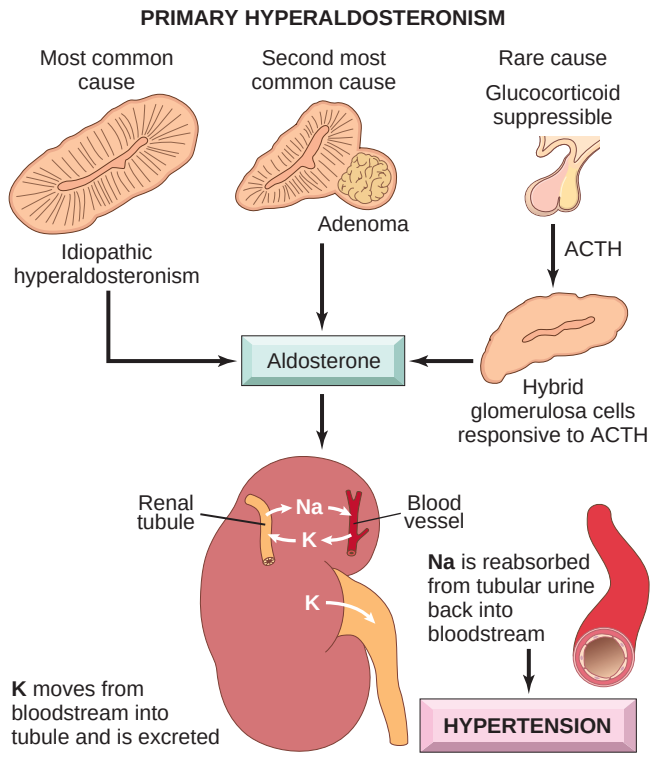

Figure 24-45 The major causes of primary hyperaldosteronism and its principal effects on the kidney.

may be secondary to an extra-adrenal cause. *Primary hyperaldosteronism* stems from an autonomous overproduction of aldosterone, with resultant suppression of the renin-angiotensin system and *decreased plasma renin activity*. **Blood pressure elevation is the most common manifestation of primary hyperaldosteronism**, which is caused by one of three mechanisms (Fig. 24-45):

- *Bilateral idiopathic hyperaldosteronism* (IHA), characterized by bilateral nodular hyperplasia of the adrenal glands, is the most common underlying cause of primary hyperaldosteronism, accounting for about 60% of cases. Individuals with idiopathic hyperaldosteronism tend to be older and to have less severe hypertension than those presenting with adrenal neoplasms. The pathogenesis of idiopathic hyperaldosteronism remains unclear, although recent studies suggest that a subset of patients with familial idiopathic hyperaldosteronism harbor germline mutations of *KCNJ5*, encoding a potassium channel.
- *Adrenocortical neoplasm*, either an aldosterone-producing adenoma (the most common cause) or, rarely, an adrenocortical carcinoma. In approximately 35% of cases, primary hyperaldosteronism is caused by a solitary aldosterone-secreting adenoma, a condition referred to as *Conn syndrome*. This syndrome occurs most frequently in adult middle life and is more common in women than in men (2:1). Multiple adenomas may be present in an occasional patient. Somatic mutations of *KCNJ5* are also present in a subset of aldosterone-secreting adenomas.
- *Glucocorticoid-remediable hyperaldosteronism* is an uncommon cause of primary familial hyperaldosteronism. In some families, it stems from a rearrangement involving chromosome 8 that places *CYP11B2* (the gene that encodes *aldosterone synthase*) under the control of the ACTH responsive *CYP11B1* gene promoter. ACTH thus stimulates the production of aldosterone synthase, the enzyme that is responsible for the last step in aldosterone synthesis. Because in this unusual circumstance aldosterone production is under the control of ACTH, it is suppressible by dexamethasone.

In *secondary hyperaldosteronism*, in contrast, aldosterone release occurs in response to activation of the renin-angiotensin system (Chapter 11). It is characterized by *increased levels of plasma renin* and is encountered in conditions such as the following:

- Decreased renal perfusion (arteriolar nephrosclerosis, renal artery stenosis)
- Arterial hypovolemia and edema (congestive heart failure, cirrhosis, nephrotic syndrome)
- Pregnancy (due to estrogen-induced increases in plasma renin substrate)

MORPHOLOGY

Aldosterone-producing adenomas are almost always solitary, small (<2 cm in diameter), well-circumscribed lesions, more often found on the left than on the right. They tend to occur in the 30s and 40s, and in women more often than in men. They are often buried within the gland and do not produce visible enlargement, a point to be remembered in interpreting sonographic or scanning images. They are bright yellow on cut section and, surprisingly, are composed of lipid-laden cortical cells that more closely resemble fasciculata cells than glomerulosa cells (the normal source of aldosterone). In general, the cells tend to be uniform in size and shape; occasionally, there is modest nuclear and cellular pleomorphism (see Fig. 24-51). A characteristic feature of aldosterone-producing adenomas is the presence of eosinophilic, laminated cytoplasmic inclusions, known as **spironolactone bodies**, found after treatment with the antihypertensive drug spironolactone. In contrast to cortical adenomas associated with Cushing syndrome, those associated with hyperaldosteronism do not usually suppress ACTH secretion. Therefore, the adjacent adrenal cortex and that of the contralateral gland are not atrophic.

Bilateral idiopathic hyperplasia is marked by diffuse and focal hyperplasia of cells resembling those of the normal zona glomerulosa. The hyperplasia is often wedge-shaped, extending from the periphery toward the center of the gland. The enlargement may be subtle, and as a rule an adrenocortical adenoma must be carefully excluded as the cause for hyperaldosteronism.

Clinical Course. **The most important clinical consequence of hyperaldosteronism is hypertension**. With an estimated prevalence rate of 5% to 10% among nonselected hypertensive patients, primary hyperaldosteronism may be the most common cause of secondary hypertension (i.e., hypertension secondary to an identifiable cause). The prevalence of hyperaldosteronism increases with the severity of hypertension, reaching nearly 20% in patients who are classified as having treatment-resistant hypertension.