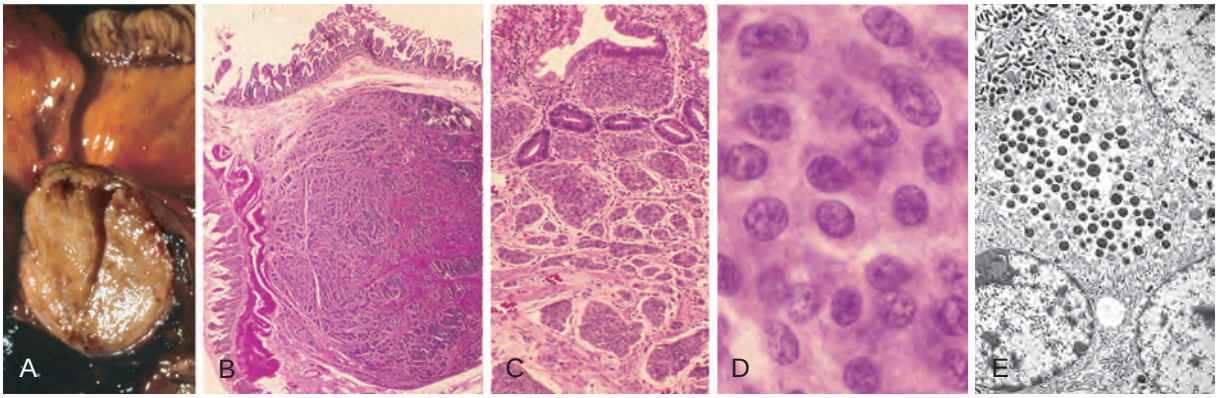

Figure 17-20 GI carcinoid tumor (neuroendocrine carcinoma). **A,** Gross cross-section of a submucosal tumor nodule. **B,** Microscopically the nodule is composed of tumor cells embedded in dense fibrous tissue. **C,** In other areas, the tumor has spread extensively within mucosal lymphatic channels. **D,** High magnification shows the bland cytology of carcinoid tumors. The chromatin texture, with fine and coarse clumps, is frequently described as a "salt and pepper" pattern. Despite their innocuous appearance, carcinoids can be clinically aggressive. **E,** Electron microscopy reveals cytoplasmic dense core neurosecretory granules.

intestine, the vasoactive substances released are metabolized to inactive forms by the liver, a "first-pass" effect similar to that exerted on oral drugs. This can be overcome by a large tumor burden or, more commonly, when tumors secrete hormones into a nonportal venous circulation. The carcinoid syndrome is therefore strongly associated with metastatic disease in the liver since the bioactive products can be released directly into systemic circulation.

The most important prognostic factor for GI carcinoid tumors is location.

- *Foregut carcinoid tumors*, those found within the stomach, duodenum proximal to the ligament of Treitz, and esophagus, rarely metastasize and are generally cured by resection. This is particularly true for gastric carcinoid tumors that arise in association with atrophic gastritis, while gastric carcinoid tumors without predisposing factors are often more aggressive.
- *Midgut carcinoid tumors* that arise in the jejunum and ileum are often multiple and tend to be aggressive. In these tumors, greater depth of local invasion, increased size, and the presence of necrosis and mitoses are associated with a worse outcome.
- *Hindgut carcinoids* arising in the appendix and colorectum are typically discovered incidentally. Those in the appendix occur at any age and are generally located at the tip. These tumors are rarely more than 2 cm in diameter and are almost always benign. Rectal carcinoid tumors tend to produce polypeptide hormones and, when symptomatic, present with abdominal pain and weight loss. Because they are usually discovered when small, metastasis of rectal carcinoid tumors is uncommon.

Gastrointestinal Stromal Tumor

A wide variety of mesenchymal neoplasms may arise in the stomach. Many are named according to the cell type they most resemble; for example, smooth muscle tumors are called *leiomyomas* or *leiomyosarcomas,* nerve sheath tumors are termed *schwannomas,* and those resembling glomus bodies in the nail beds and at other sites are termed *glomus tumors.* These are all rare and are discussed in greater detail in Chapter 26. ***GI stromal tumor (GIST)* is the most common mesenchymal tumor of the abdomen,** with annual incidences between 11 and 20 per million people. More than half of these tumors occur in the stomach. The term stromal reflects historical confusion about the origin of this tumor, which is now recognized to arise from the interstitial cells of Cajal, or pacemaker cells, of the gastrointestinal muscularis propria.

Epidemiology. Clinically silent, microscopic proliferations that may represent precursors to GIST are present in 10% to 30% of resected stomachs. These have a low mitotic index and lack pleomorphism and other features suggesting malignancy. The risk of of these benign proliferations becoming a GIST is estimated to be 1 in 2000.

The peak age at which clinically evident GISTs are recognized is approximately 60 years, with fewer than 10% occurring in individuals younger than 40 years of age. Of the uncommon GISTs in children, some are related to the *Carney triad*, a nonhereditary syndrome of unknown etiology seen primarily in young females that includes gastric GIST, paraganglioma, and pulmonary chondroma. There is also an increased incidence of GIST in individuals with neurofibromatosis type 1.

Pathogenesis. **Approximately 75% to 80% of all GISTs have oncogenic, gain-of-function mutations in the receptor tyrosine kinase KIT.** Approximately 8% of GISTs have mutations that activate a closely related receptor tyrosine kinase, platelet-derived growth factor receptor α (PDGFRA). For unknown reasons, GISTs bearing PDGFRA mutations are overrepresented in the stomach. *KIT* and *PDGFRA* gene mutations are mutually exclusive, reflecting their activities within the same signal transduction pathway. Germline mutations in these same genes are present in rare familial GISTs, in which patients develop multiple GISTs and may also have diffuse hyperplasia of Cajal cells. Both sporadic and germline mutations result in constitutively active KIT or PDGFRA receptor tyrosine kinases and produce intracellular signals that promote tumor cell proliferation and survival (Chapter 7). Some GISTs without mutated *KIT* or *PDGFRA* have mutations in