avium-intracellulare) and noninfectious (Kaposi sarcoma) complications.

- *Metastatic neoplasms* involving the adrenals are another cause of adrenal insufficiency. The adrenals are a fairly common site for metastases in patients with disseminated carcinomas. Although adrenal function is preserved in most such patients, the metastatic tumors occasionally destroy enough adrenal cortex to produce a degree of adrenal insufficiency. Carcinomas of the lung and breast are the source of a majority of metastases, although many other neoplasms, including gastrointestinal carcinomas, malignant melanoma, and hematopoietic neoplasms, may also metastasize to the adrenals.
- *Genetic causes of adrenal insufficiency* include congenital adrenal hypoplasia (*adrenal hypoplasia congenita*) and *adrenoleukodystrophy*. Adrenoleukodystrophy is described in Chapter 28. Congenital adrenal hypoplasia is a rare X-linked disease caused by mutations in a gene that encodes a transcription factor implicated in adrenal development.

MORPHOLOGY

The anatomic changes in the adrenal glands depend on the underlying disease. **Primary autoimmune adrenalitis** is characterized by irregularly shrunken glands, which may be difficult to identify within the suprarenal adipose tissue. Histologically the cortex contains only scattered residual cortical cells in a collapsed network of connective tissue. A variable lymphoid infiltrate is present in the cortex and may extend into the adjacent medulla, although the medulla is otherwise preserved (Fig. 24-49). In cases of **tuberculous and fungal disease** the adrenal architecture is effaced by a granulomatous inflammatory reaction identical to that encountered in other sites of infection. When hypoadrenalism is caused by **metastatic carcinoma**, the adrenals are enlarged and the normal architecture is obscured by the infiltrating neoplasm.

Clinical Course. Addison disease begins insidiously and does not come to attention until the levels of circulating glucocorticoids and mineralocorticoids are significantly decreased. The initial manifestations include *progressive weakness and easy fatigability*, which may be dismissed as nonspecific complaints. *Gastrointestinal* disturbances are common and include anorexia, nausea, vomiting, weight loss, and diarrhea. In individuals with primary adrenal disease, *hyperpigmentation* of the skin, particularly of sun-exposed areas and at pressure points, such as the neck, elbows, knees, and knuckles, is quite characteristic. This is caused by elevated levels of pro-opiomelanocortin (POMC), which is derived from the anterior pituitary and is a precursor of both ACTH and melanocyte stimulating hormone (MSH). By contrast, hyperpigmentation is not seen in persons with adrenocortical insufficiency caused by primary pituitary or hypothalamic disease. Decreased mineralocorticoid activity in persons with primary adrenal insufficiency results in potassium retention and sodium loss, with consequent *hyperkalemia, hyponatremia, volume depletion, and hypotension*. Hypoglycemia may occasionally occur as a result of glucocorticoid deficiency and impaired gluconeogenesis. Stresses such as infections, trauma, or surgical procedures in such patients can precipitate an acute adrenal crisis, manifested by intractable vomiting, abdominal pain, hypotension, coma, and vascular collapse. Death occurs rapidly unless corticosteroid therapy begins immediately.

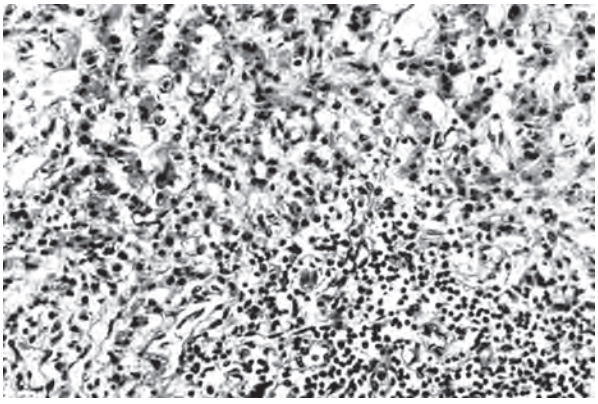

Figure 24-49 Autoimmune adrenalitis. In addition to loss of all but a subcapsular rim of cortical cells, there is an extensive mononuclear cell infiltrate.

KEY CONCEPTS

Adrenocortical Insufficiency (Hypoadrenalism)

- Primary adrenocortical insufficiency can be acute (Waterhouse-Friderichsen syndrome) or chronic (Addison disease)
- Chronic adrenal insufficiency in the developed world most often is secondary to *autoimmune adrenalitis*, which occurs in the context of one of two autoimmune polyendocrine syndromes: APS1 (caused by mutations in the *AIRE* gene) or APS2. APS1 is characterized by autoimmune attack against multiple endocrine organs and autoantibodies against IL-17.
- Tuberculosis and infections due to opportunistic pathogens associated with the human immunodeficiency virus and tumors metastatic to the adrenals are the other important causes of chronic hypoadrenalism.
- Patients typically present with fatigue, weakness, and gastrointestinal disturbances. Primary adrenocortical insufficiency also is characterized by high ACTH levels with associated skin pigmentation.

Secondary Adrenocortical Insufficiency

Any disorder of the hypothalamus and pituitary, such as metastatic cancer, infection, infarction, or irradiation, that reduces the output of ACTH leads to a syndrome of hypoadrenalism that has many similarities to Addison disease. Analogously, prolonged administration of exogenous glucocorticoids suppresses the output of ACTH and adrenal function. With secondary disease the hyperpigmentation of primary Addison disease is lacking, because levels of melanocyte-stimulating hormone are not elevated. The manifestations also differ in that secondary hypoadrenalism is characterized by deficient cortisol and androgen output but normal or near-normal aldosterone synthesis. Thus, in adrenal insufficiency secondary to pituitary malfunction, marked hyponatremia and hyperkalemia are not seen.