REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Diagnosis and Differential Diagnosis of Cushing's Syndrome

D. Lynn Loriaux, M.D., Ph.D.

From the Division of Endocrinology, Diabetes, and Clinical Nutrition, Oregon Health and Science University, Portland. Address reprint requests to Dr. Loriaux at the Division of Endocrinology, Diabetes, and Clinical Nutrition, Oregon Health and Science University, 3181 SW Sam Jackson Park Rd., L607, Portland, OR 97239-3098, or at loriauxl@ohsu.edu.

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More than a century ago, Harvey Cushing introduced the term "pluriglandular syndrome" to describe a disorder characterized by rapid development of central obesity, arterial hypertension, proximal muscle weakness, diabetes mellitus, oligomenorrhea, hirsutism, thin skin, and ecchymoses.[1] Cushing knew that this syndrome was associated with adrenal cancer,[2] and he suspected that some cases might have a pituitary component. On September 6, 1911, he performed a craniotomy on one of his patients (referred to as Case XLV) but found no pituitary tumor.[3] In his description of the case, he goes on to say that "we may perchance be on the way toward the recognition of the consequences of hyperadrenalism."[2] With time, it became clear that the disorder could be caused by small basophilic adenomas of the pituitary gland,[4] and the pluriglandular syndrome became known as Cushing's syndrome.

Fuller Albright provided the next conceptual advance in an extraordinary report, published in the first volume of the Laurentian Hormone Conference, "The Effects of Hormones on Osteogenesis in Man"[5]:

> It has been our concept that protoplasm in general, like the protoplasmic matrix of bone, is constantly being anabolized and catabolized at one and the same time; a factor which increases catabolism would lead to very much the same net result as a factor which inhibits anabolism, but there would be some differences; it is my belief that the "S" hormone [cortisol] is anti-anabolic rather than catabolic. . . . The anti-anabolism . . . is contrasted with the increased anabolism due to an excess of the "N" hormone [testosterone] in the adreno-genital syndrome. This anti-anabolism of protoplasm in Cushing's syndrome accounts for not only the osteoporosis, but the muscular weakness, the thin skin, probably the easy bruisability, and possibly the atrophy of the lymphoid tissues and thymus.

Nonetheless, in the intervening years, the physical examination of patients suspected to have glucocorticoid excess focused on the anabolic changes, essentially to the exclusion of the antianabolic changes. With the rapid increase in the rate of obesity in the general population, Cushing's syndrome can no longer be reliably separated from the metabolic syndrome of simple obesity on the basis of anabolic signs alone. However, the antianabolic changes in Cushing's syndrome are very effective in making this distinction. This review focuses on the problems introduced into the diagnosis and differential diagnosis of Cushing's syndrome by the obesity epidemic and on ways to alter the traditional approach, using the antianabolic changes of excess cortisol to separate patients with Cushing's syndrome from obese patients with the insulin-resistant metabolic syndrome.

PHYSICAL EXAMINATION

Andreas Vesalius (1514–1564) published his transformational work on human anatomy, *De Humani Corporis Fabrica Libri Septem*, in 1543. It is the book that corrected many of Galen's anatomical errors. The book was met with considerable hostility. As an example, Jacobus Sylvius (Jacques Dubois, 1478–1555), the world's leading anatomist at the time and Vesalius's former mentor, on being asked his opinion of the work, replied, "Galen is not wrong. It is man that has changed, and not for the better."[6] This was not true then, but it is true now.

Approximately one third of the U.S. population is obese. The worldwide prevalence of the metabolic syndrome among obese persons is conservatively estimated at 10%; that is, approximately 12 million people have the obesity-related metabolic syndrome.[7,8] The clinical picture of this syndrome is almost the same as that of Cushing's syndrome.[9,10] The prevalence of undiagnosed Cushing's syndrome is about 75 cases per 1 million population, or 24,000 affected persons. On the basis of these prevalence estimates, the chance that a person with obesity, hypertension, hirsutism, type 2 diabetes, and dyslipidemia has Cushing's syndrome is about 1 in 500. In Harvey Cushing's era, when obesity was rare, making the diagnosis of Cushing's syndrome was the most certain aspect of the management of this disorder. Today, making the diagnosis is the least certain aspect in the care of patients with Cushing's syndrome.

The metabolic syndrome caused by glucocorticoid hypersecretion can be differentiated from the obesity-associated metabolic syndrome with the use of a careful assessment of Albright's antianabolic effects of cortisol. These effects — osteopenia, thin skin, and ecchymoses — are present in patients with Cushing's syndrome but not in patients with simple obesity.

Patients in whom osteoporosis is diagnosed radiographically are more likely to have Cushing's syndrome than those who do not have osteoporosis, with a positive likelihood ratio of 11.[11-13] Today, a z score of –2 at the lumbar spine supports this criterion. Skinfold thickness is conveniently measured with an electrocardiographic caliper that has the points dulled with a sharpening stone and the screws tightened so that the gap is maintained when the caliper is removed from the skinfold. The skin over the proximal phalanx of the middle finger of the nondominant hand is commonly used for this measurement (Fig. 1). A thickness of less than 2 mm is considered to be thin skin. Patients who have thin skin are more likely to have Cushing's syndrome, with a positive likelihood ratio of 116 (Fig. 2).[13-15] Finally, patients who have three or more ecchymoses that are larger than 1 cm in diameter and not associated with trauma such as venipuncture are more likely to have Cushing's syndrome than are patients without such findings, with a positive likelihood ratio of 4.[13,16]

If we know the prevalence of undiagnosed Cushing's syndrome in the population of persons with the obesity-related metabolic syndrome, we can begin to calculate the probability that a person has Cushing's syndrome, using the likelihood ratios for the antianabolic features observed on physical examination. Likelihood ratios can be converted into probabilities with the use of Bayes' theorem. This conversion is markedly facilitated by the Fagan nomogram for this purpose.[17]

The prevalence of undiagnosed Cushing's syndrome is not known, but it can be estimated. Two persons per 1 million population die from adrenal cancer every year.[18] The current life span for patients with adrenocortical carcinoma, after diagnosis, is between 2 and 4 years.[19,20] Allowing 3 years to make the diagnosis, the prevalence of undiagnosed Cushing's syndrome is 6 cases per million. In most case series of Cushing's syndrome, an average of 8% of patients have adrenal carcinoma.[21] If 6 per million is 8% of the group, the total Cushing's syndrome group is 75 persons per million, or 24,000 persons. If all 24,000 patients are included in the metabolic syndrome group, comprising 12 million people, the prevalence of Cushing's syndrome is 0.002, or 0.2%. With a probability of 0.2% and a likelihood ratio of 116 for thin skin, 18 for osteopenia, and 4 for ecchymoses, the probability that a patient with these three findings has Cushing's syndrome is 95%.

URINARY FREE CORTISOL

The diagnosis of all endocrine diseases requires a clinical presentation that is compatible with the disease, as well as identification of the pathophysiological cause. An assessment for excess glucocorticoid effects can be made by measuring

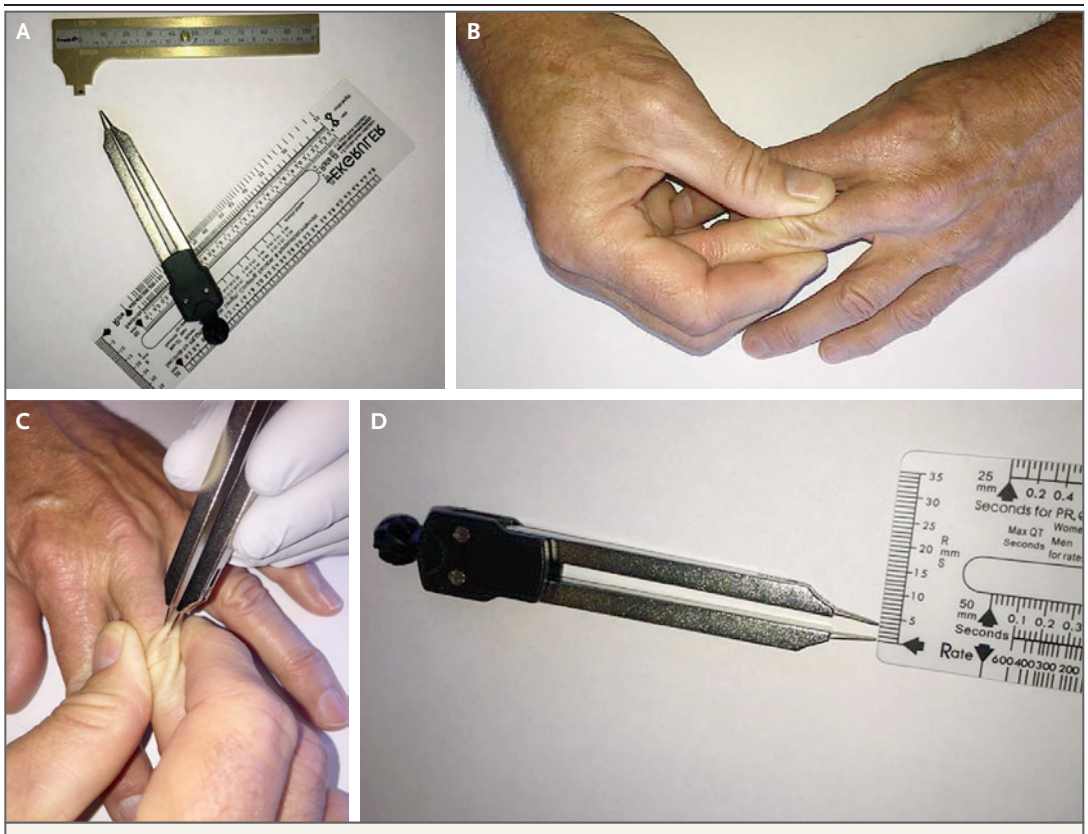

Figure 1. Measurement of Skinfold Thickness.

Skinfold thickness is measured with a caliper and a micrometer or millimeter ruler (Panel A). A skinfold is created (Panel B) and measured with the caliper (Panel C). The thickness of the skinfold is read on the ruler; the thickness is 3 mm in this case (Panel D).

the 24-hour urinary free cortisol level.[22] There are two kinds of free cortisol: plasma protein-unbound cortisol and cortisol unconjugated to sulfuric or hyaluronic acid. Protein-unbound cortisol is filtered in the glomerulus and then reabsorbed in the collecting system. About 3% of filtered cortisol ends up in the urine. This free cortisol in the urine is unconjugated. Thus, the urinary free cortisol level is a direct reflection of the free, bioactive cortisol level in plasma. The free cortisol level is quantified in a 24-hour urine sample by averaging the increased secretion of cortisol in the morning and the decreased secretion in the afternoon and at night. Urinary creatinine is also measured to determine whether the collection is complete. Creatinine levels of less than 1.5 g per day for men and less than 1 g per day for women indicate incomplete collection, and the test should be repeated in patients with these levels.

Unconjugated cortisol can be extracted directly from urine with a nonpolar lipid solvent. After extraction, the cortisol is purified by means of high-pressure liquid chromatography and then quantified with a binding assay, usually radioimmunoassay. Free cortisol also can be quantitated directly by means of mass spectroscopy. The urinary free cortisol assay of choice uses high-pressure liquid chromatographic separation followed by mass spectrometric quantitation.[23] With the use of this assay, the urinary free cortisol level in healthy adults ranges from 8 to 51 μg per 24 hours (mean [±SD], 23±8). Clinical depression increases urinary free cortisol excretion, and most studies show that the level of urinary free cortisol ranges from 10 to 60 μg per day in patients with typical clinical signs and symptoms of depression. If we use 60 μg per day as the cutoff between normal values (<60 μg per day) and elevated values (≥60 μg per day), urinary free

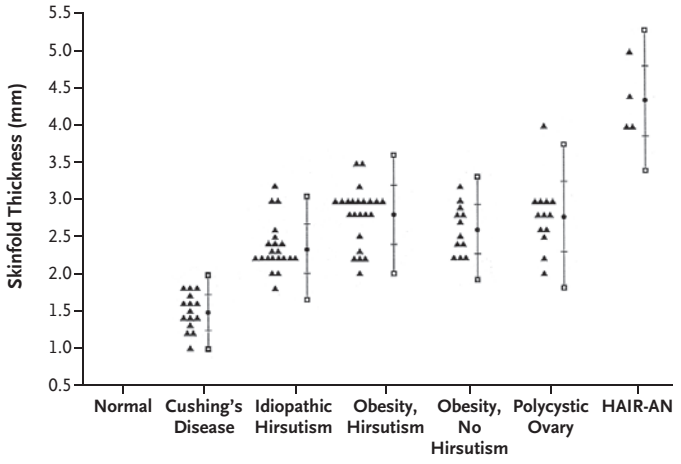

Figure 2. Comparison of Skinfold Thickness in Patients with Cushing's Syndrome and Those with Other Conditions Related to Insulin Resistance.

HAIR-AN denotes hyperandrogenism, insulin resistance, and acanthosis nigricans. Vertical bars indicate means ±2 SD. Data are from Corenblum et al.[14]

cortisol excretion of 62 μg per day or more has a positive likelihood ratio of 11.[24] Thus, in a patient presenting with obesity, hypertension, type 2 diabetes, and hirsutism who has thin skin, osteopenia, ecchymoses, and an elevated urinary free cortisol level, the probability of Cushing's syndrome is 1 (100%). For such patients, the clinician should move directly to a differential diagnostic evaluation.

DEXAMETHASONE-SUPPRESSION TEST

The dexamethasone-suppression test is commonly used in the diagnosis of Cushing's syndrome. This test was developed by Grant Liddle in the early 1960s as a differential diagnostic test to separate corticotropin-dependent from corticotropin-independent Cushing's syndrome. This is now done by measuring the plasma corticotropin level. Unfortunately, dexamethasone suppression has continued to be used as a screening test for Cushing's syndrome.

The control group for this test comprises patients with obesity and depression in whom cortisol secretion is not suppressed in response to an oral dose of 1 mg of dexamethasone at midnight. Of the current U.S. population of 360 million people, approximately one third (120 million people) are obese. Of those who are obese, 10% (12 million people) have depression. In half these patients (6 million people), the plasma cortisol level will not be suppressed in response to a dexamethasone challenge. On the basis of my estimate of the current prevalence of undiagnosed Cushing's syndrome (24,000 cases) and the estimate of the at-risk population (6 million persons), the positive predictive value of the dexamethasone-suppression test is only 0.4%. Thus, this test should not influence what the physician does next and should no longer be used for this purpose.

OUTLIERS

For patients with convincing evidence of Cushing's syndrome on physical examination and an elevated 24-hour urinary free cortisol level, the differential diagnostic process outlined below should be initiated. However, a small group of patients will not meet these criteria.

Some patients have a strongly positive physical examination but low or zero urinary free cortisol excretion. Plasma corticotropin levels are suppressed in these patients. These patients are receiving exogenous glucocorticoids. The glucocorticoid must be identified, and a plan must be made for its discontinuation. Sometimes the glucocorticoid is being given by proxy (e.g., by a parent to a child), and no history of glucocorticoid administration can be found. Nevertheless, the glucocorticoid must be identified and discontinued.

Other patients have few or no clinical signs of Cushing's syndrome but do have elevated urinary free cortisol excretion. Plasma corticotropin is measurable in these patients. They are usually identified during an evaluation for arterial hypertension. All such patients should undergo inferior petrosal sinus sampling to determine the source of corticotropin secretion. Ectopic sources are almost always neoplastic and are usually in the chest.[25] Patients with eutopic secretion usually have the syndrome of generalized glucocorticoid resistance.[26]

Finally, a few patients have convincing findings on physical examination coupled with a normal urinary free cortisol level. In such cases, the clinician should make sure that urinary free cortisol is being measured with high-performance liquid chromatography and mass spectrometry, that renal function is normal, and that the collections are complete. "Periodic" Cushing's syn-

drome must be ruled out by measuring urinary free cortisol frequently over the course of a month.[27] If these efforts fail, the patient should be followed for a year, with urinary free cortisol measurements performed frequently. No additional tests should be performed until the situation is sorted out. More tests would be likely to lead to an unnecessary surgical procedure.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Cushing's syndrome is shown in Figure 3. If plasma corticotropin is measurable, the disease process is corticotropin-dependent. If corticotropin is not measurable, the process is corticotropin-independent.

Corticotropin-dependent causes of Cushing's syndrome are divided into those in which the corticotropin comes from the pituitary (eutopic causes) and those in which the corticotropin comes from elsewhere (ectopic causes). This differentiation is made with the measurement of corticotropin in inferior petrosal sinus plasma and the simultaneous measurement of corticotropin in peripheral (antecubital) plasma immediately after corticotropin-releasing hormone stimulation of pituitary corticotropin secretion. In samples obtained 4, 6, and 15 minutes after stimulation with corticotropin-releasing hormone, eutopic corticotropin secretion is associated with a ratio of the central-plasma corticotropin level to the peripheral-plasma corticotropin level of 3 or more. Ectopic corticotropin secretion is associated with a central-to-peripheral corticotropin ratio of less than 3. The positive predictive value of this test is 1 (Fig. 4).[28]

Although some authorities suggest that inferior petrosal sinus sampling can safely be bypassed in patients with corticotropin-dependent Cushing's syndrome and a well-defined pituitary adenoma, I disagree. The incidence of nonfunctioning pituitary microadenomas is between 15% and 40%.[29] This means that up to 40% of patients with ectopic secretion of corticotropin have an incidental pituitary abnormality. If it is assumed that the pituitary abnormality is responsible for corticotropin secretion, 15 to 40% of patients with ectopic secretion of corticotropin will be misdiagnosed and submitted to a transsphenoidal exploration of the sella turcica and pituitary gland. The prevalence of ectopic corticotropin secretion in the population of patients with undiagnosed Cushing's syndrome is about 10%, accounting for 2400 patients. Up to 40% of these patients, or 960, have an incidental pituitary tumor. The mortality associated with transsphenoidal microadenomectomy is 1%.[30] If all 360 to 960 patients undergo this procedure, there will be up to 10 deaths from an operation that can have no benefit. For this reason alone, all patients with corticotropin-dependent Cushing's syndrome should undergo inferior petrosal sinus sampling to confirm the source of corticotropin secretion before any surgical intervention is contemplated.

Patients with eutopic corticotropin secretion are almost certain to have a corticotropin-secreting pituitary microadenoma. An occasional patient will have alcohol-induced pseudo–Cushing's syndrome. The slightest suggestion of alcoholism should lead to a 3-week abstinence period before any surgery is considered.[31]

Patients with ectopic corticotropin secretion are first evaluated with computed tomography (CT) or magnetic resonance imaging (MRI) of the chest. In two thirds of these patients, a tumor will be found.[25] If nothing is found in the chest, MRI of the abdominal and pelvic organs is performed. If these additional imaging studies are also negative, there are two options: bilateral adrenalectomy or blockade of cortisol synthesis. If blockade is chosen, the patient should undergo repeat scanning at 6-month intervals.[32] If no source is found by the end of the second year, it is unlikely that the source will ever be found, and bilateral adrenalectomy should be performed for definitive treatment (Doppman JL: personal communication).

Corticotropin-independent Cushing's syndrome is usually caused by an adrenal neoplasm. Benign tumors tend to be small (<5 cm in diameter) and secrete a single hormone, cortisol. The contralateral adrenal gland is suppressed by the cortisol secreted from the tumorous gland. If the value for Hounsfield units is less than 10 and the washout of contrast material is greater than 60% at 15 minutes, the tumor is almost certainly benign.[33] Such tumors can be treated successfully with laparoscopic adrenalectomy.

The syndromes of micronodular and macronodular adrenal dysplasia usually affect both adrenal glands. The nodules secrete cortisol. Corticotropin is suppressed, as is the internodular tissue of the adrenal glands. Percutaneous bilat-

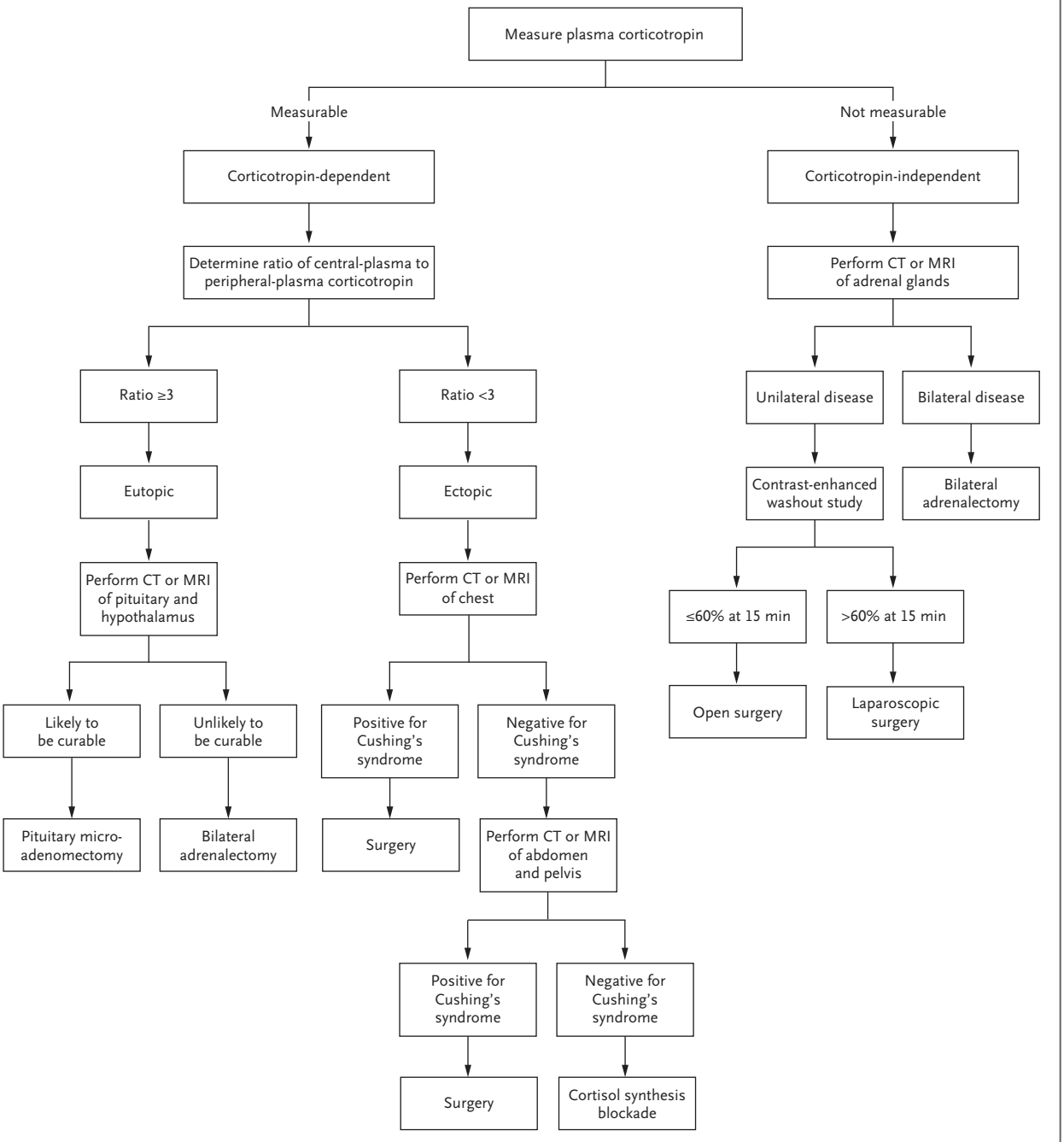

Figure 3. Differential Diagnosis of Cushing's Syndrome.

Every branch point is associated with a test that will govern what the physician does next. No test should be deleted from the evaluation, and no test should be added to the evaluation.

eral adrenalectomy, followed by glucocorticoid and mineralocorticoid treatment, is curative.

Adrenal tumors secreting more than one hormone (i.e., cortisol and androgen or estrogen) are almost always malignant. Surgical removal of all detectable disease is indicated, as is a careful search for metastases. If metastases are found, they should be removed. This usually requires an

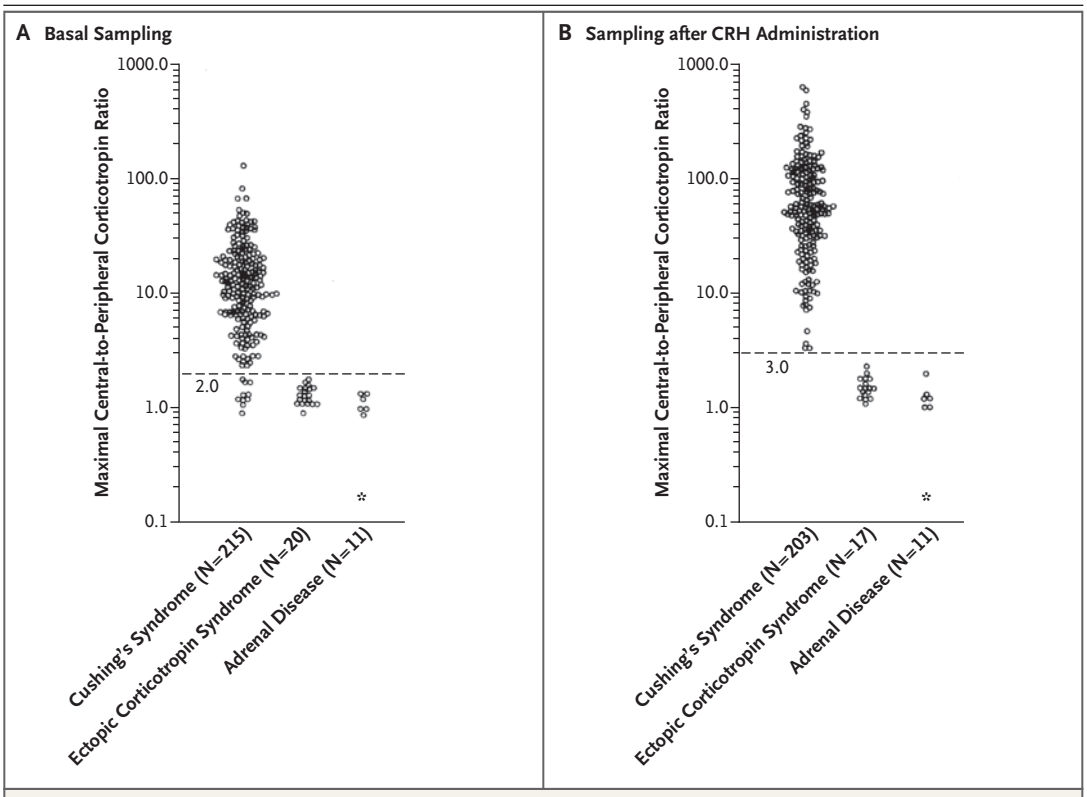

Figure 4. Maximal Ratio of Corticotropin in Inferior Petrosal Sinus Plasma to Corticotropin in Peripheral Plasma in Patients with Cushing's Syndrome, Ectopic Corticotropin Secretion, or Adrenal Disease.

Panel A shows the results of corticotropin measurement in basal samples, and Panel B shows the results in samples obtained after the administration of corticotropin-releasing hormone (CRH). Corticotropin measurement after CRH administration is superior to basal measurement for differentiating Cushing's syndrome from ectopic corticotropin secretion and primary adrenal disease. Five patients with primary adrenal disease had undetectable corticotropin in peripheral plasma before and after CRH administration (asterisks in Panels A and B). The positive predictive value of this test is 1. Data are from Oldfield et al.[28]

open adrenalectomy. It goes without saying that adrenal tumors, nodules, and metastases should be treated by the most experienced endocrine cancer surgeon available.

If the plasma cortisol level on the morning after a transsphenoidal microadenomectomy is 0, the operation was a success. The patient should be treated with oral hydrocortisone, at a dose of 12 mg per square meter of body-surface area once a day in the morning, and a tetracosactide (Cortrosyn) stimulation test should be performed at 3-month intervals. When the tetracosactide-stimulated plasma cortisol level is higher than 20 μg per deciliter (551 μmol per liter), cortisol administration can be stopped. The same rule applies in the case of a unilateral adrenalectomy. If the adrenalectomy is bilateral, cortisol, at a dose of 12 to 15 mg per square meter per day, and fludrocortisone (Florinef), at a dose of 100 μg per day, should be prescribed as lifelong therapy.

SUMMARY

The obesity epidemic has led to necessary changes in the evaluation and treatment of patients with Cushing's syndrome. The most dramatic change is the emphasis on the antianabolic alterations in Cushing's syndrome, which can provide a strong basis for separating patients with Cushing's syndrome from the more numerous patients with obesity and the metabolic syndrome. More can be done along these lines. Likelihood ratios are known for proximal muscle weakness and can be known for brain atrophy and growth failure in children.

The dexamethasone-suppression test, although

still very popular, no longer has a role in the evaluation and treatment of patients with Cushing's syndrome. Only three biochemical tests are needed: urinary free cortisol, plasma corticotropin, and plasma cortisol measurements. Urinary free cortisol excretion is the test that confirms the clinical diagnosis of Cushing's syndrome. To be trustworthy, it must be performed in the most stringent way, with the use of high-pressure liquid chromatography followed by mass spectrometric quantitation of cortisol. Measurement of plasma corticotropin is used to separate corticotropin-dependent from corticotropin-independent causes of Cushing's syndrome and to separate eutopic from ectopic secretion of corticotropin. Inferior petrosal sinus sampling should be performed in all patients with corticotropin-dependent Cushing's syndrome because of the high prevalence of nonfunctioning incidental pituitary adenomas among such patients. Measurement of plasma cortisol has only one use: determining the success or failure of transsphenoidal microadenomectomy or adrenalectomy. If the plasma cortisol level is not measurable on the morning after the operation (<5 μg per deciliter [138 μmol per liter]), the procedure was a success; if it is measurable, the operation failed. The surgeon must not administer intraoperative or postoperative synthetic glucocorticoids until the plasma cortisol level has been measured.

Successful evaluation of a patient who is suspected of having Cushing's syndrome requires an endocrinologist who is skilled in physical diagnosis. Also required is a laboratory that measures urinary free cortisol using high-performance liquid chromatography and mass spectrometry and that can measure plasma cortisol and plasma corticotropin by means of radioimmunoassay.

Inferior petrosal sinus sampling is performed by an interventional radiologist. The treatment for all causes of Cushing's syndrome, other than exogenous glucocorticoids, is surgical, and neurosurgeons, endocrine surgeons, and cancer surgeons are needed. This level of multidisciplinary medical expertise is usually found only at academic medical centers. Thus, most, if not all, patients with Cushing's syndrome should be referred to such a center for treatment.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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