MORPHOLOGY

The main lesions of Cushing syndrome are found in the pituitary and adrenal glands. The **pituitary** shows changes regardless of the cause. The most common alteration, resulting from high levels of endogenous or exogenous glucocorticoids, is termed **Crooke hyaline change.** In this condition the normal granular, basophilic cytoplasm of the ACTH-producing cells in the anterior pituitary becomes homogeneous and paler. This alteration is the result of the accumulation of intermediate keratin filaments in the cytoplasm.

Depending on the cause of the hypercortisolism the **adrenals** show one of the following abnormalities: (1) cortical atrophy, (2) diffuse hyperplasia, (3) macronodular or micronodular hyperplasia, and (4) an adenoma or carcinoma. In patients in whom the syndrome results from exogenous glucocorticoids, suppression of endogenous ACTH results in bilateral **cortical atrophy,** due to a lack of stimulation of the zonae fasciculata and reticularis by ACTH. The zona glomerulosa is of normal thickness in such cases, because this portion of the cortex functions independently of ACTH. In contrast, in cases of endogenous hypercortisolism, the adrenals either are hyperplastic or contain a cortical neoplasm. **Diffuse hyperplasia** is found in individuals with ACTH-dependent Cushing syndrome (Fig. 24-42). Both glands are enlarged, either subtly or markedly, weighing up to 30 gm. The adrenal cortex is diffusely thickened and variably nodular, although the latter is not as pronounced as seen in cases of ACTH-independent nodular hyperplasia. Microscopically, the hyperplastic cortex demonstrates an expanded "lipid-poor" zona reticularis, comprising compact, eosinophilic cells, surrounded by an outer zone of vacuolated "lipid-rich" cells, resembling those seen in the zona fasciculata. Any nodules present are usually composed of vacuolated "lipid-rich" cells, which account for the yellow color of diffusely hyperplastic glands. In contrast, in **macronodular hyperplasia** the adrenals are almost entirely replaced by prominent nodules of varying sizes (≤3 cm), which contain an admixture of lipid-poor and lipid-rich cells. Unlike diffuse hyperplasia, the areas between the macroscopic nodules also demonstrate evidence of microscopic nodularity. **Micronodular hyperplasia** is composed of 1- to 3-mm darkly pigmented (brown to black) micronodules, with atrophic intervening areas (Fig. 24-43). The pigment is believed to be lipofuscin, a wear-and-tear pigment (Chapter 2).

Primary adrenocortical neoplasms causing Cushing syndrome may be malignant or benign. Functional adenomas or carcinomas of the adrenal cortex as the source of cortisol are not morphologically distinct from nonfunctioning adrenal neoplasms (described later). Both the benign and the malignant lesions are more common in women in their 30s to 50s. Adrenocortical **adenomas** are yellow tumors surrounded by thin or well-developed capsules, and most weigh less than 30 gm. Microscopically, they are composed of cells that are similar to those encountered in the normal zona fasciculata. The **carcinomas** associated with Cushing syndrome, by contrast, tend to be larger than the adenomas. These tumors (detailed later) are unencapsulated masses frequently exceeding 200 to 300 gm in weight that have all of the anaplastic characteristics of cancer. With functioning tumors, both benign and malignant, the adjacent adrenal cortex and that of the contralateral adrenal gland are atrophic, as a result of suppression of endogenous ACTH by high cortisol levels.

Figure 24-42 Diffuse hyperplasia of the adrenal contrasted with normal adrenal gland. In cross-section the adrenal cortex is yellow and thickened, and a subtle nodularity is seen (contrast with Fig. 24-46). Both adrenal glands were diffusely hyperplastic in this patient with ACTH-dependent Cushing syndrome.

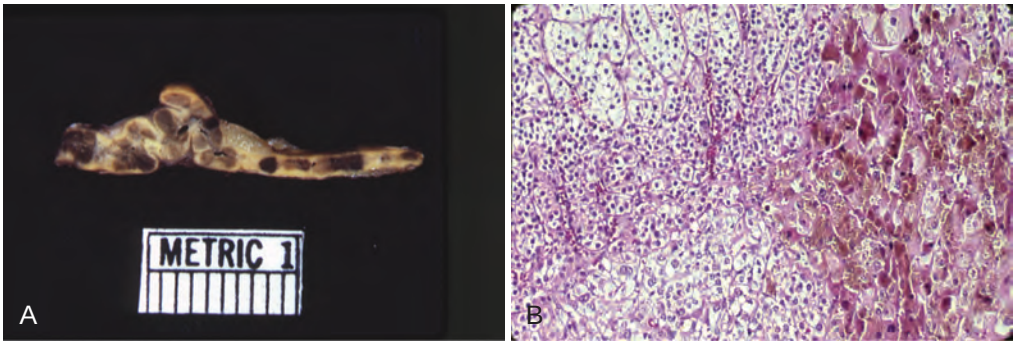

Figure 24-43 **A,** Micronodular adrenocortical hyperplasia with prominent pigmented nodules in the adrenal gland. **B,** On histologic examination the nodules are composed of cells containing lipofuscin pigment, seen in the right part of the field. (Photographs courtesy Dr. Aidan Carney, Department of Medicine, Mayo Clinic, Rochester, Minn.)