The Physiology of Anorexia Nervosa and Bulimia Nervosa

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Abstract

Eating disorders (ED) are psychological disorders that are characterized by abnormal eating, dysfunctional relationships with food, and a preoccupation with one's weight and shape. The incidence of EDs in women ranges from 0.5 to 3 % with the incidence increasing from 1963 to 2013. Currently, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) recognizes two specific EDs: anorexia nervosa (AN) and bulimia nervosa (BN), although there are subtypes associated with each. The DSM-IV-TR and the International Classification of Diseases (ICD-10) have different criteria for diagnosing AN and BN. Early identification of an ED is associated with shorter duration and fewer medical complications. Yet, it is estimated that only about 33 % of AN patients and 6 % of BN are receiving proper treatment for their illnesses. Gastrointestinal upset, fluid and electrolyte imbalances are common in AN in the short term and can eventually lead to long-term complications such as, pernicious anemia, osteoporosis, and heart disease. On the other hand, BN can cause short-term adverse effects like erosion of the teeth, enlargement of the parotid salivary glands, and acidic stomachs leading to heartburn. Long-term adverse effects caused by BN are gynecological problems, hormonal disturbances, hypercholesterolemia, and hypertension. Successful treatment of EDs should be managed with a team-based approach including the physician, psychologist, and registered dietitian.

Keywords

Physiology of anorexia nervosa • Physiology of bulimia nervosa • Genetics

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J.J. Robert-McComb et al. (eds.), *The Active Female: Health Issues Throughout the Lifespan*,
DOI 10.1007/978-1-4614-8884-2_11, © Springer Science+Business Media New York 2014

11.1 Learning Objectives

After completing this chapter, you should have an understanding of:

- The significance of an eating disorder
- The varying types of eating disorders
- Differentiating and similar signs and symptoms of each disorder
- The physiological changes that occur in anorexia nervosa and bulimia nervosa, specifically
- The potential long-term physiological consequences of anorexia nervosa and bulimia nervosa
- The importance of genetics, neurotransmitters, and key hormones in eating disorders

11.2 Introduction

Eating disorders (EDs) are psychological disorders that are characterized by abnormal eating, dysfunctional relationships with food, and a preoccupation with one's weight and shape [1]. More and more, these disorders are being recognized by medical professionals as biologically based psychiatric disorders [2]. EDs affect daily functioning and often result in physical complications and psychological distress [1]. The current *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV-TR*) [1] recognizes two specific EDs: anorexia nervosa (AN) and bulimia nervosa (BN). There are two subtypes associated with each specific ED: anorexia nervosa, restricting type (AN-R); anorexia nervosa, binge/purge type (AN-BP); bulimia nervosa, purging type (BN-P); and bulimia nervosa, non-purging type (BN-N). A third category, eating disorder not otherwise specified (EDNOS), is included for EDs of clinical significance that do not meet criteria for AN or BN. Within this broad category, there are currently three subdivisions: (1) binge-eating disorder (BED), which is currently under review and has been recommended to be included in the *DSM-IV-TR* as a specific clinical ED [3]; (2) subthreshold AN or BN (i.e., disorders very similar in symptoms or presentation to either AN or BN but not fully meeting the criteria for a diagnosis of either disorder); and (3) disorders with symptoms of both AN and BN but again not meeting the criteria for either disorder [4]. Additionally, it has been recommended that purging disorder (PD) be included in the *DSM-IV-TR* under the EDNOS classification for further review so that the appropriateness of including PD as a full-threshold ED can be determined [5].

Several characteristics that affect health outcomes are represented across EDs. Some of these characteristics include: (1) demographic characteristics; (2) experiences in adolescence; (3) low self-esteem and negative ideations; (4) medical and psychological comorbidity; and (5) issues with weight, shape, and the stereotype of beauty [6]. The majority of people with EDs experience other psychological disorders as well. Factors such as swiftness of weight loss, current weight, and chronicity of the ED are related to the intensity of the comorbid illness [7]. One study found that 56.2 % of individuals with AN, 94.5 % with BN, 78.9 % with BED, and 63.3 % with subthreshold BED met the criteria for another mental disorder, most often mood disorders, anxiety disorders, impulse control disorders, or substance use disorders [8]. Additionally, some form of personality disorder affects between 27 and 93 % of ED patients [9, 10]. Eating disturbances that do not meet full criteria for a clinical eating disorder are associated with elevated risk of depression, anxiety disorders, substance abuse, or health complications [11].

It is difficult to estimate the true prevalence of EDs due to underreporting [7, 12]. Even with considerable underreporting, the incidence of EDs has increased over the past 50 years. Increase in the prevalence of EDs might be due to improved understanding of the symptomatology and risk factors, as well as changes in diagnostic criteria, referral practices, and accessibility to help [12].

Generally, the incidence of EDs decreases with age. Many young people suffer from some form of disordered eating, whereas the incidence of EDs in women ranges from 0.5 to 3 % [13, 14]. Even though these numbers might seem low, this incidence rate is problematic as EDs are commonly

listed in the top ten causes of disability and mental illness in young women [15, 16]. Frequently, the onset age for AN and BN is between 15 and 19 [13, 15, 17, 18]. Although EDs and body dissatisfaction are typical for young women, they can occur in older women. In a randomly selected nonclinical sample of 1,000 women aged 60–70 years, more than 80 % used strategies to control their weights and over 60 % reported body dissatisfaction. Eighteen women (3.8 %) met the criteria for an eating disorder [19]. Because EDs can develop when people experience life transitions, are independent, and have an ample amount of privacy [20], one possible reason that some older women have is because they have lost their spouses, are living alone, or are at a time of transition in their lives.

As one ages, there is also a slight change in the expression of EDs. Adolescents and young women are more likely to show signs and symptoms related to AN and BN, whereas older adults may exhibit signs and symptoms more closely aligned to BED [16, 18]. These differences may exist because young people are more likely than older people to internalize cognitive distortions about body image and pressure from society to be thin [12].

At any age, EDs are complex, serious, maladaptive, and result in adverse health consequences [1, 7, 21]. EDs typically last several years and tend to have high relapse rates [11, 15, 20]. Specifically, the average duration of BN is 8.3 years, and the average duration of BED and subthreshold levels of BED is 8.1 and 7.2 years, respectively [8]. By the fifth year of the ED, the symptoms, pathology, and the clinical track of the ED will likely stabilize [22]. Unfortunately, the chronicity of EDs can ultimately result in diminished health, decreased psychosocial functioning, and compromised interpersonal interactions [7, 11, 17, 23].

Early identification of an ED is associated with shorter duration and fewer medical complications [24]. Unfortunately, recent estimates show that only about 33 % of AN patients and 6 % of BN patients are receiving proper treatment for their illnesses [12]. Comorbidity plays an important role in the treatment of EDs, as people are more likely to seek treatment for their non-ED mental health problems than for the ED itself [8]. In clinical settings, women and girls are ten times more likely than men and boys to receive treatment [7, 15, 20], but this ratio might not accurately represent the number of men and boys compared to women and girls who actually have eating disorders [20]. Thus, increased understanding of EDs is imperative so that treatment for people with EDs is more accessible and more effective.

11.2.1 Diagnostic Criteria for Anorexia Nervosa

AN is a drastic reduction in eating resulting in very low body weight [25]. Although patients with AN consume food, they eat with extreme limitations. Strict calorie and food restriction, as well as obsessive exercise, can produce an unhealthy level of weight loss in AN patients [7, 25]. Weight concerns, fear of fatness, social influence, distorted body shape, eating concerns, yearning for thinness, and body dissatisfaction are consistently found to be predictors of EDs and lie at the core of AN [11–29]. Often, the AN patient is totally preoccupied by thoughts of shape and weight, including obsession about weight gain and the perceived largeness of her body, and she often sees herself as being overweight regardless of how much weight she loses [7, 17, 18, 29]. An excess of physical activity has been recognized as hyperactivity in AN patients and is present in roughly 80 % of those with AN [30].

DSM-IV-TR [1] includes specific diagnostic criteria for AN. Initially, the individual must be at a weight that is 85 % or less of her expected weight, based on her height and her age, which is equivalent to a body mass index (BMI) of less than 18 (A BMI that falls between 18.5 and 24.9 is considered to be in the healthy range). Additionally, individuals who have started menstruating will develop secondary or functional hypothalamic amenorrhea. Amenorrhea is the absence of menstrual bleeding. Secondary amenorrhea is defined as the cessation of menses for 6 or more months sometime after menarche has occurred.

Functional hypothalamic amenorrhea is a reversible form of gonadotropin-releasing hormone deficiency commonly triggered by stressors such as excessive exercise, nutritional deficits, or psychological distress. For those girls who have not reached menarche, they will typically fail to begin menstruating at the expected time this is known as primary amenorrhea. Primary amenorrhea is the failure of menses to occur by age 16 years, in the presence of normal growth and secondary sexual characteristics. Psychological criteria include extreme disturbance in self-perception of the body and an overwhelming fear of fatness. AN patients can be further subdivided into two subtypes: restricting subtype (AN-R) and binge/purge subtype (AN-BP). The AN-R subtype describes those individuals who severely restrict their food intake and do not use compensatory behaviors, like self-induced vomiting, to compensate for calories consumed. The AN-BP subtype is diagnosed when periods of restriction are accompanied by periods of overeating and extreme compensatory purging behaviors, like self-induced vomiting. AN, particularly the restricting type (AN-R), is the most rare form of eating disorder.

Some question the validity of the diagnostic criteria for AN that are included in the *DSM-IV-TR*. The strongest debate has risen regarding the inclusion of amenorrhea. Some suggest that the differences between AN patients who do and do not menstruate are very limited [31–33]. Additionally, a large number of females use birth control or other substances that affect hormones, so it can be difficult to determine if a woman would develop amenorrhea if she were not using these substances [7]. Although some argue that fear of weight is a classic feature of AN, this fear may not be present in all individuals with AN [34]. Furthermore, the subtypes associated with AN have been questioned. The AN-R and AN-BP subtypes were originally differentiated because women in these two subgroups were thought to be different in terms of comorbidity and recovery cycles, but recent evidence suggests that the current separation might not be needed [34]. Still, others have pushed to eliminate the AN-BP subtype all together and limit AN to only those individuals who severely restrict their food intake and to include AN-BP with BN and include a low-weight specifier [35].

Another commonly used classification system for EDs and other illnesses is the *tenth edition of the International Classification of Diseases* (ICD-10). The ICD-10 specifies that patients with AN have a BMI equal to or below 17.5, which is well below the healthy range (18.5–24.9) [36]. Other ICD-10 criteria for AN include amenorrhea, weight loss that is self-induced and purposeful, a fear of fatness, and a perception of being fat. Unlike the *DSM-IV-TR* classification, the ICD-10 specifies that binge eating is an exclusionary criteria for AN. The ICD-10 criteria are based on behavioral symptoms and methods of weight loss, in contrast to the *DSM-IV-TR* that emphasizes psychological distortions and disturbances [17, 36]. Table 11.1 presents a comparison of the *DSM-IV-TR* and ICD-10 diagnostic criteria for AN.

There are different theories that attempt to explain the onset and continuation of AN. However, it is thought that a combination of genetics, environmental factors, and specific personality traits likely contributes to the development and maintenance of AN [37].

Research suggests that personality disorders most commonly associated with AN-R include avoidant, dependent, obsessive-compulsive, and borderline personality disorders [9, 38]. Additionally, anxiety and mood disorders affect about 25 % of people with AN [39], and comorbid conditions like depression, anxiety, phobias, and personality disorders might contribute to worse outcomes for AN patients [39].

It has been suggested that AN patients have lower reward sensitivity than other individuals [25]. For example, they often deny food can be satisfying; therefore, it might be easier for them to skip food because the food is not as pleasing for them as it is for people without AN.

Some research suggests that AN patients have lower levels of novelty seeking and higher levels of harm avoidance, and both factors can prevent a person from developing binge eating and purging behaviors [9, 40]. However, AN-BP patients do develop binge eating and purging behaviors, and these behaviors are intermingled with periods of fasting, excessive exercise, and other compensatory behaviors [7].

Table 11.1 Comparison of DSM-IV-TR and ICD-10 diagnostic criteria for anorexia nervosa

	DSM-IV	ICD-10
Code	307.1	F50.0
Weight	Refusal to maintain body weight at or above minimal normal weight for age and height (e.g., weight loss leading to maintenance of body weight <85 % of expected weight) or Failure to make expected weight gain during growth period, leading to weight <85 % of expected normal body weight	Body weight is maintained at least 15 % below that expected (either lost or never achieved) Quetelets's body mass index is 17.5 kg/m^2 or less or Prepubertal patients may show failure to make the expected weight gain during the period of growth
Phobia/associated behaviors	Intense fear of gaining weight or becoming fat, even though underweight DSM-IV behaviorally differentiates between types: Restricting = not engaging in binge-eating or purging behavior Binge eating/purging = regularly engaging in binging or purging behavior	Weight loss self-induced by avoidance of "fattening foods" and One or more of the following: self-induced vomiting, self-induced purging, excessive exercise, use of appetite suppressants and/or diuretics
Body perception	Disturbance in the way in which one's body weight and shape are experienced Undue influence of body weight or shape on self-evaluation or Denial of the seriousness of the current low body weight	Body-image distortion in the form of a specific psychopathology whereby a dread of fatness persists as an intrusive, overvalued idea and Patient imposes a low weight threshold on himself or herself
Amenorrhea/hormonal fluctuations	In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles (amenorrhea exists if periods occur only via hormone induction)	In women, amenorrhea, and in men, loss of sexual interest and potency (an apparent exception is the persistence of vaginal bleeds in anorexic women who are receiving replacement hormonal therapy, most commonly taken as a contraceptive pill) There may also be elevated levels of growth hormone, raised levels of cortisol, changes in the peripheral metabolism of the thyroid hormone, and abnormalities of insulin secretion
Pubertal development	Not specified	With prepubertal onset, the sequence of pubertal events is delayed or even arrested (growth ceases; in girls, the breasts do not develop and there is a primary amenorrhea; in boys, the genitals remain juvenile). With recovery, puberty is often completed normally, but the menarche is late

Source: Bulik, C. M., L. Reba, A. M. Siega-Riz, and T. Reichborn-Kjennerud. 2005. Anorexia nervosa: Definition, epidemiology, and cycle of risk. *Int J Eat Disord* 37: s2–s9. Reprinted with permission of John Wiley & Sons, Inc.

11.2.2 Diagnostic Criteria for Bulimia Nervosa

Prevalence rates of BN range from 1 to 4 %, making BN approximately three times more common than AN [6, 7, 12, 18, 39]. BN is a complex disorder characterized by recurrent binge eating, compensatory behaviors to avoid weight gain, and related behavioral and physiological symptoms. The diagnostic criteria for BN include several criteria that reflect the physical manifestation of the disorder. Specifically, the current *DSM-IV-TR* criteria indicate that all women with BN have recurrent episodes of binge eating [1].

According to the *DSM-IV-TR*, BN is characterized by compulsive, extreme binge eating followed by a compensatory method like self-induced vomiting, misuse of diuretics or laxatives, or excessive exercise to make up for the excessive amount of calories consumed. Diagnostic criteria state that this type of cyclic behavior must occur for at least 3 months, and binge eating and purging episodes are to occur at least two times per week. The main psychological factor in BN is loss of control during episodes of binge eating. Additionally, the BN patient places high importance on body weight and physical appearance. There are two subtypes of BN: The purging subtype (BN-P) includes those people who make themselves vomit or use laxative or diuretics to compensate for a binge, and the non-purging subtype (BN-N) includes those people who use other forms of compensatory behavior, such as excessive exercise or fasting [1].

An episode of binge eating is characterized by both of the following: (1) eating within any 2-h period an amount of food that is definitely larger than most people would eat; and (2) a sense of lack of control overeating or a feeling that one cannot stop eating or control what or how much is being consumed. To compensate for the large amount of food that has been consumed during the eating binge, the individual with BN engages in behaviors to prevent weight gain, such as (1) self-induced vomiting; (2) misuse of laxatives, diuretics, enemas, or other medications; (3) fasting; or (4) excessive exercise. To be diagnosed with BN using the current *DSM-IV-TR* criteria, the binge eating and compensatory behaviors must occur, on average, at least twice a week for 3 months. Another diagnostic criterion for BN is that self-evaluation is unduly influenced by body shape and weight [41].

As with AN, there is also ICD-10 criteria for BN diagnosis. The ICD-10 criteria for BN are similar to the *DSM-IV-TR* criteria. The ICD-10 criteria for BN include having an adverse relationship or preoccupation with food, engaging in binge eating and purging behaviors, and attempting to keep body weight below a level that would optimize health [36]. Table 11.2 provides a comparison of the DSM-IV-TR and ICD-10 diagnostic criteria for BN.

Table 11.2 Comparison of DSM-IV-TR and ICD-10 diagnostic criteria for bulimia nervosa

	DSM-IV-TR	ICD-10
Code	307.51	F50.2
Relationship with food	Binge/purge cycle must occur for at least 3 months, at a rate of two times per week, on average	Continued obsession with food Strong cravings Fear of weight gain
Binge eating	Eating, in 2 h or less, a portion of food that is substantially larger than most others would eat Loss of control when consuming this food	Period of overeating when are a great deal of food is eaten quickly
Purging tendencies	Recurrent methods of compensation (vomiting, diuretics, other medications, fasting or exercise)	Methods to compensate for the binge Vomiting, restriction of food intake, drug use may include appetite suppressants, thyroid treatments or diuretics
Beauty ideal	Weight and shape are a major influence in defining the identity of a BN patient	Strives to achieve a weight that is well standard weight or weight expected for a particular person

Source: Bulik, C. M., L. Reba, A. M. Siega-Riz, and T. Reichborn-Kjennerud. 2005. Anorexia nervosa: Definition, epidemiology, and cycle of risk. *Int J Eat Disord* 37: s2–s9. Adapted with permission of John Wiley & Sons, Inc.

Individuals who engage in binge eating also commonly engage in the excessive use of weight-loss supplements. According to Reba-Harrelson et al. [42] women with BN are more likely to use diet pills if they have a higher BMI, higher novelty seeking, anxiety disorders, alcohol abuse, or borderline personality disorder. Many of these characteristics are commonly found to co-occur with BN [42].

11.2.3 Eating Disorder Crossover and Identification

It is difficult for researchers to design well-controlled studies for EDs, particularly studies that will distinguish the causes and early signs of EDs. There are multiple reasons for this difficulty. For instance, it is often difficult to accumulate a large enough sample of people with EDs, and AN and BN often consist of similar or overlapping characteristics [13, 17, 37].

Although AN and BN are separate disorders, there are several traits commonly found in both AN and BN patients: Specifically, high neuroticism, perfectionism, obsessiveness, and low self-directedness are characteristic of both AN and BN. These shared traits may increase the chance of crossover from AN to BN [22]. Commonalities between AN and BN patients may be attributed to the symptom overlap between the two disorders or may help account for the high crossover rate from AN to BN [17, 22]. Other traits associated with the crossover from AN to BN include prior anxiety, childhood sexual abuse, negative affect, and improvement in the AN condition [22, 37].

The symptoms associated with AN-BP and both subtypes of BN overlap, making diagnosis difficult. A person's weight distinguishes those with BN from those with AN-BP. People with BN typically have a weight that is in the normal range, and some are overweight [43].

Similar to AN, some diagnostic criteria for BN are controversial. For example, individuals who binge eat and purge once each week rather than twice each week experience similar levels of eating-related pathology, and the definition of a binge (i.e., "an amount of food that is larger than most people would eat") is not objective or easily measurable [7].

Also, ED classification can be difficult as crossover from one form of ED to another is fairly common. It has been estimated that between 8 and 62 % of patients with AN eventually crossover to BN [17, 22]. The highest percentage of crossover occurs when restricting AN patients crossover to the binge/purge subtype of AN (AN-BP) or to BN [7, 22]. Additionally, BN can crossover to BED [16, 44]. Crossover from one ED to another typically occurs during the first 5 years of the illness; after 10 years, the rate of crossover is substantially reduced [7, 17]. Furthermore, certain personality traits in AN patients, such as novelty seeking and low self-directedness, have been associated with higher crossover probability compared to other AN patients without these traits [45]. There are theories attempting to explain why the crossover from AN to EDs with bingeing behavior occurs frequently. Several animal and historical studies have shown that restricted eating will result in binge eating later; therefore, many believe that the restricting behavior directly causes a person to begin binge eating [25].

11.3 Research Findings

11.3.1 Short-Term Adverse Effects of Anorexia Nervosa

Numerous physiological signs and symptoms are associated with AN, and many of these physical symptoms are life-threatening [39]. A summary of some of the physical consequences of AN is provided in Table 11.3.

Although numerous physical abnormalities may be found in people with AN, research findings indicate that laboratory results may be normal even in the presence of profound malnutrition [46].

The body weight of the individual with AN generally reflects the degree of calorie restriction, the severity of purging behaviors (if present), and the amount of exercise engaged in by the individual. Adults who are diagnosed with AN generally

Table 11.3 Physical consequences of anorexia nervosa

Cardiovascular	*Gastrointestinal*
Bradycardia	Abdominal discomfort
Tachycardia	Bloating/feeling of fullness
Arrhythmias	Constipation
Hypotension	Delayed gastric emptying
Fainting	Decreased gastric and intestinal motility
Dizziness	Pancreatitis
Endocrine	*Integumentary*
Amenorrhea	Dry, flaky/scaly, yellowish orange skin
Cold sensitivity	Decreased body fat
Oligomenorrhea	Lanugo (fine facial and body hair)
Anovulation	Thinning hair
	Brittle nails
Hematologic	*Central nervous system*
Anemia	Poor problem-solving skills and memory
Hypercortisolism	Decreased concentration and attention
Leukopenia	Depressed mood
Pancytopenia	Peripheral neuropathy
Thrombocytopenia	Seizures
Skeletal	*Fluids and electrolytes*
Osteopenia	Electrolyte imbalance
Osteoperosis	Dehydration
Bone fractures	Rebound peripheral edema
Stunted growth	Renal failure
	Metabolic acidosis

show extreme weight loss and may be described as thin or emaciated. Children and adolescents may not lose an extreme amount of weight, because weight loss goes against the body's natural tendency to grow larger. Rather, children and adolescents might lose smaller amounts of weight (e.g., 5–10 lb) or might not grow to a weight that would be expected for them based on their height, age, and developmental level [47].

11.3.1.1 Gastrointestinal Abnormalities

Individuals with AN frequently describe mealtime as an uncomfortable experience associated with symptoms of anxiety, such as sweating and increased pulse and respiratory rates [48]. When a person eats little food, a series of adverse consequences affect normal digestion. Food is held for longer periods in the stomach and intestines, which can produce bloating and a feeling of being full, stomachache, and constipation. Food normally passes through the stomach in about an hour, but when the consumption of food is restricted, food may stay in the stomach for 4 or 5 h [47]. So, it may be difficult for a young woman with anorexia to resume a normal pattern of eating. After eating a normal amount of food for lunch, she may still feel full when it is time for supper.

Due to malnutrition [49] and repeated episodes of binge eating [50], pancreatitis is a common occurrence in patients with eating disorders. Patients with pancreatitis may complain of steady and intense upper abdominal pain that may diffuse to the back, chest, or lower abdomen. Numerous mechanisms have the potential to cause pancreatitis, including a sudden increase in calorie intake after malnutrition or the ingestion of various medications including the laxatives and diuretics used in purging [51].

11.3.1.2 Fluid and Electrolyte Abnormalities

Individuals with AN can develop imbalances in body fluid and electrolyte levels due to prolonged malnutrition and dehydration. These imbalances can reduce fluid and mineral levels and produce a condition known as *electrolyte imbalance.* Fluid and electrolyte imbalances can become more serious when an individual also engages in purging behaviors, such as vomiting and laxative abuse. Dehydration may result from inadequate fluid intake or excessive fluid loss during purging or exercise. Dehydration leads to increased blood levels of urea, urate, and creatinine and dehydration may result in decreased urine volume and renal failure. A *rebound peripheral edema* (i.e., swelling of body tissue due to excessive fluid retention) may also occur and can contribute to a dramatic increase in body weight (approximately 10–45 lb). *Metabolic acidosis*, a condition when the body produces too much acid or the kidneys do not remove enough acid, may result from vomiting and loss of stomach acid and sodium bicarbonate. If the individual also engages in laxative abuse, the loss of alkaline bowel fluids

may result in metabolic acidosis [52]. Individuals who abuse laxatives are four times more likely to suffer serious medical complications than non-laxative abusers [53]. Reduced blood flow, and lower blood pressure have all been linked to electrolyte imbalance. Electrolytes, such as calcium and potassium, are critical for maintaining the electric currents necessary for a normal heartbeat. These imbalances can be very serious and can even be life-threatening unless fluids and minerals are replaced.

11.3.1.3 Integumentary Abnormalities

Malnutrition, loss of body fat, and dehydration can also cause changes in skin and tissues. Frequently, the skin is dry, scaly, and covered with *lanugo*, a fine, downy hair resembling that of newborn babies. Fingernails and hair are often brittle, and hair loss may occur in patches or uniformly over the scalp and other body areas [54]. A yellowish or orangish discoloration of the skin occurs in approximately 80 % of patients with AN [46]. This unusual skin color, which is "most noticeable on the palms of the hands, the soles of the feet, and the creases inside the elbows," is due to faulty metabolism of β-carotene in the liver leading an excessive level of β-carotene circulating in the blood, some of which is deposited under the skin [47].

Additionally, severe starvation has been linked to depressed mood, decreased concentration and attention, and poor problem-solving skills and memory. These problems may contribute to poor judgment about the severity of the illness and, therefore, hamper the individual's recognition of the need for treatment [48].

11.3.2 Long-Term Adverse Health Effects of Anorexia Nervosa

11.3.2.1 Hematologic and Immunologic Abnormalities

Hematologic and immunologic abnormalities are often found in patients with AN. Poor nutrition with severe weight loss often results in dramatic decreases in red blood cells, white blood cells, and blood platelets. Anemia is a common result of anorexia and starvation. One particularly serious blood problem is pernicious anemia, which can be caused by severely low levels of vitamin B_{12}. In some severe cases of AN, the bone marrow dramatically reduces its production of blood cells, a life-threatening condition called *pancytopenia.* Impairment of the immune system is also common and is believed to be a consequence of *hypercortisolism* (i.e., excessive amounts of the hormone cortisol). These effects can be corrected with nutritional improvement and weight restoration.

11.3.2.2 Skeletal Problems

Although long-term complications of AN can involve any of the body's systems, the bones are significantly affected. Since puberty is a critical time for skeletal development, developing AN during this period can interfere with the development of peak bone mass and, therefore, produce permanent long-term skeletal effects [48]. When a young child is severely underweight, there is a danger that the child's growth will be limited. However, if AN starts after puberty begins and ends before the growth plates in her bones have closed, then a young woman's growth in height will not be stunted [55].

Bone loss and decreased bone density are common problems for people with AN and is particularly prevalent in individuals with AN who have been severely emaciated for a prolonged period of time [56–58]. However, fractures of the long bones, vertebrae, and sternum have been reported in individuals with AN who have had amenorrhea for as short a period as 1 year [59]. Approximately 90 % of women with anorexia experience osteopenia (decrease in bone mass) and some have osteoporosis (brittle and fragile bones) [60]. In a study assessing decreased bone density and bone loss in women with AN, nearly half of the women had osteopenia at the hip, and 16 % had osteoporosis at the hip. More than half had osteopenia at the spine, and almost 25 % had osteoporosis at the spine. Over 90 % of women had abnormally low bone density at one or more sites in the skeleton. Additionally, weight was the factor most related to bone loss. The less a woman weighed, the more likely it was that she would have substantial bone loss [60].

In a long-term study of 103 patients with AN, osteoporosis with multiple fractures and terminal renal deficiency accounted for the most severe disabilities experienced by the patients [61]. Bone loss, osteopenia, and associated stress fractures have been linked to endocrine disturbances that alter normal hormonal mechanisms and lead to oligomenorrhea and amenorrhea [62]. Oligomenorrhea is infrequent (or, in occasional usage, very light) menstruation. More strictly, it is menstrual periods occurring at intervals of greater than 35 days, with only four to nine periods in a year. Amenorrhea is the absence of a menstrual period in a woman of reproductive age.

Dietary deficiency, low circulating estrogen levels, hypercortisolism, laxative misuse, and disturbed acid–base balance also contribute to adverse physical consequences [63]. Other factors contributing to bone loss include high levels of stress hormones (which impair bone growth) and low levels of calcium, certain growth factors, and dehydroepiandrosterone (DHEA). Skeletal problems can be minimized or prevented by early recognition and intervention, but long-term complications can be expected to occur and progress as long as an individual continues to exercise without proper nutritional intake [64]. Unfortunately, weight gain does not completely restore bone loss, but achieving regular menstruation as soon as possible can protect against permanent bone loss. The longer the eating disorder persists the more likely the bone loss will be permanent.

Over 60 % of patients with AN have leukopenia (a reduction in the number of leukocytes in the blood), and this abnormality may be related to bone marrow hypoplasia and decreased neutrophil (a granular leukocyte having a nucleus of three to five lobes) lifespan [46]. Leukopenia accompanied by a relative lymphocytosis has also been reported [59]. Normochromic anemia, normocytic anemia, and thrombocytopenia have been found in approximately one-third of patients with AN [65].

11.3.2.3 Central Nervous System Abnormalities

Disruptions in neuroendocrine and neurotransmitter systems are prevalent in people with AN and affect the brain and other parts of the body. Seizures, disordered thinking, and *peripheral neuropathy* (i.e., numbness or odd nerve sensations in the hands or feet) have all been reported. Structural changes in the brain include: widening of the sulcal spaces and cerebroventricular enlargement [66] and reductions in the size of the pituitary [67]. People with AN also demonstrate increased metabolism in the cortex and caudate nucleus [68].

11.3.2.4 Effects on Pregnancy

Research suggests that most pregnant women with a history of EDs have healthy pregnancies [69]. However, some research suggests that women who have had EDs may face higher risks for a number of complications, including cesarean sections, postpartum depression, miscarriages, complicated deliveries, and premature birth [47, 70]. In one of the few studies that investigated pregnancy outcomes for women who had a previous diagnosis of AN, a large sample of women who were discharged from hospital with a diagnosis of AN during 1973 to 1996 and who gave birth during 1983 to 2002 were compared with a large sample of healthy women who gave birth during the same years. The researchers collected information about preeclampsia (i.e., pregnancy-induced hypertension), instrumental delivery, prematurity, small for gestational age, birth weight, Apgar score, and perinatal mortality. Results showed that the main birth outcome measures in women with a history of AN were very similar to those without a history of AN. The only observed difference was a slightly lower mean birth weight for babies whose mothers had a history of AN [69]. This research suggests that women who have a history of AN and who have been treated for the disorder are often able to become pregnant and have healthy pregnancies.

11.3.3 Comorbidities and Mortality Rates for Anorexia Nervosa

11.3.3.1 Cardiovascular Abnormalities

Some of the most serious and life-threatening complications of AN result from impairment of the cardiovascular system. For example, people with AN might complain of heart palpitations,

dizziness, fainting, shortness of breath, and chest discomfort. If these cardiovascular abnormalities are not recognized and treated, they could result in death.

Heart disease is the most common medical cause of death in people with AN, and a primary danger to the heart is from abnormalities in the balance of minerals, such as potassium, calcium, magnesium, and phosphate. Prolonged starvation leads to decreased sympathetic tone in the heart and blood vessels. The heart's ability to pump and the vessels' ability to transport blood may be altered, which could result in *bradycardia* (i.e., heart beats too slowly), *tachycardia* (i.e., heart beats too quickly), or extremely low blood pressure [65]. Bradycardia may occur due to a starvation-induced metabolic decrease controlled by circulating *catecholamines* (i.e., "fight or flight" hormones released in response to stress) and a change in thyroid hormone levels. Tachycardia can occur when the circulating fluid volume decreases as a result of dehydration, and the heart is forced to pump faster to compensate for the decrease [71]. The reduction in blood pressure may lead to light-headedness or dizziness, and the individual with anorexia may experience orthostatic hypotension (lightheadedness when standing up or getting out of bed) [47]. Episodes of fainting may occur because of abnormally low blood pressure. Studies have shown that 91 % of individuals with AN have pulse rates less than 60 beats per minute [72], and up to 85 % of patients with AN also have hypotension, with blood pressures below 90/60 [73]. Individuals with AN have been found to have higher incidences of mitral valve abnormalities and left ventricular dysfunction than individuals who do not have eating disorders [74]. All of these factors contribute to a significant risk of sudden death due to cardiovascular problems in this population [75, 76].

Cardiovascular abnormalities also contribute to the coldness that people with AN experience. Because the blood circulates more slowly, a person's hands and feet turn cold and also appear blue because red blood cells have been depleted of oxygen. However, another reason that individuals with anorexia feel cold is the loss of the insulation normally provided by a thin layer fat all over the body [47].

11.3.3.2 Endocrine Abnormalities

AN affects the endocrine system by producing numerous alterations in neuroendocrine mechanisms. Changes in the hypothalamic-pituitary-adrenal axis (HPA axis) result in hypercortisolemia and increased cerebrospinal fluid (CSF) levels of corticotropin-releasing hormones. Since the hypothalamus controls the pituitary gland, pituitary function is also inhibited, resulting in alterations in the normal circulating levels of gonadotropins, cortisol, growth hormone, and thyroid hormones. As a result, prepubertal patients may have altered sexual maturation and arrested physical development and growth patterns [77].

Hormonal problems are one of the most serious effects of AN. People with AN have decreased levels of reproductive hormones, including estrogen and DHEA. Estrogen is important for heart health and bone health. DHEA, a weak male hormone, is also important for bone health. For women, these hormonal abnormalities may result in menstrual cycle disruptions, including anovulation (lack of regular ovulation), oligomenorrhea, and amenorrhea [78, 79], and these abnormalities can occur even *before* a person has lost a significant amount of weight. Estrogen levels are usually restored and menses usually resume after a person has been treated and her weight has increased. However, in some cases, menstruation may never return, resulting in infertility.

Starvation and weight loss are known to create hypothalamic abnormalities that profoundly affect other organs within the endocrine system. A chain of interrelated events begins when the hypothalamus fails to signal the release of gonadotropin-releasing hormones from the pituitary. The absence of this signal causes a decrease in luteinizing hormone (LH) and follicular-stimulating hormone (FSH) levels and inhibits the positive feedback mechanism to the ovaries. Consequently, the ovaries do not release estrogen or progesterone in normal amounts, which further inhibits the pituitary gland. Ovarian volume

and uterine volume are decreased, and the vaginal mucosa becomes atrophic [65].

Normal functioning of the thyroid gland is also disrupted in individuals who have eating disorders. Individuals with AN frequently demonstrate thyroid abnormalities as a result of decreased calorie intake and starvation. Free thyroxine (free T4) decreases to low normal levels, whereas triiodothyronine (T3) levels decrease to abnormally low levels in proportion to the degree of weight loss [65], but thyroid-stimulating hormone (TSH) levels are usually within normal range [80]. Thyroid function tests reveal low T3 levels in proportion to weight loss, low normal T4 levels, and decreased metabolic rates [65].

11.3.3.3 Mortality Rates

AN is recognized as having the highest mortality rate of any psychiatric condition in young females [15, 16, 18, 26, 81, 82]. Estimates of premature deaths in AN patients range from 5 to 6 % [7, 39]. Causes of death in women with EDs include starvation, suicide, and electrolyte imbalance [6, 12, 39, 83]. Several factors may be predictors of mortality, including having a body weight that is less than 77 lb, repeated inpatient admissions, and severe alcohol and substance use disorders [6, 84]. Adults with AN also have a high mortality rate [85, 86]. AN is also associated with elevated levels of suicide ideation and high rates of suicide [18, 83, 87].

11.3.4 Short-Term Adverse Effects of Bulimia Nervosa

Behaviors associated with BN may have few adverse consequences for individuals who briefly engage in self-induced vomiting, purging, or fasting [88]. However, when those behaviors are recurrent and persistent enough to lead to a diagnosis for BN, individuals are likely to have these physiological consequences: (1) erosion of the teeth, (2) enlargement of the parotid salivary glands, and (3) acidic stomachs leading to regurgitation of acidic stomach and heartburn [88, 89]. Signs and symptoms related to BN are listed in Table 11.4. This table is not all inclusive but lists some of the more common pathologies in BN.

Table 11.4 Signs and symptoms of bulimia nervosa

Anovulation	Hypotension
Calluses on back of hand and fingers	Integumentary
Cardiomyopathy	System
Cheilosis	Disorders
Constipation	Metabolic
Dental abscesses	Acidosis
Dental caries	Alkalosis
Diarrhea	Mitral valve prolapse
Dry, flaky skin	Muscle cramps
Dyspepsia	Musculoskeletal weakness
Endocrine disorders	Palpitations
Esophagitis	Pancreatitis
Heart failure	Pruitis
Hematemesis	Sore throat
	TetanY

Excessive vomiting causes erosion on the enamel and dentin on teeth, increasing the susceptibility to cavities and gum disease [88, 89]. It can also cause acid from the stomach to rise up to the esophagus, which leads to infections, gastro-esophageal reflux disease, and may eventually cause a ruptured esophagus [89]. Other short-term complications resulting from BN include impaired satiety, decreased resting metabolic rate, and abnormal neuroendocrine responses. These symptoms increase in severity with continued disordered eating [90]. These complications should be thought of as occurring on a continuum, and in some cases, the symptoms are reversible.

11.3.5 Long-Term Adverse Health Effects of Bulimia Nervosa

11.3.5.1 Gynecological Problems and Hormones

Gynecological problems are one of the most frequent long-term complications of EDs [91, 92]. The unsatisfactory nutrition in BN results in hormonal dysfunction, menstrual disturbances, and infertility [93]. These symptoms may be reversible with early treatment of the ED [91, 92]. Menstrual irregularities as a result of BN may be caused by weight fluctuations, nutritional deficiency, and

prolonged stress [94]. This same menstrual irregularity or oligomenorrhea can lead to polycystic ovary syndrome in individuals who are bulimic, especially if they are also obese [94, 95].

Gonadal steroids are among the many factors that influence food intake and body weight in mammals [97]. A key role of estradiol is related to food intake and energy balance. The actions of estradiol may have a gender-specific effect on the regulations of eating, which could explain why BN is more common in women than men [96]. During the estrogen-releasing cycle, the amount of food being consumed fluctuates in response to ovarian rhythms in bulimic women [97, 98].

Disturbances in hormonal regulation in BN can also lead to severe mood changes and aggressive behavior patterns. Researchers have found that individuals with BN have a decrease in plasma levels of prolactin and estradiol, and an increase in cortisol and testosterone [99, 100]. There is a positive correlation between testosterone plasma levels [101] and aggressiveness in individuals with BN that is not seen in other individuals [99, 100]. Individuals with BN tend to have a higher score when rating depressive symptoms and aggressiveness on eating-related psychopathology assessments, which suggests that BN plays a role in the modulation of aggressiveness [99].

11.3.5.2 Cardiovascular Abnormalities

Hypercholesteremia (the presence of high levels of cholesterol in the blood) is a cardiovascular risk factor associated with BN. Hypercholesterolemia is not a disease but an abnormal metabolic state that can be secondary to many diseases and can also contribute to many forms of disease, most notably cardiovascular disease [102]. Pauporte and Walsh [103] found that the mean serum cholesterol levels of patients with BN were significantly higher than the cholesterol levels of individuals in a comparison group (patients: 194 ± 36 mg/dl; comparison group: 176 ± 34 mg/dl; $t = 2.77$; df = 159; $p = 0.006$). Additionally, individuals who binge or overeat, or who are obese, are also at high risk for developing hypertension, which is another pathway to long-term cardiovascular disease [103].

Mira et al. [104] found that individuals with BN and other EDs not only had higher levels of cholesterol, but they also had lower levels of electrolytes, such as, potassium, chloride, and phosphate in the plasma. The misuse of laxatives and weight-loss supplements over time can cause these electrolyte imbalances and gastrointestinal abnormalities [104].

Cardiac autonomic regulation and stress reactivity may also be altered in BN patients due to energy restriction. Altered eating patterns in BN can result in metabolic and cardiovascular abnormalities [105]. Messerli-Bürgy et al. [106] found that heart rate stress reactivity was highest in BN patients when looking at biological stress responses. During the stress recovery stage of the laboratory stressor, heart rate variability (HRV) decreased in the participants with BN compared to a group of other women [106]. A decrease in HRV is associated with coronary artery disease and congestive heart failure [107–111]. A similar study investigated cardiac autonomic regulation and stress reactivity in relation to biochemical markers of dietary restriction in women diagnosed with BN. These investigators found that women with BN who were fasting (compared to women who had BN but were not fasting or women who did not have BN) showed increased vagal dominance and decreased sympathetic modulation during both resting and recovery periods. These results support the notion of cardiac sympathetic inhibition and vagal dominance during dietary restriction, and suggest the specificity of starvation related to biochemical changes for cardiac autonomic control [169]. Vögele et al. [105] also found that individuals with BN have higher resting cardiac vagal tone than controls [105]. Based on the findings from their studies, Murialdo et al. [112]. hypothesized that BN patients have sympathetic failure, prevalent vagal activity, and impaired sympathetic activation. These findings indicate a relationship between energy restriction and vagal dominance [112].

Elevated homocysteine levels (an amino acid in the blood) are associated with cognitive decline in dementia and healthy elderly people and are also associated with a high risk of cardiovascular diseases, stroke, and peripheral vascular disease

[113, 114]. While elevated homocysteine levels are more common in AN than BN patients, BN patients also exhibit signs of elevated homocysteine levels [114, 115]. This condition can be caused by several conditions, such as malnutrition, starvation, alcohol abuse, or genetic predisposition [116]. Deficiencies of three vitamins—folic acid (B_9), pyridoxine (B_6), or cyanocobalamin (B_{12})—can also lead to high homocysteine levels. Wilhem et al. [117] found a small decrease in levels of homocysteine following a 12-week treatment period for individuals with ED; however, the change was small and statistically nonsignificant. Nonetheless, their conclusion was that during effective treatment that concomitantly increased BMI, hyperhomocysteinemia was partially reversible. In light of the findings from Frieling et al. [114], decreasing homocysteine levels may not improve memory in an ED population. Interestingly, in a mixed group of patients (14 with AN and 12 with BN), elevated homocysteine levels were associated with normal short- and long-term verbal memory, and normal plasma homocysteine levels were associated with poorer memory performance. These results indicate that, under the special circumstances of ED, elevated homocysteine levels improve memory signaling, possibly by facilitating long-term potentiation.

11.3.5.3 Immunologic Abnormalities

Individuals with BN may also have a comprised immune system. Several studies have reported changes in immune cells and natural killer cells important for immunity in patients with AN and BN [118]. With a decrease in lymphocyte number, individuals with BN are more vulnerable to disease.

11.3.6 Comorbidities and Mortality Rates for Bulimia Nervosa

BN is a long-term disorder with a waxing and waning course. Comorbid medical and psychiatric conditions associated with BN include: (1) irritable bowel syndrome; (2) fibromyalgia; (3) mood disorders, such as major depression; (4) anxiety disorders, such as generalized anxiety disorder, panic disorder, and phobias; (5) alcoholism and substance abuse, (6) personality disorders, and (7) aggressive behavior and poor impulse control [119]. These comorbid conditions are similar for BN and AN [119].

Recent data suggest that mortality rates for BN are around 3.9 % [120]. Mortality rates are slightly higher (5.2 %) for Eating Disorder Not Otherwise Specified (EDNOS), a disorder in which an individual's behavior may meet some but not all of the diagnostic criteria for BN [120].

11.4 Contemporary Understanding of the Issues

11.4.1 Genetic Variables and Eating Disorders

An area of interest in research is the role that genetics plays in EDs. Genetic research is attempting to explicate the behavioral, neurobiological, and temperamental variables that represent the core features of both the anorexic and bulimic phenotype. However, there is shared variance between genetic variables and other risk factors, such as an individual's environment or her attempts at dieting and losing weight.

The role of genetics in the etiology of EDs has long been postulated to be a risk factor based on information about the relatives and siblings of individuals with EDs. For example, individuals are more susceptible to developing an ED if a close relative also has an ED [121]. First-degree relatives of AN persons are six times more likely to develop AN [122]. Twins have a tendency to share specific patterns of ED symptoms, such as obesity, AN, or BN [123]. The compilation of several twin studies has indicated a 48–76 % heritability in AN and 50–83 % heritability for BN [16]. However, there is little statistically relevant evidence linking AN and heritability in twin studies [122]. The importance of genetic predisposition in BN is shown by the difference in concordance rates for monozygotic and dizygotic twins. The concordance rate for BN is 23 % for monozygotic twins and 9 % for dizygotic twins

[119, 123]. In other words, when one member of a twin pair has BN, the other twin is more likely to also have BN if the twins are identical genetically than if their genetic similarity is that of any other pair of siblings. The fact that the concordance rates for BN found in twin studies are nowhere near 100 % demonstrates clearly that many factors other than genetic predisposition contribute to BN.

The role of shared environmental influences must be considered in studies of twins and other siblings, given our knowledge of the importance of environment in the development of an ED. Evidence supports a strong association between genetically determined factors, such as serotonin (5-Hydroxytryptamine [5-HT]) and dopamine (DOP) levels, and environmental risk factors; suggesting that environmental risk factors play a large role in the expression of behaviors that are also genetically determined [124]. Epigenetics, changes in gene expression, is one factor of many that bridges the gap between genetics and environmental factors. Epigenetic modifications, including the methylation of deoxyribonucleic acid (DNA), can be influenced by various environmental factors, including stress and eating behavior. Methylation of the dopaminergic genes dopamine receptor D2 (DRD2) and dopamine active transporter 1 gene (DAT1) have been exhibited in patients with AN [122]. However, others investigators have noted only a small overlap between genetically determined and environmental risk factors. Thus, there is considerable independence between these two types of risk factors in the development of an eating disorder [26, 125–129].

The behavior components of BN, such as, self-induced vomiting, have also been found to be inheritable [130]. Some have suggested that overeating or behaviors consistent with BN are related to genetically determined, dysfunctional neurotransmitter systems [131].

It is clearly understood that genetics significantly contribute to the etiology and development of BN, however, details of genetic contributions to AN remain uncertain [132]. Recent studies have suggested that focusing on the level of severity of AN, instead of simply the presence of AN, when selecting subjects is beneficial when examining genetic contributions [128]. It is a challenge to understand the link between heritability and EDs because no certain gene(s) have been connected with eating disorder phenotypes [2]. It is also estimated that it is the small contributions of many genes instead of large contributions from a few genes that aid in the development of an ED [128]. An inherent limitation in the research methodology is the difficulty in linking the symptoms of both AN and BN to one single variable, such as genetics [132].

11.4.2 Neurotransmitters and Neuropeptides

11.4.2.1 Serotonin and Tryptophan

The ingestion of food produces chemical changes in the brain that cause a variety of neurochemical responses throughout the body. Specific hormones are released to create instructional pathways for neural communication. Tryptophan is an essential amino acid that is found in many common foods, such as nuts, meats, and dairy products, and is a precursor for serotonin (5-HT). Therefore, dietary deficiency of tryptophan may lead to low levels of 5-HT. Low levels of tryptophan and 5-HT are commonly seen in individuals with psychological disorders, such as depression, AN and BN [132, 133]. A decrease in 5-HT can contribute to the abnormal eating patterns seen in individuals with BN by interfering with the homeostatic regulation of eating by the hypothalamus [134].

Serotonin is a monoamine neurotransmitter that helps the body regulate appetite, sleep patterns, and mood. As stated previously, 5-HT is biochemically derived from tryptophan and is primarily found in the gastrointestinal tract, platelets, and central nervous system of humans and animals. Regulation of serotonin is important in the pathophysiology of an ED [135, 136]. Serotonin is responsible for regulation or involvement in some of the main functions of the central nervous system, such as: control of mood, appetite, sleep, muscle contraction, pain sensitivity, blood pressure, and some cognitive functions including memory and learning [137, 138].

Serotonin transports, especially the serotonin transport protein 5-HTT (or SERT), are considered good markers for gene studies focused on eating disorders [139]. Serotonin is involved in the etiology of AN by altering physiological and behavioral functions that affect mood, impulse regulation and appetite [139]. Serotonin also influences the hyperactivity associated with AN [132]. Serotonin is likely involved in the etiology of BN by modulating physiological and behavioral functions including anxiety, perception, and appetite [140].

11.4.2.2 Neural Signaling Response to Food Consumption

The neural signaling that occurs in response to food consumption is a link in the feedback mechanisms that normally keep carbohydrate and protein intake more or less constant [141]. Carbohydrate consumption causes insulin secretion which also increases 5-HT release, whereas the consumption of protein lacks this effect on insulin. The consumption of carbohydrates causes the secretion of insulin from the pancreas into the blood, reducing plasma levels of glucose and allowing the uptake of tryptophan in the brain. Tryptophan enhances 5-HT release and also increases the saturation of tryptophan hydroxylase [136, 141]. Hydroxylase is the enzyme responsible for 5-HT synthesis. When BN patients are given a pharmacological stimulus for the production of 5-HT (serotonin-stimulated prolactin secretion), the number of their eating binges decreases [134].

Other investigators have suggested that protein should be added to the diet of BN patients in order to reduce binge eating [142]. Wurtman and Wurtman [136] reported that individuals whose eating binges consist of primarily protein have fewer eating binges than those whose eating binges consist primarily of carbohydrates [136]. In that study, individuals with BN reported less hunger and greater fullness, and consumed less food at test meals, after protein intake than after carbohydrate intake (673 kcal vs. 856 kcal). This discrepancy between protein and carbohydrate consumption during eating binges deserves attention in future research.

11.4.2.3 Receptor Subtypes for Serotinin

The pharmacology of 5-HT is extremely complex, with its actions being mediated by a large and diverse range of 5-HT receptors. At least seven different receptor subtypes (5-HT1–7) are known to exist, each located in different parts of the body and triggering different responses. Serotonin receptors include: 5HT1Dβ, 5HT2A, 5HT2C, and 5-HT7 tryptophan hydroxylase 1. Associations between a functional variant in the 5-HT transporter gene have been found with other psychiatric symptoms such as depression, alcoholism, and suicidal behavior [143]. Alleles are different forms of the DNA sequence of a particular gene. By conferring the allele-specific transcriptional activity on the 5-HT transporter gene promoter in humans, it has been found that the 5-HT transporter gene-linked polymorphic region (5-HTTLPR-a serotonin-transporter-linked promoter region) influences a constellation of personality traits related to anxiety and increases the risk for neurodevelopmental, neurodegenerative, and psychiatric disorders [144]. The S, G, and A alleles have been implicated in the transmission of an ED from mother to child [145]. It has been hypothesized that alterations in the S-allele contributes to the pathophysiology of AN and binge eating [139, 146]. Simply carrying the S-allele increases risk of AN and binge eating [139, 147].

Particularly the 5-HTTLPR (serotonin-transporter-linked promoter region) S-allele has been linked to AN, high anxiety and low levels of impulsiveness in some studies [139]. A study by Akkermann et al. [147], investigated the association between the 5-HTTLPR and binge eating to determine if the 5-HTTLPR genotype influenced the severity of binge eating. Women prone to binge eating and carrying the S-allele showed significantly higher levels of BN scores. Among these women, those with s/s genotype also had higher levels of state anxiety and a tendency for higher impulsivity [147].

Not all researchers are in agreement about the relationship of the S-allele and the pathophysiology of BN. Lee [148] found that overall EDs were significantly associated with the S-allele

and genotype, but a meta-analysis led to the conclusion that while AN was associated with the S-allele and the S carrier genotype, BN was not associated with this allele [148]. Racine et al. [149] found that the T-allele and the S-allele gene were associated with higher levels of impulsivity, but there were no main effects for the 5-HT genotypes on any binge eating measure, and interaction between genotypes, impulsivity, and dietary restraint were nonsignificant [149].

11.4.2.4 Dopamine

Another important neurotransmitter (neural messenger) that merits discussion in the pathophysiology of both AN and BN is dopamine (DOP). Dopamine is classified as a catecholamine (a class of molecules that serve as neurotransmitters and hormones). Dopamine is a precursor (forerunner) of adrenaline and another closely related molecule, noradrenaline. Central DOP mechanisms are involved in the reward and motivational aspects of eating and food choices, and they play a role in the compulsive feeding patterns observed in BN and purging disorders [150]. Foods high in fats and sugars are likely to promote DOP stimulation [151]. It has been hypothesized that deficiencies in DOP may promote reward-seeking behaviors that result in instant gratification such as carbohydrate eating binges [152–154]. The role of DOP in the pathophysiology of AN remains unclear. Some studies have shown reduced DOP levels in certain regions of the brain (the hippocampus, dorsal striatum, and hypothalamus) to be associated with starvation/food restriction in AN [155]. Also, DOP can contribute to the hyperactive characteristic in AN patients via increased concentrations of DOP in the hypothalamus [155]. However, the complexity of the body's systems and number of different pathways and receptors make targeting the role/concentration of DOP in the pathophysiology of both AN and BN difficult.

11.4.2.5 Catechol-*O*-methyltransferase

Although not classified as a neurotransmitter, catechol-*O*-methyltransferase (COMT) is an important protein in the degradation of DOP and other catecholamines in the brain, so it deserves attention in the discussion of eating disorders. It is one of several enzymes that degrade catecholamines such as DOP, epinephrine, and norepinephrine. Dysregulation of DOP has been implicated in many genetic studies related to BN [150, 151].

The COMT gene lies in a chromosomal region that is of interest in investigations of psychosis and mood disorders [145]. In particular, regions on chromosome 10 have been linked to BN and obesity [156]. However, despite a considerable research effort, a clear relationship between the genetic variation in specific chromosomes and the psychiatric phenotype has not been substantiated [157].

11.4.3 Peptides and Proteins

Individuals with an ED are less sensitive to the satiating effects of food [158, 159]. For example, after eating BN patients report lower subjective ratings of fullness than other individuals [159]. Ample evidence supports the notion that individuals with BN have a disturbance in satiation, which helps to explain the consumption of very large amounts of food that is recorded during binge meals in laboratory settings [159–163].

There are several specific physiological mechanisms that help to explain the deficit in the normal development of satiation when individuals with an ED consume food. Peptide signals from surrounding tissues communicate with the hypothalamus to control hunger and eating behavior [122]. Abnormal levels of leptin, ghrelin (the satiety peptide), cholecystokinin (CCK), and androgens have all been implicated as playing a role in food intake, satiety signaling and binge-eating behavior [164].

11.4.3.1 Leptin

Leptin is a protein hormone that plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism. It is one of the most important adipose-derived hormones [165]. Certain levels of leptin must exist in order to support menstruation; consequently low leptin levels have been linked with amenorrhea.

Low leptin levels have also been associated with AN [166, 167]. Some studies have found that individuals with BN have low levels of serum leptin [112, 168–170]. However, one study found that leptin concentrations were significantly higher in patients with BN than they were for individuals in a comparison group [171]. There is also no consensus among researchers examining ED patients about whether plasma levels of leptin are significantly related with patients' body weight or BMI [172–177].

Ghrelin is a hormone that stimulates hunger that is produced mainly by P/D1 cells lining the fundus of the human stomach and by the epsilon cells of the pancreas. Ghrelin levels increase before meals and decrease after meals. It is considered the counterpart to the hormone leptin, produced by adipose tissue, which induces satiation when present at higher levels. Both acute and chronic fasting increase ghrelin levels [122, 178]. Weight loss brought about by dieting causes ghrelin levels to rise as body weight and body fat decline. Ghrelin may blunt the appetite-reducing effect of leptin [179].

11.4.3.2 Ghrelin

Because ghrelin levels increase before meals, it would be expected that ghrelin levels are higher in individuals in the acute stage of AN. Research has found this to be true. The effects of ghrelin are unclear in those who chronically suffer from AN. However, research has shown that ghrelin levels drop in individuals with AN who are receiving treatment. This information could explain why AN patients are even more resistant to food during treatment, making the recovery process very difficult [30].

It has been suggested that individuals with BN have high ghrelin levels [180]. Supporting the hypothesis that individuals with BN have high ghrelin levels, Kojima et al. [180]. found that patients with BN exhibit elevated ghrelin levels before meals and reduced ghrelin suppression after eating. They found that postprandial ghrelin suppression was significantly attenuated in patients with BN compared to individuals who did not have BN [180]. Monteleone et al. [179] also found that the ghrelin levels of individuals with BN did not decrease as much as would be expected after a meal. In healthy women, circulating ghrelin showed a drastic decrease after food intake, whereas this response was significantly blunted for individuals with BN. The blunted ghrelin response to food ingestion for individuals with BN may explain the impaired suppression of the drive to eat following a meal, which can lead to binge eating [179]. Elevated ghrelin levels have all been found to decrease significantly after treatment, despite similar BMI, percent body fat, and leptin levels [169]. When ghrelin levels return to normal for an individual with an ED, abnormal eating behavior and depressive symptoms both improve [169].

11.4.3.3 Cholecystokinin

Cholecystokinin (CCK) is a peptide hormone of the gastrointestinal system responsible for stimulating the digestion of fat and protein. It also acts as a hunger suppressant and contributes to the feeling of satiation [181]. Individuals with BN have a reduced level of postprandial CCK compared to individuals who do not have EDs [160, 182–185].

The development of CCK and satiety has been greatly explored in BN, including gastric capacity, gastric emptying, gastric relaxation reflex and the postprandial release of CCK [41]. A significant enlarged gastric capacity has been found in women with BN compared to non-BN women [186]. This suggests that a larger amount of food must be consumed before the development of gastric signals. Along with this gastrointestinal abnormality, gastric emptying has found to be delayed in women with BN [182, 187–189]. As a result of this irregularity, there may be a delay in the development of satiety cues that result from the presence of food in the intestine. Finally, another gastrointestinal problem that arises with BN is that there is a reduced gastric relaxation occurring following food ingestion [190].

11.4.3.4 Brain-Derived Neurotrophic Factor

Lastly, certain proteins, such as brain-derived neurotrophic factor (BDNF), have been implicated in the etiology of an ED. This protein may

influence an individual's vulnerability to AN and BN [156] via regulation of apatite control [122]. Specifically, the genetic contribution of the BDNF-specific receptor neurotrophic tyrosine kinase receptor type 2 (NTRK2), is implicated in the susceptibility of developing an ED [191]. In most candidate gene association studies (CGASs), decreased levels of BDNF are typically present in those with AN [122].

It is important to note the difficulty in linking protein levels to genetic traits associated with an eating disorder. If protein levels return to normal with restored weight and proper nutrition, the disturbed protein levels may be related to improper nutrition rather than the traits associated with the eating disorder [122].

11.5 Future Directions

11.5.1 Anorexia Nervosa

> The treatment of patients with anorexia nervosa is both a science and an art. The science deals with the physical aspects that resulted from undernutrition, and the art deals with the person in whom the disorder exists [47].

Individuals with AN frequently lack insight into their problems and often deny the existence of problems related to eating. They are often reluctant to seek help from friends, family members, or health professionals, because the eating disorder becomes a lifestyle and they fear changing their habits and gaining weight. When they do seek help on their own, it may be due to severe distress over physical or psychological problems that occur as a result of the eating disorder or in conjunction with the eating disorder. In an attempt to conceal their disorder from health professionals, individuals with AN may try to hide signs of this disorder or might provide inaccurate information to the clinician [47]. For example, an individual with AN might drink a lot of water prior to being weighed by a professional or might hide weights in her clothing to increase the number on the scale.

Treatment must be specific to each individual because of the different levels of severity and because of the unique characteristics each individual with AN develops [47]. Effective treatment of individuals with AN should include weight restoration and restoring healthy eating habits. However, successful treatment of AN requires more than a focus on eating and weight gain. Focus on emotional issues that are related to the disorder and family conflicts that contribute to the disorder are also needed [47].

Successful treatment depends on the individual with AN gaining weight and maintaining a normal weight and adequate nutrition. Initially in treatment, the focus is on supporting the individual with AN and building a cooperative relationship with her while she gains weight. Because of the cognitive impairments resulting from semi-starvation, it will be difficult to deal with emotional and interpersonal problems until the individual's weight returns to the normal range [47]. Sometimes, however, the focus on weight gain may be too narrow, so that the person gains weight during treatment, but has not accepted that weight gain or changed her attitudes and perceptions related to weight and eating. Many patients with anorexia gain weight in treatment but then lose it soon after leaving treatment. Also, some treatment programs focus on rapid weight gain, which will be difficult for the individual with anorexia both psychologically and physically, and may expose the individual to some serious health risks, such as heart failure [47].

Weight restoration must be done gradually and patiently. Additionally, returning the individual with AN to a normal pattern of eating can be either easily accomplished or extremely difficult, depending on how long the disorder has persisted. She may rebel against a 2,000–3,000-cal diet because she will feel as though she is being overfed and may therefore also stop cooperating with other aspects of treatment. Therefore, enlisting the help of a dietitian can assist in educating the person about her nutritional needs. However, including too many professionals into the treatment might pose problems for the person being treated for AN, so an ideal approach might be for the therapist to work closely with the nutritionist [47]. There are also physical reasons that she will be unable to resume a normal diet immediately.

Attempting rapid weight gain in a person who has been starving may lead to excessive fluid retention with a risk of heart failure. In addition, any nourishment may be difficult for her because of her empty and shrunken stomach. So, eating may trigger nausea and vomiting, and these physical responses must be carefully distinguished from common psychological variables, such as revulsion at food and self-induced vomiting [47]. Without early, aggressive intervention, AN will most likely last for several years, and it may persist or reoccur throughout the individual's life [47]. Long-term follow-up studies reveal a mortality rate as high as 18 %, with the majority of deaths related to medical complications of the disorder [39].

Current research is focusing on the use of ghrelin agonists/antagonists and the treatment of eating disorders; however, most studies are animal based studies and only few studies have used human subjects in regards to AN. For example, ghrelin antagonists have been found to reduce the hyperactivity associated with AN but may cause appetite depression. Therefore, treatment with ghrelin antagonists is controversial. Ghrelin agonists are a possible treatment option for AN-R due to the resultant increase in food intake seen in human subjects. Yet, larger studies using human subjects are needed to clearly understand the relationship between ghrelin and AN-R and more studies need to focus on ghrelin and the AN-BP subtype [30]. Serotonin is also being considered for the use of AN treatment [132].

11.5.2 Bulimia Nervosa

There are many effective treatment options for individuals with BN, such as pharmacology (most commonly anti-depressant medications) [192], psychological treatment, therapeutic exercise such as yoga, and behavioral modification. Cognitive behavior therapy is effective in reducing the symptoms of BN and BED [193]. However, even though improvement over a short-term period is commonly found in the research literature, treatment may have a more limited effect over the longer term [194]. Vigilance is needed in helping girls and women to have healthy eating patterns and to avoid BN and other EDs in a culture that places so much emphasis on physical appearance and has such unrealistic ideals regarding the weight and shape of the human body.

It would be great if EDs could be prevented from occurring (primary prevention), but that goal seems unattainable based on the research on past prevention programs. Efforts to prevent EDs shave produced temporary results, a change in knowledge but no change in attitudes or behavior, or an increase in symptoms of eating disorders [195–197]. Unfortunately, prevention efforts can lead girls and young women to focus even more than they had before on their bodies and on dieting, and may promote unhealthy behaviors among especially vulnerable girls [47]. Another reason that primary prevention is so difficult is that any prevention programs are unlikely to have as much of an effect on girls and young women as the influence of their peers and of media messages. Therefore, the best type of prevention for an ED may be secondary prevention—identifying the early signs of trouble and starting treatment as soon as possible.

11.5.3 Secondary Prevention and Education

Health professionals must be educated about the dangers and warning signs of EDs to promote early recognition, evaluation, and treatment. Parents, teachers, and coaches who recognize common signs of an eating disorder in girls or young women should express their concerns to these individuals and their parents and should also encourage them to seek further evaluation. Because individuals often develop an eating disorder in the aftermath of a diet, overweight individuals should be encouraged to lose weight through nutritionally balanced meals and exercise rather than by strict dieting that can trigger binge eating and purging cycles [49]. Health professionals must develop realistic attitudes about body weight and shape in order to communicate information effectively and to promote appropriate preventive efforts.

Early diagnosis of an ED is related to a better prognosis because the patient is more receptive to treatment. Earlier diagnosis is an important first step for many patients and allows for intervention before the adverse eating patterns are ingrained due to repetition [85]. Vigilant friends and family can notice signs and symptoms of the ED and attempt to seek proper help. If an ED is suspected, one of the most practical screening tools to use in the primary care setting is the SCOFF questionnaire [198]. Because of its 12.5 % false-positive rate, this test is not sufficiently accurate for diagnosing eating disorders, but it is an appropriate screening tool that physicians can use as a first step in identifying and treating the ED. Although a substantial amount of progress has been made in the field of eating disorder research and treatment, there are still many questions without answers. By reading this book, you will see where we are on the journey towards better understanding and treating eating disorders.

11.6 Concluding Remarks

The key feature of AN is the refusal of the girl or woman to eat an adequate amount of food [47]. BN is an eating disorder that involves binge eating and the use of inappropriate methods to avoid weight gain [199]. There are also shared qualities, as more than half of patients diagnosed with AN-R crossover to AN-BP and approximately one-third crossover to BN during the first 5 years of being diagnosed with an eating disorder [200].

All of the physiological changes that occur in AN are caused by malnutrition or "semi-starvation" [47]. Those changes are the adaptive responses of the body to survive despite inadequate intake of food: conservation of energy, shifts in electrolyte balances, attempts to use fat and spare the body's glucose and protein, and changes in the functioning of the hypothalamus and the pituitary gland.

With fluctuating eating patterns, individuals with BN are at risk for developing cardiovascular health problems [105] such as coronary artery disease, hypertension, and congestive heart failure [107–111]. Many other adverse health conditions are also associated with the disorder such as alcoholism, panic disorder, generalized anxiety disorder, phobia, and major depression [119]. Two of the most prevalent co-occurring conditions for individuals with BN are anxiety and depression [201].

Both genetics and environmental factors (culture and family) play large roles in the behavioral, neurobiological, and temperamental variables that represent the core features of ED development. The family environment is especially important in the development of an ED, since adolescence is a particularly vulnerable age for females [199].

The psychological and physiological aspects of BN are often tightly linked [202]. Biomarkers associated with BN include, but are not limited to the dysregulation of hormones that contribute to irregular dieting behaviors, possibly through serotonergic mechanisms [41]. Alterations in 5-HT and DOP can result in the dysregulation of mood, satiety, appetite, sleep, muscle contraction, and some cognitive functions including memory and learning [137, 138]. Research does not indicate a direct relationship between pathophysiological markers and the diagnosis of AN [128].

The initial evaluation of an individual with an eating disorder must include a comprehensive physical exam and health history to rule out existing physiological pathology. Several lab tests, including a complete blood count (i.e., full blood chemistry, electrolyte profile, liver and function tests, and urinalysis) should also be performed. An EKG is essential to evaluate the cardiovascular system and to rule out potentially life-threatening arrhythmias, and a chest X-ray may be performed to evaluate heart size and placement [63].

A number of long-term complications may result from the prolonged and severe malnutrition that often accompanies eating disorders. Medical complications can be expected to progress as long as the individual continues to exercise without proper nutritional intake [64]. Inadequate nutritional intake and poor absorption of nutrients result in physical consequences, including extreme weight loss, electrolyte imbalances,

cardiac abnormalities, hormonal changes, central nervous system abnormalities, bone loss, and muscle wasting. Unfortunately, these physical consequences can result in death; therefore, adequate nutritional intake and weight restoration are vital in the treatment of an ED [39].

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