

## ENDOMETRIUM

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Endometrial carcinoma is the most common malignant neoplasm of the female genital tract. Factors associated with unopposed estrogenic stimulation, such as obesity, exogenous hormone use, and endometrial hyperplasia, are related to the development of the most common form of endometrial carcinoma—that is, the endometrioid subtype (Bokhman, 1983). More recent studies have confirmed this association by demonstrating elevated serum estrogen levels in patients with endometrioid carcinoma (Brinton et al., 1992; Potischman et al., 1996). It also has been recognized that some forms of endometrial carcinoma appear to be unrelated to hormonal factors and hyperplasia (Sherman et al., 1997). Serous carcinoma is the prototypic endometrial carcinoma that is not related to estrogenic stimulation. In the past two decades, clinicopathologic, immunohistochemical, and molecular genetic studies have provided additional data to allow for the development of a dualistic model of endometrial carcinogenesis. In this model two types of precursor lesions are proposed for the two pathways of endometrial carcinogenesis. *Atypical hyperplasia* (AH) is recognized as the precursor for the endometrioid type of endometrial carcinoma and *endometrial intraepithelial carcinoma* (EIC) as the precursor for serous carcinoma, the most common nonendometrioid subtype of endometrial carcinoma. The following discussion summarizes current knowledge about the relationship of these precursor lesions to the various forms of endometrial carcinoma.

### ATYPICAL ENDOMETRIAL HYPERPLASIA AND ITS RELATIONSHIP TO ENDOMETRIOID CARCINOMA OF THE ENDOMETRIUM

#### CLASSIFICATION AND BEHAVIOR OF ENDOMETRIAL HYPERPLASIAS

In the past, the terms *adenomatous hyperplasia* and *atypical hyperplasia* were used to denote proliferative lesions of the endometrium with varying degrees of architectural complexity and cytologic atypia (Buehl et al., 1964; Campbell and Barter, 1961; Gusberg, 1947; Gusberg and Kaplan, 1963; Gusberg et al., 1954; Hertig and Sommers, 1949; Hertig et al., 1949; Novak and Rutledge, 1948; Vellios, 1974). In addition, the term *carcinoma in situ* was proposed to describe small lesions, with or without glandular crowding, having the cytologic features of carcinoma but lacking invasion (Buehl et al., 1964; Hertig and Sommers, 1949; Hertig et al., 1949; Tavassoli and Kraus, 1978; Vellios, 1974; Welch and Scully, 1977). However, because carcinoma *in situ* was never clearly defined, the term was abandoned and, in retrospect, many of these lesions would be classified today as *hyperplasia with eosinophilic change*. Recently, Spiegel (1995) applied the term to an entirely different set of lesions that are associated with serous carcinoma (see below), adding further ambiguity to the historical confusion surrounding its clinical and biological significance. Pathologists have recognized for

decades that endometrial cancer precursors are morphologically and biologically heterogeneous. However, early studies designed to clarify the significance of these lesions were limited by the lack of standardized diagnostic criteria, failure to consider cytologic and architectural features separately, and inclusion of irradiated patients, which may have altered the natural history of the lesions studied (Beutler et al., 1963; Chamlian and Taylor, 1970; Gusberg, 1947; Hertig and Sommers, 1949; Hertig et al., 1949; McBride, 1959; Vellios, 1974; Welch and Scully, 1977). Many of these limitations have been addressed in more recent studies. Kurman et al. (1985) reported a retrospective follow-up study of 170 patients with untreated endometrial hyperplasias that were classified according to architectural and cytologic features identified in endometrial curettings. Women were followed from 1 to 27 years before undergoing hysterectomy in order to delineate the histologic features associated with an increased risk of progression to carcinoma. Lesions were classified as *hyperplasia* or *atypical hyperplasia* according to the absence or presence of nuclear atypia. One-third of the patients with hyperplasia and atypical hyperplasia were asymptomatic after the curettage, presumably because of regression of the lesion, and required no further treatment. Of the patients who required additional hormonal or surgical treatment, 69% with hyperplasia and 39% with atypical hyperplasia regressed. The proliferative process persisted in 28% of women with hyperplasia and in 27% of those with atypical hyperplasia. Two (2%) of 122 patients with hyperplasia progressed to carcinoma whereas 11 (23%) of the 48 women with atypical hyperplasia progressed to carcinoma ( $p = 0.001$ ) (Table 17-1). In a similar study, Gusberg and Kaplan (1963) found that 20% of their group of patients with "severe adenomatous hyperplasia" had uterine carcinoma when hysterectomy was done shortly

after curettage, but only 11% of those who were followed developed carcinoma.

In their study, Kurman et al. also assessed the degree of glandular complexity and crowding in an effort to identify a subgroup of lesions with an increased risk of progression to carcinoma. Thus, a proliferative lesion displaying minimal to moderate glandular complexity and crowding but lacking cytologic atypia was termed *simple hyperplasia* (Figs. 17-1 and 17-2), whereas one with marked glandular crowding was termed *complex hyperplasia* (Fig. 17-3). An endometrial proliferation displaying minimal to moderate glandular complexity and crowding accompanied by cytologic atypia was designated *simple atypical hyperplasia* (Figs. 17-4 and 17-5), whereas one demonstrating marked glandular crowding and cytologic atypia was designated *complex atypical hyperplasia* (Figs. 17-6 and 17-7). Progression to carcinoma occurred in 1 (1%) of 93 patients with simple hyperplasia, in 1 (3%) of 29 patients with complex hyperplasia, in 1 (8%) of 13 patients with simple atypical hyperplasia, and in 10 (29%) of 35 patients with complex atypical hyperplasia (Table 17-2). Simple atypical hyperplasia is an uncommon lesion. In most hyperplastic lesions, the degree of glandular crowding and complexity and level of cytologic atypia are concordant. Thus, cytologic atypia was the most useful criterion for identifying a patient with a significantly increased risk of developing carcinoma, with the presence of superimposed glandular complexity and crowding placing the patient at greater risk. This study established the classification of endometrial hyperplasias that was adopted by the World Health Organization (WHO) (Table 17-3; Scully et al., 1994). A more recent study of the behavior of endometrial hyperplasia found that most cases of endometrial hyperplasia without atypia regressed spontaneously, whereas those with complex atypical hyperplasia were much more likely to persist

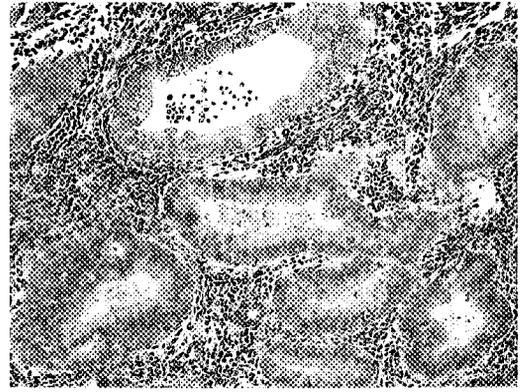
**Table 17-1.** Follow-up of Hyperplasia in Comparison with Atypical Hyperplasia (170 Patients)

Finding	Patients n	Regressed n (%)	Persisted n (%)	Progressed to Carcinoma	
				n (%)	P
Hyperplasia	122	97 (80)	23 (19)	2 (2)	0.001
Atypical hyperplasia	48	8 (58)	9 (19)	11 (23)	0.001

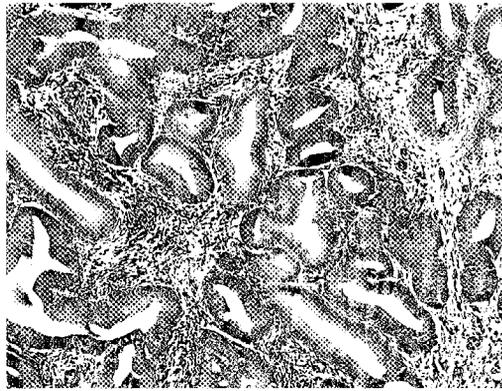
Adapted from Kurman et al., 1985, with permission.



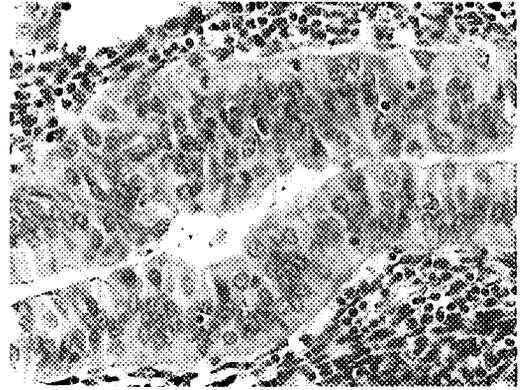
**Figure 17-1.** Simple hyperplasia without atypia. Glands are slightly crowded, cystically dilated, and have focal glandular outpouchings.



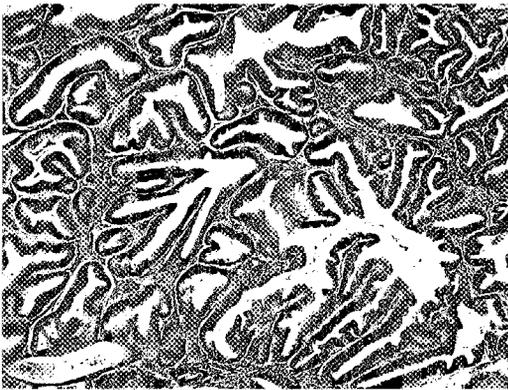
**Figure 17-4.** Simple atypical hyperplasia. Glands are slightly crowded with a moderate amount of intervening stroma.



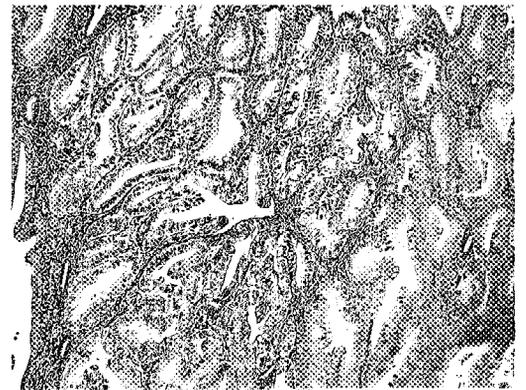
**Figure 17-2.** Simple hyperplasia without atypia. Glands are slightly more crowded than in Figure 17-1 but they are not arranged in a back-to-back fashion and there is minimal glandular complexity.



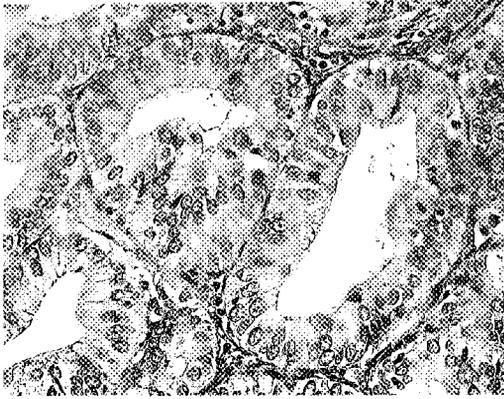
**Figure 17-5.** Simple atypical hyperplasia. Higher magnification of Figure 17-4 demonstrates cytologic atypia characterized by loss of cellular polarity, nuclear enlargement and rounding, coarse and vesicular chromatin, and occasional prominent nucleoli.



**Figure 17-3.** Complex hyperplasia without atypia. Glands are crowded in a back-to-back fashion with minimal intervening stroma. Gland outlines are complex rather than simple.



**Figure 17-6.** Complex atypical hyperplasia. Despite marked glandular crowding, individual glands are completely surrounded by stroma. The glands are not confluent and the stroma shows no evidence of desmoplasia.



**Figure 17-7.** Complex atypical hyperplasia. Crowded glands display loss of polarity, nuclear rounding, chromatin irregularities, nucleoli, and occasional mitotic figures.

(Terakawa et al., 1997). Another recent study confirmed the significance of cytologic atypia in predicting an increased risk of associated endometrial carcinoma in hysterectomy specimens (Hunter et al., 1994). Since the vast majority of atypical hyperplasias have complex architecture, complex atypical hyperplasia is associated with a significant risk of persistence and progression to carcinoma. Hence, this lesion is regarded as a direct precursor of well-differentiated endometrioid carcinoma of the endometrium. However, hyperplasia is identified in a prior endometrial specimen or in the hysterectomy specimen in only 35%–75% of women with endometrial carcinoma (Ayhan and Yarali, 1991; Beckner et al., 1985; Bokhman, 1983; Deligdisch and Cohen, 1985; Gucer et al., 1998; Kaku et al., 1996). In those reports that specified the number of hyperplasias that were classified as atypical, 14–36% of women with endometrial carcinoma had associated atypical hyperplasia

**Table 17-3.** Classification of Noninvasive Endometrial Proliferations

I. Hyperplasia
A. Simple hyperplasia
B. Complex hyperplasia
II. Atypical hyperplasia
A. Simple atypical hyperplasia
B. Complex atypical hyperplasia

(Gucer et al., 1998; Kaku, 1996). It is unclear whether failure to identify an associated atypical hyperplasia in all cases of endometrioid carcinoma reflects overgrowth of a preexisting hyperplasia by carcinoma or the development of carcinoma through a different pathway.

Some investigators have attempted to use computerized nuclear and architectural morphometric analyses of endometrial hyperplasias to predict coexistent carcinoma in hysterectomy specimens (Ausems et al., 1985; Baak, 1986; Baak et al., 1988, 1992; Dunton et al., 1996). Nuclear morphometry alone has been shown to be insufficiently sensitive and specific to properly distinguish atypical hyperplasias that are associated with carcinoma from those that are not (Ausems et al., 1985; Baak, 1986). The combination of architectural and nuclear morphometric features has been shown to identify 63%–100% of the cases of atypical hyperplasia analyzed that did not have coexistent or subsequent carcinoma. However, not all patients with atypical hyperplasia assessed as high risk for carcinoma based on morphometry had carcinoma detected on follow-up (Baak et al., 1988, 1992; Dunton et al., 1996). Although morphometric analysis is now available in many centers, it is costly and labor intensive and therefore not practical for most laboratories.

**Table 17-2.** Follow-up of Hyperplasia: Comparison of Cytologic and Architectural Abnormalities (170 Patients)

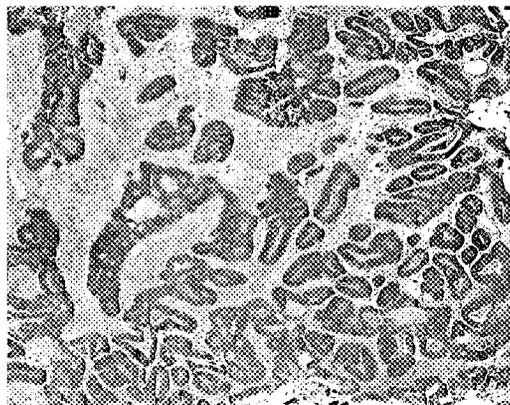
<i>Finding</i>	<i>Patients</i> n	<i>Regressed</i> n (%)	<i>Persisted</i> n (%)	<i>Progressed to Carcinoma</i> n (%)
Simple hyperplasia	93	74 (80)	18 (19)	1 (1)
Complex hyperplasia	29	23 (80)	5 (17)	1 (3)
Simple atypical hyperplasia	13	9 (70)	3 (23)	1 (8)
Complex atypical hyperplasia	35	20 (57)	5 (14)	10 (29)

Adapted from Kurman et al., 1985, with permission.

PATHOLOGIC DISTINCTION OF  
ATYPICAL HYPERPLASIA FROM  
WELL-DIFFERENTIATED  
ENDOMETRIOID CARCINOMA

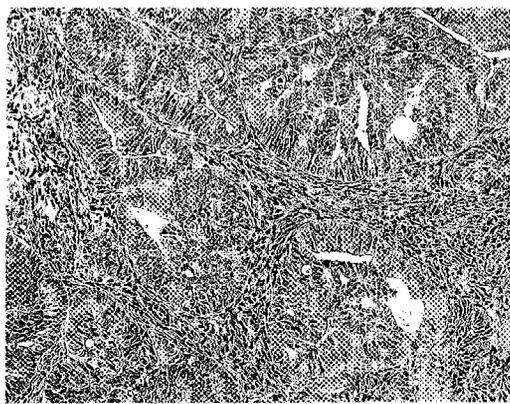
To determine specific and reproducible criteria for distinguishing atypical hyperplasia and so-called carcinoma-*in situ* from well-differentiated carcinoma in curettings, Kurman and Norris (1982) reviewed 204 curettings from the Armed Forces Institute of Pathology (AFIP) files. Cases showing the most severe forms of atypical hyperplasia, including examples of what have been regarded as carcinoma *in situ* and well-differentiated carcinoma, were selected and compared with the findings in nonirradiated hysterectomy specimens obtained within 1 month of the curettage. Degrees of cellular atypia, stratification, mitotic activity, and the presence or absence of stromal invasion (see below) were recorded. Of these features, stromal invasion was the most useful criterion for predicting the presence of a clinically significant carcinoma that had invaded the myometrium, including those that had metastasized (King et al., 1984; Kurman and Norris, 1982).

Identification of stromal invasion depended on the presence of one of the following: (1) an irregular infiltration of glands associated with cellular, reactive-appearing fibroblastic stroma (desmoplastic response); (2) a confluent glandular and/or cribriform pattern in which individual glands, uninterrupted by stroma, merge; and (3) an extensive papillary pattern. The processes that manifested the aforementioned features of invasion had to be sufficiently extensive to involve half of a low-power field measuring 4.2 mm in diameter without intervening stroma (Kurman and Norris, 1982; Norris et al., 1983). Originally, replacement of the endometrial stroma by masses of squamous epithelium was considered a rare manifestation of invasion but this criterion has subsequently been modified. Currently, masses of squamous epithelium that replace the endometrium (greater than a 2 mm<sup>2</sup> area) are interpreted as evidence of stromal invasion only if associated with a desmoplastic response or a confluent glandular pattern (Kurman and Norris, 1994). These three features are detailed below.

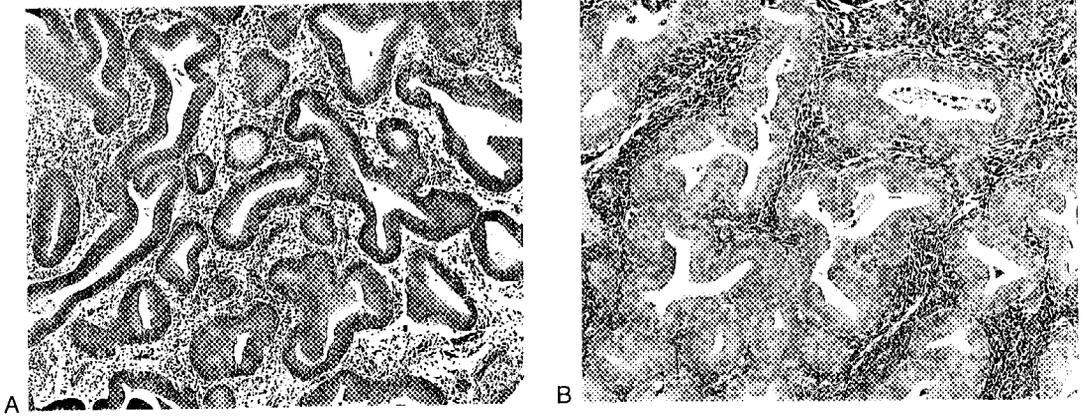


**Figure 17-8.** Well-differentiated endometrioid carcinoma. Glands are surrounded by a desmoplastic stroma that reflects stromal invasion. [From Kurman, R.J. and Norris, H.J.: Evaluation of criteria for distinguishing atypical endometrial hyperplasia from well-differentiated carcinoma. *Cancer* 49:2547-2559, 1982; with permission.]

1. A desmoplastic stromal response is characterized by altered stroma containing densely arranged, parallel, reactive fibroblasts that are more spindle shaped than the stromal cells of proliferative or hyperplastic endometrium (Figs. 17-8 to 17-10). Collagen is often prominent, unlike proliferative and hyperplastic endometria, in which it is inconspicuous. The desmoplasia is frequently maintained when neoplastic glands invade the myometrium. Frag-



**Figure 17-9.** Well-differentiated endometrioid carcinoma. Endometrial stroma is altered and replaced by fibroblasts, resulting in a desmoplastic reaction that reflects invasion.



**Figure 17-10.** Two examples of endometrial hyperplasia that lack stromal desmoplasia. *A:* Simple hyperplasia without atypia. *B:* Complex atypical hyperplasia. Glands in both examples are surrounded by stroma that resembles that seen in proliferative endometrium. The stroma surrounding the glands in *B* is compressed by the closely packed hyperplastic glands. There is no desmoplastic reaction and thus stromal invasion is absent.

ments of polyps, including the atypical adenomyomatous polyp identified by Mazur (1981), or tissue from the lower uterine segment has a fibrous stroma that can be difficult to distinguish from desmoplastic stroma. In such instances, features other than the altered stroma should be used to determine whether stromal invasion is present (see below).

2. Confluent glandular or cribriform growth is characterized by glands that are fused and lack intervening normal stroma (Figs. 17-11 and 17-12).
3. Complex papillary patterns in which multiple branching fibrous processes are lined by atypical columnar epithelium are also considered to represent carcinoma (Fig. 17-13). Hyperplasia may form papillary projections lined by stratified atypical epithelial cells, but these are confined within glandular lumina and lack fibrovascular cores.

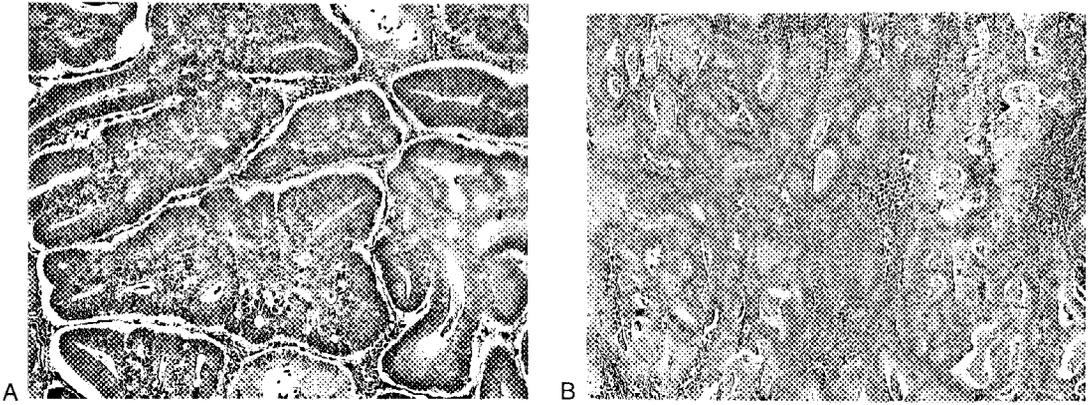
When stromal invasion was present in curettings, residual carcinoma was found in the uterus in half the cases; of these, one-third were moderately or poorly differentiated and one-fourth deeply invaded the myometrium (Table 17-4). Seven percent of women with carcinomas (stromal invasion identified in curettings) had extrauterine metastases at hysterectomy, and half of the women died of tumor.

Increasing degrees of nuclear atypia, mi-

totic activity, and stratification of cells in curettings were associated with a higher frequency of carcinoma in the subsequent hysterectomy specimen in the above study (Kurman and Norris, 1982) but were of limited value because even a mild degree of these changes was associated with carcinoma in nearly one-third of the cases. Of the residual carcinomas identified, 20% were moderately or poorly differentiated and 10% invaded the middle or outer third of the myometrium. The presence of nuclear atypia, mitotic activity, and stratification of cells in curettings, therefore, did not permit the



**Figure 17-11.** Well-differentiated endometrioid carcinoma. Confluent glandular pattern reflects stromal invasion.



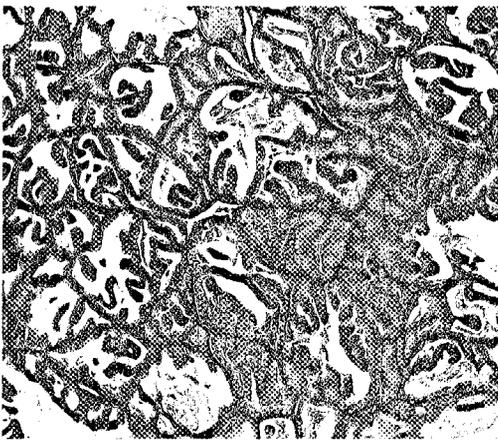
**Figure 17-12.** Well-differentiated endometrioid carcinomas. Two examples illustrate the cribriform pattern of stromal invasion. [A from Kurman and Norris, 1982, with permission.]

recognition of a biologically significant lesion in the uterus.

When stromal invasion was absent in the curettings, carcinoma was found in the uterus in only 17% of cases, and all the carcinomas were well differentiated and either confined to the endometrium or only superficially invasive (Table 17-5). None of the 89 patients whose lesions in curettings lacked stromal invasion had a recurrence. The finding of carcinoma in the uterus in 17% of patients who demonstrated only atypical hyperplasia in curettings was no higher than anticipated because similar findings had been reported by others (Campbell and

Barter, 1961; Tavassoli and Kraus, 1978). Two more recent studies, however, found higher frequencies of endometrial carcinoma (43% and 50%) in hysterectomy specimens following a diagnosis of atypical hyperplasia (Janicek and Rosenshein, 1994; Widra et al., 1995). Of the carcinomas detected in both studies, 43% were stage 1C or greater. These studies included patients who had been diagnosed by either curettage or biopsy but there were no significant differences in the frequencies with which carcinoma was detected at hysterectomy in those patients who received a curettage compared to those who had been biopsied. However, in one of these studies, the biopsy and curettage specimens were not reviewed to confirm that features of stromal invasion were absent in these specimens (Janicek and Rosenshein, 1994).

Thus, stromal invasion is the most useful feature for distinguishing atypical hyperplasia from well-differentiated carcinoma in curettings. The above findings also indicate



**Figure 17-13.** Well-differentiated endometrioid carcinoma. A complex papillary pattern is a manifestation of stromal invasion. [From Kurman and Norris, 1982, with permission.]

**Table 17-4.** Residual Carcinoma in 115 Uteri After Curettage Showing No Stromal Invasion

<i>Finding</i>	<i>Number (%)</i>
Residual carcinoma	58 (50)
Grade 1	38 (66)
Grade 2	14 (24)
Grade 3	6 (10)
Myometrial invasion	42 (72)
Inner third	28 (48)
Middle and outer thirds	14 (24)

Adapted from Kurman et al., 1982, with permission.

**Table 17-5.** Residual Carcinoma in 89 Uteri After Curettage Showing No Stromal Invasion

<i>Finding</i>	<i>Number (%)</i>
Residual carcinoma	15 (17)
Grade 1	15
Myometrial invasion	7
Depth of invasion	
1 mm or less	5
2 to 4 mm	2

Adapted from Kurman et al., 1982, with permission.

that the presence and absence of stromal invasion in curettages are correlated, respectively, with the finding of more aggressive versus low-grade carcinomas in hysterectomy specimens. More recently, another study has demonstrated that clinically significant endometrial proliferations, i.e., those that have a high likelihood of myometrial invasion, can be recognized when either sufficient architectural complexity or nuclear atypia, including prominence of nucleoli, is present (Longacre et al., 1995). In addition, the strong association of a desmoplastic stromal response with a myoinvasive lesion was confirmed.

#### REPRODUCIBILITY OF DIAGNOSIS OF ENDOMETRIAL HYPERPLASIA, ATYPICAL HYPERPLASIA, AND WELL-DIFFERENTIATED CARCINOMA

Few studies have addressed the reproducibility of the diagnosis of endometrial hyperplasia and its distinction from well-differentiated carcinoma. One study that compared diagnostic reproducibility using the 1975 and 1994 WHO classifications of endometrial hyperplasia and carcinoma found that interobserver agreement was fair to moderate with both systems (Skov et al., 1997). A subsequent study of 100 endometrial biopsy and curettage specimens ranging from proliferative endometrium to well-differentiated carcinoma found substantial interobserver agreement for diagnoses of hyperplasia and well-differentiated carcinoma but only moderate agreement for the diagnosis of atypical hyperplasia (Table 17-6; Kendall et al., 1998). Of numerous histologic features evaluated, the only feature that was associated with distinction of atypical hyperplasia from hyperplasia without atypia in multivariable logistic regression analysis was the presence of nucleoli. The features that were associated with the distinction of carcinoma from atypical hyper-

**Table 17-6.** Intra- and Interobserver Reproducibility of Diagnoses of Hyperplasia, Atypical Hyperplasia, and Well-Differentiated Carcinoma of the Endometrium

<i>Intraobserver agreement for Diagnosis of Proliferative Endometrium, Hyperplasia, Atypical Hyperplasia, Well-Differentiated Carcinoma</i>				
<i>Pathologist</i>	<i>Kappa Value</i>	<i>% Agreement</i>	<i>Interpretation</i>	
1	0.67	76	Substantial	
2	0.69	77	Substantial	
3	0.70	77	Substantial	
4	0.77	83	Substantial	
5	0.85	89	Almost perfect	
<i>Interobserver agreement for 4 diagnostic categories<sup>a</sup></i>				
<i>Diagnosis</i>	<i>Round 1</i>	<i>Interpretation</i>	<i>Round 2</i>	<i>Interpretation</i>
Proliferative endometrium	0.86	Almost perfect	0.86	Almost perfect
Hyperplasia	0.65	Substantial	0.60	Substantial
Atypical hyperplasia	0.42	Moderate	0.47	Moderate
Well-differentiated carcinoma	0.79	Substantial	0.83	Almost perfect

<sup>a</sup>Kappa values.

Data from Kendall et al. (1998).