Cell Metabolism
Commentary

A Nonadaptive Scenario Explaining the Genetic Predisposition to Obesity: The "Predation Release" Hypothesis

John R. Speakman[1,*]
[1] Aberdeen Centre for Energy Regulation and Obesity (ACERO), School of Biological Sciences, University of Aberdeen, Aberdeen, Scotland AB24 2TZ, UK
*Correspondence: j.speakman@abdn.ac.uk
DOI 10.1016/j.cmet.2007.06.004

The "thrifty gene hypothesis" suggests we evolved genes for efficient food collection and fat deposition to survive periods of famine and that now that food is continuously available, these genes are disadvantageous because they make us obese in preparation for a famine that never comes. However, famines are relatively infrequent modern phenomena that involve insufficient mortality for thrifty genes to propagate. I suggest here that early hominids would have been subjected to stabilizing selection for body fatness, with obesity selected against by the risk of predation. Around two million years ago predation was removed as a significant factor by the development of social behavior, weapons, and fire. The absence of predation led to a change in the population distribution of body fatness due to random mutations and drift. Because this novel hypothesis involves random drift, rather than directed selection, it explains why, even in Western society, most people are not obese.

Introduction

Western societies have experienced an epidemic of obesity during the twentieth century. The rapidity of the epidemic indicates it has an environmental cause. Yet, when studies have investigated the contribution of genetic and shared environmental factors on individual susceptibility to obesity, the major effect is genetic (Perusse et al., 1998). Obesity must consequently be a result of a gene by environment interaction. Some individuals have a genetic predisposition to become obese that is revealed in our modern environment. It has been widely recognized that our genetic predisposition to obesity lies in our evolutionary history. Previous evolutionary scenarios are all fundamentally similar and follow the original proposal by Neel (1962)—that obesity (and diabetes) stem from natural selection on our ancient ancestors favoring "thrifty genes," defined as conferring a phenotype of "*being exceptionally efficient in the intake and/or utilization of food*" during periods of food abundance. Neel (1962) argued that such a genotype would be advantageous for primitive humans exposed to variation in food supply because it would allow them to efficiently deposit fat stores and hence survive any subsequent period of famine. In modern society, however, with plentiful and continuous food, this thrifty genotype proves deleterious because it promotes efficient storage of fat, in preparation for a famine that never comes. There have been many papers reiterating the same general theme (e.g., Prentice, 2001, 2005; Chakravarthy and Booth, 2004; Wells, 2006; Eknoyan, 2006; Watnick, 2006).

I have previously argued the "famine and thrifty gene hypothesis" is fundamentally flawed (Speakman, 2006a, 2006b; see also Benyshek and Watson, 2006). In brief, famines are relatively rare demographic events, occurring only about once every 100 years, that probably originated during our transition to an agriculture-based society about 10,000 years ago. Where good data exist, excess mortality during famines is low, generally less than 5% per annum, and this mortality falls predominantly on the old and very young. Mortality in postreproductive adults is irrelevant for genetic selection, and differential mortality in the very young is unlikely to be biased toward lean individuals because until recently obesity was virtually unheard of in this age group.

Perhaps the strongest evidence against the thrifty gene and famine hypothesis comes from observations of adiposity in modern hunter-gatherer (HG) and subsistence agriculture (SA) populations. If there is strong selection for thrifty genes, then during periods between famines these populations should become obese. If they do not, then it is difficult to see how they would derive any survival advantage during the next famine. Table 1 summarizes some estimates of BMI in HG and SA populations. Only one study indicated that the communities were food restricted. Despite being in nonfamine conditions, the individuals all had BMIs around 19. Moreover, in the one example where a population was studied in drought conditions (Campbell et al., 2003), no significant differences in BMI were detected between a SA population undergoing a drought and a nomadic HG population that was not.

If the thrifty gene and famine hypothesis fails to adequately explain the genetic underpinning of the modern obesity epidemic, then what are the alternatives? My aim in this commentary is to introduce a novel evolutionary scenario for the modern epidemic that does not hinge on selection of thrifty genes during periods of famine. This novel scenario emphasizes the importance played by release from predation as a significant factor in our

Table 1. Body Mass Indices of Hunter-Gatherer and Subsistence Agriculture Communities during Periods between Famines

Location	Population	Activity	Sex	BMI	n	Reference
Namibia	!Kung San	HG	M	19.4	238	Kirchengast (1998)
			F	19.1		
	Kavango	SA	M	19.4	156	
			F	20.3		
Cameroon	Pygmy	HG	M and F	19.9-20.9		Kesteloot et al. (1997)
	Bantu	SA	M and F			
Australia	Aboriginal	HG	M and F	<20.0		Odea (1991)
Paraguay	Ache	SA				Bribiescas (2001)
Kenya	Ariaal	HG and SA	M and F	17.8	56	Campbell et al. (2003)
Ethiopia	Elka	SA	M	19.7	226	Alemu and Lindtjorn (1995)
			F	20.0		

HG, hunter-gatherer; SA, subsistence agriculture.

evolutionary history, combined with genetic drift.

The Challenge Facing Evolutionary Explanations of the Modern Obesity Epidemic

The major challenge facing any evolutionary explanation of the genetic predisposition to obesity is not to explain why we get obese, but rather to explain why only a fraction of the population gets that way. Even in the USA, 35% of the population still has a BMI in the "normal" range of 17.5 to 25 (Flegal et al., 2002; Ogden et al., 2006). Any scenario that postulates a selective advantage for obesity due to thrifty genes must explain why 35% of the population apparently did not inherit these genes. This is a major problem for any adaptive scenario because genes that confer even small advantages spread in the gene pool given sufficient time to propagate.

An Alternative Model for the Evolution of the Genetic Predisposition to Obesity

One way that we may gain insight into the processes that underlie body weight regulation in early hominids is to examine the regulation of body weight in modern wild animals. Studies of wild small animals indicate that they have a very strong regulatory system for body weight that is highly resistant to perturbations that are brought about, for example, by modifying their diets (e.g., Shaw's jird, *Meriones shawi*, El-Bakry et al., 1999; Siberian hamster, *Phodopus sungorus*, McElroy et al., 1986). In bank voles (*Clethrionomys glareolus*, Peacock and Speakman, 2001), for example, exposure to a high-fat diet does not cause them to gain weight (Figure 1). Rather the animals modulate their energy intake and elevate their levels of physical activity so that their weight remains stable.

It is possible to make small rodents lose weight by placing them onto caloric restriction. When this is done the animals oppose the restriction by modulating their energy budgets. Consequently, after a period of losing weight the animals come again into energy balance and remain weight stable (Hill et al., 1984; Hambly and Speakman, 2005). If the animals are then given free access to food they exhibit hyperphagia or sustained reductions in expenditure (Munch et al., 1993; Evans et al., 2005; Hambly and Speakman, 2005), generating rapid weight gain until their body masses return to control levels. Similar patterns of response to enforced restriction are observed in humans (Dulloo, 1997). The existence of a post-restriction hyperphagic response is important for two reasons. First, it

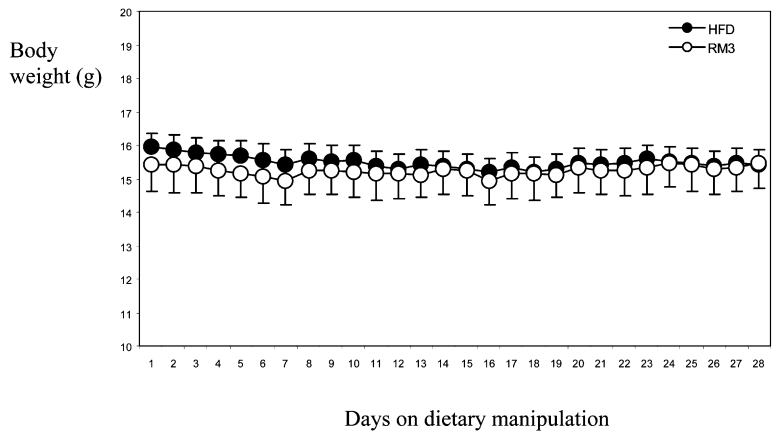

Figure 1. Response of Wild Small Mammal to High-Fat Diet

Body weights of bank voles (*Clethrionomys glareolus*) fed either a high-fat diet (HFD, 29% energy from fat, closed symbols) or standard rodent chow (RM3 pellets, 8% fat, open symbols) for a period of 28 days. The voles show complete resistance to weight gain when fed the high-fat diet (redrawn after Peacock and Speakman, 2001).

demonstrates that the animals could eat more food in the control conditions. Consequently, their intake is not constrained by some quirk of the housing conditions and must be internally controlled. They do not simply eat as much as they can, and their body mass comes to a dynamic equilibrium, where the expenditure of the expanding tissue mass balances this maximal intake (Wirtshafter and Davis, 1977; Levitsky, 2002; Speakman, 2004). The second aspect of the hyperphagia is that it suggests when the animals come off restriction they may perceive themselves to be underweight and overeat relative to controls to redress this imbalance. One interpretation of these data is that the animals have a target body weight that they regulate around by varying their food intake and energy expenditure (Kennedy, 1953; Keesey and Hirvonen, 1997; Mercer and Speakman, 2001; Figure 2A). Such homeostatic "set-point" models have, however, attracted considerable criticism because they are at odds with many features evident in patterns of change in animal and human body weight (Wirtshafter and Davis, 1977; Berthoud, 2006). An alternative interpretation is that the level of body mass is not regulated by a target, but rather is controlled by upper and lower intervention points, above and below which animals intervene to bring their body mass back into an "acceptable" range (Figure 2B: Levitsky, 2002).

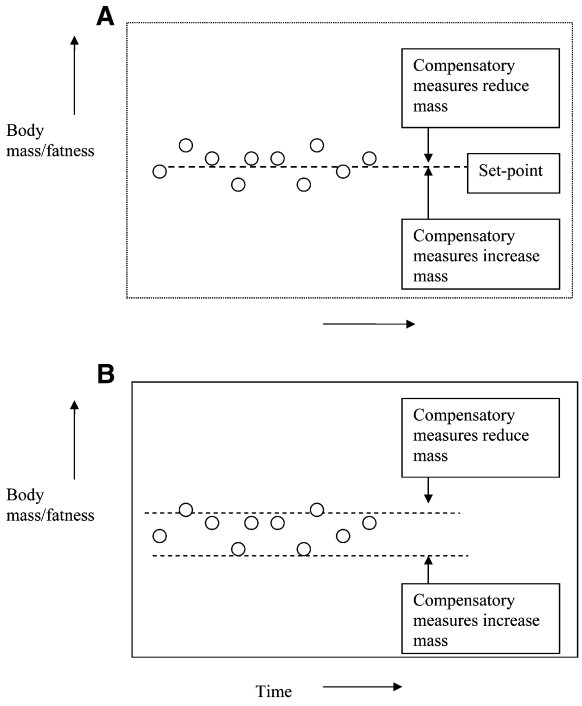

Figure 2. Models of Regulation of Body Weight and Fatness
The first (A) is the classical set-point model where compensatory measures respond as soon as the body mass or body fatness rises above or falls below the set point of the system. The second (B) has no set point but instead has upper and lower intervention levels. Body mass varies at random, or under environmental influences, between these intervention limits, and physiological compensation mechanisms are only triggered when the mass or fatness varies beyond the intervention levels.

What Features Define the Levels of These Upper and Lower Intervention Points?

Why, for example, is the lower intervention point not even lower? This question is equivalent to asking why lean humans in HG and SA societies routinely store energy to give them BMIs in the range from 18–22 (Table 1) but not BMIs in the range from 10–12. Small animals like the vole in Figure 2 probably store fat as an insurance against periods when they have no access to food supplies. Having a fat store can make a big difference for a vole. We have previously measured the level of energy demands of free-living field voles (*Microtus agrestis*) using the doubly-labeled water technique (Speakman, 1998). During winter, when voles routinely live in environments where the ambient temperature can be 30°C–40°C below their lower critical temperature, DEE is about 120 kJ/day (Speakman et al., 2003). Body fat has an energy content of about 39 kJ/g. If a 20 g vole were to store only 0.5 g of fat, then it would have enough energy available to survive for about 4 hr without feeding. There is consequently a strong selective pressure on these animals to store more fat to avoid the risk of starvation during minor periods of food insecurity. In fact voles during winter store about 3 g of fat (Krol et al., 2005), which is sufficient for them to survive without food for about 24 h. This probably allows the animals to survive any minor food security crisis they may normally encounter in the wild. There is considerable evidence, including experimental manipulations, that wild animals (mostly studied in birds) regulate their levels of body fat to match the stochasticity of food supply (e.g., Totzke et al., 2000; Cuthill et al., 2000; Fauchald et al., 2004).

The level of fat storage in HG and SA communities is probably set by similar effects. They have BMIs of 18–22 rather than 10–12 because having BMIs at this much lower level would make them susceptible to starvation during minor periods of food insecurity. The occurrence of such periods of minor food insecurity has probably not changed significantly over time as humans changed from HG to SA lifestyles (Benyshek and Watson, 2006), and the minimal level of stored fat has similarly not changed in modern societies that practice HG or SA (Table 1). Another factor of importance in setting the minimal level of fat storage is the impact that such minimal fat reserves, signaled by circulating leptin levels, have on puberty and fecundity in females. Females require a certain level of circulating leptin to initiate puberty (Ahima et al., 1997) and to reproduce (Tataranni et al., 1997). This level is presumably set by the impact that a period of food insecurity might have on the success of reproduction. As the impact of food insecurity on reproduction is likely to be greater than the impact on survival, this explains why the minimal level of fat storage in females is generally greater than that of males. The "risk of starvation" and "impact on fecundity" explain why we store the amounts of fat we do when we are lean but do not explain

why we get obese. To understand that we need to understand what selective pressures define the upper intervention point.

If voles were to store 6 or 10 g of fat they would increase their probability of surviving longer periods without food. However, there is a trade-off. Longer periods of interruption of food supply become less and less likely to occur, but carrying around 10 g of fat when you only weigh 20 g in the first place brings other problems. The risks of mortality from predation for voles are very high (Graham and Lambin, 2002), and the life expectancy of a bank vole in the wild is consequently under 4 months. Carrying around a large fat store may enhance the probability of surviving a crisis of food supply, but probably simultaneously increases the probability of being killed by a predator. This could be a direct effect because fat voles are less able to run away from predators or because lean voles can escape into refuges that their predators cannot access (Sundell and Norrdahl, 2002, Sundell and Ylonen, 2004). Alternatively it could be an indirect effect because larger size is correlated with greater energy demands (Speakman et al., 2003) and therefore requires greater food intake and a greater time spent foraging over a wider area. Greater mobility of voles has been empirically linked to greater predation risk (Banks et al., 2000; Norrdahl and Korpimaki, 1998). There is much evidence to support this idea. Bank voles in an area of Switzerland where weasels are naturally less abundant and, hence, mortality is lower were heavier (Yoccoz and Mesnager, 1998). Across smaller areas, and over time, vole body mass is negatively related to weasel density (Sundell and Norrdahl, 2002). When predators were experimentally excluded from an area in the field, bank voles (Carlsen et al., 2000) and field voles (Carlsen et al., 1999) in the predator-excluded area increased their body mass but did not in control areas. Moreover, in the laboratory, bank voles (W. Tidhar, F. Bonier, and J.R.S., unpublished data) and field voles (Carlsen et al., 1999) reduced their body mass or gained less mass when they were exposed to the feces of a predator but not in response to the feces of a nonpredator.

These twin constraints probably explain why voles (and other small mammals) have very tight regulatory systems that cannot be perturbed by changing the fat content of their food (Figure 1). Considerable research suggests that this fundamental balance of risks of starvation keeping body masses up (i.e., setting the lower intervention point) and risks of predation keeping body masses down (i.e., setting the upper intervention point) is a key component of body mass regulation in many wild animals—including both mammals and birds (e.g., Lima, 1986; Witter and Cuthill, 1993; Gosler et al., 1995; Cuthill et al., 2000).

If the dual intervention point model (Figure 3; Levitsky, 2002) is correct, it is clear that differences in individual susceptibility to obesity may stem from a separation of the upper and lower intervention points. Faced with a situation of positive energy balance, the individual with his or her upper and lower intervention points set closely together, at a low level, will enable counterregulatory measures that the person with widely separated intervention points will not. Given the data from small mammals and birds it seems most likely that the lower intervention point is set by evolutionary selection pressures relating to the risk of starvation, while the upper intervention point is set by selection pressures relating to the risks of predation.

Application of the Dual Intervention Point Model to the Evolution of Human Body Weight/Fatness

Our hominid ancestors were very likely under the same selection constraints as wild animals are today. If an individual were to store virtually no body fat (BMI around 10) they would be at risk of mortality because of the increased risk of starvation during any period of food shortage. I am not referring here to periods of famine, but to periods of a few days when the individual failed to secure food. A second and possibly much more important factor working against very low fat storage would be elevated risk of mortality during contraction of infectious diseases. Low body mass might cause poor immunocompetence, and hence individuals with very low fat contents may have been more susceptible to contracting disease and less able to fight it off. Additionally, when infected and unable to forage, these individuals would have a narrower window during which they could draw on stored reserves. Individuals with high levels of fat storage might never starve during disease episodes, but would also be selected against because they would be less able to avoid predators. This predation risk would set (in an evolutionary sense) the upper intervention point.

During the early period of human evolution between 6 and 2 million years ago (Pliocene) large predatory animals were far more abundant than they are today (Hart and Sussman, 2005). In Africa, these included several species of sabre-toothed cats such as *Megantereon,* several false sabre-toothed cats in the genus *Dinofelis,* conical-toothed cats of the genus *Homotherium,* a giant cheetah *(Acinonyx pardinensis)*, and some members of the Felinae in the genus *Panthera* that are now extinct, along with modern representatives of this genus that are still with us (lion and leopard; Turner, 1997). In addition to these members of the cat family there were also cursorial hunting hyenas (genus *Chasmaporthetes*), giant hyenas (*Pachycrocuta brevirostris*), dog-like bears (*Agriotherium*), and expanding populations of true dogs (Canids). Our ancestors (Paranthropines and Australopithecines) were considerably smaller than modern humans (Kappelman, 1996), making them potential prey to a wide range of predators. Indeed it has been suggested that the false sabre-toothed cat *Dinofelis* may have been a specialist predator on Australopithecines (Turner, 1997). Six percent to 10% of fossil bones of early hominids (*Australopithecus afarensis*) show signs of predation (Hart and Sussman, 2005), similar to levels reported in modern day African ungulates. Most bones of other Australopithecines come from assemblages that reflect predator activity (Pickering et al., 2004) consistent with the idea

that early hominids suffered high predation risks (Brain, 1981). At this stage of our evolution it seems most likely that upper and lower intervention points would have evolved to be relatively close together, and the early hominids probably had close control over their body weights, like modern day wild animals under similar constraints (e.g., Figure 1).

Several major events happened in our evolutionary history around 2 million to 1.8 million years ago. The first was the evolution of social behavior. This would have allowed several individuals to band together to enhance their ability to detect predators and protect each other from their attacks. In a similar manner some modern primates (for example, vervet monkeys [*Cercopithecus aethiops*]) have evolved complex signaling systems to warn other members of their social groups about the approach of potential predators (Cheney and Seyfarth, 1985). This alone may have been sufficient to dramatically reduce predation risk (Fuentes, 2006). A second important factor was the discovery of fire (Platek et al., 2002) and tools that could be used as weapons. Australopithecine bones found in caves do not have tools or other artifacts associated with them. The first descriptions of modified stones for use as tools date to the Oldowan site 2.6 million years ago (Susman, 1991), and systematic tool use was probably not fully developed until the appearance of *Homo habilis* and *Homo erectus* around 2 million years ago. Together fire and weapons would have been very powerful mechanisms for ancestors to protect themselves against predation, and social structures would have greatly augmented these capacities by enabling more rapid predator detection and effective group protection systems. Modern apes such as chimpanzees *(Pan troglodytes)* also use weapons such as sticks to protect themselves against predators, such as large snakes and leopards (Kortlandt, 1966), or band together for protection, and it has been concluded that bands of early hominids with even quite primitive tools could easily succeed in defending themselves in confrontations with potential predators (Treves and Naughton-Treves, 1999).

The effective removal of predation as an evolutionary force is suggested here to be the most significant evolutionary event in the regulation of our body fatness because it removes the selective pressure maintaining the upper intervention point (see also Speakman, 2004). After the evolution of social groups and the discovery of fire and weapons there would have still been strong disease-related selection against lowering of the lower intervention point but no selective pressure constraining the upper intervention point. Under this scenario mutations leading to an increase in the upper intervention point would not be removed by selection, but mutations leading to reductions in the lower intervention point would still be selected against. Over time the upper and lower intervention points would randomly drift apart.

The key aspect of this "drift" scenario is that the genetic predisposition to obesity is not interpreted to be an advantageous characteristic favored by the process of natural selection (as in the thrifty gene hypothesis). Rather it is seen as consequence of the absence of selection. As such this model is a "nonadaptive" scenario. I contend that obesity has never been advantageous to humans. Moreover, because the upward drift in the upper intervention point is presumed to have occurred at random, this explains why many individuals still regulate their body weights in the BMI range from 17.5 to 25. These individuals have simply not drifted.

Quantification of the Nonadaptive Drift Model in Upper Intervention Points

One feature of the thrifty gene hypothesis is that, despite the plethora of papers that have reiterated it over the half century since it was first formulated, it is still completely anecdotal. No one has ever attempted to quantify the predictions of the hypothesis. Can we quantify the predictions of the nonadaptive drift hypothesis for the shape of the modern obesity epidemic? To predict the distribution of upper intervention points under an absence of selection, I have modeled the pattern making the following assumptions: I have assumed that the upper intervention point is a polygenic trait that is influenced by a large number of genes, each having independent additive effects. Reviews of the genetics of obesity support this interpretation (Rankinen et al., 2006). Since these genes are presumed to be independent and additive we can simplify the model by considering the situation for a single gene with large effects. Hence, if we assume that there is a single gene governing the upper intervention point and that mutations in this gene result in increases or decreases in the set point by 8 BMI units, this is numerically equivalent to the set point being defined by many independent and additive genes, with each having a small impact on BMI. We will take as a starting point the BMI of modern HG communities as an indication of the BMIs of hominids 1.8 million years ago, approximately when the predation transition occurred. These communities have BMIs centered on a mean of around 20 (Table 1; Kirchengast, 1998; Kesteloot et al., 1997; Odea, 1991; Bribiescas, 2001; Campbell et al., 2003; Alemu and Lindtjorn, 1995). Random gene mutations occur at a rate of about one per generation (Eyre-Walker and Keightley, 1999; Crow, 1999), although the actual figure is widely disputed, and estimates range over two orders of magnitude. Human generations last about 25 years, so in 1.8 million years there have been 72,000 generations. Given that the human genome consists of about 25,000 genes (Venter et al., 2001) and assuming the mutations occur at random across the genome, then each gene has on average experienced about three random mutations since the predation transition. We will assume that mutations occurring at random are equally likely to result in an increase or a decrease in the upper intervention point (i.e., on average 1.5 mutations result in positive movements, and 1.5 mutations generate negative movements) and also that, in a single-gene model, each mutation results in an 8 point shift in BMI (either up or down).

Because mutations are discontinuous events (i.e., there is no such thing as 1.5 mutations), we will assume that the actual number of mutations follows a Poisson distribution with a mean intensity of the Poisson process equal to 1.5 mutations (up and down). Given that mutational events are presumed to occur at random, we can estimate the probability of any particular combination of numbers of mutations leading to increases and decreases in the upper intervention point by combining the respective Poisson probabilities. For example, the probability of a lineage experiencing five mutations increasing the set point is 0.00154, and the probability of experiencing three mutations decreasing the set point is 0.01305. In combination, therefore, the probability of experiencing five positive and three negative mutations comes out at $p = 0.00154 \times 0.01305 = 0.0000219$, or about two in 100,000 individuals. Since each mutation is assumed to move the upper intervention point by 8 BMI units, these individuals would have an upper intervention point BMI of $20 + (5 \times 8) - (3 \times 8) = 36$. We will assume that there is no negative impact of a high intervention point because these individuals are not selected against when there is no predation and that upper intervention points less then 20 are selected against because this leads to a conflict with the low intervention point. Thus a lineage with one positive and two negative movements in the upper intervention point will be eliminated because the resultant upper intervention point BMI is only 12. We can combine the probabilities that have resultant upper intervention points of ≥ 20 to evaluate the resultant drifted distribution (Figure 3). This distribution shows the expected pattern of variation in BMI in a population after 1.8 million years of absence of selection against high upper intervention points. This expected distribution is similar to the present (2000) distribution of BMI in the USA (Flegal et al., 2002; NHANES III data) but suggests the epidemic may still have some way to go, as the expected numbers of very obese exceed the current observation, while predicted numbers of overweight individuals are lower than observed. The important point, however, is not that the model closely predicts the modern distribution of body weights because we do not know how realistic the model assumptions are. If the upper intervention point is defined by 20 genes with an effect of 0.1 BMI units, the predicted distribution would have much lower numbers of obese, and if it were governed by 160 genes with the same effect, it would generate much greater numbers of obese. The key point is that approximate parameterization of the model results in a predicted distribution of obesity phenotypes that is not wildly discordant with the current distribution. Much better models should be possible in the future as our knowledge of the model parameters becomes more crystallized. The nonadaptive drift in upper intervention points resulting from a relaxation in predation risk starting about 1.8 to 2 million years ago therefore overcomes the key challenge facing evolutionary scenarios of explaining why only a small proportion of the population gets massively obese (BMI > 40). No formulation of the thrifty gene hypothesis has ever achieved this.

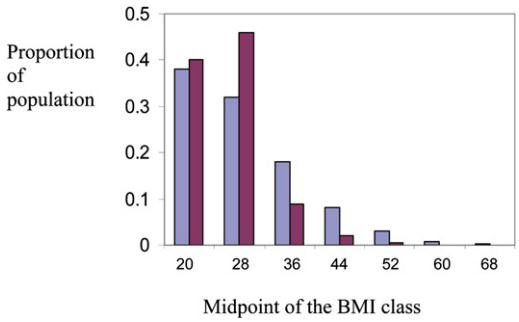

Figure 3. Predicted and Observed Variation in Body Mass Index

The expected distribution of body mass indices in a population after 1.8 million years of drift in the presence of strong selection against reduced lower intervention points, but with no selection opposing random mutations, causing increased upper intervention points to the control system (blue). The model is based on estimates for the rates of mutation per generation, human generation times, and the time period of 1.8 million years since early hominids dramatically reduced their risks of predation. The maroon bars show the distribution of BMI in the USA in 2000 (Flegal et al., 2002, NHANES III).

Implications

The model of drifted upper intervention points has several implications:

(1) The obesity epidemic is predicted by this model to have a limited extent. Once populations attain the drifted upper intervention point distribution, the epidemic will grow no worse. Unfortunately, because we know next to nothing about the genetic basis of the system, we cannot predict when this will happen. Recent evidence, however, suggests that some slowing of the epidemic in the US has already occurred (Ogden et al., 2006).

(2) If the thrifty gene hypothesis is wrong, then searching for thrifty genes is a waste of time (see also Speakman, 2006a). Conversely, an important key to understanding and potentially discovering new solutions to the obesity problem is to find the molecular basis for the upper intervention point of the system—that is, genes that control body weight/fatness successfully in lean individuals that have become mutated in the obese. Unfortunately, while we can postulate that such a system exists, and we know several likely peripheral signals that code for fat storage, we know virtually nothing about the coding in the brain to which these levels are compared to initiate compensatory responses to reduce weight. I suggest that once we know how the upper intervention point is encoded, manipulating it will become a rich source of novel pharmaceutical discovery.

(3) When the upper and lower intervention points for body weight are well separated there is scope for a wide range of factors to act that will influence the actual attained body

weight/fatness. It is between these physiological intervention points that environmental and social factors (such as affluence) can achieve significance. In the past these social and environmental factors may have been the most important factors influencing whether individuals achieved their drifted upper intervention points or not. Consequently a full theory will only be attained by merging the present physiological framework with a socio-economic and environmental perspective.

(4) Another aspect of the upper and lower intervention points being well separated is that under normal growth conditions, without free access to high energy diets, individuals would naturally sit just above the lower intervention point. This would explain why "normal weight" individuals with BMIs in the range from 20–25 show an asymmetry in their responses to energy imbalance, with greater resistance to weight loss than to weight gain (Schwartz and Niswender, 2004).

(5) Other physiological factors may be important in affecting whether individuals attain their drifted upper intervention points. One, for example, is the status of their feeding-reward system. Some individuals may rapidly move toward their upper intervention points because they have a reward system that gives them greater hedonic stimulation when they feed. By contrast, individuals with a system that is less prone to stimulation by the hedonic properties of food may migrate to their upper intervention points more slowly. This model suggests, however, that while the reward system may play a role in how rapidly individuals migrate to their intervention points, the hedonic reward system will eventually be overridden by the intervention system illustrated in Figure 2B. Consequently it is suggested that individuals with a low upper intervention point combined with a high hedonic reward system will not get fat. Association studies between the status of the reward system and body weight across a population with a diversity of intervention points may then fail to reveal an effect of the reward system despite its potential role in the rates at which individuals achieve their upper intervention points.

ACKNOWLEDGMENTS

I am grateful to many people for interesting discussions about the ideas in this paper, notably P. Grant, E. Krol, D. Wang, M. Friedman, H. Rudi-Berthoud, and D. Strickland. I would also like to thank S. O'Rahilly for his support and enthusiasm.

REFERENCES

Ahima, R.S., Dushay, J., Flier, S.N., Prabakaran, D., and Flier, J.S. (1997). J. Clin. Invest. *99*, 391–395.

Alemu, T., and Lindtjorn, B. (1995). Int. J. Epidemiol. *24*, 977–983.

Banks, P.B., Norrdahl, K., and Korpimaki, E. (2000). Proc. R. Soc. Lond. B. Biol. Sci. *267*, 1621–1625.

Benyshek, D.C., and Watson, J.T. (2006). Am. J. Phys. Anthropol. *131*, 120–126.

Berthoud, H.R. (2006). Obesity *14* (*Suppl 5*), 197S–200S.

Brain, C.K. (1981). The Hunters or the Hunted? An Introduction to African Cave Taphonomy (Chicago: University of Chicago Press).

Bribiescas, R.G. (2001). Am. J. Phys. Anthropol. *115*, 297–303.

Campbell, B., O'Rourke, M.T., and Lipson, S.F. (2003). Am. J. Hum. Biol. *15*, 697–708.

Carlsen, M., Lodal, J., Leirs, H., and Jensen, T.S. (1999). Oikos *87*, 277–285.

Carlsen, M., Lodal, J., Leirs, H., and Jensen, T.S. (2000). Int. J. Mamm. Biol. *65*, 100–109.

Chakravarthy, M.V., and Booth, F.W. (2004). J. Appl. Physiol. *96*, 3–10.

Cheney, D.L., and Seyfarth, R.M. (1985). Behaviour *94*, 150–166.

Crow, J. (1999). Nature *397*, 293–294.

Cuthill, I.C., Maddocks, S.A., Weall, C.V., and Jones, E.K.M. (2000). Behav. Ecol. *11*, 189–195.

Dulloo, A.G. (1997). Proc. Nutr. Soc. *56*, 25–40.

Eknoyan, G. (2006). Adv. Chronic Kidney Dis. *13*, 421–427.

El-Bakry, H.A., Plunkett, S.S., and Bartness, T.J. (1999). Physiol. Behav. *68*, 87–91.

Evans, S.A., Parsons, A.D., and Overton, J.M. (2005). J. Appl. Physiol. *99*, 1336–1342.

Eyre-Walker, A., and Keightley, P.D. (1999). Nature *397*, 344–347.

Fauchald, P., Tveraa, T., Henaug, C., and Yoccoz, N. (2004). Oikos *107*, 583–591.

Flegal, K.M., Carroll, M.D., Ogden, C.L., and Johnson, C.L. (2002). JAMA *288*, 1723–1727.

Fuentes, A. (2006). Social organization: social systems and the complexities in understanding the evolution of primate behavior. In Primates in Perspective, C.J. Campbell, A. Fuentes, K.C. MacKinnon, M. Panger, and S.K. Bearder, eds. (Oxford: Oxford University Press).

Gosler, A.G., Greenwood, J.J.D., and Perrins, C. (1995). Nature *377*, 621–623.

Graham, I.M., and Lambin, X. (2002). J. Anim. Ecol. *71*, 946–956.

Hambly, C., and Speakman, J.R. (2005). Obes. Res. *13*, 1548–1557.

Hart, D., and Sussman, R.W. (2005). Man the Hunted: Primates, Predators and Human Evolution (Boulder, CO, USA: Westview Press).

Hill, J.O., Fried, S.K., and DiGirolamo, M. (1984). Am. J. Physiol. *248*, R318–R327.

Kappelman, J. (1996). J. Hum. Evol. *30*, 243–276.

Keesey, R.E., and Hirvonen, M.D. (1997). J. Nutr. *127*, S1875–S1883.

Kennedy, G.C. (1953). Proc. R. Soc. Lond. B. Biol. Sci. *140*, 578–592.

Kesteloot, H., Ndam, E.C.N., Kowo, M., Njoya, O., Cobbaert, C., Sasaki, S., and Seghers, V. (1997). Nutr. Metab. Cardiovasc. Dis. *7*, 383–387.

Kirchengast, S. (1998). Ann. Hum. Biol. *25*, 541–551.

Kortlandt, A. (1966). Curr. Anthropol. *7*, 215–216.

Krol, E., Duncan, J.S., Redman, P., Morgan, P.J., Mercer, J.G., and Speakman, J.R. (2005). J. Comp. Physiol. [B] *176*, 153–163.

Levitsky, D.A. (2002). Appetite *38*, 143–148.

Lima, S.L. (1986). Ecology *67*, 377–385.

McElroy, J.F., Mason, P.W., Hamilton, J.M., and Wade, G.N. (1986). Am. J. Physiol. *250*, R383–R388.

Mercer, J.G., and Speakman, J.R. (2001). Neurosci. Biobehav. Rev. *25*, 101–116.

Munch, I.C., Markussen, N.H., and Oritsland, N.A. (1993). Acta Physiol. Scand. *148*, 335–340.

Neel, J.V. (1962). Am. J. Hum. Genet. *14*, 352–353.

Norrdahl, K., and Korpimaki, E. (1998). Ecology *79*, 226–232.

Odea, K. (1991). Clin. Exp. Pharmacol. Physiol. *18*, 85–88.

Ogden, C.L., Carroll, M.D., Curtin, L.R., McDowell, M.A., Tabak, C.J., and Flegal, K.M. (2006). JAMA *295*, 1549–1555.

Peacock, W.L., and Speakman, J.R. (2001). Physiol. Behav. *74*, 65–70.

Perusse, L., Changnon, Y.C., Rice, T., Rao, D.C., and Bouchard, C. (1998). Med. Sci. (Paris) *14*, 914–924.

Pickering, T.R., Clarke, R.J., and Moggi-Cecchi, J. (2004). Am. J. Phys. Anthropol. *125*, 1–15.

Platek, S.M., Gallup, G.G., and Fryer, B.D. (2002). Med. Hypotheses *58*, 1–5.

Prentice, A.M. (2001). Br. Med. Bull. *60*, 51–67.

Prentice, A.M. (2005). Mech. Ageing Dev. *126*, 976–981.

Rankinen, T., Zuberi, A., Chagnon, A.C., Weisnagel, S.J., Argyropoulos, G., Walts, B., Perusse, L., and Bouchard, C. (2006). Obesity *14*, 529–644.

Schwartz, M.W., and Niswender, K.D. (2004). J. Clin. Endocrinol. Metab. *89*, 5889–5897.

Speakman, J.R. (1998). Am. J. Clin. Nutr. *68*, 932S–938S.

Speakman, J.R. (2004). J. Nutr. *134*, 2090S–2105S.

Speakman, J.R. (2006a). The genetics of obesity: five fundamental problems with the famine hypothesis. In Adipose Tissue and Adipokines in Health and Disease, G. Fantuzzi and T. Mazzone, eds. (Totowa, NJ, USA: Humana Press).

Speakman, J.R. (2006b). Diab. Vasc. Dis. Res. *3*, 7–11.

Speakman, J.R., Ergon, T., Cavanagh, R., Reid, K., Scantlebury, D.M., and Lambin, X. (2003). Proc. Natl. Acad. Sci. USA *100*, 14057–14062.

Sundell, J., and Norrdahl, K. (2002). Ann. Zool. Fenn. *39*, 325–333.

Sundell, J., and Ylonen, H. (2004). Behav. Ecol. Sociobiol. *56*, 263–269.

Susman, R.L. (1991). J. Anthropol. Res. *47*, 129–151.

Tataranni, P.A., Monroe, M.B., Dueck, C.A., Traub, S.A., Nicolson, M., Manore, M.M., Matt, K.S., and Ravussin, E. (1997). Int. J. Obes. *21*, 818–821.

Totzke, U., Hubinger, A., Dittami, J., and Bairlein, F. (2000). J. Comp. Physiol. [B] *170*, 627–631.

Treves, A., and Naughton-Treves, L. (1999). J. Hum. Evol. *36*, 275–282.

Turner, A. (1997). The Big Cats and Their Fossil Relatives (New York: Columbia University Press).

Venter, J.C., Adams, M.D., Myers, E.W., Li, P.W., Mural, R.J., Sutton, G.G., Smith, H.O., Yandell, M., Evans, C.A., Holt, R.A., et al. (2001). Science *291*, 1304–1351.

Watnick, S. (2006). Adv. Chronic Kidney Dis. *13*, 428–432.

Wells, J.C.K. (2006). Biol. Rev. Camb. Philos. Soc. *81*, 183–205.

Wirtshafter, D., and Davis, J.D. (1977). Physiol. Behav. *19*, 75–78.

Witter, M.S., and Cuthill, I.C. (1993). Philos. Trans. R. Soc. Lond. B Biol. Sci. *340*, 73–92.

Yoccoz, N.G., and Mesnager, S. (1998). Oikos *82*, 85–98.