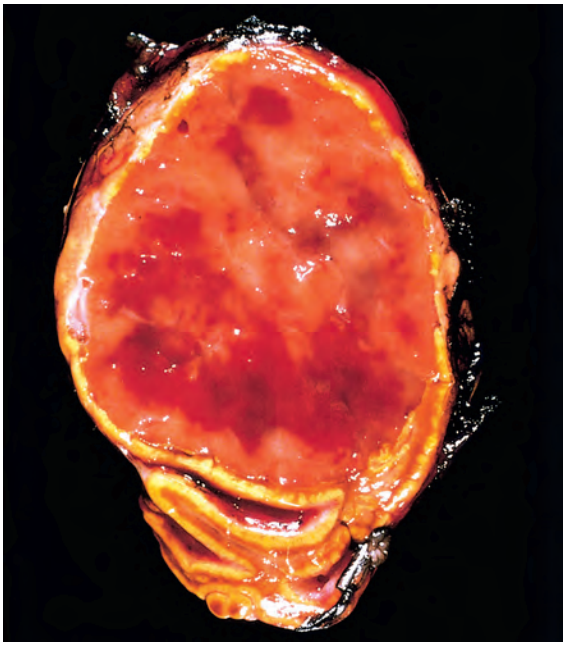

Figure 24-54 Pheochromocytoma. The tumor is enclosed within an attenuated cortex and demonstrates areas of hemorrhage. The comma-shaped residual adrenal is seen below. (Courtesy Dr. Jerrold R. Turner, Department of Pathology, University of Chicago Hospitals, Chicago, Ill.)

due to oxidation of stored catecholamines, thus the term **chromaffin**.

The histologic pattern in pheochromocytoma is quite variable. The tumors are composed of clusters of polygonal to spindle-shaped chromaffin cells or chief cells that are surrounded by supporting sustentacular cells, creating small nests or alveoli **(zellballen)** that are supplied by a rich vascular network (Fig. 24-55). Uncommonly, the dominant cell type is a spindle or small cell; various patterns can be found in any one tumor. The cytoplasm has a finely granular appearance, best demonstrated with silver stains, due to the presence of granules containing catecholamines. The nuclei are usually round to ovoid, with a stippled "salt and pepper" chromatin that is characteristic of

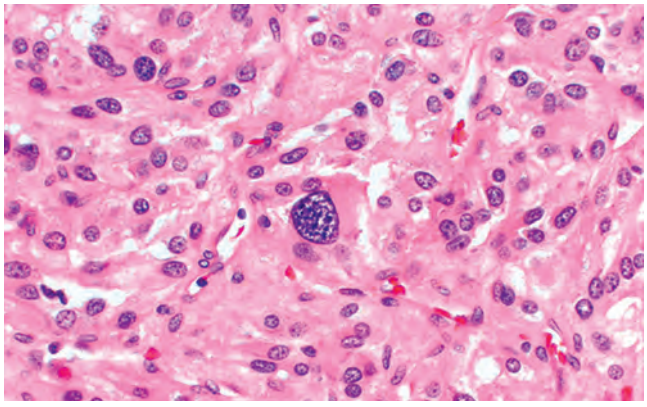

Figure 24-55 Pheochromocytoma demonstrating characteristic nests of cells ("zellballen") with abundant cytoplasm. Granules containing catecholamine are not visible in this preparation. It is not uncommon to find bizarre cells even in pheochromocytomas that are biologically benign. (Courtesy Dr. Jerrold R. Turner, Department of Pathology, University of Chicago Hospitals, Chicago, Ill.)

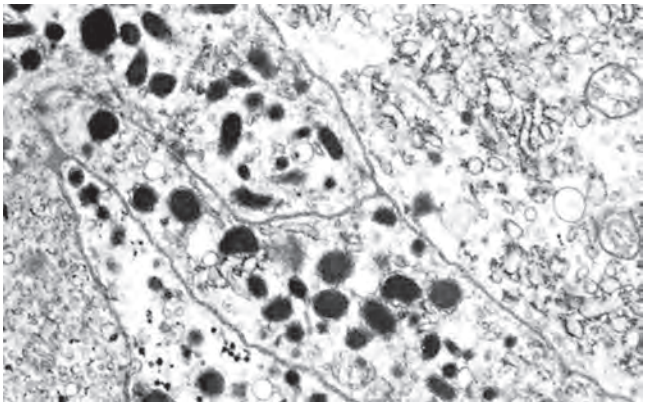

Figure 24-56 Electron micrograph of pheochromocytoma. This tumor contains membrane-bound secretory granules in which catecholamines are stored (30,000×).

neuroendocrine tumors. Electron microscopy reveals variable numbers of membrane-bound, electron-dense secretory granules (Fig. 24-56). Immunoreactivity for neuroendocrine markers (chromogranin and synaptophysin) is seen in the chief cells, while the peripheral sustentacular cells stain with antibodies against S-100, a calcium-binding protein expressed by a variety of mesenchymal cell types.

Determining malignancy in pheochromocytomas can be vexing. **There is no histologic feature that reliably predicts clinical behavior.** Several histologic features, such as numbers of mitoses, confluent tumor necrosis, and spindle cell morphology, have been associated with an aggressive behavior and increased risk of metastasis, but are not entirely reliable. Tumors with "benign" histologic features may metastasize, while bizarrely pleomorphic tumors may remain confined to the adrenal gland. In fact, cellular and nuclear pleomorphism, including the presence of giant cells, and mitotic figures are often seen in benign pheochromocytomas, while cellular monotony is paradoxically associated with an aggressive behavior. Even capsular and vascular invasion may be encountered in benign lesions. **Therefore, the definitive diagnosis of malignancy in pheochromocytomas is based exclusively on the presence of metastases.** These may involve regional lymph nodes as well as more distant sites, including liver, lung, and bone.

Clinical Course. The dominant clinical manifestation of pheochromocytoma is *hypertension*, observed in 90% of patients. Approximately two thirds of patients with hypertension demonstrate *paroxysmal episodes*, which are described as an abrupt, precipitous elevation in blood pressure, associated with tachycardia, palpitations, headache, sweating, tremor, and a sense of apprehension. These episodes may also be associated with pain in the abdomen or chest, nausea, and vomiting. *Isolated* paroxysmal episodes of hypertension occur in fewer than half of patients; more commonly, patients demonstrate chronic, sustained elevation in blood pressure punctuated by the aforementioned paroxysms. The paroxysms may be precipitated by emotional stress, exercise, changes in posture, and palpation in the region of the tumor; patients with urinary bladder paragangliomas occasionally precipitate a

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