CHAPTER 17

Evolutionary Medicine and Obesity

Developmental Adaptive Responses in Human Body Composition

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Baker and colleagues reinforce a recurrent theme about the significance of "conditioned responses" and individual variability in their work exploring fetal–adult developmental continuities. They test a variety of research models looking for consistencies in associations between fetal growth patterns and both body composition and neurological development beginning in utero and during childhood. They also include adolescence–adulthood continuities. One inference from their work is that often statistical associations are dependent on the type of method used to analyze them. Even so, one important consistent finding is that individuals who experience reduced fetal growth also experience deficits in brain size (assessed by imaging techniques and anthropomorphic measurements including head circumference) and neuron formation. When all populations and circumstances across societies were considered, they found mixed support for the link between reduced fetal growth and later fatness or obesity. They discuss the possibility that it may not be so much that the relationship is not real but that other factors also play important roles in the expression of adult phenotypes. That muscle mass, brain size, and abdominal fatness may at times be affected differentially in relationship to in utero conditions may be best accounted for, they argue, by considering the time at which each individual is measured and the possibility that later "fatness" is increased under some conditions but not others. Rather than asking if reduced fetal growth leads to later obesity, they suggest that perhaps a better strategy, one reminiscent of foraging evolutionary models (i.e., models that examine how food quantity, quality, and collecting/harvesting/preparation patterns are fitted to the local ecologies), is to ask under what conditions reduced size at birth leads to obesity—a solution that no doubt the next wave of researchers will implement.

OBESITY AND CHRONIC DISEASE IN THE MODERN WORLD

Currently, obesity looms as perhaps the greatest long-term health threat for humans in both developed and developing countries (Frisancho, 2003; World Health Organization, 1998). Because of its relationship with a host of chronic diseases, including heart disease, hypertension, and even certain forms of cancer, understanding the determinants of obesity has important implications for both clinical practice and public health strategies (Bjorntorp, 1990, 1997b; Bjorntorp & Eden, 1996). It has been suggested for over 40 years that evolutionary biology might provide important perspectives on the development of obesity (Knowler, Pettitt, Savage, & Bennett, 1981; Neel, 1962; Neel, Weder, & Stevo, 1998; West, Bailey, Coniglione, Smith, Scroggins, & Ellison, 1974). Recent epidemiological findings linking reduced fetal growth to changes in body composition at birth, during childhood, and into adulthood have renewed interest in the evolutionary origins of human obesity and the role of developmental responses in shaping the process (Cameron & Demerath, 2002; Gluckman & Hanson, 2004; Gluckman, Hanson, Moran, & Pinal, 2005; Kuzawa, 2005).

People who experienced reduced fetal growth have an increased risk of becoming obese, but their phenotype is characterized by some interesting features in addition to increased fatness. These individuals also tend to have reduced muscle mass and greater storage of body fat within the abdomen, sometimes called a centralized pattern of fatness or, colloquially, an "apple-shaped" physique (Bjorntorp, 1990, 1997; Bjorntorp & Eden, 1996; Frisancho, 2003). Reduced muscle mass and more abdominal fatness increase risk for diabetes, heart disease, and hypertension above the risk from increased fatness alone (Bjorntorp & Eden, 1996). Many studies have linked each of these aspects of body shape and composition to reduced growth in utero (Barker, Robinson, Osmond, & Barker, 1997; Cameron & Demerath, 2002; Erikkson, Forsen, Tuomilehto, Osmond, & Barker, 2001; Euser, Finken, Kejzer-Veen, Hille, Wit, & Dekker, 2005; Jaddoe & Witteman, 2006; Kahn, Narayan, Williamson, & Valdez, 2000; Kensara, Wootton, Phillipps, Patel, Jackson, & Elia, 2005; Koziel & Jankowska, 2002; Labayen, Moreno, Blay, Blay, Mesana, & Gonzalez-Gross, 2006; Laitenen, Pietilainen, Wadsworth, Sovio, & Jarvelin, 2004). Interestingly, it has been suggested that these changes might have an adaptive basis that help to prepare the growing fetus for the world it will inhabit. If so, the link between slowed growth in utero and altered physiology and body composition later in life should be explicable via developmental models adopted from evolutionary biology (Levins, 1968; Schlichting & Pigliucci, 1999).

This chapter reviews the perspective that evolutionary medicine offers for understanding the relationship between obesity and reduced fetal growth resulting in small size at birth. Two different evolutionary models of chronic disease risk may be proposed to explain obesity later in life among those born small: (1) the predictive adaptive response (PAR) and (2) the brain optimization rule. The conceptual feasibility and empirical predictions of both models are compared, then contrasted with a third, more general model, that physiological "damage" during stunted fetal growth produces all of the observed changes in adults. The predictions of each model are tested using the conclusions from epidemiological research. The chapter closes with a discussion of the implications of these findings for clinical practice and epidemiological research.

EVOLUTIONARY MEDICINE AND EVOLUTIONARY MODELS OF DEVELOPMENTAL OBESITY

The field of evolutionary medicine contends that while we may live in the Space Age, our bodies and physiology remain firmly planted in our Stone Age past (Strassman & Dunbar, 1999). Human physiology was shaped by natural selection over millions of years throughout the course of mammalian and later human evolution. Because of this, human physiology is best understood as an adaptive system, which was optimized to increase our survival and reproduction in these ancestral environments (Lappe, 1994; Nesse & Williams, 1994). If so, many human diseases may arise from—or be exacerbated by—a mismatch between a physiology prepared to meet evolutionary needs of our ancient ancestors and the very different environment in which we now live that has resulting from unprecedented and rapid cultural change during the last 10,000 years (Boyd Eaton & Eaton 1999; Nesse & Williams, 1994; Strassman & Dunbar, 1999). Advocates of evolutionary medicine suggest that both clinical practice and research on public health could be improved by incorporating these principles (Lappe, 1994). Over the past 15 years, evolutionary perspectives have increasingly been incorporated into clinical and public health research as interest in Darwinian thinking has grown among health care providers and epidemiologists (Stearns, 1999).

Evolutionary thinking is characterized by a careful consideration of how phenotypes are designed to increase biological "fitness," which can be broadly defined as the production of viable offspring (Stearns, 1999; Williams, 1966). While measuring fitness is straightforward, producing viable offspring is a complicated process that involves several steps. The offspring must survive to maturity, choose a mate, gestate and give birth to their own offspring, and finally support those offspring to their own maturity (Stearns, 1992). In mammals, the period of dependency after birth includes both lactation by the mother and an intense period of learning by the offspring before they are able to fend for themselves (Wood, 1994). This general feature of juvenile mammals is even more pronounced among primates whose offspring often do not reach maturity for several years to more than a decade (Kaplan, Hill, Lancaster, & Hurtado, 2000). These lengthened periods of dependency create evolutionary challenges.

Because the energy (usually food) available to an animal is always limited, the animal must make physiological trade-offs between spending its energy on functions including growth, maintenance of its body, locomotion, and reproduction. The relative costs and benefits of dividing resources between these competing functions ultimately determine fitness (Stearns, 1992; Zera & Harshman, 2001). As a species evolves, it must navigate an inherent antagonism between having traits that would increase fitness the most and the disruption that those traits might cause to the existing delicate balance of trade-offs between competing physiological functions. Over time, the process of natural selection tends to produce phenotypes that best balance these trade-offs and produce higher levels of fitness across the range of environments that individuals have experienced over time and space (Levins, 1968). The phenotypes that are most affected are those that directly affect survival and reproduction (Williams, 1966). Some flexibilty in the form of developmental and physiological plasticity exists, however, and it is likely that the ability to have this type of short-term developmental or physiological responses has also been favored by selection. Phenotypic plasticity is shaped by developmental experiences that induce physiological changes that probably act to increase survival, reproduction, and ultimately fitness (Levins, 1968; Bateson et. al., 2004).

Although one might not immediately equate body composition with survival, it is also shaped by physiological trade-offs that may have evolutionary benefits. During fetal growth, trade-offs between tissues such as fat and muscle can have long-term effects on body composition. During gestation, tissues experience simultaneous "critical" periods of development. During these periods, the number of cells and size of tissues such as muscle, brain, or fat may be "programmed" for the entire life course (Barker, 1995, 1997; Cameron & Damerath, 20002; Gluckman & Hanson, 2004; Gluckman et. al., 2005; McCance & Widdowson, 1974). When such "programming" occurs, it is assumed to affect later responses, making the tissues more or less responsive to the environment (Schmalhausen, 1949). When energy is limited, investments in each tissue may be altered to reflect the "preferences" of a physiological design that evolved to maximize fitness (Schlichting & Pigliucci, 1999). Zera and Harshman (2001) referred to these "preferences" as "priority rules" that can be described in models that predict how scarce nutrients during fetal development should be divided among the growing brain, musculo-skeletal system, and fat mass in order to maximize lifetime fitness. The predictions may then be tested with the results of previous research to evaluate their adequacy.

What are the most "adaptive" or fitness-enhancing responses to the environment during growth and development? Adaptive responses differ from other physiological characters because they improve survival or reproduction within specific environments (Curio, 1973; Williams, 1966). They are not simply byproducts of random processes or damage to tissues during development; instead, they link specific experiences (known as "exposures" in epidemiology) to specific physiological characteristics that clearly increase survival and reproduction within specific environments (Gould & Lewontin, 1979; Stearns, 1992). Models that emphasize adaptation through the process of development differ from other models that invoke random processes such as tissue damage during development (in which all cells have equal chances of deleterious effects) as potential explanations (Bateson et. al., 2004). In those born small but later obese, adaptive models of development predict specific relationships between brain, muscle, and fat tissues. They propose that these relationships are adaptive in nature, enhancing fitness through increases in either survival or reproduction. Developmental damage models make no such claims.

PREDICTIVE ADAPTIVE RESPONSE, BRAIN PRESERVATION, OR DEVELOPMENTAL DAMAGE?

Predictive Adaptive Response (PAR) Model: Variation in Body Composition Modulates Energy Expenditure

Gluckman and Hanson (2004) suggested the PAR model as an explanation for chronic disease. In the present context, this model suggests that lowered muscle mass, greater fat mass, and more abdominal obesity tend to co-occur in individuals who have small size at births and function as an energy-saving response to early life signals that (presumably) that the individual will face greater energetic scarcity (or more periods of scarcity) across

his or her life span. Well-developed theory borrowed from microeconomics supports this model, suggesting that in times of scarcity, individuals tend to spend or invest less and save more to avert shortfalls (Hirschleifer, 1966; Winterhalder, Lu, & Tucker, 1999). In terms of obesity among those who were born small, several physiological facts are relevant. First, the amount of energy used during activity or while at rest is largely determined by the amount of muscle that an individual has (Arslanian, 1996; Ravussin, 1995). Decreasing muscle mass lowers total energetic requirements. Second, greater fat mass results in greater energetic storage per unit of body mass. One gram of fat stores 9 kcal, while carbohydrates (which may be stored in the liver or muscles) and proteins store only 4 kcal per gram (Groff & Groper, 2000). Last, abdominal fat cells are more sensitive to hormonal signals that cause release of fats into the bloodstream (Bjorntorp, 1990, 1997a, b; Bjorntorp & Eden, 1996; Rebuffe-Scrive, Enk, Crona, Lonnroth, Abrahamsson, & Smith, 1985; Rebuffe-Scrive, Bronnegard, Nillson, Eldh, Gustaffson, & Bjorntorp, 1990; Streeten, 1993). Thus, lowering muscle mass, increasing fat mass, and storing relatively more of the total fat in the abdomen results in (1) reduced total energetic requirements, (2) greater storage against shortfalls, and (3) easier access to these stores during shortfall. A physiology characterized by these changes would be primed to perform well in environments characterized by energetic scarcity (Neel, 1962; Neel et. al., 1998). The PAR model predicts that individuals who experience reduced growth due to energetic shortfalls in utero become physiologically primed for precisely this kind of a "feast or famine" environment.

Brain Optimization Rule: The Evolution of a Trade-Off Between Brains and Brawn

The brain optimization rule model further develops the line of reasoning that physiological trade-offs may underlie some chronic diseases. It postulates that if a scarcity of nutrients occurs in utero, especially during the second trimester when the brain and muscle tissues are both in a critical period, the body will favor the growth of the brain at the expense of muscle (Barker, 1995, 1997; Yajnik, 2000, 2004). According to this model, the priority of brain tissue is accomplished by restricting sugar uptake by muscle. Normally, the hormone insulin signals all cells to take up glucose, fats, and proteins from the blood; however, in individuals who experienced reduced growth in utero, the muscle cells are induced to become resistant to the effects of insulin, thus leaving a greater amount of sugar in the blood stream to fuel brain development (Barker, 1995, 1997; Reaven, 1998; Yajnik, 2000, 2004). Since these effects occur during the critical period of muscle development, they are long term in nature and result in life-long resistance to insulin resistance (a step toward obesity and diabetes) and reduced muscle mass (Cameron and Demerath, 2002). It is important to emphasize that any proposal that a priority rule has evolved to favor brains over brawn is a hypothesis rather than an empirically documented fact. However, the proposition is plausible given the fact that an overriding trend in human evolution has been the reduction of muscle mass and increase of brain mass (Kaplan, Hill, Lancaster, & Hurtado, 2000; Klein, 1999).

The primary prediction of the brain optimization rule model is that a negative relationship between brain mass and muscle mass should be observed among people who had a small size at birth. Similarly, people who are born small, but do not have later deficits in brain mass or function as adults, should also be found to have lowered muscle mass. The model could also explain the observation that people who had small size at births tend to be fatter, perhaps due to insulin resistance induced in their muscles in utero. The body's typical response to the resistance of a tissue to a hormonal signal is to increase production of the signaling hormone (Arslanian, 1996; Groff & Groper, 2000). In the case of insulin, increased production to compensate for resistance would result in more rapid clearance of sugars from the blood, leading to quicker return of hunger after meals. This could lead to overeating and ultimately, greater fatness (Neel, 1962; Neel et. al., 1998). The brain optimization rule makes no particular prediction concerning abdominal fatness.

Developmental Damage: An Explanation Based on Clinical Pathology

Where possible, evolutionary models should always be tested against a null expectation that variation is produced by random processes (i.e., chance) or without any particular adaptive target (Curio, 1973; Stearns, 1992). In the case of relationships between reduced fetal growth and later obesity, a null model is available. The developmental damage model invokes clinical damage of tissues as a plausible, null alternative that could potentially produce all of the phenotypic changes noted people who experience reduced fetal growth and later become obese (Gluckman & Hanson, 2004; Gluckman et. al., 2005; Kuzawa, 2005). The developmental damage model suggests that all tissues should be simultaneously damaged because all of them are subject to the same lack or resources. In such a case we would expect that the growth of the brains, muscles, and fat should all be stunted. Since it is likely that the glands (hypothalamus, pituitary, adrenal glands) that produce the hormones that regulate the storage of fat in the abdomen may be damaged by the same nutritional shortfall, this endocrine damage may also contribute to abdominal obesity (Jaddoe & Witteman, 2006). If true, the developmental damage model could explain increased relative fatness in the abdomen without the need to invoke any adaptive responses across development.

Discriminating Between the Three Models

Each model makes specific predictions about the relationships that should be observed between muscle, brains, and fat in people who experienced slowed fetal growth (Table 17-1). The model of a PAR predicts that these people should have (1) lowered muscle mass, (2) greater fatness, and (3) greater abdominal fatness. It makes no statement about brain development. The brain optimization rule makes two possible predictions. From one perspective, the model might predict a negative relationship between muscle mass and brain mass. A slightly different perspective might argue that brain mass will be no different between those born small and with stunted muscle mass and those born of normal size, but will be diminished in those born small but with normal levels of muscle mass. Though it is not a specific prediction of this model, it also allows for increases in overall fat mass as a side effect of insulin resistance in muscle tissue.

The developmental damage model predicts uniform stunting of all tissues including muscles, the brain, and fat. It allows for greater relative fatness in the abdomen through damage of the endocrine glands that regulate abdominal obesity. Since the models make very specific predictions about the body composition, they may potentially be discriminated

TABLE 17-1 Evolutionary Models of Obesity Among Those Born Small: Model Predictions and Supporting Evidence[a]

Model	Discriminating predictions	Supporting evidence
Developmental damage (DD)	Brains, muscle, and fat tissues all stunted in those born small.	Simultaneous reduction in brain mass or cognitive function, muscle mass, and fat mass.
Brain optimization Rule (BOR)	Discriminated from the DD model because of non-uniform stunting of tissues. Brain preserved but muscle mass stunted in those born small.	No differences in brain growth or cognitive function in those born small, but reduced muscle mass. Allows for increased fatness, but makes no prediction about abdominal fatness.
Predictive adaptive response (PAR)	Discriminated from the DD model by specific pattern of changes: 1) reduced muscle, 2) increased fatness, 3) relatively greater abdominal fatness. Clear support requires rejection of the BOR model, with no relationship between brain and muscle development.	Strongest support with rejection of both DD and BOR models. Consistent findings relating reduced fetal growth lowered muscle mass, increased fatness, and more abdominal fatness.

[a] *Adaptive and neutral evolutionary models may be discriminated based on their predictions. The DD model requires stunting of all tissues. The BOR model is discriminated because brain development is not stunted when muscle mass is sacrificed among those born small. The PAR model is discriminated from the DD and BOR models by a clear and specific pattern of nonuniform stunting of tissues.*

through a survey of the literature reporting associations between reduced fetal growth and later obesity, brain development, and body composition. We collected the results of a large series of studies that have tested for associations between measures of size at birth and later body composition or brain development. Studies suggesting positive or negative relationships or no effect were compiled, used to arrive at a consensus of the studies' findings, and compared to the predictions of each model to determine which model has the most support. This process should reveal if either of the adaptive models better explain the findings than the null model of clinical damage to tissues.

Discriminating between all three models is complicated because some of their predictions overlap. Logically, the null model (developmental damage) should first be eliminated. If the consensus findings suggest that uniform stunting of all tissues occurs, then the developmental damage model would be supported. If not, then the alternative adaptive models should be tested, beginning with the brain optimization rule model. If brain mass is preserved while muscle mass is sacrificed among those born small, then this model would find support. The PAR model does not predict that brain mass should receive priority, but postulates that abdominal fat stores are particularly useful. Both of these predictions allow it to be distinguished from the brain optimization rule model.

EMPIRICAL SUPPORT FOR EACH MODEL

We reviewed available studies that examined associations between reduced fetal growth and both body composition and neurological development in utero and during childhood,

TABLE 17-2 Consensus Empirical Findings of Association Between Small Size Birth and Later Body Composition[a]

Outcome measure	Total studies	Increased in those born small	Decreased in those born small	No relationship	Qualitative consensus conclusion
Fat mass/percentage	12[b]	5	2	5	No clear consensus finding.
Skeletal muscle mass	7[c]	0	7	0	Small size at birth negatively impacts long-term muscle mass.
Abdominal fatness	12[d]	8	0	4	Small size at birth increases abdominal fatness.
Brain development	15[e]	0	13	2	Brain development negatively impacted by small size at birth.

[a] *The literature suggests lowered muscle mass, reduced brain development, and greater abdominal fatness among those born small. It provides only equivocal evidence of effects of reduced fetal growth on overall fatness.*
[b] *Binkin et al., 1998; Euser et al., 2005; Kensara et al., 2005; Laitenen et al., 2004; Larciprete et al., 2005; Lebayen et al., 2006; Padoan et al., 2004; Ravelli et al., 1976, 1999; Sachdev et al., 2005; Stanner et al., 1977.*
[c] *Euser et al., 2005; Hediger et al., 1998; Kahn et. al., 2000; Kensara et. al., 2005; Lebayen et al., 2005; Wells et al., 2005; Sachdev et al., 2005.*
[d] *Barker et al., 1997; Kensara et al., 2005; Koziel and Jankowska, 2002; Lebayen et al., 2006; Laitenen et al., 2004; Law et al., 1992; Malina et al., 1996; Ravelli et al., 1999; Sachdev et al., 2005; Schroeder et al., 1999; Stanner et al., 1977; Valdez et al., 1994.*
[e] *Amin et al., 1997; Georgieff et al., 1985; Gross et al., 1978; Gutbrod et al., 2000; Hack et al., 1984, 1989; Hediger et al., 1998; Kitchen et al., 1980; Monset-Couchard and Bethman, 2000; Pena et al., 1998; Stanley and Speidel, 1985; Vohr and Oh, 1983.*

adolescence, and adulthood (Table 17-2). These studies reported results measuring the effects of reduced fetal growth on later brain development, overall fatness and muscularity, and abdominal fatness. These outcomes were measured using body measurements (head circumference, body mass index, skinfold measures) as well as cellular measures of brain cell development (the reader is referred to Roche, Heymsfield, & Lohman, 1996, for several chapters reviewing these methods of assessment). Twelve studies reviewed examined relationships between reduced size at birth and later overall fatness. Seven studies tested for relationships of reduced fetal growth and later muscle mass. Fifteen studies reviewed the effects of reduced fetal growth on either head circumference or neurological development. Twelve studies tested for associations of small size at birth with later abdominal fatness.

Overall, these studies provide no support for the brain optimization rule, but fail to discriminate convincingly between the developmental damage model and the PAR. It is clear that brain mass is stunted among people who have experienced reduced fetal growth. Thirteen of 15 studies confirmed the fact that those who experienced reduced fetal growth also experienced deficits in brain size and neuron formation. Those born small also displayed reduced muscle mass: seven of seven studies reported this association.

Eight of 12 studies reported greater abdominal fatness in people who were born small. Of the 12 studies testing for relationships between reduced fetal growth and overall fatness, 5 reported greater fatness in those born small. Two studies found the opposite effect; both of these used measurements obtained through imaging technology while growth restriction was occurring in utero. Five studies found no association at all between the obesity later in life and small size at birth, which suggests that reduced fetal growth results in greater overall fatness only under certain conditions.

While the review clearly suggests that the brain optimization rule model may be rejected because simultaneous stunting of brain and muscle occurs, it does not allow one to clearly discriminate between the predictive adaptive response and developmental damage models. Observations of the reduction of both muscle and brain mass tend to support the idea that developmental damage creates the observed relationship between reduced fetal growth and body composition later in life. Two studies that were able to use medical imagery to track the effects of reduced growth in utero found these fetuses to have lower fat mass than average-sized fetuses, providing further support for the hypothesis that reduced growth in utero adversely affects all tissues (Larciprete, Valensise, Di Pierro, Vaspollo, Casalino, Arduini, et al., 2005; Padoan, Rigano, Ferrazzi, Beaty, Battaglia, & Galan, 2004). Studies of body composition in childhood, adolescence, and adulthood provide mixed results for the effects small size at birth on later fatness. At present, it appears that reduced fetal growth leads to greater fatness only under certain conditions—conditions that currently remain somewhat unclear (Cameron & Demerath, 2002).

The balance of the evidence suggests that the developmental damage model adequately explains relationships between reduced fetal growth and later body composition. These conclusions are tentative because the PAR model cannot be ruled out without findings that establish a firmer link between small size at birth to greater fatness later in life. Future studies could attempt to do this by examining relationships between reduced fetal growth and all three tissues in the same individuals, thus overcoming a shortcoming of a literature review that cannot compare differences in each of these tissues simultaneously.

Given the mixed results of the studies that investigated the link between reduced fetal growth and later fatness, it is highly likely that the factors that create this link in certain cases are quite complex. The relationship may be produced by uncontrolled confounding factors, unexamined interactions between factors, or even threshold effects (in which a threshold of growth deficit in utero must be experienced to produce the effect later in life, a threshold that may differ depending on the individual's genotype or that of the mother). The results of Ravelli, Stein, and Susser (1976) strongly suggest that greater fatness occurs in those whose mothers suffered through a famine while pregnant with them, but subsequent studies have found it difficult to replicate these effects, even in animal models (Armitage et. al., 2004). Ravelli, Stein, and Susser's (1976) study measured obesity risk in 19-year-old Dutch Army recruits whose mothers suffered semi-starvation during the World War II. During this time, caloric intakes were severely reduced among pregnant women to as little as one third of the necessary requirement for pregnant and lactating women (2100 kcal per day for 62-kg women [Insel, Turner, & Ross, 2002]). The study found a 50% increase in risk among the recruits, but these conclusions were seriously weakened when a follow-up study on 50-year-old men and women from the same cohort found no effects (Ravelli, Van der Meulen, Osmond, Barker, & Bleker, 1999). As a case in point for the difficulty in replicating such findings, a study conducted on the population

of Leningrad, which was exposed to a similar famine during World War II, failed to produce evidence of this relationship (Stanner, Bulmer, Andres, Lantseva, Borodina, Poteen, & Yudkin, 1997). While a handful of studies have suggested increased risk for obesity among those born small (Erikkson, Forsen, Tuomilehto, Osmond, & Barker, 2001), the contradictory evidence from other studies shows that other factors also play important roles in adult phenotypes (see Cameron & Demerath, 2002, for a similar opinion).

Does the failure of either evolutionary model to convincingly explain the data sound the death knell for evolutionary models for obesity? Probably not: more likely, it highlights the usefulness of further evolutionary modeling along a new, innovative line. Conditional strategies for dealing with environmental variation during postnatal growth are widespread in nature (Parker & Maynard-Smith, 1990). In the current study, for example, we applied a coarse-grained assumption that phenotypic changes occurring in utero will hold across the entire life span. In the case of muscle mass, brain mass, and abdominal fatness this assumption seems to hold, but studies of actual fetal growth restriction show that fetal fat mass is also sacrificed (Larciprete et. al., 2005; Padoan et al., 2004). Postnatal studies indicate that fatness is increased under some conditions and not under others and that these effects may vary depending upon the time at which individuals are measured. These observations suggest that conditional models of postnatal development might be viable strategies that make good evolutionary sense. Understanding these strategies could be accomplished within an evolutionary framework that models trade-offs between sets of costs and benefits and their complicated-interactions while relaxing the assumption *that in utero* effects will hold across the life span.

IMPLICATIONS FOR CLINICAL PRACTICE, EPIDEMIOLOGY, AND EVOLUTIONARY MEDICINE

Clinical practitioners face the unique challenge of integrating the results of research studies based on populations with their need to treat individuals who may have greatly differing phenotypes (Lappe, 1994). Links between epidemiological research on infectious diseases and evolutionary theory are direct—it is easy for clinical practitioners to understand that natural selection directly affects host/pathogen dynamics. Understanding chronic diseases in an evolutionary framework is more challenging. While many clinicians have embraced the evolutionary idea of "thrifty" genes (Knowler et. al., 1981; Neel, 1962), the idea that adaptive developmental responses might provide useful insights for treating patients suffering from obesity and related chronic diseases is not so straightforward. A greater understanding of the dynamic physiological responses potentially produced by evolution, as well as the limits imposed by developmental experiences, can only enhance the individual practitioner's clinical intuition. However, the incorporation of evolutionary approaches into medical practice will not alleviate each practitioner's need to interpret a research literature that often contains conflicting results. This issue is no different than other issues within evidence-based medicine. Ultimately, adding an evolutionary "intuition" (Stearns, 1992) to the deep understanding of biochemistry endowed within a medical education can enhance clinical practice within a variety of settings ranging from family practice to endocrinology.

The implications of this study are much brighter for the introduction of evolutionary models into epidemiological research and public health practice. Epidemiology works by testing of alternative hypotheses, progressively eliminating of their predictions in order to narrow the possibilities to find the most consistent relationships between experiences associated with disease and pathological outcomes (Aschengrau & Seage, 2003). The models reviewed here produced specific, testable predictions that may be falsified empirically. As such, they become useful tools for the design of epidemiological research. By generating research based on evolutionary principles, such a process promises to truly integrate evolutionary perspectives into epidemiology.

Along these lines, the findings of this study may be particularly important in shaping future evolutionary epidemiological research. Particularly, the equivocal findings regarding the relationships between reduced fetal growth and later obesity suggest that reframing research on this outcome within a framework based on conditional responses (a well-developed tool within evolutionary biology [see Parker & Maynard Smith, 1990, for a review]) might be useful. Rather than asking whether reduced fetal growth leads to later obesity, perhaps a better strategy is to ask under *what conditions* reduced size at birth leads to later obesity. Forging evolutionary models that incorporate flexible postnatal responses based on exposures in childhood and in utero may provide new and better avenues for understanding relationships between reduced fetal growth and later body composition. These perspectives would certainly be evolutionary in nature, but would incorporate additional dynamics. Moreover, they would once again produce testable hypotheses that could be examined using standard epidemiologic research designs and methods. The result could be a marked improvement in strategies to prevent obesity, which typically have been unsuccessful thus far (Caballero, 2004; Kaur, Hyder, & Poston, 2003).

Testing hypotheses derived from evolutionary models is important for the field of evolutionary medicine as well. Explanations for diseases or adaptations that seem evolutionarily plausible are really hypotheses that need to be tested. Not all phenotypes are produced by the process of adaptation—neutral variation also exists within nature (Gould & Lewontin, 1979). By testing specific, empirical predictions of evolutionary models, we stand to gain insights into whether natural selection or clinical pathology has shaped a phenotype or not. Understanding the targets of selection involved and the potential "design" of physiological responses is enhanced when specific empirical predictions are tested (see Stephens & Krebs, 1986, Chapter 13, and Parker & Maynard Smith, 1990, for useful reviews of the importance of evolutionary modeling and hypothesis testing within evolutionary biology). By putting evolutionary hypotheses to the test, practitioners of evolutionary medicine will sharpen their understanding of the nature of the characters they study while avoiding the pitfalls of evolutionary "storytelling" that occur when the criterion plausibility alone is used to understand biological variation (Gould & Lewontin, 1979).

CHAPTER 18

The Developmental Origins of Adult Health

Intergenerational Inertia in Adaptation and Disease

Christopher W. Kuzawa

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