

# Dealing with Hazardous Waists:

## Trends in the Management of OBESITY

by John H. Dirckx, M.D.

In a recent year, approximately 8 million Americans spent almost \$2 billion at commercial dieting centers, including Jenny Craig, Diet Center, Physicians Weight Loss Centers, and Weight Watchers International. Information or advice about dieting and weight control appears in virtually every issue of every women's magazine, as well as in most health and fitness publications. Calories, pounds, and inches are a perennial topic of discussion in advertising and the news media, on talk shows, and in casual conversation.

While this general obsession with overweight and its avoidance reflects, in some measure, an increasing public awareness of the adverse health consequences of obesity, its true roots lie in a culturally conditioned perception that thinness, even excessive thinness, is inherently attractive and desirable, whereas the opposite condition is repellent and undesirable. As a consequence, besides a large group of persons whose health is adversely affected by excessive body weight, our society includes another large group whose health is threatened by their determination to remain thin at all costs.

This article focuses on the nature, causes, and consequences of obesity, and some of the many ways (most of them useless and some of them perilous) in which it is treated.

### A Widespread Problem: The Nature and Prevalence of Obesity

Any discussion of obesity should logically begin with a working definition of it. Here we immediately run into trouble. If obesity means "being too fat," then how fat is too fat? Do we look at societal and esthetic norms or at actuarial tables? Do we measure absolute weight, or compare weight to height, or assess the distribution of subcutaneous fat?

Fat, or adipose tissue, consists of specialized connective tissue cells (adipocytes), each of which contains a deposit of lipid material that distends the cell membrane and pushes the

nucleus to the periphery. Adipocytes are not metabolically inert. They play an essential role in energy metabolism, synthesizing fats from carbohydrates and fatty acids and serving as a bank or storage pool of cellular fuel upon which the body can draw when dietary intake is reduced or interrupted. Adipose tissue also serves as mechanical and thermal insulation. Most of it is found in a layer of variable thickness under the skin, called the panniculus adiposus, but it also appears in the mesentery and omenta, the bone marrow, and around the kidneys.

Obesity is essentially an excess of subcutaneous fat in proportion to lean body mass. The accumulation of excessive fat in subcutaneous tissues is associated with both hypertrophy (increased size) and hyperplasia (increased numbers) of adipocytes. Ultimately this accumulation

reflects an imbalance between food intake and energy expenditure—an ongoing storage of surplus energy resources in preparation for a period of diminished rations that never comes.

The energy that a given foodstuff is capable of releasing during metabolism is measured in calories per gram. A calorie (cal) is defined as the amount of heat required to raise the temperature of 1 kg of water 1°C. For practical purposes, nutritionists measure the energy content of foods in kilocalories (1 kcal = 1000 cal). However, for many years it has been customary to refer to kilocalories simply as "calories."

An adult needs 1200-1800 calories a day to maintain basic life processes, and an additional 50-150% of this amount to meet the needs imposed by physical exertion. A sleeping person consumes 50-75 cal/hr. A person walking uphill, swimming, playing basketball, or shoveling snow may consume ten times as many, or even more. Calorie consumption, both at rest and during exertion, increases in direct proportion to body weight. One pound (0.45 kg) of body fat represents roughly 3500 calories of stored food energy.

For convenience of discussion, all foods are divided into just three categories: carbohydrate (starches and sugars from



grains, cereals, fruits and vegetables), protein (from lean meat, fish, eggs, and cheese), and fat (animal fats including butter fat, and fish and vegetable oils). Obviously many staple foodstuffs and virtually all prepared dishes consist of mixtures of these in various proportions.

Whereas one gram of protein or carbohydrate provides about 4 calories, an equal amount of fat provides 9. This proportion must be kept in mind when assessing and comparing diets. In this country, an average middle-class diet derives 50% of its calories from carbohydrate, 35% from fat, and 15% from protein. (Nutritionists currently recommend limiting dietary fat to 10-30% of total calories.)

Several objective measures have been used to quantify obesity. One way of roughly estimating obesity is to determine the *relative weight* (RW) by dividing the subject's body weight by the median desirable weight for a person of the same height and of medium frame according to actuarial tables. These tables (so named because they are based on survival statistics compiled by life insurance companies) relate weight solely to height. The tables generally provide different figures for three classes of body build (small, medium, and large frame), and some introduce the additional variable of age.

More sophisticated ways of relating weight to height are the body mass index and the ponderal index. *Body mass index* (BMI) is found by dividing the weight in kilograms by the square of the height in meters. The *ponderal index* is the weight in kilograms divided by body mass in cubic meters. (Body mass can be determined by measuring the amount of water displaced when the body is immersed.)

Unfortunately, none of the methods mentioned above can distinguish between true obesity (excess adipose tissue) and increased lean body mass. For example, a body builder with enormously overdeveloped muscles but very little subcutaneous fat would have abnormal elevations of all these indices. More useful in judging the presence of excessive subcutaneous fat deposits is the measurement of skinfold thickness with a caliper at standard sites, such as the posterior chest below the scapula and the back of the arm over the triceps muscle. Determination of the waist-to-hip ratio assesses the regional deposition of fat and differentiates the more medically significant central (male-pattern) obesity from peripheral (female-pattern) obesity.

So what constitutes obesity? A widely accepted definition is a body weight that is 20% or more in excess of ideal weight-for-height according to actuarial tables—in other words, an RW of 1.2 or more. By this definition, 34% of adults in the U.S. are obese. The National Institutes of Health has defined overweight as a BMI between 25 and 30 kg/m<sup>2</sup>, and obesity as a BMI of 30 kg/m<sup>2</sup> or more. By these criteria, 55% of adult Americans are either overweight or obese.

The term *morbid obesity*, often used to refer to a degree of overweight that involves particularly serious health risks, has no fixed meaning. It has been variously defined as a

weight that is at least 100 lb more than ideal weight according to actuarial tables; a weight that is at least twice ideal weight; and a BMI over 40. Sometimes the term just means severe obesity that doesn't respond to a medically supervised regimen of diet and exercise.

No solitary cause can account for all cases of obesity. Faulty eating habits, perhaps related to failure of normal satiety feedback mechanisms, appear to be responsible for some cases, but many obese persons neither consume more calories than nonobese persons nor eat different proportions of foodstuffs. In recent years the old dichotomy between *endogenous obesity* (due to genetic or metabolic factors) and *exogenous obesity* (due to overeating) has been largely abandoned.

Everyone has noticed that overweight tends to run in families. But is that due to a genetically transmitted disorder of metabolism or to faulty eating habits learned by imitation? Studies of obese twins have suggested the presence of genetic influences on resting metabolic rate, feeding behavior, changes in energy expenditures in response to overfeeding, and other

biochemical variables. Children adopted at birth show no correlation of their body weight with that of their adoptive parents, but an 80% correlation with that of their genetic parents. Genetic factors account for the high prevalence of obesity among African-American women. In certain inbred populations, such as the Native Americans of the southwest, there is a very high prevalence of severe obesity.

Obesity has often been thought of as an endocrine disorder. But, contrary to popular belief, overweight is not caused by malfunction of the pituitary, thyroid, or adrenal glands. (It is, however, frequently associated with hyperinsulinism and relative insulin resistance.) The gradual increase in body weight that

affects many persons as they get older (middle-aged spread) apparently results from a reduction in physical activity, not from any biochemical shifts associated with aging.

Intensive study of large populations has turned up a remarkable variety of environmental factors associated with obesity. These include socioeconomic status, region of residence, season, and family size. Persons subsisting at or below the poverty level are more likely to be overweight than those in more fortunate circumstances. Obesity is much more prevalent in the northeastern and midwestern U.S. than in the south and west. A higher prevalence of obesity is found when weight is measured during the winter than during the summer. Urban living and being part of a smaller family favor obesity.

As mentioned above, there are important gender differences in the distribution of excessive body fat. Men tend to display central or abdominal obesity (the so-called spare tire), with an increased waist-to-hip ratio, while women are more likely to have peripheral obesity, with principal adipose tissue deposits in the buttocks and thighs.

### Defining Obesity

In discussing definitions of *obesity*, one must at least mention purely subjective norms. Sometimes obesity, like beauty, is in the eye of the beholder. Perceptions of what is fat and what is not may be culturally conditioned. References to fatness in the Bible and in classical and medieval literature almost invariably equate it with prosperity, beauty, and health. Standards of feminine beauty as portrayed in the paintings of the great European masters include an abundance of subcutaneous fat. A woman psychiatrist from Russia once told me, "I didn't know I was fat until I came to America."

The prevalence of obesity has increased since the 1980s, and continues to increase in both adults and children. Public health authorities attribute this trend primarily to social factors: a reduction in the effort required by occupational and house-keeping chores due to the increasing use of machinery and computers, fast foods with high fat content, increasingly sedentary lifestyles, increasing use of transportation instead of walking, and substitution of passive for active recreations. There is some evidence that the incidence of obesity in children is linked to time spent watching television.

### Heavy Odds: The Hazards of Overweight

Obesity, which has often been called the principal nutritional disorder in the United States, is increasingly decried by health officials and educators as a major public health problem. But what's so bad about being overweight?

The adage sometimes quoted, that fat people die at increased rates from every cause except suicide and tuberculosis, probably can't be sustained by statistical proof, but it isn't far from the truth. Obesity is known to be an independent risk factor for many life-threatening and life-shortening conditions (hypertension, hypercholesterolemia, type 2 diabetes mellitus, myocardial infarction, obstructive sleep apnea, and hypoventilation syndrome) as well as for others capable of causing severe distress or disability (osteoarthritis and other orthopedic disorders, infertility, lower extremity venous stasis disease, gastroesophageal reflux disease, and urinary stress incontinence). Certain common malignancies (cancer of the colon, rectum, and prostate in men, and of the breast, cervix, endometrium, and ovary in women) occur more commonly in obese persons than in those of normal weight.

Lesser degrees of obesity can constitute a significant health hazard in the presence of diabetes mellitus, hypertension, heart disease, or other risk factors. Distribution of excess body fat in central depots (abdominal or male pattern, with an increased waist-to-hip ratio) rather than in peripheral ones (gluteal or female pattern) is associated with higher risks of many of these disorders.

Obese persons are more liable to injury than persons of normal weight. Because they move more slowly, they are more likely to be hit while crossing a street. A larger body is more unwieldy: obese persons are more likely to fall on stairs or in the shower.

An overweight person is more difficult for a physician to examine. Palpation of masses in the abdomen, breasts, or subcutaneous tissues may be virtually impossible. Excess fat also

disperses x-rays and renders other imaging techniques less useful. Overweight persons are notoriously poor candidates for thoracic and abdominal surgery, and have a much higher incidence of unsuccessful outcomes, complications, and intraoperative and postoperative mortality.

The hackneyed folk image of the jolly fat man or woman, whose obesity is somehow tied to and offset by an unfailingly amiable and cheerful disposition, is pure myth. Not least among the adverse consequences of obesity are social stigmatization, poor self-image, low self-esteem, and the anxiety and depression resulting from them.

Overweight persons face occupational discrimination, social rejection, and derision from persons of normal weight, including friends and relations, who are apt to attribute their obesity to a lack of self-discipline or even to moral degeneracy. The obese tend to have higher rates of unemployment and a lower socioeconomic status, and this is only partly related to their inability to qualify for certain jobs because of size or weight restrictions.

In public they are often the target of rude and disparaging remarks and other tokens of hostility from ignorant and ill-disposed strangers. They can't travel comfortably in compact cars, be accommodated comfortably in restaurants, or fit comfortably into seats in theaters, sports arenas, buses, or airplanes (all of which are designed to cram the maximum number of paying customers into the available space).

Excessive size of trunk and limbs makes for clumsiness in performing many of the activities of daily living. Bathing and personal hygiene may be awkward or impossible for the overweight, particularly in public facilities. Physical exercise, part of any rational program for the treatment of obesity, is often far more difficult for the obese than for persons of normal weight. Their choice in clothing is sharply limited. Euphemisms used by manufacturers and vendors of clothing who cater to overweight persons (*stout, portly, stocky, corpulent, full-figured, large framed*) can seem almost as offensive as intentionally derogatory street terms.

Surely it must be evident to even the slenderest intelligence that obesity, besides being a very prevalent condition, poses harrowing health risks and generates devastating psychological trauma.

### Fat Chance: Fad Diets and Gimmicks

The severe psychological burden of obesity, and the desire to avert or reverse some of its harmful effects on health, have

### Eating Disorders

Although we may choose to think of obesity as an *eating disorder*, that phrase is usually applied to extreme and compulsive forms of dietary deviance. Bulimia nervosa is a tendency to indulge in binge eating of high calorie foods, often daily, usually followed by self-induced vomiting, purgation with laxatives, or both in order to prevent resultant weight gain. Anorexia nervosa, by contrast, is a compulsive reduction of food intake in order to achieve or maintain an extreme and unhealthy degree of thinness. This disorder has complex psychological roots, but a grossly distorted body image plays a part in its genesis.

Neither of these eating disorders pertains directly to the topic of this article. But the point is worth noting that a marked increase in the incidence of anorexia nervosa among young women in this and other Western countries during the past three decades coincided with a change in the ideal of feminine beauty, as promoted in the mass media, advertising, and fashion design, from the well-rounded to the skeletal. This shift in public perceptions has changed what it means to be overweight or obese, and has prompted many to seek weight reduction for cosmetic rather than medical reasons.

made its victims an easy mark for an endless succession of charlatans. Not all methods of weight control can be condemned as quackery. Bariatrics is a legitimate branch of medicine that concerns itself with the prevention and treatment of obesity. However, even within the medical profession there are numerous practitioners who exploit an unwary and vulnerable public with worthless and even dangerous diets, drugs, and gadgets.

The list of unproven weight-control methods that have been promoted in recent years is long and varied. Dietary programs are among the most prominent of these. The typical gimmick diet has two features: an underlying theory or rationale that mixes a little biochemistry and physiology with a lot of hogwash, and a dietary regimen designed to take off weight by inducing drastic nutritional imbalances while avoiding a sensation of hunger. Some of these are “crash” diets meant to induce rapid weight loss by some combination of fasting and dietary hocus pocus. But the majority of them promise rapid and permanent weight loss with a minimum of effort and discomfort.

Most of these diets are flawed by irrational theory and inappropriate methodology. Many indulge in calorie juggling instead of calorie restriction, without which no diet can succeed for long. Many fad diets can lead to dangerous disturbances of biochemical equilibrium, and can deprive their followers of essential nutrients, minerals, and vitamins while imposing additional strains on already challenged cardiovascular and excretory systems.

Low carbohydrate diets (such as Dr. Atkins’ Diet Revolution, which is claimed to stimulate production of a mythical fat mobilizing hormone) seem to work at first because they force the body to break down glycogen, a complex carbohydrate stored in liver and muscle tissue that serves as an emergency energy reserve. This in turn leads to brisk water loss (diuresis) and hence reduction of body weight without significant depletion of fat stores. When glycogen stores are exhausted and fat begins to be burned to meet day-to-day energy requirements, the result is ketosis—the same life-threatening disorder that occurs when type 1 diabetes gets out of control. A diet low in carbohydrate is often high in fat, and this typically causes a dangerous elevation of plasma lipids.

Programs that emphasize high intake of protein (Complete Scarsdale Medical Diet, Doctor’s Quick Weight Loss Diet) or fruit (the Pritikin Diet, the Beverly Hills Diet) likewise induce potentially dangerous distortions of body chemistry. Many weight-loss programs require the patient to buy expensive powders, liquids, or mixes variously designated as nutritional supplements, protein spacers, or fat burners. Often these contain only a few cents’ worth of vitamins and other chemicals. Protein supplements dispensed by some weight-loss clinics have consisted largely of hydrolysates of gelatin from animal hides and hooves, markedly deficient in essential amino acids.

Another flaw of most of these diets is that they cannot be comfortably or safely continued for long periods—certainly not for a lifetime. But permanently overcoming obesity demands a permanent correction of the imbalance between caloric intake and caloric expenditure.

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A remarkable variety of prescription drugs have been used inappropriately to help control overweight by reducing appetite, altering nutritional physiology, or otherwise meddling with nature. When I was in private practice during the 1960s, I used to see patients who were being treated by bariatricians with diuretics (to squeeze out every drop of excess fluid, at the risk of inducing dangerous dehydration and electrolyte imbalance), thyroid hormone (because weight loss is a symptom of hyperthyroidism), and even digitalis (because anorexia is a symptom of digitalis intoxication!).

In addition, numerous over-the-counter agents, including herbals and so-called health food products, have been promoted as aids in weight control. Among these may be mentioned methylcellulose, which swells up after absorbing fluid in the digestive system, and thus allegedly yields a sense of satiety; confections containing mostly pure sugar with a dash of the topical anesthetic benzocaine, intended to delude the stomach into thinking it is full of food; phenylpropanolamine (the active ingredient of Dexatrim products), effective as a nasal decongestant but only marginally so as an anorexiant; and ephedrine, a bronchodilator that suppresses appetite but can dangerously elevate blood pressure.

Remember those gadgets that were supposed to achieve spot reduction of subcutaneous fat by massage or vibration? And jaw wiring, to prevent the overweight patient from eating solid food? Ear stapling? Cellulite? Fads come and fads go. One could write a whole book about ineffectual and fraudulent weight-loss methods, but my purpose here is to present a balanced and scientifically accurate survey of obesity treatments, both good and bad.

### **When Loss Is Gain: The Medical Management of Obesity**

On the positive side, there are some safe and moderately effective ways of controlling overweight. Moreover, reduction of excessive weight leads to improvement in most of the associated health risks. Obviously losing weight won’t repair osteoarthritic knees and hips, or heal a heart scarred by a previous myocardial infarction, but statistics confirm improvement in hypertension, type 2 diabetes, hypercholesterolemia, gastroesophageal reflux disease, and infertility.

All effective methods of weight reduction, with the exception of liposuction and other cosmetic surgical procedures in which subcutaneous fat is mechanically removed, work by substituting an energy deficit for an energy surplus. They do this by reducing caloric intake, increasing physical exertion, or (preferably) both. Exercise programs without dietary restriction usually fail, because exercise makes people hungry, and when people get hungry, they eat.

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The standard basic weight-reduction program calls for a restricted calorie, low-fat diet, and performance of aerobic activity of at least moderate intensity for at least 30 minutes a day. Calorie allowances are based on the patient's ideal weight (according to height, with allowances for age and frame) and basal level of physical exertion (occupational and avocational). A program that consistently takes off more than 1-1.5 lb/wk is probably too stringent. It may induce undesirable changes in body chemistry, and probably cannot and should not become a lifelong habit. The wisest way to monitor weight loss is to weigh in just once a week, so as to avoid attributing undue significance to minor variations caused by consumption of food and drink, water retention or loss, and defecation. As I often remind my patients, an 8 ounce glass of water weighs half a pound.

Although some patients are helped in achieving weight loss by anorexiants drugs, behavior modification programs, or hypnosis, the emphasis must be on establishing permanent changes in lifestyle. Surgical procedures to reduce gastric capacity or intestinal absorption of nutrients are reserved

for victims of severe obesity in whom medically supervised regimens have failed to yield weight loss. Weight reduction is not recommended during pregnancy or in patients with osteoporosis, cholelithiasis, severe mental illness, or terminal illness.

*Anorexiant*s (also called anorectics and anorexigenics) are drugs that reduce appetite. It has long been known that central nervous system (CNS) stimulants of the amphetamine class, besides promoting a heightened sense of energy and well-being and reducing the need for sleep, produce anorexia. These drugs are referred to as sympathomimetic agents because they mimic the effects of natural hormones and neurotransmitters, such as epinephrine and norepinephrine, that mediate the "fight or flight" response of the sympathetic division of the autonomic nervous system to critical challenges.

For several decades, amphetamine and its dextrorotatory isomer, dextroamphetamine, were widely prescribed as anorexiant. Because of the high risk of habituation and abuse, these drugs have long been classed by federal authorities as Schedule II controlled substances (on the same level as narcotics such as meperidine and morphine). In 1990, the alarming spread of habituation to amphetamines prompted the Food and Drug Administration (FDA) to withdraw approval of these agents for the treatment of obesity. Their use is currently restricted to the treatment of attention deficit disorder and narcolepsy.

Several amphetamine-related drugs are still approved for short-term use in curbing appetite as an adjunct to the dietary treatment of obesity (see table, Sympathomimetic Anorexiant). The primary mechanism whereby amphetamines and amphetaminelike agents lead to weight loss is thought to be reduction of appetite, but other effects on metabolism have not been excluded.

Although these drugs have their place in the management of some cases of obesity, they also have many shortcomings. Tolerance develops rapidly, so that after a few weeks of continuous treatment, appetite suppression no longer occurs with the initial dose. As with the amphetamines, psychological dependence also frequently occurs, particularly if dosage is increased to overcome tolerance. Because these drugs are sympathomimetic agents, they elevate pulse and blood pressure (often already elevated in obese persons) and may cause cardiac palpitation. Common CNS side-effects are hyperactivity, restlessness, and insomnia.

Moreover, these agents produce only modest degrees of weight loss, if any, unless combined with a full program of caloric restriction and regular exercise. Perhaps the most serious objection to their use is that, by curbing appetite temporarily and artificially, they distract from the basic issues and goals of weight control, substitute a gimmick for personal commitment to a healthful regimen, and reduce motivation for a long-term improvement in eating habits. Although FDA guidelines advise the use of anorexiant only in persons with a BMI of 30 or more (27 in the presence of certain other risk factors), patients often request and obtain them to control appetite for purely cosmetic reasons, or even simply for use as "uppers."

Other drugs with CNS effects have also been found to be useful in weight-loss programs. Dexfenfluramine is a serotonin reuptake inhibitor and releasing agent with a pharmacologic action somewhat like that of the antidepressants fluoxetine (Prozac), sertraline (Zoloft), and others. Weight loss with this agent apparently results from suppression of appetite by an increase of serotonin receptor activation in certain brain centers. Clinical studies have shown selective reduction of the appetite for carbohydrates, and have suggested that a delay in gastric emptying may also account for some of the effects of this agent on eating behavior.

Dexfenfluramine was first marketed in 1996 under the brand name of Redux. Partly because of its novel mechanism, it quickly came into wide use in bariatric clinics. The combination of dexfenfluramine and phentermine, commonly known as fen-phen, became enormously popular, and some 22 million prescriptions were written in one year for these two agents together. Dozens of primary care physicians began limiting their practices to the treatment of obesity with fen-phen.

But dexfenfluramine is by no means innocuous. Before it was released for use in this country, experience abroad had shown that prolonged administration could lead to primary pulmonary hypertension, an essentially untreatable and generally fatal disorder. In addition, by elevating plasma levels of sero-

#### **Sympathomimetic Anorexiant**

benzphetamine (Didrex)  
diethylpropion (Tenuate)  
methamphetamine (Desoxyn)  
phentermine (Adipex-P,  
Fastin, Ionamin)

tonin, dexfenfluramine can cause heart valve damage like that which occurs in carcinoid syndrome.

In July 1997 the Food and Drug Administration (FDA) warned physicians that ongoing clinical studies suggested a heightened risk of heart valve damage and primary pulmonary hypertension when dexfenfluramine is combined with phentermine. In November of the same year, in the face of several lawsuits and mounting evidence of an unacceptable risk profile, the FDA withdrew approval of dexfenfluramine.

At that point, many weight-loss clinics immediately substituted fluoxetine for dexfenfluramine in the fen-phen regimen. Although fluoxetine has FDA approval for the treatment of bulimia nervosa, its employment as an adjunct in the treatment of simple obesity is an off-label use.

In 1998 a new and unrelated agent, sibutramine, was marketed under the name of Meridia. Sibutramine inhibits the reuptake not only of serotonin but also of norepinephrine and dopamine, but it does not promote the release of any of these agents. So far, clinical trials have not identified any cases of cardiac disease or primary pulmonary hypertension induced by sibutramine. However, its use has been associated with insomnia and a rise in blood pressure in some patients.

Data are not available on the continuous use of sibutramine for more than one year. Because of the bad experience with fenfluramine, the FDA has advised caution in the long-term use of this agent. In particular, physicians are warned that when weight loss of roughly 1 lb/wk is not observed during the first four weeks of therapy, further administration of sibutramine will probably be ineffectual.

In April 1999 the FDA approved the release of an anti-obesity agent with a new mechanism of action. Orlistat, marketed as Xenical, works in the digestive system by inhibiting intestinal lipases, enzymes that digest fat. When taken in the recommended dosage (one capsule with each meal that includes fat), orlistat blocks the absorption of about one-third of ingested fat. Clinical trials in which administration of orlistat accompanied a restricted-calorie diet deriving no more than 30% of calories from fat have shown only modest success. Fewer than two-thirds of subjects lose more than 5% of total body weight in one year.

Orlistat is not absorbed systemically, and thus far its use has not been associated with serious side-effects. However, unabsorbed fat passing into the colon can cause flatulence, steatorrhea (frequent or urgent passage of greasy, bulky, foul-smelling stools), and fecal leakage. These consequences can be averted by reducing the fat content of the diet, but a patient who can be satisfied with a low-fat diet doesn't need the medicine! Because absorption of fat-soluble vitamins (A, D, E, K) and beta-carotene from foods may be significantly reduced by orlistat, these must be artificially supplemented.

Surgical procedures designed to facilitate weight loss by altering the anatomy and physiology of the digestive system are approved only for patients with severe obesity in whom medically supervised regimens have failed. The rationale of these operations is either to reduce gastric capacity (thus allowing a feeling of satiety with smaller meals) or to curtail intestinal absorption of nutrients. Some procedures combine both methods. Most operations for obesity can be performed laparoscopically.

A person who habitually overeats may have a gastric capacity of 2-3 liters. Filling such a stomach even once a day with a normal variety of foods may yield far more calories than can be expended by normal activities. Various gastric pouch procedures (reduction gastroplasties) have been devised to diminish the effective capacity of the stomach. Vertical gastric stapling is a permanent reconstructive procedure in which a pouch with a capacity of about 60 mL (2 oz) is created in the part of the stomach into which the esophagus empties. A narrow passage between this pouch and the remainder of the stomach, reinforced with synthetic mesh, retards emptying, providing a prolonged sensation of fullness with small amounts of food.

With gastric banding, still an investigational procedure at this writing, a gastric pouch is formed by the application of a band of silicone rubber around the stomach to create an hourglass shape. Unlike stapling, this procedure does not involve opening the digestive tract, and it is reversible. The device contains a balloon that permits adjustment without repeat surgery. Gastric pouch procedures have been moderately effective, but the artificial sense of postprandial satiety is not entirely gratifying to many patients, who may defeat the purpose of the procedure by nibbling constantly.

Gastric bypass (Roux-en-Y gastrojejunostomy), a more complex procedure, consists of creating a very small upper gastric pouch that is completely segregated from the remainder of the stomach. A Y-shaped connection is then formed whereby this pouch drains directly into the jejunum, while the lower, larger, segregated portion of the stomach continues to drain gastric juice into the duodenum. This procedure supposedly leads to early satiety not only by reducing the effective capacity of the stomach but by delivering foods rapidly to the small intestine for earlier absorption. Most patients who have had gastric bypass achieve and maintain substantial weight loss.

Other surgical procedures are intended to reduce absorption of ingested foodstuffs. Jejunioleal bypass, one of the earliest surgical procedures used to combat morbid obesity, consisted of shortening the effective absorptive length of the small intestine by 90% or more. Often associated with severe malabsorption, metabolic disorders, and hepatic and renal impairment, it is no longer performed.

### Diet Drugs on the Internet

Not all quackery involves the use of ineffectual remedies. Anyone who has an on-line computer and a credit card can obtain phentermine, sibutramine, and orlistat via the Internet from physicians who are willing to prescribe and dispense these agents without ever seeing or weighing the patient, much less performing a physical examination or laboratory studies, providing dietary counseling, or monitoring the effects of treatment. Patients are required to submit answers to a simple questionnaire and to waive any redress in the event of adverse consequences. This outrageous and irresponsible practice is currently legal in 39 states.

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Biliopancreatic diversion involves reimplanting the biliary and pancreatic ducts from the duodenum to the jejunum, so that digestive enzymes reach the foodstream relatively late in its passage through the small intestine. This procedure selectively reduces the absorption of fats, while permitting nearly normal absorption of protein and carbohydrate. It may be combined with a 70% gastrectomy to reduce meal size. Even with normal-sized portions of food, actual caloric intake is greatly reduced. Although the procedure is highly effective in reducing body weight, most patients suffer from steatorrhea and inadequate absorption of protein, calcium, and fat-soluble vitamins. These must be combated with a low-fat diet and aggressive nutritional supplementation.

#### **Size XL Genes?**

Efforts to find a genetic cause for obesity have focused on genes that influence the function of the hypothalamus (the part of the brain concerned with appetite, satiety, and eating behavior), the deposition of fat in adipose cells, and the efficiency of oxidative reactions involved in the expenditure of energy in tissues. Considerable interest has been aroused recently by the discovery of a "satiety hormone." Leptin is a protein, secreted by adipose tissue, that acts on a receptor site in the hypothalamus to curb appetite and increase energy expenditure as body fat stores increase. Leptin levels are reduced by fasting and increased by inflammation.

The gene encoding leptin has been identified. Laboratory mice with mutations on this gene become morbidly obese, diabetic, and infertile. Administration of leptin to these mice improves glucose tolerance, increases physical activity, reduces body weight by 30%, and restores fertility. Although mutations in the leptin gene have been found in a small number of morbidly obese human subjects with abnormal eating behavior, the majority of obese persons do not show such mutations, and have normal or elevated circulating levels of leptin.

In controlled clinical trials, both lean and overweight persons have experienced modest weight loss while receiving daily injections of leptin over a period of months. All subjects followed weight-reduction diets during the trial period. Weight loss in some subjects receiving leptin did not exceed that achieved by subjects receiving placebo, but when significant weight reduction occurred, it was proportionate to dosage. Administration of leptin seems unlikely to become a standard treatment for obesity, but only time will tell.

Fat cells (adipocytes) develop when precursor cells called preadipocytes fill up with fat. Some very obese persons have been shown to have mutations in a gene that encodes a protein

called g-2 type peroxisome proliferator-activating receptor. In such persons, a breakdown in the regulation of fat metabolism apparently leads to uncontrolled conversion of preadipocytes to adipocytes.

Disturbances in the metabolism of pro-opiomelanocortin (POMC) have been implicated as a possible source of obesity in some persons. This substance, produced in the brain and skin, is the precursor of hormones that influence adrenocortical function, skin pigmentation, food intake, and fat storage. Strains of mice that are bred to lack the gene that encodes POMC will overexpress the so-called agouti protein, become obese, and develop yellow fur. Injections of melanocortin peptides into these mice correct the obesity and restore the normal dark brown color to the fur, but do not result in weight loss in normal mice. The implications of these findings for human medicine are unknown.

**O**verweight is a medically hazardous condition with metabolic, psychological, and genetic roots. Seldom is it a manifestation of gluttony, laziness, poor self-discipline, or moral laxness. The correction of obesity generally requires a firm commitment and permanent lifestyle changes. Overweight persons who delude themselves into thinking they can achieve and maintain a healthy weight without effort or discomfort, if only they can find the right fad diet or magic pill, betray unrealistic attitudes and rarely succeed in achieving and maintaining a healthy weight.

Public health authorities and nutritionists have urged physicians to adopt a more aggressive and supportive role in combating obesity, and have issued guidelines for the identification, evaluation, and treatment of obesity in children and adults. They emphasize that diet and exercise remain the mainstays of treatment, but acknowledge the difficulties in sustaining long-term weight loss.

Pharmacologic agents approved by the FDA for long-term treatment of obesity do not work in all patients, and typically induce only modest weight loss at best. Surgical procedures designed to reduce gastric capacity or intestinal absorption of nutrients are approved only for extreme, recalcitrant obesity, and may have devastating effects on gastrointestinal function and general health.

The future will bring more precisely targeted and efficacious treatments for obesity based on a clearer understanding of the genetic, biochemical, and psychological factors underlying body weight regulation and its disorders.

John H. Dirckx, M.D., has been director of the student health center at University of Dayton, Ohio, since 1968. He is the author of *Human Diseases* (1997), *Laboratory Medicine: Essentials of Anatomic and Clinical Pathology*, 2nd ed. (1995), and *H&P: A Nonphysician's Guide to the Medical History and Physical Examination* (1991), published by Health Professions Institute.

