THE ROLE OF THE CENTRAL NERVOUS SYSTEM IN THE PSYCHONEUROENDOCRINE DISTURBANCES OF ANOREXIA AND BULIMIA NERVOSA

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CLINICAL DESCRIPTION OF ANOREXIA NERVOSA AND BULIMIA NERVOSA

Anorexia nervosa (AN) and bulimia nervosa (BN) are disorders of unknown origin that most commonly occur in women and usually have their onset in adolescence. The prevalence of AN and BN is approximately 0.5% to 1% and 1% to 3% respectively. Women with eating disorders invariably have a distorted body image and an intense fear of weight gain. Comorbid psychiatric disorders and symptoms are often present, including depression, anxiety disorders, obsessive compulsive disorder (OCD), as well as alcohol and other substance abuse.

Women with AN lose considerable body weight. To meet DSM-IV criteria for AN body weight must fall below 85% of ideal. AN is further classified as either of the restricting or binge-eating/purging type on the basis of whether or not binge-eating or purging behaviors are present. Both types of AN will be referred to as simply AN in this article. DSM-IV criteria for BN essentially involve regular, repeated binge-purge cycles with undue concern about body shape and weight in the absence of AN. BN may be further classified into either a purging or nonpurging type, on the basis of whether or not engagement in...
vomiting, laxatives, diuretics, or enemas has occurred. Both types of BN will be referred to as simply normal weight bulimia or BN in this article.

AN and BN have considerable morbidity and mortality. In fact the death rate of AN is 0.05% per year. While many people with AN and BN have a chronic course, approximately 30% to 60% recover over the long term. Over the past decade substantial gains have been made in devising specific psychologic therapies for these disorders. Moreover, psychopharmacologic studies suggest that antidepressants are useful in the acute treatment of BN.53,102 A recent study by our group showed that serotonin specific uptake inhibitor (fluoxetine) improved outcome in AN.52

NEUROENDOCRINE STUDIES IN ANOREXIA NERVOSA AND BULIMIA NERVOSA

It has been well recognized that endocrine disturbances are common in AN and BN.32,33,35,36 For example, (Table 1) it is well known that increased plasma levels of cortisol and growth hormone, a “euthyroid sick” T4 and T3 hormone profile, and decreased plasma gonadotrophin levels occur in AN and BN. Hormones such as prolactin, thyroid, growth hormone, and cortisol secretion contribute to fat, protein, and carbohydrate metabolism; they represent an important component in the regulatory mechanism for the disposition of metabolic fuels.54 Thus, it is not surprising that their secretion may be altered by malnutrition. It is important to emphasize that the peripheral endocrine abnormalities of both AN and BN reverse with clinical remission, indicating that they are “state” markers of starvation, and not traits.

Abnormal hormone secretions are most commonly found in malnourished

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<th>Table 1. NEUROENDOCRINOLOGIC FINDINGS IN ANOREXIA NERVOSA AND BULIMIA NERVOSA</th>
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<td>Anorexia Nervosa</td>
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<td>Peripheral cortisol</td>
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? not investigated/not known.
AN. In addition they are present, but to a lesser extent, in normal weight women with BN. The presence of starvation in AN is self-evident, but may not be recognized in normal weight bulimia. Although BN women often maintain a normal weight, they restrict eating when not binging and purging and may have monotonous and poorly balanced meal patterns. Pirkes found that fatty acid β-hydroxybutyric acid levels were elevated in ill BN and AN groups compared to controls. Starvation-induced depletion of hepatic glycogen stores results in free fatty acids and ketone bodies replacing glucose as the primary energy source. This shift from glycogenolysis to lipolysis and ketogenesis is associated with an increase in free fatty acids and their metabolites (i.e., β-hydroxybutyric acid) in plasma. These data show that BN subjects are nutritionally depleted in spite of their normal body weight.

The relationship of starvation and eating disorders is most clearly seen for menstrual function. Amenorrhea is required for the diagnosis of AN while oligomenorrhea occurs in approximately half of BN subjects. Similarly the pervasiveness of decreased luteinizing hormone in AN appears universal while only those BN subjects who are less than 85% of their previous high weight appear to have decreased luteinizing hormone levels.

Studies of the effects of reduced caloric intake on peripheral endocrine systems have been done in healthy women. When healthy control women were starved, they developed increased plasma levels of cortisol and of growth hormone as well as changes in thyroid hormones (normal plasma T4 and decreased plasma T3 levels). T4 essentially acts as a prohormone which is subsequently converted to the metabolically active T3 form. This euthyroid sick thyroid profile helps to reduce energy expenditure and to minimize structural protein loss in the use of amino acids for gluconeogenesis. These studies also found a decrease in plasma gonadotropin levels. These endocrine abnormalities associated with starvation in the healthy women subjects reverses with the resumption of normal eating patterns.

Aside from the effects on hormonal secretion, starvation also exaggerates comorbid psychiatric symptoms in AN and BN. For example, Pollice found that malnutrition intensifies the severity of depression, anxiety, and obsessionality in AN. The Minnesota experiment by Keys found that semistarving male conscientious objectors to military service were associated with increased depression, irritability, labile mood, decreased concentration, decreased libido, and decreased motor activity. These changes appear consistent with features of AN or BN, further extending the idea of starvation-related “state” changes influencing the behavioral as well as the endocrine milieu of AN and BN.

CENTRAL NERVOUS SYSTEM NEUROPEPTIDE FUNCTION

The realization that peripheral hormonal disturbances are a consequence of starvation in AN and BN, and not a cause of their eating disorder psychopathology, has evolved over the past 10 to 20 years. Along with this realization an understanding of how CNS neuronal pathways contribute to starvation-induced alterations in peripheral hormonal secretion has developed. This article focuses on new findings about the CNS regulation of peripheral hormonal disturbances in AN and BN and how they may be affected by starvation.

Neuropeptides are signaling substances composed of several to more than 40 amino acids. Initially their actions in the brain were thought to be limited to the regulation of essential homeostatic bodily functions such as food and water consumption and metabolism, sexuality, sleep, body temperature, pain sensation,
and autonomic function. Neuropeptides have since been localized in the CNS outside of the hypothalamus and pituitary and have been implicated in regulating more complex human behaviors such as obsessionality, mood states, risk taking, addiction, and the ability to form attachments. It is possible that some of the behavioral disturbances seen during starvation may be related to alterations in peptides.

Of particular interest to the field of AN and BN is that many neuropeptides, in concert with the monoamines, contribute to the regulation of feeding behavior. In fact, the mechanisms for controlling food intake involve complicated interplay between peripheral (i.e., taste, gastrointestinal peptides, vagal afferent nerves) and central nervous system neurotransmitters. Considerable data suggest that neurotransmitters have specific roles in regulating the structure of feeding. That is, neurotransmitters, such as norepinephrine, serotonin, opioids, and peptide YY (PYY) regulate the rate, duration, and size of meals, as well as the selection of carbohydrates and protein in animals. It is theoretically possible that the alterations in brain neuropeptide activity found in patients with AN or BN could contribute to a specific and systematic disturbance of the structure of feeding behavior.

**NEUROPEPTIDE Y AND PEPTIDE YY**

Neuropeptide Y (NPY) and PYY are thirty-six phylogenetically and structurally related amino-acid peptides that share the same super-family of receptors. These peptides are potent activators of feeding behavior in animals. NPY can be found in high concentrations in limbic structures including the hypothalamus, but is also present throughout cerebral cortex. NPY is secreted by the hypothalamic arcuate nucleus, from which it acts on the PVN hypothalamic nucleus. This activation of the PVN helps mediate increased eating, especially of carbohydrate-rich sweet foods, and reduces energy expenditure. PYY in contrast is present in the CNS at lower levels and is located in caudal brainstem and spinal cord. PYY is primarily located peripherally in endocrine cells of the lower gastrointestinal tract, where it helps mediate gastrointestinal motility and function.

Our group found that underweight anorexics had significantly elevated concentrations of cerebrospinal fluid NPY compared to healthy volunteers. In contrast, patients with AN, whether underweight or recovered, had normal CSF PYY concentrations. CSF NPY levels appeared to return to normal with recovery, although AN with amenorrhea continued to have higher CSF NPY levels. Animal studies show that increased NPY activity may represent a homeostatic mechanism to stimulate feeding. However, elevated cerebrospinal fluid NPY levels appear to be an ineffective stimulant of feeding in underweight anorexics since they are notoriously resistant to eating and weight restoration. It is important to note, however, that anorexics typically display an obsessive and paradoxical interest in dietary intake and food preparation. We cannot discount the possibility that increased NPY activity could contribute to these cognitions. Alternatively, chronic elevation of NPY could be associated with a down-regulation of the NPY receptors that modulate feeding in AN.

It is important to note that intracerebroventricular NPY administration to experimental animals produces many of the physiologic and behavioral changes classically associated with anorexia nervosa. That is, NPY administration has gonadal steroid dependent effects on luteinizing hormone secretion, suppresses
sexual activity increases corticotropin releasing hormone in the hypothalamus and produces hypotension.

Morley and colleagues found that PYY, injected ICV into rats, caused massive food ingestion to which tolerance did not develop. This powerful effect on feeding behavior in animals prompted the speculation that increased activity of PYY may contribute to bulimia. CSF PYY values for normal weight bulimic women studied when binging and vomiting were similar to controls. In contrast, CSF PYY concentrations were significantly elevated in bulimic women studied after a month of abstinence from binging and vomiting compared to healthy volunteer women and patients with AN. This CSF PYY finding has been confirmed in a new and larger group of normal weight bulimic women (Lesem M, personal communication, Washington, DC, 1986). In contrast to AN, EN patients had normal CSF NPY levels.

It is not known why CSF PYY values were normal when bulimics were studied near in time to chronic binging and vomiting behavior, yet were elevated after 30 days of abstinence. Because it is possible that dietary intake or emesis may effect CNS PYY in humans, future studies will need to determine whether chronic binging and vomiting behavior, or other state-related factors can reset the modulation of CNS PYY so that an abrupt cessation of binging and vomiting results in an overshoot of CNS PYY secretion. This appears to be possible since we have recently found normal CSF PYY levels (unpublished data) in BN women recovered for more than a year. Whatever the cause of the high CSF PYY during short-term abstinence it should be emphasized that this disturbance is of potential importance. Normal weight bulimia is a disorder with a high rate of recidivism despite treatment. Abnormally elevated CNS PYY activity in the abstinent state may contribute to a persistent drive in feeding behavior, particularly a desire for sweet foods, and the resumption of binging behavior.

LEPTIN

Leptin is the recently discovered hormone product of the mouse ob gene and human homologue gene, LEP. Leptin is secreted predominantly by adipose tissue cells, and it is thought to act as an afferent signal and regulator of body fat stores. It is thought that leptin activates receptors encoded by the db gene in the hypothalamus and ob receptors in the choroid plexus. In rodent models, defects in the leptin coding sequence resulting in leptin deficiency, or defects in leptin receptors are associated with obesity. Treatment with recombinant leptin can significantly reduce fat mass in obese and also normal weight animals in a dosage dependent manner. In humans, leptin is positively correlated with fat mass in individuals in all weight ranges and women tend to have higher concentrations than men of the same weight, presumably because of the higher proportion of body fat in females. Obesity in humans is not thought to be a result of leptin deficiency per se, but it is postulated that obesity may be associated with leptin resistance.

Malnourished and underweight AN have consistently been found to have significantly reduced plasma and CSF leptin concentrations compared to normal weight controls. This strongly implies a normal physiologic response to starvation. Mantzoros et al also reported an elevated CSF to plasma leptin ratio in AN compared to controls suggesting that the proportional decrease in leptin levels with weight loss is greater in plasma than in CSF. Similar to normal control women, leptin levels in AN are correlated with body weight and fat.
A longitudinal investigation during refeeding in anorexia nervosa patients has shown that CSF leptin concentrations reach normal values before full weight restoration, possibly as a consequence of the relatively rapid and disproportionate accumulation of fat during refeeding. This finding led the authors to suggest that premature normalization of leptin concentration might contribute to difficulty in achieving and sustaining a normal weight in AN.

Less work has examined the leptin status of individuals with BN. To date, one study has found that serum leptin concentrations in ill bulimics are similar to those of normal control women and are correlated with body mass. Recent studies from our group (unpublished data) show that plasma and CSF leptin levels are normal in long-term recovered AN and BN subjects. Taken together these data on AN and BN suggest that, similar to normal individuals, leptin is correlated with body weight and is not involved in the origin of these disorders. However leptin may still play a role in symptoms in these disorders in ill states.

Recent studies have suggested that leptin also modulates fertility. Leptin administration restores reproductive function in infertile ob/ob mice and in prepubertal mice. Although feeding of normal meals has been reported not to affect plasma leptin levels or ob mRNA expression in lean and obese humans, animal studies have found that acute fasting and refeeding rapidly decreases and increases (respectively) ob mRNA expression and that overfeeding (without weight gain) increases ob mRNA expression. Such findings have led to speculation that leptin is the metabolic signal which mediates impaired reproductive ability in conditions of extreme overweight and underweight. The potential relationship between leptin and amenorrhea in AN has been demonstrated by Kopp et al who found that leptin concentration below 1.85 μg L⁻¹ predicted lifetime occurrence of amenorrhea.

Leptin appears to play an important role in triggering adaptive response to starvation. Since weight loss generally causes leptin levels to fall in proportion to the loss of body fat mass. Acute fasting-induced weight loss appears to provoke a fall in leptin concentration that is disproportionately greater than would be expected from the amount of fat lost. This suggests that under conditions of intense food deprivation, leptin may act as an initial warning signal, instigating metabolic responses to famine, even before a significant weight/fat loss has occurred. Indeed, reduced leptin concentrations have been found to be a critical signal that initiates the neuroendocrine response to starvation, including limiting procreation, decreasing thyroid thermogenesis, and increasing secretion of stress steroids. Specifically, administration of leptin during a period of fasting partially restores testosterone and luteinizing hormone concentrations, blunts falling thyroxine levels and attenuates the rise in corticosterone and adrenocorticotropin hormone (ACTH). Leptin has these effects without affecting plasma concentrations of insulin, glucose, or ketone bodies. However, during starvation concentrations of neuropeptide Y (NPY) (a potent appetite stimulator) rise and NPY inhibits gonadotropin release and activates the HPA axis. Since leptin also inhibits starvation-induced elevations in NPY, it is likely that leptin reverses the effects of starvation by regulating the amount of hypothalamic NPY messenger RNA. In addition to decreasing NPY synthesis or inhibiting its action as an appetite stimulant, leptin is thought to decrease food intake and reduce body weight by increasing metabolic rate through activation of beta-adrenergic receptors and possibly by having its own, or other peptidemediated anorexigenic properties.
CORTICOTROPIN RELEASING HORMONE (CRH)

It is well recognized that underweight anorexics have increased plasma cortisol secretion.16,107 There has been considerable controversy concerning the pathophysiology of hypercortisolism in AN. Recent studies12,41 have supported the probability that hypercortisolism in AN is due to hypersecretion of endogenous corticotropin releasing hormone (CRH). In fact, several studies52,61 have reported elevated cerebrospinal fluid CRH levels in underweight anorexics. However, there is a normalization of elevated levels of cerebrospinal fluid CRH levels after weight gain that is associated with relative normalization of pituitary-adrenal function. Hypersecretion of CRH in underweight anorectic patients may represent a response to weight loss per se.8,29,93 Nonetheless, increased CNS CRH activity is of great theoretic interest in AN since intracerebroventricular CRH administration to experimental animals produces many of the physiologic and behavioral changes classically associated with AN, including hypothalamic hypogonadism,66 decreased sexual activity,42 decreased feeding behavior15 and hyperactivity.47 In addition, a positive relationship between hypersecretion of CRH and depression in the weight-corrected anorexics has been found. CRH hypersecretion has been linked to the symptom complex of depression.81,90

OPIOID PEPTIDES

A question has been raised as to whether altered endogenous opioid activity might contribute to disturbed feeding behavior in the eating disorders.28,72,76,98 Such speculation has been fueled by considerable data, derived primarily from animal experimentation,79 which suggests that opioid agonists increase and opioid antagonists decrease food intake. It should be noted that assessment of brain opioid activity is problematic in vivo in humans. First, there are multiple neuropeptides in the central nervous system that have opioid activity and there are a multiplicity of opioid receptors in the brain. We are not able to measure the functional activity of these peptides or receptors in vivo in humans. Second, peripheral assessment of opioid activity are compromised by the relative nonspecificity of pharmacologic probes and the probability that peripheral measures may not reflect CNS opioid function.

The relative activity of a few opioid peptides can be assessed by measuring levels of these peptides in CSF. Our group60 reported that underweight anorexics had significantly reduced cerebrospinal fluid β-endorphin concentrations compared to healthy volunteers. Cerebrospinal fluid β-endorphin levels remained significantly below normal after short-term weight restoration. Long-term weight-restored anorexics had normal cerebrospinal fluid β-endorphin concentrations. In addition, several studies have reported that CSF β-endorphin levels were reduced in women ill with BN14 (Kaye, unpublished data). β-endorphin has been shown to stimulate feeding behavior in rats when injected intraventricularly or into the medial hypothalamus.69,81 If we assume that β-endorphin activity contributes to feeding behavior in humans and hypothesize that reduced cerebrospinal fluid concentrations reflect decreased activity of this system, it is then possible that reduced β-endorphin activity contributes restricted eating in AN and BN.

Less is known about other opioid systems in eating disorders. CSF fluid dynorphin levels have been reported to be normal in all stages of AN66 and in ill BN patients.14,98 A radioisotope assay, which measures overall opioid activity, showed that underweight anorexics had an increase of cerebrospinal fluid opioid
activity. It should be noted that values of β-endorphin in cerebrospinal fluid were found to be less than 1% of the values for total opioid activity measured by the radioreceptor assay. Other investigators have reported a discrepancy between measurements of β-endorphin and total opioid activity. Thus, elevated concentrations of one or more of the other endogenous opioid peptide(s) may account for the radioreceptor assay results. Such a possibility remains to be explored.

Evidence of the involvement of opioid peptides in the mediation of the rewarding aspects of feeding has prompted studies examining the effects of the opioid receptor antagonists, naloxone and naltrexone, both in animals and humans. Repeated experiments have shown that opioid antagonists inhibit feeding and opioid agonists stimulate feeding in a variety of species including humans. Open trials of high dosages of naltrexone have been reported to reduce binge frequency in BN. However, several double-blind controlled trials using lower doses showed no effects on binge frequency or macro nutrient intake. A recent double-blind trial reported that a relatively high-dose naltrexone treatment reduced binge and purge frequency and total daily food intake, but it did not effect the ability of patients to resist the desire to binge or purge. Whether high-dose opioid antagonist treatment has a role in BN remains to be determined.

It is also possible that a disturbance of opioid function could contribute to neuroendocrine disturbances in eating disorders, such as disturbances of the HPA or HGA axis. Brain opioid pathways inhibit ACTH and cortisol release in humans and suppress pulsatile gonadotropin secretion in rats and sexually mature humans. Reproductive activity has been studied in AN by infusion of relatively nonspecific exogenous opiate antagonists. Most underweight anorexics have a blunted response of luteinizing hormone secretion after administration of opioid antagonists. Since weight restoration tends to normalize these findings, it is likely that nutritional status plays a role in abnormal luteinizing hormone response to opioid antagonists. However, the failure of opioid antagonists to increase luteinizing hormone secretion in underweight anorexics argues that some other neurotransmitter system(s) are responsible for inhibition of luteinizing hormone secretion.

**VASOPRESSIN AND OXYTOCIN**

Vasopressin and oxytocin are structurally related neuropeptides that are transported from the hypothalamus to the posterior pituitary for release into systemic circulation. In the periphery vasopressin controls free-water clearance of the kidney, whereas oxytocin promotes uterine contraction during parturition and milk let-down during the postpartum period. In addition, both are distributed in the brain, and function as long-acting neuromodulators and to exert complex behavioral effects. Oxytocin administration to rats disrupts memory consolidation and retrieval, whereas vasopressin administration enhances memory function. Importantly, effects of oxytocin appear to be reciprocal to the effects of vasopressin. For example, oxytocin antagonizes vasopressin’s promotion of consolidation of learning acquired during aversive conditioning. In addition, studies in humans show that oxytocin modulates activation of the hypothalamic pituitary adrenal axis by antagonizing vasopressin-induced ACTH release from the anterior pituitary.

Underweight patients with anorexia nervosa have abnormally high levels of centrally directed vasopressin in association with a profound defect in the
osmoregulation of plasma vasopressin. Gold et al and Demitrack et al found that underweight restrictor anorexics had reduced cerebrospinal fluid oxytocin levels. Underweight anorexics have also been found to have an impaired plasma oxytocin response to challenging stimuli. Such abnormalities tend to normalize after weight restoration suggesting that such changes may be secondary to malnutrition and abnormal fluid balance. Demitrack, Gold, and colleagues hypothesized that a low level of centrally directed oxytocin could act in concert with a high level of cerebrospinal fluid vasopressin in underweight anorexics so as to enhance the retention of cognitive distortions of the aversive consequences of eating. In other words, to impair the extinction of aversively conditioned learning. Such changes in these neuropeptides may exacerbate the tendency for restrictor anorexics to have perseverative preoccupation with the adverse consequences of food intake.

Patients with normal weight bulimia, on admission and after 1 month of nutritional stabilization and abstinence from binging and purging, had elevated CSF vasopressin concentrations but normal CSF oxytocin levels. Bulimic patients also had a significant reduction in the plasma vasopressin response to hypertonic saline. Such defects may aggravate the maintenance of adequate fluid volume and may contribute to their obsessional preoccupation with the aversive consequences of eating and weight gain.

Our group (unpublished data) has found that CSF levels of oxytocin and vasopressin are normal after long-term recovery from AN and BN. However, preliminary data suggests that high levels of oxytocin are associated with a lifetime history of anxious and obsessive traits in recovered subjects. These data suggest that oxytocin may not play a contributory role in the development of an eating disorder, but could play a role in determining whether co-morbid anxious/obsessive symptoms are present.

RELATIONSHIP OF NEUROPEPTIDE ALTERATIONS TO SYMPTOMS IN AN

The data cited above shows that multiple neuropeptide disturbances occur when people with AN and BN are engaged in pathologic eating behaviors and are malnourished. When these peptide systems have been studied after long-term recovery from AN, they have tended to be normal. Less work has been done in assessing these systems after recovery from BN, studies also suggest normalization of peptide function. The correction of these neuropeptide disturbance by weight-restoration in AN implies that such disturbances are secondary to malnutrition and weight loss and not the cause. Still, an understanding of these neuropeptide disturbances may shed light on why many anorexics cannot easily reverse their illness. First, weight loss and malnutrition appear to contribute to many anorexics entering a downward spiraling circle with malnutrition sustaining and perpetuating the desire for more weight loss and dieting. Symptoms, such as obsessions and dysphoric mood, may be exaggerated by these neuropeptide alterations and thus contribute to this downward spiral. Second, even after improved nutrition and weight gain, many people with AN have much difficulty normalizing their behavior. Since these neuropeptide disturbances do not appear to be a permanent feature or cause of anorexia nervosa, these disturbances are strongly entrenched and are not easily corrected by improved nutrition or short-term weight normalization. The fact that neuropeptide disturbances are not found after long-term recovery suggests that therapy must be sustained for months after weight normalization.
Table 2. HYPOTHETIC RELATIONSHIPS BETWEEN SYMPTOMS IN UNDERWEIGHT ANOREXICS AND NEUROPEPTIDE EFFECTS

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<tr>
<th></th>
<th>Underweight Anorexics</th>
<th>Increased NPY</th>
<th>Increased CRH</th>
<th>Decreased Leptin</th>
<th>Decreased β-endorphin</th>
<th>Increased Vasopressin</th>
<th>Decreased Oxytocin</th>
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Starvation-induced alterations of neuropeptide activity most clearly contribute to neuroendocrine dysfunctions in anorexia nervosa. For example, corticotropin releasing hormone alterations contribute to hypercortisolism and NPY alterations may contribute to amenorrhea. Normalization of brain neuropeptide systems tends to parallel the time frame for normalization of neuroendocrine function. The prolonged resumption of menses after weight correction particularly illustrates that many of these physiologic disturbances are not easily corrected by improved nutrition and may take months or even years to normalize. Alterations of neuropeptide activity (Table 2) could contribute to several other characteristic psychophysiological disturbances in acutely ill anorexics. For example, the consequences of malnutrition may perpetuate pathologic feeding behavior. Thus starvation-induced increases of corticotropin releasing hormone activity and reduced β-endorphin activity could reduce appetite. However, the same reasoning would suggest that elevated NPY activity would stimulate feeding. If such cerebrospinal fluid concentrations were to reflect the brain activity of these systems, these alterations might serve to increase the drive to feed. Underweight anorexics display an intense ambivalence about food. They resist eating and yet are inordinately preoccupied with diet and cooking. It is possible that the mixed signals about satiety and desire to feed could contribute to this confusing dissociation that anorexics often display between reduced caloric intake and obsessive thoughts about food. A relationship between neuropeptide abnormalities and cognitive or mood alterations is also possible. Disturbances of vasopressin and oxytocin could contribute to obsessive thoughts. It is well recognized that malnutrition causes substantial dysphoria in underweight anorexics and that weight restoration reduces such symptoms in most anorexics. Although speculative, it is possible that disturbances of opioids or CRH could be related to exaggeration of dysphoric symptoms in underweight anorexics.

In summary, these neuropeptide changes may explain why some anorexics develop a chronic, seemingly irreversible course. Because it may take weeks to months for improved nutrition and weight normalization to normalize these neuropeptide disturbances, it may be necessary to continue treatment for some anorexic patients for prolonged periods of time until brain neuropeptide systems have had time to normalize.

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body mass index but are independent of the respective disease. Clin Endocrinol 46:289–293, 1997
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