The Eating Disorders
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Chapter 17

New Neuroendocrine Findings in Anorexia Nervosa and Bulimia

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Anorexia nervosa is a disorder in which a patient deliberately loses weight and fails to maintain a minimal normal weight for his age and height. Bulimia nervosa is a disorder characterized by recurrent episodes of binge eating, often followed by purging of the food by vomiting. Both anorexia nervosa and bulimia are associated with pervasive endocrine dysfunction, including amenorrhea, oligomenorrhea, and thyroid disturbances. Early endocrine studies in anorectics demonstrated that the pituitary-ovarian axis showed abnormal regulation, with luteinizing hormone (LH) rhythms reverting to an immature prepubescent pattern. No studies of pituitary-ovarian function in normal-weight bulimics have yet been published. The advent of new technologies and pharmacologic challenges have made it possible to examine the hypothalamo-pituitary-adrenal (HPA) and hypothalamo-pituitary-thyroid (HPT) endocrine axes in greater detail. Inasmuch as these endocrine disturbances may parallel or reflect perturbations in mood, appetite, and behavior, they may have relevance to the etiologies of these illnesses.

HYPOTHALAMO-PITUITARY-ADRENAL (HPA) AXIS

Corticotropin-releasing factor (CRF) and thyrotropin-releasing hormone (TRH) are released by neurons in the hypothalamus and enter the pituitary portal system in the infundibulum, where they are transported to the anterior pituitary gland. Here they act upon receptors on the pituicytes to cause the release of adrenocorticotropic hormone (ACTH) and thyrotropin (TSH) respectively. Neurotransmitters appear to exert effects upon CRF, with serotonin and acetylcholine being stimulatory for the most part, and norepinephrine producing a tonic inhibitory effect [1,2,3]. Cortisol itself exerts both positive and negative feedback on ACTH, and possibly, also on CRF release. Much less is known about the neurotransmitter relationships with TRH, but the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) exert feedback inhibition on TSH and possibly also on TRH. Elevated glucorticoids also inhibit TSH release, and it has been speculated that hyperactivity of the HPA axis can cause a diminution of activity in the HPT axis [4].

In normal individuals there is a diurnal rhythm for cortisol, with an increasing number of secretory episodes occurring between 2 and 8 AM, resulting in a peak plasma level at approximately 8 AM. Then there is a gradual decline in plasma levels and secretory episodes throughout the day, leading to a nadir at approximately midnight and 2 AM [5-7]. Normally, cortisol is cleared by renal mechanisms and has an approximate half-life in plasma of 60 minutes [6]. Studies by Boyar and Doerr demonstrated that the diurnal curve in patients with low-weight anorexia is reset at a higher level and is distorted, with a more pronounced peak and loss of the

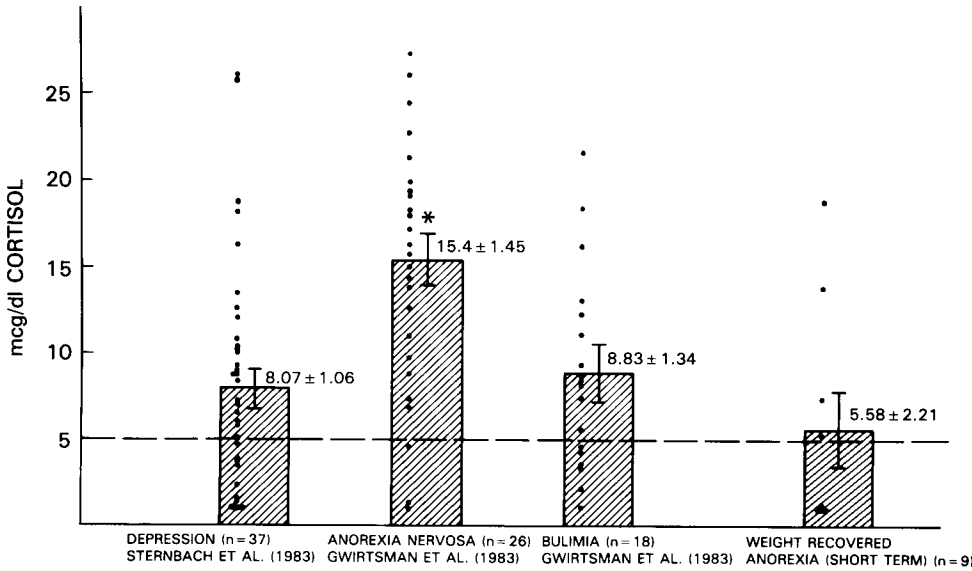


Figure 17.1 Underweight anorexic patients (AN) demonstrate the least amount of suppression to dexamethasone, with only 3 of 26 patients showing suppression below 5 mcg/dl. After short-term weight recovery, AN demonstrate more complete suppression, but a significant fraction still do not suppress. Depressives and bulimics demonstrate similar rates of nonsuppression.

nadir. Boyar felt that delayed degradation and abnormal metabolism of cortisol to tetrahydro-cortisone was the cause of this diurnal distortion, since the half-life of cortisol is prolonged to about 90 minutes in anorexia [8,9]. However, subsequent data from his own lab and by Doerr have shown that patients with anorexia show persistence of secretory bursts into the late evening, and overall, the cortisol production rate is increased in anorexia [6,9]. However, when anorexics regain weight, the diurnal cortisol pattern begins to return to normal [9,10].

In summary, then, the studies have demonstrated elevated plasma cortisols, elevated 24-hours mean plasma cortisol [7,8,11,12], distortion of the circadian cortisol rhythm, and prolonged plasma half-life of cortisol in anorexia nervosa [6-9,12]. These changes are precisely what is seen with pure protein-calorie malnutrition (PCM), and therefore probably represent an artifact of low weight or starvation [14-16]. However, there may be some differences between anorexia nervosa and pure malnutrition. First of all, the 24-hour output of urinary free cortisol (UFC) is elevated in the low-weight state of anorexia nervosa and returns to normal following weight recovery [10], while the UFC appears to be normal in malnutrition and shows no change after refeeding. This conclusion may be premature, because the excretion of free cortisol is dependent on glomerular filtration rates (GFR), and GFR may show a greater reduction in malnutrition than in anorexia. Secondly, cortisol production rate is elevated in anorexia nervosa, while it is diminished in PCM [15-17]. Furthermore, the cortisol production rate appears to decrease when patients with anorexia nervosa regain their weight, but it increases with weight recovery in PCM [10,15]. Thus, in this one parameter of cortisol metabolism, anorexics show an abnormality not seen in pure malnutrition. It is of interest that cortisol production rate and UFC are also increased in depressives [5,18], and this manifestation of HPA dysregulation in anorexia nervosa may be more closely related to the psychiatric condition than the physical state.

Efforts to perturb the HPA axis have been used in an attempt to assess its integrity in anorexia nervosa. Exogenous ACTH stimulation of the adrenal gland results in exaggerated cortisol responses in anorexics [11,19] similar to that seen in depressed patients, whereas this effect does not occur in pure malnutrition [14,15]. Metyrapone blocks the final step in cortisol synthesis from its precursor steroids. This produces a fall in cortisol levels. Such an acute drop should feed back upon the pituitary gland and produce an increase in the pituitary production of ACTH and possibly of CRF. The ACTH response to metyrapone administration is entirely normal in anorexia and in malnutrition. Thus, the

Table 17.1 Hypothalamic-Pituitary-Adrenal Axis I

	Anorexia Nervosa	Protein-Calorie Malnutrition	Depression
Basal Levels			
Plasma Cortisol	elevated	elevated	elevated
24-hour Mean Plasma Cortisol	elevated	elevated	elevated
24-hour Mean Plasma Cortisol, after Weight Recovery	normal	normal	–
Circadian Rhythm of Cortisol	preserved but distorted	–	very distorted
Metabolism			
Cortisol Production Rate (PPR) Relative to Body Size	increased	normal	increased
Change in PPR Compared with Low Weight	decreased	increased	–
Half-life of Cortisol in Plasma	increased	increased	normal
24-hour Excretion of Unconjugated ("free") Cortisol (UFC)	increased	increased	increased
Stimulation Studies			
ACTH and Cortisol Response to Metyrapone	normal	normal	normal
Cortisol Response to ACTH Stimulation	probably exaggerated	probably normal	probably normal
Suppression Studies			
Cortisol Response to Dexamethasone	Most have non-suppression	All have non-suppression	40% have non-suppression
Dexamethasone Suppression after Weight Gain	most suppress	normal	–

pituitary appears to respond normally to feedback regulation by the adrenal gland, ie, a drop in cortisol production by the adrenal gland in both anorexia and malnutrition, and the adrenal gland is probably hyperresponsive to signals from the pituitary in anorexia.

Dexamethasone is a highly potent synthetic glucocorticoid. It may be given as a single dose to suppress production of ACTH and CRF, mimicking the feedback inhibition by cortisol. This is known as the dexamethasone suppression test (DST). The general strategy is to give dexamethasone at 11 PM or midnight during the nadir of cortisol secretion, and in sufficient doses to suppress the HPA axis. Serum cortisol is sampled at 8 AM on Day 2. An extensive body of literature in psychiatry has demonstrated that the 4 PM and 11 PM time points on Day 2 have diagnostic utility in affective disorders, especially major depressive disorder with melancholia. A high percentage of control subjects, when given 1 or 2 mg dexamethasone PO at 11 PM, show complete suppression of cortisol to levels less than 2 mcg/dl, and this suppression lasts at least 24 hours. However, depressives and patients with other psychiatric disorders will show escape from suppression, usually at the 4 PM or 11 PM time points. Figure 1 shows the 4 PM postdexamethasone cortisol in patients with anorexia nervosa, bulimia, weight-recovered anorexics, and a comparison group of patients with major depression. All patients were tested using the same RIA assay with an intraassay coefficient of variability of 16.2% and a sensitivity of 1 mcg/dl. Patients with low-weight anorexia nervosa show significantly higher cortisols than depressives and bulimics (ANOVA, one-way $F=8.56$, $p=0.04$), and fewer patients with low-weight anorexia nervosa suppress. However, following weight restroration, this difference disappears. It is of note that in PCM, dexamethasone does not suppress the HPA axis, but after refeeding, suppressibility returns to normal [15]. These relationships are summarized in table 1.

Based upon these findings, we divided our sample of low-weight anorexics and normal-weight bulimics to further investigate the relationship between weight and the DST. Figure 2 demonstrates clearly that in low-weight anorexia nervosa, bulimia nervosa, and obesity, lower weight patients show significantly more nonsuppression than higher weight patients. An emerging lit-

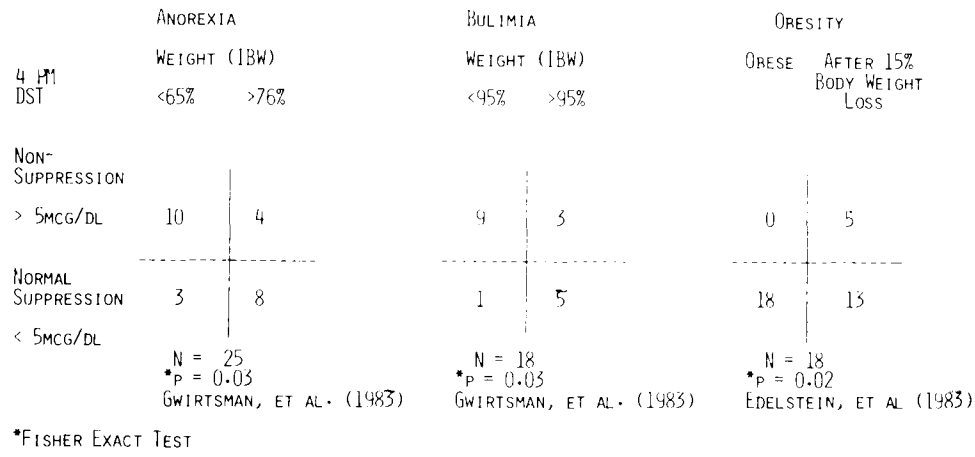


Figure 17.2 When anorexics and bulimics are divided into groups based upon weight, they appear to have different responses to dexamethasone. Anorexics below 65% of ideal body weight (IBW) and bulimics below 95% of IBW suppressed less frequently than their slightly heavier counterparts. This has also been found in obese subjects. In these populations weight was an important determinant of DST nonsuppressibility, but degree of depression was not.

erature is beginning to examine this issue in normal volunteers and depressed patients. Thus far, two studies have asserted that the HPA axis becomes disinhibited when normal volunteers lose weight by dieting [20,21], and four of seven studies have found a positive relationship between dexamethaxone nonsuppression and history of weight loss in depressives [20-26].

Thus, in patients with both low-weight anorexia and normal-weight bulimia nervosa, a number of studies have demonstrated nonsuppressibility of cortisol in response to dexamethason [8,9,12,27-31]. The relationship of this biological parameter with mood state is an important one and has been inadequately investigated. In underweight anorexics [28] we failed to find an association between the presence of depression and DST nonsuppresison. In normal-weight bulimics, we found that 5/22 (23%) of our sample met criteria for DSM III major depressive disorder, but again there was no consistent relationship with DST abnormalities. Additionally, there was no significant relationship between DST and duration and severity of illness, menstrual abnormalities, T_3 and T_4 results, family history, previous history of primary anorexia nervosa, or treatment response with antidepressant. Edelstein et al [32] also failed to find any coincident mood changes with weight loss in her obese subjects who converted to abnormal DSTs. In weight-recovered anorexic patients, a number continue to show nonsuppression [27,33]. It is interesting to speculate that dexamethasone nonsuppressibility in this group may be more related to their psychiatric condition than their physical state, since patients with pure malnutrition do not suppress either, but all recover after refeeding [15,16].

HYPOTHALAMO-PITUITARY-THYROID (HPT) AXIS

It has been known for some time that patients with anorexia nervosa show clinical signs of hypothyroidism, including cold intolerance, constipation, low basal metabolism rate (BMR), bradycardia, elevated carotene, and slowed deep tendon reflexes. As mentioned before, the HPT axis is an endocrine cascade system with T_4 and T_3 as its final end product. These hormones act to inhibit TSH and possibly also TRH [4]. The control of TSH secretion is complex and controversial and may also involve other hormones and neurotransmitters. It has been found that electrical stimulation of the anterior hypothalamus, TRH, estrogens, and possibly norepinephrine enhance the secretion of TSH, whereas periphypothalamic lesions, somatostatin, dopamine, hypercortisol states, exogenous steroids, and possibly growth hormone (GH) [34] exert inhibitory effects on TSH release [4,35]. The effects of serotonin on the HPT axis are still unclear, but there is some evidence that this neurotransmitter may be inhibitory [36].

TRH itself is found in multiple brain regions such as the pineal, the amygdala, and other limbic areas, and may be transported through the CSF to act upon the anterior pituitary [4]. Exogenous TRH also releases prolactin in normals [4] and causes abnormal secretion of GH in anorexia, chronic liver disease, mental depression, acromegaly, hypothyroidism [36], and bulimia nervosa [31,37], but not in volunteers. These differential effects and some animal data imply that TRH may be modifying the pituitary directly and also indirectly via monoaminergic pathways. In disease states that affect the integrity of such pathways, the direct stimulatory ef-

fect of TRH on the pituitary becomes unmasked [36].

Basal chemical indices of thyroid function have been well studied and there is agreement that serum total T_4 is low normal in anorexia nervosa [36,38,39-43], but free T_4 is normal [36]. T_3 is in the hypothroid range, [36,38,41,44] even lower than in myxedema [41]. It appears as if T_3 but not T_4 is extremely sensitive to nutritional state, as studies of experimental starvation in normal volunteers and obese patients [45,46] demonstrate marked decreases in T_3, and the low T_3 seen in anorexia nervosa and PCM is corrected following weight gain [42,44,47]. One study has demonstrated rises of T_3 into the hyperthyroid range in anorexics during weight gain [41]. Reverse T_3, or rT_3, is a metabolically inactive isomer of T_3 that has been found to be elevated in anorexia nervosa [35,48], experimentally starved controls, obese individuals [48] PCM, and other disease states [47]. It is thought that tissue conversion of T_4 to T_3 is routed to rT_3 as a peripheral adaptation to starvation, which returns to normal following nutritional rehabilitation [32,35,46,48].

Baseline TSH levels in anorexia nervosa are in the normal range [35,38,40,42,43,49] and do not seem altered in starved controls or overweight patients [45,48]. In normal weight bulimics, baseline T_3 and T_4 concentrations are in the normal range [31,37]. Basal TSH levels in 11 female and three male bulimics that we studied were normal at 2.0 ± 0.1 $u^{U/L}$ and 1.6 ± 0.5 $u^{U/L}$ respectively. One other study [37] found one of six patients had mildly elevated basal TSH levels.

TSH has a circadian rhythm in normals [4,50] with a peak occurring during or after the onset of sleep and a nadir in the late afternoon. Both indirect [44] and direct (Gwirtsman, Kaye, and Gold, unpublished observations) measurement of these circadian rhythms indicate a loss of the nighttime surge in anorexia nervosa, with a general resetting of the curve upwards. Although these data are still preliminary and require replication, it is interesting that in animals, both hypothyroidism and hypothalamic lesions can abolish this TSH periodicity [4], implying that such dysregulation in anorexia nervosa may reflect hypothalamic dyscontrol.

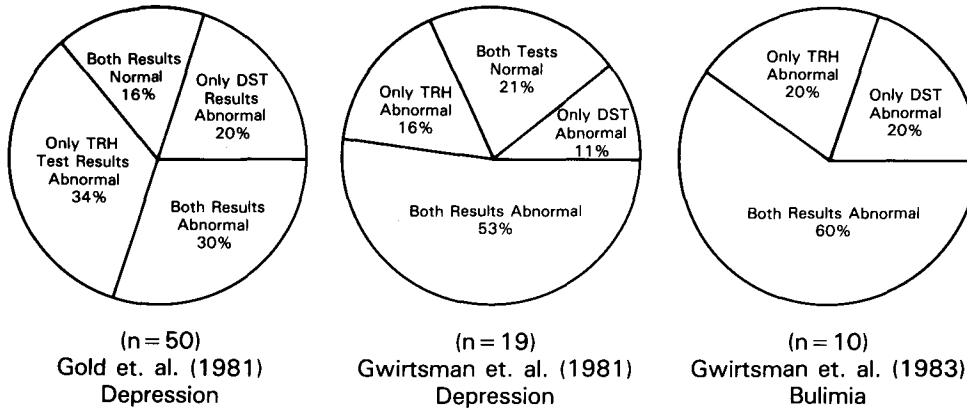
The TRH stimulation test (TST) looks at the responsivity of the pituitary gland to maximal stimulation by the hypothalamic tripeptide TRH. The TST has been found to be blunted in a sizable perentage of patients with affective disorder. A normal response to TRH is a surge of TSH release from the pituitary reaching a peak at approximately 30 minutes and attaining a magnitude of 10 to 15 ng/ml over the baseline level. This peak minus baseline difference is known as the Δ Max TSH. Generally a Δ Max TSH of less than 5 to 7 ng/ml is considered a blunted response to TRH. In clinical hypothyroidism the TSH response to TRH is exaggerated, and when this is due to disease in the hypothalamus, the peak response of Δ Max TSH is often delayed [4,40]. Several investigators have looked at this response in small samples of anorectic patients, and some show a normal curve [40,43,49], but most demonstrate a delayed response [35,38,42-44,53]. Occasionally the TSH response has been blunted [34,35,42]. These changes are not due to hypothyroidism but are probably related to hypothalamic dysfunction, perhaps a deficiency of TRH [44,49]. It should be noted that, while some studies suggest that acute starvation of volunteers [51] and obese patients [52] diminishes the TSH response to TRH, other studies have failed to find this [45,48].

Following weight gain, many anorexia patients develop a more rapid response of Δ Max TSH and fewer blunted responses are seen [35,41], but some continue to be abnormal. Additionally, underweight anorexics demonstrate pathological GH increases to TRH [34,53]. These GH responses appear to be related in an inverse fashion to the blunted TSH response [34] and only partially correct with weight gain [42]. Such pathological changes are not specific to anorexia nervosa. Prolactin responses to TRH remain normal in anorexia at low weight and following weight recovery [42]. TST abnormalities and clinical characteristics of anorexia nervosa such as depression have not been studied to our knowledge.

In normal-weight bulimia nervosa TSH responses to TRH have been found to be blunted in eight of ten females in one study [31] and one of six patients in another investigation [37]. In our sample of 18 bulimics, TST abnormalities were not related systematically to duration and severity of illness, menstrual abnormalities, T_3 and T_4, past history of anorexia nervosa, family history, presence of major depressive disorders, or treatment response to antidepressants. There was a trend for patients with blunted TSH responses to TRH to be lower weight than those with normal responses ($N=10$, $p=0.09$).

HPA AND HPT RELATIONSHIPS

In order to assess the relationship between the HPA and HPT axes, it is important to perform tests relating to both of these axes in anorexia nervosa and bulimia nervosa. In depressed patients 70% to 80% of patients demonstrate either a DST or TRH abnormality, and 30% to 40% have a disturbance on both tests [53,54] (figure 3). We are unaware of any studies that examine this relationship in anorexics or in malnourished patients. However, in a small sample of bulimic patients who weighed 95% $\pm$ 2.4% of ideal weight by (range 83% to 111%) by Metropolitan Life Insurance tables, we found that all subjects had either a DST or TRH ab-



Thyrotropin releasing hormone (TRH) test and dexamethasone suppression test (DST) abnormalities in unipolar depression and bulimia.

Figure 17.3 Two studies agree that neuroendocrine abnormalities are commonly found in depression. Only 16% to 21% of depressed individuals had no abnormality on either the TRH or DST. In ten normal-weight bulimics, the same degree of neuroendocrine dysfunction can be demonstrated. All of the bulimics had either a TRH or DST abnormality, and 6 of 10 were abnormal on both tests.

normality and six of ten or 60%, had both tests abnormal. Our bulimia nervosa patients had signs and symptoms of depression, usually meeting criteria for dysthymic disorder, but only three had symptoms that were severe enough to classify as major depressive disorder. The data collected thus far are preliminary and are insufficient to allow us to attribute the cause of the more endocrinologically disturbed patients to severity of their depressions. Similarly, there were no consistent relationships between menstrual abnormalities, nor history of anorexia nervosa, and the double DST and TST abnormality. Perhaps the neuroendocrine aberrations in these bulimic patients are related more to the behaviors of bingeing and vomiting. Studies are now underway in this laboratory to determine if this is so.

NEUROENDOCRINE-ADRENERGIC SYSTEM RELATIONSHIPS

The adrenergic system has been studied extensively in eating disorders and will be reviewed in the chapter by Kaye et al. Several studies of urinary 3-methoxy-4-hydroxy-phenylglycol (MHPG) agree that this parameter is low in underweight anorexia nervosa patients [28,55,56,57] and returns to normal with refeeding [56,57]. CSF levels of norepinephrine are normal in underweight and refed anorectics but decline in the long-term weight recovered phase [58]. Defining the relationships between the adrenergic system and the HPA and HPT axes is important in enhancing our understanding of the biophysiology of eating disorders. One study [28] demonstrates a direct relationship between DST nonsuppression and lowered MHPG in underweight anorexia nervosa. In order to explore the relationship between neuroendocrine dysfunction and the adrenergic system in normal-weight bulimia nervosa, our patients received methylphenidate stimulation tests (MST) and urinary MHPG was measured. Additionally, they were treated for their disorder with adrenergic agents.

Twenty-four hour urine MHPG was collected, preserved, and measured by methods previously described [59]. Specimens were only used for MHPG analysis if total urine volume was greater than 1,000 ml/24hours or urine creatinine was greater than 15mg/kg [60]. Low MHPG is less than 1,027 mcg/24hours for normal women [61]. The MST involves the administration of an oral amphetamine-like compound, which can have a rapid, though time-limited, mood-elevating effect on depressed patients. Seven bulimic patients were given 10 to 20 mg methylphenidate orally in open trial, and mood ratings were done before and one and two hours after the administration of the drug.

The results are as follows: Bulimics had normal mean MHPG (N=10, MHPG=1,308.7 ± 151.4 SEM) but showed a bimodal distribution, with five subjects having distinctly low MHPG (mean=808 ± 59 SEM) and five subjects having normal MHPG (mean=1,642 ± 109 SEM). These two subgroups were significantly different ($T=5.81$ $p<0.001$ $df=8$). The two subgroups discriminated by MHPG did not differ according to DST results, ideal body weight, or clinical variables. However,

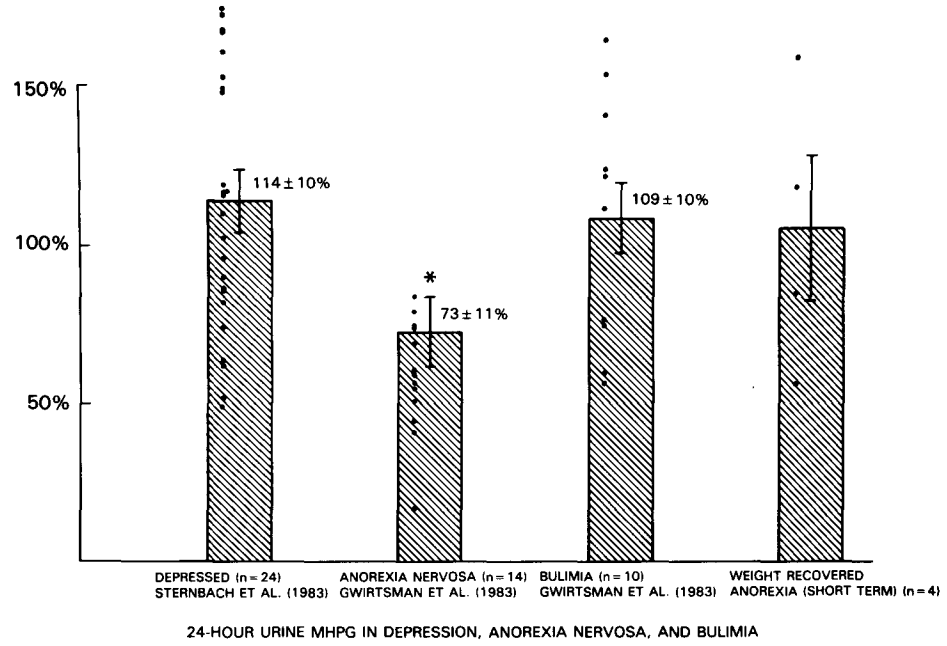


Figure 17.4 Although 24-hour urine MHPG is distinctly low in underweight anorexics, this represents only the absolute value of MHPG. When MHPG is corrected for body weight, it comes up to the normal range. Weight-recovered AN women show normal urinary MHPG, as do depressives and bulimics. Subgroups of patients have decreased urinary output of MPGH (not shown).

we did find a correlation between MHPG and TSH response to TRH ($r=0.83$, $p=0.05$). This is in contrast to the inverse correlation found in another study of depressed patients [62] and the failure to find any correlation in a sample of depressed female patients [63]. This suggests that bulimics do not merely represent a subgroup of affective disorder but may have a more distinct psychobiological identity. Figure 4 shows the MHPG values in bulimics, anorexics, and a comparison group of depressives. It is evident that anorexics have lower absolute values of MHPG (ANOVA, one-way, $F=8.58$ $p<0.05$), but this is problematic, since these values have not been corrected for percent body weight. When this is done, MHPG for underweight anorexic subjects comes up into the normal range.

Sixteen bulimics were treated with medication, two had maprotiline, nine were on tranylcypromine, two had imipramine (IMI), and three were given desipramine (DMI). Fourteen of these had depression ratings, and of these, 8 of 14, or 57%, had a definite antidepressant response [64]. Five of ten, or 50%, had a >50% improvement in binge frequency, and these patients also improved in their depression ratings ($t=-2.56$ $p=0.034$.). It was also found that patients tended to have more mood improvement with tricyclics than with nontricyclic compounds ($t=2.3$ $p=0.038$).

Four of seven patients had a definite mood-elevating effect after receiving methylphenidate. Measures of appetite were not done. This agrees with another study that demonstrated clear euphoriant effects on mood with intravenous methylamphetamine [65]. Neither urine MHPG, MST, nor treatment response to antidepressants, either adrenergic or nonadrenergic, was related in any systematic fashion to DST results. TST results could also not be consistently related to any adrenergic measure except for MHPG, and as previously mentioned, numbers were often too small to permit adequate statistical analysis. The only endocrinological parameter that predicted improvement in bulimic symtoms was the presence of normal menstrual periods ($t=-3.0$ $p=0.024$). This agrees with another study done on anorexics demonstrating a correlation between outcome and return of menses [66].

It is probably not surprising that significant relationships between adrenergic and neuroendocrine parameters did not emerge in this preliminary study, inasmuch as the sample size is small, bulimia nervosa is probably a heterogeneous disorder, and the tests done are probably neither extraordinarily specific for a single neurotransmitter, nor do they necessarily represent CNS function adequately. However, the lack of a relationship between the HPA axis and tests of adrenergic function may be quite significant in bulimia nervosa, since a direct relationship is noted in anorexia nervosa [33] and in de-

pressives [67]. Further studies looking at neuroendocrine-neurotransmitter relationships in eating disordered individuals are being undertaken in our laboratory in order to examine whether more complex system interactions will have some diagnostic specificity.

CLINICAL CONCLUSIONS

1. The dexamethosone suppression test is not useful diagnostically in patients with low-weight anorexia nervosa, since it is almost always positive regardless of mood.
2. In patients with anorexia nervosa who are weight recovered, and in normal-weight bulimics, the dexamethasone suppression test may have limited diagnostic utility. However, more study is needed here, because a definite relationship between DST nonsuppressibility and mood state has not been established.
3. The TST probably adds little diagnostically to the diagnosis of normal-weight bulimia, since most patients who are acutely ill and in the hospital will show blunted responses, regardless of mood state or family loading for affective disorder.
4. Relationships between the adrenergic system and neuroendocrine tests in eating disorders are complex and appear to be different from those found in depressives.
5. Although many bulimics appear to respond to standard antidepressant medications with improvements in mood and eating patterns, neither neuroendocrine measures nor tests of noredrenertic function predict such responses in any systematic fashion.

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