Abnormal endometrial proliferations form a morphologic continuum ranging from focal glandular crowding through various degrees of hyperplasia and carcinoma. Classifications have evolved in which degrees of proliferation are separately labeled, although objective criteria are few and only simple hyperplasia and frank carcinoma, at the extreme ends of the spectrum, are consistently identified. Proliferations composed of closely packed complex glands displaying cytologic atypia comprise a gray area in the spectrum and provide the greatest difficulty in interpretation since some carcinomas of the endometrium lack atypia and some hyperplasias show atypia to a marked degree. Terms that have been used to describe lesions in the borderline area include adenomatous hyperplasia, atypical hyperplasia, and carcinoma in situ, but criteria for distinguishing them have been loosely and variably applied by different authors, and follow-up studies that might justify and validate their existence as discrete entities are difficult to interpret meaningfully.  

Endometrial proliferations are divided into noninvasive and invasive forms. Invasive lesions comprise all types of endometrial carcinoma and are considered in Chapter 12, Endometrial Carcinoma. Noninvasive lesions are the subject of this chapter and are considered as follows: (1) a brief review of terms and classifications in use, (2) the histopathologic features of hyperplasia and metaplasia, (3) adjunctive techniques in the characterization of hyperplasia, (4) behavior of the various forms of hyperplasia, (5) hyperplasia as a precursor of endometrial carcinoma, and (6) management of patients with endometrial hyperplasia.
Terminology in a Historical Perspective

Cystic Hyperplasia
This is the most common form of hyperplasia. It is characterized by dilated glands of varying sizes lined by tall columnar or cuboidal epithelium, usually showing some degree of mitotic activity and mild stratification. The stratification and columnar shape of the cells distinguish it from cystic (senile) atrophy and the isolated inactive cystic glands occasionally observed in normal proliferative or secretory endometrium, since the latter are lined by a single layer of flattened or low cuboidal epithelium.

Adenomatous Hyperplasia
This term has been applied by different authors to describe widely differing patterns. Gusberg used it to include all categories of endometrial hyperplasia beyond cystic hyperplasia.19-21 He subdivided adenomatous hyperplasia into mild, moderate, and severe forms. Severe adenomatous hyperplasia corresponds to the pattern others designate as atypical hyperplasia. In contrast, Hertig and Sommers26 used the term adenomatous hyperplasia to denote a histologic pattern exhibiting glandular projections and budding into the surrounding stroma. Vellios45 and Buehl et al.4 used the term in a similar fashion but restricted it to endometria with little or no cytologic atypia.

Atypical Hyperplasia
This term was introduced by Novak and Rutledge40 to describe proliferative endometria characterized by a greatly increased number of glands, with very little intervening stroma. Although they described the glandular pattern as closely resembling carcinoma and described the presence of moderately large uniform nuclei, they did not mention nuclear atypia. Campbell and Barter5 used a similar terminology but divided atypical hyperplasia into grades 1, 2, and 3, depending on how closely the lesion resembled carcinoma. They used complexity of the pattern rather than cytologic atypia as the main basis for subdividing atypical hyperplasia. In contrast, Vellios45 restricted atypical hyperplasia to endometria showing degrees of cellular atypia even in the absence of glandular crowding. This discrepancy in what constitutes atypia persists in the literature in that some authors use the term atypical hyperplasia to describe abnormally complex architectural patterns regardless of cytologic atypia, whereas others limit the term to endometria with cytologic atypia regardless of architectural pattern, and some authors require that both be present.33,47

Carcinoma In Situ
The term carcinoma in situ (CIS) was introduced by Hertig et al.26,27 to describe a focal lesion with cytologic alterations in which glandular crowding was not usually a prominent feature. The cells were large, with loss of polarity and abundant amphophilic or eosinophilic cytoplasm. The nuclei were pale, with fine granular chromatin and irregular nuclear membranes, but were not hyperchromatic. The glands had some cellular disorientation, disparity in size, and duplication of lumens. Intraglandular tufting was sometimes present. Buehl et al.4 and Vellios,45 however, used the term to denote a process at the extreme end of the proliferative continuum, with cytologic and architectural features consistent with carcinoma. Nuclear hyperchromatism and irregular nuclear outlines, clumping of chromatin, enlarged nucleoli, and usually eosinophilic cytoplasm were major features. Architectural changes included intraglandular cribriform arrangements and epithelial bridges. This lesion was distinguished from well-differentiated carcinoma on the basis of crowding. If glands having the characteristics of CIS were crowded together to the point that the likelihood of stromal invasion was high, the lesion was designated invasive carcinoma. Welch and Scully47 defined CIS as a small lesion involving no more than five or six glands in which cytologic features of carcinoma are present, but in which there is no evidence of invasion. If the change involves more than five or six glands, a diagnosis of invasive carcinoma is made arbitrarily. It is clear that in some instances, invasion is impossible to identify in areas of crowded glands, just as cytologic atypia is not found in every endometrial carcinoma. Many authors do not regard CIS as a replicable diagnosis for these reasons.

Classification
Until recently, the confusion in terminology and uncertainty over the behavior of various forms of hyperplasia have led to misleading diagnoses and inappropriate treatment. A clinically useful classification should be objective and reproducible, categorizing endometrial proliferations according to their behavior. Individualized management based on the natural history of the disease can then be undertaken. The classification proposed by the International Society of Gynecological Pathologists (ISGP) takes into account the inability to recognize some fully transformed malignant cells by any technique that is presently available until invasion of the adjacent tissue occurs. Abnormal endometrial proliferations are, therefore, divided into noninvasive and invasive forms according to the presence or absence of endometrial stromal invasion.34 This classification may not necessarily distin-