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Metabolic thrift and the genetic basis of human obesity

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Abstract

Evolution has molded metabolic thrift within humans, a genetic heritage that, when thrust into our modern "obesogenic" environment, creates the current obesity crisis. Modern genetic analysis has identified genetic and epigenetic contributors to obesity, an understanding of which will guide the development of environmental, pharmacologic, and genetic therapeutic interventions.

> "The voyage was so long, food and water ran out. One hundred of the paddlers died; forty men remained. The voyagers finally reached Fitinui, then Aotona."
>
> -From "The Story of Aka", in *The Native Culture in the Marquesas* by E. S. Craighill Handy

The Rigors of Oceanic Life

Twenty thousand years ago, fifty men and thirty women launched into the waves four large wooden canoes loaded with as much food as they could bear. As they boarded, all knew that only a minority of them might reach their final destination. They were leaving their tropical island in the South Pacific, heading east. Their island's resources were no longer sufficient to support their growing population and their people were running out of food. Their mission- to cast themselves into the Pacific Ocean and travel hundreds of miles in search of fertile land- was, to say the least, hazardous. The perils they faced included storms, whales, sharks, drowning, and injury. But their greatest enemy was starvation. Depending on the time it took to find land, and their ability to catch fish or birds in transit, their food supplies might not last the voyage and all of them might enter into the early stages of starvation. And it was likely that some if not all would die of starvation before finding fertile land. If indeed they found land, it might be too far from their original island to return- in this case, their charge was to start anew-they would be become the founders of a new society.

Paleontological evidence suggests that expeditions similar to this led to human colonization of the South Pacific beginning as long as 15,000–30,000 years ago and proceeding over thousands of years until as recently as 300 AD.[1–3] In addition to the stress of periodic transoceanic voyages, for which mortality was estimated to be as high as 75%,[1] island life was far from idyllic. Early humans in the South Pacific were faced with an active, energy-intensive lifestyle, constant exposure to the elements, and limited food supplies that were

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highly susceptible to labile weather and seasons. Periodic transoceanic journeys and the rigors of oceanic life in general exerted strong selective pressure and molded of the metabolism of the Polynesian people over the course of evolution. Those that survived were capable of storing calories in the form of adipose tissue rapidly and in large amounts in times of plenty, and burning calories in a highly efficient manner during times of famine. These evolutionary pressures additionally selected for individuals whose metabolisms were capable of maintaining high blood glucose levels in the face of early starvation, an adaptive advantage that protected against the dire consequences of hypoglycemia. To put it succinctly, the metabolisms of those that survived were highly *thrifty*. This metabolic thrift provided a significant advantage during the evolution of the Polynesian peoples. In modern times, however, this evolutionary heritage has led to a prevalence of obesity and metabolic disease in Polynesians that is among the highest of any ethnic group.[4–7]

While at high risk, Polynesians are not alone in their propensity to obesity and metabolic disease. Furthermore, the Polynesian South Pacific Diaspora is but one of many examples of the pressures that food scarcity exerted on humans over the course of evolution.[8] Over two thirds of the human population in the industrialized world is currently overweight or obese, and close to one third is obese.[9] No longer restricted to a minority, overweight and obesity are in fact intrinsic aspects of the modern human condition. Why? What mechanisms underlie this phenomenon? The contributors to obesity are evolutionary, genetic, and environmental in nature. Our species has experienced millennia of selective pressures that engineered within us a genetic predisposition towards overweight and obesity. This genetic heritage was adaptive in our distant past, providing protection against the rigors of famine, but when thrust into our modern obesogenic environment, has led to the current obesity crisis.

Ice-Age Origins of Human Metabolic Thrift

Approximately 2 million years ago, an ice age radically altered earth's environment and changed the course of primate evolution. Previously, our hominid primate ancestors, like all life forms, certainly competed fiercely for limited food resources. But with the onset of the ice age, competition was amplified and the evolutionary pressures that selected for metabolic thrift increased dramatically. The constituents of the hominid diet also changed, with a transition towards a protein-rich carnivorous diet as high carbohydrate fruits and vegetables became less abundant, generating concomitant selective pressure for insulin resistance to ward off hypoglycemia. This so-called *carnivore hypothesis* explains the relationship between metabolic thrift, adipose tissue accumulation, and insulin resistance, which had its genesis long before *Homo sapiens* and underlies the pathogenesis of obesity-related diabetes.[10]

Evolutionary selection for metabolic thrift continued after the emergence of *Homo sapiens*. Early human societies first adopted agrarianism approximately 12,000 years ago, and the resulting stabilization of food supplies and increase in dietary carbohydrates led to a waning of selective pressure for insulin resistance. Due to differences in geography and climate, European populations adopted agrarianism thousands of years prior to Asian populations. As a result, modern Europeans have relatively lower rates of insulin resistance compared to

Asians as selective pressure for this metabolic trait waned earlier in ancient European populations.[10, 11] This reversal of the selective pressure for insulin resistance provides a cogent demonstration of the intimate link between environment and metabolic phenotype.

The Advantages of Adipose Tissue

Torpor, hibernation, reduced metabolic rate, and high rates of caloric intake are but a few of the many strategies that all biologic organisms employ to achieve metabolic thrift. Among these diverse strategies, excess energy storage is a dominant mechanism, and adipose tissue is the paradigm for this strategy. The chemical properties of lipids are particularly well-suited for this task. Lipids not only have a high-energy capacity, but are also water insoluble and thus amenable to storage in large quantities in cells without disrupting cellular osmotic gradients. These qualities make lipid a universal vehicle for energy storage throughout the animal kingdom. Yeast store energy in the form of intracellular lipid droplets, while the Drosophila fruit fly stores lipid in the "fat body", a master metabolic organ and a predecessor to formal adipose tissue depots and the liver of vertebrates. In higher metazoans, the liver is capable of significant lipid storage; in geese, the liver is a dominant site of lipid stores during migration, while steatosis is a near-universal feature of human obesity. Indeed, not only hepatocytes, but virtually all cells have the capacity to store lipid. But this capacity reaches its zenith in adipocytes: adipose tissue in a lean human provides sufficient energy for weeks and even months, and in the obese, this time-frame is significantly extended; one case report documents a monitored fast in excess of one year in an obese patient,[12] although such efforts are not without risk.[13]

While common throughout the animal kingdom, adipose tissue is a particularly useful strategy of metabolic thrift for humans. Adipose tissue provided an energy buffer against abrupt changes in food resources as our species left Africa 60,000–120,000 years ago to colonize virtually every habitat on the globe.[14,15] In addition, humans have relatively long gestation and neonatal maturation periods as well as large brains that require a constant supply of glucose. Adipose tissue mass as a percentage of body weight is highest during the neonatal period, when brain growth is most rapid, in order to protect against the detrimental effects of malnutrition on the developing brain. Adipose tissue continues to exert a strong influence on reproductive fitness in adulthood, as human females are infertile in the absence of sufficient adipose tissue stores. The maintenance of adequate adipose tissue reserves is thus essential for the perpetuation of our species, and as such, powerful systems have evolved to defend these reserves. Collectively these systems comprise the so-called *adipostat*, the sum of all metabolic processes that act to maintain adipose tissue mass.

The Adipostat

Obesity is considered by many to be a consequence of inadequate self-discipline or "willpower". As such, individual diet and exercise have been historical mainstays of treatment. But vast evidence demonstrates failure of such efforts in almost all cases. The reasons for this failure are based in the tightly regulated systems that control body weight and energy metabolism. The neural networks that regulate these systems are rooted not in the frontal cortex, the seat of human cognition and conscious "willpower", but rather deep in

the hypothalamus of the midbrain, an area of the brain that long predates humans. We often believe we can consciously control how much and how frequently we eat, but in fact this control is much less than we perceive. While we are capable of limiting our food intake for short periods of time, the control mechanisms for long-term regulation of body weight are well beyond our conscious control. As a result, individual dietary efforts are almost universally followed by weight regain. Obesity is highly persistent. Obese people cannot simply choose to eat less

A wide range of physiologic processes control energy homeostasis and body weight, most dominant of which in humans are those that regulate food intake. The satiety factor leptin serves as a paradigmatic regulator of food intake. Jeffrey Friedman at the Rockefeller University cloned the leptin gene in 1994, ushering in the modern era of satiety research.[16] Leptin is a hormone secreted by adipose tissue in response to a meal that binds to its receptors in the hypothalamus to effect satiety. Leptin levels wax and wane depending on prandial status throughout the day. In addition, peak post-prandial leptin levels vary over the course of weeks and months depending on adipose tissue stores. Weight loss, whether from dieting or starvation, leads to decreased post-prandial peak leptin levels, which in turn decreases post-prandial satiety, leading to a compensatory increase in food intake over weeks and months assuming food is available, thus restoring adipose tissue mass. Leptin secretion by adipose tissue is thus governed by positive and negative feedback mechanisms that act to regulate food intake over the short-term, i.e. hours and days, as well restore adipose tissue mass when depleted over the long-term i.e. weeks and months.

Much excitement accompanied Friedman's discovery as leptin was considered a potential therapy for obese humans. Excitement waned, however, as trials of exogenous recombinant leptin therapy for human obesity demonstrated poor efficacy. In addition, obese humans manifest elevated serum leptin levels as a result of their increased adipose tissue mass, a paradoxical finding not consistent with their increased food intake. These observations were explained by subsequent research demonstrating hypothalamic resistance to leptin's satiety-inducing effects in human obesity, a phenomenon that has so far limited the use of leptin as a therapeutic agent for obesity.[17, 18]

The development of leptin resistance in response to hyperleptinemia in obese humans is an example of the robust nature of the multiple redundant compensatory physiologic processes that regulate body weight. Leptin is one of many mediators that regulate satiety and hunger, and these mechanisms are similarly a subset of the many metabolic processes that control energy balance. The biochemical processes that control metabolic rate, thermogenesis, fat, protein, and glucose metabolism, and adipocyte proliferation and differentiation, are but a few of these many systems, all of which are constrained by tightly regulated allostatic feedback mechanisms that act to defend adipose tissue stores and maintain body weight within a narrow range. Conscious efforts to lose weight with dieting, while transiently successful, fail in the long run as these control systems collectively respond to weight loss with a vigorous drive to regain lost adipose tissue mass.

The *hypothalamic feeding* center is the anatomic site of central control of energy homeostasis. The hypothalamic feeding center receives afferent neural and hormonal input

from all organ systems, (e.g. leptin, ghrelin, insulin, and multiple other hormones, along with neural afferents from the gut, adipose tissue, liver, and all other tissues), assesses energy stores, and directs metabolism accordingly to maintain adequate energy reserves, primarily in the form of adipose tissue mass. The hypothalamic feeding center *set-point* defines the level of energy reserves "considered adequate" to maintain energy homeostasis, and as such, serves as an *adipostat*, which vigorously defends decreases in adipose tissue mass due to dieting, fasting, or starvation with powerful compensatory mechanisms that act to return adipose tissue stores to prior levels. Reduction in satiety hormones such as leptin, increases in hunger hormones such as ghrelin, and reduction in metabolic rate are but a few of the many counter-regulatory processes mediated by the hypothalamus that limit conscious efforts to lose weight.

In contrast to diet-induced weight loss efforts, which almost invariably fail due to these robust counter-regulatory mechanisms, bariatric surgery remains the only current efficacious therapy for human obesity. As a therapeutic tool for obesity, bariatric surgery is therefore unique in its ability to regulate and durably "reset" the adipostat. The mechanisms underlying bariatric surgery's effects on weight regulation are ill-defined but certainly multiple. Surgery clearly alters expression of gut and adipose tissue hormones, leptin included, to promote satiety and weight loss.[19] More provocative, perhaps, are data demonstrating a paradoxical increase in energy expenditure in response to surgically-induced weight loss, in contrast to the compensatory decrease in metabolic rate observed with diet-induced weight loss.[20–22] While the underlying mechanisms of this response are unclear, it suggests a unique aspect of bariatric surgery, specifically that it somehow "side-steps" compensatory counter-regulatory responses that limit diet-induced weight loss. Bariatric surgery thus provides an important model for study of regulation of the adipostat. Elucidation of the molecular and cellular mechanisms by which surgery achieves this regulation will eventually lead to novel pharmacotherapy that will permit manipulation of the adipostat and provide treatment for obesity.

Rare humans suffer from highly morbid congenital and acquired lipodystrophy syndromes characterized by a paucity of adipose tissue.[23] Why are such conditions rare while obesity is common? The answer to this question reveals an important characteristic of the systems that control body weight-these processes err towards accumulation of excess energy rather than its depletion. Accumulation of excess adipose tissue imparted little if any selective disadvantage over the course of our evolution, and in fact likely provided a strong reproductive advantage. Disorders of metabolism that cause wasting and under-nutrition, in contrast, imparted a strong selective disadvantage. As a result, wasting disorders are exceedingly rare, while obesity is quite common.

The question arises (often posed by lean people!) that if we all share the same weight regulatory mechanisms, then why are the obese unable to control their weight while lean people can? The answer to this question lies in understanding that the adipostat set-point differs amongst us all. This variability is the result of subtle differences in dosing and function of the many genes that control satiety, hunger, metabolic rate, energy utilization, and all other aspects of metabolism. These genetic differences underlie the observed heterogeneity in human body weight in general, and the obesity phenotype specifically, with

different ages of onset, different precipitating factors (e.g. pregnancy, menopause, aging), and differing capacities to achieve and maintain weight loss with dieting and exercise. These differences explain why some of us are lean while some (the majority) of us are overweight or obese. These differences underlie the genetic basis of human obesity.

The Thrifty Gene Hypothesis and the Genetic Basis of Human Obesity

In 1962, James Neel, a geneticist at the University of Michigan, proposed the *thrifty gene hypothesis*, positing that evolutionary pressures in the form of food scarcity throughout human history led to the selection of *thrifty genes*, genes that predispose to metabolic thrift to protect against the detrimental impact of famine on survival and reproductive fitness.[24] These genes were adaptive during our evolution, but in our modern, resource-rich environment, are maladaptive and lead to obesity.

The thrifty gene hypothesis, while a cogent explanation for the human tendency towards obesity, remains contested. Alternative theories, such as the shift of humans from prey to predator status (*predation release*), and random changes in gene frequency independent of selective pressures (*genetic drift*), have been proposed and were likely also active during evolution.[25,26] Others dispute the magnitude of the selective pressures exerted by famine on early humans, although these are minority arguments, as substantial data supports that famines were frequent and widespread throughout human history.[8] The thrifty gene (or genotype) hypothesis is likely an over-simplification, but nonetheless provides a useful conceptual framework for considering the evolutionary forces that predispose to obesity.

In 1962, the specific genes and their protein products that regulate metabolism, including leptin, were not yet described. Yet Neel's hypothesis formed the basis for an understanding of the genetic basis of obesity, as it posits that metabolic thrift is rooted in genetics. What evidence supports this contention? Subsequent accumulated research supporting a genetic basis for obesity is in fact quite robust and exists primarily in the form of quantitative genetic analysis of twin studies. Twin studies involve statistical analysis of large cohorts of monozygotic and dizygotic twins based on Mendelian genetic principles and permit quantification of genetic and non-genetic contributors to a given phenotype. Such analyses have been used to determine the genetic contribution to a wide range of phenotypic characteristics and disease states. Multiple twin studies demonstrate with a high degree of concordance that the predisposition towards obesity in humans is primarily genetic, with genetic factors contributing approximately 70% to the tendency towards a specific body habitus, whether it be lean or obese, with the remaining 30% deriving from non-genetic environmental contributors.[27–34] These observations beg the obvious question: if obesity is primarily genetic, then where are the thrifty genes?

Thrifty Genes, Thrifty SNPs, and Human Metabolic Diversity

The human genome is riddled with *single nucleotide polymorphisms (SNPs)*, point mutations in multiple genes present at variable frequencies in populations that cause subtle alterations in the functions of the proteins they regulate. The frequency of a given SNP within the collective genome of a human population may be low, especially if that SNP has little or no effect on the function of the gene with which it is associated. Alternatively, if a

particular SNP alters a gene's function such that it provides a selective disadvantage, it will be rapidly selected out of a population and become quite rare or cease to exist altogether. Finally, some SNPs may provide little or no advantage in one environment, but in a different environment may suddenly provide a selective advantage. In such a case, a SNP will increase rapidly in frequency within a human population as environment changes, a process referred to as *selective sweep.*[35,36] Such selection is likely responsible for the high prevalence of SNPs that predispose to insulin resistance in Polynesians, driven by the selective advantage imparted by such genes during colonization of the Pacific thousands of years ago.[37]

The many genes that regulate metabolism in humans are thought to contain a high number of SNPs. In the context of Neel's theory, thrifty SNPS and the genes that contain them, mediate metabolic thrift, and selective pressure for such SNPs dramatically increased in primates with the onset of the ice age. Subsequent human colonization of the globe further honed human metabolic thrift and tailored the genomes of human subpopulations (such as the Polynesians) based on their specific environments. The multiple SNPs scattered throughout the human genome provide a means of rapid selection, within a few generations, for genetic alleles that provide a reproductive advantage, much more rapid than spontaneous mutation required by classical Darwinian genetics. These polymorphisms thus act as a "genetic savings bank" that provides humans with a high degree of metabolic diversity that permits rapid adaptation to abrupt changes in environment, a trait that has been crucial to our success as a species.

The Search for Thrifty Genes in the Modern Era

Despite their quantitative predictive power, twin studies are not capable of identifying specific genetic loci, a task that requires methods to interrogate the genome at the nucleotide level. One such method, *genome-wide association studies* (GWAS), involves sequencing the genomes of thousands of individuals to identify SNPs, which are then correlated with disease states and phenotypic characteristics. While conceptually straightforward, such analyses are practically complex. Many SNPs lie in non-coding regions of the genome, areas that are technically difficult to study and poorly understood from a functional perspective. In addition, as GWAS analysis proceeds, it has become clear that SNPs that correlate with obesity each individually contribute only a small amount (<1–3%) to the total genetic propensity towards obesity, implicating hundreds, and possibly thousands, of contributing genes.[38,39] This is the case for SNPs associated with many chronic diseases, which, like obesity, are complex polygenic phenomena. These small effect sizes mandate study of thousands of subjects to achieve adequate power, and further complicate functional analysis. Of note, the small effect size of SNPs for any given phenotype was predicted a century ago in the form of the *infinitesimal (or geometric) model* of quantitative genetics.[40] Simply put, this model states that any given mutation will exert a minute (infinitesimal) effect on global phenotype, in part because mutations that exert large effects are likely to be maladaptive and thus rapidly selected out of a population- only small effect-size SNPs are likely to be innocuous, and in some cases adaptive, and thus preserved. As a result, functional analysis of individual SNPs is unlikely to be productive- rather, such analysis must be carried out collectively, simultaneously taking into consideration all SNPs that influence a given

phenotype.[41] Needless to say, this presents obvious obstacles when all contributing SNPs have yet to be identified.

Despite these challenges, thrifty gene candidates have begun to emerge—to date, GWAS has associated over 50 genetic loci that confer susceptibility to obesity. Some of these loci lie in genes that are clearly involved in energy balance, including the hypothalamic satiety receptor MC4R, the adipokines leptin and adiponectin and their receptors, and the adipogenic transcription factors PGC-1α, PPAR-γ, and SREBP1c. Many obesity-related SNPs, however, are associated with genes that are not clearly involved in metabolism, such as TNF-α (an inflammatory mediator), FTO (a DNA demethylase), TMEM18 (involved in neural development), CTNNBL1 (a Wnt/β-catenin-signaling family member), and ADAMT59 (associated with global tissue development).[39,42,43] These unexpected thrifty gene candidates speak to the fact that the processes that control energy homeostasis interface with virtually every aspect of our physiology, and suggest that the very definitions of thrifty genes and metabolic processes may need to be relaxed and become more inclusive. Nonetheless, GWAS shows promise as a diagnostic tool: for example, a high number of obesity-related SNPs predicts poor weight loss after bariatric surgery.[44] While the complexities are daunting, further identification of thrifty SNPs will eventually provide the potential for targeted genetic-based therapy for obesity.

Epigenetic Regulation Of Metabolism—The Thrifty Phenotype

One of the most important advances in 21st century biology will be the incorporation of *epigenetics* into classic Darwinian genetic theory. Epigenetics consists of post-fertilization modification of the genome independent of changes in DNA nucleotide sequence, including but not limited to DNA and histone methylation, myristoylation, and glycosylation. These genomic changes occur in response to environmental stimuli perceived by the developing fetus *in utero*, and are thus termed *fetal programming*. Epigenetic modifications affect both somatic and germ cells and are thus heritable, although their heritability is not as persistent as that associated with classic Darwinian spontaneous DNA mutation, and may in contrast span only one or a few generations. Epigenetic modification is a normal process during fetal development and may extend into adulthood, although phenotypic plasticity resulting from epigenetic modification is certainly greatest during fetal and neonatal periods. Epigenetic fetal programming provides a mechanism by which the genome of a developing organism can be rapidly altered in response to maternal-fetal environment, with profound effects on phenotype.

The role of epigenetic fetal programming in determining adult metabolic phenotype has been studied intensely in the last twenty years. A classic example is provided by the Dutch Hunger Winter of World War II, during which the Germans cut off food supplies to Holland, resulting in a cohort of mothers whose offspring experienced severe caloric restriction and malnutrition during pregnancy. When compared to matched offspring from subsequent healthy pregnancies from the same mothers, children born during the Dutch Hunger Winter suffered higher rates of obesity and metabolic disease as adults.[45,46] Study of similar cohorts in other geographic locations and time periods confirm the relationship between fetal malnutrition and low birth-weight, and adult obesity and metabolic disease.[47–49] Hales and

Barker proposed the *thrifty phenotype hypothesis* in 1992 to describe this phenomenon.[50] Perhaps surprisingly, subsequent research demonstrated that maternal *over*-nutrition led to similar fetal programming, as numerous studies in animals and humans demonstrate that maternal diabetes and obesity as well as high birth-weight are also associated with increased risk of adult obesity and metabolic disease in offspring.[47,49,51–53] The similar fetal metabolic response to under-and over-nutrition presents a paradox that may be rationalized as an adaptive response by the developing fetus: regardless of the direction of the stimulus, both under- and over-nutrition signal instability in environmental food resources, and thus induce similar metabolic programming, the so-called "weather forecast" analogy.[54] It is important to note, however, that this is likely a simplified hypothesis, and debate exists regarding the adaptive role of fetal metabolic programming and ability of the fetus to "predict" its future environment based on *in utero* stimuli. Others, for example, suggest that epigenetic programming is designed to adapt the fetus to variability in maternal phenotype rather than environment, a variable the fetus is more likely to be capable of "predicting" and one that also has a dramatic impact on survival.[55]

While technologies for studying the *epigenome* at the molecular level are in early stages, evidence is accumulating that confirm a correlation between fetal metabolic programming and epigenetic changes in DNA. Offspring of the Dutch Hunger Winter, for example, demonstrate decreased DNA methylation in the IGF2 gene compared to matched non-famine offspring.[56] Other studies demonstrate differences in DNA methylation between mothers and infants with intrauterine growth restriction.[57–61] Similar evidence in humans and animal models demonstrates a link between maternal over-nutrition and molecular changes in the fetal epigenome.[62–69] While in early stages, a detailed understanding of the role of the epigenome in shaping metabolic phenotype is emerging. Provocatively, these nascent data demonstrate that epigenetic phenotype can be reversed with therapy: maternal bariatric surgery-induced weight loss, for example, is associated with decreased risk of obesity in offspring, accompanied by alterations in the epigenome.[70–73]

The thrifty phenotype hypothesis complicates the interpretation of the genetics of obesity and introduces challenges in distinguishing between the effects of classical genetics and epigenetics. For example, the heritability of obesity demonstrated by twin studies may result not only from classic Darwinian genetics as previously assumed, but also from epigenetic changes shared by twin siblings who experience similar fetal stimuli. These observations blur the lines between classical genetics and epigenetics. Often touted as opposing theories, however, it is important to note that thrifty genotype and thrifty phenotype hypotheses are by no means mutually exclusive, and both contribute to the genetics of human obesity. Despite these subtleties, epigenetic-mediated fetal programming is accepted as an important contributor to the pathogenesis of obesity and metabolic disease.

Environmental Contributors

While twin studies demonstrate that obesity is, from a quantitative perspective, predominantly genetic, environment nonetheless plays a critical role. Our current obesogenic environment provides constant access to saturated fat, simple carbohydrates, and salt, dietary constituents that we encountered infrequently and in small quantities during our

evolution, and that we are hardwired to seek out and consume in large quantities. Reduced physical activity exacerbates the problem. Our Paleolithic ancestors, among whom obesity was thought to be uncommon, are estimated to have consumed one third more calories than modern humans, but were much more active,[74] illustrating the obvious point that the central variable that dictates body weight is the difference between energy intake and expenditure.

More subtle factors also contribute. Circadian rhythmicity is an important characteristic of eating behavior, physical activity, and many physiologic processes. Circadian rhythms are disrupted in our modern environment and this disruption has been clearly linked to obesity and metabolic disease.[75–77] Notably, SNPs in genes that regulate Circadian rhythms and sleep cycles are associated with obesity,[78] suggesting genetic susceptibility to this environmental risk factor. Average indoor temperatures have stabilized and increased in the last 50 years, another putative contributing factor.[79] Complex societal forces amplify the epidemic: assortative mating, the tendency for obese people to preferentially choose obese mates, is estimated to contribute substantially to the increasing prevalence of obesity.[80,81]

Most important as we consider the role of environment, however, is that we abandon the false dichotomy of nature *versus* nurture. We often consider genetics and environment to be separate and distinct forces, but the very foundation of Darwinian theory posits that genetics and environment beget one another. It is the interaction of our genetics with our modern environment that leads to the obesity phenotype. Numerous examples exist of populations thrust into industrialized societies in whom obesity, uncommon in their native environment, suddenly blossoms (e.g., Inuits, Pima Indians, Polynesians, Aboriginal Australians),[7,82–84] the result of a genetic (and/or epigenetic) background that is adaptive in one environment but maladaptive in another. These examples are paradigms for the human race as a whole, whose genetic heritage was forged in an ancient environment characterized by food scarcity, but who now find themselves in a modern obesogenic environment. Epigenetics provides a dramatic example of the relationship between environment and genetics that manifests over the course of a generation, but classic Darwinian selection involves the same intimate interplay over millennia. Obesity is not primarily caused by genetics, nor is environment the dominant culprit. Rather, it is the interaction of our genetic heritage with our modern environment that has led to a dramatic increase in the prevalence of the obesity phenotype.

Conclusion

In the distant future, genetic engineering holds the promise for therapy that targets the very thrifty genes that cause obesity. From a practical standpoint, however, immediate solutions to the obesity crisis are more likely to arise from environmental manipulation, something at which we humans are, for better or worse, quite adept. Numerous obstacles exist, not the least of which is a powerful and lucrative food industry with a vested interest in perpetuating over-consumption. Nonetheless, a nascent field of environmental engineering is emerging to address these problems.[85,86] An understanding of the genetic basis of obesity and its relationship to our modern obesogenic environment is critical to accomplish these goals. But perhaps as important, the realization that obesity results not from a character defect, but rather from powerful physiologic mechanisms rooted in a genetic heritage shaped over

millennia of evolution, provides a basis for empathy for people afflicted with a debilitating condition and subjected to deep-rooted social prejudice.

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