the capacity to adjust the timing of key life history transitions in response to stressful challenges. Mammals evolved from early reptile-like amniotes that split from amphibians more than 300 million years ago (Carroll, 1997). Because the CRF peptide and the stress hormone system are present in humans and toads, this implies that this system has been around for at least that many years, and that some of the basic components that regulate its effects on the developing organism have been conserved since then.

In light of these similarities, it seems likely that the CRF–stress hormone system present in the human fetus is built from a template that was already present in rough outline among ancient amphibians. It likely evolved a capacity to respond to developmental cues that were directly experienced by the embryo in the outside world, not unlike the functioning of the system in the modern spadefoot tadpole. With the eventual evolution of internal fertilization in placental mammals, the embryonic environment shifted inside the mother's body. This allowed the mother to buffer the embryo by maintaining a constant temperature and by mobilizing nutritional stores to offset deficits when dietary intake is scarce. But it also created new channels for the mother to communicate ecological information to the fetus—through stimulation of systems like CRF and the stress hormone axis, but by no means limited to this. As a type of sensory modality, the information

conveyed in the various nutrients and hormones crossing the placenta allow the mammalian fetus to monitor and track many features of the future environment into which it will be born and live out its life. And importantly, because this signal is communicated by the mother via the placenta, this opens up opportunities for natural selection to modify the information that the signal encodes and, as will be discussed, to enhance its reliability as a cue.

Research on the developmental origins of health and disease has documented detailed examples of fetal biological systems that are influenced by maternal nutritional or hormonal cues, and it was proposed above that a form of predictive signaling could go some way towards explaining the differences in how populations are experiencing the burden of CVD as nutrition and lifestyle change across the globe. Might these responses to prenatal nutrition also be part of a broader strategy of plasticity allowing the human fetus to shift its adaptive priorities dynamically in anticipation of the outside world? Given that most human research on early life developmental plasticity focuses on outcomes like cholesterol levels or diabetes, it is rarely certain whether these human responses might be part of a developmental strategy that initially evolved to help the organism predict and adapt to postnatal life. These traits may have great significance for human health, but their functional role or adaptive importance is more ambiguous and thus difficult to interpret. Luckily, there are clear examples of other mammals that have evolved adaptive capacities to predict their future ecology in response to prenatal cues, providing a useful starting point for considering the possible function of the responses documented in humans.

Predictive Intergenerational Signaling in Mammals: The Montane Vole

Some of the best examples of intergenerational signaling in mammals come from rodent populations that inhabit highly seasonal environments in places like Siberia and the intermountain west of North America. Here I borrow from the work of my colleague at Northwestern, Terry Horton (Horton, 1984). Starting in the early 1980s, Horton and her colleagues, then at the University of Utah, helped pioneer the study of predictive developmental responses in mammals, working with the Montane vole (*Microtus montanus*) (Negus & Berger, 1987; Negus et al., 1992). This species provides fascinating insights into the strategies of intergenerational signaling that mammals have evolved to help them adapt to dynamic environments.

Given their short life spans of 1 year or less, and the even shorter length of the breeding season, these rodents have one chance to reproduce and are forced to adopt one of several developmental strategies depending on when in the yearly cycle they are born (Negus & Berger, 1987). Individuals born in the spring enjoy a period of increasing day length and food availability. Given this, the best strategy for an animal born in the spring is to grow rapidly and mature at a young age, which allows it to reproduce during the height of the summer breeding season. This is an effective strategy, but the offspring of these matings are then born later in the same year, and thus during a very different stage in the seasonal progression—a period that will soon shift into autumn and a severe and protracted winter. If the offspring attempted to breed this late in the year, their own offspring would be too small to survive the extended winter and would die. For these later-born individuals, it thus makes sense to grow to a body size adequate to survive winter, while delaying reproduction until the following spring.

This extreme plasticity in development is an ingenious strategy. However, what is particularly fascinating about it is that an individual vole has already started to set its developmental trajectory *before birth* (Figure 18-2), before it has had a chance to experience the seasons for itself (Horton, 1984). Work by Horton and others has shown that these developmental responses are in part dependent upon the mother having an intact pineal gland, and that these predictive developmental responses in offspring may be manipulated by injecting her with the hormone melatonin during pregnancy (reviewed in Goldman, 2003). Endogenous production of melatonin by the pineal gland is regulated by the body's biological pacemaker and is acutely suppressed by sunlight, resulting in circadian dynamics in circulating melatonin that mirror cycles of light and dark. The body uses the diurnal changes in melatonin to entrain biological rhythms such as the sleep/wake cycle to the daily cycle of light and dark. It has the same effect in the vole mother, but it also crosses her placenta, providing the vole fetus with this information as well. If after birth the offspring senses increasing day length—as mirrored in the *change* in the circadian dynamics of melatonin relative to what was sensed *in utero*—it infers that it has been born early in the year, while a decrease in day length signals that birth has occurred later in summer or fall. By monitoring changes in melatonin across late gestation and the period of lactation, the offspring is able to sense the current position in the seasonal cycle, allowing it to set its long-term developmental and reproductive strategy in a predictive fashion.

This is not the end of the predictive challenge faced by the young vole, because the spring melt and the onset of new plant growth may shift by 6 weeks or more from year to year, which is a very long time for a species that matures as early as 4–6 weeks of age

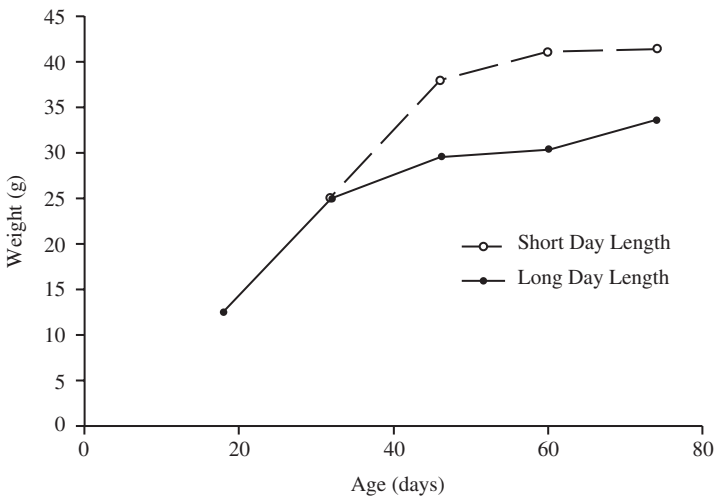

FIGURE 18-2 Postweaning growth trajectories of voles whose mothers were exposed to short (8 hours) or long (16 hours) day length during pregnancy. Postweaning photoperiod was 14 hours after weaning for all groups. To determine what season they are born in, voles monitor the change in photoperiod between gestation (via maternal melatonin) and weaning to determine whether day length is increasing or decreasing. (Adapted from Horton, 1984.)

(Negus et al., 1992). Given that the vole has a single opportunity to reproduce, it must fine-tune the timing of reproductive maturity with greater precision than it could achieve using photoperiod alone as a cue. It manages this with the aid of a second cue conveyed by the mother across the placenta. In addition to the transmission of photoperiod cues, a chemical produced in abundance by grasses during their early spring growth also passes across the placenta, providing the fetus with information about the vole's primary food resource. The presence of this metabolite in the maternal diet during pregnancy has the effect of speeding the pace of postnatal growth and reproductive maturation in offspring (Berger & Negus, 1992; Epstein et al., 1986; Frandson et al., 1993). Thus, the fetus uses information on prenatal and postnatal photoperiod to sense its position in the seasonal cycle, while additional cues from the diet provide finer-grained information on the more variable timing of plant growth during its particular year of birth.

This elaborate system of intergenerational communication has helped this short-lived species, and others with similar life histories, to thrive in challenging environments marked by extreme seasonal shifts in temperature, day length, and food availability, which are compounded by year-to-year variation in the onset of important ecological events. Similar systems of maternal–fetal signaling have been documented in other high-latitude short-lived species, including the Siberian or Djungarian hamster (*Phodopus sungorus*) (Weaver & Reppert, 1986) and the meadow vole (Lee et al., 1989).

THE FUNCTION OF DEVELOPMENTAL RESPONSES TO FETAL NUTRITION IN HUMANS

The ecology and life history of the Montane vole make this species a perfect candidate for the evolution of predictive developmental plasticity based upon maternal–fetal signaling. There are enormous shifts in ecology during the year that are regular and therefore predictable. Because this cycle is both severe and long relative to an individual vole's life expectancy, when one enters it places important constraints on that individual's possible developmental and reproductive strategies. What's more, the mother's body produces a hormone that not only signals current position within the seasonal cycle with high reliability, but also passes across the placenta to a fetus already endowed with receptors capable of sensing it. Her ingestion of certain plant metabolites is tightly correlated with the onset of spring vegetative growth, providing additional information on the availability of plant resources. Given this convergence of conditions, it is almost unthinkable that this species would *not* have evolved a capacity to fine-tune postnatal life history in response to maternal cues.

The response of the human fetus to prenatal nutrition clearly *is* an example of developmental plasticity. Less certain is whether this response is *adaptive*, implying that it evolved by natural selection to help the organism survive or reproduce. Did some of the long-term effects that fetal undernutrition have on human metabolism and physiology evolve to improve the developing organism's fit with the postnatal environment, akin to what we see in the vole and its predictive developmental plasticity? Several conditions must be met for this type of strategy to have evolved. First and most obviously, there must have been ecological variability—an ability to adjust to postnatal ecology is of no use if the ecology does not vary. This assumption seems reasonable. As generalists, humans are

not tied to narrow niches, latitudes, or climatic zones, and thus inhabit ecologies that vary in both the quantity and consistency of resource availability. The paleoclimate record shows that climate change compounded this challenge of coping with ecological variability. In contrast to the highly unusual climate stability of the past 10,000 years, the preceding millions of years were marked by chaotic shifts that led to locally rapid ecological change (reviewed by Roy et al., 1996; Potts, 1998). Data from pollen cores, ocean sediments and glacial cores show that there were large and unpredictable climate shifts that occurred on the scale of centuries and even decades. Although natural selection operating on gene frequencies can adjust a population to changing conditions, this process is slow in comparison to these shifts. Thus, our ancestors would have required more rapid modes of biological adaptation to cope with this ecological variability (Potts, 1998).

In light of this challenge, having an ability to predict the present state of the environment might provide the human fetus with certain advantages. The human and animal model literatures show that prenatal nutrition influences postnatal traits like blood pressure, glucose metabolism, and lipid metabolism. Although researchers focus on these outcomes for their obvious health significance, changes in these and other systems might also be necessary to support a shift in the organism's energetic priorities (Figure 18-3), and, thus, might be viewed as components of an adaptive response to early environments. Although speculative, there are reasons to interpret the available data in this light (see Kuzawa, 2005). For instance, lower-birth-weight individuals end up smaller as adults and have reduced muscle mass (Kensara et al., 2005; Singhal et al., 2003). The number of muscle fibers present at birth is responsive to the nutritional milieu *in utero*, which helps determine lean mass and strength throughout life (Zhu et al., 2006). Although this reduction in insulin-sensitive tissue increases risk of diabetes, from an ecological perspective smaller bodies with less metabolically active tissue have reduced nutritional requirements. There is also evidence that prenatal undernutrition has the effect of reducing

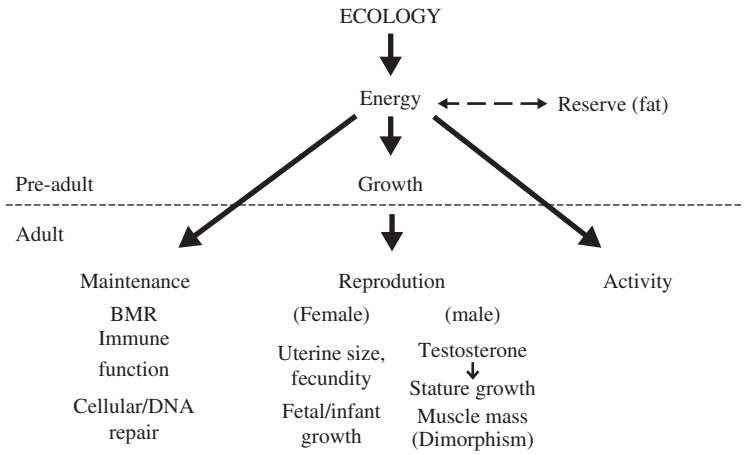

FIGURE 18-3 Organismal energy allocation. Organisms allocate a fraction of energy to growth, which is shunted into supporting reproduction upon cessation of growth. (Modified from Kuzawa, 2005.)

expenditures on other functions like reproduction and immunity (Galler et al., 1979; McDade et al., 2001; Moore et al., 2004), which might similarly be necessary to conserve resources when nutrition is scarce.

Some of the postnatal changes in the biology of specific tissues that are triggered by fetal undernutrition might further help the organism adapt to its environment. Compared to individuals of higher birth weight, the muscle of individuals born small appears to be relatively insensitive to the effects of insulin (Vaag et al., 2006), in part as a result of a reduction in the number of mitochondria (Park et al., 2003). Although insulin resistance is an important risk factor for the development of diabetes and thus CVD, this shift in glucose allocation can be viewed as a more conservative strategy of resource use. Insulin resistance in peripheral tissues has the effect of boosting delivery of glucose to non–insulin-sensitive tissues like the energy-demanding and fragile brain, perhaps at a cost to glycogen storage in muscle and thus physical endurance. Like the brain, the feto-placental unit during pregnancy also extracts glucose from the blood stream without the aid of insulin. A reduction in the use of glucose by the mother's muscle, as a result of reduced muscle insulin sensitivity established during her early development, would thus leave more glucose in the circulation to support fetal growth (see also Haig, 1993).

If such changes in energetic priorities are appropriate preparations for a marginal or less stable nutritional future, the developing organism might benefit by adjusting its strategy of metabolic partitioning in response to early life nutritional cues, that is, *if* the fetus has access to a cue that is an accurate predictor of future nutritional conditions. Given the elaborate strategy that the short-lived vole must use to predict its future, how plausible is a similar scenario of prediction in the comparatively long-lived human?

What Does Fetal Nutrition Signal About the Future in Humans?

Several questions must be considered when evaluating the potential for predictive signaling of this sort in humans. First, which resources cross the placenta and are sensed by the fetus? Second, with what, if anything, are these resources reliably correlated in the outside world? As with the vole, knowing the answer to these questions will provide a sense for what the fetus is potentially capable of "seeing" about its postnatal environment. Although assessing this is anything but straightforward, certain features of fetal biology create opportunities to evaluate this in a rough sense. During fetal life, growth rate is regulated by a different suite of hormones than during childhood and adolescence. Nutrients pass across the placenta to increase fetal insulin, which increases production of the insulin-like growth factors, which in turn stimulate skeletal growth at the growth plate and differentiation and proliferation of muscle cells (Gluckman & Pinal, 2003). Delivery of fuel substrate and insulin also drive fat deposition in the fetus during the third trimester (Symonds et al., 2003). Although an individual's growth potential is influenced by factors other than nutrition, this acute sensitivity of fetal growth to nutrition means that birth size serves as a useful, if rough, proxy for the stream of nutrients that the fetus received across the placenta. If we can identify the factors that predict birth weight, the fetus could evolve the capacity to achieve the same feat in reverse—much as the vole has done—and use intrauterine nutrition to infer these characteristics of the outside world.

So what predicts birth weight? Genetic factors generally account for at most 40% of birth-weight variation (Polani, 1974). Given the large variability in birth weight not

accounted for by genetics, it is somewhat surprising that what a mother eats during pregnancy is also not a particularly strong predictor of birth weight. This is seen in the modest effects that maternal nutritional supplementation has on birth weight. Most trials increase birth weight on the order of 25 g for each 10,000 kcal of maternal supplementation (Institute of Medicine, 1990; Kramer, 2000). Given that 10,000 kcal is enough energy to build roughly 2 kg of new tissue (Waterlow, 1981), it is clear that only a small fraction of the supplement is passing across the placenta to augment fetal growth. The relatively modest effects of pregnancy supplementation on birth outcomes attest, in part, to the effectiveness of maternal buffering mechanisms. Maternal metabolism and physiology maintain a relatively constant supply of resources to the fetus, and this dampens the impact of changes in her intake or energy status on the fetus. When nutritionally stressed, the mother's body may mobilize fat stores while reducing metabolic expenditure on nonessential functions like thermogenesis and physical activity (see Dufour & Sauther, 2002). The minor effects of pregnancy supplementation trials show that this buffering works both ways: abrupt improvements in dietary intake in the form of supplements also fail to have large effects on fetal nutrition. This is not to suggest that supplementation does not benefit both mother and fetus—supplements *do* reduce the rates of fetal growth restriction, stillbirths and neonatal death (Kramer, 2000), and supplements may have larger effects on birth weight when high-risk women are targeted (Ceesay et al., 1997). Moreover, the balance of nutrients or the adequacy of specific micronutrients in the mother's diet can have also influence fetal growth above and beyond any effects of gross macronutrient consumption (Institute of Medicine, 1990). However, for the purposes of the present discussion, the modest change in birth weight from most supplementation trials suggest that large fluctuations in what a mother consumes during pregnancy may often have comparably small effects on fetal nutrition, thus rendering these changes in the outside ecology relatively "invisible" to the fetus and its developing metabolism and biology (Kuzawa, 2005; Wells, 2003).

If large swings in the mother's dietary intake during pregnancy are not visible to the fetus, what features of the external ecology, if any, does intrauterine nutrition allow the fetus to see? Although energy intake during pregnancy is not a particularly strong predictor, weight gain during pregnancy is, because the weight of the feto-placental unit and amniotic fluid account for a large percentage of the gain (Institute of Medicine, 1990). What is perhaps more interesting is that nutritional status at the time of conception, or even before, predicts birth weight (Harding, 2003; Institute of Medicine, 1990; Rayco-Solon et al., 2005). A mother's nutritional status at conception in turn reflects her cumulative nutritional experiences in prior years. This provides important clues as to the type of information conveyed by fetal nutrition: if it serves as an ecological cue, it clearly must inform the fetus, in part, about conditions experienced by the mother in the *past*.

Additional evidence that fetal nutrition is a signal of the mother's nutritional history comes from studies that track the intergenerational predictors of birth weight. Although it is not surprising that larger mothers tend to give birth to bigger babies, studies find that different components of maternal stature predict birth weight with varying strength and that leg length tends to be a stronger predictor than trunk length (Lawlor et al., 2003). Studies that include measures of the mother's own growth show that her leg length measured during childhood is an even stronger predictor of offspring birth weight than is her leg length as an adult (Martin et al., 2004). Because childhood leg growth is among

the most nutritionally sensitive components of skeletal growth (Scrimshaw & B'ehar, 1965), these studies support the view that part of what the fetus sees in the stream of nutrition is a reflection of what the mother ate many years prior, during her own growth and development.

The intergenerational influences on fetal nutrition become particularly fascinating when we trace back even further to the mother's own intrauterine experiences as a fetus. Intergenerational correlations between maternal and offspring birth weight are high, with each kilogram increase in maternal birth weight predicting a 200-g increase in the birth weight of offspring (reviewed by Ramakrishnan et al., 1999). Several features of these correlations are worth noting. First, they tend to be independent of maternal stature or body size, suggesting that they are not merely a result of the fact that individuals born large end up as larger adults. Larger women do give birth to larger babies, but the intergenerational birth-weight correlation is independent of the mother's adult size. Second, the intergenerational correlation is strengthened after adjusting for gestational age, revealing that what is important is the nutritionally sensitive measure of fetal growth rate, rather than differences in the duration of prenatal growth (Alberman et al., 1992). Although some of this correlation is likely due to shared genes, there is also evidence for an environmentally induced component to these intergenerational effects on fetal nutrition. Women whose mothers experienced the Dutch famine winter of WWII during the first trimester of pregnancy gave birth to offspring (the grandoffspring of the original famine-exposed women) who were themselves smaller (Lumey, 1992). Thus, the intrauterine nutritional experiences of these women influenced the intrauterine nutritional environment that they provided their own offspring (Ounsted et al., 1986). The mechanisms that account for these intergenerational influences on nutrition and fetal growth remain poorly characterized, but likely involve changes in traits like placental perfusion and the size and blood flow to the uterus (Gluckman & Hanson, 2004).

Taken together, these studies provide a fascinating glimpse of what the intrauterine nutrient stream allows the fetus to "see," and, thus, what it might use this cue to infer about the world that it will be born into. Based upon the predictors of birth weight, fetal nutrition conveys information about the local nutritional ecology that stretches back into the mother's developmental past, all the way back to her own intrauterine experiences as a fetus. Because the mother's supply of nutrients to her current fetus is in part dependent upon the supply of nutrients that she received *in utero* from *her* mother, this implies that the fetus is partly seeing what the *grandmother* ate during her lifetime as well. Thus, although fetal nutrition is responsive to the mother's current nutrition and health, it is perhaps better described as a signal of her chronic intake, and one that provides something like an integrated, running average measure of the recent nutritional experiences of the matriline (Kuzawa, 2005).

THE ADAPTIVE SIGNIFICANCE OF INTERGENERATIONAL INERTIA

The preceding discussion highlights at least two interlocking processes that help link fetal nutrition with the past experiences of recent ancestors. The first is maternal buffering, which insulates fetal nutrition from acute changes in her current intake, thus decoupling

the intrauterine nutritional signal from temporary, and thus potentially misleading, cues like an illness, a drought, or a particularly abundant season (or equivalently, supplementation). The second includes intergenerational mechanisms (discussed below) that link fetal nutrition with the nutritional and growth conditions experienced by the mother during her past, extending back to her own gestational experiences and thus to the nutritional history of recent matrilineal ancestors. The effect of these dual influences is to allow a recalibration of the nutritional signal in response to ecological change, but only gradually and with a lag resulting from the lingering influence of the past (Ounsted et al., 1986; Price & Coe, 1999).

Particularly striking evidence for this lag is seen in the gradual, intergenerational increase in birth weight documented in a troop of wild macaques that experienced an abrupt improvement in nutrition after being taken into captivity (Price and Coe, 1999; Price et al., 2000). The positive trend in birth weight had not stabilized after five generations, and there was an intergenerational component to the trend, with maternal birth weight predicting birth weight of female offspring (see also Ounsted et al., 1986). This shows how a population may require multiple generations of maternal–fetal transmission to recalibrate certain aspects of developmental biology to even abrupt ecological change. I have argued elsewhere that this type of gradual intergenerational response to change, or *phenotypic inertia* (Kuzawa, 2005), improves the reliability of fetal nutrition as a signal of typical ecological conditions (Figure 18-4). A strategy of ignoring transient changes while allowing intergenerational recalibration to more sustained change could allow the fetus to track ecological shifts that are longer-term and more stable, and thus more relevant to a long-lived species.

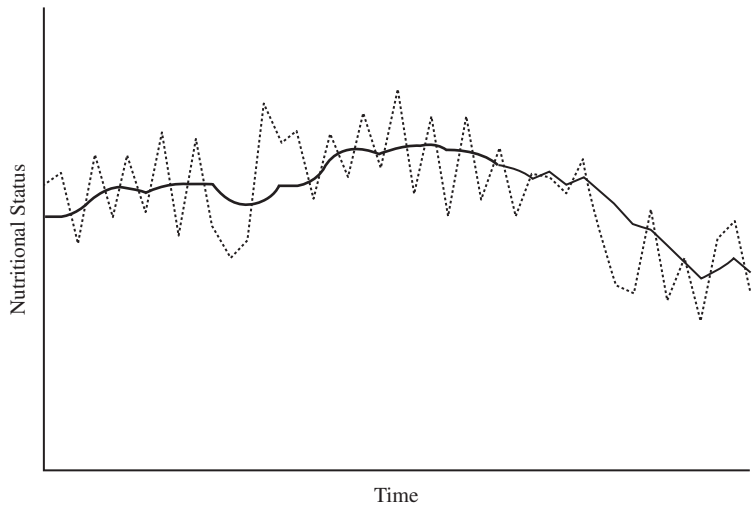

FIGURE 18-4 The hypothesized capacity for fetal nutrition to be set to a running average signal of the nutritional experiences of recent ancestors. Maternal buffering of the effect of abrupt and transient changes in nutritional status (dotted line), combined with intergenerational influences on nutrition, allows the fetus to track more gradual but sustained ecological trends (solid line). (Adapted from Kuzawa, 2005.)

Mechanisms of developmental induction and intergenerational inertia

Although the specific pathways accounting for the intergenerational continuity of fetal nutrition and growth remain poorly understood, animal experiments provide important insights into how ecological information is conveyed across generations for similar traits and systems. The best documented mechanisms for the continuity of induced phenotypic states include heritable modifications in the molecular scaffolding from which the double helix of the DNA is built, such as the attachment of an extra methyl group to cytosine ("methylation") or other changes in the conformation of chromatin (reviewed by Jablonka & Lamb, 1995, 2005). These "epigenetic" changes can influence whether and how much a gene is expressed, while leaving the DNA itself unmodified. Epigenetic changes can be induced by an environmental stimulus like nutrition, can persist across a single life cycle, and in some cases also across generations.

As the list of examples of epigenetic effects, or "epigenetic inheritance systems," continues to grow (Jablonka & Lamb, 1995; 2005), their importance to the intergenerational transmission of environmental influences on biology and health is becoming clear (Drake & Walker, 2004). One study found that restricting the protein intake of pregnant rats changed the methylation of a gene that regulates lipid metabolism (PPARα) in offspring and that methylation status was correlated with the postweaning expression of mRNA at that particular locus (Lillycrop et al., 2005). Thus, changing the environment of one generation—the pregnant mother—leads to methylation and altered gene expression in offspring after birth. Another study exposed pregnant rats to a synthetic stress hormone (dexamethasone) and measured metabolism and growth in several generations of offspring (Drake et al., 2005). The female fetuses exposed *in utero* gave birth to offspring (the grandoffspring of the treated pregnant dams) who were themselves smaller and had impaired glucose tolerance. Interestingly, this effect was not limited to the offspring of exposed mothers. The *male* treated fetuses, when crossed with a control female later in adulthood, also sired smaller offspring who were glucose intolerant. In both patrilineal and matrilineal offspring, the effect on growth and metabolism lingered into the grandoffspring generation but was reversed in great-grandoffspring.

The patrilineal inheritance in this study helps clarify one type of epigenetic "memory" that may be transmitted across generations—in this case influencing how the body allocates and uses glucose. Unlike the female's contribution to the zygote, which includes not only genes but also the cytoplasm, chromatin, organelles, and enzymes present in the egg (Bonner, 1974), sperm are believed to donate nothing more than chromosomes to the zygote at conception. As such, the finding of an inherited paternal effect strongly suggests that environmental experiences can modify the pattern of gene expression of the germ line present at conception which is then transmitted to offspring (for review, see Chong & Whitelaw, 2004). Although the specific molecular details have yet to be described for this model, the findings are consistent with the known mechanisms of epigenetic inheritance: the genes themselves clearly are not changed, because the phenotype "washes out" and reverts to its preinduced state after two generations. Another recent study found that a different prenatal treatment—maternal protein restriction—had an effect on glucose metabolism that was transmitted across two generations of offspring, this time investigated only in females (Benyshek et al., 2006). In contrast to the results of the prenatal

stress hormone protocol, not only the grand offspring but the *great*-grandoffspring of the pregnant dam exposed to protein restriction had glucose intolerance before the phenotype reverted to its preinduced state. Although not focused on early nutrition, another recent study showed that exposing pregnant rats to an endocrine disruptor around the time of sexual differentiation impairs spermatogenesis in male offspring for at least *four* generations of offspring (as many as were followed up) (Anway et al., 2005).

The early postnatal period of maternal–offspring interaction is a continued stage of plasticity and developmental induction, which gives rise to fascinating examples of epigenetic inheritance operating through distinct pathways. Michael Meaney and colleagues at McGill University have documented the molecular mechanisms underlying one such example in remarkable detail (Weaver et al., 2004). In this model, the stimulus is not nutrition, but how a mother rears her newborn pups. More nurturant mothers lick and groom their pups and also engage in a behavior called "arched back nursing" that encourages pup feeding. When compared to the pups of less nurturant mothers, the indulged pups show an attenuated physiological stress hormone response later in life when faced with a challenge or threat. Meaney's group has shown that the induced change in the stress hormone system involves changes in both the chromatin configuration and methylation status of the gene encoding the glucocorticoid receptor in a region of the brain (the hippocampus) that helps regulate stress hormone production (Weaver et al., 2004). This pattern of epigenetic inheritance occurs even when the young being raised by nurturant dams are the genetic offspring of the low nurturant dams, showing that the continuity of behavior is not merely a result of classic genetic inheritance, while an epigenetic basis for the effect is supported by the fact that the behavior is reversed by demethylation. Thus, rather than being a result of genetic inheritance or simple learning, this pattern of inheritance likely involves biological changes in gene expression in hippocampal neurons that influence how the stress hormone system is regulated. One trait that this change in stress reactivity influences is future rearing style, and amazingly, the indulged pups end up replicating a similar nurturant style when rearing their own young. Thus, in this model we have evidence for a mode of epigenetic inheritance that bypasses the zygote altogether, with an environmentally induced phenotype in one generation serving as a template for the construction of a similar phenotype in offspring.

It is highly unlikely that changes in chromatin and gene methylation in the hippocampus would result in a future rearing behavior that replicates the same chromatin and methylation changes in offspring purely by *chance*. This interpretation seems even less likely once other examples of maternal–fetal intergenerational transmission are considered, such as the lingering effect of the nutritional experiences of past generations on the intrauterine nutritional environment provided offspring. These observations, and the complexity of the epigenetic mechanisms that account for them, suggest that mammalian biology has been *designed* to allow certain nongenetic, environmentally induced phenotypic changes to be transmitted across generations (Jablonka and Lamb, 2005). As suggested above, such modes of nongenetic inheritance may have evolved to allow individuals to cope with changes that are too rapid to be tracked by the gradual process of natural selection operating on gene frequencies, but that are too slow, sustained, or extreme for our acutely responsive and reversible homeostatic processes to efficiently buffer given their limited range of response (Figure 18-5) (see Bateson, 1963).

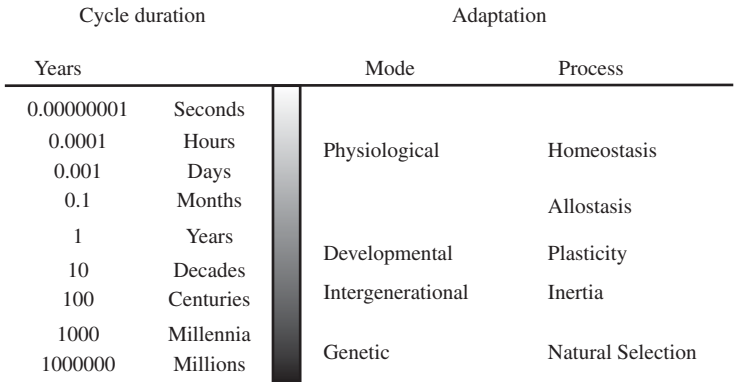

FIGURE 18-5 The spectrum of ecological change and the hypothesized role of intergenerational inertia as a mode of adaptation.

Intergenerational Inertia Versus Acute Effects as a Dimension of Developmental Adaptation

Each of these examples provides insight into the types of heritable epigenetic changes that allow the transfer of ecological information across generations, represented not in the specific sequence of DNA inherited, but in the pattern with which that DNA is expressed. The previously discussed examples of intergenerational birth-weight correlations, the effect of prenatal nutrition on the fetal growth of offspring, and the lag in the birth-weight response to nutritional change documented in the macaque population suggest that intrauterine nutrition provides the fetus with information about past ecologies, likely operating through similar, yet to be identified epigenetic pathways. At the same time, however, it is clear that a mother's gestational health or nutritional status, or stressors like smoking, have acute effects on her current birth outcome (Institute of Medicine, 1990). Thus, there are multiple influences on intrauterine signals, and the balance between them must influence the type and time depth of information that is encoded and communicated to the fetus.

It is interesting to consider how these inputs might converge to influence the signal received by the fetus. In this regard, maternal–fetal biological signaling might be analogous to the inheritance of cultural traditions, which vary markedly in their tendency to remain stable in the face of societal change. At one extreme are short-lived fads, which are selected for rapid turnover and novelty and may be learned at any stage in the life cycle. At the other are more deeply rooted traditions like language, linguistic accent, and religious belief, which have greater intergenerational staying power in the face of change. It is notable that the most stable cultural practices have a pattern of socialization dependent upon stimuli being experienced during early sensitive periods in neurocognitive development. Although humans have the ability to learn language throughout life, we are particularly efficient at learning grammatical structure and vocabulary during early childhood, when our brains are primed to latch onto and internalize what we hear (Pinker & Bloom, 1990). Our reliance upon prior generations at this age nearly ensures that we end up perpetuating linguistic patterns similar to those used in recent generations.

Thus, although language of course does change, the pace of that change is tempered by the fact that the critical period for language acquisition overlaps with the period of intergenerational dependence.

The biological and metabolic traits that are influenced by intergenerational epigenetic effects likely also vary in their relative sensitivity to current versus ancestral influences. Some plastic traits are sensitive to the mother's (or the neonate's) immediate experiences, while others have greater intergenerational stability because their mature state is—akin to our linguistic accent—established during early windows of development that overlap with, and are responsive to, the biology (or behavior) of the prior generation. The finding, reviewed above, that different experimental protocols induce phenotypic states that persist across two, three, or four generations of offspring before reverting to the preinduced state suggests that epigenetic information is not only transmitted across generations, but that the strength of inertia—the weighting of past versus current influences—is itself potentially modifiable. It seems likely that the number of generations across which an induced developmental effect lingers might itself be modified by natural selection, allowing information to be integrated, and a running average calculated, across different intergenerational time frames (Kuzawa, 2005).

To conclude this section, the minimum requirements for the evolution of a system of adaptive developmental plasticity, as outlined above, appear to be in place in humans: not only are humans confronted by different types of nutritional ecologies, but the biological effects of prenatal responses to nutrition could benefit the organism faced with this ecological variation. The fetus has access to a cue that is a reasonable indicator of the average, recent state of the ecology, boosting the likelihood that these adjustments will be well-matched to postnatal realities. Finally, there is a growing list of mechanisms to account for the intergenerational transfer of environmental information through nongenetic pathways, providing evidence that evolution has favored such strategies in mammals. Together these observations boost the plausibility that adaptive fetal plasticity could have evolved under the influence of natural selection.

INTERGENERATIONAL INERTIA AND HUMAN HEALTH

The vole and human illustrate two distinct strategies that species varying dramatically in life history and ecology have evolved to predict postnatal conditions from prenatal cues. The vole uses a combination of hormonal and chemical cues of maternal origin to predict its *future* position within a regular seasonal cycle of changing day length, temperature, and ecological productivity. This feat of forward-looking prediction is only possible because its dominant ecological cycle is not only regular, but also severe and prolonged relative to its life expectancy. The vole is not concerned with the nutritional experiences of ancestors during prior years, but instead with ensuring that its own single reproductive effort is well timed with respect to the present year's seasonal transitions. The vole uses at least three cues to achieve its sophisticated strategy of forward-looking prediction: it establishes whether day length is increasing or decreasing by calculating the change in photoperiod—first measured *in utero* via maternal melatonin signaling, and again after weaning. Starting before birth, it also senses the concentration of plant metabolites present in the maternal diet, which signal the presence of early spring vegetative growth.

Using this combination of cues, the vole manages to home in with reasonable precision on an appropriate developmental and reproductive strategy that helps ensure that its single shot at reproduction is well timed.

Unlike the vole, the human fetus will live through hundreds of seasons and has no comparable large-scale cycle to entrain its much longer life history to prior to birth. In many ways, the challenge faced by the human fetus is thus opposite that of the vole: to ignore the specific season of birth to a certain extent, and to minimize the impact of any extreme or unusual conditions that may be present during that particular gestation, such as might be expected during a particularly good or bad year or season. Humans have faced considerable ecological and nutritional variability, but unlike the forward-looking vole, the longer-term trends that we confront and must adapt to follow no predictable cycle. The human fetus is therefore forced to adopt the very different strategy of adjusting nutritional expectations on the basis of information reflecting conditions experienced by *past* generations. A "backward-looking" cue is likely the most useful strategy available to the human fetus, because there simply is no basis for predicting the future, other than by hedging that conditions will remain about the same as experienced by recent ancestors. By smoothing out the effect of any short-term seasonal or year-to-year perturbations, the buffering of fetal nutrition by maternal metabolism, combined with the intergenerational averaging of nutritional information conveyed to the fetus, should increase the fidelity of this signal, boosting its value as a guide when constructing the developing body and its future metabolic priorities.

It is not difficult to imagine how this same capacity to anchor metabolic expectations to a signal of average recent nutritional experiences could backfire, heightening risk for metabolic disease, when change is not only abrupt but sustained. Today, powerful ripples are sent through the global human nutritional ecology by institutions like industrial agriculture, which has increased the affordability of concentrated sources of calories like refined sugar and oil (Drewnowski & Popkin, 1997). Additional ripples come with the mechanization of our lives and changing patterns of activity. Human locomotion is increasingly powered by hydrocarbons rather than dietary energy, while employment options are often limited to sedentary occupations that require minimal physical exertion (Popkin & Gordon-Larsen, 2004). As a result of these changes, energy balance is shifting into the surplus column in many populations, and humankind is putting on extra body fat at an alarming rate (see Chapter 3). As emphasized in the introduction to this chapter, populations experiencing a particularly rapid pace of nutritional and lifestyle change are often predisposed to CVD. The model presented here outlines one adaptive feature of mammalian biology that may backfire when conditions change rapidly, thus helping explain some of this heterogeneity in the global CVD epidemic.

The now common finding that CVD risk is highest among individuals who were born small but later put on weight is consistent with the hypothesis of developmental mismatch, as it suggests that experiencing improved nutrition between birth and adulthood can exacerbate the effects of a compromised fetal environment (Fagerberg et al., 2004; Oken and Gillman, 2003). Developmental mismatch could help explain why stunting—a measure of early life undernutrition—is a risk factor for obesity in some populations experiencing rapid nutritional transition (Florencio et al., 2003; Popkin et al., 1996; Steyn et al., 1998). The model is also supported by the finding that poor gestational

nutrition is *not* associated with elevated CVD risk in populations that remain marginally nourished in adulthood (Moore et al., 2001). If the mismatch hypothesis is correct, populations shifting rapidly from low to higher nutritional status would be expected to experience a period of transition marked by high CVD risk, followed by a gradual intergenerational recalibration of expectations to the new, more abundant nutritional plane (Gluckman & Hanson, 2005; Prentice and Moore, 2005). It has been argued that this type of gradual resetting of expectations could go some way towards explaining the recent decline in CVD in populations that already experienced peak rates of CVD earlier in the twentieth century, like the United States and western Europe (Barker, 1994).

Although a model of developmental adaptation predicts that transitional populations will eventually recalibrate and experience a reduction in CVD risk, there may be situations in which this does not occur. Diabetes relates to birth weight in a U-shaped fashion, and thus is more common among individuals who were either small *or* large at birth (Huang et al., 2006). This may lead to an unusual intergenerational pattern of disease transmission when nutritional environments change rapidly. An individual undernourished as a fetus is more prone to develop diabetes if nutrition improves and he or she gains weight. Gestational diabetes in the next generation of mothers, in turn, increases the flow of glucose and insulin across the placenta, leading to a fetus (grandoffspring) born with excessive body fat and altered glucose metabolism. Large or macrosomic babies have an increased risk of developing obesity and diabetes themselves, thus potentially setting in motion an intergenerational cycle of mutually reinforcing diabetic pregnancies and diabetic offspring. In this way, a particularly rapid pace of change may shift a population from a pattern of chronic undernutrition to an intergenerational susceptibility to obesity and diabetes. A mechanism of this sort has been proposed as an explanation for the very high rates of gestational diabetes among certain Native American populations in the United States, notably the Pima (Benyshek et al., 2001), and the emerging epidemic of metabolic disease on the Indian subcontinent (Yajnik, 2004).

Conditions such as poverty can also create a form of mismatch in the absence of rapid social change, and this can have an important, sustained influence on disease patterns in certain societies and demographic subgroups. In contrast to global trends in adult dietary intake and energy balance, the health and nutritional status of infants and young children remains tied to conditions that influence risk for infectious disease, including sanitation, crowding, and the availability of clean water. Many populations from developing nations that are experiencing weight gain as adults still have relatively high rates of early life undernutrition and growth stunting tracing to factors like childhood diarrhea and respiratory tract infections. If the developmental mismatch model is correct, there are dueling forces at work in these individuals, who enter a world that is nutritionally challenging, but gradually shift into positive energy balance and weight gain as they age. Because infant nutritional status remains tightly linked to poverty, while adult energy balance is increasingly decoupled from traditional economic barriers, this could also lead to mismatch, not because the ecology is changing, but because the *experience* of that ecology—poverty—differs by age. There is evidence for such patterns of concurrent early life undernutrition and adult overnutrition in the same populations, as suggested, for instance, in the finding of a co-occurrence of obese and malnourished individuals in the same household (e.g., Garrett & Ruel, 2005).

Revising the Model of Chronic Disease Epidemiology: Genes, Environment and Developmental Biology

The developmental processes reviewed in this chapter point to the need for an amended model of metabolic disease epidemiology. The traditional perspective, which views health as a product of our genome interacting with our own environment and lifestyle, is clearly not complete. Developmental and epigenetic processes also leave a lingering imprint on our biology that trace to formative environmental experiences during early life and are influenced to varying degrees by the historical experiences of ancestors prior to our own conception. The complexity of interactions generated by these influences is now becoming clear. As one example, genes that influence cholesterol metabolism have been shown to have effects on lipid profiles that depend upon the birth weight of the carrier of that allele (Garces et al., 2002; Infante-Rivard et al., 2003). Similar interactions with birth weight have been found for genes that influence insulin resistance (Cambien et al., 1998; Vu-Hong et al., 2006), bone mineral metabolism (Dennison et al., 2004), and blood pressure (te Velde et al., 2005), among others. As discussed in this chapter, birth weight, in turn, is a marker that partially reflects the historical nutritional experiences of *prior* generations. It thus seems clear that our health is a product of our genes interacting not solely with our *own* lived experiences, but also with the experiences of our immediate ancestors (Jablonka, 2004).

Although developmental responses to early environments may modify the effects of the genes that we inherit, they also reveal why it is no longer acceptable to uncritically assume that unexplained biological differences between populations trace to genes, even when those differences are already present at birth. This is particularly true when membership in a population or subgroup is established according to socially defined criteria, such as the labeling in the United States of individuals with any visible African ancestry as African American ("hypodescent"). I close this chapter with this example as it illustrates the power of a developmental model of adult health to challenge us with new ideas about the causes of social disparities in conditions like CVD. It is well established that African Americans have higher rates of hypertension, diabetes, and CVD mortality than their U.S. non-Hispanic white counterparts. When studies find that race is still a significant predictor of these conditions after adjusting for certain lifestyle and socioeconomic characteristics, it is not uncommon for researchers to suggest that the residual effect of race must indicate as-yet-undiscovered black–white differences in gene frequencies (see Cooper & Kaufman, 1998). This conflation of biological difference with genetics is one of the more pervasive errors committed in the modern study of biology and health, and in this case it is brought into question by the fact that U.S. blacks *also* have lower birth weights than their white counterparts (Alexander et al., 1999), which we now know is a risk factor for hypertension, diabetes, and CVD.

One may question whether black–white differences in birth weight and cardiovascular risk might both be the result of a common set of genetic differences between these groups. Although I am aware of no evidence to support this interpretation, recent research points to the power of developmental environments to shape these health disparities. In a study of birth records of recent immigrants to the United States, immigrants from the Caribbean and Africa, many of whom come from privileged socioeconomic positions in their home countries, were found to have a birth weight distribution nearly identical to

that of U.S. whites upon arrival (David & Collins, 1998). This equivalence was short lived. Among subsequent generations born in the United States, the birth weight distribution of the offspring of African immigrants eventually shifted to the left, en route to a convergence with the lower African American mean (Collins et al., 2002). What is particularly fascinating is that the European immigrants in this study responded to the U.S. environment in opposite fashion: their birth weights were *lower* than the U.S. white mean upon arrival, but *increased* with each passing generation born in the United States.

These opposing biological responses were far too rapid to be the result of changes in gene frequencies (Boas, 1912). Instead, they reveal that living in the United States has different implications for the intrauterine environments that U.S. blacks and U.S. whites experience prior to birth. Whether from Europe or Africa, after several generations the birth-weight distributions of each group of immigrants and their descendents come to resemble those of their U.S. ethnic counterparts. If we believe the findings of this study, which had a sample in excess of 91,000, the widely documented black–white difference in birth weight is not likely the result of genes (David & Collins, 1997). Although the causes of the lower birth weights of African Americans and these offspring of African immigrants are not fully understood, factors associated with minority status, such as discrimination and racism, have been shown to increase the risk of prematurity and fetal growth restriction (e.g., Collins et al., 1998; Dole et al., 2004). This chapter, in turn, has reviewed evidence that this disparity in the gestational environment could help explain the prominent race-based U.S. health disparities in adult diseases like hypertension, diabetes, and CVD, all of which are more common in individuals born small. Indeed, a recent analysis of data from the biracial Bogalusa Heart Study cohort found that the black–white difference in hypertension in this sample was no longer significant after models adjusted for birth weight (Cruickshank et al., 2005; see also Fang et al., 1996).

Thus there is growing evidence, albeit indirect, for a developmental origin of some of the most prominent U.S. health disparities (Pike, 2005; see also Chapter 6). And yet, far more research continues to search for genetic explanations for these group differences (Cooper & Kaufman, 1998), despite the minor importance of racial categories or population membership as an explanation of human genetic variation (Serre & Paabo, 2004). I use this example not to question the influence of genetic structure on human biology and health, but to underscore why a model of disease that is limited to the inheritance of DNA base sequences, current environments, and the interaction between them is no longer complete or acceptable. Studies documenting developmental and intergenerational influences on health show how some seemingly hardwired and even inherited traits may be, at their core, the result of phenotypic strategies designed to maintain and transmit environmental information across life cycles and even generations. This can lead to mismatch when conditions change rapidly, as highlighted in this review. But these same mechanisms of intergenerational transmission could also amplify health disparities when unfavorable conditions, such as discrimination and stress, are chronically experienced (Figure 18-6). In the case of African American health disparities, the experience of stress during pregnancy and the passage of stress hormones across the placenta could initiate many of the same fetal responses as undernutrition and with similar long-term biological health risks for offspring (Seckl & Meaney, 2004; Worthman and Kuzara, 2005; see also Chapter 6).

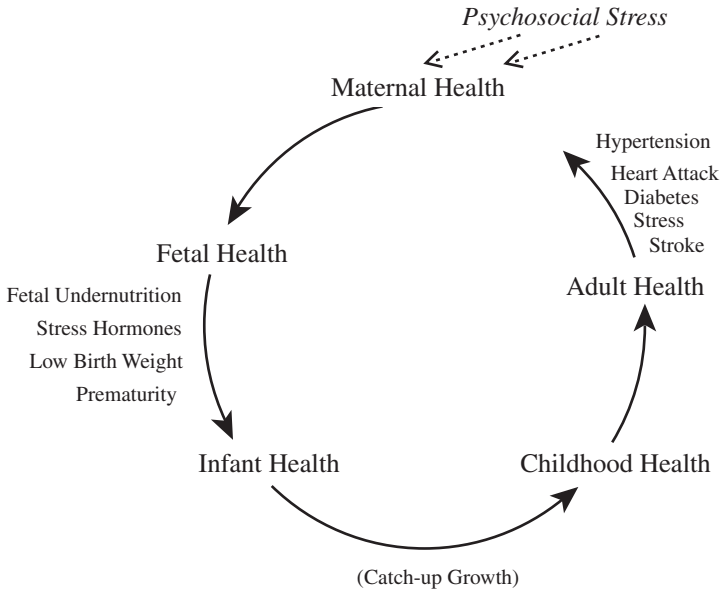

FIGURE 18-6 Model of the intergenerational amplification of health disparities in the absence of rapid social change.

Whether triggered by stress, nutrition, or other stimuli, the mechanisms of maternal–fetal signaling reviewed in this chapter are neither "genetic" nor "environmental" as traditionally defined. Although they involve potentially heritable changes in the expression of specific genes, these epigenetic changes are initiated in response to the environment. As such, they help blur the distinction between genetic and environmental influences on biology and health. The complex systems of inheritance that they undergird may have originally evolved to help organisms cope with environmental change that is beyond the narrow reach of homeostasis and its buffering capacity, but too abrupt to be visible to the more powerful, yet more gradual process of natural selection operating on gene frequencies. This chapter has reviewed evidence that even the capacity for developmental adaptation on this more rapid time scale may be outstripped by the contemporary pace of cultural and social change. In the case of nutrition, when early life signals are discordant with postnatal realities, the risk of metabolic disease may be elevated, thus linking the environmental experiences of recent ancestors with the diseases of the present.

On a more positive note, as the pace of environmental change attenuates, we can hope that the biology of future generations will recalibrate, having read the nutritional messages of the present and adjusted, over several generations, to the new nutritional world that we now inhabit. And our generation must help send this message to future generations by ensuring that today's pregnant mothers and their newborn offspring are well nourished. If the model presented in this chapter is correct, nutritional expectations are designed to shift in response to change that is sustained across multiple generations.

Nutritional interventions that target not only pregnant mothers, but also follow up with their nutritionally sensitive young, should help lift the nutritional expectations of offspring generations, with health benefits that echo into the future.

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