

# Current Status of Medical and Surgical Therapy for Obesity

EDWARD C. MUN, GEORGE L. BLACKBURN, and JEFFREY B. MATTHEWS

Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

The incidence of obesity (especially childhood obesity) and its associated health-related problems have reached epidemic proportions in the United States. Recent investigations suggest that the causes of obesity involve a complex interplay of genetic, environmental, psychobehavioral, endocrine, metabolic, cultural, and socioeconomic factors. Several genes and their protein products, such as leptin, may be particularly important in appetite and metabolic control, although the genetics of human obesity appear to involve multiple genes and metabolic pathways that require further elucidation. Severe obesity is frequently associated with significant comorbid medical conditions, including coronary artery disease, hypertension, type II diabetes mellitus, gallstones, nonalcoholic steatohepatitis, pulmonary hypertension, and sleep apnea. Long-term reduction of significant excess weight in these patients may improve or resolve many of these obesity-related health problems, although convincing evidence of long-term benefit is lacking. Available treatments of obesity range from diet, exercise, behavioral modification, and pharmacotherapy to surgery, with varying risks and efficacy. Nonsurgical modalities, although less invasive, achieve only relatively short-term and limited weight loss in most patients. Currently, surgical therapy is the most effective modality in terms of extent and duration of weight reduction in selected patients with acceptable operative risks. The most widely performed surgical procedure, Roux-en-Y gastric bypass, achieves permanent (followed up for more than 14 years) and significant weight loss (more than 50% of excess body weight) in more than 90% of patients.

The notion that obesity is the result of a lack of willpower on the part of affected individuals is simplistic, unscientific, and counterproductive in combating this disease. It is increasingly clear that the regulation of body weight is dependent on multiple biologic factors modified by various environmental and psychosocial factors. The food intake of an average adult matches energy expenditure within 0.17% per decade,<sup>1</sup> indicating the presence of a biologic regulatory system with remarkable precision in energy metabolism. Although the influence of genetic factors on the expression of obesity has been demonstrated repeatedly,<sup>2-4</sup> the re-

cent explosion in the prevalence of obesity is most likely caused by environmental and behavioral changes. Nevertheless, recent advances in the genetics of obesity and in energy metabolism should yield new insights into fundamental physiologic regulatory processes and may lead to more effective and specific therapies.

The degree of obesity is most conveniently quantified by the body mass index (BMI) because of its ease of calculation and relatively accurate correlation with body fat content. BMI represents a ratio of weight and body surface area, expressed as weight (kilograms) divided by the square of height (square meters). Conventional categories of relative body weight corresponding to BMI are shown in Table 1.<sup>5</sup> Using these categories, more than half of all adults<sup>6</sup> and approximately a quarter of all children are overweight (BMI > 25) or obese (BMI > 30),<sup>7</sup> and 18% of all Americans are obese (BMI > 30).<sup>8,9</sup> Approximately 280,000 annual deaths are estimated to be attributable to obesity in the United States.<sup>10</sup> Four of 5 obese people have at least one debilitating illness associated with the underlying obesity. In developed countries, obesity is more common among those of lower socioeconomic status. The prevalence of obesity is higher in certain ethnic groups such as African Americans and Mexican Americans. U.S. public health officials indicate that obesity currently is not effectively addressed (Healthy People 2010). For example, in a recent community-based study over a 3-year period, more than half (53.7%) of the subjects gained weight, whereas only a quarter (24.5%) were able to avoid a weight gain, and successful weight loss and maintenance were seen in less than 5% (4.6%).<sup>11</sup> The urgency of the current weight problem is also reflected by the most recent top 10 leading health indicator list, in which the top 2 are physical activity and obesity, which rank above tobacco use. Many epidemiology studies have documented a close relationship between increasing adiposity and death

---

*Abbreviations used in this paper:* BMI, body mass index; GBP, gastric bypass; LCD, low-calorie diet; LFD, lower-fat diet; NPY, neuropeptide Y; VBG, vertical banded gastroplasty; VLCD, very low-calorie diet.

© 2001 by the American Gastroenterological Association

0016-5085/01/\$35.00

doi:10.1053/gast.2001.22430

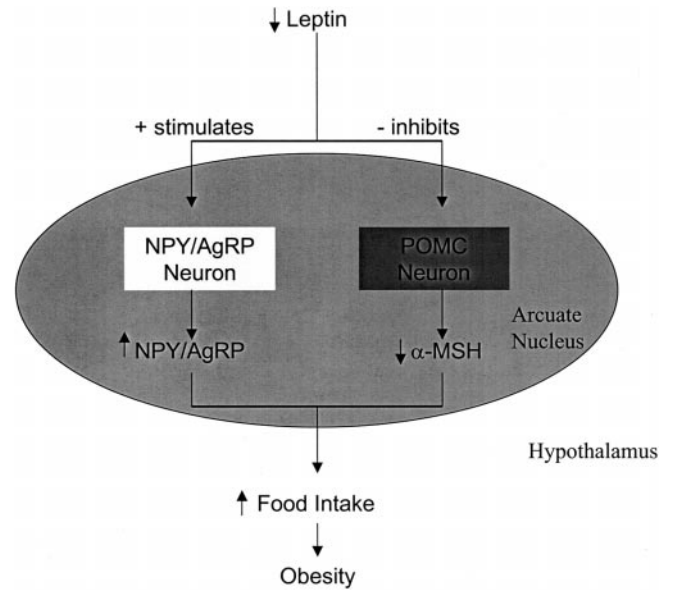
**Table 1.** Classification of Obesity

Obesity class		BMI (kg/m <sup>2</sup> )
Underweight		<18.5
Normal		18.5–24.9
Overweight		25.0–29.9
Obesity	I	30.0–34.9
	II	35.0–39.9
Extreme obesity	III	≥40.0

Data from US Department of Health and Human Services.<sup>5</sup>

rates.<sup>12–15</sup> Figure 1 represents one of many BMI versus mortality curves, illustrating an exponential increase in mortality risk with obesity. A recent prospective study again confirmed that obesity is closely associated with an increased risk of death from all causes, including cardiovascular disease and cancer.<sup>16</sup>

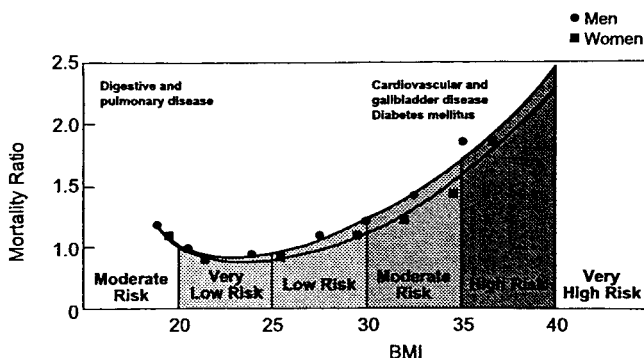
The mechanisms regulating overall energy balance and weight are incompletely understood. In 1994, the *ob* gene and its protein product leptin were identified by positional cloning from *ob*<sup>-/-</sup> mice.<sup>17</sup> Leptin, a 167–amino acid protein produced by adipocytes, appears to be an afferent signal for satiety in mice.<sup>18</sup> In *ob*<sup>-/-</sup> mice, the lack of functional leptin leads to hyperphagia and obesity, and its replacement reverses the weight gain. Although both leptin deficiency<sup>19</sup> and a leptin receptor defect<sup>20</sup> have been identified in humans, only a handful of cases can be attributed to these; almost all obese human patients instead display leptin resistance.<sup>18,21</sup> The role of leptin in humans is not as straightforward as in mice, although it appears to be an important metabolic signaling molecule that regulates energy expenditure as well as food intake.<sup>22</sup> Leptin receptors are richly expressed in the arcuate nucleus of the hypothalamus, which expresses several key molecules regulating food intake (Figure 2). These include neuropeptide Y (NPY) and agouti-related protein, which increase food intake, as well as pro-opiomelanocortin, a precursor of  $\alpha$ -melanocyte-stimulating hormone, and cocaine- and amphet-



**Figure 2.** Effects of leptin on food intake. A decreased plasma level of leptin activates NPY/agouti-related protein neurons in the arcuate nucleus of the hypothalamus, resulting in increased expression of both NPY and agouti-related protein. Increased NPY and agouti-related protein release then stimulates food intake and subsequent weight gain. At the same time, pro-opiomelanocortin neurons in the same region of the hypothalamus are inhibited by leptin deficiency. A resultant decrease in  $\alpha$ -melanocyte-stimulating hormone expression and release leads to reduced activity in melanocortin-mediated anorexia, and thus increased food intake and weight gain.

amine-regulated transcript, which decrease food intake (Figure 2).<sup>23–25</sup> Mutations in pro-opiomelanocortin and a melanocyte-stimulating hormone receptor have been demonstrated to be associated with obesity and leptin resistance.<sup>26,27</sup>

Adaptive thermogenesis (regulated production of heat) is an important element of energy expenditure. Some of the key agents in the regulation of thermogenesis such as uncoupling proteins<sup>28,29</sup> and peroxisome proliferator-activated receptor  $\gamma$  coactivator 1<sup>30</sup> appear to be modulated by leptin.<sup>31,32</sup> Human leptin trials for the treatment of obesity are currently in progress. Because most obese patients have leptin resistance, the potential of high-dose exogenous leptin for antiobesity therapy is uncertain, although the analogous strategy of insulin treatment for insulin-resistant type II diabetes mellitus has been successful. Decreased leptin levels may, at least in part, be responsible for high failure rates in diet therapy of obesity. The notion of combining leptin replacement with a diet is an attractive possible new approach to the medical management of obesity. Activation of thermogenesis and lipolysis by stimulation of the  $\beta_3$ -adrenergic receptor is another avenue for new drug development.



**Figure 1.** Mortality risk increases with obesity. Adapted and reprinted with permission.<sup>133</sup>

## What Is Morbid About Morbid Obesity?

Severe obesity is associated with the development of a variety of medical conditions, thus the term *morbid obesity*. Premature mortality has been repeatedly observed in severely obese patients.<sup>16,33,34</sup> Some of the contributing conditions include coronary artery disease, hypertension, type II diabetes mellitus, sleep apnea syndrome, obesity hypoventilation syndrome, and necrotizing panniculitis. Morbid obesity is also associated with numerous other disabling conditions such as chronic venous stasis disease, osteoarthritis, urinary incontinence, gastroesophageal reflux disease, fatty liver, cholelithiasis, idiopathic intracranial hypertension (pseudotumor cerebri), sex hormone dysfunction, and clinical depression. Many of these comorbidities are closely related to the increased intra-abdominal pressure and sagittal abdominal wall diameter.<sup>35</sup> Increased risk is observed in obese patients for the development of various cancers, including breast, colon, uterine, and prostate cancer. Table 2 lists various obesity comorbidities encountered in the clinical setting.

## Does Weight Loss Reduce the Morbidity of Obesity?

The purpose of treatment for obesity is to restore normal metabolic and organ function. It should be remembered that the goal of any antiobesity therapy is not to reduce weight per se, but to reduce the disability and morbidity, and thus to increase the quality of life. The rationale for treatment of obesity is not only the increased mortality attributable to obesity, but also the numerous lines of evidence suggesting that weight loss reduces risk factors for comorbid disease.<sup>5</sup> A modest to moderate loss of excess weight (the difference between actual weight and the ideal body weight for a given height) achieved by life-style changes has been shown to reduce blood pressure in overweight hypertensive<sup>36,37</sup> and nonhypertensive patients,<sup>38</sup> to improve serum lipid profile (reduced triglyceride and total and low-density lipoprotein cholesterol levels, along with increased high-density lipoprotein cholesterol levels),<sup>39,40</sup> and to improve glucose tolerance and fasting glucose levels in normoglycemic and diabetic patients.<sup>41-43</sup> Diet, exercise, and standard behavior modification have been the traditional methods, but these do not always work by themselves. Pharmacologic treatments have yielded mixed results over the years, with some patients responding well but others not at all. Recently, a new generation of drugs promises hope for treatment of those with clinically

**Table 2.** Obesity Comorbidities

Cardiovascular system
Coronary artery disease
Hypertension
Congestive heart failure
Cor pulmonale, pulmonary hypertension
Deep vein thrombosis
Pulmonary embolism
Respiratory system
Obstructive sleep apnea
Asthma
Obesity hypoventilation syndrome
Endocrine system
Type II diabetes mellitus
Glucose intolerance, decreased insulin sensitivity
Dyslipidemia (hypercholesterolemia, hypertriglyceridemia)
Amenorrhea, dysmenorrhea
Polycystic ovary syndrome
Infertility
Hirsutism
Gynecomastia
Breast cancer
Gastrointestinal and abdominal wall system
Gastroesophageal reflux
NASH, fatty liver
Cholelithiasis
Colon cancer
Hernias (umbilical, epigastric, incisional, inguinal)
Musculoskeletal system
Degenerative joint disease, osteoarthritis
Chronic low back pain
Genitourinary system
Urinary stress incontinence
Hypogonadism
Uterine cancer
Prostate cancer
Integument
Venous stasis disease
Superficial thrombophlebitis
Cellulitis, panniculitis, candidiasis
Increased postoperative wound infection
Psychoneurologic system
Clinical depression
Migraine headache
Idiopathic intracranial hypertension (pseudotumor cerebri)
Cerebrovascular accident (stroke)

significantly obesity, but to date these therapies have not been shown to be effective for cases of severe obesity.

Surgical treatments for obesity in general achieve more profound and long-lasting weight loss and improve or resolve most comorbidities of severe obesity. In addition to the improvements in hypertension,<sup>44,45</sup> serum lipid levels,<sup>46</sup> and diabetes mellitus,<sup>47,48</sup> weight reduction by surgery improves respiratory insufficiency caused by sleep apnea and obesity hypoventilation syndrome,<sup>49,50</sup> reflux esophagitis,<sup>51,52</sup> pseudotumor cerebri,<sup>53</sup> and venous stasis ulcers.<sup>35</sup> However, a more recent study by Sjostrom et al.<sup>54</sup> shows differential effects of long-term (8 years) surgical weight loss on diabetes and hypertension. Although surgical weight loss was associated with sig-

nificant reduction in both diabetes and hypertension at 2 years, by 8 years the incidence of hypertension in the surgical group was the same as that in matched controls. Despite the clear benefits seen with surgical weight reduction, several key questions remain: Does the degree of improvement of obesity comorbidities by surgery reduce the complications of those conditions, and thereby translate into a longer life and improved quality of life for the patients? Is the degree of improvement offset by the risk of surgical complications? What is the cost (or benefit) of such treatment to society? The Swedish Obese Subjects (SOS) study is one of the few longitudinal investigations attempting to answer these fundamental questions.

### Medical Therapy

Capitalizing on the increased market for obesity therapy, numerous commercial programs have sprung up across the United States and formed a thriving multi-billion dollar industry. These nonsurgical programs are classified into 4 basic approaches: diet, exercise, behavior modification, and drugs. Accumulating data reveal the effectiveness of these modalities in inducing modest weight loss in many participants; however, these approaches are usually effective only in the short run, and indefinite continuation of such treatments is usually difficult for patients to sustain. Studies are ongoing, particularly in search of safe and effective drug therapies directed against the molecular defects of obesity.

### Diet Therapy

Theoretically, it should be a simple matter to achieve weight loss by dieting, producing an energy deficit in which intake is less than energy expenditure. As so many can attest by their own personal experience, this approach is far more difficult to put into action in an environment where delicious, high-calorie foods are abundant and easily obtained. This inherent difficulty is well illustrated by the typical results of many diet programs, in which early weight loss is achieved by most patients, but the weight loss is not maintained over the long term.

A comprehensive and critical evaluation of multiple dietary clinical trials was carried out by an expert panel convened by the National Institutes of Health (NIH) in 1998 in an effort to establish evidence-based guidelines for the treatment of obesity.<sup>5</sup> Despite confounding factors from various studies, several key conclusions could be agreed upon. First, dietary caloric reduction is indeed associated with weight loss. Low-calorie diets (LCDs) consisting of 1000–1200 kcal/day can reduce total body

weight by an average of 8% over 3–12 months. Very low-calorie diets (VLCDs) with 400–500 kcal/day produce greater initial weight loss than LCDs, but the long-term (>1 year) weight loss is not different from that of LCDs. Second, a change in diet composition by fat reduction is associated with weight loss. Lower-fat diets (LFDs), deriving 20%–30% of calories from fat, help promote weight loss by producing a reduced caloric intake. LFDs coupled with total caloric reduction produce greater weight loss than LFDs alone. LFDs produce weight loss primarily by decreasing caloric intake. Based on these findings, the panel recommends (1) LCDs for weight loss in overweight and obese patients and (2) reduction of fat as part of an LCD to reduce calories. Because there is little evidence that LFDs per se cause weight loss independent of caloric reduction, reduction in total caloric intake is the most important factor in weight loss.

Carbohydrate restriction has been the basis for several popular diets in the past, and has recently been resurrected as the “Atkins diet” and the “zone diet.”<sup>55,56</sup> The basic premise of low-carbohydrate diets is that excessive carbohydrates induce increased levels of insulin that promote transport and storage of fat. Low-carbohydrate diets, consisting inevitably of high levels of protein and fat, promptly induce depletion of liver glycogen storage and systemic ketosis resulting from oxidation of fat. However, short-term weight loss on such diets seems to be caused in large part by the loss of water and electrolytes.<sup>57</sup> This is particularly true during the initial diet phase, in which heavily hydrated glycogen is catabolized to meet energy requirements and maintain blood glucose. Low-carbohydrate, high-protein diets seem particularly effective in suppressing hunger, possibly because of branched-chain amino acid content.<sup>58</sup> Thus, the weight loss may not necessarily be attributable solely to the composition of the diet, but also to reduced total caloric intake. Additionally, a more recent study showed that weight loss is not different between low- and high-carbohydrate diets,<sup>59</sup> indicating that total energy intake, not nutrient composition, determines weight loss. Because long-term studies are not yet available, the long-term safety and efficacy of low-carbohydrate, high-protein/fat diets remain to be established.

### Exercise

In our modern, technology-driven age, an ever-increasing number of labor-saving conveniences and gadgets contribute to the reduction in average daily energy expenditure that favors the development of obesity.<sup>60</sup> Although physical activity and exercise are key factors in successful weight reduction programs, the contribution

of exercise to weight loss is modest at best. For example, approximately 40 miles of walking is required to metabolize 1 kg of fat. The effect of exercise on weight loss is variable, but most studies show only a small reduction (~2 kg),<sup>37,61,62</sup> and some show no benefit at all.<sup>63,64</sup> Furthermore, most studies show that weight loss induced by exercise alone is inferior to that achieved by diet alone.<sup>37,64,65</sup> However, exercise is probably independently important to the well-being of overweight and obese individuals because physical activity increases maximal oxygen uptake and thus cardiorespiratory fitness.<sup>37,63,64</sup> Moreover, maintenance of weight loss is facilitated by regular exercise.<sup>66</sup> Unfortunately, the unrealistic expectations of weight loss from exercise regimens that are promoted by many commercial enterprises may lead to disappointment and discontinuation of exercise. Development of a consistently achievable exercise program for each overweight patient is essential. Although it is difficult, even the most obese patients may be able to participate in some form of appropriately designed physical activity.

### Behavior Therapy

Conditioning probably plays a major role in many behavioral disorders. Like Pavlov's dog, who salivated at the sound of a bell, overweight and obese individuals become conditioned to the repeated association of, for example, pizza and beer with watching sporting events on television. Thus, behavior therapy in obesity is to identify cravings and weaken or disconnect the triggering events that lead to overeating. However, the effectiveness of behavior therapy alone against obesity is modest compared with that reported in other conditions such as depression, anxiety, and bulimia,<sup>67</sup> and it is best combined with other weight loss modalities. When behavior therapy was combined with diet therapy in the form of an LCD or VLCD, maintenance of weight loss at 1 year was better than with diet alone.<sup>68,69</sup> Similarly, drug therapy with fenfluramine was shown to achieve a better weight loss at 6 months, and better maintenance at 1 year, when combined with behavior therapy.<sup>70</sup> Long-term (1–5 years) follow-up of these patients, however, indicates that most of the subjects in the group regain the lost weight in the absence of continued behavioral intervention.<sup>69,71</sup> A recent NIH expert panel recommends that behavior therapy be an adjunct treatment for weight loss and weight maintenance.<sup>5</sup>

### Pharmacotherapy

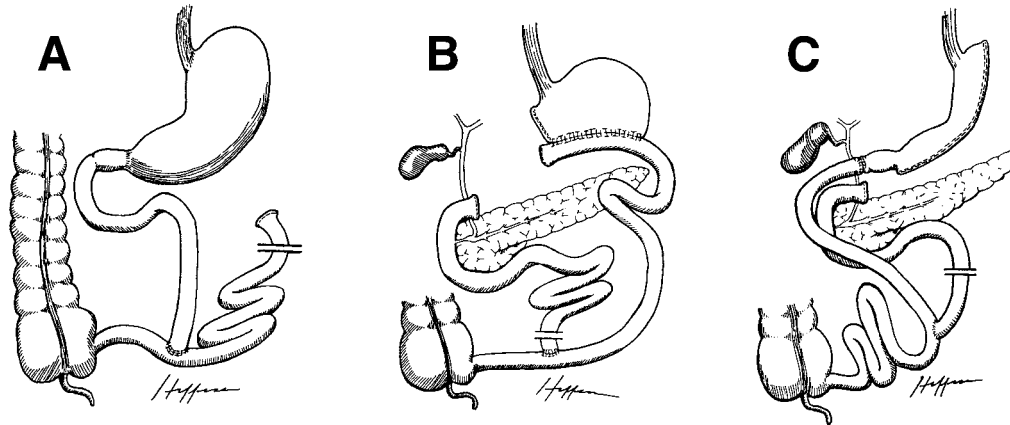
Although somewhat effective, drug therapy, like other nonsurgical modalities, achieves only a modest (~10%) weight reduction and requires continued use to

maintain this result. In addition, the dangerous adverse effects associated with some drugs, including addiction with amphetamines<sup>72</sup> and valvular heart disease with fenfluramine plus phentermine (fen-phen),<sup>73</sup> have given pharmacotherapy for obesity a bad reputation. However, recent advances in understanding of molecular mechanisms of weight regulation may yet lead to the development of new classes of antiobesity drugs.

Most antiobesity drugs can be classified into 2 major groups by their mechanisms of action: appetite suppression and/or stimulation of thermogenesis and intestinal fat absorption. Fenfluramine and its *d* isomer dexfenfluramine increase central serotonin release and induce anorexia and weight loss. In one study, dexfenfluramine showed a small but statistically significant advantage in weight loss when 35% of the subjects taking dexfenfluramine (compared with 17% of the placebo group) were able to lose at least 10% of their initial weight.<sup>74</sup> Phentermine is a central adrenergic agonist that leads to appetite suppression and weight loss.<sup>72</sup> Combination therapy with serotonergic (fenfluramine) and the catecholaminergic (phentermine) agents was demonstrated to be effective in weight reduction<sup>75,76</sup> and became widely popular until an unusual form of valvular heart disease in women taking this combination was reported in 1997<sup>73</sup> and confirmed in other studies.<sup>77–79</sup> These agents were subsequently withdrawn from the market in 1998. Phentermine alone does not appear to increase valvular heart disease.

Sibutramine, a  $\beta$ -phenethylamine, is a selective inhibitor of the reuptake of both serotonin and norepinephrine and is used more widely since the discontinuation of fenfluramine and dexfenfluramine. It induces both decreased food intake and increased thermogenesis.<sup>80–82</sup> Weight loss induced by sibutramine was shown to be comparable to that induced by dexfenfluramine.<sup>83</sup> In another study, patients taking sibutramine maintained a continued weight loss of 15% over a 1-year period after an initial diet-induced weight loss, and those in the placebo group regained the weight they initially lost.<sup>84</sup> Patients using sibutramine should be monitored for sympathomimetic side effects, including any tachycardia and hypertension.

Orlistat, an inhibitor of pancreatic lipase, decreases fat absorption in the intestine. Orlistat blocks digestion of approximately 30% of ingested dietary triglyceride<sup>85</sup> and has been shown to achieve a weight loss of ~10% (compared with ~5% in the control group).<sup>86,87</sup> However, since the induction of fat malabsorption is its basis of action, it is rather common that steatorrhea develops with orlistat if enough fat is ingested during a meal.<sup>88</sup>



**Figure 3.** Malabsorptive bariatric procedures. (A) Jejunioileal bypass; (B) biliopancreatic diversion; (C) duodenal switch.

Caffeine, ephedrine, and the combination of these 2 drugs can reduce food intake and cause thermogenesis by increasing oxygen consumption.<sup>89,90</sup> The combination of caffeine and ephedrine has been shown to be more effective in inducing weight loss than placebo, caffeine, or ephedrine alone.<sup>91,92</sup> The weight loss difference between the combination regimen and placebo is relatively small, and neither agent alone produced significantly more weight loss than placebo.<sup>91</sup> Major adverse effects of these agents include tachycardia and palpitations, and the combination of caffeine and ephedrine is not currently approved by the U.S. Food and Drug Administration.

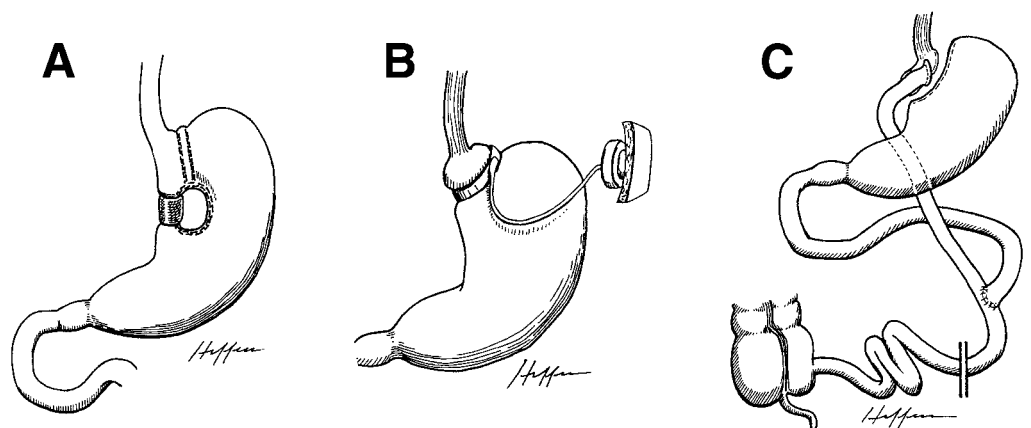
Recent insights into the molecular mechanisms of satiety and thermogenesis present a window of opportunity for novel pharmacotherapies. Potential strategies include targeting the central regulation of food intake using leptin (and leptin analogues), leptin receptor agonists, melanocortin receptor (MC4R) agonists, NPY antagonists, and cocaine- and amphetamine-regulated transcript receptor agonists. Potential drugs that target thermogenesis regulation are also promising, and these include  $\beta_3$ -adrenergic receptor agonists and agents that activate or increase uncoupling proteins. A major intestinal fatty acid transporter (FATP4) has recently been

identified<sup>93</sup>; specific inhibitors of this transporter could be effective in blocking fat absorption, although the potential for steatorrhea, as with orlistat, must be acknowledged.

Currently, indications for the use of pharmacotherapy for obesity are a BMI of 30 or a BMI of 27 with obesity-related comorbidities. However, no data show that drug treatment of otherwise healthy obese subjects prevents future complications or improves long-term outcome. Moreover, long-term weight loss data are not available. Most patients regain weight once any drug therapy is discontinued, and the success of pharmacotherapy demands life-style changes in diet, exercise, and behavior to increase its effectiveness.

### Surgical Therapy

Bariatric procedures for weight reduction share 2 major designs: intestinal malabsorption and gastric restriction. Malabsorptive procedures (Figure 3) involve rearrangement of the small intestine to decrease the functional length or efficiency of the intestinal mucosa for nutrient absorption. Restrictive operations (Figure 4) involve creation of a small neogastric pouch and gastric



**Figure 4.** Restrictive bariatric procedures. (A) VBG; (B) adjustable gastric banding; (C) Roux-en-Y GBP.

outlet to decrease food intake. Various procedures have evolved from combinations of these 2 principles. Patient selection criteria for surgical treatment of obesity were developed at a 1991 NIH Consensus Development Conference Panel and include patients with BMI > 40 or BMI > 35 with obesity-related medical comorbidities.<sup>94</sup> Additional criteria used by most bariatric surgeons as general guidelines are listed in Table 3. The goals of surgery are to induce and maintain significant loss of excess weight through a safe operation and to improve or resolve many of the comorbid medical problems so that quality of life is enhanced and prolonged. A successful outcome of bariatric surgery depends on several factors. First and foremost is a well-informed and well-educated patient with realistic expectations. It is simply unrealistic to expect total or near-total loss of excess weight with unchanged dietary habits and this expectation can result in patient dissatisfaction postoperatively. A multidisciplinary team capable of providing all aspects of preoperative and postoperative care is thought to be crucial in addressing multiple potential difficulties in the care of these complex patients. Optimally, the team should include dedicated surgeons, internists, psychiatrists, dietitians, nutritionists, and nurses.

## Malabsorptive Procedures

### Jejunioleal Bypass

The first bariatric operation was jejunioleal bypass,<sup>95</sup> in which an anastomosis of proximal jejunum (14 inches from the ligament of Treitz) to the terminal ileum (4 inches from the ileocecal valve) is created, leaving an extended loop excluded from the food stream (Figure 3A). The jejunioleal bypass is exclusively a malabsorp-

tive procedure because the stomach is not modified to limit food intake. Although this operation requires no significant changes in eating habits to induce weight loss, it was plagued by an unacceptable level of serious complications, including hepatic failure,<sup>96</sup> cirrhosis,<sup>97</sup> oxalate kidney stones, bypass enteritis, arthritis, and multiple metabolic deficiencies such as protein malnutrition, metabolic bone disease, hypocalcemia, and vitamin B<sub>12</sub> and vitamin D deficiency.<sup>98</sup> This procedure is no longer performed, and the poor experience with jejunioleal bypass caused a stigma to be associated with bariatric surgery and probably hindered more widespread application of improved operations for obesity. Survivors of this procedure should be evaluated for liver and renal dysfunction and for conversion to a more acceptable anatomic construction whenever possible.

### Biliopancreatic Diversion and Duodenal Switch

This procedure uses malabsorption of nutrients because its principal antiobesity mechanism is diversion of biliary and pancreatic secretions to the distal 50 cm of the ileum (Figure 3B).<sup>99</sup> A small degree of gastric restriction is added by performing a distal (80%) gastrectomy. The combination of gastroileostomy (rather than gastrojejunostomy), a very long biliopancreatic limb, and a very short common channel results in significant maldigestion and malabsorption of nutrients. This procedure is highly effective in inducing weight loss, particularly in "supermorbid" obese patients (BMI > 50). However, significant metabolic complications can occur, such as protein calorie malnutrition, metabolic bone disease, and deficiencies in fat-soluble vitamins, iron, calcium, and vitamin B<sub>12</sub>.<sup>99,100</sup> Most bariatric surgeons are reluctant to perform biliopancreatic diversion as a first-line antiobesity procedure.<sup>35,100</sup> The duodenal switch procedure (Figure 3C) is a modified form of biliopancreatic diversion that connects the jejunum (rather than ileum) to the proximal duodenum, thus taking advantage of dumping physiology as with Roux-en-Y gastric bypass (GBP).<sup>101-103</sup>

**Table 3.** Eligibility Criteria for Surgery

Eligibility criteria
BMI > 40 or BMI > 35 with obesity-related comorbidities
Age 16-65 yr
Acceptable medical/operative risks
Proof of failed attempts at nonsurgical weight reduction
Motivated, psychologically stable patient with realistic expectations
Patient capable of understanding the procedure and possible complications
Commitment to prolonged life-style changes
Supportive family/social environment
Commitment to long-term follow-up
Ineligibility criteria
Unsolved history of alcohol or substance abuse
History of schizophrenia, severe depression, particularly suicidal ideation
Hostile uncooperative behavior
Unacceptable medical risk
Hostile uncooperative family environment

## Restrictive Procedures

### Gastroplasty

Gastroplasty involves pure restriction of the storage capacity of the stomach to decrease consumption of solid foods. These procedures entail the use of surgical stapling devices and are thus commonly referred to as gastric stapling operations. Initially, gastroplasty consisted of horizontal partitioning of the stomach into a small proximal pouch and a large distal remnant,<sup>104,105</sup> which communicate through a narrow channel or stoma.

Later this was modified by Mason to a vertically oriented gastroplasty with the staple line extending upward from the angle of His, with a mesh-band reinforcement at the stoma on the lesser curvature, and was termed vertical banded gastroplasty (VBG) (Figure 4A).<sup>106</sup> VBG was designed to avoid 2 common causes of failure of horizontal partitioning gastroplasty: pouch and stomal dilation. The vertical staple line was primarily to exclude the fundus of the stomach, which was thought to dilate relatively easily, while polypropylene mesh encircling the stoma was used to prevent dilation.

However, a high incidence of stomal stenosis or staple line dehiscence has also been reported with VBG.<sup>107</sup> Although the small pouch and stoma effectively deter ingestion of large boluses of food, many patients learn out of frustration to cheat with high-calorie liquids such as milkshakes. Long-term weight maintenance after VBG has been disappointing, despite the rapid weight loss seen in the first 1–2 years: Nightengale et al.<sup>108</sup> found that only 38% of the patients were able to maintain at least 50% of the excess weight loss at 3 years, and Howard et al.<sup>109</sup> reported a smaller series in which no patient could maintain a 50% excess weight loss by 5 years. Sugerman et al.<sup>110</sup> also found that the mean loss of excess weight was only approximately 38% at 3 years. In these randomized prospective trials, weight loss after VBG was inferior to that after Roux-en-Y GBP, leading many bariatric surgeons to abandon gastroplasty as a primary antiobesity procedure.<sup>35,111</sup>

### Gastric Banding

Gastric banding, another pure gastric restrictive procedure in which a prosthetic band is encircled around the proximal stomach to compartmentalize it into a small pouch and a large remnant, was initially described by Bo and Modalsli.<sup>112</sup> The absence of a staple line and of the associated risk of staple line dehiscence is a theoretical advantage of this procedure. An adjustable gastric band (Figure 4B) was later introduced in which a subcutaneous saline port connected to the adjustable band allows changes in the stoma size.<sup>113</sup> This device may be placed laparoscopically,<sup>114,115</sup> making it an attractive new device. The results are widely variable but will probably prove comparable to those of VBG.<sup>116–118</sup> Westling et al.<sup>119</sup> reported a 56% loss of excess weight at 2 years in 90 patients, but with a disappointing 35% conversion to Roux-en-Y gastric bypass. The adjustable gastric band is not yet available in the United States pending the results of a multicenter trial in progress.

### Gastric Bypass

Based on the observation that patients with a small proximal gastric remnant after subtotal gastrectomy experienced significant weight loss, GBP was first used to treat obesity by Mason and Ito in 1969.<sup>120,121</sup> The original operation partitioned the stomach into a small proximal cardia and a distal bypassed stomach, with a loop gastrojejunostomy to drain the proximal pouch. Various modifications have been introduced since then, such as Roux-en-Y gastrojejunostomy (Figure 4C),<sup>122</sup> in situ compartmentalization of stomach without division,<sup>123</sup> and lengthening of the Roux limb.<sup>124</sup> This procedure is primarily a restrictive operation in that ingestion of a large meal is prevented by a small gastric pouch and a narrow stoma. In addition, the gastrojejunostomy configuration of this operation uses dumping physiology (characterized by lightheadedness, nausea, palpitations, diaphoresis and/or abdominal pain, and diarrhea) as a negative conditioning response when a high-carbohydrate liquid meal is ingested. Thus, after a purely restrictive operation such as VBG, sweets eaters resistant to weight loss because of dietary indiscretions such as high-carbohydrate liquid meals may lose significant weight if their anatomy is reconfigured to Roux-en-Y GBP.<sup>52</sup> Dumping symptoms in response to oral glucose occur specifically in GBP but not in VBG patients, and this phenomenon is closely associated with an elevated serum enteroglucagon level.<sup>125,126</sup>

Both procedures, VBG and GBP, are endorsed by the NIH Consensus Development Panel, but GBP has been shown to be superior to VBG in weight reduction in several randomized, prospective comparisons<sup>109,110,127</sup> and has emerged as the gold standard operation.<sup>8</sup> Long-term maintenance of weight loss after GBP has been excellent. Pories et al.<sup>48</sup> reported a series with 58%, 55%, and 49% loss of excess weight at 5, 10, and 14 years from surgery, respectively. More recently, Jones reported a 62% loss of excess weight at 10 years.<sup>111</sup> Modifications that enhance the malabsorptive effects of Roux-en-Y GBP include lengthening the Roux limb (thus shortening the distal common digestive channel). “Long-limb GBP,” in which the Roux limb is 150 cm long, compared to the standard 50–75 cm,<sup>124</sup> “distal GBP,” and “very very long Roux limb GBP,” in which the distal common digestive channel is shortened to 50–100 cm,<sup>100</sup> may achieve better weight loss in super-obese (BMI  $\geq$  50) patients, although the potential for debilitating malnutrition and vitamin deficiencies exists.

With recent advances in minimally invasive surgical techniques, laparoscopic GBP has become feasible.<sup>128–131</sup> This technically intensive procedure carries a significant

**Table 4.** Complication Rates After Roux-en-Y Gastric Bypass

Complications	%
<b>Perioperative</b>	
Mortality	1.5
Wound infection	11.7
Wound seromas	5.8
Anastomotic stenosis	3.0
Splenic laceration	3.0
Subphrenic abscesses	2.5
Readmission	8.2
Reoperation	2.8
<b>Late</b>	
Vitamin B <sub>12</sub> deficiency	40.0
Anemia	39.0
Incisional hernia	23.9
Readmission	38.1
Depression	23.4
Staple line dehiscence	15.1
Gastritis	13.2
Cholelithiasis	11.4
Bile reflux	8.7

Data from Pories et al.<sup>48</sup>

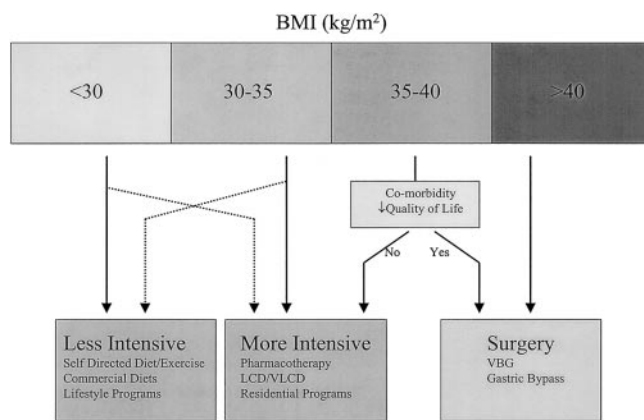
learning curve and requires careful patient selection, including minimal prior upper abdominal surgery, and should initially be reserved for patients at the lower end of the morbid obesity spectrum. In selected patients, laparoscopic GBP can be performed safely and may have advantages of a shorter hospital stay and faster recovery.<sup>131,132</sup>

The perioperative mortality rate of GBP is approximately 1%, and the risk of early postoperative complications is approximately 10%. Major gastrointestinal complications after gastric bypass include anastomotic ulcer, gastrointestinal bleeding, ulcer in bypassed stomach or duodenum, torsion of the Roux limb with volvulus, closed loop obstruction, stomal stenosis, and gallstone formation associated with rapid weight loss. The follow-up series published by Pories et al.<sup>48</sup> is one of the most comprehensive (608 patients) and the longest (14 years), and a summary of the complication rates in their series is shown in Table 4. Perioperative mortality is largely attributable to sepsis and pulmonary embolus. Wound complications are relatively common in the early postoperative periods. Late complications are dominated by stoma complications (stenosis, ulcer, dilation), staple line disruption, and micronutrient deficiencies. Close affiliation with gastroenterologists who are familiar with the complications of these procedures is a key to the successful long-term treatment of these patients. Because most of the stomach and the duodenum is bypassed in this procedure, potential deficiencies of iron, calcium, thiamine, and vitamin B<sub>12</sub> exist; thus, daily supplements and periodic monitoring of the patient are needed to prevent these deficiencies. Although uncommon, delayed

recognition of Wernicke–Korsakoff syndrome from thiamine deficiency may result in serious, irreversible neurologic deficits. Therefore, long-term metabolic surveillance is mandatory in all GBP patients, and patient commitment to prolonged postoperative follow-ups must be a prerequisite to surgery.

**Summary**

Obesity is a serious chronic medical problem that is increasing at an alarming rate. Although its exact pathogenesis is under intense investigation, it is unlikely that a single gene is responsible for the development of obesity in humans. Significant obesity is associated with numerous comorbid conditions that respond to various therapies directed toward a reduction of excess weight. The goal of treatment of obesity is to improve or resolve comorbid conditions and to improve the quality of life by restoring metabolic and organ function. Available treatment modalities include combinations of diet, exercise, life-style modifications, and adjunctive use of pharmacotherapy and surgery. Nonsurgical modalities provide less invasive initial therapies that should be recommended to all overweight and moderately obese patients. Although safe and effective pharmacotherapeutic agents are currently limited in number and choice, recent advancements in the field of appetite and weight regulation promise more specific and effective drug therapies in the



**Figure 5.** Treatment algorithm for obesity (BMI ≥ 30 kg/m<sup>2</sup>). Overweight (BMI 25–30 kg/m<sup>2</sup>) individuals are encouraged to focus on self-directed diets, exercise, and other life-style modifications to induce a modest and achievable weight reduction and avoid further weight gain. Failure of this approach or the presence of other obesity-related risk factors (i.e., hypertension, diabetes) calls for more intensive approaches. Obese (BMI 30–40 kg/m<sup>2</sup>) individuals must be structured into regimented programs with close monitoring for optimal weight loss and long-term maintenance. If weight reduction attempts have failed in morbidly obese (BMI ≥ 40 kg/m<sup>2</sup>) and severely obese (BMI 35–40 kg/m<sup>2</sup>) patients with accompanying comorbid conditions or significant reduction in quality of life, surgical therapy should be considered.

future. Surgical therapy is the most effective modality for treatment of severe obesity. Any individual with obesity should be evaluated carefully for associated comorbidities and risks. Appropriate levels of therapeutic modalities based on the severity of obesity and the associated risks should be offered to patients (Figure 5). A multidisciplinary approach, including expert medical, psychological, and nursing supervision with skilled nutrition, exercise, and behavior counseling, is advocated for patients with medically significant obesity. The end result is to provide appropriate and well-screened patients with a safe and effective means of decreasing morbidity from a wide range of disease states.

## References

- Weigle DS. Appetite and the regulation of body composition. *FASEB J* 1994;8:302–310.
- Stunkard AJ, Foch TT, Hrubec Z. A twin study of human obesity. *JAMA* 1986;256:51–54.
- Stunkard AJ, Sorensen TI, Hanis C, et al. An adoption study of human obesity. *N Engl J Med* 1986;314:193–198.
- Cardon LR, Carmelli D, Fabsitz RR, Reed T. Genetic and environmental correlations between obesity and body fat distribution in adult male twins. *Hum Biol* 1994;66:465–479.
- Expert Panel. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. Bethesda, MD: National Institute of Health, National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services, Public Health Service, 1998.
- Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960–1994. *Int J Obes Rel Metab Disord* 1998;22:39–47.
- Troiano RP, Flegal KM. Overweight prevalence among youth in the United States: why so many different numbers? *Int J Obes Rel Metab Disord* 1999;23(suppl 2):S22–S27.
- Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA* 1999;282:1523–1529.
- Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the United States, 1991–1998. *JAMA* 1999;282:1519–1522.
- Allison DB, Fontaine KR, Manson JE, Stevens J, VanTallie TB. Annual deaths attributable to obesity in the United States. *JAMA* 1999;282:1530–1538.
- Crawford D, Jeffery R, French S. Can anyone successfully control their weight? Finding of a three year community-based study of men and women. *Int J Obes* 2000;24:1107–1110.
- Lee IM, Manson JE, Hennekens CH, Paffenbarger RS Jr. Body weight and mortality. A 27-year follow-up of middle-aged men. *JAMA* 1993;270:2823–2828.
- Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *N Engl J Med* 1995;333:677–685.
- Lindsted K, Tonstad S, Kuzma JW. Body mass index and patterns of mortality among Seventh-day Adventist men. *Int J Obes* 1991;15:397–406.
- Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. The effect of age on the association between body-mass index and mortality. *N Engl J Med* 1998;338:1–7.
- Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 1999;341:1097–1105.
- Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994;372:425–432. (erratum, *Nature* 1995;374:479.)
- Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, Collins F. Effects of the obese gene product on body weight regulation in ob/ob mice. *Science* 1995;269:540–543.
- Montague C. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* 1997;387:903–908.
- Clement K, Vaisse C, Lahlou N, Cabrol S, Polloux V, Cassut D, Gourmeien M, Dina C, Chabant J, Lacorta JM, Basdevant A, Bougneres P, Lebouc Y, Froguel P, Guy-Grand B. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* 1998;392:398–401.
- Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, Fei H, Kim S, Lallone R, Ranganathan S. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat Med* 1995;1:1155–1161.
- Lowell BB, Spiegelman BM. Towards a molecular understanding of adaptive thermogenesis. *Nature* 2000;404:652–660.
- Erickson JC, Hollopeter G, Palmiter RD. Attenuation of the obesity syndrome of ob/ob mice by the loss of neuropeptide Y. *Science* 1996;274:1704–1707.
- Fan W, Boston BA, Kesterson RA, Hruby VJ, Cone RD. Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. *Nature* 1997;385:165–168.
- Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature* 2000;404:661–671.
- Krude H, Biebermann H, Luck W, Horn R, Brabant G, Gruters A. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat Genet* 1998;19:155–157.
- Yeo GS, Farooqi IS, Aminian S, Halsall DJ, Stanhope RG, O'Rahilly S. A frameshift mutation in MC4R associated with dominantly inherited human obesity (letter). *Nat Genet* 1998;20:111–112.
- Klingenberg M, Echtay KS, Bienengraeber M, Winkler E, Huang SG. Structure-function relationship in UCP1. *Int J Obes Rel Metab Disord* 1999;23(suppl 6):S24–S29.
- Klingenberg M, Huang SG. Structure and function of the uncoupling protein from brown adipose tissue. *Biochim Biophys Acta* 1999;1415:271–296.
- Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell* 1998;92:829–839.
- Elias CF, Aschkenasi C, Lee C, et al. Leptin differentially regulates NPY and POMC neurons projecting to the lateral hypothalamic area. *Neuron* 1999;23:775–786.
- Scarpace PJ, Matheny M, Pollock BH, Tumer N. Leptin increases uncoupling protein expression and energy expenditure. *Am J Physiol* 1997;273:E226–E230.
- Drenick EJ, Bale GS, Seltzer F, Johnson DG. Excessive mortality and causes of death in morbidly obese men. *JAMA* 1980;243:443–445.
- Sjostrom LV. Mortality of severely obese subjects. *Am J Clin Nutr* 1992;55:516S–523S.
- Kellum JM, DeMaria EJ, Sugerman HJ. The surgical treatment of morbid obesity. *Curr Probl Surg* 1998;35:791–858.
- MacMahon S, Cutler J, Brittain E, Higgins M. Obesity and hypertension: epidemiological and clinical issues. *Eur Heart J* 1987;8(suppl B):57–70.
- Anderssen S, Holme I, Urdal P, Hjermann I. Diet and exercise intervention have favourable effects on blood pressure in mild hypertensives: the Oslo Diet and Exercise Study (ODES). *Blood Press* 1995;4:343–349.
- Cutler JA. Randomized clinical trials of weight reduction in non-hypertensive persons. *Ann Epidemiol* 1991;1:363–370.

39. Hellenius ML, de Faire U, Berglund B, Hamsten A, Krakau I. Diet and exercise are equally effective in reducing risk for cardiovascular disease. Results of a randomized controlled study in men with slightly to moderately raised cardiovascular risk factors. *Atherosclerosis* 1993;103:81-91.
40. Dengel JL, Katzel LI, Goldberg AP. Effect of an American Heart Association diet, with or without weight loss, on lipids in obese middle-aged and older men. *Am J Clin Nutr* 1995;62:715-721.
41. Heller SR, Clarke P, Daly H, Davis I, McCulloch DK, Allison SP, Tattersall RB. Group education for obese patients with type 2 diabetes: greater success at less cost. *Diabetes Med* 1988;5:552-556.
42. Nilsson PM, Lindholm LH, Schersten BF. Life style changes improve insulin resistance in hyperinsulinaemic subjects: a one-year intervention study of hypertensives and normotensives in Dalby. *J Hypertens* 1992;10:1071-1078.
43. Agurs-Collins TD, Kumanyika SK, Ten Have TR, Adams-Campbell LL. A randomized controlled trial of weight reduction and exercise for diabetes management in older African-American subjects. *Diabetes Care* 1997;20:1503-1511.
44. Foley EF, Benotti PN, Borlase BC, Hollingshead J, Blackburn GL. Impact of gastric restrictive surgery on hypertension in the morbidly obese. *Am J Surg* 1992;163:294-297.
45. Carson JL, Ruddy ME, Duff AE, Holmes NJ, Cody RP, Broline RE. The effect of gastric bypass surgery on hypertension in morbidly obese patients. *Arch Intern Med* 1994;154:193-200. (erratum, *Arch Intern Med* 1994;154:1770.)
46. Olsson SA, Petersson BG, Sorbris R, Nilsson-Ehle P. Effects of weight reduction after gastroplasty on glucose and lipid metabolism. *Am J Clin Nutr* 1984;40:1273-1280.
47. Herbst CA, Hughes TA, Gwynne JT, Buckwalter JA. Gastric bariatric operation in insulin-treated adults. *Surgery* 1984;95:209-214.
48. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, Barakat HA, deRamon RA, Israel G, Dolezal JM. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg* 1995;222:339-352.
49. Sugerman HJ, Baron PL, Fairman RP, Evans CR, Vetrovec GW. Hemodynamic dysfunction in obesity hypoventilation syndrome and the effects of treatment with surgically induced weight loss. *Ann Surg* 1988;207:604-613.
50. Sugerman HJ, Fairman RP, Sood RK, Engle K, Wolfe L, Kellum JM. Long-term effects of gastric surgery for treating respiratory insufficiency of obesity. *Am J Clin Nutr* 1992;55:597S-601S.
51. Kim CH, Sarr MG. Severe reflux esophagitis after vertical banded gastroplasty for treatment of morbid obesity. *Mayo Clin Proc* 1992;67:33-35.
52. Sugerman HJ, Kellum JM, Jr., DeMaria EJ, Reines HD. Conversion of failed or complicated vertical banded gastroplasty to gastric bypass in morbid obesity. *Am J Surg* 1996;171:263-269.
53. Amaral JF, Tsiaris W, Morgan T, Thompson WR. Reversal of benign intracranial hypertension by surgically induced weight loss. *Arch Surg* 1987;122:946-949.
54. Sjostrom CD, Peltonen M, Wedel H, Sjostrom L. Differentiated long-term effects of intentional weight loss on diabetes and hypertension. *Hypertension* 2000;36:20-25.
55. Atkins R. *Dr. Atkins' new diet revolution*. New York: Avon, 1992.
56. Sears B, Lawren W. *The zone*. New York: Harper Collins, 1995.
57. Rabast U, Vornberger KH, Ehl M. Loss of weight, sodium and water in obese persons consuming a high- or low-carbohydrate diet. *Ann Nutr Metab* 1981;25:341-349.
58. Hannah JS, Dubey AK, Hansen BC. Postingestional effects of a high-protein diet on the regulation of food intake in monkeys. *Am J Clin Nutr* 1990;52:320-325.
59. Golay A, Allaz AF, Morel Y, de Tonnac N, Tankova S, Reaven G. Similar weight loss with low- or high-carbohydrate diets. *Am J Clin Nutr* 1996;63:174-178.
60. James WP. A public health approach to the problem of obesity. *Int J Obes Rel Metab Disord* 1995;19(suppl 3):S37-S45.
61. King AC, Haskell WL, Taylor CB, Kraemer HC, DeBusk RF. Group vs home-based exercise training in healthy older men and women. A community-based clinical trial. *JAMA* 1991;266:1535-1542.
62. Frey-Hewitt B, Vranizan KM, Dreon DM, Wood PD. The effect of weight loss by dieting or exercise on resting metabolic rate in overweight men. *Int J Obes* 1990;14:327-334.
63. Verity LS, Ismail AH. Effects of exercise on cardiovascular disease risk in women with NIDDM. *Diabetes Res Clin Pract* 1989;6:27-35.
64. Bertram SR, Venter I, Stewart RI. Weight loss in obese women—exercise v. dietary education. *S Afr Med J* 1990;78:15-18.
65. Wood PD, Stefanick ML, Dreon DM, Frey-Hewitt B, Garay SC, Williams PT, Superko HR, Fortmann SP, Albers JJ, Vranizan KM. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. *N Engl J Med* 1988;319:1173-1179.
66. Kayman S, Bruvold W, Stern JS. Maintenance and relapse after weight loss in women: behavioral aspects. *Am J Clin Nutr* 1990;52:800-807.
67. Wadden TA, Foster GD. Behavioral treatment of obesity. *Med Clin North Am* 2000;84:441-661.
68. Wadden TA, Stunkard AJ. Controlled trial of very low calorie diet, behavior therapy, and their combination in the treatment of obesity. *J Consult Clin Psychol* 1986;54:482-488.
69. Wadden TA, Foster GD, Letizia KA. One-year behavioral treatment of obesity: comparison of moderate and severe caloric restriction and the effects of weight maintenance therapy. *J Consult Clin Psychol* 1994;62:165-171.
70. Craighead LW, Stunkard AJ, O'Brien RM. Behavior therapy and pharmacotherapy for obesity. *Arch Gen Psychiatry* 1981;38:763-768.
71. Wadden TA, Berkowitz RI, Vogt RA, Steen SN, Stunkard AJ, Foster GD. Lifestyle modification in the pharmacologic treatment of obesity: a pilot investigation of a potential primary care approach. *Obes Res* 1997;5:218-226.
72. Bray GA. Use and abuse of appetite-suppressant drugs in the treatment of obesity. *Ann Intern Med* 1993;119:707-713.
73. Connolly HM, Cray JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, Schaff HV. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997;337:581-588. (erratum, *N Engl J Med* 1997;337:1783.)
74. Guy-Grand B, Apfelbaum M, Crepaldi G, Gries A, Lefebvre P, Turner P. International trial of long-term dexfenfluramine in obesity. *Lancet* 1989;2:1142-1145.
75. Weintraub M, Hasday JD, Mushlin AI, Lockwood DH. A double-blind clinical trial in weight control. Use of fenfluramine and phentermine alone and in combination. *Arch Intern Med* 1984;144:1143-1148.
76. Weintraub M. Long-term weight control: the National Heart, Lung, and Blood Institute funded multimodal intervention study. *Clin Pharmacol Ther* 1992;51:581-585. (erratum, *Clin Pharmacol Ther* 1992;52:323.)
77. Jick H, Vasilakis C, Weinrauch LA, Meier CR, Jick SS, Derby LE. A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. *N Engl J Med* 1998;339:719-724.
78. Khan MA, Herzog CA, St. Peter JV, Hartley GG, Madlon-Kay R, Dick CD, Asinger RW, Vessey JT. The prevalence of cardiac valvular insufficiency assessed by transthoracic echocardiography in obese patients treated with appetite-suppressant drugs. *N Engl J Med* 1998;339:713-718.
79. Weissman NJ, Tighe JF Jr, Gottdiener JS, Gwynne JT. An assess-

- ment of heart-valve abnormalities in obese patients taking dexfenfluramine, sustained-release dexfenfluramine, or placebo. Sustained-Release Dexfenfluramine Study Group. *N Engl J Med* 1998;339:725-732.
80. Rolls BJ, Shide DJ, Thorwart ML, Ulbrecht JS. Sibutramine reduces food intake in non-dieting women with obesity. *Obes Res* 1998;6:1-11.
  81. Hansen DL, Toubro S, Stock MJ, Macdonald IA, Astrup A. Thermogenic effects of sibutramine in humans. *Am J Clin Nutr* 1998;68:1180-1186.
  82. Seagle HM, Bessesen DH, Hill JO. Effects of sibutramine on resting metabolic rate and weight loss in overweight women. *Obes Res* 1998;6:115-121.
  83. Hanotin C, Thomas F, Jones SP, Leutenegger E, Drouin P. A comparison of sibutramine and dexfenfluramine in the treatment of obesity. *Obes Res* 1998;6:285-291.
  84. Apfelbaum M, Vague P, Ziegler O, Hanotin C, Thomas F, Leutenegger E. Long-term maintenance of weight loss after a very-low-calorie diet: a randomized blinded trial of the efficacy and tolerability of sibutramine. *Am J Med* 1999;106:179-184.
  85. Hauptman JB, Jeunet FS, Hartmann D. Initial studies in humans with the novel gastrointestinal lipase inhibitor Ro 18-0647 (tetrahydrolipstatin). *Am J Clin Nutr* 1992;55:309S-313S.
  86. Sjostrom L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppe-schaar HP, Krempf M. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. *Lancet* 1998;352:167-172.
  87. Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, Heimbürger DC, Luens CP, Robbins DC, Chung J, Heymsfield SB. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA* 1999;281:235-242. (erratum, *JAMA* 1999; 281:1174.)
  88. Hill JO, Hauptman J, Anderson JW, Fujioka K, O'Neil PM, Smith DK, Zavoral JH, Aronne LJ. Orlistat, a lipase inhibitor, for weight maintenance after conventional dieting: a 1-y study. *Am J Clin Nutr* 1999;69:1108-1116.
  89. Astrup A, Lundsgaard C, Madsen J, Christensen NJ. Enhanced thermogenic responsiveness during chronic ephedrine treatment in man. *Am J Clin Nutr* 1985;42:83-94.
  90. Astrup A, Buemann B, Christensen NJ, Toubro S, Thorbok G, Victor OJ, Quaade F. The effect of ephedrine/caffeine mixture on energy expenditure and body composition in obese women. *Metabolism* 1992;41:686-688.
  91. Astrup A, Breum L, Toubro S, Hein P, Quaade F. The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in obese subjects on an energy restricted diet. A double blind trial. *Int J Obes Rel Metab Disord* 1992;16:269-277.
  92. Toubro S, Astrup A, Breum L, Quaade F. The acute and chronic effects of ephedrine/caffeine mixtures on energy expenditure and glucose metabolism in humans. *Int J Obes Rel Metab Disord* 1993;17(suppl 3):S73-S77, S82.
  93. Stahl A, Hirsch DJ, Gimeno RE, Munreddy S, Ge P, Watson N, Patel S, Kotler M, Ramondi A, Tartaglia LA, Lodish HF. Identification of the major intestinal fatty acid transport protein. *Mol Cell* 1999;4:299-308.
  94. NIH conference: gastrointestinal surgery for severe obesity. Consensus Development Conference Panel. *Ann Intern Med* 1991;115:956-961.
  95. Payne JH, DeWind LT. Surgical treatment of obesity. *Am J Surg* 1969;118:141-147.
  96. Halverson JD, Wise L, Wazna MF, Ballinger WF. Jejunoileal bypass for morbid obesity. A critical appraisal. *Am J Med* 1978; 64:461-475.
  97. Kroyer JM, Talbert WM Jr. Morphologic liver changes in intestinal bypass patients. *Am J Surg* 1980;139:855-859.
  98. Sugerma H. Gastric surgery for morbid obesity. In: Zinner MJ, ed. Maingot's abdominal operations. Stamford, CT: Appleton & Lange, 1997:1057-1077.
  99. Scopinaro N, Gianetta E, Adami GF, Friedman D, Traverso E, Marinari GM, Cuneo S, Vitale B, Ballari F, Colombini M, Baschieri G, Bachi V. Biliopancreatic diversion for obesity at eighteen years. *Surgery* 1996;119:261-268.
  100. Murr MM, Balsiger BM, Kennedy FP, Mai JL, Sarr MG. Malabsorptive procedures for severe obesity: comparison of pancreaticobiliary bypass and very very long limb Roux-en-Y gastric bypass. *J Gastrointest Surg* 1999;3:607-612.
  101. Lagace M, Marceau P, Marceau S, Hould FS, Potvin M, Bourque RA, Biron S. Biliopancreatic diversion with a new type of gastrectomy: some previous conclusions revisited. *Obes Surg* 1995;5:411-418.
  102. Marceau S, Biron S, Lagace M, Hould FS, Potvin M, Bourque RA, Marceau P. Biliopancreatic diversion, with distal gastrectomy, 250 cm and 50 cm limbs: long-term results. *Obes Surg* 1995; 5:302-307.
  103. Marceau P, Hould FS, Simard S, Lebel S, Bourque RA, Potvin M, Biron S. Biliopancreatic diversion with duodenal switch. *World J Surg* 1998;22:947-954.
  104. Gomez CA. Gastroplasty in morbid obesity. *Surg Clin North Am* 1979;59:1113-1120.
  105. Pace WG, Martin EW Jr, Tetirick T, Fabri PJ, Carey LC. Gastric partitioning for morbid obesity. *Ann Surg* 1979;190:392-400.
  106. Mason EE. Vertical banded gastroplasty for obesity. *Arch Surg* 1982;117:701-706.
  107. MacLean LD, Rhode BM, Sampalis J, Forse RA. Results of the surgical treatment of obesity. *Am J Surg* 1993;165:155-162.
  108. Nightengale ML, Sarr MG, Kelly KA, Jensen MD, Zinsmeister AR, Palumbo PJ. Prospective evaluation of vertical banded gastroplasty as the primary operation for morbid obesity. *Mayo Clin Proc* 1991;66:773-782.
  109. Howard L, Malone M, Michalek A, Carter J, Alger S, Van Woert J. Gastric bypass and vertical banded gastroplasty—a prospective randomized comparison and 5-year follow-up. *Obes Surg* 1995;5:55-60.
  110. Sugerma HJ, Starkey JV, Birkenhauer R. A randomized prospective trial of gastric bypass versus vertical banded gastroplasty for morbid obesity and their effects on sweets versus non-sweets eaters. *Ann Surg* 1987;205:613-624.
  111. Jones KB Jr. Experience with the Roux-en-Y gastric bypass, and commentary on current trends. *Obes Surg* 2000;10:183-185.
  112. Bo O, Modalsli O. Gastric banding, a surgical method of treating morbid obesity: preliminary report. *Int J Obes* 1983;7:493-499.
  113. Kuzmak L. Stoma adjustable silicone gastric banding. *Prob Gen Surg* 1992;9:298-317.
  114. Belachew M, Legrand M, Vincenti V, Deffechereux T, Jourdan JL, Monami B, Jacquet N. Laparoscopic placement of adjustable silicone gastric band in the treatment of morbid obesity: how to do it. *Obes Surg* 1995;5:66-70.
  115. O'Brien PE, Brown WA, Smith A, McMurrick PJ, Stephens M. Prospective study of a laparoscopically placed, adjustable gastric band in the treatment of morbid obesity. *Br J Surg* 1999; 86:113-118.
  116. Belachew M, Legrand M, Vincent V, Lismonde M, Le Docte N, Deschamps V. Laparoscopic adjustable gastric banding. *World J Surg* 1998;22:955-963.
  117. Doldi SB, Micheletto G, Lattuada E, Zappa MA, Bona D, Sonvico U. Adjustable gastric banding: 5-year experience. *Obes Surg* 2000;10:171-173.
  118. Forsell P, Hellers G. The Swedish Adjustable Gastric Banding (SAGB) for morbid obesity: 9 year experience and a 4-year

- follow-up of patients operated with a new adjustable band. *Obes Surg* 1997;7:345–351.
119. Westling A, Bjurling K, Ohrvall M, Gustavsson S. Silicone-adjustable gastric banding: disappointing results. *Obes Surg* 1998;8:467–474.
  120. Mason EE, Ito C. Gastric bypass. *Ann Surg* 1969;170:329–339.
  121. Ito C, Mason EE, Besten LD. Experimental studies on gastric bypass versus standard ulcer operations. *Tohoku J Exp Med* 1969;97:269–277.
  122. Griffen WO Jr, Young VL, Stevenson CC. A prospective comparison of gastric and jejunioileal bypass procedures for morbid obesity. *Ann Surg* 1977;186:500–509.
  123. Alden JF. Gastric and jejunioileal bypass. A comparison in the treatment of morbid obesity. *Arch Surg* 1977;112:799–806.
  124. Brolin RE, Kenler HA, Gorman JH, Cody RP. Long-limb gastric bypass in the superobese. A prospective randomized study. *Ann Surg* 1992;215:387–395.
  125. Meryn S, Stein D, Straus EW. Pancreatic polypeptide, pancreatic glucagon and enteroglucagon in morbid obesity and following gastric bypass operation. *Int J Obes* 1986;10:37–42.
  126. Kellum JM, Kuemmerle JF, O'Dorisio TM, Rayford P, Martin D, Engle K, Wolf L, Sugerman HJ. Gastrointestinal hormone responses to meals before and after gastric bypass and vertical banded gastroplasty. *Ann Surg* 1990;211:763–771.
  127. Sugerman HJ, Londrey GL, Kellum JM, Wolf L, Liszka T, Engle KM, Birkenhauer R, Starkey JV. Weight loss with vertical banded gastroplasty and Roux-Y gastric bypass for morbid obesity with selective versus random assignment. *Am J Surg* 1989;157:93–102.
  128. Wittgrove AC, Clark GW, Tremblay LJ. Laparoscopic gastric bypass, roux-en-Y: preliminary report of five cases. *Obes Surg* 1994;4:353–357.
  129. Naitoh T, Gagner M, Garcia-Ruiz A, Heniford BT, Ise H, Matsuno S. Hand-assisted laparoscopic digestive surgery provides safety and tactile sensation for malignancy or obesity. *Surg Endosc* 1999;13:157–160.
  130. Schauer PR, Ikramuddin S, Gourash WF. Laparoscopic roux-en-Y gastric bypass: a case report at one-year follow-up. *J Laparoendosc Adv Surg Tech A* 1999;9:101–106.
  131. de la Torre RA, Scott JS. Laparoscopic roux-en-Y gastric bypass: a totally intra-abdominal approach—technique and preliminary report. *Obes Surg* 1999;9:492–498.
  132. Wittgrove AC, Clark GW. Laparoscopic gastric bypass, Roux-en-Y—500 patients: technique and results, with 3–60 month follow-up. *Obes Surg* 2000;10:233–239.

---

Received September 26, 2000. Accepted November 29, 2000.

Address requests for reprints to: Edward C. Mun, M.D., Harvard Medical School, Department of Surgery, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, Massachusetts 02215. e-mail: emun@caregroup.harvard.edu; fax: (617) 667-2978.

Drawings of bariatric procedures were provided by Dr. Alejandro Heffess.

Dr. Blackburn has worked as a consultant and/or received research grants from pharmaceutical companies whose medications are discussed in this article.