(Chapter 7). The cancers appear 15 to 40 years after the first exposure.

- ***Schistosoma haematobium*** infections in endemic areas (Egypt, Sudan) are an established risk. The ova are deposited in the bladder wall and incite a brisk chronic inflammatory response that induces progressive mucosal squamous metaplasia and dysplasia and, in some instances, neoplasia. Seventy percent of the cancers are squamous, the remainder being urothelial or, least commonly, glandular.
- **Long-term use of analgesics** is implicated, as it is in analgesic nephropathy (Chapter 20).
- **Heavy long-term exposure to cyclophosphamide**, an immunosuppressive agent, induces, as noted, hemorrhagic cystitis, and increases the risk of bladder cancer.
- **Irradiation**, often administered for other pelvic malignancies, increases the risk of urothelial carcinoma. In this setting, bladder cancer occurs many years after the irradiation.

Several acquired genetic alterations have been observed in urothelial carcinoma, many of which lead to constitutive activation of growth factor receptor signaling cascades (Chapter 7). Some of these alterations are strongly associated with tumor histopathology. These include gain-of-function mutations in *FGFR3*, which are found predominantly in noninvasive low-grade papillary carcinomas and result in constitutive activation of the FGFR3 receptor tyrosine kinase. In contrast, loss-of-function mutations in the *TP53* and *RB* tumor suppressor genes are almost always seen in high-grade and, frequently, muscle invasive tumors. Other genetic alterations are not as tightly associated with tumor histologic features. Activating mutations in the *HRAS* oncogene are freqeuntly found, particularly in low-grade, noninvasive tumors. Recalling that RAS signal transducers act downstream of receptor tyrosine kinases such as FGFR3, it is not surprising that *HRAS* and *FGFR3* mutations are generally mutually exclusive in bladder cancer.

Particularly common (occurring in 30% to 60% of tumors) are losses of genetic material on chromosome 9 (including monosomy or deletions of 9p and 9q). These abnormalities are often the only chromosomal changes present in superficial noninvasive papillary tumors and occasionally in noninvasive flat tumors, suggesting that these are early events in the evolution of bladder carcinomas. The 9p deletions (9p20) span a region that includes the tumor suppressor gene *CDKN2A,* which encodes the cyclin-dependent kinase inhibitor p16/INK4a and ARF, a protein that augments p53 function (Chapter 7). Several different tumor suppressor genes have been proposed to be the target of deletions on chromosome 9q, including *PTCH*, which encodes a negative regulator of the Hedgehog signaling pathway, and *TSC1*, which encodes a negative regulator of mTOR signaling. On the basis of these findings, a model for bladder carcinogenesis has been proposed. In this two-pathway model, low-grade superficial papillary tumors are characterized by *FGFR3* and *RAS* mutations and chromosome 9 deletions. Of these, a minority may then lose *TP53* and/or *RB* function and progress to invasion. In the second more aggressive pathway, noninvasive high-grade flat or papillary lesions are initiated by *TP53* mutations and, with loss of chromosome 9 and acquisition of other, still to be characterized mutations, progression to invasion ensues (Chapter 7).

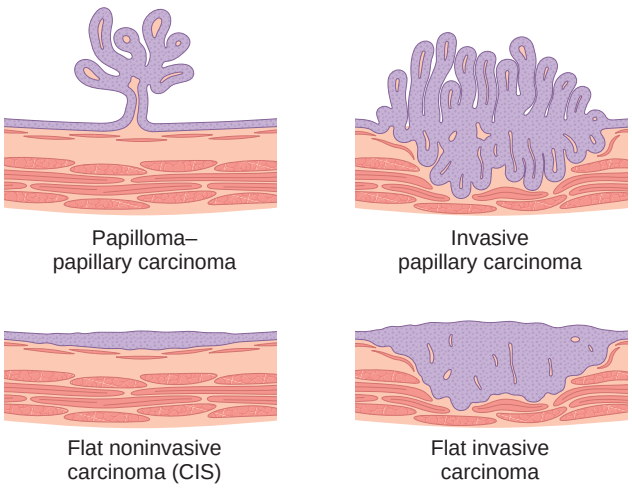

Figure 21-6 Four morphologic patterns of bladder tumors. CIS, Carcinoma in situ.

MORPHOLOGY

The appearance of urothelial tumors varies from purely papillary to nodular or flat (Fig. 21-6). Most arise from the lateral or posterior walls at the bladder base. Papillary lesions are red, elevated excrescences ranging in size from less than 1 cm in diameter to large masses up to 5 cm in diameter (Fig. 21-7). Multiple discrete tumors are often present. As noted, the histologic features encompass a spectrum from benign papilloma to highly aggressive anaplastic cancers. Overall, the majority of papillary tumors are low grade.

- **Papillomas** represent 1% or less of bladder tumors, and are usually seen in younger patients. These tumors typically arise singly as small (0.5 to 2 cm), delicate, structures, superficially

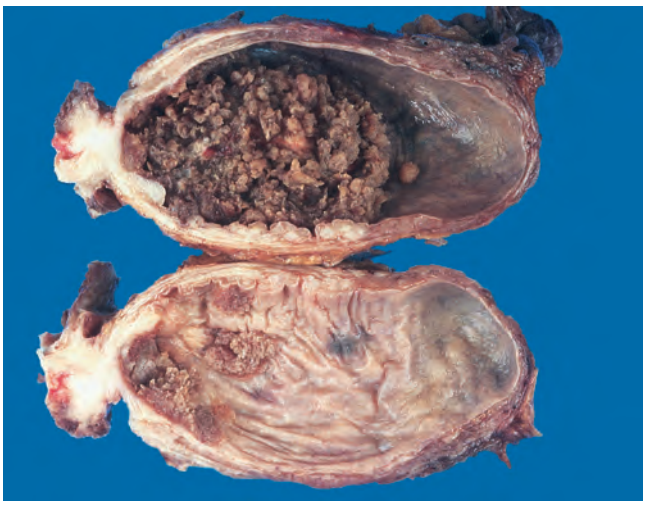

Figure 21-7 Cross-section of bladder with upper section showing a large papillary tumor. The lower section demonstrates multifocal smaller papillary neoplasms. (Courtesy Dr. Fred Gilkey, Sinai Hospital, Baltimore, Md.)