

Adrenal Insufficiency

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CASE PRESENTATION

A 44-year-old woman whose medical history was remarkable only for chondrocalcinosis of the knees was referred to the endocrinology department to exclude a metabolic or hormonal problem. The patient complained of several weeks of fatigue, somnolence, pain in the large joints, nausea, and decreased appetite. Her symptoms had appeared gradually, without a clear precipitating event. She had also noted an unintentional 11-kg weight loss over a period of 6 months, associated with reduced appetite and occasional nausea. Her past medical history was remarkable for the fact that in her early 30s she had had a period of amenorrhea lasting approximately 1 year. After blood work, a physician had told her that "my pituitary was not working and that I would not be able to become pregnant." Subsequently, however, her periods returned spontaneously, and she had 4 natural pregnancies.

On the review of systems, the patient denied any change in her skin color or texture, in bowel habits, dizziness, chest pain, shortness of breath, polyuria, polydypsia, headaches, or visual changes. Her periods were coming monthly, with normal flow. She was taking no medications, with the exception of acetaminophen as needed for knee pain. Physical examination showed a well-appearing woman who weighed 69.5 kg and stood 166 cm tall,

A 44-year-old woman reported several weeks of fatigue, somnolence, pain in the large joints, nausea, and decreased appetite. She had also noted an unintentional 11-kg weight loss over a period of 6 months. She had a remote history of amenorrhea, but she was presently menstruating regularly. She was taking no medications, with the exception of acetaminophen as needed for knee pain. The diagnosis of adrenal insufficiency (AI) was considered. Serum cortisol level after adrenocorticotropin hormone (ACTH) stimulation was abnormal. Because her plasma ACTH level was not increased, a diagnosis of secondary AI (due to deficiency in ACTH) was made. Magnetic resonance imaging of the brain performed to exclude the presence of a sellar or suprasellar mass showed reduction in size of the pituitary gland and an increased cerebrospinal fluid content within the sella, consistent with a partially empty sella. The patient's symptoms improved rapidly with hydrocortisone therapy but during follow-up, the dose of hydrocortisone was found to be excessive. Important differences exist between primary and secondary AI, and the diagnosis of secondary AI may be challenging. The therapy of AI should be carefully tailored to the requirements of the individual patient.

JAMA. 2005;294:2481-2488

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with a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) of 25.2. Her recumbent blood pressure was 115/80 mm Hg, her heart rate 74/min, her respiratory rate 12/min, and her temperature 36.5°C. The patient had no significant blood pressure or heart rate change after 1 minute in the upright position. The skin and buccal mucosa had no hyperpigmentation or hypopigmentation. The thyroid gland was palpable but without abnormalities. There was no cervical or axillary adenopathy. Examination of the heart showed a regular rate and rhythm with normal cardiac sounds and no murmurs. The lungs were clear to auscultation and the abdomen was benign. Visual fields were full by confrontation, and the neurological examination was nonfocal.

Upon examination of her laboratory studies, the electrolytes were normal (sodium 141 mEq/L, potassium 3.6 mEq/L), as were her creatinine and blood urea nitrogen levels. Blood hemoglobin was normal (13 g/dL). At 10 AM, serum cortisol and plasma adrenocorticotropin hormone (ACTH) levels were 4.0 µg/dL (normal range, 5-20 µg/dL) and 9 pg/mL (normal range, 6-60 pg/mL), respectively. The serum level of free thyroxine (T_4) was 1.2 ng/dL (15.4 pmol/L) (normal range,

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Grand Rounds Section Editor: David S. Cooper, MD, Contributing Editor, JAMA.

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0.18-1.6 ng/dL [2.32-20.59 pmol/L]), with a thyroid-stimulating hormone of 3.3 mIU/mL (normal range, 0.5-4.5 mIU/mL). An ACTH stimulation test was performed. Sixty minutes after the intravenous injection of 1 to 24 synthetic ACTH (250- μ g intravenous), the serum cortisol was 7 μ g/dL (normal, >18 μ g/dL).

Magnetic resonance imaging of the brain, performed to exclude the presence of a sellar or suprasellar mass, showed reduction in size of the pituitary gland, mild leftward deviation of the pituitary stalk, and an increased cerebrospinal fluid content within the sella, consistent with a partially empty sella, but no tumor mass or cyst.

The patient started taking hydrocortisone (20 mg in the morning and 10 mg in the afternoon). Two months later, she reported significant improvement of all her symptoms and a 6-kg weight gain. Six months later she was feeling well, but her weight had increased to 94 kg (24.5 kg in 9 months of therapy; BMI, 34.1), with preferential accumulation of adipose tissue in her abdomen. Her hydrocortisone dose was reduced to 10 mg in morning and 5 mg in afternoon, without any relapse of her symptoms. Three and half years later, she was still doing well with the same hydrocortisone dose and her weight was 87 kg (BMI, 31.5). She was still having regular periods. The insulin-like growth factor 1 was low at 71 ng/mL (normal range, 90-360 ng/mL).

DISCUSSION

This patient has symptoms and biochemical evidence of adrenal insufficiency (AI), as shown by her abnormal cortisol response to ACTH (the interpretation criteria of the ACTH stimulation test will be discussed below). Her AI is secondary to reduced ACTH secretion rather than due to a primary disease of the adrenal glands, as indicated by the inappropriately normal plasma ACTH level. The past history of amenorrhea is consistent with the possibility that the patient has a pituitary pathology, possibly a pituitary

adenoma that infarcted, leaving an "empty sella."¹ Although ACTH deficiency with normal thyroid-stimulating hormone and gonadotropin secretion (judged by the resumption and continuation of normal menses) is rare, it has been described before in a similar setting.² The low serum insulin-like growth factor 1 in a patient with hypopituitarism strongly suggests growth hormone deficiency.³

The etiology, diagnosis, and therapy of primary and secondary AI, as well as the differences between these 2 disease states, are reviewed herein. The major hormones of the hypothalamic-pituitary-adrenal (HPA) axis are shown in the FIGURE.

Classification of AI

Adrenal insufficiency develops when a large part of the function of the adrenal glands is lost. Primary AI is caused by processes that damage the adrenal glands or by drugs that block cortisol synthesis. In contrast, secondary AI results from processes that reduce the secretion of ACTH by the pituitary gland due to a pituitary or hypothalamic pathology; although the latter, due to deficit of corticotrophin-releasing hormone (CRH), is sometimes called tertiary AI. In this review, both forms are included in the secondary AI group. Both primary and secondary AI can develop either slowly, over several weeks or months, or acutely, with catastrophic consequences that may lead to cardiovascular collapse and death. The classification and common etiologies of primary and secondary AI are shown in the Figure.

Primary AI. In developed countries, the most frequent cause of primary AI is autoimmune adrenalitis. In the developing world, on the other hand, tuberculosis most likely remains the more common cause of adrenal failure.^{4,5} In young males, adrenoleukodystrophy (or the less severe adrenomyeloneuropathy) must be considered. This disease, transmitted as a recessive X-linked trait, is due to the accumulation of very long chain fatty acids

in the adrenal glands and in the central nervous system. Therefore, the clinician should perform a careful neurological examination in young males with primary AI, keeping in mind that AI can appear long before neurological symptoms.⁶ Several infectious processes known to be associated with AIDS, particularly *Cytomegalovirus*, *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, *Toxoplasma gondii*, *Mycobacterium avium intracellulare*, *Pneumocystis jiroveci*, and *Histoplasma capsulatum*, may lead to adrenal gland destruction. Among medications, ketoconazole (an antifungal) and etomidate (a general anesthetic) can cause AI.⁷

Secondary AI. The most common cause of secondary AI is the abrupt discontinuation of long-term administration of glucocorticoids. There is a great individual variability in susceptibility to suppression of the HPA axis by exogenous glucocorticoids; therefore, the presence of AI cannot be predicted reliably by the dose and duration of glucocorticoid use.⁸ Several weeks of exogenous glucocorticoid administration are required for the development of AI.⁹ Intramuscular, intra-articular, and even inhaled or topical glucocorticoids can cause significant suppression of the HPA axis.^{10,11} Similarly, megestrol acetate, a synthetic progestational agent used to increase appetite in a variety of cachexia-inducing illnesses, can suppress ACTH secretion at doses of more than 160 mg/d, leading to secondary AI.¹²

Secondary AI can be caused by pituitary adenomas, craniopharyngiomas, pituitary surgery, lymphocytic hypophysitis, and a wide variety of other neoplastic, inflammatory, and infectious processes involving the sellar or suprasellar area. Pituitary or whole brain irradiation can cause AI up to several years after its completion.¹³ Finally, traumatic brain injury and subarachnoid hemorrhage can cause AI that may not manifest itself until several months after the acute event.¹⁴

In the failing pituitary gland, ACTH secretion is usually the last function to

be lost. As the present case illustrates, however, exceptions to this rule occur. The patient had ACTH deficiency (and possibly growth hormone deficiency) despite the presence of normal thyroid and gonadotropin function. Such exceptions are more frequent in postirradiation hypopituitarism.¹³

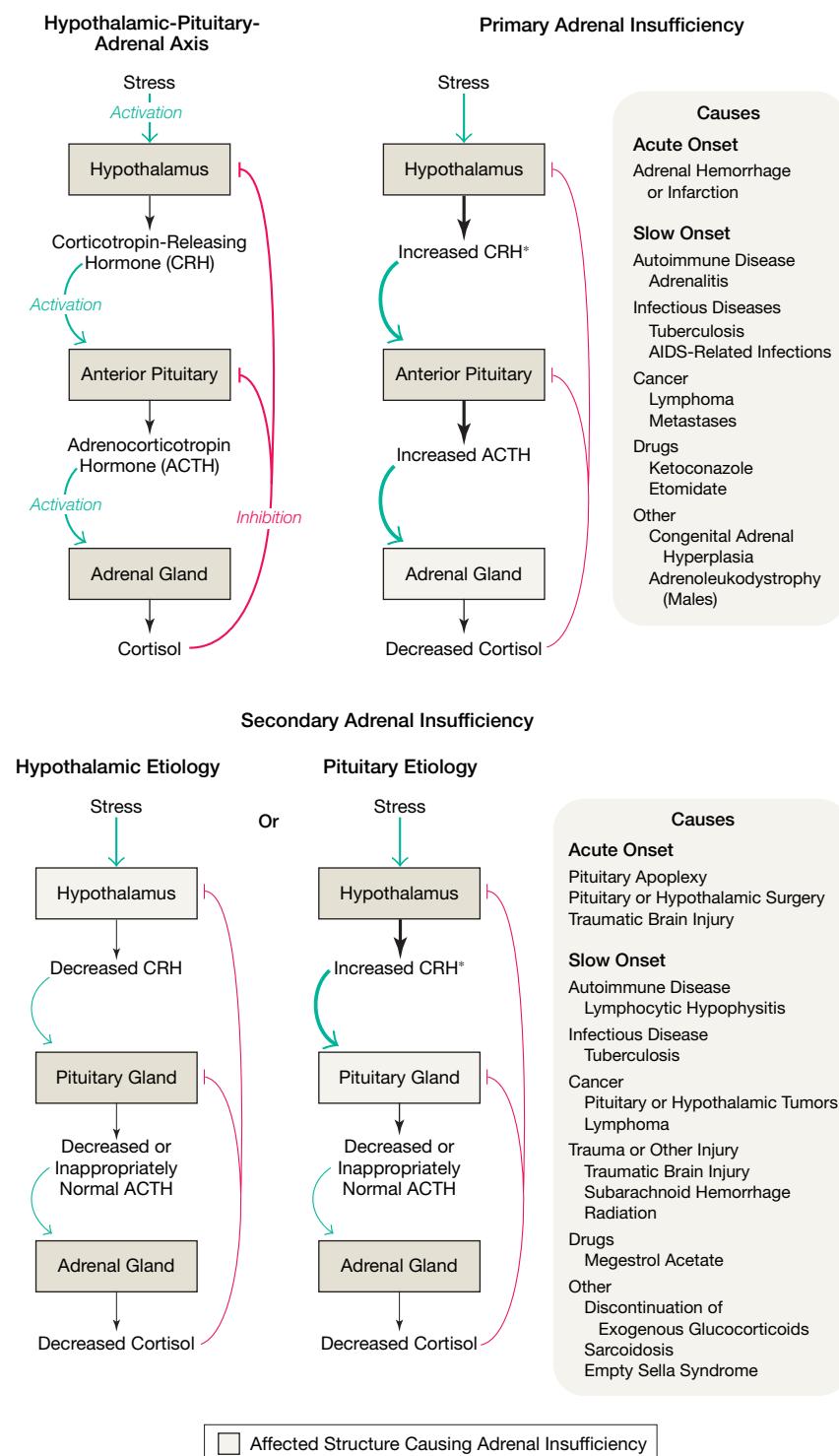
Clinical Presentation

The development of acute AI is potentially lethal. The physician must consider AI as a possible cause of unexplained deterioration of cardiovascular status. Adrenal hemorrhage or infarction occurs in patients who are severely ill from underlying conditions, including sepsis, pulmonary embolism, acute renal failure, acute myocardial infarction, and heart failure.^{15,16} The presence of antiphospholipid antibodies or pharmacological anticoagulation can lead to adrenal hemorrhage or infarction.¹⁷

Patients with slow onset AI usually complain of being chronically fatigued. They often report joint pain, lack of appetite, unintentional weight loss, abdominal pain, nausea, and diarrhea. Primary AI, in contrast with secondary AI, is often associated with lack of aldosterone as well as cortisol. Consequently, symptoms and signs of mineralocorticoid deficiency (salt-craving, postural hypotension, electrolyte abnormalities) usually indicate primary AI. For any given level of morning serum cortisol, patients with primary AI have more severe symptoms than patients with secondary AI.¹⁸ Patients with secondary AI are often able to function relatively well during unstressed periods, and they may manifest cardiovascular instability or hypoglycemia only when they undergo physical stress.

Hyperpigmentation of the skin and of the mucosae resulting from the melanocyte-stimulating activity of β -lipotropin, which derives from the same precursor as ACTH, is observed only in primary AI. Although hyperkalemia is observed only in primary AI, hyponatremia can also occur in secondary AI, as the result of reduced glomerular fil-

Figure. Hypothalamic-Pituitary-Adrenal Axis and Causes of Primary and Secondary Adrenal Insufficiency



*Although CRH in the hypophyseal portal system cannot be measured, it is likely increased.

tration rate, increased antidiuretic hormone secretion, and possible concomitant central hypothyroidism. Patients with primary AI caused by autoimmune adrenalitis are at risk for other manifestations of autoimmune disease, such as vitiligo, Hashimoto thyroiditis, pernicious anemia, and type 1 diabetes mellitus. TABLE 1 illustrates some of the contrasts between primary and secondary AI.

Diagnosis of AI

Once AI is suspected, a variety of tests may be used to evaluate adrenal function. A stepwise approach helps maintain cost-effectiveness in screening all the patients in whom this potentially dangerous (and treatable) disease is suspected.

Nonstimulated Serum Cortisol. The initial test in an ambulatory patient should be a 6- to 8-AM measurement of serum cortisol and plasma ACTH. This approach exploits the fact that serum cortisol level peaks in the early morning hours. A careful social and work history should be obtained before order-

ing this test, as shift workers or patients with unusual sleep-wake patterns may have altered cortisol circadian rhythm.¹⁹ This test is helpful if the serum cortisol level is more than 18 µg/dL (normal adrenal function) or less than 3 µg/dL (indicates AI).⁴ In the latter case, plasma ACTH level will distinguish between primary and secondary AI. In primary AI, the ACTH level is almost invariably more than 100 pg/mL, while in secondary AI, plasma ACTH can be either low or inappropriately normal (when serum cortisol is reduced).

In patients with severe physical stress, serum cortisol level should be more than 18 µg/dL at any time of the day.⁴ One exception is the patient with severe hypoproteinemia, because albumin and cortisol-binding globulin normally bind approximately 90% of circulating serum cortisol. In patients who are severely ill with serum albumin values of less than 2.5 g/L, the total cortisol is often markedly lower than 18 µg/dL; however, the free fraction of cortisol may be normal. In such patients, the total serum cortisol is less reliable than free cor-

tisol as an index of AI.²⁰ Unfortunately, direct measurement of free serum cortisol is not yet widely available, and there is no formula to correct serum cortisol according to albumin or total protein level. For this reason, patients diagnosed with AI in the intensive care unit based on serum cortisol should be retested in the outpatient setting before being committed to a life-long glucocorticoid treatment.

If an ambulatory patient has a morning serum cortisol level of between 3.1 and 17.9 µg/dL, some sort of dynamic test of adrenal function is essential. The test options for the assessment of adrenal function are summarized in TABLE 2. None of the available stimulation tests is ideal in terms of sensitivity and specificity. Consequently, the test results must be interpreted in the context of the clinical scenario. The choice of the test depends on several factors, including the experience of the physician and practical considerations related to test performance.

Insulin-Induced Hypoglycemia (Insulin Tolerance Test). The insulin tolerance test (ITT) measures the patient's cortisol response to hypoglycemia induced by the intravenous administration of insulin. This test is often considered the criterion standard because it assesses the ability of the entire HPA axis to respond to the stressful situation of hypoglycemia.²¹ Following insulin (0.1 IU/kg) administration, blood is drawn during symptomatic hypoglycemia (glucose should decrease to less

Table 1. Signs and Symptoms of Primary and Secondary Adrenal Insufficiency (AI)

	Primary AI	Secondary AI
Skin and mucosae	Dark	Pale
Potassium	High	Normal
Sodium	Low	Normal or low
Associated diseases	Primary hypothyroidism, type 1 diabetes mellitus, vitiligo, neurological deficit (adrenoleukodystrophy, males only)	Central hypogonadism or hypothyroidism, growth hormone deficiency, diabetes insipidus, headaches, visual abnormalities

Table 2. Synopsis of the Dynamic Tests Available to Assess Adrenal Function

	Test				
	ITT	Metyrapone	CRH	Conventional-Dose ACTH	Low-Dose ACTH
Stimulus	Insulin, 0.1-0.15 IU/kg intravenously	Metyrapone, 30 mg/kg by mouth at midnight (maximum, 3000 mg)	Ovine CRH, 1 µg/kg intravenously	1-24 ACTH, 250 µg intravenously (or intramuscularly)	1-24 ACTH, 1 µg intravenously
Blood drawing time points	30, 45, 60, and 90 min	8 AM following morning	15, 30, and 60 min	30 or 60 min	30 min
Measurements	Serum cortisol, blood glucose	Serum cortisol and 11-deoxycortisol	Serum cortisol	Serum cortisol	Serum cortisol
Cutoff	Serum cortisol >18 µg/dL, if glucose decreased <40 mg/dL	Serum 11-deoxycortisol >7 µg/dL, with serum cortisol <5 µg/dL	Serum cortisol >18.5 µg/dL	Serum cortisol >18 µg/dL	Serum cortisol >18 µg/dL

Abbreviations: ACTH, adrenocorticotropin hormone; CRH, corticotrophin-releasing hormone; ITT, insulin tolerance test. SI conversion: To convert glucose to mmol/L, multiply by 0.0555.

than 40 mg/dL [<2.22 mmol/L]). In obese patients with insulin resistance, the usual dose of insulin should be increased to 0.15 IU/kg.²² A serum cortisol peak of more than 18 μ g/dL is considered normal. The ITT has the advantage that it can also test the growth hormone reserve in patients with pituitary or hypothalamic disease. It is contraindicated in patients older than 60 years, and in those with history of seizures, or with documented or suspected coronary artery disease. It requires close medical supervision and trained personnel. Even the ITT has some limitations in terms of reproducibility and clear cutoff levels.^{21,23} It has been proposed that to improve its specificity glucose should decrease to less than 30 mg/dL (<1.67 mmol/L), with accompanying potential higher risks.²³

Metyrapone Test. The metyrapone test measures the ability of the HPA axis to respond to an acute reduction in serum cortisol levels. Metyrapone inhibits 11-hydroxylase, the enzyme involved in the last step of cortisol synthesis. This inhibition causes a decrease in cortisol that results (in a healthy patient) in a compensatory increase in ACTH and in the cortisol precursor, 11-deoxycortisol. This test is simple, relatively inexpensive, very sensitive, and requires a single blood drawing.²⁴ The administration of metyrapone (30 mg/kg; maximal dose, 3000 mg) occurs at midnight, and blood is drawn the following morning at 8 AM for cortisol and 11-deoxycortisol.²⁵ In response to metyrapone, serum cortisol level should decrease to less than 5 μ g/dL, and 11-deoxycortisol should increase to more than 7 μ g/dL. Recently, it has been proposed that the sum of cortisol and 11-deoxycortisol should be more than 16.5 μ g/dL.²⁵ Although some authors recommend that this test should be performed only during a hospital admission, a large retrospective series found it to be safe and suitable for the outpatient setting.²⁶ Regrettably, the intermittent availability of metyrapone limits its applicability in the United States.

CRH Stimulation Test. The CRH stimulation test measures the ability of the pituitary gland to secrete ACTH in response to CRH and the ability of the adrenal gland to respond with an increase in cortisol to the increase in circulating ACTH. Ovine CRH (1 μ g/kg) is injected intravenously, and cortisol is measured after 15, 30, and 60 minutes. The test has been proposed as a way to differentiate secondary (pituitary disease) from tertiary (hypothalamic disease) AI. However, a serum cortisol cutoff that allows high sensitivity (18.5 μ g/dL) is faulted by very low specificity (33%).²⁷ The lack of multiple studies involving large numbers of patients and the high cost of CRH have greatly limited its use.

ACTH Stimulation Test. The ACTH stimulation test is based on the inability of a diseased adrenal gland to respond acutely to the injection of ACTH by secreting cortisol. In the conventional ACTH stimulation test, 250 μ g of synthetic (1-24) ACTH is injected intravenously (or intramuscularly), and serum cortisol levels are measured at 30 or 60 minutes. A serum cortisol level of more than 18 μ g/dL at either time point constitutes a normal response, independent of baseline level and time of day. Although some healthy individuals can peak below this cutoff level, a peak of less than 15 μ g/dL is invariably abnormal.²⁸

The choice of the 250- μ g dose is based solely on the fact that ACTH comes in 250- μ g vials. However, with this dose, ACTH reaches plasma levels that are approximately 1000 times the values observed in maximally stressed healthy individuals, thereby potentially causing a falsely normal cortisol response by an adrenal gland that is in fact partially impaired.²⁹ Based on this observation, Dickstein et al³⁰ proposed the use of a more physiological low ACTH dose (1 μ g) to identify milder forms of secondary AI. They showed that in healthy individuals, the 1- μ g dose causes a similar increase in serum cortisol at 30 minutes, with a decline at 60 minutes.³⁰ Because ACTH is packaged only in 250- μ g vials, it must

be diluted to reach lower concentrations (ie, 1 μ g/mL), and it can be kept at 4°C for up to 4 months without any decline in biological activity.³¹

In several studies, the low-dose ACTH stimulation test has been shown to be more sensitive for diagnosing mild secondary AI than the traditional 250- μ g test, but not as sensitive as the ITT or metyrapone tests.^{24,32-35} However, a recent meta-analysis has found the sensitivity and specificity of the 2 tests to be not significantly different in the diagnosis of secondary AI.²⁸ Both doses perform equally well for the diagnosis of primary AI, even in mild cases.^{28,36} Using the low-dose test, most authors recommend using a 30-minute serum cortisol cutoff of 18 μ g/dL. When the results of this test are borderline (peak serum cortisol between 15 and 18 μ g/dL), confirmation by either the metyrapone test or ITT should be performed.^{24,28}

There are sporadic reports of possible dangers of missing the diagnosis of secondary AI using the 250- μ g test.³⁷ However, it has not yet been proven in a large cohort whether patients who pass the high-dose test but fail the low-dose test actually benefit from glucocorticoid therapy.

As long-term reduction in ACTH secretion is needed to develop adrenal atrophy, any form of ACTH stimulation test generates false-negative results in patients with a recent onset of ACTH deficiency, such as those who have recently undergone pituitary surgery or had a pituitary infarction. The reduction in ACTH secretion must be chronic (>1 month) and probably severe to cause atrophy of the adrenal glands.

Because the low-dose test is simple to perform, potentially more sensitive than the high-dose test, and less expensive (many patients can be tested with a single 250- μ g ACTH vial), it should be the routine procedure used in the evaluation of potential cases of both primary and secondary AI.

Identifying the Cause of AI

Once the diagnosis of AI is established, the physician must determine its cause.

Table 3. Equivalency Table of Commonly Used Glucocorticoids*

	Glucocorticoids				
	Hydrocortisone	Cortisone Acetate	Prednisone	Prednisolone	Dexamethasone
Relative potency	1	0.8	4	5	25-50
Equivalent dose, mg	20	25	5	4	0.5
Biological half-life, h	8-12	8-12	18-36	18-36	36-54

*Adapted from Krasner.⁹

In primary AI, the age of the patient, associated morbidities, clinical picture, and medical history must guide the decisions regarding work-up. Measurement of anti-adrenal antibodies may help the diagnosis of autoimmune adrenalitis. This test is highly specific but not 100% sensitive.³⁸ Measurement of very long chain fatty acids must be obtained if adrenoleukodystrophy is suspected. Computed tomography imaging of the adrenals may unveil hemorrhagic, metastatic, or infectious diseases. Adrenal biopsy may occasionally be needed. In secondary AI, in the absence of a history of exogenous glucocorticoid exposure, magnetic resonance imaging of the sellar region is mandatory, as secondary AI may be the presenting feature of a neoplastic process in the pituitary or the hypothalamus.

Therapy

Glucocorticoids. Glucocorticoids are the main therapy for all forms of AI. Although several kinds of glucocorticoids can be used, hydrocortisone (10-12.5 mg/m² per day) is preferred because its short half-life mimics most closely the normal cortisol circadian rhythm. This dose of hydrocortisone is not associated with reduced bone mineral density.³⁹ The downside is that hydrocortisone must be given twice or 3 times a day.⁴⁰ The classic dose of 30 mg/d (20 mg in the morning and 10 mg in the afternoon) is probably excessive in most patients, particularly patients with secondary AI, as shown by today's patient, who gained a significant amount of weight with this dose. Other glucocorticoids may be administered, keeping in mind their potencies relative to that of hydrocortisone (TABLE 3).^{9,41} Long-acting glucocorticoids are preferred

when, together with replacement therapy, one wants to suppress ACTH secretion, such as in congenital adrenal hyperplasia.

Because there is no good biochemical index to help determine the right glucocorticoid dose to reduce long-term adverse effects on bone and other tissues, the smallest amount that improves the patient's symptoms is recommended.⁴² In patients with glucocorticoid-induced AI, using a small dose may accelerate the recovery of the HPA axis.⁹ In some patients who have mild secondary AI and no symptoms during everyday life, hydrocortisone may be required only during periods of physical stress. In contrast with the approach to treating primary hypothyroidism, when restoration of a normal thyroid-stimulating hormone is an important target of therapy, in the treatment of primary AI, attempting to normalize plasma ACTH levels is not recommended because this invariably results in overdosing and the induction of an iatrogenic Cushing syndrome state.⁴³ In patients who are also hypothyroid, thyroid hormones should never be replaced before administering glucocorticoids; euthyroidism may trigger an adrenal crisis by accelerating the metabolism of cortisol. Similarly, growth hormone therapy can accelerate cortisol metabolism, thereby requiring adjustment of hydrocortisone dosing.⁴⁴

The cytochrome P450 CYP3A4 isozyme is involved in the hepatic metabolism of glucocorticoids. Therefore, patients who are taking drugs that may increase (phenytoin, rifampin, barbiturates) or decrease (protease inhibitors) the function of this enzyme may need higher or lower doses of glu-

corticoids, respectively.^{45,46} In patients who are taking protease inhibitors, significant adrenal suppression may occur within few months of therapy with inhaled steroids.⁴⁷

Women usually do not need adjustment in their dose of glucocorticoids during pregnancy, but in case of protracted first trimester vomiting, parenteral administration may be needed.

Every patient with AI should wear a medical alert bracelet or necklace stating the need for glucocorticoids in case of an emergency. An emergency glucocorticoids injection kit should be prescribed to patients who live or travel to remote areas, where they may not have readily available medical assistance.

Mineralocorticoids. Patients with primary AI also need mineralocorticoid therapy. The only drug available is fludrocortisone. Its dose ranges in most cases between 0.05 and 0.2 mg/d, usually in a single dose. The dose is adjusted according to the patient's symptoms, including orthostatic dizziness and salt craving, and to serum potassium and plasma renin activity. Suppressed plasma renin activity is a useful marker of fludrocortisone overdose. In the absence of orthostatic symptoms or of significant changes in the blood pressure or heart rate during orthostatic maneuvers, however, the fludrocortisone dose should not be increased even if the plasma renin activity is increased to mild or moderate levels. Overdosing of fludrocortisone can cause fluid retention, edema, and hypertension.

Androgen. In women with AI, dehydroepiandrosterone replacement improves well-being and sexuality.⁴⁷ As dehydroepiandrosterone is considered a dietary supplement in the United States, it is not regulated by the US Food and Drug Administration. Arlt et al⁴⁸ showed that patients treated with 50 mg/d of dehydroepiandrosterone increase their serum dehydroepiandrosterone-sulfate and testosterone levels; therefore, these measurements can be used to determine adequateness of the supplement and the patient's adherence.

Therapy During Stress. During illnesses, the glucocorticoid dose should be increased. One reasonable approach is to double the maintenance dose in the setting of fevers (temperatures $>38^{\circ}\text{C}$), major dental procedures (tooth extractions or root canals), or invasive diagnostic procedures (gastroscopy, colonoscopy, cystoscopy, or bronchoscopy). Patients with AI are more likely to develop cardiovascular instability when they have a disease that causes vomiting or diarrhea. In these situations, in addition to the increased glucocorticoid requirement, they may not properly absorb the oral therapy. For this reason, patients with AI should go the emergency department if they experience multiple episodes of vomiting and/or diarrhea.

The glucocorticoid doses commonly used during major stress (major surgery, severe infection, myocardial infarction)—80 to 100 mg of hydrocortisone every 8 hours—are probably excessive and not based on any clear evidence. Patients with intact adrenal function secrete between 75 and 150 mg/d in response to major surgery.⁴⁹ Therefore, the maximal dose recommended is 50 mg of hydrocortisone every 8 hours. When such a dose is administered, there is no need to prescribe fludrocortisone even in patients with primary AI, because the high doses of hydrocortisone will activate the mineralocorticoid receptor. It is possible that even this dosage is excessive in patients with secondary AI. A small study⁵⁰ showed that among patients with glucocorticoid-induced AI (taking a mean daily prednisone dose of 18.8 mg) undergoing major surgery, a group treated with the usual prednisone dose and a group that received stress-dose glucocorticoids had no difference in perioperative complications.

Patients with septic shock whose total serum cortisol increases by less than 9 $\mu\text{g}/\text{dL}$ in response to 250 μg of ACTH have lower mortality when treated with hydrocortisone (50 mg every 6 hours) plus fludrocortisone (0.05 mg/d).⁵¹ This benefit is likely a pharmacological effect and does not necessarily classify these patients as having AI.

CONCLUSION

The symptoms of AI are nonspecific and this disease often goes undiagnosed for extended periods of time, with the risk of potential serious consequences. Therefore, physicians must suspect it in the presence of the symptoms described earlier, particularly in patients with a history of autoimmune diseases or signs or symptoms consistent with hypopituitarism. The work-up must be step-wise and should start from the least expensive test (morning serum cortisol). Adrenal insufficiency needs to be suspected in severely ill patients with cardiovascular instability. In this setting, glucocorticoids should be administered empirically while waiting for the results of a pretreatment serum cortisol.

Confirming the diagnosis of partial secondary AI may be challenging and repeated testing may be needed before committing a patient to a lifelong glucocorticoid therapy. As both lack of needed treatment and not warranted glucocorticoids are dangerous, in dubious cases the decision of whether to treat a patient with suspected AI should be left to practitioners who have experience in the field. Glucocorticoids need to be prescribed judiciously, using the lowest possible dose that improves the patient's symptoms to avoid long-term adverse effects on bone, blood pressure, body composition, and glucose metabolism.

Financial Disclosures: None reported.

Acknowledgment: I thank John Stone, MD, and Simeon Margolis, MD, PhD, from the Department of Medicine, Johns Hopkins University, for critically reviewing the manuscript. No compensation was given to either of them.

REFERENCES

1. Robinson DB, Michaels RD. Empty sella resulting from the spontaneous resolution of a pituitary macroadenoma. *Arch Intern Med.* 1992;152: 1920-1923.
2. Hatazoe T, Murakami Y, Umaki I, Sohmiya M, Hu HY, Kato Y. Isolated adrenocorticotrophic hormone deficiency associated with growth hormone deficiency and empty sella. *Intern Med.* 1995;34:688-691.
3. Hartman ML, Crowe BJ, Biller BM, Ho KK, Clemmons DR, Chipman JJ; HypoCCS Advisory Board and US HypoCCS Study Group. Which patients do not require a GH stimulation test for the diagnosis of adult GH deficiency? *J Clin Endocrinol Metab.* 2002;87: 477-485.
4. Oelkers W. Adrenal insufficiency. *N Engl J Med.* 1996;335:1206-1212.
5. Kelestimur F. The endocrinology of adrenal tuberculosis: the effects of tuberculosis on the hypothalamo-pituitary-adrenal axis and adrenocortical function. *J Endocrinol Invest.* 2004;27:380-386.
6. Moser H, Dubey P, Fatemi A. Progress in X-linked adrenoleukodystrophy. *Curr Opin Neurol.* 2004; 17:263-269.
7. Magill SS, Puthanakit T, Swoboda SM, et al. Impact of fluconazole prophylaxis on cortisol levels in critically ill surgical patients. *Antimicrob Agents Chemother.* 2004;48:2471-2476.
8. Schlaghecke R, Kornely E, Santen RT, Ridderkamp P. The effect of long-term glucocorticoid therapy on pituitary-adrenal responses to exogenous corticotropin-releasing hormone. *N Engl J Med.* 1992;326: 226-230.
9. Krasner AS. Glucocorticoid-induced adrenal insufficiency. *JAMA.* 1999;282:671-676.
10. Mahachoklertwattana P, Sudkronrayudh K, Direkwatertanachai C, Choubtum L, Okascharoen C. Decreased cortisol response to insulin induced hypoglycemia in asthmatics treated with inhaled fluticasone propionate. *Arch Dis Child.* 2004;89:1055-1058.
11. Mader R, Lavi I, Luboshitzky R. Evaluation of the pituitary-adrenal axis function following single intraarticular injection of methylprednisolone. *Arthritis Rheum.* 2005;52:924-928.
12. Ron IG, Soyfer V, Goldray D, Inbar MJ, Weisman Y. A low-dose adrenocorticotropin test reveals impaired adrenal function in cancer patients receiving megestrol acetate therapy. *Eur J Cancer.* 2002;38: 1490-1494.
13. Toogood AA. Endocrine consequences of brain irradiation. *Growth Horm IGF Res.* 2004;14 (suppl A):S118-S124.
14. Aimaretti G, Ambrosio MR, Di Somma C, et al. Traumatic brain injury and subarachnoid hemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury. *Clin Endocrinol (Oxf).* 2004;61:320-326.
15. Xarli VP, Steele AA, Davis PJ, Buescher ES, Rios CN, Garcia-Bunuel R. Adrenal hemorrhage in the adult. *Medicine.* 1978;57:211-220.
16. Siu SC, Kitzman DW, Sheedy PF 2nd, Northcutt RC. Adrenal insufficiency from bilateral adrenal hemorrhage. *Mayo Clin Proc.* 1990;65:664-670.
17. Espinosa G, Santos E, Cervera R, et al. Adrenal involvement in the antiphospholipid syndrome: clinical and immunologic characteristics of 86 patients. *Medicine (Baltimore).* 2003;82:106-118.
18. Vallotton MB. Endocrine emergencies: disorders of the adrenal cortex. *Baillieres Clin Endocrinol Metab.* 1992;6:41-56.
19. Touitou Y, Motohashi Y, Reinberg A, et al. Effect of shift work on the night-time secretory patterns of melatonin, prolactin, cortisol and testosterone. *Eur J Appl Physiol Occup Physiol.* 1990;60:288-292.
20. Hamrahan AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. *N Engl J Med.* 2004;350:1629-1638.
21. Pfeifer M, Kanc K, Verhovec R, Kojianic A. Reproducibility of the ITT for assessment of GH and cortisol responses in normal and hypopituitary adult men. *Clin Endocrinol (Oxf).* 2001;154:17-22.
22. Cordido F, Alvarez-Castro P, Isidro ML, Casanueva FF, Dieguez C. Comparison between insulin tolerance test, growth hormone (GH)-releasing hormone (GHRH), GHRH plus acipimox and GHRH plus GH-releasing peptide-6 for the diagnosis of adult GH deficiency in normal subjects, obese and hypopituitary patients. *Eur J Endocrinol.* 2003;149:117-122.
23. Nye EJ, Grice JE, Hokings GI, et al. The insulin hypoglycemia test: hypoglycemic criteria and reproducibility. *J Neuroendocrinol.* 2001;13: 524-530.
24. Soule S, van Zyl Smit K, Parolis G, et al. The low dose ACTH stimulation test is less sensitive than the overnight metyrapone test for the diagnosis of secondary hypoadrenalinism. *Clin Endocrinol (Oxf).* 2000; 53:221-227.

25. Berneis K, Staub JJ, Gessler A, Meier C, Girard J, Muller B. Combined stimulation of adrenocorticotropin and compound-S by single dose metyrapone test as an outpatient procedure to assess hypothalamic-pituitary-adrenal function. *J Clin Endocrinol Metab.* 2002;87:5470-5475.

26. Fiad TM, Kirby JM, Cunningham SK, Mckenna TJ. The overnight single-dose metyrapone test is a simple and reliable index of HPA axis. *Clin Endocrinol (Oxf).* 1994;40:603-609.

27. Schmidt IL, Lahner H, Mann K, Petersenn S. Diagnosis of adrenal insufficiency: evaluation of the corticotropin-releasing hormone test and basal serum cortisol in comparison to the insulin tolerance test in patients with hypothalamic-pituitary-adrenal disease. *J Clin Endocrinol Metab.* 2003;88:4193-4198.

28. Dorin RI, Qualis CR, Crapo LM. Diagnosis of adrenal insufficiency. *Ann Intern Med.* 2003;139:194-204.

29. Mayenknecht J, Diederich S, Bahr V, Plockinger U, Oelkers W. Comparison of low and high dose corticotrophin stimulation test in patients with pituitary disease. *J Clin Endocrinol Metab.* 1998;83:1558-1562.

30. Dickstein G, Shechner C, Nicholson WE, et al. Adrenocorticotropin stimulation test: effects of basal cortisol level, time of the day and suggested new sensitive low dose test. *J Clin Endocrinol Metab.* 1991;72:773-778.

31. Dickstein G, Arad E, Shechner C. Low-dose ACTH stimulation test. *Endocrinologist.* 1997;7:285-293.

32. Abdu TAM, Elhaddad TA, Neary R, Clayton RN. Comparison of the low dose short synacthen test (1 µg), the conventional dose short synacthen test (250 µg), and the insulin tolerance test for assessment of the hypothalamic-pituitary-adrenal axis in patients with pituitary disease. *J Clin Endocrinol Metab.* 1999;84:838-843.

33. Dokmetas HS, Colak R, Kelestimir F, Selcuklu A, Unluhizarcı K, Bayram F. A comparison between the 1-microg adrenocorticotropin (ACTH) test, the short ACTH (250 microg) test, and the insulin tolerance test in the assessment of hypothalamo-pituitary-adrenal axis immediately after pituitary surgery. *J Clin Endocrinol Metab.* 2000;85:3713-3719.

34. Courtney CH, McAllister AS, McCance DR, et al. Comparison of one week 0900 serum cortisol, low and standard dose synacthen test with a 4 to 6 weeks insulin hypoglycemia test after pituitary surgery in assessing HPA axis. *Clin Endocrinol (Oxf).* 2000;53:431-436.

35. Suliman AM, Smith TP, Labib M, Fiad TM, McKenna TJ. The low-dose ACTH test does not provide a useful assessment of the hypothalamic-pituitary-adrenal axis in secondary adrenal insufficiency. *Clin Endocrinol (Oxf).* 2002;56:533-539.

36. Laureti S, Arvat E, Candeloro P, et al. Low dose (1 µg) ACTH test in the evaluation of adrenal dysfunction in pre-clinical Addison's disease. *Clin Endocrinol (Oxf).* 2000;53:107-115.

37. Streeten DH, Anderson GH Jr, Bonaventura MM. The potential for serious consequences from misinterpreting normal responses to the rapid adrenocorticotropin test. *J Clin Endocrinol Metab.* 1996;81:285-290.

38. Falorni A, Laureti S, Nikoshkov A, et al. 21-hydroxylase autoantibodies in adult patients with endocrine autoimmune diseases are highly specific for Addison's disease: Belgian diabetes registry. *Clin Exp Immunol.* 1997;107:341-346.

39. Chikada N, Imaki T, Hotta M, Sato K, Takano K. An assessment of bone mineral density in patients with Addison's disease and isolated ACTH deficiency treated with glucocorticoid. *Endocr J.* 2004;51:355-360.

40. Mah PM, Jenkins RC, Rostami-Hodjegan A, et al. Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency. *Clin Endocrinol (Oxf).* 2004;61:367-375.

41. Malchoff CD, Carey RM. Adrenal insufficiency. In: *Current Therapy in Endocrinology and Metabolism.* St Louis, Mo: Mosby; 1997:142-147.

42. Peacey SR, Guo CY, Robinson AM, et al. Glucocorticoid replacement therapy: are patients over treated, and does it matter? *Clin Endocrinol (Oxf).* 1997;46:255-261.

43. Oelkers W, Diederich S, Bahr V. Diagnosis and therapy surveillance in Addison's disease: rapid adrenocorticotropin (ACTH) test and measurement of plasma ACTH, renin activity and aldosterone. *J Clin Endocrinol Metab.* 1992;75:259-264.

44. Swords FM, Carroll PV, Kisalu J, Wood PJ, Taylor NF, Monson JP. The effects of growth hormone deficiency and replacement on glucocorticoids exposure in hypopituitary patients on cortisone acetate and hydrocortisone therapy. *Clin Endocrinol (Oxf).* 2003;59:613-620.

45. Lamberts SWJ, Bruining HA, De Jong FH. Corticosteroid therapy in severe illness. *N Engl J Med.* 1997;337:1285-1292.

46. Eagling VA, Back DJ, Barry MG. Differential inhibition of cytochrome P450 isoform by the protease inhibitors ritonavir, saquinavir and indinavir. *Br J Clin Pharmacol.* 1997;44:190-194.

47. Samaras K, Pett S, Gowers A, McMurchie M, Cooper DA. Iatrogenic Cushing's syndrome with osteoporosis and secondary adrenal failure in human immunodeficiency virus-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: six cases. *J Clin Endocrinol Metab.* 2005;90:4394-4398.

48. Arlt W, Callies F, van Vlijmen JC, et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med.* 1999;341:1013-1020.

49. Salem M, Tainsh RE Jr, Bromberg J, Loriaux DL, Chernow B. Perioperative glucocorticoid coverage: a reassessment 42 years after emergence of a problem. *Ann Surg.* 1994;219:416-425.

50. Glowniak JV, Loriaux DL. A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. *Surgery.* 1997;121:123-129.

51. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA.* 2002;288:862-871.