

**Treatment.** The usual approach to treatment of PEM includes three phases. The first relatively brief phase (24–48 hr) is a stabilization phase. During this phase, dehydration, if present, is corrected and antibiotic therapy is initiated to control infection. Because of the difficulty of estimating hydration, oral rehydration therapy is preferred. If intravenous therapy is necessary, estimates of dehydration should be reconsidered frequently, particularly during the first 24 hr of therapy.

The second phase includes continued antibiotic therapy with appropriate changes if the initial combination was not effective and introduction of a diet providing maintenance requirements of energy and protein (~75 cal/kg and ~1 g/kg/24 hr of protein) along with adequate electrolytes, trace minerals, and vitamins. This phase usually lasts for an additional week to 10 days. If the infant is unable to take the feedings from a cup or bottle, administration of feedings by nasogastric tube rather than by the parenteral route is preferred.

By the end of the second phase, any edema that was present has usually been mobilized, infections are under control, the child is becoming more interested in his or her surroundings, and his or her appetite is returning. The child is then ready for the final phase of treatment, which consists primarily of feeding. He or she should be switched gradually to a recovery diet providing up to 150 kcal/kg/24 hr and 4 g/kg/24 hr of protein. After adjustment to this diet, the child can be fed ad libitum. Once ad libitum feedings are allowed, intakes of both energy and protein can be substantial.

In developing countries, this phase is often carried out at home. However, continued hospitalization is much more effective. This allows further focus on maternal education, which is crucial for continued effective treatment as well as prevention of additional episodes.

Iron therapy usually is not started until this final phase of treatment so as to prevent binding of iron to already limited stores of transferrin, which, in turn, may interfere with the protein's host defense mechanisms. There also is concern that free iron during the early phase of treatment may exacerbate oxidant damage, precipitating clinical kwashiorkor or marasmic kwashiorkor in a child with clinical marasmus.

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## Chapter 43

# Obesity *Patricia A. Donohoue*

There has been a significant increase in the prevalence of overweight and obesity in the United States, despite nationwide efforts at reducing fat intake to prevent cardiovascular disease. In pediatrics, the consequences of this epidemic are the occurrence of “adult” diseases in youth, such as type 2 diabetes mellitus, hypertension, and hyperlipidemia.

The definition of obesity may vary depending on the source of the information, but most health care providers agree that indi-

viduals whose body mass index (BMI) (weight in kilograms divided by the square of the height in meters; kg/m<sup>2</sup>) exceeds the age-gender-specific 95th percentile are obese (see Fig. 15–2A and B). Those whose BMI is between the 85th and 95th percentiles are overweight and are at increased risk for obesity-related co-morbidities (see also Chapter 41). In adults, it is generally considered that an individual whose BMI is more than 30 kg/m<sup>2</sup> is obese. High BMI correlates with excess body fat in all age groups and in both genders, with the exception of persons with very high muscle mass (e.g., “body builders”). Data for age and gender BMI percentiles are derived from the National Health and Nutrition Examination Survey III (NHANES III) and are available from the Centers for Disease Control and Prevention ([www.cdc.gov/nchs/about/major/nhanes](http://www.cdc.gov/nchs/about/major/nhanes)).

**Etiology.** The regulation of body fat stores and the etiology of human obesity are multifactorial, reflecting complex interactions between genetic background, environmental stimuli, and developmental processes. During the stage of human evolution when food was obtained through strenuous physical activity (e.g., hunting, digging) and periods of prolonged fasting and famine were constant threats, genotypes developed to favor energy storage. In the environment of plentiful and easily accessible high-calorie food, these so-called thrifty genotypes are highly prevalent and, unfortunately, are now detrimental. This gene-environment interaction must be considered in the prevention and treatment of obesity.

An important factor in maintenance of body weight is the relationship between body weight and total energy expenditure. The trend toward returning to a specific set point for body weight is powerful and results not only from a reduction in total energy expenditure in response to weight loss but also from an increase in energy expenditure with weight gain. There are multiple genetic factors controlling this set point. There is ethnic variability in resting energy expenditure; it is higher in white than in black prepubertal girls and higher in white than in black prepubertal children, independent of percent body fat and sex. Genetic factors may also influence the lower physical activity and resting energy expenditure observed in infants who later become obese children. The genetic control of energy expenditure and heat production may be involved in the etiology of obesity. Energy expenditure and heat production are controlled by interactions with sympathetic neurons and mitochondrial uncoupling proteins, among other systems.

The importance of environmental factors on body size is underscored by the marked increase in obesity over the past 20 yr, a time period whose brevity precludes a significant change in the gene pool. The prevalence of obesity is increasing dramatically not only in adults but also in youth, as demonstrated in the Muscatine Study (Table 43–1). The prevalence is significantly higher, and the trend is even more pronounced in minority groups in the United States, particularly in adult females (Table 43–2). The same minority female preponderance occurs in

**TABLE 43–1. Prevalence of Overweight in Muscatine, IA, Schoolchildren\***

Year (n)	12–14 yr	15–17 yr	18 yr	Total Percent
<b>Females</b>				
1971 (1,072)	17.5	16.3	25.0	17.4
1981 (906)	18.7	17.9	20.0	18.4
1992 (1,139)	31.4	30.0	22.7	30.5
<b>Males</b>				
1971 (978)	16.8	11.9	26.9	15.4
1981 (921)	19.6	16.5	10.8	17.9
1992 (1,191)	28.5	21.8	33.9	25.9

\*Age-gender adjusted BMI > 85th percentile.

TABLE 43-2. Prevalence of Obesity (BMI > 30.0 kg/m<sup>2</sup>) by Race-Ethnic Group: United States, 1988-1994

	Age Group (yr)							Total Age-Adjusted
	20-29	30-39	40-49	50-59	60-69	70-79	80+	20-74 yr
<b>Men</b>								
Non-Hispanic white	12.0	17.1	22.7	30.6	25.3	20.4	7.7	20.0
Non-Hispanic black	19.1	20.3	22.3	21.5	25.6	19.5	11.1	21.3
Mexican-American	13.3	17.9	32.9	37.1	26.6	18.5	4.4	23.1
<b>Women</b>								
Non-Hispanic white	13.1	22.4	22.6	33.5	28.3	23.7	14.3	22.4
Non-Hispanic black	23.4	35.5	44.6	50.1	45.4	38.3	20.5	37.4
Mexican-American	22.4	34.7	44.7	43.0	39.1	24.3	19.1	34.2

youth and is particularly apparent at the onset of puberty and at the time of menarche. The pattern of increasing obesity prevalence has been observed throughout the United States and has accelerated over the past 10 yr. The impact of environment on the epidemic of obesity includes unfavorable trends in food intake and physical activity, as well as barriers to reversing these trends. Other examples of the impact of environment on body size are the development of obesity in patients who have survived leukemia or who have suffered hypothalamic damage, especially patients treated for craniopharyngioma.

The importance of heredity on body size has been demonstrated in multiple studies of dizygotic and monozygotic twins and of adopted individuals and their biologic siblings. Studies of twin pairs have consistently demonstrated higher concordance for body size among monozygotic than dizygotic twins. In adult adoptees and their biologic siblings, both full and half siblings, there is a significant correlation of BMI in biologic siblings across the entire distribution of body sizes.

In large unrelated populations from several ethnic groups, there is statistical evidence for recessive gene effects on body size variables, including BMI, abdominal visceral fat, relative fat pattern, and obesity. Longitudinal studies have demonstrated familial aggregation of obesity and cardiovascular risk. Examples of these include the Muscatine Study, the Bogalusa Heart Study, the San Antonio Family Heart Study, the HERITAGE Study, the Québec Family Study, and studies of American Pima Indians.

**Epidemiology.** The prediction of risk of adult obesity during childhood is based on several factors. Blood pressure, blood lipid levels, and obesity in childhood track into adulthood. Thus, childhood obesity itself is a predictor of adult obesity and of higher than expected adult morbidity and mortality regardless of the presence of overweight in adulthood. The prevalence of clinically significant obesity-related morbidities in youth is rising and predicts earlier onset of more severe problems in young adults. The increase in type 2 diabetes among children and adolescents is directly related to the obesity epidemic.

Parental obesity, particularly maternal, is predictive of childhood obesity. High birthweight is also a predictor of later obesity, and the most important factor contributing to high birthweight is maternal diabetes and, to a lesser degree, maternal obesity. The relative risk of developing obesity in young adulthood is higher for young children if they have obese parents and higher for older children if they themselves are obese (Table 43-3).

The influence of deficient physical activity on the development of obesity is reflected in the NHANES III data. Lack of physical activity is directly related to television viewing, and hours of television are significantly correlated to weight gain during the growing years. In a study of schoolchildren in California, reduction in television viewing significantly reduced the rate of weight gain in a study of third graders, when compared with third graders with no intervention. Among children

8-16 yr of age, the prevalence of obesity was positively associated with hours of television viewing, even when controlling for age, race, income, caloric intake, and physical activity.

### Pathogenesis

**ANIMAL MODELS OF SINGLE GENE DEFECTS.** In rodents, multiple examples of naturally occurring single gene mutations producing obesity are known and form the basis for a candidate gene approach to identify the genes responsible for human obesity (Table 43-4). Several human counterparts of these rodent obesity syndromes have been identified. The prototypic obese mice with single gene defects are the obese (*ob/ob*, *Lep<sup>ob</sup>*) and diabetes (*db/db*, *Lepr<sup>db</sup>*) autosomal recessive mutations. If present on the same genetic background strain, they cause identical phenotypes of severe hyperphagia, obesity, type 2 diabetes, defective thermogenesis, and infertility due to hypogonadotropic hypogonadism. The mutant gene responsible for the phenotype in *Lep<sup>ob</sup>* mice encodes a protein termed *leptin*, which is deficient in these animals. The gene encoding human leptin has been studied extensively, but with the exception of leptin deficiency caused by rare *LEP* gene mutations its importance in altered human satiety and abnormal body size determination has not been clearly demonstrated. Studies of this genetic locus in populations, and in large panels of obese and/or diabetic individuals, have failed to demonstrate linkage or mutations. The cloning of the leptin receptor gene *Lepr* led to characterization of the mutations causing the mouse *db/db* phenotype and its rat homologues, the Zucker fatty (*fa/fa*) and obese Koletsky phenotypes. Thus, mutation of the same gene, *Lepr*, occurred spontaneously in three different strains and produced the same phenotype. Mice that are heterozygous for either the *ob* or the *db* mutation have body composition and leptin homeostasis phenotypes that are intermediate between homozygous wild type and mutant animals. Severe early-onset human obesity caused by a mutant leptin receptor has been identified in three female siblings. These homozygotes had failure of pubertal development and reduced growth hormone and thyroid-stimulating hormone secretion. In

TABLE 43-3. Odds Ratios for Obesity in Young Adulthood According to Obesity Status in Childhood and Parents' Obesity Status

Age (yr)	Obese as Child	Number of Obese Parents	
	Yes vs No	1 vs 0	2 vs 0
1-2	1.3	3.2	13.6
3-5	4.7	3.0	15.3
6-9	8.8	2.6	5.0
10-14	22.3	2.2	2.0
15-17	17.5	2.2	5.6

Data from Whitaker RC, Wright JA, Pepe MS, et al: Predicting obesity in young adulthood from childhood and parental obesity. *N Engl J Med* 1997; 337:869-73.

TABLE 43-4. Rodent Obesity Mutations, Human Regions of Synteny, and Human Homologues

	Mutation	Gene	Mode of Inheritance (Autosomal)	Rodent Chromosome	Human Syntenic Region	Human Mutation Described	Mutant Protein
<b>Mouse</b>	Agouti	<i>A<sup>y</sup></i>	Dominant	2	20q11	No*	ASP
	Diabetes	<i>db</i>	Recessive	4	1p31	Yes	Lepr
	Fat	<i>fat</i>	Recessive	8	4q21	No†	Carboxypeptidase
	Obese	<i>ob</i>	Recessive	6	7q31	Yes	Leptin
	Tubby	<i>tub</i>	Recessive	7	11p15	No	Phosphodiesterase
<b>Rat</b>	Fatty	<i>fa</i>	Recessive	5	1p31	Yes	Lepr
	Corpulent	<i>fa<sup>K</sup></i>	Recessive	5	1p31	Yes	Lepr

\* ASP prevents binding of  $\alpha$ MSH to its receptor MC4R. Several MC4R mutations are associated with human obesity.

† CPE is required for normal prohormone processing by prohormone convertase 1 (PC1). PC1 mutations are associated with human obesity. ASP = agouti signaling protein; Lepr = leptin receptor; CPE = carboxypeptidase E.

linkage studies of large populations, the leptin receptor locus seems more important than the leptin locus in its contribution to variability in body size.

The tubby (*tub*) mutation in mice is an autosomal recessive trait that is associated with less severe obesity and insulin resistance than *ob* or *db*, is not associated with significant hyperphagia, causes variable degrees of hyperlipidemia depending on background strain, and is more severe in males than females. The phenotype also includes retinal degeneration and sensorineural hearing loss similar to the human Usher, Alström, and Bardet-Biedl syndromes, but human *TUB* mutations have not yet been described.

In the fatty (*fat/fat*) mouse, the recessively inherited mutation causes hyperinsulinemia without hyperglycemia and postpubertal obesity that is less severe than that seen in *ob/ob* or *db/db* mice. The "hyperinsulinemia" is caused by hyperproinsulinemia. The molecular defect is in the gene encoding carboxypeptidase E (CPE), an endoprotease required for normal processing of prohormones to active hormones, including proinsulin to insulin and pro-opiomelanocortin (POMC) to adrenocorticotrophic hormone (ACTH), melanocyte-stimulating hormone (MSH),  $\beta$ -endorphin, and  $\beta$ -lipoprotein. The role of CPE mutations in human obesity is unknown; however, a possible correlate has been described in which there are mutations of the prohormone convertase 1 (PC1) gene. These patients have obesity along with impaired processing of insulin, leading to diabetes, hyperproinsulinemia, and ACTH deficiency from impaired processing of POMC. Several individuals with mutations of the *POMC* gene have been identified, and they have severe early-onset obesity as well as ACTH deficiency. They also have red hair, whereas their family members do not.

The yellow mutation of agouti mice is a dominant trait that causes yellow coat color (rather than the wild-type hairs that are banded black and yellow), obesity, and diabetes. This was the first rodent obesity gene to be cloned, and subsequently dozens of agouti yellow alleles have been identified, which vary in their phenotypic expression. The molecular defect in the most dominant form *Ay* is a deletion in the 5' regulatory region. This results in overproduction of agouti signaling protein (ASP) through ectopic expression of normal agouti mRNA in many tissues, rather than its normal site of expression, which is limited to the skin. ASP and another similar peptide, agouti-related peptide (AgRP), act as antagonists of native ligand binding to melanocortin receptors 1–4 (MC1R through MC4R), each of which is expressed differentially in specific tissues. Although ASP mutations have not yet been described in humans, several MC4R mutations are now known to be associated with obesity. Up to 10% of obese subjects (adults and youth) in Germany and France have MC4R mutations. The prevalence rate appears to be lower in the United States. The dominant nature of these mutations is most likely caused by haploinsufficiency and not a dominant negative effect.

**CONTROL OF FEEDING.** Energy intake and expenditure is under the control of complex interactions between peripheral signaling and effector systems and neuroendocrine systems. The hormone leptin is an important component of this complex system. Plasma levels of leptin correlate with fat mass and are higher in females than males. As has been demonstrated in animals, human leptin is made almost exclusively in adipose tissue and acts centrally in the hypothalamus by modifying two effector systems. Low plasma concentrations of leptin and insulin (e.g., during fasting and weight loss) increase food intake and decrease energy expenditure by stimulating neuropeptide Y (NPY) synthesis, and perhaps by inhibiting sympathetic activity and other catabolic pathways. High leptin and insulin concentrations (e.g., during feeding and weight gain) decrease food intake and increase energy expenditure through release of melanocortin and corticotropin-releasing hormone (CRH), among others. The list of neuropeptides that are known to alter energy balance is growing rapidly. Many of these are listed in Table 43–5. Among the more important peptides that stimulate feeding are orexins A and B, which are secreted by the hypothalamus, and ghrelin, which is secreted by the stomach.

**THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS.** It has been demonstrated in multiple animal models that adrenalectomy obliterates or attenuates the obesity syndromes

TABLE 43-5. Central Nervous System Proteins (Neuropeptides) Involved in Energy Homeostasis

Neuropeptide	Regulation by Adiposity Signal (Leptin or Insulin)
<b>Orexigenic</b> (stimulates feeding)	
Neuropeptide Y*	Decreased
Agouti related peptide*	Decreased
Melanin-concentrating hormone	Decreased
Orexin A and B (hypocretin 1 and 2)	Decreased
Galanin	Unknown
Norepinephrine	Unknown
Gherlin	Unknown
<b>Anorexigenic</b> (inhibits feeding)	
$\alpha$ -Melanocyte-stimulating hormone*	Increased
Corticotropin-releasing hormone*	Increased
Thyrotropin-releasing hormone*	Increased
Cocaine- and amphetamine-regulated transcript*	Increased
Interleukin-1 $\beta$ *	Increased
Urocortin*	Unknown
Glucagon-like peptide 1	Unknown
Oxytocin	Unknown
Neurotensin	Unknown
Serotonin	Unknown

\*Exerts effects on both energy intake and expenditure that result in a change in energy stores.

Majority of information obtained with permission from Schwartz MW, Woods SC, Porte D Jr, et al: Central nervous system control of food intake. *Nature* 2000;404:661–71.

expressed in genetically obese rats and mice, in diet-induced obesity, and in hypothalamic obesity. Treatment with only trace quantities of glucocorticoid causes rapid return of the obesity, indicating heightened sensitivity to the steroid. In humans and animals with hypercortisolemia, obesity is prominent. However, in adrenalectomized animals, the effects seen could result from a combination of glucocorticoid deficiency alone or in combination with the secondary elevation of hypothalamic CRH and pituitary ACTH production. In animal studies, CNS administration of CRH as well as a related hormone, urocortin, mimics the events seen in the "stress response," including anorexia. These data suggest that therapeutic manipulations of the HPA axis could alter the phenotype of certain genetically obese individuals.

**POLYGENIC MODELS.** The polygenic mouse models of obesity have allowed identification of multiple genetic loci within individual strains that modify obesity, plasma cholesterol levels, specific deposition of body fat depots, and propensity toward development of obesity on a high-fat diet. These polygenic models more closely resemble the human obesity phenotypes than single gene models; however, the single gene defects producing recessive traits, dominant traits, promoter alterations, and those subject to parental imprinting must also be considered candidates for genetic effects in human obesity.

**GENE-TARGETING AND EFFECTS ON BODY FAT/FEEDING.** Gene targeting of a variety of genes has been used to study obesity. These, along with other relevant animal models, are summarized in Table 43–6, and they demonstrate both monogenic and polygenic effects on body size variables.

**Clinical Manifestations.** Human obesity in rare instances may be associated with defects at a single genetic locus. These include Prader-Willi, Bardet-Biedl, and Alström syndromes, in which the causes of obesity are unknown. The presence of these syndromes can usually be detected by demonstration of the typical dysmorphic features on physical examination. Certain hormonal aberrations, such as hypothyroidism, Cushing syndrome, and generalized hypothalamic dysfunction, can result in excessive weight gain. However, these conditions are rarely identified among the typical patients who present for evaluation of obesity.

In children, obesity is most often associated with tall stature, slightly advanced bone age, and somewhat early puberty. In most patients with obesity, rapid growth in height precludes the diagnosis of hypothyroidism and hypercortisolism. By contrast, hypothyroidism and cortisol excess cause delayed skeletal devel-

opment, short stature, and delayed puberty. Many obese youth also have **acanthosis nigricans**, a hypertrophic hyperpigmentation of the skin most commonly seen on the posterior neck and in skin creases. This condition is associated with insulin resistance and a higher risk of developing type 2 diabetes.

**Laboratory Findings, Diagnosis, and Differential Diagnosis.** Obesity can be diagnosed in most cases by simple inspection of the patient. If needed, BMI can be plotted on BMI growth curves (see Fig. 15–2) to identify those who are over the 95th percentile. Early identification of children at risk includes the demonstration of early adiposity rebound. Examination of BMI curves (see Fig. 15–2) shows that BMI reaches a nadir after infancy and then rebounds. If this rebound occurs early, especially if the BMI is already high for age, there is a significantly increased risk of developing obesity.

Hypothyroidism and hypercortisolemia can be ruled out by demonstrating normal free thyroxine and thyroid-stimulating hormone levels and 24 hr urinary free cortisol or diurnal salivary cortisol levels. If patients have severe early-onset obesity, out of proportion to the family history, one of the single gene defects mentioned earlier may need to be considered. Leptin levels can help in the diagnosis of leptin deficiency or resistance, and screening for genetic mutations is possible in several research laboratories.

The most important tests in the evaluation and follow-up of obese patients are those that evaluate cardiovascular disease risk and diabetes risk. These include plasma lipid profiles, fasting glucose and insulin levels, and hemoglobin A1C. It may also be necessary to perform studies to test for sleep apnea.

**Complications.** The 2001 Surgeon General's Call to Action ([www.surgeongeneral.gov/topics/obesity/calltoaction](http://www.surgeongeneral.gov/topics/obesity/calltoaction)) states that there has been a reversal of gains made in cardiovascular health over the recent past, owing to the huge increase in obesity prevalence. Obesity-associated co-morbidities include significantly increased risks for diabetes, cardiovascular disease, cancer, respiratory disease (asthma, sleep apnea), infertility, degenerative joint disease, proteinuria, depression, anxiety, and discrimination both in social life and in the workplace. Obesity shortens life span through its co-morbidities; and the earlier the onset, the shorter the life. It is a chronic disease that requires chronic therapy.

**Prevention.** Community-wide efforts need to be directed toward increasing physical activity and changing dietary habits. Increasing the safety of streets and playgrounds may be necessary in some settings, but the resources for this are often absent. Responsibility for promoting and organizing opportunities for nutritional education and for increasing physical activity for all citizens should be shared by schools, community organizations, and places of worship. Enhancement of physical education programs should be a priority of the school systems. School meal programs should provide healthy choices for students; vending machines in schools should not provide high-calorie beverages and snacks. Pediatric health care providers should counsel obese parents about the risk of childhood obesity in their children. Breast-fed infants are less likely to develop adult obesity than bottle-fed infants, and this should be communicated to expectant parents.

**Treatment.** Reduction of dietary calories and fat and increasing dietary fiber are recommended. Diets that are lower in carbohydrates may be useful in some individuals, but the basic goal should be reduction in energy intake and increase in energy expenditure. Any increase in physical activity is good, with regular aerobic exercise being the goal. This should be accompanied by a decrease in television viewing and computer games.

**MEDICATIONS.** Medical therapeutic options for treatment of obesity are not very promising. Therapy must be long term and ongoing, as is the case with treatment of hypertension and

**TABLE 43–6. Transgenic Models for Altered Body Size or Body Fat**

Increased	Decreased	No Change on Normal Diet
MC4R-KO	Dopamine D <sub>1</sub> receptor KO	CRH KO
5-HT2c receptor KO	UCP-1 overexpression	NPY KO
CRH overexpression	Tyrosine phosphatase 1B KO	TNF- $\alpha$ KO
BAT ablation	GLUT4 KO	UCP 3 KO
$\beta_3$ -AR KO (+/-)	MCH KO	
GLUT4 overexpressed in fat	LPL overexpression in muscle	
NPY receptor 1 KO	PKA RII $\beta$ KO	
Nhlh2 gene KO	PPAR $\gamma$ KO heterozygotes	
11 $\beta$ -HSD-1 overexpressed in fat		

MC4R = melanocortin receptor 4; KO = knockout; 5-HT2c = 5-hydroxytryptophan 2c; CRH = corticotropin-releasing hormone; BAT = brown adipose tissue;  $\beta_3$ -AR =  $\beta_3$ -adrenergic receptor; GLUT4 = glucose transporter 4; NPY = neuropeptide Y; Nhlh2 = one of two helix-loop-helix transcription factors expressed in the developing mouse nervous system; UCP = uncoupling protein; MCH = melanin-concentrating hormone; LPL = lipoprotein lipase; PKA RII $\beta$  = protein kinase A regulatory subunit II  $\beta$ ; PPAR = peroxisome proliferator-activated receptor; TNF = tumor necrosis factor; 11 $\beta$ -HSD-1 = 11 $\beta$ -hydroxysteroid dehydrogenase type 1.

diabetes. Anti-obesity drugs are not approved for prolonged use or for use in youth. They have not been extensively tested for safety over long periods of time, may only benefit a minority of patients, and may be associated with serious cardiovascular side effects. The major classes of drugs are those that reduce food intake (monoamine oxidase inhibitors, sympathomimetic drugs), those that increase energy expenditure (ephedrine, caffeine), and those that inhibit fat absorption (orlistat). The use of agents to induce dietary fat malabsorption has been only minimally successful and is associated with significant intestinal discomfort if not accompanied by a low-fat diet. Metformin, a glucose-sensitizing agent developed for use in type 2 diabetes, has shown promise in helping obese patients adhere to a diet; the diet itself may be nearly equally effective over the long term. Certain neuropeptide agonists and antagonists are being developed as therapeutic agents. The roles of some of these compounds in energy homeostasis are shown in Table 43–5.

The use of recombinant leptin in humans resulted in a modest and highly variable loss of weight (loss of fat mass) that was dose related and occurred in both lean and obese subjects. Leptin treatment in the rare leptin-deficient patients produced a rapid reduction in weight and increase in energy expenditure; antibodies to leptin developed after several months of treatment. The impact of these antibodies on efficacy has not yet been demonstrated.

**SURGERY.** Surgical therapy to reduce the volume of the stomach may be successful in the long term in some patients. Procedures to bypass the absorptive surfaces of the intestine have been associated with many complications, the most predictable being nutritional deficiencies. Surgery to remove fat (liposuction), if used alone, is not a long-term solution. However, it may be a useful cosmetic adjunct in patients who are successful with diet and exercise, with or without surgical gastroplasty.

**GOALS OF TREATMENT.** As with adults, it is rarely possible for obese youth to achieve an “ideal body weight” for height. The initial goal should be a 10% reduction in weight for older children; in adults, this modest degree of loss is associated with a decrease in plasma lipids, blood pressure, fasting insulin, and other co-morbidities such as asthma symptoms. For younger children, severe caloric restriction may result in an unacceptable decrement in height velocity. In many younger children, simply preventing further weight gain for a period of time will achieve the same goals. In all age groups, permanent lifestyle changes are required. This is not unlike the lifestyle changes needed for optimal control of diabetes, hyperlipidemia, and hypertension. The most significant impact on the obesity epidemic will have to be achieved through patient education and prevention. At present, there is limited value for genetic counseling, but there may be an increasing role as more genetic defects are described.

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## Chapter 44

# Vitamin Deficiencies and Excesses

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Vitamins are essential nutrients that must be supplied exogenously either as part of a well-balanced diet or as supplements. The functions of vitamins are summarized in Table 44–1, and the daily reference intakes for infants and children are summarized in Table 40–1. Deficiency states are uncommon in developed countries except, perhaps, among some food-insecure families (see Chapter 42). In contrast, deficiency states (see Table 44–1) are quite common in many developing countries.

Toxicity results from excessive intakes of the fat-soluble vitamins A and D, but toxicity from excessive intakes of the water-soluble vitamins is rare. The vitamin-dependent states are also summarized in Table 44–1.

### VITAMIN A

*Vitamin A* is a generic term encompassing all  $\beta$ -ionone derivatives other than provitamin A carotenoids. These include retinol, retinyl ester, retinal and retinoic acid, and the vitamin A alcohol, ester, aldehyde, and acid. *Provitamin A carotenoids* is a generic term for all carotenoids that have the biologic activity of  $\beta$ -carotene. They or their derivatives with vitamin A activity are required in the diets of adults as well as of infants and children.

$\beta$ -Carotene is partially absorbed into the intestinal lymphatics. The remainder is cleaved into two molecules of retinol. Dietary retinyl ester is hydrolyzed to retinol in the intestine, esterified with palmitic acid in the mucosal cells, and stored in the liver as retinyl palmitate, which can be hydrolyzed to free retinol for transport by retinol-binding protein to its site of action. Zinc also is required for this mobilization. Normal plasma values of retinol are 20–50  $\mu\text{g}/\text{dL}$  in infants and 30–225  $\mu\text{g}/\text{dL}$  in older children and adults.

The liver content of vitamin A is low at birth but is rapidly augmented by the large amounts in colostrum and breast milk as well as infant formulas. Other foods (vegetables, fruits, eggs, butter, liver) or vitamin supplements also provide vitamin A. Cooking, canning, and freezing of foodstuffs results in only small losses of vitamin A, but it is destroyed by oxidizing agents. Thus, risk of vitamin A deficiency is small in healthy children receiving a well-balanced diet. However, vitamin A deficiency can also result from inadequate intestinal absorption secondary to chronic intestinal disorders or fat malabsorption syndromes. Low dietary intake of fat can also result in low vitamin A absorption, and low dietary protein intake can result in deficient