DIAGNOSIS OF ENDOCRINE DISEASE

Differentiation of pathologic/neoplastic hypercortisolism (Cushing's syndrome) from physiologic/non-neoplastic hypercortisolism (formerly known as pseudo-Cushing's syndrome)

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Abstract

Endogenous hypercortisolism (Cushing's syndrome) usually implies the presence of a pathologic condition caused by either an ACTH-secreting neoplasm or autonomous cortisol secretion from a benign or malignant adrenal neoplasm. However, sustained or intermittent hypercortisolism may also accompany many medical disorders that stimulate physiologic/non-neoplastic activation of the HPA axis (formerly known as pseudo-Cushing's syndrome); these two entities may share indistinguishable clinical and biochemical features. A thorough history and physical examination is often the best (and sometimes only) way to exclude pathologic/neoplastic hypercortisolism. The presence of alcoholism, renal failure, poorly controlled diabetes and severe neuropsychiatric disorders should always raise suspicion that the presence of hypercortisolism may be related to physiologic/non-neoplastic Cushing's syndrome. As late-night salivary cortisol and low-dose dexamethasone suppression have good sensitivity and negative predictive value, normal studies exclude Cushing's syndrome of any form. However, these tests have imperfect specificity and additional testing over time with clinical follow-up is often needed. When there is persistent diagnostic uncertainty, secondary tests such as the DDAVP stimulation test and the dexamethasone-CRH test may provide evidence for the presence or absence of an ACTH-secreting tumor. This review will define and characterize the numerous causes of physiologic/non-neoplastic hypercortisolism and provide a rational clinical and biochemical approach to distinguish it from pathologic/neoplastic hypercortisolism (true Cushing's syndrome).

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Invited authors' profiles

James W Findling, MD, and **Hershel Raff, PhD**, began their scientific collaboration as post-doctoral fellows at the University of California-San Francisco. They have been colleagues at the Medical College of Wisconsin and Aurora St Luke's Medical Center for over thirty years. Dr Findling is Clinical Professor of Medicine and Dr Raff is Professor of Medicine, Surgery, and Physiology at the Medical College of Wisconsin. Dr Raff is also Director of the Endocrine Research Laboratory at Aurora St Luke's Medical Center/Aurora Research Institute. Their clinical research focuses on the diagnosis and management of pituitary–adrenal disorders. They have made original contributions in the development of inferior petrosal ACTH sampling and late-night salivary cortisol for the diagnosis and differential diagnosis of Cushing's syndrome.

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Introduction

Endogenous hypercortisolism – Cushing's syndrome – is one of the most challenging diagnostic problems in clinical endocrinology. Neoplastic (pathologic) Cushing's syndrome is usually due to an ACTH-secreting neoplasm or to autonomous cortisol secretion from a benign or malignant adrenal neoplasm. Non-neoplastic (physiologic) hypercortisolism is common in many medical disorders such as chronic alcoholism, chronic kidney disease and psychiatric conditions (Table 1). This phenomenon has been called the 'pseudo-Cushing's syndrome'. Patients with chronic physiologic hypercortisolism may have features that are indistinguishable from pathologic Cushing's syndrome. Sometimes pseudo-Cushing's syndrome has been used to characterize patients with a Cushingoid habitus without convincing laboratory evidence of increased cortisol secretion. Consequently, the term pseudo-Cushing's syndrome is imprecise and has led to confusion. This review will characterize the Cushing's syndromes as either neoplastic (pathologic) endogenous hypercortisolism or non-neoplastic (physiologic) with the understanding that sustained cortisol excess in either condition can lead to similar clinical and biochemical findings. We have recently reviewed aspects of this issue (1).

The hypothalamic–pituitary–adrenal (HPA) axis generates a basal, circadian cortisol rhythm and increases cortisol secretion in response to a wide variety of external and internal stimuli – 'stress' is the general term used to

describe stimulus-induced activation of the HPA axis. In laboratory animals, sustained or intermittent stress may result in biochemical and physical manifestations of endogenous corticosteroid excess (2, 3, 4, 5, 6). As early as the 1950s, Hane and Robertson demonstrated marked elevations in plasma 17-hydroxycorticosteroids accompanying sexual maturation and spawning of Pacific salmon as they endured their fluvial migration up the Sacramento River (7). Marked hyperplasia of the adrenocortical tissue was found, and the salmon demonstrated clinical features of glucocorticoid excess including central redistribution of fat, cutaneous wasting and superficial fungal infections associated with the immunosuppressive effects of glucocorticoids (Fig. 1). Interestingly, these salmon with glucocorticoid excess also had evidence of coronary artery disease similar to patients with Cushing's syndrome (8, 9). Of course, this biologic phenomenon contributes to the death of the salmon and

Table 1 Causes of endogenous hypercortisolism.

Neoplastic pathologic hypercortisolism (Cushing's syndrome)

- ACTH-secreting neoplasm
 - Pituitary (Cushing's disease)
 - Non-pituitary (ectopic ACTH)

Adrenal neoplastic disease

- Adrenocortical adenoma
- Adrenocortical carcinoma
- Bilateral adrenal nodular disease
 - Primary pigmented micronodular hyperplasia
 - Primary bilateral macronodular hyperplasia

Non-neoplastic-physiologic hypercortisolism (formerly known as pseudo-Cushing's syndrome)

- Phenotype similar to neoplastic hypercortisolism
 - Alcoholism and alcohol withdrawal
 - Chronic kidney disease
 - Depression/neuropsychiatric disease
 - Glucocorticoid resistance
 - Uncontrolled diabetes mellitus
- Phenotype not similar to neoplastic hypercortisolism
 - Starvation/malnutrition—*anorexia nervosa*
 - Pregnancy
 - Chronic intense exercise

Figure 1

Pacific salmon before fluvial migration up the Sacramento River (A) and subsequent overt clinical manifestations of glucocorticoid excess with central redistribution of fat and cutaneous wasting (B) and superficial fungal infections due to immunosuppression (C). Photos were taken in 1958 and provided as a gift from Dr Satoshi Hane.

probably should not be characterized as ' piscine pseudo-Cushing's syndrome'.

In humans, chronic or intermittent increases in hypothalamic–pituitary–adrenal (HPA) axis activity has been observed in many medical disorders associated with psychological, inflammatory, chemical and physical stressors (10, 11, 12). Laboratory findings in these patients can overlap with states of pathologic hypercortisolism and cause significant diagnostic confusion. We will describe some of medical disorders associated with hypercortisolism and provide insights on approaches to distinguish them from patients with true pathologic, neoplastic Cushing's syndrome. It is important at the outset to emphasize that the state of the art in this area needs additional comprehensive studies to understand the clinical importance of non-neoplastic (physiologic) hypercortisolism and how best to distinguish it from the pathologic Cushing's syndromes.

Physiologic (non-neoplastic) hypercortisolism: phenotypes similar to pathologic Cushing's syndrome

The majority of non-neoplastic states of hypercortisolism are mediated by subtle activation of the HPA axis primarily through neural pathways with input to the paraventricular nuclei of the hypothalamus (2). Much like pathologic hypercortisolism, a recurring theme in most of these situations is attenuated sensitivity to glucocorticoid negative feedback that may lead to mild increases in cortisol similar to those found in subclinical Cushing's syndrome (13). We emphasize that the effects of small increases in cortisol may summate over time to provide significant, longitudinal glucocorticoid exposure resulting in some of the features of pathologic glucocorticoid excess (14).

Alcohol-induced hypercortisolism

Excessive alcohol intake increases cortisol secretion acutely and chronically (15, 16). In the late 1970s, it was recognized that alcoholic patients have many of the signs and symptoms of Cushing's syndrome (17, 18). These clinical features often resolve with abstinence from alcohol (17, 18, 19). Alcohol-induced cortisol hypersecretion is primarily mediated through the activation of hypothalamic corticotropin-releasing hormone (CRH) secretion into the portal veins leading to the anterior pituitary (20, 21, 22, 23). Alcohol-induced increases in

vasopressin secretion may also be a factor as hypothalamic vasopressin of parvocellular and magnocellular origin augments the response to CRH (23, 24, 25). Impaired peripheral clearance of cortisol probably due to hepatic dysfunction may contribute to the hypercortisolemic state in alcoholics (26). The presence of persistent liver function abnormalities – particularly if the AST is much greater than the ALT (27) – raises concern for excessive alcohol consumption.

Patients with alcohol-induced hypercortisolism have increased late-night salivary cortisol and urinary measurements of corticosteroids (26, 28, 29). Overnight dexamethasone suppression testing and assessment of stress-induced ACTH secretion often yields abnormal results (28, 30). The dexamethasone–CRH test may also be abnormal during active alcohol consumption and cannot be used to differentiate alcohol-induced hypercortisolism from pathologic Cushing's syndrome (31). On the other hand, there may be no ACTH response to stimulation with desmopressin acetate (DDAVP) in alcohol-induced Cushing's syndrome (similar to healthy subjects) in contrast to patients with Cushing's disease (32). The challenge in the evaluation of alcohol-induced hypercortisolism and its differentiation from patients with pathologic Cushing's syndrome is heightened because some patients can be less than forthright about the magnitude of their chronic alcohol consumption. Although the majority of patients with alcohol-induced Cushing's syndrome have either normal or increased plasma ACTH, adrenal nodular disease and subnormal plasma ACTH has been reported (33).

Depression/neuropsychiatric disorders

Many neuropsychiatric disorders have been associated with increases in HPA axis activity (34). Most forms of major depression – especially psychotic depression – have increased HPA axis activity (35). Decreases in the sensitivity of the glucocorticoid and possibly the mineralocorticoid receptors may lead to resistance to cortisol negative feedback (35). In addition, successful psychopharmacotherapy tends to normalize HPA axis function; ineffective therapy often correlates with persistent hypercortisolism (34). Many of these patients have an abnormal low-dose dexamethasone suppression test as well as increased late-night and urine cortisol (36). In fact, mental health specialists have utilized both the low-dose dexamethasone suppression and the dexamethasone–CRH tests to characterize these disorders and their response to therapy (37). This makes proper

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differentiation of the cause of hypercortisolism very challenging as neoplastic/pathologic Cushing's syndrome is often complicated by significant neuropsychiatric illnesses (38). The DDAVP stimulation test has not been studied sufficiently in depressive illness to depend on it as a diagnostic tool. As the dexamethasone–CRH test is used in the diagnosis of depression, biochemical discrimination between true pathologic Cushing's syndrome and physiologic stimulation of the HPA axis from neuropsychiatric disorders can be very challenging (37).

Chronic kidney disease (CKD)

End-stage renal failure is associated with alterations in cortisol control and abnormal dexamethasone-induced cortisol suppression (39, 40, 41). Some patients with end-stage renal failure receiving hemodialysis have a disrupted circadian rhythm, and others only have subtle increases in late-night cortisol (42). The mechanism for the increase in cortisol in CKD is not a decrease in renal clearance of cortisol as plasma ACTH is typically increased in these patients. Hypercortisolism appears to be generated by the activation of the HPA axis presumably from hypothalamic origin and may correlate with increases in C-reactive protein suggesting that the high inflammatory state of chronic kidney disease may be the underlying etiology. The secondary tests outlined below (dexamethasone–CRH or DDAVP) have not been evaluated in patients with end-stage kidney disease.

Type 2 diabetes, insulin resistance and the metabolic syndrome

Pathologic Cushing's syndrome may be an unsuspected finding in patients with type 2 diabetes mellitus with a prevalence as high as 3% (43, 44, 45, 46, 47). The converse is also true in that patients with diabetes mellitus with poor glycemic control may have an activated HPA axis (48). Increased late-night salivary cortisol concentrations have been found in some patients with poorly controlled type 2 diabetes mellitus (49). Furthermore, subtle disruptions of pituitary–adrenal function may contribute to insulin resistance and the development of the metabolic syndrome (50). Glycemic fluctuations do not have a major correlation with salivary cortisol excretion in diabetes mellitus (51). A concept of 'tissue-specific' Cushing's syndrome has been suggested in patients with obesity, the metabolic syndrome and insulin resistance suggesting

that increased adipose expression of 11- β -hydroxysteroid dehydrogenase 1 may generate increased tissue cortisol levels (52). Subtle abnormalities in HPA axis function in diabetic patients with poor glycemic control should be interpreted with caution.

Glucocorticoid resistance

Cortisol resistance is a familial receptor-mediated disorder with increased androgen and cortisol production in healthy-appearing individuals (53). As the index cases are usually diagnosed in adulthood, cortisol resistance is partial and accompanied by compensatory increases in indices of HPA axis activity as well as excessive secretion of adrenal androgens and adrenal corticosteroid biosynthetic intermediates with salt-retaining activity (54). These patients do not have the typical catabolic features of cortisol excess such as cutaneous wasting, abdominal striae, myopathy and low bone density. The usual presentation includes features of mineralocorticoid excess such as hypokalemia and hypertension (54). Increases in plasma ACTH and cortisol secretion are usually present, and some patients may have bilateral adrenal enlargement. Features of androgen excess can be present in women including hirsutism, acne, menstrual irregularities and oligomenorrhea with decreased fertility (53). Consequently, the presence of significant biochemical ACTH-dependent hypercortisolism in the absence of any physical features of cortisol excess should raise concern about a glucocorticoid resistance syndrome.

Physiologic (non-neoplastic) hypercortisolism: phenotypes not similar to pathologic Cushing's syndrome

Clinical disorders and conditions associated with the activation of the HPA axis may have significant sequelae of hypercortisolism, but their features are rarely confused with pathologic Cushing's syndrome.

Anorexia/starvation equivalent disorders

Starvation associated with eating disorders (anorexia nervosa) activates the HPA axis with varying degrees of hypercortisolism (55, 56). Patients with anorexia nervosa have an attenuated ACTH response to CRH probably due to negative feedback of cortisol on the corticotrophs of the anterior pituitary (57). Interestingly, the dexamethasone–CRH test may also be abnormal in patients with anorexia

(58). DDAVP does not stimulate ACTH in these patients, which is similar to healthy subjects (55). Severity of bone loss and hypothalamic amenorrhea correlates with the degree of hypercortisolism in women (59, 60). In addition, there is increased bone mineral fat related to cortisol excess (56).

Starvation equivalent disorders may also be associated with hypercortisolism. Patients in the intensive care unit for long periods of time have significant loss of muscle mass and catabolism mediated in part by hypercortisolism (61). Increases in cortisol have also been observed in healthy women undergoing low-calorie dieting and increased morning cortisol levels have been demonstrated in women with significant weight loss after bariatric surgery (62). It seems logical that chronic wasting in catabolic states associated with many chronic medical conditions may be related, in part, to HPA axis activation and endogenous hypercortisolism.

Pregnancy

Salivary and serum free cortisol levels increase during pregnancy, particularly in the third trimester (63, 64, 65). The increase in total cortisol is primarily due to the increases in corticosteroid-binding globulin as pregnancy progresses, but the increase in free, biologically active cortisol is ACTH mediated (63, 66). The increase in plasma ACTH has been attributed to the secretion of CRH from the placenta, the increase in progesterone acting as a glucocorticoid antagonist, a decrease in glucocorticoid negative feedback sensitivity and the production of ACTH from the placenta (63). CRH-binding protein also increases during pregnancy, which may prevent the stimulatory effects of placental CRH on the maternal pituitary gland (67, 68, 69). The actual diagnosis of Cushing's syndrome is uncommon in pregnancy as hypercortisolism usually attenuates hypothalamic-pituitary-gonadal function. Nonetheless, pathologic Cushing's syndrome can cause complications in pregnancy, and the diagnosis must be based on overt clinical and biochemical evidence of hypercortisolism (63).

Intense chronic exercise

Chronic exercise, particularly of high intensity, may result in mild elevations of cortisol secretion even in the resting state. Although highly trained runners may have increased evening concentrations of ACTH and cortisol in the basal state, they have diminished exercise-induced

cortisol levels compared to sedentary or moderately trained runners (70). This adaptation of the HPA axis is proportional to the degree of physical training and provides elite runners a means to handle a higher work load with less pituitary-adrenal activation (70).

Multiple sclerosis

Patients with multiple sclerosis may also have increased activity of the HPA axis, the mechanism of which may be an increased inflammatory state and cytokine stimulation (71). Brain lesions in the hypothalamic and other critical areas may be involved in this disruption of normal hypothalamic control.

Obstructive sleep apnea

One might expect that obstructive sleep apnea, with its frequent hypopneas leading to hypoxia, might activate the hypothalamic-pituitary-adrenal axis. However, patients with obstructive sleep apnea do not appear to have an activation of pituitary-adrenal function and nor have significant alterations of HPA axis function been consistently found (72, 73).

Clinical differentiation: physiologic vs pathologic hypercortisolism

A detailed history and good physical examination are critical first steps in evaluating patients with suspected hypercortisolism, regardless of the potential etiology. Patients with chronic alcoholism, major depressive illness or the possibility of opioid use or abuse are often the most challenging and require meticulous attention to their signs, symptoms, history and physical examination. Underestimation of alcohol intake and failure to admit to negative behaviors in chronic alcoholics is particularly problematic. A high index of suspicion is needed, and sometimes, clues such as persistent elevations in liver function tests may be helpful. Although opioids can acutely suppress the activity of the HPA axis, their discontinuation can lead to an abrupt recovery and even overcompensation (74). As a result, patients who use significant amounts of narcotics may have confusing biochemical findings related to HPA axis function. This rollercoaster effect on pituitary-adrenal function in opioid-treated patients may actually cause some evidence of overall cortisol excess as measured by increases in hair cortisol concentration (75).

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Neuropsychiatric disorders may lead to the activation of the HPA axis and cause cortisol hypersecretion thereby presenting the clinician with a significant diagnostic challenge. Mental health specialists may be needed to assist with the characterization and classification of these neuropsychiatric disorders. This is particularly so as a wide variety of neuropsychiatric disorders including obsessive compulsive disorder, bipolar disorder, schizophrenia and the onset of major depression have been described in patients with pathologic hypercortisolism (38). Poorly controlled diabetes mellitus should be corrected before interpreting subtle increases in HPA axis activity. End-stage renal failure can obfuscate a diagnosis of pathologic Cushing's syndrome unless there are overt clinical or radiological imaging abnormalities. However, a normal late-night salivary cortisol is helpful in discounting the diagnosis of endogenous Cushing's syndrome in patients with chronic kidney disease (42).

As emphasized previously, the physical examination may occasionally be helpful; however, most patients in whom there is diagnostic uncertainty have mild biochemical cortisol excess and, rarely, have overt clinical manifestations of hypercortisolism. On the other hand, some patients with alcohol-induced hypercortisolism may have obvious clinical features of Cushing's syndrome including facial fullness with plethora, violaceous striae and proximal myopathy and edema (18, 28, 32, 33). Most patients with pathologic hypercortisolism have objective clinical manifestation of cortisol excess such as hypertension, diabetes/pre-diabetes, low bone density with fracture and hirsutism/oligomenorrhea.

Biochemical differentiation of physiologic and pathologic hypercortisolism

Routine testing

The Endocrine Society guidelines for the diagnosis of suspected pathologic Cushing's syndrome exploit three different aspects of disruption of normal physiology (76). These include (1) the failure to achieve a normal nadir in late-night cortisol assessed by the measurement of increased late-night salivary cortisol, (2) the failure to suppress morning serum cortisol after overnight 1 mg dexamethasone suppression and (3) increase in the excretion of free cortisol in the urine. All these laboratory studies have been evaluated and are available world-wide.

Although late-night salivary cortisol and the overnight low-dose dexamethasone suppression test may have false-positive results, normal levels of late-night salivary

cortisol and appropriate suppression of cortisol after dexamethasone after the overnight 1 mg dexamethasone suppression test (post-dexamethasone cortisol $<1.8 \mu\text{g/dL}$ ($<50 \text{ nmol/L}$)) makes the diagnosis of pathologic Cushing's syndrome very unlikely (77). Urine free cortisol excretion should not be used as a screening test for suspected hypercortisolism because of its poor sensitivity for the detection of neoplastic Cushing's syndrome (76). Even with this caveat, marked elevations of urinary free cortisol excretion (3–4 times the upper limit of normal) are highly suggestive of pathologic Cushing's syndrome and may be useful in the confirmation of the diagnosis (76). Although relatively rare, cyclical or intermittent Cushing's syndrome may be associated with discordant testing and provide further diagnostic uncertainty (78). In patients with a high index of clinical suspicion, repeated studies may be needed over time to make an accurate diagnosis. If the patient is restless and not willing to wait, second-line testing described below may be necessary to differentiate pathologic and physiologic hypercortisolism.

Imaging

It is not useful to perform imaging studies to distinguish between pathologic and physiologic hypercortisolism. The presence of small or ephemeral abnormalities on magnetic resonance imaging (MRI) of the pituitary in 10–20% of normal subjects will only cause further diagnostic confusion and patient angst (79), so imaging of the pituitary should only be done when the biochemical diagnosis of pathologic ACTH-dependent Cushing's syndrome has been established. Although bilateral inferior petrosal sinus sampling (IPSS) with CRH stimulation is essential in the diagnostic confirmation of Cushing's disease in patients with a normal pituitary MRI, it does not distinguish pathologic hypercortisolism from those of physiologic origin (80). The discovery of an incidental adrenal mass by computed tomography (CT) of the abdomen may warrant an evaluation of potential cortisol hypersecretion. Nonetheless, adrenal imaging is not an index of adrenal function. In fact, adrenal size evaluated by imaging can be remarkably discordant with cortisol secretion (81, 82).

Secondary tests

DDAVP stimulation and the dexamethasone–CRH test have been used to discriminate patients with pathologic

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Table 2 Dexamethasone–CRH test vs DDAVP test to distinguish pathological (Cushing's syndrome) and physiological (pseudo-Cushing's) hypercortisolism. All told for Cushing's syndrome, there were 322 patients with Cushing's disease, 2 with ectopic ACTH syndrome and 5 with adrenal Cushing's syndrome. There were a total of 145 pseudo-Cushing's patients.

	Pseudo-Cushing's diagnoses	Cutoffs/criteria for Cushing's syndrome	Performance	
			Sensitivity	Specificity
Dex-CRH test				
(91)	Obesity, eating disorders, withdrawal from substance abuse, depression, bipolar, other psych diagnoses	SC: >38 nmol/L (>1.4 µg/dL)	100%	100%
(94)	Truncal obesity, PCOS, depression, EtOH	SC: >38 nmol/L (>1.4 µg/dL)	100%	63%
(95)	EtOH, eating disorders, depression	SC: >38 nmol/L (>1.4 µg/dL)	100%	50%
(92)	EtOH, depression	SC: >38 nmol/L (>1.4 µg/dL)	NoMeds: 93%	NoMeds: 92%
			Meds: 88%	Meds: 75%
(83)	EtOH, PCOS, depression, heart failure, cirrhosis	SC: >87 nmol/L (>3.2 µg/dL)	94%	100%
DDAVP test [†]				
(96)	EtOH, depression, PCOS	ACTH: >6 pmol/L (>27 pg/mL)	87%	91%
(94)	Truncal obesity, PCOS, depression, EtOH	ACTH: >6 pmol/L (>27 pg/mL)	82%	90%
(85)	Depression, EtOH, PCOS, panic disorders, bulimia	ACTH: >6 pmol/L (>27 pg/mL)	75%	90%
		Basal SC: >331 nmol/L (>12.0 µg/dL) and ACTH: >4 pmol/L (>18 pg/mL)	90%	92%

[†]ACTH was measured as Δ Plasma ACTH; ACTH, adrenocorticotropic hormone; SC, serum cortisol; CRH, corticotropin-releasing hormones; DDAVP, desmopressin; EtOH, alcohol; NoMeds/Meds: patients divided into those who were not or were taking medications known to interfere with dexamethasone metabolism; PCOS, polycystic ovary syndrome.

hypercortisolism who typically respond from those with physiologic hypercortisolism (Table 2).

DDAVP stimulation

Corticotroph adenomas can express specific vasopressin receptors (V1b). As a result, desmopressin acetate administration can stimulate ACTH secretion in patients with Cushing's disease (83, 84, 85, 86). On the other hand, the response to DDAVP is typically small or absent in healthy subjects and those with physiological hypercortisolism (83, 84, 85, 86). The test is usually performed in the morning with plasma ACTH and serum cortisol levels measured before and 15-, 30- and 60-min after DDAVP (10 µg intravenously) administration. Few side effects have been reported, but the patients should limit fluid intake for 6–8 h after the test. The sensitivity, specificity, positive predictive value and negative predictive value for DDAVP stimulation are reportedly good when differentiating between physiologic and pathologic hypercortisolism (Table 2).

Using a DDAVP-induced increase in plasma ACTH of >6 pmol/L (>27 pg/mL) as a cut-off for Cushing's disease, the test resulted in sensitivities between 75% and 87% and specificities between 90% and 91%. Notice that Table 2 highlights those studies that specifically identified a group of patients with pseudo-Cushing's syndrome

as a comparator to patients with proven pathologic Cushing's syndrome. Most studies have shown that there is some overlap between patients with pathologic Cushing's syndrome, obese control subjects and patients with physiologic states of cortisol excess.

Tirabassi *et al.* found that using a basal serum cortisol of >331 nmol/L (>12.0 µg/dL) as a criterion combined with a lower cut-off for the DDAVP-induced increase in ACTH (Δ 4 pmol/L (Δ 18 pg/mL)), the sensitivity could both be improved to 90% without an appreciable decrease in specificity (85, 86). These two studies likely reported data from many of the same patients and therefore the derived criteria for the DDAVP stimulation test were similar. Data from otherwise healthy obese subjects and the number and variety of patients with physiologic hypercortisolism are limited in some of the studies investigating the DDAVP stimulation test.

Patients with chronic alcoholism have a minimal, if any, response to DDAVP but only a few patients have been carefully studied (32). In patients with depression, there appears to be blunted ACTH and cortisol responses to DDAVP, although variable results have been reported (87). One possible limitation to all stimulation tests is the lack of harmonization of ACTH assays (88). Normative data for most ACTH assays after DDAVP stimulation are lacking, and the dynamic range of ACTH and cortisol responses in normal subjects (non-obese and obese) is not clear.

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In addition, some patients with ectopic ACTH-secreting tumors and hypercortisolism may have an ACTH response to DDAVP providing further potential confusion (84, 89).

A positive ACTH response to DDAVP (before or after dexamethasone) may be the earliest diagnostic indicator of recurrent Cushing's disease preceding elevations in both urinary cortisol and late-night salivary cortisol (90). Despite its many limitations and the need for additional studies, the DDAVP stimulation test may add some valuable diagnostic information when the diagnosis of pathologic/neoplastic Cushing's syndrome is uncertain.

Dexamethasone–CRH test

The dexamethasone–CRH test was initially described in 1993 as a means of distinguishing patients with true pathologic Cushing's syndrome due to Cushing's disease from those with hypercortisolism from a physiologic cause and the term 'pseudo-Cushing's syndrome' was born (91). Although some protocols have varied from the initial published approach, dexamethasone (0.5 mg) is typically given orally for eight doses over several days prior to the morning administration of CRH after which plasma ACTH and cortisol measurements were obtained at baseline at 15 and 30 min. To obtain optimal results, the patient may need to be hospitalized, which makes this test prohibitively expensive. Although the initial report found that a serum cortisol concentration $>1.4 \mu\text{g/dL}$ ($>39 \text{ nmol/L}$) in response to CRH after dexamethasone suppression was considered true Cushing's syndrome with 100% specificity, subsequent studies used receiver-operator curve analysis to more precisely calculate sensitivity and specificity (Table 2).

Alwani *et al.* (83) recently found that a higher cut-off for the serum cortisol response to CRH after dexamethasone suppression was necessary to improve the specificity (100%) albeit with a slightly lower sensitivity (94%) compared to prior studies (Table 2). It was also found that increased late-night salivary cortisol and the evening-to-morning cortisol ratio aided in the diagnostic approach. Adding to this is the fact that many commonly used medications can interfere with dexamethasone metabolism (92), which makes the reliability of this test even more questionable in patients with concomitant medical and psychiatric disorders requiring pharmacotherapy (Table 2).

As previously mentioned, the dexamethasone–CRH test is used by psychiatrists in the evaluation of patients with depression (37). In fact, this is currently

the most frequent application of this test in the United States. Typically, the neuropsychiatric approach is to give dexamethasone only once (the night before CRH administration) so the test compliance is less rigorous for the patient. As patients with depressive disorders tend to have augmented cortisol response to CRH after dexamethasone administration, there is significant concern about the predictive value of a positive test in patients who are depressed and have evidence of biochemical hypercortisolism.

Summary and conclusions

Activation of the hypothalamic–pituitary–adrenal axis is a major adaptive response to any challenge to homeostasis. Several clinical situations and medical disorders may cause chronic or intermittent stimulation of the HPA axis and result in a state of hypercortisolism that may have similar clinical and biochemical features as the Cushing's syndrome. These states of physiologic or non-neoplastic hypercortisolism have been characterized as pseudo-Cushing's syndrome; however, as observed in salmon swimming upstream (Fig. 1), the clinical features of HPA axis activation may be anything but 'pseudo,' and it seems as if the terms physiologic or non-neoplastic hypercortisolism are more appropriate. Chemical (alcohol), psychological (major depressive illness), inflammatory (end-stage renal failure) and physical (chronic intense exercise) stressors create a state of cortisol excess that may cause significant biochemical and clinical diagnostic confusion with the well-characterized neoplastic/pathologic forms of the Cushing's syndrome. We also speculate that there are other currently unstudied subacute and chronic medical conditions that stimulate HPA axis activity sufficiently to have significant physiologic consequences.

The most valuable clinical tool for discriminating between physiologic and pathologic Cushing's syndrome is a thorough history and physical examination. Clinicians need to be cognizant of the fact that certain common disorders such as alcoholism, chronic kidney disease, neuropsychiatric illness and poorly controlled diabetes are associated with abnormalities in HPA axis function. Moreover, patients with significant biochemical hypercortisolism, but without overt physical or metabolic evidence of Cushing's syndrome, should be evaluated with skepticism. Analytic errors, surreptitious use of steroids and glucocorticoid resistance should be considered. On the other hand, patients who appear Cushingoid (and there are certainly many of

them) but who have normal late-night salivary cortisol measurements and suppress cortisol appropriately during a low-dose dexamethasone suppression test are very unlikely to have pathologic hypercortisolism (with the unusual exception of a truly intermittent/cyclical disorder). Accordingly, the best screening tests for the diagnosis of hypercortisolism are late-night salivary cortisol and the overnight dexamethasone suppression test. These tests have the best sensitivity and negative predictive value. Of course, their major limitation (like all tests for assessing endogenous cortisol excess) is their imperfect specificity.

If there is diagnostic uncertainty, it is always prudent to re-evaluate the patient in 6–12 months. However, if the patient or the endocrinologist has significant angst, secondary tests such as DDAVP stimulation or dexamethasone–CRH are recommended. Both of these tests seem to perform similarly, but, quite frankly, have not undergone extensive enough evaluation in many conditions associated with hypercortisolism let alone in obese subjects with Cushingoid features. In addition, patients with some conditions associated with cortisol excess such as depression and active alcohol abuse have abnormal dexamethasone–CRH testing. We suggest that endocrinologists use these tests with caution and not substitute their outcome for good clinical judgment.

As more patients undergo consideration for hypercortisolism for common medical problems (obesity, diabetes, hypertension, osteoporosis and adrenal nodules) and with the widespread use of the internet for self-diagnosis, establishing the diagnosis of the Cushing's syndrome will be increasingly recognized as one of the most challenging in all of clinical medicine. When the patient (or the endocrinologist) is unsatisfied with the diagnostic conclusion, it is often valuable to refer the patient to a center with special expertise in the diagnosis of Cushing's syndrome. To paraphrase our previous assertion, clinicians who have never missed the diagnosis of Cushing's syndrome or have never been humbled by attempting to establish its cause should refer their patients with suspected hypercortisolism to someone who has (93).

Declaration of interest

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