Medical Progress

OBESITY

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Obesity is the most common and costly nutritional problem in the United States, affecting approximately 33 percent of adults.1 Health care costs directly attributable to obesity amount to approximately $68 billion per year, and an additional $30 billion per year is spent on weight-reduction programs and special foods.2 Nevertheless, treatment directed toward the long-term reduction of body weight is largely ineffective, and 90 to 95 percent of persons who lose weight subsequently regain it.3,4

The level of energy storage, or fatness, at which the risk of morbidity increases is determined on an actuarial basis. The body-mass index (the weight in kilograms divided by the square of the height in meters) is easy to calculate and is sufficiently correlated with direct measures of body fatness (e.g., as measured by hydrodensitometry) to be useful in defining obesity clinically.5 A body-mass index greater than 28 is associated with a risk of morbidity, such as stroke, ischemic heart disease, or diabetes mellitus, that is three to four times the risk in the general population.6 A central distribution of body fat (ratio of waist circumference to hip circumference, >0.90 in women and >1.0 in men) is associated with a higher risk of morbidity and mortality than a more peripheral distribution of body fat (waist:hip ratio, <0.75 in women and <0.85 in men) and may be a better indicator of the risk of morbidity than absolute fat mass.7 Obesity in childhood appears to increase the risk of subsequent morbidity, whether or not obesity persists into adulthood.8

This review examines our current understanding of the pathogenesis of obesity, as well as other important aspects of this topic. Recent comprehensive reviews are also available:2,5,9-11

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REGULATION OF ENERGY STORAGE, INTAKE, AND EXPENDITURE

The primary form in which potential chemical energy is stored in the body is fat (triglyceride) (Table 1). The high caloric density and hydrophobic nature of triglyceride permit efficient energy storage without adverse osmotic consequences. The first law of thermodynamics, which states that the amount of stored energy equals the difference between energy intake and work, is uniformly applicable to biologic systems. The amount of triglyceride in adipose tissue is the cumulative sum over time of the differences between energy (food) intake and energy expenditure (mainly resting metabolism and physical activity). Although homeostatic mechanisms keep this difference very close to zero (see below), very small imbalances over a long period can have a large cumulative effect. The current availability of highly palatable, calorically dense foods and a sedentary lifestyle promote weight gain. For example, nonobese adults ingest about 900,000 kcal of food per year. About 3500 kcal of chemical energy is contained in 0.45 kg (1 lb) of adipose tissue. If intake exceeded expenditure by 2 percent daily for a year, the result would be an increase of 18,000 kcal, or approximately 2.3 kg (5 lb). Because energy expenditure increases as weight increases, the weight gained would somewhat compensate for this imbalance. However, the 9.1 kg (20 lb) of weight gained by the average American man or woman between the ages of 25 and 55 years represents a remarkably small net imbalance between energy intake and expenditure—an excess intake of about 0.3 percent of ingested calories.13

This degree of control is achieved by coordinate effects on energy intake and expenditure mediated through endocrine and neural signals that emanate from adipose tissue14 and the endocrine,15 neurologic,16 and gastrointestinal17,18 systems and are integrated by the central nervous system.16 Short-term (daily) food intake is not closely correlated with energy expenditure or energy stores in adults19 or children.20 One or more mechanisms are needed to integrate short-term determinants of energy intake (e.g., hepatic glycogen content, fatty-acid oxidation, and plasma glucose17,21) with more direct monitoring of long-term energy stores (fat mass).22,23 Such integration is central to the regulation of body fat stores (Fig. 1 and 2).

The relative constancy of energy storage is the result of the coordinate activity of a complex system with components ranging from the highest cortical centers to the adipocytes; no single node or loop in
the system functions in isolation. As shown in Figure 2, a large number of factors originating throughout the body send afferent signals to a smaller number of functional centers in the central nervous system, which then mediate interactions with efferent pathways to regulate energy expenditure (e.g., through the sympathetic and parasympathetic nervous systems and thyroid hormones) and energy intake (through eating behavior).24,26,27,30

The substances shown in Figure 2 interact at many levels. For example, the effect of cholecystokinin on satiety is increased by estradiol and insulin and is dependent on parasympathetic afferents,31,32 and the release of insulin is increased by cholecystokinin and parasympathetic efferents and inhibited by sympathetic efferents.18,33 The redundancy and interactions within this system make it unlikely that pharmacologic or surgical manipulation of a single component will lead to long-term resolution of obesity.

**NEUROPHYSIOLOGY OF FEEDING**

Numerous biopsychological factors impinge on eating behavior. The arcuate and paraventricular nuclei in the ventromedial hypothalamus are parts of a system integrating body composition with energy intake and expenditure.35 Afferent neural (vagal and cholinergic) stimuli and hormonal stimuli (e.g., insulin, cholecystokinin, leptin, and glucocorticoids) related to metabolic status are received in the hypothalamus, where they modulate the release of peptides known to affect food intake and efferent signals to the hypothalamic–pituitary axis (resulting in endocrine mediation of fuel disposition) and the autonomic nervous system (resulting in energy expenditure and insulin release).36 In rats, lesions of the ventromedial hypothalamus (or the median forebrain bundle) that disrupt these nuclei and contiguous tracts cause hyperinsulinemia, hyperphagia, and hypometabolism. The resulting obesity is maintained by

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**Table 1. Energy Storage in a 70-kg Man and a 30-kg Child.**

<table>
<thead>
<tr>
<th>Energy</th>
<th>Site</th>
<th>70-kg Man* (kg kcal stored)</th>
<th>30-kg Child† (kg kcal stored)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglyceride</td>
<td>Adipose tissue</td>
<td>15 105,000</td>
<td>4.5 31,500</td>
</tr>
<tr>
<td>Protein</td>
<td>Muscle</td>
<td>6 25,000</td>
<td>1.5 6,250</td>
</tr>
<tr>
<td>Glycogen</td>
<td>Liver and muscle</td>
<td>0.19 760</td>
<td>0.13 500</td>
</tr>
<tr>
<td>Glucose or lipid</td>
<td>Body fluids</td>
<td>0.025 100</td>
<td>0.011 40</td>
</tr>
</tbody>
</table>

*Data are from Rosenbaum and Leibel.4†Data are from Cahill.12

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**Figure 1. Metabolic Changes after Weight Gain or Loss in Adults.**

Data are from Leibel et al.,24,25 Landsberg and Young,26 and Danforth and Burger.27

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appropriate adjustments of food intake and energy expenditure, suggesting that the lesions have altered a set-point mechanism for regulating body weight. Although there has been considerable interest in dietary composition and weight fluctuations as determinants of body composition, these factors do not have major roles in the pathogenesis of obesity. Both protein and carbohydrate can be metabolically converted to fat, and there is no evidence that changing the relative proportions of protein, carbohydrate, and fat in the diet without reducing caloric intake will promote weight loss. However, fat has a higher caloric density than protein and carbohydrate, and its contribution to the palatability of foods promotes the ingestion of calories.

**METABOLIC EFFECTS OF WEIGHT PERTURBATION**

The responses of both lean and obese humans to experimental perturbation of body weight support the hypothesis that body fat content is regulated, making it unlikely that behavior can be the sole determinant of obesity. The 24-hour energy expenditure per unit of lean body mass is similar in lean and obese subjects at their usual body weight. Small (10 percent) decreases in body weight result in declines in energy expenditure that persist despite a caloric intake that is sufficiently reduced to maintain the lower weight. Thus, a formerly obese person requires approximately 15 percent fewer calories to maintain a “normal” body weight than a person of...
the same body composition who has never been obese.\textsuperscript{25,42,43} This decline in 24-hour energy expenditure reflects approximately an 18 percent decrease in resting energy expenditure (resting cardiorespiratory work, maintenance of transmembrane ion gradients, and so forth) and approximately a 25 percent decrease in nonresting energy expenditure (energy expended in physical activity), suggesting that the reductions in energy expenditure may be due in part to changes in the efficiency with which skeletal muscle converts chemical energy to mechanical work.\textsuperscript{44} These reductions in energy expenditure persist in adults who have maintained a reduced body weight for three to five years.\textsuperscript{43} Lean and obese subjects have equivalent increases in energy expenditure during the maintenance of an increased body weight.\textsuperscript{25}

In both obese and lean subjects who lose weight, there is an almost inevitable recidivism, with the lost weight rapidly regained.\textsuperscript{54} The regained weight is probably due to physiologic factors that act to maintain the usual body weight, even when it is high.

In genetically obese rodents (see below), metabolic efficiency is increased or calories are preferentially stored as fat during the first few weeks of life, before the development of obesity.\textsuperscript{45} Some adults\textsuperscript{46} and children\textsuperscript{47} who later become obese have lower rates of energy expenditure than nonobese persons. In addition, both formerly obese adults\textsuperscript{48} and those who later become obese\textsuperscript{46,49} oxidize fat more slowly than do obese adults or nonobese adults who do not later become obese, making the formerly or subsequently obese more prone to accumulate fat. The observation that a decreased expenditure of energy and an increased propensity to store fat may precede the development of obesity (i.e., that the subsequently obese person is similar to the formerly obese person) suggests that the extra body fat in the obese person in some way corrects for low energy expenditure.

**FUTILE CYCLES**

In animals, some regulation of energy balance is achieved through metabolic cycles that consume ATP without producing useful biochemical work (futile cycles) — for example, simultaneous lipolysis and glyceride synthesis in fat cells and glycolysis and gluconeogenesis in the liver.\textsuperscript{50} Although small changes in energy expenditure through these cycles could theoretically affect body weight over time, there is little evidence that the cycles are important in energy homeostasis in humans.\textsuperscript{51} Substrate oxidation uncoupled from ATP generation in brown adipose tissue has also been hypothesized to be a mechanism for regulating body energy stores.\textsuperscript{52} Although brown adipose tissue is present in neonates, the extent to which it persists into adulthood and whether its amount or function in obese or formerly obese persons differs from that in persons who have never been obese are controversial.\textsuperscript{53} A protein (uncoupling protein 2) has recently been identified that uncoupled substrate oxidation from the generation of ATP in white adipose tissue and muscle and that is up-regulated in mice fed high levels of fat.\textsuperscript{54,55} These findings suggest but do not prove that uncoupled mitochondrial respiration may act as an energy buffer in humans.\textsuperscript{56}

**CHEMICAL MEDIATORS OF ENERGY HOMEOSTASIS**

**Insulin**

Plasma insulin concentrations are proportional to the adipocyte volume.\textsuperscript{52} Insulin gains access to the central nervous system through a saturable transport system and reduces food intake by inhibiting the expression of neuropeptide Y, enhancing the anorectic effects of cholecystokinin and inhibiting neuronal norepinephrine reuptake.\textsuperscript{15,57} Insulin does not reduce neuropeptide Y messenger RNA (mRNA) in genetically obese Zucker \textit{(fa/fa)} rats.\textsuperscript{15,16} Since \textit{fa} is a mutation in the leptin receptor,\textsuperscript{58} the lack of an effect of insulin on neuropeptide Y mRNA in \textit{fa/fa} rats suggests that insulin reduces food intake through an effect on leptin-mediated signaling (see below).

**Cholecystokinin**

Cholecystokinin, a peptide secreted from the duodenum in the presence of food, reduces food intake.\textsuperscript{18} There are two types of cholecystokinin receptors: type A predominates in the gastrointestinal system, and type B predominates in the brain, especially in the nucleus of the tractus solitarius and area postrema.\textsuperscript{39} Only type A receptors bind the bioactive C-terminal octapeptide of cholecystokinin. The anorectic effect of cholecystokinin is blocked by abdominal vagotomy,\textsuperscript{60} suggesting that the primary site of action of cholecystokinin is in the periphery. Cholecystokinin does not cross the blood–brain barrier\textsuperscript{61} — further evidence that duodenal cholecystokinin does not directly affect central systems of energy homeostasis. However, cholecystokinin is synthesized in the brain, and intracranial administration of cholecystokinin results in a feeling of satiation.\textsuperscript{62}

**Other Endocrine and Peptide Signals**

Numerous other hormones modulate fat storage through their effects on energy intake (e.g., glucocorticoids and glucagon), energy expenditure (e.g., androgens and thyroid and growth hormones), or the partitioning of stored energy between lean tissue and fat.\textsuperscript{63} In addition, in some genetically obese animals or those with obesity due to experimentally induced lesions in the ventromedial hypothalamus, adrenalectomy ameliorates the obesity, suggesting that treatment with glucocorticoid antagonists may be effective in some cases of obesity in humans.\textsuperscript{64} Other gut peptides, including gastrin-releasing peptide, neuromedin B, enterostatin, and amylin, may
also contribute to the regulation of energy balance in humans.18

Leptin

Leptin, encoded by the Lep gene (Table 2),65 is synthesized in and secreted from adipose tissue and is a potential afferent signal of fat stores. In humans this gene is referred to as LEP. Systemic or intracerebroventricular administration of leptin reduces food intake and increases energy expenditure, resulting in reduced body fat and restoration of insulin-sensitive glucose disposal in ob/ob (leptin-deficient) mice.56-69 Very high doses of leptin have similar effects in nonobese animals.70 Administration of leptin in rats deprived of food corrects many of the neuroendocrine changes (e.g., the decrease in the release of thyroid hormone) that occur as a result of food deprivation71 but does not alter the rate of weight loss. By virtue of its effects on growth hormone–releasing and gonadotropin-releasing hormones, the leptin-mediated signal may provide a critical link between somatic energy stores, on the one hand, and growth and fertility, on the other.72 The characteristics of this system are consistent with the concept of a lipostatic set point for weight regulation.22

The expression of leptin in adipose tissue is increased by insulin,73 glucocorticoids,74 and estrogens and is decreased by β-adrenergic agonists and possibly by androgens.75,76 Leptin probably contributes to energy homeostasis in part by decreasing neuropeptide Y mRNA or blocking its action as an appetite stimulant (see below). However, transgenic mice lacking the neuropeptide Y gene still respond to the anorexigenic effects of leptin,27 suggesting that it also acts through mechanisms that are independent of neuropeptide Y.

Although leptin exerts potent antiobesity effects in leptin-deficient rodents, its role in the pathogenesis or treatment of obesity in humans is unclear. Tentative linkage of some measures of adiposity to the region of the LEP gene has been reported in some groups of extremely obese whites78,79 and in a Hispanic population80 but not in the Pima Indians, in whom obesity and diabetes are extremely common.81 However, most obese persons do not have any abnormalities in the coding sequence for leptin.82,83

Plasma leptin concentrations are increased in obese humans in direct proportion to body fat mass.70 Within a given fat depot, the expression of leptin mRNA is proportional to adipocyte volume,84 and rates of leptin production per unit of fat mass and of leptin clearance from the circulation are similar in obese subjects and those who have never been obese.85 Unlike ob/ob mice, in which the administration of leptin normalizes insulin-mediated glucose disposal, obese subjects with high plasma leptin concentrations have a resistance to insulin,86 and leptin diminishes the sensitivity to insulin in human cells in vitro.87

Although rodents are more sensitive to intracerebroventricular administration of leptin than to peripheral administration,69 whether leptin must enter the cerebrospinal fluid to act in the brain is not known. In nonobese subjects, the cerebrospinal fluid leptin concentration is about 5 percent of the plasma concentration, whereas in obese subjects, the percentage is lower, apparently because of the saturation of the system mediating the transfer of leptin from plasma to cerebrospinal fluid.88 In addition, the proportion of circulating leptin that is bound to protein in lean subjects is approximately twice that in obese subjects.89 The disproportionately low cerebrospinal fluid leptin concentrations in obese subjects may reflect a degree of resistance to leptin.

During weight loss, plasma leptin concentrations and the expression of leptin mRNA in adipose tissue are reduced to a level below that predicted by the change in fat mass,90,91 No significant changes in plasma leptin concentrations, other than those predicted by the increased fat mass, have been noted.

Table 2. Mutations in Obese Rodents.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Gene Product</th>
<th>Rodent Homologue</th>
<th>Chromosome</th>
<th>Human Homologue</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lep</td>
<td>ob</td>
<td>Leptin</td>
<td>6 (mouse)</td>
<td>7q31.3</td>
<td>Central effects resulting in decreased food intake and increased energy expenditure</td>
<td></td>
</tr>
<tr>
<td>Lepr</td>
<td>db</td>
<td>Leptin receptor</td>
<td>4 (mouse)</td>
<td>1p32</td>
<td>Leptin signal processing, transport or clearance (?)</td>
<td></td>
</tr>
<tr>
<td>Lepr</td>
<td>fa</td>
<td>Leptin receptor</td>
<td>5 (rat)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cpe</td>
<td>fat</td>
<td>Carboxypeptidase E</td>
<td>8 (mouse)</td>
<td>11p15</td>
<td>Prohormone (including neuropeptide) processing</td>
<td></td>
</tr>
<tr>
<td>Tub</td>
<td>tub</td>
<td>Phosphodiesterase</td>
<td>7 (mouse)</td>
<td>4q32 (?)</td>
<td>Hypothalamic cellular apoptosis (?)</td>
<td></td>
</tr>
<tr>
<td>Agouti</td>
<td>Ay</td>
<td>Agouti signaling protein</td>
<td>2 (mouse)</td>
<td>20q11.2</td>
<td>Blocking of melanocortin-4 receptor</td>
<td></td>
</tr>
</tbody>
</table>

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during weight gain\textsuperscript{93} (and unpublished data). The relation between fat mass and plasma leptin is not altered by the maintenance of an elevated or reduced body weight\textsuperscript{94} (and unpublished data). Variations in the fat content of isocaloric diets have no effect on plasma leptin concentrations.\textsuperscript{94} No statistically significant correlations have been noted between plasma leptin concentrations per unit of fat mass and measures of 24-hour energy expenditure per unit of fat-free mass at usual body weight or after a loss or gain of weight.\textsuperscript{92,95}

In the aggregate, these findings suggest that the primary role of leptin may be to indicate whether somatic fat stores are sufficient for growth and reproduction. If the stores are inadequate — as reflected by a decline in plasma leptin concentrations to a level below a threshold that may be genetically and developmentally set — the result is hypophagia, low energy output, and infertility. Plasma leptin concentrations above this threshold may have a minimal physiologic effect or none. Hence, obese humans with high plasma leptin concentrations have neither hypophagia nor hypermetabolism.

**Leptin Receptors**

If leptin is a major afferent signal to the central nervous system regarding fat mass, human obesity may be the result of mutations or allelic variations in the leptin receptor, exemplified in diabetic (\textit{db/db}) mice\textsuperscript{96} and Zucker fatty (\textit{fa/fa}) rats.\textsuperscript{97} The leptin receptor is widely expressed (in the brain, lungs, kidneys, muscle, and adipose tissue). Distinct forms of the receptor apparently serve to transport leptin in the circulation and across cell membranes, and one isoform couples ligand binding to intracellular signaling of the action of leptin.\textsuperscript{98} If obesity in humans were due to a mutation affecting the ability of the leptin receptor to couple to its effector molecules, then obese persons might be expected to have higher plasma leptin concentrations than predicted on the basis of their fat mass, but this is not the case.\textsuperscript{76}

**Neuropeptide Y**

Neuropeptide Y links afferents reflecting the nutritional status of the organism from the endocrine, gastrointestinal, and central and peripheral nervous systems to effectors of energy intake and expenditure (Fig. 2). The peptide is synthesized by cell bodies in the arcuate nucleus of the hypothalamus and transported axonally to the paraventricular nucleus, where the highest concentrations are found.\textsuperscript{99} (Neuropeptide Y is also synthesized and released from the adrenal gland and sympathetic nerves, but it does not cross the blood–brain barrier.\textsuperscript{100})

Neuropeptide Y is a potent central appetite stimulant. The expression of neuropeptide Y mRNA is increased by insulin and glucocorticoids and decreased by leptin and estrogen.\textsuperscript{100,101} In rodents, food deprivation is associated with an increase in hypothalamic production of neuropeptide Y mRNA.\textsuperscript{102} The injection of neuropeptide Y into the paraventricular nucleus in rats stimulates food intake and increases lipoprotein lipase activity in white adipose tissue while decreasing sympathetic nervous system activity and thermogenesis in brown adipose tissue.\textsuperscript{103} Thus, centrally administered neuropeptide Y produces coordinate effects on energy intake and output that favor weight gain. Despite evidence of the physiologic importance of neuropeptide Y in energy homeostasis, neuropeptide Y–knockout mice have normal body fat and food intake, with normal hyperphagia when food is withheld.\textsuperscript{77} These findings highlight the extraordinary redundancy of systems regulating caloric storage.

**GENETIC FACTORS**

In most humans, body fitness is a continuous, quantitative trait that reflects the interactions of development and environment with genotype. Studies in twins, adoptees, and families\textsuperscript{4} indicate that as much as 80 percent of the variance in the body-mass index is attributable to genetic factors. Heritability is estimated to be as high as 30 to 40 percent for factors such as adipose-tissue distribution (the ratio of upper-body fat to lower-body fat), physical activity, resting metabolic rate, changes in energy expenditure in response to overeating, certain aspects of eating behavior, food preferences, lipoprotein lipase activity, maximal insulin-stimulated glyceride synthesis, and basal rates of lipolysis.\textsuperscript{4,5}

Given the importance of energy stores to individual survival and reproductive capacity,\textsuperscript{4,104} the ability to conserve energy in the form of adipose tissue would at one time have conferred a survival advantage.\textsuperscript{105} For this reason, humans are presumably enriched with genes that favor energy intake and storage and diminish energy expenditure. However, the combination of easy access to calorically dense foods and a sedentary lifestyle has made the metabolic consequences of these genes maladaptive.\textsuperscript{105} The increasing prevalence of obesity in the United States (approximately a 30 percent increase in the past decade),\textsuperscript{1,106} the inverse relation between obesity and social class, and the secular trend toward increasing obesity\textsuperscript{4} provide clear evidence of potent environmental influences on adiposity. Although numerous environmental factors, such as television watching and low family income,\textsuperscript{4} have been implicated, no single factor is causative. Nevertheless, the increasing prevalence of obesity clearly indicates that environmental manipulation (e.g., changes in diet and physical activity) may alter or prevent some aspects of obesity.

Thus, aside from several single-gene disorders resulting in obesity (e.g., the Prader–Willi, Bardet–Biedl, Alström, and Cohen syndromes), each of which
is associated with other striking dysmorphic features, obesity is probably due in most cases to subtle alterations in interactions between genetic and environmental factors that favor the net deposition of calories as fat. Segregation analyses in which the familial transmission of obesity was examined have provided evidence of the segregation of major genes that influence the body mass index (accounting for 20 to 35 percent of variation). The heritability of early-onset obesity may be considerably higher than that of adult-onset obesity. What is likely to be most strongly inherited is the rank order of the amount of body fat per unit of lean body mass among persons in a given environment.

Obesity is an example of a phenotype that is not likely to be attributable to a single gene unless it is extreme (body-mass index, >60) or present in an isolated population group. Because obesity can develop only from an excess of energy intake over expenditure, the search for candidate obesity genes has focused on those that have a role in energy metabolism. Extended families, sibling pairs, and subjects within distinct ethnic or geographic populations are examined for links between obesity and molecular markers for candidate genes on the basis of metabolic factors (e.g., the β3-adrenergic receptor, the glucose transporter, the glutamate-gated receptor, and Na+/K−ATPase). Obesity syndromes in humans and obesity genes in rodents (e.g., the genes for leptin and the leptin receptor).

Mice and rats with single-gene mutations resulting in obesity have been studied extensively in an effort to understand the physiologic and biochemical basis of the most salient aspects of their phenotype: increased food intake, reduced energy expenditure, preferential storage of calories as fat, and susceptibility to non-insulin-dependent diabetes mellitus. All the extant rodent genes in which mutations cause obesity have been cloned (Table 2) and have counterparts in humans. Obesity and non-insulin-dependent diabetes mellitus have been linked to a region (chromosome 1p22–p31) that contains the leptin receptor. Although sequence variation has been reported in some exons of the leptin-receptor gene, none of these variations have yet been identified in humans, one person has recently been described who has a phenotype remarkably similar to that of the fat mouse and a mutation in prohormone convertase, an endoprotease that cleaves pairs of basic amino acid residues in these same pro-hormones just before carboxypeptidase E exerts its action. The identification of these rare mutations underscores the need for further investigation in humans of possible allelic variations in these and other genes that studies in animals have pinpointed as central to systems of energy homeostasis.

Some investigators have examined genes that may regulate responses to an obesity-promoting environment. Inbred strains of rats and mice differ widely in their susceptibility to spontaneous and diet-induced obesity. Several groups have mapped some of the relevant genes to specific regions in the rodent genome, using crosses between strains at the extremes of the phenotype of interest (e.g., high and low body fat or high and low susceptibility to obesity with a high-fat diet). Some of the quantitative trait loci that have been identified are in regions of single genes known to cause obesity syndromes (Table 2), raising the possibility that allelic variation at these loci accounts for some portion of the heritable variation in body fat stores in rodents.

Another approach to the identification of genes related to the phenotype of obesity is to look for linked genetic intervals in the entire genome of subjects from families in which obesity is common. The feasibility of this approach depends on the number of genes responsible for the phenotype in affected subjects, the total number of relevant genes in the population, and the strength of an effect attributable to any locus. This approach is efficient for the study of single-gene disorders with high penetrance but is problematic for the study of multiple-gene disorders with genetic heterogeneity as well as strong environmental influences on phenotypic expression, such as obesity.

**TREATMENT**

The aim of weight reduction should be to decrease morbidity rather than to meet a cosmetic standard of thinness, and obese persons should be encouraged to set reasonable short-term goals for weight loss, bearing this aim in mind. They must
recognize that any lifestyle alterations, in the form of increased exercise or decreased caloric intake, made to lose weight will need to be continued indefinitely if the lower body weight is to be maintained. In general, maintaining a reduced weight through exercise and a diet that does not require medical supervision, without resorting to surgery or drugs, is more likely to be successful in persons with mild obesity than in those with severe obesity.\textsuperscript{28} Despite the widespread use of various pharmacologic and surgical therapies since the 1950s, the prevalence of obesity continues to increase, and the results of treatment remain unsatisfactory.\textsuperscript{2} Approximately two thirds of persons who lose weight will regain it within one year, and almost all persons who lose weight will regain it within five years.\textsuperscript{124}

**Lifestyle Modification**

**The Role of Dietary Composition**

The composition of the ideal or most healthful diet is not known. However, weight-reducing diets that consist of drastically altered proportions of nutrients may be dangerous\textsuperscript{125,126} and no more effective than diets that contain at least minimal amounts of protein, essential fatty acids, vitamins, and minerals, according to age-specific recommendations,\textsuperscript{127} and are low in saturated fat. Given our current knowledge of the effects of diet on morbidity, it is logical to assume that such a diet, especially if combined with regular exercise, will diminish the severity of cardiovascular risk factors (e.g., hyperlipidemia), even though it may not affect body composition.\textsuperscript{128} There is some evidence that low-fat diets may enhance short-term weight loss\textsuperscript{129} and, if continued, help maintain the reduced body weight.\textsuperscript{130}

**The Role of Exercise**

Increased physical activity not only increases caloric expenditure but also promotes dietary compliance. Exercise may increase the desire for foods that are high in carbohydrates and reduce the desire for foods that are high in fat.\textsuperscript{131} Thus, treatment programs for obesity that include physical activity may be more successful than those that do not. Different types of exercise may affect fuel use differently. Intermittent exercise (high intensity followed by low intensity) results in a greater reduction in weight and fat than continuous exercise of low-to-medium intensity that involves expending the same number of calories.\textsuperscript{131,132}

**The Role of Behavior Modification**

Although psychological disturbances are not often the primary cause of obesity, behavior modification based on an analysis of the circumstances in which a person tends to eat and the particular meaning of eating for that person can be helpful for weight reduction. Experts in this approach recommend that persons receive advice or counseling in a stable group setting for a long period and that close contact with the therapist and members of the group be maintained after weight has been lost.

**Drug Therapy**

The amphetamine-like actions of sympathomimetic drugs (phentermine, phenmetrazine, phenidimetrazine, diethylpropion, mazindol, and phenylpropanolamine) that increase brain concentrations of catecholamines or act directly on catecholamine receptors to increase the activity of $\beta$-adrenergic systems (resulting in decreased appetite or increased energy expenditure) or decrease the activity of $\alpha$-adrenergic systems (resulting in increased appetite or decreased energy expenditure) make the drugs unsuitable for obese persons with evidence of cardiovascular disease.\textsuperscript{2,28} Serotonin-reuptake inhibitors have recently been favored as appetite suppressants. The newest of these agents, fenfluramine, was approved for use by the Food and Drug Administration (FDA) in 1996. The serotonergic drugs do not raise blood pressure or increase the metabolic rate and are usually well tolerated. The combination of phentermine and fenfluramine has found favor on the basis of a four-year study of 121 subjects; the average weight loss was 11 kg (24 lb) at two years and 9.4 kg (21 lb) at three years (with no sustained weight loss in the control group), although fewer than half the subjects completed the study.\textsuperscript{133} Whenever the drugs were stopped, weight was promptly regained. Fluoxetine and other selective serotonin-reuptake inhibitors used for the treatment of depression promote some weight loss for at least five to six months. Serotonin-reuptake inhibitors may increase the likelihood of primary pulmonary hypertension,\textsuperscript{134} although it has been argued that for obese persons, the benefit of weight reduction with the use of these drugs outweighs the risk associated with their use.\textsuperscript{135} However, recent observations by Connolly et al. (to be published in the August 28 issue of the *Journal*) suggest that valvular heart disease may be associated with the use of fenfluramine and phentermine.

Sibutramine, a drug with both catecholaminergic and serotonergic agonist effects, is now in the last stages of evaluation for approval by the FDA. Other drugs under development include $\beta_3$-adrenergic-receptor agonists and other chemicals that act to increase caloric expenditure (e.g., BRL 26380A and ephedrine) and a lipase inhibitor (tetrahydrolipstatin) that prevents the digestion and absorption of ingested fats. No currently available therapy addresses the central mechanisms regulating body weight. Although the administration of leptin causes weight loss in some leptin-deficient rodents, most obese persons do not have a deficiency of this protein.\textsuperscript{76,91} Since plasma leptin concentrations fall during hy-
pocaloric intake,91 the administration of leptin might prove useful in promoting adherence to dietary regimens and maintenance of reduced body weight.27

Given the central role of neuropeptide Y in the modulation of eating behavior, antagonists of the action of neuropeptide Y may lower body weight. Other potential treatments are listed in Table 3. Any drug therapy should be administered with recommendations for dietary modifications and exercise.

Surgical Therapy

Surgery is usually recommended only for persons with severe obesity (body-mass index, >40) or those with less severe obesity (body-mass index, 35 to 40) who have coexisting conditions.28 Jejunoileal shunts lead to substantial weight reduction, and 10 years after surgery, approximately 80 percent of patients remain at least 10 percent below their preoperative body weight.28 This procedure, however, frequently results in symptoms related to the presence of a blind loop. The more commonly performed procedure is gastric reduction (gastroplasty) with or without an intestinal bypass. Gastroplasty with a bypass can initially result in substantial weight loss, and approximately 80 percent of patients remain at least 10 percent below their preoperative body weight for 10 years after surgery, although the success rate is substantially lower in patients with a craving for foods high in carbohydrates.28 The efficacy of the procedure is probably due to the increased sense of fullness with a reduced gastric volume and the symptoms of “dumping” associated with the passage of gastric contents into the intestines, which act as deterrents to eating. Excess consumption of liquid or semisolid foods can negate the benefits of surgery. Patients who undergo gastroplasty must be followed carefully for possible intestinal obstruction and electrolyte disturbances.

<table>
<thead>
<tr>
<th>TARGET OF TREATMENT</th>
<th>GOAL</th>
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<tbody>
<tr>
<td>Adipocyte transcription factors (peroxisome proliferator-activated receptor γ2)</td>
<td>Decrease differentiation of adipocytes from fibroblasts136</td>
</tr>
<tr>
<td>Tumor necrosis factor</td>
<td>Interfere with insulin action and ameliorate insulin resistance by decreasing effects on skeletal muscle137</td>
</tr>
<tr>
<td>Specific endogenous anorectic substances (e.g., cholecystokinin) or appetite stimulants (e.g., neuropeptide Y)</td>
<td>Develop pro-satiety agents from an understanding of neuro-hormonal mediation of eating behavior128,136 (e.g., recent identification of butabindide, an inhibitor of the cholecystokinin-inactivating peptidase)</td>
</tr>
<tr>
<td>Primary signals regarding body composition or central control of energy balance</td>
<td>Alter central mechanisms for regulating body weight rather than appetite or energy expenditure, thereby invoking all systems of body-weight regulation to achieve and maintain a reduced weight</td>
</tr>
<tr>
<td>Specific genes (leptin receptor, leptin, and antisense neuropeptide Y)</td>
<td>Manipulate promoters to increase expression of satiety factors (e.g., leptin) or decrease expression of appetite stimulants (e.g., neuropeptide Y)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

Clinical research and studies in animals have produced substantial evidence that body weight is regulated in humans and have identified some of the substances that mediate this regulation with respect to food intake, energy expenditure, and fat accrual. The insights gained from these investigations will have profound effects on lay and professional perceptions of the causes of obesity. At the least, these insights should alleviate the social stigma associated with a condition properly regarded as a medical problem that results, in most instances, from very complex interactions between genetic susceptibilities and environmental and developmental factors. Whether these insights can be parlayed into effective prophylaxis and therapy remains to be seen. The medical community should be skeptical of quick pharmacologic fixes for obesity and should continue to support the view that alterations in diet and physical activity — though extremely difficult to implement and sustain — will always be central components of prevention and treatment.

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