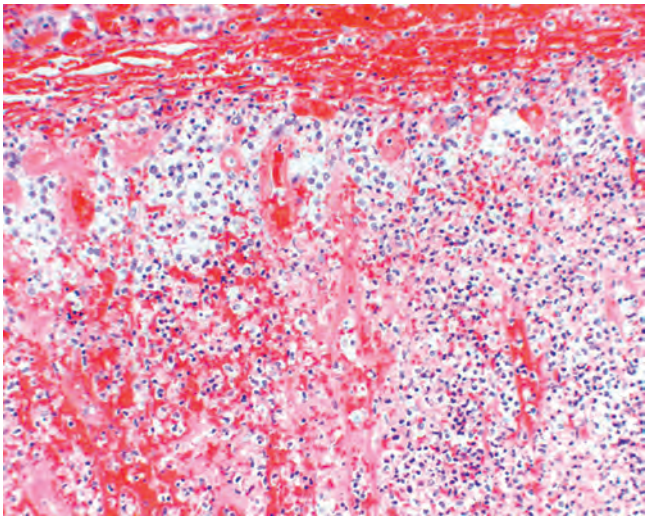

Figure 24-48 Waterhouse-Friderichsen syndrome. At autopsy, the adrenals were grossly hemorrhagic and shrunken; microscopically, little residual cortical architecture is discernible.

- Rapidly developing adrenocortical insufficiency associated with massive bilateral adrenal hemorrhage

Waterhouse-Friderichsen syndrome can occur at any age but is more common in children. The basis for the adrenal hemorrhage is uncertain but could be due to direct bacterial seeding of small vessels in the adrenal, the development of disseminated intravascular coagulation, or endothelial dysfunction caused by microbial products and inflammatory mediators. Whatever the basis, the adrenals are converted to sacs of clotted blood, which obscures virtually all of the underlying detail. Histologic examination reveals that the hemorrhage starts within the medulla near thin-walled venous sinusoids, then suffuses peripherally into the cortex, often leaving islands of recognizable cortical cells (Fig. 24-48). Prompt recognition and appropriate therapy must be instituted immediately, or death follows within hours to a few days.

Primary Chronic Adrenocortical Insufficiency (Addison Disease)

In an article published in 1855, Thomas Addison described a group of patients suffering from a constellation of symptoms, including "general languor and debility, remarkable feebleness of the heart's action, and a peculiar change in the color of the skin" associated with disease of the "suprarenal capsules" or, in more modern parlance, the adrenal glands. Addison disease, or chronic adrenocortical insufficiency, is an uncommon disorder resulting from progressive destruction of the adrenal cortex. In general, clinical manifestations of adrenocortical insufficiency do not appear until at least 90% of the adrenal cortex has been compromised. The causes of chronic adrenocortical insufficiency are listed in Table 24-10. Although all races and both sexes may be affected, certain causes of Addison disease (e.g., autoimmune adrenalitis) are much more common in whites and in women.

Pathogenesis. A large number of diseases may affect the adrenal cortex, including lymphomas, amyloidosis, sarcoidosis, hemochromatosis, fungal infections, and adrenal hemorrhage, but more than 90% of all cases are attributable to one of four disorders: autoimmune adrenalitis, tuberculosis, AIDS, or metastatic cancers.

- *Autoimmune adrenalitis* accounts for 60% to 70% of cases; it is by far the most common cause of primary adrenal insufficiency in developed countries. As the name implies, there is autoimmune destruction of steroidogenic cells. Autoantibodies to several key steroidogenic enzymes (21-hydroxylase, 17-hydroxylase) have been detected in these patients. Autoimmune adrenalitis can occur in one of two clinical settings:
  - *Autoimmune polyendocrine syndrome type 1* (APS1), also known as autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy (APECED), is characterized by chronic mucocutaneous candidiasis and abnormalities of skin, dental enamel, and nails (ectodermal dystrophy) in association with a combination of organ-specific autoimmune disorders (autoimmune adrenalitis, autoimmune hypoparathyroidism, idiopathic hypogonadism, pernicious anemia) that result in immune destruction of target organs. APS1 is caused by mutations in the autoimmune regulator *(AIRE)* gene on chromosome 21q22. AIRE is expressed primarily in the thymus, where it functions as a transcription factor that promotes the expression of many peripheral tissue antigens. Self-reactive T cells that recognize these antigens are eliminated (Chapter 6). In the absence of AIRE function, central T-cell tolerance to peripheral tissue antigens is compromised, promoting autoimmunity. Individuals with APS1 develop autoantibodies against IL-17 and IL-22, which are the principal effector cytokines secreted by T_H17 T-cells (Chapter 6). Because these two T_H17-derived cytokines are crucial for defense against fungal infections, it is not surprising that patients develop chronic mucocutaneous candidiasis.
  - *Autoimmune polyendocrine syndrome type 2* (APS2) usually starts in early adulthood and presents as a combination of adrenal insufficiency and autoimmune thyroiditis or type 1 diabetes. Unlike in APS1, mucocutaneous candidiasis, ectodermal dysplasia, and autoimmune hypoparathyroidism do not develop.
- *Infections*, particularly tuberculosis and those produced by fungi, may also cause primary chronic adrenocortical insufficiency. *Tuberculous adrenalitis,* which once accounted for as much as 90% of cases of Addison disease, has become less common with the development of antituberculous agents. With the resurgence of tuberculosis in most urban centers and the persistence of the disease in developing countries, however, this cause of adrenal insufficiency must be kept in mind. When present, tuberculous adrenalitis is usually associated with active infection in other sites, particularly in the lungs and genitourinary tract. Among fungi, disseminated infections caused by *Histoplasma capsulatum* and *Coccidioides immitis* may result in chronic adrenocortical insufficiency. AIDS sufferers are at risk for developing adrenal insufficiency from several infectious (cytomegalovirus, *Mycobacterium*