ABSTRACT Obesity represents one of the most serious global health issues with ~310 million people presently affected. It develops because of a mismatch between energy intake and expenditure that results from behavior (feeding behavior and time spent active) and physiology (resting metabolism and expenditure when active). Both of these traits are affected by environmental and genetic factors. The dramatic increase in the numbers of obese people in Western societies reflects mostly changing environmental factors and is linked to reduced activity and perhaps also increased food intake. However, in all societies and subpopulations, there are both obese and nonobese subjects. These differences are primarily a consequence of genetic factors as is revealed by the high heritability for body mass index. Most researchers agree that energy balance and, hence, body weight are regulated phenomena. There is some disagreement about exactly how this regulation occurs. However, a common model is the “lipostatic” regulation system, whereby our energy stores generate signals that are compared with targets encoded in the brain, and differences between these drive our food intake levels, activity patterns, and resting and active metabolisms. Considerable advances were made in the last decade in understanding the molecular basis of this lipostatic system. Some obese people have high body weight because they have broken lipostats, but these are a rare minority. This suggests that for the majority of obese people, the lipostat is set at an inappropriately high level. When combined with exposure to an environment where there is ready availability of food at low energy costs to obtain it, obesity develops. The evolutionary background to how such a system might have evolved involves the evolution of social behavior, the harnessing of fire, and the development of weapons that effectively freed humans from the risks of predation. The lipostatic model not only explains why some people become obese whereas others do not, but also allows us to understand why energy-controlled diets do not work. Drug-based solutions to the obesity problem that work with the lipostat, rather than against it, are presently under development and will probably be in regular use within 5–10 y. However, several lines of evidence including genetic mapping studies of quantitative trait loci associated with obesity suggest that our present understanding of the regulatory system is still rudimentary. In particular, we know nothing about how the target body weight in the brain is encoded. As our understanding in this field advances, new drug targets are likely to emerge and allow us to treat this crippling disorder.

KEY WORDS: • obesity • genetics • environment • review

Background

It is an ironic and rather sad fact that the two major nutritional problems that presently face the world are that ~600 million people face severe energy deficits and starvation while at the same time, ~320 million people face a problem of chronic energy surplus and obesity (1). In some cases, these problems exist alongside one another (2), but obesity is predominantly a problem of Westernized societies. In the last few years it has become an increasing problem throughout most of the world (e.g., 3–6). By 2000 the obesity problem had already grown to such an extent that the World Health Organization declared it was the greatest health threat facing the West (7). Obese people carry around excessive amounts of body fat, which in the absence of more direct measures, is generally estimated by combining measures of height and weight. The most common method of combining these measures is to divide body weight in kilograms ($W$) by the height in meters ($h$) multiplied by itself (i.e., $W/h^2$). This is
called the body mass index (BMI). On the BMI scale, people with an index >25 but <30 are said to be overweight, and people with an index >30 are defined as obese. Although these definitions have been adopted by the WHO, there are several well-recognized problems with this index. In particular, it does not reflect body fatness changes very well when a person is also changing his or her height over time. Consequently, BMI cannot be used to reliably gauge the body fatness of children. In addition, bodybuilders and some athletes, who have developed large amounts of muscle tissue, may also be misclassified as obese. Generally, however, in most adults, BMI correlates reasonably closely to body fatness (which is measured by more sophisticated scanning and imaging devices), particularly if combined with measures such as the waist circumference.

Despite its limitations, the preferred use of BMI is justified on historical grounds. During the 1930s, U.S. life insurance companies analyzed the factors that influence the probability that someone would redeem a life insurance policy (which generally meant a person died). Based on redemptions of ~5,000,000 policies issued in the 1930s, the factor the companies decided was the most effective predictor of mortality was BMI. In fact, the life insurance companies discovered that mortality was lowest for individuals with BMIs between 20 and 25. Above this range, mortality increased, and it increased dramatically when BMI was >30. Conversely, mortality also increased when BMI fell to <20. This pattern of increase at high and low BMIs is at least partly influenced by the heterogeneous nature of the population involved, which included both smokers and nonsmokers. Smokers dominated the low-BMI classes throughout the 1940s–1960s, before the health effects of smoking were widely acknowledged. When only nonsmokers were examined, the dramatic rise in mortality at low BMI was much reduced although not entirely removed. The normal BMI range for minimal mortality in nonsmokers is presently suggested to be from 18.5 to 24.9.

**Effects of obesity on mortality**

Among both smokers and nonsmokers, mortality increases as BMI increases >25. This is because there is a direct link between body fatness and susceptibility to many degenerative diseases (6,10). The most important of these is type 2 diabetes. The risk of developing type 2 diabetes for someone with a BMI of 35 compared to someone with a BMI of 22 is 40–90-fold and appears to be greater in obese females than males (11). Diabetes increases the risk of circulatory disorders and cardiovascular disease and is the most common cause of blindness in people aged <60 yr. Increased body fatness is also an independent risk factor for hypertension and cardiovascular disease. Some cancers (particularly breast cancer) are increased in relation to body fatness, although whether this is a problem of impaired early detection using existing techniques in the obese patient is not clear. Obesity is also a risk factor for several respiratory disorders including sleep apnea (12). The obese patient is more likely to be depressed and taking antidepressant medications, more likely to suffer joint problems, and also more likely to suffer from skin disorders.

Because of the medical complications associated with obesity, there is a statistically significant increased risk of mortality once BMI increases >25. Because the original data were derived for mostly white persons living in the U.S., there has been recent discussion over the relevance of this cut-off point for different ethnic groups (13). In particular, in Asians and Chinese, mortality has already started to increase at a BMI of 23–24. If a person has a BMI >30, then on average, his or her expected life span is reduced by 9 yr compared to someone with a BMI of 20–22 (14). There are ~30,000 premature deaths in the UK annually that can be attributed to obesity (14). For comparison, this is about the same number of individuals who die of lung cancer (~33,000 annually). Throughout Europe, the deaths attributable to obesity exceed 300,000 annually, which ~1 in every 13 recorded deaths (15).

The health consequences of obesity combined with the fact that many people are affected by it has significant economic consequences. In the UK, these costs were quantified in 2000 by the National Audit Office (13) to be ~£500 million annually in direct health care costs and a further £2 billion annually in wider costs to the economy. In the U.S., the total economic costs of obesity in 1997–1998 were estimated at ~$92.6 to 99.2 billion annually when normalized to 2002 dollars (16–18). Similar data are available for most Western societies that indicate the present costs of obesity generally run at ~5–8% of health-care spending (18–22).

The effects of obesity on health outcome appear to be reversible if the person in question loses weight. This is important, because it is not entirely clear yet what the mechanisms are by which obesity predisposes someone to a particular disease. Based on the correlative evidence alone, obesity might be linked to elevated disease risks by a genetic pleiotropy; that is, a genetic problem leads a person not only to develop obesity, but the same problem, in association with a Western lifestyle, independently elevates the disease risk. If this were true, simply reducing the level of body fatness would not remove the underlying cause of the elevated disease risk. However, several recent studies consistently show improvements in associated health outcomes for people who were obese but have sustained weight loss for protracted periods. Consequently, it is obesity itself and not a shared underlying genetic lesion that causes elevated disease risk.

The exact mechanisms by which obesity leads to the development of disease is an area of intense study. This is because it is not obesity itself but rather the health consequences that are the issue. If the nature of the causal link between obesity and health problems could be elucidated, then developing therapies that break that link might be a feasible solution to the problem. This is obviously attractive, because it would mean people could continue to pursue a Western lifestyle while avoiding the negative consequences. There are two basic alternatives that have been proposed to link obesity with diabetes. The first suggests that because obese people have much higher circulating levels of free fatty acids, in muscles, these might compete with circulating glucose. This leads to persistently elevated circulating glucose levels, elevated insulin secretion, and ultimately, insulin resistance. The alternative suggestion is that some products secreted by fat tissue actively interact with insulin to generate insulin resistance or promote insulin sensitivity. Some important secretions from adipose tissue in this respect are TNF-α (23,24), adiponectin (25,26), and resistin (26,27). Blocking the signals that link obesity to diabetes may be an effective therapy for obesity-mediated diabetes, but this approach is only likely to address one disease consequence at a time. Hence, a much more useful approach is to actually try...
to eliminate all the disease consequences at once by treating obesity itself.

Energy balance and obesity

Obesity is a problem of imbalance between energy intake and expenditure. Total energy demands can be partitioned into several different compartments. The requirement to sustain general cellular processes is known as the basal metabolic rate (BMR). BMR is measured under strict conditions whereby the subject is completely inactive, is not digesting food, and is at a thermoneutral temperature. If we sit quietly, we burn more energy than BMR, and this is generally called the resting metabolic rate (RMR). After food ingestion, our metabolic rate rises further; when we start to move around, it increases even more and is termed active energy expenditure. To balance our total energy expenditure, we eat food. In the short term, expenditure and intake do not match closely, because we feed in discreet bouts, whereas expenditure is a continuous process. Because of the laws of thermodynamics, which state that energy can neither be created nor destroyed, the imbalance between intake and expenditure requires that we also have the capacity to temporarily store energy. Generally, the equation is food energy intake = energy expenditure + energy storage. We store energy as fat, because it is much denser than carbohydrate and also does not require large amounts of water for storage. Given the energy-balance equation, it is clear that obesity results from too little energy, or doing both.

The obesity phenomenon is usefully considered as having two different facets. The first is the temporal trend in the prevalence of overweight and obese people over time, particularly over the last 25 y. Most people alive today (in 2004) were also alive in 1980. Consequently, the expansion of the prevalence of obesity between 1980 and 2004 must reflect changes that have occurred in our behavior (activity and food intake) that are dependent on the changing environment rather than the effects of population genetics. The second facet is the differential susceptibility of individuals to the problem. Whatever environment or time period we choose, we find a mix of obese and lean people. These differences may reside in the microstructure of the environment experienced by each individual or may depend on genetic differences. An important point to recognize is that genetics and environmental factors exert their effects on energy balance and obesity via effects on our behavior and physiology (Fig. 1). There is no direct link between our genes and our body weight or fatness. This is frequently misunderstood as is evidenced by discussions about whether obesity is caused by our genes or our behavior (e.g., 28). As Figure 1 makes clear, these are not alternative causal agents. Behavior and genes are different levels of the same causal framework. The question of “genes or behavior” makes no more sense than the question of “behavior or energy balance.” Consequently, although we might say that obesity has a large genetic component to it, this doesn’t mean that the obese have somehow miraculously deposited enormous quantities of body fat without eating too much food, or expending too little energy, or doing both.

Facet one: trends in obesity over time

The prevalence of overweight and obesity in people has increased dramatically in the last 30–50 y. For example, in 1980, 7% of the UK population was classified as obese. By 2000 this was 20%. Overweight subjects comprised ~20% of the UK population in 1980. By 2000 this was 45%. Consequently, the majority of current UK society is either obese or overweight (7). The UK numbers are on the high side but are typical of many European nations (1). In the U.S., the progression of obesity is ~3–4 y ahead of the problem in Europe; 2003 estimates suggest that 31% of the population is obese (BMI > 30) (29). Moreover, obesity has even greater prevalence in some subpopulations. For example, the prevalence of obesity in black populations across the entire U.S. is ~5% higher than in colocalized white populations (30), and for black females,
prevalence is even higher with ~50% obese. Socioeconomic class and education also appear to be important factors, with the lowest educated groups having ~5% higher prevalence than more educated subpopulations (31,32). Similar demographic patterns are reported for almost all Westernized societies. In addition, there are signs that this problem has achieved truly global distribution during the last decade; many Asian, South American, and African nations report that obesity rates are increasing rapidly (3–6,33).

It is easy to identify some correlated societal trends to the obesity epidemic. One of the factors believed to be important is television viewing (34–39). By the early 1970s, televisions were already a virtually ubiquitous household feature in the U.S. and most of Europe. What has changed is the amount of programming. We now have a choice of many different channels to watch 24 h/d: there is always something to catch our attention and potentially keep us watching. By the late 1990s it was estimated that 20% of children in the U.S. were watching >6 h of television every day. Parental ratings of how much television a child watches are positively associated with the child’s BMI (35), and having a television in a child’s bedroom is a significant risk factor for obesity (37); also, television viewing is negatively associated with engagement in physical activity (38,40). However, significant differences appear to exist in the associations within different ethnic subpopulations, which suggest that the linkages are complex (39). In adults, it was suggested that the association between television viewing and BMI is stronger in women than in men (36,41), but other studies have not reported this difference (42).

Many other changes in activity patterns have occurred over the last 50 y or so. In the 1950s most people in Western societies walked around a range of small local shops to do the week’s shopping. This has been almost completely replaced by one-stop, out-of-town hypermarkets, where one can park conveniently close to the store, buy everything in a large cart that doesn’t have to be carried around, and then drive it all home. There is no doubt that these changes were largely facilitated by the spread of car ownership. Out-of-town supermarkets could not have been a commercial proposition in the 1950s, because only a small sector of the population could have used them. Another factor in temperate zones where it is cold in the wintertime is the work involved in heating one’s home. The spread of central heating systems has replaced the hard work that it took to keep coal fires burning. The domestic appliance market has also made enormous inroads into the labor that typified housework in the 1950s and 1960s. Washing machines, vacuum cleaners, dishwashers, spin dryers, and tumble dryers have all reduced domestic work chores. Our addiction to domestic appliances is such that we now have devices that take any effort out of even the most trivial of tasks, such as electric toothbrushes and carving knives.

At the same time that there have been changes in activity patterns, there have also been large changes in eating habits. Key dietary behavior shifts include greater consumption of food away from the home (43) and large increases in total energy from salty snacks, soft drinks, and pizza (44,45). Despite these changes, some studies suggest that total daily energy intake has declined (46,47), but other studies suggest an increase (44), and yet others find no significant trends (48,49). At national levels, however, food sales statistics show that for almost all food types, the same amount of food or more is presently being purchased per individual compared with 20 y ago. This is particularly the case for confectionery items.

Over the last two decades, fat consumption has declined in parallel with the increased prevalence of obesity in both the U.S. (50) and Europe (48), and the decline is matched by a parallel increase in carbohydrate consumption (48,49).

It is clear that social changes involved activity reductions, and this was potentially combined with an increase in energy consumption. We should be cautious, however, about drawing simple cause-and-effect arguments from these correlations with the spread of obesity. For example, enrollments at health clubs have also expanded over the same period that obesity has increased. In addition, the stimulation of television and the availability of cheap electric lighting means that on average, individuals spend 2 h less each day asleep compared with the 1920s (51). Time spent sleeping is positively associated with obesity (42), so this change should be protective. Despite these caveats, some intervention studies have assessed the roles of different factors. Studies in the U.S. were performed to try to intervene in children’s television viewing habits to determine the impact on body fatness. These interventions show a significant effect on body weight. Surprisingly however, this was not because the children adopted more active lifestyles when deprived of their viewing time. Rather, the major differences were in the consumption of snack foods: the children ate these when watching television, but not when engaged in alternative pursuits (even sedentary ones).

**Facet two: Individual differences in susceptibility**

The second facet of the obesity problem is that despite living in similar environments, not everyone gets obese. This effect can be traced to individual differences in behavior and physiology. Millions of people eat regularly at burger bars, yet others never visit them. In contrast, some people exercise regularly, whereas others almost never do. Some of these differences reflect substructuring of the environment in which we live. For example, middle-class areas may have better provision of parks and cycle paths, which encourage recreational activity. This is only part of the explanation, however, because whatever environment or sector of the community is chosen, it is populated by a mix of obese and lean people. One explanation for these differences is that for everyone, there are subtle differences in lifetime-accumulated experience and social factors that lead to differences in behavior and physiological energy expenditure. This experience may include the period spent in utero. An alternative viewpoint is that these behavioral differences have a large genetic component to them. This model suggests that, when immersed in the same environment, some people develop obesity because their genetic constitution is such that they are more likely to adopt behaviors or have physiologies (such as low RMRs) that lead them into positive energy balance.

Calculations indicate that the heritability of BMI is high. Accordingly, studies of monozygotic and dizygotic twins raised apart and together and pairs of adopted and nonadopted “virtual twins” indicate the variation in body mass that is explained by genetic factors is also very high. A meta-analysis recently indicated that the average variation explained by genetic factors was 77%, and that shared environmental factors were insignificant (52). Faced with this information, it is important to recognize what exactly is being said. A common response to the suggestion that shared environments are unimportant is to point out that if one were to take a pair of twins and keep one of them locked up with minimal food for years on end, the deprived twin would not develop the same BMI as the twin given free access to food; hence it is “obvious” that environment must be important. However, although this hypothetical experiment would probably yield the suggested
result, such extreme environments are seldom encountered in Western society. It appears that once certain environmental requirements are met, additional variability in the environment becomes relatively unimportant and genetic factors predominate. A counterexample to the starved-twin scenario clarifies this point: if I had an enormous refrigerator in my house continuously stocked full of food, it would probably have no effect on my actual food intake if I were provided with a second, similarly continuously stocked refrigerator. Once I have met a certain minimal environmental requirement, additional variation in the environment is irrelevant, and this appears to be the present situation in Western society. Illustrating this point further, the average income in the U.S. (in 2002 figures) was $272,000 annually; therefore, it is possible to purchase one’s entire daily energy requirements for ~$5/d (~5% of the average annual income).

In this context, the changing prevalence of obesity over time must be a gene-environment interaction effect. Addressing the genetic side of this interaction is potentially a far more tractable problem than addressing the environmental component by reengineering society, because the level at which interventions might ultimately be made is the individual rather than the society as a whole. There is a clear need, therefore, to understand the genetic bases of food intake, energy expenditure, and hence, energy-balance variations.

Regulation of energy balance

There is a generalized opinion that energy balance, and hence, body weight and/or fatness, are phenomena that are regulated (e.g., 53–57). The origins of this idea seem to reside in calculations of the potential impacts of imbalances in our energy intake and expenditure. For example, on average, a typical candy bar contains ~250 kcal (1 MJ) of energy. If over the last 23 y I had eaten a candy bar more than my energy expenditure every day, I would have accumulated 23 × 365 × 1000 kJ = 8395 MJ of extra energy. Because 1 kg of fat tissue contains ~33 MJ of energy (58), the 8395 MJ would be equivalent to deposition of ~254 kg of fat tissue! Even if I had eaten a candy bar above my requirements only once each week, I would have accumulated 36 kg of body fat. If such small imbalances in our intake and expenditure can have such major impacts on body weight, the argument is that these phenomena normally must be regulated in some manner. However, this calculation involves several dubious assumptions. It is assumed that all of the excess energy is deposited as fat, and that the deposited fat tissue expends no energy. More realistic assumptions about the nature of the deposited tissue and the energy expenditure of that tissue lead to the conclusion that trivial imbalances in our energy balance generally lead to trivial changes in our body weight (see, for example, 59–61).

Development of obesity actually requires quite severe imbalances in our intake and expenditure can have such major impacts on body weight, the argument is that these phenomena normally must be regulated in some manner. However, this calculation involves several dubious assumptions. It is assumed that all of the excess energy is deposited as fat, and that the deposited fat tissue expends no energy. More realistic assumptions about the nature of the deposited tissue and the energy expenditure of that tissue lead to the conclusion that trivial imbalances in our energy balance generally lead to trivial changes in our body weight (see, for example, 59–61).

Three alternative models of energy-balance regulation involve feedback from energy imbalance into energy intake and expenditure. In one model, food intake and energy expenditure are stochastically variable from day to day and independent of each other (A). The resultant variations in energy balance translate into storage of lean and fat tissue controlled by the p ratio. Lean and fat tissue also directly affect the levels of energy expenditure. In the second model, there is memory of the historical energy balance that feeds back onto food intake and energy expenditure (B). If an animal spends a period in energy deficit under this model, it will feed back an impetus to increase intake and reduce expenditure. Alternatively overconsumption will lead to converse feedback, reduced intake, and increased expenditure. In the third model, the same feedbacks relative to historical energy balance come from the fat and lean tissue reserves rather than historical memory (C).

FIGURE 2

Three alternative models of energy-balance regulation involve feedback from energy imbalance into energy intake and expenditure. In one model, food intake and energy expenditure are stochastically variable from day to day and independent of each other (A). The resultant variations in energy balance translate into storage of lean and fat tissue controlled by the p ratio. Lean and fat tissue also directly affect the levels of energy expenditure. In the second model, there is memory of the historical energy balance that feeds back onto food intake and energy expenditure (B). If an animal spends a period in energy deficit under this model, it will feed back an impetus to increase intake and reduce expenditure. Alternatively overconsumption will lead to converse feedback, reduced intake, and increased expenditure. In the third model, the same feedbacks relative to historical energy balance come from the fat and lean tissue reserves rather than historical memory (C).
individually defined parameter under genetic control or whether it is instead variable and itself dependent on body composition such that when subjects have large fat reserves, they preferentially mobilize and deposit fat, but during lean periods, they reduce the p ratio and start to mobilize protein as well and thus autoregulate (to some extent) their body composition (60). Several arguments suggest it is unlikely that the p ratio is individually fixed (63).

The p-ratio model can explain many features of energy balance without the need to invoke any regulatory signals generated by lean or fat tissues, particularly if the p ratio is fixed genetically (59). The model, however, is an inadequate description of phenomena related to energy regulation (60–63). The main difficulty faced when using this model is explaining patterns of intake that occur after periods of food deprivation. During food deprivation, subjects tend to reduce their expenditure more than can be accounted for by the loss of metabolizing tissue (64–66). On refeeding, they also tend to exhibit post-restriction hyperphagia. These patterns would not emerge if intake and expenditure were independent stochastic variables linked only to storage by the p ratio. The salient issue is this: When we have been food deprived, where do the feelings of hunger come from that cause us to subsequently overeat and reduce our energy expenditures to redress the previous energy imbalance? Two basic possibilities exist. First, there may be a sensing mechanism that monitors the extent of energy imbalance by the fluxes of nutrients related to intake and expenditure. The “glucostatic” model of food intake regulation (67) is this type of energy balance–regulation model. By this hypothesis, feeding behavior is regulated by fluctuations in circulating levels of glucose, which are sensitive to patterns of both energy expenditure and intake. Thus if glucose-sensing centers in the brain detect a drop in circulating glucose levels, feeding is stimulated, and feeding is then terminated by the increase in circulating glucose. Glucose status, therefore, acts as a sensor for immediate energy balance. This is, however, a signal that monitors only the short-term flux of energy. It is likely that animals, including humans, have also evolved mechanisms to monitor patterns of energy imbalance over much more protracted periods. This could be an accumulated memory of energy balance (Fig. 2B) or, an alternative source of such signals is the energy stores themselves.

The third class of model therefore invokes a feedback loop (Fig. 2C) generated from the stored energy (fat and lean tissue stores) (61,68–70). This could work in several different ways, but two models predominate. One mechanism is that energy intake and expenditure rates are tied into the sizes of the energy stores by an amplification mechanism (71). When stores are large, the signals from the stores do not stimulate feeding very much but have a strong effect on expenditure. Conversely, when the stores get smaller, the effect on expenditure is diminished and the effect on feeding is increased. The second way this might operate is by reference to a target store size that is encoded centrally (72–75). Because most energy is stored as fat, the suggestion is that the regulated body component is body fatness (with lean body mass dragged along by some unknown mechanism in the p ratio). Other models are also feasible where lean mass is directly regulated (68). The regulation of body fatness by reference to a centrally encoded target is generally attributed to Kennedy (69) and is called the “lipostatic” model of body weight regulation.

At present, the exact nature of the regulatory model for energy balance and body weight remains uncertain, and separating the alternatives models is not easy. In particular, the feedback from an accumulated memory of the status of energy balance (model 2) and feedback from the stored reserves (model 3) might be difficult to resolve. This is because in most circumstances, the two factors move in parallel. It is seldom the case that someone could accumulate an energy deficit but not affect levels of their stores and vice versa. To test between these models, therefore, requires an experimental design that separates the different effects. If the system works as envisaged in model 2 (Fig. 2B), with a memory of energy deficit feeding back to drive intake and expenditure, then it seems likely that this memory will decay over time. For example, if I starved you for 24 h, you would feel hungry the next day. If I gave you free access to food the day after you had starved, you would overeat to compensate for the missing intake. However, if I stopped you from overeating for a week after your starvation day, but gave you enough to balance your energy demands, and then gave you free access to food, you would probably not feel as hungry as you did the day after you had starved. This is because the memory of the energy deficit had receded because of the intervening time spent in energy balance. This decline in the force of memories of energy deficit over time could be used to separate regulation by model 2 from model 3 (Fig. 2C). The design is as follows: a set of subjects is placed on an energy-restricted diet that provides fewer calories in food than they were expending with a resultant loss of body weight (fat and lean tissue). At the same time, they accumulate memory of energy deficit. After a suitable period of restriction (of say, 3 mo), the subjects are randomized into one of two groups. Group 1 is taken off the diet immediately and given free access to food. Group 2 is fed enough food to keep the body mass constant and is regulated on a daily basis for an additional intervention period of 3 mo and is then given free access to food. At the end of this period, group 2 will have the same body fat and lean stores as group 1, but will have been fed in energy balance for 3 mo. Hence, if it is the size of the stores that drives the hyperphagic responses, the extent of hyperphagia in the release phase of the experiments will be the same for the two groups. In contrast, if it is the memory of energy deficit that drives the hyperphagic response, group 1 will have a much stronger hyperphagia than group 2, because the memory of deficit will have receded over the 3 mo that group 2 was fed in energy balance. In general, the more time spent feeding in energy balance, the lower will be the predicted hyperphagic response.

These experiments have not yet been performed, but would be extremely informative. It seems likely that elements of all three different models are important. First, short-term signals probably play a critical role in switching feeding behavior on and off and in regulating short-term activity patterns. The p ratio is an important aspect of nutrient allocation that governs how energy surpluses and deficits are translated into body composition, whereas long-term signals that potentially interact with centrally encoded targets provide an overall orchestration of the short-term regulation mechanisms.

There is some experimental support for this regulatory framework. Many studies show that when subjects are food deprived, they compensate for the deprivation by reducing their energy expenditure. Although less frequently performed, the converse, increasing expenditure in response to overfeeding, is also observed (e.g., 76,77). Perhaps the most comprehensive study was that of Leibel et al. (78), who placed obese and lean subjects in a protocol where they were systematically under- or overfed to produce differences in their body weights by ~10%. The researchers then examined the compensatory responses in the subjects’ energy-expenditure patterns. As anticipated by the model, when subjects were underfed, they responded to the energy deficit by decreasing their expenditure more than could...
be accounted for by the mass change, whereas under conditions of energy surplus during the overfeeding part of the study, they responded by elevating their energy expenditure. The contributions of changes in RMR and nonresting energy expenditure to these compensations were about equal. In other studies, differential responses to overfeeding are reported: some individuals gained body weight whereas others did not. The extent of the weight gain was dependent on the extent to which the subjects performed spontaneous activities to burn off the excess energy (79–81).

During the 1950s at about the same time that ideas were evolving about lipostatic, proteostatic, and glucostatic mechanisms of energy regulation, a spontaneous mutant mouse occurred at The Jackson Laboratory in the U.S. This mouse, which became excessively fat, was called the ob/ob mouse, because it was clear that the original mutation was a single-gene recessive defect that caused its obesity. When heterozygous ob/+ mice breed together, one quarter of the offspring are homozygous ob/ob mutants, and they feed voraciously relative to their littermates. They also have reduced metabolic rates and lower body temperatures, and as they get older, they become less active. In combination, this leads to a dramatic energy imbalance, and the mice become very obese. On average, by 12 wk of age, they weigh almost twice as much as their heterozygous and wild-type littermates. Since that time, many other natural, mutant, fat mice and rats have been developed and bred by the major mouse- and rat-breeding companies such as the db/db diabetic mouse, the fa/ta fat rat, and the tub/tub tubby mouse.

A series of elegant parabiosis experiments with ob/ob and db/db mice were performed to try to elucidate the nature of the genetic defects that these mice harbor (82,83). Parabiosis involves surgically joining the blood circulation of pairs of mice with the result that any circulating factor in the blood of one animal is passed to the other and vice versa. When the fat ob/ob mouse was joined together in parabiosis with a lean wild-type mouse (+/+), the ob/ob mouse started to eat less food and to lose body weight. However, when a fat db/db mouse was joined in parabiosis to a wild-type +/+ mouse, something radically different happened. The db/db mouse was unaffected, but the wild-type mouse started to eat less food and eventually died of starvation. Joining together ob/ob and db/db mice had a similar result to joining up ob/ob to +/+ mice: the ob/ob mouse reduced its food intake and started to lose weight, but the db/db mouse continued to eat and remained fat.

These experiments provided strong support for the lipostatic model (69). It was clear that the ob/ob mice have a defect in the signal that tells them how fat they are. In the absence of this signal, the mice “think” that they are dangerously thin relative to their target, and they therefore elevate their food intake and suppress their metabolism and body temperature so that their body weight increases to meet the target. In parabiosis with wild-type mice, ob/ob mice start to get a signal from the fat in the lean mouse’s body, and they suppress their food intake and normalize their body temperatures. Because this also happens when ob/ob mice are in parabiosis with db/db mice, the db/db mutation cannot also be a problem with the signal. The mutation in db/db mice must actually be a problem with reading the signal in the brain. Hence, the db/db mice also “think” that they are dangerously thin, and effect changes in their food intake and expenditure to bring their fatness up to target. When db/db mice are placed in parabiosis with wild-type mice, there is no effect on their food intake, because they are already producing lots of the signaling factor (it just isn’t being read), so getting more of a signal from the wild-type mouse has no effect. However, for the wild-type mouse the situation is more serious, because in parabiosis with a db/db mouse, a wild-type mouse receives a massive signal from the db/db animal; “thinking” it is massively over its target, the wild-type mouse shuts down its food intake to try to lose weight. Because the db/db partner keeps eating, however, there is always a signal telling the wild-type mouse not to eat, and eventually it dies of starvation. Despite these insights, it was another 20 y before the signaling compound was finally identified. The mutation causing the ob/ob mouse signal was a single-base mutation in a gene located on chromosome 6 (84) (mapped to chromosome 7 in humans). The consequence of this mutation was that instead of the gene signaling the production of a full-length 167-amino acid protein, the presence of a premature stop codon caused a much shorter, nonfunctional protein to be produced. The signal protein was called leptin from the Greek root leptos, which means thin, because the animals that had full-length leptin were lean.

In the seminal paper on leptin (84), it was shown that leptin is produced exclusively in adipose tissue, which is as one might anticipate for a compound that acts as a lipostatic signal of the size of body fat stores. Subsequent work shows other sites of production at much lower levels in developing fetuses, placenta (85–88), and stomach (89). When recombinant leptin was injected into ob/ob mice, the animals ate less food and dramatically declined in body weight (90–95). Other features of the genetic pathology were also normalized, including for example, the ability to sexually mature and breed (96). Moreover, in wild-type mice, exogenous leptin also reduced the animals’ body weight, as one might anticipate if the mice received an erroneous signal about the size of their body fat stores (90–92). In mice with targeted transgenic overexpression of leptin production, there is a dramatic decrease in body fatness (97).

The leptin receptor (Ob-R) is a cytokine receptor (98) with several splice-variant forms including a short form (Ob-Ra) and a long form (Ob-Rb). The long form of the leptin receptor contains an intracellular signaling domain that is missing from Ob-Ra. The dominant intracellular signaling mechanism appears to act via the Janus kinase/signal transduction and activation of transcription pathway (99). Leptin binding (100) and receptor–localization studies revealed that Ob-Ra is found in the choroid plexus (101), and Ob-Rb is expressed in large quantities in several nuclei of the hypothalamus, particularly the arcuate nucleus (ARC) (102,103), and also in the brain stem (104). The location of the signaling form of the leptin receptor in the hypothalamus was significant, because early brain-lesioning studies on rodents showed that removing segments of the hypothalamus has a profound effect on several motivational processes including feeding behavior. It is now known that two types of neurons in the ARC receive the peripheral leptin signal (102–105). One type known as neuropeptide Y/Agouti-related protein (NPY/AgRP) neurons coexpress NPY, and AgRP (106) have projections that can be traced into the brain stem to the paraventricular (PVN) nucleus and to the second type of cell that receives the leptin signal in the ARC. The second type of neurons is called pro-opiomelanocortin/cocaine amphetamine–regulated transcript (POMC/CART) neurons (107,108). POMC/CART neurons also receive projections from neurons in other brain areas that express serotonin (5-HT) and have 5-HT receptors on their surfaces.

Both POMC/CART and NPY/AgRP neurons project to cells in the PVN that express melanocortin-4 receptors (MC4-Rs) and also to cells in the ventromedial nucleus that express melanocortin-3 receptors (MC3-Rs). Both of these melanocortin receptors are G protein–coupled receptors. POMC/CART neurons secrete α-melanocyte–stimulating hormone.
(α-MSH), whereas NPY/AgRP neurons secrete AgRP. α-MSH is an agonist, and AgRP is an antagonist of both MC4-Rs and MC3-Rs (109). When leptin molecules from the periphery dock with their receptors on NPY/AgRP neurons in the ARC, there is suppression of NPY release (110,111) and reduction in γ-aminobutyric acid (GABA) release at the synapses where the NPY/AgRP neurons meet the POMC/CART neurons. Under the GABA-mediated disinhibition and combined with direct leptin stimulation, the POMC/CART neurons release α-MSH at the MC4-Rs on PVN neurons at the same time that the antagonist AgRP derived from the leptin-stimulated NPY/AgRP neurons is reduced. Secretion of α-MSH depends on successful cleavage of the POMC molecules, which is brought about by the proconvertase-1 enzyme. Additionally, the stimulatory effect of α-MSH appears to depend critically on its acetylation status, which is also under regulatory control of acetylase-deacetylase enzymes. The increased α-MSH and reduced AgRP levels stimulate the MC4-Rs with two downstream effects. First, the sympathetic system is stimulated and releases noradrenaline at peripheral cells that express β-adrenergic receptors. In brown adipose tissue in rodents, this produces an immediate stimulation of metabolic rate. At the same time, food intake is inhibited. The resultant negative energy balance causes leptin levels to decrease. This reduced signal has the opposite effects in the ARC nucleus: NPY/AgRP cells are stimulated to release NPY; POMC/CART cells are inhibited (directly and indirectly), and at the MC4-Rs in the PVN, AgRP release is enhanced, whereas-αMSH level is reduced. This leads to reduced sympathetic activity, reduced energy expenditure, and stimulated feeding behavior.

There is now considerable evidence that the leptin system interplays with other signals that may also be involved in long- and short-term regulation. The best-characterized of these so far is insulin. Like leptin, the secretion of insulin is proportional to the magnitude of the body fat stores. Neurons in the ARC that express the leptin receptor also often express the insulin receptor IR-1. The insulin receptor signals via the phosphoinositide 3-kinase pathway, and there is suggestion (112) that intracellular interaction between leptin signaling and insulin signaling may exist. Insulin is known to inhibit NPY (113), and animals with reduced numbers of insulin receptors have elevated food intake consistent with increased NPY levels (114). Insulin may act as a long- and short-term signal given its responsivity to altered glucose levels after feeding. Similar short-term signals include glucose and free-fatty acids themselves and peptides secreted from the gut such as cholecystokinin (115), ghrelin (116), and peptide YY$_{3-36}$ (PYY$_{3-36}$, 117), receptors for which also colocalize to ARC cells.

The situation in humans is likely to be more complex than in rodents because of the input of cortical-level processes (118). Moreover, we are aware that endogenous cannabinoids and the serotonergic and opioid-dopaminergic (119) systems are also involved, but the details of the interactions presently remain obscure. Nevertheless, this model potentially explains why many people are able to regulate their body weight over periods of many years. Whenever one puts on too much weight, leptin, insulin, and probably other signals are generated that reduce food intake and increase energy expenditure until the signals and weight are normalized. Whenever one loses weight, the opposite occurs: the multiple signals decrease in frequency, food intake is stimulated, and energy expenditure is suppressed to regain the missing weight.

One major argument against the lipostatic theory of weight control is the fact that so many people are presently obese. If such a system operates, the argument goes, then clearly it cannot be very effective. However, even if lipostats exist, obesity may develop for two reasons. First, obese people may have broken lipostats; or, second, the lipostats in obese people may be set at very high target levels. After the discovery of leptin, there was immediate interest in whether obesity was a result of deficient leptin production—a broken lipostat. Obese people might have abnormalities in their ability to produce leptin in much the same way as the leptin-deficient ob/ob mouse. Imagine, for example, if my leptin production was only half of the normal rate. My brain would think that I was only half as fat as I actually am, and it would encourage me to eat more food and expend less energy until my fat content was high enough to redress the leptin-production deficiency. If this were the case, the potential to cure obesity would be in sight: one could treat people with leptin (or drugs to mimic its action or stimulate natural leptin production) to trick the brain into thinking that one was fatter than was actually the case. The regulatory system would then downregulate food intake and increase energy expenditure to redress the balance. The only downside is that this would need to be a lifelong treatment, because discontinuation would lead to decreased leptin levels and resultant weight regain. However, the euphoria over the potential of leptin was short lived, because it was found (120–124) that in general, fat people have very high leptin concentrations, which is as might be expected from their high body fatness if their leptin-production systems were working correctly. The vast majority of obese people do not have leptin-production deficiencies or defects in their leptin receptors (125).

An interesting exception was two children from Cambridge, UK (126). These children were <10 y old when they were discovered, but they already had ravenous, insatiable appetites. This had resulted in extreme obesity that had forced their parents to seek hospital treatment for them. These children were massively obese; for example, the older child, aged 10 y, already weighed 110 kg. Both children had no detectable levels of circulating leptin in their blood. Additional investigations showed they had a recessive mutation in their leptin gene that prevented leptin production. Once the defect was diagnosed, the children were treated with recombinant leptin. With daily injections, their dramatic weight-gain trajectories and compulsive-eating behavior were reversed (127). Since this time, other families have also been described with leptin-production deficiencies including a family of three people from Turkey whose body weights almost halved when they received daily leptin injections for 10 mo.

An interesting subpopulation of the obese are individuals that are heterozygous for the leptin deficiency. These individuals have lowered leptin production for their body fatness levels, and as a consequence they are on average more obese than their homozygous wild-type relatives (128). These heterozygous individuals are also extremely rare but provide an important point of principle regarding the functioning of the lipostatic control mechanism. Some individuals have been identified with loss-of-function mutations for the leptin receptor Ob-Rb. A small group of individuals has also been identified with mutations in the POMC gene, which makes them unable to secrete α-MSH (129,130). Because these subjects do not secrete α-MSH onto the MC4-Rs in the PVN, they have a perpetually stimulated appetite and develop obesity. A second consequence of this mutation is the subjects have bright-red hair (130) because of an absence of α-MSH interacting on MC1-Rs in the periphery (131). However, the most important single-gene defects of which we are presently aware concern polymorphisms of the MC4-R itself (132–134). Many polymorphisms have been identified in this gene (135) most of which do not have any functional significance (136).
Some key polymorphisms of MC4-R are associated with obesity, and in most populations that have been studied to date, mutations of this gene account for \( \sim 3–5\% \) of all morbid obesity (133). Overall then, completely broken lipostats explain only a small portion of the total numbers of obese and overweight people. What about the genetic “mis-setting” of lipostats at high targets, which then interact with the environment to generate the temporal and spatial patterns of susceptibility that we presently observe? Is this a feasible alternative explanation for the high prevalence of obesity? The negative-feedback model of body weight regulation has many similarities with thermostatic temperature regulation in a house (137). In that system, a room-temperature sensor compares the actual and desired room temperatures, and an effector system (the radiators) can be modulated to bring actual and desired states into balance. We can understand the interplay between genes and the environment by using this thermostatically heated–house analogy. Imagine houses have a whole range of thermostatic temperature set points from cold to hot. If the houses were all in the arctic and were poorly insulated, then all the house temperatures would be cold because even those with high set points (or broken thermostats) couldn’t get as hot as their thermostats want them to be because the capacity of their heating systems wouldn’t be able to match the heat loss through their roofs. This is equivalent to the genetic system being environmentally constrained. However, if the houses were all in the tropics, where the environmental temperature is much warmer, then those with high target temperatures (or broken systems) would reach their high temperatures. This is equivalent to the genetic system being released from environmental constraint.

The key point is that actual house temperatures depend on both the thermostat characteristics and the environment in which the houses are located. Our genes may predispose us to obesity, but genes can only be expressed in environments, and it is the gene-environment interaction that is most important. Obese people might have high target body fatness settings in their lipostats that result in actual high body fatness in Western societies where there is ready access to high-energy–content foods. Presently in rural, primitive farming communities, and in the past in Western societies, people might have (or have had) high target settings or breakage in their regulation systems. However, if they had to work 12 h/d digging fields or chasing prey, they may have been unable to ever consume sufficient food to reach this target.

**Evolutionary context**

One difficulty with this interpretation is understanding the evolutionary processes that might result in systems evolving with such variable individual lipostat settings. Our knowledge about the evolution of body-weight–regulation mechanisms in humans is poor. Generally, arguments tend to paint simplistic adaptive scenarios emphasizing that storing large amounts of fat might at some point have been selectively advantageous (e.g., because it would provide increased resistance to starvation: the so-called thrifty gene hypothesis. The main problem with such “adaptive” scenarios, however, is understanding why such an advantageous genotype would not rapidly replace the disadvantageous “non-thrifty” genotype, and make everyone in modern society susceptible to obesity. This problem is seldom recognized in such adaptive landscapes.

Studies of wild animals suggest that stored body fat is actually regulated under stabilizing selection as part of a dynamic tradeoff between the risks of starvation, which promote fat storage, and the risks of predation, which promote leanness (138–147). Because early humans likely also faced these contrasting selective pressures, they probably also evolved a regulatory system (i.e., a lipostatic system) that promotes fat storage to avoid starvation but also prevents excessive fat storage to avoid predation (148). The set point of this system may have been temporarily variable because of the differing selective pressures at different times of year. Several key events in human evolution likely have dramatically reduced the risks of predation. These include the evolution of social behavior, which allows groups of humans to drive away predators and alert each other of the presence of danger. Such behaviors are also observed in modern-day groups of apes and monkeys such as vervet monkeys, which have evolved complex signals to indicate the approach of different types of predators (149–152). The harnessing of fire \( \sim 1.8 \) million y ago (153) and the construction of tools to actively aid defense would further enhance protection against the threat of predation. Under this release from constraint, it is feasible to imagine that target set points might drift upward at random because they would have no selective consequences as long as actual body weights were constrained by food supply. This would remove the strong selection that imposed an upper limit on fat storage, but defense against energy deficits would still be strongly selected for. This asymmetry accords with modern experience (154). In this evolutionary scenario, the capacity to deposit enormous fat stores is not seen as adaptive; hence there is no need to explain why the trait did not spread through the entire population. Several hundred generations later, when faced with the Western lifestyle, the continued absence of strong selection on the lipostat target would result in a diversity of targets and the consequent diversity of body-fatness phenotypes that we presently observe. One additional prediction from this hypothesis is that the greatest release from the constraints at the upper boundary of regulation should occur in those populations that have been most liberated from the risks of predation. There is no lower risk than living in a completely predator-free environment, and although such environments are uncommon, small remote islands generally have no predators that are likely to pose a risk to humans. It is perhaps significant that the greatest levels of obesity in modern populations occur in Pacific Islanders, where some islands have \( >70\% \) of people in the obese category (e.g., Tonga; 155).

**Why conventional behavioral (energy restriction) approaches to weight loss don’t work**

The most-common treatment prescribed for obesity and overweight is to engage in an energy-restricted diet. Indeed in many countries, before obese subjects can be prescribed drugs to assist them, they need to have tried this option first. Moreover, this is a method of choice for attempting to reduce weight by overweight subjects (and people in the normal weight range). Recent surveys suggest that at any one time, 40% of people in Western societies may be engaged in some form of energy restriction. Vast numbers of options are open to people, and a large dieting industry caters to these needs. Many organized “dieting clubs” promote calorie restriction as the method of choice for regaining control of body weight. Unfortunately, almost all of these approaches provide the promise of short-term success coupled with long-term failure. If one consumes a low calorie–intake diet that provides less energy than one expends, the result is reduced energy storage that is manifested as a loss of body tissue, some of which is fat and some of which is lean, depending on one’s p ratio, which varies with how fat one already is and perhaps also the rate of
weight loss. Whatever is claimed to be the mechanism, all successful weight-reduction diets work on the principle of energy deficit. The major differences between diets are the effects that they have on our short-term perceptions of hunger and their side effects on other systems. Presently, popular diets such as the Atkins diet rely on large quantities of dietary protein almost to the exclusion of carbohydrate. The scientific basis for this diet is that there appears to be a hierarchy of macronutrient effects on perceptions of hunger: fat is least satisfying, carbohydrates next, and finally, the most satiating macronutrient is protein (156). A diet that provides an energy deficit, where most of the calories come from protein, therefore leaves one feeling less hungry than if the same deficit came from a fiber-dominated diet. But weight loss is the same for the same energy deficit. The difference is that because perceptions of hunger are different, it may be easier to adhere to a high-protein diet than a high-fiber diet, and the longer one stays on a diet, the more weight is lost.

Potentially major problems exist with high-protein/low-carbohydrate diets. First, these diets are generally deficient in micronutrients (which can be rectified by taking a vitamin supplement) and also, possibly, in carbohydrates that are important for optimal function of the central nervous system. Second, a high protein intake is generally coupled with a high saturated fat intake and a high serum cholesterol level, both of which are implicated as causal factors in cardiovascular disease, cancer, and stroke independent of the obesity they engender. Urinary calcium excretion increases with high protein intake. Moreover, bowel cancer is strongly negatively correlated with dietary fiber content, and so excluding fiber from the diet enhances the risk of developing bowel cancer. Processing high protein loads may also increase the risk of kidney failure because of the concomitant high rate of urea production. These high-protein/low-carbohydrate diets are consequently only appropriate for the short term. Even then, the benefits of weight loss need to be balanced against the negative side effects. During 2001, the American Heart Association and the World Cancer Research Fund both came down heavily against these diets as aids in the fight against obesity. A meta-analysis of high-protein diet interventions and their effects concluded that high-protein diets do result in greater weight loss than conventional diets, but that one of the largest potential problems they pose is increased calcium excretion in urine, which may ultimately contribute to excess bone loss (157).

The most beguiling aspect of all energy-controlled diets is that in the short term, they do result in significant weight loss. If one is in caloric deficit, then one’s feedback mechanisms respond by attempting to minimize the magnitude of the difference between what is being eaten and what the body requires. One becomes lethargic, and activity level and resting metabolic rate are reduced (78). Consequently the rate of weight loss slows as the time under restriction progresses, and eventually a steady state is reached where the reduced intake is matched by reduced energy expenditure. To sustain additional weight loss requires an even more stringent reduction in energy intake. The weight that has been lost is maintained only with sustained dietary control.

The only way to permanently lose weight on a diet is to stay permanently on the diet or replace it with some alternative form of caloric intervention like exercise (158). This is because once the diet is stopped, body fat content is considerably lower than the body’s target fatness; the body produces low levels of leptin and other signals to indicate it is “under target.” The major impetus of the lipostatic regulation system is to redress this imbalance by compelling the individual to eat more food. To emphasize this, it is noteworthy that an almost 100% successful, permanent treatment for obesity is surgical intervention such as gastric banding. This works because it forces people to comply with calorie restriction forever.

We can understand why calorie-restricted diets don’t work for weight control by reconsidering the analogy of the thermostat in a house (137). Imagine your thermostat is set very high and your house is hot. You aren’t happy with this situation, but because you don’t know how the thermostat works, you call in an “expert” who opens the sitting-room window. There is an immediate improvement in the house temperature. Over the next few days, the house cools to a more comfortable level, but it is still a bit too warm; you need to open another window to keep the temperature decreasing. Eventually you reach a desirable temperature. Somebody comes by and says that you might have exposed yourself to some risks by opening your windows like that: your kids might get colds in the drafts, and you might get burgled. You decide after a while that having the windows open is not a great idea, and you close them. Immediately the temperature starts to rise again, and soon you are back to your boiling-hot house. Energy-restriction diets are like attempts to fix your house temperature by opening a few windows. They are effective, but they only work as long as you stay on them, and they sometimes have undesirable side effects. Usually, discontinuing the diet results in you regaining the original weight (159). In fact, the diet food—products industry is a multibillion-dollar enterprise because diets work in the short term, but the population of potential customers is never seriously diminished by the diets themselves.

Alternative approaches: working with the lipostat rather than against it

If leptin works in leptin-deficient subjects (127), then could it be used in other obese people to trick their brains into thinking they are even fatter than they are? After all, leptin administration to mice that had no genetic problems in producing leptin caused weight loss (91), and individuals that are heterozygous for the loss-of-function mutation respond as expected from their lower leptin levels (128). Moreover, transgenic mice overexpressing leptin almost completely lose their body fat (97), and appetite loss in subjects at high altitude appears to be linked to elevated leptin concentrations (160). Clinical trials with leptin started in the late 1990s. The largest trial (161) included ~75 obese patients who were given daily leptin injections as different doses. The subjects were also prescribed a diet that over the 6-mo study period was expected to result in weight loss of ~12 kg. The study revealed that subjects on placebo treatment lost on average only 1.4 kg, whereas those on the highest doses of leptin (0.3 mg/kg) lost five times as much (7.1 kg). Although this modest weight loss is lower than anticipated (12 kg) given the prescribed diet, it is clear that the people on leptin treatment found it easier to adhere to the dietary prescription. The major problem, however, is the dose of leptin required to obtain this result involved an injection of ~30 mg of leptin each day (161). With the present (2004) price of recombinant leptin of approximately $100/mg, this treatment would cost $3,000/d. This is unlikely to be the sort of treatment that could be envisaged for large numbers of patients in general therapy, because it would cost more than treating the health consequences of the obesity. In addition, ~15% of the patients on the trial receiving leptin exhibited moderate to severe allergic reactions at the injection sites.

Although leptin has not provided the solution it once promised, it does provide some reassurance that the system in humans is not radically different to that in rodents. Using
animal models, therefore, is the best hope we have of finding general solutions to the obesity problem. If leptin production is not the problem, then other possibilities are that the leptin fails to cross the blood-brain barrier (162) or the signal is not read properly by the receptor system (both contributing to so-called leptin resistance). In the last couple of years, there has been enormous interest in other signals from the periphery that may play a role in signaling energy status to the brain and may therefore be putative targets for drug development. The two major ones are ghrelin, which is a growth hormone secretagogue produced by the stomach, and PYY3-36, which is also a gut-derived signaling compound. The effects of these compounds remain controversial, and a vigorous debate is presently occurring over their effects on body-weight control.

The future

Although we have seen spectacular advances in our understanding of the molecular basis of body-weight regulation during the decade since the discovery of leptin, and within the next decade we are likely to see drugs on the market that work with this system rather than against it to produce weight loss, there is still a great deal that we do not understand. Three sources of information serve to quantify the extent of our present ignorance about the control system and its interrelationship with obesity, as follows: 1) genetic mapping studies, which identify the specific regions of the genome where polymorphic loci are associated with variation in body weight; 2) actions of drugs that produce effects on body weight for which the mechanism is unclear including drugs that have weight gain as an unexpected side effect; and 3) examination of the lipostatic model itself, so we can see areas where our understanding is deficient.

Genetic mapping studies aim to identify quantitative trait loci (QTL) where important genes are located that influence body weight. QTL mapping involves studying the genomes of families where there is divergence in the BMIs of the two parents. When such individuals produce offspring, these children inherit half their genetic material from their father and half from their mother. Each of these contributions is a mixture of the DNA that the parents inherited from their parents. By using genetic markers along the genome, it is possible to trace which bits of chromosome have been inherited by which children and associate this with the development of obesity in those children. Across many such pedigrees, it is possible to identify regions of the genome where variations generate variability in BMI. These regions are known as QTL. Chagnon et al. (163) summarized the QTL-mapping studies performed to date and identified 68 different QTL regions of the human genome where significant associations were found between body fatness (normally BMI) and polymorphic variation. These are spread across all chromosomes except the Y chromosome. Seven of these loci were confirmed in multiple (between two and five) studies. Interestingly, few of these map closely to candidate genes for compounds presently known to be component parts of the lipostatic system. That we do not know the candidate genes at these major loci is a strong message that our understanding of this system and the manner in which it works is still rather rudimentary.

The second line of evidence concerning our ignorance derives from drug effects on appetite and energy balance, and that we do not fully understand how they work relative to the lipostatic system. First, one of the two pharmaceuticals licensed for the treatment of obesity falls into this class. Sibutramine is a 5-HT–reuptake inhibitor that produces significant weight loss. There is an indication that the actions of leptin and serotonin interact (164), but as yet this is poorly understood. Second, a phenomenon that is reported by marijuana users is that smoking the drug stimulates appetite. The discovery of endogenous cannabinoid receptors (CB-1), which are putative drug targets, has led to the development of agonist and antagonist drugs that bind to these receptors. There are already CB-1 antagonist drugs that appear to generate significant reductions in appetite and weight loss (165). The details of how they work, however, beyond interacting with the CB-1 receptor, is unclear. Finally, there is a whole class of drugs that have weight gain as a side effect of their use. These include many of the antipsychotic treatments for schizophrenia such as clozapine and olanzapine (166–168). Significant weight gain on these drugs appears to include a combination of effects on expenditure and intake (166). The drugs are known to be active at many types of receptors in the brain including histamine, dopamine, and 5-HT receptors (169). Their mode of action relative to the established network downstream from leptin is unclear.

If we consider the model of the lipostatic system, it is evident that there are large blanks in our understanding of how this system actually works. We know some of the signals that emanate from the periphery to indicate energy status, but we don’t know how many other signals there might be and the timescales over which they are important. How partitioning of energy (the p ratio) is controlled also remains unclear. There has been considerable debate about the nature of transport processes for the peripheral signals across the blood-brain barrier (162) and whether defects in these systems interfere with efficient signaling, but little progress has been made along these lines. Intracellular signaling once the main compounds hit their target receptors has been actively studied, and considerable progress has been made in understanding how leptin and insulin modulate gene-expression profiles in their target neurons. Initial events downstream from leptin are starting to become clear. However, the interactions beyond the MC4-Rs in neurons within the PVN are far less understood. Generally published models have arrows that emerge from this point to feeding behavior and energy expenditure, but the detailed mechanisms of how feeding behavior and expenditure are controlled are vague. As our understanding of this area blossoms, there will likely be a whole range of new targets to which pharmaceutical intervention may be possible. In the effector system, the molecular basis of variability in resting metabolism (170) and the way that activity levels are regulated remain virtually unknown.

One area that we still know very little about is the nature of the encoding of the lipostatic target weight. Several small-animal models appear to be particularly suitable for investigating this phenomenon including animals that alter their body weight in response to changing seasons (171,172). We do know that these changes are signaled by altered photoperiod; by switching the photoperiod, it is possible to move animals from one level of regulation to another. An example of such a switch occurs in the bank vole Clethrionomys glareolus (173). When bank voles maintained in cold conditions are exposed to a short photoperiod, they have a low body mass and relatively little fat storage. If the photoperiod is altered to yield a long day (16 h of light), the animals put on weight for a period of ~2 wk until they are ~10% heavier (Fig. 3A). Most of this weight gain is fat tissue. They then reestablish control at this higher level. This pattern of change appears to involve a shift in the target of the lipostatic system.

By extracting RNA from the hypothalami of short- and long-day bank voles, we can compare the gene-expression profiles of the major genes known to be involved in the lipostatic system.
The results of this comparison are illustrated in Figure 3B. This comparison shows that some genes are differentially regulated, in particular, the CART gene is upregulated in the long-day group (173). This potentially indicates that CART has some involvement in the lipostatic regulatory set point. Another small-animal model system that is extensively characterized with respect to responses to photoperiod is the Siberian hamster *Phodopus sungorus*. On exposure to short photoperiods, hamsters lose body weight and reestablish control at a much lower level where ~30% of the body weight has been lost (Fig. 4A). Gene-expression profiles that compare long- and short-photoperiod hamsters are also shown in Figure 4B (172). Some parallel changes in the patterns for bank voles and hamsters are apparent. In particular, the upregulation of CART is observed. Interestingly CART was recognized in candidate-gene screenings in humans as a potential candidate for influencing obesity (163), although other studies of polymorphism linkages between the CART gene and obesity suggest that the effects are mostly on regional fat distribution (163a). These studies are in their infancy, but the potential is clear. Once we know which genes are involved in setting the lipostat target, we can start to think about manipulating the system. These manipulations could include production of agonists and antagonists to the gene products and their receptors to turn someone with a high target weight into someone with a low target weight.

How far in the future is this dream of manipulating body weight by target resetting? Inevitably, progress depends on making key breakthroughs in gene identification and control and the development of suitable pharmaceuticals. Because drug evaluation and testing generally takes about a decade, this could become a reality in 15–20 y. Drugs that mimic or interfere with other components of the lipostatic system are already in phases 2 and 3 of development and should be available to health care practitioners within the next 5–10 y. Meanwhile, the main alternative strategy is willpower. This does work, but for a permanent solution, this needs permanent lifetime commitment and struggle. The evidence suggests that few people are able to sustain this. At present, the only alternative solution that has almost guaranteed success is forced adherence to energy restriction by surgical intervention. Surgical intervention in 20% of the population is, however, beyond the capacity of health care systems to deliver.

Drugs that manipulate the lipostatic system will provide a valuable advance in the fight against obesity. Using these drugs at the same time as calorie restriction means that patients will no longer need to perpetually fight against the impetus of their regulatory systems. Rather, we will use the system that controls body weight to take it to a level that we want instead of an arbitrary setting that is based on genetic inheritance. The effect of treatment would be gradual, but unlike conventional approaches that fight against one’s genes, an individual would work with his or her genes, which will make the entire process considerably easier. However, it should be clear that whatever manipulation is envisaged, its success will only last as long as the manipulation continues. If we administer drugs that lower the lipostatic set point, they will only help suppress body fatness.
as long as the set point is altered. Once the drugs are discontinued, the set point will (presumably) readjust to the original level and the system will provide an impetus to regain body weight. The same is true for all of the drugs that are based on mimicking peripheral signals. Once the signal has gone, the impetus to replace it by increasing fitness will return. Although they are valuable, such drugs will need to be lifelong treatments if they are to be effective. The ultimate “holy grail” solution is to permanently switch the system so that the effects are also permanent. Whether this is even possible without some form of gene therapy (174,175) that may be politically unacceptable is presently unknown.

Conclusion

Obesity is a serious condition that presently affects ~320 million people; an additional 800 million people are overweight. Differences among individuals in their susceptibility to obesity probably reflect, in large part, their genetic constitutions. Differences among individuals in their susceptibility to obesity are presently unknown. If they are to be effective. The ultimate “holy grail” solution is on mimicking peripheral signals. Once the signal has gone, the body weight. The same is true for all of the drugs that are based original level and the system will provide an impetus to regain increased serum leptin levels. Diabetes 48: 14:672.

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QUERIES - nutrition08119q

[AQ1] Has your meaning been retained in this sentence? “Generally, however, in most adults, BMI correlates reasonably closely to body fatness (which is measured by more sophisticated scanning and imaging devices), particularly if combined with measures such as the waist circumference (8).”

[AQ2] OK to insert “is termed” in this sentence? “After food ingestion, our metabolic rate rises further; when we start to move around, it increases even more and is termed active energy expenditure.”

[AQ3] Insertion of “process” in this sentence OK? “In the short term, expenditure and intake do not match closely because we feed in discreet bouts whereas expenditure is a continuous process.”

[AQ4] Has your meaning been retained in this edited sentence? “Given the energy balance equation, it is clear that obesity results from either food intake being too high, expenditure being too low (through low RMR and/or activity expenditures), or a combination of both.”

[AQ5] In this sentence, change to “UK numbers” OK? “The UK numbers are on the high side but are typical of many European nations (1).”

[AQ6] Edits to this sentence OK? “For example, the prevalence of obesity in black populations across the entire U.S. is ~5% higher than in colocalized white populations (30), and for black females, prevalence is even higher with ~50% obese.”

[AQ7] In this sentence, change from “children” to “child” throughout OK? “Parental ratings of how much television a child watches are positively associated with the child’s BMI (35), and having a television in a child’s bedroom is a significant risk factor for obesity (37); also, television viewing is negatively associated with engagement in physical activity (38,40).”

[AQ8] Edits to this sentence OK? “At national levels, however, food-sales statistics show that for almost all food types, the same amount of food or more is presently being purchased per individual compared with 20 y ago.”

[AQ9] Has your meaning been retained in this sentence? “Accordingly, studies of monozygotic and dizygotic twins raised apart and together and pairs of adopted and nonadopted “virtual twins” indicate the variation in body mass that is explained by genetic factors is also very high.”

[AQ10] Insertion of “deprived” in this sentence OK? “A common response to the suggestion that our shared environments are unimportant is to point out that if one were to take a pair of twins and keep one of them locked up with minimal food for years on end, the deprived twin would not develop the same BMI as the twin given free access to food; hence it is “obvious” that environment must be important.”

[AQ11] Sentence edited as meant, that circulating glucose has a feedback mechanism? “Thus if glucose-sensing centers in the brain detect a drop in circulating glucose levels, feeding is stimulated, and feeding is then terminated by the increase in circulating glucose.”

[AQ12] Vice versa meant here? “It is seldom the case that someone could accumulate an energy deficit but not affect levels of their stores and vice versa.”

[AQ13] Insertion of “energy” in this sentence correct? “Many studies show that when subjects are food deprived, they compensate for the deprivation by reducing their energy expenditure.”

[AQ14] Has your meaning been retained in this edited sentence? “The extent of the weight gain was dependent on the extent to which the subjects performed spontaneous activities to burn off the excess energy (79–81).”

[AQ15] In these two sentences, changing “they” to db/db mice correct? “Hence the db/db mice also “think” that they are dangerously thin, and effect changes in their food intake and expenditure to bring their fatness up to target. When db/db mice are placed in parabiosis with wild-type mice, there is no effect on their food intake, because they are already producing lots of the signaling factor (it just isn't being read), so getting more of a signal from the wild-type mouse has no effect.”
Moreover, we are aware that endogenous cannabinoids and the serotonergic and opioid-dopaminergic (119) systems are also involved, but the details of the interactions presently remain obscure.

OK to add “in frequency” to this sentence? “Whenever one loses weight, the opposite occurs: the multiple signals decrease in frequency, food intake is stimulated, and energy expenditure is suppressed to regain the missing weight.”

OK to change “and” to “or” since both situations don’t exist in one person? “First, obese people may have broken lipostats; or second, the lipostats in obese people may be set at very high target levels.”

Correct to change “identify” to “indicate” in this sentence? “Such behaviors are also observed in modern-day groups of apes and monkeys such as vervet monkeys, which have evolved complex signals to indicate the approach of different types of predators (149–152).”

Has your meaning been retained in this sentence? “Second, a high protein intake is generally coupled with a high saturated fat intake and a high serum cholesterol level, both of which are implicated as causal factors in cardiovascular disease, cancer, and stroke independent of the obesity they engender.”

Insertion of “concomitant” OK? “Processing high protein loads may also increase the risk of kidney failure because of the concomitant high rate of urea production.”

OK to put this text into list format for clarity? Edits to sentences (for parallel structure) OK? “Three sources of information serve to quantify the extent of our present ignorance about the control system and its interrelationship with obesity, as follows: 1) genetic mapping studies, which identify the specific regions of the genome where polymorphic loci are associated with variation in body weight; 2) actions of drugs that produce effects on body weight for which the mechanism is unclear including drugs that have weight gain as an unexpected side effect; and 3) examination of the lipostatic model itself, so we can see areas where our understanding is deficient.”

Clozpine meant (rather than clozopine)? “These include many of the antipsychotic treatments for schizophrenia such as clozapine and olanzapine (166–168).”

“Screenings” meant? “In particular, the upregulation of CART is observed. Interestingly CART was recognized in candidate-gene screenings in humans as a potential candidate for influencing obesity (163), although other studies of polymorphism linkages between the CART gene and obesity suggest that the effects are mostly on regional fat distribution (163a).”

Has your meaning been retained in this sentence? “Presently research efforts are geared toward identifying and ultimately manipulating the control system for body weight so that solutions can work in harmony with (instead of against) one’s genes.”

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Changes to Ref. 62 (Girardier, 1994) and added information (as per PubMed) correct?
For Ref. 71, please complete the citation information with title of article (or book chapter), journal or book title, volume no., pages; if the citation is a book, also include publisher’s name and location.

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Reference 119 has only first page number. Is this an Abstract? If not, please provide the last page number if article is longer than one page.

For Ref. 128 (Farooqi et al., 2001), change to article title (as per PubMed) correct?

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