

Chapter 166

Nutrition, Behavior, and the Developmental Origins of the Metabolic Syndrome

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Abbreviations

LDL Low density lipoprotein
FOAD Fetal origins of adult disease

166.1 Introduction

A handful of unifying perspectives have guided theory and even research related to the metabolic syndrome and its associated abnormalities. A broad look at the most popular of these adds another dimension to the clinical knowledgebase that we have and also helps us to better characterize findings and unknowns. This chapter will take such an approach and attempt to highlight some of the outstanding perspectives in an attempt to reconcile the metabolic syndrome with the goals and frame of reference of this book. First, of course, it is important to have a handle on what the metabolic syndrome represents nosologically and why it can be such a difficult construct to get a firm grip on.

The metabolic syndrome is a combination of medical disorders that present in a clustered fashion and result in increased risk for cardiovascular disease and diabetes. Also known as syndrome x, and the insulin resistance syndrome, this multifactorial disease was identified over 80 years ago but has shown a striking increase, worldwide, in the last 2 decades. The rise in international prevalence and clinical interest is closely associated with the global epidemic of obesity and diabetes; however, the metabolic syndrome includes other comorbid disorders, including cardiovascular disease. Symptoms and features include: glucose intolerance (type 2 diabetes, impaired glucose tolerance or impaired fasting glycemia); high blood pressure (hypertension); central obesity (visceral adiposity); increased LDL cholesterol; and dyslipidemia (elevated triglycerides) (Table 166.1). These conditions have a tendency to co-occur in individuals more often than they present alone. For this reason, they have been grouped into the encompassing diagnosis of the metabolic syndrome which is known to present in a variety of different ways in different people. Partly because the constellation of metabolic abnormalities can be slightly different for virtually every person, there is still some contention over which features are central etiologically.

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Table 166.1 The key features of the metabolic syndrome

Obesity	Increased total body fat, abdominal or central fat distribution, increased visceral fat
Insulin resistance	Hyperinsulinemia
Dyslipidemia	Hypertriglyceridemia, decreased HDL cholesterol, increased LDL cholesterol
Impaired glucose tolerance	Type 2 diabetes mellitus
Hypertension	High or deranged blood pressure

The defining disorders of the metabolic syndrome and their components

Table 166.2 Diagnosis of the metabolic syndrome

Increased waist circumference	>102 cm in men, >88 cm in women
Elevated triglycerides	>150 mg/dL or 1.7 mmol/L
Decreased HDL cholesterol	<40 mg/dL in men, <50 mg/dL in women
Blood pressure	>130/85 mmHg or active treatment for hypertension
Fasting glucose	>110 mg/dL or active treatment for hyperglycemia
The National Cholesterol Program requires that at least three of the above five criteria be met for a diagnosis of the metabolic syndrome	

In 2005 the Adult Treatment Panel III of the National Cholesterol Education Program (2001) defined diagnosis as three or more of five states listed in Table 166.2. The International Diabetes Federation, the European Group for the Study of Insulin Resistance, and the World Health Organization, and others have each identified unique sets of diagnostic criteria. This disparity in diagnostic definition has created some concern and confusion, although all three systems are relatively similar.

Making comparisons of prevalence for different populations is difficult because different published studies utilize different diagnostic criteria, although a standardized, international definition should abet these difficulties. Sex and ethnic origin predict large amounts of variation in prevalence. The prevalence is also highly age-dependent. Prevalence in the USA (in the national health and nutrition examination survey) increased from 7% in participants between the ages of 20 and 29 to 44% in participants between 60 and 69 (Ford et al. 2002). The majority of diagnoses are given to older, obese individuals who have a degree of insulin resistance. Until recently, the metabolic syndrome was regarded as a disease of old age, yet now, with increasing rates of obesity and diabetes in young people, it is commonly diagnosed in children. As in adults, susceptibility of children to the metabolic syndrome increases with worsening obesity.

The etiology and pathophysiology of the metabolic syndrome are extremely complex and have only partially been elucidated. Currently, it is debated whether obesity or insulin resistance is the cause of the metabolic syndrome, or if it can be attributed to a more obscure metabolic derangement (Table 166.3). The disorder, like its features, is highly heritable, and the large genetic component helps health practitioners to identify at-risk individuals if their family medical history is known. The main treatments include calorie restriction and dieting, physical exercise, and occasional drug prescription. The individual diseases that make up the metabolic syndrome are usually treated individually; diuretics and ACE inhibitors for hypertension, cholesterol drugs for elevated LDL cholesterol, and triglyceride levels and various drugs for insulin resistance. More information about treatment and clinical recommendations is given in Table 166.4.

The prevalence of the metabolic syndrome has increased severalfold in the last few decades. In these same decades, fast food and processed foods have become internationally ubiquitous, and physical exercise has been engineered out of our daily routines. It is clear that the metabolic syndrome is a product of the modern environment which has done much to increase sedentary behavior and the overconsumption of unhealthy foods. It is thought that humans were not “designed” to live this type of lifestyle, which is to say that we were not naturally selected to have genes that prepare us for it. Our hunting and gathering ancestors were probably only rarely afflicted by such unhealthy lifestyles or their metabolic consequences.

Table 166.3 Behavior and the metabolic syndrome

Pituitary adrenal abnormalities: hypercortisolemia, stress behavior
Reduced physical activity, sedentariness
Reduced ability to cope with stress, elevated stress hormone levels
Substance abuse: smoking, alcohol, others
Increased food intake: hyperphagia, increased dietary fat content
Sex hormone abnormalities

A brief list of some of the behavioral abnormalities closely associated with the metabolic syndrome

Table 166.4 Therapeutic intervention for the metabolic syndrome

Obesity	Behavior modification, caloric restriction, regular exercise
Atherogenic diet	Reduce trans fats, saturated fats, dietary cholesterol, and total fat
Cigarette smoking	Complete smoking cessation
HDL	Advise adding fibrates or nicotinic acid to diet
Hypertension	Lifestyle therapy, advice antihypertensive drugs
LDL	Advise LDL cholesterol-lowering drugs
Elevated glucose	Lifestyle therapy, advice hypoglycemic agents
Physical inactivity	60 min of moderate-intensity exercise daily
Prothrombotic state	Advise low dose aspirin therapy

A very brief summary of clinical recommendations for the individual disorders of the metabolic syndrome

166.2 The Thrifty Genotype

The same genes that cause humans to be susceptible to diabetes, heart disease, and obesity in modern times may have protected us from starvation and famine during ancestral times. This hypothesis was first put forward in 1962 by James Neel in an article entitled: “Diabetes mellitus: a ‘thrifty’ genotype rendered detrimental by ‘progress.’” Neel coined the phrase “thrifty genotype” referring to the probably very large complement of genes that would have helped our ancestors’ metabolisms to be economical and prudent with the foods that they hunted and gathered (Neel 1982). Not only did their meals contain a smaller proportion of sugar and fat, but our ancestors also had to engage in prolonged physical activities to obtain them. Interestingly, adopting a “paleolithic diet” consisting primarily of fruit, vegetables, and meat is an increasingly popular dietary regimen. Neel pointed out that not only are our bodies engineered to expect a different diet, but they are also probably expecting extreme food shortages, something modern people only very rarely encounter. His thesis, refined in subsequent articles, was that adaptations that allowed organisms to minimize metabolism and providently lay down fat reserves would produce a survival advantage during periods of nutritional scarcity (Neel 1999). A good deal of research has indicated that the environment of human adaptedness, and wild environments in general, are marked by periods of “boom and bust” where periods of plenty are interspersed among periods of food shortage or famine. This concept was initially generated to allow an evolutionary explanation for the existence of diabetes, but has since been generalized toward the metabolic syndrome and become widely adopted. The mainstay of this conceptual standpoint is that our inherited propensity for energy conservation probably only translates into obesity and metabolic disease in modern times and may have protected individuals, particularly those with the “thriftiest genotypes” from starvation in ancestral times (Table 166.5).

Thrifty benefits have been attributed to the individual components of the metabolic syndrome. A smaller, weaker, yet less energy-expensive heart may confer the ability to minimize energy expenditure in the heart in order to mitigate the risk of starvation (Barker 1998; Barker et al. 2002). In modern times people that express this once adaptive phenotype no longer enjoy the benefits because the excess of fat and cholesterol consumed by these individuals puts a serious strain on their “thrifty” heart, making

Table 166.5 Diet and behavior, then and now

Prehistoric foraging individual	Modern day individual
Caloric uncertainty	Caloric stability
Moderate to high physical activity	Low physical activity
Dietary balance	Dietary excess
Insulin sensitivity in muscle cells	Insulin resistance in muscle cells
Metabolic efficiency	Metabolic dysregulation
Reproductive advantage	Presumed reproductive disadvantage
A comparison of health and ecological features between a typical forager and modern individual on a Westernized diet with an inactive lifestyle	

them susceptible to heart or cardiovascular disease (Ridley 2003). A similar tradeoff is presumed to exist for insulin signaling. The beta cells of the pancreas release insulin in response to carbohydrate intake facilitating the metabolism of carbohydrates. An exaggerated pancreatic response (seen in the metabolic syndrome) results in hyperinsulinemia (high circulating levels of insulin) that leads to increased lipogenic activity and ultimately the storage of fats in adipose tissue. Such metabolic tendencies for increased adiposity may have helped individuals in the past to be frugal with fats and to store more fat, yet today they lead to obesity. Type 2 diabetes mellitus has been characterized as a disorder that is a prototypic example of this kind of evolutionary tradeoff. It has been thought for decades now that, on a cellular and organ system level, the disorder represents a thrifty condition – insulin resistance – that would have only rarely manifested as disease in the ancestral environment, because at that time individuals had no access to refined sugar or processed foods. The current literature holds that insulin resistance, brought about by genes for type 2 diabetes, represents a finely tuned physiological state and that its cellular and molecular pathways have been refined by natural selection over millions of years to help organisms conserve blood sugar. Insulin causes cells to rapidly take up blood sugars and increase the rate of their cellular processes thereby increasing total metabolic output. The defective insulin receptors, seen in cells of people with insulin resistance, might have helped to conserve these blood sugars in the past, but now that our diets feature dramatically higher levels of refined sugar; insulin resistance results in blood sugar levels that are vastly too high. Elevated blood sugar, hyperglycemia, can cause a variety of systemic and organ problems through the glycation and damaging of important biomolecules, seen frequently in diabetes. In all of these examples, biological mechanisms malfunction badly once they are forced to face our unhealthy modern diets (Table 166.6). It is now thought that many individual physiological pathways involved in the metabolic syndrome may represent ancient methods of energy conservancy (Eriksson et al. 2001).

Population genomics has identified some very interesting trends in geographic susceptibility to the metabolic syndrome, which provide corroborating evidence for the thrifty genotype theory. This widely accepted interpretation emphasizes that populations of preagricultural, foraging individuals who live in areas where, until recently, food has been relatively unpredictable have much higher prevalence of thrifty genes (Neel 1982). The traits that these genes code for probably helped these individuals survive during prolonged periods of scarcity or were maintained because historically these individuals were not exposed to high calorie diets (Valencia et al. 1999). Today, the incidence of the metabolic disease remains highest among populations where an economy of foraging existed until recently. Unfortunately, people in these areas such as Native Americans, Aboriginal Australians, and Pacific Islanders have an unusually high prevalence of the metabolic syndrome now that they have been exposed to the modern “diet of affluence.” This genetic variation between human populations is akin to other known forms of anthropological adaptation to environment. Unknown to many, there are several examples of selective pressures acting on humans even in the last 50,000 years. Lactase persistence is one example, where populations in Europe and elsewhere

Table 166.6 Medical risks associated with a westernized diet

Metabolic state	Implications for foragers	Implications for moderns
Adiposity	Healthy fat retention	Excessive fat retention
Insulin resistance	Healthy levels of blood sugar	Excessive levels of blood sugar
Beta cell Responsiveness	Metabolism of carbohydrates	Hyperinsulinemia
Thrifty heart	Healthy, efficient heart	Heart burdened by high body fat
Glucose intolerance	Normoglycemia	Hyperglycemia

A comparison between a typical forager and an obese modern individual with respect to the end result of individual metabolic states

retained the ability to digest lactose into adulthood because of the domestication of cattle and the importance of the ability to derive calories from milk.

The Pima Indians in Arizona and the Nauru people from the Micronesian South Pacific Islands appear to have particularly thrifty genotypes (Dowse et al. 1991). Both populations are thought to have endured repeated episodes of food shortage and starvation. They live and have long lived in relatively isolated, unpredictable, and in the case of the Pima, desolate areas. Fascinatingly, the Nauru people have traveled among remote islands in the Pacific during many, several-week-long canoe voyages. Historical accounts attest that many individuals in these canoes died of starvation during the trips, perhaps creating a Nauru founder population of highly starvation adapted people. When exposed to a Western lifestyle in the twentieth century, obesity and type 2 diabetes increased drastically in the Pima and Nauru. For some time, these two groups had among the highest age and sex-adjusted incidence rates of type 2 diabetes, around 25 per 1,000 people per year for the Pima (Schulz et al. 2006).

A variety of animal studies echo these genographic studies in humans. Diabetes commonly afflicts zoo animals, and an epidemic has been described of captive populations of primates, whose lifestyle approximates the sedentary, high-calorie lifestyle of First World urban humans (Diamond 2003). Ecological support for the thrifty genotype hypothesis comes from studies with leptin-deficient (*ob/ob*) and leptin receptor-deficient (*db/db*) mice (Coleman 1979). Heterozygous animals, which have a significant tendency toward obesity and diabetes when fed *ad libitum*, survived longer during fasting than the wild-type animals, even when matched for body weight. This trend has been observed outside of the laboratory too. Certain animals that are well adapted to frequent food shortages, such as desert mammals, show increased susceptibility to the features of the metabolic syndrome when they are able to feed *ad libitum*. The Israeli sand rat is a prime example. It is highly predisposed to developing metabolic disease including insulin resistance, obesity, and diabetes when put on the western lab rat diet. The symptoms reverse quickly when its food is restricted or it is placed back in its natural environment (Haines et al. 1965). Fascinatingly, it is known that the facets of the metabolic syndrome in humans, including diabetes, can be reversed by diet, exercise, and weight loss. This decline and even disappearance of diabetes symptoms happened to thousands of Parisians during the 1870–1871 famine associated with the siege of Paris (Zimmet 1997).

Even though the thrifty gene hypothesis has been challenged in its particulars, the aspects discussed here have been well accepted in the medical and ethological literatures. The thrifty genotype model is not meant to account for all instances of metabolic disease, but does seem to offer a high degree of explanatory power for the metabolic pandemic of modern times. Far from being a liability, a tendency to be fine tuned for having a lower metabolism would have been an asset to survival in the Plio-Pleistocene because it would have helped individuals to conserve calories. That individual species, or some individuals within a species, have this tendency has important biomedical ramifications, and further research and experimentation in this area should help to clarify the underpinnings and tradeoffs involved in energy homeostasis. Several successful animal models, like the ones mentioned,

are thought to have helped to elucidate some of the key genes and pathways involved in impaired energy balance regulation. Interestingly, the genes that one is born with are not the only predisposing factors, as the next section will illustrate; the environment can play a large role as well.

166.3 The Developmental Origins of the Metabolic Syndrome

It is now widely accepted that the risk for a number of metabolic diseases may be affected by circumstances before birth. Professor David Barker and colleagues have produced a large amount of data, since 1994, showing that low birth weight increases susceptibility to noninsulin-dependent diabetes mellitus, hypertension, and coronary heart disease (Barker 1998) later in life. By analyzing epidemiological data for cohorts whose birth records are available, and following these individuals into adulthood, Barker, Hales and others have shown that birthweight, length, body proportions, and placental weight are highly associated with later metabolic disease incidence (Philips 1998) or risk factors for those diseases (hypertension, glucose intolerance, hyperlipidemia) (Barker, 1994, 1998). In addition to having increased adipose tissue mass in adulthood, low birth weight individuals have a tendency to store adipose tissue centrally and have a lower lean mass. Reduced muscle has been reported to contribute heavily to a lowered basal metabolic rate and is expected to reduce capacity for exercise (Kensara et al. 2005). These associations between birth size and disease are often apparent from childhood, hold in a large number of different populations, and have given rise to the term “fetal origins of adult disease” (FOAD) (Law and Shiell 1996; McKeigue 1997).

The biological changes responsible for metabolic alterations are attributed to epigenetic programming, also called phenotypic plasticity. Epigenetic programming occurs when an environmental cue creates a change in gene expression. Even small changes in gene expression and protein regulation, early on, can cause large phenotypic changes with time. Developmental geneticists closely adhere to the idea that a single genotype can give rise to, or canalize, a variety of different phenotypes depending on the programming effects of the early environment. Intrauterine programming is a well-established biological phenomenon, and there are many well-known examples, affecting organisms from plants to humans. In this case, an environmental stimulus, experienced during gestation, is thought to lead to impaired fetal growth and diminution in size at birth, although “catch-up” growth in childhood is the norm. This stimulus or cue also leads to altered homeostatic mechanisms such as the regulation of blood pressure or insulin sensitivity, which in turn results in susceptibility to the metabolic syndrome later in life. Exactly what this cue or stimulus is, has been open to debate. The majority of models in this literature point to undernutrition (Langley 1997) but some emphasize the contribution of other forces, such as placental dysfunction, or excessive fetal exposure to glucocorticoids.

Evidence for undernutrition as the underlying, environmental stimulus in this association comes from three sources: (1) the aforementioned epidemiological associations; (2) animal models; and (3) historical pseudo-experiments. Birth weight is readily altered in experimental animals by manipulating maternal nutrition during fetal development. A reliable way to decrease a rat’s size at birth is by reducing the proportion of protein in the diet of their pregnant mothers. Like humans and other mammals, these rats show catch-up growth in youth, but soon thereafter exhibit tendencies toward obesity, elevated blood pressure (Langley and Jackson 1994), and impairments in glucose tolerance (Desai et al. 1995). Glucose intolerance seen in low-protein exposed offspring is contributed to by a reduction in pancreatic beta cell mass, reduced insulin secretion, and peripheral tissue insulin resistance. These symptoms are worsened by the presence of obesity in an additive manner (Petry et al. 1997) and, as in humans, worsened symptoms lead to reduced longevity in rats and mice (Ozanne and Hales 2004).

Restriction of total calories during pregnancy, without respect to protein composition, has been shown to result in rat offspring that are hyperphagic, hyperinsulinemic, obese, hypertensive, and significantly less physically active (Harding 2001). Again, analogous to what we see in our own species, these symptoms are accentuated by a highly palatable or high-fat diet later in life. High levels of catch-up growth after early deprivation have been shown to be related to skeletal muscle insulin resistance, reduced thermogenesis, and increased insulin sensitivity in adipose tissue (Cettour-Rose et al. 2005). Another parallel in this domain that is directly relevant to human health is the finding that diets of saturated fats lead to detrimental effects on glucose homeostasis in fetally deprived rats whereas diets containing polyunsaturated fatty acids had beneficial effects (Siemelink et al. 2002). Similar studies designed to reduce maternal nutrition during pregnancy have led to comparable results in rats, mice, guinea pigs, and sheep.

Peripheral signals that indicate the size of adipose stores such as circulating factors and the hormone leptin are received and integrated by the central nervous system, primarily at the hypothalamus and brainstem. If adipose stores are sufficient or large, changes in these signaling systems, such as the increase in leptin hormone, induce the nervous system to inhibit feeding and promote energy expenditure. Offspring of undernutrition pregnancies have been shown to demonstrate leptin insensitivity, high body weight, and increased food intake in adult life (Harding 2001). Whether early food restriction acts at the level of the hypothalamus to predispose to this “thrifty behavior” is currently not clear. There is very little doubt though that maternal undernutrition in animals leads to diminished size, altered behavior, and permanent alterations in metabolism, and that this is consistent with disease susceptibility observed in human studies.

The second source of evidence for the efficacy of maternal undernutrition in the programming of the metabolic syndrome comes from historical pseudo-experiments. A popular example, the Dutch Hunger Winter, was a season of extreme food shortage in the Netherlands between 1944 and 1945. Ravelli and colleagues compared data on 300,000 19-year-old males that were born before, during, or after this famine (Ravelli et al. 1976). The study revealed that the nutritional limitations imposed by severe nutritional deprivation lead to offspring with reduced birth size, and increased risk of glucose intolerance, and obesity in adult life. The cohorts that were most affected were the offspring of the mothers whose first two trimesters of pregnancy coincided with the famine. Similar historical pseudo-experiments, with well documented medical data that are consistent with the findings of the Dutch Hunger Winter, have occurred in Asia and elsewhere.

Another body of literature has taken this programming concept a step further and attributed adaptive or evolutionary value to sensitivity to programming (Barker et al. 2002). Evolutionary significance has been attributed to the programming that occurs due to nutritional deprivation, and even to altogether different programming models, such as early life stress. Neonatal rats, when exposed to various stressors, show permanent changes in hypothalamic structure and systemic responses to stress (Barbazanges et al. 1996; Francis et al. 1996) and these responses have been characterized as representing predictive actions to better prepare the animal for predation risk and environmental adversity (Zhang et al. 2004). In a similar manner, the thrifty phenotype hypothesis contends that the permanent changes in metabolic homeostasis represent evolutionarily adaptive programming that decreases susceptibility to starvation.

166.4 The Thrifty Phenotype

It is clear that Hales and Barker, like Neel before them, appreciated the evolutionary implications of their hypotheses. They explicitly proposed that this metabolic response to a nutritionally poor early environment was a predictive, adaptive response that would maximize chances of surviving postnatally in conditions of ongoing deprivation. Also, like Neel, they appreciated the fact that this prediction represents a

tradeoff and is subject to being inaccurate. If, unexpectedly, the postnatal environment provides plentiful nutrition these individuals will be at increased risk of metabolic disease.

The phenotypic characteristics of many organisms ranging from plants to insects to mammals are known to show plastic responses to environmental events, many of which are thought to represent adaptive, defensive responses, or reproductive strategies (Via and Lande 1985). This phenotypic plasticity through differential gene expression is often cued by maternal condition and is known to create profound alterations in the phenotypes of developing organisms. The thrifty phenotype hypothesis (Hales and Barker 1992, 2003 2001) has been used widely by researchers from different disciplines to interpret studies showing that maternal malnutrition is a strong risk factor for the metabolic syndrome (Wells). According to this hypothesis, phenotypes that are programmed by prenatal malnutrition to express low metabolic rates enjoy a survival advantage under deprived circumstances; however, if such a thrifty fetus is born into an environment marked by nutritional abundance, it will face increased risk of negative health consequences (Bateson et al. 2004). Conversely, robust phenotypes that express larger size and rapid metabolism are thought to increase reproductive success when resources are more plentiful, but are more susceptible to starvation if exposed to nutritional shortage. Specialists now believe that the association between maternal malnourishment and the offspring's proclivity for a low metabolism is adaptive specifically because the mother's deprived condition during pregnancy is often predictive of the environment into which the fetus will be born. It has been established that many animals share similar metabolic responses to environmental cues and this requires us to concede that our own tendency to react plastically may derive from phylogenetically earlier forms because of a shared evolutionary history (Crespi and Denver 2005).

Epigenetic processes are the biological basis for programming effects. Chemicals such as acetyl or methyl groups attach themselves to promoter regions of genes in specific tissues. Fine and intricate control of gene expression has been taken to suggest that the programming effects have been maintained through evolution because of their adaptive advantage rather than representing maladaptive effects of developmental disruption such as teratogenesis (Hanson and Gluckman 2008). It has been shown that, in animals, these epigenetic effects, for instance DNA methylation, can be passed down to successive generations along with the altered phenotypic expressions. In fact, due to alterations in the epigenome that are maintained during the creation of gametes, the effects of early life undernutrition may be transmitted to subsequent generations without repetition of the immediate insult in the second generation (Drake and Walker 2004). Many researchers believe that there may be an adaptive advantage in long term intergenerational programming, and that information about a grandparent's environment will help a developing animal in its "environmental forecasting."

Many fully grown animals are well known to demonstrate consistent adaptive responses to starvation that help to minimize energy expenditure, even of the order of a few days. Starvation evokes several immediate physiological changes, the most dramatic of which include suppression of metabolic rate, increased adiposity, reduction of thyroid and growth hormone levels, a reduction in fertility (through the suppression of gonadal function), and an increased activation of the hypothalamic–pituitary–adrenal axis (Schwartz et al. 1995; Flier 1998). Unlike animals programmed prenatally for thrift though, these predictive metabolic measures reverse largely after the animal resumes its normal diet. It is also well accepted that seasonal cycles of metabolic alterations occur in hibernating mammals. Many animals that hibernate are insulin insensitive for months before they go into hibernation and exhibit increased adiposity. When they wake up in the spring they are lean and insulin sensitive once again (Scott and Grant 2006). These other examples of phenotypic plasticity are comparable to intrauterine programming in many ways and researchers could potentially learn much from contrasting these models.

The brains of experimental animals that were exposed to early nutritional deprivation seem to be buffered from growth restriction in moderate cases, but can show definite changes in severe ones.

Reductions in the number of cells in certain regions as well as in synapses and white matter evince that programming effects, that may involve thrift, take place in the brain as well. Recent studies using imaging techniques show that gray matter is reduced in humans subjected to intrauterine growth restriction, and that catch up growth may not occur (Tolsa et al. 2004). The present author has offered explanatory hypotheses for these and related observations elsewhere (Reser 2006). It is possible that a large number of different metabolic and organ systems may be affected by epigenetic programming involving predictive adaptive responses. Further, integrative research, incorporating the viewpoints from different levels of biological and medical analysis, should help to provide a clearer picture of what we refer to today as “thrift.”

166.5 Applications to Other Areas of Health and Disease

The thrifty genotype hypothesis posits that certain human genes that are associated with increased risk for metabolic disease today were naturally selected in the past because they helped their bearers to be more “thrifty” with energy stores. According to this hypothesis, phenotypes that express low metabolic rates enjoy a survival advantage under deprived circumstances. However, they face increased risk of negative health consequences when sugars and fats are artificially abundant, as they are in many countries today. The thrifty phenotype hypothesis posits that all of us have windows of susceptibility to thrifty programming that enable us to create permanent readjustments in homeostatic systems in an obsolete attempt to aid survival.

Today, the costs of the metabolic syndrome are well documented and well understood, but the prehistoric, defensive manifestations are obscured, at least at first glance, because of discrepancies between the ancestral environment and the modern environment. Many traits that are known to have been defensive in the ancestral environment are now seen as maladaptive in the present (an “environmental mismatch”) and the science of evolutionary medicine attempts to identify and characterize these traits. Researchers have identified many such “pathological” conditions such as anxiety, cystic fibrosis, diarrhea, fever, inflammation, pain, sneezing, sickle cell anemia, and vomiting and have helped to show that they actually represent evolved defenses that would have promoted survival and the likelihood of reproductive success (Williams and Nesse 1998).

The merits of the thrifty genotype and phenotype hypotheses include the implications that they generate for understanding past, current, and future trends in disease (Pollard). The historical and evolutionary forces that are apparent are still largely abstract when measured against our biomedical knowledge, and it is clear that during our journey of reconciling the two, they will continue to influence and provide predictions for each other. The notion that the human genome bears witness to past struggles for survival against starvation allows us a new context within which to view the responses of the human body. A person’s physiological response to dieting will reflect our ancestors’ adaptive responses to seasonal hunger, just as their response to abundant calories and fats will reflect our ancestors’ beneficial responses to harvest seasons. Furthermore, the thrifty phenotype hypothesis informs us that early, prenatal effects and even effects that were inherited from grandparents can cause the same anachronistic responses.

The cause of fetal malnutrition in present day populations is different from what it used to be. In the ancestral past the majority of examples of fetal malnutrition and intrauterine growth restriction probably would have come from starvation. Today, especially in affluent countries, it primarily stems from circulatory problems that are secondary to uteroplacental dysfunction, a relatively rare but epidemiologically constant condition. These modern fetuses, restricted by uteroplacental dysfunction, misinterpret their situation and prepare for nutritional scarcity when they will, in fact, encounter the opposite scenario.

Anthony Philipps explains that these findings have important implications for obstetrics and prenatal nutrition. It is imperative that circulatory assessments be made earlier in pregnancy, that more reliable ways to ascertain placental villous blood flow are developed, and that more sophisticated fetal growth measures are devised and used widely.

The identification and mapping of both thrifty genes and epigenetic markers will help to evaluate these hypotheses, but more importantly, will help inform medical research. Many critical aspects remain to be explored: (1) Where are the alleles for thrifty genes? (2) At what points during development do these windows of susceptibility exist? (3) What are the signaling pathways through which an environmental cue is translated into a developmental response? (4) Which developmental responses persist beyond a single generation and how? (5) How long do we have to wait, and how many people have to die prematurely from the metabolic syndrome for natural selection to remove the thrifty genes from our gene pool?

The observations discussed here have been extensively replicated and the theories discussed have been widely espoused but both are – and perhaps for good reason – still discussed, questioned, and debated. Many of these observations are not invariable and the causal pathways are still quite far from being transparent. It is thought that the concepts of the “thrifty genotype” and “thrifty phenotype” can be consistent and reconciled with one another. Sometimes, though, it is clear that they are mutually exclusive explanatory alternatives such as when it is not known if a low birth weight is inherited or acquired. Validity and applicability of these hypotheses is certainly open for dispute. Thrifty genes may not be identified for decades and even given the recent advances in genetic analysis are a rather nebulous concept today. One would assume that thrifty alleles would influence processes such as lipolysis, fuel oxidation, and skeletal muscle glucose metabolism, but it is difficult to say. The 2007 genome-wide association studies on type 2 diabetes mellitus provided promising data, and more refined genetic tools will provide a more complete picture of the genetic and epigenetic complexity of the metabolic syndrome.

Animal models are not always directly comparable to the human situation, but should continue to offer insight into mechanism. Long-term studies in humans are expensive and time-consuming but they will help to clarify the pertinent issues too. It is evident that this line of research has major ramifications for public health policy. Health care funding may be more prudently spent on informing and improving pregnancy care rather than on the contingent metabolic disorders which manifest decades later and cost many times more to treat. If overeating and sedentary behavior are determined during prenatal development to the degree that this literature implies, this may explain why public health initiatives to improve exercise and dieting in adults with metabolic symptoms are largely ineffective.

There is a large literature that addresses these concepts from different angles, and much is known about the similarities in predisposition for metabolic disease between people and animals (Gluckman and Hanson 2004). There is still much that is unknown though, and whether the broad, ultimate, evolutionary hypotheses have to be largely altered or just fine tuned, it is becoming clear that metabolic disease may very simply stem from the fact that our behavior, diet, and nutrition are so different from the way they used to be.

Summary Points for the Developmental Origins of the Metabolic Syndrome

- The metabolic syndrome represents a cluster of metabolic derangements that are risk factors for obesity, type 2 diabetes mellitus, and cardiovascular disease.
- There is currently a worldwide epidemic of obesity and diabetes that is due to unhealthy eating and poor exercise. These are probably issues that our hunting and gathering ancestors would rarely have been exposed to, because they were probably rarely exposed to excess, but commonly exposed to famine.

- The human gene pool probably contains many thrifty genes that would have helped our ancient ancestors to survive food shortages and starvation. For example, a tendency to efficiently take up ingested fats into fat stores would have increased the likelihood of survival.
- The physiological states that cause us to be susceptible to facets of the metabolic syndrome probably all had ecological utility in the past. This is supported by animal models.
- Many mammals and it seems humans too can be programmed for thrift if they are exposed to severe undernutrition early in development. This programming may be a predictive adaptive response to environmental cues signaling that the environment is nutritionally poor.
- The thrifty phenotype that is created from these programming effects is highly susceptible to metabolic disease.
- Future findings in this literature should have serious implications for public health and the treatment of the metabolic syndrome.

Definitions

Dyslipidemia: Refers to a disruption of the levels of lipid in the blood. In western societies, most dyslipidemias are hyperlipidemias; an elevation of lipids, often due to diet, lifestyle, or prolonged elevations of insulin.

Glucose tolerance: The ability of the body to adapt to a relatively large dose of glucose. This ability is usually diminished in diabetics and is used to diagnose diabetes mellitus. A fasting subject ingests around 75 g of glucose, and blood glucose is measured at intervals. In diabetics the concentration is higher and takes longer to return to baseline value.

Genotype: The genetic constitution of a cell or organism. The genotype contains the information, in the form of DNA, which dictates how the cell or organism develops and interacts with its environment.

Hypercortisolemia: High amounts of circulating cortisol, an essential glucocorticoid steroid hormone, and the major hormone secreted by the adrenal glands.

Hyperglycemia: A complex metabolic condition characterized by high levels of blood glucose in the circulation, usually a result of insufficient or ineffective insulin production in either type 1 or type 2 diabetes mellitus.

Hyperphagia: Refers to an abnormal appetite or increased eating of food, often associated with abnormalities in the hypothalamus.

Hypertension: High blood pressure or force of blood on the vessel walls of the arteries.

Hypothalamic–pituitary–adrenal axis: This is a neuroendocrine system in the body responsible for regulating stress physiology. Brain areas that sense threat signal the hypothalamus, which communicates hormonally to the pituitary which hormonally signals the adrenal glands to secrete adrenaline and cortisol.

Insulin resistance: A condition in which cells, especially those comprising muscle, fat, and liver tissue fail to be properly receptive to the messages of the hormone insulin. Because insulin promotes the extraction of glucose from the blood, allowing cells to meet their metabolic needs, insulin resistance is associated with elevated levels of blood glucose.

Metabolic syndrome: A combination of metabolic disorders that commonly present together, and increase the risk of developing diabetes and cardiovascular disease.

Phenotype: An observable characteristic of an organism, such as a trait, property, or behavior. Phenotypes develop from the interaction between an organism's genes and its environment.

Visceral fat: The accumulation of fat around the internal organs of the torso. It is associated with the "apple shape," belly fat, central obesity, and a high waist to hip ratio.

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