9 Etiologies of Obesity

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KEY POINTS

- Obesity is an exceedingly complex group of diseases and probably should be characterized as a syndrome.
- Simply overeating does not result in long-term obesity.
- More than 350 genes or gene markers have been identified that are associated with obesity and may contribute to the etiology of obesity in animals and humans.
- The etiologies that contribute to obesity that physicians can influence include dietary and exercise patterns, endocrine and metabolic diseases, and drugs.
- More research is needed to uncover the causes of obesity and to develop therapies.

1. INTRODUCTION AND OVERVIEW

This chapter examines some of the evidence to date for the various etiologies of obesity. Table 1 provides an outline of the chapter and the major factors thought to contribute to the etiology of obesity.

The common feature of all obese people is an excess accumulation of adipose tissue. However, obesity is not a single disease. More than 300 different genes and gene markers have been identified that are associated with obesity (*see* Chapter 18 for a discussion on recent research on the genetics of obesity), and there are numerous environmental factors that appear to be necessary for the expression of obesity *(1–2)* (*see* Table 2). A prevailing current hypothesis is that, in most people, obesity is the interaction of the environment and a genetic predisposition to accumulate excess adipose tissue. Usually, both the genetic factor(s) and the environmental factors must be present for obesity to occur. This hypothesis is undoubtedly true for the vast majority of obese people. The previous belief of many lay people and health professionals that obesity is simply the result of a lack of willpower and an inability to discipline eating habits is no longer defensible (*see* Chapter 24 for a summary of lay and professional attitudes about obesity) despite its continued popularity. It is likely that few or no cases of obesity are simply the result of overeating, rather than a more complex interaction of environmental and genetic factors. The classic studies of Sims et al. *(3)* provide evidence that simply

From: *The Management of Eating Disorders and Obesity, Second Edition*
Edited by: D. J. Goldstein

Table 1
Chapter Overview

overeating does not result in long-term obesity. In these studies, forced overfeeding of young lean males resulted in weight gain averaging only about 21% over baseline, despite dramatic increases in energy intake for months. Furthermore, this overfeeding did not result in long-term obesity *(3)*.

The hypothesis that obesity is almost always a product of a genetic predisposition interacting with the environment has been challenged by recent evidence that animals infected with certain viruses develop obesity *(4–6)*. Preliminary data suggest that one or more of these viruses may contribute to obesity in humans, but additional research must be done. As is shown here, we are only in our infancy of understanding of the etiologies of obesity.

2. GENETIC FACTORS CONTRIBUTING TO OBESITY

2.1. Single-Gene Defects

Single-gene defects as models of obesity in animals have been known for many years, and more recently have been described in humans *(1)*. The two most prominent single-gene defects that cause obesity in animals and/or humans include *ob/ob* and *db/db*, the genes coding for leptin and leptin receptor, respectively. Others include the *agouti, tubby*, and *proopiomelanocortin* genes *(1)*. Coleman's *(7–9)* early descriptions of two mouse models, the obese (*ob/ob*) and the obese and diabetic (*db/db*), stimulated a series of research studies that culminated with the identification of the gene defects responsible for each of these disorders. The *ob* gene, first described by Zhang et al. *(10)*, codes for leptin.

Table 2
Potential Explanations Advanced for the Epidemic of Obesity

1. Reduced activity
   a. Greater affluence, more cars, less heavy labor
   b. Cable TV, increased channels
   c. Computers in workplace and home
   d. Computer games, handheld and desktop
   e. Fears of violence or kidnapping of children
   f. Organized sports for children, reduced outside playing time
2. Changes in food intake
   a. Increasing affluence among population, food more affordable
   b. Easier access to food in environment
   c. Expansion of fast food sources and availability
   d. Change in character of food (high fat, refined carbohydrates)
   e. Larger portion sizes
3. Two-income families, less attention to meal preparation
4. Worldwide epidemic of obesity-producing virus

Leptin is made in adipose tissue and is postulated to signal the brain regarding insufficiency of food intake and decreasing levels of adipose tissue stores in the body. Leptin deficiency is an autosomal recessive trait that produces massive obesity in ob/ob mice and in a small number of humans reported with this defect *(10–15)*. Coleman *(7,8)* showed that ob/ob mice must be food restricted to half of the energy intake of their lean siblings to achieve a comparable body weight, and even then, their body fat is greater.

When injected with leptin, both ob/ob mice and humans lose weight down toward the levels of their unaffected siblings *(11–13,16)*. The altered gene in the db/db mouse codes for the leptin receptor, and apparently results in a defective or absent receptor site. Defects in the comparable gene in rats produce the Zucker obese rat model. Neither db/db mice nor Zucker rats lose weight when injected with leptin.

Only a tiny fraction of obese people have a single-gene disorder as the etiology of their obesity. Such individuals tend to gain weight continually until they die of some complication of obesity. Recent studies have identified a very small number of humans with leptin deficiency, and a somewhat larger number with leptin receptor defects *(14–18)*. It has been disappointing to learn that obese people have high levels of leptin, and appear to be resistant to its action in reducing body fat *(19)*.

There are several other rare obesity syndromes owing to genetic or familial causes as reviewed by Chagnon et al. *(1)* and Bray et al. *(20)*. For example, the Prader-Willi syndrome (obesity, mental retardation, short stature, small hands and feet) probably represents a mutation in affected individuals *(20)*. Of the 24 genes specifically identified with human obesity *(1,21)*, most contribute only very modestly to the obesity in a given individual. Bouchard et al. *(21)* maintain a constantly updated website on the human obesity genome at http://obesitygene.pbrc.edu.

2.2. Polygenic Obesity

In the majority of both animals and humans, the genetic contribution to obesity is not a single-gene defect, but is the result of a combination of genetic factors (Chapter 18

summarizes recent advances in the genetics of human obesity with emphasis on leptin and the leptin receptor). As noted earlier, Bouchard, Chagnon and colleagues *(1)* identified more than 300 genes or gene markers that are involved in the etiology of obesity, and 24 chromosomes have genes or gene markers that definitely contribute to obesity *(21)*. Some genes promote obesity and some appear to be protective. The implications of this number of genes being involved in obesity are that there may be dozens to thousands of different types of obesity.

2.3. Clinical Studies

Twin studies provide the most impressive clinical evidence that genetic factors play an important role in the etiology of obesity in humans *(22–25)*. Stunkard et al. *(23)* studied identical and nonidentical twins who were reared together and others who were reared apart. They found a high correlation of body weight among identical twins, even if they were reared apart, and concluded that as much as 70% of the variance of obesity could be attributed to genetic factors. Allison et al. *(24)* confirmed these results in a separate set of 53 twin pairs from multiple countries. They concluded that the heritability of body mass index was between 0.50 and 0.70 *(24)*. Bouchard et al. *(25)* did very careful studies in twins who were isolated in the Canadian wilderness with no access to foods other than those provided by the investigators. Identical twins were overfed for a period of 100 d and the gains in body weight and adipose tissue were evaluated. There was a closer association of both body weight and intra-abdominal adipose tissue (visceral fat) within twin pairs compared to among twin pairs. Recent studies suggest that the heritability of obesity in twins may differ among the sexes *(22)*.

Bogardus et al. *(26)* evaluated potential mechanisms by which genetic factors may contribute to obesity. Studies of resting metabolic rate show that the variation within families is less than the variation among families. This study suggests that energy metabolism is involved in regulating the body weight, and may contribute to the etiology of obesity. Potential candidate genes that could affect energy metabolism are the genes for the various uncoupling proteins. Uncoupling protein-1 (UCP-1) in brown fat plays a major role in energy metabolism in rodents, but there appears to be little brown fat in adult humans. Fleury et al. *(27)* first described the links between uncoupling protein-2 (UCP-2) and obesity and hyperinsulinemia. However, many studies have not been able to associate genetic differences in UCP with the prevalence of obesity *(1,25,28)*. Even when associated, the contribution of UCP mutations to obesity is very small, about 1–3% of the variance.

3. ENVIRONMENTAL FACTORS CONTRIBUTING TO OBESITY

3.1. Environmental Programming of Genetic Expression

Although the gene pool of an individual is fixed at conception, environmental factors may determine how these genes are expressed. There is intense interest on the role of environmental factors during intrauterine life and early infancy in the production of disease later in life.

3.1.1. Intrauterine Factors

The German blockade of the Netherlands during World War II resulted in many pregnant women undergoing starvation during some or most of their pregnancies. People

born during the "Dutch famine" have been followed by their government for many years and in 1976, Ravelli et al. *(29)* reported that there was an increased prevalence of obesity in this population. If mothers were starved during the first 6 mo of pregnancy, the progeny were obese and had the "metabolic syndrome" in later life. If starved in the last 3 mo, progeny tended to be thinner than normals.

Epidemiological studies demonstrate that babies with a low birth weight and particularly babies who are born small for gestational age have a higher prevalence of obesity in adulthood *(30)*. The causes for small-for-dates babies are not clear, but abnormalities of the placenta may play a role. Low birth weight may be the result of a number of environmental factors including maternal undernutrition and smoking. Conversely, babies with high birth weights, and particularly those whose mothers had gestational diabetes, are at increased risk for obesity *(30–32)*.

Animal studies have confirmed that nutritional and hormonal manipulations during intrauterine life lead to obesity and metabolic syndrome in adulthood. Female rats exposed to an intrauterine environment of gestational diabetes produced by giving the drug streptozotocin to their mothers during pregnancy, develop gestational diabetes when they grow up and become pregnant *(33)*. This effect may go out to three generations.

Rhesus monkeys whose mothers were injected with androgen during pregnancy develop obesity, insulin resistance, and a syndrome similar to polycystic ovary syndrome when they become adults *(34,35)*.

3.1.2. Environmental Factors in Early Development

Overfeeding shortly after birth may lead to obesity and diabetes later in life in both humans and animals *(36,37)*. Underfeeding shortly after birth has been postulated to result in obesity later in life in humans, but studies are inconclusive *(36)*.

It is apparent that numerous environmental factors have the ability to alter gene expression. This effect may not be confined to fetal or early life. The phenomenon of sudden weight gain in adult humans and animals in response to environmental stressors that leads to obesity that then persists has been noted by many clinicians. For example, rats fed a high-fat diet for a brief period will become obese, but lose the weight if returned to a chow diet. If the high-fat diet is given for an extended time, permanent obesity ensues. Similar mechanisms may be operating in humans.

3.2. Familial and Ethnic Factors

Environmental factors of a familial nature including ethnic food preferences, eating patterns, dietary composition differences (e.g., high-fat diets), and activity levels, play a role in the etiology of obesity. Studies of energy expenditure in individuals and families show that differences are greater between families vs within families *(26)*. This may be the result of genetic factors affecting energy metabolism, but could also be owing to learned patterns of activity. Different ethnic groups demonstrate marked differences in the character and amounts of foods eaten. Factors that may influence total calorie intake include the frequency and timing of eating and the use of spices, oils and fats, and preferred food sources (e.g., rice, wheat).

3.3. Diet Composition and Eating Patterns

In considering factors that may have played a role in the epidemic of obesity, increases in food intake are high on the list (Table 2). People in the United States and across the

Table 3
Mechanisms of Obesity on High-Fat Diets

1. Increased food intake
   a. Increased energy content of fat for same volume or weight
   b. Greater palatability of high-fat foods
   c. Generally lower chewing and swallowing time for high-fat foods
   d. Lower degree of satiety from high-fat foods
2. Greater efficiency of storage with excess intake
3. Differences among individuals in oxidation of dietary fatty acids

world are becoming more affluent and able to afford more food and more commercially prepared foods, which tend to have a higher energy density. Ease of access to food has increased with more restaurants, especially fastfood restaurants that have quite inexpensive, high-fat, high-calorie foods as their staples. Portion sizes have increased since the 1980s. With more leisure-time activity, especially watching TV, food intake increases.

Excessive calorie intake above daily energy requirements is necessary for the development of obesity, but it is incorrect to assume that simple overeating is responsible for all obesity. As noted in Chapter 19, there is evidence that the quality of the foods ingested also is important in producing obesity. In animal studies, diets high in fat produce a greater degree of obesity than those high in carbohydrate (CHO). There are several reasons that increased dietary fat produces obesity (Table 3). Fat contains more than twice as many calories per gram as protein or CHO. Eating the same volume of food results in much greater energy intake on a high-fat diet than on a low-fat diet. Also, high-fat foods are more palatable than low-fat foods. Fat adds a desirable "mouth feel" to foods that animals and humans prefer. Fatty foods are usually low in dietary fiber, are softer, and require less time to chew and swallow than other types of foods. This is particularly true of high-fat desserts. Because there is less processing time for high-fat foods, it is easier to eat larger amounts. Finally, there is evidence that high-fat foods do not produce satiety as well as do high-CHO foods *(38)*. Experiments in which subjects were fed a high- or low-fat preload before a meal showed that total energy intake was greater with the high-fat preload. The subjects did not perceive the increased energy of the preload, ate a comparably sized meal, and thus obtained a greater total energy intake. Tremblay et al. *(39)* noted that the combination of a high-fat appetizer and simultaneous consumption of alcohol results in a significantly higher total energy intake as compared to an equicaloric low-fat, no-alcohol appetizer.

The predisposition to gain fat on a high-fat diet is partially genetically determined. West et al. *(40)* studied nine strains of inbred mice. Within each strain, half of the mice were fed a high-fat diet, the other half was fed a low-fat diet, and the differences in weight gain and fat gain were determined. There were marked differences in weight and fat gain, supporting the Flatt hypothesis, although differences in food intake contributed to the fat gain. Rissanen et al. *(41)* reported on human twins who differed in body weight and had different preferences for dietary fat. The fatter twin preferred and ate more fat than the leaner twin. This suggests that although genetic factors are important, environmental factors play a major role in the preference for dietary fat and its contribution to obesity.

Ravussin and Smith *(42)* postulated that some humans, upon gaining weight, lose the ability to make new fat cells to store the excess fat in adipose tissue, so they begin to deposit fat in muscle, liver, and other tissues. This produces insulin resistance and contributes to the metabolic syndrome and to diabetes. More studies are needed to prove this theory.

Fat is stored more efficiently than CHO or protein when the diet contains more energy than is necessary for weight maintenance *(43–46)*. The cost of storing excess fat as a percentage of ingested energy is significantly less than the cost of making fat from CHO or protein. The capacity of different people or animals to oxidize fat in the diet to match fat intake varies from individual to individual. Many animals or humans are able to increase fat oxidation to match fat intake only after some degree of fat storage. Flatt *(44,45)* has postulated that on changing from a low- to a high-fat diet, individuals who lack the ability to match fat oxidation to fat intake will gain weight. The rationale for this hypothesis is that there are only two fates for ingested fat: oxidation or storage. Humans have a very limited capacity to convert any of the energy in fat to either protein or CHO *(44,45)*. Therefore, if the percentage of fat in the diet increases, fat oxidation must immediately increase to prevent storage of the additional fat calories.

The ability to oxidize fat apparently is influenced by genetic factors. Boozer et al. *(47)* demonstrated that not all calories are equal when they fed four groups of rats a similar number of kcal, but different percentages of fat. The rats on the high-fat diet (48% of kilocalories as fat) gained almost 50% more body fat over a 6-wk period than rats on an equicaloric low-fat diet (12% of kilocalories as fat). Similar observations have been made in humans. Danforth noted that comparable weight gain with overfeeding required many fewer kilocalories on a high-fat diet than on a low-fat diet *(48)*. Lissner et al. *(49)* kept calories constant, but switched from a high-fat to a low-fat diet, and noted weight loss. Prewitt et al. *(50)* also switched from a high-fat to a low-fat diet and found that the subjects could not maintain body weight, despite increasing the daily energy intake of low-fat foods.

The studies above suggest that the level at which body weight is regulated is determined in part by the percentage of fat calories in the diet. Not all investigators agree. The arguments pro and con are summarized in two editorials by Bray and Popkin vs Willett, respectively *(51,52)*.

3.4. Amount of Physical Activity

The amount of daily physical activity clearly contributes to the maintenance of body weight (*see* Chapter 13 on the role of exercise). Obese people are less active than lean people. Prentice and Jebb *(53)* observed that obesity is more common in lower vs upper socioeconomic groups, and that the factor that correlated best with the degree of obesity was activity. Degree of obesity was negatively correlated with daily physical activity.

Explanations for the epidemic of obesity focus on changes in activity since the 1980s in the United States (Table 2). With increasing affluence and mechanization, there are more cars, labor-saving devices, and less need for heavy labor. Greater penetration in homes of televisions, computers, and computer games increases sedentary time, especially for children. Fear of violence, secondary to drug dealing, and fear of kidnapping influence parents to keep children in the house or to limit outside exercise to organized sports. Long car travel to little league games, soccer practice, and so forth mean less actual time playing outside for children.

It is important to recognize that greater activity levels do not necessarily require greater amounts of formal exercise. Although all exercise is activity, the activities of daily living make an important contribution to total daily energy expenditure. Zurlo et al. *(54)* studied subjects in their indirect calorimeter facility and found that spontaneous activity, or "fidgeting," was correlated with body weight and adiposity. The difference in energy expenditure from "fidgeting" amounted to as much as 600 kcal/d, an amount that could account for a sizable difference in body weight. These findings were confirmed by Levine et al. *(55)*. It is not clear whether deliberately attempting to increase fidgeting will assist in weight loss or maintenance, but encouragement by physicians for patients to try as much as possible to minimize inactivity may be helpful. Epstein et al. *(56)* found that this strategy was useful in treating childhood obesity. Children were limited to a fixed amount of time in sedentary activities, and left to their own devices during nonsedentary times. Another group was assigned specifically to exercise. The decreased sedentary-behavior group had a decrease in overweight of 20 vs 13% for the exercise group, and at 1 yr, the differences were 19 vs 9%. Gortmaker et al. *(57)* and Robinson et al. *(58)* evaluated the role of TV viewing on obesity in children. TV clearly contributes to obesity in children, and reducing time watching TV was effective in preventing obesity.

3.5. Drugs

It is not well recognized, but numerous drugs may produce an increase in food intake or body weight. Glucocorticoids produce fat gain, particularly truncal adiposity, in a high percentage of users. Insulin and oral hypoglycemics (sulfonylureas and thiazolidinediones) promote weight and adipose tissue gain in diabetics. Phenothiazines, atypical antipsychotic agents, and some antidepressants, such as tricyclics and selective serotonin reuptake inhibitors, may produce weight gain. Cyproheptadine and valproic acid also have been implicated in the etiology of obesity in some patients. Finally, β-adrenergic antagonists such as propranolol are postulated to reduce sympathetic nervous system activity and lead to weight gain or difficulty in losing weight.

3.6. Stress

3.6.1. Emotional Stress

Several types of stress may contribute to obesity; perhaps the most studied of which is emotional stress. Depression is associated with weight gain in about 10 to 20% of cases. Weight gain is particularly common in seasonal depression (seasonal affective disorder [SAD]), which occurs in the winter months predominantly in northern latitudes. Some studies have suggested that SAD and its associated weight gain may be treated by exposure to artificial sunlight. On an anecdotal basis, many patients report that the onset of obesity occurred with some major emotionally stressful event in their lives. However, it is difficult to identify a suitable control group for such events. Multiple studies have shown that surgery, such as tonsillectomy, is associated with an increased incidence of obesity compared to unoperated controls in the period after surgery *(59,60)*.

3.6.2. Central Nervous System Damage

Injury to selected areas of the central nervous system (CNS) from accidents or neoplasms is known to cause obesity in a small number of patients *(61)*. Probably the most common type of injury is head trauma from automobile accidents. Pituitary or hypotha-

lamic tumors are the most common types of neoplasms associated with the onset of obesity *(61)*.

3.6.3. Surgical Procedures

Surgical procedures in the CNS may produce trauma to critical areas and produce obesity *(61)*. However, there are many anecdotal cases of obesity following surgery on other parts of the body, as noted for obesity after tonsillectomy. It is unclear whether damage to the CNS occurs during surgery in these cases, or if there is some other factor that alters CNS biochemistry. Animal studies show that lesions of the ventromedial hypothalamus, for example, leads to massive obesity, which is then defended by the body's normal mechanisms against starvation *(62)*.

3.6.4. Infectious Diseases

An ominous potential etiology of obesity is that of infectious disease. Bray *(61)* reported a small number of patients who developed obesity after tuberculosis or other infections of the CNS that produced anatomical damage. Such bacterial infections causing obesity are rare and the CNS mechanisms easily understood. What is more disquieting is the possibility that viral infections may cause obesity. There are seven known animal models of virus-induced obesity. Lyons et al. *(63)* described massive obesity that occurred in mice after infection with canine distemper virus, a virus that is similar to human measles virus. Carter et al. *(64)* described obesity and stunting in chickens resulting from a rous-associated virus. Several strains of scrapie agent produce obesity, apparently by damaging the brain *(65)*. Borna virus produces widespread abnormalities including lympho-monocytic inflammation of the hypothalamus, hyperplasia of pancreatic islets, elevated serum glucose and triglycerides levels, stunting, and an increased body fat *(66)*. Dhurandhar et al. *(67)* described an unusual type of obesity in chickens in India owing to an avian adenovirus. This adenovirus caused the deposition of increased visceral fat, but paradoxical reductions in serum cholesterol and triglycerides. In a small study, about 20% of obese humans selected randomly from an obesity treatment program in Bombay, India, had antibodies that reacted with this chicken adenovirus *(68)*. The patients with antibodies weighed significantly more and had significantly lower serum cholesterol and triglycerides. Dhurandhar and Atkinson demonstrated that infection with a human adenovirus, Ad-36, produced increased adipose tissue and paradoxically lower serum cholesterol and triglycerides in chickens, mice, and nonhuman primates *(5,6)*. Obese humans who have antibodies to Ad-36 have lower serum cholesterol and triglycerides than do antibody negative individuals *(69)*. More research is urgently needed to determine whether obesity in humans may be due to viral infections.

4. ENDOCRINE AND METABOLIC DISEASES AS AN ETIOLOGY OF OBESITY

Endocrine disease is a commonly sought etiology of obesity, but is rarely found (Chapter 21 includes discussions of the evaluation of obese patients in obesity treatment programs). Thyroid disease is most often blamed for causing obesity, particularly in adolescents. However, hypothyroidism very rarely produces significant weight gain and treatment of thyroid deficiency rarely results in much weight loss. In the experience of the author, the presence of hypothyroidism makes it difficult for patients to lose weight

while participating in an obesity treatment program, but with thyroid hormone replacement, weight loss in response to diet, exercise, and behavior modification including diet and exercise, with or without drug therapy, proceeds as predicted. An unusual cause of obesity reported by anecdote is hyperthyroidism. The author has taken care of four patients who reported the onset of weight gain simultaneously with the onset of symptoms suggestive of hyperthyroidism, and who were documented with elevated thyroid hormone levels and depressed thyroid-stimulating hormone (TSH) levels. Because thyroid disease is commonly found in obese patients, it is wise to check the serum thyroxine (T4) and TSH before starting a weight-reduction program.

Cushing's syndrome resulting from treatment with exogenous glucocorticoids is the most common form of endocrine obesity. Weight gain with glucocorticoid treatment may be large, in the range of 25 to 50 kg in extreme cases. Weight gain of these levels in spontaneously appearing Cushing's disease (pituitary tumor) or Cushing's syndrome owing to an adrenal adenoma certainly may be seen, but these diseases are exceedingly rare. Insulinomas are another rare cause of endocrine obesity. They promote deposition of adipose tissue and overeating due to periods of hypoglycemia.

Pseudohypoparathyroidism, hypothalamic disease, and hypogonadism are very rare causes of obesity. Although the average physician is not likely to ever see such patients in the primary care of medicine, endocrine diseases should be kept in mind because they are associated with treatable conditions that may markedly improve quality of life for these unfortunate people.

5. ABNORMAL REGULATION OF BODY WEIGHT OR BODY FAT

Keesey *(62,70)* advanced the hypothesis that individuals have a "body weight set point" that represents a body weight or an adipose tissue mass that is defended from change. Not all authors agree with this concept *(44,45,71)*. Flatt *(44,45)* suggested that the apparent "regulation" of body weight is the result of a confluence of factors that eventually lead to a stable body weight. If the equilibrium is disturbed, there are compensatory changes and a "settling" of the body weight or body fat at a new level. In the final analysis, the argument may be about semantics, but it is quite clear that the body weights of animals and humans do fluctuate in a fairly narrow range, and that single perturbations such as reduction of daily energy intake promote biochemical changes in the body that limit the reduction in weight and adipose tissue mass *(62,70)*. Conversely, overfeeding results in compensatory changes that limit weight gain. These biochemical changes, particularly in the case of underfeeding, are perfectly understandable survival traits that undoubtedly have been incorporated into the gene pool of all living creatures to deal with the periodic shortages of food or even famines that plagued the world for most of the time that life has been on Earth. Because surpluses of food have been rare throughout history, it would not be surprising that the mechanisms to deal with overfeeding are not as powerful as those dealing with underfeeding. These biochemical responses cause little inconvenience or health problems for the normal-weight individual who wishes to lose weight for cosmetic purposes. However, for the significantly obese person who needs to lose weight for health purposes, these "protective" mechanisms are frustrating indeed.

The discovery of leptin and its effects on body fat stores has given credence to the concept of regulation of fat stores in the body *(7–19)*. Leptin signals the brain regarding the amount of fat that is stored in the body, and abnormal genes for leptin or leptin

receptors are associated with massive obesity in humans and animals. Treatment with leptin reduces body fat content of genetically obese mice, normal mice, and mice made obese by feeding a high-fat diet *(11–13)*. However, serum leptin levels are strongly correlated with adipose tissue mass *(19)*, suggesting that leptin "resistance" occurs. These data illustrate that leptin is not part of a simple negative feedback regulatory loop.

It appears that lowering the fat content of the diet from 35% of kilocalories, which is the typical American diet, to about 20% or less, which is the diet of primitive cultures, may lower the level at which body weight is defended. Likewise, exercise or increased activity may lower the defended body weight. These have been incorporated into behavioral treatments of obesity, but with a poor success rate. Obesity drugs and obesity surgery, particularly jejuno-ileal bypass surgery and gastric bypass surgery, are more passive methods of lowering the level at which body weight is regulated *(72,73)*. Other chapters (*see* Chapter 20) in this book discuss the success of treatment of obesity with these methods. More research is needed to determine if there is active regulation of body weight as postulated in the "body weight set point" theory, or if weight regulation is simply an interaction of a variety of factors that influence food intake, activity levels, and metabolic rate.

6. CONCLUSION

Obesity is an exceedingly complex group of diseases and probably should be characterized as a syndrome. With research in the area only just begun, more than 350 genes or gene markers have been identified that are associated with obesity and may contribute to the etiology of obesity in animals and humans. This suggests that there may be thousands of different types of obesity. The presence of a genetic tendency to obesity does not mean that obesity is inevitable, since environmental factors are critical for the expression of the genetic potential. Physicians should be aware of the factors that contribute to obesity that can be manipulated, such as dietary and exercise patterns, endocrine and metabolic diseases, and drugs. Research into obesity and its etiologies has been sparse, but the accelerating pace of research into obesity promises to provide new answers and point the way to new treatments for obesity.

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