Pathogenesis. **Autoimmune gastritis is associated with loss of parietal cells, which are responsible for secretion of gastric acid and intrinsic factor.** The absence of acid production stimulates gastrin release, resulting in hypergastrinemia and hyperplasia of antral gastrin-producing G cells. Lack of intrinsic factor disables ileal vitamin B_{12} absorption, which ultimately leads to vitamin B_{12} deficiency and a slow-onset megaloblastic anemia *(pernicious anemia)*. Reduced serum pepsinogen I concentration results from chief cell destruction. Although *H. pylori* infection can cause gastric atrophy and hypochlorhydria, it is not associated with achlorhydria or pernicious anemia. This is because, in contrast to the diffuse atrophy of autoimmune gastritis, the damage in *H. pylori* gastritis is multifocal and leaves patches of residual parietal and chief cells.

CD4+ T cells directed against parietal cell components, including the H+,K+-ATPase, are considered to be the principal agents of injury in autoimmune gastritis. This is supported by the observation that transfer of H+,K+-ATPase-reactive CD4+ T cells into naïve mice results in gastritis and production of H+,K+-ATPase autoantibodies. There is no evidence of an autoimmune reaction to chief cells, suggesting that these may be lost through gastric gland destruction during autoimmune attack on parietal cells. If autoimmune destruction is controlled by immunosuppression, the glands can repopulate, demonstrating that gastric stem cells survive and are able to differentiate into parietal and chief cells.

Autoantibodies to parietal cell components, most prominently the H+,K+-ATPase, or proton pump, and intrinsic factor are present in up to 80% of patients with autoimmune gastritis. However, these antibodies are not thought to be pathogenic because neither secreted intrinsic factor nor the luminally oriented proton pump are accessible to circulating antibodies, and passive transfer of these antibodies does not produce gastritis in experimental animals. Nevertheless, the presence of these autoantibodies is a useful diagnostic tool.

MORPHOLOGY

Autoimmune gastritis is characterized by diffuse mucosal damage of the oxyntic (acid-producing) mucosa within the body and fundus. Damage to the antrum and cardia is typically absent or mild. With diffuse atrophy, the oxyntic mucosa of the body and fundus appears markedly thinned, and rugal folds are lost. If vitamin B_{12} deficiency is severe, nuclear enlargement (megaloblastic change) occurs within epithelial cells. Neutrophils may be present, but the inflammatory infiltrate is typically composed of lymphocytes, macrophages, and plasma cells, often in association with lymphoid aggregates and follicles. The superficial lamina propria plasma cells typical of *H. pylori* gastritis are absent, and the inflammatory reaction is deeper and centered on the gastric glands (Fig. 17-13*A*). Loss of parietal and chief cells can be extensive. When atrophy is incomplete, residual islands of oxyntic mucosa may give the appearance of multiple small polyps or nodules. In other areas, small surface elevations may represent sites of intestinal metaplasia, characterized by the presence of goblet cells and columnar absorptive cells (Fig. 17-13*B*). Although present in most patients, endocrine cell hyperplasia can be difficult to appreciate on hematoxylin and eosin-stained sections. This hyperplasia, which can be clearly demonstrated with immunostains for proteins such as chromogrannin A, parallels the degree of mucosal atrophy and is a physiologic response to decreased acid production. Over time, hypergastrinemia can stimulate endocrine cell hyperplasia in the fundus and body. Rarely, this may progress to form small, multicentric, low-grade neuroendocrine (carcinoid) tumors.

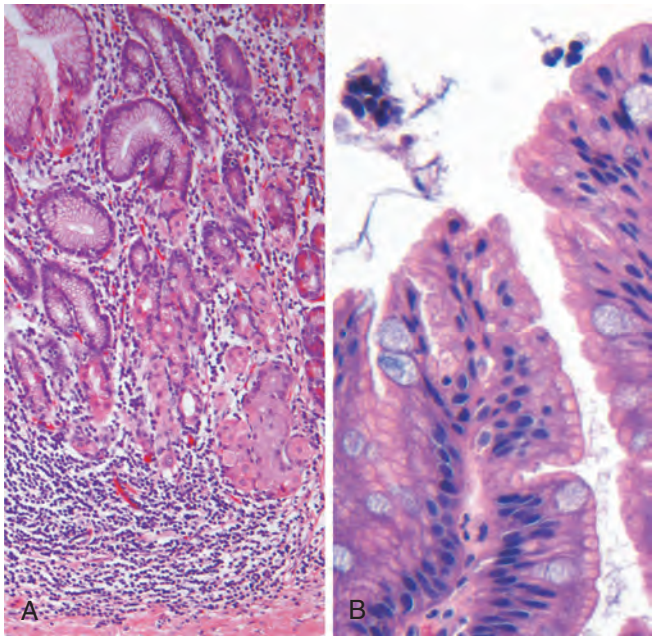

Figure 17-13 Autoimmune gastritis. **A,** Low-magnification image of gastric body demonstrating deep inflammatory infiltrates, primarily composed of lymphocytes, and glandular atrophy. **B,** Intestinal metaplasia, recognizable as the presence of goblet cells admixed with gastric foveolar epithelium.

Clinical Features. Antibodies to parietal cells and to intrinsic factor are present early in the disease course. Progression to gastric atrophy probably occurs over 2 to 3 decades, and anemia is seen in only a few patients. Because of the slow onset and variable progression, patients are generally diagnosed only after being affected for many years; the median age at diagnosis is 60. Slightly more women than men are affected. Pernicious anemia and autoimmune gastritis are often associated with other autoimmune diseases including Hashimoto thyroiditis, insulin-dependent (type I) diabetes mellitus, Addison disease, primary ovarian failure, primary hypoparathyroidism, Graves disease, vitiligo, myasthenia gravis, and Lambert-Eaton syndrome. These associations, along with concordance in some monozygotic twins and clustering of disease in families, support a genetic predisposition. In general, about 20% of relatives of individuals with pernicious anemia also have autoimmune gastritis, although they may be asymptomatic. Despite this strong genetic influence, autoimmune gastritis stands apart from many other autoimmune diseases in that there is little evidence of linkage to specific HLA alleles.

Clinical presentation may be linked to symptoms of anemia (Chapter 14). Vitamin B_{12} deficiency may also cause atrophic glossitis, in which the tongue becomes smooth and beefy red, epithelial megaloblastosis, malabsorptive