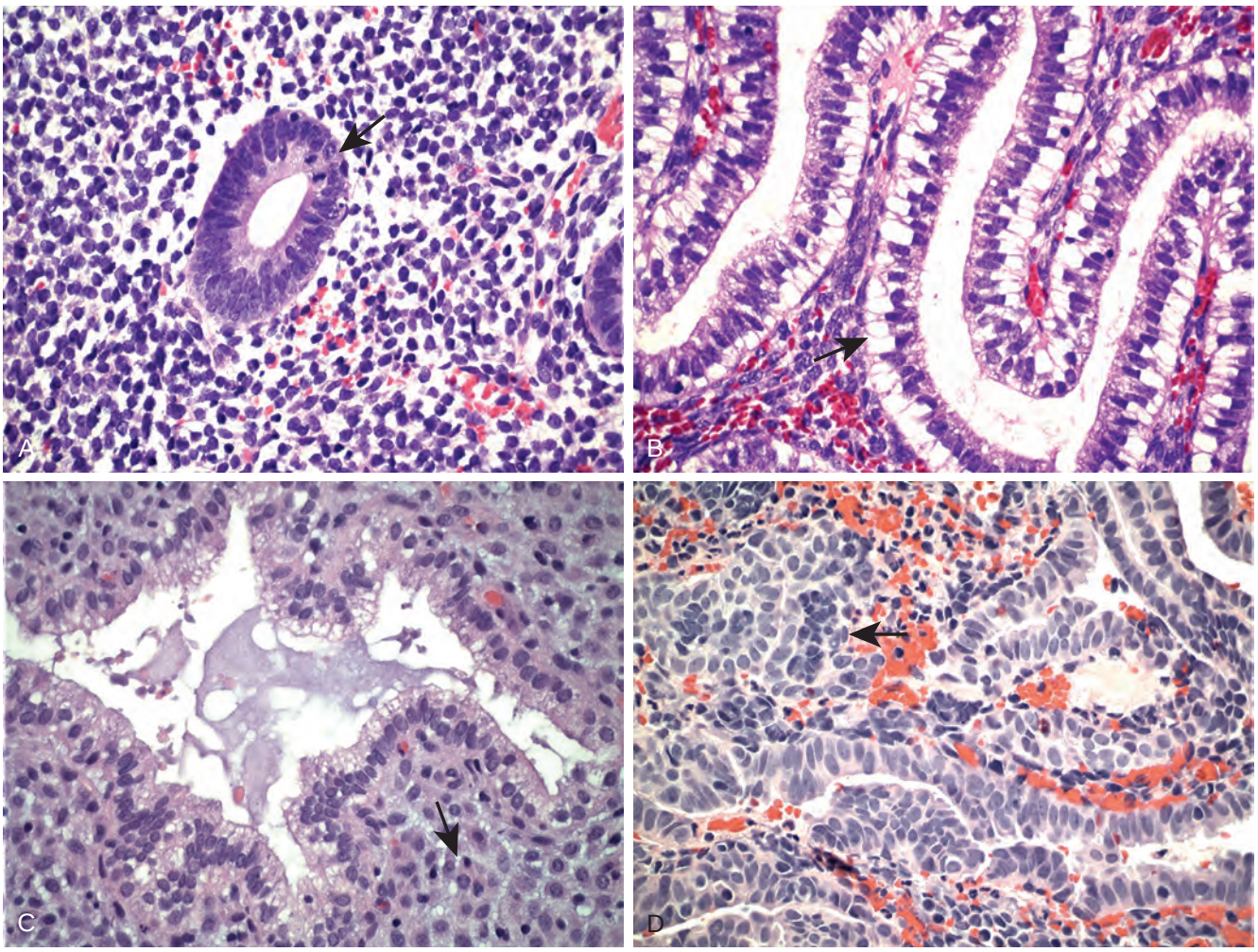

Figure 22-19 Histology of the menstrual cycle. **A,** Proliferative phase with mitoses *(arrow)*. **B,** Early secretory phase with subnuclear vacuoles *(arrow)*. **C,** Late secretory exhaustion and predecidual changes *(arrow)*. **D,** Menstrual endometrium with stromal breakdown *(arrow)* (see text).

the glands are tortuous, producing a serrated appearance. This serrated or "saw-toothed" appearance is accentuated by secretory exhaustion and shrinkage of the glands.

- *Stromal changes in the late secretory phase*, due predominantly to progesterone, are important for dating the endometrium. Prominent spiral arterioles appear by days 21 to 22 accompanied by an increase in ground substance and edema between the stromal cells. By days 23 to 24, stromal cell hypertrophy, increased cytoplasmic eosinophilia (*predecidual change*) and a resurgence of stromal mitoses appear (Fig. 22-19*C*). Predecidual changes spread throughout the functionalis during days 24 to 28 and are accompanied by a sparse infiltrate of neutrophils and lymphocytes, which in this context are considered normal.
- With the dissolution of the corpus luteum and the subsequent drop in progesterone levels, the functionalis degenerates and bleeding into the stroma occurs, followed by stromal breakdown and onset of the next menstrual cycle (Fig. 22-19*D*).

Much of the action of the ovarian hormones on the endometrium occurs through their cognate nuclear receptors and perhaps even by receptor-independent mechanisms. During the proliferative phase, estrogen drives the proliferation of both glands and stroma, sometimes by promoting "cross-talk" between these two cell types. For example, much of the effect of estrogen on glandular proliferation occurs via stromal cells, which in response to estrogen produce growth factors (e.g., insulin-like growth factor 1 and epidermal growth factor) that bind receptors expressed on the epithelial cells. During the secretory phase, progesterone down-regulates the expression of estrogen receptor in both the glands and the stroma, and as a result endometrial proliferation is suppressed. Progesterone also promotes the differentiation of the glands and causes functional changes in the stromal cells. Endometrial stem cells have been identified and there is recent data to suggest that they play a central role in the regeneration of the endometrium after menses. They may also contribute to the development of ectopic endometrial tissue and endometrial cancer.

Functional Endometrial Disorders (Dysfunctional Uterine Bleeding)

Although abnormal uterine bleeding can be caused by well-defined pathologic conditions, such as chronic endometritis, endometrial polyps (Fig. 22-20*C*), submucosal