distal tubular flow rate, in addition to secondary hyperaldosteronism. Thiazides have a greater effect on plasma K^+ concentration than loop diuretics, despite their lesser natriuretic effect. The diuretic effect of thiazides is largely due to inhibition of the Na^+-Cl^- cotransporter NCC in DCT cells. This leads to a direct increase in the delivery of luminal Na^+ to the principal cells immediately downstream in the CNT and cortical CD, which augments Na^+ entry via ENaC, increases the lumen-negative potential difference, and amplifies K^+ secretion. The higher propensity of thiazides to cause hypokalemia may also be secondary to thiazide-associated hypocalciuria, versus the *hypercalciuria* seen with loop diuretics; the increases in downstream luminal calcium in response to loop diuretics inhibit ENaC in principal cells, thus reducing the lumen-negative potential difference and attenuating distal K^+ excretion. High doses of penicillin-related antibiotics (nafcillin, dicloxacillin, ticarcillin, oxacillin, and carbenicillin) can increase obligatory K^+ excretion by acting as nonreabsorbable anions in the distal nephron. Finally, several renal tubular toxins cause renal K^+ and magnesium wasting, leading to hypokalemia and hypomagnesemia; these drugs include aminoglycosides, amphotericin, foscarnet, cisplatin, and ifosfamide (see also "Magnesium Deficiency and Hypokalemia," below).

Aldosterone activates the ENaC channel in principal cells via multiple synergistic mechanisms, thus increasing the driving force for K^+ excretion. In consequence, increases in aldosterone bioactivity and/or gains in function of aldosterone-dependent signaling pathways are associated with hypokalemia. Increases in circulating aldosterone (hyperaldosteronism) may be primary or secondary. Increased levels of circulating renin in secondary forms of hyperaldosteronism lead to increased angiotensin II and thus aldosterone; renal artery stenosis is perhaps the most frequent cause (Table 63-4). Primary hyperaldosteronism may be genetic or acquired. Hypertension and hypokalemia, due to increases in circulating 11-deoxycorticosterone, occur in patients with congenital adrenal hyperplasia caused by defects in either steroid 11β-hydroxylase or steroid 17α-hydroxylase; deficient 11β-hydroxylase results in associated virilization and other signs of androgen excess, whereas reduced sex steroids in 17α-hydroxylase deficiency lead to hypogonadism.

The major forms of *isolated* primary genetic hyperaldosteronism are familial hyperaldosteronism type I (FH-I, also known as glucocorticoid-remediable hyperaldosteronism [GRA]) and familial hyperaldosteronism types II and III (FH-II and FH-III), in which aldosterone production is not repressible by exogenous glucocorticoids. FH-I is caused by a chimeric gene duplication between the homologous 11β-hydroxylase (*CYP11B1*) and aldosterone synthase (*CYP11B2*) genes, fusing the adrenocorticotropic hormone (ACTH)–responsive 11β-hydroxylase promoter to the coding region of aldosterone synthase; this chimeric gene is under the control of ACTH and thus repressible by glucocorticoids. FH-III is caused by mutations in the *KCNJ5* gene, which encodes the G-protein-activated inward rectifier K^+ channel 4 (GIRK4); these mutations lead to the acquisition of sodium permeability in the mutant GIRK4 channels, causing an exaggerated membrane depolarization in adrenal glomerulosa cells and the activation of voltage-gated calcium channels. The resulting calcium influx is sufficient to produce aldosterone secretion and cell proliferation, leading to adrenal adenomas and hyperaldosteronism.

Acquired causes of primary hyperaldosteronism include aldosterone-producing adenomas (APAs), primary or unilateral adrenal hyperplasia (PAH), idiopathic hyperaldosteronism (IHA) due to bilateral adrenal hyperplasia, and adrenal carcinoma; APA and IHA account for close to 60% and 40%, respectively, of diagnosed hyperaldosteronism. Acquired somatic mutations in *KCNJ5* or less frequently in the *ATP1A1* (an Na^+/K^+ ATPase α subunit) and *ATP2B3* (a Ca^{2+} ATPase) genes can be detected in APAs; as in FH-III (see above), the exaggerated depolarization of adrenal glomerulosa cells caused by these mutations is implicated in the excessive adrenal proliferation and the exaggerated release of aldosterone.

Random testing of plasma renin activity (PRA) and aldosterone is a helpful screening tool in hypokalemic and/or hypertensive patients, with an aldosterone:PRA ratio of >50 suggestive of primary hyperaldosteronism. Hypokalemia and multiple antihypertensive drugs may alter the aldosterone:PRA ratio by suppressing aldosterone or increasing PRA, leading to a ratio of <50 in patients who do in fact have primary hyperaldosteronism; therefore, the clinical context should always be considered when interpreting these results.

The glucocorticoid cortisol has equal affinity for the mineralocorticoid receptor (MLR) to that of aldosterone, with resultant "mineralocorticoid-like" activity. However, cells in the aldosterone-sensitive distal nephron are protected from this "illicit" activation by the enzyme 11β-hydroxysteroid dehydrogenase-2 (11βHSD-2), which converts cortisol to cortisone; cortisone has minimal affinity for the MLR. Recessive loss-of-function mutations in the *11βHSD-2* gene are thus associated with cortisol-dependent activation of the MLR and the syndrome of apparent mineralocorticoid excess (SAME), encompassing hypertension, hypokalemia, hypercalciuria, and metabolic alkalosis, with suppressed PRA and suppressed aldosterone. A similar syndrome is caused by biochemical inhibition of 11βHSD-2 by glycyrrhetinic/glycyrrhizinic acid and/or carbenoxolone. Glycyrrhizinic acid is a natural sweetener found in licorice root, typically encountered in licorice and its many guises or as a flavoring agent in tobacco and food products.

Finally, hypokalemia may also occur with systemic increases in glucocorticoids. In Cushing's syndrome caused by increases in pituitary ACTH (Chap. 406), the incidence of hypokalemia is only 10%, whereas it is 60–100% in patients with ectopic secretion of ACTH, despite a similar incidence of hypertension. Indirect evidence suggests that the activity of renal 11βHSD-2 is reduced in patients with ectopic ACTH compared with Cushing's syndrome, resulting in SAME.

Finally, defects in multiple renal tubular transport pathways are associated with hypokalemia. For example, loss-of-function mutations in subunits of the acidifying H^+-ATPase in alpha-intercalated cells cause hypokalemic distal renal tubular acidosis, as do many acquired disorders of the distal nephron. Liddle's syndrome is caused by autosomal dominant gain-in-function mutations of ENaC subunits. Disease-associated mutations either activate the channel directly or abrogate aldosterone-inhibited retrieval of ENaC subunits from the plasma membrane; the end result is increased expression of activated ENaC channels at the plasma membrane of principal cells. Patients with Liddle's syndrome classically manifest severe hypertension with hypokalemia, unresponsive to spironolactone yet sensitive to amiloride. Hypertension and hypokalemia are, however, variable aspects of the Liddle's phenotype; more consistent features include a blunted aldosterone response to ACTH and reduced urinary aldosterone excretion.

Loss of the transport functions of the TALH and DCT nephron segments causes hereditary hypokalemic alkalosis, Bartter's syndrome (BS) and Gitelman's syndrome (GS), respectively. Patients with classic BS typically suffer from polyuria and polydipsia, due to the reduction in renal concentrating ability. They may have an increase in urinary calcium excretion, and 20% are hypomagnesemic. Other features include marked activation of the renin-angiotensin-aldosterone axis. Patients with antenatal BS suffer from a severe systemic disorder characterized by marked electrolyte wasting, polyhydramnios, and hypercalciuria with nephrocalcinosis; renal prostaglandin synthesis and excretion are significantly increased, accounting for much of the systemic symptoms. There are five disease genes for BS, all of them functioning in some aspect of regulated Na^+, K^+, and Cl^- transport by the TALH. In contrast, GS is genetically homogeneous, caused almost exclusively by loss-of-function mutations in the thiazide-sensitive Na^+-Cl^- cotransporter of the DCT. Patients with GS are uniformly hypomagnesemic and exhibit marked hypocalciuria, rather than the hypercalciuria typically seen in BS; urinary calcium excretion is thus a critical diagnostic test in GS. GS is a milder phenotype than BS; however, patients with GS may suffer from chondrocalcinosis, an abnormal deposition of calcium pyrophosphate dihydrate (CPPD) in joint cartilage (Chap. 339).

Magnesium Deficiency and Hypokalemia Magnesium depletion has inhibitory effects on muscle Na^+/K^+-ATPase activity, reducing influx into muscle cells and causing a secondary kaliuresis. In addition,