The adrenal glands are paired retroperitoneal organs situated on the anteromedial surface of each kidney. The adrenal cortex, constituting 85% to 90% of the gland, arises embryologically from the mesoderm and can be subdivided into the zona glomerulosa, zona fasciculata, and zona reticularis. Each zone produces steroid hormones from a common precursor, pregnenolone. The zona glomerulosa produces the mineralocorticoid aldosterone, and the zona reticularis and zona fasciculata produce the glucocorticoid cortisol, as well as androgens and estrogens. Within the cortex lies the adrenal medulla, consisting of catecholamine-secreting chromaffin cells derived embryologically from neuroectoderm.

Glucocorticoids play key roles in cellular metabolism, immunosuppression, and antiinflammation. Regulated by the hypothalamus-pituitary-adrenal axis, adrenocorticotropic hormone (ACTH) is secreted by the anterior pituitary in a diurnal rhythm, with a morning peak and a midnight nadir. Aldosterone primarily controls salt and fluid balance. Regulated by the renin-angiotensin-aldosterone axis, it is synthesized and secreted in response to increased levels of angiotensin II, hyponatremia, or hyperkalemia.

The catecholamines epinephrine, norepinephrine, and dopamine are produced from the precursor tyrosine. Once synthesized, catecholamines are stored in vesicles and released by exocytosis with stimulation of preganglionic nerves. Responses include inotropy and chronotropy of the heart, vasoconstriction, bronchodilation, lipolysis, increased metabolic rate, and pupillary dilation.\(^1,2\)

**CUSHING SYNDROME**

Cushing syndrome, characterized by Harvey Cushing in 1932,\(^3\) stems from long-term glucocorticoid exposure. Cushing syndrome is most commonly caused by exogenous therapeutic steroids. Endogenous causes are classified based on ACTH elevation. ACTH-dependent forms include pituitary adenoma (Cushing’s disease) and ectopic ACTH or corticotropin-releasing hormone (CRH) production. ACTH-independent forms include adrenal adenoma, carcinoma, and hyperplasia. Conditions resulting in hypercortisolism, representing “pseudo-Cushing” states include major depression, alcoholism, morbid obesity, and poorly controlled diabetes.\(^5\) These patients apparently have an overactive hypothalamus and increased CRH with appropriate, although blunted, negative feedback on the pituitary.\(^5\)

The prevalence of endogenous Cushing syndrome is estimated at 2 to 13 cases per million people annually.\(^5,6\) Cushing syndrome accounts for approximately 0.2% of patients with hypertension\(^7\) and 2% to 3% of those with poorly controlled type 2 diabetes.\(^8\) Among the most common causes, the breakdown is pituitary disease (68% to 70%), ectopic ACTH (12% to 17%), and adrenal adenoma or carcinoma (15% to 20%).\(^4–6\)

Symptoms of Cushing syndrome begin gradually, usually with uncontrollable weight gain and fat redistribution. Patients characteristically develop truncal obesity, moon facies, or a buffalo hump. Fat may be deposited in unusual places such as the supraclavicular area, temporal fossa, or popliteal fossa. Comparison with old photographs helps with diagnosis. Dermatologic changes include thinning of the skin, easy bruising or impaired wound healing, facial erythema from telangiectasias, acne, characteristic wide purple striae, and hirsute or fine villous hair growth. Patients may experience amenorrhea, oligomenorrhea, or decreased libido. Proximal muscle wasting is evidenced by difficulty climbing stairs or rising from a seated position. Hypertension, impaired glucose tolerance, overt diabetes mellitus, and lipid abnormalities subsequently increase the risk of atherosclerotic cardiovascular disease. Depression is seen in 50% of patients.\(^6\)
**BIOCHEMICAL DIAGNOSIS**

Once Cushing syndrome is clinically suspected, biochemical tests can confirm the diagnosis (Fig. 1). Twenty-four-hour urinary free cortisol is useful as a screening test. Multiple specimens are needed, because at least one in four specimens will have normal free cortisol in 10% to 15% of patients with Cushing syndrome.Urinary free cortisol has good sensitivity and specificity, both ranging from 96% to 100%.9,10

Other tests to differentiate patients with hypercortisolism from normal patients with Cushingoid features are the low-dose dexamethasone suppression test (LDDST), late-night serum or salivary cortisol, and the dexamethasone-CRH test. In normal individuals, dexamethasone, a potent glucocorticoid, suppresses the hypothalamic-pituitary axis and decreases levels of ACTH and cortisol. In the traditional LDDST, 0.5 mg of dexamethasone is administered orally every 6 hours for 2 days, during which urine is collected for measurement of 17-hydroxycorticosteroids. In modified LDDSTs, plasma cortisol may be measured or the test may be performed overnight with a one-time 1 mg dexamethasone dose. The LDDST has a sensitivity of 78% to 86% and a specificity of 92% to 93%.11

Late-night serum cortisol measurement depends on the loss of diurnal rhythm even in patients with mild Cushing syndrome, although the nighttime nadir is preserved in patients with pseudo-Cushing syndrome. Studies have reported sensitivity of 96% to 100% and specificity of 77% to 100%.10,12 This test has traditionally required an inpatient setting for 48 hours to avoid falsely elevated cortisol secondary to stress.12 Alternatively, a nighttime salivary specimen, which correlates with plasma free cortisol, can be obtained at home without undue stress. Midnight salivary cortisol levels show comparable sensitivity and specificity to plasma cortisol.9,13

A more recent test combines the LDDST and CRH stimulation test. In Cushing’s disease, the pituitary adenoma is resistant to low-dose dexamethasone suppression and yet responds to CRH, resulting in increased cortisol. Conversely, pituitary corticotrophs in patients with adrenal adenomas will be both suppressed by low doses of dexamethasone and have a blunted response to CRH. A plasma cortisol measurement 15 minutes after
CRH administration yielded 100% sensitivity and 100% specificity compared with patients with pseudo-Cushing or normal controls.14

**Differential Diagnosis**

Once the biochemical diagnosis of Cushing syndrome has been established, the cause must be elucidated. Simultaneous measurement of ACTH and cortisol distinguishes ACTH-independent from ACTH-dependent Cushing syndrome. Because some patients have cyclical cortisol levels, multiple samples are recommended.4 If ACTH is suppressed, indicating ACTH-independent disease, patients proceed to adrenal imaging, usually noncontrast computed tomography (CT).

If ACTH is elevated on at least one serum measurement, a high-dose dexamethasone suppression test should be performed to distinguish between ACTH-dependent causes. Pituitary-based disease retains glucocorticoid receptors, so that with sufficiently high doses of dexamethasone, ACTH secretion will be suppressed by at least 50%. Ectopic ACTH production should not respond to dexamethasone. If the diagnosis remains in doubt, inferior petrosal sinus sampling, a CRH stimulation test, or a metyrapone stimulation test may be performed.4,5

Pituitary imaging may be helpful in planning the surgical approach but does not necessarily assist in the diagnosis, because 40% to 65% of pituitary adenomas are occult.4,5,8 CT and/or magnetic resonance imaging (MRI) of the chest and abdomen helps diagnose or localize ectopic ACTH or CRH sources.

**Treatment**

The treatment of ACTH-independent disease is unilateral adrenalectomy for adenoma or carcinoma and bilateral adrenalectomy for bilateral hyperplasia. Ectopic disease should be surgically resected when possible. Treatment for pituitary adenoma is hypophysectomy followed by radiotherapy if this fails. Chemotherapy or radiotherapy may be necessary if metastases develop.4 Medical management is useful in several different situations, such as a temporizing approach until definitive surgical therapy, after surgical failure, if a source cannot be localized, in patients waiting for pituitary radiotherapy to take effect, as a palliative measure, or if the patient is not a surgical candidate. Patients should be monitored to avoid adrenal insufficiency. First-line agents are generally adrenolytic therapy such as metyrapone, ketoconazole, mitotane, aminoglutethimide, or etomidate. A second category of medications, although much more variable in nature and less clearly understood, is neuromodulatory agents such as dopamine agonist bromocriptine, 5-HT antagonists cyproheptadine or ritanserin, so-

**Hyperaldosteronism**

Primary aldosteronism, described by Conn in 1955,16 is classically associated with hypertension and hypokalemia, although many patients are asymptomatic. Hypokalemia may cause muscle cramping, palpitations, urinary frequency, nocturia, or polydipsia. Marked hypokalemia manifests as muscle weakness, tetany, paresthesias, or even paralysis. Metabolically, patients may have mild alkalosis, hypernatremia, or high urinary potassium excretion. Hyperaldosteronism should be suspected in patients with severe hypokalemia after diuretic therapy.17,18

Aldosterone-producing adenomas (APAs) and bilateral adrenal hyperplasia (BAH) are the most common causes of primary aldosteronism19,20; less frequent causes are unilateral adrenal hyperplasia, adrenocortical carcinoma, glucocorticoid-suppressible hyperaldosteronism, or an ectopic aldosterone-producing tumor.19,20 Glucocorticoid-suppressible hyperaldosteronism is autosomal dominantly inherited and results in expression of a chimeric gene which encodes hybrid steroids.18 Aldosterone production parallels the circadian rhythm of ACTH and is suppressed by glucocorticoid administration.17

In patients with essential hypertension, the prevalence of primary aldosteronism was traditionally considered to be 0.5% to 1% when only hypokalemic patients were screened. If all patients with essential hypertension are screened for primary aldosteronism, the prevalence rises significantly, up to 5% to 13%. Although hypokalemia manifests itself only in patients with severe hyperaldosteronism, most patients with primary aldosteronism are normokalemic and thus have been previously overlooked.19,20

**Biochemical Diagnosis**

In addition to hypokalemia, patients with primary hyperaldosteronism characteristically have increased plasma aldosterone concentration (PAC) and suppressed plasma renin activity (PRA). These tests are not useful screening tests owing to the diurnal and day-to-day variation in aldosterone concentration and the high false-positive rate for suppressed PRA due to low renin levels in 30% of hypertensive patients. The PAC/PRA ratio is a generally accepted screening test; it will be persistently elevated in patients with primary hyperaldosteronism despite antihypertensive medications or dietary salt balance.21
Although this test lacks standardization, a PAC/PRA ratio of greater than 20 or 30 ng/dL per ng/mL/hr warrants further investigation. The diagnosis of primary hyperaldosteronism is then confirmed using an aldosterone suppression test. In normal patients, sodium loading suppresses aldosterone, but aldosterone remains elevated in patients with hyperaldosteronism. Patients may be salt loaded orally followed by measurement of 24-hour urinary aldosterone excretion. Urinary sodium documents adequate salt loading. High intake of sodium can aggravate kaliuresis, so potassium must be repleted. Alternatively, sodium may be administered intravenously followed by measurement of PAC. The antihypertensive medications least likely to interfere with these tests are alpha-adrenergic receptor blockers and guanethidine. These tests will be inaccurate for patients taking spironolactone or angiotensin-converting enzyme inhibitors.

**Differential Diagnosis**

As with Cushing syndrome, once the biochemical diagnosis of primary aldosteronism is established, additional testing distinguishes the different subtypes to guide management. The postural stimulation test entails measurement of PAC after an 8-hour overnight recumbency and again after 4 hours of erect posture. Patients with APA show less sensitivity to small changes in angiotensin II that occurs with upright posture relative to patients with BAH; a decrease in plasma aldosterone indicates an APA. However, this test has fallen out of favor, because it does not lateralize a lesion and a small subset of patients with APA will respond to angiotensin II and will, therefore, be falsely categorized as having BAH. Although a positive posture test has a positive predictive value close to 100%, its sensitivity for APA is only 30% to 63%.

Adrenal CT is recommended; unilateral macroadenomas (more than 1 cm) on CT likely represents APAs, especially in young patients. Adrenal CT scans have a sensitivity of 58% to 75% for detecting APAs. However, the adrenal glands may appear normal, have microadenomas, or have bilateral lesions, in which case additional evaluation is recommended if the clinical suspicion for APA is high. Adrenal vein sampling, although invasive and technically difficult, is the reference standard to diagnose primary aldosteronism. The rates of successful bilateral catheterization range from 68% to 97%. Cortisol is measured to verify that the adrenal veins were successfully catheterized. Normalized aldosterone levels are compared with an inferior venacaval sample. A ratio of dominant to nondominant normalized aldosterone of at least 4 is indicative of an APA or unilateral hyperplasia.

**Treatment**

Once the subtype of primary hyperaldosteronism has been determined, treatment aimed at minimizing the effects of hypertension or hypokalemia is implemented. The treatment for APA or unilateral adrenal hyperplasia is adrenalectomy. Hypertension completely resolves in approximately one third of patients. BAH and glucocorticoid suppressible hyperaldosteronism require medical treatment, usually spironolactone.

**PHEOCHROMOCYTOMA**

Pheochromocytomas arise from chromaffin cells of the adrenal medulla or extraadrenal paraganglionic tissue and secrete catecholamines, usually epinephrine or norepinephrine. Extraadrenal sites include the paraaortic sympathetic chain, organ of Zuckerkandl, renal hilum, urinary bladder, chest, and neck. The annual incidence is 2 to 8 cases per million people. They occur with equal frequency between men and women and at any age, but primarily from age 30 to 50. On autopsy series, pheochromocytomas have been found in 0.05% to 0.13% of patients. Often called the “10% tumor,” approximately 10% are bilateral, extraadrenal, multifocal, malignant, familial, recur after surgery, or occur in children. Familial syndromes associated with pheochromocytoma include multiple endocrine neoplasia types IIA and IIB, von Hippel-Lindau, neurofibromatosis, tuberous sclerosis, Sturge-Weber, and ataxia-telangiectasia. Approximately 50% of patients have sustained hypertension with or without paroxysms, 45% are normotensive between paroxysms, and the remaining 5% are normotensive. Pheochromocytomas occur in 0.05% to 0.5% of hypertensive patients. The paroxysms, or crises, may occur spontaneously or be triggered by changes in position, increased abdominal pressure, anxiety, exercise, trauma, surgery, labor, or ingestion of certain foods or drugs. Patients commonly complain of episodic headaches, tachycardia or palpitations, or diaphoresis with these paroxysms. Less common symptoms include nausea, pallor, flushing, dizziness, abdominal pain, dyspnea, angina, tremors, anxiety, and visual disturbances. Although variable among patients, paroxysms tend to occur in a stereotypical pattern for each patient. Spells generally last minutes to 1 hour, but can last as long as 1 week and can occur a few times a year to hourly. Patients who should be screened for pheochromocytoma include those with paroxysms, labile blood pressure, hypertension not amenable to a multidrug regimen, a familial history of pheochromocytoma or other neuroendocrine disease linked with pheochromocytoma, or a paradoxical rise in blood pressure with antihyperten-
sive medication, especially beta-blockers. The differential diagnosis includes hyperthyroidism, panic disorder or other anxiety state, menopause, migraine headaches, and unstable angina.

**DIAGNOSIS**

There has been much debate over the most preferred laboratory test. Plasma catecholamines and 24-hour urinary metanephrines or catecholamines are generally accepted as screening tests; they are approximately equal in sensitivity and specificity. The sensitivity has ranged from 71% to 100% and the specificity from 80% to 100% in various studies. Urinary vanillylmandelic acid has a slightly decreased sensitivity and increased specificity relative to these tests. False-negative results can occur, especially if specimens are taken during a normotensive period. Larger tumors may release relatively smaller amounts of catecholamines and higher amounts of metabolites, because catecholamines are metabolized within the tumor. Smaller tumors, in contrast, will release larger amounts of active hormone into the blood stream and correspondingly fewer metabolites. Elevated serum epinephrine suggests pheochromocytoma in the medulla or organ of Zuckerkandl, because phenylethanolamine-N-methyltransferase converts norepinephrine to epinephrine in these sites.

Recent evidence has supported plasma-free metanephrine as a diagnostic study, with a sensitivity and specificity of 99% and 89%, respectively. Free plasma metanephrines levels may be more consistent, as they are constantly released as tumor metabolism products. Theoretically, this increases sensitivity, because it eliminates the need to collect samples during a paroxysm. Some have argued that the decreased specificity of this test will lead to an unjustifiable increase in false-negative cases. Other investigators have shown promise with fractionated plasma metanephrines.

Provocative tests include the clonidine suppression and glucagon stimulation tests. The clonidine suppression test is used when a patient has moderately elevated values of screening plasma catecholamines, between 1000 and 2000 pg/mL. After oral administration of clonidine, the sympathetic outflow from the brain will be blocked in neurogenic causes of hypertension. After 3 hours, the plasma catecholamines will fall to less than 500 pg/mL in patients without pheochromocytoma. The glucagon stimulation test is useful if the screening studies are negative but clinical suspicion remains high. Glucagon injection stimulates a pheochromocytoma to secrete catecholamines. A threefold rise or a rise greater than 2000 pg/mL is diagnostic. The glucagon stimulation test is rarely used secondary to the risk of inciting a hypertensive response. If it is absolutely necessary in an equivocal patient, oral medications such as prazosin or nifedipine can be given before the injection to prevent a hypertensive crisis; these medications will not affect the catecholamine levels measured.

Pheochromocytomas can be localized using ultrasound, CT, MRI, or scintigraphy. With its low cost and easy accessibility, ultrasonography is a useful first-line study; however, its sensitivity is only 83% to 89%. CT and MRI are comparable in localizing intraabdominal lesions, with a sensitivity of 89% to 100%. MRI has an advantage in detecting extraadrenal disease and so has improved specificity. On T2-weighted MRI images, pheochromocytomas are generally hyperintense, distinguishing them from most other masses. Ultrasonography and MRI have been used in pregnant patients with good success. Scintigraphy using 131I-MIBG (metaiodobenzylguanidine) is helpful for localizing complex lesions, such as those that are extraadrenal, recurrent, multifocal, or malignant. It is generally only used if other imaging scans have been inconclusive secondary to its cost and limited availability. 131I-MIBG has a slightly lower sensitivity than CT or MRI, but near perfect specificity. There is little indication for invasive angiography with the success of these other imaging modalities. Once localized, fine needle aspiration must be avoided, because it can precipitate a hypertensive crisis.

**TREATMENT**

The treatment of pheochromocytoma is operative. Surgical cure is possible as long as there are no metastases. Patients must be medically optimized to avoid a hypertensive crisis. This entails treating the hypertension, expanding the intravascular volume, and controlling any cardiac arrhythmias. An alpha-adrenergic antagonist such as phenoxybenzamine is primarily used; calcium channel blockers or angiotensin-converting enzyme inhibitors can be added if necessary. Patients can replenish salt and fluid orally. If a beta-blocker is needed to control arrhythmias, it is imperative that the alpha-blockade be established first. Intraoperatively, care must be taken to avoid anesthetic agents that precipitate catecholamine secretion.

Patients are generally followed up postoperatively with biochemical testing; imaging is not routinely necessary. However, no histologic or clinical criteria have been determined that can distinguish benign from malignant disease.

**INCIDENTALOMA**

Adrenal incidentalomas are defined as clinically silent adrenal masses found on abdominal imaging performed for nonadrenal causes. Incidentalomas
are now the most common adrenal mass encountered.\(^3\) Incidentalomas may be significant because of malignancy or hormonal production. Autopsy studies have indicated a prevalence ranging from 1% to 8.7% (mean 2.3%). The prevalence increases with age, from 0.2% for younger patients to 6.9% for patients older than 70 years old.\(^4\) On radiologic series, the prevalence of CT-diagnosed incidentaloma ranges from 0.35% to 4.4%.\(^4\) Although adrenal adenomas are the most common, the differential diagnosis includes other tumors such as adrenocortical carcinoma, pheochromocytoma, soft-tissue tumors, lymphoma, or metastasis, as well as cysts, hemorrhage, or infection.\(^4\) Approximately 16% are hyperfunctioning, 5% represent adrenocortical carcinoma, and 2% are metastases.\(^4\) The risk of adrenocortical carcinoma increases with size. At less than 4 cm, the chance of malignancy is 2%, from 4.1 to 6 cm, the risk is 6%, and at greater than 6 cm, the risk is 25%.\(^2\) Hyperfunctioning lesions may represent pheochromocytoma, hyperaldosteronoma, mild hypercortisolism, or virilizing or feminizing tumor.\(^2\) Hypercortisolism is most common, seen in 9% of patients.\(^4\)

The workup of incidentalomas includes radiologic and biochemical examination (Fig. 2). CT scan is the preferred radiologic modality. CT findings indicating benignity include homogenous round or oval appearance with smooth well-defined borders, less than 10 Hounsfield units, and size less than 3 cm.\(^4\) Hounsfield units less than 10 has a sensitivity of 74% and specificity of 96% for predicting adenoma.\(^4\) Features typical for adrenocortical carcinoma include size larger than 5 cm, central necrosis, tumor calcification, or evidence of nodal, hepatic, or venous spread.\(^4\) If a mass is indeterminate on CT, MRI or radionuclide scintigraphy can characterize the lesion further. Both opposed-phase chemical shift MRI and scintigraphy have high accuracy in distinguishing adenomas from nonadenomas.\(^4\) Although ultrasonography may identify incidentalomas and can distinguish cystic from solid structures, it has low sensitivity for smaller lesions and cannot adequately characterize known lesions.\(^4\)

The biochemical workup of an incidentaloma consists of the screening tests previously described, including urinary free cortisol, LDDST, urinary catecholamines and metanephrines, serum potassium, and the PAC/PRA ratio.\(^2\) If needed, testosterone, dehydroepiandrosterone sulfate, or estradiol levels can be used to evaluate for viriliz-
ing or feminizing tumors. Other primary tumors should be excluded; percutaneous biopsy is useful for suspected metastasis. Treatment of a clinically hyperfunctioning lesion is adrenalectomy. Patients with subclinical pheochromocytoma should also undergo surgery because of the risk of a hypertensive crisis, in which subclinical hypercortisolism or hyperaldosteronism may be carefully observed. Adrenalectomy should also be performed for nonfunctioning incidentalomas greater than 6 cm or rapidly enlarging incidentalomas. Masses 4 to 6 cm can be observed or operated on, depending on the other characteristics. If metastasis is revealed on workup, adrenalectomy has not been shown to be beneficial.

**ADRENOCORTICAL CARCINOMA**

Adrenocortical carcinoma is a rare entity representing 0.05% to 0.2% of all cancers, with an annual incidence of 0.5 to 2 per million people. It occurs at any age and has a bimodal distribution, with peaks at 5 years and 40 to 50 years. There is a female predominance, and the lesions are bilateral in 2% to 10% of cases. Forty-six percent present with clinically evident endocrine abnormality and more may be subclinically active. Cushing syndrome is seen in 30% to 40% of patients. Virilization occurs in 20% to 30%, but predominantly in children. Hyperaldosteronism and feminization occur rarely. Otherwise, patients may present with a palpable mass, abdominal or back pain, fullness, weight loss, nausea, anorexia, weakness, or fevers. The workup includes both radiologic and biochemical examination. Adrenalectomy is the mainstay of treatment, even if the mass cannot be completely excised. Mitotane has been used adjuvantly or if surgery is not feasible, although the results have been mixed. The prognosis is poor, with a recurrence rate of 35% to 85% and mean survival of 18 months.

**LAPAROSCOPIC ADRENALECTOMY**

Laparoscopic adrenalectomy has become increasingly more common since first described in 1992. The benefits are typical of laparoscopic procedures—faster return to regular diet, shorter hospital stay, shorter convalescence, and decreased analgesic requirement. Although most adrenal masses are amenable to laparoscopy, it is contraindicated for large adrenocortical carcinomas, especially if local invasion or venous thrombus exists.

**CONCLUSIONS**

The complex hormonal function of the adrenal glands encompasses many aspects of normal bodily function. An adrenal mass may present as an incidental finding or with symptoms of hormonal excess. Biochemical function and the risk of malignancy must be evaluated when considering adrenalectomy.

**REFERENCES**