ACTH deficiency can occur alone, but in some instances, it is only one component of panhypopituitarism, associated with multiple trophic hormone deficiencies. Secondary disease can be differentiated from Addison disease by demonstration of low levels of plasma ACTH in the former. In patients with primary disease the destruction of the adrenal cortex reduces the response to exogenously administered ACTH, whereas in those with secondary hypofunction there is a prompt rise in plasma cortisol levels.

MORPHOLOGY

In cases of hypoadrenalism secondary to hypothalamic or pituitary disease **(secondary hypoadrenalism)**, depending on the severity of ACTH deficiency, the adrenals may be moderately to markedly decreased in size. The small, flattened glands usually retain their yellow color as a result of a small amount of residual lipid. The cortex may be reduced to a thin ribbon composed largely of zona glomerulosa. The medulla is unaffected.

Adrenocortical Neoplasms

It should be evident from the preceding sections that functional adrenal neoplasms may be responsible for any of the various forms of hyperadrenalism. Adenomas and carcinomas are about equally common in adults; in children, carcinomas predominate. While most cortical neoplasms are sporadic, two familial cancer syndromes are associated with a predisposition for developing adrenocortical carcinomas: Li-Fraumeni syndrome, in patients who harbor germline *TP53* mutations (Chapter 7), and Beckwith-Wiedemann syndrome, a disorder of epigenetic imprinting (Chapter 10).

Functional adenomas are most commonly associated with hyperaldosteronism and Cushing syndrome, whereas a virilizing neoplasm is more likely to be a carcinoma. However, not all adrenocortical neoplasms elaborate steroid hormones. *Functional and nonfunctional adrenocortical neoplasms cannot be distinguished on the basis of morphologic features.* Determination of functionality is based on clinical evaluation, and measurement of hormones or hormone metabolites in the blood.

MORPHOLOGY

Most **adrenocortical adenomas** are clinically silent and are usually incidental findings at autopsy or during abdominal imaging for an unrelated cause (see the discussion of adrenal "incidentalomas" later). The typical cortical adenoma is a well-circumscribed, nodular lesion up to 2.5 cm in diameter that expands the adrenal (Fig. 24-50). In contrast to functional adenomas, which are associated with atrophy of the adjacent cortex, the cortex adjacent to nonfunctional adenomas is normal. On cut surface, adenomas are usually yellow to yellow-brown because of the presence of lipid.

Microscopically, adenomas are composed of cells similar to those populating the normal adrenal cortex. The nuclei tend to be small, although some degree of pleomorphism may be encountered even in benign lesions ("endocrine atypia"). The cytoplasm of the neoplastic cells ranges from eosinophilic to vacuolated, depending on their lipid content (Fig. 24-51). Mitotic activity is generally inconspicuous.

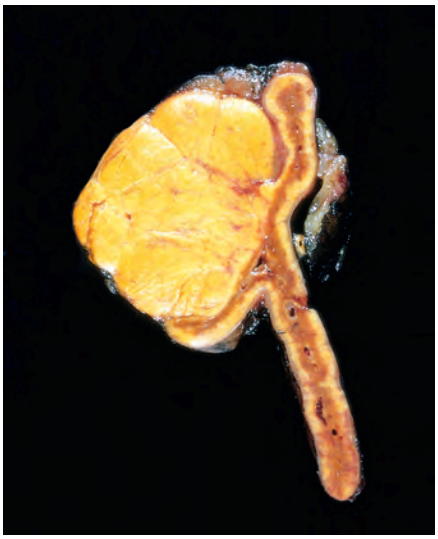

Figure 24-50 Adrenal cortical adenoma. The adenoma is distinguished from nodular hyperplasia by its solitary, circumscribed nature. The functional status of an adrenal cortical adenoma cannot be predicted from its gross or microscopic appearance.

Adrenocortical carcinomas are rare neoplasms that can occur at any age, including childhood. They are more likely to be functional than adenomas and are often associated with virilism or other clinical manifestations of hyperadrenalism. In most cases adrenocortical carcinomas are large, invasive lesions, many exceeding 20 cm in diameter, which efface the native adrenal gland (Fig. 24-52). The less common, smaller, and better-circumscribed lesions may be difficult to distinguish from an adenoma. On cut surface, adrenocortical carcinomas are typically variegated, poorly demarcated lesions containing areas of necrosis, hemorrhage, and cystic change. Adrenal cancers have a strong tendency to invade the adrenal vein, vena cava, and lymphatics. Metastases to regional and periaortic nodes are common, as is distant hematogenous spread to

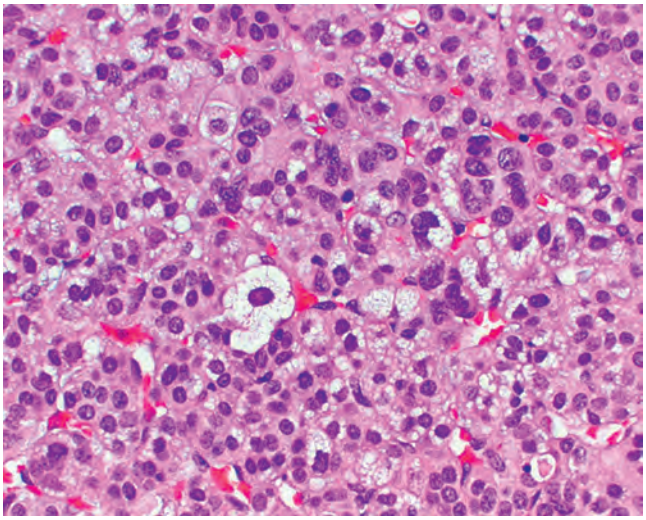

Figure 24-51 Histologic features of an adrenal cortical adenoma. The neoplastic cells are vacuolated because of the presence of intracytoplasmic lipid. There is mild nuclear pleomorphism. Mitotic activity and necrosis are not seen.