

# Stress-Induced Hypocortisolemia Diagnosed as Psychiatric Disorders Responsive to Hydrocortisone Replacement

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**ABSTRACT:** In patients of all ages, many disorders labeled as psychiatric may actually be due to hormonal insufficiencies. For example, cortisol deficiency is rarely taken into account in a medical or psychiatric work-up, so persons with mild to moderate cortisol insufficiency are for the most part relegated to receiving a psychiatric diagnosis when, in fact, the same disorder is represented. However, the symptoms of cortisol insufficiency appear to closely parallel such psychiatric disorders as post traumatic stress disorder (PTSD) and addictions. There has been some question of whether substance abuse *causes* a hypocortisolemic state. In reviewing the literature and obtaining detailed histories of addicted patients, it appears that childhood trauma, also known as “early life stress” (ELS), instead may elicit a hypocortisolemic state. This leads some to self-medicate with an addictive substance to quell the pain of a cortisol insufficiency, both physical and emotional. In fact, the literature supports the concept that addictive substances increase cortisol in predisposed patients. Patients with a variety of psychiatric disorders including addictions were found to have signs and symptoms of mild or moderate hypocortisolemia. Generally, an appropriate comprehensive examination supported a diagnosis of cortisol insufficiency. For the most part, these patients were successfully treated with physiologic doses of bio-equivalent hydrocortisone, along with replacement of any other deficient hormone. By correcting underlying hormonal insufficiencies, many patients improved, with some patients having a total reversal of psychiatric symptoms. It is therefore reasonable to evaluate and treat hormonal insufficiencies with hormones prior to using psychotropic medication.

**KEYWORDS:** stress; trauma; cortisol; PTSD; hormones; substance abuse; aging; paranoia; irritability; hostility; startle; alcoholism; psychotropic; DSM

Exponentially expanding medical knowledge, intensified by the advance of computer-oriented technologies, has furthered the development of medical specialization, which in turn has spawned even more highly focused subspecialties. This is advantageous in that complex medical and especially surgical procedures require a higher level of expertise and therefore more intense educational training. Unfortunately, this level of expertise has been at the cost of a cohesive, holistic perspective. The problem is complicated by the relative lack of communication between the dif-

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ferent disciplines.<sup>1</sup> The same medical problems appear to have discipline-specific diagnoses with various treatment methods based on specialty-driven approaches.

The problem of this fragmented approach to medicine was further complicated by a subtle transformation to symptom-based treatment. This shift in part is due to a decrease in time allocated for patient visits. Limits on third-party reimbursements to physicians impose time constraints on patient care. In some studies, primary care physicians average about ten minutes per patient.<sup>2</sup> In one study the average time for a patient interview was 6.7 minutes.<sup>3</sup> Clearly these brief visits are not conducive to a comprehensive approach to patient care. However, an expeditious approach using symptom relief, is preferable to the costly and time-consuming explorations of a possible underlying problem. This quick, symptom-centered approach to medicine has been described by some as "McMedicine."

The imposition of time constraints created a need for rapid resolutions to patients' problems. This need was met by a pharmaceutical industry that produced and continues to produce medications providing symptom relief. The patient feels better and a minimal amount of time is required of the doctor. Whatever the problem, there is a pill offering an "antidote." For example, patients with insomnia are given a soporific medication. If the patient feels depressed, there is an antidepressant for him. In fact, in the United States, medications offering symptom relief are advertised directly to the public so that patients can ask doctors for a specific brand of medication to relieve their symptoms.<sup>4,5</sup>

Psychiatry fits well into this symptom-based paradigm because psychiatric diagnoses are based on symptom clusters. Psychiatry has developed unique diagnoses based on the Diagnostic and Statistical Manual (DSM), the current version being DSM IV-TR. The original purpose of developing such a manual was to standardize international research parameters. With a world-wide consensus about the exact identity of a mental problem, shared research information multiplies the usefulness of the data and provides greater validity to the knowledge gained. The ultimate purpose of developing research parameters was to discover the etiology, appropriate treatment, and prevention of mental problems.<sup>6</sup>

On the basis of a variety of statistically derived symptom clusters and the array of behavioral responses to emotional discomfort, the manual sorted them into specific diagnostic groupings. These classifications are decided on by a DSM committee that continually revises the criteria by including or excluding various symptoms. The classifications were not meant to replace an etiologically based diagnosis. In fact, it is clearly stated in the DSM that a psychiatric diagnosis is made only if the symptoms are not caused by a medical disorder or by the effects of alcohol or drugs.<sup>6</sup> Therefore, a psychiatric diagnosis is, by definition, one of exclusion.

In reality, however, if the primary complaint is emotional, with the presenting symptoms consistent with a DSM-defined disorder, then the initial diagnosis can be considered a psychiatric disorder. This may mistakenly eliminate a search for any known medical problems that can produce the same symptoms. Diagnostic codes give the psychiatric determinations some validity. It then appears quite appropriate to give the patients psychotropic medications to treat diagnostically indicated and coded psychiatric problems. Pharmaceutical company studies of drugs specifically designed to treat these psychiatric disorders, based on DSM criteria, legitimize the diagnosis. These double-blind placebo-controlled trials of drugs become the basis of what has been called "evidence-based treatment."

**TABLE 1. Comparing post-traumatic stress disorder and cortisol insufficiency**

Post-traumatic stress syndrome	Low cortisol
Intense psychological stress to external cues	Anxious, nervous
Intense response to external cues of trauma	Poor stress tolerance
	Hypersensitivity to environment
	Stress-induced fatigue
<i>Avoidance</i>	
Avoids thoughts of trauma	Absent minded
Avoids activities, places, etc.	Forgetful
Decreased interest and participation in activities	Feeling spacey, confused
Feeling detached from others	Depression
Feeling future foreshortened	Depression
<i>Increased symptoms of arousal</i>	
Trouble falling/staying asleep	Hypersensitivity of all senses
Hypervigilant	Paranoid feelings
Irritable or outbursts of anger	Irritable/hostile
Trouble concentrating	Concentration problems
Exaggerated startle response	Poor stress tolerance

However, because psychiatrically diagnosed disorders are not etiologically derived, the designated therapies are based on treating symptoms. Additionally, patients may not be aware of any other indicators of a medical problem possibly associated with the emotional symptoms and would not mention them to the physician during their brief visit. Additionally, the diagnosis was already made. This negates the necessity of any further investigation into a cause.

Moreover, primary care physicians are encouraged to look for psychiatric disorders, especially depression. When the symptoms fit the diagnosis of depression they are urged to treat these patients with antidepressants.<sup>5</sup> If the patients' depressive symptoms respond to an antidepressant, it further reduces the likelihood of finding a physiologic problem that can be treated. Unfortunately, using a psychiatric diagnosis without further investigation into a possible cause is not necessarily a benign treatment choice. An example of this is the depression that is a manifestation of hypothyroidism. If patients with this particular depression remain untreated for hypothyroidism, a number of morbid conditions can develop, the most damaging of which is dilated cardiomyopathy or congestive heart failure.<sup>7,8</sup> Clearly, hormones have functions beyond the effects on emotions.

With aging, hormone deficiencies are a fact, as most of the body's hormones diminish. However, hormone deficiencies, not merely as a product of aging, may cause symptoms categorized as psychiatric disorders. Hormone deficiencies can generate emotional symptoms, create perceptual distortions, and affect the ability to think. Even so, patients are given a psychiatric diagnosis without an adequate investigation into a treatable medical cause. A side-by-side comparison of a hormone deficiency and a psychiatric diagnosis shows that they have same symptoms<sup>9</sup> (TABLE 1).

It is apparent that the psychiatric diagnoses of post-traumatic stress syndrome (PTSD) and hypocortisolemia have the same symptoms.<sup>6,9</sup> Of the symptoms listed for PTSD in DSM IV-TR, not all are not required to make the diagnosis. For a diagnosis of PTSD, two requirements are essential. The person must have been exposed to a traumatic event during which he or she witnessed the death of another or experienced physical harm, or even the threat of physical harm, to self or others. The second absolute requirement is that the person's response to the experience be intense fear, helplessness, or horror. In children, this manifests as disorganized or agitated behavior and can occur any time a child feels unsafe and incapable of dealing with intense fear. Basically, it can be any traumatic event or even a chaotic environment that creates intense fear. In the category of "re-experiencing the traumas" only one of the following conditions is required: intrusive thoughts of the event, dreams or nightmares, flashbacks, an intense response to the external cues of the trauma, or intense psychological stress to external cues. Of these choices, the last two items easily fit most cases of hypocortisolemia. In the category of "avoidance or numbing of feelings," only three of five of the following conditions is required: avoids thoughts of trauma; avoids activities, places, etc.; decreased interest and participation in activities; feeling detached from others; or feeling that the future is foreshortened. In the category of "increased symptoms of arousal" only two of the following items are necessary for the diagnosis of PTSD: trouble falling or staying asleep, irritability or outbursts of anger, trouble concentrating, hypervigilant, or an exaggerated startle response. Additionally, for the diagnosis of PTSD, the symptoms have to last more than a month and impair functioning in social, occupational, and other areas.<sup>6</sup>

Patients with hypocortisolemia can easily meet diagnostic criteria for PTSD. They can feel anxious or nervous, have poor stress tolerance, be hypersensitive to the environment, with a hypersensitivity to sound, light, taste, smell, and touch. Additionally, many patients experience extreme fatigue after a stressful situation. They can often feel depressed, spacey, absent-minded, forgetful or confused. All these symptoms can be interpreted as being avoidant and thus consistent with PTSD symptoms. The hypocortisolemic symptoms of sensory hypersensitivity, paranoia, irritability, hostility, problems concentrating, and an intolerance to stress can readily correspond to the PTSD subcategory of increased arousal.<sup>9</sup>

Additionally, the symptoms of hypocortisolemia may be interpreted as meeting the diagnostic criteria for numerous other psychiatric disorders.<sup>6</sup> For example, children who present with disorganized or agitated behavior and meet diagnostic criteria for PTSD can also be viewed as having the mood fluctuations of a bipolar II disorder. Concentration difficulties are given the designation of attention deficit disorders (ADD). The psychiatric journals abound with discussions of bipolar II disorders misdiagnosed as ADD.<sup>10</sup> At times they are categorized as comorbid disorders.

Even a mild to moderate cortisol insufficiency can produce certain emotional states that are common to a variety of psychiatric disorders. Emotional states can generate distinctive patterns of behavior. Furthermore, behavior is influenced by individualized interpretations of stress, the severity of the insufficiency, and cultural differences. Given these differences, it is not surprising that the manifestations of hypocortisolemic symptoms can also be assigned to a multiplicity of psychiatric diagnoses such as PTSD, ADD, depression, bipolar disorder, anxiety disorders, and personality disorders.

Poor stress tolerance, a symptom associated with hypocortisolemia, may be due to compensatory surges of adrenalin creating a fearful emotional state that leaves patients feeling overwhelmed. They have difficulty tolerating “one more thing” and thus can feel trapped by others or by life’s circumstances. Life feels unmanageable, out of control, giving patients the perception that they are victims, at the mercy of everyone and everything. Taken to the extreme it can be seen as paranoia. In addition to inducing fear, adrenalin excesses intensify the senses to the point of sensory overload. In fact, patients may be so sensitive that they can even feel the pain of others. This hypersensitivity coupled with an undercurrent of fear may help create a pessimistic attitude, perhaps to the point of being classified as depression.<sup>1</sup>

A lack of sufficient cortisol with a compensatory adrenalin release may cause some patients to feel irritable or hostile. Emotional extremes because of an adrenergic overload may result in a behavioral response of anxious outbursts or explosions of anger.<sup>12</sup> Accusatory expressions, for some, may be a way to dispel, through projection, intolerable emotions, such as fear or guilt. All these behaviors can be seen as personality features when they may be no more than a response to hypocortisolemia.<sup>6</sup> Not all people who are hypocortisolemic choose to behave in this manner. There is a choice, or free will, whereby people may change their perceptions and alter their behavior. The option to choose behavior alters physiologic response, emotional reactions, and even the balance of hormones.<sup>13-16</sup>

Numerous studies have shown that people with PTSD have low cortisol.<sup>17-20</sup> Although traumatized, other people with an adequate amount of cortisol did not go on to develop PTSD.<sup>21</sup> In fact, cortisol normally might even increase ten-fold during a traumatic event and then return to normal levels when the trauma ends. This is a healthy response to a physical or emotional stress. A healthy stress response triggers a release of adrenalin in addition to a cortisol increase.<sup>9</sup> Contrary to the general public’s erroneous concept that cortisol creates stress, the role of cortisol is to facilitate a healthy adaptation to a particular stressor. Cortisol mobilizes glucose to provide the fuel necessary for surviving a fearful event. Cortisol also counters the damaging physiologic response to stress by limiting inflammation and suppressing hyperimmunity.<sup>9,22</sup>

The term “adrenal burnout” has been used to describe an abnormal physiologic response to stress. At first, usually in childhood, the adrenal gland is thought to release enough cortisol in a crisis, but with ongoing trauma and a continuous outpouring of cortisol there is a point when the adrenal gland can no longer produce enough cortisol resulting in an inadequate response to stress. In these people, even though cortisol levels rise, the amount may not be enough to meet their needs.

A negative feedback loop regulates the release of cortisol from the adrenal cortex. Without pathology, the adrenal gland is well regulated by hypothalamic and pituitary mechanisms. Insufficient quantities of cortisol stimulate an increase in the hypothalamic production of cortisol-releasing hormone (CRH). CRH then increases the pituitary release of adrenocorticotrophic hormone (ACTH). The larger amounts of ACTH released by the pituitary gland would normally induce the adrenal glands to release the necessary amount of cortisol. In people with a relative insufficiency, even though there is an increase in the amount of cortisol, it is still inadequate to support an optimal response to stress.

The effect of an inadequate cortisol level can be debilitating, especially to the brain. Cortisol facilitates neuronal utilization of glucose for energy to allow the cell

to function and live. Neurons cannot survive without glucose. Without energy, brain cell function is severely limited.<sup>23</sup> In essence, the brain begins to shut down. Brain cells go into survival mode and diminish or cease making neurotransmitters. This decrease in brain activity may be perceived as a loss of pleasure or depression. To coin a phrase, “a screaming boredom” seems to be a fitting description for the feeling evoked by the brain’s need to survive. This state, viewed from a DSM perspective, may fill the requirements for a variety of diagnoses, depression, ADD, with or without hyperactivity, and the anxiety spectrum disorders. This partially functioning state invoked by low brain glucose can also fit the diagnosis of chronic fatigue syndrome.<sup>24</sup> It is not surprising that with a limited ability to utilize brain cells that stressful situations evoke intolerance and a limited ability to cope. In this case, challenging situations become crises.<sup>23</sup>

A limited supply of glucose to the brain causes an endogenous response in at least three ways. A perceived hypoglycemic state induces glucose hyperphagia or an overwhelming drive to eat sweets or carbohydrates, which are readily converted to glucose.<sup>25</sup> There may also be an intense drive to have something that increases cortisol for that particular person, such as coffee, alcohol, or drugs. This response to a particular substance is not universal and appears to be mediated by a genetic predisposition.

Another response to cortisol insufficiency is the rapid conversion of the prohormone thyroxine (T4) to the activated form of triiodothyronine (T3).<sup>26,27</sup> This also increases the brain’s ability to utilize glucose. Adrenalin has a similar effect. The lack of adequate fuel for brain cells is a danger signal to the adrenal medulla to respond with surges of adrenalin.<sup>28</sup> Though compensatory measures are essential to allow the brain to utilize glucose, they can cause a multitude of problems. The combination of T3 and adrenalin surges produces intense physiologic effects.<sup>26</sup> The emotional interpretation of these bodily processes and resultant behavior is determined by each person based on individual attitudes and cultural biases.

As specified in the DSM, psychiatric diagnoses are defined by specific groupings of symptoms and categories of behavior. However, the responses to the same physiologic responses, surges of T3 and adrenalin, are sweating, shaking, an increase in heart rate, palpitations, and the feelings associated with a “fight or flight” reaction. These biologic events induce the subjective feelings of anxiety, fear, and paranoia along with the possible behavioral effects of an increased startle response, irritability, hostility, or anxious outbursts. The variety of emotional and behavioral responses correlates with an array of psychiatric diagnoses such as PTSD, panic disorder, numerous anxiety disorders, substance abuse disorders, and even personality disorders.<sup>6</sup>

A relative hypocortisolemic state may underlie or at least exacerbate stress-related medical problems. Chronic fatigue syndrome may be due to relative hypocortisolemia that would lead to an inadequate supply of glucose to cells, especially in the brain cells, resulting in low energy.<sup>29</sup> Fibromyalgia may be the result of an unchecked inflammatory response in the muscles and skin due to inadequate cortisol.<sup>24</sup> Irritable bowel syndrome (IBS) may also be linked to a dysregulation of the HPA axis.<sup>30</sup> An inadequate release of cortisol in response to a stress can, in the genetically predisposed, lead to inflammation and swelling of the bowel walls that would result in the symptoms associated with IBS. Other disorders connected to a relative insufficiency of cortisol are the autoimmune disorders, such as rheumatoid arthritis or

lupus. Because cortisol modulates the immune system, in those prone to autoimmune disorders, an inadequate amount might exacerbate or perhaps even trigger a hyperimmune state.

Because many of the medical problems caused by a cortisol insufficiency respond, at least in part, to antidepressants, and in particular serotonin reuptake inhibitors (SSRIs), it may be possible that SSRIs induce an increase in cortisol. In spite of a lack of financial incentive to study antidepressant effects on the production of cortisol, there are a few studies, with paroxetine and sertraline, that do show an increase in cortisol in cortisol-deficient patients.<sup>31–33</sup>

A hormone imbalance as a cause of depression has been postulated since the 1970s. At times patients with psychiatrically diagnosed disorders were noted to have high levels of cortisol. Attempting to find a laboratory marker for depression, there were a number of studies that used a low evening dose of dexamethasone to check for the effect on cortisol the following morning. A normal response results in cortisol suppression. The hypothesis that depression is linked to nonsuppression was not supported. Using dexamethasone as a diagnostic tool was abandoned because only about half of the depressed patients showed cortisol suppression with dexamethasone.<sup>21</sup>

Some depressed patients have high cortisol levels and an excess of CRH. The hypothalamus continues to release CRH, an apparent malfunction in the negative feedback loop. A proposed mechanism is that cortisol, although excessive in blood, has limited access to the brain because of the blood–brain barrier, the capillary network supplying the brain. The blood–brain barrier also restricts entry to excessive or harmful substances. Lining the capillary endothelium, a molecular sentry, a phosphorylated glycoprotein (P-gp), acts to limit the amount of cortisol allowed to cross into the brain. Pariente and others found that the antidepressants they studied appeared to block P-gp at the blood–brain barrier, allowing more cortisol to enter the brain and hypothalamus, thus shutting down excessive CRH production.<sup>33</sup> Perhaps this may be, at least in part, the mechanism of antidepressant action. If this is correct, then P-gp may limit cortisol entry into the brain regardless of blood cortisol levels. Antidepressants may still allow for cortisol to pass through to the brain, enabling glucose to provide energy to brain cells. Theoretically, P-gp's limiting cortisol entry into the brain may be the reason why a cortisol-deficient patient does not respond to cortisol replacement.

It is not surprising to find that a condition of low cortisol may be one of the driving forces that lead people to alcoholism or substance abuse. The patients with PTSD, prone to developing an addiction, seem to do so because the particular addicting substance increases their cortisol.<sup>34</sup> This hypothesis seems to be validated by the studies done with alcoholics and naltrexone. Studies at Rockefeller University and Yale showed that alcohol increases cortisol in alcoholics and also that naltrexone appears to increase and stabilize cortisol levels through HPA activation.<sup>35</sup> This naltrexone-mediated increase in cortisol may also be the mechanism for reducing alcohol craving.<sup>34,35</sup>

People with addictions appear to have stress-related hypocortisolemia with a genetic predisposition to have cortisol levels rise with their particular substance of abuse.<sup>12</sup> Because caffeine is known to increase cortisol,<sup>36</sup> it is interesting to note that Alcoholics Anonymous meetings often include coffee, sweets, and drama. This ubiquitous availability of sweets at meetings may be due to a sugar craving from

**TABLE 2. Other symptoms of hypocortisolemia**

Diarrhea with stress	Cravings for:
Irritable bowel syndrome	sweets
Sore throat	pasta, bread
Flu-like symptoms	salty food
Achy skin	pickles, vinegar
Headaches	lemon
Trouble staying hydrated	spicy food
Fatigue more in afternoon	Autoimmune disorders
Stress-induced fatigue	arthritis
Low blood pressure	lupus
Need to keep moving	obsessive–compulsive disorders?
Allergies	multiple sclerosis?
Sinusitis	schizophrenia?

hypocortisolemia and the drama may be helpful in providing more adrenalin, another compensatory mechanism.<sup>28,37,38</sup>

In addition to emotional and behavioral symptoms, many somatic symptoms are associated with hypocortisolemia, although most patients do not manifest all the symptoms<sup>9</sup> (TABLE 2). The digestive tract problems associated with hypocortisolemia, particularly under stressful circumstances, consist of diarrhea, abdominal cramping, irritable bowel symptoms, and nausea with or without vomiting. Other symptoms commonly linked with inflammation are flu-like symptoms, achy skin, a sore throat, sinusitis, headaches, and painful joints and muscles. With a decrease in cortisol, patients who are genetically predisposed will express a hyperimmune state. Allergies flare and autoimmune conditions, such as rheumatoid arthritis, lupus, or multiple sclerosis, worsen with stress, indicating a possible association to a hypocortisolemic state. In that cortisol supports the circulatory system, lowered levels of cortisol can result in low blood pressure with orthostatic hypotension, with patients reporting momentary visual loss or a dizziness when standing up abruptly. If the levels of cortisol become extremely low, the result can be circulatory collapse or shock. Some unusual food preferences or cravings, in various combinations, seem to be a component of this condition and can consist of a need for sugar or carbohydrates such as bread or pasta, salty food, pickles, vinegar, lemon, and or spicy foods.<sup>9</sup> Fatigue, often but not necessarily in the afternoon, is a common feature of hypocortisolemia. Frequently, stressful conditions induce fatigue<sup>9</sup> (TABLE 2). At times some patients will have excessive amounts of nervous energy and seem to be “highly charged.” This may be do to the compensatory release of adrenalin in hypocortisolemia. In fact, high-risk activities or novelty-seeking behaviors are associated with PTSD and therefore with hypocortisolemia.<sup>17,38,39</sup>

In addition to the emotional, behavioral, and somatic symptoms, many patients with hypocortisolemia may have physical signs as well. Some patients with autoimmune disorders may also have vitiligo, a spotty depigmentation of the skin. Many patients have hyperpigmentation at pressure points such as joints, elbows, knees,

knuckles, and palmar creases. A brown pigmentation also can be seen below the eye in some of the patients. Scars acquired after the onset of a cortisol insufficiency will be pigmented, while earlier scars are not pigmented. Clothing pressure can also create pigmented areas such as pigment under bra straps or at the waistline from the pressure of belts. Pigmented areas are not seen in all patients with cortisol insufficiency. The presence of hyperpigmentation requires melanocytes that are able to produce melanin and presupposes an intact pituitary gland able to produce an excess of adrenocorticotrophic hormone (ACTH) in response to hypocortisolemia.<sup>40</sup>

Laboratory evaluations, though necessary, may not always corroborate even obvious clinical signs and symptoms. This may be due to laboratory testing limitations. One problem is the evanescent property of cortisol. In that cortisol release and utilization is an adaptive mechanism to any stress, fluctuations in levels would be expected. Blood drawing traumatizes some patients. Other patients may be harried by time constraints with the need to rush to work or their next scheduled activity. In these patients, the blood levels will be higher than in patients who are relatively calm. The amount of a hormone is not the only constituent that determines an adequate hormonal response. Other factors influence the efficacy of any hormone.<sup>41</sup>

Hormones exist in the blood in two states, bound to a protein and in the "free" state, or unbound. Total cortisol is a level of both bound and unbound factions, and often appears on laboratory reports as merely "cortisol." If the amount of total cortisol is within the reference range or even appears to be above the reference range, the actual amount of useful cortisol might still be very low. When a hormone is bound to a protein carrier it is slated for elimination and not available for use by the body. For cortisol, the principle protein carrier is transcortin, also called cortisol binding globulin (CBG). When CBG is present in excessive amounts, as seen in women on oral contraceptives or even those who take oral estrogen, the amount of CBG increases dramatically, greatly diminishing the amount of available cortisol in spite of a high total cortisol level.<sup>42,43</sup>

Another issue is the lack of clinical laboratory standardization. This is an international problem. Each laboratory uses different equipment, different reagents, and a variety of individual clinical pathologists who interpret the results.<sup>44,45</sup> The samples obtained to determine reference ranges are collected from the first three thousand or so results of a test ordered by doctors. These results are then used to determine the standard range by applying the concept of a bell-shaped curve. The statistical model maintains that ninety-five percent of the samples fall within two standard deviations from the mean and thus determines the reference range. Unfortunately, the samples used to make this determination are from patients who have the specific abnormalities being investigated.<sup>46,47</sup>

A 24-hour collection of urine for cortisol and cortisol metabolites is also helpful in that it is not at merely one point in time like a blood test. Instead, it is an average value for the day. Even though this may add some knowledge of the patient's physical state, not all patients who present with signs and symptoms have a low 24-hour urinary free cortisol, although they may have abnormally low levels of cortisol metabolites, suggesting that even though cortisol is available it is not being utilized. The symptoms of hypocortisolemia, in these cases, are postulated to be due to a defect in the cellular receptors for cortisol. However, these patients still respond to physiologic doses of hydrocortisone.<sup>41</sup> It is essential to remember that laboratory testing is merely an adjunct to the evaluative process and is not intended to replace good med-

ical judgment based on a comprehensive history and an examination of patients for signs and symptoms of a disorder.

Another test frequently done in patients presenting with hypocortisolemia is the stimulation of the adrenal gland using an ACTH analogue, Cortrosyn<sup>®</sup>. This is a method to determine whether the source of hypocortisolemia is due to primary adrenal insufficiency or from a secondary adrenal insufficiency due to inadequate amounts of pituitary ACTH or a hypothalamic insufficiency of cortisol-releasing hormone (CRH). The test has been performed by injecting 250 micrograms of Cortrosyn<sup>®</sup>, although this amount is considered excessive by some studies, in that all but the patients with the most severe forms of hypocortisolemia respond to this dose. Several studies suggest that a 1-microgram dose can uncover the mild to moderate cases of low cortisol.<sup>48</sup> Again, a laboratory evaluation is not intended to replace good medical judgment.

In spite of a variety of laboratory testing results, patients demonstrating the signs and symptoms of mild to moderate hypocortisolemia appear to respond to low physiologic doses of hydrocortisone in a number of studies. Patients with symptoms of hypocortisolemia who were diagnosed with chronic fatigue syndrome, responded to low doses of hydrocortisone.<sup>50</sup> Additionally, patients identified as having PTSD who are given low doses of cortisol at the time of the trauma do not seem to develop symptoms of PTSD.<sup>49,51</sup>

In the aging population, hormone insufficiencies and hormone treatments are commonplace. However, a cortisol insufficiency is often overlooked in spite of the presence of signs and symptoms. The cause may not be due to aging, but to a long-standing deficiency exacerbated by aging. Over time, most patients develop a variety of coping skills for mild to moderate cortisol insufficiency, at times known as a low adrenal reserve. If fatigue, pain, memory deficits, and concentration difficulties worsen, they are then attributed to "getting old."

Some studies describe an increase in serum cortisol in the elderly. However, they may still manifest the signs and symptoms of a hypocortisolemia. As in some younger people, cellular cortisol receptors may be less sensitive. This limits cortisol function in spite of seemingly adequate levels. Testing for cortisol and its metabolites in a 24-hour urine sample will show high or normal urinary free cortisol with below normal metabolites, the total amount of hydroxycorticosteroids.<sup>41</sup> Other studies of older patients actually demonstrate a decrease in serum cortisol. This is thought to be due to an age-related decrease in adrenal cortex sensitivity to ACTH.<sup>52</sup> Additionally, the signs and symptoms of a relative cortisol deficiency correspond to the symptoms normally associated with aging.

Moreover, when elderly patients have symptoms that are primarily emotional, or demonstrate behavioral dysfunction, they are readily diagnosed with a psychiatric disorder and are treated with psychotropic medications. As physicians, we have an obligation to include a thorough evaluation of each patient despite age, prior to making a psychiatric diagnosis, which by definition is a diagnosis of exclusion. Furthermore, in addition to medication side effects, treating symptoms with psychotropic medications may mask any underlying medical problems, which can result in continued, perhaps progressive morbidity and possibly mortality. The most important element of providing good patient care is the ability to make an accurate diagnosis by obtaining a good history and performing a physical exam. Treating the underlying problem is a better approach to patient care. In the case of a relative cortisol insuffi-

ciency, if patients are treated with physiologic doses of hydrocortisone, the symptoms for the most part abate.<sup>41,51</sup> Once a medical diagnosis can be either ruled out or confirmed and treated, then a psychiatric diagnosis and treatment with psychotropic medications may be appropriate and perhaps even necessary.

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