ELSEVIER

Physiology & Behavior 81 (2004) 359–374

PHYSIOLOGY & BEHAVIOR

Eating disorders: clinical features and pathophysiology

Diane Alix Klein*, B. Timothy Walsh[1]

Columbia University/NYSPI, Unit #98, 1051 Riverside Drive, New York, NY 10032, USA

Abstract

Anorexia nervosa (AN) and bulimia nervosa (BN) are disorders of eating and weight-related behavior that together afflict some 1–3% of women in the United States. One of the remarkable features about each of the eating disorders is how persistent the disordered eating behavior becomes once it has begun. Substantial psychological, social, and physiological disturbances are associated with eating disorders, and it has been very difficult to disentangle those factors that may result from the disturbed behavior from the factors that may have predisposed individuals to, or precipitated the development of, the disorder. This article will briefly review the definitions, phenomenology, and identified risk factors for development of each of the major eating disorders. Pathophysiology will be discussed, with a particular focus on candidate factors that might sustain disordered eating behavior, as informed by clinical and basic science research. Future research directions will be suggested.

Keywords: Pathophysiology; Anorexia nervosa; Bulimia nervosa

1. Overview

An eating disorder may be defined as a persistent disturbance of eating behavior or a behavior intended to control weight, which significantly impairs physical health or psychosocial functioning, and is not secondary to a general medical condition or another psychiatric disorder [1]. The most widely recognized eating disorders are anorexia nervosa (AN) and bulimia nervosa (BN). The salient feature in AN is the refusal to maintain a minimally normal body weight; BN is characterized by recurrent episodes of binge eating followed by inappropriate behaviors aimed to avoid weight gain, such as self-induced vomiting. Binge-eating disorder (BED) is a more recently defined syndrome that features recurrent episodes of overeating, without inappropriate compensatory behaviors. A large number of people exhibit problematic eating behavior that might warrant a diagnosis of eating disorder, yet, does not fall clearly into a particular diagnostic category. Under the current psychiatric nomenclature of the *Diagnostic and Statistical Manual of the American Psychiatric Association-Fourth Edition* (*DSM-IV*; [2]), these persons would be diagnosed as having "eating disorder not otherwise specified" (or an "atypical eating disorder").

One of the remarkable features about each of the eating disorders is how persistent the disordered eating and/or dieting behavior becomes once it has begun. Substantial psychological, social, and physiological disturbances are associated with eating disorders, and it has been very difficult to disentangle those factors that may result from the disturbed behavior from the factors that may have predisposed individuals to, or precipitated the development of, the disorder. This article will briefly review the definitions, phenomenology, and identified risk factors for development of each of the well-defined eating disorders, AN and BN. Pathophysiology will be discussed, with a particular focus on candidate factors that may sustain disordered eating behavior, as informed by clinical and basic science research. Future research directions will be suggested.

2. Anorexia nervosa (AN)

2.1. Definition

AN, literally "a nervous loss of appetite", is derived from the Greek orexis, appetite. The syndrome was first described in medical literature nearly simultaneously by Sir William Gull in England and Ernest-Charles Lasegue in France, in the 1870s. Their descriptions of the cardinal

* Corresponding author. Tel.: +1-212-543-6944; fax: +1-212-543-6606.

E-mail addresses: dk2127@columbia.edu (D.A. Klein), btw1@columbia.edu (B.T. Walsh).

[1] Tel.: +1-212-543-5752.

0031-9384/$ – see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.physbeh.2004.02.009

features of severe weight loss, amenorrhea, psychological disturbances, and increased activity are reflected with only small modification in modern diagnostic criteria for the disorder as outlined in *DSM-IV*.

DSM-IV requires four criteria to be present for the diagnosis of AN. The core feature of AN is a relentless pursuit of thinness and refusal to maintain body weight at a minimally acceptable standard for age and height. This is suggested to be 85% of expected weight. A second essential feature is the intense fear of gaining weight or becoming fat. Third, individuals with AN place undue value on weight and typically exhibit disturbed perceptions of their own body shape and size. Lastly, postmenarchial females with the disorder are amenorrheic. *DSM-IV* furthermore recognizes two clinical subtypes of AN, the restricting and the binge-eating/purging type. Individuals with the former accomplish weight loss primarily through fasting or excessive exercise; individuals with the latter attempt to reduce weight through such behaviors as self-induced vomiting or laxative abuse. Many individuals progress from the restricting to the binge/purge subtype [3], but despite this phenomenological evolution, the restricting subtype is sometimes considered to be phenomenologically distinct.

2.2. Epidemiology

The lifetime prevalence of the full syndrome of AN among women is an estimated 0.5–2% [4–6]. Some recent studies have suggested that this number is growing, although there is disagreement [7]. Importantly, a number of persons exhibit partial forms of the syndrome and do not meet the diagnostic criteria for AN. AN disproportionately affects women, at a ratio of 10 to 20:1 females–males. Historically, the typical patient presenting for treatment of AN in North America has been a Caucasian adolescent female of middle-to-upper socioeconomic background. While persons of other ethnic groups do present for treatment for the disorder, the preponderance of women in the United States affected by AN are still Caucasian [8]. Participation in certain activities and professions, including dance, fashion modeling, and sports, in which low-fat mass is considered to be advantageous (e.g., distance running), seems to be associated with higher rates of eating disorders in both genders.

2.3. Etiology

The genesis of disordered eating behavior, in general, and AN, in particular, appears to be multifactorial. While several apparent risk factors have been identified, there is no known direct cause. The low incidence of AN makes it difficult to study prospectively, and for any given exposure or vulnerability, many more persons possess the risk factor than develop the disorder. A likely model features an interaction of several biological, psychological, and environmental risk factors, as discussed below. It appears that factors that initiate disordered eating and dieting behavior are distinct from those that maintain the behavior once it becomes problematic [9].

2.4. Susceptibility factors and exposures

2.4.1. Genetic/familial

There is good evidence that genetic factors play a role in vulnerability to eating disorders. According to family studies, the lifetime risk of AN or BN among female relatives of an individual with an eating disorder is 7 to 20 times that of the general population [10]. The transmission of this susceptibility appears to be at least, in part, genetic, as monozygotic twin pairs have higher concordance rates of AN than do dizogotic twins. Overall, an estimated 58–76% of the variance in the occurrence of AN may be related to genetic factors. The remainder of the variance in AN is not explained by either genetics or shared environmental experience and is believed to stem from nonshared or unique environmental effects. These include differential experiences among siblings in the same household, such as different treatment by parents, peer groups, and life experiences [11].

Which specific heritable feature or features confer vulnerability to an eating disorder is a compelling question. The concept of an ‘‘obsessive-compulsive spectrum’’ of disorders has gained recent attention, featuring obsessive-compulsive disorder (OCD), obsessive-compulsive personality disorder (OCPD), and body dysmorphic disorder (BDD); eating disorders have been included in this theoretical spectrum [12]. These syndromes are thought to share certain phenomenology, associated features, and, arguably, familial transmission. While it does not appear to be the case that AN is coinherited with OCD per se [13], there is evidence to suggest the cotransmission of AN and obsessive personality traits [13,14]. Such findings have fostered the hypothesis that a broader phenotype exists, featuring perfectionism, rigidity, and propensity for behavioral constraint, of which AN is one possible expression.

Because CNS serotonin function is clearly involved in the regulation of food intake and has also been implicated in obsessive-compulsive spectrum disorders [15], some attempts to determine a biological marker for such a trait have focused on genes involved in the serotonergic system, including transporter and receptor polymorphisms. Other attempts to establish a heritable vulnerability for eating disorders have focused on genes involved in body weight regulation and feeding, such as leptin, the melanocortin MC receptor, and estrogen receptor genes, as implicated in animal feeding models. Most of such investigations, which assess for higher than expected transmission of particular polymorphisms in persons with AN or BN, have yielded negative or inconsistent results [16]. However, large-scale molecular genetic studies are underway to ascertain genetic underpinnings of eating disorders.

Like most other major psychiatric disorders (e.g., depression, bipolar disorder), AN is likely not to result directly

from a polymorphism of one particular gene, but rather at least a "two-hit" (or a "multiple-hit") process wherein a trait, linked to a certain gene or set of genes, is expressed under particular environmental circumstances. Gene dosing effects may also play a role. Conceivably, vulnerability to AN could be conferred by any of a number of traits including a tendency towards behavioral rigidity, a diminished sensitivity to orexigenic signals, a heightened sensitivity to the reinforcing effects of starvation or exercise, or a tendency towards excessive locomotor activity in the setting of weight loss, among others. These might only be manifest in the setting of dieting behavior, a social environment that emphasizes thinness, and/or participation in strenuous physical activity. An alternative phenotype might be expressed in a different cultural setting or gender. Identification of the factors involved in the pathogenesis of disordered dieting behavior should continue to fuel investigations of genes conferring the vulnerability to the development of AN.

2.4.2. Temperament/personality

Personality and temperamental traits identified in persons with AN include greater harm avoidance, conscientiousness, persistence, and perfectionism than the general population [17]. Additionally, a higher frequency of perfectionism and obsessional symptomatology has been demonstrated among women recovered from AN [17,18], as assessed by such tools as the Temperament and Character Inventory (TCI; [19]), the Multidimensional Perfectionism Scale [20], and the Yale-Brown Obsessive Compulsive Scale [21,22]. Such retrospective assessments may be complicated by the effects of a period of illness. Hence, while it is likely that these characteristics premorbidly increase vulnerability in AN, the possibility that an episode of AN produces these psychological changes cannot be excluded.

2.4.3. Developmental factors

AN most commonly develops during adolescence or young adulthood and rarely begins prepubertally. The proximity of puberty and the development of secondary sex characteristics to the usual age of onset of AN suggest that puberty itself may be a risk factor. Psychological reactions to the maturing body, changing peer relationships, and new life challenges might play a role in the development of AN. Furthermore, estrogen and other reproductive hormones affect mood and feeding behavior in both animals and humans [23]. That AN tends to appear as the hypothalamic–pituitary–gonadal axis is maturing (and that it occurs predominantly in women) raises the possibility that some individuals express sensitivity to these changes in the development of eating-disordered behavior. Additionally, the development of motivational brain circuitry that occurs during adolescence is speculated to render young people more vulnerable to addictive disorders [24]. While the link between eating disorders and disorders of drug use remains to be established, the same processes that render a developing individual vulnerable to such maladaptive behaviors, as drug use, might also influence the development of disordered eating behavior. Finally, psychological stress may play some role in the initiation of the disturbance and in relapses among those who do achieve remission. An examination of each of these factors, the role of gonadal hormones, developing motivational neurocircuitry, and stress on the initiation or maintenance of reduced food intake and excessive physical activity in animals could lend important insight into their potential roles in the pathogenesis of AN.

2.4.4. Sociocultural influences

Sociocultural influences have been implicated in eating disorders, particularly in the initiation of the disordered behavior. Popular media not only equates beauty with a slender, sometimes cachectic, physique, but also promulgates means by which this might be achieved, in advertisements for diet regimens and fitness clubs. Children in the United States and United Kingdom endorse dieting concerns and behavior as early as age eight [25]. This phenomenon is more pronounced in Westernized cultures, where eating disorders appear to be more prevalent. As Western media is exported, so is vulnerability to eating-disordered behavior; studies of women on the Fiji Islands, for example, isolated from Western cultural influences until 1995, demonstrate a sharp rise in disordered eating attitudes and behavior with introduction of Western media [26]. However, the occurrence, albeit infrequent, of AN in nonindustrialized countries, and the existence of descriptions of the syndrome dating to the 1600s [27], argue that factors other than current cultural imperatives regarding shape and weight play an important role in development of eating disorders.

2.5. Clinical features

Weight loss in AN is usually accomplished primarily through a reduction in food intake, which often progresses through stages. Initial rationing may mirror current dietary trends and may seem innocent in its inception. First, desserts, then meat, and then all foods that could potentially contain fat may be eliminated; vegetarianism may be claimed to justify progressive substitution of energy—poor food choices for energy-dense ones. Increased attention is paid to the nutrient and caloric content of food, and an individual usually arrives at a regimen of "safe" foods. This might feature as little as a few leaves of lettuce or pieces of fruit per day, and frequently does not vary at all from day to day. Drinking of fluids is often restricted as well, although may also be abnormally enhanced. Patients with AN consume fewer calories over 24 hours and consume meals of reduced caloric content compared with normal individuals; they also tend to eat more slowly, with frequent pauses in eating [28,29].

As weight loss progresses, thinness becomes an increasingly salient goal. Growing attention is paid to body weight, shape, and size. Varied techniques may be employed to

estimate and measure these, and rituals may develop around such assessments, which may be repeated multiple times daily. Weight loss confers profound, if fleeting, reassurance; weight gain is viewed as failure deserving of self-punitive measures including further restriction and increased exercise. Idiosyncratic rules develop around when, what, and how much a person permits herself to eat and around how much exercise is required. As the disorder progresses, these rules become increasingly inflexible.

At the outset of the disorder, weight loss may be socially reinforced. Particularly, if a person is overweight initially, early dieting successes may be met with approval from family and friends. Continued weight loss, to the point of cachexia, eventually elicits concern, which may be reinforcing for some individuals and discomfiting to others, particularly when it threatens to interfere with continued weight loss. Under pressure to gain weight, individuals often turn to deception, claiming to ''already have eaten'' and consuming up to liters of fluid (''water-loading''), or carrying concealed heavy items when being weighed. Not uncommon, an individual with AN may be able to hide weight loss from family members with loose-fitting clothes, and a 30- to 40-pound weight loss may go unnoticed.

Social avoidance usually facilitates progressive weight loss. Persons with AN may eschew situations and events in which eating would be required. Psychological concomitants of starvation, including irritability, poor concentration, and fatigue, render social interaction less rewarding as well. The behavioral repertoire of an individual with AN often constricts to include little more than rituals associated with exercise and eating, and work. With declining interest and performance, investment is withdrawn from other activities that had reinforcing value prior to the development of the disordered dieting, such as extracurricular and social outlets. The loss of these reinforcers has detrimental effects. Not only does it disrupt previously learned eating patterns and social cues for eating, but as well, a paucity of alternative investments heightens the relative salience of dieting behavior and thinness to the individual with AN.

The stereotypic nature of the daily existence of such individuals, and, more generally, the typical course of AN, harken to other behavioral disorders such as alcoholism. In the latter, the pursuit of a substance or activity that is initially rewarding ultimately becomes severely maladaptive. With physiological and/or psychological tolerance, increasing amounts of time and energy are subsumed in an attempt to achieve a rewarding effect, or simply to stave off symptoms of withdrawal. A restricted behavioral repertoire with limited alternative reinforcers is characteristic of substance dependence. Indeed, AN has been likened to an addictive disorder [30]. However, cardinal behavioral and psychological features of addiction, including intoxication, craving, dependence, and withdrawal, have yet to be systematically demonstrated in AN. Furthermore, it remains unclear which aspect or aspects of AN might be so potently reinforcing. While it has been suggested that starvation-induced endogenous opioids and/or stimulation of the dopaminergic system play a role in sustaining the behavior [31], this remains to be demonstrated. The finding however that food deprivation in rats, which enhances the hedonic responses to food, also increases the motivational value of nonfood rewards, including as psychostimulants [32] and intracranial self-stimulation [33], does suggest that whatever behaviors are reinforcing in AN, might be so to a greater degree due to this apparent reward-potentiating effect of starvation. An exploration of the mechanisms underlying this potentiation may provide insight into processes of reinforcement in AN.

AN is a strikingly refractory behavioral disorder. The dieting behavior appears to interact with underlying vulnerabilities and environmental factors to produce alterations in the choices, learned responses, and drives that are expressed in AN. Below are described a number of features associated with the syndrome of AN. While causality is unclear in the majority of these, some or all have the potential to contribute to the maintenance of the irrational pursuit of weight loss that characterizes AN.

2.6. Associated features

2.6.1. Overactivity

Overactivity is a feature of AN that is repeatedly referenced and incompletely understood. Considered by some to be a hallmark feature of the syndrome, excessive physical activity is frequently seen in patients with AN at some point during its course. Overactivity may take various forms including a planned excess of sports, walking, or other physical activity, with the apparent goal of further catabolism. Even maintenance of a rigid posture, isotonic contractions, and excessive standing are known by patients with AN to consume more calories than rest will, and are frequently practiced on inpatient treatment units. Fidgeting and restless movements that appear to be nonvolitional are also observed, however, suggesting that starvation itself might elevate activity levels. Exercise-induced stimulation of the dopaminergic system has been suggested as a possible causal factor [31], but no clear mechanism has been identified. Indeed, few attempts have been made to quantify locomotor activity in AN. It remains undetermined whether overactivity occurs in a subset only or in all of patients with AN, and at what particular stage in the illness it presents. Furthermore, while it has been argued that excessive activity contributes to difficulties in restoring and maintaining weight in recovering individuals, possibly by reducing appetite or increasing caloric needs, this has not yet been demonstrated experimentally.

Sometimes, excessive sports activity and strenuous exercise coincide with the onset of strict dieting, which ultimately progresses to AN. Several investigators conclude that such activity is a possible independent risk factor for AN, or activity anorexia [34]. Significantly, the most widely accepted animal model of AN [35] is that of activity anorexia. In this model, previously free-feeding rats are

provided only 1 h/day of access to food, at the same time, an activity wheel is made accessible for the rest of the day. While rats simply provided with restricted food access learn to maintain their weights by consuming more food during that single hour, animals that are provided access to the running wheel increase their physical activity such that they lose weight. Strikingly, animals inducted into this regimen will progressively choose to run, to the extent that they will ultimately die of emaciation. This model lends credence to the hypotheses that exercise is more reinforcing to a semi-starved individual and that exercise itself may confer some reinforcing value to food avoidance. An investigation of the neurochemistry underlying this behavior in rats may provide insight into factors that foster overactivity in some persons with AN.

2.6.2. Altered drive to eat

Hunger is often denied by persons with AN, but the name of the disorder is somewhat of a misnomer, as AN is not primarily a disorder of appetite loss. Persons with AN do behave, however, as though the normal excitatory control of eating behavior is disrupted. At the same time, its inhibitory counterpart, satiety, seems to be enhanced. When compared with both individuals with BN and noneating-disordered controls, individuals with AN endorsed lower hunger ratings and higher fullness ratings during the course of test meals [28,36,37]. The normal reciprocal relationship between these two states as well was disturbed in these individuals. And compared with normal individuals, persons with AN demonstrated a weakened correlation between gastric contents and hunger, suggesting diminished perception of this somatic state [38]. On neuropsychological testing, however, individuals with AN have been found to be distracted by food-related cues, suggesting that food is a salient stimulus [39]. Most patients with AN indeed endorse thinking about food nearly constantly, despite eating only small amounts of it.

Most patients describe learning early in the course of their illness to ignore hunger sensations to succeed at weight loss. This selective inattention may be facilitated by the effects of starvation itself, including delayed gastric emptying [40], which could act to enhance satiety, starvation-induced endogenous opioid release, elevated cortisol, or other processes that could simultaneously enhance anorexigenic signaling. Such processes are not unique to AN, but would be universal and adaptive to any organism that has to function in a state of chronic starvation. What distinguishes individuals with AN is the choice that they make to avoid the food in ample supply in their environments.

Various molecules have been implicated in the stimulatory and inhibitory control of eating behavior, a number of which have been assayed in individuals with AN. For the most part, orexigenic hormones are found in elevated concentrations in individuals with AN, consistent with at least a partial compensatory response to starvation; anorexigenic signals are generally reduced. One possible exception is leptin. This peptide hormone, secreted by adipose cells in proportion to fat mass and active in the CNS, appears to play a role in the tonic control of ingestive behavior. Leptin is found in reduced levels in plasma among women with AN, as would be predicted from their low-fat mass [41]. However, when a curve was created to depict the relationship between leptin levels and percent body weight in people over a range of body weights and then extrapolated to low body weights, leptin levels in persons with AN were greater than predicted by this curve [42]. Furthermore, during recovery, leptin levels have been found to normalize prior to normalization of body weight [43], suggesting that leptin might be interfering with the drive to eat. It is unknown whether similar levels occur in persons who are severely underweight due to other causes. It is also unknown as to how such abnormal levels would translate to the behavioral abnormalities observed in AN, although the finding that leptin has effects in CNS reward pathways [44] suggests that it could possibly alter the reinforcing value of food for an individual.

Studies do suggest abnormalities in the reward value of food among individuals with AN. While the perception of taste intensity appears to be intact, hedonic ratings of tastes of test solutions are shifted such that sweet solutions are preferred, while high-fat solutions are considered aversive [45–47]. This is reflected in clinical presentations of patients with AN, who report repulsion by high fat content in food and demonstrate avidity for sweet substances, particularly those without nutritive value (e.g., artificially sweetened diet beverages). The mechanism for this shift is unknown, and two separate processes might be involved. An aversion to high-fat solutions might reflect a form of conditioned aversion to perceived calories, overriding what otherwise would be (and is, in food-deprived animals) a preference for more concentrated fat sources [48]. These hedonic differences appear to persist in individuals with AN following treatment, at least in the short term [45,47], which raises the possibility of an underlying trait related to preference for sweet substances, versus an enduring effect from a period of starvation.

2.6.3. Cognitive and mood abnormalities

One of the most remarkable perceptual changes in AN is that of distorted body image. Cachectic individuals may endorse the belief that they are actually too heavy, a phenomenon that may seem suggestive of a delusion, although reality testing is otherwise intact. Sometimes, the individual acknowledges being thin or even underweight but persists in identifying a particular body aspect that is fat, or simply does not acknowledge the life-threatening consequences of being severely underweight.

A host of neuropsychological abnormalities has been identified among persons acutely ill with AN, including in the domains of memory, attention, concentration, and motor speed [49–51]. These functional abnormalities have been associated in some, but not all [49,52], neuroradiographic studies with structural brain abnormalities including enlarged cerebral ventricles and diffusely atrophic frontal

lobes [53]. Additionally, neuropsychological deficits may be linked to elevations in cortisol level seen in the acutely underweight state [54], although this association as well lacks consistent support. It is unclear whether and to what extent cognitive and radiographic abnormalities resolve with weight restoration; discrepancies among studies may reflect disparities in patient recovery status at follow-up testing. Attempts to demonstrate specific neurocognitive deficit syndromes, such as right parietal dysfunction, which might account for distorted body image, or executive dysfunction, which might explain cognitive rigidity observed in AN, have similarly yielded mixed results [55–58]. In general, however, the presence of cognitive deficits in the acutely starved state is likely to contribute to the irrational preoccupation with food and body weight and to the difficulty of conducting psychotherapy with these individuals.

Mood disturbance is common in the underweight state of AN; some 21% to 91% of patients have been reported to demonstrate depressive symptoms during the acute phase of AN [59]. Other psychological symptoms frequently reported in the acutely underweight state include obsessionality and irritability. These often abate with weight restoration and are likely not unique to AN. For ethical reasons, few data exist on the effects of starvation in normal humans other than in extreme conditions of deprivation. One study conducted during the Second World War, using healthy male conscientious war objectors, documented intense preoccupation with food and eating. Seemingly irrational rituals developed around food consumption; these men also demonstrated loss of humor, irritability, and diminished social interest [60]. The mechanisms mediating such changes are unclear. However, an intriguing analogue to the obsessive and ritualistic behavior observed among starving people may be the hoarding behavior in food-restricted rats that increases with a decline in body weight [61]. Corticosteroids and leptin have been suggested to mediate these behaviors; definitive demonstration of this in an animal model could lend insight into the food-related, and perhaps even the generalized, obsessionality observed in persons with AN.

2.6.4. Neurotransmitter disturbances

A number of the mood and cognitive abnormalities evidenced by individuals with AN have been hypothesized to be linked to abnormalities in CNS serotonin function. Increased serotonergic responsiveness has been linked to psychopathological characteristics of OCD, overly inhibited behavior in animals, anxious and obsessive behavior in humans, and harm avoidance [59]. Furthermore, pharmacologic manipulations demonstrate association between increased synaptic serotonin and inhibition of feeding behavior [62]. Although serotonergic regulation of mood and appetite arise from different loci in the CNS, such associations have prompted the investigation of the serotonin function in persons with AN.

The measurement of the serotonin metabolite 5-HIAA in lumbar CSF provides an indirect global measure of presynaptic release of the neurotransmitter in the CNS. Early studies demonstrated reductions in CSF 5-HIAA levels in underweight patients with AN when compared with their weight-restored state and control values [63,64], although this has not been a universal finding [65]. Reductions in the metabolites of other neurotransmitters, including dopamine and norepinephrine, have also been described in underweight patients with AN [63,66]. Reexamination of the same patients shortly after weight restoration has shown that CSF 5-HIAA values tend to normalize [64], as do the metabolites of other neurotransmitter metabolites. Interestingly, however, persons recovered from AN for longer periods of time appear to have elevated levels of CSF 5-HIAA. Not only are these significantly higher than in their underweight state, but also higher than levels of CSF 5-HIAA found in normal individuals [67]. It has been suggested that these elevated levels of CSF 5-HIAA reflect a premorbid trait of hyperserotonergic function among individuals with AN [59], which has been argued to underlie trait obsessionality.

Abnormal serotonin function might thus account, in part, for individual differences in the vulnerability to develop AN, possibly by means of predisposition to cognitive and behavioral rigidity. However, another process would seem to be involved in the increased obsessionality that accompanies starvation. This phenomenon has been observed both in underweight individuals with AN [68], as well as in starved men without any preexisting obsessionality [60]. Given the above finding of reduced CSF 5-HIAA in acutely underweight individuals with AN, it seems likely that another neurochemical mechanism contributes to the increased obsessionality observed in acute starvation.

A number of other hormones have been found to be deranged in starvation, including cortisol (elevated; [69]), CSF vasopressin (increased postrecovery in binge/purge AN participants; [70,71]), and CSF oxytocin (normal in recovered [70] and acutely ill AN-B/P participants [72] but decreased in underweight individuals with restricting subtype of AN [72]). A number of these hormones are involved in learning and behavior [73], and in the modulation of neurotransmitter systems [74]. Whether and how derangements in these or other neurochemicals could contribute to the cognitive, affective, and behavioral abnormalities observed in AN are intriguing questions as yet unanswered.

It should be noted that majority of studies to date examining the brain neurochemical changes in AN have relied upon highly indirect measures, i.e., CSF levels. While the interpretive strength of this literature is low, recent advances in molecule-specific brain imaging show promise for providing more definitive answers to the neurochemical abnormalities associated with AN. Future research in this area is anticipated.

2.7. Physical complications, treatment and prognosis

Numerous physical and laboratory abnormalities accompany starvation. Most of these are accommodations to

reduce metabolic expenditure. Blood pressure and pulse are abnormally low. Thyroid abnormalities seen in AN include low levels of the active hormone, T3 (triiodothyrone). Vasopressin secretion by the posterior pituitary is disturbed, and a clinical picture of partial diabetes insipidus may result. Amenorrhea reflects hypothalamic dysfunction and is characterized by low levels of LH and FSH, as well as reduced estrogen and progesterone. In males with AN, a similar hypogonadism occurs with decreased testosterone levels. Diminished libido is found in both genders. While these abnormalities generally improve with weight restoration, osteopenia is one physical problem that does not. Such medical morbidity, in promoting the lassitude and fatigue that many individuals with AN demonstrate, likely contributes to the restricted behavioral repertoire that characterizes AN.

The crucial immediate goal in the treatment of AN is weight restoration. Until the physical and psychobiological effects of weight loss are reversed, little can be gained from other treatment modalities including psychotherapy and medication. Depending on the severity of the illness, inpatient hospitalization may be necessary to initiate weight restoration. A diet of 2000–4000 kcal/day can be implemented with close supervision of meals and curtailment of exercise. Psychotherapy, both group and individual, is a critical adjunct as weight restoration proceeds. The secondary aims of treatment include correcting the irrational commitment to weight loss and preventing relapse. Despite the frequent presence of mood and anxiety disturbances, antidepressant medications are generally unhelpful in the acutely underweight state, possibly due to the diminished availability of dietary precursors to serotonin [75]. Selective serotonin re-uptake inhibitors (SSRIs) may be useful following weight restoration, however [76]. Trials are underway to determine whether atypical antipsychotics (e.g., olanzapine) are useful, as these appear to reduce cognitive rigidity and anxiety in OCD and are associated with weight gain in other patient populations.

AN is a chronic illness in some 20% of those who develop it, and an additional 5% to 10% percent ultimately die of complications of AN, including suicide. Outcome studies further suggest that slightly fewer than half of patients with AN will make full recovery from the disorder, and a final third will experience partial remission but continue to evidence at least some eating-disordered symptomatology [77].

2.8. Future directions

In summary, AN is a disorder of abnormal dietary restraint that develops primarily in young women and becomes devastatingly persistent in a significant proportion of those it affects. Factors that seem to predispose to development of the disorder include perfectionism and rigidity; these may also influence its recurrence and persistence. Neurochemical changes associated with starvation may perpetuate the disordered behavior by distorting cognition and reward processes and altering the choices, learning, and drives involved in eating behavior. Further research in such areas identified above might lend insight into factors that maintain AN and, in turn, ultimately yield novel, and sorely needed, treatment approaches.

3. Bulimia nervosa

3.1. Definition

The term bulimia is thought to derive from the Greek words *bous* and *limos*, and translates literally to ‘‘ox hunger’’ [78]. Overeating has presumably been a problem for humans for millennia, and the practice of vomiting after eating also dates back thousands of years [79]. However, it was not until 1979 that the clinical syndrome of BN was formally described, in an article published by Russell [80]. In 1980, BN was recognized as a disorder in *DSM-III*. Modest modifications have been made to the yield the current *DSM-IV* criteria.

The essential behavioral feature of BN is recurrent episodes of binge eating, involving consumption of an excessive amount of food, with a subjective sense of loss of control. Binge eating episodes are associated with inappropriate behavior aimed at avoiding weight gain, most often self-induced vomiting. To meet *DSM-IV* criteria for BN, both overeating episodes and inappropriate compensatory behaviors must occur, on average, at least twice a week for 3 months. Additionally, the psychological feature of overconcern with shape and weight must be present. Finally, a diagnosis of BN is not applied to a patient currently meeting criteria for AN. Body weight is usually normal in persons with BN; if body weight is less than 85% of IBW and amenorrhea is present, the diagnosis of AN, binge-eating/purging subtype, is almost always more appropriate.

In *DSM-IV*, a subtyping scheme was introduced for BN in which patients are classed as having either the purging or the nonpurging type of BN, where the latter utilize only excessive exercise and/or fasting in attempt to avoid weight gain. This distinction is supported by clinical differences between the two groups, including among purging bulimics, a greater likelihood of electrolyte disturbances, greater psychiatric comorbidity, and lower body weight. Furthermore, the majority of research data on patients with BN pertain to those with the purging type.

3.2. Epidemiology

BN is a more common disorder than AN is; the lifetime prevalence is estimated at some 1–3% of women, with a similar additional fraction exhibiting partial forms of the disorder [81,82]. As in AN, the majority of persons seeking treatment for BN are women, with a male-to-female ratio of approximately 1:10. BN typically develops during late

adolescence or early adulthood; research suggests that women born after 1960 have a higher risk of developing the disorder than do those born before 1960 [81]. Dieting usually precedes the onset of binge eating, although a significant subgroup reports binge eating prior to the onset of dieting [83]. Like AN, BN is also more prevalent in Western cultures, where palatable food is plentiful, yet thinness is valued.

3.3. Etiology/vulnerability factors

Many of the same environmental factors that predispose to development of AN are risk factors for BN. A history of AN itself has been cited as a risk factor for BN, as some studies suggest that 20–30% of persons with BN have, at some point in their lives, met criteria for AN [10]. Additionally, family studies demonstrate higher levels of both BN and AN occurring in the same families, suggestive of a shared environmental and/or genetic liability [84].

In contrast to AN, BN is associated with a higher-than-expected prevalence of childhood and parental obesity, suggesting that a predisposition towards obesity may also increase vulnerability to this eating disorder [85]. Additionally, early experiences of critical comments by family about weight, shape and eating have been identified as more common in patients with BN [86]. This may be related to the apparent risk that dieting behavior confers on the development of bulimia.

Patients with BN have been found to have higher rates of anxiety and mood disorders, particularly, major depressive disorder and dysthymic disorder, in addition to personality and drug abuse disorders [81]. Studies of comorbidity have found up to 75% of lifetime prevalence of an affective disorder among participants with BN [87]. In addition, elevated rates of affective disorders have been found among family members of persons with BN. Such findings have led some to suggest that a genetic diathesis for depression might predispose an individual to the development of bulimia [88]. The nature of the relationship between depression and bulimia remains unclear.

3.3.1. Personality and temperament

Studies of temperament in persons with BN have found elevated measures of novelty seeking, impulsivity [89], and harm avoidance [90,91,92]. Greater negative emotionality and stress reactivity [93], as well as higher rates of personality disorders [94], have also been found among individuals with BN. Some of these features persist even after recovery; women recovered from bulimia for greater than a year were found to have elevated scores on measures of reactivity to stress, negative emotionality, perfectionism, social insecurity, and feelings of ineffectiveness [95]. As some of these abnormalities could be enduring effects of repeated engagement in an alienating and unwanted behavior, it is not possible to conclude that these traits preceded the BN. Findings of increased levels of perfectionism and stress reactivity in noneating-disordered relatives of probands with BN compared with controls [96] do, however, support the possibility that such disturbances reflect underlying traits with a familial foundation. Regardless of whether stress reactivity and negative emotionality are state or trait functions, it could be predicted that they would pose added challenges to a person attempting to recover from BN.

Several studies have reported an increased prevalence of substance-use disorders and self-injurious behaviors, such as self cutting and suicide attempts, among patients with BN [97,98]. Elevated rates of substance-use disorders have also been demonstrated among family members of person with BN [13]. Women with both BN and substance-use disorders have been found to demonstrate a greater degree of psychopathology, and their family members as well, to have higher rates of substance use, antisocial behavior, impulsivity, and affective instability, than those of women with BN and no substance use disorder [99]. Such findings have fostered speculation that this cluster of behaviors might reflect a general propensity to impulsive and self- (and/or other-) directed aggressive behavior, of which the repeated binge eating and purging of BN might be one of several possible expressions. Such a propensity in a subgroup of persons with BN could be one vulnerability factor in the development of the disorder. The concept of a ‘‘multi-impulsivist’’ has been forwarded, featuring an individual who engages in stealing, self-injury, suicide attempts, and substance abuse, in addition to BN. Findings have been equivocal, however, as to whether such a distinct subgroup exists among individuals with BN [100,101].

3.3.2. Developmental

Early reports suggested a specific association between BN and a history of sexual abuse. Indeed, such a history does occur more often among persons with BN than among those without any psychiatric illness. Follow-up studies comparing persons with BN with controls with other psychiatric illness reveal, however, that this apparent risk factor is not specific for BN. History of sexual abuse appears to be, rather, a nonspecific risk factor for psychiatric illness later in life [102]. The majority of persons with BN and eating disorders, in general, were not exposed to early sexual trauma. However, data suggest that those who were exposed experience a worsened course of BN [103].

3.4. Clinical features

As with AN, thinness has tremendous psychological salience for individuals with BN, and behaviors aimed at achieving weight loss are usually present at the onset of the disorder. BN typically begins in late adolescence or early adulthood, during or following a diet. At some point, a behavioral method is discovered that promises to rid the body of unwanted calories. Enlightenment may come from a friend, teammate, or popular media. Usually, this method is manually induced vomiting, although emetics, such as syrup

of ipecac, are sometimes used. Patients also abuse laxatives, enemas, and diuretics, although these methods only produce apparent weight loss through fluid shifts. Patients have been known to inappropriately obtain stimulant medication and thyroid hormone replacement and, those with diabetes, to omit insulin administrations in attempts to lose weight.

Initially, great satisfaction may be experienced that appealing food may be eaten without weight gain. However, as the disorder progresses, perceived control over eating diminishes. Inappropriate compensatory behaviors and self-imposed caloric restriction stimulate hunger and binge eating; a vicious cycle develops. Frequency and duration of binge eating episodes tend to increase, as does the amount consumed. The range of stimuli that can provoke a binge also expands. Feelings of low mood, rejection, anxiety, and frustration often precede binges, which appear to become learned responses to adverse emotional states. Some patients describe a feeling of numbness during a binge-eating episode, and attribute anxiolytic and dysphoria-alleviating effects to the behavior [104,105]. Other triggers include boredom and use of alcoholic beverages or other disinhibiting substances. Binge-eating episodes may also be planned, with food procured and stored for a later time when gorging can occur without interruption. Binges tend to occur in the late afternoon or evening, and almost always while alone [104]. Usually, great effort is expended to maintain this behavior in secret and to conceal evidence of the activity. Purging behavior usually occurs immediately following a binge and may confer a sense of relief that a person is rid of unwanted calories. However, self-loathing and frustration often ensue.

Despite the common report of carbohydrate craving, pure carbohydrates, such as fruits, are not commonly eaten during binge episodes. Rather, the macronutrient composition of a binge meal has been found to not differ significantly from that of a normal control's meal [106] or to reflect an increase proportion of high-fat, as well as high-sugar, foods [107]. Food consumption does often greatly exceed that of normal individuals, ranging from several hundred to greater than 10,000 calories per binge-eating episode. On the low end, the amount consumed in a binge meal may be consistent with the size of a normal meal; what distinguishes it as a binge-eating episode is the subjective loss of control that accompanies the eating. Patients with BN often eat very rapidly during a binge, although variants of bulimic behavior, including rumination, chewing, and spitting out food, and picking at food over the course of hours so as to consume very large quantities, have also been described.

Many bulimics identify "forbidden foods", certain desirable foods that predispose them to lose control of their eating and binge eat. These are contrasted with "safe foods" that do not trigger binges. What determines forbidden status is often idiosyncratic, but likely relates to a learned association between the consumption of these foods and subsequent disinhibition of eating behavior. Evidence does support heightened arousal in this population with exposure to these foods. The phenomenon of "cue reactivity" has been demonstrated in BN with respect to the sight, smell, and taste of typical binge foods [108]. In this experimental design, used in addiction research to predict likelihood of relapse to substance abuse, individuals with BN reported a greater urge to binge and higher levels of stress and physiological arousal to selected binge/favorite food cues compared with a control group. These findings suggest that the processes that sustain the consumption of drugs of abuse might bear relevance on those that sustain binge eating in persons with BN. Further exploration of phenomena of addiction in persons with BN is required to establish such a connection.

An animal model that provides striking parallels to these aspects of BN is that developed by Hagan et al. [109,110]. In this model, rats that have been cycled through periods of caloric restriction and refeeding, despite a return to ad lib feeding and normal body weight, engaging in binge-like overeating when stressed with foot shock [110]. Furthermore, it has been demonstrated that hyperphagia tends to occur primarily on highly palatable food, as opposed to chow, suggesting that it is driven by reward as opposed to metabolic need. Finally, these investigators have most recently shown that exposure to a morsel of highly palatable food was adequate to trigger overeating of chow in rats that experienced both caloric restriction and stress [109], analogous to the cue reactivity research described above. While the cognitive aspects of binge eating in women with BN (as with any psychiatric disorder) are difficult to model in animals, and purging behavior is not represented in this model, this paradigm does show considerable promise as a means to gain further insight into the mechanisms sustaining binge-eating behavior.

As with AN, the cycle of binge eating and purging that characterizes BN is likely sustained at least, in part, by factors engendered by the behavior itself. Intermittent dietary restriction, cognitive, and mood abnormalities, and physiologic changes with binge eating likely contribute to BN by impairing the normal inhibitory and excitatory controls of eating. Thus, associated abnormalities described below may be both resultant of, and contributory to, the behavioral disturbance. The majority of research in BN has focused on abnormalities in inhibitory controls overeating (satiety), as are described below. However, the enhanced excitatory stimulation of eating and enhanced reward value associated with food also appear to play a significant role in the perpetuation of this behavioral disturbance and will likely be a topic of increasing focus in future research.

3.5. Associated abnormalities

3.5.1. Impaired satiety: behavioral evidence

A landmark advance in eating disorders research was the finding that binge-eating behavior could be elicited in the laboratory setting, both in naturalistic studies [111,112] and in structured meal studies [113]. The former, in which

individuals with BN were provided ad libitum access to food over a 24- to 48-h period, showed that approximately a third of meals taken by this group were very large when compared with the control participants' intake, and that these meals contributed to overall greater caloric consumption in participants with BN than in controls. Structured meal studies have involved providing a meal to participants with instructions either to binge eat or to "eat as you normally would"; eating behavior and subjective measures are then assessed. When provided a meal and instructions to binge eat, BN patients have been found to eat significantly more food than noneating disordered controls [113,114]. After the meals, hunger ratings of patients were higher than the hunger ratings of the controls, and satiety ratings were lower. Patients with BN also consumed significantly more of a single-item meal [114] and failed to exhibit sensory-specific satiety, the normal decrease in pleasantness of a particular food after it has been eaten [115].

Other studies of eating in BN employed preloads of food to assess satiety, which was measured behaviorally by the amount of reduction in intake of a subsequent test meal. When the participants were served a soup, preload of varying size, followed by a test meal, patients with BN ate considerably more than did the control participants overall, but they did reduce their intake of the test meal after the larger preload [116]. This suggests that some inhibitory control of eating does function in patients with BN during binge eating, but that its activity is sufficient to terminate eating only after the consumption of an abnormally large amount of food. In studies of eating microstructure using single meals, some patients with BN were found to speed up their eating as a meal progressed, in contrast to noneating disordered individuals who slowed down as more food was consumed [117]. This abnormal acceleration suggests a diminished sensitivity to cues, such as gastric stretch, as meal size increases.

Patients with BN tend to demonstrate overly restrained eating in circumstances when they are not binge eating, which has generally been attributed to cognitive factors. In laboratory settings, when instructed not to binge eat (and/or when there is no opportunity to later purge), patients with BN have been found to consume smaller meals compared with the control participants and to select foods with lower fat content than the controls did [118]. This may reflect the overconsciousness of the impact of food on weight control and/or the overrestriction to compensate for a deficiency in normal satiety.

3.5.2. Potential mechanism of impaired satiety

An extensive body of evidence, largely from animal research, suggests that satiety is determined by postingestive events in the upper gastrointestinal tract. Several phenomena relevant to the development of satiety have been explored in BN, including gastric capacity, gastric emptying, gastric relaxation reflex, and the postprandial release of cholecystokinin (CCK).

3.5.3. Gastric capacity

Several studies have examined gastric capacity in women with BN. Estimates of stomach capacity have been obtained by filling a balloon with water and measuring the maximum volume that a participant could tolerate, measuring volume required to produce a given rise of intragastric pressure, and by measuring subjective fullness ratings. These measurements have revealed significantly enlarged gastric capacity in women with BN and in nonbulimic participants who binge eat, when compared with nonbinge-eating controls [119,120]. Furthermore, the amount of a test meal consumed correlated significantly with gastric capacity, as did self-reported binge intake [120]. Assuming that gastric capacity was not abnormal prior to the onset of binge eating, these findings suggest that the behavior itself may affect stomach functioning so that a larger quantity of food must be consumed before the development of gastric signals important to the termination of the meal.

3.5.4. Gastric emptying

A second abnormality in GI function found in patients with BN is that of delayed gastric emptying. Delayed exit of nutrients from the stomach has been demonstrated by several investigators [121–124]. Whole-gut transit has also been found to be significantly delayed, with a tendency for delay of mouth-to-cecum transit, as well [40]. Other studies [120,125,126] failed to find significant delays in gastric emptying between patients and controls. Discrepancies in findings may be related to differences in technique and in meal size and content. Delayed gastric emptying could contribute to the bloated feelings cited as precipitants to purging and might also delay the development of satiety cues that result from the presence of food in the small intestine.

3.5.5. Gastric relaxation

A third functional GI abnormality that has been suggested to occur in BN is that of reduced gastric relaxation occurring following food ingestion. Our group conducted an initial study using a gastric barostat, showing that patients with BN, compared with controls, demonstrated significant reduction of the normal gastric relaxation that occurs following food ingestion [127]. These abnormalities appear similar, in some ways, with those described in patients with Type I diabetes mellitus and autonomic neuropathy, who have delayed gastric emptying, impaired gastric relaxation, and disturbances in sensations of gastric fullness.

3.5.6. Cholecystokinin

Animal and human work has clearly documented that the release of CCK from cells in the duodenum, in response to the presence of nutrients, is a key contributor to the development of satiety. The role of CCK in BN has been examined in several settings. While it does not appear that basal CCK levels are abnormal in BN [128], several studies have demonstrated impaired CCK release following test meals [129–131], with greater blunting with increasing

meal size [121]. Blunted CCK response is furthermore accompanied by diminished subjective postprandial satiety in some of these participants, although there is not always a direct correlation between CCK levels and satiety ratings [121]. The mechanism for impaired CCK release in BN has not been definitively determined, but it is possible that disturbances in stomach function, such as delayed gastric emptying, contribute to this. It is also possible that impaired CCK release could be related to serotonergic dysfunction, as serotonergic treatments have been found to improve CCK abnormalities [129,132]. Whether this reflects a direct effect of the treatment or of normalization of eating behavior is not clear. Furthermore, it remains open to investigation as to whether CCK infusion in individuals with BN could reverse satiety deficits.

3.5.7. Vagal activity

The afferent vagus nerve mediates satiation by carrying afferent signals from the gut to higher brain areas. The possibility of abnormal vagal function in BN has been raised and may be supported by findings of increased pain threshold in bulimic patients [133,134]. Because somatosensory pain is modulated by the vagus nerve, it has been argued that this functional decrease in signal transduction reflects the overstimulation of afferent vagal fibers. This decrease in ascending vagal transmission could similarly account for the diminished satiation in BN patients [135]. This rationale led to a trial in BN of ondansetron, an antiemetic frequently used in oncology. Ondansetron is an antagonist of 5-HT3 receptors, found on chemosensitive afferent vagal fibers in the gastric mucosa. In one randomized, double-blind, placebo-controlled trial using 25 patients with BN, treatment was associated with a significantly greater decrease in binge eating following vomiting than placebo [135]. Additionally, the number of normal meals was reported to be increased. While this finding does not conclusively prove that vagal overload contributes to the impaired satiety in bulimic patients, or that the reversal of this putative factor is what improves symptoms, it does suggest an interesting direction of future investigation.

3.5.8. Serotonergic function in BN

Evidence for impaired serotonergic function in BN stems from several sources. First, a number of investigations have demonstrated abnormalities in indirect measures of serotonergic function, as will be described briefly below. Second, the frequent occurrence of mood and impulse-control disorders in patients with BN, each linked to abnormalities in serotonergic function [136], is consistent with an abnormality in this system. Finally, double-blind, placebo-controlled trials of serotonergic antidepressant medications have shown these to be efficacious in reducing binge-eating and purging behavior, regardless of whether clinical depression is present [137].

A method commonly used to assess serotonin status in BN has been the peripheral administration of an agent, such as fenfluramine, mCPP, or 5-hydroxytryptophan, that acts through the central serotonergic system to stimulate the release of a hormone, such as prolactin. Compared with normal individuals, patients with BN have been found to show reduced responses to such stimuli [138,139]. This response, furthermore, may correlate with the severity of behavioral disturbance; in one study, prolactin response to fenfluramine was found to be significantly decreased in persons who engaged in binge eating at a high frequency (greater than twice daily) [140]. In addition, results of assays believed to reflect serotonergic turnover also suggest reduced activity in BN, although these are less consistent. While one study found that particpants actively engaging in bulimic behavior to have normal levels of CSF 5-HIAA [141], another study found that this metabolite was low in participants who binge-ate more than twice daily [142].

The origin of serotonergic dysfunction in persons with BN is an intriguing question. Prospective studies examining such measures in individuals who go on to develop BN are not available. Abnormalities in the serotonergic system, including elevated levels of CSF 5-HIAA and altered 5-HT2A receptor density, have been demonstrated in persons who have been abstinent from BN for greater than a year [143,144]. However, it is not clear what relationship these bear on the status of the serotonergic system prior to the onset of the BN, as the possibility of enduring effects of the disorder cannot be excluded. Evidence collected from women actively engaging in dieting behavior is particularly likely to be affected by the behavior. Research has found dieting to lower plasma levels of the serotonin precursor tryptophan, which could, in turn, reduce CNS serotonin production [145]. Functional supersensitivity of 5-HT2C receptors has been found following a period of dieting, further supporting the possibility that dieting lowers central 5-HT [146]. After a period of caloric restriction, blunted prolactin release to fenfluramine challenge has also been found; women appear to be more sensitive to this effect than are men [147]. Thus, it is likely that at least a component of the serotonergic dysfunction found in persons with BN is state related. Interestingly, the possibility exists that this state itself further contributes to the behavioral abnormalities that characterize BN.

Serotonin has been implicated in human and animal studies in the inhibition of eating behavior. The activation of serotonergic pathways, particularly in the region of the medial hypothalamus, contributes to postprandial satiety [62]; pharmacological agents that increase central serotonergic transmission have been found to reduce the rate of eating and meal size [148,149]. It has been suggested that disturbances in serotonin function could impair the termination of eating episodes in persons with BN [150]; further investigation of this hypothesis is warranted. It is also possible that diminished serotonin function contributes to the initiation of binge-eating episodes. Given the association between reduced serotonergic activity and impulsivity in other patient populations [136], it has been postulated that

such a deficit in persons with BN could lower the threshold to initiate a binge-eating episode. The link between impulsivity and serotonergic dysfunction (specifically, impaired platelet 5-HT uptake) in persons with BN has been supported by some evidence, as has the link between symptom severity in BN and diminished 5-HT activity [151]. However, it is not clear that it is impulsivity per se that mediates this association, as other studies have failed to find a correlation between measures of impulsivity and binge frequency [152]. Other mood states associated with reduced serotonergic transmission, such as dysphoria, might also contribute to the urge to binge eat in BN.

Several studies, using the acute tryptophan depletion (ATD) paradigm, have investigated the response of women with BN to reductions in serotonin. Oral intake of a mixture of large neutral amino acids (LNAA), which compete with tryptophan for availability to the brain, is thought to produce a deficit in CNS tryptophan and a transient reduction in brain serotonin synthesis and release [153]. ATD in normal individuals can produce transient depressive symptoms; women appear to be more susceptible to these effects than men are, and persons with a history of depression are more susceptible than those without [154]. Persons with BN subjected to this paradigm have demonstrated particular sensitivity, with increased irritability, labile mood, retarded affect, and caloric intake of a test meal [155,156]. Kaye et al. [157] found women with BN to have significantly greater increase in peak depression, mood lability, sadness, and desire to binge after ATD, although actual food intake was not increased, possibly due to food presentation. No effects on these parameters in BN patients were demonstrated in another study, possibly due to the different concentration of amino acid preparation used in the depletion procedure [158]. As the production of dysphoric mood with ATD is considered to be a marker of depressive disorders, this effect is not specific to BN. Many of the patients in these studies were also depressed. While these findings do not demonstrate causality between lowered serotonin, dysphoric mood state, and binge eating in persons with BN, they are consistent with the existence of a depressive diathesis among bulimic patients, which could be triggered by dieting behavior.

3.5.9. Leptin

Leptin additionally has been implicated in BN. Several studies have found serum leptin levels in patients with BN to be abnormally low [41,42,159,160]; one study reported a trend toward inverse correlation between frequency of binge-eating episodes and serum leptin concentration [161]. The significance of these findings persists even when body weight and/or percent body fat is taken into account. Participants who had achieved remission from BN were also found, in one study, to have abnormally low leptin levels [161], although not in another [162]. How such findings might relate to abnormalities in the drive to eat apparent in persons with BN is unclear.

3.6. Morbidity, prognosis and treatment

The natural course of BN is more benign than that of AN. Serious medical morbidity, such as gastric rupture or esophageal tear, is rare. Dental erosion from repeated bathing of the teeth in gastric acid is the commonest physical complication of longstanding BN. Painless swelling of the parotid glands is sometimes present, yielding "chipmunk" facies. Electrolyte abnormalities may result from the abuse of laxatives and diuretics, and from loss of gastric acid.

Patients with BN, on the whole, tend to be more amenable to treatment than are patients with AN [163]. Two treatment approaches have clearly been identified as beneficial in BN. The first is a short-term (4–6 months) psychological treatment, cognitive behavioral therapy, which focuses on restructuring the maladaptive thoughts and behaviors that perpetuate the cycle of bingeing and purging [164]. The second treatment is antidepressant therapy. Initially, the use of antidepressant medications was based on the association between BN and mood disturbance. However, antidepressant medications have been demonstrated to be effective in reducing the frequency of binge-eating episodes, regardless of whether depressed mood is present. Over a dozen double-blind, placebo-controlled studies have demonstrated that antidepressants help reduce binge frequency [165].

Despite the efficacy of these treatments, many patients do relapse. A recent meta-analysis examined 88 outcome studies and showed that 5–10 years following presentation for BN, some 50% had achieved full recovery, while 20% continued to meet full criteria for BN. Another 30% had experienced relapse into bulimic symptoms. Treatment studies showed improved outcome in the short term, when compared with naturalistic outcome studies, but limited impact over the longer term [166].

3.7. Future directions

In summary, BN is a behavioral disorder featuring recurrent episodes of binge eating associated with inappropriate attempts to avoid weight gain. As with AN, BN is a disorder of the motivated behavior, eating, with BN featuring an apparently abnormally enhanced drive to eat and/or ineffective mechanisms of satiety. These abnormalities may, to some degree, be a product of the behavior itself, fostering a self-perpetuating cycle. The underlying traits of affective dysregulation and impulsivity may further contribute to dysregulation of eating behavior and may be enhanced by dieting behavior, possibly through serotonergic mechanisms. Reinforcement of abnormal eating patterns may occur through the same reward pathways that reinforce normal eating behavior. Further research is needed to determine the presence and extent of abnormalities in the excitatory controls of feeding behavior in individuals with BN, and how these could contribute to the persistence of this disorder.

Acknowledgements

This work was supported in part by grants MH65024 and MH42206 from the National Institutes of Health.

References

[1] Fairburn CG, Walsh BT. Atypical eating disorders. In: Fairburn CG, Brownell KD, editors. Eating disorders and obesity: a comprehensive textbook. New York: Guilford Press; 2002. p. 171–77.
[2] Diagnostic and statistical manual of mental disorders. 4th ed.: American Psychiatric Association. Washington (DC), 1994;154.
[3] Eddy KT, Keel PK, Dorer DJ, Delinsky SS, Franko DL, Herzog DB. Longitudinal comparison of anorexia nervosa subtypes. Int J Eat Disord 2002;31:191–201.
[4] Walters EE, Kendler KS. Anorexia nervosa and anorexic-like syndromes in a population-based female twin sample. Am J Psychiatry 1995;152:64–71.
[5] Favaro A, Ferrara S, Santonastaso P. The spectrum of eating disorders in young women: a prevalence study in a general population sample. Psychosom Med 2003;65:701–8.
[6] Striegel-Moore RH, Dohm FA, Kraemer HC, Taylor CB, Daniels S, Crawford PB, et al. Eating disorders in white and black women. Am J Psychiatry 2003;160:1326–31.
[7] Fombonne E. Anorexia nervosa. No evidence of an increase. Br J Psychiatry 1995;166:462–71.
[8] Crago M, Shisslak CM, Estes LS. Eating disturbances among American minority groups: a review. Int J Eat Disord 1996;19:239–48.
[9] Walsh BT, Devlin MJ. Eating disorders: progress and problems. Science 1998;280:1387–90.
[10] Klump KL, Kaye WH, Strober M. The evolving genetic foundations of eating disorders. Psychiatr Clin North Am 2001;24:215–25.
[11] Klump KL, Wonderlich S, Lehoux P, Lilenfeld LR, Bulik CM. Does environment matter? A review of nonshared environment and eating disorders. Int J Eat Disord 2002;31:118–35.
[12] McElroy SL, Phillips KA, Keck PEJ. Obsessive compulsive spectrum disorder. J Clin Psychiatry 1994;55:33–51 [Suppl.].
[13] Lilenfeld LR, Kaye WH, Greeno CG, Merikangas KR, Plotnicov K, Pollice C, et al. A controlled family study of anorexia nervosa and bulimia nervosa: psychiatric disorders in first-degree relatives and effects of proband comorbidity. Arch Gen Psychiatry 1998;55:603–10.
[14] Bellodi L, Cavallini MC, Bertelli S, Chiapparino D, Riboldi C, Smeraldi E. Morbidity risk for obsessive-compulsive spectrum disorders in first-degree relatives of patients with eating disorders. Am J Psychiatry 2001;158:563–9.
[15] Hollander E. Treatment of obsessive-compulsive spectrum disorders with SSRIs. Br J Psychiatry 1998;35:7–12 [Suppl.].
[16] Hinney A, Remschmidt H, Hebebrand J. Candidate gene polymorphisms in eating disorders. Eur J Pharmacol 2000;410:147–59.
[17] Halmi KA, Sunday SR, Strober M, Kaplan A, Woodside DB, Fichter M, et al. Perfectionism in anorexia nervosa: variation by clinical subtype, obsessionality, and pathological eating behavior. Am J Psychiatry 2000;157:1799–805.
[18] Srinivasagam NM, Kaye WH, Plotnicov KH, Greeno C, Weltzin TE, Rao R. Persistent perfectionism, symmetry, and exactness after long-term recovery from anorexia nervosa. Am J Psychiatry 1995;152:1630–4.
[19] Cloninger CR, Przybeck TR, Svrakic DM, Wetzel RD. The temperament and character inventory (TCI): a guide to its development and use. St. Louis (MO), center for psychobiology of personality. St. Louis, MO: Washington University; 1994.
[20] Frost RO, Marten P, Lahart C, Rosenblate R. The dimensions of perfectionism. Cogn Ther Res 1990;14:449–68.
[21] Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown Obsessive Compulsive Scale: I. Development, use, and reliability. Arch Gen Psychiatry 1989;46:1006–11.
[22] Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR, et al. The Yale-Brown Obsessive Compulsive Scale: II. Validity. Arch Gen Psychiatry 1989;46:1012–6.
[23] Geary N. Estradiol, CCK and satiation. Peptides 2001;22:1251–63.
[24] Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am J Psychiatry 2003;160:1041–52.
[25] Shapiro S, Newcomb M, Loeb TB. Fear of fat, disregulated-restrained eating, and body-esteem: prevalence and gender differences among eight- to ten-year-old children. J Clin Child Psychol 1997;26:358–65.
[26] Becker AE, Burwell RA, Gilman SE, Herzog DB, Hamburg P. Eating behaviours and attitudes following prolonged exposure to television among ethnic Fijian adolescent girls. Br J Psychiatry 2002;180:509–14.
[27] Vandereycken W, Van Deth R. From fasting saints to anorexic girls. New York: New York Univ. Press; 1994.
[28] Sunday SR, Halmi KA. Micro- and macroanalyses of patterns within a meal in anorexia and bulimia nervosa. Appetite 1996;26:21–36.
[29] Hadigan CM, Anderson EJ, Miller KK, Hubbard JL, Herzog DB, Klibanski A, et al. Assessment of macronutrient and micronutrient intake in women with anorexia nervosa. Int J Eat Disord 2000;28:284–92.
[30] Davis C, Claridge G. The eating disorders as addiction: a psychobiological perspective. Addict Behav 1998;23:463–75.
[31] Pierce WD, Epling WF. Theoretical developments in activity anorexia. In: Epling WF, Pierce WD, editors. Activity anorexia: Theory, Research and Treatment. Malwah (NJ): Lawrence Erlbaum Associates; 1996. p. 23–41.
[32] Cabeza de Vaca S, Carr KD. Food restriction enhances the central rewarding effect of abused drugs. J Neurosci 1998;18:7502–10.
[33] Carr KD. Augmentation of drug reward by chronic food restriction. Behavioral evidence and underlying mechanisms. Physiol Behav 2002;76:353–64.
[34] Davis C, Kennedy SH, Ravelski E, Dionne M. The role of physical activity in the development and maintenance of eating disorders. Psychol Med 1994;24:957–67.
[35] Smith GP. Animal models of human eating disorders. Ann N Y Acad Sci 1989;575:63–72.
[36] Halmi KA, Sunday SR. Temporal patterns of hunger and fullness ratings and related cognitions in anorexia and bulimia. Appetite 1991;16:219–37.
[37] Hetherington MM, Rolls BJ. Eating behavior in eating disorders: response to preloads. Physiol Behav 1991;50:101–8.
[38] Robinson PH. Perceptivity and paraceptivity during measurement of gastric emptying in anorexia and bulimia nervosa. Br J Psychiatry 1989;154:400–5.
[39] Sackville T, Schotte DE, Touyz SW, Griffiths R, Beumont PJ. Conscious and preconscious processing of food, body weight and shape, and emotion-related words in women with anorexia nervosa. Int J Eat Disord 1998;23:77–82.
[40] Kamal N, Chami T, Andersen A, Rosell FA, Schuster MM, Whitehead WE. Delayed gastrointestinal transit times in anorexia nervosa and bulimia nervosa. Gastroenterology 1991;101:1320–4.
[41] Monteleone P, Fabrazzo M, Tortorella A, Fuschino A, Maj M. Opposite modifications in circulating leptin and soluble leptin receptor across the eating disorder spectrum. Mol Psychiatry 2002;7:641–6.
[42] Frederich R, Hu S, Raymond N, Pomeroy C. Leptin in anorexia nervosa and bulimia nervosa: importance of assay technique and method of interpretation. J Lab Clin Med 2002;139(2):72–9.
[43] Mantzoros C, Flier JS, Lesem MD, Brewerton TD, Jimerson DC. Cerebrospinal fluid leptin in anorexia nervosa: correlation with nutritional status and potential role in resistance to weight gain. J Clin Endocrinol Metab 1997;82(6):1845–51.

[44] Fulton S, Woodside B, Shizgal P. Modulation of brain reward circuitry by leptin. Science 2000;287:125–8.
[45] Sunday SR, Halmi KA. Taste perceptions and hedonics in eating disorders. Physiol Behav 1990;48:587–94.
[46] Simon Y, Bellisle F, Monneuse MO, Samuel-Lajeunesse B, Drewnowski A. Taste responsiveness in anorexia nervosa. Br J Psychiatry 1993;162:244–6.
[47] Drewnowski A, Halmi KA, Pierce B, Gibbs J, Smith GP. Taste and eating disorders. Am J Clin Nutr 1987;46:442–50.
[48] Kimura F, Endo Y, Fujimoto K. Vigorous intake of oil emulsion caused by chronic food deprivation remains after recovery in rats. Physiol Behav 2003;78:107–15.
[49] Kingston K, Szmukler G, Andrewes D, Tress B, Desmond P. Neuropsychological and structural brain changes in anorexia nervosa before and after refeeding. Psychol Med 1996;26:15–28.
[50] Mathias JL, Kent PS. Neuropsychological consequences of extreme weight loss and dietary restriction in patients with anorexia nervosa. J Clin Exp Neuropsychol 1998;20:548–64.
[51] Green MW, Elliman NA, Wakeling A, Rogers PJ. Cognitive functioning, weight change and therapy in anorexia nervosa. J Psychiatr Res 1996;30:401–10.
[52] Laessle RG, Krieg JC, Fichter MM, Pirke KM. Cerebral atrophy and vigilance performance in patients with anorexia nervosa and bulimia nervosa. Neuropsychobiology 1989;21:187–91.
[53] Katzman DK, Christensen B, Young AR, Zipursky RB. Starving the brain: structural abnormalities and cognitive impairment in adolescents with anorexia nervosa. Semin Clin Neuropsychiatry 2001; 2:146–52.
[54] Laessle RG, Fisher M, Fichter MM, Pirke KM, Krieg JC. Cortisol levels and vigilance in eating disorder patients. Psychoneuroendocrinology 1992;17:475–84.
[55] Grunwald M, Ettrick C, Assmann B, Dahne A, Kraus W, Busse F, et al. Deficits in haptic perception and right parietal theta power changes in patients with anorexia nervosa before and after weight gain. Int J Eat Disord 2001;29:417–28.
[56] Maggia G, Bianchi B. Differential hemispheric involvement in anorexia nervosa. Eat Weight Disord 1998;3:100–9.
[57] Jones BP, Duncan CC, Brouwers P, Mirsky AF. Cognition in eating disorders. J Clin Exp Neuropsychol 1991;13:711–28.
[58] Fassino S, Piero A, Daga GA, Leombruni P, Mortara P, Rovera GG. Attentional biases and frontal functioning in anorexia nervosa. Int J Eat Disord 2002;31:274–83.
[59] Kaye WH. Anorexia nervosa, obsessional behavior, and serotonin. Psychopharmacol Bull 1997;33:335–44.
[60] Franklin JC, Schiele BC, Brozek J. Keys A: observations of human behavior in experimental semistarvation and rehabilitation. J Clin Psychology 1948;4:28–45.
[61] Cabanac M, Gosselin C. Ponderostat: hoarding behavior satisfies the condition for a lipostat in the rat. Appetite 1996;27:251–61.
[62] Blundell JE. Serotonin manipulations and the structure of feeding behaviour. Appetite 1986;7:39–56 [Suppl.].
[63] Kaye WH, Ebert MH, Raleigh M, Lake R. Abnormalities in CNS monoamine metabolism in anorexia nervosa. Arch Gen Psychiatry 1984;41:350–5.
[64] Kaye WH, Gwirtsman HE, George DT, Jimerson DC, Ebert MH. CSF 5-HIAA concentrations in anorexia nervosa: reduced values in underweight subjects normalize after weight gain. Biol Psychiatry 1988;23:102–5.
[65] Gerner RH, Cohen DJ, Fairbanks L, Anderson GM, Young JG, Scheinin M, et al. CSF neurochemistry of women with anorexia nervosa and normal women. Am J Psychiatry 1984;141:1441–4.
[66] Kaye WH, Frank GK, McConaha C. Altered dopamine activity after recovery from restricting-type anorexia nervosa. Neuropsychopharmacology 1999;21:503–6.
[67] Kaye WH, Gwirtsman HE, George DT, Ebert MH. Altered serotonin activity in anorexia nervosa after long-term weight restoration. Does elevated cerebrospinal fluid 5-hydroxyindoleacetic acid level correlate with rigid and obsessive behavior? Arch Gen Psychiatry 1991; 48:556–62.
[68] Pollice C, Kaye WH, Greeno CG, Weltzin TE. Relationship of depression, anxiety, and obsessionality to state of illness in anorexia nervosa. Int J Eat Disord 1997;21:367–76.
[69] Kaye WH, Gwirtsman HE, George DT, Ebert MH, Jimerson DC, Tomai TP, et al. Elevated cerebrospinal fluid levels of immunoreactive corticotropin-releasing hormone in anorexia nervosa: relation to state of nutrition, adrenal function, and intensity of depression. J Clin Endocrinol Metab 1987;64:203–8.
[70] Frank GK, Kaye WH, Altemus M, Greeno CG. CSF oxytocin and vasopressin levels after recovery from bulimia nervosa and anorexia nervosa, bulimic subtype. Biol Psychiatry 2000;48:315–8.
[71] Kaye WH. Neuropeptide abnormalities in anorexia nervosa. Psychiatry Res 1996;62:65–74.
[72] Demitrack MA, Lesem MD, Listwak SJ, Brandt HA, Jimerson DC, Gold PW. CSF oxytocin in anorexia nervosa and bulimia nervosa: clinical and pathophysiologic considerations. Am J Psychiatry 1990; 147:882–6.
[73] Liberzon I, Trujillo KA, Akil H, Young EA. Motivational properties of oxytocin in the conditioned place preference paradigm. Neuropsychopharmacology 1997;17:353–9.
[74] Kaye WH. Central nervous system neurotransmitter activity in anorexia nervosa and bulimia nervosa. In: Fairburn CG, Brownell KD, editors. Eating disorders and obesity. New York: The Guilford Press; 2002. p. 272–7.
[75] Attia E, Haiman C, Walsh BT, Flater SR. Does fluoxetine augment the inpatient treatment of anorexia nervosa? Am J Psychiatry 1998; 155:548–51.
[76] Kaye WH, Nagata T, Weltzin TE, Hsu LK, Sokol MS, McConaha C, et al. Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. Biol Psychiatry 2001;49:644–52.
[77] Steinhausen HC. The outcome of anorexia nervosa in the 20th century. Am J Psychiatry 2002;159:1284–93.
[78] Stunkard A. A history of binge eating. In: Fairburn CG, Wilson GT, editors. Binge eating: nature, assessment, and treatment. New York: Guilford Press; 1993. p. 15–34.
[79] Nasser M. A prescription of vomiting: historical footnotes. Int J Eat Disord 1993;13:129–31.
[80] Russell G. Bulimia nervosa: an ominous variant of anorexia nervosa. Psychol Med 1979;9:429–48.
[81] Kendler KS, MacLean C, Neale M, Kessler R, Heath A, Eaves L. The genetic epidemiology of bulimia nervosa. Am J Psychiatry 1991;148:1627–37.
[82] Garfinkel PE, Lin E, Goering P, Spegg C, Goldbloom DS, Kennedy S, et al. Bulimia nervosa in a Canadian community sample: prevalence and comparison of subgroups. Am J Psychiatry 1995;152: 1052–8.
[83] Haiman C, Devlin MJ. Binge eating before the onset of dieting: a distinct subgroup of bulimia nervosa? Int J Eat Disord 1999;25: 151–7.
[84] Strober M, Freeman R, Lampert C, Diamond J, Kaye W. Controlled family study of anorexia nervosa and bulimia nervosa: evidence of shared liability and transmission of partial syndromes. Am J Psychiatry 2000;157:393–401.
[85] Fairburn CG, Doll HA, Welch SL, Hay PJ, Davies BA, O'Connor ME. Risk factors for binge eating disorder: a community-based, case-control study. Arch Gen Psychiatry 1998;55:425–32.
[86] Fairburn CG, Welch SL, Doll HA, Davies BA, O'Connor ME. Risk factors for bulimia nervosa. A community-based case-control study. Arch Gen Psychiatry 1997;54:509–17.
[87] Brewerton TD, Lydiard RB, Herzog DB, Brotman AW, O'Neil PM, Ballenger JC. Comorbidity of axis I psychiatric disorders in bulimia nervosa. J Clin Psychiatry 1995;56:77–80.
[88] Kassett JA, Gershon ES, Maxwell ME, Guroff JJ, Kazuba DM, Smith AL, et al. Psychiatric disorders in the first-degree relatives

of probands with bulimia nervosa. Am J Psychiatry 1989;146: 1468–71.
[89] Diaz-Marsa M, Carrasco JL, Saiz J. A study of temperament and personality in anorexia and bulimia nervosa. J Personal Disord 2000;14:352–9.
[90] Fassino S, Abbate-Daga G, Amianto F, Leombruni P, Boggio S, Rovera GG. Temperament and character profile of eating disorders: a controlled study with the Temperament and Character Inventory. Int J Eat Disord 2002;32:412–25.
[91] Kleifield EI, Sunday S, Hurt S, Halmi KA. The Tridimensional Personality Questionnaire: an exploration of personality traits in eating disorders. J Psychiatr Res 1994;28:413–23.
[92] Brewerton TD, Hand LD, Bishop ERJ. The Tridimensional Personality Questionnaire in eating disorder patients. Int J Eat Disord 1993; 14:213–8.
[93] Pryor T, Wiederman MW. Measurement of nonclinical personality characteristics of women with anorexia nervosa or bulimia nervosa. J Pers Assess 1996;67:414–21.
[94] Bulik CM, Sullivan PF, Joyce PR, Carter FA. Temperament, character, and personality disorder in bulimia nervosa. J Nerv Ment Dis 1995;183:593–8.
[95] Stein D, Kaye WH, Matsunaga H, Orbach I, Har-Even D, Frank G, et al. Eating-related concerns, mood, and personality traits in recovered bulimia nervosa subjects: a replication study. Int J Eat Disord 2002;32:225–9.
[96] Lilenfeld LR, Stein D, Bulik CM, Strober M, Plotnicov K, Pollice C, et al. Personality traits among currently eating disordered, recovered and never ill first-degree female relatives of bulimic and control women. Psychol Med 2000;30:1399–410.
[97] Bulik CM, Sullivan PF, Carter FA, Joyce PR. Lifetime comorbidity of alcohol dependence in women with bulimia nervosa. Addict Behav 1997;22:437–46.
[98] Paul T, Schroeter K, Dahme B, Nutzinger DO. Self-injurious behavior in women with eating disorders. Am J Psychiatry 2002;159:408.-11.
[99] Lilenfeld LR, Kaye WH, Greeno CG, Merikangas KR, Plotnicov K, Pollice C, et al. Psychiatric disorders in women with bulimia nervosa and their first-degree relatives: effects of comorbid substance dependence. Int J Eat Disord 1997;22:253–64.
[100] Fahy T, Eisler I. Impulsivity and eating disorders. Br J Psychiatry 1993;162:193–7.
[101] Welch SL, Fairburn CG. Impulsivity or comorbidity in bulimia nervosa. A controlled study of deliberate self-harm and alcohol and drug misuse in a community sample. Br J Psychiatry 1996;169: 451–8.
[102] Kendler KS, Bulik CM, Silberg J, Hettema JM, Myers J, Prescott CA. Childhood sexual abuse and adult psychiatric and substance use disorders in women: an epidemiological and co-twin control analysis. Arch Gen Psychiatry 2000;57:953–9.
[103] Sullivan PF, Bulik CM, Carter FA, Joyce PR. The significance of a history of childhood sexual abuse in bulimia nervosa. Br J Psychiatry 1995;167:679–82.
[104] Abraham SF, Beumont PJ. How patients describe bulimia or binge eating. Psychol Med 1982;12:625–35.
[105] Heatherton TF, Baumeister RF. Binge eating as escape from self-awareness. Psychol Bull 1991;110:86–108.
[106] Walsh BT, Kissileff HR, Hadigan CM. Eating behavior in bulimia. Ann N Y Acad Sci 1989;575:446–54.
[107] Gendall KA, Sullivan PE, Joyce PR, Carter FA, Bulik CM. The nutrient intake of women with bulimia nervosa. Int J Eat Disord 1997;21:115–27.
[108] Staiger P, Dawe S, McCarthy R. Responsivity to food cues in bulimic women and controls. Appetite 2000;35:27–33.
[109] Hagan MM, Chandler PC, Wauford PK, Rybak RJ, Oswald KD. The role of palatable food and hunger as trigger factors in an animal model of stress induced binge eating. Int J Eat Disord 2003;34: 183–97.
[110] Hagan MM, Wauford PK, Chandler PC, Jarrett LA, Rybak RJ, Blackburn K. A new animal model of binge eating: key synergistic role of past caloric restriction and stress. Physiol Behav 2002;77:45–54.
[111] Weltzin TE, Hsu LK, Pollice C, Kaye WH. Feeding patterns in bulimia nervosa. Biol Psychiatry 1991;30:1093–110.
[112] Kaye WH, Weltzin TE, McKee M, McConaha C, Hansen D, Hsu LK. Laboratory assessment of feeding behavior in bulimia nervosa and healthy women: methods for developing a human-feeding laboratory. Am J Clin Nutr 1992;55:372–80.
[113] Kissileff HR, Walsh BT, Kral JG, Cassidy SM. Laboratory studies of eating behavior in women with bulimia. Physiol Behav 1986;563–70.
[114] Guss JL, Kissileff HRFX. Effects of glucose and fructose solutions on food intake and gastric emptying in nonobese women. Am J Physiol 1994;267:R1537–44.
[115] Hetherington M, Rolls BJ. Sensory-specific satiety in anorexia and bulimia nervosa. Ann N Y Acad Sci 1989;575:387–98.
[116] Hadigan CM, Walsh BT, Devlin MJ, LaChaussee JL, Kissileff HR. Behavioral assessment of satiety in bulimia nervosa. Appetite 1992; 18:233–41.
[117] Guss JL, Kissileff HR. Microstructural analyses of human ingestive patterns: from description to mechanistic hypotheses. Neurosci Biobehav Rev 2000;24:261–8.
[118] Rolls BJ, Andersen AE, Moran TH, McNelis AL, Baier HC, Fedoroff IC. Food intake, hunger, and satiety after preloads in women with eating disorders. Am J Clin Nutr 1992;1093–103.
[119] Geliebter A, Hashim SA. Gastric capacity in normal, obese, and bulimic women. Physiol Behav 2000;74:743–6.
[120] Geliebter A, Melton PM, McCray RS, Gallagher DR, Gage D, Hashim SA. Gastric capacity, gastric emptying, and test-meal intake in normal and bulimic women. Am J Clin Nutr 1992;56:656–61.
[121] Devlin MJ, Walsh BT, Guss JL, Kissileff HR, Liddle RA, Petkova E. Postprandial cholecystokinin release and gastric emptying in patients with bulimia nervosa. Am J Clin Nutr 1997;65:114–20.
[122] Cuellar RE, Kaye WH, Hsu LK, VanThiel DH. Upper gastrointestinal tract dysfunction in bulimia. Dig Dis Sci 1988;33:1549–53.
[123] Kiss A, Bergmann H, Abatzi TA, Schneider C, Wiesnagrotzki S, Hobart J, et al. Oesophageal and gastric motor activity in patients with bulimia nervosa. Gut 1990;31:259–65.
[124] Shih WJ, Humphries L, Digenis GA, Castellanos FX, Domstad PA, DeLand FH. Tc-99 m labeled triethelene tetraamine polysterene resin gastric emptying studies in bulimia patients. Eur J Nucl Med 1987;13: 192–6.
[125] Robinson PH, Clarke M, Barrett J. Determinants of delayed gastric emptying in anorexia nervosa and bulimia nervosa. Gut 1988;29: 458–64.
[126] Hutson WR, Wald A. Gastric emptying in patients with bulimia nervosa and anorexia nervosa. Am J Gastroenterol 1990;85:41–6.
[127] Walsh BT, Zimmerli E, Devlin MJ, Guss J, Kissileff HR. A disturbance of gastric function in bulimia nervosa. Biol. Psychiatry 2003;54(9):929–933.
[128] Phillipp E, Pirke KM, Kellner MB, Krieg JC. Disturbed cholecystokinin secretion in patients with eating disorders. Life Sci 1991;48: 2443–50.
[129] Geracioti TDJ, Liddle RA. Impaired cholecystokinin secretion in bulimia nervosa. N Engl J Med 1988;319:683–8.
[130] Geracioti TDJ, Kling MAJR, Kanayama S, Rosenthal NE, Gold PW, Liddle RA. Meal-related cholecystokinin secretion in eating and affective disorders. Psychopharmacol Bull 1989;444–9.
[131] Pirke KM, Kellner MB, Friess E, Krieg JC, Fichter MM. Satiety and cholecystokinin. Int J Eat Disord 1994;15:63–9.
[132] Brambilla F, Brunetta M, Draisci A, Peirone A, Perna G, Sacerdote P, et al. T-lymphocyte concentrations of cholecystokinin-8 and beta-endorphin in eating disorders: II. Bulimia nervosa. Psychiatry Res 1995;59:51–6.
[133] Faris PL, Raymond NC, deZwaan M, Howard LA, Eckert ED, Mitchell JE. Nociceptive, but not tactile, thresholds are elevated in bulimia nervosa. Biol Psychiatry 1992;32:462–6.
[134] Raymond NC, Eckert ED, Hamalainen M, Evanson D, Thuras PD,

Mitchell JE, et al. A preliminary report on pain thresholds in bulimia nervosa during a bulimic episode. Compr Psychiatry 1999;40:229–33.
[135] Faris PL, Kim SW, Meller WH, Goodale RL, Oakman SA, Hofbauer RD, et al. Effect of decreasing afferent vagal activity with ondansetron on symptoms of bulimia nervosa: a randomised, double-blind trial. Lancet 2000;355:792–7.
[136] Oquendo MA, Mann JJ. The biology of impulsivity and suicidality. Psychiatr Clin North Am 2000;23:11–25.
[137] Walsh BT. Treatment of bulimia nervosa with antidepressant medication. J Clin Psychopharmacol 1991;11:231–2.
[138] Brewerton TD, Mueller EA, Lesem MD, Brandt HA, Quearry B, George DT, et al. Neuroendocrine responses to *m*-chlorophenylpiperazine and L-tryptophan in bulimia. Arch Gen Psychiatry 1992; 49:852–61.
[139] Levitan RD, Kaplan AS, Joffe RT, Levitt AJ, Brown GM. Hormonal and subjective responses to intravenous meta-chlorophenylpiperazine in bulimia nervosa. Arch Gen Psychiatry 1997;54:521–7.
[140] Monteleone P, Brambilla F, Bortolotti F, Maj M. Serotonergic dysfunction across the eating disorders: relationship to eating behaviour, purging behaviour, nutritional status and general psychopathology. Psychol Med 2000;30:1099–110.
[141] Kaye WH, Ballenger JC, Lydiard RB, Stuart GW, Laraia MT, O'Neil P, et al. CSF monoamine levels in normal-weight bulimia: evidence for abnormal noradrenergic activity. Am J Psychiatry 1990;147:225–9.
[142] Jimerson DC, Lesem MD, Kaye WH, Brewerton TD. Low serotonin and dopamine metabolite concentrations in cerebrospinal fluid from bulimic patients with frequent binge episodes. Arch Gen Psychiatry 1992;49:132–8.
[143] Kaye WH, Greeno CG, Moss H, Fernstrom J, Fernstrom M, Lilenfeld LR, et al. Alterations in serotonin activity and psychiatric symptoms after recovery from bulimia nervosa. Arch Gen Psychiatry 1998;55:927–35.
[144] Kaye WH, Frank GK, Meltzer CC, Price JC, McConaha CW, Crossan PJ, et al. Altered serotonin 2A receptor activity in women who have recovered from bulimia nervosa. Am J Psychiatry 2001;158:1152–5.
[145] Anderson IM, Parry-Billings M, Newsholme EA, Fairburn CG, Cowen PJ. Dieting reduces plasma tryptophan and alters brain 5-HT function in women. Psychol Med 1990;20:785–91.
[146] Cowen PJ, Clifford EM, Walsh AE, Williams C, Fairburn CG. Moderate dieting causes 5-HT2C receptor supersensitivity. Psychol Med 1996;26:1155–9.
[147] Walsh AE, Oldman AD, Franklin M, Fairburn CG, Cowen PJ. Dieting decreases plasma tryptophan and increases the prolactin response to D-fenfluramine in women but not men. J Affect Disord 1995; 33:89–97.
[148] Simansky KJ. Serotonergic control of the organization of feeding and satiety. Behav Brain Res 1996;73:37–42.
[149] Brewerton TD. Toward a unified theory of serotonin dysregulation in eating and related disorders. Psychoneuroendocrinology 1995;20: 561–90.
[150] Jimerson DC, Lesem MD, Kaye WH, Hegg AP, Brewerton TD. Eating disorders and depression: is there a serotonin connection? Biol Psychiatry 1990;28:443–54.
[151] Steiger H, Young SN, Kin NM, Koerner N, Israel M, Lageix P, et al. Implications of impulsive and affective symptoms for serotonin function in bulimia nervosa. Psychol Med 2001;31:85–95.
[152] Wolfe BE, Jimerson DC, Levine JM. Impulsivity ratings in bulimia nervosa: relationship to binge eating behaviors. Int J Eat Disord 1994;15:289–92.
[153] Delgado PL, Charney DS, Price LH, Aghajanian GK, Landis H, Heninger GR. Serotonin function and the mechanism of antidepressant action. Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. Arch Gen Psychiatry 1990;47: 411–8.
[154] Ellenbogen MA, Young SN, Dean P, Palmour RM, Benkelfat C. Mood response to acute tryptophan depletion in healthy volunteers: sex differences and temporal stability. Neuropsychopharmacology 1996;15:465–74.
[155] Weltzin TE, Fernstrom JD, McConaha C, Kaye WH. Acute tryptophan depletion in bulimia: effects on large neutral amino acids. Biol Psychiatry 1994;35:388–97.
[156] Weltzin TE, Fernstrom MH, Fernstrom JD, Neuberger SK, Kaye WH. Acute tryptophan depletion and increased food intake and irritability in bulimia nervosa. Am J Psychiatry 1995;152:1668–71.
[157] Kaye WH, Gendall KA, Fernstrom MH, Fernstrom JD, McConaha CW, Weltzin TE. Effects of acute tryptophan depletion on mood in bulimia nervosa. Biol Psychiatry 2000;47:151–7.
[158] Oldman A, Walsh A, Salkovskis P, Fairburn CG, Cowen PJ. Biochemical and behavioural effects of acute tryptophan depletion in abstinent bulimic subjects: a pilot study. Psychol Med 1995;25: 995–1001.
[159] Baranowska B, Wolinska-Witort E, Wasilewska-Dziubinska E, Roguski K, Chmielowska M. Plasma leptin, neuropeptide Y (NPY) and galanin concentrations in bulimia nervosa and in anorexia nervosa. Neuroendocrinol Lett 2001;22:356–8.
[160] Brewerton TD, Lesem MD, Kennedy A, Garvey WT. Reduced plasma leptin concentrations in bulimia nervosa. Psychoneuroendocrinology 2000;25:649–58.
[161] Jimerson DC, Mantzoros C, Wolfe BE, Metzger ED. Decreased serum leptin in bulimia nervosa. J Clin Endocrinol Metab 2000;85: 4511–4.
[162] Gendall KA, Kaye WH, Altemus M, McConaha CW, La Via MC. Leptin, neuropeptide Y, and peptide YY in long-term recovered eating disorder patients. Biol Psychiatry 1999;46:292–9.
[163] Vitousek K, Watson S, Wilson GT. Enhancing motivation for change in treatment-resistant eating disorders. Clin Psychol Rev 1998;18: 391–420.
[164] Fairburn CG, Norman PA, Welch SL, O'Connor ME, Doll HA, Peveler RC. A prospective study of outcome in bulimia nervosa and the long-term effects of three psychological treatments. Arch Gen Psychiatry 1995;52:304–12.
[165] Zhu AJ, Walsh BT. Pharmacologic treatment of eating disorders. Can J Psychiatry 2002;47:227–34.
[166] Keel PK, Mitchell JE. Outcome in bulimia nervosa. Am J Psychiatry 1997;154:313–21.