from cross-over of promoter sequences between the *CYP11B1* and *CYP11B2* genes that are involved in glucocorticoid and mineralocorticoid synthesis, respectively (Fig. 406-1). This rearrangement brings *CYP11B2* transcription under the control of ACTH receptor signaling; consequently, aldosterone production is regulated by ACTH rather than by renin. The family history can be helpful because there may be evidence for dominant transmission of hypertension. Recognition of the disorder is important because it can be associated with early-onset hypertension and strokes. In addition, glucocorticoid suppression can reduce aldosterone production.

Other rare causes of mineralocorticoid excess are listed in Table 406-3. An important cause is excess binding and activation of the mineralocorticoid receptor by a steroid other than aldosterone. Cortisol acts as a potent mineralocorticoid if it escapes efficient inactivation to cortisone by 11β-HSD2 in the kidney (Fig. 406-7). This can be caused by inactivating mutations in the *HSD11B2* gene resulting in the syndrome of apparent mineralocorticoid excess (SAME) that characteristically manifests with severe hypokalemic hypertension in childhood. However, milder mutations may cause normokalemic hypertension manifesting in adulthood (type II SAME). Inhibition of 11β-HSD2 by excess licorice ingestion also results in hypokalemic hypertension, as does overwhelming of 11β-HSD2 conversion capacity by cortisol excess in Cushing's syndrome. Deoxycorticosterone (DOC) also binds and activates the mineralocorticoid receptor and can cause hypertension if its circulating concentrations are increased. This can arise through autonomous DOC secretion by an adrenocortical carcinoma, but also when DOC accumulates as a consequence of an adrenal enzymatic block, as seen in congenital adrenal hyperplasia due to CYP11B1 (11β-hydroxylase) or CYP17A1 (17α-hydroxylase) deficiency (Fig. 406-1). Progesterone can cause hypokalemic hypertension in rare individuals who harbor a mineralocorticoid receptor mutation that enhances binding and activation by progesterone; physiologically, progesterone normally exerts antimineralocorticoid activity. Finally, excess mineralocorticoid activity can be caused by mutations in the β or γ subunits of the ENaC, disrupting its interaction with Nedd4 (Fig. 406-7), and thereby decreasing receptor internalization and degradation. The constitutively active ENAC drives hypokalemic hypertension, resulting in an autosomal dominant disorder termed *Liddle's syndrome*.

Clinical Manifestations Excess activation of the mineralocorticoid receptor leads to potassium depletion and increased sodium retention, with the latter causing an expansion of extracellular and plasma volume. Increased ENaC activity also results in hydrogen depletion that can cause metabolic alkalosis. Aldosterone also has direct effects on the vascular system, where it increases cardiac remodeling and decreases compliance. Aldosterone excess may cause direct damage to the myocardium and the kidney glomeruli, in addition to secondary damage due to systemic hypertension.

The clinical hallmark of mineralocorticoid excess is hypokalemic hypertension; serum sodium tends to be normal due to the concurrent fluid retention, which in some cases can lead to peripheral edema. Hypokalemia can be exacerbated by thiazide drug treatment, which leads to increased delivery of sodium to the distal renal tubule, thereby driving potassium excretion. Severe hypokalemia can be associated with muscle weakness, overt proximal myopathy, or even hypokalemic paralysis. Severe alkalosis contributes to muscle cramps and, in severe cases, can cause tetany.

Diagnosis Diagnostic screening for mineralocorticoid excess is not currently recommended for all patients with hypertension, but should be restricted to those who exhibit hypertension associated with drug resistance, hypokalemia, an adrenal mass, or onset of disease before the age of 40 years (Fig. 406-12). The accepted screening test is concurrent measurement of plasma renin and aldosterone with subsequent calculation of the aldosterone-renin ratio (ARR) (Fig. 406-12); serum potassium needs to be normalized prior to testing. Stopping antihypertensive medication can be cumbersome, particularly in patients with severe hypertension. Thus, for practical purposes, in the first instance the patient can remain on the usual antihypertensive medications, with the exception that mineralocorticoid receptor antagonists need to be ceased at least 4 weeks prior to ARR measurement. The remaining antihypertensive drugs usually do not affect the outcome of ARR testing, except that beta blocker treatment can cause false-positive results and ACE/AT1R inhibitors can cause false-negative results in milder cases (Table 406-4).

ARR screening is positive if the ratio is >750 pmol/L per ng/mL per hour, with a concurrently high normal or increased aldosterone (Fig. 406-12). If one relies on the ARR only, the likelihood of a false-positive ARR becomes greater when renin levels are very low. The characteristics of the biochemical assays are also important. Some labs measure plasma renin activity, whereas others measure plasma renin concentrations. Antibody-based assays for the measurement of serum aldosterone lack the reliability of tandem mass spectrometry assays, but these are not yet ubiquitously available.

Diagnostic confirmation of mineralocorticoid excess in a patient with positive ARR screening result should be undertaken by an endocrinologist as the tests lack optimized validation. The most straightforward is the saline infusion test, which involves the IV administration of 2 L of physiologic saline over a 4-h period. Failure of aldosterone to suppress below 140 pmol/L (5 ng/dL) is indicative of autonomous mineralocorticoid excess. Alternative tests are the oral sodium loading test (300 mmol NaCl/d for 3 days) or the fludrocortisone suppression test (0.1 mg q6h with 30 mmol NaCl q8h for 4 days); the latter can be difficult because of the risk of profound hypokalemia and increased hypertension. In patients with overt hypokalemic hypertension, strongly positive ARR, and concurrently increased aldosterone levels, confirmatory testing is usually not necessary.

Differential Diagnosis and Treatment After the diagnosis of hyperaldosteronism is established, the next step is to use adrenal imaging to further assess the cause. Fine-cut CT scanning of the adrenal region is the method of choice because it provides excellent visualization of adrenal morphology. CT will readily identify larger tumors suspicious of malignancy but may miss lesions smaller than 5 mm. The differentiation between bilateral micronodular hyperplasia and a unilateral adenoma is only required if a surgical approach is feasible and desired. Consequently, selective adrenal vein sampling (AVS) should only be carried out in surgical candidates with either no obvious lesion on CT or evidence of a unilateral lesion in patients older than 40 years, because the latter patients have a high likelihood of harboring a coincidental, endocrine-inactive adrenal adenoma (Fig. 406-12). AVS is used to compare aldosterone levels in the inferior vena cava and between the right and left adrenal veins. AVS requires concurrent measurement of cortisol to document correct placement of the catheter in the adrenal veins and should demonstrate a cortisol gradient >3 between the vena cava and each adrenal vein. Lateralization is confirmed by an aldosterone/cortisol ratio that is at least twofold higher on one side than the other. AVS is a complex procedure that requires a highly skilled interventional radiologist. Even then, the right adrenal vein can be difficult to cannulate correctly, which, if not achieved, invalidates the procedure. There is also no agreement as to whether the two adrenal veins should be cannulated simultaneously or successively and whether ACTH stimulation enhances the diagnostic value of AVS.

Patients younger than 40 years with confirmed mineralocorticoid excess and a unilateral lesion on CT can go straight to surgery, which is also indicated in patients with confirmed lateralization documented by a valid AVS procedure. Laparoscopic adrenalectomy is the preferred approach. Patients who are not surgical candidates, or with evidence of bilateral hyperplasia based on CT or AVS, should be treated medically (Fig. 406-12). Medical treatment, which can also be considered prior to surgery to avoid postsurgical hypoaldosteronism, consists primarily of the mineralocorticoid receptor antagonist spironolactone. It can be started at 12.5–50 mg bid and titrated up to a maximum of 400 mg/d to control blood pressure and normalize potassium. Side effects include menstrual irregularity, decreased libido, and gynecomastia. The more selective MR antagonist eplerenone can also be used. Doses start at 25 mg bid, and it can be titrated up to 200 mg/d. Another useful drug is the sodium channel blocker amiloride (5–10 mg bid).

In patients with normal adrenal morphology and family history of early-onset, severe hypertension, a diagnosis of GRA should be