atrophic gastritis and intestinal metaplasia. As a result, the incidence of diffuse type gastric cancer, which was previously low, is now similar to intestinal type gastric cancer.

The depth of invasion and the extent of nodal and distant metastases at the time of diagnosis remain the most powerful prognostic indicators in gastric cancer. Local invasion into the duodenum, pancreas, and retroperitoneum is common. In such cases efforts are usually focused on chemotherapy or radiation therapy and palliative care. However, when possible, surgical resection remains the preferred treatment for gastric adenocarcinoma. With surgical resection, the 5-year survival rate of early gastric cancer can exceed 90%, even if lymph node metastases are present. In contrast, the 5-year survival rate for advanced gastric cancer remains less than 20%. Because of the advanced stage at which most gastric cancers are discovered in the United States, the overall 5-year survival is less than 30%.

Lymphoma

Although extranodal lymphomas can arise in virtually any tissue, they do so most commonly in the GI tract, particularly the stomach. In allogeneic hematopoietic stem cell and organ transplant recipients, the bowel is also the most frequent site for Epstein-Barr virus-positive B-cell lymphoproliferations. This preferential location is most likely because the deficits in T-cell function caused by oral immunosuppressive agents (e.g., cyclosporine) are greatest at intestinal sites of drug absorption. Nearly 5% of all gastric malignancies are primary lymphomas, the most common of which are indolent extranodal marginal zone B-cell lymphomas. *In the gut these tumors are often referred to as lymphomas of mucosa-associated lymphoid tissue (MALT), or MALTomas*. This and other lymphomas of the gut are discussed in Chapter 13.

Pathogenesis. Extranodal marginal zone B-cell lymphomas usually arise at sites of chronic inflammation. They can originate in the GI tract at sites of preexisting MALT, such as the Peyer patches of the small intestine, but more commonly arise within tissues that are normally devoid of organized lymphoid tissue. *In the stomach, MALT is induced, typically as a result of chronic gastritis. H. pylori* infection is the most common inducer in the stomach and, therefore, is found in association with most cases of gastric MALToma. Remarkably, *H. pylori* eradication results in durable remissions with low rates of recurrence in most MALToma patients.

Three translocations are associated with gastric MALToma, the t(11;18)(q21;q21) and the less common t(1;14)(p22;q32) and t(14;18)(q32;q21). The t(11;18)(q21;q21) translocation brings together the apoptosis inhibitor 2 *(API2)* gene on chromosome 11 with the "mutated in MALT lymphoma," or *MLT*, gene on chromosome 18. This creates a chimeric *API2-MLT* fusion gene that encodes an API2-MLT fusion protein. The t(14;18)(q32;q21) and t(1;14)(p22;q32) translocations cause increased expression of intact MALT1 and BCL-10 proteins, respectively.

Each of the three translocations has the same net effect, the constitutive activation of NF-κB, a transcription factor that promotes B-cell growth and survival. Antigen-dependent activation of NF-κB in normal B and T cells requires both BCL-10 and MLT, which work together in a pathway downstream of the B- and T-cell antigen receptors. Thus, *H. pylori*–induced inflammation may trigger NF-κB activation through the MLT/BCL-10 pathway in MALTomas that lack these translocations. Removal of this stimulus may explain why these tumors tend to respond to *H. pylori* eradication. In contrast, NF-κB is constitutively active in tumors bearing translocations involving *MLT* or *BCL10*, and *H. pylori* treatment is ineffective. Other tumor characteristics, including invasion to the muscularis propria or beyond and lymph node involvement, also correlate with failure of *H. pylori* eradication to induce remission.

As with other low-grade lymphomas, MALTomas can transform into more aggressive tumors that are histologically identical to diffuse large B-cell lymphomas. This is often associated with additional genetic changes, such as inactivation of the tumor suppressor genes that encode p53 and p16. As one might guess, MALTomas that have undergone such transformation are not responsive to *H. pylori* eradication.

MORPHOLOGY

Histologically, gastric MALToma takes the form of a dense lymphocytic infiltrate in the lamina propria (Fig. 17-19*A*). Characteristically, the neoplastic lymphocytes infiltrate the gastric glands focally to create **diagnostic lymphoepithelial lesions** (Fig. 17-19*A*, inset). Reactive-appearing B-cell follicles may be present, and, in about 40% of tumors, plasmacytic differentiation is observed. At other sites GI lymphomas may disseminate as discrete small nodules (Fig. 17-19*B*) or infiltrate the wall diffusely (Fig. 17-19*C*).

Like other tumors of mature B cells, MALTomas express the B-cell markers CD19 and CD20. They do not express CD5 or CD10, but are positive for CD43 in about 25% of cases, an unusual feature that can be diagnostically helpful. In cases lacking lymphoepithelial lesions, monoclonality may be demonstrated by restricted expression of either κ or λ immunoglobulin light chains or by molecular detection of clonal IgH rearrangements. Molecular analysis is being used increasingly to identify tumors with translocations that predict resistance to therapy.

Clinical Features. The most common presenting symptoms are dyspepsia and epigastric pain. Hematemesis, melena, and constitutional symptoms such as weight loss can also be present. Because gastric MALTomas and *H. pylori* gastritis often coexist and have overlapping clinical symptoms and endoscopic appearances, diagnostic difficulties may arise, particularly in small biopsy specimens.

Carcinoid Tumor

Carcinoid tumors arise from the diffuse components of the endocrine system and are now properly referred to as *well-differentiated neuroendocrine tumors.* The term carcinoid, or "carcinoma-like," was applied because these tumors tend to have a more indolent clinical course than GI carcinomas. Most are found in the GI tract, and more than 40% occur in the small intestine (Table 17-6). The tracheobronchial tree and lungs are the next most