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30 Beyond Feast–Famine: Brain Evolution, Human Life History, and the Metabolic Syndrome

Christopher W. Kuzawa

EXPLAINING THE MODERN METABOLIC DISEASE EPIDEMIC: THE THRIFTY GENOTYPE HYPOTHESIS AND ITS LIMITATIONS

Today, more than 1 billion people are overweight or obese, and the related condition of cardiovascular disease (CVD) accounts for more deaths than any other cause (Mackay et al., 2004). Why this epidemic of metabolic disease has emerged so rapidly in recent history is a classic problem for anthropologists concerned with the role of culture change in disease transition (Ulijaszek and Lofink, 2006). In 1962, the geneticist James Neel proposed an explanation for this phenomenon that looked for clues in the "feast–famine" conditions that he believed our nomadic, foraging ancestors faced in the past. Given the unpredictability of food resources in natural ecologies, Neel suggested that a "thrifty" metabolism capable of efficiently storing excess dietary energy as body fat when food was abundant would have provided a survival advantage during later periods of shortage. In the wake of the rapid dietary and lifestyle change in recent generations, and the comparatively slow pace of genetic change, these foraging-adapted genes would now be "rendered detrimental by progress" (Neel, 1962), leading to obesity and diabetes. While a useful way to think about obesity generally, variations on this idea have been proposed to help explain the high rates of metabolic disease among populations believed to have experienced especially severe nutritional conditions in the past, including the diabetes-prone Pima Indians of the American Southwest (Knowler et al., 1982), and several groups of South Pacific Islanders who have among the highest rates of obesity in the world (Dowse and Zimmet, 1993; McGarvey, 1994).

The thrifty gene hypothesis was one of the first uses of evolutionary reasoning to shed light on a human disease, and is thus a classic example of evolutionary or "Darwinian" medicine (see Nesse and Williams, 1994; Stearns and Koella, 2008; Trevathan et al., 2008). The idea that obesity and related diseases result from a "discordance" or "mismatch" between our ancient genes and our rapidly changing lifestyle and diet is now widely accepted, and it seems clear that obesity must be more common today in large part because we are eating more and expending less than our ancestors traditionally did (Eaton and Konner, 1985; see Chapter 28 of this volume). Despite the intuitive appeal of these ideas, the hypothesis is not without limitation. For one, it helps explain why we gain weight in a modern environment of nutritional abundance, but says very little about the syndrome of metabolic changes that account for the diseases that accompany obesity (Vague, 1955; Kissebah et al., 1982). While excess weight gain in general is unhealthy, it is specifically fat deposition in the visceral or abdominal region that accounts for the bulk of its adverse effects on health. Visceral fat has unique metabolic properties that contribute to prediabetes states like insulin resistance when deposition in this depot is excessive (Reaven, 1988; Wellen and Hotamisligil, 2003). The simple idea that our bodies are famine adapted may help explain why we are prone to gaining weight when we eat too much, but it says little about the metabolic symptoms that make weight gain unhealthy.

The sole focus of the hypothesis on genes is also outdated in light of newer evidence that biological susceptibility of developing these adult diseases is also elevated among individuals who experienced poor nutrition during early life (Barker et al., 1989; Gluckman and Hanson, 2006). A large research literature has demonstrated that the body's responses to early life nutrition subsequently influences that individual's risk for developing adult diseases like diabetes and CVD, a process described as nutritional "programming" (Lucas, 1991) or "induction" (Bateson, 2001). For instance, CVD and the rate of CVD mortality in adulthood are inversely related to size at birth – a measure of fetal nutrition – in places like the UK, Sweden, India, and the Philippines (Kuzawa and Adair, 2003;

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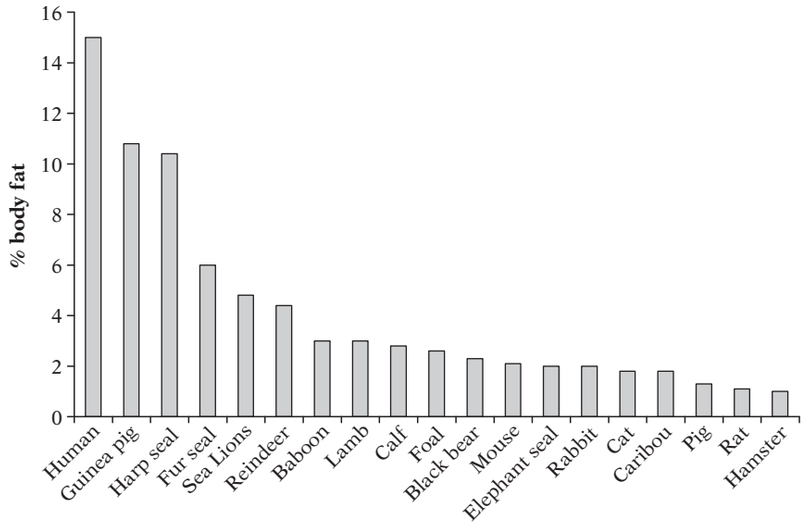
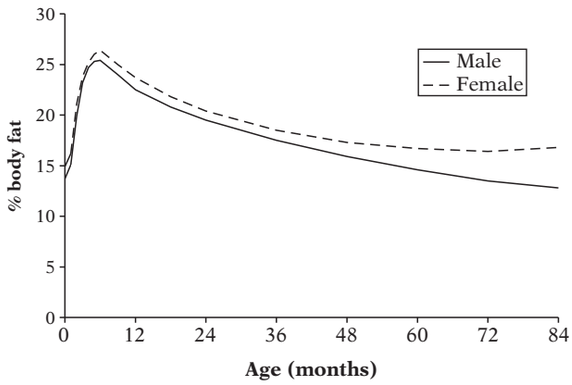


30.1. Percentage of body fat at birth in mammals. Adapted from Kuzawa (1998).

Yajnik, 2004; Lawlor et al., 2005). Individuals who were born small also experience durable changes in biological systems that contribute to CVD, as reflected in their higher risk of depositing fat in the visceral region, or of developing high blood pressure, impaired glucose tolerance or diabetes, or high cholesterol (Adair et al., 2001; Kuzawa and Adair, 2003). When the dietary intake of pregnant rats and sheep is restricted, their offspring have much the same set of outcomes as we see in humans born small (McMillen and Robinson, 2005; Fernandez-Twinn and Ozanne, 2006). This finding suggests that the body has an ability to induce a "thrifty phenotype" that is better suited to survival in nutritionally challenging environments. It also illustrates why a purely gene-based model of metabolic disease evolution is incomplete (Hales and Barker, 1992).

A third limitation of the thrifty genotype hypothesis is that it merely *assumes* that famine was the key source of selection on human metabolism without considering the actual causes of that stress and the ages at which it is most severe (Kuzawa, 1997). There are reasons to question whether our distant foraging ancestors experienced a major burden of famine, which archaeological and contemporary ethnographic data suggest only emerged as an important problem after the evolutionarily recent development of agricultural subsistence (Cohen and Armelagos, 1984; Benyshek and Watson, 2006). Given this, famine may have been a relatively weak force of selection on the human gene pool (Speakman, 2006).

Additional support for this interpretation comes from the growth pattern of body fat in humans, shown in Figure 30.1. In humans, body fat makes up a larger percentage of weight at birth than in any other



30.2. Age changes in percentage body fat in humans. Data from Davies and Preece (1989), pp. 95–97.

mammal studied thus far (Kuzawa, 1998). This is followed by a continued period of rapid fat deposition during the early postnatal months. In well-nourished populations, adiposity reaches peak levels during the first year of life before gradually declining to a nadir in childhood, when humans reach their lowest level of body fat in the lifecycle (Figure 30.2). If the threat of famine is what drove the human tendency to build up fat reserves, it is not obvious why children's bodies should do so little to prepare for these difficult periods. The lower priority placed upon maintaining an energy reserve by middle childhood suggests that the background risk of starvation faced by our ancestors – "famine" – was small in comparison to the nutritional stress experienced during the preceding developmental period. A prereproductive life history stage that does

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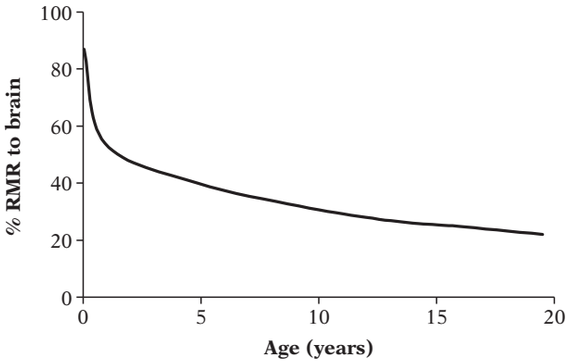
not prioritize energy storage is difficult to reconcile with the assumption that famine was the major nutritional challenge faced by human populations.

In this chapter, I review the causes, consequences, and adaptive solutions to the nutritional stress of infancy and childhood in hopes of shedding light on the evolution of human metabolism. Viewing human nutritional stress through a developmental lens helps identify ages when human metabolism has likely been under strongest selection. I will show how two traits that are central to the adverse health consequences of obesity in overnourished adults – visceral fat and insulin resistance – likely evolved as components of an energy backup system that reprioritizes the allocation of prized energy and glucose during a crisis, thus allowing the body to shunt resources from nonessential functions to critical organs like the brain (for discussion of the function of insulin resistance during pregnancy, see Haig, 1993). Demands placed on this system are greater during infancy and early childhood than at any other age of the lifecycle, suggesting that some of the evolutionary seeds of adult metabolic disease may trace to selection pressures operative during early life. In addition, evidence for developmental plasticity in this backup system and the adult diseases that it contributes to suggests that its priorities may be adjusted in response to nutritional and other stressors experienced early in the life cycle. A developmental approach to the evolution of human metabolic disease underscores the importance of the body's internal strategies of allocating finite resources – in addition to the external stress of famine – as key to understanding the contemporary epidemic of metabolic disease.

A DEVELOPMENTAL PERSPECTIVE ON ENERGY STRESS IN HUMAN EVOLUTION: THE DEVELOPMENTAL BOTTLENECK

Humans have been described as naturally obese (Pond, 1997), a characterization which is particularly fitting at birth as human newborns are born with more body fat than any other species (Kuzawa, 1998). Attempts to explain our unusual "baby fat" have traditionally looked to our hairlessness for clues, and it is widely assumed that natural selection compensated for our loss of fur with a layer of insulative body fat (e.g., Hardy, 1960; Morris, 1967). A competing perspective notes that this excess adipose tissue is well-suited to serve as a backup energy supply for another distinctive human trait: our large brains (Kuzawa, 1998). Brains have among the highest metabolic rates of any tissue or organ in the body, and they are quickly damaged in the event of even temporary disruption in energy supply. Neuronal tissues are costly because they must be maintained in a state far from thermodynamic equilibrium,



30.3. Percentage of resting metabolic rate (RMR) devoted to the brain by age in humans. Data adapted from Holliday (1986).

which requires a constant redistribution of ions across the cell membrane using energy-dependent ion pumps. Humans are exceptional in the quantity of this costly tissue that they must sustain, and it has been estimated that greater than 80% of the body's metabolism is devoted to the brain in the newborn (Figure 30.3).

It is a notable feature of human metabolism that total metabolic rate measured in adulthood (for instance, calories expended per day) is not increased above other mammals of similar body size despite our highly encephalized state (Armstrong, 1983). Thus, brain expansion must have been matched by a reduction in other energetically expensive tissues (Armstrong, 1983). Human evolution was marked by a movement to more energy-dense and easy to digest foods (Leonard and Roberton, 1992, 1994), which may have allowed a reduction in the size and energy requirements of the metabolically costly gut (Aiello and Wheeler, 1995). This reduction in gut expenditure may have helped offset our increased brain needs in adult life (Aiello and Wheeler, 1995), but this seems less likely during infancy and childhood. The size of the brain relative to the body is far larger in the human neonate and infant than in the adult, and as a result, the body's total energy requirements are likely elevated at this age relative to other similarly sized mammalian and primate newborns (Foley and Lee, 1991). Moreover, unlike energy expended on other tissues or systems, brain metabolism may not be reduced to conserve energy during a period of shortage, but instead must be maintained within narrow limits to avoid permanent damage (Owen et al., 1967). Thus, our large brains impose a double burden on metabolism during infancy: they increase demand for energy while restricting flexibility in metabolic expenditure when nutritional supply is disrupted.

Other factors that are commonly experienced during infancy can impede the supply of nutrients, ensuring that negative energy balance is a regular occurrence at this age in most populations. We are

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born with a naïve adaptive immune system, and must therefore come into contact with (and be infected by) specific pathogens to acquire the repertoire of antibodies necessary to protect us from future infection. Initially, newborns enjoy immune protection from several maternal sources. The first is in the form of maternal immunoglobulin G (IgG) antibodies acquired across the placenta. In addition, exclusively breast-fed infants are shielded from exposure to pathogens, and also enjoy passive immune protection from maternal secretory antibodies (sIgA) in breast milk. As a result, newborns are often quite healthy in the early postnatal months. However, both sources of passive immune protection eventually wane. As energy requirements outstrip the supply capacity of breast milk by roughly 6 months of age, less sterile complementary foods must be introduced, and infectious disease becomes unavoidable in all but the most sanitary environments. These childhood infections, in turn, are a source of nutritional stress, and indeed, it is primarily through their effects on nutritional status that they compromise health and contribute to mortality during infancy and childhood (see Scrimshaw, 1989, for review). Once sick, a child loses appetite and this may be compounded in some cultures by the withholding of food by caretakers (Scrimshaw, 1989). The common diarrheal diseases reduce nutrient absorption and digestion, while the fevers associated with many viral infections can increase metabolic rate and thus energy expenditure. The specific symptoms may vary by illness, but the pattern of nutritional depletion that accompanies infections has the effect of suppressing immune function, leaving the infant more prone to future infection and a compounding cycle of nutritional stress (Pelletier et al., 1995).

The human infant thus faces a profound energetic dilemma: at precisely the age when they are most dependent upon provisioning by caretakers to maintain the high and obligatory energy needs of their large brains, they are likely to be cut off from that supply chain as a result of illness and the nutritional stresses of weaning. It is this confluence of factors, and the synergy between nutritional stress and compromised immunity, that accounts for much of the high infant mortality in many societies (Pelletier et al., 1995). Natural selection likely favored neonatal adiposity as a strategy to prepare for these difficult periods. It is easy to imagine how infants with a genetic predisposition to deposit copious quantities of energy as fat prior to weaning would be better represented among the subset who survive to adulthood to reproduce and pass on their genes (Kuzawa, 1998).

It is important to note that these sources of energy stress have largely receded by mid childhood: children have already acquired antibodies against the major pathogens that they are likely to confront. As a result, infections and periods of negative energy balance decline to a small fraction of their high prevalence during the postweaning period. Because older children are far less likely to have to rely upon energy reserves for survival, it is easy to see why the human body places lower priority on maintaining sizeable body fat stores by this age.

Thus, the unique energetic stressors of early life have left an imprint on the developmental pattern of fat deposition in humans, represented by intensive investment in the tissue in the run-up to the stresses of weaning, and a gradual decline in the priority given to maintaining this reserve at older and more resilient ages. But this merely shows that the body is prioritizing the allocation of energy to an energetic buffer. This energy backup must have also been accompanied by the evolution of an efficient distribution and delivery system. Because the brain accounts for 50–80% of the body's energy usage during the first few years of life, we should expect that this delivery system – human metabolism – will be organized around the goal of ensuring a constant supply of energy to this fragile and costly organ. The availability of dietary nutrients is variable and often unpredictable, and as we will see next, human metabolism manages this risk by rapidly modifying energy allocation in response to changes in intake and expenditure. Multiple cues signaling nutritional stress induce a similar response that achieves a common end: stored fats are mobilized for use, while glucose is spared for the brain at the expense of less critical functions like muscle.

TISSUE-SPECIFIC INSULIN RESISTANCE AS A LIFE HISTORY STRATEGY

Although long-term changes in fat stores are monitored by the brain through the effects of fat-derived hormones like leptin, short-term changes in energy metabolism are regulated in a more distributed fashion by organs like the pancreas, and also by the tissues themselves, which alter their own uptake and use of glucose in response to changes in circulating hormones and the supply of nutrients. A sudden glut of glucose or other substrate in the blood stream is sensed by the beta cells of the pancreas, which secrete insulin into the circulation. Insulin stimulates glucose uptake by tissues throughout the body, initiating a negative feedback process that helps re-establish normal basal glucose concentrations. The tissues that are not responsive to insulin are few, but prominently include the organ most vulnerable to energy shortage – the brain (Seaquist et al., 2001). While this may at first seem paradoxical, this tissue-specific pattern of insulin sensitivity provides the body with the ability to modify partitioning of glucose between the brain and other tissues by increasing

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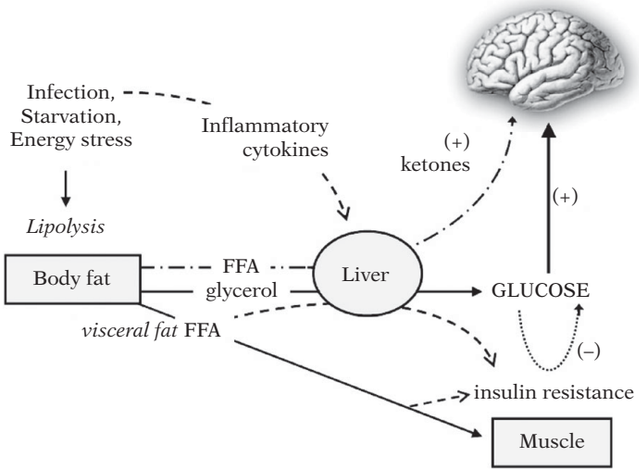

30.4. How body fat and insulin resistance protect the brain. During a crisis, stored triglycerides are broken down into free fatty acids (FFA) and glycerol. Glycerol enters the liver as a gluconeogenic substrate, thus increasing the pool of available glucose. Free fatty acids enter the liver where they are converted to ketone bodies, which the brain uses as a substitute energy substrate. Free fatty acids also induce insulin resistance in the liver and muscle, which spares glucose for the brain. When the nutritional stress is caused by infection, inflammatory cytokines reach the liver and also spare glucose by inducing insulin resistance in liver and muscle.

or decreasing insulin-mediated glucose uptake in the periphery (e.g. muscle, liver, body fat).

How this system of resource partitioning works is well illustrated by cases of accidental insulin overdose. When insulin-dependent diabetics inject themselves with too much insulin, this can be fatal, because it "overfeeds" the insulin-sensitive periphery, leaving nothing to fuel the insulin-independent brain (Waring and Alexander, 2004). Reducing insulin-mediated uptake in the periphery has the opposite effect, as it reduces glucose use in tissues like muscle, leaving more to be delivered to the brain. The body has two means of decreasing peripheral glucose use to spare the brain when confronted with nutritional stress. The first is to reduce insulin production, which reduces glucose uptake in the periphery. Secondly, the body can influence where glucose is used with greater precision by increasing or decreasing insulin sensitivity on a tissue-by-tissue basis. Skeletal muscle is a key player in this flexible system. Because it is the largest consumer of glucose, the body's response to changes in energy status prominently involves modulating muscle glucose uptake by changing insulin sensitivity in this tissue. The brain is an important arbiter of this response. The brain may not be insulin sensitive, but it does express insulin receptors and can also sense the adequacy of the supply of glucose that it receives. In the event that cerebral glucose flux is attenuated, the brain helps ensure its own glucose supply by inducing peripheral insulin resistance via effects on the sympathetic nervous system and other pathways. In addition to these direct effects of the brain, some of the change in glucose partitioning is co-ordinated directly by the affected peripheral tissues, as discussed in greater detail below.

From the perspective of adult metabolic disease, this reduced insulin-stimulated uptake of glucose by skeletal muscle forces the body to increase – and eventually deplete – its production of insulin in type II diabetes (formally noninsulin dependent diabetes, or adult-onset diabetes). However, adopting instead the perspective of a young organism managing a finite energy supply, insulin resistance in a tissue-like skeletal muscle allows the body to shift its priorities of glucose allocation – away from peripheral tissues and toward the fragile and energy demanding brain (Figure 30.4).

HOW VISCERAL FAT AND INSULIN RESISTANCE HELP PROTECT THE BRAIN DURING A CRISIS

Given these design features, it is not surprising that insulin resistance is triggered during states associated with negative energy balance, such as starvation, infection, or trauma (Jensen et al., 1987; Childs et al., 1990). During a fast, free fatty acids (FFA) are first mobilized from the metabolically active visceral adipose depot, which is secreted into the portal circulation that drains into the liver. Fat mobilization from this depot is achieved by innervation of the tissue by sympathetic nerve fibers and, unlike other fat depots, these effects are relatively insensitive to the anti-fat mobilizing effects of insulin (van Harmelen et al., 2002; Hucking et al., 2003). The liver interprets the sudden appearance of FFA in the portal circulation as a signal that the body is being forced to mobilize fat from this depot, and reprioritizes metabolism to protect the supply of glucose to the brain. This is achieved by increasing hepatic glucose production while also inducing insulin resistance in the liver and in skeletal muscle, thus reducing glucose uptake (Kabir et al., 2005). In addition, FFA in the circulation are taken up to be used as energy by tissues like muscle, which directly induces insulin resistance (Roden et al., 1996).

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Similar changes in how the body uses glucose are seen in response to the stress of infection or trauma. The body's first response to an infection includes inflammation, which helps mobilize immune and non-immune resources as a first line of defense against tissue invasion and injury (Fernandez-Real and Ricart, 1999, 2003). Inflammation is initiated in the liver in response to signals indicating tissue injury, such as the appearance of proteins that signal the presence of bacteria, or by molecules called cytokines produced by immune cells like macrophages. Interestingly, in obese individuals visceral adipose tissue is an important source of these cytokines, which, like FFA, are secreted from fat cells into the portal circulation where they induce a similar constellation of changes in energy metabolism as they reach the liver (Tsigos et al., 1999). Why these overfilled fat cells secrete proinflammatory cytokines is currently a focus of intensive research, and there are interesting leads. One is that adipocytes and the immune cells that secrete inflammatory cytokines (macrophages) are closely related cells that share similar patterns of gene expression (Wellen and Hotamisligil, 2003). It is also of interest that fat cells secrete some cytokines as they swell in size, perhaps helping the cell avoid overfilling or rupturing (McCarty, 1999). Regardless of the mechanism underlying the inflammatory effects of excessive body fat, it seems very likely that these cells are now sending signals that, in the past, would have been reliable indicators of infection or trauma rather than obesity. It is ironic to think that the metabolism of the overfed individual today, whose swollen fat cells produce high levels of cytokines, may be tricked by their obesity into sensing an inflammatory challenge or threat, inappropriately initiating the same constellation of metabolic adjustments designed to cope with starvation or infection.

What is clear is that multiple signals of nutritional stress or trauma – whether FFA or cytokines – help link the highly labile fat depot of the abdomen with metabolic adjustments co-ordinated by the liver (Figure 30.4). Not unlike the effects of FFA in the portal circulation, these cytokines induce a state of peripheral insulin resistance, while also mobilizing FFA stored in visceral fat for use as energy. These FFA also bathe the liver, and thus further contribute to insulin resistance through the pathways described above (Pickup and Crook, 1998; Orban et al., 1999).

The evolutionary perspective adopted here, emphasizing the importance of the brain metabolism and the pattern and sources of nutritional stress, helps clarify the logic underlying metabolic adjustments that lie at the heart of the metabolic syndrome: when the body is confronted with a challenge to energy balance, such as starvation or infection, the less critical, peripheral tissues shift to using fats mobilized from adipose tissue, which saves the more easily metabolized and desirable energy substrate of glucose for use by the brain. As peripheral insulin resistance helps the body control where glucose is used, it seems likely that these general features of human metabolism were forged in the evolutionary crucible of early life nutritional stress. As emphasized above, the challenge of fueling the brain, and thus the need to reduce insulin-mediated uptake in the periphery during undernutrition or infection, is most acute, common, and life-threatening at this age. The need to buffer brain glucose must place an important constraint on any response to nutritional stress during fetal life, infancy, and early childhood, when the brain demands the equivalent of 50% or more of the body's total available energy (e.g. Childs et al., 1990).

HOW PRENATAL NUTRITION HELPS FINE TUNE THE SETTINGS OF THE BODY'S ENERGY BACKUP SYSTEM

As previously alluded to, there is now a great deal of evidence that individuals born small have higher risk of developing conditions like diabetes and CVD. The present discussion provides an opportunity to speculate on the function of these biological changes, for they prominently involve resetting how the body prioritizes traits like visceral adiposity and insulin resistance (for a review see Kuzawa et al., 2007). Although most human research in this field has documented relationships between early life nutrition and metabolic disease risk factors in later childhood, adolescence, or adulthood, a handful of studies have now investigated these same outcomes in infants and young children – the age when the allocation of scarce glucose may be most critical for survival, and thus, when these metabolic pathways may have been under particularly strong evolutionary pressure. What these studies find is that, compared to their age mates who were better-nourished prior to birth, individuals born small tend to put on more visceral fat and become more insulin resistant as they gain weight (Soto et al., 2003; Ibanez et al., 2006). Metabolic changes in glucose use and visceral fat are already detectable in the first year of life, showing that a body with a prior history of prenatal nutritional stress is not only prone to adult disease, but also handles its energy and substrate differently during late infancy and early childhood.

Why the body adopts this strategy when prenatal nutrition is scarce is uncertain, but two possibilities seem plausible. Firstly, glucose-sparing adjustments could be important for protecting the brain during prenatal life when intrauterine nutrition is compromised (Hales and Barker, 1992). The challenge of protecting the brain, as outlined above, does not begin at birth, and nutritional shortfall in utero can result when

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fetal demand for energy outstrips maternal supply across the placenta (Harding, 2001). By this reasoning, then, an adjustment made in utero to boost immediate survival may have unintended side-effects after birth (Hales and Barker, 1992).

The second and not mutually exclusive possibility is that some of the adjustments have been shaped for benefits accrued after birth (Gluckman et al., 2005). To the extent that poor prenatal nutrition or maternal stress are correlated with the world that the fetus will be born into, these signals could allow it to modify the priorities of energy use, including the settings of this backup system, to match the severity of postnatal nutritional stress or challenge that it is likely to face (for more on fetal nutrition as an anticipatory cue see Bateson, 2001; Kuzawa, 2005; Wells, 2007; Kuzawa, 2008). These adjustments could help the infant manage its precarious metabolic state and survive this developmental bottleneck of early life nutritional stress when conditions are difficult. But this shift in metabolic priorities would also have the effect of accentuating the metabolic derangements that accompany weight gain when nutrition is chronically abundant. When a previously undernourished body is confronted with excess nutrition, a strategy of prioritizing visceral fat deposition and sparing glucose becomes a liability, increasing risk of developing the metabolic syndrome, diabetes, and CVD as an adult. In other words, if there are "thrifty genes" they code not for static properties but for flexible strategies, or reaction norms. This ability to flex may help match the body's metabolism to nutritional stress early in life, but this may plant the seeds for metabolic diseases caused when nutrition is chronically abundant later in life.

BEYOND FEAST–FAMINE: FRAGILE BRAINS AND METABOLIC PLASTICITY

In proposing the thrifty gene hypothesis, Neel made the elegant point that we gain insights into modern human diseases by reconstructing the environments and stressors that our ancestors faced, as this provides a sense for what our bodies and biology are designed to expect. I have tried to show how we can approach human metabolism from a developmental perspective to hone this exercise in reverse-engineering. Rather than inferring past selection from the default clinical perspective of adult obesity or diabetes, the developmental approach developed in this chapter began by isolating ages of high mortality to identify when metabolism is most critical for survival. Identifying the sources of nutritional stress at the ages of peak nutritional mortality provides clues into the types of biological responses or strategies that would have been available to natural selection to work around this stress, thereby increasing survival and thus genetic fitness. Because the nutritional stress of weaning occurs prior to reproductive maturity, it represents a "developmental bottleneck" through which any metabolic genes must first pass before being passed on to offspring (Kuzawa, 1998). This selection would help ensure that traits that increase early life survival would stabilize into the pattern of human ontogeny across many generations of differential survival. I have argued that body fat, especially the rapidly mobilized visceral fat depot, and the ability to reprioritize glucose allocation by inducing insulin resistance, may be two examples of metabolic traits that could be beneficial to an infant faced with the challenge of buffering its most critical functions like the brain during the common nutritional stressors confronted at this age.

The developmental influences on these metabolic traits show that the genes favored by natural selection do not determine the organism's metabolic state in a simple one-to-one fashion. Not only does adult health depend upon the interaction between one's genome and lifestyle, as long appreciated, but the body also appears to have a capacity to adjust the settings and priorities of its metabolism in response to early nutritional experiences and to cues conveyed by the mother across the placenta. These biological responses may be viewed as examples of the well-known importance of developmental plasticity as a mode of human adaptability (Lasker, 1969; Frisancho, 1993; also see Chapter 2 of this volume). Organisms must cope with ecological and social change on a variety of time scales, spanning rapid and reversible changes (e.g., breakfast followed by a fast until lunch) to much longer trends that take years, decades, generations, or longer to unfold (e.g., extended droughts, migrating to a new ecology, an ice age) (Potts, 1998). Genes are effective at tracking the slowest, most gradual changes in ecology and diet, while homeostasis buffers rapid and reversible changes. Developmental adjustments made in response to early life nutrition operate on an intermediate time scale, allowing the organism to change its settings more rapidly than could be achieved by natural selection, but in a fashion that is more durable and stable than what the body achieves via homeostasis (Kuzawa, 2005).

In this sense, our metabolisms may not be all that different from other systems that have a capacity to adjust long-term settings to local conditions via developmental responses, illustrated classically by the important effects of developmental experience on systems like the brain, the immune system, and the skeleton. Many of the body's systems are built from a genetic architecture that evolved through natural selection, but that – by design – rely upon information about local ecology acquired during early development to complete their construction. There is little doubt that

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the size, configuration, and attachments of the body's skeletal elements evolved through natural selection operating on gene frequencies. However, because individuals are idiosyncratic in their behavior and thus the mechanical loadings that they will impose on their skeletons, natural selection constructed a system that has an exquisite capacity to compensate for biomechanical strain, and to organize developmentally around the pattern of use and disuse in the individual. Perhaps it should come as no surprise that the body's priorities of energy allocation, which are so critical for survival, should have a similar capacity. After all, humans do not merely vary in their culture, pathogen ecology, and pattern of physical activity, but also in their diet, nutritional sufficiency, and exposure to metabolically demanding stressors. These physiological and metabolic "loadings" may be hidden from view, but they are just as critical as components of the individual's adaptive strategy. The ability to adjust metabolic settings to local conditions might help humans prepare for important adaptive challenges, like the severity of infant and early childhood nutritional stress outlined here. However, this same flexibility may also carry longer-term costs to health in modern environments, especially if scarcity-adapted metabolic priorities adopted early in life are later confronted with chronic overnutrition and weight gain (Gluckman et al., 2005).

It remains to be determined which of these ideas about the function of these traits are correct in detail. What does seem clear is that our metabolisms are designed to do more than survive the crisis of famine. Identifying the ages and causes of nutritional stress and nutritional mortality – both external and internal to the body itself – will be critical if we hope to understand how natural selection responded to this stress, and the legacy of these adaptations for the current global plague of metabolic disease.

DISCUSSION POINTS

1. Human babies are born with more body fat than any other mammal – including seals. What might explain the evolution of this unusual trait?
2. The human brain is energetically very costly, especially early in the lifecycle. What are some of the ways that evolution may have changed human biology to allow the evolution of a large brain size in humans?
3. It is well known that diseases like diabetes and cardiovascular disease "run in families," reflecting a genetic contribution. Yet, these diseases have emerged as major public health problems in a few short generations – which is not enough time for gene frequencies to change substantially. How do we reconcile these observations?
4. This chapter argues that developmental adaptations made by the fetus to nutritional stress could contribute to a higher risk for diabetes later in life. What are these adaptations and how might they be beneficial early in life?
5. Chronic diseases often negatively impact health and survival late in the lifecycle – when one's genome has already been passed on via offspring to the next generation. Discuss how selection pressures operating early in the lifecycle might influence the evolution of diseases with late life negative impacts.
6. If we ask "What are the causes of the diabetes epidemic?", a public-health or medicine-inspired answer to this question might note that many people are eating too much and gaining weight, among other factors, which leads to insulin resistance. What types of answers does an evolutionary approach to this problem inspire, and how are they different from a public health or medical approach?

ACKNOWLEDGEMENTS

Dan Benyshek, Dan Eisenberg, Peter Ellison, Lee Getler, David Haig, Elizabeth Quinn, Melanie Vento, and two anonymous reviewers provided helpful comments on various drafts of this paper.

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