Modern science versus the stigma of obesity

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Obese people, who are already subject to adverse health effects, are additionally victimized by a social stigma predicated on the Hippocratic nostrum that weight can be controlled by 'deciding' to eat less and exercise more. This simplistic notion is at odds with substantial scientific evidence illuminating a precise and powerful biologic system that maintains body weight within a relatively narrow range. Voluntary efforts to reduce weight are resisted by potent compensatory biologic responses. This article will review some of this evidence, together with promising avenues of research. Further progress in understanding and treating obesity will come not from repetition of anachronistic preconceptions but rather from the rigorous scientific approach that has driven advances in so many other areas of medicine.

People often reserve their harshest judgments for those conditions about which the least is known. So, mental illness was once thought to be sign of the devil incarnate, ulcer disease was a result of an inability to deal with stress, colitis was a disorder of the high-strung and AIDS was a personal failing. Even cancer was a disease imbued with shame, with the afflicted hidden from view and seldom spoken of. Substance abusers and compulsive gamblers are now appropriately considered to have disorders that require treatment. In these and other instances, advances in our understanding of the underlying pathology have led to a greater acceptance of those affected by these conditions. There is, however, an unfortunate exception to this trend.

Today, is there a group more stigmatized than the morbidly obese? In most circles, the conventional wisdom on obesity's cause has not changed appreciably from the time of Galen, who clearly held obese individuals responsible for their state, or of Shakespeare, who, through Henry IV, hurled a barrage of insults at Falstaff, referring to him as "fat-witted", "chair-breaker" and "mare-cripler"[1,2]. Through the ages, obese individuals have been held accountable for their condition. Today in the United States, more than 60% of people are either overweight (body mass index (BMI, height/weight^2 in m/kg^2) >25) or obese (BMI >30). Morbidly obese individuals (BMI >40) number in the millions. Can it be that, as many believe, these millions of people deserve their fate because they lack discipline?

The commonly held belief that obese individuals can ameliorate their condition by simply deciding to eat less and exercise more is at odds with compelling scientific evidence indicating that the propensity to obesity is, to a significant extent, genetically determined. The heritability of obesity is equivalent to that of height and greater than that of almost every other condition that has been studied[3–5]—greater than for schizophrenia, greater than for breast cancer, greater than for heart disease and so on. Although environmental factors contribute to changes in the incidence of obesity over time, individual differences in weight are largely attributable to genetic factors[6,7]. So, although the current environment, in which almost everyone has essentially unlimited access to calories, can account for an average weight gain of 7–10 pounds over the past decade in the United States, it is genetics and not the environment that accounts for a large proportion of the marked differences in individual body weight in our population today.

Some of the genes that regulate body weight have been identified, disclosing a robust physiological system that maintains weight within a narrow range (generally 10–20 pounds)[6,8]. These genes balance calorie intake and energy expenditure with considerable precision. Weight loss on the part of the obese is met with compensatory responses by these genes, which act to resist weight change in part through a decrease in metabolism and an increase in hunger[9]. For this reason, most people who lose weight by dieting eventually regain it[10,11]. In a growing subset of people, the molecular pathology of obesity is completely understood, and for some of them highly effective therapies for weight loss are available[8,12,13].

All of the above indicates that morbid obesity is not a personal choice but a disease. Like those with hypertension, which increases the risk of strokes or heart attacks, morbidly obese individuals are at one extreme of the distribution for a continuous trait (adiposity) and are at an increased risk for numerous conditions that shorten life, including diabetes, heart disease, hypertension and cancer[14–16]. Collectively, these diseases are known as the metabolic syndrome. In the aggregate, they are the principal causes of morbidity and mortality in the Western world, leading many to conclude that obesity is the disease of the twenty-first century[16].

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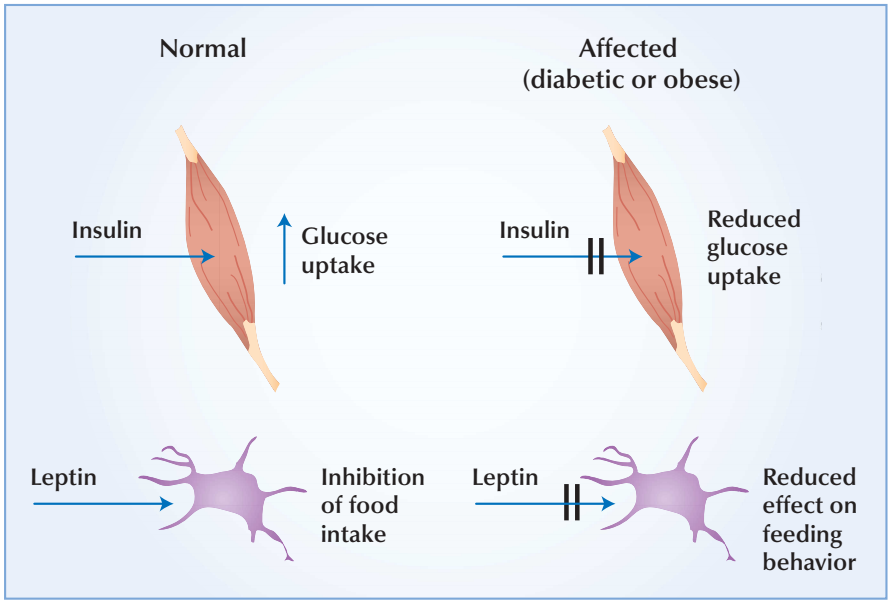

Figure 1 Leptin resistance and obesity. Leptin resistance and obesity (bottom) are analogous to insulin resistance and type 2 diabetes (top), respectively, in several aspects. In both cases, affected individuals frequently have high circulating levels of the hormone despite being diabetic (in the case of insulin) or obese (in the case of leptin). In addition, affected individuals show a reduced response to treatment with exogenous hormone as compared to those who are unaffected. One notable difference is that almost all type 2 diabetics will respond to insulin if a high enough dose is given, whereas only a subset of obese subjects lose weight when given high doses of exogenous leptin. The pathophysiology and treatment of diabetes have been advanced by a fuller understanding of the abnormalities of insulin signal transduction in insulin-resistant tissues such as skeletal muscle. Similarly, obesity research will be advanced by a fuller understanding of the basis of leptin resistance at its sites of action in the brain and potentially other tissues. Several genes, including those encoding PTP1b and SOCS3, have been shown to contribute to leptin resistance, thus identifying new potential drug targets for the treatment of obesity. Nevertheless, leptin resistance is not necessarily a result of abnormalities in the cells that respond directly to leptin, but could result from alterations elsewhere in the neural system that regulates food intake and body weight. For example, mutations affecting MC4R lead to leptin resistance, despite the fact that these neurons bearing MC4R are downstream of the leptin-responsive POMC neurons. Hedonic reward pathways could also lead to leptin resistance even further downstream. A complete understanding of leptin resistance may require understanding how the numerous inputs that regulate complex, motivation behaviors are integrated.

Why is it, then, that the views of scientists who study this health problem have not found their way into the minds of the public or even a significant proportion of the scientific community? Perhaps it is because, in contrast to almost every other disorder, common views on obesity are shaped by a lifelong set of personal experiences having to do with one's own efforts to manage one's weight. Perhaps it is because these views are shaped by a constant barrage of advertisements from the diet industry, which has a multibillion-dollar interest in promoting the view that weight can be controlled through volition alone. Perhaps it is because, by contrast to other stigmatized disorders, obesity is immediately evident and tends to elicit a set of atavistic and often ill-informed responses. Perhaps it is because humans prefer to believe that that the conscious wish to be trim is an element of our 'free will' and should therefore dominate the neural mechanisms that drive us to eat.

What is now known should be sufficient to end the opprobrium of the obese. To end the stigma of obesity, the scientific community must communicate more effectively a growing body of compelling evidence indicating that morbid obesity is the result of differences in biology and not a personal choice.

Ten years ago, little was known about the biological system that regulates weight. Although it was known that the hypothalamus regulates food intake and metabolism, the molecular elements of the relevant neural circuits were not known. Whereas it was known that the basic laws of physics governed energy balance in mammals (as in all creatures), the ways in which cellular metabolism is controlled were unknown. Whereas it was known that obesity is highly heritable, none of the causal genes had been identified.

Here I briefly review recent progress and potential opportunities in obesity research in four areas: the neuroanatomical basis of feeding behavior, the molecular mechanisms that regulate food intake, the molecular mechanisms that regulate energy consumption and the genes that cause obesity. This review is not meant to be exhaustive, but to provide a few examples of how new scientific findings rebut the view that obesity is a result of a character flaw and to highlight opportunities for future research.

Neural control of food intake

Everyone knows what it feels like to skip a meal or to refrain from enjoying that alluring cheesecake. From this shared experience comes the conclusion that obese people restrain themselves less well than the lean. The problem with this view is that it ignores the basic neural system that controls the drive to eat and the variability of its potency in different individuals.

The neural system that regulates body weight and appetite is centered in the hypothalamus, a brain region that has changed little from fish to humans, except in terms of its connections to higher cortical centers, which are more developed in primates[17]. The hypothalamus has a major role in controlling most basic life-sustaining drives, including thirst, sexual behavior, temperature and feeding, which it precisely balances against energy expenditure[18]. In humans, these basic drives can be opposed by higher cognitive drives centered in the cortex, such as the wish to weigh less. However, whereas we are aware of the conscious desire to eat less, the basic drive to eat is subconscious; we cannot 'hear its voice' but simply experience its effect.

The belief that we can control our weight with volition alone assumes that although the basic neural network that regulates weight, appetite and energy balance is relevant for all animals including nonhuman primates, this system has been rendered inactive in humans. It is more likely, however, that the development of the human cortex has provided a counterweight to this basic regulatory system in the form of the conscious desire to eat less. Thus although voluntary changes in behavior can often effect short-term weight change, available scientific evidence suggests that over the long term the neural centers that control appetite overcome motivational factors and the lost weight is regained. A fuller understanding of the intrinsic difficulty in losing weight will thus require the elucidation of how relevant sensory and cognitive inputs are integrated to regulate feeding and other complex motivational behaviors (see below).

A balanced view of the causes of obesity would acknowledge the potency of the basic circuits that regulate food intake and focus on the relative potency of this drive relative to that of conscious motivation. For reasons that are becoming well understood, the neural system that regulates energy balance sets adipose tissue mass at a higher level in the obese than in the lean. Furthermore, after weight loss, this system speaks at least as loudly in the obese as in the lean. So, when obese individuals lose weight, hunger is increased and energy expenditure is reduced, both of which usually overcome the conscious desire to be thin. The perceived lack of discipline of obese individuals is thus likely to reflect a heightened biological drive to eat more and regain weight. The ability of leptin to reduce the ravenous appetite of individuals who lack this hormone illustrates this point.

Leptin and the regulation of food intake

Leptin is a 142-amino-acid peptide that functions as an afferent signal in a negative feedback loop that maintains body weight within a relatively narrow range[19]. This endocrine system also links changes in nutritional state to adaptive changes in almost every physiological system, including neuroendocrine function, metabolism and immune function[7,19].

Mutations in the leptin gene result in an insatiable appetite, morbid obesity and numerous clinical abnormalities, all of which are corrected by leptin treatment[12,13,20]. Subjects who are heterozygous for the leptin mutation also develop obesity that is not as severe as in homozygotes[21]. Although leptin treatment can normalize appetite in this rare yet highly instructive case, volitional factors are completely incapable of controlling it.

Weight loss results in a fall in plasma leptin levels[22]. Decreased leptin, in turn, leads to a state of positive energy balance with increased hunger and decreased metabolism, both of which act to restore baseline weight[19]. Starved animals also show alterations in hunger, neuroendocrine function, reproductive capacity, immune function and insulin sensitivity, all of which are ameliorated by leptin replacement[19,23].

Low leptin levels are also seen in human and rodent lipodystrophy—the congenital or acquired absence of adipose tissue[24,25]. Individuals with lipodystrophy also have increased hunger, significant alterations in hypothalamo-pituitary function with secondary amenorrhea, diabetes and insulin resistance, and abnormal immune function. In this and other clinical settings in which endogenous leptin levels are low, leptin replacement ameliorates all of these abnormalities, including the increased appetite that such individuals manifest[26,27].

These studies confirm that leptin has potent biological effects in humans and raise the possibility that obese individuals with low leptin levels might also lose weight after treatment with this hormone. Leptin treatment of obese humans has variable effects[28]. It is unknown whether obese individuals with low leptin levels respond more robustly than the rest of the obese population, but the effects of leptin in other conditions in which the levels of this molecule are low suggest that they might. About 5–10% of obese people (and a significant proportion of lean people with type 2 diabetes) have low leptin levels. The effect of leptin in these individuals needs to be studied[22].

Weight gain is associated with increased leptin levels and, in general, obese subjects have significantly elevated plasma leptin[22]. In humans or animals with normal weight, treatment with leptin in physiological amounts leads to loss of adipose tissue, weight loss and a significant increase in insulin sensitivity[28,29]. This is not the case, however, in most obese hyperleptinemic humans or animals: only a subset of these subjects lose weight in response to leptin[28,29]. The analogy to the reduced effects of insulin on hyperinsulinemic people with type 2 diabetes suggests that obesity is the result of leptin resistance (see **Fig. 1**).

A key objective in understanding the pathophysiology of obesity will therefore be the elucidation of the cellular response to leptin that is abrogated in leptin-resistant states. This task is made more challenging by the fact that, excepting some effects of leptin on skeletal muscle and other peripheral tissues[7,30], the brain is the principal site of leptin action.

The leptin receptor is expressed in several brain regions, including key hypothalamic nuclei that regulate body weight[31]. In general, leptin appears to inhibit pathways that stimulate food intake (orexigenic) and stimulate

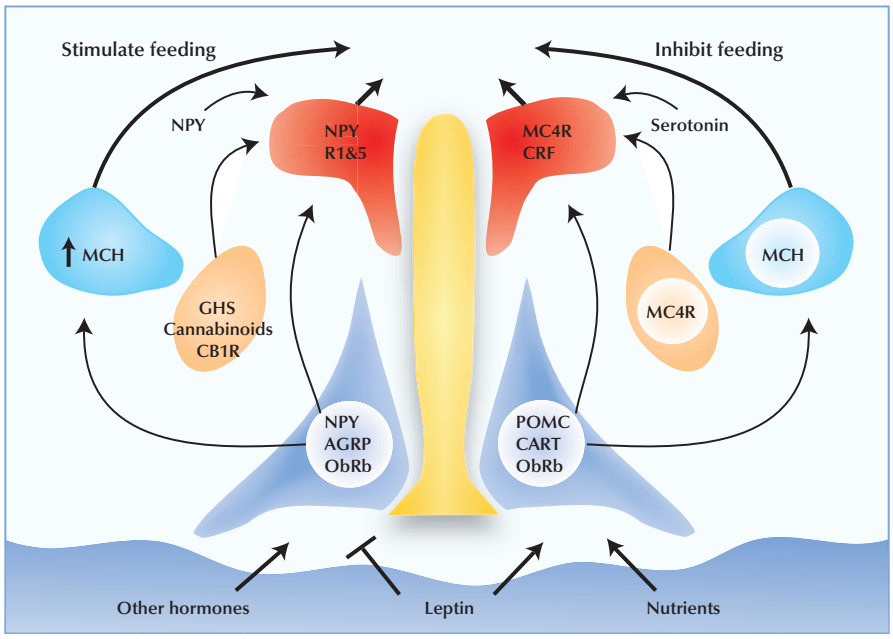

Figure 2 The neural circuit regulating food intake and body weight. Leptin modulates the activity of neural circuits in the hypothalamus and other brain regions including the brainstem. In the hypothalamus, leptin inhibits neurons that increase food intake including those expressing NPY and AGRP and potentiates neurons that reduce food intake including neurons expressing POMC. Both of these sets of neurons coexpress the leptin receptor, ObRb. MCH, endogenous cannabinoids and classical neurotransmitters such as serotonin are also elements of this neural circuit, which is also modulated by other hormones and nutrients. Mutations in genes in this pathway are now known to account for ~5% of morbid human obesity, the majority of which are in MC4R (the receptor for αMSH, a product of the gene encoding POMC). Mutations in the genes encoding leptin, the leptin receptor, POMC itself, and PC1, an enzyme that processes neuropeptides, also cause obesity in humans. Further studies of this neural circuit, including the identification of other neural mediators, are likely to provide new approaches for treating obesity by inhibiting pathways that increase weight and/or activating pathways that reduce weight. CART, amphetamine-regulated transcript (neuropeptide); CB1R, cannabinoid receptor-1; CRF, corticotrophin-releasing factor; GHS, growth hormone secretagogue receptor (also known as the ghrelin receptor); R1&5, NPY receptors 1 and 5.

pathways that inhibit feeding (anorexigenic) (see **Fig. 2**). Neuropeptide (NPY), Agouti gene–related peptide (AGRP), melanin-concentrating hormone (MCH) endogenous cannabinoids and ghrelin are examples of orexigenic neuromodulators, whereas serotonin, norepinephrine and αMSH (α-melanocortin-stimulating hormone, a product of the pro-opiomelanocortin (POMC) precursor protein) are anorexigenic signals[7,32–35]. Importantly, in addition to leptin, these neural pathways also respond to other hormonal and metabolic signals[7,36].

A fuller understanding of leptin resistance will require that all of its cellular sites of action be identified as a prerequisite to understanding the cellular responses that are reduced in the leptin-resistant state. This could open avenues to ameliorate leptin resistance directly or activate pathways downstream of it. Leptin activates the JAK-Stat signaling system, and Stat3, SHP2, PI3K and phosphodiesterase 3B have been shown to participate in leptin signaling[37–40]. Evidence from mice carrying point mutations in the gene encoding the leptin receptor indicates that different signaling pathways are probably activated in different neuronal types[41]. Recent research has shown that the genes encoding PTP1b and SOCS-3 and other genes contribute to leptin resistance in the CNS, and indicates that inhibition of these molecules could enhance leptin action and reduce weight[42,43]. However, leptin resistance need not be evident in cells that are direct targets of this hormone and could be the result of effects elsewhere in the neural circuit that regulates food intake. For example, absence of the melanocortin-4 receptor (MC4R) leads to leptin resistance downstream of POMC-containing neurons, which are a direct target of leptin[8,29,34,44]. In addition, leptin leads to the rapid rewiring of neurons in the arcuate nucleus, suggesting that the basis of leptin resistance is more complex than if it were mediated by alterations in a single cell type[45].

Leptin sensitivity can also be modulated by environmental factors. For example, exposure to a highly palatable, high-fat diet leads to obesity in some genetically susceptible mouse strains but not others[46]. A possible mechanism for the effects of diet on leptin sensitivity is suggested by studies of transgenic mice that constitutively overexpress leptin[47]. On a normal diet, these animals are extremely lean. However, when fed a palatable high-fat diet, these animals no longer respond to leptin and become obese. One explanation for this result is that the increase in lipids alters signaling in the hypothalamus[36]. Another possibility is that the hedonic value of the diet leads to leptin resistance, perhaps by modulating reward pathways that intersect with leptin-activated pathways. Indeed, feeding is a reward-driven behavior, and the potent effects of leptin on reward pathways confirm a direct interplay between this molecule and hedonic stimuli[48,49].

Feeding has an important motivational component. Visual, gustatory and olfactory stimuli, gastrointestinal signals, emotional cues and higher cognitive inputs are all integrated to produce a decision to eat[7,18]. Although the nucleus accumbens is known to have a major role in controlling reward behaviors, the site of the neural center that integrates inputs relevant for feeding is not known[18]. The development of new methods for tracing polysynaptic neural circuits[50] might improve our delineation of the neural circuit that regulates feeding.

There are other unresolved issues with respect to the physiological roles of leptin and its therapeutic potential. As mentioned above, leptin resistance can result from altered signaling in the neural circuit that regulates feeding[7]. Yet in other cases, leptin resistance appears to result from a defect in its ability to gain access to feeding centers in the brain[7,29,51,52]. The mechanisms responsible for leptin uptake across the blood-brain barrier (BBB) are unknown. In some regions, leptin appears to gain access at circumventricular organs, which lack a BBB, whereas in other regions there appears to be an active transport mechanism, the elements of which are unknown[53]. Leptin-binding proteins in plasma may play a role in this process. Leptin circulates bound to other proteins, including a soluble form of its receptor, and in a 'free' form[54]. It is currently not known whether the free or the bound form is bioactive.

There is also direct evidence that the circuit that responds to leptin is regulated by neurotransmitters such as serotonin[33]. A drug previously used for the treatment of obesity was Fen-Phen, a combination of fenfluramine (a serotonin agonist) and phentermine (a norepinephrine agonist), both of which are anorexigenic[55,56]. Amphetamines also cause weight loss by enhancing norepinephrine signaling, whereas sibutramine, a

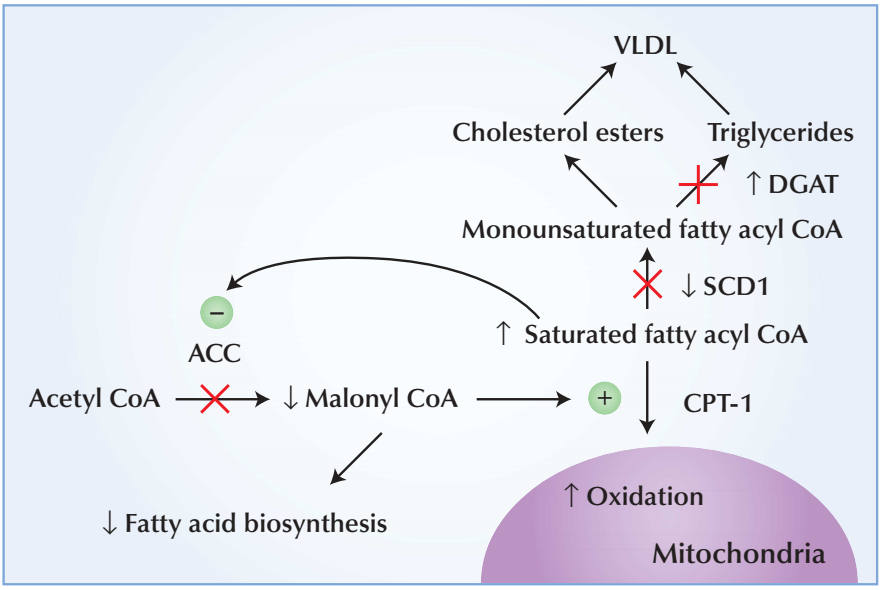

Figure 3 Biochemical pathway regulating cellular fatty acid metabolism and energy expenditure, showing the mechanism underlying increased fatty acid oxidation. The rate-limiting step in fatty acid oxidation is the uptake of fatty acids into mitochondria by carnityl palmityl transferase-1 (CPT-1), a system that shuttles fatty acids into mitochondria. This shuttle is normally inhibited by malonyl CoA, a three-carbon fatty acyl CoA generated from acetyl CoA by ACC-2. Decreased levels od malonyl CoA results in increased fatty acid metabolism and energy expenditure. Thus, a mutation of the gene encoding ACC-2 results in increased energy expenditure and resistance to obesity. A similar effect is seen with mutations in *Scd1*, which encodes stearoyl CoA desaturase, in mice with asebia. This enzyme catalyzes the synthesis of monounsaturated fatty acids from saturated fatty acids. Saturated fatty acids potently inhibit ACC allosterically whereas monounsaturated fatty acids do not, suggesting that mutations in *Scd1* secondarily reduce ACC activity. This has been shown directly in studies of mice with asebia. Finally, mutations affecting DGAT, another enzyme in this pathway, also produce similar effects, suggesting that modulation of this pathway could provide a means to reduce weight by increasing energy expenditure.

drug that causes some weight loss, inhibits reuptake of serotonin and norepinephrine[32]. An opportunity that has not been fully exploited is to develop new agonists for the specific serotonin and norepinephrine receptors that mediate the antiobesity effect of Fen-Phen and related compounds. Although the HT2c serotonin receptor subtype has been shown to be involved in the regulation of feeding in animals, it is not known which serotonin receptor regulates feeding in humans[57].

Another possibility is to develop agents that modulate the neural circuits of feeding and energy balance with efficacy equivalent to Fen-Phen's but without significant toxicity. Endogenous cannabinoids are important for the response to leptin deficiency, and recent data indicate that rimonadant, an inhibitor of the cannabinoid receptor CB1R, can reduce body weight in a significant number of subjects[7,58]. Further studies of the circuit that responds to leptin will provide additional therapeutic opportunities. Drugs that inhibit orexigenic pathways or stimulate anorexigenic pathways are already in development, and it can be anticipated that such agents will have beneficial effects.

Energy expenditure

In 1783, Lavoisier and Laplace built the first calorimeter by enclosing an animal or burning charcoal in a chamber surrounded by a block of ice. Using this device they showed that the bioenergetics of living organisms and inanimate systems are fundamentally the same[59]. In both cases, energy was generated by the consumption of oxygen, leaving carbon dioxide and water as byproducts.

In a critical extension of this fundamental advance, von Helmholtz showed that living organisms obey the first laws of thermodynamics, which states that the amount of energy in a closed system must remain constant[60]. What this means is that for the weight of an organism to remain constant, the amount of energy eaten must equal the amount of energy consumed by metabolism. Any imbalance between food intake and energy expenditure results in a change in the amount of stored energy, mainly fat.

The implications of this simple equation are frequently underappreciated in discussions about the causes of obesity. Body weight is remarkably stable in humans. The average human consumes one million or more calories per year, yet weight changes very little in most people. These facts lead to the conclusion that energy balance is regulated with a precision of greater than 99.5%, which far exceeds what can be consciously monitored[61]. For example, the error rates of the calorie listings on food labels are in many cases greater than 10%, as assessed by calorimetry[62].

Discussions of the causes of obesity generally focus on the importance of food intake in the energy-balance equation. However, several lines of evidence indicate that energy expenditure is tightly regulated and that subconscious alterations of energy expenditure have a powerful, perhaps dominant, influence on body weight. Energy expenditure is highly variable and, in prospective studies, people with lower rates of energy expenditure develop obesity more frequently than people with high rates[63]. In other studies, overfeeding twin pairs increased their energy expenditure to a variable extent and subjects with the lowest increases gained the most weight[64,65]. These studies also established that the effect of overfeeding on energy expenditure is highly heritable.

Energy expenditure refers to the total number of calories expended per 24 hours, which depends on metabolic rate, activity and the thermogenic effects of feeding. Voluntary physical exercise represents only a small fraction of our daily caloric use, and the propensity to gain weight correlates better with total energy expenditure and nonexercise activity[63,65]. Exercise by itself has not been shown to be highly effective in treating obesity because the increased energy use from exercise is generally offset by increased caloric intake.

Energy expenditure falls significantly after weight loss[9]. So, an obese person who had gone from 300 to 200 pounds would have to consume considerably fewer calories to maintain this new weight than a person who started out at 200 pounds. This fact, combined with the increased hunger that is manifest after significant weight loss, undoubtedly contributes to the high relapse rate seen after dieting. An extreme example of this can be inferred from the analysis of outcomes after bariatric surgery. This procedure alters gastrointestinal anatomy to reduce caloric intake beyond what could be achieved volitionally. Although people who undergo bariatric surgery lose a significant amount of weight, nearly all remain clinically obese[66]. This result is consistent with animal studies showing that genetically obese animals become obese even when their food intake is restricted to that of control mice[67]. The implication is that something metabolically different about morbidly obese individuals results in obesity independently of their caloric intake.

These clinical findings suggest that directly increasing energy expenditure is an alternative strategy for inducing weight loss. This premise has already been tested in humans using dinitrophenol, which uncouples mitochondrial respiration. This agent successfully induces weight loss in humans but has unacceptably high toxicity[68]. Thyroid hormone also reduced weight by increasing energy expenditure, but was again toxic[68]. The development of selective thyroid hormone agonists that increase energy expenditure with no side effects could provide clinical benefit in a manner analogous to the use of selective estrogen receptor modulators as an alternative estrogen.

Recent animal studies have identified other genes that, when mutated, increase energy expenditure and lead to resistance to obesity despite markedly increased food intake. Three of these encode enzymes in the fatty acid biosynthesis pathway—acetyl CoA decarboxylase-2 (ACC-2), diacylglycerol acetyl transferase (DGAT) and stearoyl CoA desaturase-1 (SCD-1) (**Fig. 3**)[69,70]. Indeed, leptin has been shown to suppress SCD1 expression, and leptin's effect in increasing energy expenditure is at least partially attributable to the suppression of this enzyme[70]. These findings suggest that inhibiting fatty acid biosynthesis or storage leads to a secondary increase in fatty acid oxidation and to a lean phenotype. Drugs that inhibit this biochemical pathway could provide new ways of reducing weight.

Other molecules that activate energy expenditure include the PGC-1 coactivator, which activates mitochondrial biogenesis and cellular programs that promote energy expenditure, and the PPARδ nuclear hormone receptor[71,72]. Similarly, the sympathetic nervous system has a profound influence on energy expenditure. Animals with a knockout of all three β-adrenergic receptors develop massive obesity as a result of an inability to dissipate energy normally when caloric intake is increased[73]. The site of β-adrenergic action responsible for this effect is not known, and a fuller understanding of this and other mechanisms that control energy balance may provide a new avenue for the development of therapies for obesity.

Genetics

The most compelling evidence that obesity is genetically determined comes from genetic analyses. Twin, adoption and familial aggregation studies have led to the conclusion that genes contribute to the development of obesity with estimates of heritability of 0.7–0.8. This means that most of the variance in the incidence of obesity is attributable to genetic factors[3–5].

In addition to congenital leptin deficiency, the genetic basis for obesity is known in several instances. Mutations in the genes encoding the leptin receptor, POMC (and αMSH), PC1 or MC4R (the receptor for αMSH) lead to forms of obesity that are inherited in mendelian fashion[44,74,75]. These genes encode components of the neural pathway that regulates energy balance. Altogether, about 5% of childhood morbid obesity can be accounted for by single-gene defects, most of which are in MC4R. The frequency of mendelian inheritance of morbid obesity is therefore higher than that of most complex disorders. Moreover, there is a high rate of consanguinity among a core of morbidly obese children in whom mutations in the known obesity genes have been excluded. This observation strongly suggests that there are additional, as-yet-unidentified mendelian forms of obesity (S. O'Rahilly, personal communication).

In the remainder of the population, obesity is the result of genes interacting with environmental factors. Although environmental factors contribute to changes in the distribution of weight in populations over time, they do not account by themselves for the marked variation in weight evident in the population; genes interacting with environmental factors do[6,76]. There is substantial evidence that alleles which predispose to obesity may have conferred a selective advantage in times of hardship and that, when food is more readily available, these alleles lead to obesity. For example, the frequency of obesity is highly variable in different populations and is most severe in populations that previously lived in adverse conditions[6,77]. Indeed, the development of leptin resistance in harsh conditions would have led to latent obesity and might have provided a selective advantage.

Several genetic loci linked to obesity in the general population have been mapped, and continuing advances in human genetics will undoubtedly lead to the identification of genetic variants that predispose to obesity[8,76]. These genes are likely to encode additional components of the physiological system that regulates nutritional state. Their identification will provide important insights into the ways in which genes, environmental and developmental factors interact to maintain weight at an optimal level for a given set of conditions.

Conclusion

Obesity and the metabolic syndrome are considered to be diseases of the twenty-first century. Hippocrates wrote that the obese should "eat only once a day and take no baths and sleep on a hard bed and walk naked as long as possible"[1,2]. Progress in this area will require that we move beyond this 2,000-year-old prescription and instead develop strategies that are based on twenty-first-century science.

Although population-based measures to reduce weight are intrinsically difficult to implement, they will need to be an important element of any strategy for dealing with the public health consequences of obesity. In this regard, modest weight loss (5–10 pounds) confers a significant health benefit and is achievable with changes in lifestyle, such as modest restriction of food intake and increased exercise[78]. However, such measures are not generally effective for the long-term maintenance of significant weight loss, especially in morbidly obese individuals[10]. For these people, help will come with the identification of the genes that predispose to obesity, a fuller understanding of their function and a deeper knowledge of how their activity is modulated by environmental, developmental, emotional and psychological factors. This level of understanding will provide the foundation for the development of effective therapies. Such therapies will undoubtedly have to include drugs or, as aptly put by J. Flier, the medical community would effectively "abandon a major segment of the population to an unhealthy fate"[7].

Obesity research is one of the most dynamic areas in biology and is at the nexus of physiology, neurobiology, biochemistry, bioenergetics, genetics, nutrition and other areas of science. We can only hope that advances in our understanding of the causes of this condition will lead to changes in the perception of what it means to be obese in a world of harsh judgments and facile conclusions that are not supported by a growing set of scientific facts. The stigma of obesity should be discarded, enabling this disease to join with other conditions that required that we look beneath the surface.

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