17 Uterus

The endometrium is a cycling glandular and stromal layer overlying the myometrium of the uterus. The appearance varies widely across different phases of the menstrual cycle, pregnancy, and menopause. Common reasons for performing an endometrial biopsy include the following:

- Abnormal vaginal bleeding
- A "thickened endometrial stripe" found on ultrasound, suggesting hyperplasia or carcinoma
- Part of an infertility workup
- Follow-up study for women with a history of hyperplasia who have been conservatively treated with hormones

The reason for the biopsy will influence your approach to the slide. Regardless of history, start by differentiating between atrophic, inactive, proliferative, secretory, and hormone-treated endometrium. On low power, survey the epithelium to get a feel for the glands and stroma:

- *Atrophic* endometrium has a low gland-to-stroma ratio, and the glands are thin, with an almost cuboidal epithelium, and no mitoses. In biopsy specimens, they tend to come off in thin strips that look like hair pins (Figure 17.1).
- *Inactive to proliferative* endometrium has a fuller, blue look to the stroma and a gland-to-stroma ratio of about 1:1 in proliferative endometrium (less in inactive). The glands are simple tubular structures that stand out as dark blue "donuts" with pseudostratified nuclei (slight variation in nuclear location, but predominantly basal) and columnar epithelium (Figure 17.2). If mitoses are readily visible in the glands, the endometrium is proliferative. Absence of mitoses indicates an inactive endometrium.
- *Secretory* endometrium has prominent spiral arterioles and variably edematous stroma so that the stromal cells look almost like naked nuclei floating in water. The glands are notable for cytoplasmic secretory vacuoles and secretions in the lumen (Figure 17.3). Later secretory stroma begins to get decidualized, or acquires pink cytoplasm, and the glands lose their vacuoles and acquire low cuboidal pink cells, ragged luminal edges, and a tortuous spiral shape. You should not see mitoses in secretory glands.
- *Progestin-treated* endometrium, like gestational endometrium, has a very decidualized stroma (plump pink cells with visible cytoplasm), but is paired with attenuated, flattened gland epithelium (Figure 17.4). These changes are due to the unopposed progesterone exposure. Unopposed estrogen, on the other hand, has a proliferative effect, and increases the chance of hyperplasia or carcinoma. (Tamoxifen acts as an estrogen agonist in the endometrium.)

Why are the endometrial characteristics important? Secretory endometrium, almost by definition, is not hyperplastic. Once you have established secretory change, you (usually) do not need to agonize over crowded glands. Because progesterone pushes the endometrium toward secretory change, it is used as treatment for hyperplasia; if you can prod the endometrium to complete the cycle and shed, the hyperplasia may go away.

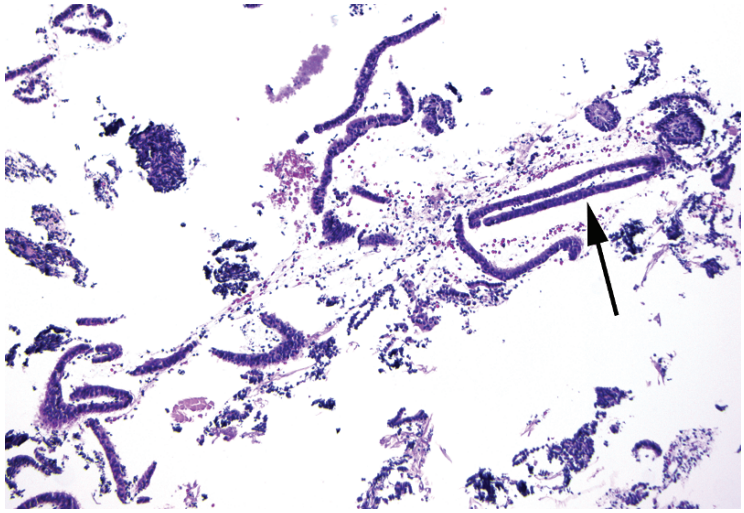

Figure 17.1. Atrophic endometrium. When curetted, the epithelium typically comes off in thin strips resembling hairpins (arrow). The specimen is also scant.

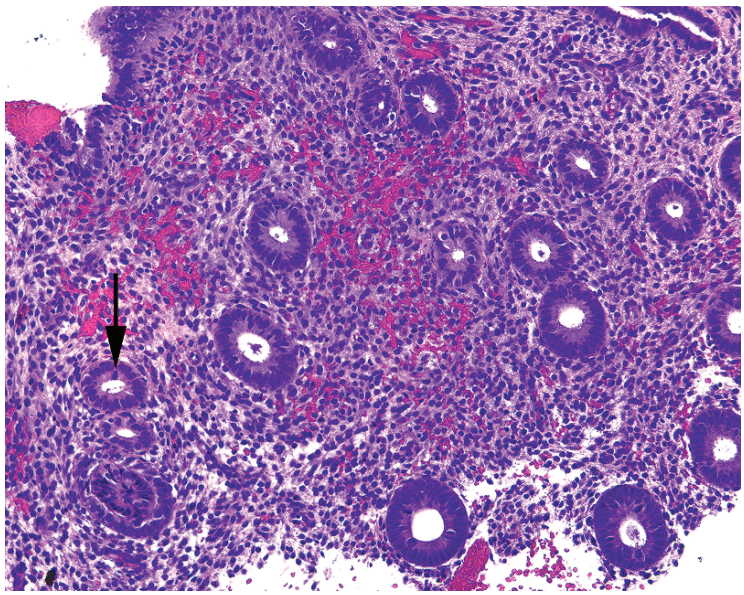

Figure 17.2. Proliferative endometrium. Multiple donut-shaped glands are visible, with dark oblong nuclei and frequent mitoses (arrow).

Next, within the biopsy fragments, look for possible causes of bleeding:

- *Benign endometrial polyp*: Benign endometrial polyps are composed of fibrotic (pink and spindly) stroma, thick-walled vessels, and usually nonfunctional (atrophic) and/or cystically dilated glands (Figure 17.5).
- *Endometrial stromal breakdown*: The stroma takes on a blurry blue look as it condenses into small dense aggregates ("blue balls"). The associated surface epithelium shows eosinophilic metaplasia, becoming almost oncocytic in appearance. Fibrin thrombi in vessels and neutrophils are also common features (Figure 17.6). The background endometrium may be end secretory (in normal menstrual bleeding) or proliferative (in dysfunctional bleeding).

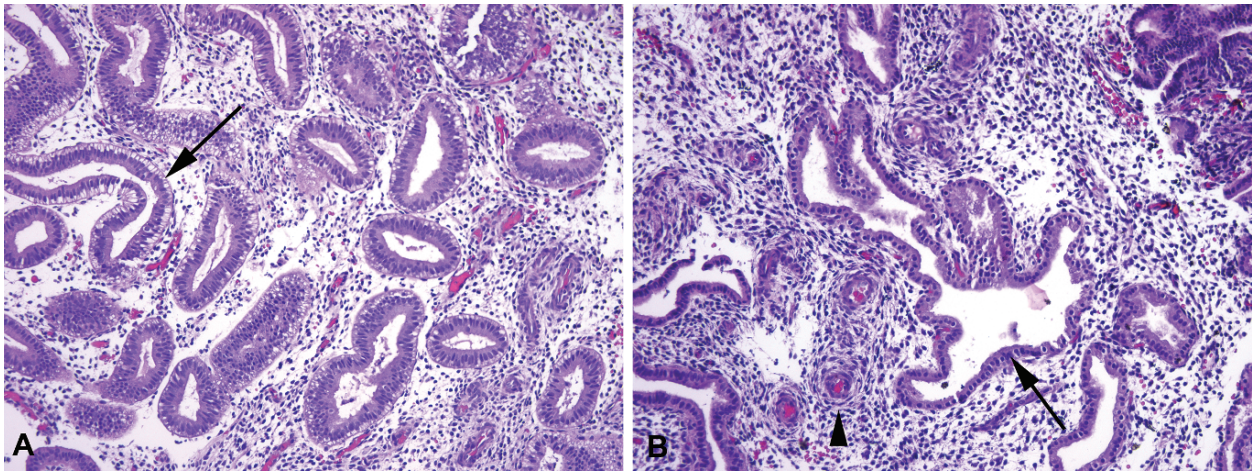

FIGURE 17.3. Secretory endometrium, various phases. **(A)** In early secretory endometrium, the glands have become tortuous in shape, and prominent cytoplasmic vacuoles are present (subnuclear, in this example; arrow). **(B)** Later in the secretory phase, the cytoplasmic vacuoles are gone, and the epithelium is more cuboidal in shape, with small round nuclei (arrow). The stroma is edematous, and early decidualization (accumulation of pink cytoplasm) is beginning around the spiral arteries (arrowhead).

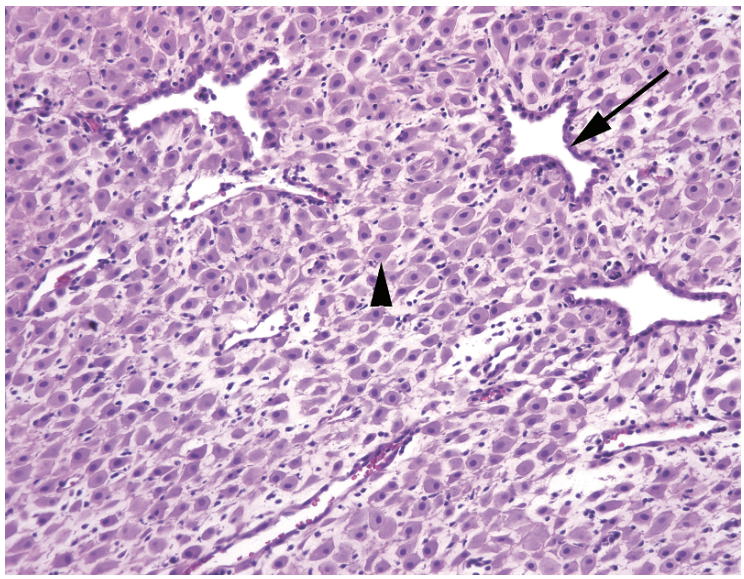

FIGURE 17.4. Progestin-treated endometrium. The glands are still tortuous in shape, like secretory endometrium, but the epithelium is markedly thinned (arrow). The stromal cells are decidualized (arrowhead), which means they have plump pink cytoplasm and distinct cell borders.

- Endometritis: The diagnosis of *acute endometritis* requires microabscesses and epithelial destruction; the presence of neutrophils alone may just indicate menstrual breakdown. *Chronic endometritis* is diagnosed by the presence of plasma cells. In general, the stroma takes on a blue spindly look, and there are increased numbers of lymphocytes; these features should prompt you to crawl around at 20× looking for plasma cells (Figure 17.7).
- *Disordered proliferative endometrium*: Disordered proliferative endometrium is notable for a mixture of cystically dilated, budding, and tubular glands in a proliferative setting, with only focal glandular crowding. It occurs during anovulatory cycles.
- *Atrophy*: Atrophy, described earlier, is responsible for about half of all cases of abnormal postmenopausal bleeding.

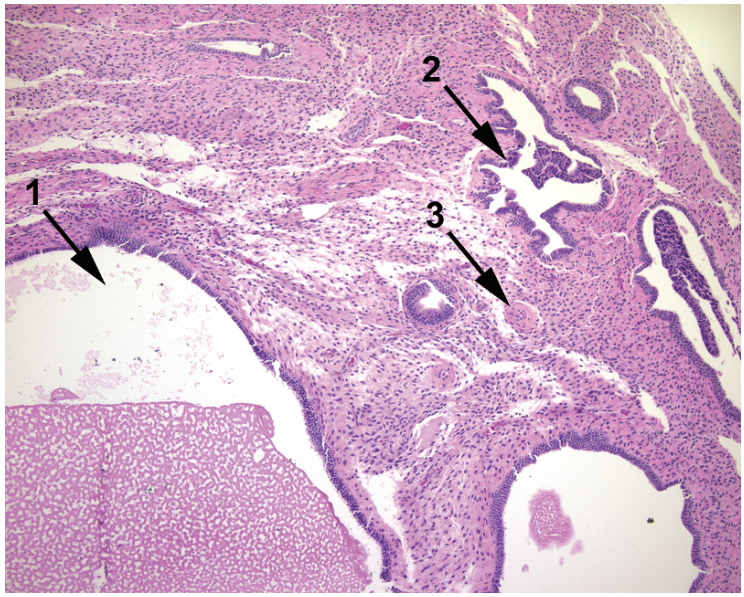

Figure 17.5. Benign endometrial polyp. This polyp shows cystic dilation of glands (1), secretory-type epithelium (2), and thickened arteries (3). The stroma is also pink, indicating a high collagen content.

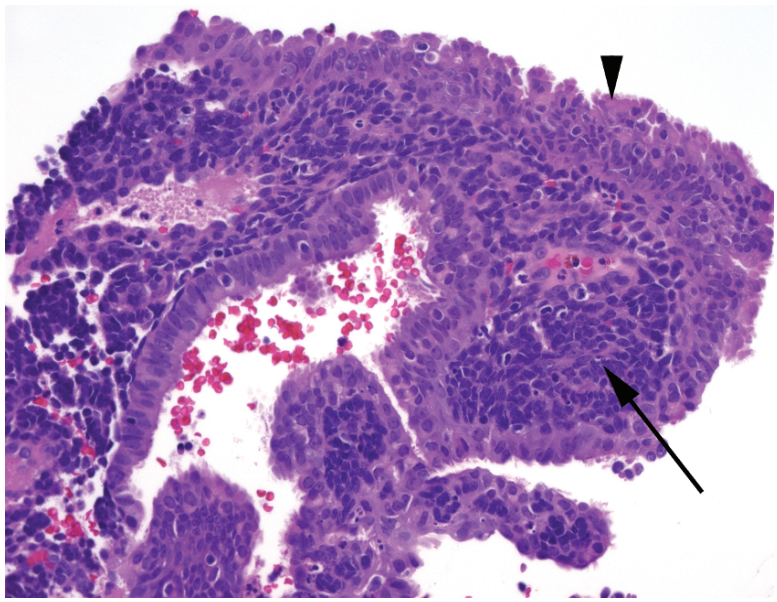

Figure 17.6. Endometrial stromal breakdown. The stroma is condensed into an extremely blue mass of tightly packed cells (arrow). The overlying epithelium is expanded into papillary tufts of pink cells, some with cilia, which is a metaplastic change (arrowhead).

Hyperplasia

Hyperplasia is defined as an increase in the gland-to-stroma ratio, and you will notice it as "crowded glands" in a proliferative setting. Endometrial hyperplasia is categorized with two criteria: architecture (simple vs. complex) and cytology (with or without atypia). The term *dysplasia* is not applied to endometrium. There are varying degrees of hyperplasia:

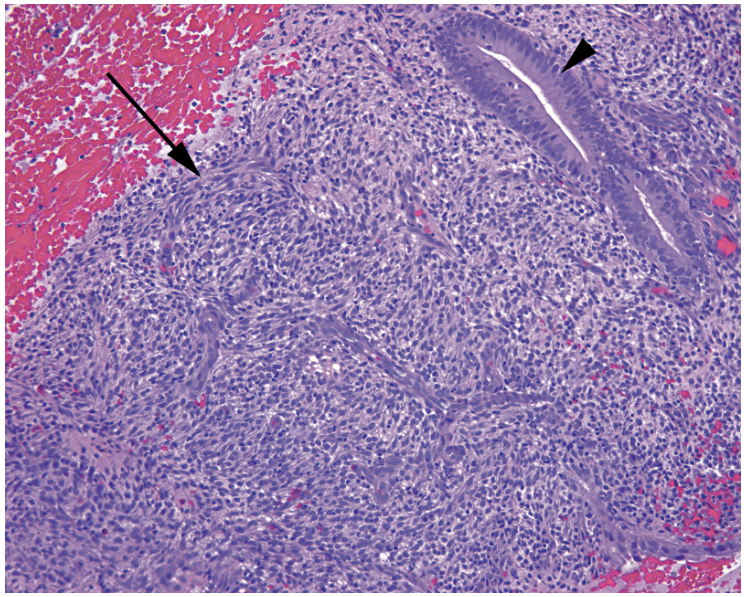

FIGURE 17.7. Chronic endometritis. At low power, the diagnostic plasma cells are not visible, but the spindly, swirling blue stroma (arrow) should be a clue to look more closely. The epithelium here is proliferative (arrowhead).

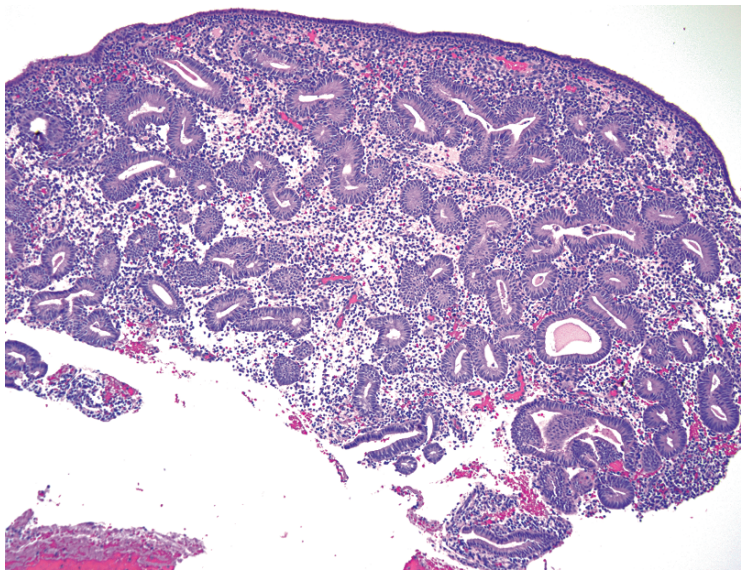

FIGURE 17.8. Simple hyperplasia. In this biopsy specimen, the glands appear proliferative and are too crowded (the gland-to-stroma ratio is greater than 1). The cells resemble normal endometrium and are not atypical.

- Simple hyperplasia: Simple hyperplasia almost always occurs without atypia. It appears as crowded, tubular, or minimally branched glands (Figure 17.8).
- Complex hyperplasia: Complex hyperplasia can occur with or without atypia. It appears as back-to-back glands with little stroma (even more crowded than in simple hyperplasia), and the glands have increasingly complex, branched outlines.
- Atypical hyperplasia: The definition of atypia varies among organs. In the endometrium, the *normal* proliferating gland has hyperchromatic, pseudostratified, elongated nuclei and

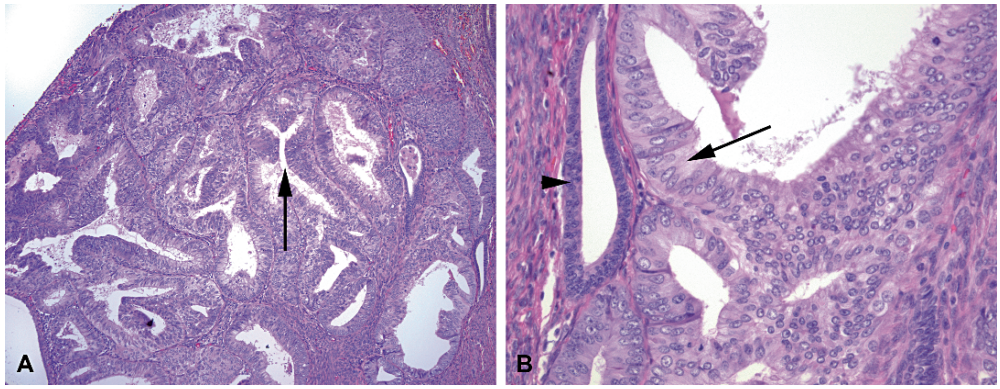

Figure 17.9. Complex atypical hyperplasia. **(A)** At low power, the glands are very crowded, even back to back, and the gland lumens have become branching and irregular (arrow). **(B)** At high power, comparing the hyperplastic epithelium (arrow) with normal residual glands (arrowhead), the hyperplastic cells have round nuclei, and pale, vesicular chromatin with prominent nucleoli, diagnostic of atypia.

frequent mitoses. This appearance in other organs, such as the colon, may make you think of low-grade dysplasia (such as a tubular adenoma). In endometrial *atypia*, the nuclei become round and pale or vesicular because of the chromatin clumping up and migrating to the nuclear membrane (Figure 17.9). Nucleoli may be prominent. The nuclei lose polarity and are seen at all levels of the epithelium (stratified). Nuclei are larger and show increased variability in size and shape. The cytoplasm becomes more eosinophilic than in nonatypical glands. Atypia is present or absent but is not graded.

- Complex atypical hyperplasia: Complex atypical hyperplasia (CAH) is a precursor to carcinoma. Florid cases of CAH may in fact be hard to distinguish from well-differentiated endometrial carcinoma—so much so that experts may disagree. The concept of "carcinoma in situ" is not used in the endometrium, but CAH is fairly equivalent to it.

Do not be fooled by artifactual crowding in a biopsy. When glands are scraped out of the uterine cavity, they may clump together and look crowded. You need to find an intact piece of endometrium to evaluate the gland to stroma ratio. Also, beware of calling hyperplasia in the setting of an endometrial polyp (they are often crowded) or secretory endometrium.

The Infertility Workup

When evaluating an endometrial biopsy specimen for infertility, first rule out the conditions listed earlier that can cause bleeding. Some infertility centers request that you date the endometrium, estimating the cycle day by histology. They are looking for a luteal phase defect, which is defined as a disparity of over 3 days between the calendar date and the histologic date in two consecutive biopsy specimens.

Proliferative endometrium cannot be dated. The first secretory change occurs, on average, on day 16 or so of a 28-day cycle. This change is the appearance of clear secretory vacuoles at the base of the epithelial cells, below the nuclei. When you see just a few of these in a generally proliferative endometrium, it is called *interval endometrium*. Beyond that day, specific histologic criteria are as follows:

Days 16 to 20: glands are the most helpful feature
- Day 16: subnuclear vacuoles, pseudostratified nuclei
- Day 17: subnuclear vacuoles, but with an orderly row of nuclei (the "piano key" look)
- Day 18: vacuoles above and below nuclei
- Day 19: few vacuoles, found only above nuclei; orderly row of nuclei, no mitoses
- Day 20: peak secretions in lumen and ragged luminal border, vacuoles rare

From days 21 to 28, the glands change little. They are exhausted and appear low columnar with orderly nuclei, no mitoses, and ragged luminal edges. They may also have degenerative apical vacuoles—tricky to discern from days 19 to 20. After day 21, the stroma is the key:

Day 21: beginning of stromal edema; secretion continues
Day 22: peak stromal edema with naked nuclei
Day 23: spiral arteries become prominent
Day 24: periarteriolar cuffing with predecidua (stromal cells around the arteries begin to get plump pink cytoplasm, creating a pink halo around the vessels)
Day 25: predecidual change under the surface epithelium
Day 26: decidual islands coalesce, lymphocytes begin to infiltrate stroma
Day 27: many neutrophils in a solid sheet of decidua, with focal necrosis and hemorrhage
Day 28: prominent necrosis, hemorrhage, clumping, and break up

Changes of Pregnancy

Gestational endometrium is a solid sheet of decidua. Decidual cells are plump polygonal cells with pink to lavender cytoplasm and small oval nuclei. The glandular epithelium becomes almost papillary in nature with a hypersecretory appearance.

Well-formed glands with ballooning, cleared-out cytoplasm and wildly pleomorphic nuclei are characteristic of the Arias-Stella reaction, a normal reaction to pregnancy (Figure 17.10). The changes can be focal. The lack of mitoses or infiltration differentiates this from clear cell carcinoma, as does the age of the patient (clear cell is usually postmenopausal) and the surrounding gestational changes.

In a patient with a history of pregnancy, you may see a placental site nodule: aggregates of intermediate trophoblastic cells, which have scattered large nuclei that look atypical, within hyaline nodules. Placental site nodules should be well-circumscribed. They are the benign remnants of old implantation sites (see Figure 16.8 in Chapter 16).

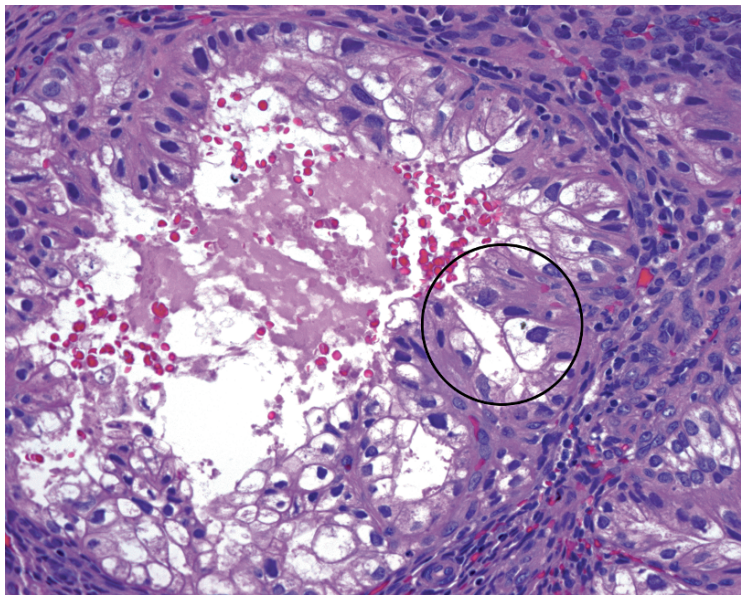

Figure 17.10. Arias-Stella reaction. Glands in the gestational endometrium can show bizarre cytology, including cleared-out cytoplasm and large hyperchromatic irregular nuclei (circle).

Types of Metaplasia

Metaplasia by itself is a benign process; however, metaplasia is often accompanied by hyperplasia. Still, it is important to recognize these cell varieties and not call them cancer. The less ominous sounding word *change* may be used instead of *metaplasia*. Cell types include the following:

- Tubal metaplasia: luminal cilia in an epithelium that looks slightly plumped up and cleared out (If you overlook the cilia, the nuclei may appear atypical.)
- Squamous metaplasia: swirling islands of immature squamous cells and, rarely, keratinization
- Mucinous metaplasia: mucinous, endocervical-type cells
- Eosinophilic metaplasia: increased eosinophilic cytoplasm; cells can proliferate in glands to the point of looking papillary (If the cells merge to form syncytial papillary tufts, it is papillary syncytial metaplasia.)
- Clear cell change: clear cells

Endometrial Malignancies

The endometrium has two cell types that can transform: glandular and stromal. Glandular cells give rise to several types of carcinoma, including endometrioid, serous, and clear cell. The stromal cells give rise to stromal sarcomas; these are entirely different from the leiomyosarcomas of the myometrium.

Endometrioid carcinoma is the most common type of endometrial cancer. It usually occurs in postmenopausal women (80% of cases), like its precursor lesion, complex atypical hyperplasia. Be cautious about diagnosing either type in a young woman, although it can happen.

Endometrioid carcinoma, in its well-differentiated form, closely resembles atypical endometrial glands. Architecturally, they are fused and complex and cover large areas without intervening stroma (Figure 17.11). The overall pattern may appear cribriform or villoglandular (like a villous adenoma of colon). The tumor may be limited to endometrium or may

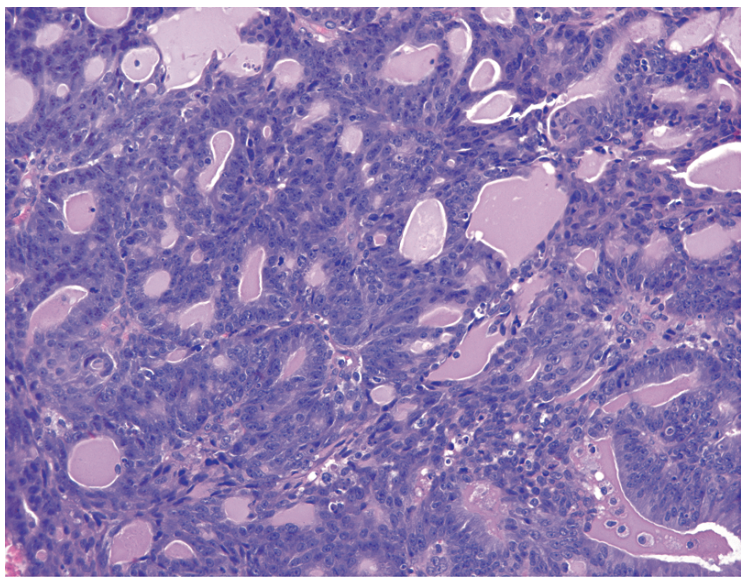

Figure 17.11. Endometrioid carcinoma. Foci of well-differentiated endometrioid carcinoma can be difficult to distinguish from complex atypical hyperplasia. However, the complicated proliferation of fused and cribriform glands in this biopsy specimen is diagnostic of carcinoma. The nuclei in this example resemble those of complex atypical hyperplasia.

invade myometrium or adjacent organs; the extent determines *stage*. The *grade* is determined by cytology and architecture. High grade tumors are equivalent to "poorly differentiated."

FIGO (International Federation of Gynecology and Obstetrics) grade 1: The tumor is <5% solid, where *solid* means sheets of cells that have lost their glandular differentiation. Areas of squamous metaplasia (common) are not counted as solid areas.
FIGO grade 2: The tumor is 6%–50% solid.
FIGO grade 3: The tumor is >50% solid.

Significant nuclear atypia (one of those features that require experience to judge) can raise the grade by one level unless the tumor is already grade 3. Variants of endometrioid carcinoma include those with squamous differentiation, a villoglandular variant, a secretory variant, and a ciliated cell variant. These variants are identified only when the majority of the tumor takes on that morphology.

Serous carcinoma is a separate tumor pathway, leading to a distinct type of carcinoma. Serous carcinoma is not associated with hormonal exposure or endometrial hyperplasia. It is considerably more aggressive than endometrioid carcinoma and tends to be diagnosed in older women. It is, by definition, high grade and therefore is not graded.

Histologically, it resembles serous carcinoma of the ovaries (formerly known as *papillary serous*). Therefore, its hallmark is a papillary architecture, although this is not required for diagnosis. The papillae have broad or fine fibrovascular cores with complex branching (Figure 17.12). The cells are notable for extreme atypia, including cherry-red nucleoli, bizarre mitoses, and multinucleated cells. As in the ovary, psammoma bodies are common.

The precursor lesion is believed to be *endometrial intraepithelial carcinoma* (EIC), a transformation of the surface epithelium, especially in polyps in older women. EIC is not quite analogous to carcinoma in situ, because EIC itself has metastatic potential. EIC, like serous carcinoma, is often associated with a *p53* mutation leading to overexpression. An immunostain for *p53* is sometimes used to confirm the diagnosis. Histologically, EIC appears as an abrupt transition on the surface from benign atrophic epithelium to pleomorphic, enlarged, atypical, mitotically active cells (Figure 17.13).

Clear cell carcinoma, like serous carcinoma, occurs primarily in older women, has no relation to hormone exposure or hyperplasia, and has a poor prognosis. Histologically, it will

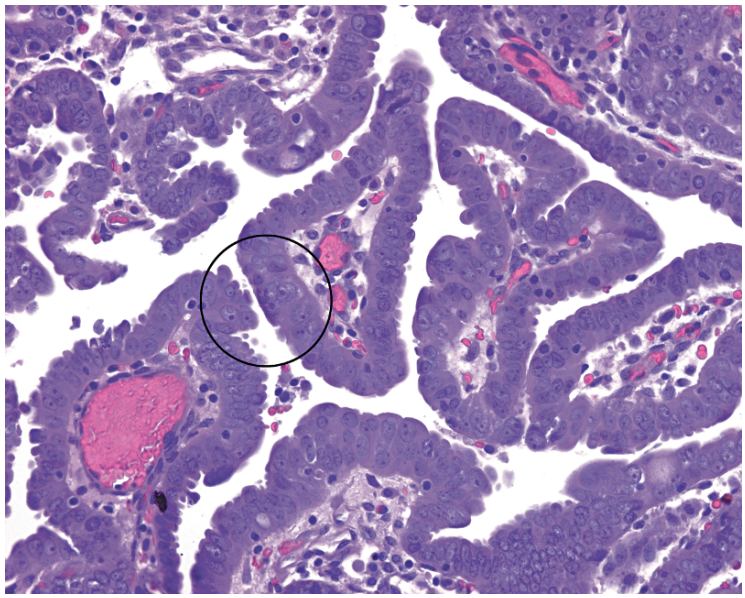

Figure 17.12. Serous carcinoma. Papillary structures are lined by atypical nuclei with prominent nucleoli (circle).

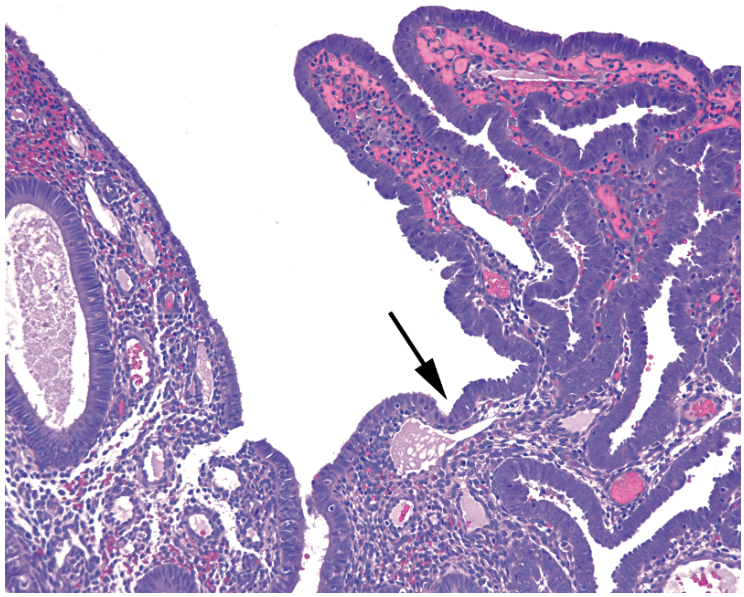

Figure 17.13. Endometrial intraepithelial carcinoma. There is an abrupt transition (arrow) from normal surface epithelium (left) to malignant cells (right). The cells of endometrial intraepithelial carcinoma resemble those of serous carcinoma.

remind you of clear cell neoplasms in other organs (such as renal cell). The cytoplasm is glycogen-rich and clear, the cell borders are distinct, and the architecture can be tubular, papillary, or solid. It may be mistaken for secretory endometrioid carcinoma but has much more nuclear pleomorphism. Like serous carcinoma, this tumor is high-grade by definition. Other rare types of carcinoma include squamous, mucinous, transitional cell, undifferentiated, and small cell carcinoma.

Endometrial stromal sarcoma is a rare malignancy of the endometrial stromal cells. The difference between a benign stromal nodule and a low-grade endometrial stromal sarcoma is in the interface with the surrounding tissue—sarcomas are infiltrative. These sarcomas have minimal atypia and few mitoses, as well as a prominent plexiform vascular proliferation (like the normal spiral arteries gone wild). The high-grade endometrial stromal sarcoma, however, has marked atypia and bizarre mitoses, like most high-grade sarcomas.

Malignant mullerian mixed tumor (carcinosarcoma) is a mixed tumor consisting of malignant glands in a sarcomatous stroma. It appears as a recognizable carcinoma, such as endometrioid type, with adjacent sarcomatous cells (large angular pleomorphic nuclei) in the stroma (Figure 17.14). Other soft tissue elements, like skeletal muscle or cartilage, may also show up. It is similar in concept to a carcinosarcoma of other organs.

In contrast, an *adenosarcoma* is a neoplasm with benign glands and a malignant stroma. An *adenofibroma* is benign glands with benign stroma. These tumors are similar to the phyllodes tumor of the breast, which can range from malignant to benign stroma.

Myometrium

The most common neoplasm of the uterus is actually the leiomyoma, a benign smooth muscle tumor of the myometrium. These tumors can be huge, multiple, myxoid, even necrotic, and still benign. Although benign, many are removed for symptomatic relief. When sampling these at the grossing bench, what you are looking for are areas that are different in texture from the typical rubbery dense consistency; areas of necrosis, hemorrhage, or dense white foci should be sampled.

The classic *leiomyoma* is a spindle cell lesion with intersecting fascicles of elongated cells, typically intersecting at right angles (Figure 17.15). The nuclei are long and thin with fine pale

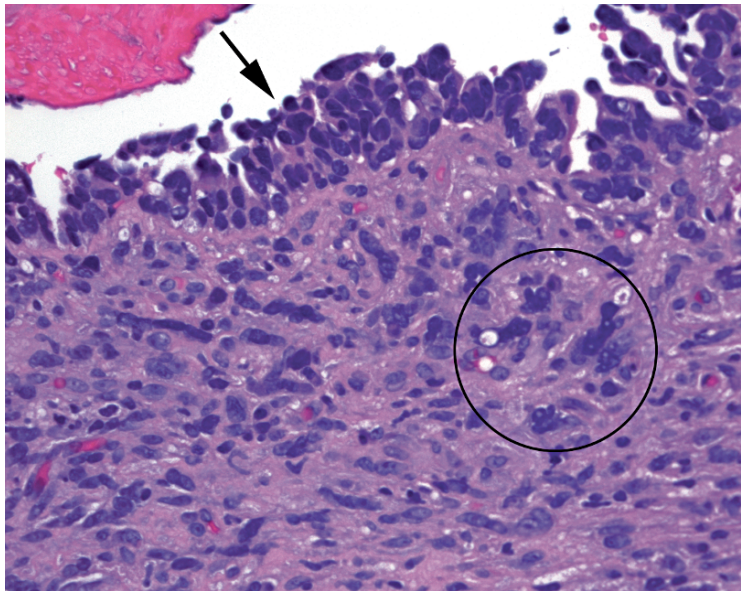

Figure 17.14. Malignant mullerian mixed tumor. This tumor is defined by the presence of carcinomatous cells in the epithelium (arrow) and sarcomatous cells in the stroma (circle). The carcinomatous cells are hyperchromatic and crowded; elsewhere in this biopsy specimen there were malignant glands. The sarcomatous cells are hyperchromatic, large, and irregular in shape, similar to malignant fibrous histiocytoma–type cells found in other sarcomas (see Chapter 28).

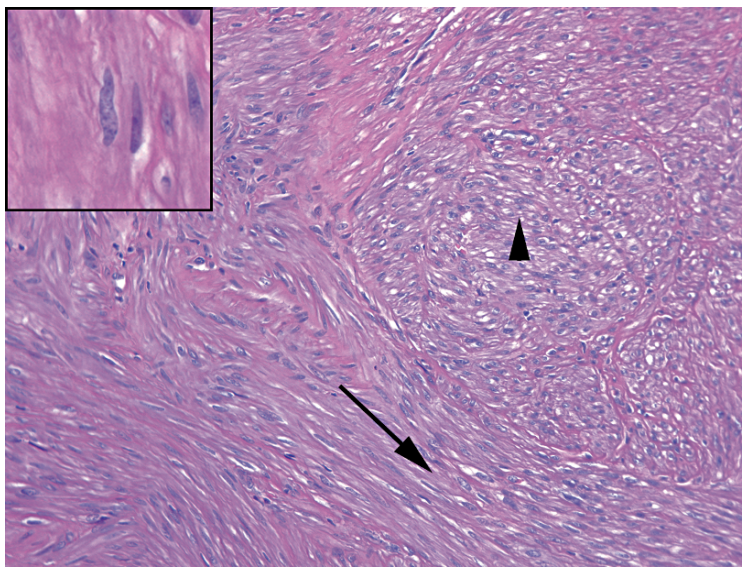

Figure 17.15. Leiomyoma. The low-power impression is that of fascicles or bundles of cells, some parallel to the slide (arrow) and some coming out at right angles (arrowhead). **Inset**: The nuclei are tapered and pale, with occasional paranuclear vacuoles, and sometimes show "corkscrew" morphology, as though the nucleus was twisted longitudinally. (Dog owners may liken this lumpy shape to something else.)

chromatin and small nucleoli. You may also see "corkscrew" nuclei, which are characteristic of smooth muscle. The stroma may be fibrotic, edematous, myxoid, or even hemorrhagic; these are all permissible degenerative changes in the absence of nuclear atypia or a high mitotic rate.

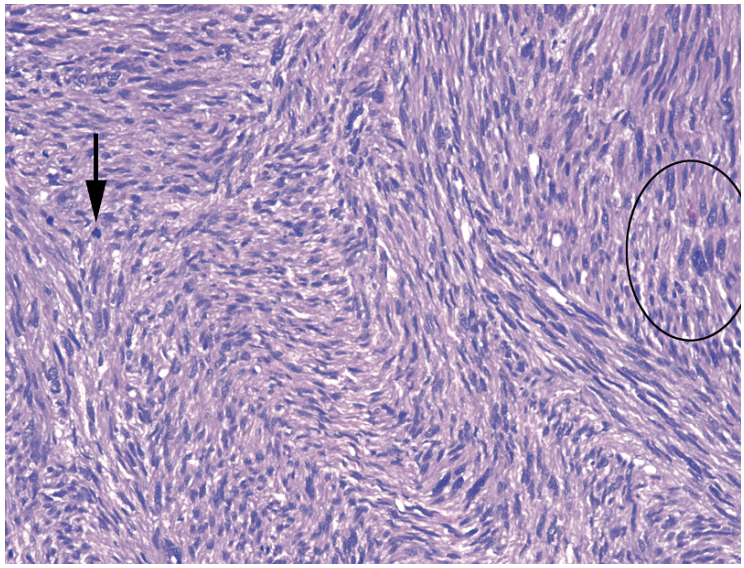

Figure 17.16. Leiomyosarcoma. The threshold for diagnosing leiomyosarcoma in the uterus is high. This lesion should be a much more cellular version of the leiomyoma, with mitoses (arrow), atypical and pleomorphic cells (circle), and necrosis (not seen here).

Leiomyosarcoma tends to present as a large, solitary mass and is not thought to arise from preexisting leiomyomas. It may resemble the fascicular leiomyoma, but mitotic activity must be high, over 10 per 10 high-power fields, and cytologic atypia should be prominent (Figure 17.16). (In sarcomas, atypia takes the form of large dark nuclei with crisp, irregularly shaped nuclear borders.) The third feature is coagulative necrosis. The threshold for diagnosing leiomyosarcoma is quite high in the uterus, unlike a leiomyomatous lesion found in the soft tissue or retroperitoneum, for example. In the uterus, atypia without mitotic activity, or mitoses without atypia, should discourage you from calling a sarcoma.

Adenomatoid tumor is a benign proliferation of mesothelial origin. It often occurs on the serosal surface of the uterus, resembling a leiomyoma both grossly and microscopically. The mesothelial tumor cells induce a smooth muscle proliferation that is probably often mistaken for leiomyoma. However, on close inspection, you will see small clefted spaces between the muscle bundles, lined by cuboidal cells forming gland-like or angiomatoid lumens. The cells can appear epithelial by histology and in fact would stain for cytokeratins. Accidentally missing it and calling it a leiomyoma does no harm to the patient; mistaking it for metastatic adenocarcinoma would be disastrous, however. Unlike adenocarcinoma, it should stain for calretinin.