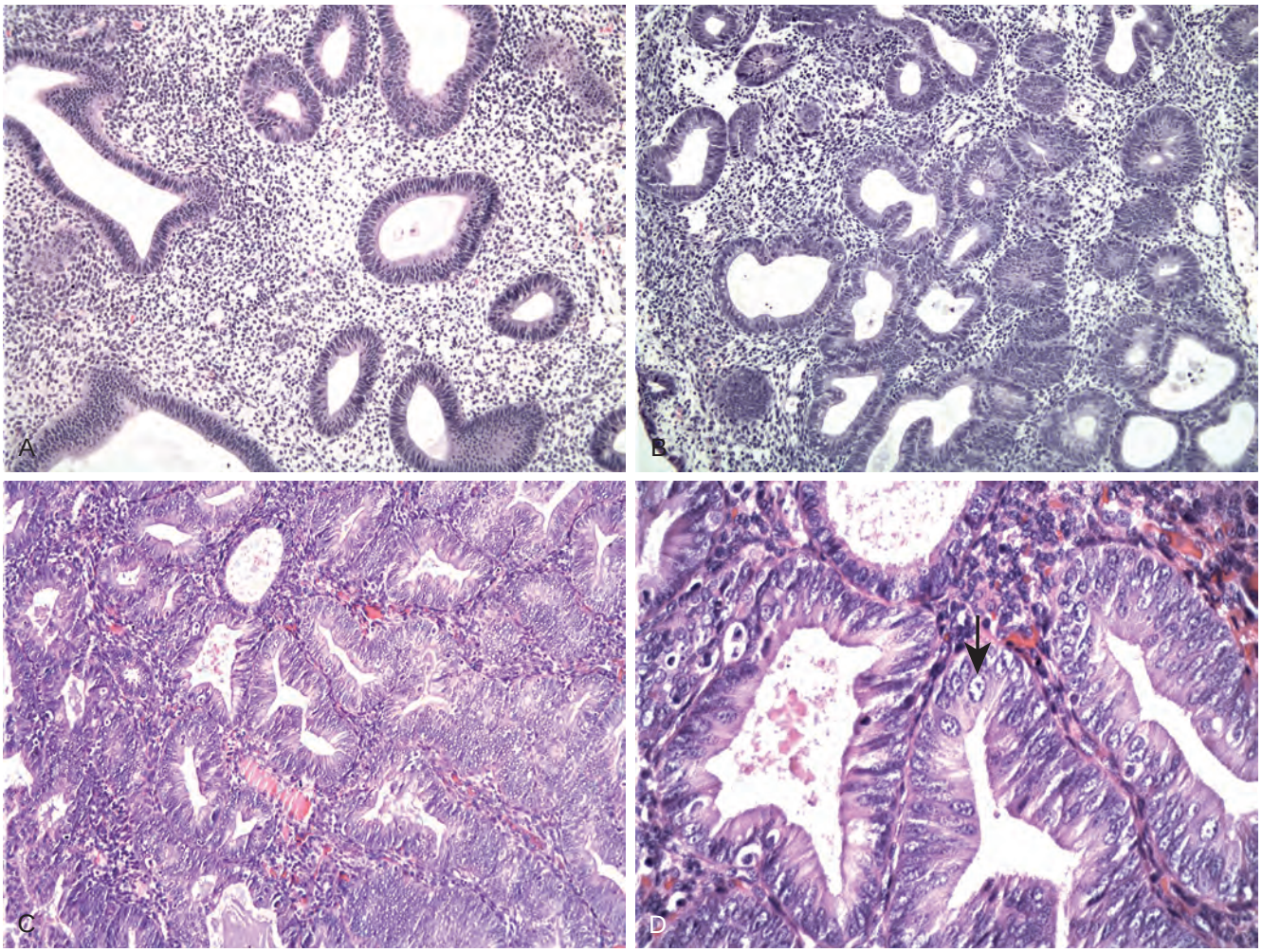

Figure 22-23 Endometrial hyperplasia. **A,** Hyperplasia without atypia. Note architectural abnormalities including mild glandular crowding and cystic glandular dilatation. **B,** Hyperplasia without atypia demonstrating increased glandular crowding with areas of back-to-back glands and cytologic features similar to proliferative endometrium. **C,** Atypical hyperplasia with further increase in glandular crowding and abnormal cytologic features. **D,** High magnification of atypical hyperplasia showing rounded, vesicular nuclei with prominent nucleoli *(arrow)*.

all invasive cancer in women, excluding skin cancer. At one time endometrial carcinoma was far less common than cancer of the cervix, but earlier detection and eradication of the precursor lesions of cervical carcinoma, coupled with an increase in endometrial carcinomas in younger women, have reversed this ratio. In 2012 in the United States, 47,130 new endometrial cancers and 8010 deaths were predicted. Worldwide there are approximately 280,000 new cases of endometrial cancer per year.

Pathogenesis. Clinicopathologic studies and molecular analyses support the classification of endometrial carcinoma into two broad categories referred to as type I and type II (summarized in Table 22-4). Because of their distinct pathogenesis, they are discussed separately.

Type I (Endometrial) Carcinoma. These are the most common type, accounting for approximately 80% of cases. Most are well differentiated and mimic proliferative endometrial glands and, as such, are referred to as *endometrioid carcinoma*. As discussed earlier, they typically arise in the setting of endometrial hyperplasia and like endometrial hyperplasia they are associated with (1) obesity, (2) diabetes (abnormal glucose tolerance is found in more than 60%), (3) hypertension, (4) infertility, and (5) unopposed estrogen stimulation.

As with other cancers, development of endometrial carcinoma involves the stepwise acquisition of several genetic alterations in tumor suppressor genes and oncogenes. In hysterectomy specimens containing both atypical hyperplasia and carcinoma, identical *PTEN* mutations have been identified in each component, supporting the view that atypical hyperplasia is a precursor to carcinoma and that *PTEN* mutations occur before the development of overt carcinoma (Fig. 22-24*A*).

Sequencing of the genomes of type I endometrioid carcinomas has shown that the most common mutations act to increase signaling through the PI3K/AKT pathway, which is a hallmark of this particular tumor type. As mentioned earlier, PI3K/AKT signaling somehow augments expression of estrogen receptor-dependent target genes in endometrial cells. Type I endometrial carcinomas