13 A FRAMEWORK FOR THE TREATMENT OF OBESITY: EARLY SUPPORT

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> *What a curious attitude scientists have—"we still don´t know that; but it is knowable and it is only a matter of time before we get to know it!" As if that went without saying.*
>
> — Wittgenstein, 1980

Introduction

Although obesity is a growing problem and many of its medical consequences are becoming manifest even in children (Drake et al., 2002), most methods of treating obese children and adults are only marginally successful (Norris et al., 2005; Padwal & Majumdar, 2007; Summerbell et al., 2003). Several assumptions underlie these methods. For example, recent studies in neuroscience and molecular genetics have led Spiegel and colleagues (2005) to suggest that obesity is a "hypothalamic disease" and a "complex genetic disease," and Nath and colleagues (2006) to suggest that "understanding . . . abnormal regulation of energy metabolism through to dysfunction of molecular mechanisms—will pave the ways for development of new treatment strategies". These assumptions bring Wittgenstein's quote to mind. They express the belief (hope) that it is only a matter of time before the problem of obesity is solved. But the limited success of presently used approaches to curb obesity could reflect the possibility that the underlying assumptions are only partially correct. The second part of Wittgenstein's quote should encourage us to consider this possibility. The discussion that follows briefly reviews and evaluates some contemporary assumptions concerning the cause of obesity and the proper approach to its treatment. The chapter then provides an alternative framework and reports preliminary results of treating extremely obese adolescents and obese patients with binge-eating disorder using a method based on this framework.

The Energy Intake–Energy Expenditure Mismatch

Diet and body weight

The relationship between diet and health has long been studied (Oddy, 2003). For example, Keys and colleagues (1963) reported that the incidence of coronary heart disease markedly decreased during periods of reduced intake of food—fat in particular. These observations stimulated interest in the relationship between fat intake and health, including body weight, and provided the basis for the recommendations that fat intake should be reduced. However, recent large-scale trials offer little support for the possibility that intake of low-fat diets reduces body weight more than marginally in the intermediate term; indeed, weight rebound is the decided norm (Howard et al., 2006).

Interestingly, although the body mass index (BMI; measured in kilograms per square meter) has increased recently in, for example, men in Great Britain (Figure 13.1A), self-reported daily energy intake displays the opposite trend (Figure 13.1B; DEFRA, 2001). However, self-reported data on food consumption must be viewed with caution; it is well known that consumption is understated, sometimes by as much as 25% (Swan, 2004). For example, American men and women reported consuming 2347 and 1658 kilocalories a day, respectively, in 1994 to 1996 (Cutlet et al., 2003); and the corresponding numbers for British men and women in 1991 were virtually the same—2313 and 1632 kilocalories per day, respectively (Swan, 2004). This is less than the caloric requirement for maintaining a normal body weight.

For an analysis of changes in consumption over time, however, underreporting may not represent a problem, if it can be assumed to be constant (Cutlet et al., 2003). The decreasing trend in intake (see Figure 13.1B) is therefore likely to represent a real time-dependent decrease in the consumption of food. And even if the data do not take into consideration snacking between meals, which contributes significantly to overall caloric intake (Cutler et al., 2003), it is still estimated that the total caloric intake in men in Great Britain has decreased during the last 20 years (Swan, 2004).

Thus, although BMI has increased during the last 30 years, probably reflecting increasing adiposity, there has been a parallel decrease in the reported daily intake of carbohydrate, fat, and protein (Figure 13.1C and D). The reason for the mismatch between intake and expenditure of energy is unknown, but it challenges the assumption that body weight is physiologically regulated. Alternatively, it calls the validity of the BMI for defining obesity into question, or it reveals a basic lack of understanding about the relationship between intake and BMI.

Diet interventions

Attempts to reduce BMI by means of diets containing reduced carbohydrate, fat, or protein have been minimally successful. Such diets typically yield weight losses

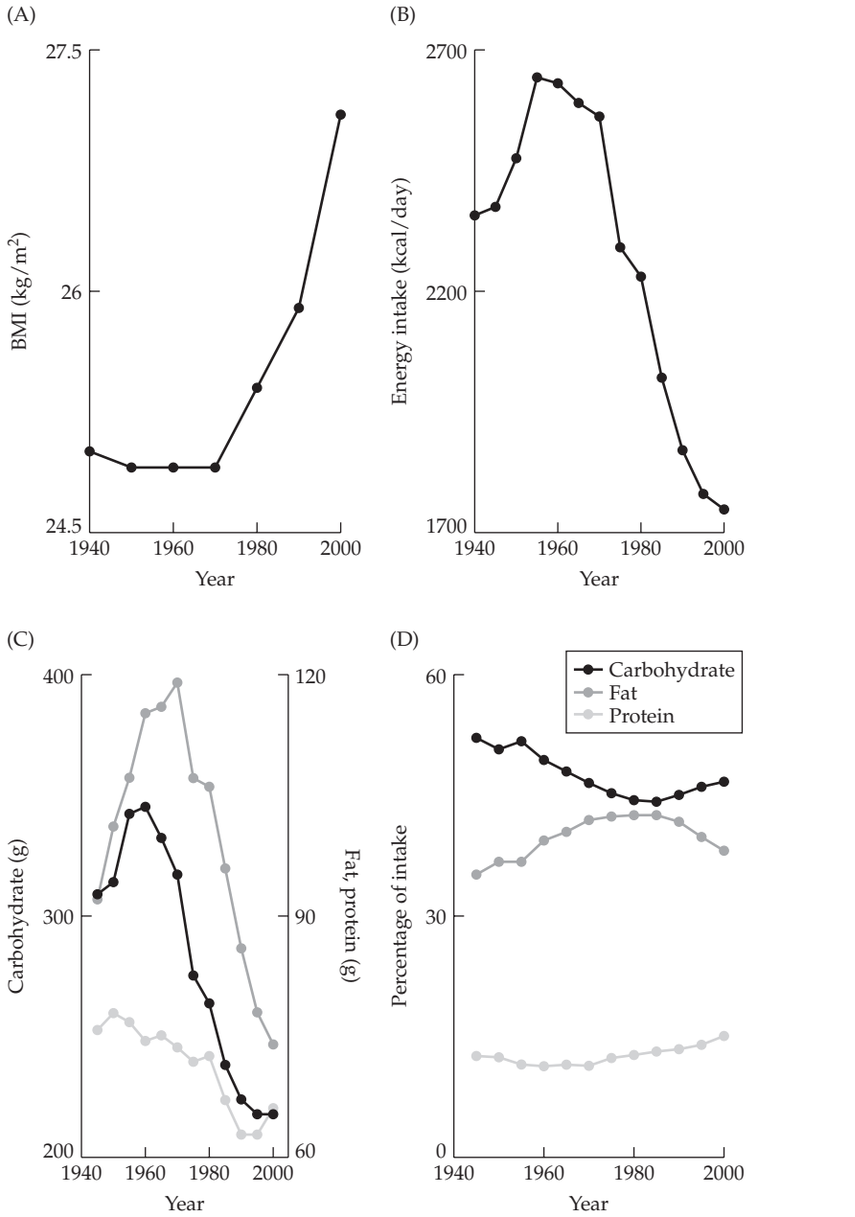


FIGURE 13.1 Body mass index (A), total energy intake (B), and intake of carbohydrate, fat, and protein expressed as total intake (C) and percentage of total intake (D) from 1970 to 2000. (Data from Floud, 1998; the National Health Service, 2004; and the Department of the Environment, Food and Rural Affairs, 2001; reproduced with permission.)

of between 2.1 and 3.2 kilograms within a year in adults who have an average BMI of 35 (Dansinger et al., 2005). A diet reduced in fat content yielded an average weight loss of 2.2 kilograms within a year in a sample of 20,000 women aged 50 to 79 years who had an average BMI of 29.1. However, this effect was reduced to 0.4 kilogram during a 7.5-year period of follow-up (Howard et al., 2006). Reducing carbohydrate intake may prove more helpful, although the long-term health effects have not been extensively studied (Adam-Perrot et al., 2006).

Interestingly, weight loss recorded among participants on a low-carbohydrate diet was found to be related to a reduction in caloric intake, not specifically to reduced carbohydrate intake and it was recently pointed out that the amount of food eaten rather than the type of diet is the important factor for reducing body weight (Dansinger & Schaefer, 2006). When implemented into clinical practice, currently used weight loss diets, while having some effects on health—for example, reduced risk of cardiovascular disease—have very small, generally unsustainable effects on body weight. No evidence suggests that one diet is more effective than another (Malik & Hu, 2007).

Summary of the intake–expenditure mismatch

It seems unlikely that a change in the intake of a single nutrient—for example, carbohydrate or fat—can explain more than a small part of the variation in the BMI, which is a likely reason that dietary interventions have rather small, transient effects on the BMI. Despite the publicity (and subsequent denouement) of some diets that constrain intake of a single macronutrient, there is no evidence that dieting consistently affects body weight.

The Hypothalamus and Eating Behavior

Homeostasis

Most neuroscience research on eating behavior and body weight, including obesity, rests on the assumption that energy balance is homeostatically controlled so that constancy is maintained across a range of conditions. For example, following food restriction and weight loss, overeating occurs until the original body weight is reattained. The converse holds when obesity is induced through forced feeding. This topic is continually being revisited, and there are many excellent recent reviews (e.g., Beck, 2006). The theory of homeostatic regulation of body weight dates back to the first half of the twentieth century and was summarized as a hypothalamic theory of motivation by Stellar in 1954. Stellar hypothesized that eating (and other types of motivated behavior as well) is a function of the activity of excitatory and inhibitory, anatomically separate "centers" in the hypothalamus (Stellar, 1954). The theory remains essentially the same today, with the exception that excitation and inhibition of eating are now thought to be chemically mediated and, at least to some extent, anatomically overlapping. It is also

recognized that the neural network engaged in eating is distributed beyond hypothalamic "centers" to brainstem and limbic areas (Grill & Kaplan, 2002).

The instability of body weight in rats and humans in the face of an energy-dense food cornucopia makes it unlikely that body weight is controlled, so much as simply attained. Yet the homeostatic view is maintained. For example, Murphy and Bloom (2006) argue that "energy balance is a homeostatic system" but suggest that it is unlikely that the recent increase in obesity is caused by a deficit in this system. Their alternative is that "the regulatory system is unable to cope with the current context of cheap–high energy foodstuffs". However, the recent increase in the BMI is not the only example that human body weight is not maintained at a stable level.

Historically, at least through the late nineteenth century, body weight has been quite variable, dictated mainly by the economic and social factors of the times, with periods of decreases and increases long before the present, conspicuous increase (Floud, 1998). This historical view suggests a flexibility in eating strategies, with its consequent changes in body weight, that has allowed individuals to cope with periods of plenty and little, albeit often at a cost to health (Fogel et al., in press; Oddy, 2003).

Feedback from adipocytes to the brain

The hypothalamic homeostatic theory predicts that when energy intake is reduced for some time, fat is depleted and hormonal signals from adipocytes are down-regulated. The brain senses the change and adapts by up-regulating neurotransmitters, often peptides that are thought to stimulate food intake. One of the best studied of these so-called *orexigenic* peptides is neuropeptide Y (NPY), which is controlled by leptin, an *anorexigenic* peptide secreted by adipocytes. In line with the hypothesis, many studies have shown that NPY stimulates food intake and leptin inhibits it (Beck, 2006; see Chapter 3).

The physiological importance of the endocrine part of this theory has not been convincingly demonstrated. For example, to cause a reduction of body weight, leptin must be given in doses that increase plasma levels of leptin tenfold above normal levels (Rosenbaum et al., 2005). Moreover, doses of NPY that typically stimulate food intake in, for example, rats are also very high and have never been validated against endogenous levels under physiological circumstances (O'Shea et al., 1997). Thus, although there is some coherence in support of roles for NPY and leptin in feeding control, the defining and necessary criterion of the physiological level has not yet been met. Other difficulties will be addressed in the discussion that follows.

Although protocols for testing the details of ingestive behavior in experimental animals have been available for many years (Toates & Rowland, 1987), the amount of food eaten per time unit remains a commonly used indirect measure of eating behavior (Keen-Rhinehart & Bartness, 2007). Emphasis on this lone measure is surprising because it has been recognized for close to a century that

eating, like other motivated behaviors, consists of two phases: *appetitive* (the search for a particular object, or commodity) and *consummatory* (the terminal *fixed* act elicited by that object; Craig, 1918; Sherrington, 1906).

The appetitive and consummatory phases can be studied separately. For example, infusing a solution of sucrose directly into the mouth of a rat circumvents the need for appetitive ingestive behavior, making it possible to measure consummatory ingestive behavior selectively. If, by contrast, the rat has to work for or search out the sucrose solution before ingestion, the amount consumed is a function of both appetitive and consummatory ingestive behaviors. As will be seen, these measures provide very different profiles of eating behavior.

In tests selective for consummatory ingestive behavior, NPY and leptin exert effects on sucrose intake that are opposite those found in tests measuring both appetitive and consummatory responses (Ammar et al., 2000). For example, when ingesting sucrose from a drinking spout located inside a test cage, rats ingest less when leptin is infused into the cerebral ventricles (Figure 13.2A). In contrast, when they receive sucrose via intraoral infusion, intracerebroventricular infusion of leptin stimulates intake (Figure 13.2B). The same paradoxical effect is obtained with intracerebroventricular NPY. More is drunk from the spout, and, paradoxically, less is received from intraoral infusions when NPY is received in the ventricles (see Figure 13.2). In short, whereas NPY stimulates intake in conventional tests, it inhibits intake in a test selectively measuring consummatory ingestive behavior. Conversely, leptin reduces intake in the conventional test, but it markedly stimulates consummatory ingestive behavior, causing a 50% increase in intake of sucrose infused intraorally.

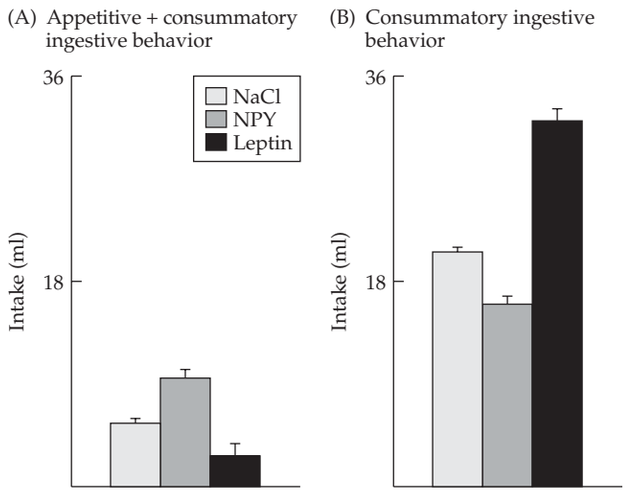


FIGURE 13.2 Intake of a 1-molar solution of sucrose available from a bottle (A) or infused intraorally at a rate of 0.5 milliliters per minute (B) in male rats. (Data from Ammar et al., 2000, reproduced with permission.)

These findings demonstrate that classification of peptides, and perhaps also of neural networks as orexigenic and anorexigenic requires further elaboration. This distinction is especially important if one conceptualizes overeating as an addictive state. The line demarcating appetitive from consummatory may shift with chronic overeating, making the individual more vulnerable to subtle cue changes that might have otherwise been ignored when at normal weight and eating normal meals at a normal rate.

Implementing the hypothalamic theory clinically

The test described in the preceding section (see Figure 13.2) was motivated by the clinical observation that although patients with anorexia nervosa do not eat enough to sustain body weight—indeed, some die from undernutrition—they routinely display behavior in anticipation of a meal that might correspond to appetitive ingestive behavior in rats. Videotape recordings showed that anorexic patients spent more time on food preparation activities, such as cutting, moving, breaking, and mixing food before eating, than did a control group; and of course they ingested less food than did control subjects (Tappe et al., 1998). This observation was interpreted as a means by which the patient could delay eating, but this sense of purpose may not be necessary. "Playing" with the food may reflect enhancement of appetitive ingestive behavior at the expense of consuming the food.

Anorexic patients, of course, have depleted fat stores and, correspondingly, low levels of leptin in the blood; as a consequence, the level of NPY is elevated in the cerebrospinal fluid (Gendall et al., 1999). Interestingly, evidence suggests that the synthesis of NPY is also up-regulated in the brain in anorexia nervosa (Goldstone et al., 2002). These endocrine changes are consequences of the starved condition of the patients, and they are reversed upon weight restoration (Gendall et al., 1999). The endocrine scenario in anorexia nervosa is inconsistent with the idea that there are hypothalamic (and extrahypothalamic) homeostatic mechanisms that, in the case of starvation, excite eating behavior in order to maintain constant body weight. However, the same scenario is consistent with the experimental maneuvers described in Figure 13.2. Hence, we suggest that the high level of NPY in the brain of anorexic patients is an endocrine adaptation that allows the search for food (i.e., display of appetitive ingestive behavior) at the expense of eating food (i.e., display of consummatory ingestive behavior).

This hypothesis has been confirmed by recent studies on the hamster, a hoarding species. Food deprivation and subsequent replenishment of food or treatment with NPY cause an increase not in eating but in hoarding and other measures of appetitive ingestive behavior (Keen-Rhinehart & Bartness, 2007). The conclusion that NPY is an "orexigen" is based on observations of rats infused with very high doses of NPY into the brain and provided with food during a limited period of time (Beck, 2006). When this conclusion is implemented beyond the rat in a conventional test, it fails. For example, although NPY can stimulate short-term food

intake in the hamster, there is no effect on 24-hour intake, and merely reducing the temperature during testing turns NPY into an inhibitor of eating (Paul et al., 2005).

Benoit and colleagues (2005) reported that the stimulatory effect of NPY on carbohydrate intake (NPY is considered particularly potent in stimulating the intake of this macronutrient; Beck, 2006) may be an artifact of the way rats are trained during testing. There was no effect of NPY in rats that had become thoroughly accustomed to the testing situation (Benoit et al., 2005). Together these findings argue against the idea that NPY is always an orexigen. They support the alternative idea that, in starvation, NPY selectively stimulates appetitive behavior and, at the same time, inhibits consummatory ingestive behavior (Ammar et al., 2000; Södersten et al., 2006a,b). Stated differently, NPY, and perhaps other peptides, assumes different roles dependent on physiological context (Södersten et al., 2006a). This physiological ambiguity should restrain the therapeutic use of such peptides.

The problem with leptin resistance

As the previous discussion has indicated, the reciprocal relationship between leptin and NPY interpreted within the hypothalamic homeostatic framework fails to explain the behavior of starved humans. But what about obesity? When rats eat palatable foods (cafeteria feeding), there is a gradual increase in the level of leptin in the blood and, as a neuroendocrine concomitant, a decrease in the synthesis of NPY in the brain (Beck, 2006). However, the brain eventually adapts, and when the rat is obese, the synthesis of NPY in the brain is back to the normal level (Beck, 2006). Obese rats do not respond to treatment with leptin by eating less food; leptin "insensitivity" develops in parallel with the development of obesity and an adjustment in the synthesis of NPY by the brain (Beck, 2006). Thus, as a corollary to the hypothalamic theory, leptin "insensitivity" is thought to develop in parallel with the development of obesity and an adjustment in the synthesis of NPY by the brain (Beck, 2006). This corollary is clearly circular and brings to mind the explanation of why opium induces sleep that was offered by Molière's doctor: "It is because opium has a soporific nature." As Bernard (1865/1927) pointed out long ago, a label is not an explanation.

The concept of leptin insensitivity makes it even more difficult to understand when leptin is a physiological inhibitor of feeding. Perhaps never. Recall that doses of leptin that are well beyond the physiological range are necessary to reduce intake. In addition, endogenous leptin is not effective during cafeteria feeding, because in this situation the rats gradually become leptin-insensitive—indeed, obese. During obesity development, leptin is apparently never able to stop rats from eating. In fact, with weight gain, a positive feedback cycle might ensue with leptin facilitating rather than inhibiting cafeteria feeding and, hence, obesity (Zhang & Scarpace, 2006).

Behavioral changes during cafeteria feeding do not accord with the idea that leptin restricts body weight gain. However, the same changes are consistent with

the finding that leptin stimulates consummatory ingestive behavior in circumstances that require minimal effort to obtain food (Ammar et al., 2000). Interestingly, humans also overconsume food when it is easily available (Cutler et al., 2003; Wansink, 2004), although it remains to be demonstrated whether leptin has a role in this situation. Together these findings raise the interesting possibility that, rather than inhibiting hunger (and therefore feeding), leptin may be acting on the mediators of sensory-specific satiety that cause omnivores to switch from one food to the next (see the epilogue).

Especially in the obese, palatable foods may circumvent certain homeostatic systems that might govern feeding. The possibility must be considered and evaluated that leptin may stimulate intake when eating does not demand substantial appetitive behavior (Ruffin et al., 2004). It follows that leptin may enhance intake in today's ambience, in which food is easily and conveniently available, with many commercial inducements and conditioned reminders. Such enhancement is consistent with the rightward shift of the consummatory appetitive divide, thereby making eating in the obese more vulnerable to cues that might otherwise be ignored. The idea that leptin might recruit different neural networks that determine behavioral strategy to deplete or replenish energy stores was first suggested by Fulton and colleagues (2000). Hence, in obesity leptin might further reduce physical activity and increase eating (Franks et al., 2007). Although not studied to our knowledge, such a mechanism might be favorably "looked upon" by hibernators that eat to the point of obesity and beyond.

The leptin–NPY neuroendocrinology of obese rats (for a full description, see the excellent review by Beck, 2006) is also inconsistent with that of obese humans. Unlike in obese rats (Beck, 2006), high leptin levels in humans reduce NPY synthesis in the brain (Goldstone et al., 2002). The brains of obese humans are not insensitive to leptin. This observation begs the question, If leptin is an inhibitor of food intake and NPY is an "orexigen," why do the obese eat too much food? The hypothalamic theory of body weight regulation cannot answer this question.

Summary of the hypothalamus and eating behavior

de Castro and Plunkett (2002) have made the point that food intake in humans living in normal environments is not controlled in the precise manner predicted by homeostatic models, particularly of the one-factor genre. Instead, human eating behavior is affected by "uncompensated" factors—that is, factors that escape homeostatic control (de Castro & Plunkett, 2002). Not surprisingly, then, drugs that have been used within the homeostatic framework and have often targeted only one "compensated" factor have very small effects on the body weight of obese patients (Despres et al., 2005; Padwal & Majumdar, 2007; Pi-Sunyer et al., 2006; Van Gaal et al., 2005). An analysis of the neural networks mediating eating behavior should consider the possibility that the effect of a peptide, as well as other neurotransmitters, varies depending on physiological state (Södersten et al., 2006b). Thus a new approach is called for to complement the determinis-

tic physiological model of the control of eating behavior in humans. Behavioral methods of treating disordered eating, including overeating in the obese, must be attuned to the factors that co-opt physiological control.

Obesity Surgery: Relapse in 30 Minutes

Surgery is effective

The most effective treatment of radical obesity is surgical intervention (Näslund & Kral, 2006). Currently, to qualify, the patient's BMI must equal or exceed 35 kg/m^2. There are three types of obesity surgery: one that limits the capacity of the stomach, one that reduces the absorption of ingested food, and one that combines these two methods (Näslund & Kral, 2006). Each procedure causes marked weight loss and alleviates the medical consequences of obesity—for example, diabetes—even before weight loss (Näslund & Kral, 2006). In the long term, there can be no question of the health-promoting effect of gastric surgery for obesity, ranging from a decrease in mortality to improvement in lifestyle (Sjöström et al., 2004).

Because currently used surgical treatments for obesity are irreversible, the function of mechanisms normally engaged during eating cannot be assessed after surgery. It has been suggested that the reduction of diabetic symptoms after surgery is partly mediated by alterations in gastrointestinal hormone secretion (Näslund & Kral, 2006), which, of course, exerts ingestive control (see Chapter 3), while also affecting pancreatic endocrine function directly (Vilsboll & Holst, 2004). For example, surgical gastric bypass decreases the BMI more than surgically restricting gastric capacity. This distinction may reflect differences in the hormonal consequences of the operation (Korner et al., 2006). If differences in hormone secretions were causally related to differences in BMI reduction after the operation, the endocrine consequences of surgery would be expected also to cause changes in eating behavior. Reversible obesity surgery, such as implanting an adjustable gastric band (Forsell & Hellers, 1997), provides an opportunity to examine whether changes in eating after the operation persist after gastric restriction has been reversed.

Reversible effect of gastric banding on eating behavior

One study focused on eating in nine Swedish women who had been treated with gastric banding for obesity. They averaged 27 years of age at the time of the operation, and each had made several unsuccessful attempts to lose weight. A silicone gastric band was tied around the upper part of the stomach about 15 centimeters from the cardia. The volume of the pouch between cardia and band was 5 to 7 milliliters. The band was connected to a nasogastric tube that was exteriorized and connected to a subcutaneous port anchored to the lower part of the sternum, thereby making the band accessible from the outside. The band was filled with 5 to 7 milliliters of a radiology-contrast medium during surgery, and it was adjusted at monthly intervals thereafter. For further details on the surgery and the postoperative procedures, see Forsell and Hellers, 1997.

The women ate regular food (manufactured by Findus in Bjuv, Sweden; amounting to 580 kilojoules, or 140 kilocalories; and consisting of 5.5 grams of protein, 6 grams of fat, and 16 grams of carbohydrate per 100 grams of food), measured using a Mandometer in a procedure that will be described later in the chapter. This procedure includes rating of satiety at regular intervals postoperatively. The women were tested twice, with a week between the tests, before gastric banding. They were monitored postoperatively at monthly intervals, and the band was adjusted; that is, fluid was either infused or withdrawn. They were retested about 15 months after surgery. Then, 1 to 3 days later, they were tested again, about 30 minutes after the gastric band was evacuated, thereby allowing the complete stomach to participate. The band was then refilled, and the women were tested with the band filled a week later—that is, with stomach contracted. Following this test, the band was again evacuated, and 1 to 3 days later the patients were studied again. The procedures were approved by the ethics committee of the Karolinska Institute.

Figure 13.3 shows that the BMI of these women was markedly reduced (about 35%) 1 year after the operation, presumably because of chronic feeding reduc-

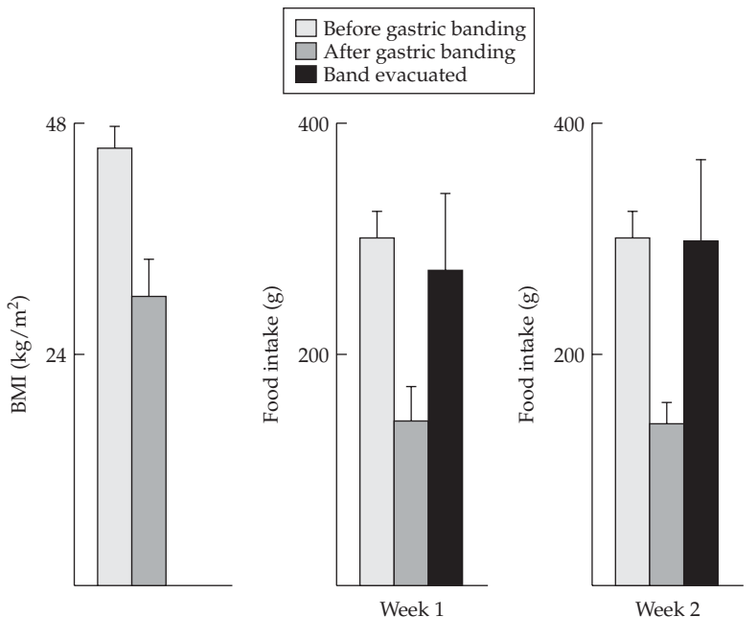


FIGURE 13.3 Body mass index in nine women before and 15 months after gastric banding. The women were tested twice for eating behavior and satiety before and after gastric banding, with a week between the tests. The gastric band was evacuated 1 to 3 days after the test, and filled for each of the two tests after gastric banding.

tion. This finding is supported by reduced food intake (about 50%) in both tests with the band filled. Figure 13.3 also shows that the diminished food intake was immediately reversed when the stomach was returned to full capacity (Week 1). Refilling the band reduced intake in a test 1 week later to the same level as the week before, and evacuating the band once more increased intake to the same level as before the gastric banding 15 months earlier (Week 2). Interestingly, the perception of satiety was similar under the three conditions (data not shown), demonstrating that the surgical effects did not cause fundamental change in either the patients' eating or the perception of small and large meals. This is of particular meaning in the light of "constant" satiety ratings after both tests. That is, satiety reflects meal completion, and not the amount consumed. This finding is reminiscent of studies by Rolls that examined the effects of eating meals of different sizes, which showed that satiety ratings were stable within an individual regardless of meal size. See the epilogue for a more complete discussion.

Summary of obesity surgery

Restraining gastric capacity for 15 months markedly affected the amount of food eaten by obese women and, consequently, their BMI. However, the effect on food intake was reversed immediately with gastric relief. The conditions that curtail meal size when the gastric band is constricted reflect minimized gastric capacity and not a fundamental reorganization of central control mechanisms. Food intake adapts to rapid changes in gastric capacity. Inhibitory neural control of eating does not develop as a result of peripheral constraints even over a relatively long period of time. The time to imprint the feeding system surgically, with all of its concomitant changes, has passed. Other strategies are called for. In short, although surgical interventions are effective in reducing body weight in obese patients, their cost (about 20,000 US dollars in 2007), surgical risk, and other negatives make it unlikely that these methods can be used for population-based treatment of obesity (Padwal & Majumdar, 2007).

An Alternative Framework

A framework is not a detailed hypothesis or set of hypotheses; rather, it is a suggested point of view for an attack on a scientific problem, often suggesting testable hypotheses. Biological frameworks differ from frameworks in physics and chemistry because of the nature of evolution. Biological systems do not have rigid laws, as physics has. Evolution produces mechanisms, and often sub-mechanisms, so that there are few "rules" in biology which do not have occasional exceptions.

A good framework is one that sounds reasonably plausible relative to available scientific data and that turns out to be largely correct. It is unlikely to be correct in all the details.

A framework often contains unstated (and often unrecognized) assumptions.

— Crick and Koch, 2003

Because of the demonstrated null to modest success of presently used methods to treat obesity (with the exception of surgery) and the sometimes questionable assumptions on which the methods are based (identified at the start of the chapter), a new framework should be useful. Here the term *framework* is used as suggested by Crick and Koch (2003).

This situation is similar to one that arose several years ago in an examination of methods used at that time to treat anorexia nervosa and other eating disorders. These methods were also marginally effective, being based on assumptions that did not take into consideration either the physiology of starvation or the biology of the brain (Södersten et al., 2006a,b). To paraphrase Crick and Koch (2003), a point of view was developed to attack the problem of anorexia nervosa. Two suggestions were made: first, that disordered eating emerges because starvation recruits a brain substrate for reward; second, that anorexic behavior is maintained through conditioning to the situations in which the reward was originally provided (Bergh & Södersten, 1996).

This framework was plausible, given the data available from animal studies. Food deprivation enhances dopamine release in the terminal region of the mesolimbic dopamine neurons in the ventral striatum. The mesolimbic dopamine system is engaged in behavioral events perceived as rewarding (see Chapter 4). Moreover, norepinephrine neurons of the locus coeruleus are activated indirectly via the enhanced secretion of corticotropin-releasing factor in a state of food deprivation. The cell bodies of the locus coeruleus, which project to mid- and forebrain structures, are engaged when attentional mechanisms are activated and constitute a neural substrate required for learning (reviewed by Zandian et al., in press). This framework suggested testable clinical hypotheses. First, patients with anorexia nervosa and other eating disorders should be able to relearn how to eat. Second, because starvation induces increased physical activity and reduced body temperature (Wang et al., 2006), anorexic hyperactivity should be reduced if the patients are kept warm, as was first suggested by Gull in 1874.

The effect of combining these interventions was evaluated in a randomized, controlled trial against a control group that received no treatment (Bergh et al., 2002). The randomized, controlled trial is considered to be the gold standard to determine the effectiveness of clinical interventions because it parallels the proper procedure of basic science (Smith, 2006). Relatively few exclusion criteria were used; patients with unspecified eating disorders and those who were in need of acute medical attention did not participate. Both anorexic (n = 19) and bulimic (n = 13) patients were included. The anorexics were younger (median 16 years old; range 10–33) than the bulimics (median 19 years old; range 15–54). The duration of the illness (2 years; range 0–21) and the number of previous treatments (3; range 1–15) were similar between the anorexic and bulimic groups

and not used as exclusion criteria. The median BMI of the anorexic patients was 15 (10.8–17.5); that of the bulimic patients was in the normal range (21.6; 17.9–31.8), with the exception of one obese patient. Symptoms of depression, anxiety, and obsession are seen in all eating-disorder patients, including the patients in this study, who also scored high on an eating-disorder inventory.

These patient characteristics are similar to those of patients participating in many other studies, with the exception that many fewer exclusion criteria were adopted for this study. In addition, anorexia and bulimia were considered to be two phases of the same disorder. Most commonly, anorexic and bulimic patients are kept separate when the effect of treatment is evaluated. The hope in using few exclusion criteria was to demonstrate that the principles of treatment were applicable to at least two feeding disorders with partially overlapping characteristics.

A successful outcome was characterized by the following criteria: (1) BMI should return to normal and be sustained in the anorexic patients. (2) Bulimics should stop binge-eating for at least 3 months. (3) Eating behavior, psychiatric profile, and laboratory tests should become normal. Patients should be able to state (4) that food and body weight were no longer problems and (5) that they had to return to school or professional activities. To be in remission, a patient had to meet all these criteria. These are strict remission criteria, which are generally not met in most outcome studies on patients with eating disorders (Södersten et al., 2006b).

Figure 13.4 shows that treatment significantly affected the number of patients going into remission. Half of the treated patients went into remission within

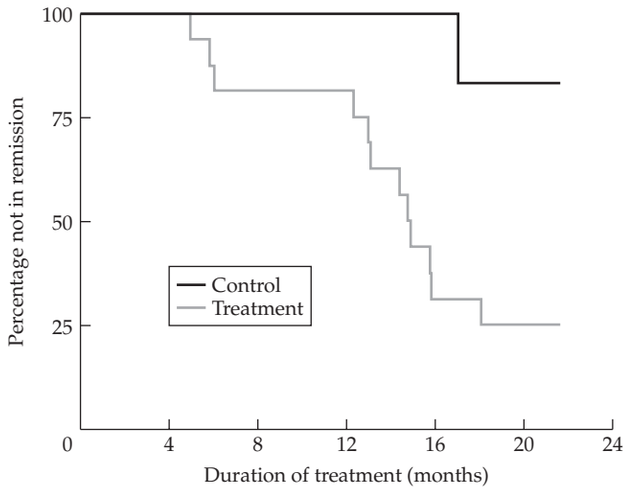


FIGURE 13.4 Outcome of treatment versus no treatment of patients with anorexia or bulimia nervosa. Each group contained 16 patients. (Data from Bergh et al., 2002, reproduced with permission.)

an average of 14 months, but only one of these treated patients went into remission spontaneously.

Because relapse is a serious problem once patients with eating disorders have been treated to the point of remission (Walsh et al., 2006), patients are followed for 5 years after treatment. Fewer than 10% of the patients relapse during this period of follow-up (Bergh et al., 2002).

These results show that the treatment had a major effect. To paraphrase Crick and Koch (2003) once more, this framework for anorexia nervosa has, so far, turned out to be largely correct, although of course it is unlikely to be correct in all details. For example, it is not known which, if any, of the interventions that were used is more important than any other.

A treatment of obesity

"A framework often contains unstated (and often unrecognized) assumptions" (Crick and Koch, 2003). An assumption that emerged from the framework for anorexia is that obesity is at the opposite extreme of the same continuum as anorexia. In line with this view, it was recently pointed out that, from a metabolic perspective, "caloric restriction [i.e., starvation] and metabolic syndrome [i.e., obesity] lie at the opposite ends of the same spectrum and so involve an overlapping set of regulators" (Guarente, 2006) Starvation and obesity are also at different ends of the same continuum from a behavioral perspective. Thus, whereas anorexic patients display reduced consummatory ingestive behavior and increased appetitive ingestive behavior (Tappe et al., 1998; discussed earlier), obese subjects behave in the opposite way. That is, compared to normal-weight subjects, they eat more if the food is easily available but less if eating demands an effort (Sclafani & Springer, 1976; Schachter, 1971).

The tests of this hypothesis were perhaps somewhat unusual. Presented with a choice between nuts with or without shells, obese subjects readily ingested nuts with no shells but ignored the nuts if it was necessary to remove the shells before eating them. By contrast, the presence or absence of the shell was irrelevant for normal-weight subjects, who were less likely to eat nuts without shells and more likely to eat nuts with shells than were obese subjects (Schachter, 1971). Furthermore, obese subjects were less likely to eat Chinese food with chopsticks, a more demanding task, than with silverware; whereas normal-weight subjects were more likely to try the chopsticks (Schachter, 1971). These interesting early studies have recently been extended by several observations that convenient access to food facilitates eating (Wansink, 2004), and a recent theory suggests that "reductions in the time costs of food" are a main cause of obesity (Cutler et al., 2003).

On the basis of these observations, it should be possible to treat obesity using procedures conceptually similar to those used for the treatment of anorexia nervosa. Whereas anorexics are encouraged to increase their eating rate, obese subjects are encouraged to slow down their eating.

A core intervention in anorexia treatment is changing the patient's eating pattern. Therefore, it was predicted that the pattern of eating behavior, and not the patient's psychological state, is what had to be addressed. Anorexic patients with BMIs as low as <14 kg/m^2 (n = 27) and up to 17.5 (n = 18), with psychological symptoms that differed markedly from normal on a standardized self rating scale (Svanborg & Åsberg, 1994), were studied (Zandian et al., in press). The hypothesis was verified: relearning how to eat normalized both the BMI and the psychological symptoms in both groups of anorexics studied, including those with extraordinary low BMIs (Zandian et al., in press).

These findings predicted that gaining *control of obese individuals' meal patterns*, as in anorexics, would alleviate their symptoms. A radical additional prediction was that the critical variable was not the type of food eaten so much as the meal patterns.

Normal human eating behavior

Humans show a big variation in the amount of food they consume from day to day (Figure 13.5). Under normal conditions, many individuals control their eating, protecting against eating too little rather than eating too much. Because this pattern of behavior is practiced for long periods of time, such individuals are at greater risk of becoming overweight (Periwal & Chow, 2006). In addition, considering that food intake in humans in everyday life is affected by a variety of factors, most of which are not compensated for by homeostatic controls (de Castro & Plunkett, 2002; Cutler et al., 2003; Wansink, 2004), humans were hypothesized to require external support to reduce body weight. Curtailing the peaks and troughs of the daily variation in food intake (Periwal & Chow, 2006) might protect against eating too much and, in the long term, against obesity and its return.

A pilot study on obese adolescents

PATIENTS Seven girls (median age 15.5 years; range 11–17) were recruited from the Childhood Obesity Clinic in Bristol, England. Their median BMI was 39.1 kg/m^2 (34.4–50.5), and they were considered resistant to standard therapy such as diet intervention and programs for physical activity. Six children had at least one obese parent, three had at least one absent parent, four had at least one parent who was being treated either for alcoholism or a psychiatric illness, and two were not attending school. Extensive social problems were universal within the group. The patients were not dysmorphic and had no underlying endocrine or metabolic cause for their obesity. Together, the extreme obesity and the social situation of these patients made them poor candidates for successful interventions, as their records indicated.

One patient, a 13-year-old with a BMI of 50.5, has a heterozygous mutation of the melanocortin-4 receptor (MC4R) gene (Farooqi et al., 2003). Insufficiency of this receptor in humans is thought to be "the most common monogenetic *cause*

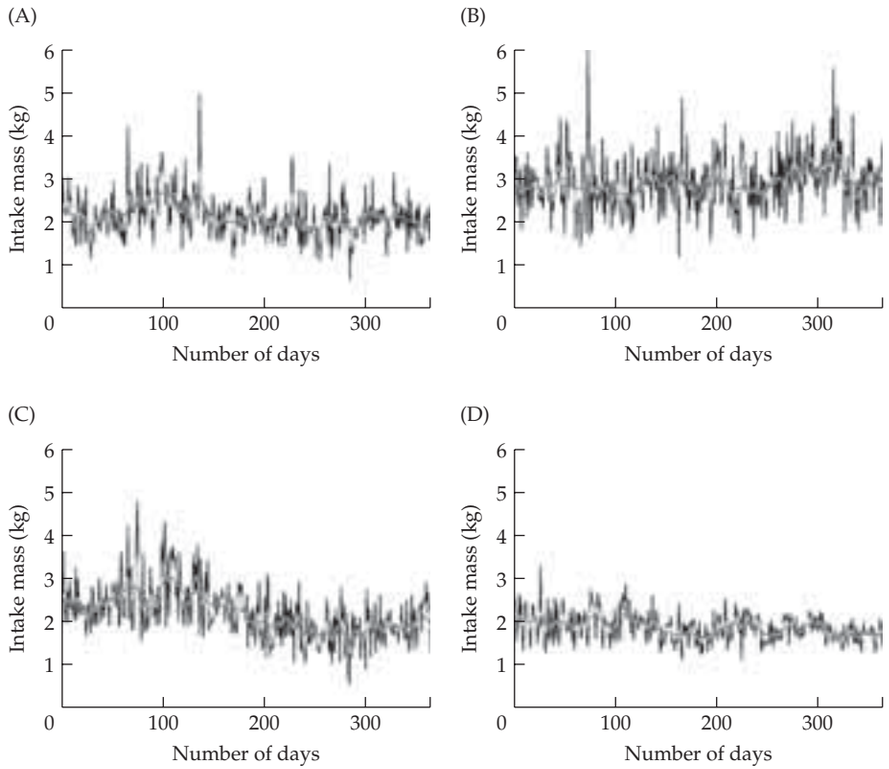


FIGURE 13.5 Daily food intake in four humans. (Data from Periwal and Chow, 2006, reproduced with permission.)

of severe obesity" (Farooqi et al., 2003, italics added), and humans with this deficiency are considered unable to regulate their eating behavior because a neural satiety mechanism has been disrupted (Cone, 2005). The possibility that the morbid obesity of this patient might be reduced by a change in eating habit was particularly interesting.

APPARATUS, QUESTIONNAIRES, AND PROCEDURE The patients were trained to eat using the Mandometer, a scale that is connected to a computer. A plate of food is placed on the scale, and the computer stores the weight loss of the plate during feeding to yield a curve of eating rate. At regular intervals, a rating scale appears on the computer screen. The patient indicates her experience of fullness on the monitor, which is also stored. This process yields a curve of satiety development. A screening test at admission identified a target rate of food intake for each patient, which was programmed into the computer and used to train nor-

mal eating patterns. A linear depiction of eating rate was displayed on the computer screen and the patient was asked to adjust her eating to this function. Such adjustment was possible because the patient could see her own eating rate appear on the screen during the meal. The following values were used for the training curve: breakfast, 125 to 250 grams eaten within 6 to 10 minutes; morning and afternoon snacks, 100 to 120 grams eaten within 5 to 10 minutes; and lunch and dinner, 290 to 400 grams eaten within 12 to 15 minutes.

A sigmoid curve, starting at 0 and ending at 10, for training meal-associated satiety (Bergh et al., 2002) was displayed on the monitor at 1-minute intervals at all meals, and the patient rated her level of fullness by pressing on a touch screen. Healthy volunteers ate 300 to 350 grams within 10 to 15 minutes and rated their satiety at about 5 to 6 under these conditions (Bergh et al., 2002). In this protocol it is important not to modify patients' diets but rather to allow them to choose a wide variety of food and drink. The reason is that the patients said that they often felt hungry when on diets and they felt ashamed of being both overweight and hungry. Patients were able to use the Mandometer in their home settings with each dinner because the device is lightweight, is easy to carry, and runs on rechargeable batteries.

Patients also filled in the Eating Disorder Inventory, a self-rating questionnaire for eating-disorder symptoms (Garner, 1991), and the Comprehensive Psychopathological Rating Scale Self-Rating Scale for Affective Syndromes (CPRS-SA; Svanborg & Åsberg, 1994). The CPRS-SA measures obsessive-compulsive behaviors, anxiety, and depression. Body weight and height were determined at monthly to bimonthly visits. The patients were also tested using the training system without the normal eating guide to evaluate change in rate and amount eaten.

RESULTS On average, patients initially ate a large amount of food (median 413 grams; range 219–775) at a high rate (median 40 grams per minute; range 20–50) when unassisted by training. These measures were reduced significantly—food intake to a median of 290 grams (168–344; $p = 0.043$), eating rate to a median of 20 grams per minute (13–29; $p = 0.028$; Wilcoxon test)—within on average 62 days (42–185) of treatment and before any change in BMI could be observed. The perception of satiety was low in three patients, but it normalized rapidly and was normal in the other patients (data not shown).

Two patients failed to comply with the treatment. One had lost weight at the time of dropout (BMI = –1.3 after 142 days of treatment), and one had gained weight (BMI = 2.4 after 364 days of treatment). The five other patients had remained in the study for a mean of 617 days (482–651) when treatment was terminated. Figure 13.6 shows that there was a significant change in BMI accrual before and during treatment.

Three patients (Patients 7, 8, and 10; Figure 13.7) had improved BMI; their BMIs decreased by 2.3, 3.4, and 8.8 kg/m^2, respectively. At follow-up 7 months after treatment, their BMIs had increased only slightly—by 0.4, 0.5, and 0.9 kg/m^2, respectively—and it remained low at follow-up 1 year after treatment in two patients—having changed by –0.5 and 1.7 kg/m^2, respectively—com-

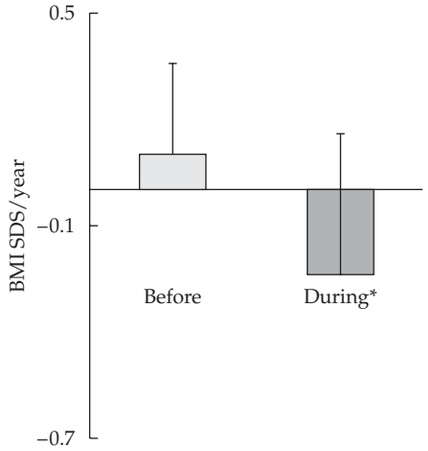


FIGURE 13.6 Change in BMI before and during treatment in five obese children. Standard deviation scores (SDSs) were generated from the 1990 British growth data using LMS curves generated by the Child Growth Foundation (Cole et al., 1998) and converted to change per year. The BMI development before treatment was based on a mean of 330 (318–384) days. *$p = 0.024$, paired t-test.

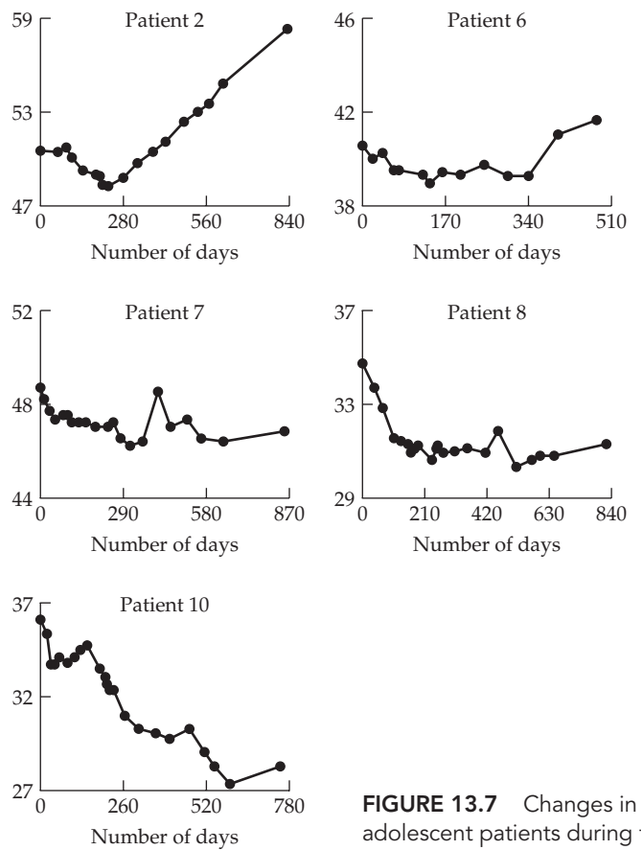


FIGURE 13.7 Changes in BMI in five obese adolescent patients during treatment.

pared to the value at the end of treatment. The third patient had also lost weight 1 year after treatment, but she had been treated with orlistat outside the study protocol during one month, so her data were not considered.

None of the patients showed signs of having an eating disorder, as indicated by normal scores on the Eating Disorder Inventory (data not shown), and the three patients who managed to reduce their body weight also had normal levels of psychiatric symptoms on the CPRS-SA rating scale (data not shown).

The two other patients (Patients 2 and 6; Figure 13.7) also improved their BMIs initially. The level of psychiatric symptoms was initially high in these patients but decreased as they lost weight. However, maternal suicidal intent led to an increase in psychiatric symptoms and BMI in one of these patients (Patient 6), who was prescribed antidepressant medication.

Interestingly, the patient who has an MC4R gene mutation and an extremely high BMI (50.5) at the start of the study (Patient 2) initially reported that she could not feel satiety. At that time she consumed a very large test meal (600 grams) at a very high rate (50 grams per minute). By contrast, after 62 days of treatment she reported being able to feel full for the first time ever, and she consumed a normal test meal (312 grams) at a normal rate (16 grams per minute). Unfortunately, paternal interference in compliance with treatment led to weight regain and an increase in psychiatric symptoms.

DISCUSSION All patients in this preliminary study had been previously treated without success using standard lifestyle modification. All had major social problems, reflecting their living in dysfunctional settings. The prognosis for these adolescent girls was bleak. Yet five of the seven, including one who dropped out of the program, lost weight during training; and three maintained this improvement for one-half to a full year after treatment. Two other patients also improved their BMIs initially, but increased complexities in their already complicated home situations may have compromised their ability to lose additional weight.

Although these results must be viewed with caution, it is interesting that body weight was affected at all, because the patients were morbidly obese and had proven resistant to treatment. All of these patients would have met the exclusion criteria commonly used in studies on the effect of pharmacological interventions to combat obesity (e.g., Despres et al., 2005; van Gaal et al., 2005). Yet the effect obtained in three patients was as large as, or larger than, that reported in previous pharmacological studies (e.g., Despres et al., 2005; van Gaal et al., 2005).

When first tested, six of the seven patients either ate an abnormally large meal or ate at an abnormally high rate. Only one participant (BMI = 34.7) ate a normal-sized meal (330 grams) at a normal rate (20 grams per minute). More interestingly, eating rate normalized in all patients before an effect on BMI was observed (within, on average, 2 months of treatment). Patients were intentionally not required to modify their diet. These pilot results generate the hypothesis that normal eating behavior may be a prerequisite for losing weight and more important than a change in diet.

The melanocortin system in the hypothalamus and brainstem is thought to play a role in satiety and body weight regulation, and "haploinsufficiency of the MC4R in humans is the most common monogenetic cause of severe obesity" (Farooqui et al., 2003). In line with this hypothesis, the patient with the MC4R gene mutation in the present study had a very high BMI (50 kg/m^2) and ate a very large meal (600 grams) at a very high rate (50 grams per minute) when first tested. She also reported being unable to perceive satiety. However, and more interesting, as she learned to eat a normal-sized meal at a normal rate, she reported feeling fullness for the first time, and she lost weight. Perhaps equally interesting, she experienced simultaneous relief from psychiatric symptoms. Unfortunately, because of parental interference, she was unable to comply with the study protocol for more than about 330 days, and at that time she relapsed into weight gain and developed psychiatric symptoms again.

Although the data from this patient must be interpreted with caution, they raise the possibility that normal eating behavior and the perception of satiety are possible in the absence of functional MC4Rs. As a corollary hypothesis, we suggest that obese patients with genetic "disorders" may be more dependent on external support for the control of body weight than are patients without such "disorders." The term *disorders* is in quotation marks here because under normal human conditions—that is, marked variations in the availability of food as discussed earlier—it has been suggested that mutation of the MC4R is a "thrifty" genotype (Cone, 2000) rather than a disorder.

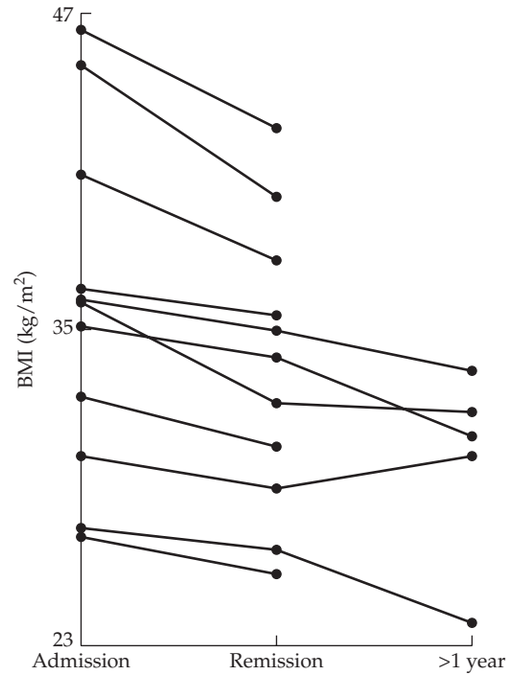
Weight reduction in patients with binge-eating disorder

In 1959, Stunkard pointed out that about 15% of patients who are obese have a pattern of eating behavior characterized by loss of control and overeating of large quantities of food, which is referred to as *binge-eating disorder* (*BED*). Behaviorally, BED patients are similar to bulimic patients, but they do not vomit and, as a consequence, they are obese. Behavioral methods are often ineffective in reducing body weight in BED patients (Stunkard & Alison, 2003), but pharmacological treatment, although often associated with unpleasant side effects, can be effective (Appolinario et al., 2003). Obesity surgery can also be effective, but BED can persist after surgery (Latner et al., 2004). The present framework predicts that reversal of disordered eating is important for reducing body weight in obese patients. The results of a preliminary study of BED patients verify this derived hypothesis.

PATIENTS Eighteen female BED patients (median 34 years old, range 22–61; median BMI 36, range 25–46.3) were treated with the Mandometer procedure described earlier. No exclusion criteria were adopted.

RESULTS Three of the patients are still in treatment. The other patients were treated to the point of remission in a median of 9 months (3–15). Three of the

FIGURE 13.8 Loss of body weight in 11 adult women with binge-eating disorder from admission to remission and at a 1-year follow-up.



four women who had been treated surgically lost weight, decreasing BMI from 44.2 to 40.2, 27.6 to 24.6, and 25.4 to 23.6, respectively; the fourth patient gained weight, increasing BMI from 28 to 30.3.

Figure 13.8 shows that all other patients lost weight. Four have maintained their reduced weight for at least 2 years (2, 3, 3, and 5 years, respectively). Another patient lost only a little weight, which she had regained by the 1-year follow-up. The rest of the patients have not yet had extensive follow-up.

DISCUSSION These results from BED patients offer further early support for the hypothesis that control of eating behavior is an important intervention in the management of obesity, although the method described here has not yet brought body weight down to the normal level in more than one patient (BMI = 23.8 at the bottom right in Figure 13.8). The fact that the BED patients had a highly variable BMI at admission, varying as much as from a minimum of 25 to a maximum of 46.3, offers further support for this hypothesis.

Summary

This chapter is founded on the confluence of three factors concerning obesity:

1. The failure of even contemporary homeostatic approaches to feeding to gain any traction on what is rapidly becoming a leading worldwide public health issue in nonpoor societies.
2. The abject failure of all diets, since their inception almost a century ago, to effect body weight loss during the intermediate or long term. Weight that is lost through dieting is reinstated after a leveling-off period. For some, this cycle of weight loss and reinstatement is repeated many times over.
3. The success of the approach to feeding disorders (namely, the disorders of anorexia nervosa and bulimia—both disorders of insufficient intake and retention) on the opposite end of the spectrum described here is encouraging.

Together, these considerations have given rise to a framework to counteract obesity. Because success in the most difficult instance predicts success in less difficult cases, the new framework was tested in seven women with a mean BMI of 39.1. Six of the seven reduced both meal size and eating rate through the feedback procedure, and three of the six either held their weight loss or even extended it when the treatment phase terminated. These early data, along with the data from very obese patients with binge-eating disorder, are of interest because the prognoses for patients of this stature were dim in the extreme. Because this is the first preliminary report of this approach, there is room for improvement either by combining eating changes with appropriate exercise regimes and/or by introducing variants in Mandometer usage. Because the approach is simple and far less expensive than other forms of dieting, it should become readily available in the public sector.[1]

Acknowledgments

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[1] A randomized, controlled trial using a Mandometer in 100 obese adolescents, some carrying an MC4R mutation currently conducted through the Bristol obesity clinic, should further inform these preliminary findings.

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