

ADIPOSE TISSUE AND ADIPOKINES IN HEALTH AND DISEASE

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Developmental Perspectives on the Origins of Obesity

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Abstract

This chapter reviews the developmental pathways contributing to the origin of obesity. Evolutionary considerations are emphasized. At birth more than half of a human baby's metabolism is devoted to the brain and it is suggested that the extreme neonatal and early childhood adiposity of humans is an adaptation to provide an energy reserve during periods of nutritional stress arising from infections and the process of weaning. This chapter also reviews the substantial experimental and clinical evidence for prenatal and early postnatal factors in the development of obesity. Developmental pathways that may lead to obesity include fetal undernutrition caused by an impaired intrauterine environment, fetal overnutrition and macrosomia caused by maternal diabetes, and infant overnutrition caused by excessive early feeding. There is evidence for interactions between these pathways and for intergenerational influences. Finally, this chapter discusses the implications for the global obesity epidemic of mismatch between the genotype, environment, and lifestyle, and underlines the potential role of inappropriate adaptive responses during development in populations undergoing rapid nutritional transition.

Key Words: Obesity; evolution; development; environment; fetal nutrition; developmental plasticity; adaptive responses; prediction; mismatch.

1. UNDERSTANDING OBESITY REQUIRES A DEVELOPMENTAL AND EVOLUTIONARY PERSPECTIVE

Ever since Neel's proposition of the "thrifty gene" hypothesis more than 40 yr ago (1), evolutionary explanations for the origins of human obesity have assumed that our tendency to put on weight in a modern environment is the vestige of a trait that was beneficial under the more austere nutritional conditions of the past. Neel proposed that, for millions of years during the Paleolithic, humans and our hominin ancestors survived as roaming bands of foragers who faced an unpredictable food supply. Given this, an ability to capitalize on any excess energy by efficiently depositing it as fat during periods of "feast" would have boosted the chances of surviving the inevitable future "famine." We inherited our genes from ancestors who survived these recurrent ecological crises, which now leave us prone to obesity and diabetes in a contemporary environment of nutritional abundance.

Neel's hypothesis was invaluable for stimulating interest in the evolutionary origins of human obesity. In particular, the thrifty gene model heightened awareness that the environment can change more rapidly than the genome, potentially leading to novel diseases through "mismatch" between genes and environment. Despite these important contributions, the hypothesis has difficulty explaining more recent advances in our understanding of the obesity epidemic and its health sequelae. As crosscultural data accumulate, the heterogeneity in the prevalence and health consequences of obesity are not easily reconciled with a purely gene-based model of obesity risk (2). Observations among societies experiencing ongoing nutritional transitions in Asia, Latin America, and elsewhere document a heightened metabolic disease risk for a given level of body mass index or adiposity (3–5). The hypothesis would need to be modified to explain this. Additionally, there is now evidence that famine was less common among our foraging ancestors than presumed by Neel's model (6), raising doubts about its central assumptions (2). Further complexities arise as etiological insights change; for example, current understanding of the pathogenesis of obesity-related disease now includes a significant role for immune activation, and this is not easily encompassed within the model (7).

That human metabolism is not primarily crafted to survive famine is suggested by a closer examination of the developmental trends in body composition that characterize the human lifecycle. As illustrated in Fig. 1, body fat in humans constitutes a larger percentage of weight at birth than in any other mammal so far studied (8). This is followed by a continued fast pace of fat deposition during the early postnatal months. In well-nourished populations, adiposity reaches peak levels at around the age of weaning before gradually declining to a nadir in childhood, when humans reach their lowest level of adiposity in the lifecycle before again increasing in the prepubertal phase. If the threat of famine is what molded the human metabolic propensity to deposit and maintain extra body fat, it is not obvious why children's bodies should do so little to prepare for these difficult periods. These developmental changes in body composition suggest that the evolutionary forces that selected for the size of the energy buffer during early life were primarily aimed at defending against nutritional stress that has largely subsided by mid-childhood. Indeed, the low priority placed on maintaining an energy reserve during childhood suggests that the background risk of starvation faced by our ancestors may have been smaller than often thought.

This chapter first reviews the nutritional ecology of the period spanning mid-gestation through early childhood and consider the influence that natural selection operating at this age may have had on the modern human genome and the risk of metabolic disease. We adopt a developmental perspective to move beyond Neel's model and take into account the sources and age-specific intensity of nutritional stress and natural selection. There is now substantial evidence that developmental responses to early nutritional environments can modify our genetic pattern of ontogenesis (developmental plasticity), with lasting effects on our physiology and metabolism. Secondly, we discuss evidence for several developmental pathways now known to link early environmental experiences, including nutrition, to later metabolism, weight gain, and disease. Just as Neel emphasized the past adaptive significance of genes, these newly discovered and potentially adaptive modes of developmental response may provide greater flexibility in the face of ecological change than can be achieved through the slow process of genetic change.

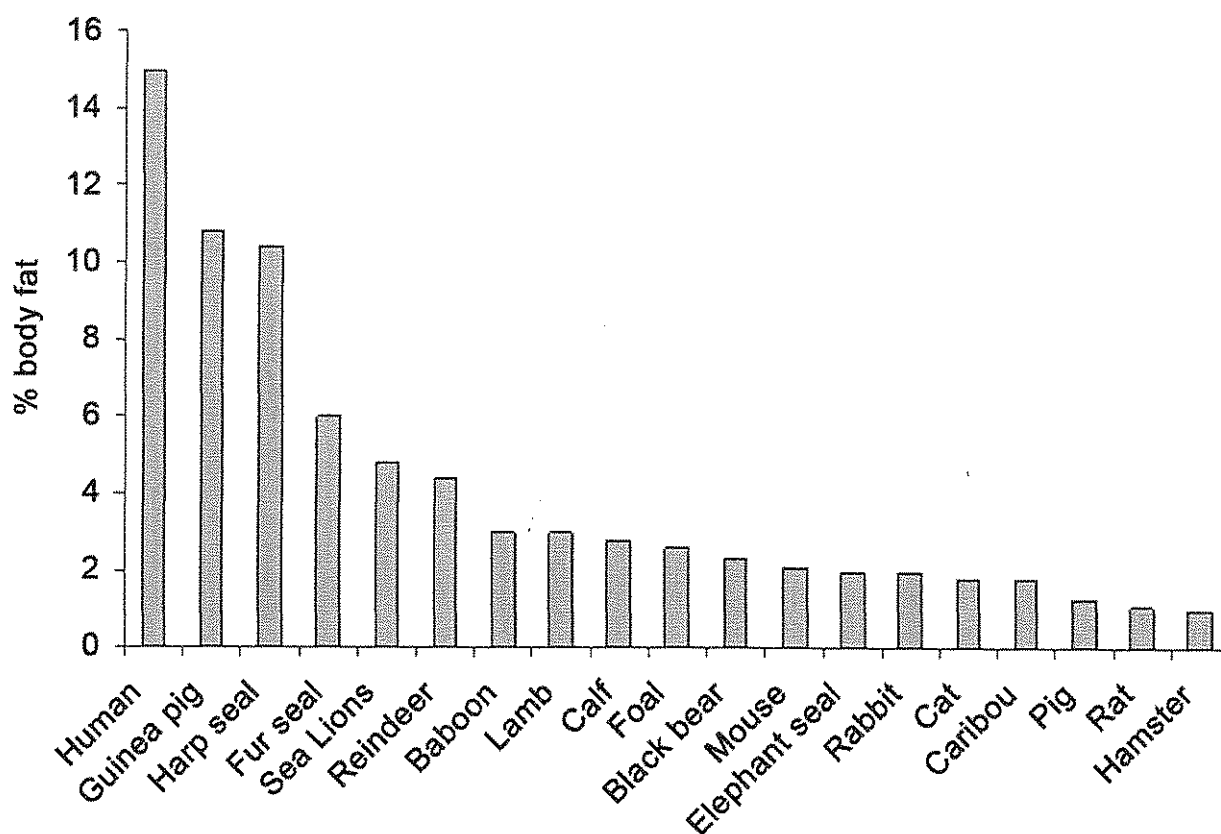


Fig. 1. Percentage of body fat at birth in mammals. Adapted from ref. 8.

These considerations underscore the need to take development seriously in studies of metabolic disease. We conclude by speculating that the accelerating pace of the global obesity epidemic and its rising disease burden may be the result of two related forms of mismatch: that between the human genome and the novel lifestyle of contemporary human populations and, in more rapidly changing environments, that between the constraints imposed by developmental processes together with early nutrition and the environment and lifestyle subsequently experienced in adulthood.

2. DEVELOPMENTAL PERSPECTIVE ON ENERGY BALANCE IN HUMAN EVOLUTION

Humans are unusual with respect to their high level of natural “obesity” (9). This trait is particularly obvious at birth, when humans have more body fat than any other species (8). Explanations for our distinctive “baby fat” have traditionally proposed that it is related to loss of body hair, and it is widely assumed that natural selection compensated for this by increasing the layer of insulative body fat (10,11). 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 (8). Humans are exceptional in the size of their brains, and at birth more than half of the body’s metabolism is devoted to this organ (12). Unlike energy expended on other tissues or systems, brain metabolism is less flexible during a period of nutrient shortage, and must be maintained within narrow limits. Thus, our large brains impose a double burden on metabolism during infancy: they increase demand for energy while restricting the flexibility of metabolic requirements when that demand is not met.

Other factors common during infancy can impede the supply of nutrients, ensuring that negative energy balance is a frequent occurrence at this age in most populations. We are born with a naïve adaptive immune system and must become exposed to specific pathogens to acquire the repertoire of antibodies necessary to protect us from future infection. Exclusively breastfed infants are initially shielded from exposure to pathogens and gain some passive immunity through their milk, so that they are often quite healthy in the early postnatal months. But, as energy requirements outstrip the supply capacity of breast milk by roughly 6 mo of age, less sterile supplemental 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 early-life mortality and poor childhood growth (*see ref. 13 for a review*). The ensuing nutritional depletion has the effect of suppressing immune function, leaving the infant more prone to future infection and thus a compounding cycle of nutritional stress.

Human infants thus face a profound energetic dilemma: at the age when they are most dependent on provisioning by caretakers to maintain the high and inflexible metabolic requirements of their large brains, they are also at risk of separation from that supply chain as a result of illness and the nutritional stresses of weaning. It is this confluence of factors, and the link between nutritional stress and immature immune function, that accounts for much of the high infant mortality in many societies (*14*). And this is where evolution has likely favored neonatal adiposity as a strategy. It is not difficult to imagine how infants with a predisposition to deposit fat prior to weaning might be better represented among the subset who survive to adulthood to reproduce and pass on their genes (*8*). Infants typically experience not a single infection, but cycles of infection followed by recovery. Thus, it is those infants who efficiently replenish their energy reserves during recovery intervals who will be better equipped energetically to survive any future illness. From this perspective, the infant experiencing cycles of illness faces a metabolic challenge not unlike Neel's proposed recurrent episodes of feast and famine.

The evolutionary imprint of this energetic stress is most conspicuous in our distinctive adiposity at birth, indicating that the process of fat deposition begins much earlier, during gestation itself—as does the challenge of protecting a relatively large brain. The size of the brain is large relative to body size throughout late gestation and the fetal brain is relatively protected under conditions of fetal undernutrition. Recent studies also show visceral fat to be conserved in the face of fetal undernutrition (*15,16*). Thus, early human development, beginning *in utero* and continuing into early childhood, is an energetically precarious stage in the lifecycle, even though the supply line of nutrients and common causes of nutritional insufficiency shift at parturition and at weaning.

These sources of energy stress have largely receded by mid-childhood: the fraction of total metabolism required by the brain has declined substantially and children have already acquired immunity against the major pathogens that they are likely to face. It thus makes sense that the human body places little priority on maintaining sizable body fat stores by this age. This would of course *not* be true if famine were the main source of selection on human body composition and metabolism, in which case we should expect no decline in adiposity in childhood.

3. DEVELOPMENTAL PATHWAYS TO OBESITY

Given that infant and child mortality is highest as a result of developmentally mediated undernutrition during the earliest stages of the lifecycle, natural selection operating at this age may have had an important influence on the evolution of human metabolism. It is notable, for instance, that the challenge of surviving recurrent infections shares similarities with Neel's vision of a feast–famine scenario, and might be expected to favor the rise of similar metabolic-disease predisposing genes. In this sense, early life might be likened to an “ontogenetic bottleneck” through which any adult metabolic traits must first pass (17). Although all humans experience this age of heightened energetic vulnerability, there is much variation in the environments that individuals experience, which determines whether they will be forced to rely on such contingencies as brain sparing, lipolysis, or rapid replenishment of body fat. There is now considerable experimental evidence that one's early nutritional experiences, both *in utero* and during infancy, may act through developmental plasticity to permanently influence traits such as appetite, tissue-specific insulin sensitivity, and weight gain (18). As will be discussed, there is much interest in establishing whether these responses have an adaptive basis, and if so, whether they are primarily designed to serve a short- or long-term adaptive function (17–21). What is certain is that these responses can have profound long-term implications for the risk of gaining excess body weight and the metabolic consequences of that weight gain. There is increasing evidence for at least two and possibly three developmental pathways that can lead to obesity; these will be discussed separately.

3.1. Fetal Undernutrition Pathway

There is a considerable body of epidemiological data relating an impaired intra-uterine environment to the development of later central adiposity. For instance, studies of elderly populations show greater visceral adiposity among individuals who were born small (22). Children of smokers, who experience prenatal hypoxia and are likely to be born small, are more likely to develop obesity (23). Studies of the Dutch winter famine of 1944–1945, where previously well-nourished women were exposed to Nazi-imposed severe rationing, show that those who were pregnant during the famine gave birth to offspring who subsequently became obese (24).

Experimentally, it can be demonstrated that animals born to undernourished mothers are relatively more obese; this is particularly evident if the offspring are placed on a high-fat diet after birth (25). The obesity induced by these early life exposures has both central and peripheral components. In both the rat (26) and sheep (27,28), changes in the neuroendocrine anatomy in the hypothalamus are described following nutritional limitations induced *in utero*. Animals born after adverse fetal manipulation also tend to be hyperphagic and to have a preference for fatty foods. They are also sarcopenic and mature to have peripheral insulin resistance, fatty liver, and truncal obesity (29).

Such observations have generally been made in the context of studies of the early life antecedents of maturity-onset diabetes and heart disease—the so-called developmental (or fetal) origins of adult disease paradigm. There is now a large body of epidemiological, clinical, and experimental data showing that an adverse intrauterine environment predicts a variety of physiological and metabolic traits that are consistent with a greater risk of lifestyle diseases in later life, including but not limited to obesity. For instance,

both impaired pancreatic islet cell function and greater insulin resistance are reported among individuals born small (30), or among rats or sheep exposed to undernutrition as fetuses (31). There have been major reviews of the developmental origins model recently (21,32,33).

Within this literature, there has been debate as to whether it is the initial impaired nutritional environment or the delayed response of rapid postnatal catch-up growth that is causally related to these later-life health consequences (34). The experimental data show that the rate of weight gain is related to both the prenatal and the postnatal nutritional exposure of the growing rat (25,29) and a number of experiments or clinical observations, such as the Dutch famine data, suggest that there is a clear fetal component. The clinical data also suggest that the propensity for obesity is in part prenatally determined. For instance, whereas subcutaneous fat at birth is linearly related to later body weight, visceral fat is not reduced in smaller babies (15,16), suggesting that the tendency for visceral obesity can be induced *in utero*, or that such individuals preferentially protect deposition and maintenance of visceral depots. In perhaps the most studied cohort, from Helsinki, adults who developed diabetes or insulin resistance were born small and did not show catch-up in weight during the early postnatal years. However, they did experience an earlier childhood adiposity rebound and put on weight faster in late childhood (35). Not dissimilar but more limited data are reported from an Indian cohort (36).

Genetic polymorphisms clearly impact on the interaction between the developmental environment and long-term phenotypic outcomes. For example, a polymorphism in the PPAR γ gene is associated with an elevated risk of insulin resistance in adults but only if birthweight was reduced. Presence of the polymorphism in the absence of fetal growth impairment is not associated with an increased risk of insulin resistance (37). Recent studies have shown similar interactions between polymorphisms in a number of loci, birth size phenotype, and later disease risk. These include the angiotensin converting enzyme gene (38), plasma cell glycoprotein-1 (39), glucokinase (40), and the vitamin D receptor (41). In such analyses, birthweight is likely to generally be a surrogate for an adverse intrauterine environment rather than causally related, but in some cases—for example, the glucokinase mutation (40)—the polymorphism may affect insulin sensitivity or action, adding directly to the strength of the association as insulin is an important regulator of fetal growth (42).

But although there are clearly genetic influences, the thrifty genotype model cannot explain the experimental or clinical data linking early undernutrition to elevated adult metabolic disease risk, or findings such as research on the Dutch winter cohort discussed above. An adaptive explanation for such observations was first proposed by Hales and Barker (19), who suggested that smaller babies make a number of adaptations *in utero* to survive, including inducing insulin resistance, which leave them more able to cope in a poor postnatal environment but which also made them more at risk of disease in later life. As with the thrifty gene hypothesis, this “thrifty phenotype” model has limitations. For instance, it cannot explain the continuous relationship between birth size and later disease risk that can be seen even in infants above the mean birthweight, nor can it explain why growth-retarded infants tend to protect visceral adiposity at birth. It also assumes that insulin resistance is present at birth, and both clinically and experimentally this appears not to be the case (43,44). In some cases growth-retarded neonates

indeed appear to have heightened insulin sensitivity (43). It also assumes that slowed growth rate is a central adaptation to a compromised prenatal nutritional environment, yet many of the experimental associations do not rely on birthweight; this is also the case in some clinical observations such as the Dutch famine data (45,46) and some recent cohort studies (35,47). Finally, the hypothesis cannot explain developmental induction in the face of physiological challenges other than nutrition. The thrifty phenotype concerned itself only with glucose/insulin metabolism, whereas subsequent work has shown effects on myriad other systems (21,48). A recent study of children conceived by *in vitro* fertilization shows them to be taller, leaner and to have heightened insulin sensitivity (49), suggesting that fetal responses to environmental manipulation need not act only in a direction toward “thriftiness.” Thus, a more comprehensive model is needed if we are going to explain the broader pattern of responses, of which obesity is one manifestation.

A more general adaptive model based on the concept of predictive adaptive responses and developmental mismatch has recently been proposed (50,51). The mismatch model suggests that all fetuses (and embryos) across the full range of environments sense their environment and, based on such cues, set their life course strategy, mediated by epigenetic processes, according to the environments they predict that they will meet postnatally (21,52,53). In particular, if the fetus predicts an adverse nutritional environment it will induce strategies such as preserving fat mass at the expense of metabolically costly muscle (sarcopenia) while reducing expenditures on other structures and costly physiological functions, including immune function, investment in reproduction, and cellular maintenance functions that normally delay the onset of aging (18,48,54). The model can provide an explanation of why a population undergoing rapid nutritional transition is at greater risk (18).

The underlying mechanisms in this case would require a capacity to predict future conditions on the basis of early life cues, which may be nutritional but could also be, for example, endocrine or oxidative stress, and to respond developmentally in an appropriate fashion. Modeling shows that such predictive responses need not be completely accurate to provide a fitness advantage (51,55). Moreover, it has been argued that the fidelity of the prenatal nutritional cue may be enhanced by maternal buffering mechanisms and intergenerational effects on fetal nutrition (17). For instance, fetal growth rate—and, by implication, fetal nutrition—is predicted not only by the mother’s current nutrition but also by her nutritional status prior to pregnancy (56), which reflects her cumulative nutritional experiences in the years prior to conception. Birthweight is also predicted by the mother’s (but not the father’s) own growth rate during both childhood and during her fetal life, and by extension, the nutritional conditions experienced by the grandmother as conveyed *in utero* to the mother as a fetus. Such intergenerational influences on fetal nutrition and growth are well established (57). By integrating nutritional information across several generations, fetal nutrition may provide a higher-fidelity cue of typical conditions than might otherwise be possible (17).

It is also important to note in this context that the fetal environment is, with the exception of gestational diabetes, always nutritionally constrained to varying degrees (21,58,59). The processes of maternal constraint have evolved particularly in monotocous species to limit fetal growth to match the maternal size phenotype, so that vaginal delivery is possible in a species with a uniquely large head but a pelvis narrowed by the adoption of an

upright posture. The mechanisms of fetal growth limitation are poorly understood, but may involve both utero-placental function and interactions between the maternal and paternal genomes via the imprinted IGF-2 system (60). It has been suggested that maternal constraint has had the additional evolutionary advantage of moving fetal development toward a set-point favoring predictive adaptation matched to a nutritionally deprived environment (51). This might provide an additional fail-safe protection for the infant. As constraint operates even in normal pregnancies, this limits the range of nutritional environments that the infant can be matched to postnatally, and as a result of improved access to food and more sedentary lifestyles more children and adults are now placed in environments above this limit. Disease risk is enhanced as a result.

Constraint and developmental induction can well extend into the neonatal period, as the neonate is entirely dependent on the mother for nutrition. Recent studies provide some support for this model. For example, if neonatal rat pups born to undernourished mothers are treated in the neonatal period with leptin, they do not become obese even if placed on a high-fat diet (29), suggesting that the predictive trajectory can be altered by neonatal manipulation.

In this model, then, factors that reduce the fidelity of the predictive cue can lead to a developmentally based mismatch between biology and environment, not unlike Neel's proposal of a gene-environment mismatch (59,61). Indeed, the processes mediating the predictive mechanisms must have been selected and preserved through evolution, rather than have Neel's thrifty genes. The fidelity of the predictive cues may be reduced by factors such as faulty maternal transduction (for example, maternal smoking inhibiting transplacental nutrient transfer) or severe maternal constraint limiting nutrient supply to the fetus (for example, young or primiparous mothers) or by genetic polymorphisms affecting mechanisms regulating nutrient delivery to fetal tissues (39). The signal may also have low fidelity as a result of rapid environmental or nutritional change, as exemplified by populations experiencing a "nutrition transition" to higher intake of dietary energy and fats coupled with reduced physical expenditure (3,61). Under these circumstances, the nutritional cue conveyed to the fetus may become inaccurate as the environment changes, thereby heightening risk of metabolic derangements as individuals poorly nourished early in life gain weight. This proposal may help explain why the BMI is a particularly strong predictor of hypertension, diabetes, or heart disease in nations like China, Brazil, and the Philippines, all of which are experiencing an ongoing, rapid nutritional transition of recent onset (3,62). Conversely, the finding that compromised birth outcome does not predict elevated adult risk for cardiovascular disease in The Gambia, where poor nutritional conditions have not improved, is also consistent with this model (63).

3.2. Fetal Overnutrition Pathway

In addition to these effects of prenatal undernutrition, it is well recognized that the fetuses of diabetic mothers are born with relative obesity, suggesting a separate pathway linking prenatal nutrition with later risk of metabolic disease. Maternal hyperglycemia leads to fetal hyperglycemia and fetal hyperinsulinemia, which promotes excessive fat deposition during the third trimester. The degree of subcutaneous adiposity is increased even under conditions of subclinical maternal hyperglycemia. The increased adiposity in fetal life may then be magnified by postnatal overnutrition, and the obesity that is generated often, in turn, leads to type 2 diabetes (64).

3.3. *Multigenerational Influences*

The situation across generations is more complex, and available data suggest that it is possible to begin with either prenatal undernutrition or overnutrition and to stabilize on a pattern of intergenerational macrosomia and diabetes. Mothers who were born as macrosomic babies are themselves at risk of gestational diabetes and thus of “transmitting” macrosomia to the next generation. Alternatively, mothers born in an impaired intrauterine environment are at greater risk, because of their altered insulin sensitivity, of developing subclinical or gestational diabetes, as discussed above, and may subsequently give birth to a macrosomic infant at heightened risk of developing obesity as a result (65). This intergenerational sequence has been suggested as an explanation for the extremely high prevalence of diabetes among some Native American groups (2). In India, where mothers are small owing to nutritional limitations in childhood and intergenerational stunting, women who give birth to infants in the upper tertile of the birth-weight range (mean 3300 g, mean for whole sample 2700 g) are more likely to develop type 2 diabetes within 8 yr than are women who deliver smaller babies (66). Thus it would appear that when the mother is small, she may give birth to a relatively small baby, although relatively large for that population, and that this baby then follows the overnutrition pathway.

3.4. *Infant Overnutrition Pathway*

Although there are conflicting data, recent systematic reviews concur that breastfeeding confers some protection against the development of childhood and adult obesity (67,68). In turn, these studies imply that feeding infant formula or cow’s milk results in a greater risk of obesity. This could reflect the greater caloric and protein load of cow’s milk, which can lead to overnutrition in infancy, or as yet unidentified beneficial effects of other breast milk components, such as growth factors or hormones such as leptin. In rats, high nutrition in infancy can induce both peripheral and central components of obesity, involving changes in both local depots and hypothalamic neuroendocrine pathways (69,70). The effect is apparent in both premature and term infants, suggesting that it is early feeding that is particularly sensitizing to the development of later obesity (71). A recent long-term cohort study identifying an association between adult obesity and rapid weight gain in the first week of life of formula-fed infants tends to confirm a deleterious effect of early overnutrition rather than an intrinsic protective effect of breastfeeding (72).

Although the studies are not comparable, either in terms of populations or their historical and geographical situations, there is an unexplained paradox: one group of studies suggests the importance of infant overnutrition as predisposing to obesity (34), whereas a separate group of studies points to lower birthweight and underweight in infancy followed by earlier adiposity rebound in childhood as the causative factors (35,36). This suggests that there are likely to be two or more independent developmental pathways that may link infant nutrition with later weight gain. Alternatively, they may be both reflections of a common pathway informed by pattern of growth in which a constrained nutritional environment (fetal or infant) is followed by a nutritionally enriched environment. The degree of constraint varies, some pregnancies are more constrained than others (58), and the speed, nature, and degree of nutritional transition can vary; all influence the pattern of developmental plasticity and the degree of mismatch and thus the

disease risk (18). Additionally there is clearly genetic variation influencing the outcome of environmental interactions during development (37). Even though the specifics of the pathways involved remain unclear, this does not diminish their substantial contribution to disease risk, a contribution that is still not widely realized. Calculations performed on the basis of birthweight, weight at 1 yr, and weight at 11 yr suggest that abnormal patterns of fetal and infant growth could account for roughly 50% of the risk of heart disease and non-insulin-dependent diabetes (73). This is a fertile area for ongoing research.

4. CONCLUSIONS

In the more than four decades since Neel's publication of the thrifty gene hypothesis, obesity has been viewed as the result of an ancient metabolism adapted to feast-famine conditions, now thrust into a modern world of chronic nutritional excess. Famine or other ecological crises may indeed have been among the most important sources of nutritional mortality among our adult ancestors, but this should not be extrapolated uncritically to the human lifecycle as a whole. Before reaching adulthood, humans first must survive the energetic turmoil and high mortality associated with gestation, parturition, and weaning, exacerbated by a relatively large and energetically demanding brain and compounded by the inevitable infections of childhood. If human metabolism is "designed" to survive nutritional stress, we have argued that the nutritional stress of early life is likely to have left a more prominent evolutionary imprint on our metabolic homeostasis and modes of adaptive response than has famine. As one example of the potential utility of the model discussed above, the intimate ties between infectious disease and nutritional stress during early life provide a useful starting point for considering the interconnections between metabolic and inflammatory processes that are now recognized as central to the metabolic syndrome.

The extensive research documenting the developmental origins of health and disease (DOHaD) paradigm makes it clear that susceptibility to obesity and metabolic disease is not dictated solely by one's inherited genome and adult lifestyle, but is also powerfully influenced by developmental processes initiated by nutrition *in utero* and continuing into the postnatal period. As discussed, one proposal we favor to explain these findings states that fetal, and perhaps infant, nutrition acts as a cue for predicting future nutrition, thus allowing the organism to adaptively modify its metabolism, physiology, and life history characteristics in a predictive fashion. That fetal undernutrition can lead in certain circumstances to a greater predisposition to weight gain, or a greater sensitivity to the adverse health effects of weight gain, intuitively supports this proposition of early life prediction, for it shows that undernutrition contributes strongly to heightened future disease risk only when conditions have changed significantly between birth and adulthood. Also supporting this model is the finding that, when environments do not change and individuals poorly nourished early in life remain marginally nourished as adults, the risk of obesity-related conditions is not elevated (63).

If prediction were the rule across the full range of early environments, we might expect prenatal overnutrition to protect against the adverse health effects of overnutrition later in life. There is some evidence that this might be the case in the absence of pathological causes of fetal overnutrition. Whereas infants born thin and who become fat as children are at greater risk of later disease, children born with a high ponderal index and who have a high ponderal index in childhood are at no particular enhanced risk (74). Experimental exposure to high-cholesterol diets *in utero* induces

greater postnatal cholesterol tolerance in pigs (75). High prenatal nutrition is associated with longevity in mice (76), whereas after birth it is undernutrition that is associated with longevity.

The contrary situation of macrosomia caused by maternal diabetes is likely to be a recent pathological development reflecting the very different nutritional environments of modern humans compared with conditions prevalent in the Paleolithic and Neolithic. Maternal undernutrition was likely to be far more common during hominin evolution than was gestational diabetes, which—like obesity itself—has emerged as a health problem only in recent generations. As is true for all biological systems, developmental responses to early environments must have limits within which they are designed to operate, reflecting the range of expected conditions likely to have been experienced by our ancestors. This system may now be pushed by chronic intergenerational excess to a state rarely expressed phenotypically in the past.

Although questions remain regarding the function of early-life developmental plasticity, the available data are sufficient to propose a tentative revised model for the origins of obesity and related diseases. The model includes two forms of mismatch, each reflecting adaptive processes operating on different temporal scales. The first is a process of gene–environment mismatch akin to that proposed by Neel. This could help explain the general human tendency to gain weight under modern conditions of reduced energy expenditure and increased intake, and for metabolic conditions such as insulin resistance to be triggered inappropriately by factors such as novel proinflammatory features of the environment. The second form of mismatch is based on developmental plasticity, as documented by the DOHaD literature, which may help to explain the heterogeneity in the obesity epidemic and its consequences. When conditions change markedly within a single generation, or when early-life predictive signals have low fidelity, this may lead to additional mismatch and metabolic disturbance. As emphasized, these latter effects could help explain some of the important features of disease transitions in populations experiencing a particularly rapid pace of dietary and lifestyle change (77).

This mismatch model potentially helps to explain some features of the modern obesity epidemic that are not addressed by a gene-centered model and is also consistent with the growing appreciation of the role of developmental processes, including plasticity, in adaptation and evolution among a wide range of organisms (78–80). Natural selection has favored a range of strategies to help our ancestors manage the vagaries of ecology and nutrition, including a genetic architecture with an appropriate set of metabolic priorities and flexibility in developmental processes capable of responding more quickly to changing conditions than would be possible via genetic change alone (52). Although these processes may have allowed efficient tracking of gradual changes in past environments, especially the more threatening situations of reduced nutrition, their adaptive capacities are now overtaxed, leading to metabolic disease, when they are confronted with the evolutionarily unprecedented pace of change in modern environments.

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