continuous or intermittent treatment throughout adult life—is a concept that is receiving more attention. In this context, the risk-benefit and quality-of-life analyses of pharmacologic treatment become increasingly important. Vigorous dialog between health care professionals, patients, the research community, and regulatory authorities is needed to define, in objective and quantifiable terms, the minimum efficacy required to justify long-term treatment. Safety considerations are critical. For example, because women make up the largest group seeking treatment for obesity, potential drugs must be tested in long-term studies for possible undesired effects on reproductive function and hormonal status.

Innovative drugs will be most effective when they are used as adjuncts to, rather than substitutes for, lifestyle changes to improve the metabolic fitness, health, and quality of life for obese individuals. Such drugs will likely be part of sequential or combined treatment programs tailored to individual patients. In summary, although the path to innovative medicines for obesity is strewn with many obstacles, the recent progress in the "new science" of obesity provides hope that the future of obesity treatment will be bright.

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Eating Disorders: Progress and Problems

B. Timothy Walsh* and Michael J. Devlin

Recent research on Anorexia Nervosa and Bulimia Nervosa has yielded an increasingly detailed understanding of the range of biological and psychological abnormalities associated with these eating disorders. Inherited vulnerabilities, cultural pressures, and adverse individual and family experiences all appear to contribute to the onset of extreme dieting, binge eating, and purging. Once initiated, these behaviors give rise to multiple physiological disturbances, some of which may serve to perpetuate the illness. Although there have been substantial advances in the management of Bulimia Nervosa, the goal of offering effective treatment to all individuals with eating disorders remains elusive. This article reviews current thinking on the etiology and treatment of the two major eating disorders and a related syndrome, Binge Eating Disorder.

Over the past 25 years, Anorexia Nervosa (AN) and Bulimia Nervosa (BN), the two officially recognized eating disorders, have become a major focus of attention among both the research community and the general public. Together these illnesses affect about 3% of women over their lifetime, and BN, the more common disorder, appears to be increasing in incidence. The causes of AN and BN remain enigmatic. Cultural and environmental factors are thought to play a role, as eating disorders are generally more common in industrialized than in developing nations. The possible etiologic role of biological factors has been difficult to study because the disorders are relatively rare and because good animal models do not yet exist. Although significant strides have been made in developing effective treatments for BN, AN remains difficult to treat, especially over the long term. Here we provide an overview of recent progress.

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Anorexia Nervosa: An Old Enigma

AN is among the most disabling and lethal of psychiatric disorders. Although it is sometimes attributed to the widespread practice of dieting among women in the late twentieth century, the first case of AN was reported 300 years ago and by 1874 the syndrome was already well described (*1*).

The essential features of the illness (Table 1) have not varied since these initial descriptions. AN is a disorder in which adolescents or young adults, mostly females, become engaged in a relentless and successful pursuit of thinness that results in serious weight loss. AN is characterized by prominent behavioral, psychological and physiological disturbances, including increased physical activity; depression; obsessional preoccupation with food; reductions in heart rate, blood pressure, and metabolic rate; increased cortisol production; and a profound decrease in the production of estrogen (or, in males, testosterone) (*2*, *3*). The changes in estrogen levels are responsible for the amenorrhea that is one of the defining characteristics of AN in women.

The prominent physiological disturbances of patients with AN have long led to speculation that their profoundly abnormal behavior is caused by a primary biological abnormality. Disruptions of the gastrointestinal tract, the pituitary, the hypothalamus, and various neurotransmitters have been postulated to be causal factors in the development of AN. However, the observation that most of these physiological disturbances resolve with normalization of body weight argues against their role as etiological factors.

Recent studies of serotonin and leptin in AN patients illustrate the challenge of determining whether the physiological abnormalities are a cause or a consequence of the disorder. The neurotransmitter serotonin is involved in physiological systems relevant to AN. Increases in brain serotonin function lead to reductions in food intake, and decreases in brain serotonin function are associated with depression. Cerebrospinal fluid (CSF) levels of the major serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), are low in underweight individuals with AN but then rise to above normal levels in individuals who have made long-standing recoveries (*4*). This finding has led to speculation that a premorbid disturbance in serotonergic function might be a risk factor for the development of AN. Low CSF levels of 5-HIAA are associated with impulsive behavior, such as suicide attempts. By extrapolation, the high levels of 5-HIAA in recovered patients could be a correlate of perfectionism and rigidity, characteristics seen in many individuals with AN before the illness develops.

Leptin is a hormone secreted by fat cells that appears to play an important role in the regulation of body fat stores. Consistent with their reduced mass of fat tissue, underweight individuals with AN have low serum levels of leptin and these increase with weight gain (*5*). Nonetheless, there are a few indications that alterations in leptin regulation may play a role in the persistence of AN. For example, during recovery, normalization of leptin levels (CSF and plasma) appears to precede normalization of body weight; this may contribute to the difficulties patients experience with attaining and maintaining normal weights.

Such findings, while intriguing, fall well short of establishing a causal link between biological aberrations and AN. Prospective clinical studies, which would establish whether biological disturbances such as serotonergic abnormalities predate the development of the eating disorder, are very difficult because of the low incidence of AN. Furthermore, in order to establish a causal relationship, the purported etiological factors would need to be manipulated and shown to have an effect on the development or course of the illness. Without such studies, we must remain cautious in our interpretation of the numerous biological abnormalities that characterize this illness.

Current treatments for AN are aimed at normalizing body weight, correcting the irrational preoccupation with weight loss, and preventing relapse. The specific interventions used to achieve these goals include admission to a hospital or a day-treatment program where a diet providing 2000 to 4000 calories per day is prescribed, meals and exercise are closely supervised, and psychological counseling is provided. Patients are universally reluctant to gain weight and have difficulty cooperating with these interventions. Despite these challenges, most specialized eating disorder units are successful in restoring body weight, but long-term correction of the psychological disturbances is less satisfactory, and relapse is common (*3*).

Patients with AN often exhibit symptoms of other psychiatric disorders. Many are depressed and many are obsessed with thoughts about weight and eating, and engage in compulsive rituals, suggestive of obsessive-compulsive disorder. Yet, despite the clear efficacy of medications such as fluoxetine (Prozac) in the treatment of depression and obsessive-compulsive disorder, these drugs appear to be of little benefit during the weight-gain phase of treatment of AN (*6*, *7*). However, a recent study reported that patients receiving fluoxetine after weight restoration in a hospital had a lower rate of relapse during the succeeding year than did patients receiving placebo (*8*). These paradoxical findings have prompted speculation that the weight-related physiological disturbances of AN, such as changes in brain neurotransmitter levels, interfere with the neurochemical effects of medications that are useful for the treatment of similar symptoms in normal-weight individuals.

Many individuals who develop AN during adolescence and young adulthood eventually make full recoveries. However, for at least 50% of these patients, the long-term outcome is not as good. The frequency of depression is high, and social and occupational functioning is often impaired. Many individuals remain irrationally concerned about weight gain and never achieve a normal body weight. The mortality, due to complications of starvation or from suicide, is substantial, approximately 5% per decade of follow-up (*9*).

In addition, not all of the physical problems associated with AN disappear with weight gain. One example is bone density. AN typically develops at the time of life when bone mass should reach its peak, and AN is associated with diminished bone density and with the risk of pathological fractures, particularly in chronic cases (*10*). The decrease in bone density is likely due to multiple factors, including decreased calcium intake, reduced estrogen secretion, and increased levels of cortisol. Weight recovery and the resumption of regular menstruation lead to improvement, but there are indications that bone density may never attain normal levels, leaving individuals at risk for serious osteoporosis later in life. Furthermore, estrogen replacement therapy, which is effective in preventing osteoporosis in post-menopausal women, appears to be largely ineffective in women with AN (*11*).

Table 1. Key diagnostic features of eating disorders.

Anorexia Nervosa
Body weight voluntarily maintained at below normal level
Intense fear of gaining weight or becoming fat
Amenorrhea (in females)
Bulimia Nervosa
Large uncontrolled eating binges at least twice weekly
Inappropriate compensatory behavior (e.g., vomiting)
Self-esteem closely linked to body weight/shape
Binge Eating Disorder
Large uncontrolled eating binges at least twice weekly
No regular use of inappropriate compensatory behaviors
Marked distress about binge eating

Bulimia Nervosa: A Recent Addition

Humans have probably engaged in occasional eating binges whenever adequate food supplies have been available, and the

practice of vomiting after overeating dates back thousands of years (*12*). However, official recognition of an eating disorder characterized by excessive food consumption ("binge eating") and by inappropriate behavior to avoid weight gain (such as self-induced vomiting) did not occur until 1980 when the American Psychiatric Association provided criteria for the diagnosis of BN (Table 1). There are clear links between AN and BN. Both disorders occur primarily among young women, both are characterized by an exaggerated concern about body shape and weight, and about one-third of patients who present for treatment with BN have past histories of AN. However, in contrast to individuals with AN, who are by definition significantly underweight, most individuals with BN are of normal body weight.

BN was officially recognized as a psychiatric disorder in part because of the increasing number of individuals who were presenting for treatment. Several studies in the early 1980s suggested that the frequency of BN among college women in the United States might be of epidemic proportions. More recent investigations using better methodology and stricter diagnostic criteria concluded that the lifetime prevalence among women is 1 to 3%, and that a comparable percentage of women have less severe variants of the disorder (*13*, *14*). Thus, BN is more common than AN, which has a lifetime prevalence among women of ~0.5%, but the physiological disturbances are much less severe and there is almost no associated mortality.

How does overeating get started, and why is it hard to stop? Many BN patients report that their eating binges began in the context of or immediately following a diet, and many continue to restrict their caloric intake when they are not binge eating. Psychological factors also seem to be critical in that patients frequently suffer from depression, which has been linked to disturbances in eating behavior. In addition, a variety of nonspecific individual and familial risk factors for psychiatric disorders, such as a history of sexual abuse, seem to increase an individual's chances of developing BN (*15*).

There is good evidence that individuals with BN, like those with AN, have abnormalities in serotonergic function (*16*). The method most commonly used to assess serotonin status in BN has been the administration of an agent, such as fenfluramine or 5-hydroxytryptophan, that acts through the central serotonergic system to stimulate the release of a hormone, such as prolactin. Compared to normal individuals, patients with BN show reduced responses to such stimuli. Because serotonin is involved in the development of satiety, disturbances in serotonin function may contribute to the persistence of the binge eating. In addition, abnormalities in the functioning of peripheral satiety mechanisms may contribute to the disorder. For example, in some patients, the capacity of the stomach is enlarged and the release of the satiety hormone cholecystokinin (CCK) following a meal is blunted (*17*). Disturbances in these physiological control mechanisms may impede the resumption of normal eating behavior (Fig. 1).

Two useful approaches have been developed for the treatment of BN. The first is a short-term (4 to 6 months) form of psychological treatment called cognitive behavioral therapy (CBT). CBT focuses on the patients' preoccupation with body shape and weight and the persistent dieting, as well as on the binge eating and purging. Patients are directed to monitor the thoughts, feelings, and circumstances surrounding binge–purge episodes, to cease dieting and begin regular eating, and to systematically challenge their assumptions linking weight to self-esteem. CBT has been demonstrated to be helpful, and there is evidence of persistent benefit four years after treatment (*18*).

The second approach, the use of antidepressant medications, such as desipramine (Norpramin) and fluoxetine (Prozac), was initially based on the association between BN and mood disturbance. Over a dozen double-blind, placebo-controlled studies have demonstrated that antidepressants help patients reduce binge frequency; however, only a minority of patients achieve full remission, and the limited data available suggest that there is a considerable rate of relapse once the medication is discontinued (*6*, *19*).

Despite these advances, current treatment methods for BN have limitations. Even in the best of hands, antidepressant medication and CBT fail for 33% to 50% of patients, so new interventions are sorely needed. In addition, therapists with expertise in CBT may be difficult to find outside of established centers, and several investigators have begun to explore the utility of self-help manuals that are based on the principles of CBT (*20*).

Cultural Imperatives

Strong circumstantial evidence suggests that cultural factors play an important role in the development of eating disorders. Reports of AN and BN emanate predominantly from the industrialized world, where food is plentiful and thinness—particularly for women—is equated with attractiveness. In the United States, 27% of

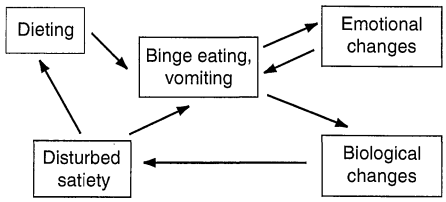

Fig. 1. Bulimia Nervosa (BN) is thought to be perpetuated by the interactions of behavioral, biological, and psychological factors. The biological changes associated with BN include enlargement of gastric capacity, slowed gastric emptying, and inhibited release of the intestinal satiety hormone cholecystokinin. Depression is one of the emotional changes commonly associated with BN. Adapted with permission from M. J. Devlin *et al.*, *Am. J. Clin. Nutr.* **65**, 114 (1997).

adolescent girls who view themselves as being at the "right weight" are nonetheless trying to lose weight, compared to less than 10% of adolescent boys (*21*). This disparity in desired body size and the high rate of dieting behavior among women are frequently invoked to explain the disproportionate occurrence of eating disorders among females. Similarly, the low incidence of eating disorders among non-Caucasians has been attributed to differences among ethnic groups in ideal body image; for example, black women, who do not commonly develop eating disorders, tend to express less dissatisfaction with their bodies than do white women of similar weight (*22*).

Familial factors also play a role in the development of eating disorders. The lifetime risk of AN or BN among female relatives of an individual with an eating disorder is 2 to 20 times that in the general population (*23*). By examining the rate of concordance of eating disorders in monozygotic and dizygotic twins, several studies have investigated the relative contributions of shared environment and shared genes in the familial aggregation of eating disorders (*13*, *24*). Although there is substantial variability among studies, overall the results suggest that a significant portion of the risk for developing an eating disorder is inherited. Heritable factors may be important in explaining the occurrence of AN long before the current cultural imperative to lose weight and in cultures where thinness is not so highly valued (*25*).

BED: Another Eating Disorder?

Although eating disorders have historically been associated with underweight or normal-weight individuals, disturbances among the obese have been noted for many years (*26*). The degree to which they contribute to the onset or maintenance of obesity,

however, is unknown. Binge Eating Disorder (BED), a syndrome first described six years ago (*27*), is characterized by eating binges, much like those seen in BN, but not followed by vomiting or any other means of counteracting the binge (Table 1). This syndrome may be at least as prevalent as BN but it is more evenly distributed in terms of gender and age. In weight loss clinics, about one-quarter to one-third of patients meet criteria for BED.

Are binge eaters really different? Laboratory studies of eating behavior have confirmed that obese patients with BED do in fact eat more than their equally overweight non-BED counterparts when instructed to binge (*28*). This suggests that binge eating is not simply a matter of perception. Binge eating also appears to be associated, independent of weight, with a greater frequency of psychiatric problems such as depression, larger and more frequent weight fluctuations, and more severe weight-related distress. These findings suggest that the distinction between obese binge eaters and non-binge eaters is a meaningful one (*29*).

What makes an individual vulnerable to BED and what triggers the onset of binge eating in those who are at risk? A predisposition to obesity and the presence of nonspecific risk factors for psychiatric disorders, such as adverse childhood experiences and parental depression, both appear to increase a person's likelihood of developing BED (*30*). Why one individual with these risk factors becomes an obese binge eater, another remains normal weight but suffers from BN, and a third ends up as a normal-weight healthy eater remains unanswered. Clearly there are risk factors and protective factors, on an individual, familial, and cultural level, that influence the development of binge eating in ways that we are only beginning to understand.

Whether the diagnosis of BED is useful in guiding treatment is a question that cannot yet be definitively answered because our knowledge base is derived from preliminary clinical trials. The challenge for those beginning to study treatment for overweight binge eaters has been to choose between treatment interventions that are designed to eliminate binge eating and those aimed primarily at weight loss. One area of disagreement is the role of dieting. Most mainstream weight control treatments encourage some degree of self-denial and a high level of dietary control. In contrast, clinicians treating patients with AN and BN see dieting as highly problematic, and the frequent progression from dieting to binge eating in normal-weight patients with eating disorders is well documented. Whether obese binge eaters can both normalize their eating and lose weight, and what sorts of treatments can best help them to achieve and maintain these goals, are the central questions of several ongoing clinical trials.

Future Directions

As is apparent from this brief review, the etiology and pathophysiological mechanisms of AN, BN, and BED are poorly understood. However, there are reasons for optimism. Advances in molecular genetics may permit the identification of genes that predispose individuals to develop AN or BN. Our expanding knowledge of biological factors involved in the regulation of body weight, such as leptin, may also yield insight into the pathophysiology of eating disorders. Studies of patients who have made full and lasting recoveries from eating disorders should help disentangle biological abnormalities that are a consequence of the illness from those that precede the symptomatic state and contribute to onset and maintenance. Greater knowledge of the pathophysiology of eating disorders should lead to innovative approaches to treatment and prevention. In particular, a clearer understanding of the similarities and differences between the disorders may facilitate the extension of treatments of known efficacy in BN to AN and BED.

The presumed etiological role of cultural factors has prompted attempts to modify the impact of these influences and thereby prevent the development of eating disorders. To date, broad-based prevention programs, which aim to increase public awareness of the health risks of inappropriate methods of weight loss, and to encourage resistance to the cultural obsession with thinness, have been generally unsuccessful. In fact, there are suggestions that such programs may actually do more harm than good, and this is currently a point of controversy in the field (*31*). Clarification of the interplay between cultural and biological factors in the development and maintenance of eating disorders will hopefully permit more accurately targeted and effective interventions.

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