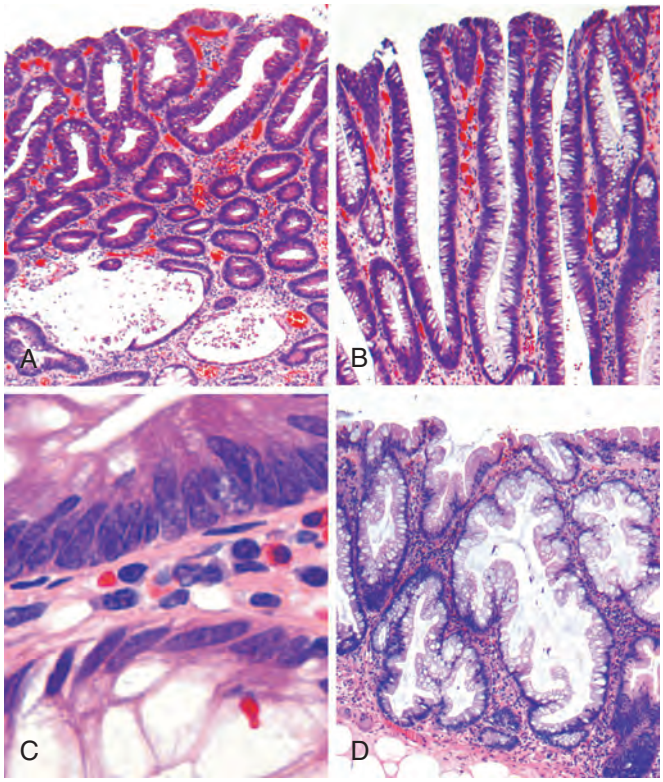

Figure 17-46 Histologic appearance of colonic adenomas. **A,** Tubular adenoma with a smooth surface and rounded glands. Active inflammation is occasionally present in adenomas, in this case, crypt dilation and rupture can be seen at the bottom of the field. **B,** Villous adenoma with long, slender projections that are reminiscent of small intestinal villi. **C,** Dysplastic epithelial cells (top) with an increased nuclear-to-cytoplasmic ratio, hyperchromatic and elongated nuclei, and nuclear pseudostratification. Compare to the non-dysplastic epithelium below. **D,** Sessile serrated adenoma lined by goblet cells without cytologic features of dysplasia. This lesion is distinguished from a hyperplastic polyp by extension of the neoplastic process to the crypts, resulting in lateral growth. Compare to the hyperplastic polyp in Figure 17-44A.

but does not confer an increased risk of cancer in other polyps within the same patient.

Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder in which patients develop numerous colorectal adenomas as teenagers. It is caused by mutations of the adenomatous polyposis coli, or *APC*, gene, which you will recall is a key negative regulator of the Wnt signaling pathway (Chapter 7). Approximately 75% of cases are inherited, while the remaining appear to be caused by de novo mutations.

At least 100 polyps are necessary for a diagnosis of classic FAP, but as many as several thousand may be present (Fig. 17-48). Except for their remarkable numbers, these growths are morphologically indistinguishable from sporadic adenomas. In addition, however, flat or depressed adenomas are also prevalent in FAP, and microscopic adenomas, consisting of only one or two dysplastic crypts, are frequently observed in otherwise normal-appearing mucosa.

Colorectal adenocarcinoma develops in 100% of untreated FAP patients, often before age 30 and nearly always by age 50. As a result, prophylactic colectomy is the standard therapy for individuals carrying *APC* mutations. Colectomy prevents colorectal cancer, but patients remain at risk for neoplasia at other sites. Adenomas may develop elsewhere in the GI tract, particularly adjacent to the ampulla of Vater and in the stomach.

FAP is associated with a variety of extraintestinal manifestations including congenital hypertrophy of the retinal pigment epithelium, which can generally be detected at birth, and therefore may be an adjunct to early screening. Specific *APC* mutations have been associated with the development of other manifestations of FAP and partly explain variants such as Gardner syndrome and Turcot syndrome (Table 17-11).

Some polyposis patients without *APC* loss have bi-allelic mutations of the base-excision repair gene *MYH* (also referred to as *MUTYH*). This autosomal recessive disorder is termed *MYH*-associated polyposis. The colonic phenotype is similar to attenuated FAP, with polyp development at later ages, the presence of fewer than 100 adenomas, and the delayed appearance of colon cancer, often at ages of 50 or older. In addition, serrated polyps, often with *KRAS*

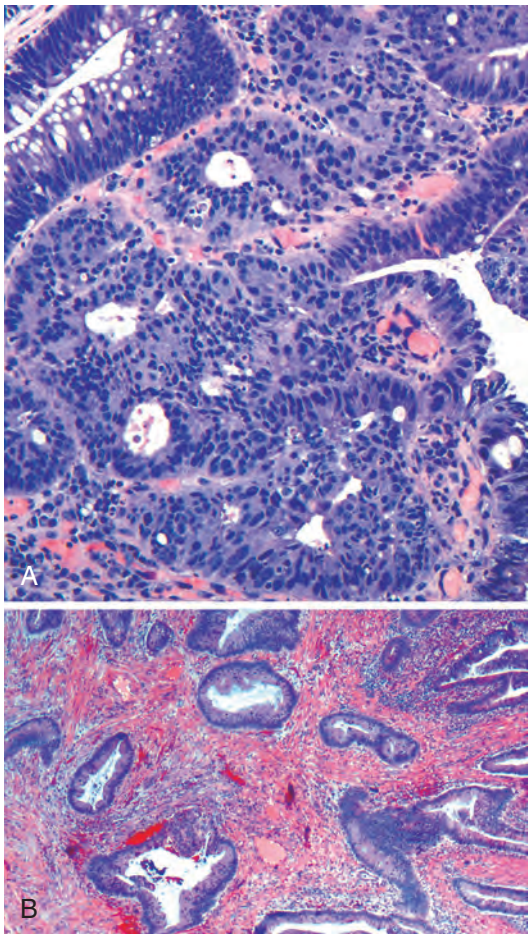

Figure 17-47 Adenoma with intramucosal carcinoma. **A,** Cribriform glands interface directly with the lamina propria without an intervening basement membrane. **B,** Invasive adenocarcinoma (left) beneath a villous adenoma (right). Note the desmoplastic response to the invasive components.