What is Pseudo-Cushing's? By Theodore Friedman, MD, PhD

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Cushing's syndrome is a rare disorder which can severely affect the patient. Symptoms of patients with Cushing's syndrome include weight gain, easy bruising, menstrual irregularities, increased appetite, trouble sleeping, depression or mood swings, anxiety, fatigue and altered mentation (trouble concentrating or decreased memory) (1-3). Physical abnormalities include new onset obesity (primarily in the abdominal and buttock regions), buffalo hump, filling in of the regions above the collarbone, thinning of the extremities, rounding and reddening of the face, thin skin, decreased muscle strength, high blood pressure, stretch marks and excess hair growth in women. Although some patients may have most or all of these signs and symptoms so that the diagnosis of Cushing's syndrome may be easy to make, other patients may have mild Cushing's syndrome and come to their health care providers at an early stage of the disease. This is especially true as Cushing's syndrome has been publicized in the lay literature (4) and with the proliferation of Internet-related information sites and Cushing's support groups, more patients are aware that Cushing's syndrome may explain their medical problems. Thus, patients are seeking medical attention earlier. However, other medical conditions may also result in some of the signs, symptoms and laboratory abnormalities seen in patients with Cushing's syndrome, without the patient actually having Cushing's syndrome. These conditions are called pseudo-Cushing's states and include conditions such as severe stresses (illness or emotional stress), alcoholism or alcohol withdrawal and psychiatric conditions such as depression, panic disorders and psychotic conditions. The pathophysiology leading to increased cortisol production in alcoholism and depression is discussed below. Pseudo-Cushing's states are classically defined as those conditions associated with increased cortisol production [usually measured by urinary free cortisol (UFC) measurements] but with less clinical signs and symptoms than true Cushing's syndrome. Resolution of the underlying primary condition leads to disappearance of the signs and symptoms of Cushing's syndrome. In this chapter, we will also discuss conditions which mimic the clinical stigmata of Cushing's syndrome, but lack elevated cortisol production.

The psychiatric conditions causing pseudo-Cushing's states, such as depression, are quite common and a patient with one of these conditions may appear similar to the rarer patient with Cushing's syndrome. Thus, it is quite important to determine if the patient has Cushing's syndrome or a pseudo-Cushing's state in a time- and cost-effective manner, because if a patient with a pseudo-Cushing's state is missed diagnosed as having Cushing's syndrome, that patient could undergo needless and potentially harmful testing and also unnecessary surgery. On the other hand, if a patient truly has Cushing's syndrome, it would be important to confirm the diagnose and eliminate the possibility of a pseudo-Cushing's state, so that the etiology of the Cushing's syndrome can be determined and the patient receive the appropriate surgery. It is important to make the diagnosis of Cushing's syndrome before investigating the type of Cushing's syndrome (differential diagnosis), as the tests employed in the latter require the patient to be hypercortisolemic.

Conditions Leading to Pseudo-Cushing's States

Both physiological and non-physiological conditions can lead to elevated cortisol production, leading to some signs and symptoms of hypercortisolism (Table 1). The physiological conditions include stresses associated with surgery and severe illness, and emotional, caloric and aerobic stress. Rosmond et al., (5) found that stress-related cortisol secretion was associated lack of diurnal variation of cortisol, cortisol levels after dexamethasone suppression, central obesity, hypertension, hyperlipidemia and insulin-resistance. The pathophysiological conditions include both alcoholism (6, 7) and psychiatric disorders (8, 9). Poorly controlled diabetes is also associated with hypercortisolism (10, 11). The hypercortisolism of alcoholism has been described much more frequently in Europe (6, 12-14); it may be rarer in the United States. Wand and Dobs (15) estimated that 5% of the alcoholic population in the Baltimore area had clinical signs of hypercortisolism. The psychiatric disorders leading to a pseudo-Cushing's states commonly confused with Cushing's syndrome include depression and anxiety disorders. Depression leading to increased cortisol production is quite common and is discussed below. Anorexia nervosa and bulimia usually do not present with symptoms of Cushing's syndrome. Renal failure leading to high cortisol production, while rare, poses significant diagnostic and therapeutic problems (16-18). Severe obesity may lead to mild elevations in cortisol production, however in both obesity and renal failure, most of the other stigmata of Cushing's syndrome are lacking.

Primary glucocorticoid receptor resistance (19-21) leads to elevated cortisol levels and may also be confused with Cushing's syndrome. The diminished feedback by glucocorticoids leads to high levels of ACTH and cortisol. Since hypertension and hyperandrogenism leading to hirsutism, acne, and oligomenorrhea exist, the patients may present with some symptoms of Cushing's syndrome. However, the classic end-organ effects of hypercortisolism including easy bruising, thin skin, and proximal muscle weakness, are absent.

Excessive fluid intake due to psychogenic polydipsia or diabetes insipidus has recently been described to cause an elevation in urinary cortisol excretion (22). In these conditions, it is hypothesized that high urinary volumes results in a loss of the renal medullary gradient and the inability to reabsorb cortisol occurs.

Finally, a common and often difficult to diagnose cause of increased cortisol levels associated with the stigmata of Cushing's syndrome is factitious glucocorticoid intake (23). The patient may be taking hydrocortisone, prednisone, dexamethasone or other synthestic glucocorticoid or rarely, ACTH. Cortisol levels may be high (in the case of hydrocortisone) or low (in then case of prednisone or dexamethasone) depending on whether the glucocorticoid cross-reacts with the cortisol assay. In exogenous glucocorticoid intake, ACTH levels are low and imaging may show atrophic adrenal glands. The patient is frequently in the medical profession, presents with severe symptoms of a rapid onset and is often quite impatient in demanding a rapid work up. A high degree of suspicion is needed to uncover this disorder, which is associated with a high morbidity and mortality.

The normal circadian rhythm of cortisol is maintained (see below) in renal failure, excessive fluid intake, glucocorticoid resistance, renal failure and most psychiatric conditions, allowing these conditions to be distinguished from Cushing's syndrome.

Other Conditions Which May Mimic Cushing's syndrome

In addition to pseudo-Cushing's states in which cortisol production is increased, there exists other states, with normal cortisol production which nevertheless, may mimic Cushing's syndrome (Table 1). The most common of these conditions is obesity and particularly the central obesity associated with the metabolic syndrome (24) [previously called syndrome X (25)]. Although cortisol production may be mildly increased (26-29) in some obese patients, direct evidence of hypercortisolism is usually absent and the cortisol levels are only mildly elevated. Similarly, polycystic ovary syndrome (PCOS) while associated with some signs and symptoms of hypercortisolism such as hirsutism, central obesity and oligomenorrhea, is characterized by eucortisolemia. Usually a careful history and physical can separate patients with these obesity or PCOS from those with true Cushing's syndrome.

Patients with adult pituitary growth hormone (GH) deficiency may present with symptoms similar to those of Cushing's syndrome. These include weight gain accompanied by central obesity, low energy and fatigue, reduced muscle strength, altered lipid composition and impaired psychological sense of well-being (30). GH deficiency should be suspected in patients with previous insults to their pituitary including surgery, radiation and presence of a pituitary tumor. Idiopathic adult GH deficiency is infrequently reported, but may exist. Patients with a history of pituitary damage should be evaluated by either two GH stimulation tests (arginine, L-dopa, GHRH, clonidine or exercise) or with an insulin tolerance test. In patients without a history of pituitary damage, the paradigm for evaluation is less clear. A prudent approach in patients with symptoms of GH deficiency would be to initially measure a serum IGF-1 level. If the value is in the lower 25% for the patient's age and sex, to then perform either the two GH stimulation tests mentioned above or the insulin tolerance test. Patients with GH deficiency are eucortisolemic.

Recently, it was noted that human immunodeficiency virus-1 (HIV)-positive patients, especially those on retroviral protease inhibitors have many of the signs and symptoms of Cushing's syndrome, including new onset central obesity, dorsocervical fat accumulation (buffalo hump), hyperlipedemia and abnormal glucose homeostasis (31-34). These abnormalities have been called protease inhibitor-associated lipodystrophy (PIAL) (35). In a study of HIV-positive patients on protease inhibitors, decreased UFC but increased 17-hydroxysteroid (17-OHS) excretion was found (35). Serum and urine cortisol were found to suppress normally to dexamethasone. The authors concluded that altered cortisol production was unlikely to explain the central obesity (35). Although it was thought that the altered fat distribution was due to the protease inhibitors, a recent report in HIV-infected women suggests that the body fat changes occurs regardless of protease inhibitor use (36). Thus the HIV-induced malnutrition of patients not on protease inhibitors may mask the central obesity, which would be further exacerbated by weight gain and increased adiposity after protease inhibitor treatment (36). While this condition is quite interesting, it is unlikely that these patients will be mistaken for patients with true Cushing's syndrome.

On the other hand, there are two conditions which although rarely described in the literature may completely mimic Cushing's syndrome, but are not associated with systemic hypercortisolism. These include hyper-responsivity of the glucocorticoid receptor and impaired catabolism of cortisol at the level of the tissue. One patient has been studied with symptoms of hypercortisolemia, but low UFC levels (37-39). The patient's fibroblasts were isolated and found to be hyper-responsive to glucocorticoids. Although only one patient with this condition has been described in the literature, others may exist but have eluded being diagnosed, as screening tests (UFCs or dexamethasone suppression) would likely be normal in patients with this condition and the patient would probably not be further evaluated. Interestingly, a polymorphism at the glucocorticoid receptor was found in 6% of normal Dutch men and was consistent with cortisol hyper-responsivity associated with significantly greater cortisol suppression by dexamethasone, higher body-mass index and lower bone density than non-carriers (40).

Glucocorticoid action at the pre-receptor level is regulated, in part, by 11β-hydroxysteroid dehydrogenase (11β-HSD), an enzyme which interconverts bioactive cortisol and bioinactive cortisone (41). There are two isoforms of this enzyme, 11β-HSD1, a low-affinity enzyme present in omental fat, hepatic, gonadal and neural tissues and 11β-HSD2, a high affinity enzyme present in the colon and kidney. In omental fat cells, 11β-HSD1 predominately converts cortisone to cortisol (42, 43), while in the kidney, 11β-HSD2 predominantly inactivates cortisol, protecting the non-selective mineralocorticoid receptor from cortisol excess. Since patients with Cushing's syndrome have central obesity, Stewart and colleagues (42, 44) proposed that enhanced conversion of cortisone to cortisol by 11β-HSD1 in the omentum may lead to similar symptoms of hypercortisolism in patients without true Cushing's syndrome. Patients with excess 11β-HSD1 would have normal plasma and urine levels of cortisol, but have symptoms of hypercortisolism. There are no specific inhibitors of 11β-HSD1 currently available; licorice and carbenoxolone inhibit both 11β-HSD1 and 11β-HSD2 and may cause mineralocorticoid hypertension. This condition, although not yet documented, may explain the findings of eucortisolemic individuals with the stigmata of Cushing's syndrome.

Pathophysiology of Pseudo-Cushing's States

Explanations for the hypercortisolemia in the pseudo-Cushing's states of depression and alcoholism have been proposed. Patients with depression, particularly melancholic depression (45) have hypercortisolemia and it is thought that the primary defect is at or above the level of the hypothalamus (45-48). This hypothesis is based on the following evidence: 1) The ACTH response to exogenous corticotrophin-releasing hormone (CRH) is attenuated, indicating that the pituitary corticotroph is appropriately restrained by the negative feedback of the elevated levels of glucocorticoids. 2) Baseline evening plasma cortisol levels are elevated in depressed patients, but the cortisol response to CRH is similar as normals. 3) Depressed patients have an increased response to exogenous ACTH compared to controls. 4) Normal controls receiving a continuous infusion of CRH have a similar degree of hypercortisolism as those with depression. 5) Cerebrospinal levels of CRH are elevated in patients with depression. To integrate these findings, it is hypothesized that endogenous CRH is elevated in depression, with this being the earliest abnormality. The adrenal glands would then hypertrophy leading to the increased response of cortisol to ACTH. Cortisol feedback to the corticotroph would remain present [although also blunted as depressed patients have reduced suppression to dexamethasone (49-51)], so that exogenous CRH causes a blunted ACTH response, but a normal cortisol response. This theory is supported by the finding of adrenal enlargement in depressed patients (52). In conclusion, depression is likely a state of CRH excess, while true Cushing's syndrome is a state of CRH deficiency. This difference is exploited in many of the tests designed to distinguish Cushing's syndrome from pseudo-Cushing's states.

In experimental animals given alcohol, there is a hypersecretion of CRH along with a partial reduction in the pituitary to both suppression by glucocorticoid and stimulation by CRH (53, 54). The increased CRH secretion may be at the hypothalamic or suprahypothalamic level (i.e. limbic cortex) (55). It is further postulated that in alcohol abusers, the decreased responsiveness to CRH is due to either down-regulation of the CRH receptors in the pituitary or alcohol's influence on transmembrane signal transduction (56-58). Moreover, in alcoholism, there appears to be impaired binding of cortisol to cortisol-binding globulin (CBG), leading to elevated levels of free cortisol (59). Another possible explanation for pseudo-Cushing's syndrome in patients with alcohol abuse is impaired hepatic metabolism of cortisol (60). Finally, genetic influences may determine why only some alcoholics develop pseudo-Cushing's syndrome (61, 62).

Initial Workup of Patients with Possible Hypercortisolism

What should an Endocrinologist do if a patient has some of the signs and symptoms of Cushing's syndrome? Patients should have a careful history and physical looking for findings specific for Cushing's syndrome. Attention should be directed to the time course of the symptoms (new, sudden onset of weight gain and other symptoms suggest Cushing's syndrome, while long-standing, non-progressing symptoms suggest pseudo-Cushing's states). Comparison with old pictures is often very helpful. New onset sleep disturbances, including frequent awakening with associated daytime fatigue are frequent in Cushing's syndrome. Typically, but not always, the obesity of Cushing's syndrome is centripetal, with a wasting of the arms and legs, distinct from the generalized weight gain seen in idiopathic obesity. Rounding of the face (moon facies) and a dorsocervical fat pad ("buffalo hump") occur in non-Cushing's syndrome-related obesity, while facial plethora and supraclavicular and temporal filling are more specific for Cushing's syndrome. Thinning of the skin on the top of the hands is a very specific sign in younger adults with Cushing's syndrome and should always be examined. Once a careful history and physical is performed, patients suspected of having hypercortisolemia should begin their laboratory investigation to distinguish between true Cushing's syndrome and other states. It is recommended that UFC measurement should be the initial screening test for patients suspected of hypercortisolemia as this test has a high degree of sensitivity and is easy to perform. Low-dose dexamethasone screening has many disadvantages compared to UFC measurement (see below) and although capable of providing useful information, cannot be recommended over UFC determinations.

I recommend measurement of three 24-hour urine samples for UFC. An elevated UFC on at least one occasion was found in 184/194 (95%) with Cushing's syndrome (63). This test is a good screen to help determine if the patient has Cushing's syndrome, is completely normal, or has an intermediate value and requires further testing to distinguish between pseudo-Cushing's states and Cushing's syndrome. Patients need to be instructed to discard the first morning void and then collect all urine until the next morning void. If all the UFCs are in the normal range (usually less than 50 or 90 μg/d (138 or 248 nmol/L), depending on the assay), it is unlikely that the patient has Cushing's syndrome. If some of the UFCs are more than 3.5 times the upper limit of normal (usually more than 175 or 315 μg/day; 491 or 870 nmol/L, depending on the assay), the patient probably has Cushing's syndrome and should have a work-up to determine the etiology of the Cushing's syndrome. If the patient's UFCs fall in the range between the upper limit of normal and 3.5 times the upper limit of normal, the patient needs to have further tests to distinguish between Cushing's syndrome and pseudo-Cushing's states. Once the initial screen (UFC) has determined that the patient has hypercortisolism, more sophisticated tests are needed to make the diagnosis of Cushing's syndrome.

Tests to Distinguish Pseudo-Cushing's States from Cushing's syndrome

There are many tests which can be done to distinguish between mild Cushing's syndrome and pseudo-Cushing's states (Table 2). The distinction between these two groups is the consideration of importance, as patients with severe Cushing's syndrome can probably be easily identified and normal patients can also be easily excluded. For this reason, the diagnostic accuracy for older tests which were based on separating normal volunteers from those with severe Cushing's syndrome are probably not relevant. The two very good, relatively new tests to help the Endocrinologist distinguish between mild Cushing's syndrome and pseudo-Cushing's states in those patients with a mildly elevated UFC, are the diurnal plasma cortisol test and the dexamethasone-CRH test. Salivary nighttime cortisol tests are also promising. Other tests including the low-dose dexamethasone test, loperamide test, insulin-tolerance test, CRH test, morning plasma free cortisol and pituitary imaging, while capable of providing additional information for the evaluation of Cushing's syndrome, exhibit an overlap between mild Cushing's syndrome and pseudo-Cushing's states and are probably inferior to the diurnal plasma cortisol and the dexamethasone-CRH test. There is no role for morning plasma total cortisol levels or petrosal sinus sampling.

Diurnal Cortisol Tests

The disruption of the circadian rhythm of cortisol (and ACTH) is a distinguishing characteristic of Cushing's syndrome. Normally cortisol reaches a peak in the early morning and a nadir around midnight (64). The normal range for morning plasma cortisol is broad; patients with Cushing's syndrome, pseudo-Cushing's states and normals have an overlap of their morning plasma cortisol levels, making this test unsuitable to use to diagnose Cushing's syndrome (65). The diurnal serum cortisol test, which measures a midnight serum cortisol level, takes advantage of the fact that normal patients and patients with pseudo-Cushing's states have much lower levels in the evening and at night, while patients with Cushing's syndrome have high cortisol levels at night. Newell-Price et al., (66) described the use of this test to distinguish between patients with Cushing's syndrome and normal volunteers in subjects who were hospitalized for at least 2 days prior to sampling. A sleeping midnight plasma cortisol of greater than 50 nmol/L (1.8 μg/dl) was found in all patients with confirmed Cushing's syndrome, but none of the normal volunteers. This test was superior to the low-dose dexamethasone-suppression test (see below) in which 3 patients with Cushing's syndrome suppressed to low dose dexamethasone with a morning plasma cortisol value of greater than 50 nmol/L (1.8 μg/dl). Unfortunately, no patients with pseudo-Cushing's states were included in this study, nor were patients with mild Cushing's syndrome particularly studied. Additionally, hospitalization of patients for 3 days to perform this test is impractical.

Papanicolaou et al. (67) used the midnight serum cortisol to distinguish patients with Cushing's syndrome from those with pseudo-Cushing's states. A midnight cortisol value greater than 7.5 μg/dl (208 nmol/L) correctly identified 225/234 patients with Cushing's syndrome, while a value less then this cutoff was found in all 23 patients with pseudo-Cushing's states. Thus the specificity was 100% and the sensitivity was 96%. The test failed in a few patients with mild Cushing's syndrome (UFC less than 200 μg/day) and those who were episodic secretors of cortisol. This study compared the two groups needing differentiation, those with pseudo-Cushing's states and those with mild Cushing's syndrome. The study did, however, only examine hospitalized patients. Because of the timing of the required blood draw, this test may require a hospital admission as it is often difficult to obtain blood at midnight in an outpatient setting.

Because of the difficulty in obtaining blood at midnight, salivary cortisol was used to distinguish between Cushing's syndrome and pseudo-Cushing's states (68). This test is based on the finding that salivary cortisol is in equilibrium with plasma free cortisol and is independent of saliva production. This study examined 11 P.M. salivary cortisol in 39 patients with proven Cushing's syndrome, 39 patients referred for possible Cushing's syndrome, but in whom the diagnosis was excluded or not firmly established (RO) and 73 normal volunteers. The average 11 P.M. salivary cortisol was 20 times higher in the patients with Cushing's syndrome than the other two groups. Using a cutoff of 3.6 nmol/L (0.13 μg/dl), 36/39 patients with Cushing's syndrome had an elevated value, while 37/39 of the RO group and 38/39 of the normal volunteers had values less than the cut-off. The sensitivity and specificity of this test was 92% and 96%, respectively. Using a different assay and studying a smaller number of patients, Papanicolaou et al., (69) also found that salivary cortisol levels can distinguish between patients with Cushing's syndrome and those with pseudo-Cushing's states. The fact that the upper limit of normal for this assay was 0.5 μg/dl while that of the Raff et al., (68) study was 0.13 μg/dl, demonstrates that the salivary cortisol results have to be standardized at each laboratory. Recently, Dr. Findling has made the salivary cortisol test readily available to patients by distribution a packet which includes the salivette for collecting the saliva and instructions for mailing the sample to Aurora Laboratories. Samples are stable and can be collected in the patients' home and mailed in. This test looks promising, however, it hasn’t been tested on enough patients with pseudo-Cushing’s states.

Dexamethasone-CRH Test

Another recommended test to distinguish between mild Cushing's syndrome and pseudo-Cushing's states in those patients with a mildly elevated UFC is the dexamethasone-CRH test. This test combines two tests, the low-dose dexamethasone suppression test (LDDST) and the CRH test which individually are good but not great at distinguishing between pseudo-Cushing's states and Cushing's syndrome. As discussed below, the dexamethasone test takes advantage of the fact that in patients with Cushing's syndrome, dexamethasone ineffectively suppresses the production of pituitary ACTH. CRH stimulates the pituitary to secrete ACTH which leads to an increase in cortisol levels. Patients with Cushing's syndrome have a larger increase in plasma ACTH and cortisol levels than in normal individuals or those patients with pseudo-Cushing's states. Although these tests individually are helpful to diagnose Cushing's syndrome, many patients with pseudo-Cushing's states also respond to them in a similar manner as those with Cushing's syndrome, making them not the ideal test to use individually. Yanovski et al., (9) elected to combine the two tests and gave 39 patients with Cushing’s syndrome and 19 patients with pseudo-Cushing’s states dexamethasone (0.5 mg) 4 times a day for 2 days starting at 12 noon (last dose at 6 A.M.). At 8 A.M. on the day of the last dose, the patients received intravenous ovine CRH (1 μg/kg) and cortisol and ACTH were measured at various times. All patients with Cushing’s syndrome had mild hypercortisolemia (UFC between 250 and 1000 nmol/d; 90-362 μg/d) so that UFCs between patients with Cushing’s syndrome and pseudo-Cushing’s states completely overlapped. A plasma cortisol greater than 1.4 μg/dl (38 nmol/L) measured 15 minutes after the CRH injection correctly identified all patients with Cushing’s syndrome, while a value less than 1.4 μg/d identified all patients with pseudo-Cushing’s states (100% sensitivity and specificity). In contrast, the low dose dexamethasone test, had a 74% specificity and 69% sensitivity when 17-OHS was measured on the second day of dexamethasone administration and 100% sensitivity and 56% sensitivity when UFCs were measured. The CRH stimulation test without dexamethasone pretreatment had 100% specificity and 64% sensitivity. This study has the advantage of comparing the dexamethasone-CRH test to other popular tests (LDDST and CRH test) in the same group of patients with mild Cushing’s syndrome and pseudo-Cushing’s states and clearly showed the superiority of the dexamethasone-CRH test in this group of patients. The main drawbacks to this test is that it requires a lot of steps and the drug (CRH), while no longer investigational, is expensive. A subsequent paper (70), found, as expected, that the dexamethasone-CRH test completely distinguished patients with Cushing’s syndrome from normal volunteers.

There are other tests (listed in Table 2) that may help distinguish between Cushing's syndrome or pseudo-Cushing's states. Although unable to completely distinguish these two groups as well as the above mentioned diurnal cortisol tests and dexamethasone-CRH tests, low dose dexamethasone tests, the insulin tolerance test, the desmopressin test and the loperamide test can provide useful information. The IL-6 test is investigational, but may be helpful in the future. Low dose dexamethasone tests are still widely performed.

Low dose dexamethasone tests

These tests are based on the fact that patients with Cushing’s syndrome are resistant to suppression by low dose dexamethasone. Dexamethasone suppression is frequently abnormal in patients with depression (49-51), the very group designed to exclude. In the overnight dexamethasone suppression test (71, 72), 1 mg of dexamethasone is given orally at 11 P.M., and a plasma cortisol is drawn the following morning at 8 A.M. A plasma cortisol greater than 5 µg/dl (138 nmol/L) suggests hypercortisolism. In the LDDST (73), dexamethasone (0.5 mg) is given every 6 hours for eight doses. A UFC greater than 10 µg/day (28 µmol/day) or a 17-OHS greater than 2.5 mg/day (6.9 µmol/day) on the second day of dexamethasone is consistent with Cushing’s syndrome. These tests have been found to misclassify as many as 6% of patients with Cushing’s syndrome and 15% of patients with pseudo-Cushing’s state. Patients with major depression(43%), other psychiatric disorders (8-41%), obesity (13%) and the chronically ill (23%) do not suppress to overnight dexamethasone (74, 75). An additional problem is the variable metabolism of dexamethasone in patients receiving medicines such as rifampin, phenobarbital or phenytoin) or in patients with renal or hepatic failure (76, 77). Most importantly, estrogens raises CBG and since the RIA for cortisol measures total cortisol, high false positive rates are seen in women taking estrogen (78). To increase the specificity of the overnight dexamethasone test, the cut-off of post-dexamethasone serum cortisol was proposed to be 1.8 µg/dl (138 nmol/L) (79). However, it was recently reported that 19% of patients with Cushing’s syndrome had a suppressed serum cortisol of less than 5 µg/dl (138 nmol/L) and a much larger percentage had a serum cortisol less than 1.8 µg/dl (80, 81). Thus, the low dose dexamethasone tests can neither be considered sensitive nor specific to distinguish between Cushing's syndrome or pseudo-Cushing's states. For these reasons, collection of urine for measurement of 24 hour urinary free cortisol excretion is likely to be a better screening test for Cushing's syndrome (81, 82). For those patients already suspected of having Cushing’s syndrome, the dexamethasone-CRH test is likely to be a better test than the LDDST to confirm Cushing’s syndrome (9).

Insulin Tolerance Test

The insulin tolerance test (ITT) measures the pituitary corticotrophs' ability to secrete ACTH in response to the stress of insulin-induced hypoglycemia. After an overnight fast, intravenous regular insulin (0.15 unit/kg) is given as a bolus. Blood samples for glucose, ACTH and cortisol are obtained at 0, 30, 60, and 90 minutes. An adequate level of hypoglycemia (a blood glucose concentration of less than 40 mg/dl or a decrease of more than 50% of the baseline concentration) needs to be obtained and a physician should be present during the test. An increase of plasma cortisol or ACTH by more than two-fold compared to baseline is considered a normal response. Patients with pituitary Cushing's disease usually fail to respond to the stress of hypoglycemia and do not have an increase in ACTH and cortisol. This is perhaps a result of depressed CRH neurons in these patients. The corticotrophs of most patients with pseudo-Cushing's states respond appropriately to stimuli and an appropriate increase in ACTH and cortisol will occur. The ITT has about an 75% predictive value in discriminating between Cushing's syndrome and pseudo-Cushing's states (8, 75, 83) and is likely inferior than the dexamethasone-CRH test or diurnal cortisol tests. It is now rarely performed.

<u>Desmopressin Test</u>

Desmopressin, a vasopressin analog which stimulates corticotrophs, was found to stimulate ACTH in 14 of 14 patients with Cushing’s syndrome, but not in 20 normal patients and 11 patients with depression (84). All the depressed patients lacked stigmata of hypercortisolism and most of them had normal cortisol excretion. Additionally, other studies have found that some patients with Cushing’s syndrome do respond to desmopressin (85, 86). Again, the lack of a true group of hypercortisolemic patients with pseudo-Cushing’s state, preclude this study from being recommended.

<u>Loperamide Test</u>

The loperamide test is based on the fact that opiates decrease plasma ACTH and cortisol levels possibly because the precursor for ACTH, POMC, also contains the endogenous opiate, β-endorphin. Thus, opiates would be expected to decrease POMC levels and decrease ACTH secretion. It was postulated that patients with pseudo-Cushing’s state would have this feedback intact, while those with Cushing’s syndrome would lack this feedback. The opiate agonist, loperamide (immodium), a drug used to treat diarrhea, is given at a dose of 16 mg at 8:30 A.M and 3 samples (basal, 180 and 210 min after drug) are obtained (87). In 41 patients with confirmed Cushing’s syndrome, loperamide did not suppress the cortisol levels below 138 nmol/L (5 μg/dl), while in 104 of 110 patients referred for evaluation of Cushing’s syndrome, which was subsequently ruled out, the cortisol value suppressed to less than 138 nmol/L (5 μg/dl) at either 150 or 210 min (88). However in the group in which Cushing’s syndrome was ruled out, it was unclear if the patients were hypercortisolemic. In a small study comparing the overnight dexamethasone test and the loperamide, the dexamethasone test was found to have higher specificity when patients with depression were evaluated (89). The loperamide test needs to be studied in more patients with mild Cushing’s syndrome and pseudo-Cushing’s state before it can be endorsed.

Interleukin-6 (IL-6) Test

IL-6 is a cytokine which stimulates the hypothalamic-pituitary axis via the CRH neuron in animals and was found to stimulate plasma cortisol and ACTH in normal volunteers (90). As pseudo-Cushing's states are marked by CRH excess while in Cushing’s syndrome, there is a deficiency of CRH, it was postulated that injection of IL-6 could distinguish between the two groups. The authors expected that IL-6 would stimulate plasma cortisol and ACTH in patients with pseudo-Cushing's states, but not in those patients with Cushing’s syndrome. Thirty four patients with Cushing’s syndrome and 9 patients with pseudo-Cushing's states received a single injection of IL-6 (3 μg/kg) (91). ACTH (maximum response at 90 minutes) and cortisol (maximum response at 120 minutes) rose in the patients with pseudo-Cushing's states, but not in those with Cushing’s syndrome. An ACTH at 90 minutes and cortisol at 120 minutes was able to completely separate the groups. This study has only been reported in abstract form and IL-6 is an investigational drug, making its use limited. We await further studies using this interesting agent.

Tests Not Recommended to Distinguish Between Cushing's syndrome and Pseudo-Cushing's States

There are also tests (Table 2) that are not helpful in making the distinction between Cushing's syndrome or pseudo-Cushing's states and may actually be confusing if done before the diagnosis of Cushing’s syndrome is made. Inferior petrosal sinus sampling (IPSS), an excellent test to differentiate the etiologies of confirmed Cushing’s syndrome, measures ACTH in the petrosal sinuses draining the pituitary compared to simultaneously drawn levels from the periphery. The test is usually given with CRH. Yanovski et al. (92) proposed that IPSS would be able to separate patients with Cushing’s syndrome from those with pseudo-Cushing’s states and speculated 3 findings in patients with Cushing’s syndrome compared to those with pseudo-Cushing’s states: 1) that the ACTH concentrations in the petrosal sinus compared to the periphery would be higher, 2) that there would be more of difference in the ACTH concentrations between the petrosal sinuses and 3) that CRH administration would not stimulate ACTH concentrations in the suppressed petrosal sinus. They studied 7 normal volunteers, 9 patients with pseudo-Cushing’s states and 40 patients with Cushing’s syndrome. Contrary to their expectations, all 3 groups had elevated petrosal to central ACTH concentrations, had lateralization of one petrosal sinus and responded similarly to CRH administration. Thus, IPSS can not be used to distinguish patients with Cushing’s syndrome from those with pseudo-

Cushing’s states and may actually be misleading if performed before the diagnosis of Cushing’s syndrome is made.

Pituitary MRI is also very good for localizing a pituitary tumor once the diagnosis of Cushing's syndrome is made, however it is not recommended to distinguish between Cushing's syndrome and pseudo-Cushing's states. This is because up to 10% of normal individuals have what radiologists read as a pituitary tumor on MRI (incidentalomas) (93). If a patient without Cushing’s syndrome only has a pituitary MRI performed which shows an adenoma, she/he may be inappropriately diagnosed as having CD and undergo unnecessary surgery.

As stated above, a morning plasma cortisol is also not able to distinguish between mild Cushing’s syndrome and pseudo-Cushing’s state. Similarly, a plasma free cortisol while higher in patients with Cushing’s syndrome than those with pseudo-Cushing’s state also exhibited too much overlap between the two groups to be used clinically to exclude pseudo-Cushing’s state (65).

Treatment of Pseudo-Cushing’s States and Conclusions

The distinction between Cushing's syndrome and pseudo-Cushing's states is often difficult, leading to frustration for both patient and physician. To prevent this frustration, working closely with a good Endocrinologist who sees many patients with Cushing's syndrome is needed. Patience is also needed. With time, most patients will "declare themselves" and develop a clearer picture consistent with either Cushing's syndrome or a pseudo-Cushing's state. While waiting, treating the underlying psychiatric condition (if present) is often helpful. In some patients, a trial of low dose ketoconazole (200 mg twice a day) may be helpful in that if the patient improves on this treatment, clinically relevant hypercortisolism is probably present, while if the patient does not improve, most likely the patient’s symptoms are unrelated to hypercortisolism. This trial can not reliably be used to distinguish between Cushing’s syndrome and pseudo-Cushing’s states as both groups may improve on ketoconazole. Liver function tests and signs of adrenal insufficiency need to be monitored on this drug. The tincture of time is the best cure!

Table 1: Pseudo-Cushing States

High Cortisol Secretion Rate without Convincing Clinical Features of Cushing Syndrome

<u>Stress</u>

- Surgery
- Severe illness
- Emotional
- Caloric
- Aerobic

<u>Alcoholism</u>

- Long-term active alcoholism
- Ethanol withdrawal

<u>Psychiatric Disorders</u>

Depression (particularly melancholic depression)
Anorexia Nervosa
Bulimia
Psychoses
Panic Disorders
Renal Failure
Severe Obesity
Primary Glucocorticoid Receptor Resistance
Excessive Fluid Intake (Psychogenic Polydipsia or Diabetes Insipidus)
Factitious Glucocorticoid Intake
Uncontrolled Diabetes

Conditions with Eucortisolemia Which May Mimic Cushing's Syndrome
Obesity
Metabolic Syndrome
Polycystic Ovary Syndrome
Growth Hormone Deficiency
HIV Infection
Glucocorticoid Hyper-Responsivity
Impaired Cortisol Catabolism

Table 2: Tests to Distinguish Pseudo-Cushing's States from Early Cushing's Syndrome

Recommended
Urinary Free Cortisol
Dexamethasone-CRH Test
Diurnal Plasma Cortisol Tests
Diurnal Salivary Cortisol Tests

Possibly Recommended
Low-dose Dexamethasone Test
Loperamide Test
Naloxone Stimulation Test
IL-6 Test

Not Recommended
Morning Plasma Cortisol Levels
Petrosal Sinus Sampling
Pituitary MRI

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