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If Body Fatness is Under Physiological Regulation, Then How Come We Have an Obesity Epidemic?

John R. Speakman

Key State Laboratory of Molecular Developmental Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Chaoyang, Beijing, China; and Institute of Biological and Environmental Sciences, University of Aberdeen, Aberdeen, Scotland, United Kingdom
j.speakman@abdn.ac.uk

Life involves a continuous use of energy, but food intake, which supplies that energy, is episodic. Feeding is switched on and off by a complex array of predominantly gut-derived peptides (and potentially nutrients) that initiate and terminate feeding bouts. Energy is stored as glucose and glycogen to overcome the problem of the episodic nature of intake compared with the continuous demand. Intake is also adjusted to meet immediate changes in demands. Most animals also store energy as fat. In some cases, this serves the purpose of storing energy in anticipation of a known future shortfall (e.g., hibernation, migration, or reproduction). Other animals, however, store fat in the absence of such anticipated needs, and in this case the fat appears to be stored in preparation for unpredictable catastrophic shortfalls in supply. Fat storage, however, brings disadvantages as well as advantages, in particular an increased risk of predation. Hence, many animals seem to have evolved a dual intervention point system preventing them from storing too little or too much fat. The physiological basis of the lower intervention point is well established, but the upper intervention point is much less studied. Human obesity can potentially be understood in an evolutionary context as due to drift in the upper intervention point following release from predation 2 million years ago (the drifty gene hypothesis) combined with a stimulus in modern society to overconsume calories, possibly attempting to satisfy intake of a limiting micro- or macro-nutrient like protein (the protein leverage hypothesis).

The laws of thermodynamics dictate that energy can be neither created nor destroyed but only transformed (first law). However, there is an overall directionality in the transformation, such that, in a closed system, disorder (entropy) increases (second law). Living organisms cannot evade these fundamental physical principles, and they have major consequences. Living things have such low entropy that they need to continuously fight against the impetus for entropy to increase. The physiological reality of these physical laws is that complex proteins, lipids, DNA, and RNA become damaged and corrupted, and must be continuously recycled and rebuilt in a complex integrated system if they are to maintain their function. Doing this requires the transformation of large amounts of energy. The summed total of all these metabolic processes means that, even when an organism is outwardly doing nothing, it still uses up large amounts of energy to sustain its physiology. Living is about much more than staving off the rampaging flow of entropy increase. All organisms must grow, move around to find mates and food, defend themselves against attack by parasites, viruses, and bacteria, and reproduce. These processes also all require energy. The requirement by life for energy is continuous. It is what separates the states of life and death.

Although energy can be used to sustain many different life processes, in animals it can be obtained only by feeding. Apart from some primitive organisms like filter feeders, feeding cannot be continuous, because if it was it would interrupt engagement in the other aspects of being alive. There is consequently a temporal mismatch in the energy utilization process and the energy provisioning process. Since energy cannot be created or destroyed, this means that animals need to have

some mechanism(s) to store energy so that the episodic supply can be matched to the continuous requirement. These physical facts that underpin the energy utilization processes in living organisms raise some interesting biological questions that are the focus of the present article. How is the balance of intake and expenditure regulated? What are the storage mechanisms? How are the levels of storage regulated? What are the evolutionary forces that control these regulatory mechanisms? What are the physiological factors that underpin this regulation? Most importantly, if there really is a regulatory system controlling body fatness, then why do we find ourselves in the middle of an obesity epidemic? Why did it all go wrong?

Short-Term Regulation of Food Intake and Energy Balance

During intake of a meal, human subjects report a progressive decline in feelings of hunger: satiation. Satiation is dependent on the nature of the food. Most people will have experienced the phenomenon of feeling completely satiated by the intake of savory food but still being able to eat a dessert: sensory-specific satiation. The signals that underpin satiation include direct distension of the gut, communicated directly to the brain via the vagus nerve. In addition, digested nutrients stimulate the release of a plethora of hormones that are released sequentially along the alimentary tract as ingested food passes and is absorbed (FIGURE 1). These anorexic hormones include cholecystokinin (CCK), glucogon-like peptide 1 (GLP1), vasoactive intestinal polypeptide (VIP), peptide YY (PYY), neurotensin (NT), oxyntomodulin (OXM), enterostatin, apolipoprotein A-IV (APO), gastrin-releasing peptide (GRP), and neuromedin B (NMB) (reviewed in Refs. 3, 13, 16, 31, 48, 53, 59). L-cells in the alimentary tract that secrete some of these hormones have been shown to have taste receptors and short-chain fatty acid receptors on their luminal surfaces, which detect digested nutrients and mediate the release of the hormones (32). Different hormones have diverse distributions along the alimentary tract, and they differ in their responses to the various ingested nutrients. They also have separate target populations in the brain. The main target populations of neurons are located in the brain stem, notably the nucleus of the solitary tract (NTS) and the arcuate nucleus (ARC) of the hypothalamus.

Many of the gut hormones feed back onto the gut, delaying motility (e.g., GLP-1 and PYY) and feed-forward to the pancreas, liver, and adipose tissue to prepare these tissues for the surge nutrients about to be absorbed. The liver, pancreas and adipose tissue also release hormones that affect appetite, including amylin, pancreatic polypeptide, and insulin from the pancreas (2, 12, 44, 55), possibly adropin from the liver (39), and many adipokines secreted from adipose tissue, including leptin, tumor necrosis factor-α, and interleukin-6. At the point feeding is terminated, the feeling of hunger is at a minimum. To distinguish the processes underpinning (lack of) hunger occurring between meals from those occurring within meals (satiation), the phenomenon between meals is called satiety. Satiety progressively declines after a meal is terminated, until reduced satiety stimulates the resumption of feeding. This decline in satiety is not simply linked to the reduced levels of the hormones stimulated by the feeding event, since repleting individual hormones during the inter-meal interval seldom delays meal onset significantly. However, this may just be because the system has massive redundancy (FIGURE 1), and it is the overall tenor of the change in multiple hormones that is more important. This reduction in levels of anorexic hormones is combined with an increase in another hormone, ghrelin, produced by the stomach, which acts in the hypothalamus as an appetite stimulant (15, 38, 49, 74).

Although the cycle of meal-based eating is preserved in many situations, the total intake of food is sensitive to changes in the levels of energy expenditure. For example, increased energy demands due to elevated levels of exercise, cold exposure, or reproduction all stimulate food intake (some examples from Refs. 33 and 35 are shown in FIGURE 2). These increases can include modulations of both meal size (reduced satiation effect of feeding) and satiety (reduced meal-to-meal interval). This is not only apparent temporally when demands change within an individual but also between individuals that differ in their energy requirements. For example, larger individuals have greater energy demands, and to meet these demands they have greater food intake. It has been recently suggested that a major factor stimulating food intake differences between individuals is the level of fat-free mass (5) or RMR (6). The mechanisms that underpin this response of food intake to balance the overall levels of expenditure remain unclear.

Over the short term, energy intake and expenditure may be balanced by the level of expenditure directly stimulating the level of intake, and any residual surplus or shortfall being supplied by mobilization or storage of glucose and glycogen. A useful analogy for this process is a regular bank account. Money is periodically deposited into the account (food intake) where it is stored temporarily (glucose and glycogen stores) and is depleted by continuous spending (energy expenditure). The presence of the bank account acts as an essential

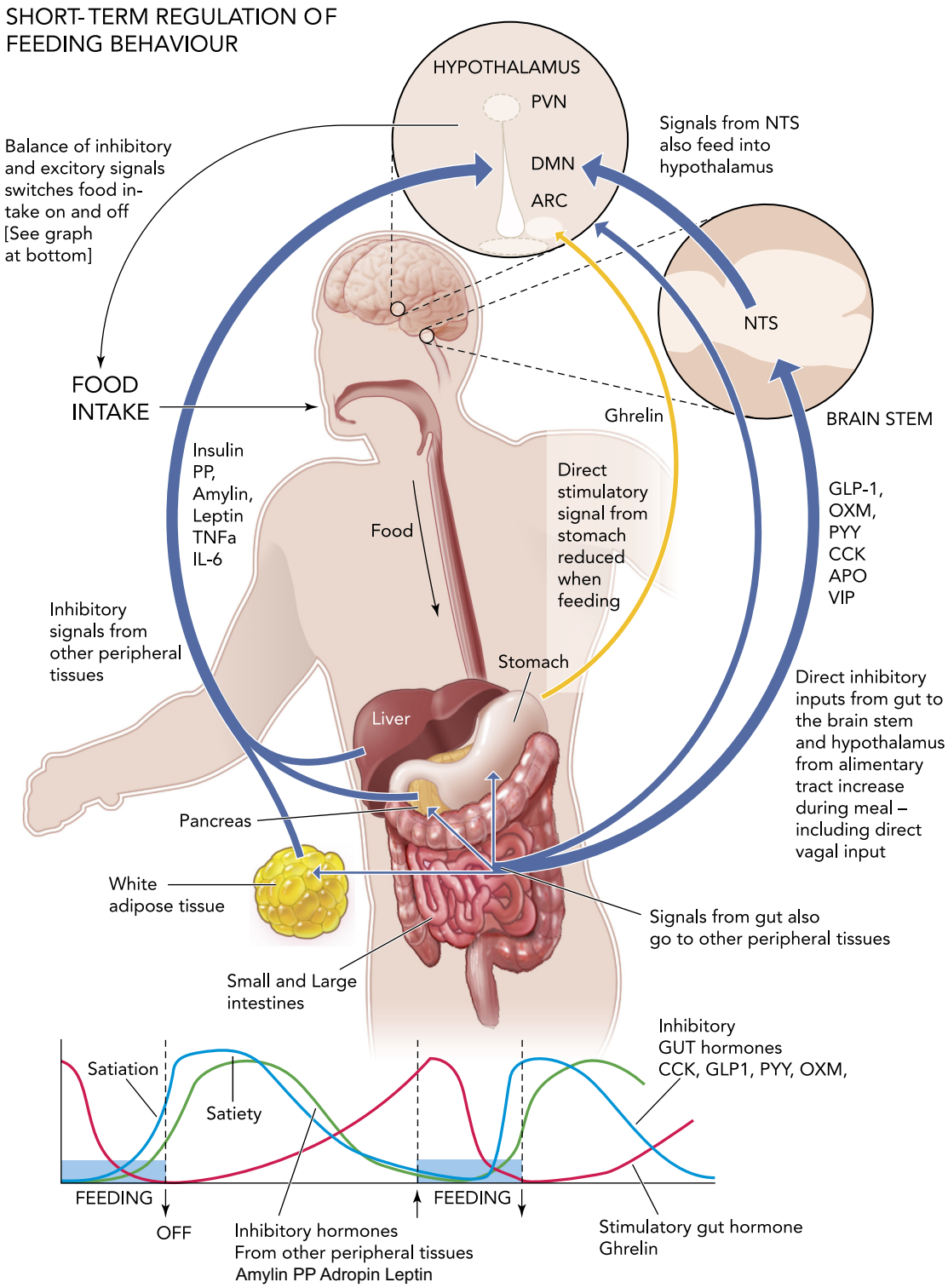

FIGURE 1. **Diagram showing the short-term regulation of food intake**
When food enters the alimentary tract, it stimulates production of several inhibitory compounds (blue arrows at *right* of diagram) that go to the brain stem [nucleus of the solitary tract (NTS)] and hypothalamus [arcuate nucleus (ARC)] and inhibits production of a stimulatory compound produced by the stomach (Ghrelin) (orange arrow at *right*). These compounds also target other peripheral tissues such as the liver, pancreas, and white adipose tissue, which generate another set of inhibitory signals that also pass to the hypothalamus (blue arrow at *left*). In addition, direct distension of the alimentary tract acts as an inhibitory signal via the vagal nerve. The consequence of these increased inhibition signals combined with the reduced stimulatory signal (see time course plot at the bottom) is that feelings of hunger decline (satiation), and feeding eventually stops. Once feeding stops, the inhibitory signals eventually decline, the stimulatory signal increases (reduced satiety), and eventually food intake is reinitiated.

buffer between the discontinuous income and continuous spending.

Long-Term Regulation of Energy Balance and Fat Storage

There are numerous situations where the linkage between energy requirements and food intake cannot be sustained, because it is impossible in a given situation to get enough food to meet the demands. In these instances, animals need a more long-term storage mechanism, and this is generally provided by body fat and protein. Retaining the bank account analogy, body fat is rather like a savings account. During periods when food is abundantly available, animals can deposit energy into this savings account so that it is available for periods in the future when demand will exceed supply (34). There are clear limits in the utility of this method, and in many circumstances storing energy external to the body may be a much better option since the amount that can be stored is much greater. But this latter strategy is prone to problems that do not beset internal storage, such as forgetting where it was stored, decay and attack by fungi, and getting it stolen. Nevertheless, storing energy outside the body is a widely used strategy (e.g., Ref. 22), and some aspects of the physiological mechanisms underlying it are starting to emerge (4).

Some animals store fat in anticipation of a clearly defined, predictable event, such as migration or hibernation (34). However, fat storage is a more widely observed phenomenon, including (very conspicuously) in humans. Why do such non-migrating, non-hibernating animals store fat? And how is the level regulated? A popular idea regarding such fat storage is that it serves as a reserve for unanticipated shortfalls in food supply. Because animals cannot switch off their demands and the reserves of glycogen and glucose are able to supply energy for only a limited period, fat storage may act as an insurance policy against such stochastic shortfalls. This idea has been called the thrifty gene hypothesis (11, 18, 41, 50, 56–58, 77, 78). During complete starvation, individuals storing more fat can survive longer than individuals who store less (65, 71), hence the thrifty gene hypothesis posits that, under conditions of uncertain food supply, genes promoting fat storage will be positively selected. The probability of a catastrophic failure of supply, however, diminishes as the duration of the period without food increases (FIGURE 3A). If an individual stores only very little fat, there is a strong probability that at some point it will encounter an energy crisis, and as a consequence it will die. There is accordingly very strong selection against storing very low amounts of fat. As individuals store more and more fat, the possibility that they will encounter a supply crisis

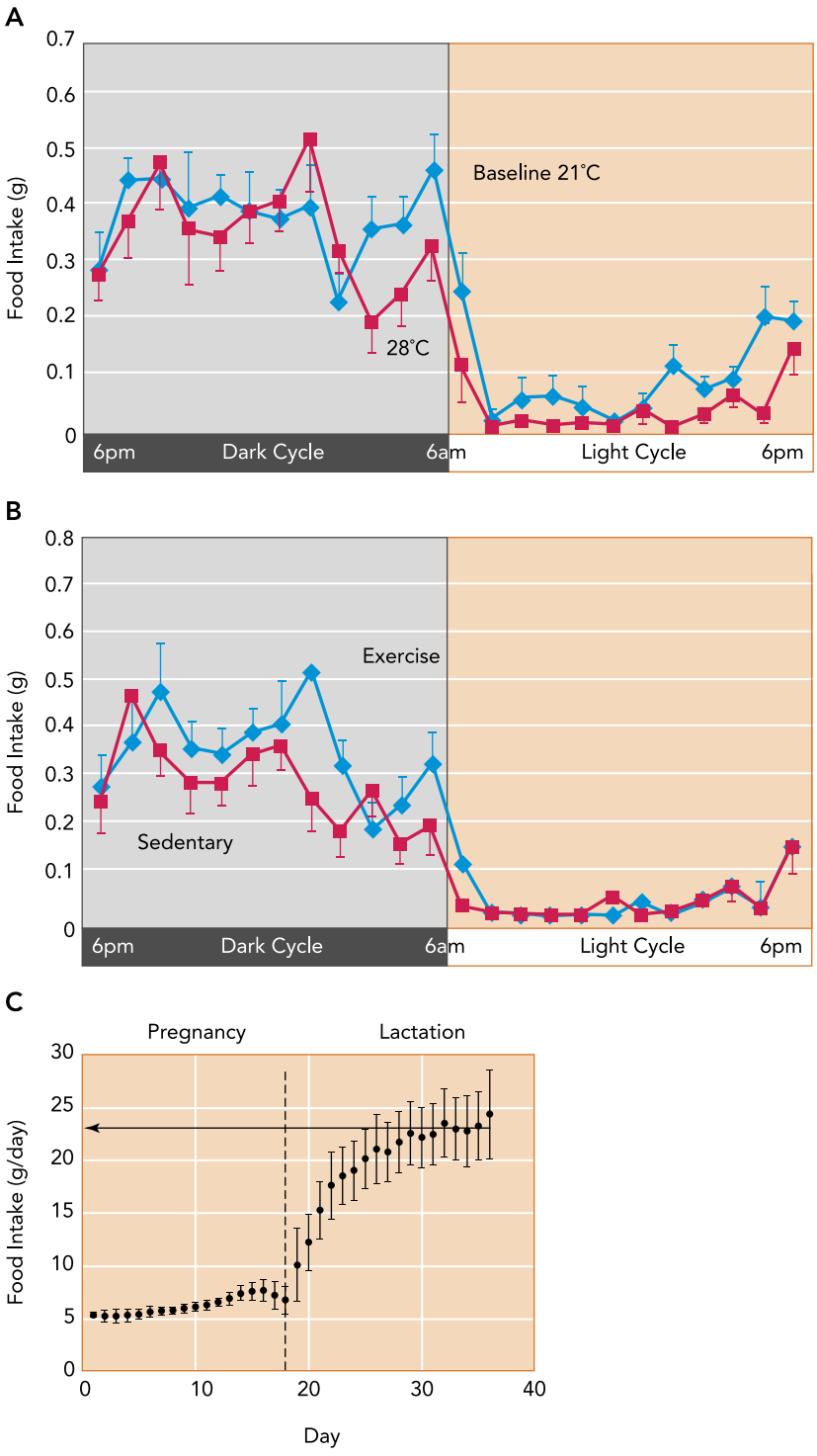

FIGURE 2. **Three examples of the effects of energy expenditure changes on food intake**
A: the 24-h cycle of food intake in mice housed at 21°C and then following their transfer to 28°C where energy demands are lower. After transfer to the hot conditions, the food intake declined (from Ref. 35). *B*: the cycle of 24-h intake of mice that were provided with running wheels to stimulate their activity compared with the same mice without wheels. Again the intake was higher when the animals expended greater levels of energy on exercise (from Ref. 35). *C*: the daily food intake throughout pregnancy and lactation in mice. The intake at peak lactation (23 g/day) is 4.6 times that of the mice at the start of pregnancy (5 g/day) only 30 days earlier (from Ref. 33).

necessitating that level of energy storage gets progressively smaller. The selection pressure to store increasingly large amounts of fat therefore gets smaller and smaller. However, as emphasised in FIGURE 3A, the selection pressure always remains positive. This raises a major problem with the thrifty gene idea. If the avoidance of starvation was the only criterion that governed the level of fat storage, then one would predict that individuals should always maximize their fat storage levels, and the world should be populated only by massively obese animals (and humans). Why does this not happen?

Going back to the savings account analogy, the suggestion that animals and humans should always be maximally fat is a bit like saying we should all have huge savings accounts containing more than a million dollars. Clearly, we all do not have such large savings accounts because the discrepancy between our income and expenditure does not allow us to deposit so much into the savings reserve. Animals and humans may be similarly constrained in their energy balance. The supply of food may be limited and hence not permit them to deposit enormous fat stores. The thrifty gene argument is that food is generally constrained in supply. When there is a glut of food, individuals respond by eating more and depositing it as fat, but their capacity to deposit enormous reserves is limited because food supply seldom remains in glut for any period of time. Individuals that have thrifty genes favoring deposition of fat in periods of glut would therefore be highly selected for, but in many situations fat storage is environmentally constrained. By this hypothesis, the modern human obesity epidemic is because we currently find

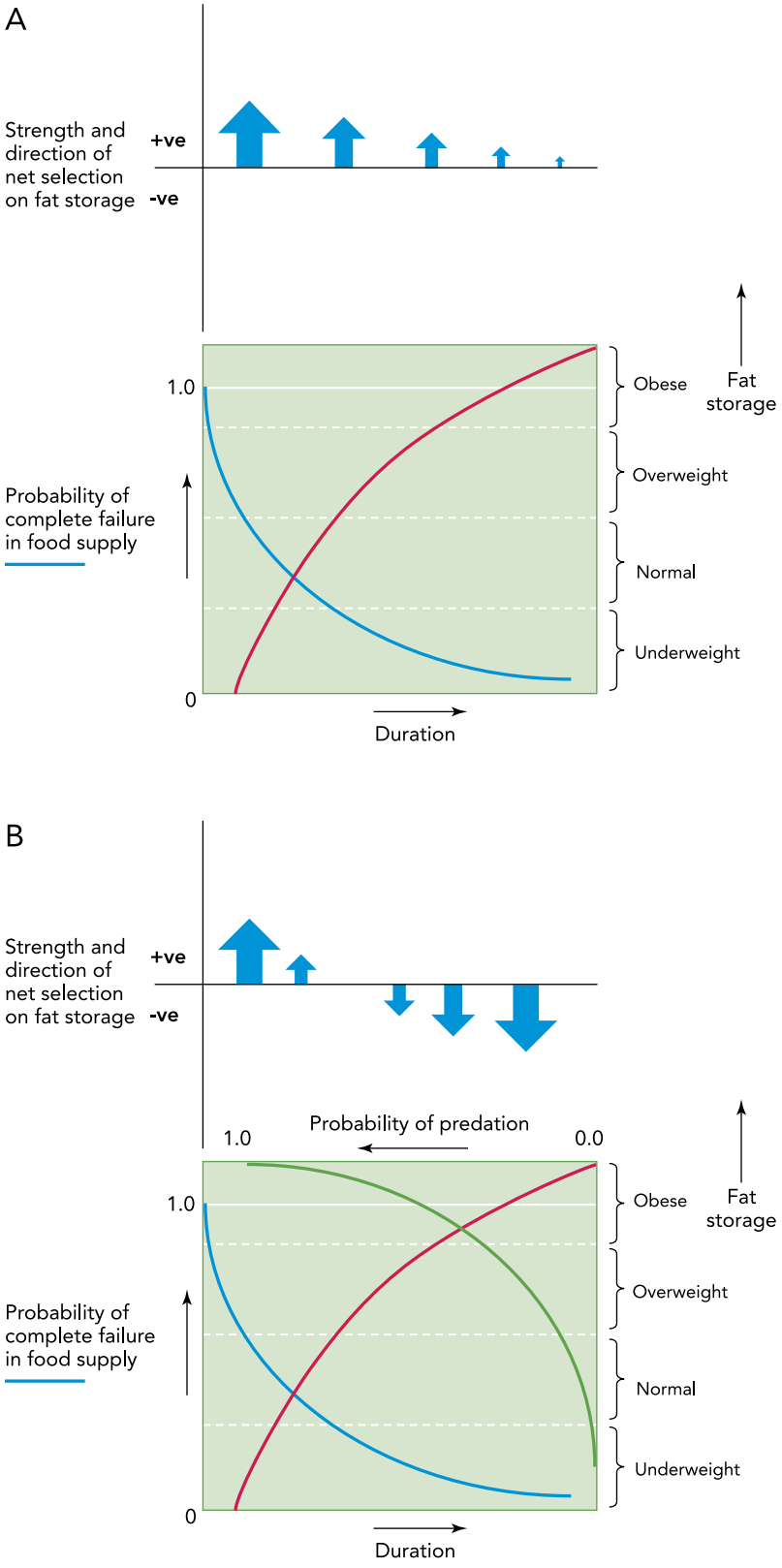

FIGURE 3. **Schematic representations of the idea that body fatness is evolutionarily selected and the twin roles of starvation and predation**
A: schematic representation of the idea that body fatness is evolutionarily selected by the risk of catastrophic failure in food supply. The blue line shows the probability of a catastrophic failure of food supply during the lifespan of an animal (*left*, *y*-axis) as a function of duration of the event (*x*-axis). Very-short-duration events are almost certain to occur ($P = 1.0$), and the probability declines as duration increases but never reached zero. The red line shows survival duration (*x*-axis) as a function of fat storage (*right*; *y*-axis). Fatter animals live longer under complete starvation than thinner ones. The arrows at the *top* show the direction and strength of selection on fat storage. When animals are underweight, their survival duration is short and the probability of them encountering a catastrophic failure of food supply of such a duration is high. Thus the selection to increase fat storage is high and positive. As fatness increases, the survival duration gets longer and the probability of a fatal event of that duration correspondingly lower, so the force of selection on fatness declines but never becomes negative. *B*: schematic representation of the twin roles of starvation and predation on evolution of fat storage. The effects of fatness on survival duration (red) and the probability of a catastrophic failure in food supply of a given duration (blue) are as in FIGURE 3A. However, now the risk of predation (*top*; *x*-axis) as a function of fat storage (*right*; *y*-axis) is also included (green line). The same selection direction and strength pertain at low levels of fat storage because the risk of predation at such levels is virtually zero. However, as fatness increases, the increasing risk of predation offsets the benefits in relation to starvation risk, creating first a zone of no directional selection and eventually increasing selection to reduce body fatness.

ourselves in an environment where food supply is never constrained, and our thrifty gene physiology pushes us toward massive fat storage. The wide differences between countries in their obesity rates are then presumed to reflect where they stand in the transition process from being food limited to food unlimited.

It is a nice idea, but there are several serious flaws in it. One problem with the argument is that the amount of extra food we need to develop massive obesity is not large. The difference between a food-constrained situation and a food-unconstrained situation would only be very small. Plus, there is much evidence to suggest that, in wild animals, the food supply is not constrained at all. Consider, for example, the effects highlighted above concerning the differences between individuals in their energy demands and how that relates to their food intake (FIGURE 2). During summer, when many individuals are breeding, some females will be at peak lactation, some pregnant and some between breeding events. Their intakes will be very different depending on their demands. The food supply must be sufficient to accommodate the intake of the animals with the greatest requirements (e.g., those lactating), so for all other individuals it must be available in excess. Why then do the animals that are not lactating eat the same amounts of food and use the surplus above their demands to deposit a fat store? A similar argument pertains to the differences in demand between small and large individuals. If there is enough energy available to supply the demands of large individuals, then for small individuals it must always be in excess. Another line of argument against food being normally limited and animals responding to unlimited food by becoming obese is that when wild animals are brought into captivity and given unlimited food supplies, they normally do not become obese. It might be argued this is a consequence of the stress of captivity, but when the converse is done and food is provided in the wild, an experiment performed frequently by ecologists, animals do not generally respond in a manner suggesting their previous supplies were limited (7, 69). Finally, for most humans in Western society, food supplies massively exceed energy requirements,[1] yet even in the fattest nations on earth, obesity is found in only 30–35% of individuals, and a population of individuals comprising ~20% remains stubbornly lean (20, 21). These arguments all suggest the thrifty gene model is incorrect, or at best only part of the story.

One idea is that fat storage not only brings advantages but also disadvantages, the most conspicuous of which is the risk of predation (9, 10, 24, 29, 43, 45). This might come about in several ways. Large individuals may be less agile or have lower maximal speeds to evade predators, or it may be because larger individuals have greater energy requirements so that they may have to forage for longer, and during foraging they are most likely to be predated. There is strong empirical evidence that predation risk is related to body size across a wide variety of taxa. Hence, although there may be a selection pressure from starvation risk pushing body fatness upward (a selection pressure that becomes progressively weaker as mass increases; FIGURE 3A), there is a countervailing pressure in the opposite direction. At some point, the diminishing advantages of avoiding starvation become offset by the risk of predation, and there will be strong selection favoring animals that do not exceed this limit (FIGURE 3B).

The Dual Intervention Point Model

One way to envisage this scenario is that there are two intervention points: at low and high levels of fatness (FIGURE 4) (70). Between these points, body fatness probably plays little part in the regulation of food intake. This zone is where social and psychological factors driving body fatness act. However, if fatness falls below the lower intervention point, then physiological mechanisms will be enabled that stimulate intake to bring fatness back into the "acceptable zone." On the other hand, if fatness increases too much, then similar physiological stimuli will be enabled to reduce intake. This idea is called the "dual intervention point" model (42, 67, 70).

There has been considerable work to elucidate the molecular underpinnings of the system that regulates the level of body fatness. A major feature of such models is the molecule leptin, discovered 20 years ago as a signal generated by fat that is mutated in the ob/ob mouse (86). The classical model by which leptin is presumed to operate is that it interacts with two populations of neurons in the arcuate nucleus of the hypothalamus, both of which carry the long form of the leptin receptor but express different neuropeptides (23, 47, 60, 81, 82). One cell type expresses neuropeptide Y (NPY) and agouti-related protein (AgRP), whereas the other type expresses pro-opiomelanocortin (POMC) and cocaine- and amphetamine-related transcript (CART). In the classical model, low leptin levels

[1]A person in the U.S. earning the minimum wage of $7.25 per hour and working a standard 38-h week would have an annual income of about $14,300. Assuming half of this was available to buy food, this person could buy annually 2,865 McDonalds happy meals (~8 per day), containing ~3,700 calories, ~47% more than the daily intake requirement of a man and 84% more than the daily intake requirement of a woman. In 2013, it was estimated that earners of minimum wage had lower income than those on welfare in the majority of states in the U.S.

stimulate the NPY/AgRP cells and inhibit the POMC/CART cells. Since AgRP is a natural agonist of melanocortin receptors, whereas POMC is cleaved to form, among other things alpha melanoctye stimulating hormone (aMSH), an endogenous antagonist of the same receptors, this leads to stimulation of melanocortin 4 receptors located in the paraventricular nucleus, and this, along with the stimulated NPY and inhibited CART, acts to promote food intake. Over the last 15 years, this model has become increasingly complex (e.g., Refs. 40, 51, 62) and now includes a direct role for nutrients being sensed in the brain (e.g., Ref. 37), interactions with other compounds expressed on neurons in other hypothalamic nuclei (e.g., Refs. 17, 52, 63), other compounds within the same neurons (e.g., Refs. 14, 27, 73, 79, 83, 84), and systems outside the hypothalamus, including the reward system in the nucleus accumbens (36, 75, 76) and the brain stem (46, 85), where the gut hormones primarily interact. Thus the long-term signaling related to fatness interacts with the short-term signaling related to individual meals (above).

Presentations of this system generally always report it as consisting a two-sided "homeostatic response": low leptin producing a stimulation of intake and reduction in expenditure, thereby elevating fat stores, and high leptin generating the reverse effects (e.g., Refs. 23, 60). The most robust demonstrations of significant effects, however, relate predominantly to the impact of low fatness and fasting (e.g., Ref. 1), and it seems likely that this control system really pertains only to the phenomenon of low body fatness stimulating intake to replete fat levels (see also Ref. 61). Our understanding of the other end of the regulatory framework (what happens when fat levels are too high) remains much more rudimentary. It seems apparent, however, that the regulatory control is not symmetrical. That is, low leptin may be a critical signal for low fat stores that fall into the lower intervention zone and enable a whole series of mechanisms that stimulate intake, and perhaps reduce energy expenditure to drive positive energy balance, and restore fat levels above the intervention point. However, high leptin, although correlated with body fatness, does not seem to play as important a role at the upper intervention point. This provides a context for understanding why leptin does not work as an obesity treatment (28). If leptin is not used by the machinery that codes for the upper intervention point to signal that fat levels are too high, then giving more leptin will not stimulate that system to reduce intake, increase expenditure, and drive weight down. In this light, understanding how the upper intervention limits operate should be a key future goal.

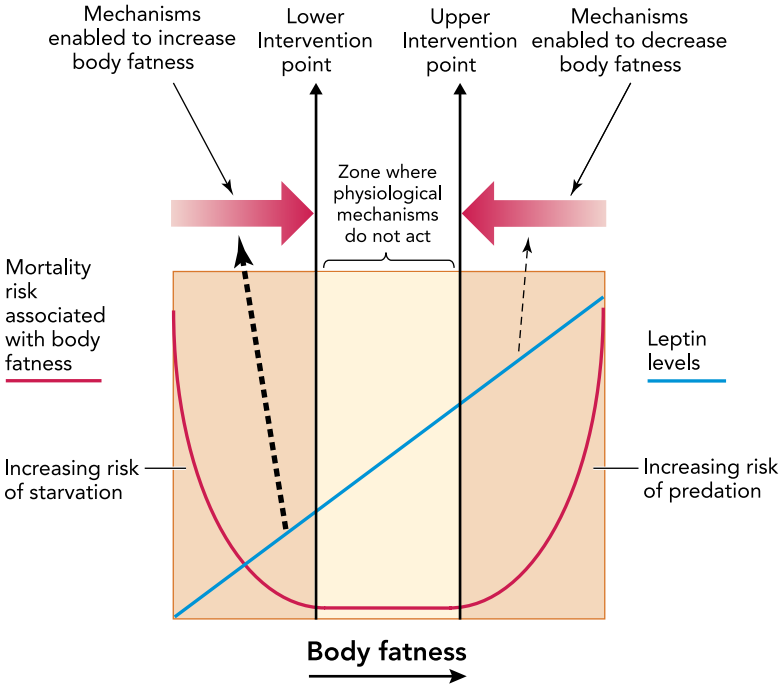

FIGURE 4. **Schematic representation of the dual intervention point model**
Mortality risk follows a U-shaped function of body fatness, increasing at low levels of fatness because of the risk of starvation and increasing at high levels because of the predation risk. At the base of the U, physiological mechanisms likely do not act to regulate body fatness. However, below the lower intervention and above the upper intervention points, mechanisms are enabled to increase and reduce fatness, respectively. Leptin levels (blue) increase in relation to body fatness. Low levels of leptin appear to be crucially involved in the mechanisms that turn on the mechanisms that increase fatness (thick dotted black arrow), but high levels of leptin appear to be less important for switching on the mechanisms that reduce fatness above the upper intervention point (thin dotted black arrow).

So Why Do We Get Fat?

If animals (and humans) have such a system regulating their body fatness, then it is pertinent to ask why we have an obesity crisis. Why, when individuals started to increase in body weight, did their physiological systems not intervene, preventing them from greater weight gain? One idea for why this happened is related to our evolutionary history and our changing exposure to predators and hence the risk of predation (67, 68). Early solitary hominins such as *Australopithecus* were probably heavily predated. There is abundant evidence supporting this suggestion. Fossil australopithecine bones frequently carry traces of predator attacks (8, 54), and the populations of predators in Africa at the time were extremely diverse and abundant, including some species (e.g., *Dinofelis*) believed to be specialist hunters of australopiths. Today, humans falling victim to predation is extremely rare. Hence, at some point in our history, we became released from the massive predation risks experienced by *Australopithecus*. This probably happened ~2 million years ago with the emergence of *Homo erectus*, a species that was social,

used weapons, and discovered fire (67). These three factors probably dramatically reduced predation risk, supported by the absence of signs of predation on *H. erectus* fossils, in contrast to those of *Australopithecus*. If predation fell to a level where it was a sufficiently rare event that it was no longer closely linked to body weight, then the selective pressure sustaining the upper intervention point (or zone) would be removed. However, although the selective pressure would have gone, the machinery would still be present in most individuals. The absence of selection is not in itself a sufficient force to remove this machinery, so what would happen is that, over time, random mutations would happen and, in the absence of selection, the prevalence of these mutations would drift. This genetic drift would be aided by the fact that the effective population size in our early history was relatively small (19, 26). The position of the upper intervention point might therefore change in some individuals, but in others it would remain unchanged, depending on these random drifting mutations. This idea has therefore been called the "drifty gene" hypothesis (68). Consistent with this viewpoint, the major polymorphisms that have been linked to BMI in genome-wide association studies (GWAS) studies are almost all located adjacent to genes that appear unrelated to the lower intervention point system (72, 80).

The massively reduced risk of predation in our evolutionary history linked to subsequent random mutations in the control system for the upper intervention point provides an evolutionary context for understanding why individuals vary enormously in their levels of obesity. However, it is incomplete because it does not explain why individuals overeat in modern society, allowing them to increase to their drifted upper intervention points. This might be because, historically, food supplies were limited, but in the light of the arguments provided above this seems unlikely. Something else may have previously capped our intake, but in modern society this restriction has been removed. One idea is that we eat not only for energy but to supply macro- and micronutrients. Historically, it may have been that our demands for these micronutrients were all met by the intake of energy. Hence, there was no strong compulsion to overeat, and as long as individuals did not allow their fat levels to fall outside the regulated limits, the regulation of food intake would depend only on the interplay of gut hormones periodically switching it on and off, with minimal additional input mediated via fat storage levels. However, in modern society, some critical micro- or macronutrient may be deficient in our diets. We may therefore be stimulated to over consume energy by a nutrient-specific hunger signal related to this critical macronutrient. Satisfying the needs for this nutrient might then drive us into positive energy balance, and we may gain weight, but once we reach our variable upper intervention points, this weight gain may be resisted. This would explain why some people become obese but others do not. Interestingly, this would actually also imply that those who had low intervention points might not be obese but might also be obtaining insufficient supplies of this nutrient. A candidate for the critical nutrient is protein (30, 64, 66), which is suggested to leverage energy intake when it is supplied at low levels, the "protein leverage" hypothesis. Interestingly, FTO the first gene identified as linked to BMI by GWAS, has been suggested recently to be potentially involved in regulation of protein intake via sensing of essential amino acids (25). The protein leverage hypothesis provides an understanding of the potential stimulus that drives people to overconsume calories in modern society, and the drifty gene hypothesis provides an understanding for why, under that pressure, some people get obese but others do not. Together, they provide a mutually supportive framework for understanding the etiology of the epidemic, reconciling the apparently disparate observations that at the individual level energy balance appears regulated, whereas at the population level there is an obesity problem.

Testing the Hypotheses

Combined together the drifty gene and the protein leverage hypotheses provide a cogent "evolutionary" model reconciling the observations that body adiposity appears at the individual level to be a regulated phenomenon, although at the population level we are in the middle of an obesity epidemic. Moreover, the hypotheses provide an explanation for why there is such diversity in the levels of observed adiposity in modern society. As previously highlighted, explaining this diversity of response has eluded previous attempts to understand the evolutionary context of the obesity epidemic, for example, in the thrifty gene hypothesis. However, although these hypotheses provide a cogent explanation of the phenomena, that does not mean they are correct, and it is reasonable to ask how the hypotheses might be tested. In this final section, I consider such possible tests for both the drifty gene and protein leverage hypotheses.

The key aspect of the drifty gene hypothesis is that the genes responsible for imposing an upper limit on our weight gain have not been subject to strong selection but have rather drifted during the past 2 million years of our evolution. At present, we do not know what these genes are. Hence, a priority for physiological research should be to aim to characterize the physiological control system that

limits weight gain. As discussed above, this does not seem to be simply the inverse of the system that attempts to cope with weight loss. Studies of animal models are likely to be a fundamental aspect of this characterization in the same way that they have made an immeasurable contribution to our understanding of the regulatory system that counteracts food shortage and weight loss. A clue, however, to the genetic elements that may form an important part of this regulatory system are the genes located nearby to single nucleotide polymorphisms (SNPs) that have been identified from GWAS to be linked to adiposity (BMI) (e.g., Ref. 72). The drifty gene hypothesis (68), by definition, predicts that these polymorphisms will not have been subjected to intense recent selection, whereas the most recent incarnation of the thrifty gene hypothesis (57, 58) suggests that such intense selection must have occurred. Reduced diversity of polymorphic variation at sites immediately adjacent to the target SNPs, reflecting a selective sweep, would be a clear indication that strong selection had occurred in the recent past, and this would provide a direct refutation of the drifty gene hypothesis. Patterns of linkage disequilibrium adjacent to the GWAS SNPs might be one mechanism to identify whether such selective sweeps have occurred adjacent to the loci in question.

The protein leverage hypothesis posits that a key factor driving excess consumption is the relatively low protein content of diets relative to their calorie contents in modern societies. If individuals do consume primarily to meet their needs for protein rather than for energy, then one would anticipate that levels of protein intake would be relatively static across different populations independent of the type of diet, and across different times in a single population, whereas calorie consumption would be highly variable (and dependent on the protein-to-energy ratio). Simpson and Raubenheimer (64) presented data for the U.S. compiled from the FAOSTAT database, which suggested that, although energy derived from carbohydrate and fat increased from ~10 MJ/day in 1961 to 14 MJ/day in 2000, the intake of energy from protein remained almost static at 2,000 kJ/day. Moreover, compiling data from the same database for 13 different countries showed that the prevalence of obesity was strongly correlated with the decline in percentage protein intake in the diet between 1970 and 2000. Although interesting, one potential criticism of these data, however, is that the FAOSTAT database is only a very crude instrument to gauge actual energy and macronutrient intakes, reflecting as they do food supply rather than food consumption. Indeed, the very poor nature of our ability to record population or individual level food intake in any meaningful quantitative manner hinders any attempt to test this idea. Nevertheless, the model presented by Simpson and Raubenheimer (64) makes a very clear prediction that when the percentage protein in the diet falls below 14%, this will drive overconsumption and obesity, and increasingly so as the percentage declines, whereas a diet containing >14% would be largely protective. This prediction should pertain at both individual and population levels.

In conclusion, energy balance is regulated on different temporal scales, from minutes to hours, dependent on storage of glucose and glycogen, to days and weeks, related to storage of fat. The dual intervention point model suggests body fatness is regulated by two systems, one at the lower margin preventing stores from being too low, dictated by the risk of starvation, and one at the upper margin preventing stores being too large, dictated by the risk of predation. We can understand the obesity epidemic as due to genetic drift in this upper target due to the reduction in predation risk over the last 2 million years. Paradoxically, given their relative importance in producing the obesity epidemic, we know a great deal about the physiology underpinning the lower intervention system but relatively little about the upper intervention system. Consistent with this view, most of the genetic polymorphisms linked to obesity have not been located in the system that regulates the lower intervention point. ■

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