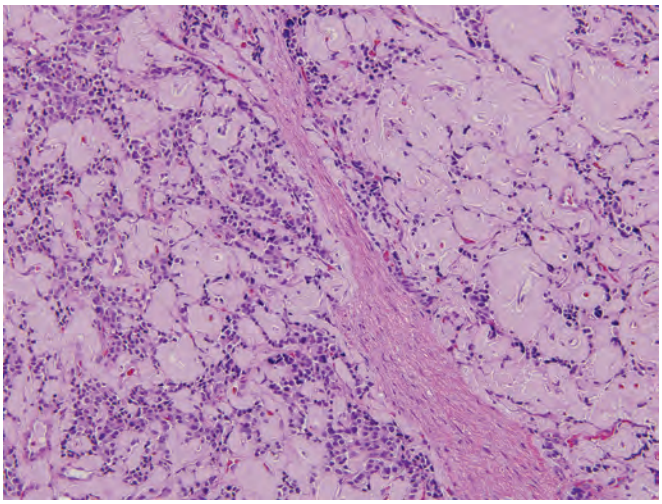

Figure 24-41 Pancreatic endocrine neoplasm ("islet cell tumor"). The neoplastic cells are monotonous and demonstrate minimal pleomorphism or mitotic activity. There is abundant amyloid deposition, characteristic of an insulinoma. Clinically, the patient had episodic hypoglycemia.

MORPHOLOGY

More than half of gastrin-producing tumors are locally invasive or have already metastasized at the time of diagnosis. In approximately 25% of patients, gastrinomas arise in conjunction with other endocrine tumors, as part of the MEN-1 syndrome (see later); MEN-1-associated gastrinomas are frequently multifocal, while sporadic gastrinomas are usually single. As with insulin-secreting tumors of the pancreas, gastrin-producing tumors are histologically bland and rarely show marked anaplasia.

In the Zollinger-Ellison syndrome, hypergastrinemia gives rise to extreme gastric acid secretion, which in turn causes **peptic ulceration** (Chapter 17). The duodenal and gastric ulcers are often multiple; although they are identical to those found in the general population, they are often unresponsive to therapy. In addition, ulcers may occur in unusual locations such as the jejunum; **when intractable jejunal ulcers are found, Zollinger-Ellison syndrome should be considered**.

Clinical Features. More than 50% of the patients have diarrhea; in 30%, it is the presenting symptom. Treatment of Zollinger-Ellison syndrome involves control of gastric acid secretion by use of H^+K^+-ATPase inhibitors and excision of the neoplasm. Total resection of the neoplasm, when possible, eliminates the syndrome. Patients with hepatic metastases have a shortened life expectancy, with progressive tumor growth leading to liver failure usually within 10 years.

Other Rare Pancreatic Endocrine Neoplasms

α-*cell tumors (glucagonomas)* are associated with increased serum levels of glucagon and a syndrome consisting of mild diabetes mellitus, a characteristic skin rash (necrolytic migratory erythema), and anemia. They occur most frequently in perimenopausal and postmenopausal women and are characterized by extremely high plasma glucagon levels.

δ-*cell tumors (somatostatinomas)* are associated with diabetes mellitus, cholelithiasis, steatorrhea, and hypochlorhydria. They are exceedingly difficult to localize preoperatively. High plasma somatostatin levels are required for diagnosis.

VIPoma (watery diarrhea, hypokalemia, achlorhydria, or WDHA syndrome) induces a characteristic syndrome that is caused by release of vasoactive intestinal peptide (VIP) from the tumor. Some of these tumors are locally invasive and metastatic. A VIP assay should be performed on all patients with severe secretory diarrhea. Neural crest tumors, such as neuroblastomas, ganglioneuroblastoma, and ganglioneuromas (Chapter 10) and pheochromocytomas (see later) can also be associated with the VIPoma syndrome.

Pancreatic carcinoid tumors producing serotonin and an atypical carcinoid syndrome are exceedingly rare. *Pancreatic polypeptide-secreting endocrine tumors* present as mass lesions as even high plasma levels of this hormone fail to cause symptoms.

Some pancreatic and extra-pancreatic endocrine tumors produce two or more hormones. In addition to insulin, glucagon, and gastrin, pancreatic endocrine tumors may produce ACTH, MSH, ADH, serotonin, and norepinephrine. These *multihormonal tumors* are to be distinguished from the MEN syndromes (discussed later), in which a multiplicity of hormones is produced by tumors in several different glands.

ADRENAL GLANDS

Adrenal Cortex

The *adrenal glands* are paired endocrine organs consisting of a cortex and a medulla, which differ in their development, structure, and function. In essence the cortex and medulla are two glands packaged as one structure. The adrenal cortex has three zones. Beneath the capsule is the narrow layer of zona glomerulosa. An equally narrow zona reticularis abuts the medulla. Intervening is the broad zona fasciculata, which makes up about 75% of the total cortex. The *adrenal cortex* synthesizes three different types of steroids: (1) *glucocorticoids* (principally cortisol), which are synthesized primarily in the zona fasciculata and to a lesser degree in the zona reticularis; (2) *mineralocorticoids*, the most important being aldosterone, which is generated in the zona glomerulosa; and (3) *sex steroids* (estrogens and androgens), which are produced largely in the zona reticularis. The *adrenal medulla* is composed of chromaffin cells, which synthesize and secrete *catecholamines*, mainly epinephrine. Catecholamines have many effects that allow rapid adaptations to changes in the environment.

Diseases of the adrenal cortex can be conveniently divided into those associated with hyperfunction and those associated with hypofunction.