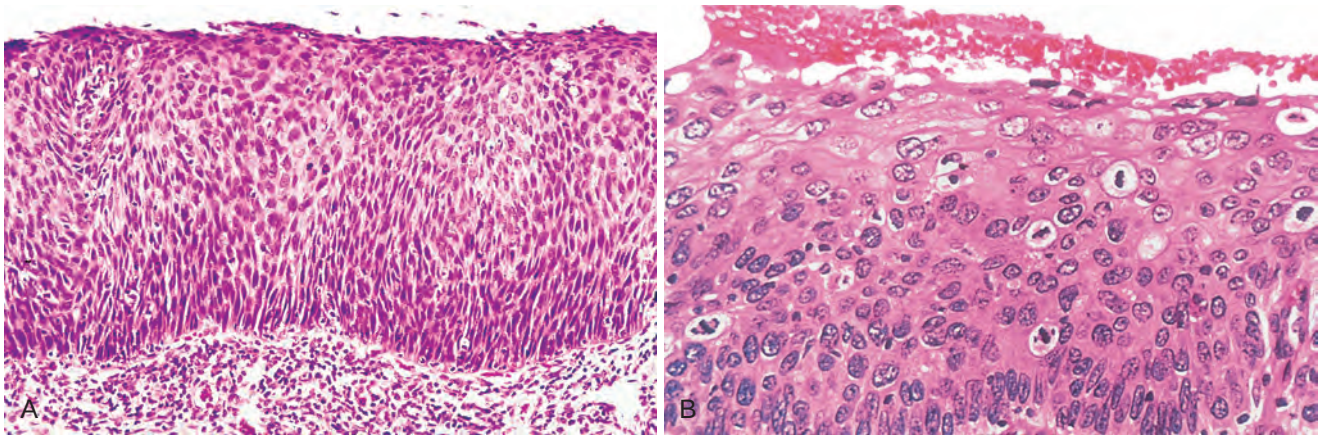

Figure 7-10 **A,** Carcinoma in situ. A low-power view shows that the epithelium is entirely replaced by atypical dysplastic cells. There is no orderly differentiation of squamous cells. The basement membrane is intact, and there is no tumor in the subepithelial stroma. **B,** A high-power view of another region shows failure of normal differentiation, marked nuclear and cellular pleomorphism, and numerous mitotic figures extending toward the surface.

the local environment. For example, gastroesophageal reflux damages the squamous epithelium of the esophagus, leading to its replacement by glandular (gastric or intestinal) epithelium more suited to an acidic environment.

Dysplasia is a term that literally means "disordered growth." It is encountered principally in epithelia and is characterized by a constellation of changes that include a loss in the uniformity of the individual cells as well as a loss in their architectural orientation. Dysplastic cells may exhibit considerable pleomorphism and often contain large hyperchromatic nuclei with a high nuclear-to-cytoplasmic ratio. The architecture of the tissue may be disorderly. For example, in dysplastic squamous epithelium the normal progressive maturation of tall cells in the basal layer to flattened squames on the surface may fail in part or entirely, leading to replacement of the epithelium by basal-appearing cells with hyperchromatic nuclei. In addition, mitotic figures are more abundant than in the normal tissue and rather than being confined to the basal layer may instead be seen at all levels, including surface cells.

When dysplastic changes are marked and involve the full thickness of the epithelium, but the lesion does not penetrate the basement membrane, it is considered a preinvasive neoplasm and is referred to as *carcinoma in situ* (Fig. 7-10). Once the tumor cells breach the basement membrane, the tumor is said to be *invasive*. Dysplastic changes are often found adjacent to foci of invasive carcinoma, and in some situations, such as in long-term cigarette smokers and persons with Barrett esophagus, severe epithelial dysplasia frequently antedates the appearance of cancer. Moreover, some mutations associated with full blown cancers (described later) may be present in even "mild" dysplasias. Thus, although **dysplasia may be a precursor to malignant transformation, it does not always progress to cancer**. With removal of the inciting causes, mild to moderate dysplasias that do not involve the entire thickness of epithelium may be completely reversible. Even carcinoma in situ may persist for years before it becomes invasive. Finally, while it should be noted that dysplasia often occurs in metaplastic epithelium, not all metaplastic epithelium is dysplastic.

Local Invasion

The growth of cancers is accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue, whereas nearly all benign tumors grow as cohesive expansile masses that remain localized to their site of origin and lack the capacity to infiltrate, invade, or metastasize to distant sites. Because benign tumors grow and expand slowly, they usually develop a rim of compressed fibrous tissue called a *capsule* that separates them from the host tissue. This capsule consists largely of extracellular matrix deposited by stromal cells such as fibroblasts, which are activated by hypoxic damage resulting from the pressure of the expanding tumor. Such encapsulation does not prevent tumor growth, but it creates a tissue plane that makes the tumor discrete, readily palpable, moveable (non-fixed), and easily excisable by surgical enucleation (Figs. 7-11 and 7-12). There are a few exceptions to this rule, however. For example, hemangiomas (neoplasms composed of tangled blood vessels) are often unencapsulated and permeate the site in which they arise (e.g., the dermis of the skin and the liver); when such lesions are extensive, they may be unresectable.

In contrast, malignant tumors are, in general, poorly demarcated from the surrounding normal tissue, and a well-defined cleavage plane is lacking (Figs. 7-13 and 7-14). Slowly expanding malignant tumors, however, may develop an apparently enclosing fibrous capsule and may push along a broad front into adjacent normal structures. Histologic examination of such "pseudoencapsulated" masses almost always shows rows of cells penetrating the margin and infiltrating the adjacent structures, a crablike pattern of growth that constitutes the popular image of cancer.

Next to the development of metastases, invasiveness is the most reliable feature that differentiates cancers from benign tumors. Most malignant tumors do not recognize normal anatomic boundaries and can be expected to penetrate the wall of the colon or uterus, for example, or fungate through the surface of the skin. Such invasiveness makes their surgical resection difficult or impossible, and even if the tumor appears well circumscribed it is