ANXIETY AND ENDOCRINE DISEASE

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It is our goal in this article to review the literature and define those endocrinological diseases that often include anxiety states as part of their initial presentation or as a characteristic symptom seen during their course. Understanding the mechanism by which anxiety develops as a routine part of these neuroendocrinological disorders may help us understand the organic basis of anxiety disorders. Research using new neurochemical, neuroanatomical and brain imaging techniques may further define the structural and physiological underpinnings of the anxiety disorders.

Biochemical Basis of Anxiety

Recent work suggests that some patients may be biochemically more sensitive to the development of anxiety symptoms in the presence of particular diseases. Mathew *et al*[1 2] have reported that patients with generalized anxiety disorders have higher plasma catecholamine levels than normal controls. These patients may down regulate catechol receptors as a result of these higher plasma concentrations and thus experience reduced receptor sensitivity in their adrenergic nervous system. Other investigators, however, have failed to confirm these findings.[3 4] Abelson et al have noted that patients with generalized anxiety have a blunted growth hormone response to clonidine (an $alpha_2$-partial agonist) stimulation , suggesting a decreased sensitivity of $alpha_2$ adrenergic receptors.[5] It may be that higher levels of catecholamines lead to down regulation of selective patients' post-synaptic $alpha_2$-adrenoceptors.

Brawman-Mintzer and Lydiard[6] in reviewing research data in this area suggest that patients at risk for generalized anxiety disorder may have deficits in the regulatory mechanisms of the hypothalamic-pituitary-axis associated with an abnormal response to stress. They hypothesize that such patients are more sensitive than controls in terms of the number and intensity of symptoms that they develop

following a panic challenge paradigm, and that they are therefore biologically distinct from patients with a primary panic disorder. The generalized anxiety patients appear to have alterations in the sensitivity of their central benzodiazepine receptors, abnormalities of serotonergic function and alteration of their 5-HT1 and 5-HT2 receptors. These researchers also cite data to suggest abnormalities in the cholecystokinin system in patients who develop severe anxiety, as well as significant changes in brain activity in this population.

Wu et al[7] noted higher relative metabolic rates in the brains of patients with generalized anxiety disorder, particularly in the occipital temporal (right posterior temporal lobe) and frontal lobes (left interior frontal gyrus), as well as in the cerebellum. They also noted decreased absolute metabolic activity in the area of the basal ganglion, the cingulate gyrus, the temporal lobes, the amygdala, and the hippocampus of these patients. Patients with general anxiety disorder had significant increases in activity in their basal ganglion and right parietal lobes and a decrease in metabolism in their right temporal and occipital lobes during vigilant tasks. When benzodiazepines were administered to these patients, cerebral glucose metabolism over the cortical surface, particularly the occipital cortex and in the limbic system and basal ganglion, diminished markedly.

Brawmin-Mintzer and Lydiard[6] summarized the currently existing data and suggest that there are several cellular structural abnormalities and changes in regulatory mechanisms that may be important biological components in the production of anxiety. Maladaptive responses to stressful stimuli occur in the locus ceruleus-norepinephrine-sympathetic nervous system, the hypothalamic-pituitary-axis, and the cholecystekinen system. Other abnormalities have been noted in the 5-HT and GABA-modulating systems.[6]

Gray[8] proposes a behavioral inhibition system as a model for anxiety disorder. In this system he defines the neuroanatomic circuits that modulate response to stress. When overstimulated, these systems produce persistent anxiety states in humans. The septohippocampal system processes threat-relevant stimuli. Discharge of this system increases arousal. Noradrenergic and serotonergic stimulation to the septohippocampal area activates the system, which in turn generates impulses to the limbic structures and the prefrontal cortex.

Medical conditions that alter the hypothalamic-pituitary-axis or which alter transmitter or receptor function may impact this system and produce anxiety-like states. Neuroimaging data provides support for this concept. It is hoped that further research into this area will help define the biological correlates of medically induced and primary anxiety disorders.

Diagnosis and Coding.

DSM-IV establishes specific criteria for determining that a mental disorder is due to a general medical condition. "There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.[9] When a mental disorder is due to a general medical condition, one does not diagnose the primary psychiatric disorder with the same symptom, but rather codes the symptom secondary to the general medical condition. Thus, with anxiety one would not code 300.02, generalized anxiety disorder, but rather 293.89, anxiety disorder due to a general medical condition. The 293.89 code may be used for those specific presentations of anxiety states which include generalized anxiety symptoms, panic attacks, obsessions and/or compulsions. When the 293.89 code is used, it is important that the anxiety symptoms be well defined and prominent and that there is evidence from history, physical examination and laboratory

findings that these symptoms are a physiological consequence of the patient's general medical condition.

Clinicians should also be sure that the disturbance is not better accounted for by some other mental disorder such as an adjustment disorder with secondary anxiety brought on by the diagnosis of a disease. This diagnosis should not be used if anxiety symptoms occur only during the course of a delirium. Finally, the anxiety symptoms associated with the medical disorder must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Endocrine Diseases and Conditions Associated with Anxiety Symptoms

The first step in defining whether an anxiety disorder is due to a general medical condition is to establish the presence of a general medical condition that is often associated with the production of anxiety symptoms. The DSM-IV defines the most common endocrinological conditions associated with anxiety states as hyper- and hypothyroidism, hypoglycemia, pheochromocytoma, and hyperadrenocorticism.[10] Anxiety may also occur following the exogenous administration of estrogens, progesterone, thyroid preparations, insulin, steroids and birth control pills.[11] Popkin,[12] in addressing the issue of endocrine disorders presenting with anxiety, suggests that anxiety states frequently occur in association with adrenal dysfunction, Cushing's Disease, Carcinoid syndrome, hyperparathyroidism, pseudohyperparathyroidism, hyperglycemia, hyperinsulinemia, pancreatic tumors, pheochromocytoma and thyroid diseases including hyperthyroidism, hypothyroidism and thyroiditis. Popkin cautions that prospective, carefully controlled studies on the etiology of anxiety in these conditions are lacking. The studies that are cited are almost exclusively case reports. He argues for more structured and careful research into the organic basis of these conditions.[13]

Jefferson and Marshall[14] identified hyperthyroidism, hypoglycemia, pheochromocytoma, and

hyperadrenalism as the medical illnesses most often associated with anxiety symptoms and most frequently misdiagnosed initially as a primary anxiety disorder.

Hall et al in a study of medically induced anxiety disorder found thyroid disorders, *i.e.*, hyper- and hypothyroidism and thyroiditis, to be the most frequent medical conditions misdiagnosed as primary anxiety disorder.[11] Other common medical causes for anxiety in their study included hypoglycemia, Addison's and Cushing's Disease, hyper- and hypoparathyroidism, and diabetes mellitus. Rarer causes included various virilizing tumors and hypo- and hyperpituitarism.

Differentiating Anxiety Associated with Medical Illnesses from Primary Anxiety Diseases.

After the clinician has established the presence of a general medical condition known to be associated with significant anxiety symptoms, he/she should undertake a careful and comprehensive assessment of the factors necessary to link the two conditions. Although there are no absolute guidelines, certain associations are helpful in establishing this connection. Are the onset of the symptoms temporally related? Is there a temporal association between the exacerbation or remission of the general medical condition and the enhancement or abatement of anxiety symptoms? Do anxiety symptoms disappear when the primary medical condition is treated? Are features that are atypical of a primary anxiety disorder present such as the usual age of onset, the initial presentation, type of onset, or an absence of family history? The clinician should also judge whether the disturbances that are present may be better accounted for by the presence of a primary anxiety disorder, a substance induced anxiety disorder, or an adjustment disorder brought on by the diagnosis of a primary medical condition.

In earlier work, reviewing patients who were felt to suffer from psychiatric symptoms caused by primary physical illness, Hall et al found that neurological and endocrine disorders were etiologically

responsible for half of the medically induced anxiety symptoms encountered. In comparing these patients to patients with primary anxiety disorders seen in clinic, certain characteristics differentiated the patients with organic anxiety from those who suffered from a primary or psychogenic anxiety disorder. 1.) Patients with anxiety secondary to underlying medical illnesses tended to have disease characteristic fluctuations in the severity and duration of their anxiety or panic attacks. 2.) There was a clear cut association between the progression of their anxiety and their underlying disease. 3.) Medically induced anxiety disorders were most likely to have onset before the age of 18 or after the age of 35 in patients with a negative personal and family psychiatric history of anxiety or affective disorders and in patients who had not previously suffered from anxiety symptoms.

Conversely, the patients with primary anxiety disorders often presented with a history of other psychiatric symptoms including phobia, conversion symptoms, etc. and were much more likely to historically have suffered a recent major psychosocial stress or loss. Patients with primary anxiety disorders often had acutely developing symptoms as compared to the insidiously developing anxiety of medically ill patients. It was rare for these patients to have a history of anxiety persisting for more than two years.[11]

Anxiety in medical patients.

It is difficult to neatly compartmentalize organically induced from psychogenically induced anxiety symptoms in medically ill patients, as anxiety symptoms are ubiquitous in medical outpatient clinics and in patients admitted to hospital with severe disease. Estimates of significant anxiety in an outpatient clinic range from 10 to 20% of patients.[15] Wells et al[16] found that more than 11% of persons with chronic medical conditions experienced a recent anxiety disorder. These findings were drawn from

conclusions based on the review of a sample of 2554 patients with one of eight chronic medical conditions. These researchers found that patients with chronic medical conditions had a significantly higher adjusted lifetime prevalence of anxiety disorder than did those without. Their results were statistically significant for the presence of recent anxiety disorders at the $P<0.005$ level. In trying to determine whether an underlying medical illness physiologically causes the patient's psychiatric symptoms as compared to the anxiety symptoms representing a reaction to the stress of the illness, Schuckit applied some of the criteria noted above.[17] He found that between 10 and 40% of medical patients with anxiety disorder had what he considered to be an organic etiology for their psychiatric symptoms.

In their study of 2554 patients, Wells et al were able to show that "The only psychiatric disorders uniquely associated with current, active, chronic medical conditions were anxiety disorders, suggesting that the association between anxiety disorders and chronic medical conditions develops *more quickly* than associations between medical conditions and other psychiatric disorders."[18] In reviewing data from other studies[19] Wells et al suggests that a careful evaluation for underlying physical disorders, particularly diabetes and heart disease be undertaken in patients with primary anxiety disorders.

Sherbourne et al[20] studied a group of 2,494 patients with hypertension, diabetes, and heart disease, assessing the group for depressive disorders, lifetime panic disorders, phobia, and general anxiety disorder. They found that medical patients with depression had higher rates of panic disorder than did non-depressed medical patients, 17% vs. 10.9%. They also noted that concurrent phobia and generalized anxiety disorder were elevated in both groups, but were more common among the

depressed patients than the medically ill patients without depression, 25% vs. 10.4%. They noted that 14% to 66% of the primary care patients had at least one concurrent anxiety disorder. Between 54.6% and 72.9% of the patients reported an unmet need for care of their personal and emotional problem when seen in family practice clinics.

Meredith et al[21] in reviewing data from 2,189 general medical patients with and without co-morbid anxiety disorders who were seen in medical clinic and who were part of the medical outcome study, noted that patients with co-morbid anxiety disorders and primary medical conditions were more likely to receive treatment for their anxiety disorder than were patients who presented with anxiety disorders without accompanying medical problems. The use of psychosocial counseling and psychotropic medication was greater for patients with depression and anxiety than for patients without depression who had chronic medical conditions. The authors concluded that anxiety disorders co-occurring with another disease (a medical illness or depression) increased the likelihood that the patient would receive counseling or be treated with a psychotropic medication when seen in the general medical sector.

Brief Review of Specific Disorders

Space does not allow a detailed description for each of the endocrine disorders associated with anxiety states; however, we will attempt in the following pages to touch on some of the more interesting and pertinent literature associated with several of these disorders.

Anxiety disorders in patients with diabetes mellitus

Popkin et al[22] noted a lifetime prevalence of 28% for generalized anxiety disorders in the 140 candidates they evaluated for pancreas transplantation. They also noted a lifetime prevalence for major

depressive disorder of 19.3%. Neither anxiety nor depression increased the risk for unfavorable transplantation outcome.

Lustman et al,[23] using structured interview techniques in a sample of patients with type 1 and type 2 diabetes reported a lifetime prevalence of phobic disorders of 26.5% and of generalized anxiety disorders of 41%. These findings are six to seven times greater than that reported for the general population in the Epidemiological Catchment Area (ECA) study.[24] Lustman et al also showed that the poorer a patient's glucose control (*i.e.*, the higher the HbA1C) the greater their lifetime incidence of psychiatric illness.[23]

Popkin et al, in a brilliant series of studies from the University of Minnesota[25] showed that 51% of a group of patients with longstanding type 1 diabetes mellitus received one or more significant psychiatric diagnoses. The lifetime prevalence of major depression was comparable for female and male diabetics, and both evidenced rates that were significantly higher than that seen in their first degree relatives or in the general population. These investigators showed that the prevalence of generalized anxiety disorder (31.7%) was 3 times that which occurred in first degree relatives (9.5%). They noted that Lustman had similarly observed high rates of generalized anxiety disorders in both type 1 and type 2 diabetics, 44.4% and 37.5% respectively.[23]

Peyrot and Rubin[26] studied 634 patients in an out-patient diabetes education program for the presence of depression and anxiety. Depression occurred in 41.3% of patients. Anxiety disorders were reported in 49.2% of the patients. The rates were considerably higher than the 10% to 20% incidence reported in the general medical population. These authors reported that the probability of disturbance ranged from 5-7% for those patients with the lowest risk profile to 82-92% for those

patients with the highest risk profile. The presence of diabetes-related complications was the only disease factor that was associated with a higher risk of disturbance for both depression and anxiety. Women, particularly those with less education, were at greatest risk. They concluded that diabetes is associated with an increased risk of psychological disturbance, particularly for those patients with more diabetic-related complications. They also concluded that socio-demographic factors accounted for much of the risk differential among patients with diabetes.

Lustman et al[27] studied 58 patients with poor glycemic control, 16 of whom (27.6%) had symptoms of generalized anxiety disorder. The patients were placed in a randomized double blind, placebo controlled eight-week trial, using alprazolam up to 2 mg a day as the active agent. They demonstrated a statistically significant reduction in glycosylated hemoglobin level in the patients treated with alprazolam compared to those receiving a placebo ($P=0.04$). Treatment effect was not a function of compliance behavior. They concluded that a short course of alprazolam improved glucose regulation in patients with a history of poor diabetes control. They felt that the effect was not directly related to concomitant changes in the patient's anxiety. The authors believed that the alprazolam treatment of anxious patients with poorly controlled diabetes may result in decreased anxiety and improved glucose regulation through independent mechanisms.

Okada et al,[28] in an interesting Japanese study, evaluated the effects of reducing stress on 20 patients with type 2 diabetes, 10 male and 10 female. Patients were treated with an anxiolytic (fludiazepam) for 12 weeks. Glycosylated hemoglobin levels were monitored. Patients took anxiety scale tests to evaluate their level of anxiety. Improvement in the trait anxiety scores was correlated with decreases in glycosylated hemoglobin levels. $P<0.01$ The authors concluded that suppressing anxiety

in patients with type 2 diabetes reduced their glycosylated hemoglobin levels. These authors in another study showed that the high-density lipoprotein/cholesterol levels of these patients increased significantly after the administration of the anxiolytic, but other aspects of their lipid profile were unchanged. They concluded that the improvement of stress in patients with non-insulin-dependent diabetes mellitus increased their high-density lipoprotein levels.[29]

Akinlade et al[30] studied and compared the emotional and cognitive function of 37 insulin-dependent diabetics with 46 non-insulin-requiring diabetics using the Hospital Anxiety and Depressive Scale (HID) and Mini Mental State Examination (MMSE.) Five percent of the insulin-requiring diabetics and four percent of the non-insulin-requiring diabetics had significant clinical anxiety; while 37.8% of the insulin-requiring diabetics and 15.2% of the non-insulin-requiring diabetics had significant depression. The prevalence rate for depression for the entire cohort was 25.3%, while the rate for significant anxiety disorders was 4.8%. Cognitive function in both groups was normal.

Anxiety Disorders in Patients with Thyroid Hormone Disturbance

Anxiety and hypothyroidism

Rogers et al[31] examined the prevalence and characteristics of medical illness in 711 patients who were enrolled in the Harvard-Brown Anxiety Disorders Research Program (HARP), a multi-center, longitudinal study of anxiety disorders. They noted that patients with panic disorder and co-morbid major depressive disorder had significantly higher rates of reported medical illnesses than anxiety disordered patients who did not suffer with concurrent depression. When they compared the rates of medical illness for their subjects to those of the Rand Health Insurance experiment, they found the prevalence of peptic ulcer disease, angina and thyroid disease to be disproportionately increased.

They noted that 2% of the males in the study and 9% of the females in the study had thyroid disease, while 1.3% of the men and 4.1% of the women suffered from diabetes mellitus. The prevalence of thyroid disease in women was higher than expected in the general population. It was not increased in men. The study noted that patients who also suffered from panic disorder were more likely to have an underlying medical illness causing their anxiety, particularly thyroid disease in women.

Psychiatric presentations are often the first sign of hypothyroidism, occurring as the initial symptoms in approximately 2% to 12% of reported cases, with organic mental deficits being the most frequently reported initial symptoms.[32] Anxiety and progressive mental slowing associated with diminished recent memory, speech deficits and diminished learning ability are the characteristic initial progression of symptoms.

Spontaneous hypothyroidism occurs predominantly in women between the ages of 40 and 60. Physical symptoms generally seen include weakness, fatigue, cold intolerance, diminished libido, lethargy, dry skin, headaches, and menorrhagia. Physical signs include brittle nails, thin, course hair; slowed pulse, and pallor. Delayed return of deep tendon reflexes is also commonly encountered. Later symptoms include perceptual changes in taste, smell, vision and hearing; reduced or absent perspiration, weight gain, pallor, hoarseness, peripheral edema, muscle cramps, dyspnea and angina. Amenorrhea or menorrhagia and galactorrhea may also be seen.

The development of severe anxiety disorders in hypothyroid states are as much or more related to the rapidity of change of thyroid hormone levels as they are to the absolute levels encountered. Whether the cause of hypothyroidism is auto-immune or follows thyroidectomy, oblation of the gland by radioactive iodine, the ingestion of medicines such as lithium carbonate, or is associated with thyroid

cancer, the neuropsychiatric symptoms are similar.

The incidence of myxedema madness as an initial presentation of hypothyroidism has diminished dramatically since the late 1880s when it occurred in almost 50% of cases. Today psychosis is reported to occur in between one to fifteen percent of patients.[33] Anxiety disorders, on the other hand, occur in between 30% and 40% of patients developing acute hypothyroidism.[34]

The most characteristic picture of patients with rapidly developing myxedema is one of progressive anxiety with generalized agitation. Patients may experience a progressive disorientation, persecutory delusions, hallucinations, and bouts of lethargy alternating with periods of extreme restlessness. They are often extremely irritable, delusional, and paranoid and may complain of auditory and visual hallucinations. Hypersexuality, irritability, suspicion, delusions, inability to concentrate, and failing memory are all conspicuous signs of rapidly developing thyroid disease.[34]

Slowly progressive changes in thyroid hormone levels are more likely to be associated with a picture of chronic anxiety, increased fatiguability and psychomotor slowing. The severity of mental symptoms are greater in elderly patients and, as noted, in patients with rapidly changing thyroid hormone levels.[34] In a study of patients with Hashimoto's thyroiditis, anxiety was a prominent initial symptom at the time that the condition was diagnosed. It was often associated with a lability of mood, withdrawal from normal duties due to perplexity, and in severe cases, generalized agitation, disorientation, and persecutory delusions as well as extreme restlessness.[35]

The anxiety associated with significant hypothyroidism usually resolves within days to months following the initiation of treatment. The clinician must remember that the central nervous system effects of profound hypothyroidism may not fully clear for two to twelve months after successful treatment.

Sleep and growth hormone production during sleep have been shown to be disturbed for weeks to months following the replacement of thyroid hormone. Return of these functions to normal seems to be related to the cessation of the anxiety states that these patients experience.[34] Kales et al[36] have shown that patients' improvement parallels restoration of their normal sleep patterns, and, in fact, note that the return of a normal sleep pattern is an excellent predictor of treatment outcome.

Anxiety and Hyperthyroidism

Hyperthyroidism is one of the most frequently encountered endocrine diseases. It most commonly occurs in women between the ages of 20 and 40. Graves' disease usually presents with a diffuse goiter and ocular disturbances. The most frequent symptoms seen at onset include anxiety, fatigue, irritability, cold intolerance, fine tremor, a sensation of somatic restlessness, insomnia, excitability, lability of mood, nervousness, weight loss, increased sweating, palpitations, impaired coordination, doubts, and persistent fear. Weight loss is unusual as most of these patients have a ravenous appetite. Patients also complain of difficulty focusing their eyes, pressure symptoms related to goiter, diarrhea, and irregular rapid heart rate.[34]

Other causes of hyperthyroidism include toxic adenoma, iodine-induced hyperthyroidism in patients with multinodular goiters, exogenous thyroid hormone ingestion, struma ovarii, iatrogenic hyperthyroidism, hydadidiform mole, and TSH secreting tumors of the pituitary.

Between 1% and 20% of hyperthyroid patients have been reported to present with psychosis. Current best estimates suggest about 5% present initially with psychotic symptoms.[34] Between 30% and 40% present with conspicuous complaints of anxiety, nervousness, apprehension, dread, depression, restlessness, diminished concentration, forced thinking, emotional lability, and

hyperkinesia.[34]

Trepacz et al[37] report a high prevalence of general anxiety disorder in a series of patients with untreated Graves' disease. Ettigi and Brown[38] note that hyperthyroidism is almost inevitably associated with mental changes, the most common including nervousness, apprehension, restlessness, inability to concentrate, marked emotional lability and hyperkinesia. These patients often present as hyperactive individuals with specific complaints of anxiety and "nervousness." A fine generalized tremor may be present, and the patient reports an internal sensation of feeling shaky or jittery. Family members often remark about personality changes and increases in both irritability and emotional lability. Jefferson and Marshall point out that the nervousness of the hyperthyroid patient is dissimilar to that seen in the patient with a primary anxiety neurosis in that it is characterized by "restlessness, shortness of attention span, and a need to move about."[14]

Popkin and MacKenzie[39] note that the behavioral changes of hyperthyroidism are numerous and useful in differentiating it from a primary anxiety neurosis or a neurasthenia. Patients with hyperthyroidism are differentiated from primary anxiety states as "in thyroid dysfunction, sleeping pulse will remain accelerated; sedated pulse will exceed 80; palms will be dry and warm, not cold and clammy; fatigue will be accomplished by a desire to be active; and cognitive dysfunction is more prominent than in neurasthenia."

Cognitive effects clear rapidly with restoration of normal thyroid levels, in contradistinction to the slow return to normal function often seen in patients with significant hypothyroidism.[34] Whybrow et al[40] note the elevation of schizophrenia and paranoid scales on the MMPI when patients are hyperthyroid and psychotic. They report that these changes clear quickly following treatment and note

that the behavioral manifestations of hyperthyroidism clear rapidly with treatment. They are toxic phenomenon related to elevated levels of circulating thyroid hormone.

MacCrimmon et al[41] noted MMPI changes in hyperthyroid patients suggestive of hysterical somatization. These investigators noted that such changes rapidly returned to normal following treatment. They suggested that the behavioral, neurotic and psychotic manifestations of hyperthyroidism were related more to disease induced biochemical abnormalities than to the patient's previous personality pattern.

Paschke et al[42] studied 15 female patients with Graves' disease, administering psychological tests at the time that their hyperthyroidism was first diagnosed and then following them through their course of antithyroid treatment. Psychological testing was obtained when the patients achieved a biochemically euthyroid state. Patients were subsequently followed while being treated with antithyroid drugs or surgery. The investigators noted that patients' psychological parameters showed considerable change as their thyroid status improved. The psychiatric symptoms most prevalent while patients were hyperthyroid included anxiety, depression, irritability and exhaustion. Patients often described themselves as anxious, nervous, irritable, tired, without energy, exhausted, and fatigued. 75.5% complained of significant anxiety when first evaluated. The authors felt that the most consistent psychological pattern seen in these patients consisted of a mixture of severe anxiety with depression, exhaustion, a decreased ability to concentrate, irritability and extroversion. The investigators noted the cessation of anxiety and irritability at the time that the patients achieved a euthyroid state. Depression took one month following the development of a euthyroid state before normalizing, whereas the personality changes took three months to subside after the patient became euthyroid. It was noteworthy

that the type of thyroid therapy made no difference in the course of the patient's psychological symptoms, *i.e.*, patients who became euthyroid from drug treatment vs. those who became euthyroid from surgery responded similarly. The authors noted that there was no relationship between the severity of disruption of thyroid hormone level and symptoms, but there was significant correlation between a return to normal thyroid function and a return to normal psychological function. There was no correlation noted between psychological test scores and the degree of autoimmune dysfunction seen in these patients. The authors concluded that patients with Graves' disease developed significant anxiety manifested as a constant personality trait when compared to the control group.

If the estimated 60% to 75% incidence of severe anxiety in patients with hyperthyroidism is correct, one could conclude that with the 300,000 new cases estimated to occur in the United States this year, that a significant number of these patients will be initially seen by psychiatrists. They are likely to evidence other signs and symptoms of hyperthyroidism when seen, specifically, nervousness, weight loss, heat intolerance, warm skin, excessive perspiration, easy fatiguability, muscular weakness, diarrhea, fine tremor, and a wide-eyed stare with possible protrusion of the eyes.[43]

Hall[34] notes that the most frequent initial presentation of hyperthyroidism centers on complaints of anxiety and nervousness. The most frequent misdiagnoses of hyperthyroidism is that of generalized anxiety disorder. This diagnosis is particularly likely in the early stages of the disease when patients present with anxiety, increasing irritability, emotional lability and personality change. Kathol and Dalahunt[44] report that when DSM-III criteria are used, the incidence of depression and generalized anxiety disorder is three to four times higher in hyperthyroid patients than that expected in the general population.

Panic disorder/agoraphobia and thyroid disease

Matsubayashi et al[45] report on two patients with Graves' disease who initially presented while euthyroid with a panic disorder. Four and five years after the panic disorder began, these patients developed hyperthyroidism. Antithyroid drug treatment reduced psychiatric symptoms. The authors suggest that panic disorder may not only be a consequence of Graves' disease but may precede its onset and potentially predispose to its development.

Orenstein et al[46] interviewed 144 consecutive female psychiatric patients and found that those with a lifetime history of either panic disorder or agoraphobia with panic attacks were more likely than the other patients to report a history of hyperthyroidism or goiter in themselves or in their first degree relatives. This personal history of hyperthyroidism or goiter was found almost exclusively in the subgroup of patients who presented with symptoms of panic/agoraphobia who also had a lifetime history of major depression.

Lesser et al[47] measured indices of thyroid function in 165 subjects who had a DSM-III diagnosis of panic disorder with or without phobic avoidance. These investigators noted that the patients with these conditions reported a higher prevalence of thyroid illness by history compared to that encountered in the general population. However, less than one percent had current thyroid dysfunction. Patients who also had a history of a major depressive episode had a higher prevalence of thyroid disease by history. Indices of thyroid functions, however, were not correlated with severity of panic attacks or phobias.

Lesser et al[47] noted a low order of occurrence of active thyroid disease in patients with panic disorder. In an eight-center drug treatment study of 165 consecutively recruited panic disorder patients,

there was a higher reported incidence of thyroid disease than would have been expected in the general population. However, when specific thyroid testing was undertaken by T3, T4, TSH and free thyroxine index, fewer than one percent of these patients had any laboratory evidence of current thyroid disease. Rag[48] also noted a low incidence of thyroid disease in the panic disorder patients that they evaluated. Matuzas et al[49] reported significantly different findings in their study of 65 self-referred patients with panic attacks, examining them for cardiac defects and thyroid abnormalities. Fifty percent of these patients evidenced mitral valve prolapse on both cardiac auscultation and echocardiography. Twenty-six percent of the women had thyroid abnormalities. Seventeen percent had elevated thyroid microsomal antibodies. There was no relationship between those patients who had mitral valve prolapse and those who evidenced thyroid abnormalities. The authors suggested that panic attacks, mitral valve prolapse, and autoimmune thyroid disorders, are associated. Forty-six of these 65 patients also met criteria for agoraphobia and would have been classified as agoraphobic with panic attacks. The 50% prevalence of mitral valve prolapse was approximately ten times higher than the 5% to 7% estimated in the general population. Twenty-five percent of the women ages, 30 to 40, had positive antithyroid antibodies, compared to 5% to 13.8% of women of similar age in the general population. The authors suggested that the prevalence of thyroid antibody titers was elevated in patients with panic attacks.

Nemeroff[50] et al had previously noted that 8 of 53 patients (15%) suffering from depression had elevated thyroid microsomal antibody titers. Orenstein et al[46] noted that of 144 consecutive female psychiatric patients interviewed, that those with a life-time history of either panic disorder or agoraphobia with panic attacks were more likely than other patients to report a history of

hyperthyroidism or goiter in themselves or in their first degree relatives. A personal history of hyperthyroidism or goiter was found almost exclusively in the subgroup of patients with panic/agoraphobia who also had a lifetime history of major depression. These investigators noted a 13% prevalence of hyperthyroidism among patients who had a history of depression/panic/agoraphobia. Their data was very similar to the 11% prevalence for a history of hyperthyroidism and agoraphobia/panic disorder reported by Lesser.[47]

Emanuele et al[51] reported on four cases of coexistent agoraphobia and hyperthyroidism, where the patients reported a fear of crowded or confined spaces, difficulty traveling away from home or places of safety, and the development of panic attacks. All of their patients had typical signs and symptoms of Graves' disease and unequivocal laboratory evidence of hyperthyroidism at the time of their psychiatric diagnosis. The agoraphobia preceded the onset of thyrotoxicosis in all of these patients. They noted that the anxiety experienced by their hyperthyroid patients was unrelenting, whereas the panic attacks that occurred with agoraphobia tended to be intermittent and provoked by readily identifiable situations. Their hyperthyroid patients experienced a constant tachycardia that persisted during sleep. While the rapid heartbeat seen in the primary anxiety and panic disorder patients was intermittent. They noted that the hyperthyroid patients had warm moist skin rather than the cold clammy skin associated with primary anxiety disorders. The tremor that they experienced was high frequency and low amplitude in contrast to the course tremor that is often seen with primary anxiety disorders. The hyperthyroid patients also complained of the proximal myopathy commonly seen with thyrotoxicosis. These authors noted that with appropriate treatment of the hyperthyroidism, the agoraphobia rapidly improved. Restoration of a euthyroid state, without concomitant psychotherapy,

resulted in the cessation of agoraphobia with restoration of the patient's ability to function normally in the community. The investigators noted, however, that the diagnosis of agoraphobia delayed the diagnosis of hyperthyroidism in all the patients in this study and made it impossible for one patient to comply with therapeutic recommendations until advanced thyrotoxicosis developed and was diagnosed and treated two and a half years later.

Noyes et al[52] compared 41 subjects with generalized anxiety disorder who had never experienced panic attacks with 71 subjects who presented with panic disorder. They found that among the general anxiety disordered subjects, co-existing major depression was associated with the presence of simple phobia and thyroid disorders.

Conclusions

Although space does not permit a more detailed review, a critical review of the literature[15 17 39 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75] shows relationships between medically induced anxiety and hyper-and hypoglycemia,[76 77 78 79] hyper-[80] and hypoparathyroidism,[81 82 83] hyper- and hypopituitarism,[84 85 86 87] hyper- and hypoestrogenemia,[88 89 90 91] hyper-[92 93] and hypoandrogenemia,[88 89] hyperprolactinemia,[94 95 96 97 98] hyper-[99] and hypocalcemia,[85] hyper- and hypothyroidism, hyperadrenalism (Cushing's disease),[81 100 101 102 103 104 105 106 107 108 109] adrenal insufficiency,[106 110] growth hormone deficiency,[111 112] pituitary microadenoma[88] and pheochromocytoma.[13 113 114 115 116 117]

As I hope we have demonstrated, endocrine disorders can and do produce both cognitive and behavioral signs of anxiety, panic disorder, and at times even obsessional symptoms in patients. These changes are generally not specific and cannot be easily compartmentalized diagnostically. They are often variable in their presentation and fluctuate in their severity. To properly evaluate patients for these

disorders, one must first entertain in the differential diagnosis the medical disorders that are associated with these conditions. The patient should receive a comprehensive history and physical examination as well as careful laboratory screening. The initial evaluation should carefully define the sequence of symptoms encountered and how they evolved, determine both personal and family histories for these endocrinological disorders, and include a detailed review of systems which is often helpful. Physical examination may define signs and symptoms that distinguish between endocrine disorders and primary anxiety and panic states. Once proper diagnosis and treatment are instituted, symptoms usually clear. As noted by Popkin,[13] "Systematic studies with diagnostic rigor and careful attention to demonstrating the etiological relationship between the anxiety disorder and endocrine disease are few," but as we hope we have demonstrated, such studies are increasing in both frequency and import. The older literature consists predominantly of case reports. The newer literature, however, does justify the construct of secondary anxiety disorders caused by endocrine disease. Defining the differences between the endocrine-produced anxiety states and "primary anxiety disorders" will represent a significant research challenge in the decades ahead.

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