

# The Endometrium

## Pathologic Principles and Pitfalls

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• **Context.**—Endometrial tissue specimens are commonly encountered in daily practice. It is well known that a number of problematic diagnostic scenarios occur relative to these specimens.

**Objective.**—To emphasize practical aspects of endometrial specimen handling and reporting, with selected comments on common diagnostic pitfalls, including (1) the diagnosis of endometrial intraepithelial carcinoma in atrophic endometrial biopsy specimens, (2) evaluation of adequacy of endometrial sampling specimens, (3) problems in diagnosing and measuring the depth of myometrial invasion in endometrial carcinoma, (4) the question of metastasis versus independent primaries in concurrent carci-

nomas of endometrium and one or both ovaries, (5) the problematic differential diagnoses between type 1 (primarily endometrioid) and type 2 (primarily serous) adenocarcinomas, and (6) atypical hyperplasia and proposed classification systems for its replacement.

**Data Sources.**—Published literature, consensus statements, and personal experience.

**Conclusions.**—A systematic approach to the handling and reporting of endometrial specimens reduces the potential for omission and error. Recognition of diagnostic pitfalls and practical approaches to their resolution help improve quality.

(*Arch Pathol Lab Med.* 2007;131:372–382)

Although most diagnostic pathologists encounter numerous endometrial specimens in their daily practice, many perplexing problems are still encountered when dealing with these specimens. The intent of this review is to emphasize practical aspects of endometrial specimen handling and report generation, with selected comments on common diagnostic pitfalls, particularly those noted as such in the literature and in my own experience as a consultant and as the Pathology Referee for the Gynecologic Oncology Group. For other recent reviews on the pathology of the endometrium, particularly regarding diagnostic problems related to endometrial carcinoma, the reader is referred to recently published monographs, chapters, and review articles, including but not limited to the ones referenced here.<sup>1–10</sup>

### THE ENDOMETRIAL BIOPSY OR CURETTAGE SPECIMEN

The approach to any endometrial sampling specimen, whether from an outpatient biopsy or a formal curettage, should be dictated by the clinical indication for submission of the specimen. In the great majority of cases, the indication will be one of the following: (1) evaluation of infertility/preparation for in vitro fertilization; (2) evaluation of abnormal vaginal bleeding (postmenopausal or during the reproductive years); and (3) follow-up of a pre-

vious cytologic or histologic diagnosis. Regardless of the indication, the approach to examination of the specimen is similar, although the information expressed in the final surgical pathology report will differ. The example that most easily comes to mind is that, in a biopsy or curettage performed for abnormal bleeding, the diagnosis of “late secretory phase” or even “secretory phase” will usually suffice, whereas if the procedure had been performed as part of an infertility workup, the specific menstrual cycle or postovulatory date should be provided in as accurate a manner as possible. Although guidelines and checklists are available for the examination and reporting of endometrial specimens involving carcinomas,<sup>11,12</sup> I am unaware of a similar effort related to the reporting of all endometrial biopsy or curettage specimens, and have attempted to provide some guidelines in Table 1. It should be emphasized that this checklist was designed by me rather than by a committee, and I am sure that other pathologists reviewing it will be able to provide useful additions, alterations, and deletions.

### Evaluation of Endometrial Biopsy/Curettage Adequacy

A determination that applies to endometrial sampling specimens, regardless of the clinical indication, is the evaluation of adequacy, although an unremarkable specimen that is adequate for one indication may not necessarily be sufficient for another. In Table 1, I present some suggestions on reporting (or at least thinking about) this evaluation. Obviously, the amount of endometrial tissue present in a specimen will depend on a number of factors, including the amount of endometrium present in the uterus (less in atrophy, more in hyperplasias and most carcinomas, and so forth), the type of procedure performed (curettage is expected to yield more endometrial tissue than the usu-

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Accepted for publication August 16, 2006.

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The author has no relevant financial interest in the products or companies described in this article.

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**Table 1. Checklist for Reporting Endometrial Biopsy/Curettage Diagnoses\***

|   |   |
|---|---|
| <p>Clinical indication</p> <p>Dysfunctional or other abnormal cyclic bleeding _____</p> <p>Perimenopausal/postmenopausal bleeding _____</p> <p>Before _____ or during _____ menopausal hormone replacement</p> <p>Hormonal evaluation (eg, infertility, habitual abortion) _____</p> <p>Evaluation of artificial cycle prior to IVF _____</p> <p>Follow-up of previous diagnosis of _____</p> <p>Missed/incomplete/inevitable abortion _____</p> <p>Other (specify) _____</p> <p>No history provided _____</p> <p>Specimen type</p> <p>Biopsy (specify instrument used) _____</p> <p>Curettage _____</p> <p>Specimen adequacy</p> <p>Satisfactory for evaluation _____</p> <p>Evaluation limited by</p> <p>Scant endometrial tissue _____</p> <p>Surface endometrium only _____</p> <p>Lower uterine segment only _____</p> <p>Obscuring blood _____</p> <p>Necrotic debris _____</p> <p>Iatrogenic effect (specify) _____</p> <p>Other (specify) _____</p> <p>No endometrial tissue present _____</p> <p>Nonendometrial tissue present (include diagnosis if indicated)</p> <p>Endocervix _____</p> <p>Ectocervix _____</p> <p>Myometrium _____</p> <p>Adipose tissue _____</p> <p>Other _____</p> | <p>Diagnosis</p> <ol style="list-style-type: none"> <li>1. Unremarkable cycling endometrium<br/>Phase _____<br/>Date (if required) _____</li> <li>2. Atrophy _____</li> <li>3. Abnormally cycling endometrium<br/>(specify pattern) _____</li> <li>4. Bleeding endometrium, NOS _____</li> <li>5. Gestational changes (check all appropriate)<br/>Decidua _____<br/>Arias-Stella phenomenon _____<br/>Chorionic villi _____<br/>Trophoblast _____<br/>Fetal parts _____<br/>Abnormal gestational changes (specify) _____<br/>Other (specify) _____</li> <li>6. Iatrogenic changes (specify) _____</li> <li>7. Endometritis (specify pattern and etiology if identifiable) _____</li> <li>8. Polyp(s) _____</li> <li>9. Metaplastic and related changes<br/>(specify) _____</li> <li>10. Reactive atypia of known cause<br/>(specify) _____</li> <li>11. Glandular atypia of undetermined significance _____</li> <li>12. Stromal atypia of undetermined significance _____</li> <li>13. Endometrial hyperplasia<br/>Simple: _____ Complex: _____</li> <li>14. Atypical endometrial hyperplasia:<br/>Simple: _____ Complex: _____</li> <li>15. Endometrial carcinoma: type: _____<br/>Grade (if appropriate) _____<br/>Amount _____</li> <li>16. Other benign or malignant tumor<br/>(specify) _____</li> <li>17. Other (specify) _____</li> </ol> |
|---|---|

\* IVF indicates in vitro fertilization; NOS, not otherwise specified.

al outpatient biopsy), and the experience and competence of the operator. Somewhat surprisingly, there has been very little published about the criteria for considering an endometrial sampling specimen as adequate or inadequate (most gynecologists and other surgeons prefer the term *insufficient* because they seem to believe that *inadequate* somehow reflects on themselves).

In general terms, I believe that an adequate specimen should contain both glandular and stromal tissue from the fundus, although the exact amount of such tissue will vary with the clinical indication for the procedure, the age of the patient, and the pathologic diagnosis. For purposes of illustration, Figure 1, A and B, presents examples of biopsy specimens (seen here in their entirety) that I would consider, respectively, inadequate and adequate (although perhaps barely so). If an adequate but minimal specimen consists of atrophic endometrium (Figure 2), and this is within the spectrum of diagnostic possibilities, no further comment is necessary in most cases. If, on the other hand, a specimen of similar size is interpreted as atypical hyperplasia, the prudent pathologist would want to note the possibility that a larger specimen (formal curettage or hysterectomy) might well reveal the presence of an underlying carcinoma.

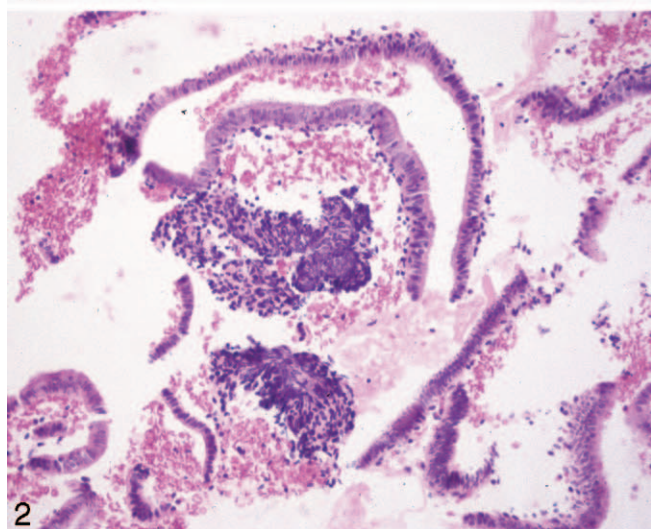
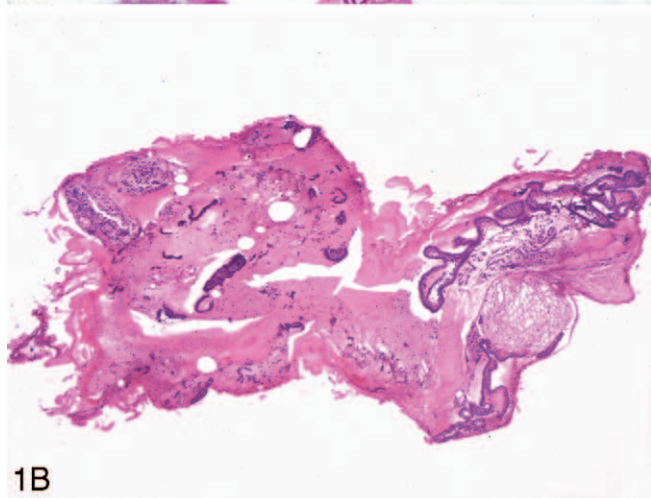
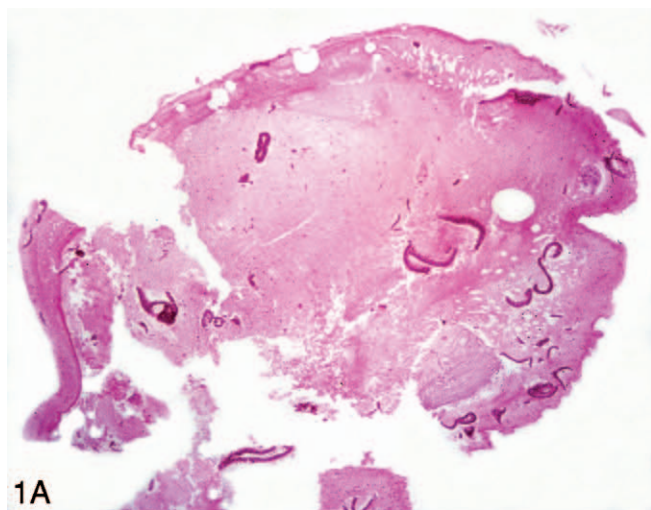
It should also be noted that the presence of nonendometrial tissue in an endometrial sampling specimen should be indicated in the surgical pathology report, perhaps as suggested in Table 1. Obviously, any diagnosable abnormality in such tissues (such as cervical intraepithelial neoplasia or a submucous leiomyoma) should be re-

ported as well. The presence of myometrium is particularly important to note in a curettage specimen submitted for or after an abortion because this finding may indicate a higher risk for subsequent intrauterine synechiae (Asherman syndrome).<sup>13</sup>

Another extrinsic tissue that should be reported when seen in endometrial sampling specimens is adipose tissue. If a "floater" or pickup from another case can be ruled out, the presence of adipose tissue is at least strongly suggestive of perforation of the uterus by the curetting instrument. Although most of these cases seem to result in no short-term or long-term damage to the patient, I still consider this to be a "critical value" (to be reported immediately and directly to the clinician) when it is encountered. Table 2 lists my other critical values, including a newly diagnosed malignancy or atypical hyperplasia, and the absence of gestational tissue in situations in which its presence is clinically anticipated. In the latter instance, the pathologist should remember that the definition of gestational tissues includes trophoblast as well as intact chorionic villi and fetal parts, but does not include decidualized endometrial stroma or endometrial glands exhibiting Arias-Stella phenomenon. Both of the latter conditions can be seen not only in extrauterine gestations but also in many nongestational situations. If necessary, the presence of single trophoblastic cells can be confirmed by an immunostain for cytokeratin (for which they are always reactive) as well as for human chorionic gonadotropin or human placental lactogen. Additional findings that might be reportable in some situations include the unexpected

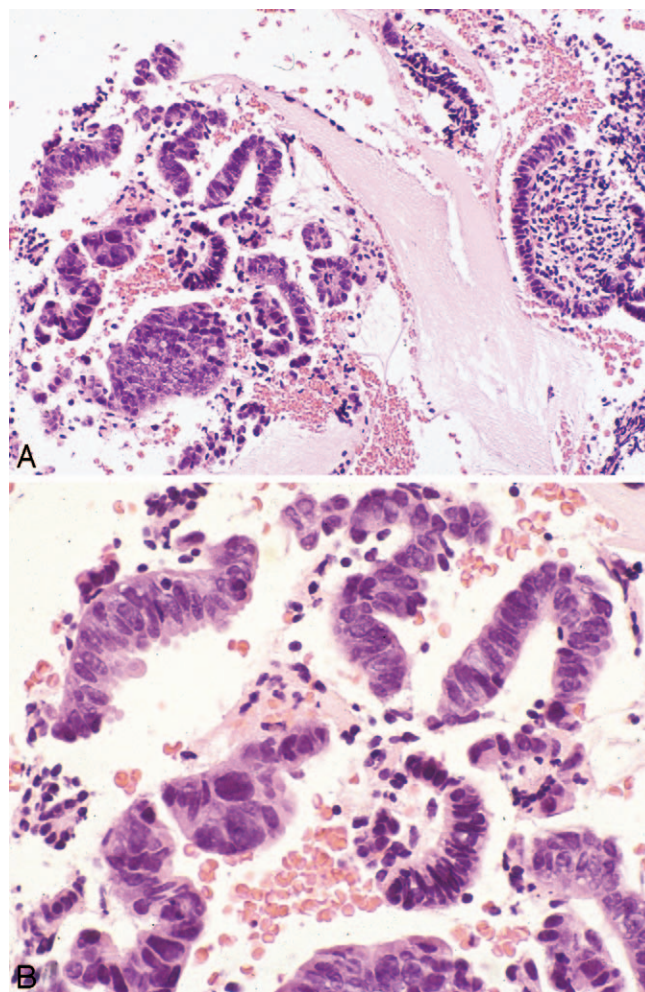
**Table 2. Critical Values (Justifying Telephone Notification) in Endometrial Sampling Specimens**

|   |
|---|
| Presence of adipose tissue<br>Newly diagnosed malignancy or atypical hyperplasia<br>Absence of gestational tissues (villi, trophoblast) when clinically anticipated |
|---|



**Figure 1.** Two endometrial biopsy specimens interpreted as insufficient/inadequate (A) and barely adequate (B). Each photomicrograph includes the entire specimen (hematoxylin-eosin, original magnification  $\times 4$ ).

**Figure 2.** Endometrial biopsy from 64-year-old woman interpreted as "atrophy." Small nests of atrophic stroma are interspersed among the atrophic glandular component (hematoxylin-eosin, original magnification  $\times 10$ ).



**Figure 3.** Endometrial intraepithelial carcinoma in atrophic endometrial curettage specimen. A, This illustration shows almost the entire specimen received. It consists mostly of isolated surface epithelium, with only a few tissue fragments containing stroma (hematoxylin-eosin, original magnification  $\times 10$ ). B, At higher magnification, a few strips of epithelium show marked nuclear atypia and enlargement (hematoxylin-eosin, original magnification  $\times 20$ ). An immunostain for p53 was strongly reactive (not shown).

presence of gestational products and the finding of a specimen insufficient for interpretation.

It should also be remembered that it is important to look carefully at atrophic and otherwise scant endometrial specimens. It is in specimens such as these that the pathologist is particularly likely to miss the presence of an endometrial intraepithelial carcinoma, the putative precursor of invasive serous (and perhaps clear cell) adenocarcinoma of the endometrium.<sup>14-16</sup> Figure 3, A and B, illustrates a typical example of a small focus of endometrial intraepithelial carcinoma in an atrophic curettage specimen. I have had the unfortunate experience of seeing other

such cases in which the original pathologist missed the endometrial intraepithelial carcinoma diagnosis and the patient later developed disseminated serous carcinomatosis, resulting in malpractice litigation. Endometrial intraepithelial carcinoma and serous carcinoma will be discussed in more detail later in this article.

A final comment on the subject of endometrial biopsy and curettage specimens concerns the number of levels (step sections) needed for diagnosis. In my own laboratory—and I believe in most laboratories in this country—3 levels are generally obtained, but a recent study suggested that this could be reduced to 2 without sacrificing diagnostic accuracy.<sup>17</sup> The authors of this study also concluded that “in order to reduce diagnostic error, laboratories should focus on reducing observer variation rather than increasing the number of levels examined.”

### EXAMINATION AND REPORTING OF HYSTERECTOMY SPECIMENS

As with endometrial sampling by biopsy or curettage, hysterectomies are performed for numerous reasons, and the examination of the specimen and the final surgical pathology report issued depend in large measure on the clinical questions to be answered. As reflected in the billing codes authorized for different types of hysterectomy specimens, it is assumed that hysterectomies performed for cancer (whether endometrial, myometrial, or cervical) will require the most extensive examination, uteri removed for prolapse will demand the least, and everything else will be somewhere in between these two extremes. Because “everything in between” might represent the majority (or at least the plurality) of hysterectomies examined by the pathologist, these should perhaps be considered first.

One of the most common hysterectomy specimens, if not *the* most common, is that performed for uterine leiomyomata. Indeed, even many other lesions identified pathologically are initially received with a clinical diagnosis of “fibroids.” Because leiomyomas are so common and leiomyosarcomas so rare, it is a safe assumption that 99% or more of all uterine smooth muscle tumors seen in an average pathology practice will be benign leiomyomas.<sup>18–20</sup> Thus, the general rules presented here for sampling in these cases assumes that the tumor or tumors within the uterus are clinically and grossly typical for benign leiomyomas. In this situation, we recommend rather minimal sampling, usually consisting of one section of the largest tumor and one or two others of other tumors selected at random. More extensive sampling will generally be required in instances of clinical, gross pathologic, or microscopic variations from the norm. Clinically, if something in the history suggests the possibility of a diagnosis other than the usual benign leiomyoma(s), more careful sampling will be indicated; one example might be if the patient is 70 rather than 30 years of age and/or is described as having a rapidly growing tumor. At the gross pathologic level, any lesion other than the typical firm, white, whorled tumor that pops up from the surrounding cut surface should prompt more careful investigation. Even in the presence of softening, hemorrhage, cystic degeneration, yellow or tan discoloration, and the like, the majority of such lesions will turn out to be benign, but the proportion will be far less than the 99% or more seen in otherwise typical smooth muscle nodules.

In addition to leiomyosarcoma, it should be remem-

bered that some of these grossly atypical presentations will result from endometrial stromal tumors rather than those of smooth muscle differentiation. A grossly infiltrative lesion, or one that extends as wormlike plugs into vessels, obviously also calls for more careful sampling for microscopic examination. Finally, sometimes the need for more sections is not recognized until the examination of initial “pilot” sections; histologic findings that may reveal the need for further examination include hypercellularity, nuclear atypia, numerous mitotic figures, foci of necrosis, an epithelioid or non-smooth muscle morphologic appearance, and various combinations of these features. Certainly, in any of these situations, the pathologist should prefer to err on the side of oversampling rather than that of undersampling.

Some uteri removed for fibroids in which softer lesions are found, or in which a diffuse myometrial hypertrophy is present, will turn out to have adenomyosis. As with smooth muscle tumors, most cases of adenomyosis are totally benign and require fairly minimal sampling. If glands within the adenomyotic foci are sparse, the differential diagnosis with low-grade endometrial stromal sarcoma should be raised,<sup>21</sup> whereas an excess of glands might suggest the possibility of an endometrial hyperplasia or carcinoma extending into (or even arising within) foci of adenomyosis.

Sampling of endomyometrium in uteri removed for prolapse generally consists of 1 or 2 sections. Because most of these uteri are atrophic, a single section can usually be submitted to include endometrium, myometrium, and serosa. If any significant pathology is suspected as a result of gross examination, more sections obviously need to be submitted.

The examination of hysterectomy specimens submitted with a diagnosis of a malignant tumor should be considerably more extensive. As mentioned previously, published protocols endorsed by the College of American Pathologists<sup>11</sup> and the Association of Directors of Anatomic and Surgical Pathology<sup>12</sup> have been published as guidelines for practicing pathologists, and these recommendations will be summarized only briefly in the present report. The uterus initially should be inspected externally, and the external margins inked for microscopic identification. In the usual radical hysterectomy, the specimen will include parametrium, although if a lesser procedure is performed, the most external layer may be uterine serosa. Although most authors recommend opening the uterus from both lateral aspects, I generally prefer to open it anteriorly because most endometrial carcinomas arise from the posterior surface. If initial gross examination indicates an anteriorly based tumor, the approach can be modified appropriately.

The ultimate goal in the examination of a cancerous hysterectomy specimen should be to confirm the presence of residual tumor after the initial sampling, to sample enough of it for adequate typing and grading, and to determine the extent of spread within the specimen (myometrium, serosa, parametrium, lymphatic/vascular spaces, cervix, and attached uterine adnexa). Table 3 indicates these goals and summarizes briefly the observations to be included in the surgical pathology report. When a tumor of sufficient size is seen grossly, an additional goal should be to obtain a portion of it for possible flow cytometric, molecular, and other studies.

The amount of sampling for microscopic examination

**Table 3. Hysterectomy for Carcinoma\***

|                                     |
|-------------------------------------|
| Location/size/extent of tumor       |
| Key to sections submitted           |
| Type, grade, benign endometrium     |
| Myoinvasion/LVSI                    |
| Other organs/margins/washings       |
| Special studies (eg, ER/PR, ploidy) |

\* LVSI, lymphatic/vascular space invasion; ER/PR, estrogen receptor/progesterone receptor.

varies according to the pre-hysterectomy diagnosis as well as the size of the uterus and the gross findings therein. In a small uterus, which is more likely to contain either a serous carcinoma or no or minimal residual tumor, the entire uterine corpus can often be submitted without incurring the wrath of the histotechnologists. If a large tumor is seen grossly, about 6 good sections will usually suffice, although I am unaware of any published data that prove that either 6 sections are better than 5, or that 7 are not better than 6. Most importantly, sections near the tumor should (if at all possible) continue into the myometrium and ultimately to the serosa, and should also include adjacent grossly benign endomyometrium (Figure 4). If the myometrium is too thick for such sections to appear on a single slide, they may be divided in 2 parts each as illustrated in Figure 4, with documentation of this

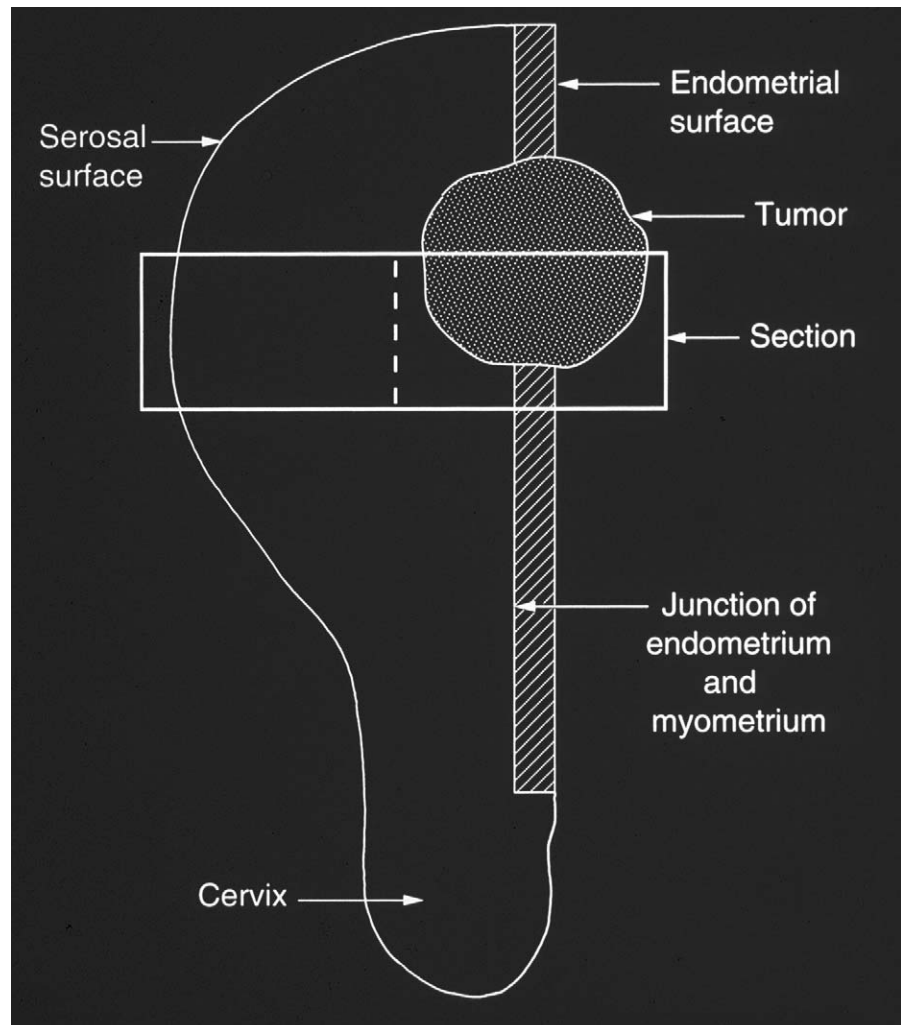
spatial arrangement in the gross description or summary of sections. The importance of having an adjacent benign endomyometrial junction becomes clear when it is time to assess the depth of myoinvasion of a tumor in which the base of the exophytic portion is not clearly identifiable.

In these cancerous hysterectomy specimens, it is also important to examine the cervix and (when included in the specimen) the uterine adnexa. Many pathologists recommend treating the cervix like a cone biopsy, with the entire cervix (or at least its upper portion) submitted in toto. This is probably not necessary if gross examination of the uterus reveals that the primary tumor is far from the internal os. Because the patients with endometrial carcinoma are usually postmenopausal, the ovaries accompanying the involved uteri are generally either small and atrophic or large and obviously involved by tumor. On occasion, however, microscopic foci of cancer may be seen in an ovary of normal size and gross appearance, so it is important to submit at least 2 sections of each ovary as well as several of the fallopian tubes. If a staging laparotomy has been performed, the specimens submitted by the operating surgeon should be submitted following the usual protocols for such procedures.

#### The Hysterectomy for Endometrial Atypical Hyperplasia

Although the diagnosis of endometrial hyperplasia would appear to be intermediate between that of lei-

**Figure 4.** Diagrammatic representation of the ideal sectioning of an endometrial carcinoma and adjacent benign endomyometrium that best demonstrates the depth of myoinvasion. As indicated, 2 sections rather than 1 may be submitted if the myometrial thickness does not allow inclusion to the serosal surface in one section. (Reprinted with permission from Silverberg.<sup>11</sup>)



**Table 4. Carcinoma of the Corpus Uteri—International Federation of Gynecology and Obstetrics Staging Classification (1988)**

| Stage | Features   |
|-------|--|
| IA    | Tumor limited to endometrium   |
| IB    | Invasion of up to half of myometrium                                       |
| IC    | Invasion of more than half of myometrium                                   |
| IIA   | Endocervical glandular involvement only                                    |
| IIB   | Cervical stromal invasion  |
| IIIA  | Tumor invasion of serosa and/or adnexa and/or positive peritoneal cytology |
| IIIB  | Vaginal metastases   |
| IIIC  | Metastases to pelvic and/or para-aortic lymph nodes                        |
| IVA   | Tumor invasion of bladder and/or bowel mucosa                              |
| IVB   | Distant metastases, including intra-abdominal and/or inguinal lymph nodes  |

myoma and of endometrial carcinoma in terms of sampling requirements, in actuality these hysterectomy specimens may require even more extensive sampling than the documented cases of carcinoma. Again, there are no prospective studies documenting how many sections are needed in these cases, but it is the rule of my institution to submit all of the endometrium unless the specimen is so large that this would involve more than 20 or 30 sections. The reason for this is the by now fairly extensive literature documenting that, at least for atypical hyperplasia, carcinoma can be identified in approximately 40% of immediate hysterectomy specimens, and 10% to 20% of these carcinomas are myoinvasive.<sup>22,23</sup> Thus, in the absence of a grossly visible tumor, extensive sampling is necessary to investigate the possibility of an occult carcinoma, as well as to rule out the possibility of myoinvasion. It should be emphasized that the reports on associated carcinomas in hysterectomy specimens relate only to atypical hyperplasias, but the distinction between complex hyperplasia and atypical complex hyperplasia has been shown to be difficult enough that one must assume that even a lesion diagnosed as complex hyperplasia without atypia might harbor a carcinoma in the subsequent hysterectomy specimen.<sup>24</sup>

#### THE SURGICAL PATHOLOGY REPORT IN CASES OF ENDOMETRIAL CARCINOMA

The subject of adequate reporting of endometrial carcinoma specimens has been addressed by both the College of American Pathologists and the Association of Directors of Anatomic and Surgical Pathology, as discussed previously, and will thus be summarized fairly briefly here.<sup>11,12</sup> In a biopsy or curettage specimen, the major features to be reported when carcinoma is present are (1) histologic type; (2) histologic grade (if appropriate; serous and clear cell adenocarcinomas are, by definition, not graded); (3) the diffuse or focal nature of the carcinomatous change, as well as its possible limitation to an endometrial polyp or polyps; (4) changes in the accompanying benign endometrium (specifically, endometrial hyperplasia, atypical hyperplasia, or intraepithelial carcinoma); and (5) the presence of myometrial and/or cervical invasion, if identifiable in the specimen.

In a hysterectomy specimen, the reader is referred again to Figure 4 for the appropriate gross sampling of the specimen. The items to be recorded in the surgical pathology report include all of those listed previously for the biopsy or curettage specimen, as well as the presence and depth of myometrial extension in the uterine corpus, the presence or absence of lymphatic/vascular space invasion, and

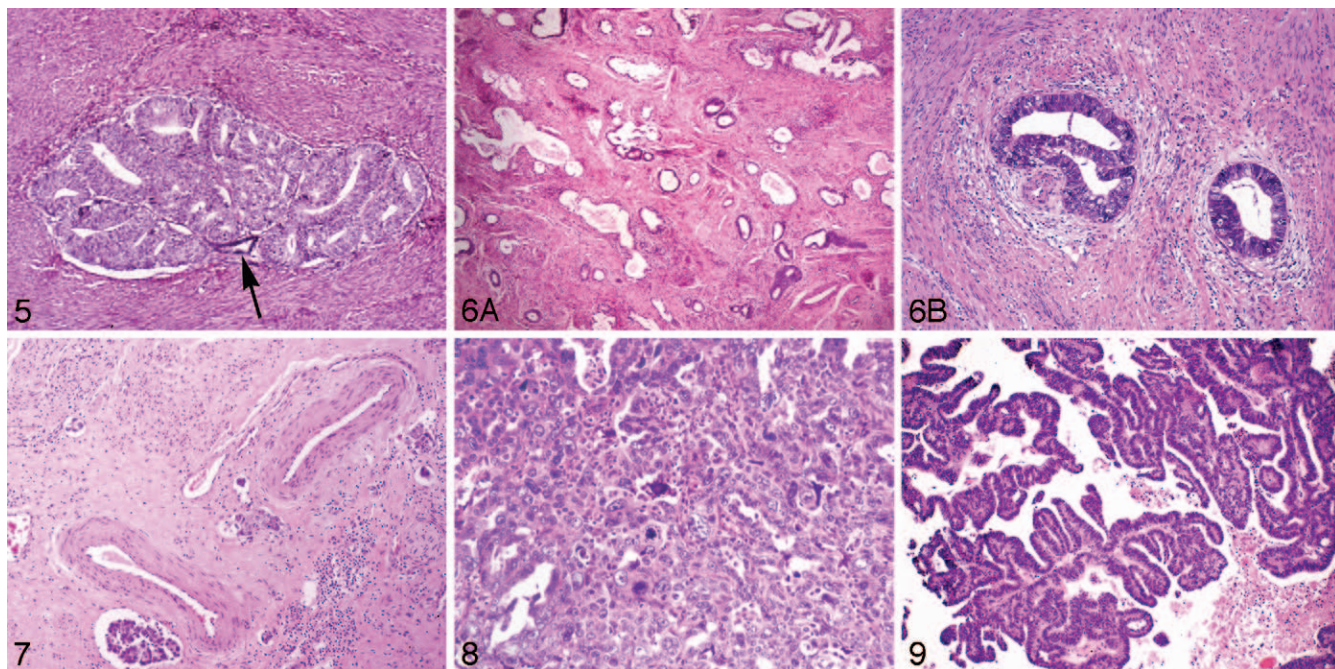
the possible involvement of uterine serosa, parametrium, cervix, and other sites included in the resection that would raise the pathologic stage of the tumor (Table 4).

#### Myoinvasion

A few comments on myoinvasion in endometrial carcinoma are worthy of note here. First, myoinvasion can be reported in 3 different fashions: (1) depth of tumor combined with thickness of myometrium at the point of deepest invasion, (2) proportion/percentage of myometrium involved by invasive carcinoma (expressed in thirds or halves of myometrial thickness), and (3) distance in millimeters from uterine serosa. Except for the third of these, sections showing both myoinvasive tumor and adjacent benign endomyometrial junction (as indicated in Figure 4) are required. Therefore, number 3 represents a fall-back technique of expressing depth of invasion if adequate sections are not available.

It should not be assumed, however, that the measurement of distance from serosa is an inferior method as several studies have validated the prognostic significance of this system.<sup>25</sup> In general, the preferred system would be to indicate specific measurements for both the depth of myoinvasion (from the endomyometrial junction) and the myometrial thickness at that point (eg, "tumor invades 5 mm into a 12-mm thick myometrium at its deepest point of invasion"). The prognostic significance of this sort of measurement is also well documented in the literature.<sup>2,26–28</sup> It has also been documented that intraoperative pathologic evaluation for myoinvasion by gross inspection of the hysterectomy specimen with or without frozen section can be accurate and clinically useful, although the main problem is the selection of the appropriate field to examine and freeze.<sup>29–31</sup>

Although the clinical importance of myoinvasion in the prognosis and treatment of endometrial carcinoma is without question, it must be pointed out that there are major pitfalls for the pathologist in the investigation of this parameter. In the study of Jacques and colleagues,<sup>32</sup> the most frequent discrepancy by far between original and review diagnoses in cases of endometrial carcinoma pertained to the evaluation of myoinvasion, the usual combination being a diagnosis of superficial (or occasionally even deep) myoinvasion in the original report and a review diagnosis of carcinoma limited to the endometrium. The main reason for this problem is the well-known but not always well-appreciated fact that the endomyometrial junction, rather than always being represented by a straight line, is often a series of hills and valleys, presenting the opportunity for an endometrial tumor to penetrate



**Figure 5.** Well-differentiated endometrioid adenocarcinoma involving a deeply seated myometrial focus of adenomyosis. Note the smooth contour of the nest of tumor, absence of surrounding desmoplastic response, and a residual benign endometrial basaloid gland (arrow) (hematoxylin-eosin, original magnification  $\times 10$ ).

**Figure 6.** Well-differentiated endometrioid adenocarcinoma invading the myometrium in a single-gland pattern with minimal desmoplastic response. A, Low magnification view (hematoxylin-eosin, original magnification  $\times 4$ ). B, Detail of one focus in which desmoplastic response surrounds well-differentiated neoplastic glands (hematoxylin-eosin, original magnification  $\times 20$ ).

**Figure 7.** Endometrial adenocarcinoma with invasion of lymphatics between and surrounding large blood vessels. Note the lymphoid infiltrate, which may be all that is seen in initial sections (hematoxylin-eosin, original magnification  $\times 10$ ).

**Figure 8.** Endometrial adenocarcinoma with glandular and solid pattern displaying bizarre nuclear atypia, including the presence of large eosinophilic nucleoli. Elsewhere in this tumor, more classic papillary and mazelike patterns of serous carcinoma were present (hematoxylin-eosin, original magnification  $\times 20$ ).

**Figure 9.** Well-differentiated endometrioid adenocarcinoma of villoglandular type. The simple papillae are lined by cells with only modest atypia, whose nuclei are parallel to one another and perpendicular to the basement membrane (hematoxylin-eosin, original magnification  $\times 10$ ).

into the valleys and appear to be within the myometrium without actually having invaded the myometrium. When this observation is added to the propensity of endometrium to extend as diverticula into the myometrium as adenomyosis, this creates yet another pitfall in the distinction of intramyometrial *extension* into adenomyosis versus true myometrial *invasion* by carcinoma.<sup>2,26,33</sup> Useful histologic features indicating an extension into adenomyosis include tumor in round nests rather than angular nests, with well-preserved basement membrane and without an adjacent desmoplastic stromal response, and often with some residual benign endometrial glands or stroma at the periphery of the nests of tumor (Figure 5 and Table 5). As a general rule, if the presence of myoinvasion in an endometrial carcinoma is suggested but not proven in a hysterectomy slide, it is almost always better to assume the lack of myoinvasion rather than its presence. Remember also that occasional endometrial carcinomas appear to arise within foci of adenomyosis, without involving the overlying surface endometrium. This situation cannot be confirmed without multiple sections showing the absence of overlying carcinoma.<sup>34</sup>

The clinical significance of the distinction between endometrial carcinoma truly invading the myometrium and that extending only into superficial tongues of endometri-

um or foci of adenomyosis lies in the fact that the latter is virtually always associated with cure by hysterectomy alone, and true myoinvasion indicates the potential for distant metastases and tumor-related mortality.<sup>2,26,28,33</sup>

Another aspect of myometrial invasion by endometrial carcinoma that presents a pitfall for the pathologist is the pattern that has been reported as the adenoma malignum pattern,<sup>4,35</sup> diffusely infiltrating invasion,<sup>36</sup> the single-gland pattern,<sup>37</sup> and the minimal-deviation invasive pattern.<sup>38</sup> Regardless of the term used, this refers to an uncommon but not rare pattern of myoinvasion in which single well-differentiated neoplastic glands infiltrate diffusely through the myometrium (and often into the cervix as well) while invoking a minimal desmoplastic response, thus mimicking a minimal-deviation adenocarcinoma or adenoma malignum of endocervical origin. Rather than being overdiagnosed, this pattern of invasion is often missed and misinterpreted as adenomyosis with a minimal-to-absent stromal component. An example of this type of invasion is shown in Figure 6, A and B. Once encountered initially, this pattern is recognizable and similar in almost every case. If carefully searched for, some desmoplastic reaction can invariably be found around at least some of the infiltrating glands. Although this pattern of myoinvasion is thought by some authors to be associ-

**Table 5. Differential Diagnosis of Myoinvasion**

| Feature                         | Extension into Adenomyosis | True Myoinvasion      |
|---------------------------------|----------------------------|-----------------------|
| Surface carcinoma               | Usually present            | Always unless treated |
| Connection to surface carcinoma | Often                      | Less often            |
| Borders of tumor nests          | Rounded                    | Angular               |
| Benign glands/stroma in nests   | Often                      | No                    |
| Stroma around nests             | Normal myometrium          | Reactive              |
| Adenomyosis elsewhere           | Usually                    | Sometimes             |

ated with a poorer prognosis,<sup>36</sup> most studies have not confirmed this observation.

**Lymphatic/Vascular Space Invasion**

Lymphatic/vascular space invasion has been studied somewhat less extensively than myometrial invasion in endometrial carcinoma hysterectomy specimens, but the general consensus is that this finding in a hysterectomy specimen is associated with a much greater risk of lymph node metastasis, distant dissemination, and death.<sup>39,40</sup> Although the accuracy and reproducibility of the diagnosis of lymphatic/vascular space invasion has not been studied in a systematic manner, it is my impression that most pathologists have little difficulty recognizing this feature when it exists. A potential pitfall occurs, however, when initial sections reveal only perivascular lymphocytic infiltrates without obvious nests of tumor cells in lymphatic spaces.<sup>41</sup> An example of this finding is illustrated in Figure 7. When this finding is encountered in a hysterectomy specimen for endometrial carcinoma, the pathologist should obtain deeper levels of the block, and obvious lymphatic/vascular space invasion will usually manifest itself in these levels.

**Pathologic Upstaging of Endometrial Carcinoma**

As indicated in Table 4, a number of findings in a hysterectomy specimen can lead to pathologic upstaging of an endometrial carcinoma previously assumed to be stage I. Particularly important to discuss here are involvement of the cervix and one or both ovaries. As indicated in the staging schema, the surgical pathology report should distinguish between endocervical glandular involvement (manifested by downward extension of carcinoma along the endocervical surface, with occasional or diffuse penetration into underlying glands) and involvement of the cervical stroma by neoplasm, similar to the patterns seen in myometrial invasion. In some instances (especially when the endocervical tumor is present in surface epithelium and/or glands only) the endocervical neoplasm may actually be a separate primary adenocarcinoma in situ or invasive adenocarcinoma. In the case of invasive adenocarcinoma, the distinction is probably not significant clinically as the prognosis and treatment of stage IIb endometrial adenocarcinoma and of stage Ia endocervical adenocarcinoma are almost identical. On the other hand, an adenocarcinoma in situ of the endocervix associated with a nonmyoinvasive endometrial adenocarcinoma with a favorable histology would probably usually be treated less aggressively than a stage IIa adenocarcinoma of otherwise similar appearance; in this situation, because the distinction can be quite difficult, it is important to remember that extensive myoinvasion, lymphatic/vascular space invasion, or other evidence of extension beyond stage I or II would provide the rationale for aggressive postoperative

therapy. It should also be remembered that reactive changes of the endocervical epithelium seen in association with endometrial carcinoma may be misinterpreted as endocervical glandular involvement by cancer.<sup>42</sup>

In the case of adenocarcinoma involving the endometrium and one or both ovaries, a somewhat different set of criteria apply. First, if the ovarian lesions are truly metastatic, the endometrial cancer is in pathologic stage III, and the prognosis is considerably poorer. On the other hand, most patients with synchronous endometrial and ovarian carcinomas are young and have well-differentiated endometrioid adenocarcinomas, and most patients in this situation probably have concurrent primary carcinomas of endometrium and ovary.<sup>43-46</sup> Suggestions for distinguishing metastases from independent primary tumors in this situation at the clinical and routine pathologic levels are presented in Table 6. More accurate distinctions can probably be made by molecular studies,<sup>44,45</sup> but clinical data suggest that the exact sites of involvement and histologic appearance of the synchronous tumors are so closely related to prognosis that these expensive studies are not necessary in most cases.<sup>44,46</sup> Basically, if both tumors are low-grade endometrioid and involved sites are limited to uterine corpus and ovary, the prognosis is favorable, while type 2 (serous and clear cell) carcinomas, high-grade endometrioid carcinomas, and involvement of other stage III sites in addition to ovary portend a grave prognosis.

Finally, it should be remembered that all additional specimens beyond the hysterectomy and associated organs should be correlated in the final surgical pathology report for an endometrial cancer. Thus, the results of staging laparotomy, including lymph nodes, should be reported and included in the final staging, as should the peritoneal washing cytology report, if it is available in the same institution. Although a positive peritoneal washing cytology upstages an endometrial carcinoma to stage IIIa, it is still debated whether upstaging based solely on this finding does or does not affect the clinical outcome.<sup>47</sup> Nev-

**Table 6. Ovarian Metastases From Endometrial Carcinoma Versus Separate Primaries**

| Favor Metastasis            | Favor Synchronous Primaries |
|-----------------------------|-----------------------------|
| Older                       | Younger                     |
| Deep myoinvasion            | No myoinvasion              |
| Type 2/high-grade carcinoma | Low-grade endometrioid      |
| No endometriosis            | Endometriosis               |
| Other metastases            | No other metastases         |
| Multinodular                | Uninodular                  |
| Primarily surface involved  | Primarily deep              |
| Vascular involvement        | No vascular involvement     |
| Monoclonal                  | Not monoclonal              |

ertheless, I am aware of at least one malpractice action based on the failure of a pathologist to correlate the peritoneal cytology report with the hysterectomy surgical pathology report in a case of endometrial carcinoma.

### CHALLENGES OF TYPE 2 CARCINOMAS

Although it was first suggested in 1983 that there might be 2 different pathogenetic types of endometrial carcinoma,<sup>48</sup> it took another decade before this principle became widely accepted.<sup>49</sup> Current classification systems now divide endometrial carcinomas into type 1 (consisting of most endometrioid and mucinous adenocarcinomas) and type 2 (represented largely by serous and clear cell adenocarcinomas).<sup>9</sup> It is still not entirely clear whether high-grade endometrioid carcinomas belong in the type 1 or type 2 category, and most rare types (such as transitional cell, squamous cell, glassy cell) are generally kept separate.

It is now well known that type 1 endometrial carcinomas are pathogenetically related to endometrial hyperplasias, that they tend to be low grade and low stage when first diagnosed, that they tend to occur in somewhat younger (albeit usually postmenopausal) women, that they are related to exogenous and endogenous hyperestrogenism, that they often are associated with PTEN (phosphatase and tensin homologue) inactivation, and that their prognosis is generally favorable. On the other hand, type 2 carcinomas occur in older women, are usually found in atrophic rather than hyperplastic endometria, are unrelated to estrogenic abnormalities, have p53 rather than PTEN irregularities, are often diagnosed with disseminated disease, and have a much poorer prognosis.

Although most type 1 and type 2 endometrial carcinomas are easily placed in the correct category, a few pitfalls still exist for the unwary pathologist. These are largely based on the former nomenclature of *papillary serous carcinoma*, which suggested that all serous carcinomas were papillary and all papillary carcinomas of the endometrium were serous. This false impression has been corrected in part by the deletion of the adjective "papillary" from the official nomenclature for serous carcinoma, but occasional problems still remain because some serous carcinomas have a predominantly glandular architecture and some endometrioid carcinomas are predominantly or exclusively papillary.

In the new World Health Organization classification of endometrial neoplasms, the comment is made in the table on grading of type 1 endometrial adenocarcinomas that "bizarre nuclear atypia should raise the grade by 1 (i.e., from 1 to 2 or 2 to 3) but may also signify type II differentiation."<sup>9</sup> In fact, I believe that the dissociation between a glandular architecture and marked nuclear atypia is more often than not a marker of serous carcinoma rather than a higher grade endometrioid carcinoma (Figure 8). A recent report in which such tumors were studied found that the clinical and immunohistochemical profiles of these tumors resembled those of serous rather than endometrioid carcinomas.<sup>50</sup> Another report also indicated that many grade 3 endometrioid adenocarcinomas were immunohistochemically more closely related to serous than to low-grade endometrioid adenocarcinomas.<sup>51</sup> In practice, at my institution we perform p53 and estrogen and progesterone receptor immunohistochemical evaluation on most tumors of this sort, and generally find that they are strongly and diffusely reactive for p53 and negative for estrogen and progesterone receptor; in this situ-

ation, we diagnose them as serous carcinomas and recommend that they be treated as such.

The other pitfall in the differential diagnosis between endometrioid and serous (or clear cell) carcinomas results from the fact that a small but significant proportion of well-differentiated endometrioid adenocarcinomas are of villoglandular type.<sup>52,53</sup> These tumors are characterized by long, slender papillae lined by uniform columnar cells with their long axes parallel to one another and perpendicular to the basement membrane, as typically encountered in low-grade endometrioid carcinomas (Figure 9). The large, rounded, dysplastic, bizarre nuclei with prominent eosinophilic nucleoli that are encountered in serous carcinomas are absent, as are the usual exfoliation of tumor cells and nests of cells into lumens and frequent psammoma bodies. Mitotic figures (often atypical) and multinucleate cells, solid nests of bizarre cells, and prominent tumor necrosis are also more common in serous carcinomas. When serous carcinomas are papillary, secondary papillae are often seen perpendicular to the main core, while the papillae of villoglandular adenocarcinomas are less complex and never form labyrinthine or mazelike spaces. As with other endometrioid adenocarcinomas, adjacent benign endometrium associated with the villoglandular type is often hyperplastic, while endometrium adjacent to serous carcinoma is usually atrophic and often reveals endometrial intraepithelial carcinoma.<sup>14-16</sup> As anticipated, the prognosis of villoglandular adenocarcinomas is similar to that of other low-grade endometrioid adenocarcinomas and far better than that of serous carcinomas.<sup>52,53</sup>

The question of the natural history of endometrial carcinomas with a mixture of type 1 and type 2 elements is also not completely resolved. The classic studies suggested that any tumor with more than 25% of a serous component would behave like a serous carcinoma, but recent publications have suggested that as little as 10% (and possibly even less) might confer a poor prognosis.<sup>54</sup> It is worth noting that the current World Health Organization publication addressing tumors of the uterus states that, "It is generally accepted that 25% or more of a type II tumour implies a poor prognosis, although the significance of lesser proportions is not well understood."<sup>9</sup>

Finally, when considering small foci of serous (and, to a lesser extent, clear cell) carcinoma, mention should be made of the concept of *minimal serous carcinoma*.<sup>55,56</sup> This term has been used in recent publications to combine the noninvasive lesion endometrial intraepithelial carcinoma<sup>14-16</sup> and small (less than 11 mm in one report) superficially invasive serous carcinomas limited to the endometrium. The few series reported thus far suggest that, when patients with these lesions are subjected to careful staging laparotomy, about one third of them have serous carcinoma outside the uterus; these patients with disseminated disease all do poorly, while the ones with disease limited to the endometrium have thus far shown excellent survival. More cases of this sort need to be studied to determine whether these results hold up, but the important lesson at this point for the pathologist is to recommend full staging laparotomy even for patients with these minimal lesions.

### THE PROBLEM OF ATYPICAL ENDOMETRIAL HYPERPLASIA

Although hyperplastic (and putatively preneoplastic) lesions of the endometrium have been known for decades

by a variety of names, since the 1985 publication of Kurman and colleagues,<sup>57</sup> the lesions have generally been divided architecturally into simple and complex, and cytologically into atypical hyperplasia and hyperplasia without atypia. Based in part on the study by Kurman et al, as well as others reporting similar data in usually smaller series of cases, the assumption was made that those lesions showing cytologic atypia (atypical hyperplasias), particularly when combined with a complex architectural appearance (complex atypical hyperplasia or atypical complex hyperplasia), were those most likely to progress to endometrial adenocarcinoma if untreated. Rates of progression were reported based on series of women in whom a diagnosis of hyperplasia or atypical hyperplasia was made and hysterectomy was not performed until anywhere from 1 to 25 or more years later. Although the absolute values for proportions of cases with an eventual diagnosis of carcinoma varied from series to series, atypical complex hyperplasia always showed by far the highest rate of progression, with actual figures varying from 20% to 40% or greater.

Also beginning in the 1980s, however, publications have appeared that challenged this concept on the basis of 2 types of observations: (1) atypical complex hyperplasia has been reported to be a poorly reproducible diagnosis, with experts differing in significant proportions of cases not only with referring pathologists but also with each other<sup>24,58,59</sup>; and (2) carcinoma can be found in uteri removed within 1 or 2 months after the diagnosis of atypical hyperplasia in a significant proportion of cases, making it unclear whether those carcinomas diagnosed many years later really represent progression or merely persistence.<sup>22,23</sup> Indeed, in the largest study to date of immediate hysterectomy after a diagnosis of atypical hyperplasia, 40% of women had carcinoma in the hysterectomy specimen—which is actually a higher proportion than the “progression” rates reported in many other studies.<sup>23</sup> In this latter study,<sup>23</sup> when the original diagnosis of atypical hyperplasia was altered to adenocarcinoma by a consensus of the study pathologists, about two thirds of these uteri were positive for carcinoma, and even 15% of the uteri in women whose biopsy diagnoses had been downgraded to less than atypical hyperplasia had carcinoma.

There would appear to be 2 ways of dealing with the current situation. One would be to try to find out what is wrong with the current system in order to improve both the diagnostic reproducibility and the positive predictive value of a diagnosis of atypical complex hyperplasia, and studies are currently under way in this area. The other way of dealing with the data reported would be to change the system entirely and adopt an entirely new terminology that would be both more predictive and more reproducible.

Two main candidates have merged as potential replacements for atypical complex hyperplasia and associated terms. The first of these combines simple and complex hyperplasias as *hyperplasia*, and combines the atypical hyperplasias with a subset of well-differentiated endometrioid adenocarcinomas as *endometrial neoplasia*.<sup>60</sup> This system has the advantage of combining lesions (atypical complex hyperplasia and low-grade endometrioid adenocarcinoma) that may be difficult to distinguish from one another and are often treated in the same way, but has the disadvantage of requiring the subset of carcinomas included in the endometrial neoplasia category to be sepa-

rated from more advanced adenocarcinomas, which are still labeled as such.

The second (and, in my opinion, the more likely to be successful) classification system continues to use the term *hyperplasia* for histologic changes produced by unopposed estrogens, and premalignant endometrial disease (as identified by integrated molecular genetic, histomorphometric, and clinical outcome data) is classified as *endometrial intraepithelial neoplasia* (EIN).<sup>61</sup> In this system, the diagnostic criteria for EIN include (1) architecture (gland area exceeding that of stroma, usually in a localized region), (2) cytologic alterations (cytology differing between the architecturally crowded focus and background endometrium), and (3) lesional size (the maximal linear dimension of the lesion should exceed 1 mm because smaller lesions have an unknown natural history). The advocates of this system have cautioned users to exclude benign mimics and carcinomas, although it remains to be determined how effectively this can be done in routine surgical pathology practice. It should be noted that EIN is not just a new name for atypical complex hyperplasia; indeed, in one recent report 18 (78%) of 23 cases of complex atypical hyperplasia were reclassified as EIN, but so were 8 (44%) of 18 complex hyperplasias without atypia and 2 (4%) of 56 simple hyperplasias without atypia.<sup>61</sup> In the same report, EIN was found to have a high level of reproducibility among the participating pathologists, and to be a better predictor of carcinoma on follow-up than was atypical hyperplasia. Although this system appears to have many advantages, studies with both larger numbers of cases and more pathologists from different institutions not associated with the original investigators are needed before EIN is fully accepted as the heir apparent to atypical complex hyperplasia. It also must be demonstrated that EIN is as reliably distinguished from well-differentiated adenocarcinoma as it is from lesions of lesser severity than EIN. It should be noted that the developers of the EIN system have established a Web site with an online interactive tutorial and a training series of cases for those readers who wish to learn more about this system; it can be accessed at [www.endometrium.org](http://www.endometrium.org).

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