karyotypes, but approximately 40% have a simple chromosomal abnormality. Several cytogenetic subgroups are recognized, including tumors with rearrangements of chromosomes 12q14 and 6p involving the *HMGIC* and *HMGIY* genes, respectively, which are also implicated in a variety of other benign neoplasms. Both genes encode closely related DNA-binding factors that regulate chromatin structure. Recently, mutations in the *MED12* gene have been identified in up to 70% of uterine leiomyomas. The *MED12* gene encodes a component of Mediator, a multiprotein complex that stimulates gene expression by serving as a bridge between long-range DNA regulatory elements (so-called enhancers) and gene promoters. The effect of *MED12* mutations on gene expression in leiomyomas is an area of active investigation.

MORPHOLOGY

Leiomyomas are sharply circumscribed, discrete, round, firm, gray-white tumors varying in size from small, barely visible nodules to massive tumors that fill the pelvis. Except in rare instances, they are found within the myometrium of the corpus. Only infrequently do they involve the uterine ligaments, lower uterine segment, or cervix. They can occur within the myometrium (intramural), just beneath the endometrium (submucosal) or beneath the serosa (subserosal) (Fig. 22-28*A*).

Whatever their size, the characteristic whorled pattern of smooth muscle bundles on cut section usually makes these lesions readily identifiable. Large tumors may develop areas of yellow-brown to red softening.

Leiomyomas are typically composed of bundles of smooth muscle cells that resemble the uninvolved myometrium (Fig. 22-28*B*). Usually, the individual muscle cells are uniform in size and shape and have the characteristic oval nucleus and long, slender bipolar cytoplasmic processes. Mitotic figures are scarce. Benign variants of leiomyoma include atypical or bizarre (symplastic) tumors with nuclear atypia and giant cells, and cellular leiomyomas. Both have a low mitotic index, helping to distinguish these benign tumors from leiomyosarcomas. An extremely rare variant, **benign metastasizing leiomyoma**, is a uterine leiomyoma that extends into vessels and spreads hematogenously to other sites, most commonly the lung. Another variant, **disseminated peritoneal leiomyomatosis**, presents as multiple small peritoneal nodules. Both are considered benign despite their unusual behavior.

Leiomyomas of the uterus, even when large or numerous, may be asymptomatic. Common signs and symptoms include abnormal bleeding, urinary frequency due to compression of the bladder, sudden pain from infarction of a large or pedunculated tumor, and impaired fertility. Myomas in pregnant women increase the frequency of spontaneous abortion, fetal malpresentation, uterine inertia (failure to contract with sufficient force), and postpartum hemorrhage. Malignant transformation to leiomyosarcoma, if it occurs at all, is extremely rare.

Leiomyosarcomas

These uncommon malignant neoplasms are thought to arise from the myometrium or endometrial stromal precursor cells, rather than leiomyomas. In contrast to leiomyomas, leiomyosarcomas have complex, highly variable karyotypes that frequently include deletions. Like leiomyomas, a subset contains *MED12* mutations, a genetic aberration that appears to be virtually unique to uterine smooth muscle tumors.

MORPHOLOGY

Leiomyosarcomas grow within the uterus in two somewhat distinctive patterns: (1) bulky, fleshy masses that invade the uterine wall or (2) polypoid masses that project into the uterine lumen (Fig. 22-29*A*). They exhibit a wide range of cytologic atypia, from extremely well differentiated to highly anaplastic (Fig. 22-29*B*). The distinction from leiomyoma is based on nuclear atypia, mitotic index, and zonal necrosis. With few

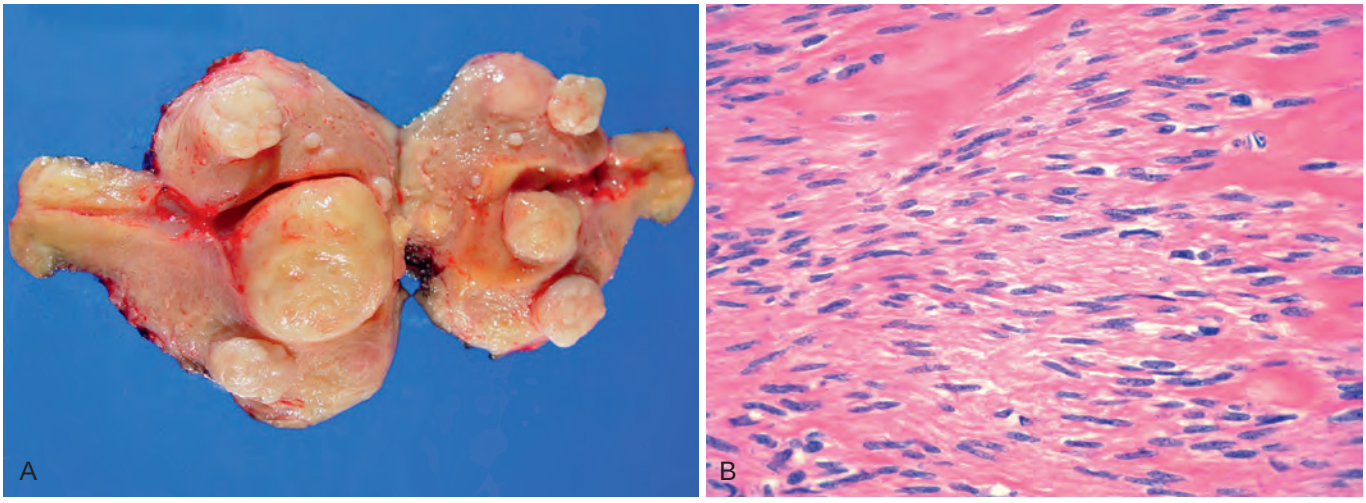

Figure 22-28 Leiomyomas of the uterine myometrium **A,** The uterus is opened to reveal multiple tumors in submucosal (bulging into the endometrial cavity), intramural, and subserosal locations that display a firm white appearance on sectioning. **B,** Leiomyoma showing well-differentiated, regular, spindle-shaped smooth muscle cells associated with hyalinization.