families with hereditary nonpolyposis colorectal carcinoma (HNPCC, discussed in Chapter 17). This defect creates a mutator phenotype, leading to more rapid accumulation of mutations that may by chance alter the function of cancer genes and thereby drive tumor development. In sporadic endometrioid carcinomas, loss of expression of DNA mismatch repair genes is commonly caused by epigenetic silencing (via promoter hypermethylation). Finally, loss-of-function mutations in *TP53* are present in approximately 50% of poorly differentiated carcinomas. Since *TP53* mutations are lacking in well-differentiated endometrioid carcinomas, these mutations are thought to be late events involved in tumor progression.

MORPHOLOGY

Endometrioid carcinoma can take the form of a localized polypoid tumor or a tumor that diffusely infiltrates the endometrial lining (Fig. 22-25*A*). Spread generally occurs by myometrial invasion followed by direct extension to adjacent structures/organs. Invasion of the broad ligaments may create a palpable mass. Dissemination to the regional lymph nodes eventually occurs, and in the late stages, the tumor may metastasize to the lungs, liver, bones, and other organs.

Endometrioid adenocarcinomas demonstrate glandular growth patterns resembling normal endometrial epithelium. There are three histologic grades: **well differentiated** (grade 1) (Fig. 22-25*B*), composed almost entirely of well-formed glands; **moderately differentiated** (grade 2) (Fig. 22-25*C*), showing well-formed glands mixed with areas composed of solid sheets of cells, which by definition make up 50% or less of the tumor; and **poorly differentiated** (grade 3) (Fig. 22-25*D*), characterized by greater than 50% solid growth pattern. Well differentiated tumors may be distinguished from hyperplasias by lack of intervening stroma.

Up to 20% of endometrioid carcinomas contain foci of squamous differentiation. Squamous elements may be histologically benign-appearing when they are associated with well-differentiated adenocarcinomas. Less commonly, moderately or poorly differentiated endometrioid carcinomas contain squamous elements that appear frankly malignant. Current classification systems grade the carcinomas based on glandular differentiation alone and ignore areas of solid squamous differentiation.

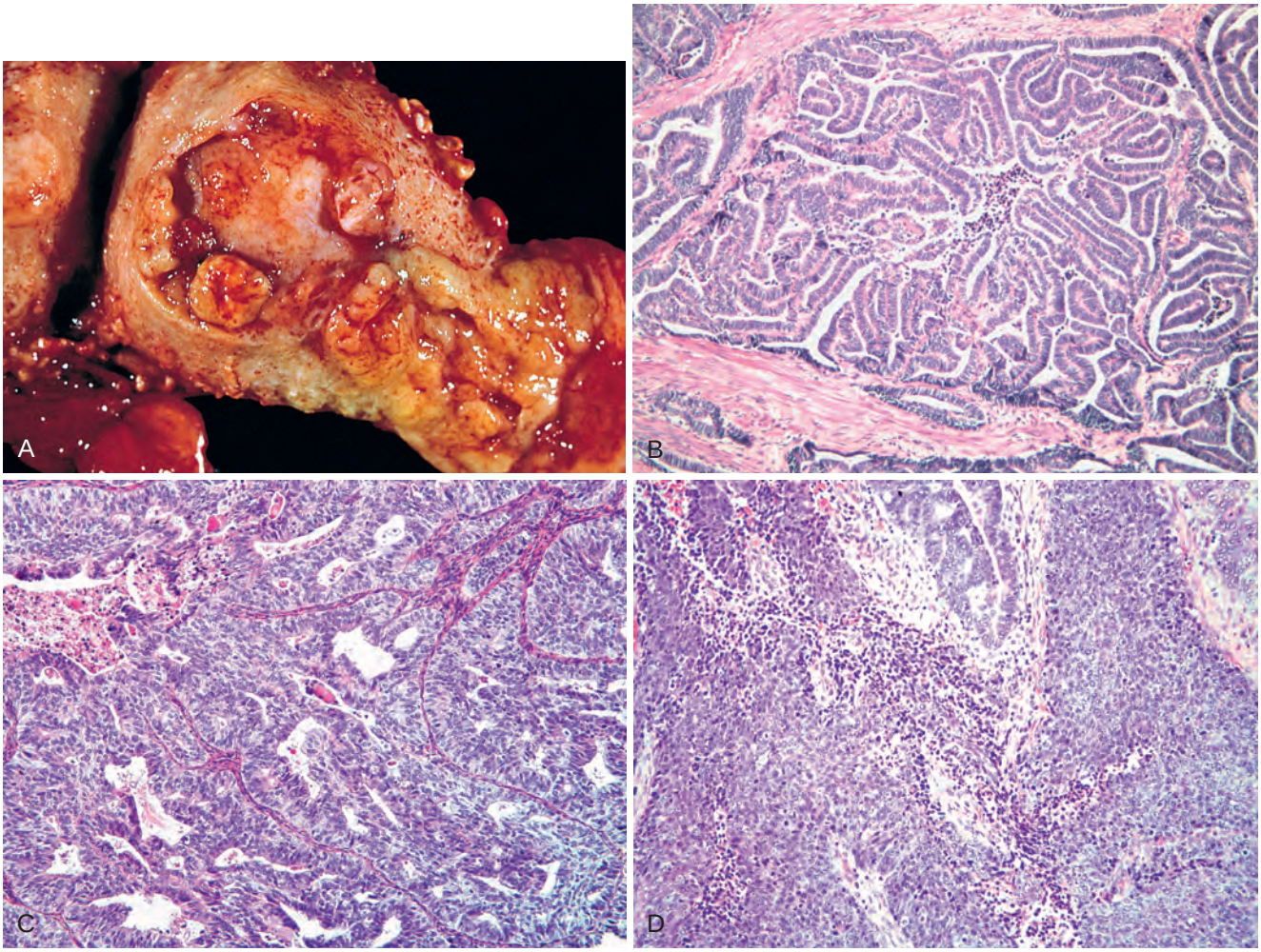

Figure 22-25 Type I endometrial carcinoma. **A,** Endometrial adenocarcinoma presenting as a fungating mass in the fundus of the uterus. **B,** Well-differentiated (grade 1) endometrioid adenocarcinoma with preserved glandular architecture but lack of intervening stroma. **C,** Moderately differentiated (grade 2) endometrioid adenocarcinoma with glandular architecture admixed with solid areas. **D,** Poorly differentiated (grade 3) endometrioid adenocarcinoma with a predominantly solid growth pattern.