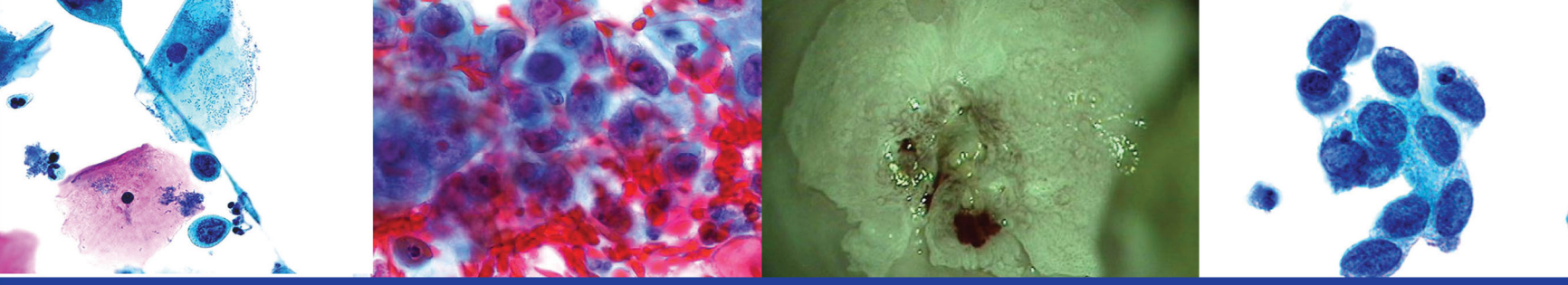
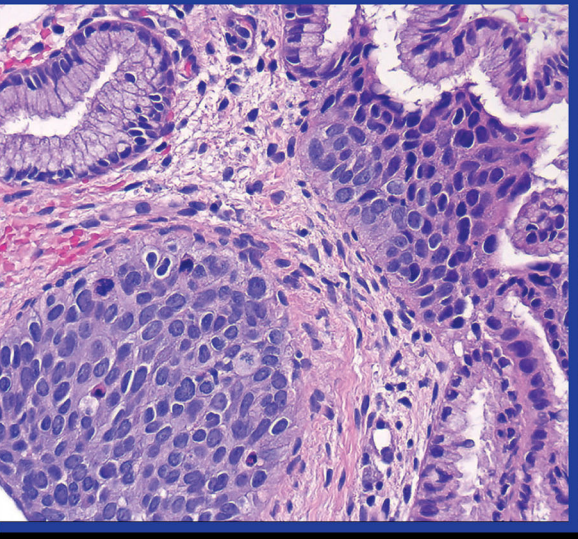
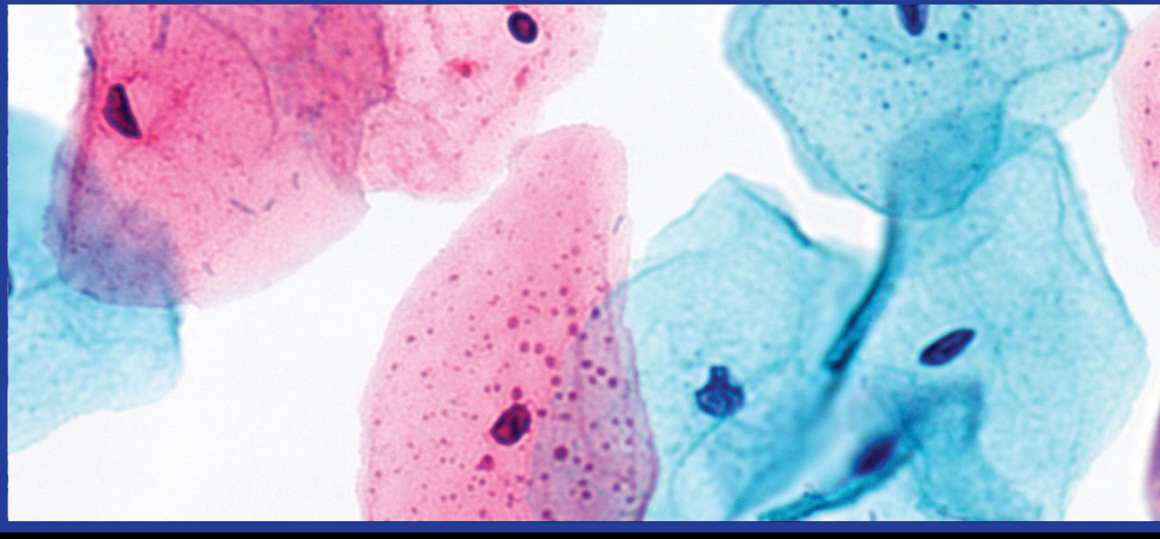


ATLAS OF GYNECOLOGIC CYTOPATHOLOGY

WITH HISTOPATHOLOGIC CORRELATIONS





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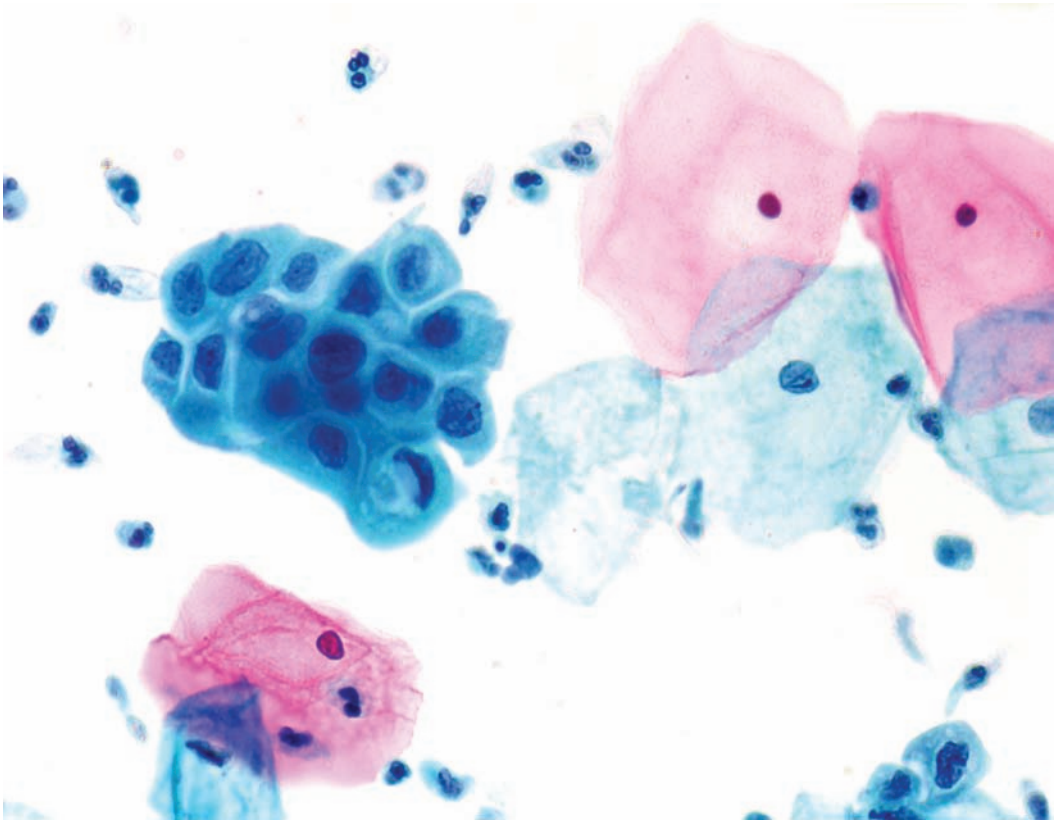

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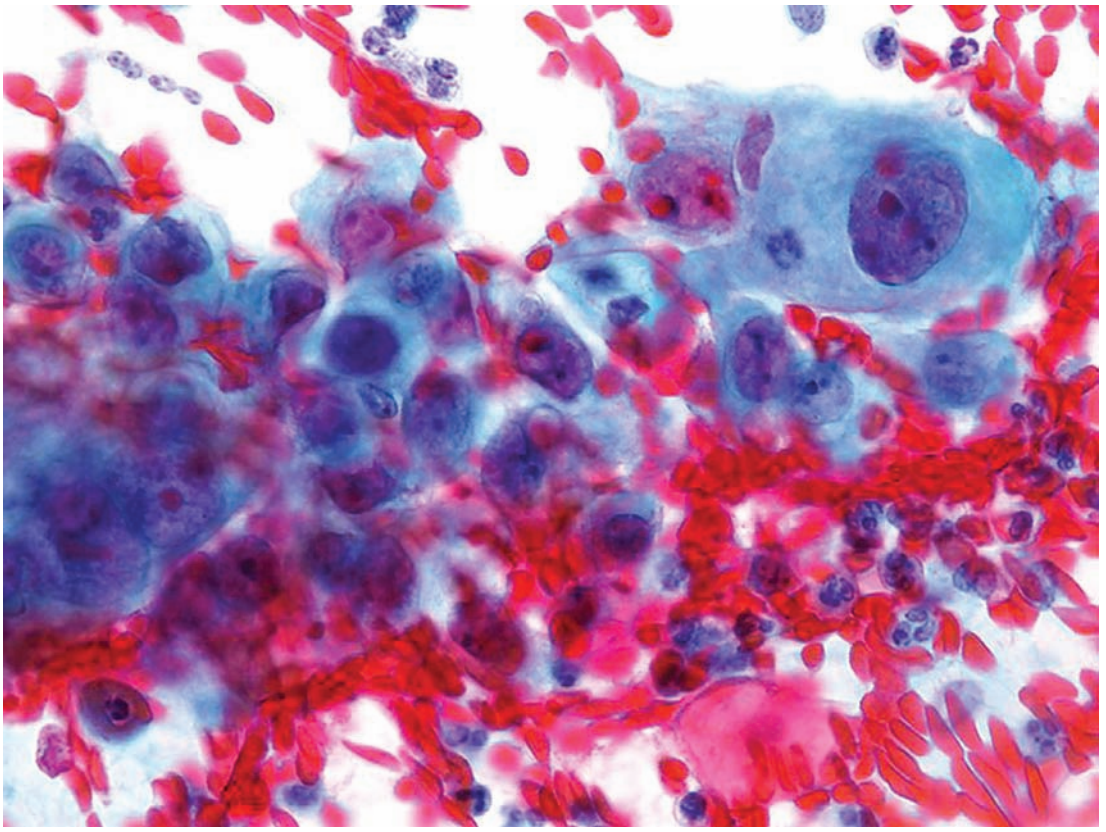

Atlas of Gynecologic Cytopathology

With Histopathologic Correlations

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We dedicate this book to our mentors, whose knowledge we were given to share.

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Foreword

The practice of cytopathology is an art and a science that depends on meticulous observation of morphologic features of cytologic material, and correlating the images with recognized histopathologic characteristics and the presenting clinical findings. In this scenario, the interaction between the pathologist and the treating physician is critical in order to ensure optimal care for our patients who demand, and deserve, nothing less. Nowhere is this more notable than in gynecologic diseases, where an open communication among cytopathologists, colposcopists, and gynecologic oncologists/surgeons is of paramount importance. It is a pleasure to pen a foreword to this outstanding work, which achieves these goals in a remarkable way.

Atlas of Gynecologic Cytopathology With Histopathologic Correlations draws from the vast library of material at Johns Hopkins, an institution that is renowned worldwide in the fields of cytopathology and gynecologic pathology. The entire spectrum of gynecologic diseases that a pathologist may encounter in the day-to-day practice is presented in a well-organized format. The volume is divided into 12 chapters along the lines of the Bethesda System for Reporting Gynecologic Cytology, the standard accepted by the profession in the United States and most of Europe. Carefully selected high-resolution images illustrate the cytomorphologic characteristics and the differential diagnostic problems associated with cervical lesions. The clarity, color reproduction, and field selection of these exquisite figures achieve the difficult goal of conveying the three-dimensional (3-D) images seen though the actual lens of a microscope in a 2-D image format. Drs. VandenBussche, Ali, and Rosenthal, internationally recognized experts in the field, who have the experience of practicing the discipline and the talent of transmitting the information as mentors, have authored this valuable and elegant text. The collaboration of Dr. Vang, a notable gynecologic pathologist, in authoring this volume enriches our understanding of the histologic correlations. The newer automated processing and screening devices are well represented in this atlas, a definite advantage to the volume. Experience with these techniques, the introduction of new molecular testing, and our understanding of the evolution of cervical diseases have dramatically changed over the last decade. This dictated a parallel change of management and prevention protocols for cervical neoplasia. The inclusion of a chapter on the new guidelines of the American Society for Colposcopy and Cervical Pathology (ASCCP) for managing cervical lesions makes it an excellent up-to-date resource for pathologists, and helps them to understand the implication of their diagnosis on management.

Despite a plethora of atlases and textbooks on cytopathology, *Atlas of Gynecologic Cytopathology With Histopathologic Correlations* is clearly a most welcome addition to the cytopathology literature. It is a practical, succinctly written, and superbly illustrated volume. The inclusion of colposcopic and histopathologic correlation enhances its value to cytopathologists and surgical pathologists alike, regardless of the extent of their experience. The authors should be commended on this excellent work.

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Preface

The Pap test has had a remarkable history, essentially in establishing the field of cytopathology and greatly contributing to the prevention of cervical cancer worldwide. In spite of numerous controversies and challenges throughout the decades, the Pap test remains one of the most utilized and successful cancer screening tests and has been adapted to meet the needs of modern patients and physicians. Although it is uncertain how the development of human papillomavirus testing and vaccination will affect the future use of the Pap test, pathologists and trainees must remain intimately familiar with the cytomorphologic characteristics of the cervicovaginal cytology samples as well as their histopathologic correlates. Educational curricula for cytomorphology criteria, laboratory methodologies, and quality assurance/quality control processes learned over the years from the Pap test form a foundation on which the rest of cytopathology expands.

The intention of this atlas is to expose the reader to high-quality images that represent the various morphologies seen within each diagnostic category. The images are coupled with captions that direct the reader's attention to important histomorphological features and provide high-yield, updated information about each entity. The atlas may be used as a study guide or as a quick reference next to the microscope.

The authors humbly dedicate this book to their mentors. Christopher VandenBussche thanks his mentors, from whom he continues to learn: Drs. Syed Ali, Yener Erozan, and Dorothy Rosenthal. Dr. Syed Ali owes his entire academic success to the most wonderful teachers he had the privilege to be trained with: Drs. Dorothy Rosenthal, Yener Erozan, and Steven Hajdu. Dr. Dorothy Rosenthal was mentored by George Wied and Leopold Koss, to whom she owes enormous gratitude for their contributions to her professional education. Russell Vang would like to acknowledge Drs. Robert Kurman and Brigitte Ronnett for their mentoring over the years, as well as continued support and encouragement, and to Evelyn Hinton, his division's administrative coordinator, for her invaluable assistance.

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Atlas of Gynecologic Cytopathology

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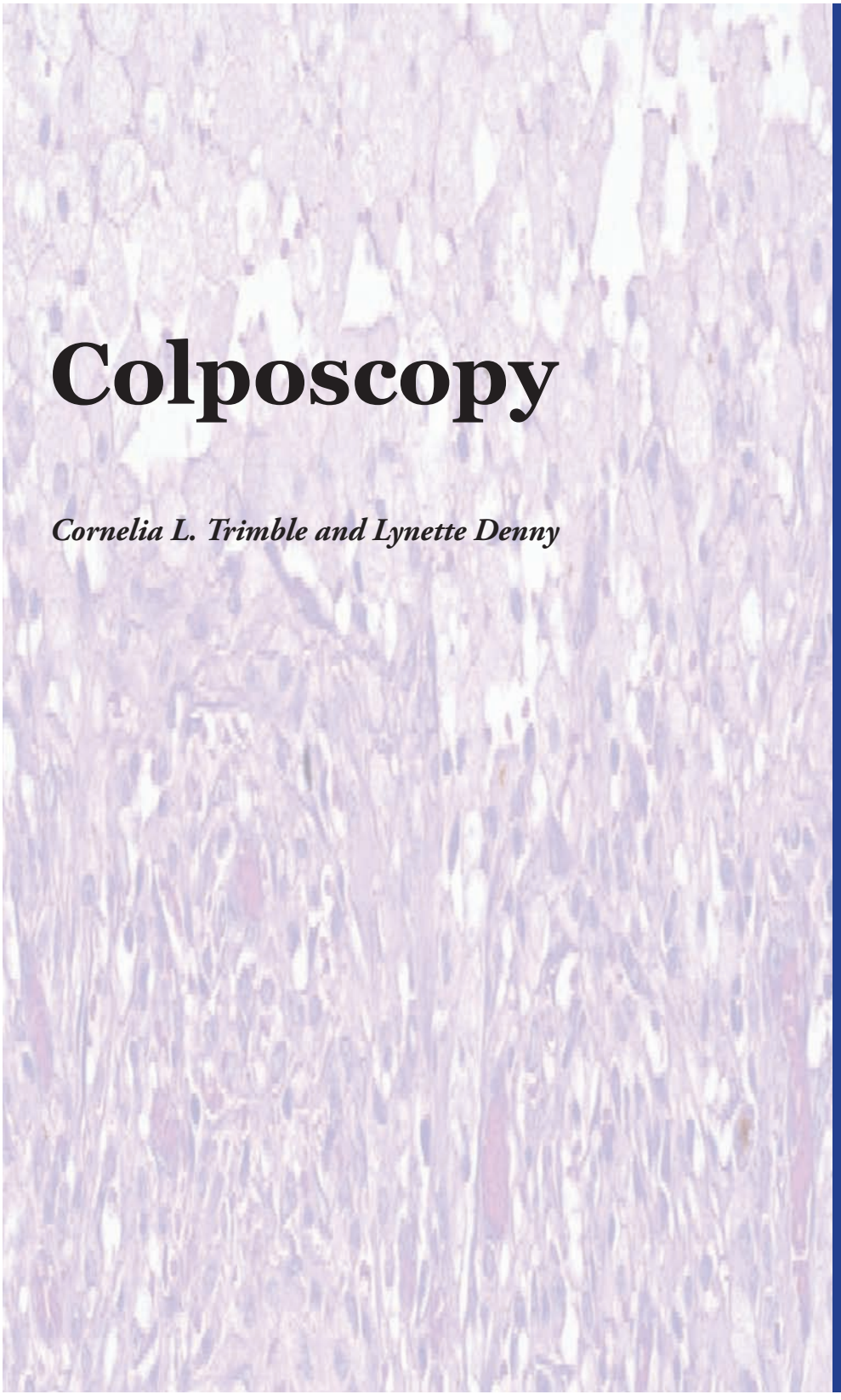
Atlas of Gynecologic Cytopathology: With Histopathologic Correlations



1

Colposcopy

Cornelia L. Trimble and Lynette Denny

Colposcopy is performed by applying a 3% acetic acid (vinegar) solution to the cervical mucosa, and viewing through a green filter. The first step is to determine whether one is able to visualize the entire squamocolumnar junction (SCJ). Most human papillomavirus (HPV)-associated lesions occur at the SCJ. As dysplastic cells have a far greater nuclear-to-cytoplasmic ratio than normal mature squamous cells, they dehydrate much more easily than normal cells, thereby becoming opaque (acetowhite). Although many conditions, including inflammation, can increase the nuclear-to-cytoplasmic ratio, dysplastic lesions are typically sharply demarcated, and have pathognomonic patterns of neovasculature: punctation and mosaicism. If a lesion is subtle, it may be helpful to apply Lugol's (iodine) solution to the mucosal surface. Glycogen turns black when exposed to iodine. Because dysplastic and malignant cells often lack normal glycogen content, normal cells tend to appear darker than dysplastic or malignant cells. The colposcopist should be aware that the application of Lugol's solution can cause an artifact in the tissue, which may skew the interpretation of the histology.

Punctation is the gross appearance of neovasculature that has formed perpendicular to the mucosal surface, typically described as being either "fine" or "coarse." Mosaicism involves aborization of the neovasculature. The neovasculature associated with cervical intraepithelial neoplasia is relatively uniform in caliber, in contrast to that in inflammatory conditions, in which vessels are tortuous, irregular, and have varying caliber.

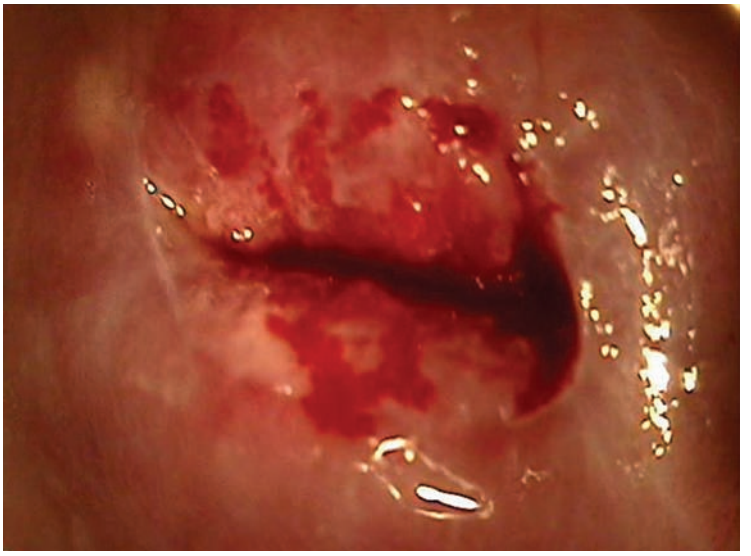


Figure 1.2a — Normal Cervix, No Green Filter. The entire squamocolumnar junction is visible.

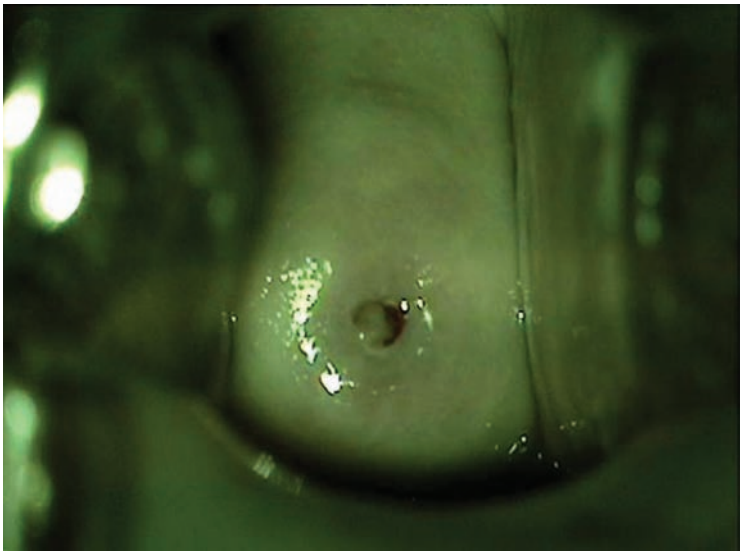


Figure 1.1 — Normal Cervix, Gross Appearance, Green Filter. The squamocolumnar junction is just inside the cervical os, and is not visible.

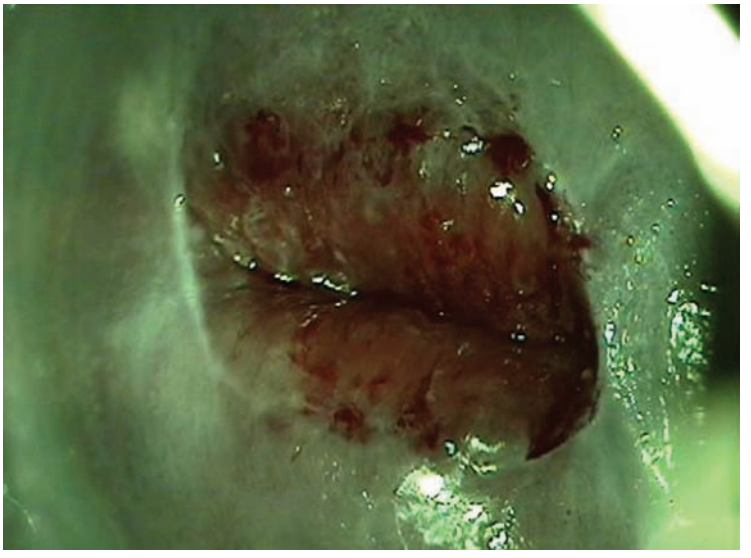


Figure 1.2b — Normal Cervix, Dilute Acetic Acid Wash, Green Filter. Same cervix as in Figure 1.2a, but with a green filter. No acetowhite areas are visible.

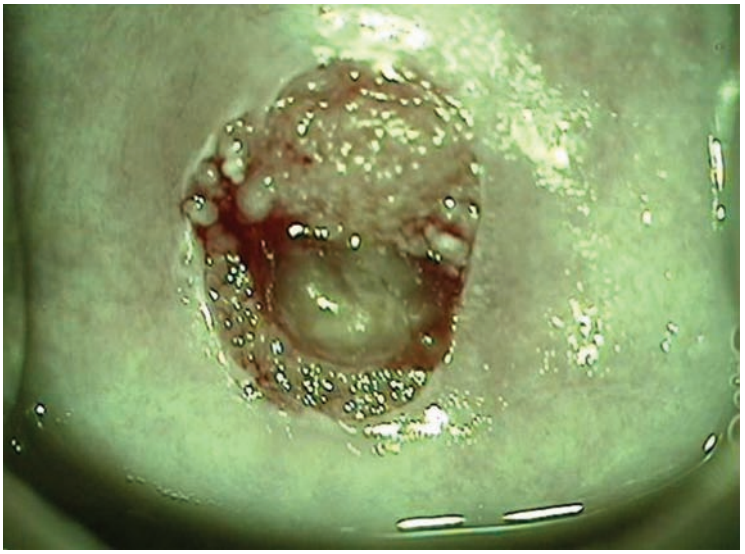


Figure 1.3 — Normal Cervix. Another example of the squamocolumnar junction, visible circumferentially.

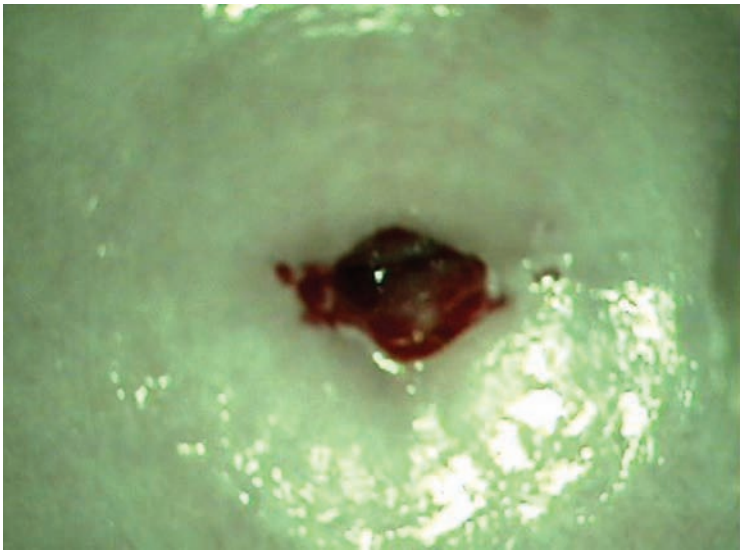


Figure 1.4 — Normal Cervix. The squamocolumnar junction is visible 360°, but the transformation zone is just inside the os.

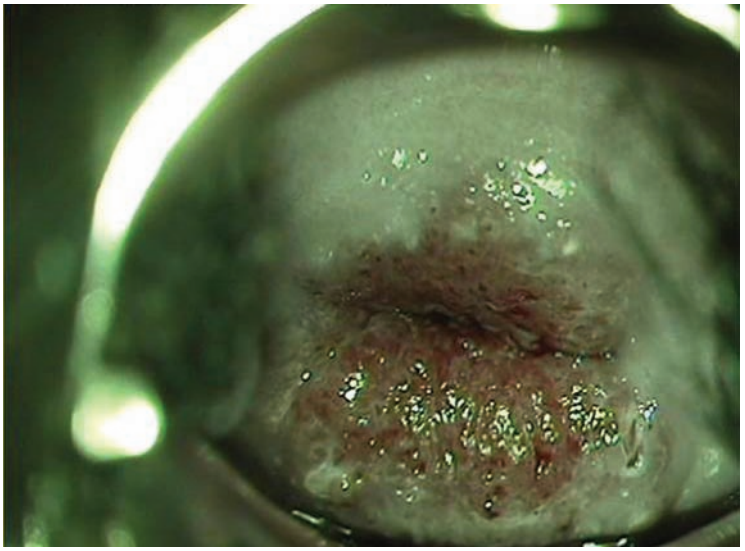


Figure 1.5 — Chronic Cervicitis and Squamous Metaplasia. The endocervical tissue at the transformation zone is slightly friable.

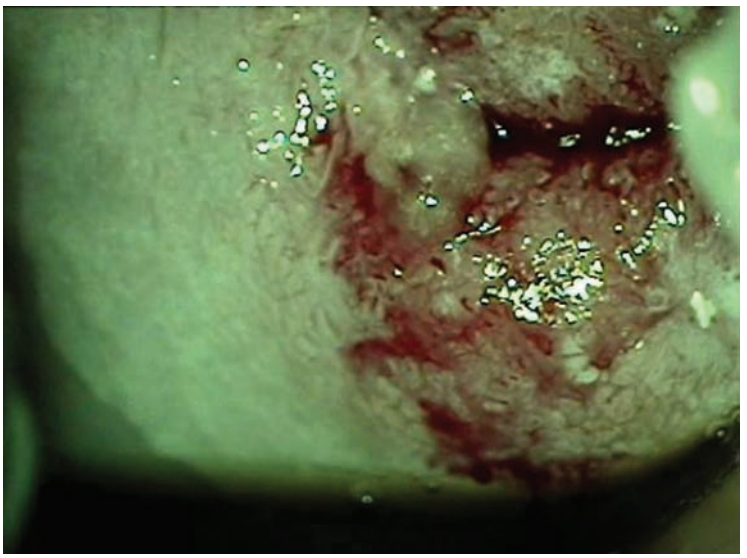


Figure 1.6 — Chronic Cervicitis and Squamous Metaplasia. The acetowhite epithelium has irregular vasculature and is not sharply demarcated.

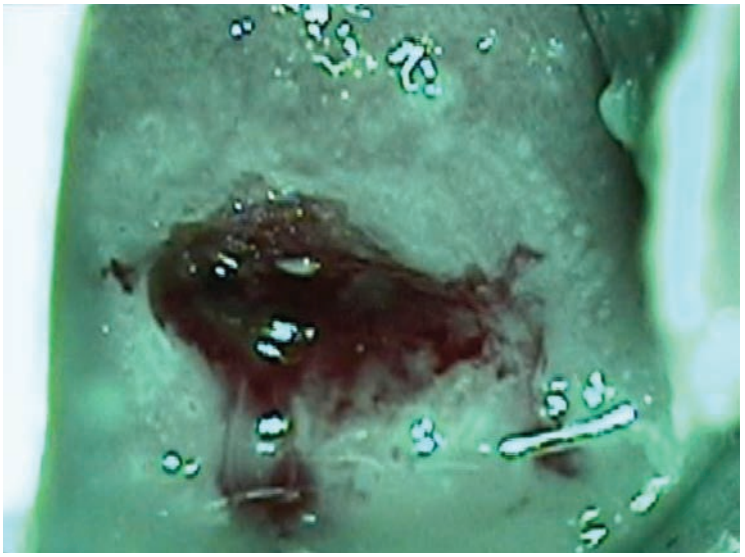


Figure 1.7 — Chronic Cervicitis and Squamous Metaplasia. Acetowhite areas at the squamocolumnar junction from 7 o'clock to 10 o'clock appear punctate; this represents metaplastic areas surrounding the gland openings. The cobblestone appearance of the acetowhite epithelium from 1 o'clock to 3 o'clock is more representative of low-grade squamous intraepithelial lesion (LSIL).

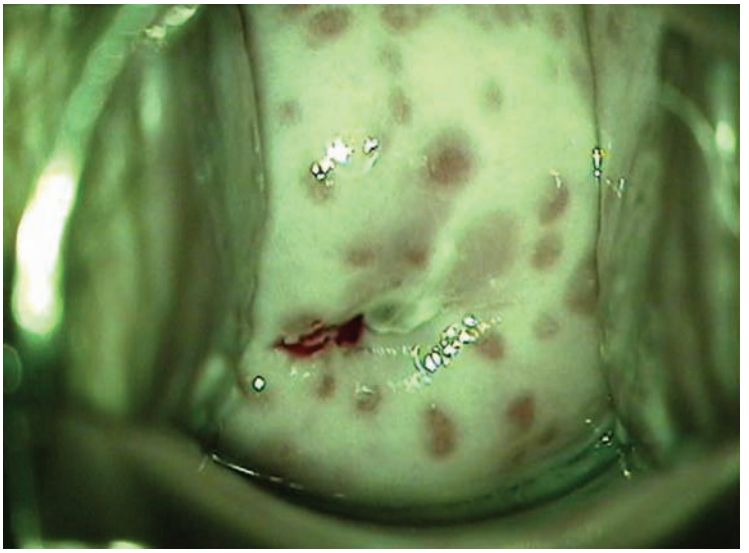


Figure 1.8 — Chronic Cervicitis and Squamous Metaplasia. This pattern of petechiae is known as "strawberry cervix." It can be seen in both infectious and noninfectious cervicitis.

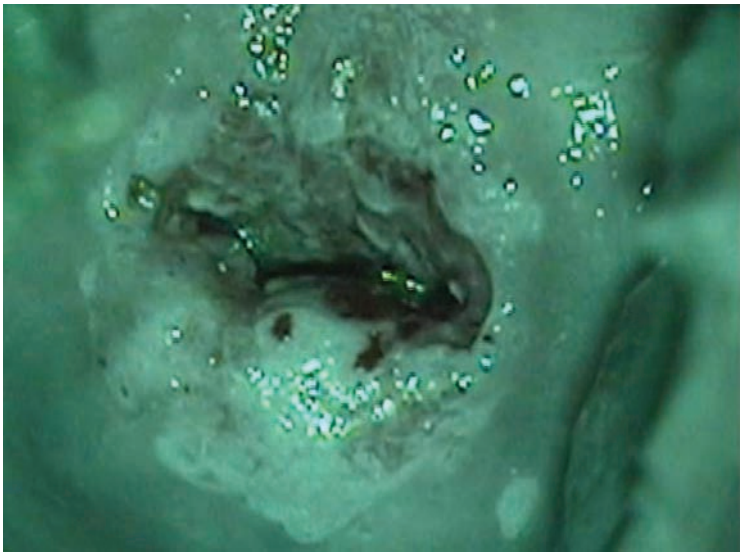


Figure 1.9 — Low-Grade Squamous Intraepithelial Lesion (LSIL). Sharply demarcated acetowhite epithelium is identifiable posteriorly, from 4 o'clock to 8 o'clock; the upper limit of the lesion is visible.

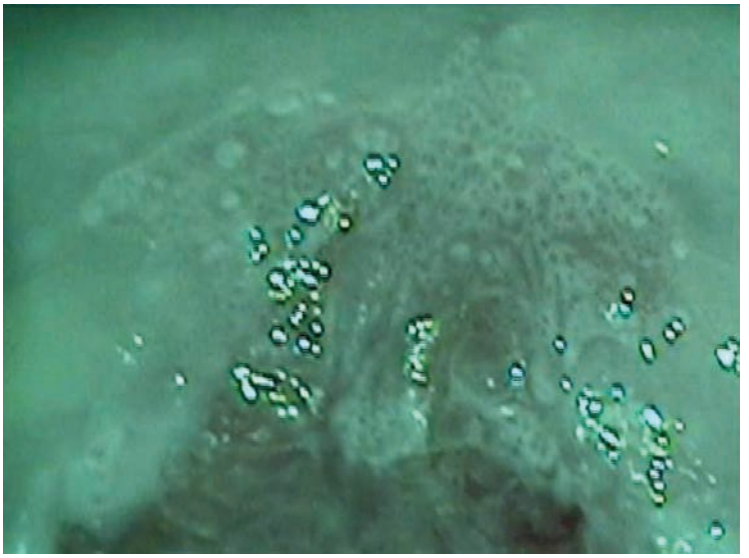


Figure 1.10 — Low-Grade Squamous Intraepithelial Lesion (LSIL). This higher magnification image of the cervix depicted in Figure 1.9 shows the anterior squamocolumnar junction, with chronic cervicitis and squamous metaplasia around the gland openings.

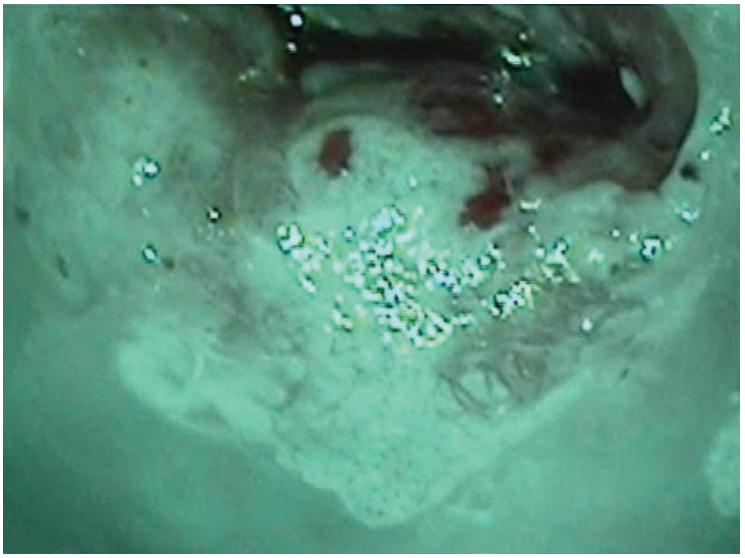


Figure 1.11 — Low-Grade Squamous Intraepithelial Lesion (LSIL). This image is the posterior squamocolumnar junction of the cervix depicted in Figure 1.9, showing dense acetowhite epithelium with fine mosaicism from 5 o'clock to 7 o'clock. The upper limit of the lesion is visible.

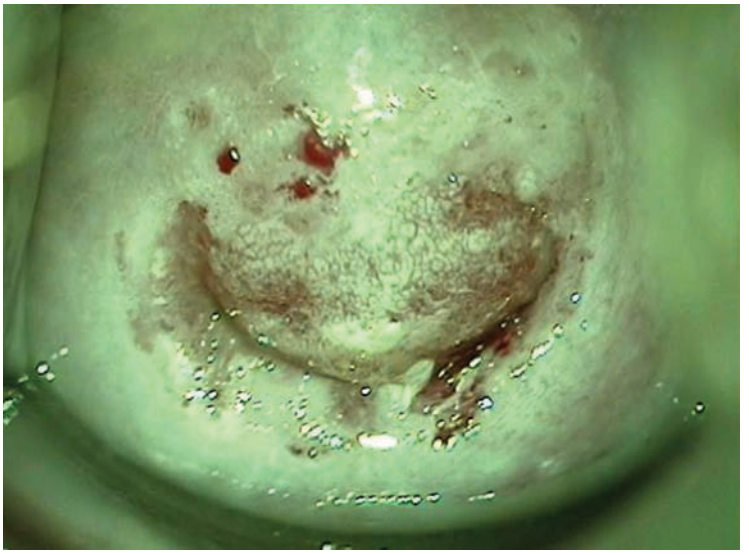


Figure 1.12 — Low-Grade Squamous Intraepithelial Lesion (LSIL). A clear example of fine mosaicism is seen from 10 o'clock to 2 o'clock.

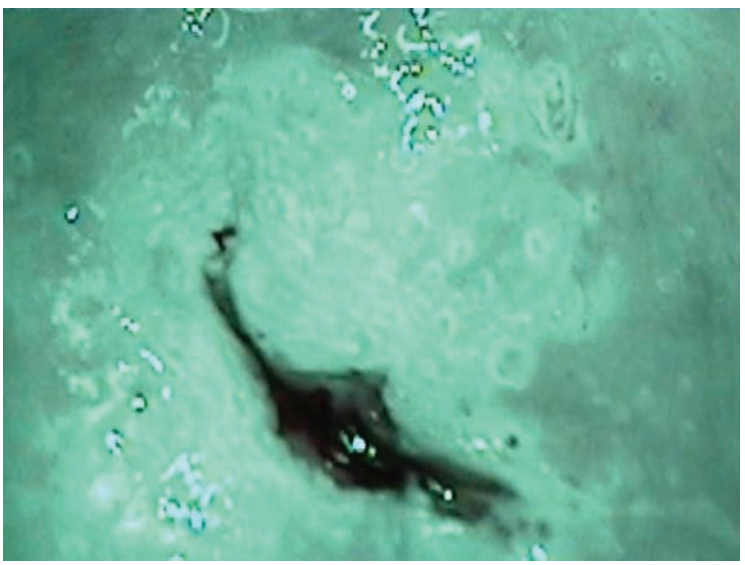


Figure 1.13 — Low-Grade Squamous Intraepithelial Lesion (LSIL) in a Background of Chronic Cervicitis and Squamous Metaplasia. Acetowhite epithelium with diffuse margins is present posteriorly, more sharply demarcated, and with fine mosaicism from 9 o'clock to 1 o'clock.

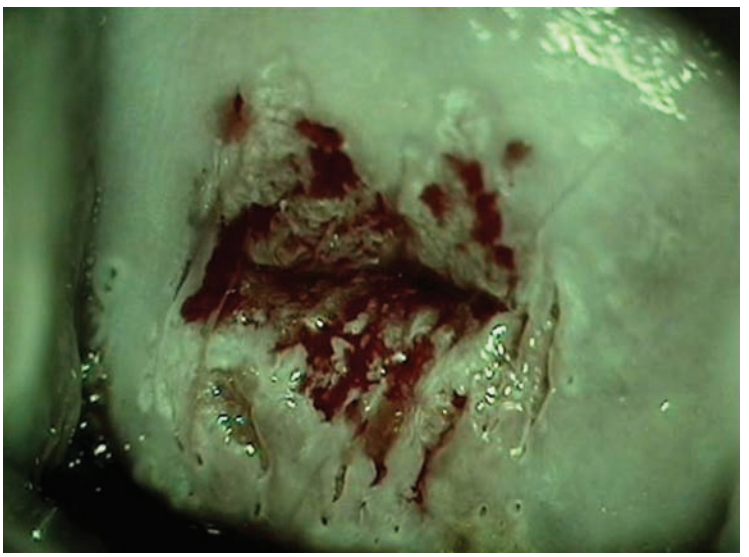


Figure 1.14 — Low-Grade Squamous Intraepithelial Lesion (LSIL). The ectropion is friable (cervicitis), and a rim of acetowhite epithelium with fine mosaicism is visible anteriorly, from 10 o'clock to 1 o'clock, and posteriorly, from 7 o'clock to 8 o'clock.

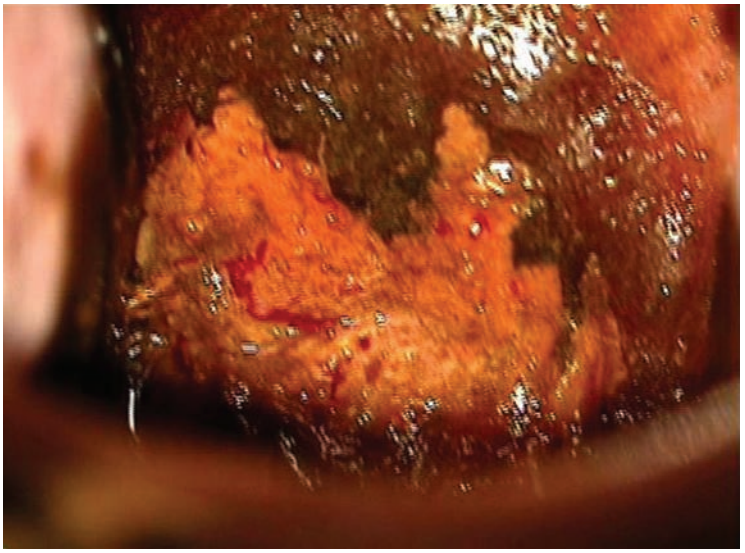


Figure 1.15 — Low-Grade Squamous Intraepithelial Lesion (LSIL), Lugol's Solution. This image is the same cervix depicted in Figure 1.14, showing the anterior portion of the squamocolumnar junction. The discrete margins of the lesion are easily identified.

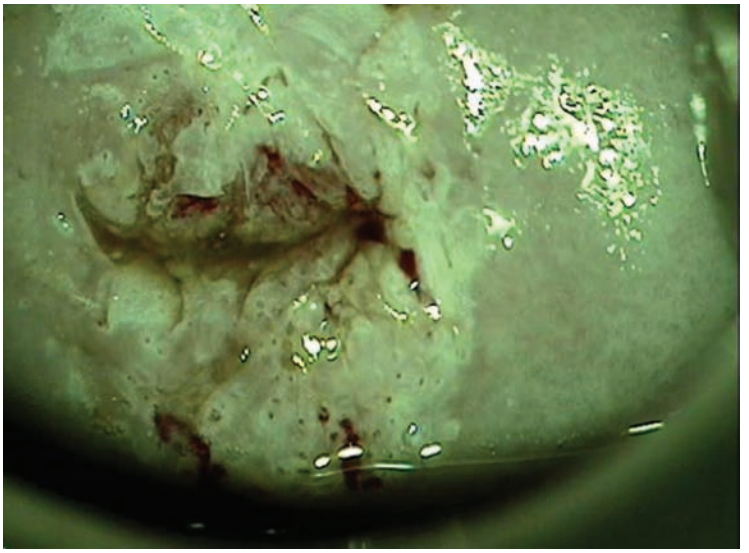


Figure 1.16 — Low-Grade Squamous Intraepithelial Lesion (LSIL) in a Background of Chronic Cervicitis and Squamous Metaplasia. Posteriorly, the acetowhite epithelium is nearly translucent. Gland openings are easily identified. Anteriorly, nearly out of the frame, more sharply demarcated acetowhite epithelium with fine mosaicism is visible.

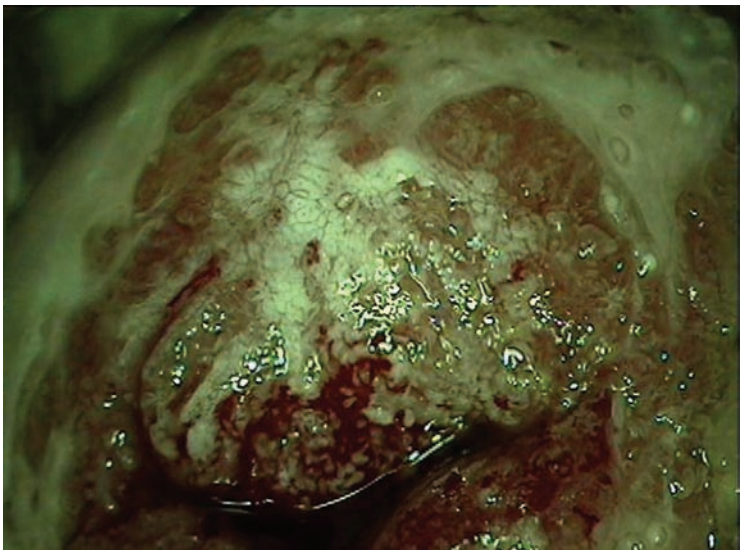


Figure 1.17 — High-Grade Squamous Intraepithelial Lesion (HSIL). Sharply demarcated dense acetowhite epithelium is identifiable at the squamocolumnar junction and demonstrates fine mosaicism.

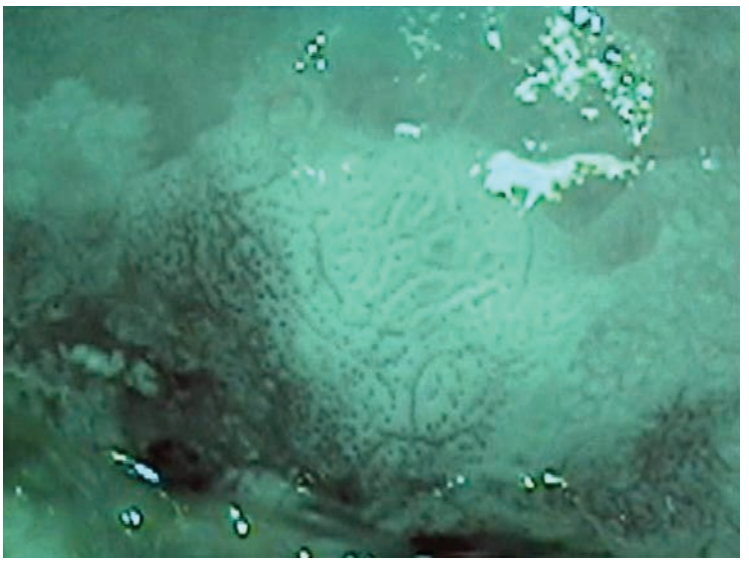


Figure 1.18 — High-Grade Squamous Intraepithelial Lesion (HSIL). Sharply demarcated acetowhite epithelium can be seen with a slightly different pattern of mosaicism.

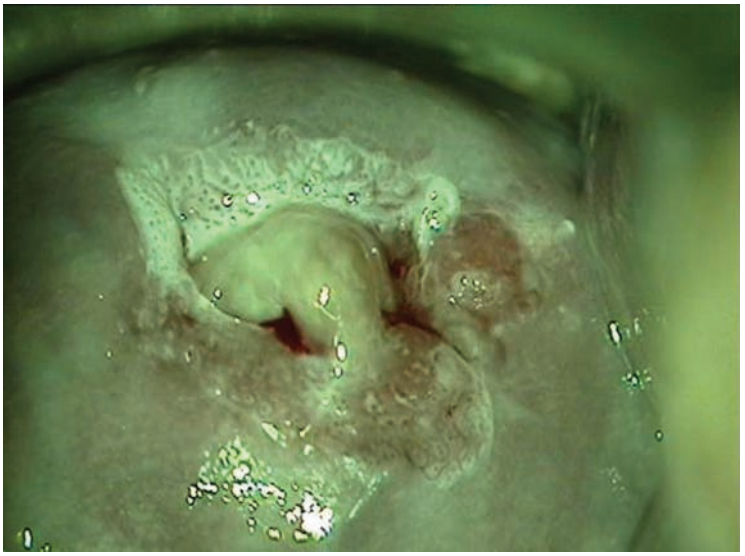


Figure 1.19 — High-Grade Squamous Intraepithelial Lesion (HSIL). The lesion can be seen between 10 o'clock and 2 o'clock. The more translucent area from 4 o'clock to 9 o'clock is likely to be LSIL.

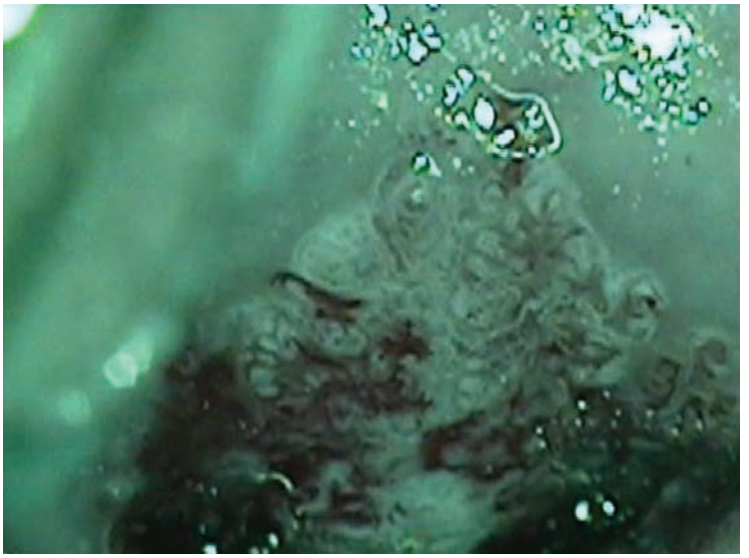


Figure 1.20 — High-Grade Squamous Intraepithelial Lesion (HSIL). The sharply demarcated acetowhite epithelium demonstrates coarse mosaicism.

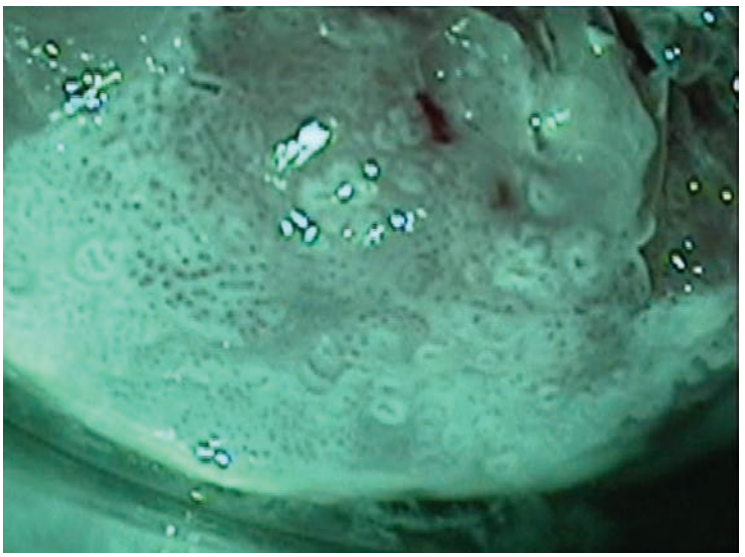


Figure 1.21 — High-Grade Squamous Intraepithelial Lesion (HSIL). The lesion can be seen posteriorly and extends from the squamocolumnar junction to the portio.

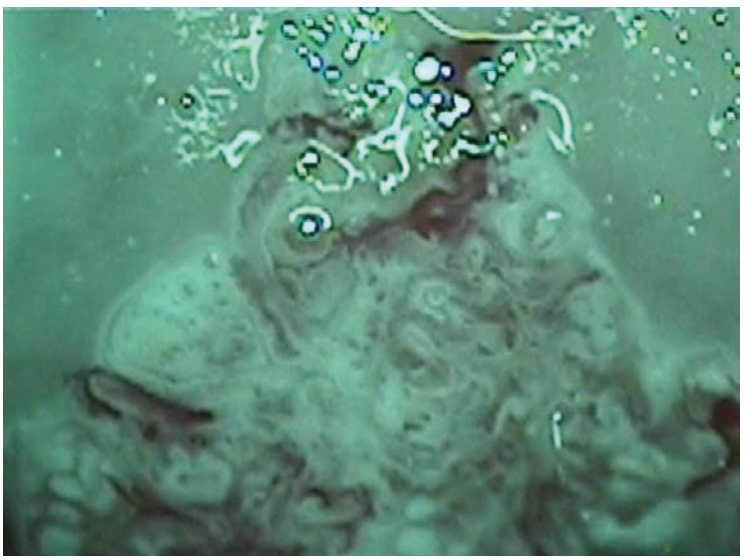


Figure 1.22 — High-Grade Squamous Intraepithelial Lesion (HSIL). Dense acetowhite epithelium with coarse punctation is present.

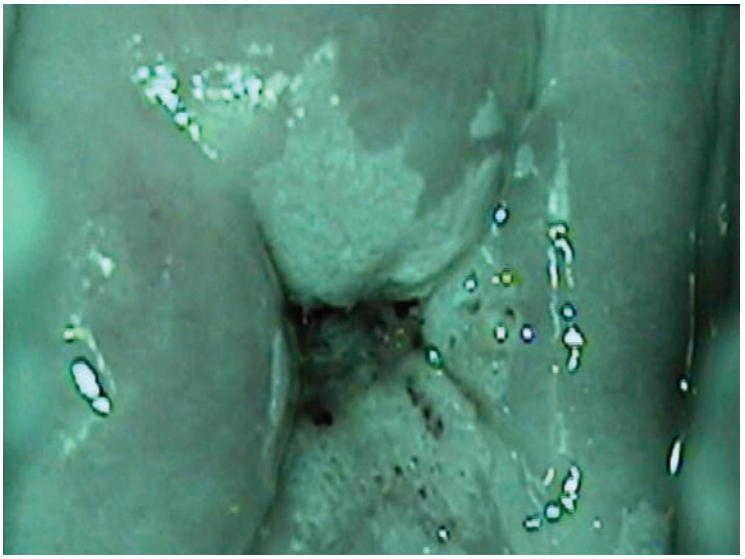


Figure 1.23 — High-Grade Squamous Intraepithelial Lesion (HSIL). The lesion is circumferential and multifocal.

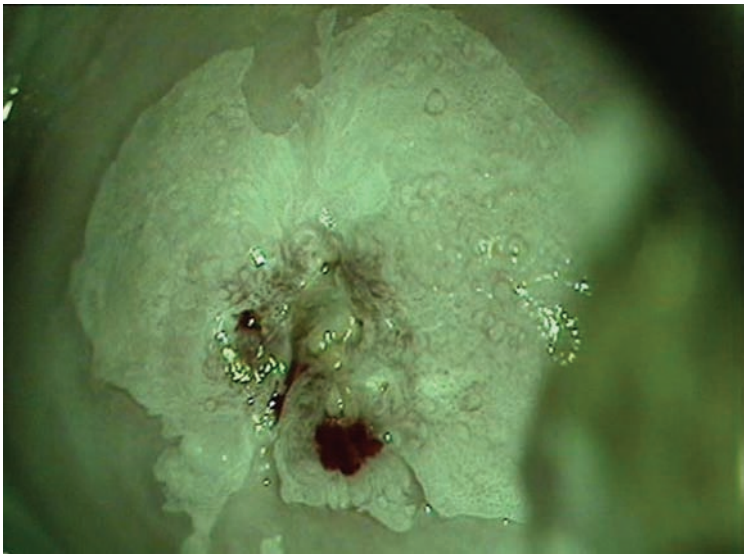


Figure 1.24 — High-Grade Squamous Intraepithelial Lesion (HSIL). This lesion is sharply demarcated, with easily identifiable fine mosaicism, circumferentially.

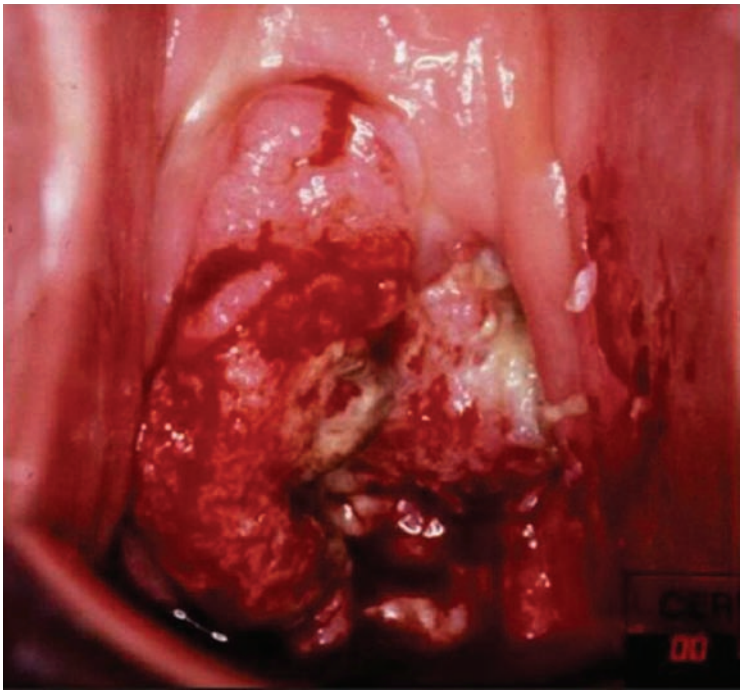
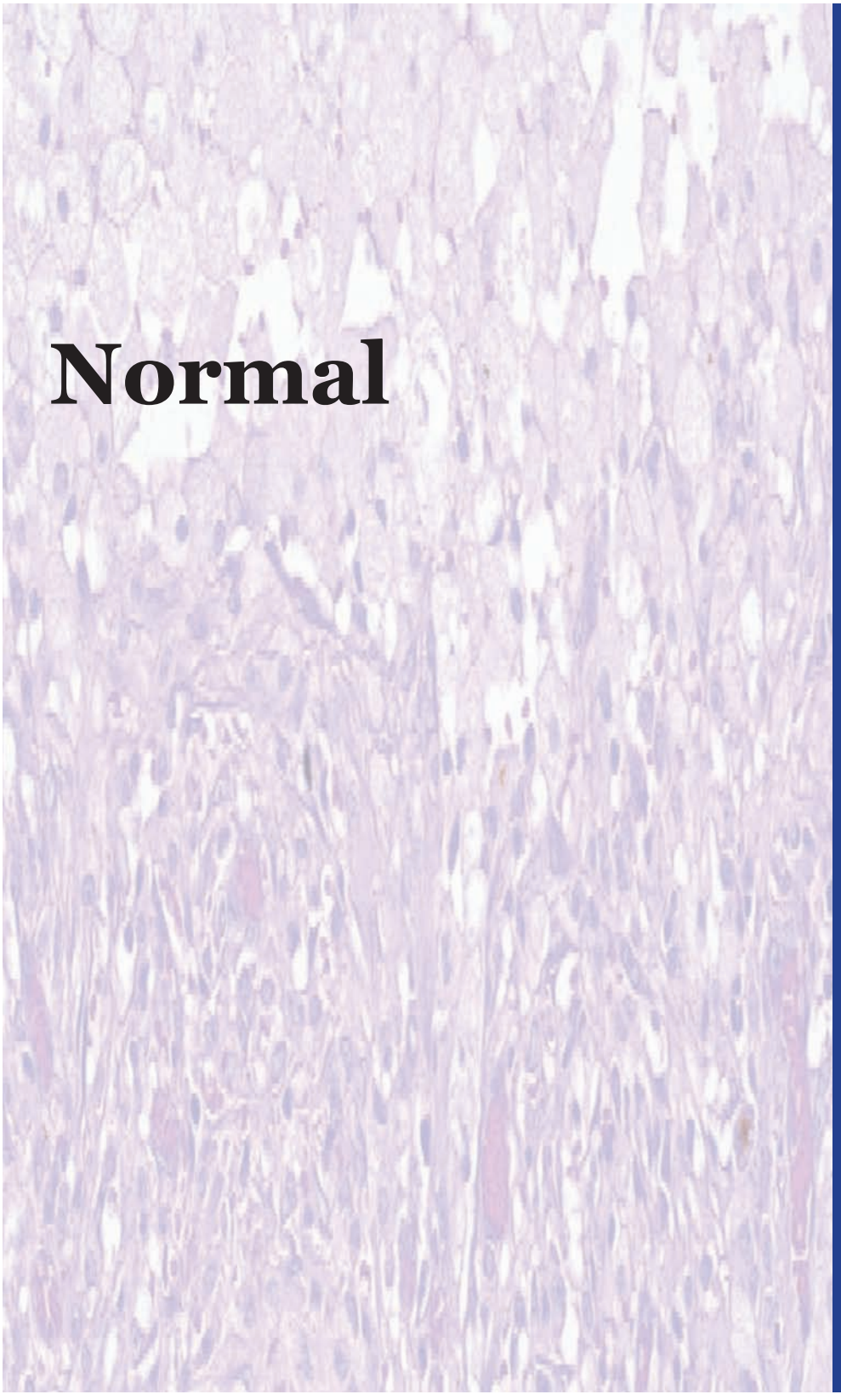


Figure 1.25 — Squamous Cell Carcinoma. The lesion is raised, irregular, and friable. The vasculature is tortuous.



Normal

2

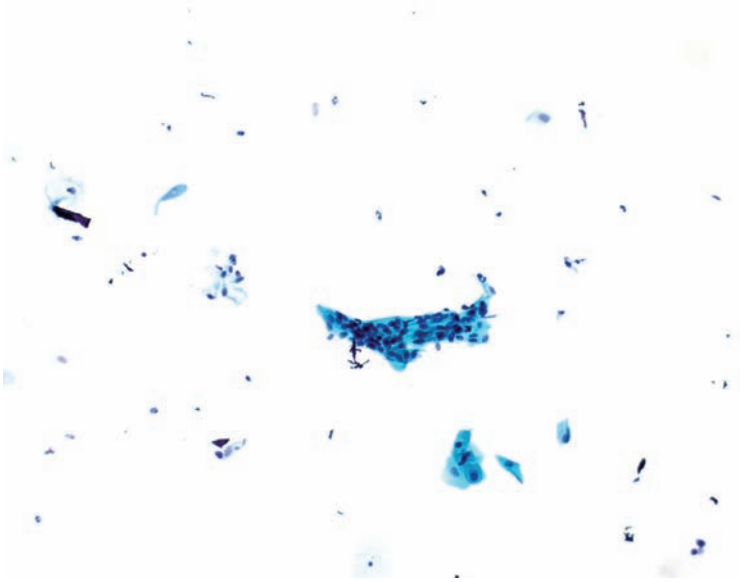


Figure 2.1 — Scant Cellularity With Large Fragments (Liquid Based; Low Power). Before calling a sample inadequate, cellular fragments need to be examined under high power to make sure that they are not atypical, deserving of an interpretive category.

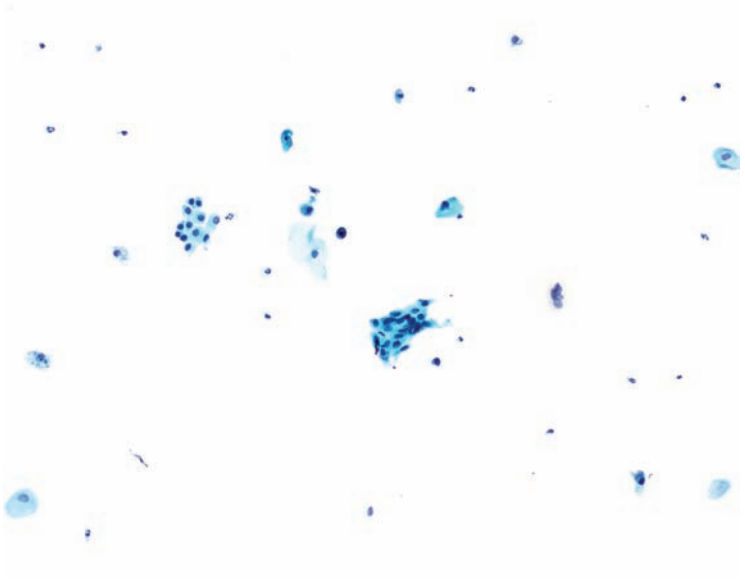


Figure 2.2 — Scant Cellularity With Fragments and Dark Single Cells (Liquid Based; Low Power). In addition to careful examination of fragments, individual cells must be scrutinized for nuclear abnormalities before declaring the sample inadequate.

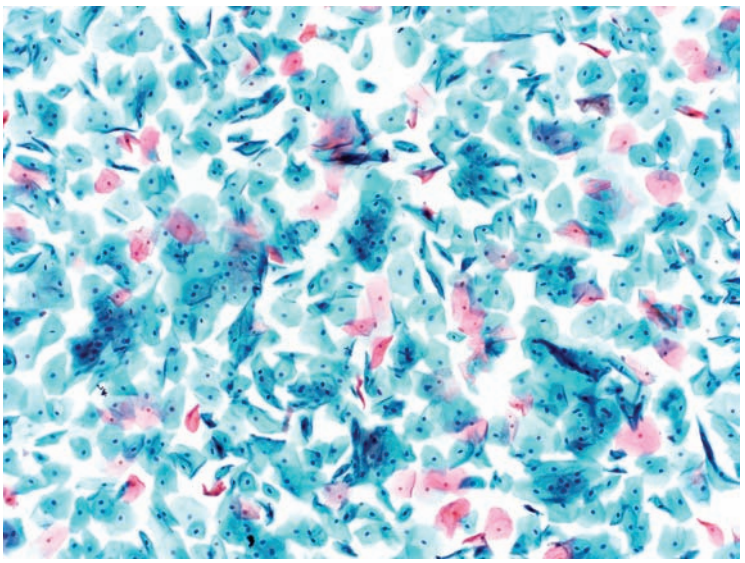


Figure 2.3 — Squamous Cells of Good Cellularity and Staining (Liquid Based; Low Power). This example of a well-prepared, well-stained liquid-based preparation displays the "thin layer," not monolayer, quality of the SurePath™ method.

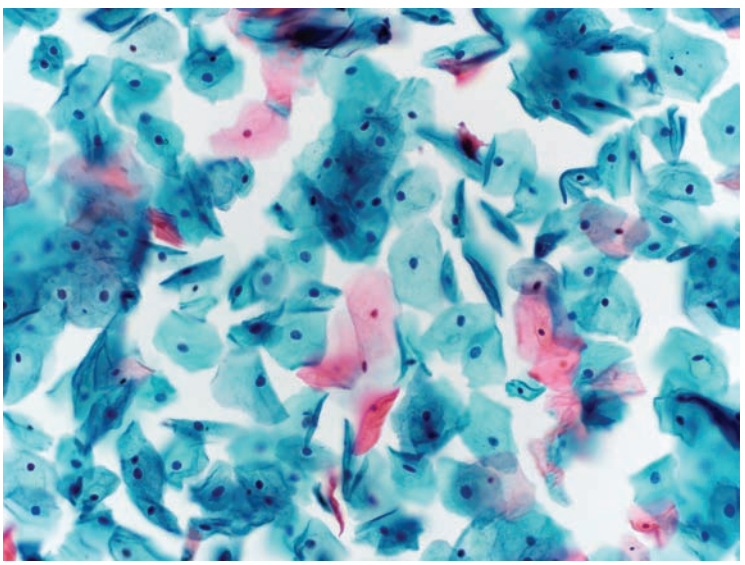


Figure 2.4 — Squamous Cells in a Liquid-Based Preparation (Liquid Based; Medium Power). Liquid-based preparations have deservedly achieved great popularity in the United States because of the even and somewhat random distribution of cells without air-drying artifact, and with generally clear background.

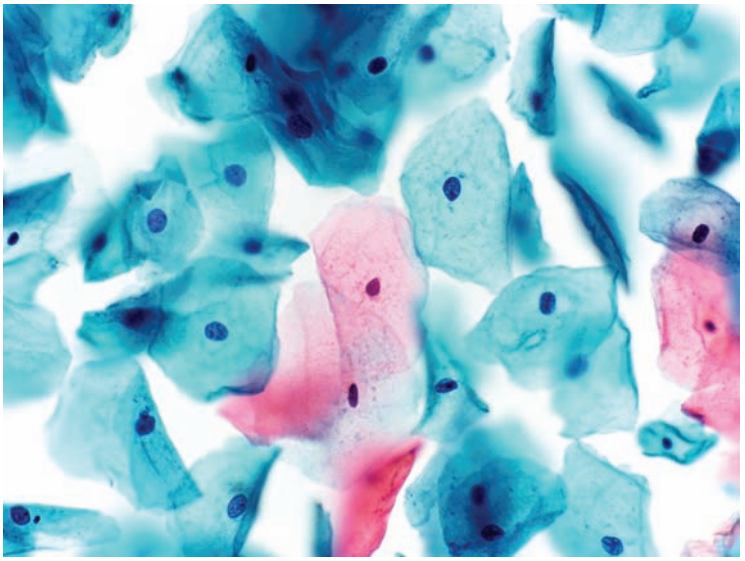


Figure 2.5 — Squamous Cells in a Liquid-Based Preparation (Liquid Based; High Power). Crisp nuclear detail and distinct cytoplasmic quality are appreciated in this SurePath preparation. Intermediate nuclei are the "internal control" for all Pap test samples and need to be consistently stained throughout the sample to establish normal chromatin criteria. Superficial nuclei are approximately half the size of intermediate nuclei and are more hyperchromatic, which is not an abnormal feature, but just a reflection of maximum maturation before the cell extrudes the nucleus and dies.

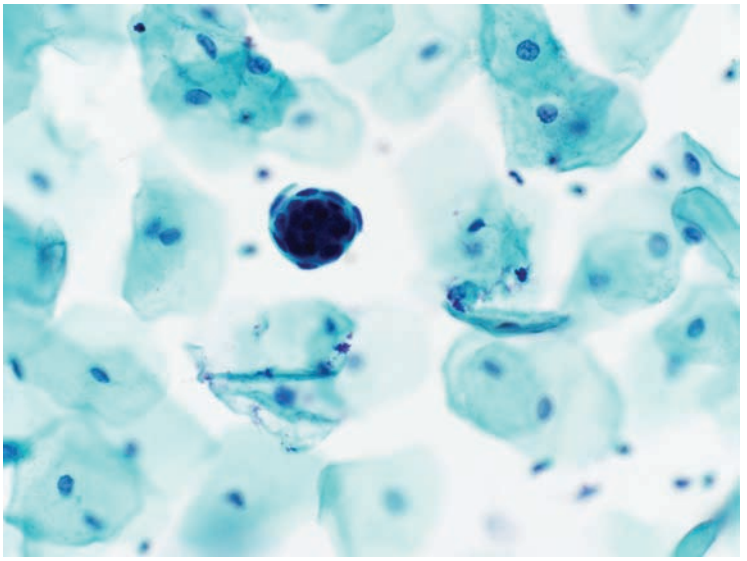


Figure 2.6 — Benign Squamous Pearl (Liquid Based; Medium Power). On low power, this structure would be an "eye catcher." On higher power, its identity is appreciated because of the thin nuclei wrapped around the periphery of the cluster. An endometrial wreath would have rounder peripheral nuclei.

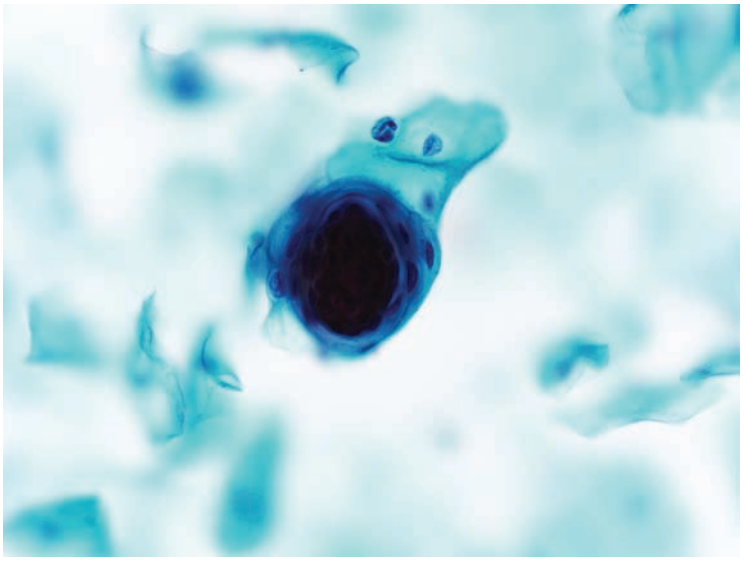


Figure 2.7 — Benign Squamous Pearl (Liquid Based; High Power). Always a challenge to photograph, these three-dimensional structures require careful focus to determine their origin, squamous or endometrial, and the presence of nuclear atypia. This squamous pearl has small nuclei at the periphery and attached benign metaplastic cells, confirming the cell of origin and its benign character.

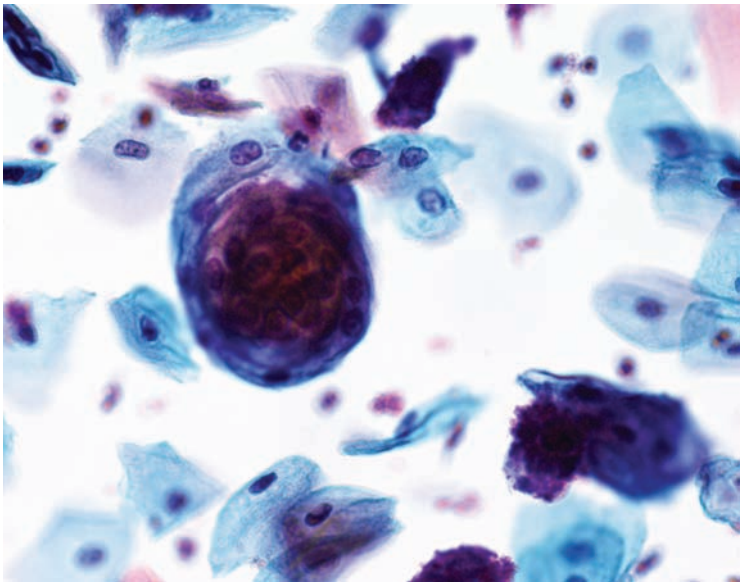


Figure 2.8 — Squamous Pearl (Liquid Based; High Power). Most squamous pearls are difficult to photograph because of the density of the central portion. This pearl reveals most of the central nuclei, and shows the peripheral layering of the epithelial cells. Such flattening of the cells with low nuclear-to-cytoplasmic (N/C) ratios separates them from endometrial whorls that have peripheral cells that are not flattened and have higher N/C ratios.

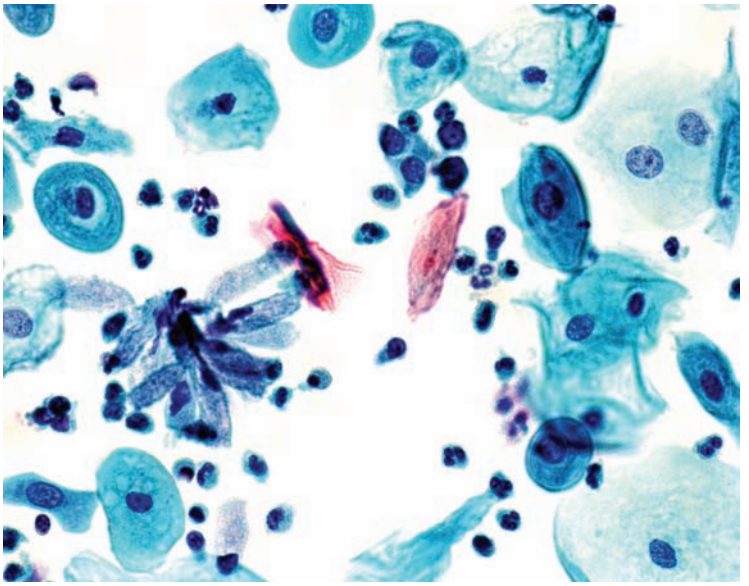


Figure 2.9 — Assorted Benign Cells (Liquid Based; Medium Power). On the left side of the frame is a fan of endocervical cells immediately recognized by their tall mucous columns of cytoplasm. Numerous parabasal cells surround the endocervical groups in an arc. The maturation of squamous cells can be appreciated in the smaller intermediate and more mature intermediate cells on the right half of the frame.

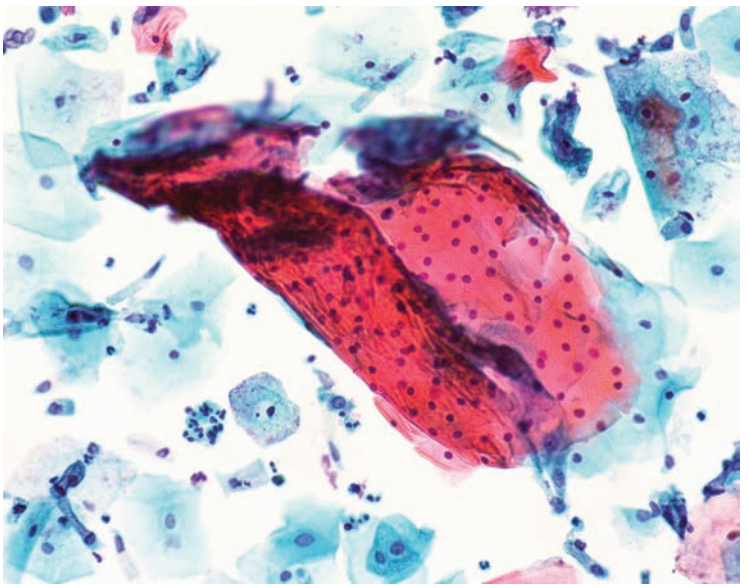


Figure 2.10 — Large Sheet of Benign Squamous Epithelium (Liquid Based; Medium Power). This large fragment of benign epithelium reflects the gentle disaggregation of the SurePath method. Because of optimal fixation and staining, the fragment is transparent, allowing full appreciation of the nuclear detail and N/C ratios.

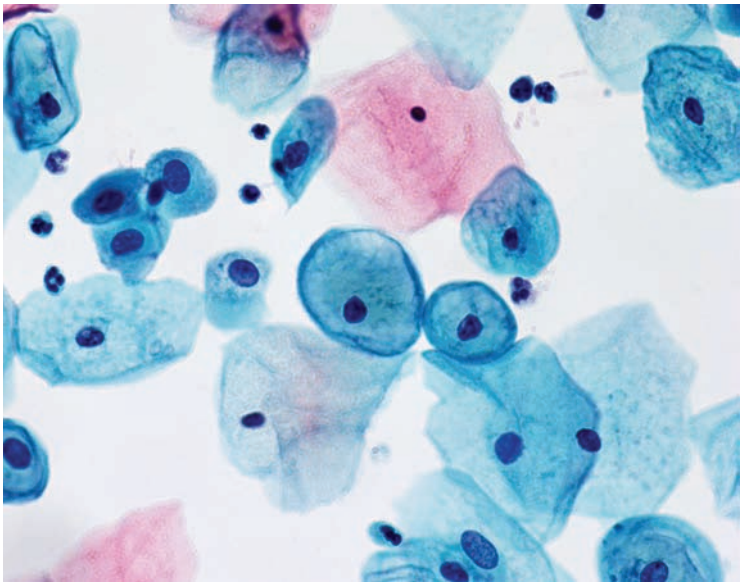


Figure 2.11 — Assorted Squamous Cells (Liquid Based; High Power). Two central cells have cytoplasmic peripheral rims, not to be mistaken for the greater peripheral thickening seen in koilocytes. These cells are a result of the progesterone effect, and have been called "navicular" cells because of the eccentric location of the nuclei and often pyramidal cytoplasmic shape. Smaller cells to the left of the center have opaque cytoplasm, higher N/C ratios, and larger nuclei than any of the other cells in the photograph. They are parabasal cells. Most of the squamous cells in the figure are intermediate in maturation. The total picture is consistent with the second half of the menstrual cycle, pregnancy, or impending menopause.

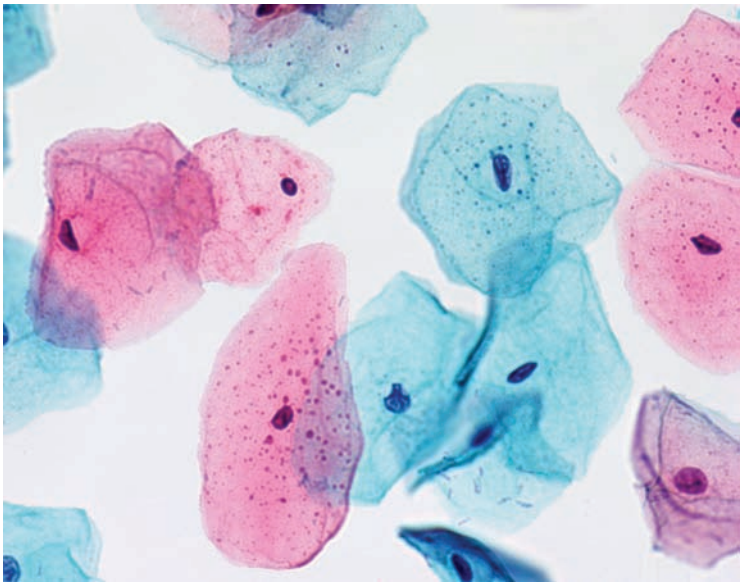


Figure 2.12 — Superficial Squamous Cells (Liquid Based; High Power). When squamous cells mature, they manifest cytoplasmic and nuclear changes. The nuclei become smaller, hyperchromatic, and incapable of reproduction. The cytoplasm changes color from blue to pink, but not always in synchrony with the nuclear changes. The age of the nucleus determines the age of the cell. Keratohyalin granules are a reflection of keratin maturity. Therefore, the cells with pyknotic nuclei and keratohyalin granules are considered superficial regardless of the cytoplasmic color.

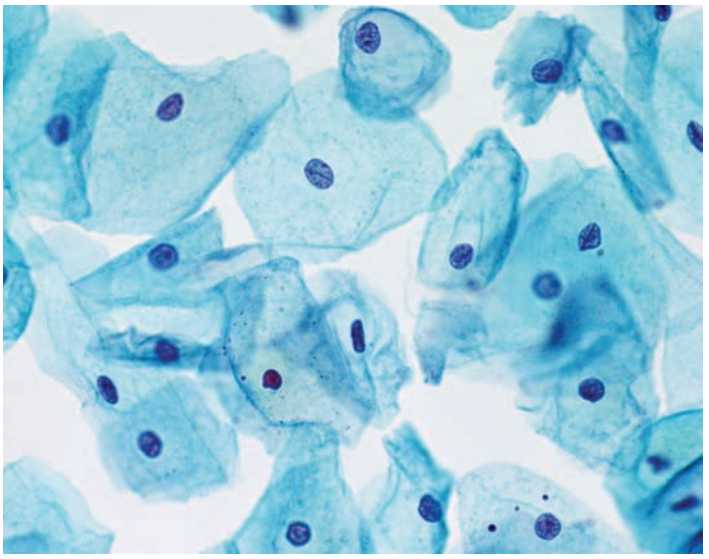


Figure 2.13 — Intermediate Squamous Cells (Liquid Based; High Power). All of these cells have blue cytoplasm and most have open (vesicular) chromatin. The cell at the top of the frame is a navicular cell, still considered an intermediate squamous cell. A few cells have pyknotic nuclei, indicating a higher level of maturity than the others, without squamous maturation. They would be categorized as superficial if cell counts were being performed.

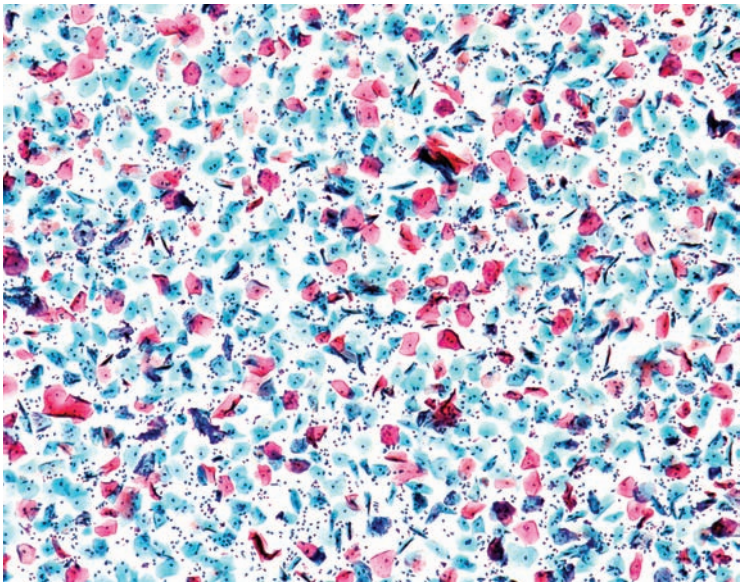


Figure 2.14 — Mixed Maturation Pattern (Liquid Based; Low Power). A mixture of intermediate and superficial squamous cells is a normal phenomenon for a woman at mid-cycle.

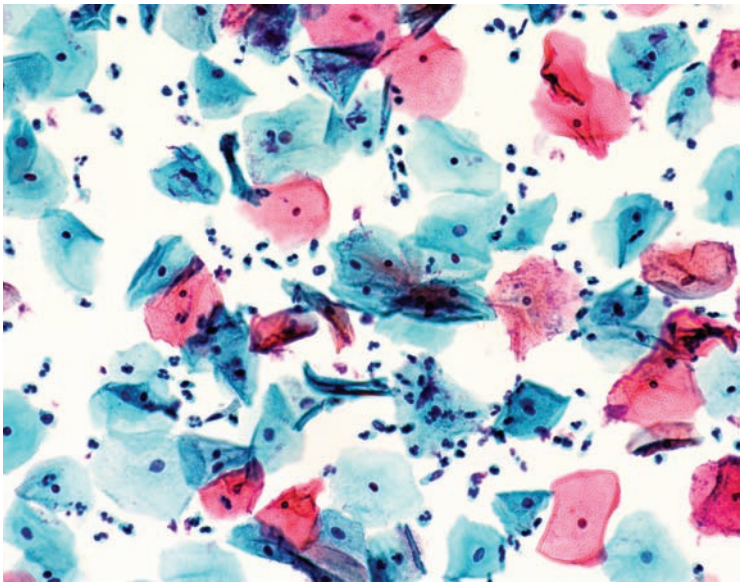


Figure 2.15 — Benign Squamous Cells (Liquid Based; Medium Power). Despite the inflammatory cells, none of the squamous cells are obscured. A gray dusting of a few of the epithelial cells indicates a shift in vaginal flora, secondary to predominance of coccoid bacteria.

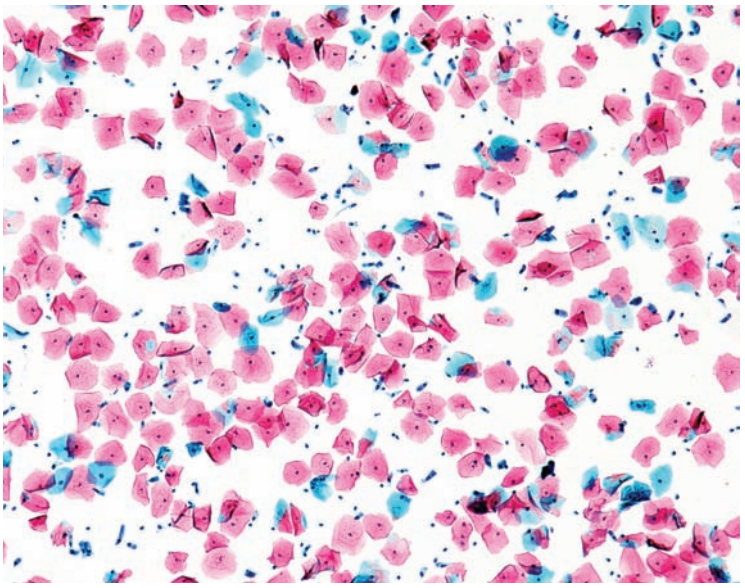


Figure 2.16 — Superficial Squamous Cells (Liquid Based; Low Power). The majority of cells are superficial squamous, indicating a predominance of estrogen rather than progesterone. This pattern reflects either the first half of the menstrual cycle or exogenous estrogen.

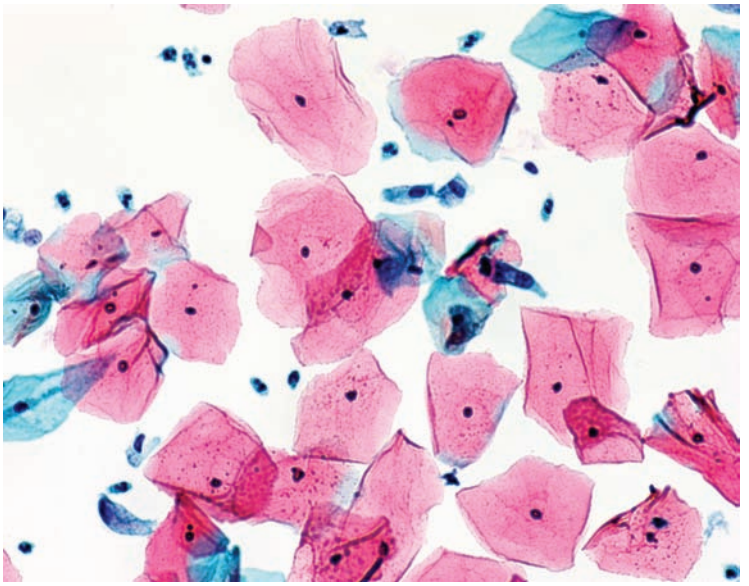


Figure 2.17 — Superficial Squamous Cells (Liquid Based; Medium Power). Higher magnification of Figure 2.16 displays the maturity of the cells. There is not enough inflammation to attribute the maturation to irritation, but to hormonal influence.

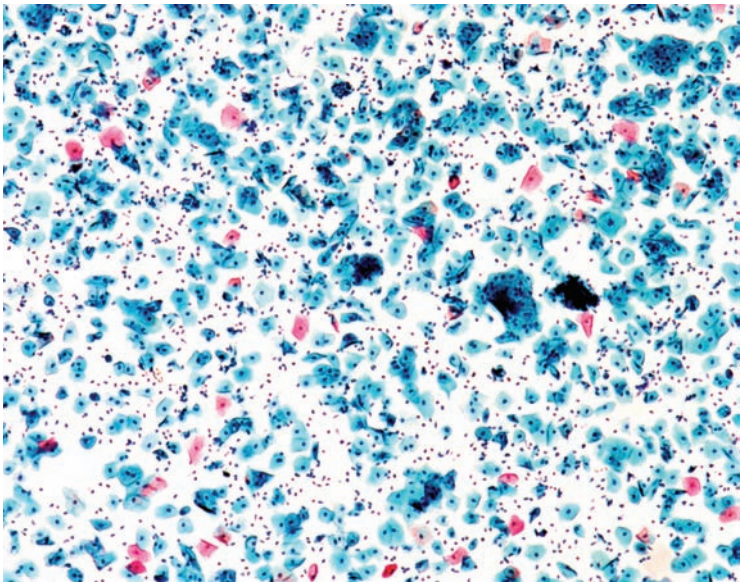


Figure 2.18 — Intermediate Maturation Pattern (Liquid Based; Low Power). When mostly intermediate cells are present, this represents a progesterone-predominant influence. The cause can be pregnancy, second half of the menstrual cycle, birth-control pills, or low estrogen due to impending menopause.

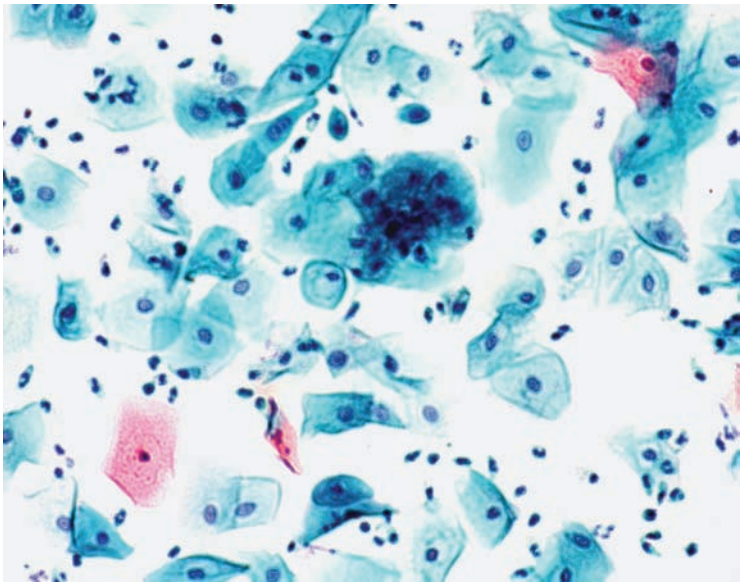


Figure 2.19 — Intermediate Maturation Pattern (Liquid Based; Medium Power). Despite the numerous neutrophils, the predominant cells are either intermediate or parabasal, supporting a hormonal basis for the population of cells.

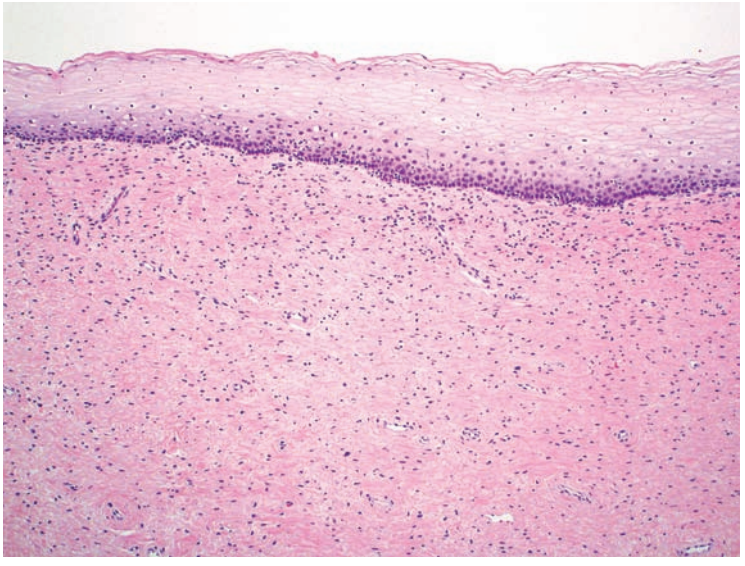


Figure 2.20 — Normal Cervical Squamous Epithelium (Hysterectomy) (Hematoxylin and Eosin [H&E] Stain; Medium Power). This section specifically is from the ectocervix. Note the absence of glands within the stroma. This example shows the typical thickness of the stratified squamous epithelium of the cervix.

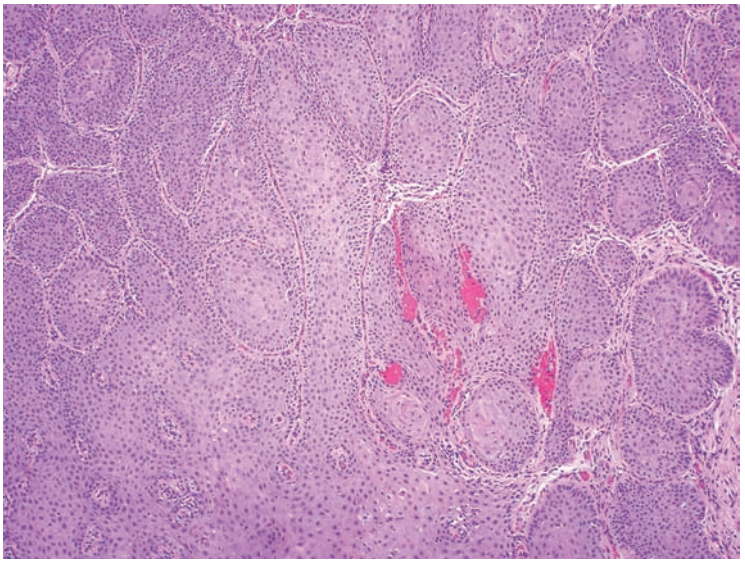


Figure 2.21 — Normal Cervix With Florid Squamous Metaplasia Involving Endocervical Glands (Hysterectomy) (H&E Stain; Intermediate Power). At low-power magnification, this pattern can cause concern for invasive squamous cell carcinoma. However, closer magnification, as seen here, shows partially tangential orientation with an orderly pattern of mostly rounded nests within the stroma. These nests lack the angulated forms, haphazard arrangement, and desmoplastic stroma that are found in carcinoma. The degree of squamous differentiation is mature, and the squamous epithelium lacks nuclear atypia. Other areas (*not shown here*) will contain a background of partly involved endocervical glands. If needed, immunostains for p16 will not show the typical diffuse strong pattern of staining seen in high-risk human papillomavirus (HPV)-related lesions.

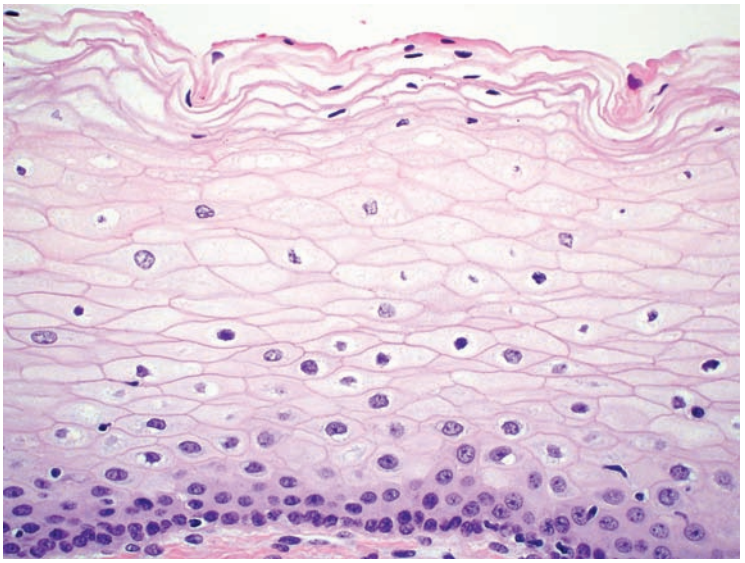


Figure 2.22 — Normal Cervical Squamous Epithelium (Hysterectomy) (H&E Stain; High Power). The bottom of the epithelium is composed of the basal layer, which contains a single layer of epithelioid cells with small round nuclei, slightly dark chromatin, and a relatively high N/C ratio. Superficial to that are one to two layers of parabasal cells, which are morphologically similar to the basal layer except for a mild increase in nuclear size, slightly increased amount of cytoplasm, and slightly more nuclear pallor. The next layer above is composed of intermediate squamous cells, which are morphologically similar to the parabasal cells, but the former have more abundant cytoplasm. The top of the squamous epithelium consists of a few layers of superficial squamous cells. When compared with the lower layers, these cells show much more flattening of cell shapes and nuclei that are darker, smaller, and flatter. Note that the nuclei of the squamous cells within each layer are uniform with an even chromatin distribution and without significant enlargement or variation in size or shape. The orderly maturation from the bottom to top of the squamous epithelium (ie, differentiation from a basaloid appearance with epithelioid morphology, round nuclei, and a high N/C ratio in the bottom of the epithelium to acquisition of more cytoplasm with a low N/C ratio in the middle of the epithelium and flattened cells with smaller and flatter nuclei in the top of the epithelium) is lost in squamous intraepithelial lesions.

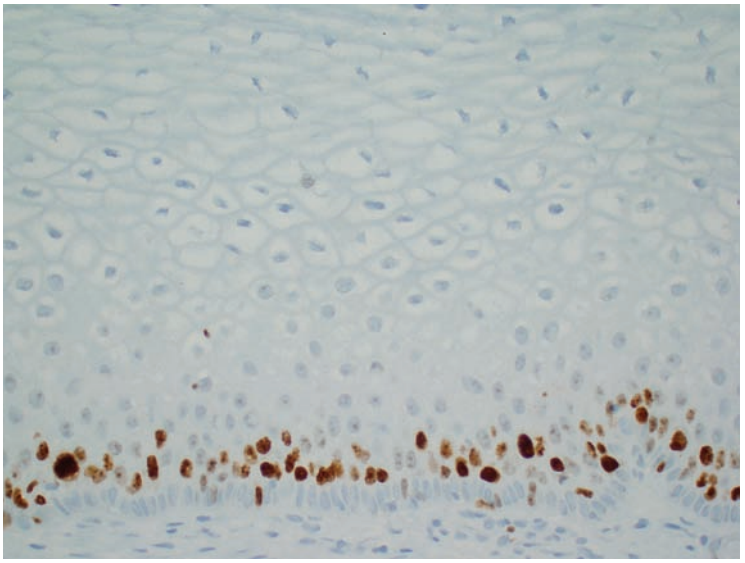


Figure 2.23 — Normal Cervical Squamous Epithelium (Hysterectomy) (Ki-67 Immunohistochemical Stain; High Power). Note that staining for Ki-67 is essentially absent in the basal layer and is present only in the parabasal layers. Specifically, proliferation is not present in the middle or upper layers of the squamous epithelium, which is in contrast to squamous intraepithelial lesions.

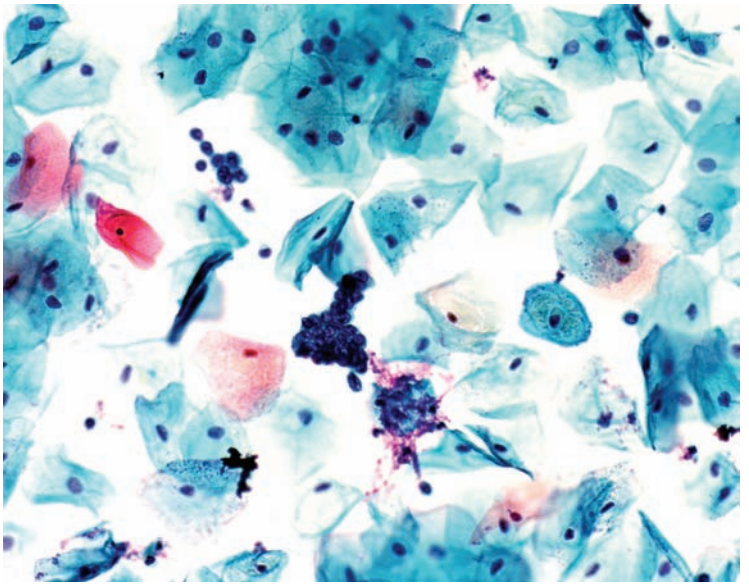


Figure 2.24 — Benign Endocervical Cells From a Gland Neck (Liquid Based; Low Power). Round nuclei tightly clustered may be considered a hyperchromatic crowded group (HCG), which deserves close attention.

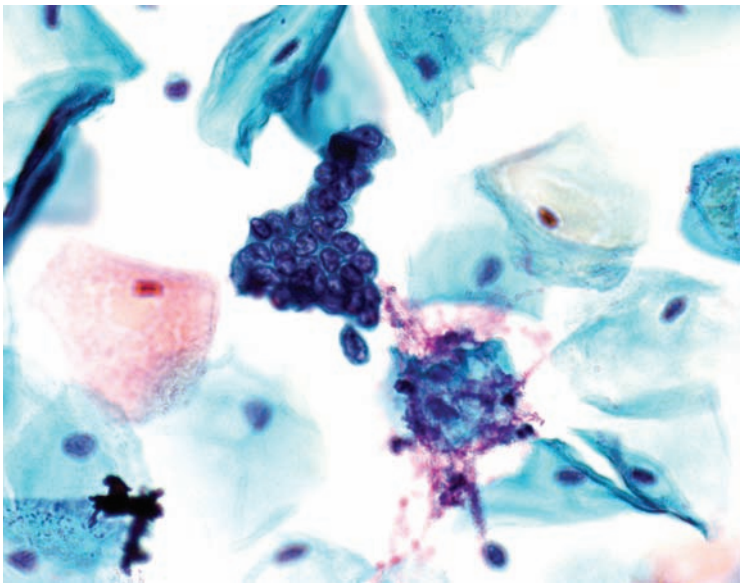


Figure 2.25 — Benign Endocervical Cells From a Gland Neck (Liquid Based; Medium Power). The single cell falling off the group gives us an opportunity to appreciate the bland chromatin and the thin nuclear rim. The lack of feathering in the group discards adenocarcinoma in situ (AIS) as a possibility and absent terminal plate or cilia excludes the lower uterine segment.

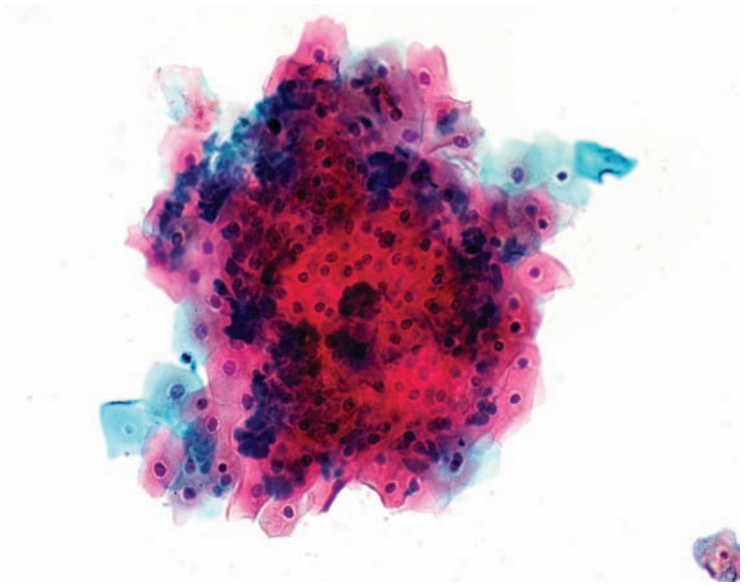


Figure 2.26 — Benign Squamous Cells in Layers (Liquid Based; Medium Power). Although often considered a "monolayer," the sample produced by liquid-based cytology (LBC) is more appropriately called "thin layer," because even the most vigorous processing method would not separate all cells. The benefit of the Papanicolaou stain is the ability to focus through the thick groups and see most cells in detail.

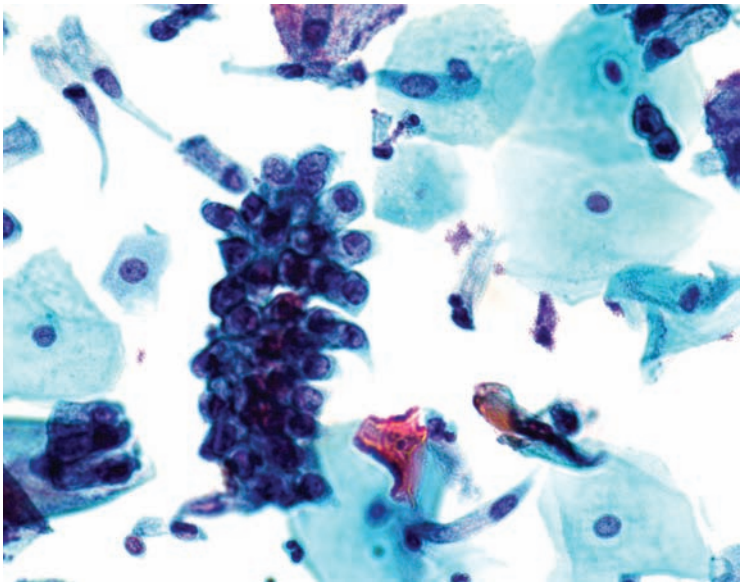


Figure 2.27 — Benign Endocervical Cells With Cytoplasmic Tails (Liquid Based; High Power). Not to be mistaken for the "feathering" of AIS, these tails simply reflect the attachment of cells to the basement membrane. The individual cells in the upper left portion of the frame also have tails, but their nuclei are very small, in contrast to the feathered cells of an AIS, in which the nuclei occupy at least two thirds of the volume of the cell. Nuclei in the fragment are round and pale, whereas nuclei in an AIS lesion are oval and hyperchromatic.

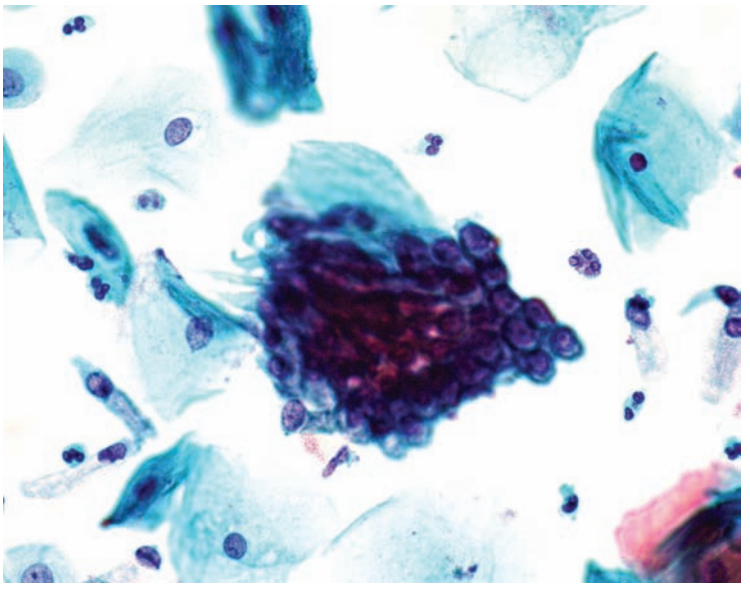


Figure 2.28 — Endocervical Cells With Cytoplasmic Tails (Liquid Based; High Power). Worthy of careful inspection, this HCG could be considered from a high-grade lesion because of its crowded nuclei and tails. However, the nuclei are round and pale. They are most likely plucked from an endocervical gland neck.

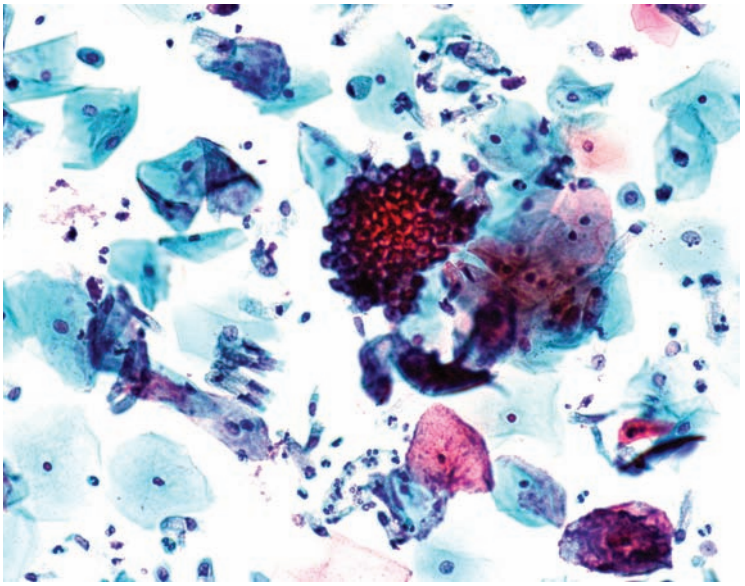


Figure 2.29 — Various Presentations of Benign Endocervical Cells (Liquid Based; Low Power). Individual endocervical cells are lined up in parallel with their tall columns of cytoplasm. A large fragment in the center of the field displays a honeycomb arrangement, created when the fragment lands on the slide either top up or down. Careful focus will reveal cytoplasm or nuclei, all at the same time.

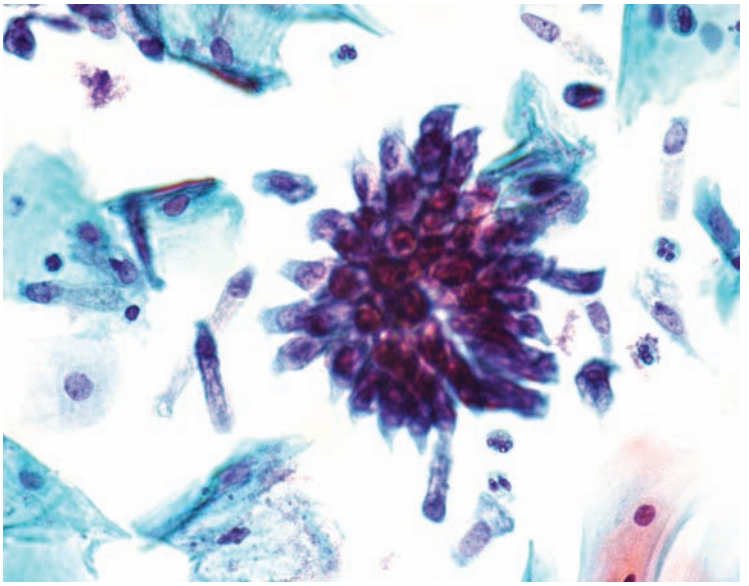


Figure 2.30 — Benign Endocervical Cells (Liquid Based; Medium Power). Appearing like petals of a chrysanthemum, these endocervical cells display the low N/C ratios of benign cells. Single cells also display the same criteria.

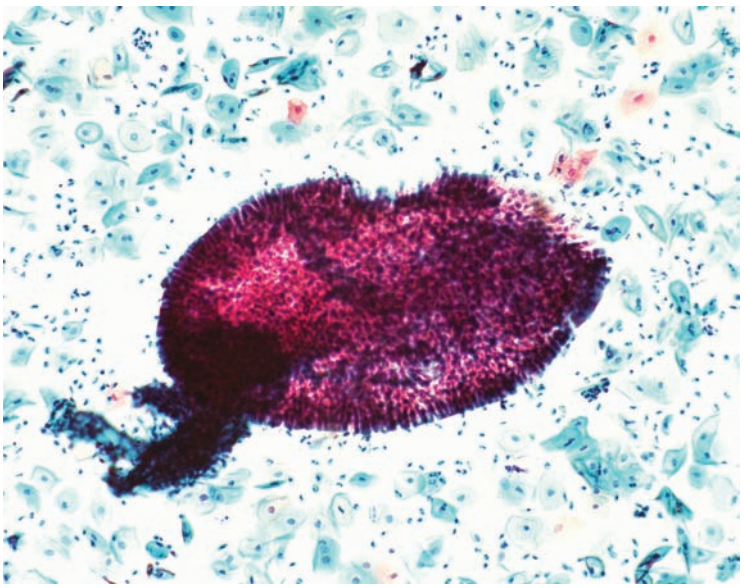


Figure 2.31 — Large Endocervical Fragment (Liquid Based; Very Low Power). Large tissue fragments are not uncommon since the adoption of vigorous sampling devices. The tissue still needs careful scrutiny to check for neoplasia. This benign fragment may be from a polyp because of the vascular support.

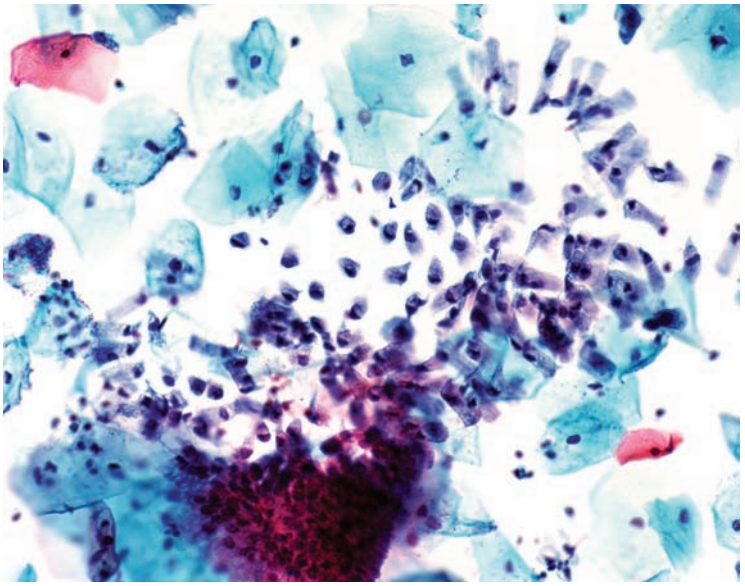


Figure 2.32 — Endocervical Cells, Disaggregated (Liquid Based; Medium Power). Endocervical groups are commonly seen in liquid-based preparations, but because of mechanical forces, they often disaggregate. When assessing Pap slides for the transformation zone component, single cells should be sought if groups are absent.

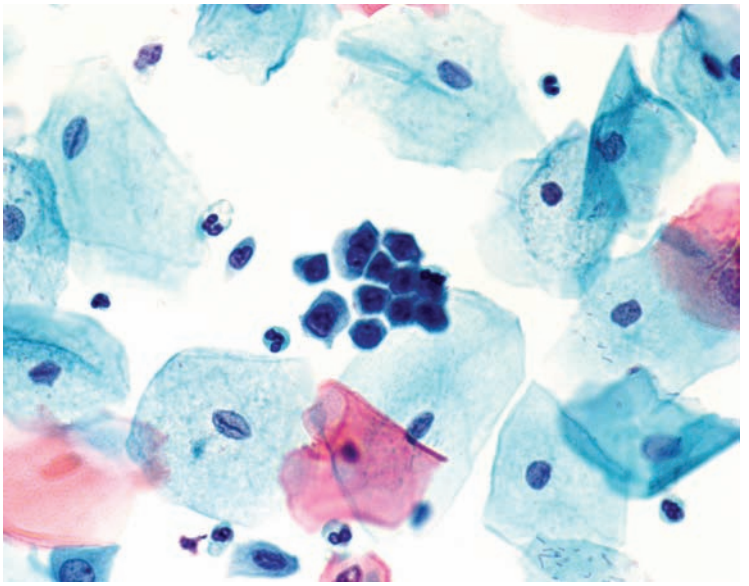


Figure 2.33 — Endocervical Cells, En Face (Liquid Based; High Power). When endocervical cells fall on the slide with either their mucosal or basal portions in the same focal plane, they appear to have high N/C ratios. Focus through the cells and all the cytoplasm or nuclei will come into focus at the same time. This is one way to distinguish these benign columnar cells from atypical metaplastic cells that will not have glandular cytoplasm.

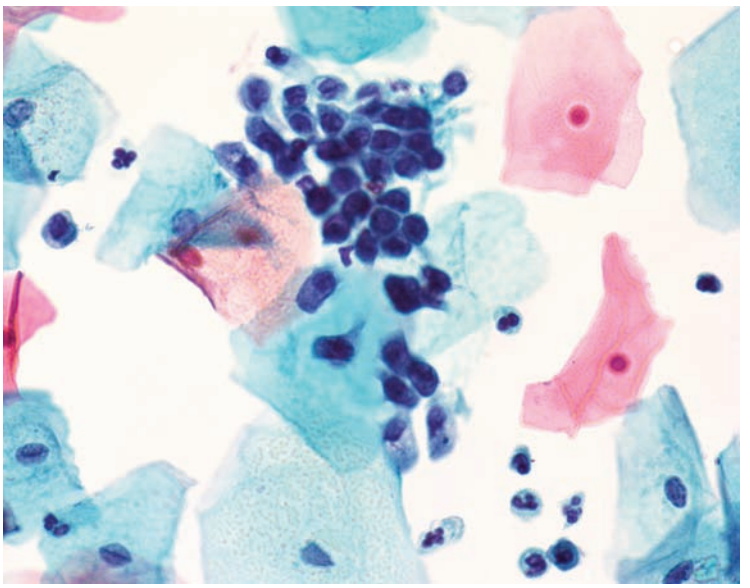


Figure 2.34 — Endocervical Cells, En Face and in Profile (Liquid Based; High Power). Another view of endocervical cells demonstrating the many appearances of these columnar cells. Note that the size and chromatin of the nuclei are similar regardless of how the cells present.

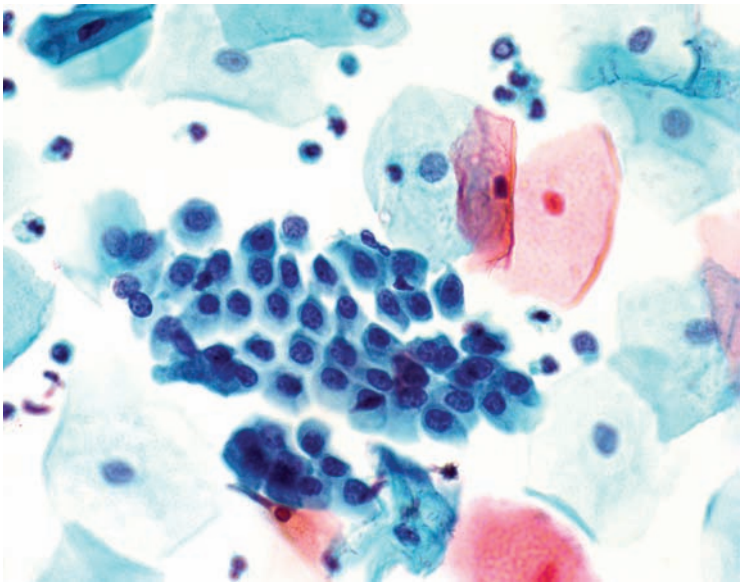


Figure 2.35 — Endocervical Cells, Some With Metaplastic Changes (Liquid Based; High Power). Some of the cells in this group have opaque cytoplasm and high N/C ratios, whereas others have transparent columns of cytoplasm. Comparison of all nuclei will assure that the cells are benign if chromatin is pale, shapes are round, and size is similar. If the metaplastic cells are dissimilar, then an atypical metaplasia should be considered, and the entire slide carefully searched for more atypical cells.

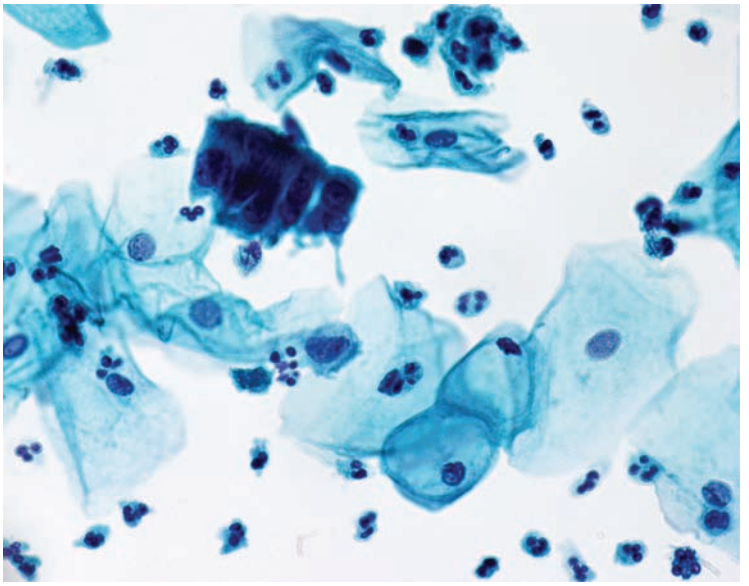


Figure 2.36 — Endocervical Cells With Terminal Bars (Liquid Based; High Power). The straight edge along the luminal surface of these cells indicates terminal bars or plates, indicating origin in the lower uterine segment. Cilia may also be present on such cells. Opposite ends of the cells contain cytoplasmic tails, not to be mistaken for "feathering." These cells have low N/C ratios, whereas, feathered cells in an AIS would have nuclei occupying at least two thirds of the column of cytoplasm.

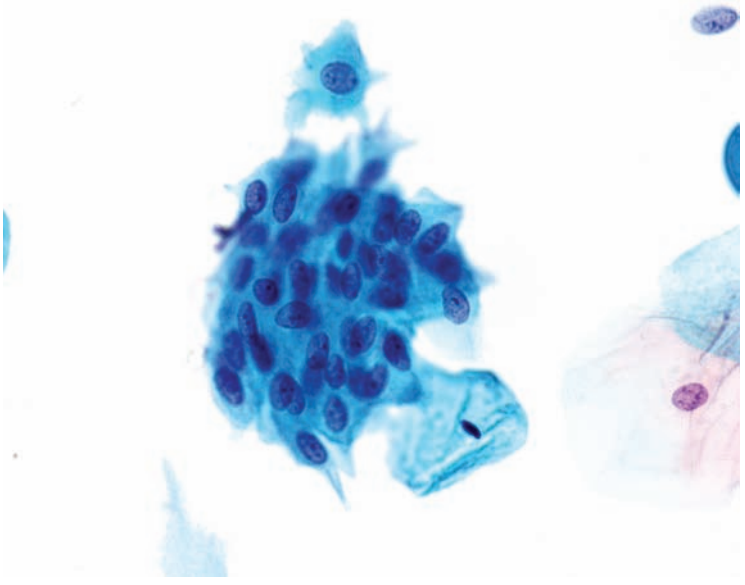


Figure 2.37 — Endocervical Cells With Metaplastic Changes (Liquid Based; Medium Power). Opaque cytoplasm indicates squamous differentiation. However, the nuclei in these cells are oval and vesicular, and the cytoplasmic tails indicate the points of attachment to the basement membrane, typical of endocervical cells. The cell at the top of the photograph has similar nuclear features, but is distinctly metaplastic because of its central nucleus and multiple cytoplasmic tails due to the mosaic arrangement in the epithelium. Endocervical cells will have only one tail.

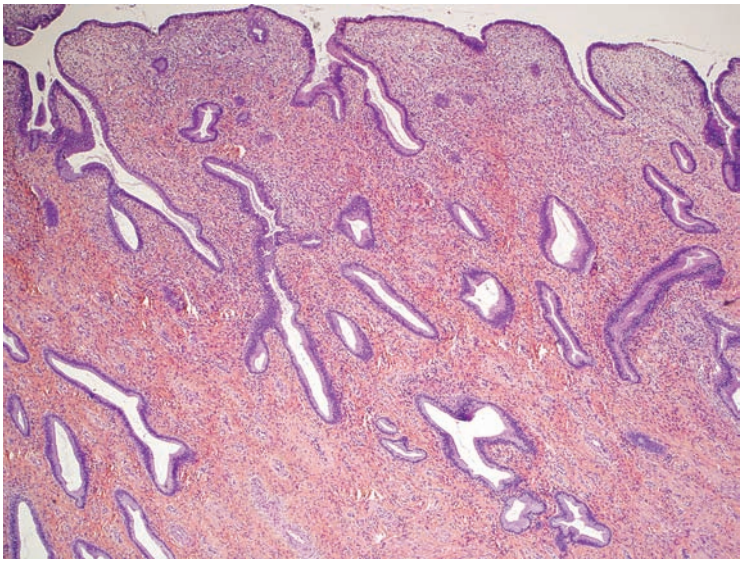


Figure 2.38 — Benign Endocervical Mucosa (Hysterectomy) (H&E Stain; Intermediate Power). The surface mucosa is rugated. Deeper, simple glands with limited branching are present within stroma. The glands are arranged in an orderly fashion and separated by abundant stroma.

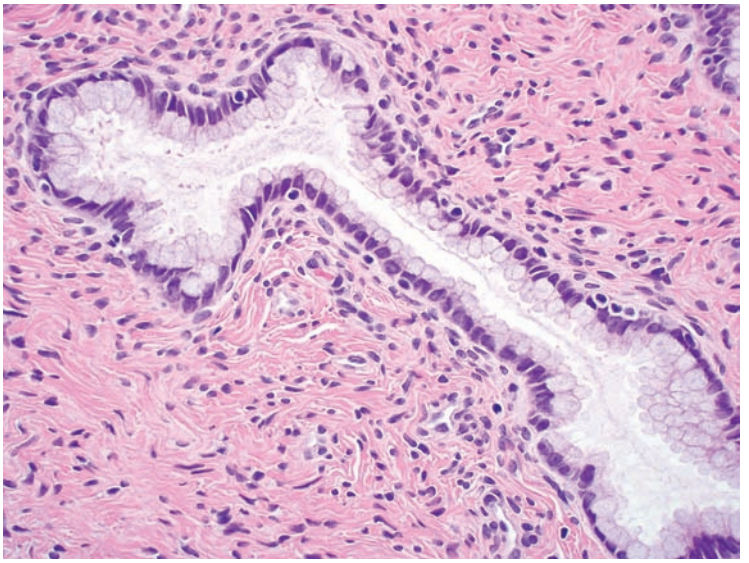


Figure 2.39 — Normal Endocervical Mucosa (Hysterectomy) (H&E Stain; High Power). The glands are simple and lined by columnar cells. The nuclei are basally situated and mostly round. They have slightly dark chromatin and evenly distributed chromatin without prominent nucleoli or mitotic activity. Abundant mucinous cytoplasm is present.

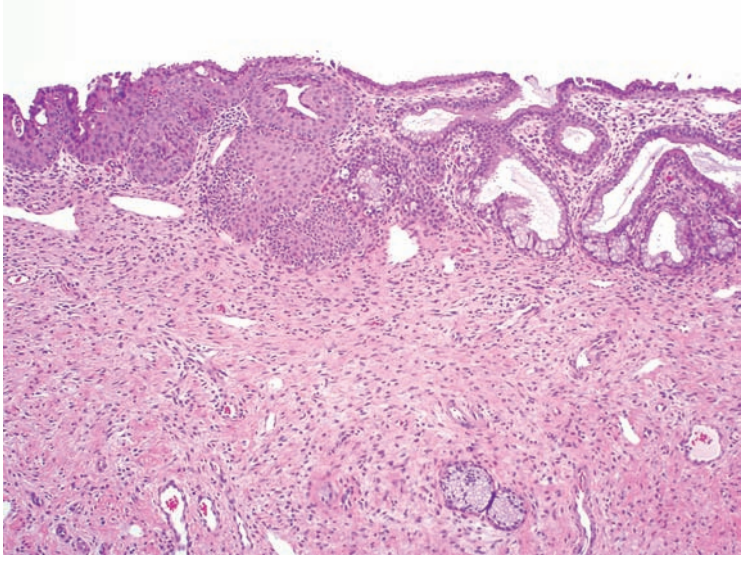


Figure 2.40 — Normal Endocervical Mucosa (Transformation Zone) (Hysterectomy) (H&E Stain; Intermediate Power). The transformation zone consists of squamous and glandular epithelia. The portion of the cervix shown in this example is predominantly composed of endocervical glands with areas of squamous metaplasia. Some of the glands are almost entirely replaced by squamous metaplasia, in which the superficial-most aspect of the mucosa retains an intact single layer of endocervical glandular epithelium.

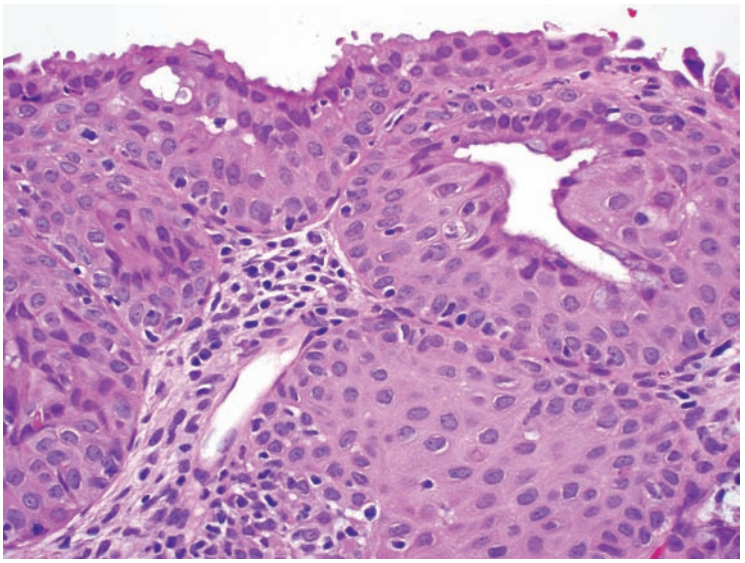


Figure 2.41 — Normal Endocervical Mucosa (Transformation Zone) (Hysterectomy) (H&E Stain; High Power). The squamous metaplasia in this example is mostly located underneath an intact single layer of endocervical glandular epithelium. Note the bland and uniform nuclei and low nuclear-to-cytoplasmic ratio of the squamous metaplastic cells. This pattern in which an overlying layer of endocervical glandular epithelium is preserved is usually a helpful clue to recognize that a focus of concern represents metaplasia as opposed to a squamous intraepithelial lesion; however, the latter can occasionally undermine overlying normal endocervical glandular epithelium.

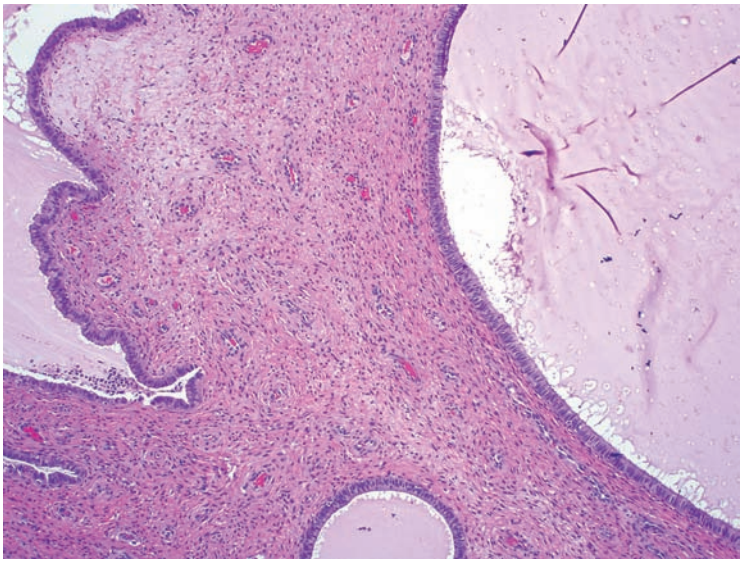


Figure 2.42 — Normal Lower Uterine Segment (Hysterectomy) (H&E Stain; Intermediate Power). The lower uterine segment is a histologically ill-defined zone between the cervix and endometrium. However, architectural and cytologic mixtures of endocervical- and endometrial-type epithelium can be found. In this example, mucinous epithelium of the type usually seen in the endocervix is present on the left, and endometrioid epithelium with pseudostratification and tubal metaplasia is noted on the right and bottom center. The stroma is similar to that seen in the endocervix.

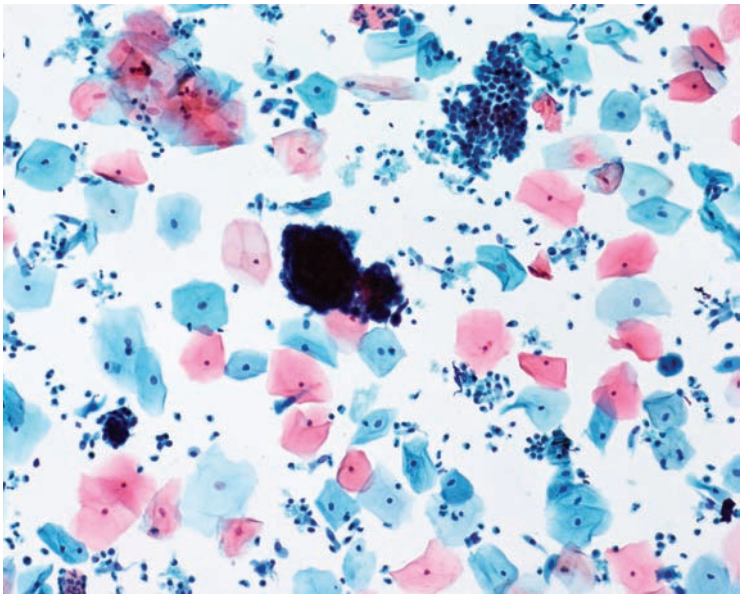


Figure 2.43 — Glandular Groups of Different Cell Types (Liquid Based; Low Power). These two large tissue fragments are obviously different. The one in the upper right quadrant has separated cells, and the central fragment is tightly clustered. Although higher power is needed for definite identification, the former is more likely an endocervical group and the latter an endometrial wreath.

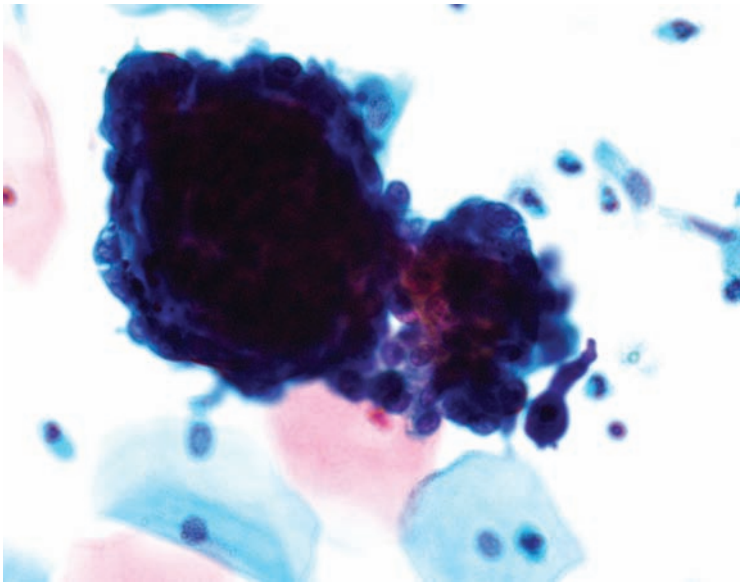


Figure 2.44 — Endometrial Wreath (Liquid Based; High Power). A closer look at the central fragment in the previous figure confirms the endometrial origin of the cells. The term wreath is derived from the similarity with circular home decorations. Here the glandular cells encircle the central stromal cells and display a double-contoured architecture. This type of tissue is usually seen during the menstrual exodus, a result of spontaneous exfoliation, not mechanical scraping.

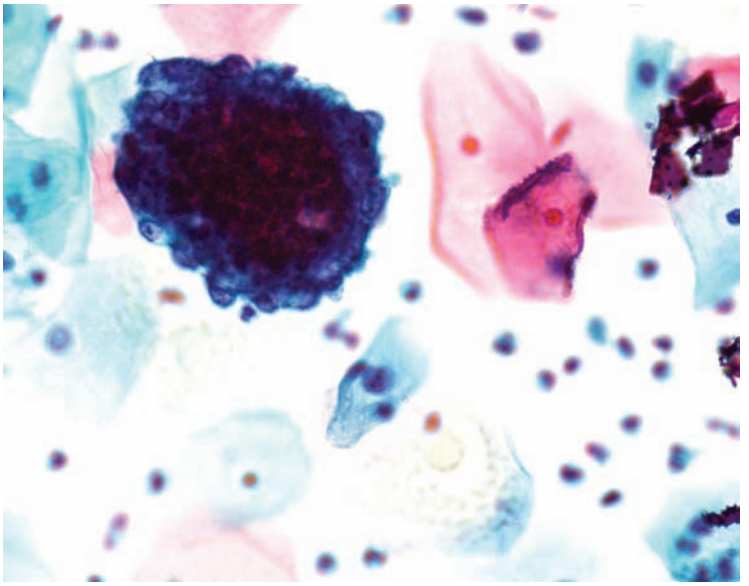


Figure 2.45 — Benign Endometrial Cells (Liquid Based; High Power). Compare with benign endocervical cells to appreciate that the endometrials appear thicker in the center of the group and uniformly thinner around the periphery. In the outer layer are the epithelial cells, and the center contains the stromal cells. Such a circular group is spontaneously shed, as contrasted with an exfoliated lower uterine segment by a sampling device.

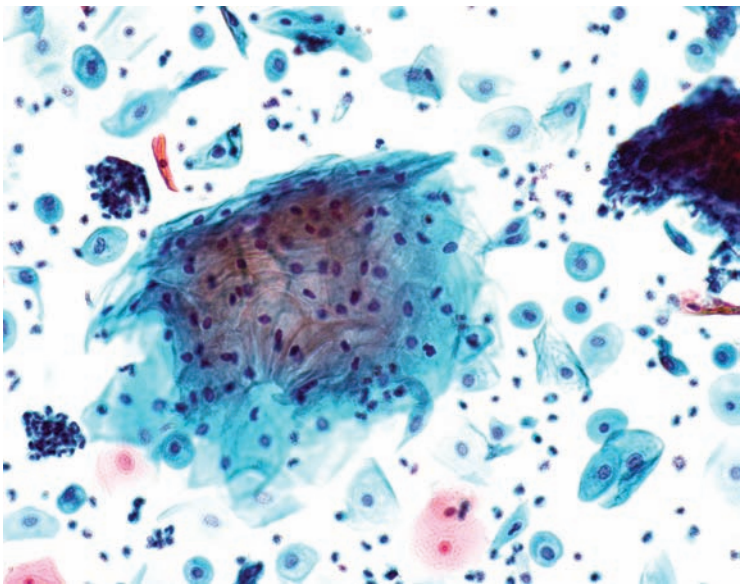


Figure 2.46 — Hyperchromatic Crowded Groups (HCG) (Liquid Based; Medium Power). Always deserving of attention, HCGs may contain a variety of cell types and may range from benign to high-grade in situ lesions. Only by inspection under high power can their properties be realized, but not always identified with certainty. Any uncertainty needs to be reflected in the report with a request for further studies.

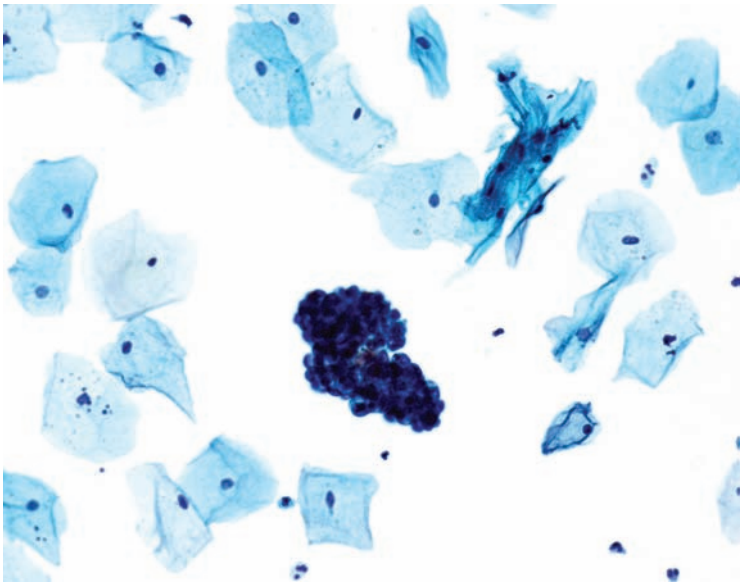


Figure 2.47 — Endometrial Cells (Liquid Based; Medium Power). An eye-catching group of cells needs closer attention. The menstrual history and evidence of prior uterine abnormalities are important factors.

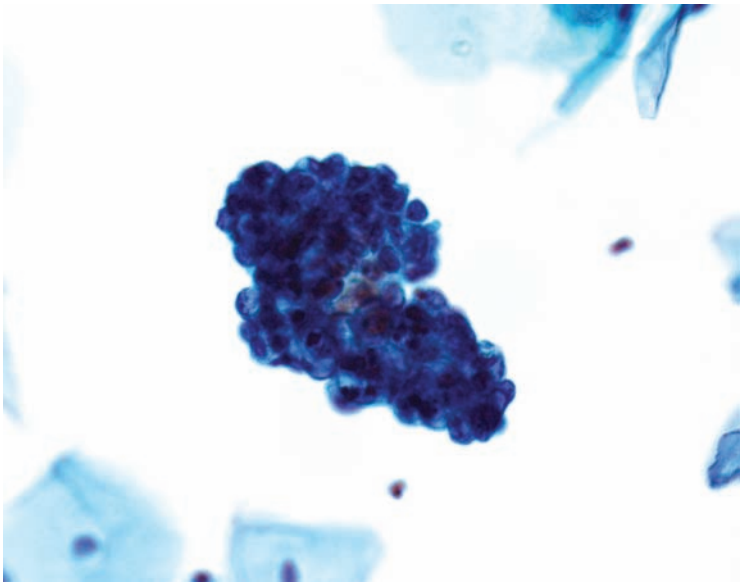


Figure 2.48 — Endometrial Cells (Liquid Based; High Power). Tightly clustered small cells are always noteworthy. Their identification can be difficult. If the patient is menstruating, their designation as endometrial cells makes sense. However, these could also be small cells from a cervical neoplasm, a rare occurrence. Any indecision should be communicated to the clinician with a request for further studies to define the cells.

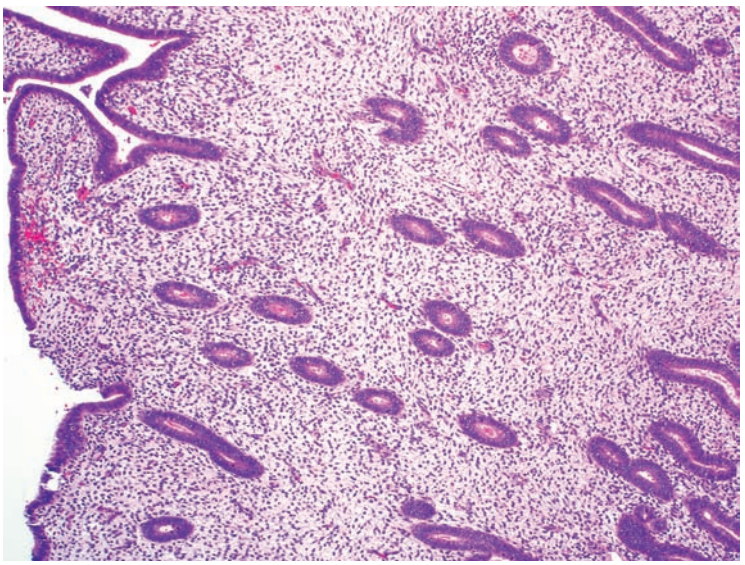


Figure 2.49 — Proliferative Phase Endometrium (Hysterectomy; H&E Stain; Intermediate Power). The glands are simple, tubular, and separated by abundant stroma, and the gland-to-stroma ratio is 1:1 or less. The surface is lined by the same type of epithelium that the glands are composed of. The stroma is cellular with small round blood vessels.

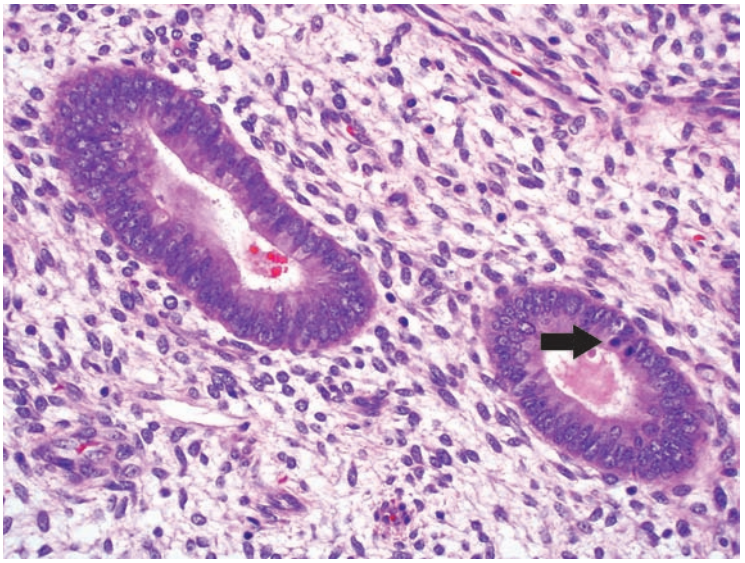


Figure 2.50 — Proliferative Phase Endometrium (Hysterectomy) (H&E Stain; High Power). The glands are simple and tubular. They are lined by pseudostratified epithelium, which consists of columnar cells, round to columnar nuclei, and a moderate amount of pink cytoplasm. The nuclei have stippled chromatin, occasionally evident nucleoli, and a mitotic figure (*arrow*). The stroma is cellular and contains round to oval nuclei with scant cytoplasm. Small round and thin elongated blood vessels can be seen.

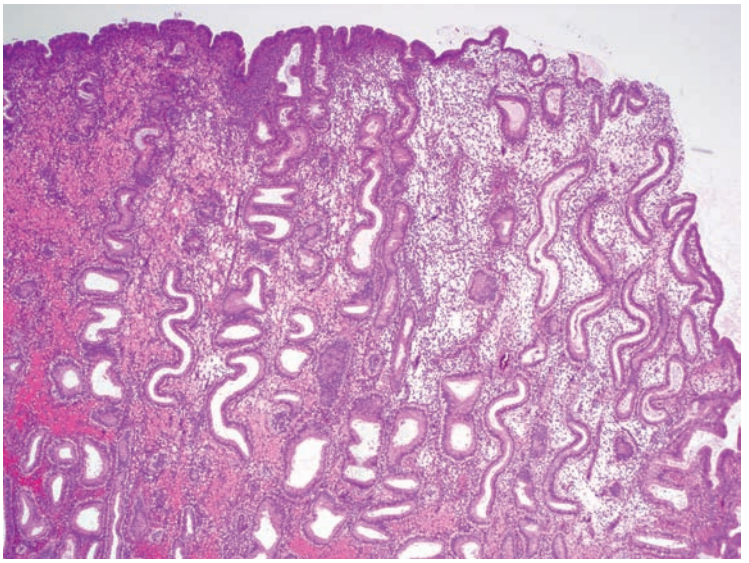


Figure 2.51 — Secretory Phase Endometrium (Hysterectomy) (H&E Stain; Low Power). The endometrium is typically thicker in the secretory phase compared with the proliferative phase. In contrast to the proliferative phase endometrium, the glandular architecture is usually more complex. In this example, the glands are notably coiled. The degree of stromal edema varies according to the day of secretory endometrium (maximal, day 21–22). Here, substantial stromal edema is present.

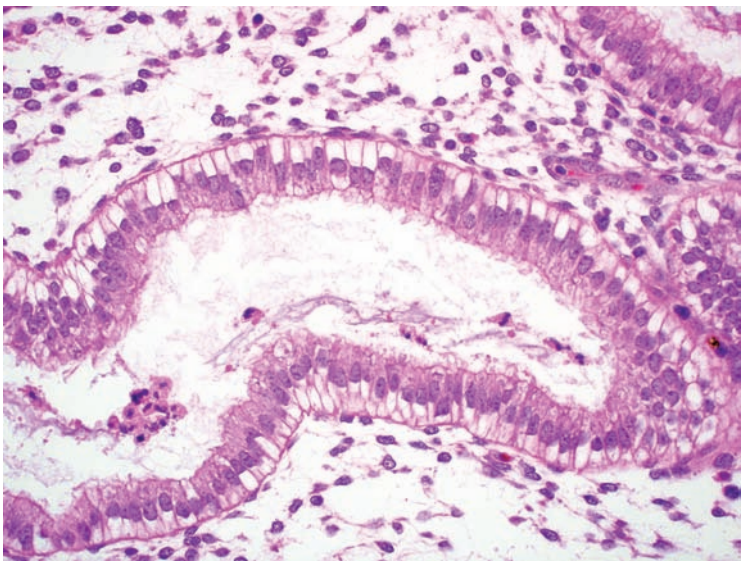


Figure 2.52 — Secretory Phase Endometrium (Hysterectomy) (H&E Stain; High Power). The cytologic appearance of the glands varies according to the day of secretory endometrium. In this example, the presence of subnuclear vacuoles is consistent with day 17. Note that, in contrast to the usual appearance of proliferative phase glands, those in the secretory phase have more rounded nuclei, paler and even chromatin, and a relative absence of pseudostratification, mitotic activity, prominent nucleoli, and tubal metaplasia. The cytoplasm tends to be paler and the luminal surface (in other examples) more irregular compared with proliferative phase glands. Furthermore, substantial stromal edema is present in this example.

3

Infectious Organisms

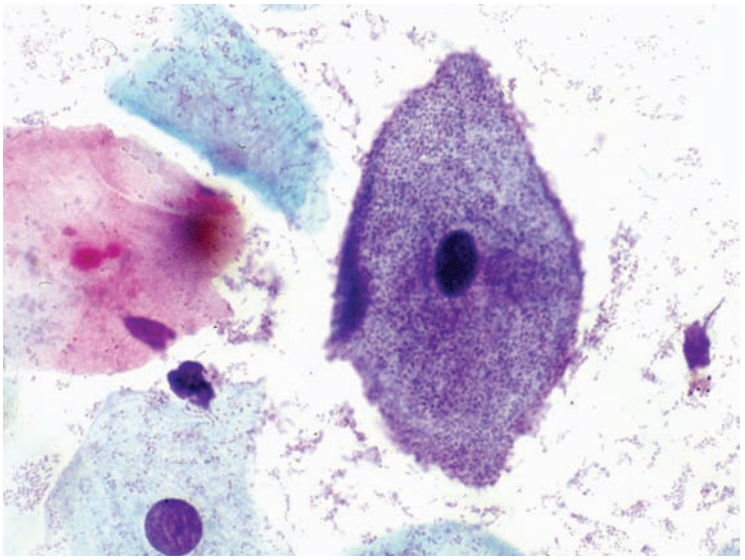


Figure 3.1 — Bacterial Vaginosis (Conventional; High Power). Individual epithelial cells are dusted by the bacteria of *Gardnerella vaginalis* and a mixture of other anaerobic bacteria, upsetting the normal flora of the vagina. Most of the bacteria coat the cells, so-called clue cells, but a scattering of cocci may be seen in the background. Although the condition is considered an infection, there is usually little or no host response, unless another vaginal infection accompanies. There is still debate as to whether this condition is sexually transmitted, or is a consequence of constitutional factors, such as diabetes, obesity, poor hygiene, and so on.

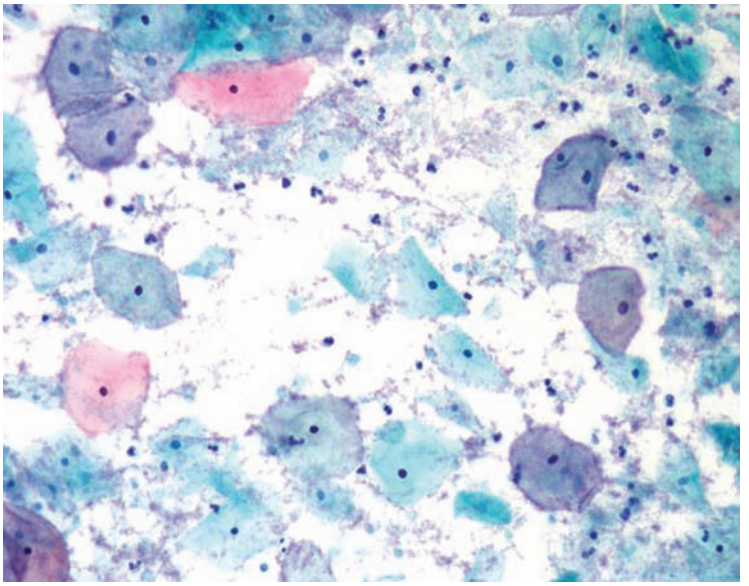


Figure 3.2 — Excess Bacteria, Rule Out Bacterial Vaginosis (Conventional; Low Power). Although some of the epithelial cells are coated with bacteria, there are also much free bacteria in the background, as well as scattered leukocytes. This is the picture of a nonspecific bacterial infection, possibly caused by *Gardnerella* species as well as other rods and cocci.

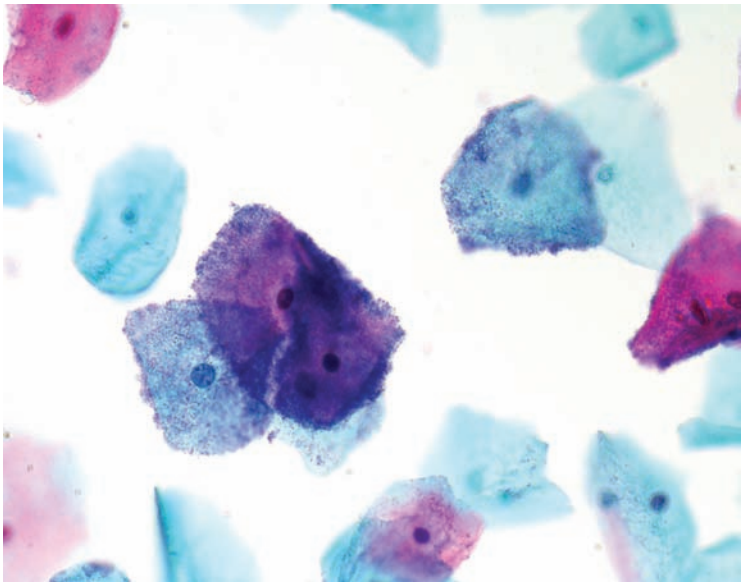


Figure 3.3 — Classic Bacterial Vaginosis (Liquid Based; Medium Power). Bacteria discretely coat the epithelial cells without any overflow onto the background. This is undoubtedly caused by *Gardnerella vaginalis*, but culture is still needed for positive identification.

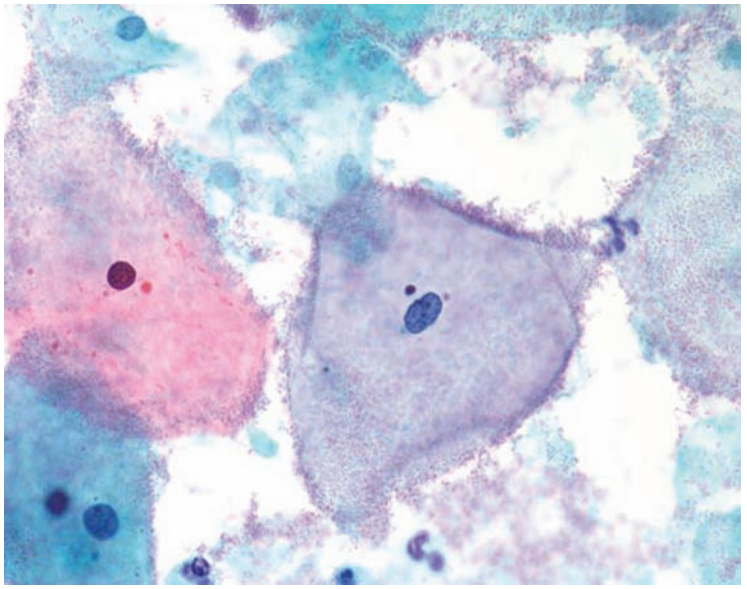


Figure 3.4 — False Clue Cells (Liquid Based; High Power). Although bacteria coat the epithelial cells, they are more notable at the cell periphery and in the background. Compare with previous figures. "Purists" would argue that a completely clean background is necessary to make the diagnosis of bacterial vaginosis. Culture is really the only way to verify the type of bacteria.

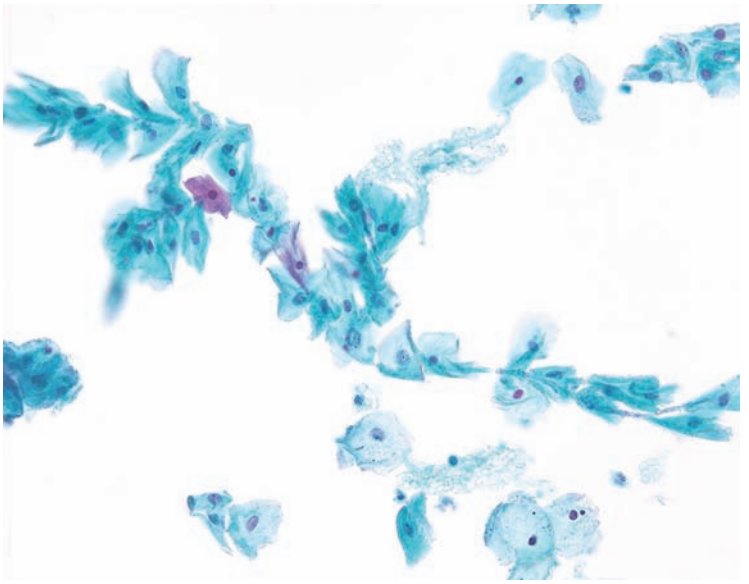


Figure 3.5 — *Candida* Species (Liquid Based; Low Power). *Candida* may be a commensal yeast, or provoke an inflammatory reaction, usually when the yeast form grows in excess to escape normal competition from *Lactobacilli*. This is often a result of antibiotic treatment for non-gynecologic reasons that kills the resident bacteria of the vagina. *Candida* organisms may grow as hyphae or pseudohyphae at body temperature, or often as budding yeasts.

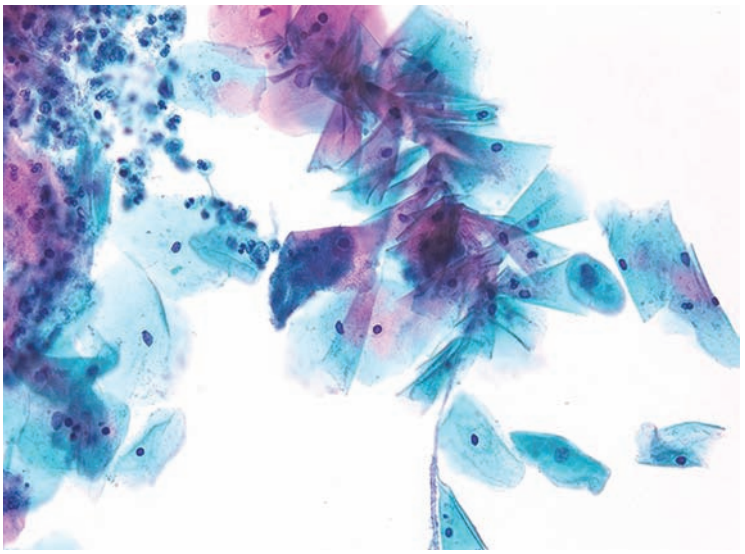


Figure 3.6 — *Candida* Species (Liquid Based; Low Power). Squamous epithelial cells appear to be skewered by the *Candida hyphae* (shish-kabob effect). Although there are leukocytes in an adjacent area, the involved epithelial cells lack any inflammatory reaction.

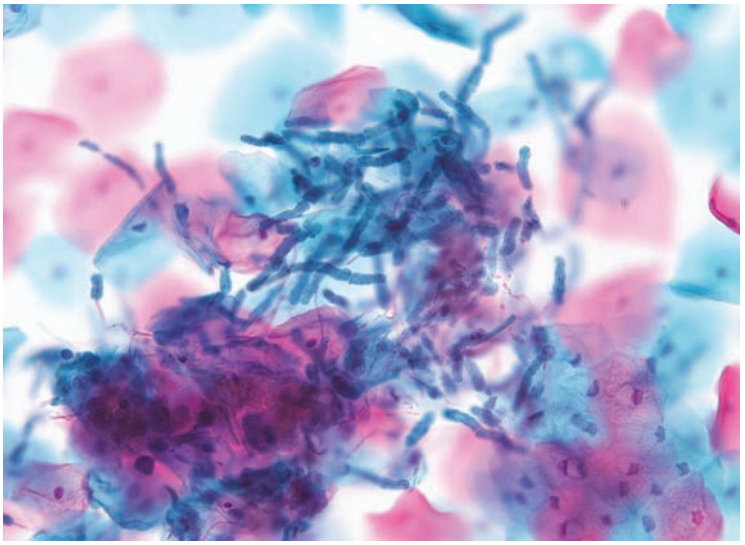


Figure 3.7 — Hyphae, Probably *Candida* (Liquid Based; Medium Power). Although *Candida albicans* is the most common fungus involved in the female genital tract, others can also be present, for example, *Candida glabrata*, smaller than *C. albicans*. Rather than trying to speciate for a Pap diagnosis, considering a general category of "Yeast forms" is most prudent.

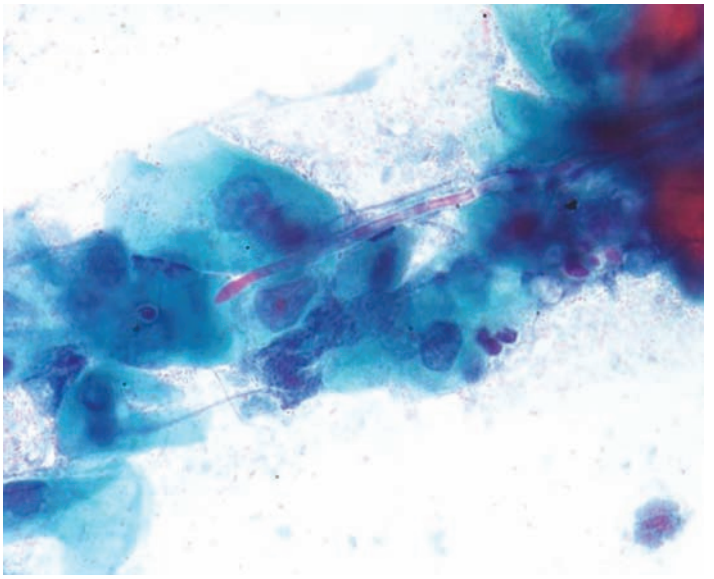


Figure 3.8 — Atypical Squamous Cells of Uncertain Significance (ASC-US) Associated With Fungal Hyphae (Conventional; High Power). Nonspecific epithelial changes may be seen with fungal infections even in the absence of inflammatory cells. The hyphae invade the mature squamous epithelial layers creating a response of enlarged nuclei with increased nuclear-to-cytoplasmic (N/C) ratios, but without cytoplasmic halos either small or large. ASC-US is an appropriate category, but do not be surprised if the human papillomavirus (HPV) result is negative, especially if the patient is older than 30 years.

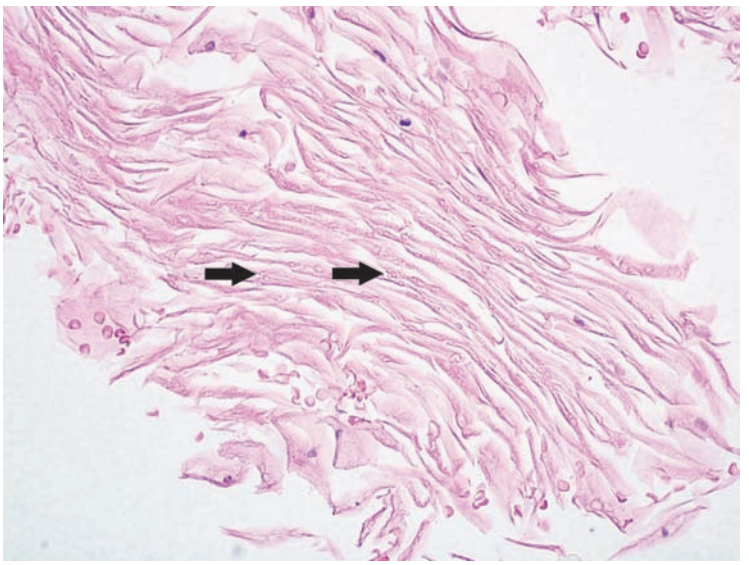


Figure 3.9 — Fungi Consistent With *Candida* Species (Vaginal Biopsy) (Hematoxylin and Eosin [H&E] Stain; High Power). Within this detached fragment of squamous epithelium, occasional yeast forms are present (*highlighted with contrast*; *arrows*). Note the size compared with red blood cells. Hyphal forms are also present but are nearly imperceptible in this example. Only an insignificant amount of inflammatory cells is present. In many cases, fungal forms may not be recognized on H&E stains without high-power magnification with contrast.

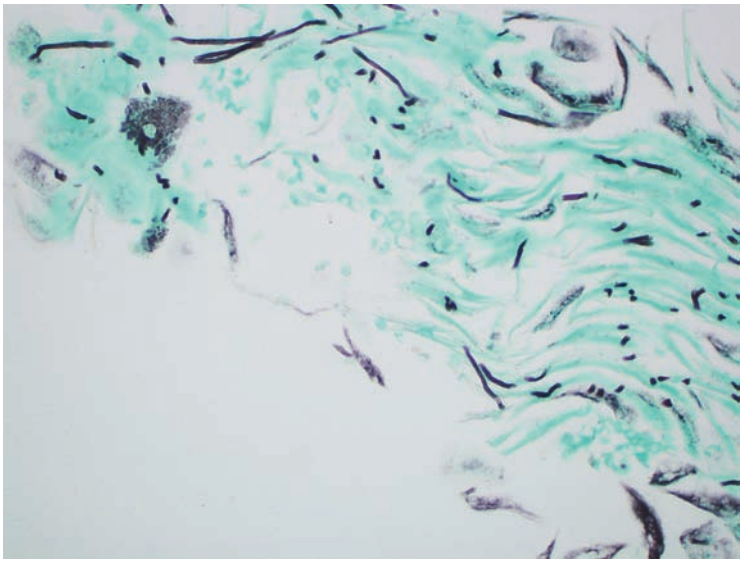


Figure 3.10 — Fungi Consistent With *Candida* Species (Vaginal Biopsy) (Gomori Methenamine Silver [GMS] Stain; High Power). Within this detached fragment of squamous epithelium, numerous yeast and hyphal forms are present (same case as in Figures 3.3–3.9). The fungi are stained black while the squamous epithelium is light green. Note the size of yeasts compared with red blood cells. In this example, the latter are green. However, red blood cells may occasionally be stained black in other cases.

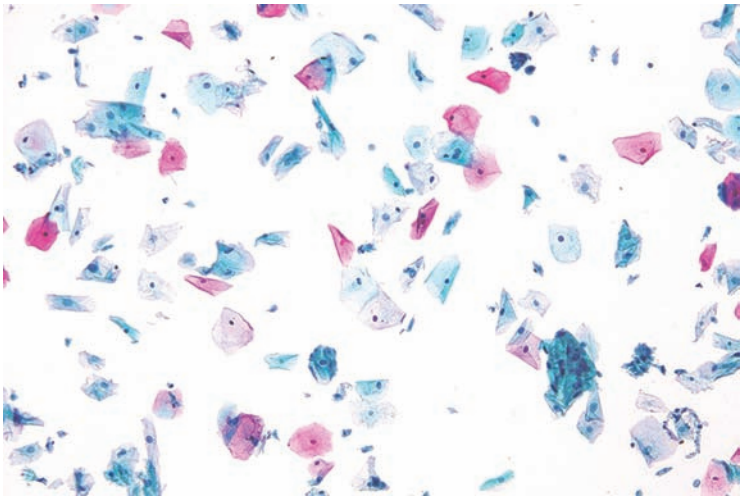


Figure 3.11 — *Trichomonas vaginalis* (Liquid Based; Low Power). Although trichomonads usually evoke an acute inflammatory response, they sometimes do not. Low power is not very dramatic, although the parasites can be appreciated if considered. They are about the size of leukocytes, but without dark nuclei.

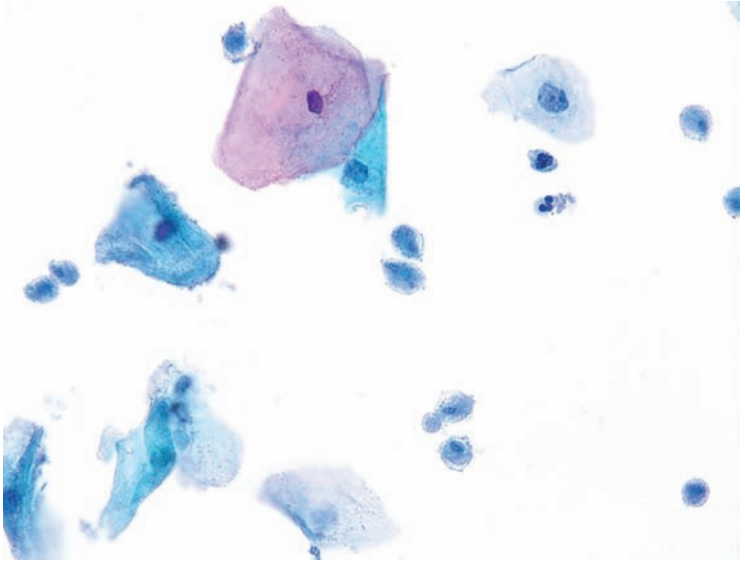


Figure 3.12 — *Trichomonas vaginalis* (Liquid Based; Medium Power). It is the most common nonviral sexually transmitted infection globally, and it usually does not provoke an inflammatory response. The protozoan is of the same size or slightly larger than a neutrophil, and on Pap stain, has a slightly grayer color. Characteristic features are not always evident, but the oval shape, axostyle (tail) at one end, and pink granules distinguish them from leukocytes that have lost their nuclei.

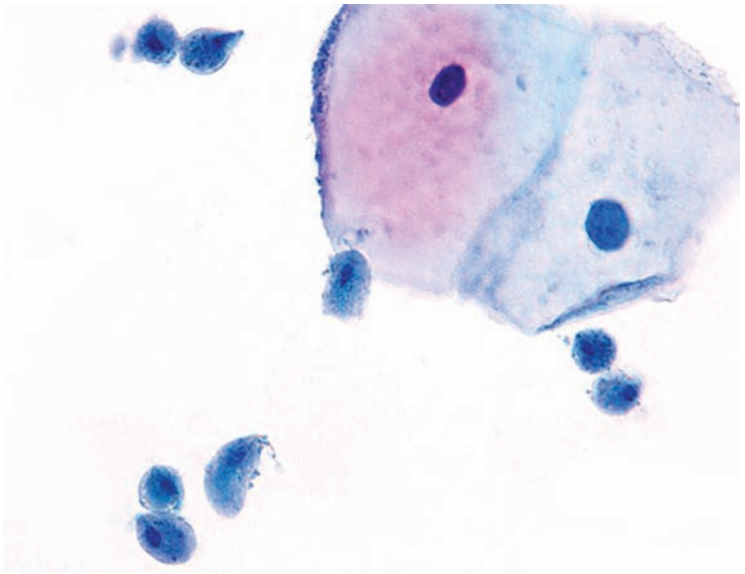


Figure 3.13 — *Trichomonas vaginalis* (Liquid Based; High Power). The variation in size and pointed ends of these ovoid parasites are helpful identifiers, but the solitary small dark nucleus in the gray-green cytoplasm of each parasite is definitive. Note the clean background.

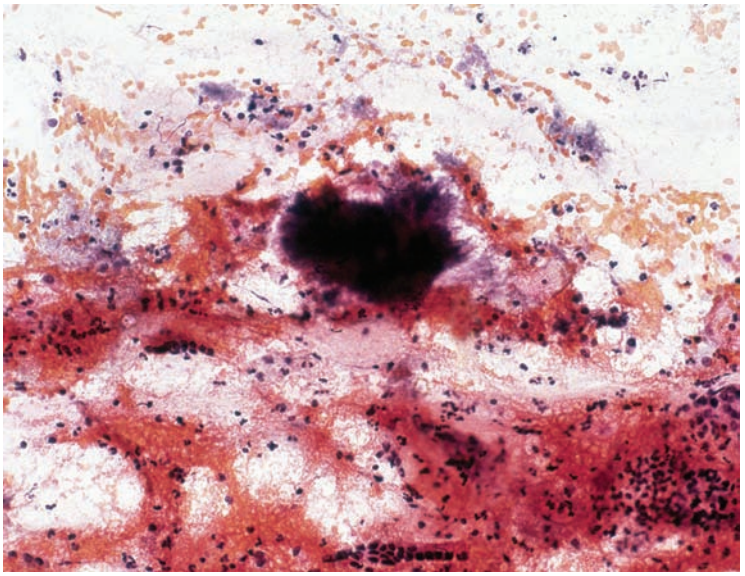


Figure 3.14 — *Actinomyces* (Conventional; Low Power). This organism was almost unknown in the female genital tract until the introduction of intrauterine devices (IUDs). The best way to appreciate them is to view them on low power, where they appear as "dust-balls." Unlike *Actinomyces* from the oropharynx, colonies from the female genital tract do not usually display central "sulfur granules."

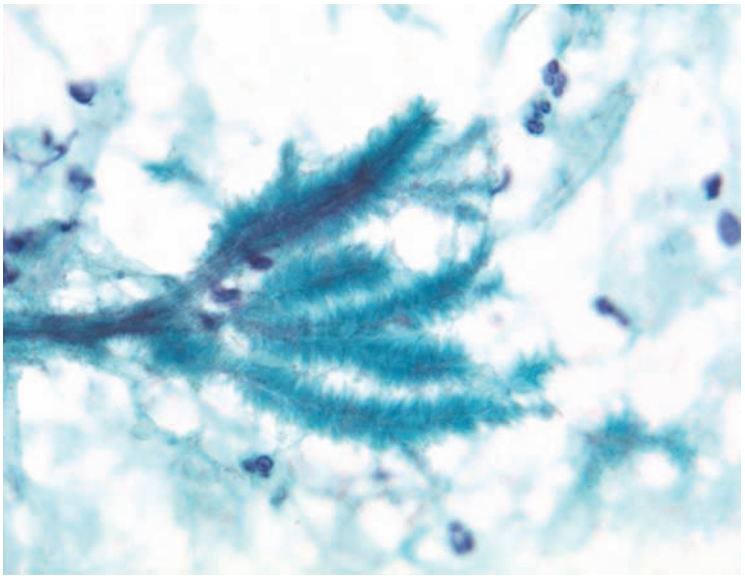


Figure 3.15 — *Actinomyces* (Conventional; High Power). The thin filaments that radially extend from the center of the colony are coated with rod-shaped or coccoid bacteria, providing the fuzzy appearance. The bacterial forms are produced by the breakdown of the mycelial filaments. These are anaerobic organisms, which explains their propensity to grow best in the fallopian tube, causing a tubal abscess. Otherwise, the organism is generally innocuous.

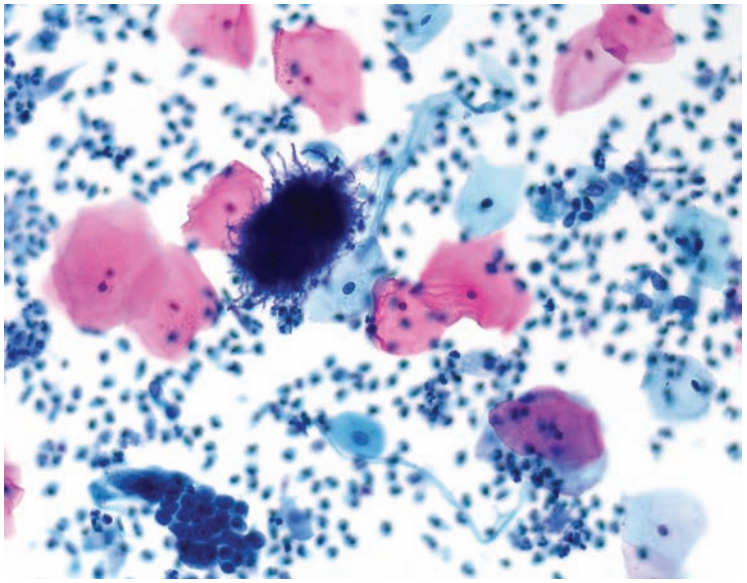


Figure 3.16 — *Actinomyces* (Liquid Based; Medium Power). This presentation is typical of a patient with an IUD and a possible infection secondary to this gram-positive organism. However, its presence usually is not associated with pathology; hence, clinical correlation is necessary.

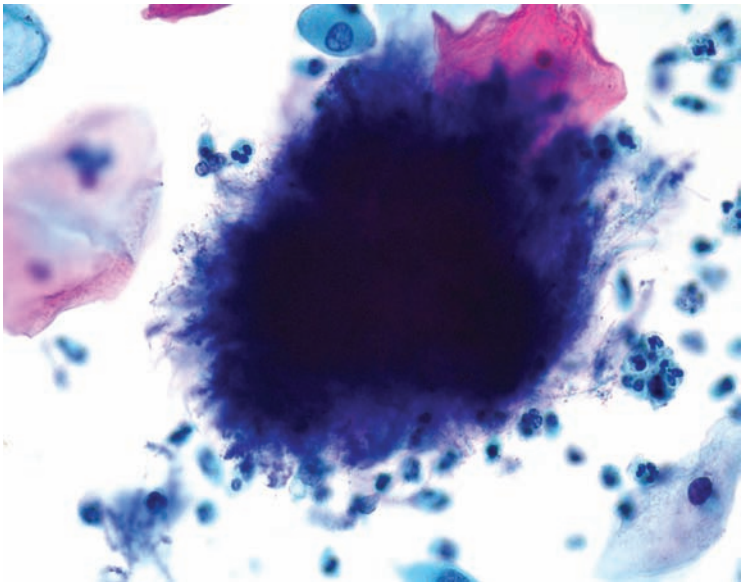


Figure 3.17 — *Actinomyces* (Liquid Based; High Power). A closer look at the colony in Figure 3.16 reveals radially extending filaments supporting the bacterial organisms, altogether considered a mycelial colony.

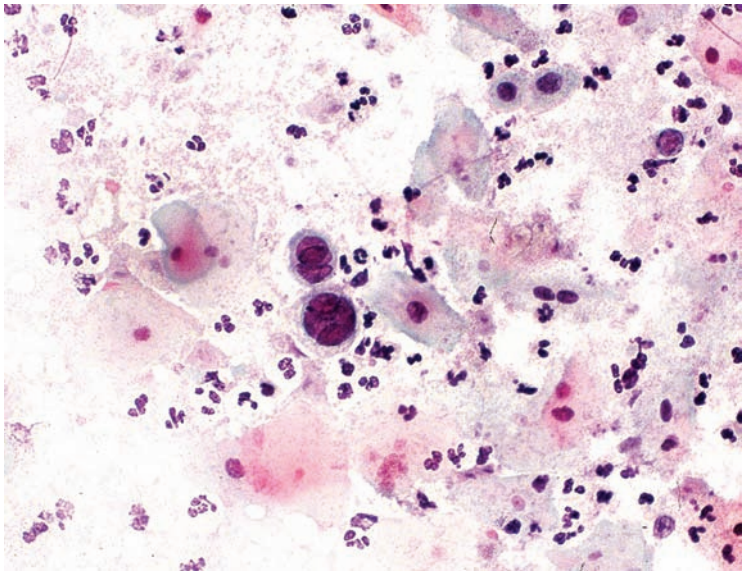


Figure 3.18 — Herpes Simplex Virus (HSV) (Conventional; Moderate Power). Infection with HSV is common in sexually active women, but is rarely diagnosed on Pap tests, because the active infection lasts for only 2 to 3 weeks. The cellular changes are classic and definitive, involving only the nuclear chromatin and often creating multinucleated cells with minimal cytoplasmic rims. Acute inflammation in a background of serum usually accompanies the cells, reflecting a ruptured vesicle in which the virus propagates.

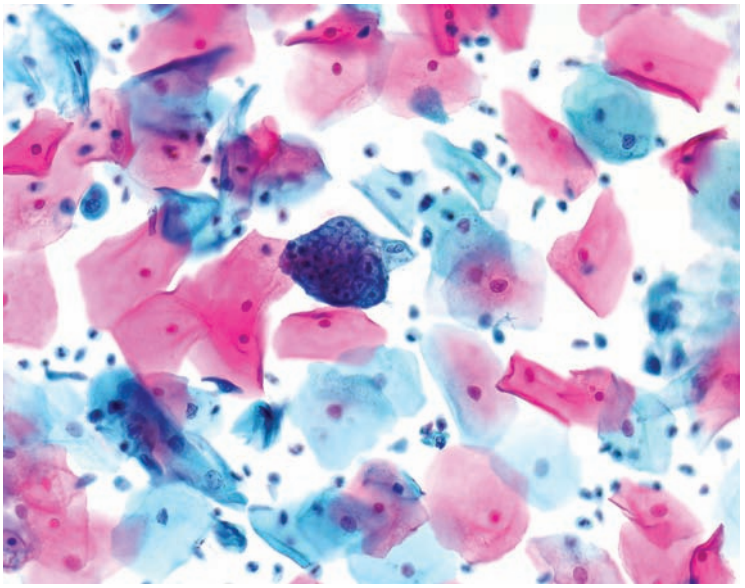


Figure 3.19 — Herpes Simplex Virus (HSV) (Liquid Based; Medium Power). The multiple nuclei contain single intranuclear inclusions that are surrounded by a halo. Nuclei are compressed together, molding against each other. Cytoplasm is virtually invisible.

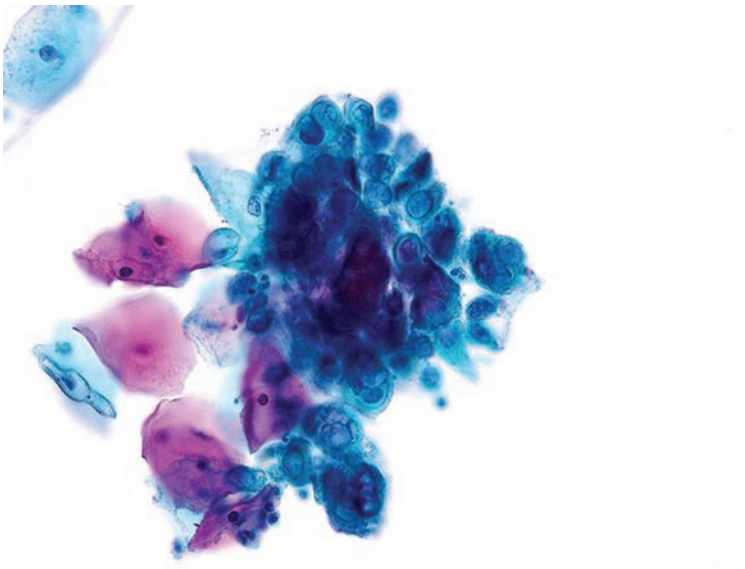


Figure 3.20 — Herpes Simplex Virus (HSV) (Liquid Based; High Power). This large epithelial fragment is unusual in that all cells appear to be infected with HSV. The nuclear changes demonstrate the ground glass disintegration of chromatin. Multinucleation is present but not in every cell.

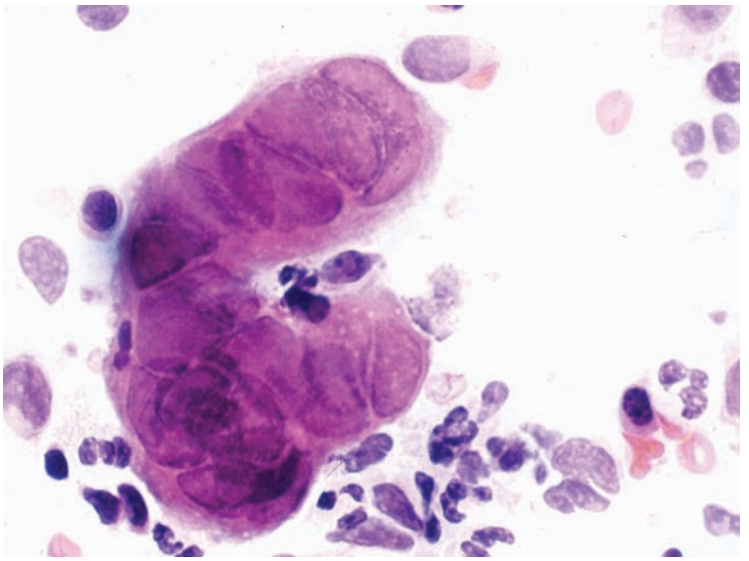


Figure 3.21 — Herpes Simplex Virus (HSV) (Conventional; High Power). Multinucleation with characteristic molding of one nucleus flattened against the other is diagnostic of HSV. The ground glass appearance of nuclear chromatin and thickened nuclear membranes complete the morphologic details. When these changes are observed in the Pap test of a pregnant woman, immediate notification to the clinician is mandatory, as HSV can be life threatening to the fetus.

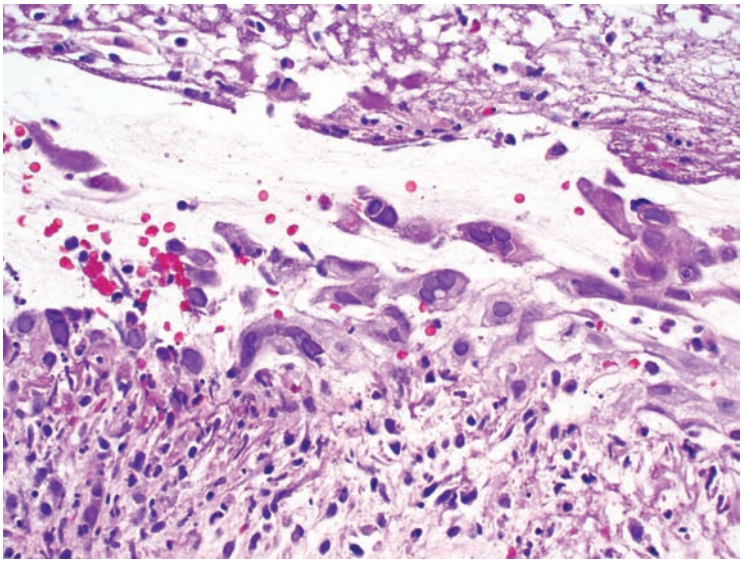


Figure 3.22 — Herpes Simplex Virus (HSV) (Cervical Biopsy) (H&E Stain; High Power). Viral inclusions are present within detached individual and clusters of squamous cells in the middle third of the photograph. The nuclei are enlarged and show a "ground glass" appearance with nuclear molding or syncytia. Abundant pink cytoplasm is also noted. The lower third of the photograph contains an ulcer bed, while necrotic debris and inflammatory cells are present in the upper third. In this setting of ulceration and inflammation, the presence of squamous cells with viral inclusions may be overlooked at low-power magnification.

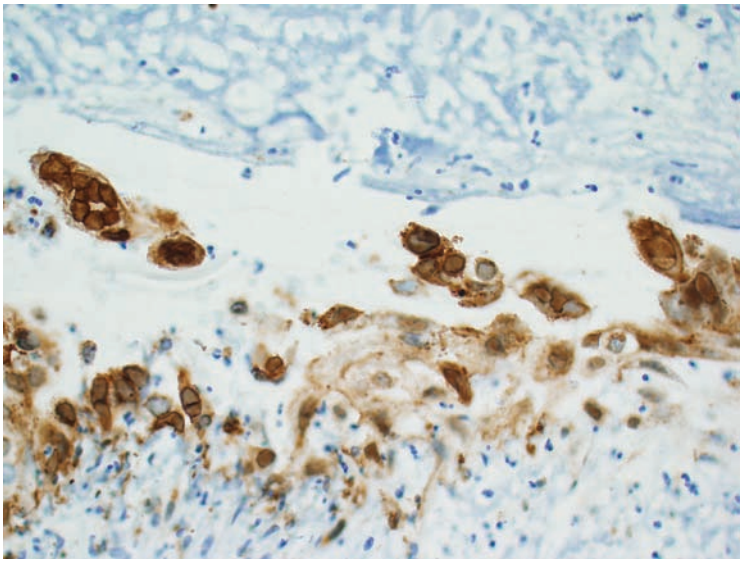


Figure 3.23 — Herpes Simplex Virus (HSV) (Cervical Biopsy) (HSV Immunohistochemical Stain; High Power). The intranuclear viral inclusions in the detached individual and clusters of squamous cells (same case as in Figures 3.3–3.22) show staining for HSV. Nuclear syncytia are particularly evident at the far left center. Note that positivity is also present in the cytoplasm of the infected squamous cells, indicating that the viral antigen is not confined to only the nuclei.

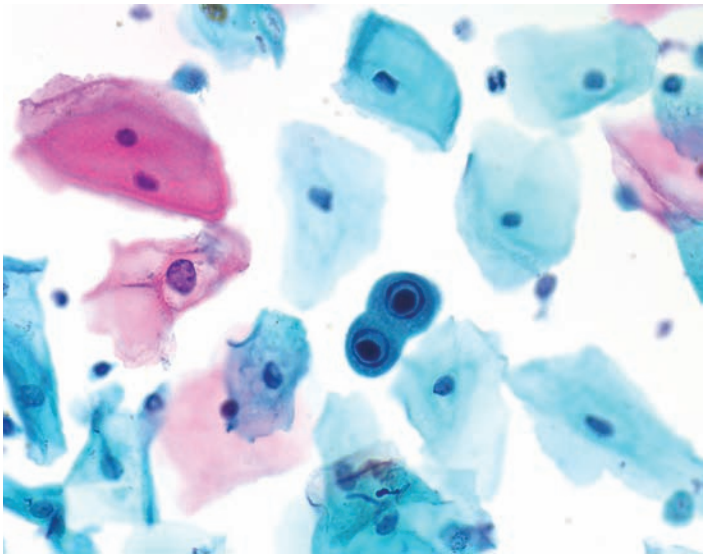


Figure 3.24 — Cytomegalovirus (CMV) (Liquid Based; Medium Power). Similar to HSV, CMV infects the nuclear DNA, enlarging the cell and sometimes producing daughter cells, although not like the multinucleated molding of HSV. As the name implies, the size of the cell is characteristically enlarged, and there is always a large nuclear inclusion surrounded by a halo. The marginated chromatin creates a thickened nuclear rim. Occasionally, cytoplasmic satellite inclusions are present. The cytoplasm is classically opaque and well defined.

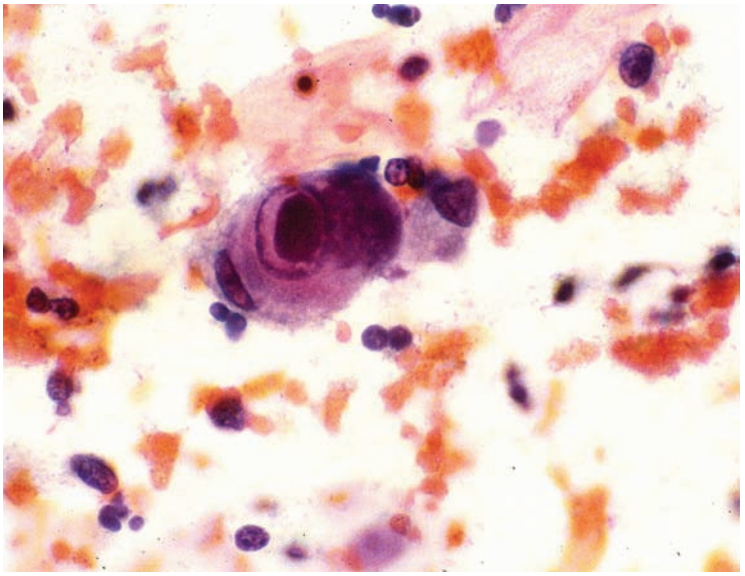


Figure 3.25 — Cytomegalovirus (CMV) (Conventional; High Power). A well-defined halo surrounds the large purple nuclear inclusion. A tiny satellite inclusion can be seen at 6 o'clock. Other nuclei in the cell group do not appear to be infected, as they are smaller than the infected cell, and the nuclei have none of the CMV features.

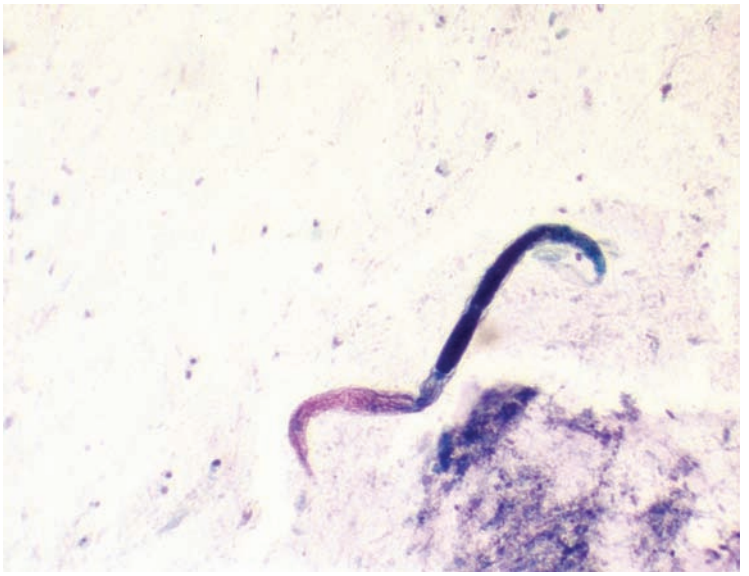


Figure 3.26 — *Strongyloides* (Conventional). *Strongyloides* in a vaginal smear! This could be mistaken for a synthetic fiber or another inconsequential artifact. Consultation with a parasitology expert is recommended.

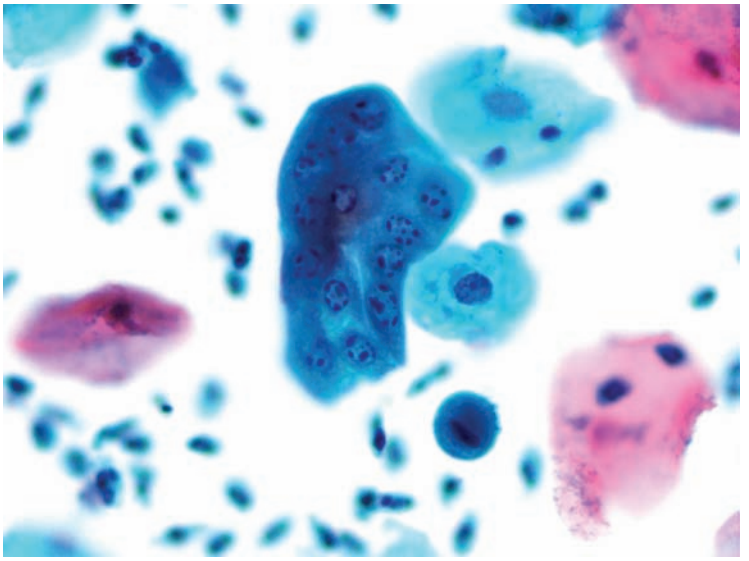


Figure 3.27 — Adenovirus (Liquid Based; High Power). This infection is rarely seen in Pap tests, and unless the nuclear features are this characteristic, these can be considered degenerative changes. Clinically, the patient may complain of symptoms related to a bladder infection or diarrhea. The female genital tract is usually asymptomatic, and the cytologic changes just reflect a nearby infection.

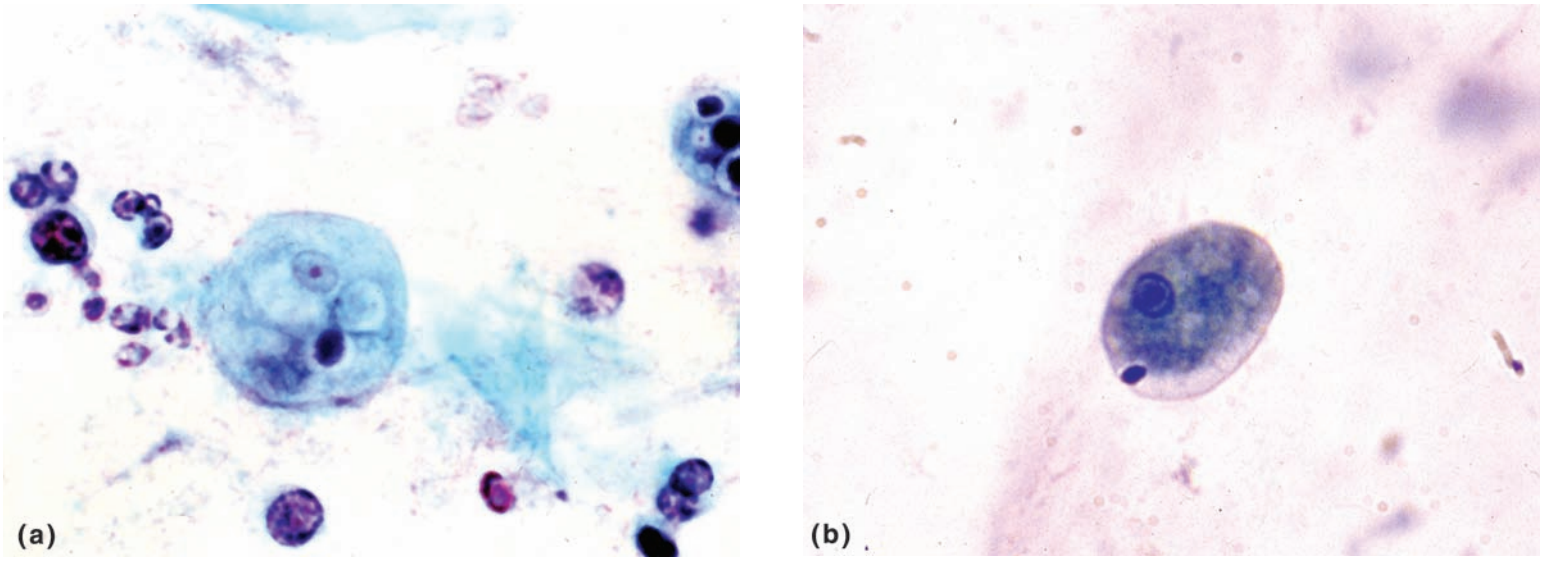


Figure 3.28 — (a, b) *Acanthamoeba gingivalis* (Conventional; High Power). Although rarely observed in routine practice, these protozoa may be encountered in women with IUDs and frequently accompanies *Actinomyces* infection.

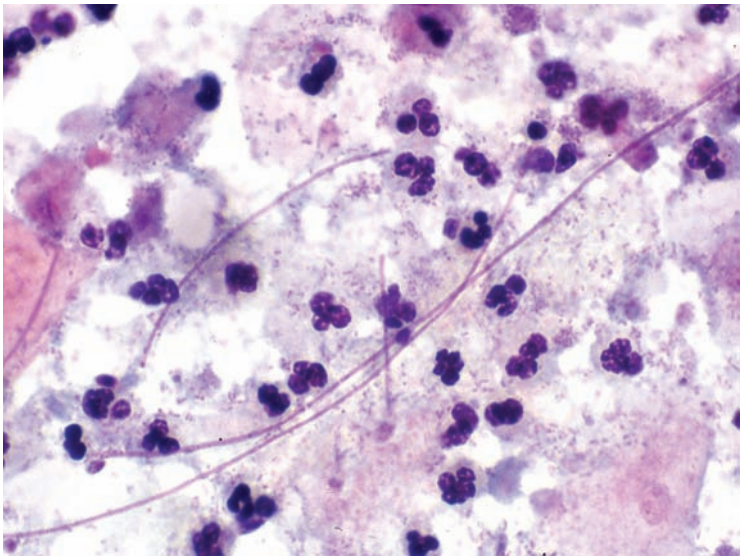


Figure 3.29 — Leptothrix (Conventional; High Power). This filamentous organism is a common partner to trichomonads in the vagina, but may also be seen alone. It is nonpathogenic but implies an imbalance in the normal vaginal flora, allowing overgrowth of pathogenic bacteria that can cause bacterial vaginosis. It may mimic *Lactobacillus acidophilus*, "good" bacteria, but its filaments are longer and they often loop.

4

Negative for Intraepithelial Lesion and Malignancy

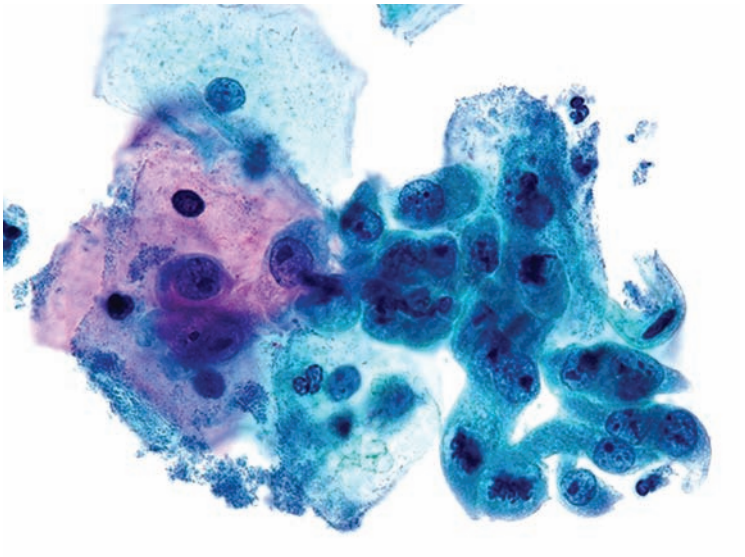


Figure 4.1 — Reactive Changes (Liquid Based; High Power). Endocervical cells tend to display reactive changes more prominently than squamous cells in the same sample, complete with mitotic figures. As long as the mitosis appears normal, the process could be considered benign. Other reactive features include prominent nucleoli and enlarged nuclei. Chromatin is uniformly distributed and finely granular.

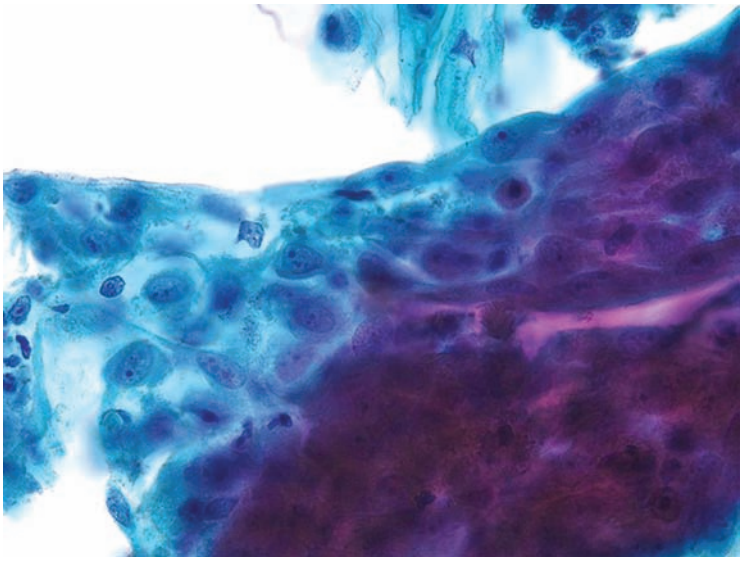


Figure 4.2 — Reactive Changes (Liquid Based; High Power). In contrast to the previous figure, this group of cells is arranged in a sheet with a mosaic arrangement. Cytoplasm is more opaque than endocervical cells and intercellular connections reflect squamous differentiation. Nuclei are similar to endocervical cells with obvious but small nucleoli.

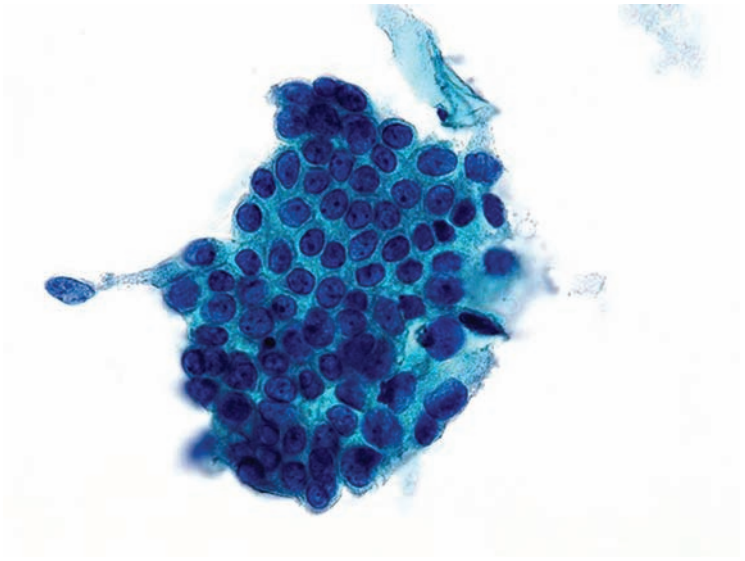


Figure 4.3 — Reactive Changes (Liquid Based; High Power). These are endocervical cells, identified by the textured/bubbly cytoplasm. The cytoplasmic borders are also shared, a characteristic of glandular epithelium. Nuclei are moderately enlarged.

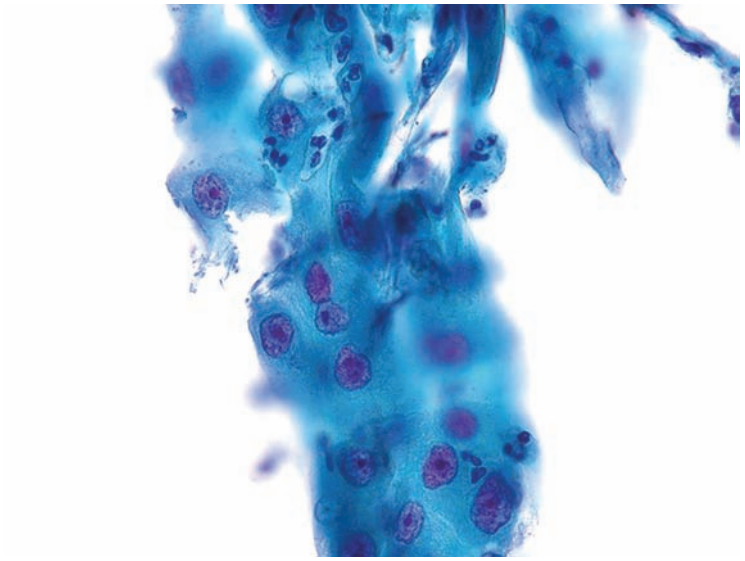


Figure 4.4 — Reactive or Repair (Liquid Based; High Power). A sheet of epithelial cells has characteristics of both squamous and glandular cells, because it reflects the reparative process in which it is engaged. When a breach in epithelium occurs, the intact edges heal toward the center, and are concerned only with covering the wound, not with differentiating. Cytoplasm is reflective of squamous cells (protective), and nuclei are similar to endocervical cells, the more reproductive component of the cervical epithelium. Nucleoli reflect the active reproductive state of the tissue. Mitoses may also be seen.

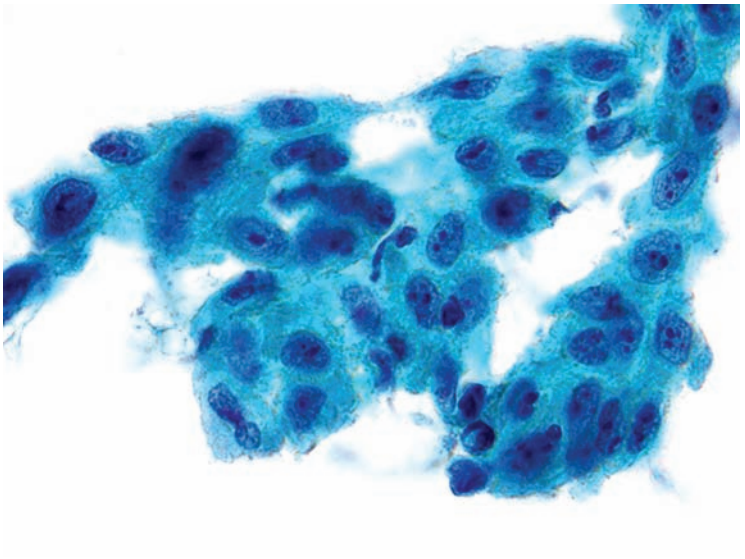


Figure 4.5 — Reactive or Repair (Liquid Based; High Power). This sheet of epithelial cells bears resemblance to the previous image, but the cytoplasm is a bit more delicate, suggesting its origin in the endocervical portion of the cervical os.

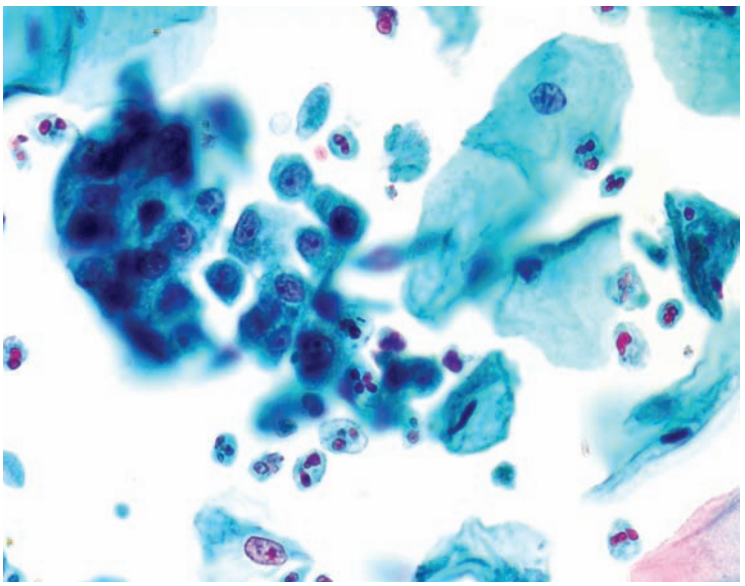


Figure 4.6 — Reactive or Metaplastic (Liquid Based; High Power). The separation of each of these cells places them in a metaplastic category. Nuclei are uniform and round, the same size and shape as the intermediate cell to the right of the group. The metaplastic cells contain nucleoli, reflecting their capability of dividing.

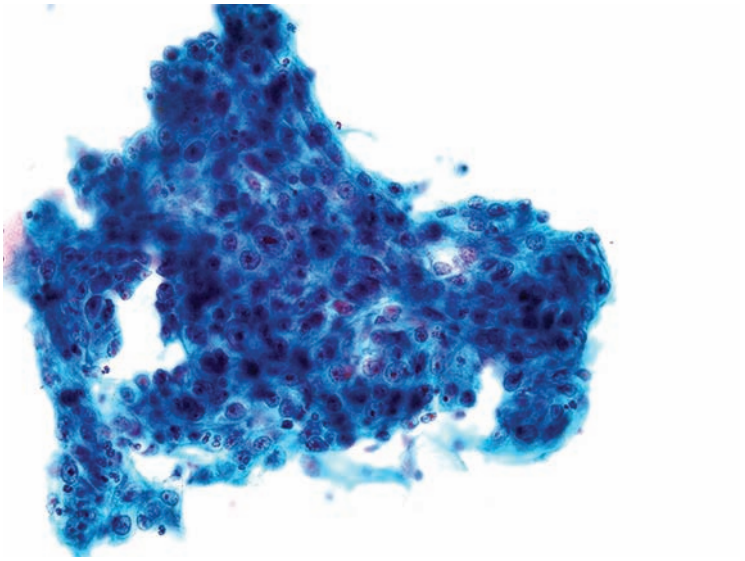


Figure 4.7 — Repair (Liquid Based; Medium Power). The characteristics of prominent nucleoli and uniform size and shape of nuclei place this fragment into a "typical repair" category. It should be interpreted as a benign change. Care should be taken not to overinterpret reparative changes as dysplastic or malignant.

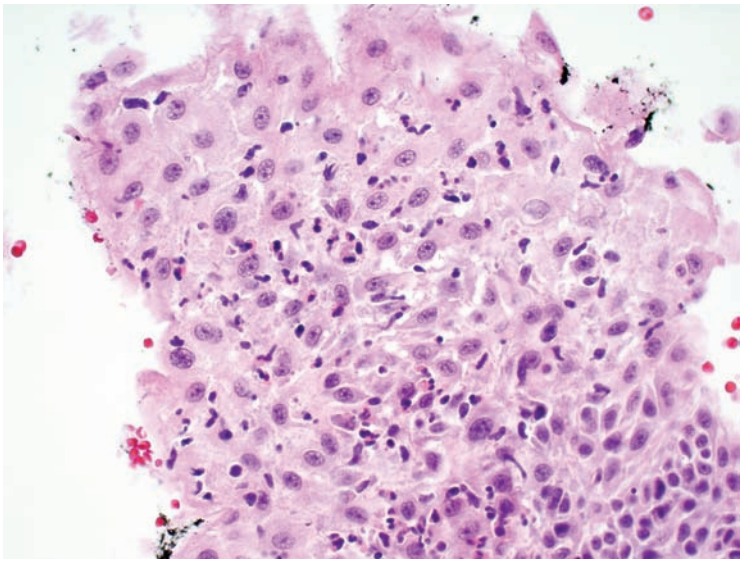


Figure 4.8 — Atypical Cervical Squamous Mucosa With Reactive or Reparative Changes (Biopsy) (Hematoxylin and Eosin [H&E] Stain; High Power). The squamous cells exhibit nuclear enlargement; however, the nuclei are fairly uniform. Prominent nucleoli, even/pale chromatin, smooth nuclear membranes, and a low nuclear-to-cytoplasmic ratio are present, and mitotic activity is absent. The squamous epithelium contains numerous inflammatory cells and some degree of intercellular edema. The bottom right corner of the photograph shows tangentially sectioned parabasal epithelium. The above-combined features are in contrast to those of a squamous intraepithelial lesion. An immunohistochemical stain for p16 would not show the typical diffuse strong pattern seen in high-grade squamous intraepithelial lesions and a subset of low-grade squamous intraepithelial lesions. Determining the Ki-67 proliferation index for the squamous cells in this setting is difficult because of the numerous inflammatory cells that would show confounding staining.

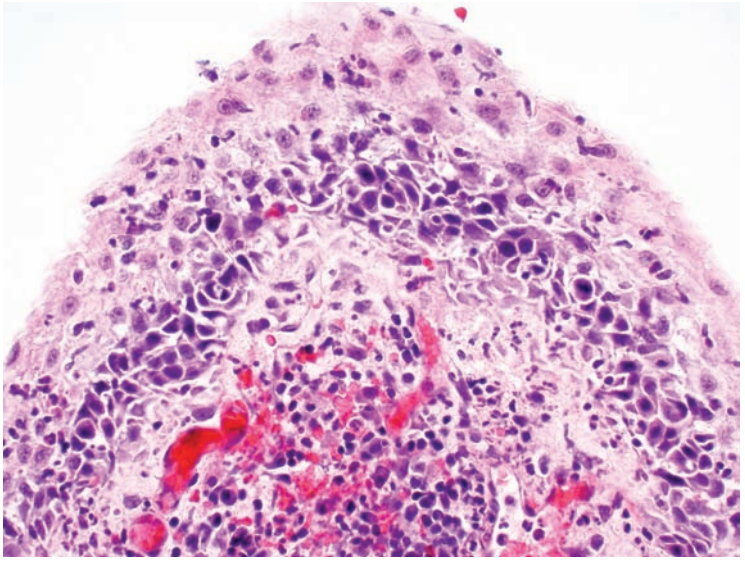


Figure 4.9 — Atypical Cervical Squamous Mucosa With Reactive or Reparative Changes (Biopsy) (H&E Stain; High Power). The squamous epithelium shows cytologic features similar to those seen in Figures 4.4 to 4.8. Note the prominent nucleoli. Also, the parabasal epithelium is somewhat prominent in this example and can cause concern for a high-grade squamous intraepithelial lesion at low-power magnification. Nonetheless, the cytologic features in this case are consistent with a reactive or reparative process and insufficient for the diagnosis of a squamous intraepithelial lesion. Moreover, immunohistochemical stains for p16 would help exclude the possibility of a high-grade squamous intraepithelial lesion. Immunostains for Ki-67, nevertheless, would be noncontributory, because the parabasal layer would be expected to show proliferative activity. In addition to inflammatory cells within the squamous epithelium, abundant inflammation is present in the stroma. When notable inflammation is present, reactive or reparative changes should always be considered in the differential diagnosis of atypical squamous epithelium. However, it is important to consider that, on occasion, squamous intraepithelial lesions can be inflamed. Thus, the presence of inflammation by itself does not exclude the possibility of a squamous intraepithelial lesion.

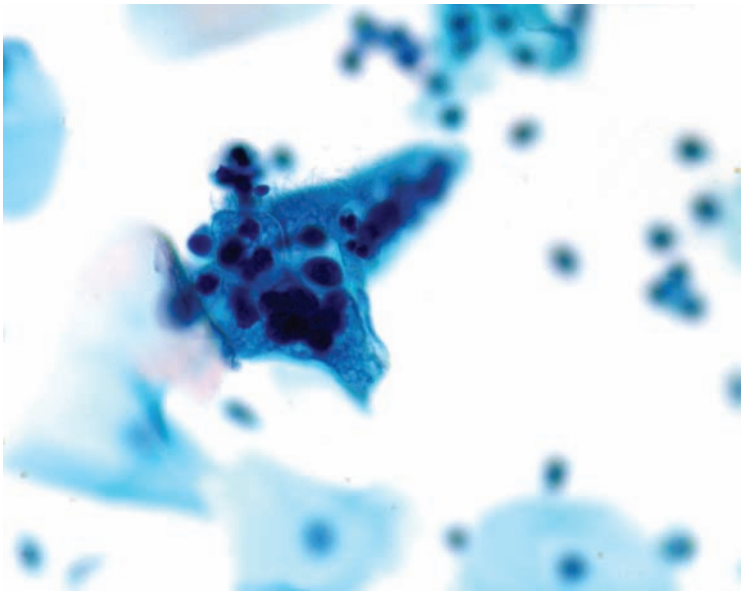


Figure 4.10a — Tubal Metaplasia (Liquid Based; High Power). Endocervical cells from the junction between the endocervical canal and the endometrial cavity naturally have cilia, which assist migrating sperms from the vagina. This is not a true metaplasia, but the term has become entrenched in the literature.

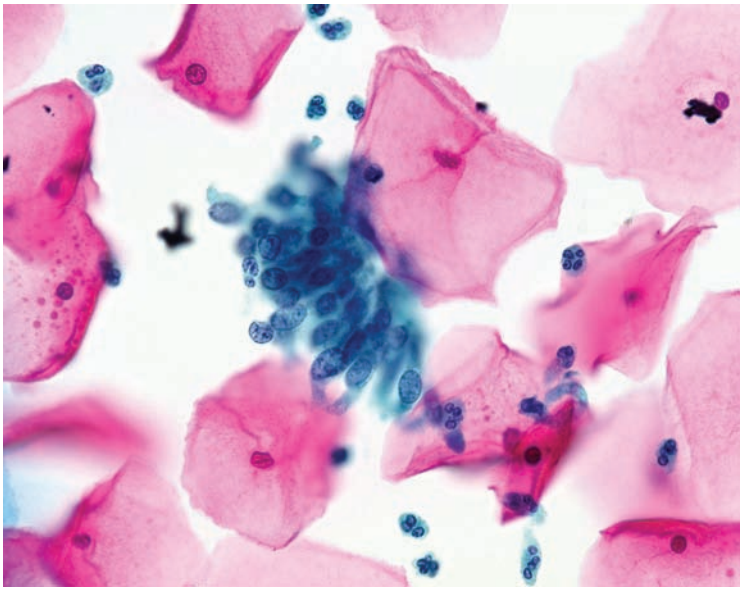


Figure 4.10b — Tubal Metaplasia (Liquid Based; High Power). This strip of endocervical cells appears stratified and the nuclei almost appear to form a feathered border, a feature that is associated with adenocarcinoma in situ. However, some cells have cilia present at the tips, indicating that these are benign ciliated endocervical cells and not a glandular lesion. In addition, the cells are not hyperchromatic and have a bland chromatin pattern.

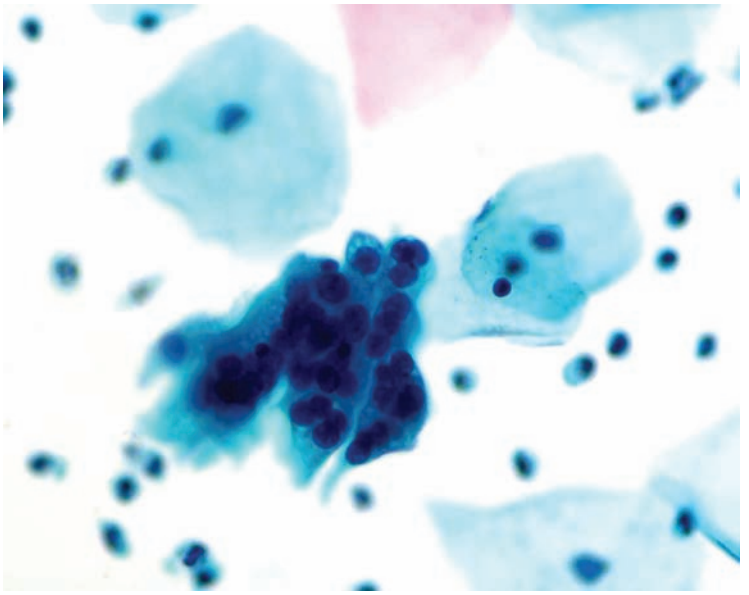


Figure 4.10c — Tubal Metaplasia (Liquid Based; High Power). The cells in this group are hyperchromatic and the nuclei overlap, two concerning features that often result in tubal metaplasia being mistaken for a glandular lesion. However, one edge of the fragment is smooth, indicating the presence of a terminal bar; furthermore, the terminal bar is ciliated. In some instances, cilia may not be as easily identifiable as the terminal bar.

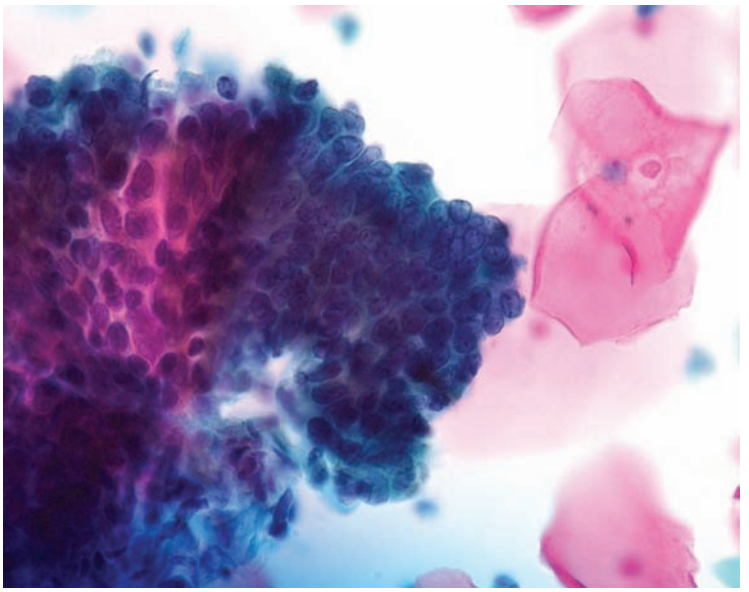


Figure 4.10d — Tubal Metaplasia (Liquid Based; Medium Power). This fragment contains cells with dark, overlapping nuclei with irregular borders. The cells have increased nuclear-to-cytoplasmic (N/C) ratios. These features are highly atypical and provide a dramatic example of how tubal metaplasia can mimic adenocarcinoma. The top left corner of the fragment contains cells that are unmistakably ciliated. This reassuring finding may only be seen focally in large tissue fragments.

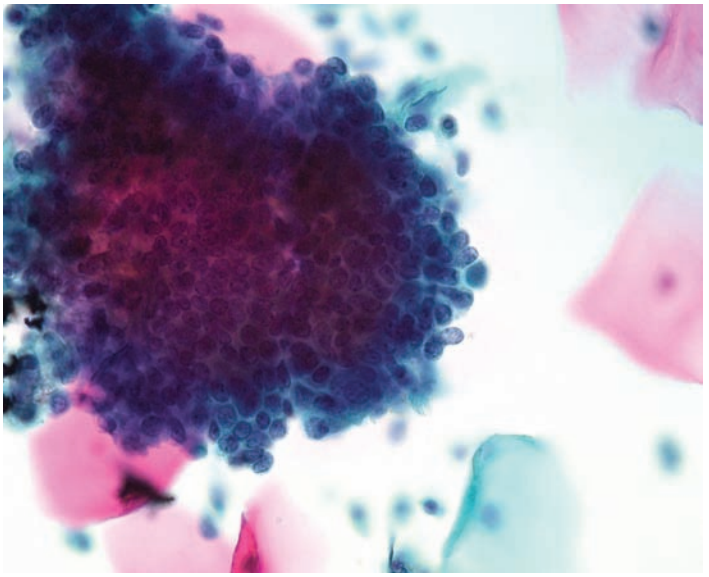


Figure 4.10e — Tubal Metaplasia (Liquid Based; Medium Power). This fragment provides a second example of how atypical tubal metaplasia can appear. It is easy to focus on the atypical features and hyperchromasia, which appears most prominent in the center of the fragment. However, the fragment edges contain ciliated cells and, perhaps more obviously, cells with distinct terminal bars. The sharp "flat" edge of the cytoplasm created by a terminal bar is not seen in adenocarcinomas.

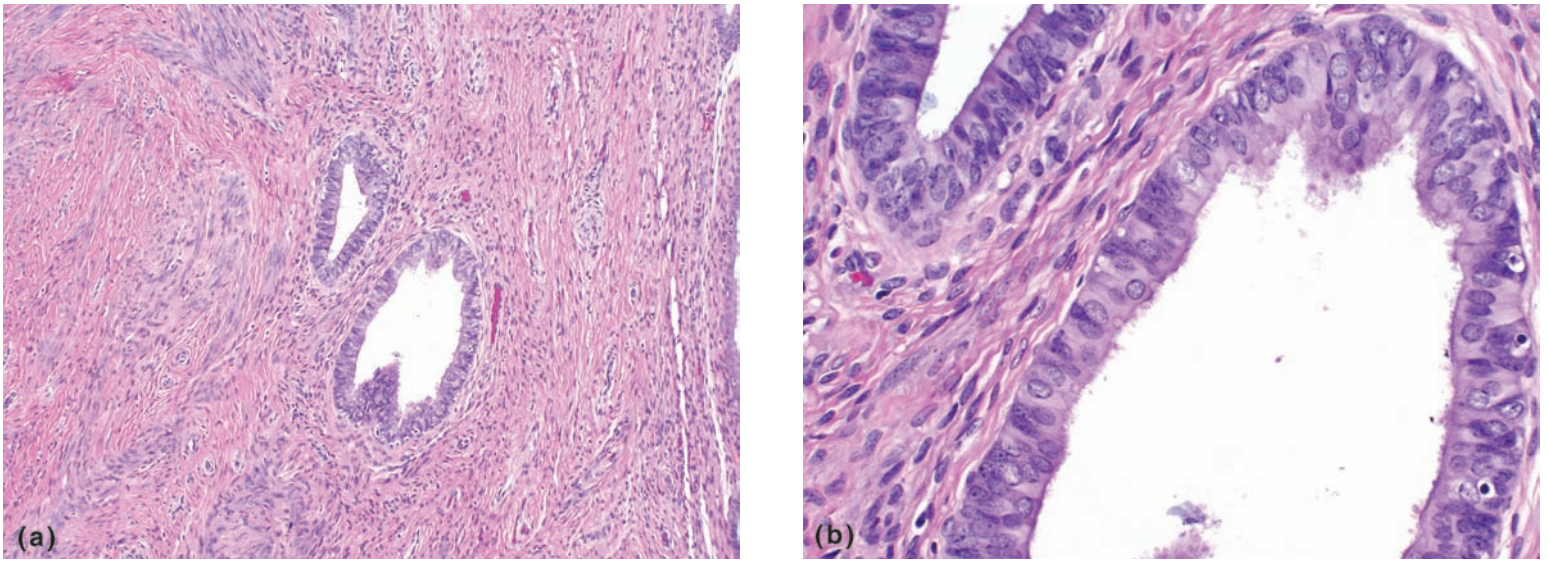


Figure 4.11 — Cervical Tubo-Endometrioid Metaplasia (Hysterectomy) (H&E Stain; (a) Intermediate and (b) High Power). At lower power magnification, these glands appear dark and may create concern for endocervical adenocarcinoma in situ. However, on higher power magnification, the glandular epithelium exhibits features similar to endometrial epithelium with tubal metaplasia. In this example, the epithelium is pseudostratified with columnar cells showing round to oval nuclei. Some cells have dark nuclei, which are within the spectrum seen in the proliferative-phase endometrium. The cells with round nuclei, abundant pink cytoplasm, and luminal cilia represent tubal metaplasia. Note that the lack of nuclear enlargement, hyperchromasia, and mitotic activity are in contrast to adenocarcinoma in situ. Although tubal metaplasia is usually a helpful clue arguing against a diagnosis of adenocarcinoma in situ, uncommon variants of the latter have been described. Performing immunohistochemical stains for p16 and Ki-67 assists in facilitating the diagnosis. Adenocarcinoma in situ shows diffuse strong staining for p16 and a high proliferation index, whereas tubo-endometrioid metaplasia usually has no focal, or patchy expression of p16 and a low proliferation index.

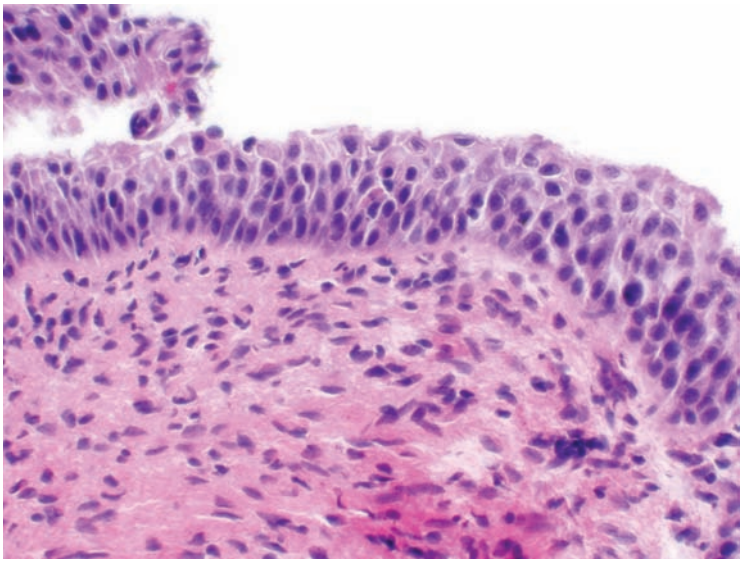


Figure 4.12a — Atypical Immature Squamous Metaplasia (AIM) (Biopsy) (H&E Stain; High Power). The squamous epithelium is somewhat attenuated. It does not exhibit full maturation, the cells show a high N/C ratio, and the morphologic features are suspicious for hyperchromasia. Mitotic figures are not present, and the nuclei are not significantly enlarged. The features based on morphology alone, therefore, are not completely definitive for a diagnosis of high-grade squamous intraepithelial lesion (HSIL) (see Chapter 6). However, the differential diagnosis concerns immature squamous metaplasia versus HSIL.

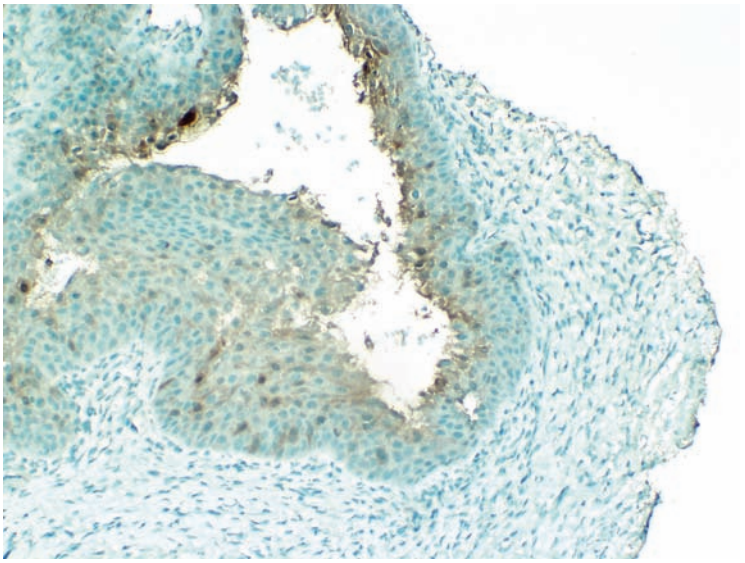


Figure 4.12b — Atypical Immature Squamous Metaplasia (AIM) (Biopsy) (p16 Immunohistochemical Stain; Intermediate Power). Focal staining for p16 is present, and this specimen lacks the usual diffuse pattern associated with high-risk human papillomavirus (HPV)-related lesions.

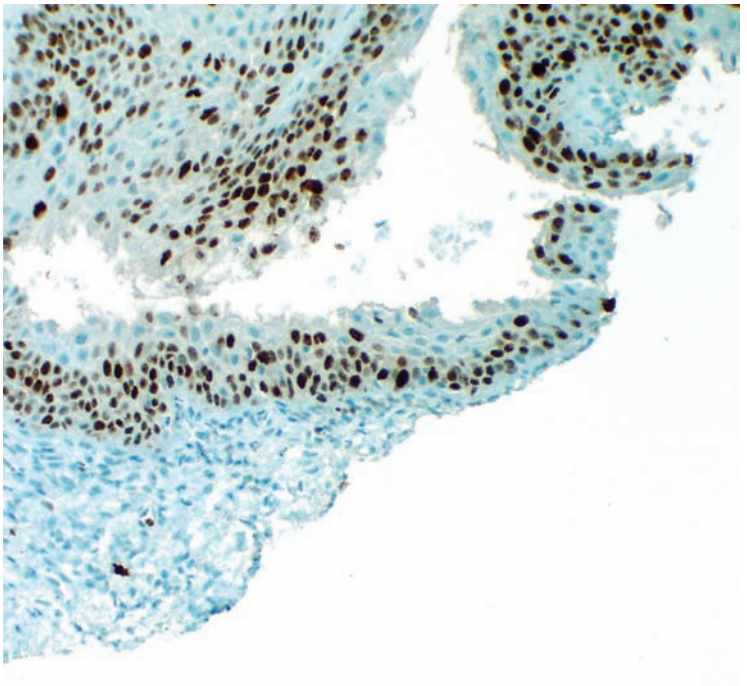


Figure 4.12c — Atypical Immature Squamous Metaplasia (AIM) (Biopsy) (Ki-67 Immunohistochemical Stain; Intermediate Power). Proliferative activity is mostly restricted to the parabasal layers. The Ki-67 index is difficult to determine because of the partially tangential orientation of the tissue section. Nonetheless, in some areas that are more perpendicularly oriented, there is slightly increased proliferation in the upper half of the attenuated squamous epithelium. These combined morphologic and p16/Ki-67 immunohistochemical findings are interpreted as being more compatible with a diagnosis of immature squamous metaplasia (or AIM) as opposed to HSIL. The term AIM has been used variably between pathologists. Here, it is used to describe cases having some features suggestive of HSIL but lacking sufficient morphologic findings to unequivocally establish that diagnosis. Thus, it is a descriptive diagnosis that captures the atypical nature of the case but which also designates it as a form of immature squamous metaplasia rather than HSIL. Immunohistochemical stains for p16 (and potentially Ki-67) can assist in resolving this differential diagnosis. HSIL typically exhibits diffuse p16 expression with a high Ki-67 index. It should be noted that rare cases of HSIL with unequivocal morphology may have non-diffuse patterns of p16. A diagnosis of AIM should only be rendered after technically satisfactory immunohistochemical stains for p16 (and potentially Ki-67) have been performed. For cases with ambiguous morphology and in which the p16 immunostain cannot be performed or interpreted due to technical reasons, which therefore limits the ability to evaluate a potential HSIL, it may be prudent to use a descriptive diagnosis indicating that the possibility of HSIL cannot be excluded (eg, "Atypical immature squamous metaplasia, cannot exclude HSIL"). To avoid confusion on behalf of the clinician, when making a diagnosis of AIM, it may be useful to write a comment section in the pathology report explaining the diagnostic dilemma and that the case does not qualify as HSIL. Immunostaining for Ki-67 is not necessary for diagnosing HSIL if the morphology and p16 result are concordant. Per the CAP-LAST consensus guidelines, the routine addition of Ki-67 to p16 immunohistochemistry is not recommended; however, for cases in which p16 immunohistochemistry is inconclusive or technically inadequate, use of Ki-67 may be considered. Specifically, when the differential diagnosis concerns HSIL versus atrophy/transitional cell metaplasia or immature squamous metaplasia, a Ki-67 stain can be useful if the p16 stain is difficult to assess. It is, nonetheless, important to recognize that interpreting a Ki-67 stain in tangentially oriented tissue or attenuated mucosa may be problematic.

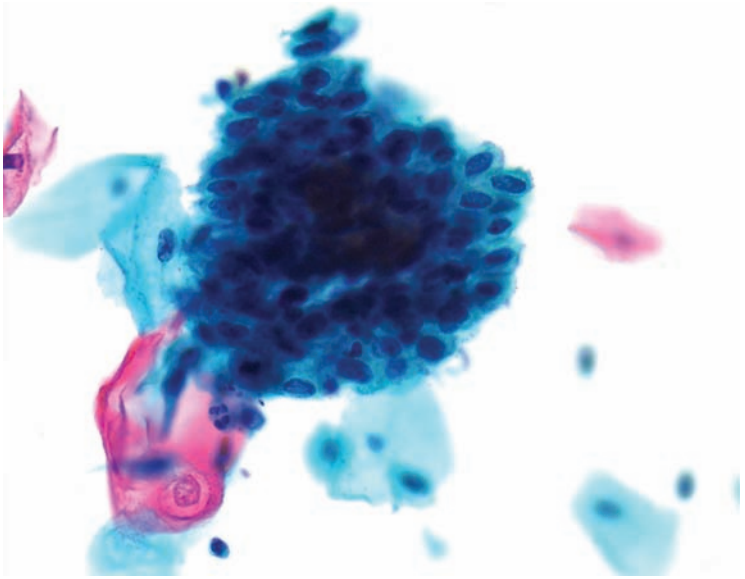


Figure 4.13 — Transitional Metaplasia (Liquid Based; High Power). A relatively new terminology, this epithelial change can easily be confused with HSIL. Careful focus through the hyperchromatic crowded group (HCG) will enable the appreciation of small oval nuclei, smooth nuclear outlines, and fine chromatin. Compare with photos of HSIL or immature squamous metaplasia.

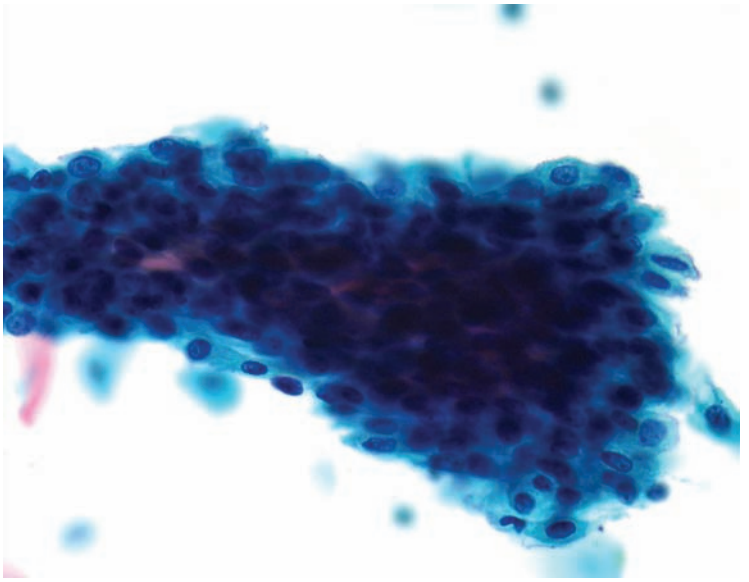


Figure 4.14 — Transitional Metaplasia (TM) (Liquid Based; High Power). Squamous metaplasia has features similar to TM, except for the round shape of nuclei and pavement arrangement. TM has a uniformly polarized pattern, strikingly similar to benign urothelium, hence the name.

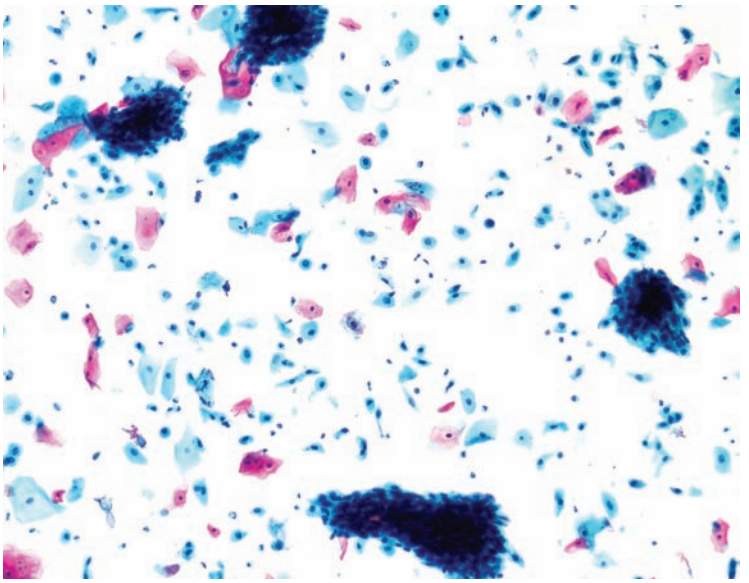


Figure 4.15 — Transitional Metaplasia (Liquid Based; Low Power). The darkness of these HCGs is worrisome, and demands careful scrutiny of every group before declaring the change benign.

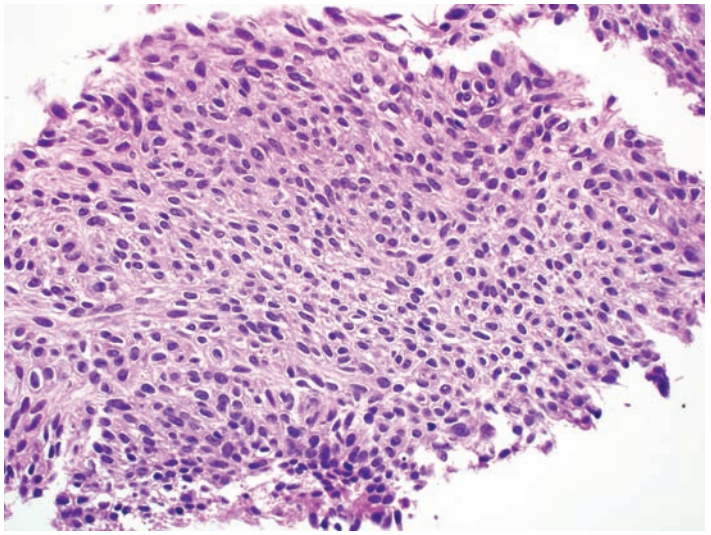


Figure 4.16a — Benign Cervical Squamous Mucosa With Atrophy or Transitional Cell Metaplasia (Endocervical Curettage) (H&E Stain; High Power). This detached and tangentially oriented fragment of squamous epithelium can cause concern for HSIL at low-power magnification because of the increased cellularity and slightly elevated N/C ratio. However, on high power, the cells lack the hyperchromasia and mitotic activity of HSIL. Atrophy and transitional cell metaplasia often show overlapping features. The slight elongation of nuclei with a suggestion of spindling or streaming is more typical of transitional cell metaplasia, although other cases have more well-developed longitudinal grooves of the nuclei.

Figure 4.16b — Benign Cervical Squamous Mucosa With Atrophy or Transitional Cell Metaplasia (Endocervical Curettage) (p16 Immunohistochemical Stain; Intermediate Power). Overexpression of p16 is not present.

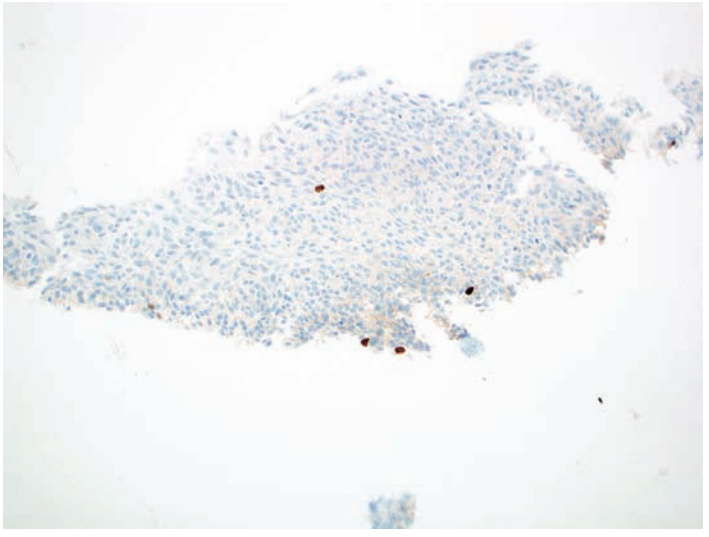


Figure 4.16c — Benign Cervical Squamous Mucosa With Atrophy or Transitional Cell Metaplasia, Histologic Section (Endocervical Curettage) (Ki-67 Immunohistochemical Stain; Intermediate Power). The proliferation index is 0%, and only rare Ki-67-positive lymphocytes are seen. These combined immunohistochemical findings (p16/Ki-67) argue against a diagnosis of HSIL.

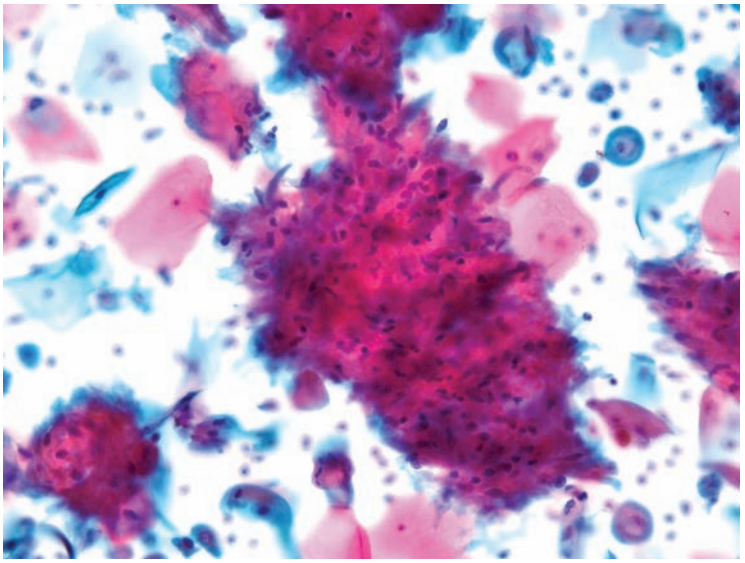


Figure 4.17 — Granuloma (Liquid Based; Medium Power). Granulomatous inflammation in the female genital tract is usually a result of prior surgery in the area. However, a granulomatous lesion, such as granuloma gravidarum, or less likely, a mycobacterial infection should be considered if an operative procedure has not occurred.

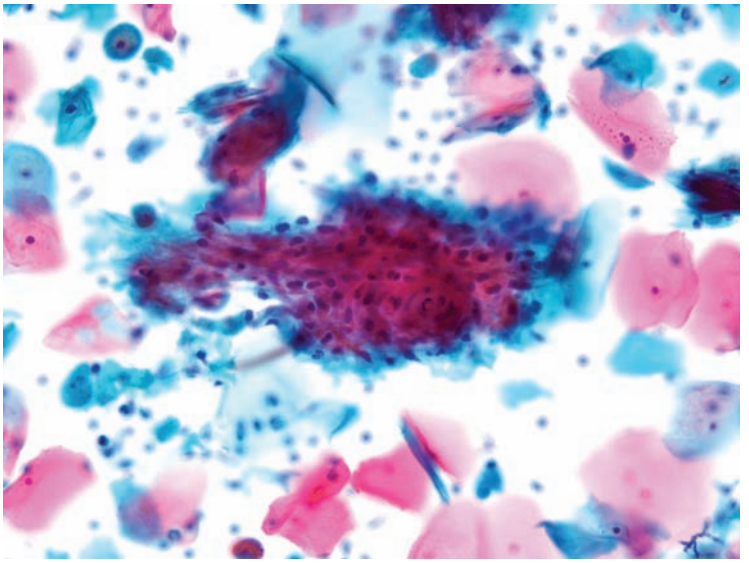


Figure 4.18 — Granuloma (Liquid Based; Medium Power). Classic cellular components can be found in a granuloma, that is, lymphocytes, macrophages, and fibroblasts. Careful search for foreign materials may be rewarding.

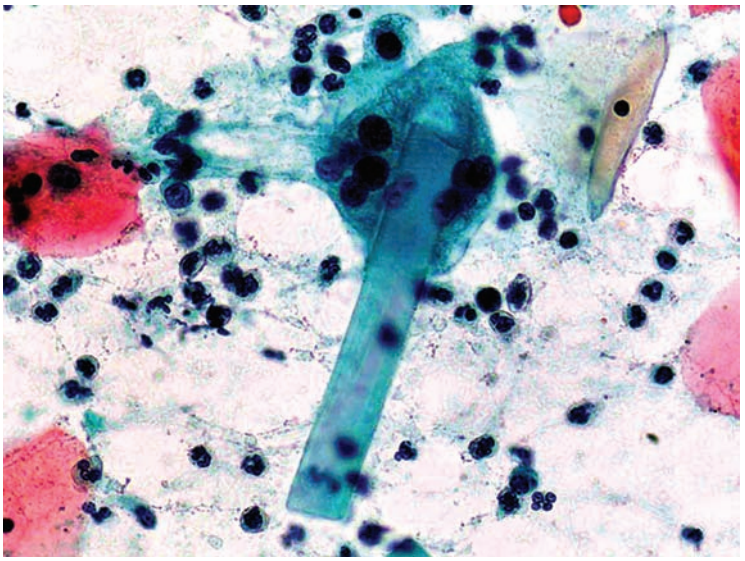


Figure 4.19 — Suture Granuloma (Liquid Based; High Power). When a foreign material, such as this suture fragment, is surrounded by histiocytes, the reason for the granulomatous reaction is obvious.

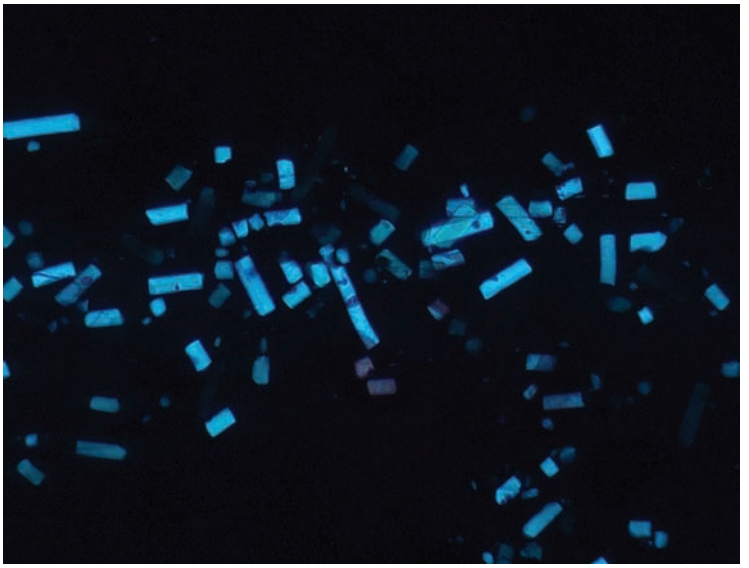


Figure 4.20 — Suture Granuloma (Liquid Based; Polarized Light). Some foreign material conveniently polarizes. When granulomatous inflammation is present, use of polarized light may prove very helpful.

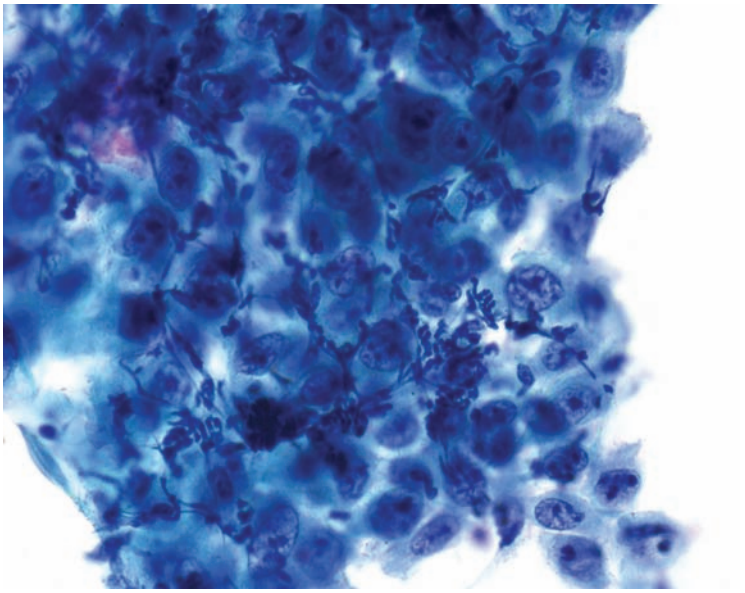


Figure 4.21 — Pemphigus Vulgaris (Liquid Based; High Power). This skin lesion may be found in many areas of the body; hence, a history should be elicited if the disease is suspected on a Pap. The cellular separations suggest a common squamous metaplasia. However, the enlarged nuclei have prominent nucleoli and characteristic speckled chromatin. Acute inflammation completes the picture. Pemphigus has long been a favorite disease to include in "unknown" panels at cytology conferences.

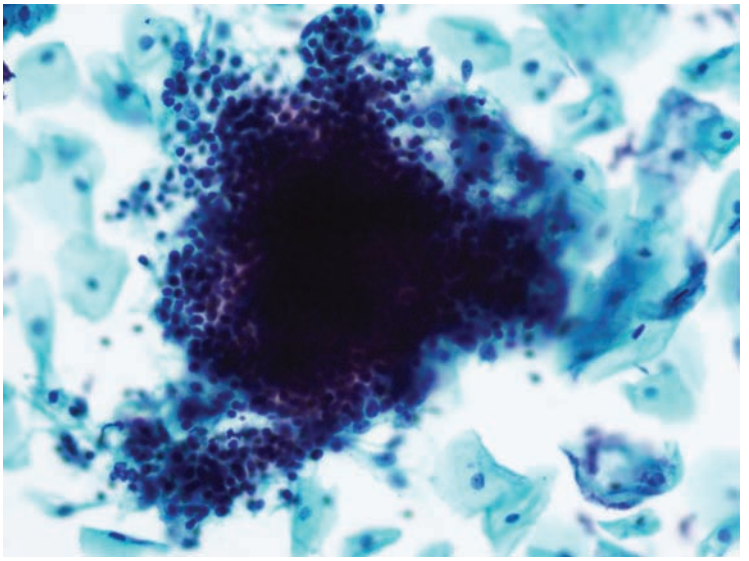


Figure 4.22 — Follicular Cervicitis (Liquid Based; Medium Power). While neutrophils are commonly seen in Pap test samples, mononuclear cells are typically found in less abundance. Quite the reverse pattern is seen in tissue samples from the cervix. Follicular cervicitis is an exaggeration of chronic inflammation in the cervical submucosa, and is retrieved in a Pap test only when the lymphoid follicle has thinned the squamous epithelium sufficiently to allow the Pap sampler to break through. Differential diagnosis includes endometrial cells, and less likely, small cell neuroendocrine carcinoma.

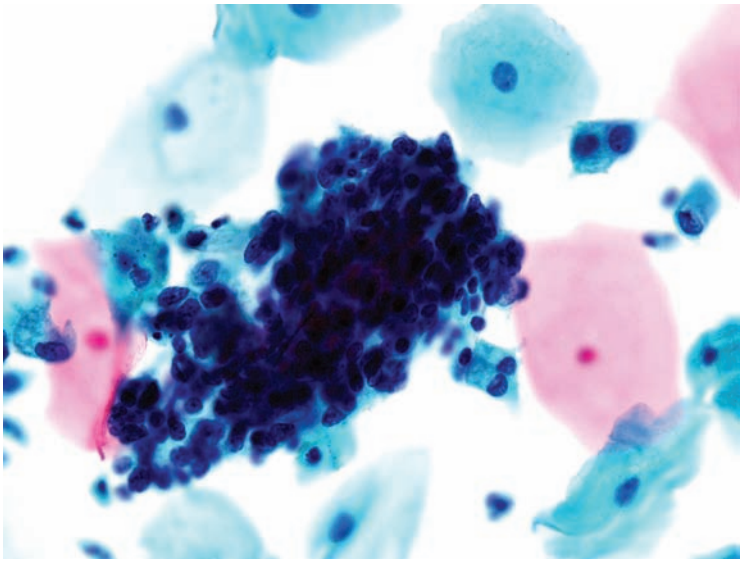


Figure 4.23 — Follicular Cervicitis (Liquid Based; High Power). Careful evaluation of the cell population enables identification of lymphocytes, monocytes, and follicular center cells. Endocervical cells adjacent to the lymphoid cells have more cytoplasm and paler nuclear chromatin.

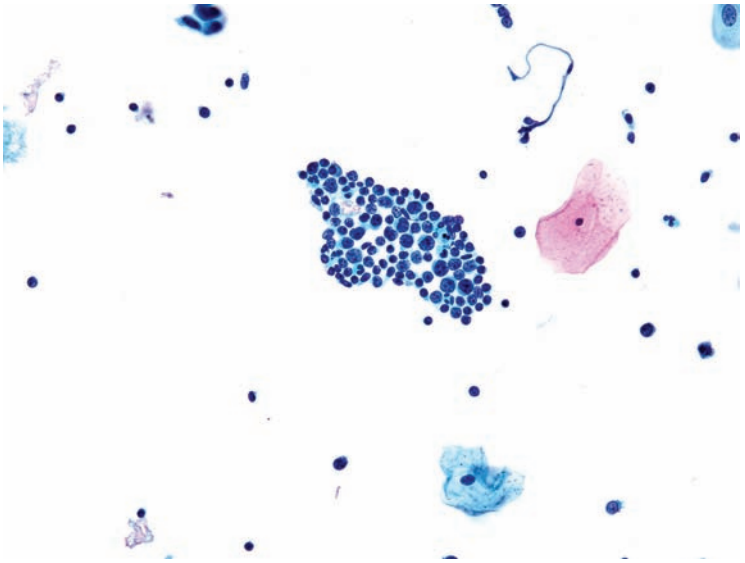


Figure 4.24 — Follicular Cervicitis (Liquid Based; Medium Power). Although the cells do not adhere tightly as in a true tissue fragment, they do aggregate even after the mechanical rigors of liquid processing. They are easily spotted on lower power, as distinct from the epithelial cells present in every Pap.

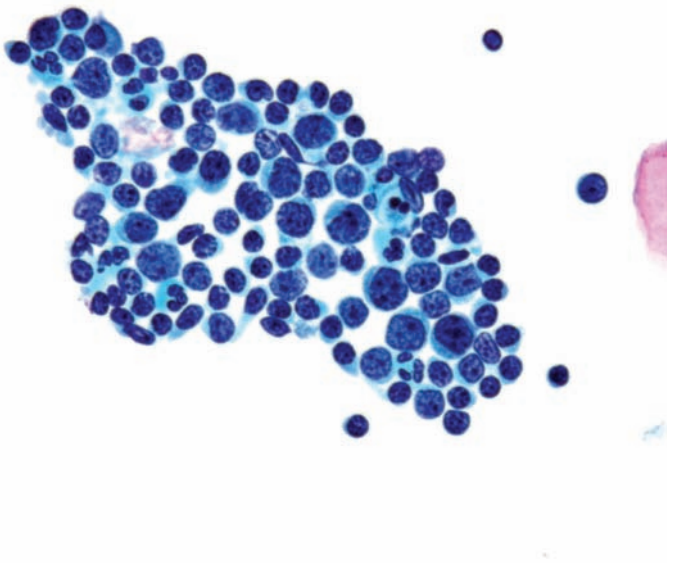


Figure 4.25 — Follicular Cervicitis (Liquid Based; High Power). This magnification allows clear identification of the various mononuclear cells to be expected in follicular cervicitis. Some of the larger cells may resemble blasts. If a history of lymphoma or leukemia is discovered, involvement of pelvic organs is a consideration, a reflection of the "sanctuary phenomenon," whereby systemic chemotherapy is only minimally effective in pelvic organs, similar to the central nervous system. Most often, however, the larger cells are only stimulated lymphoid cells. When primarily detached, these high N/C ratio cells can be confused with an HSIL.

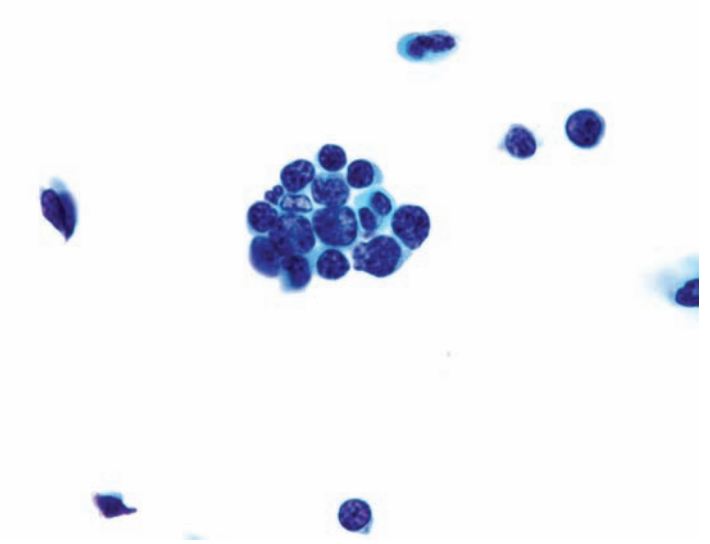


Figure 4.26 — Follicular Cervicitis (Liquid Based; High Power). This small group of round cells is suspicious for a neoplasm, as many of the cells are identical and large. One or two appear to mold, making the lesion suspicious for a small-cell neuroendocrine tumor. However, careful focusing will negate that impression, and the single lymphocytes in the background confirm the benign diagnosis.

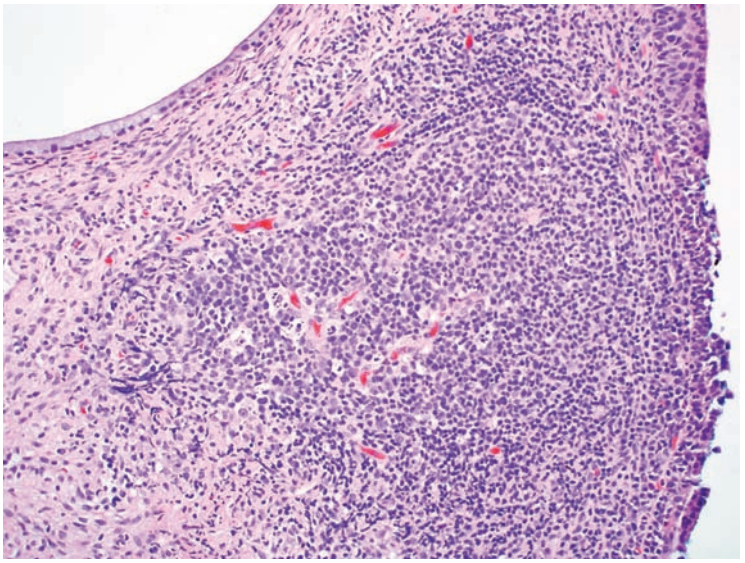


Figure 4.27 — Follicular Cervicitis (Cone Biopsy) (H&E Stain; Intermediate Power). Underneath the surface mucosa of the cervix (*far right*) is a prominent lymphoid follicle within the stroma. It exhibits the same histologic features seen in reactive follicles in lymph nodes, including a germinal center (with tingible-body macrophages and a mixture of small and large lymphoid cells) with a mantle of small lymphocytes. An association between follicular cervicitis and *Chlamydia* infections has been recognized. Cases of florid reactive lymphoid hyperplasia of the cervix (so-called lymphoma-like lesion) can simulate lymphoma, especially in small biopsies.

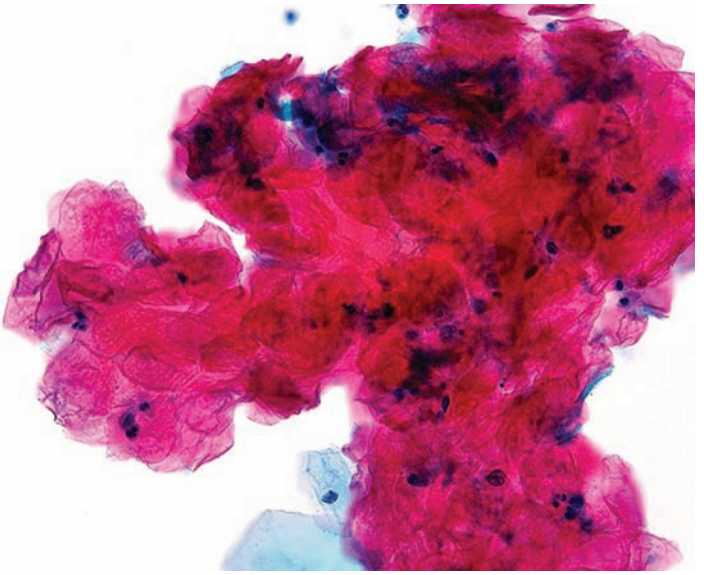


Figure 4.28 — Hyperkeratosis (Liquid Based; Medium Power). A large fragment of anucleated squames is unusual and urges careful search for a keratinizing neoplasm. If none is found, the hyperkeratosis may be due to uterine prolapse alone, or with use of a pessary. Clinical correlation is needed to define the reason for the keratosis.

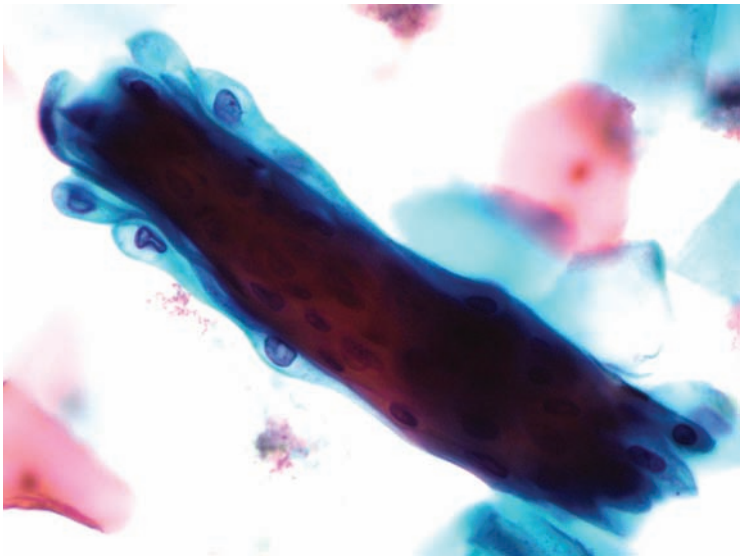


Figure 4.29 — Parakeratosis (Liquid Based; High Power). In contrast to the anucleated squames in Figure 4.28, these nucleated cells are configured in a parallel strip. If all cells have the same small-size nuclei, and are in an ordered pattern, the diagnosis is benign. Compare with atypical parakeratosis.

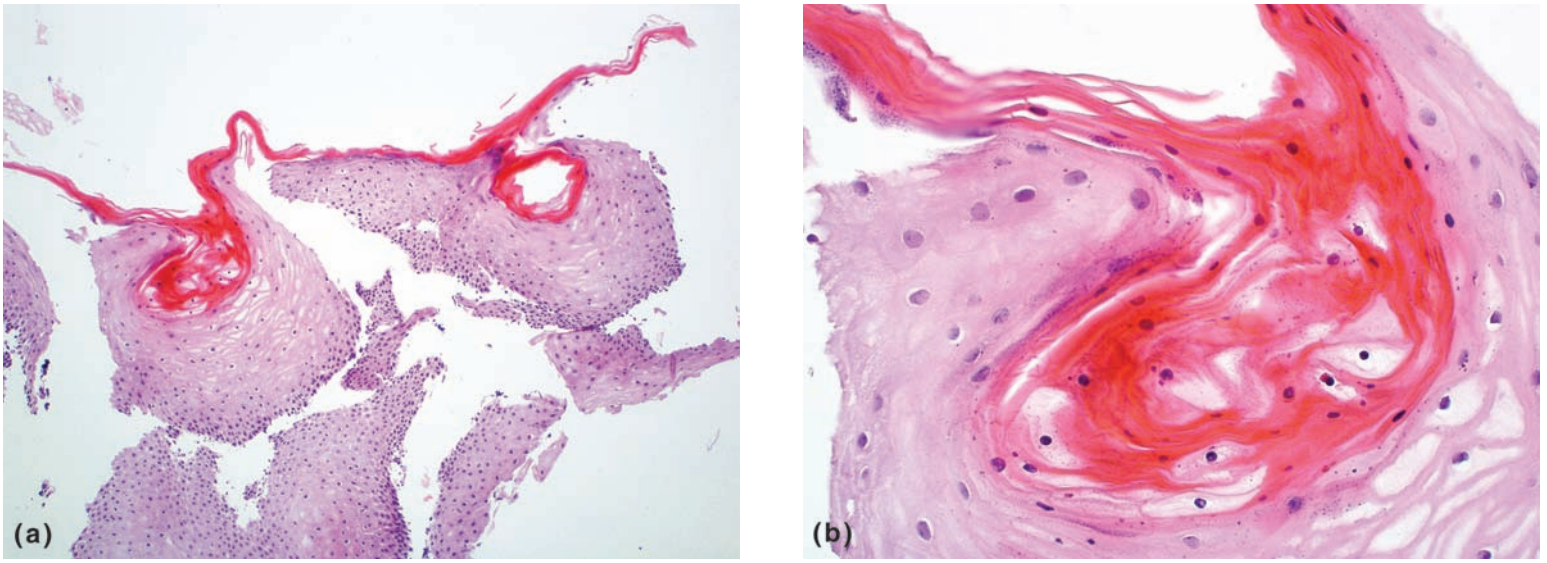


Figure 4.30 — Benign Cervix With Hyperkeratosis or Parakeratosis (Biopsy) (H&E Stain; (a) Intermediate and (b) High Power). The majority of the squamous epithelium is unremarkable and shows normal maturation. However, the surface is involved by hyperkeratosis or parakeratosis. Parakeratosis, particularly in a markedly fragmented biopsy, can create concern for a keratinizing squamous intraepithelial lesion. The bland appearance of the background squamous epithelium in this example, along with the absence of significant nuclear abnormalities in the parakeratotic layer, argue against a squamous intraepithelial lesion. Also, Ki-67 immunohistochemical stains should not show increased proliferative activity. Hyperkeratosis or parakeratosis by itself is nonspecific, but hyperkeratosis can be associated with uterine prolapse.

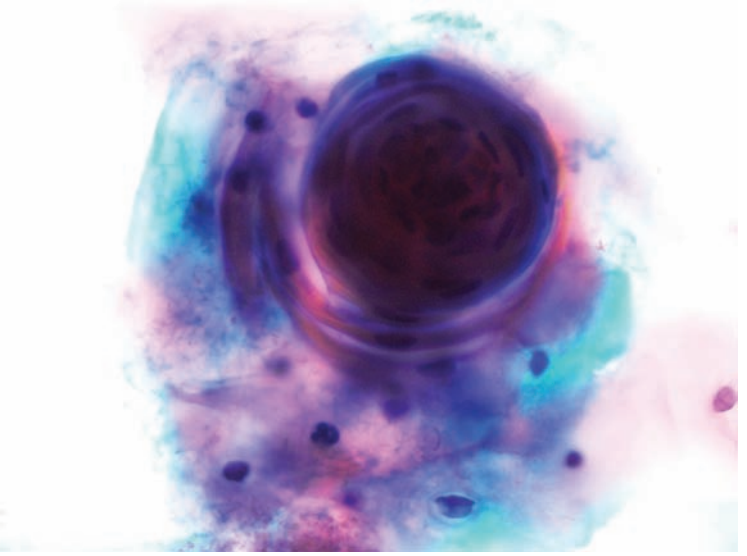


Figure 4.31 — Benign Pearl (Liquid Based; High Power). Before koilocytes were recognized as the hallmark of HPV infection, squamous pearls were considered the sign of a squamous wart in conventional Pap smears. A pearl is essentially parakeratosis in a whorled pattern, and represents tips of the wart. As in parallel parakeratosis, if the nuclei are small and similar, then the lesion is completely benign; if nuclei are larger, dissimilar, and of irregular shapes, then a neoplasia is to be considered.

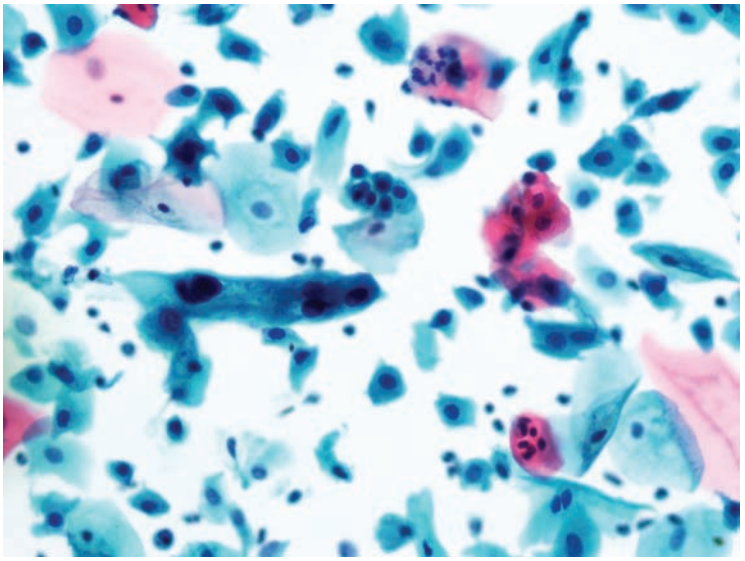


Figure 4.32 — Radiation Changes (Liquid Based; Medium Power). Radiation directly to the pelvic organs causes atrophy as well as abnormal cells. The changes are less dramatic than pictured in older texts because radiation is now more directed and causes less damage than when originally used to control cancers. The cells in this figure have pulled cytoplasm, similar to reparative changes. Note the surrounding parabasal atrophy.

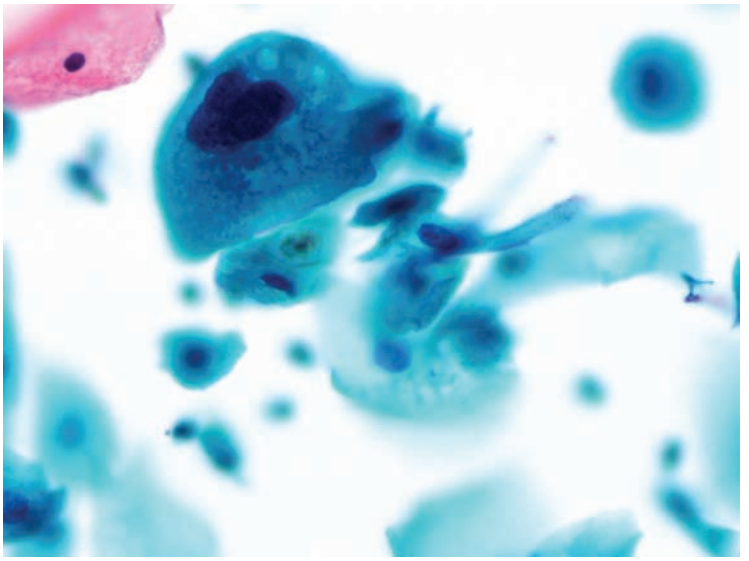


Figure 4.33 — Radiation Change (Liquid Based; High Power). Nuclei may be vacuolated and abnormal in density. However, the N/C ratios remain normal. Changes such as these used to be called "radiation dysplasia," until time and tissue studies revealed that no dysplasia had resulted from the radiation treatment. Over time, most of these changes disappear.

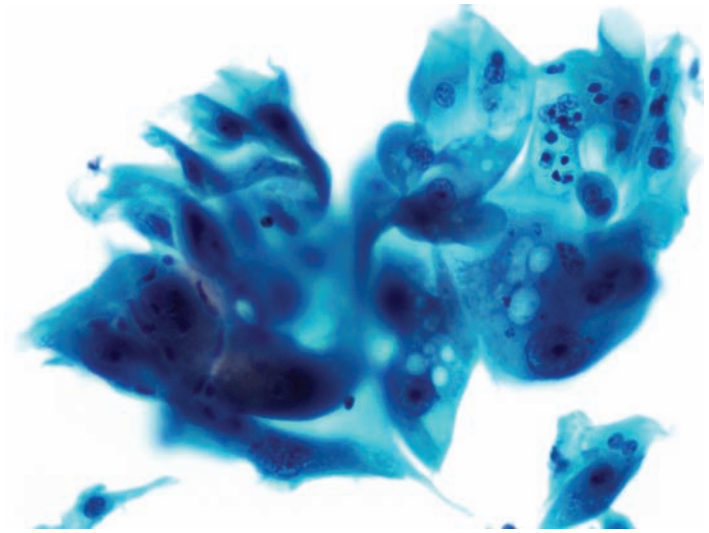


Figure 4.34 — Radiation Change (Liquid Based; High Power). Dramatic radiation changes include greatly enlarged cells with pulled cytoplasm, vacuoles in nuclei and cytoplasm, and embedded neutrophils. Note that the N/C ratios are low. Multinucleation and prominent nuclei attest to the rapid turnover of these cells.

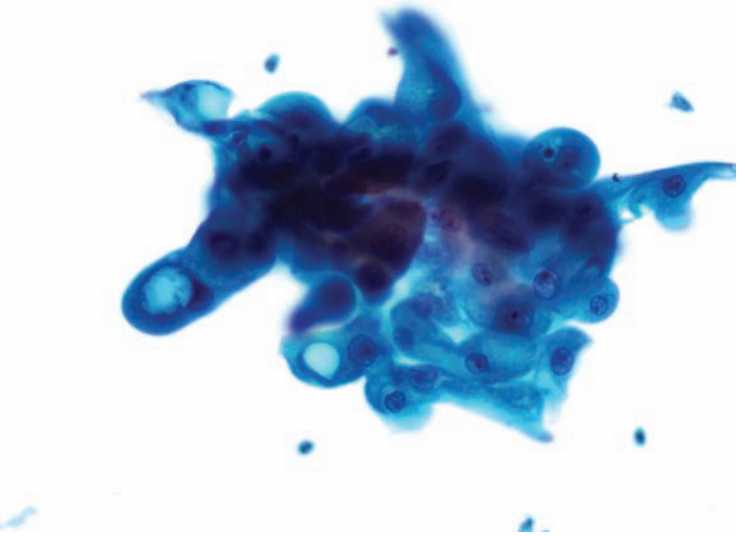


Figure 4.35 — Radiation Change (Liquid Based; Medium Power). Less dramatic than Figures 4.4 to 4.34, but nonetheless eye-catching, these changes are similar to repair. The vacuoles in opaque cytoplasm are the clues that radiation is the culprit.

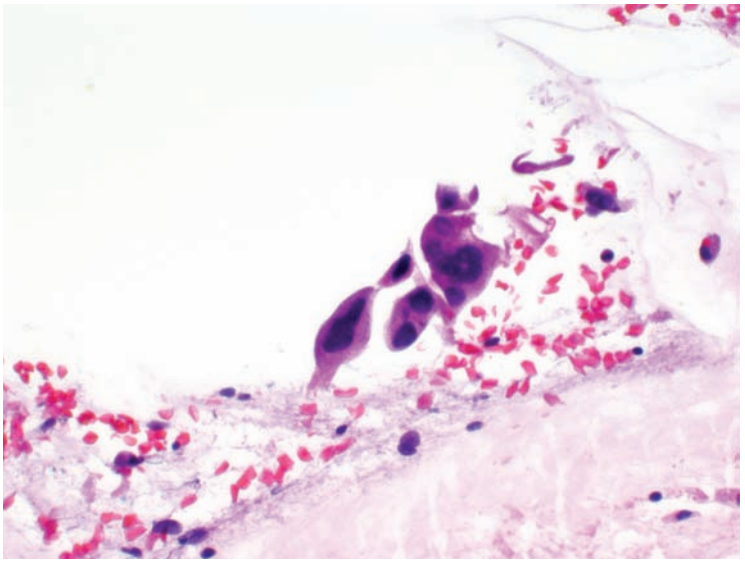


Figure 4.36 — Cervical Squamous Cells With Radiation Atypia Endocervical Curettage (ECC) (H&E Stain; High Power). This example shows detached squamous cells with enlarged dark nuclei with "smudgy" features. Mitotic figures are absent, and abundant amphophilic cytoplasm with a low N/C ratio is present. The cells also show some suggestion of multinucleation. These combined morphologic findings, in the context of the known history of radiation therapy in this patient, are consistent with atypia due to radiation changes.

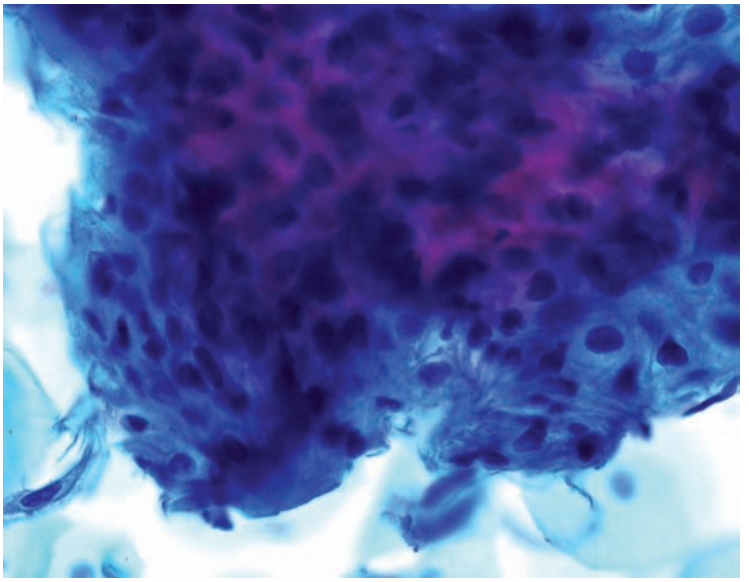


Figure 4.37 — Parabasal Atrophy (Liquid Based; High Power). Compact cells with relatively high N/C ratios could mistake this fragment for transitional metaplasia. However, nuclei here are round and cytoplasm is more abundant than in transitional metaplasia.

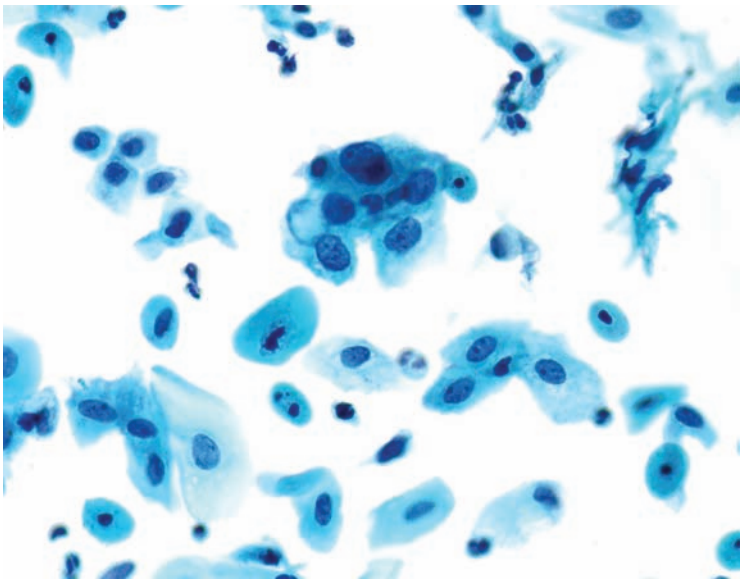


Figure 4.38 — Parabasal Atrophy (Liquid Based; High Power). When seen in small groups or singly, the atrophic changes can be appreciated. Chromatin is uniform among cells, regardless of size or N/C ratio. If some are degenerated, then they may appear darker. If intact well-preserved cells have more hyperchromatic nuclei, then a neoplasm should be considered, and an HPV test should be ordered to confirm infection.

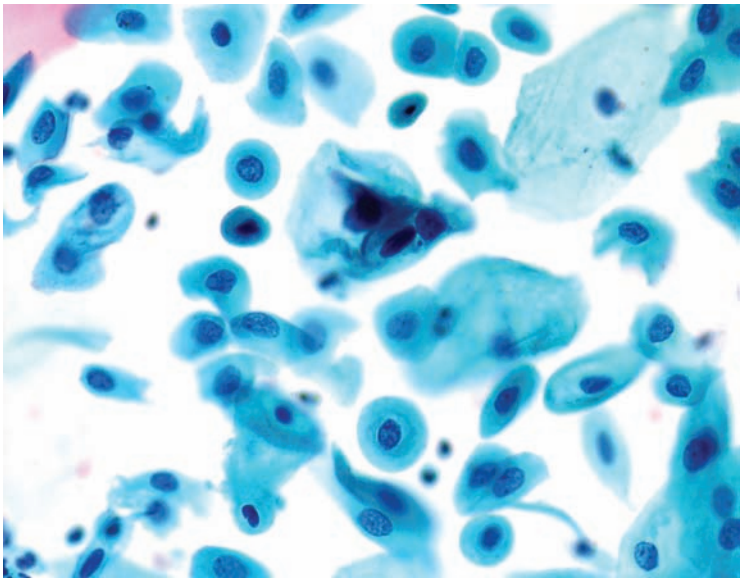


Figure 4.39 — Parabasal Atrophy (Liquid Based; High Power). Not every cell will be atrophic; hence, it is expected to see some intermediate squamous cells, and perhaps an occasional superficial cell, especially if there is some inflammation.

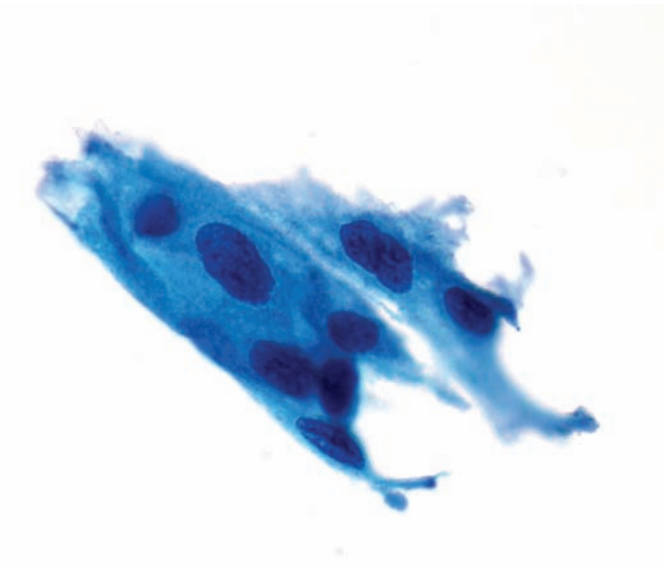


Figure 4.40 — Parabasal Atrophy (Liquid Based; High Power). This group of cells could easily be classified as atypical squamous cells (ASC) because of the enlarged and slightly irregular nuclei. In this case, a short course of topical estrogen could completely clear the changes. A reflex HPV test could also be performed; if negative, the changes are attributable to atrophy. If HPV positive, the patient would be directed to colposcopy.

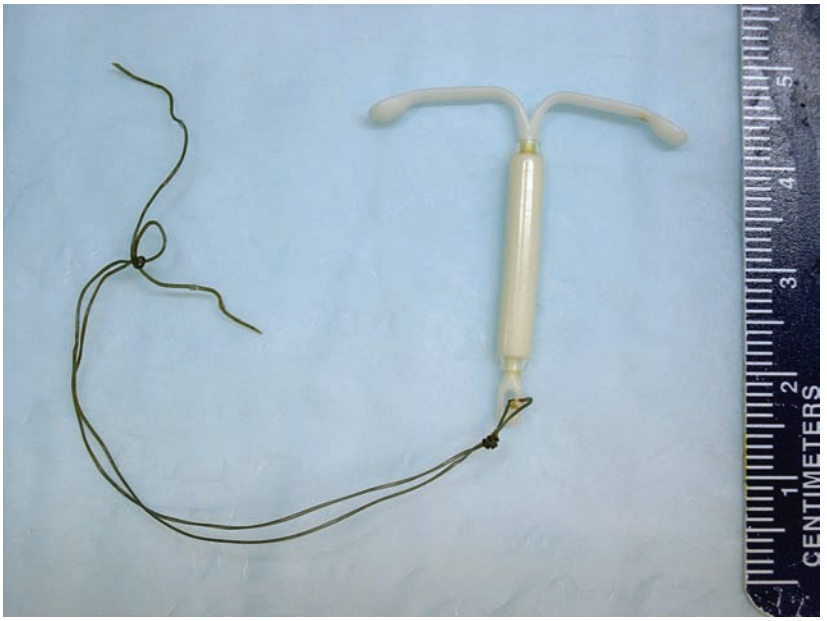


Figure 4.41 — Intrauterine Device (IUD) (Gross Specimen). An IUD is a reversible intrauterine form of contraception. The two most commonly used IUDs are the copper and hormonal types. This example is of the hormonal type (Mirena). It is a local and continuous levonorgestrel-releasing intrauterine system. It is composed of a T-shaped polyethylene frame with a white cylinder steroid reservoir and brown polyethylene removal threads. The T-body measures 3.2 mm in both the vertical and horizontal dimensions. It is inserted into the uterine cavity in the vertical position with the arms being located in the superior portion of the cavity while the threads are inferior. The associated histologic changes in the endometrium are typical of progestin effects, characterized by abundant decidualized stroma and inactive glands. The Mirena IUD should be removed after 5 years.

5

Low-Grade Squamous Intraepithelial Lesion

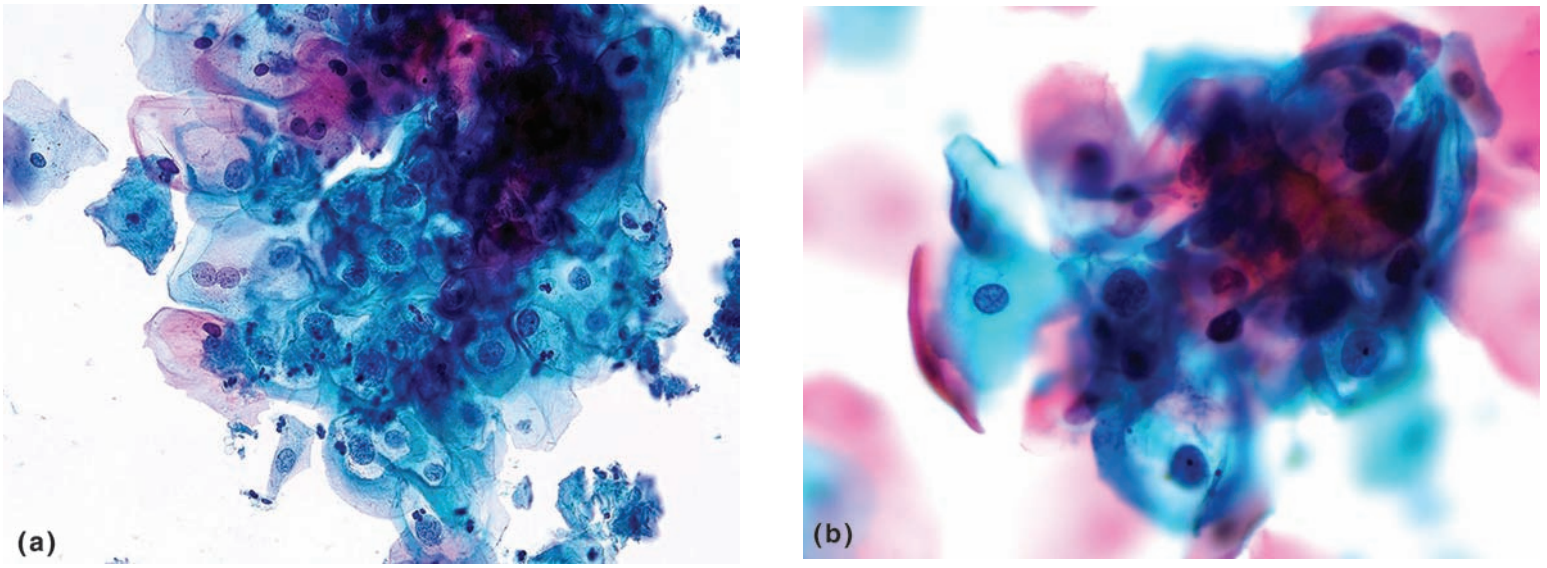


Figure 5.1 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; [a] Medium Power, [b] High Power). Well-defined large cytoplasmic halos with centrally placed enlarged nuclei are the hallmarks of a human papillomavirus (HPV) low-grade lesion. The enlarged nuclei are displaying only early changes, probably not yet integrating the virus into their genome. At this stage of infection, when the cells rupture as they die, the virions are released into the vagina and are capable of transmission to another wounded epithelium.

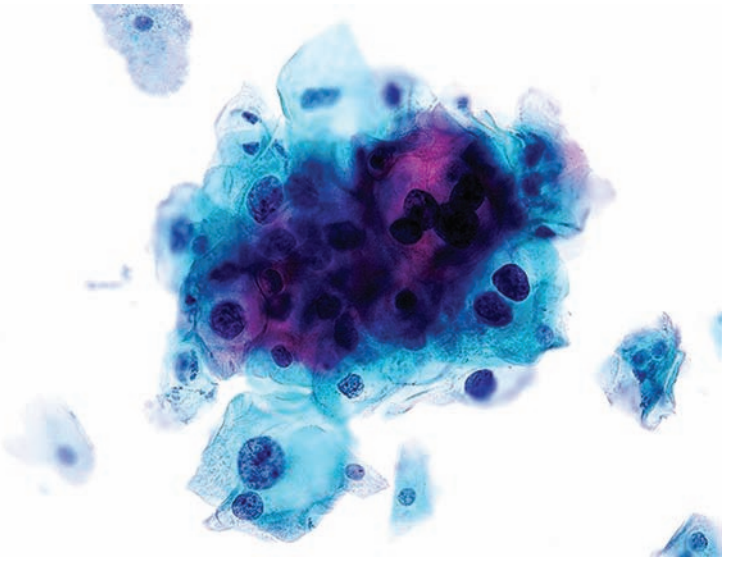


Figure 5.2 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; High Power). Most of the nuclei in this group of cells are round with minimally altered nuclear chromatin. However, a few nuclei are irregular in shape and hyperchromatic. Although these could be degenerated changes, they could imply that viral integration of the stem cells has occurred, and that this epithelium is not likely to clear the infection but progress to a higher grade lesion.

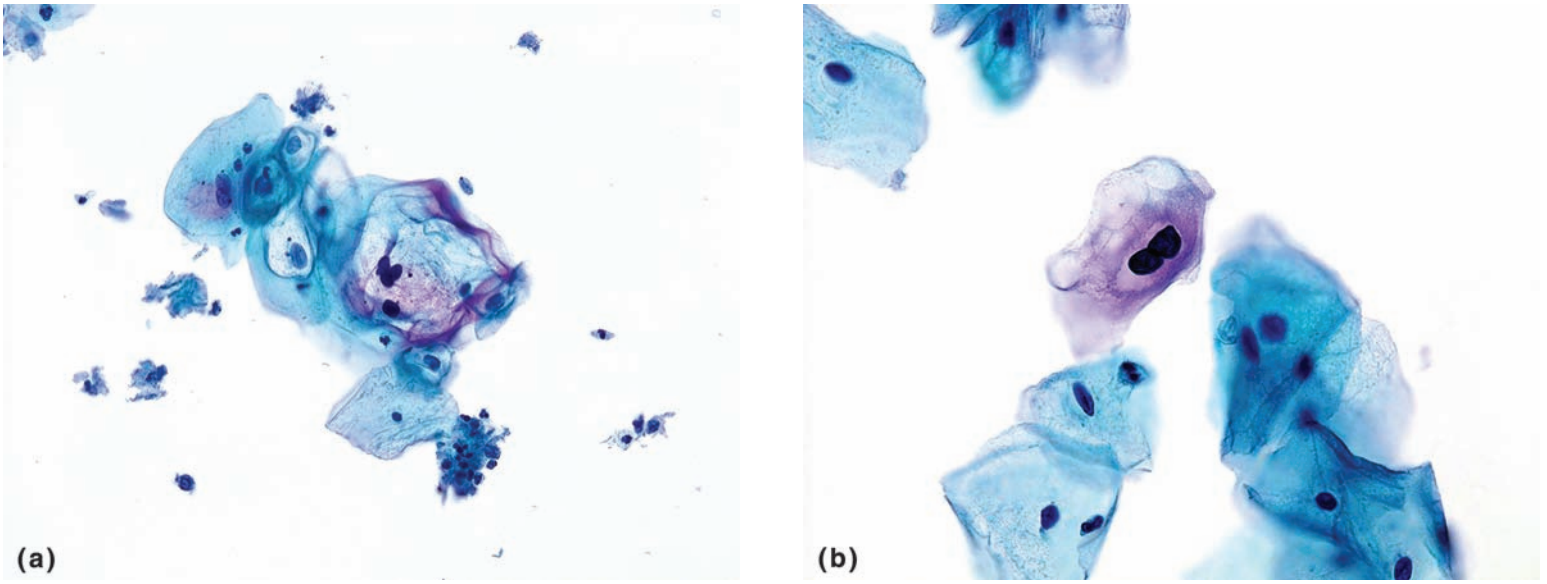


Figure 5.3 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; Medium Power). Multinucleation is a common characteristic of low-grade infections. The internal boundaries of the koilocytes are sharp and the outer rim of cytoplasm is densely opaque. Although there are inflammatory cells in this field, they are probably from another infection, as HPV does not elicit an inflammatory response.

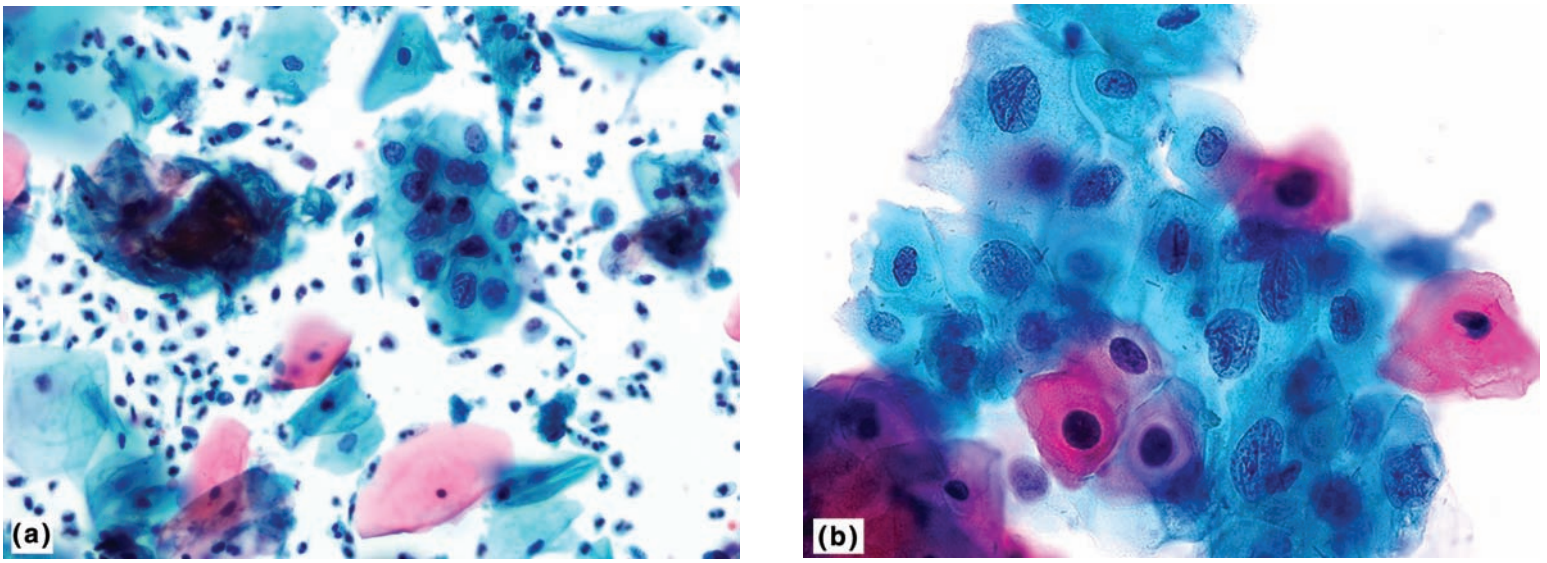


Figure 5.4 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; [a] Medium Power, [b] High Power). Koilocytes are not requisite for the interpretation of LSIL. However, when cells do not contain distinct halos, and have enlarged nuclei with irregular nuclear shapes and coarse chromatin, an interpretation of high-grade squamous intraepithelial lesion (HSIL) (cervical intraepithelial neoplasia grade 2 [CIN2]) should be considered. Certainly, more than one cell group will contribute to the final decision.

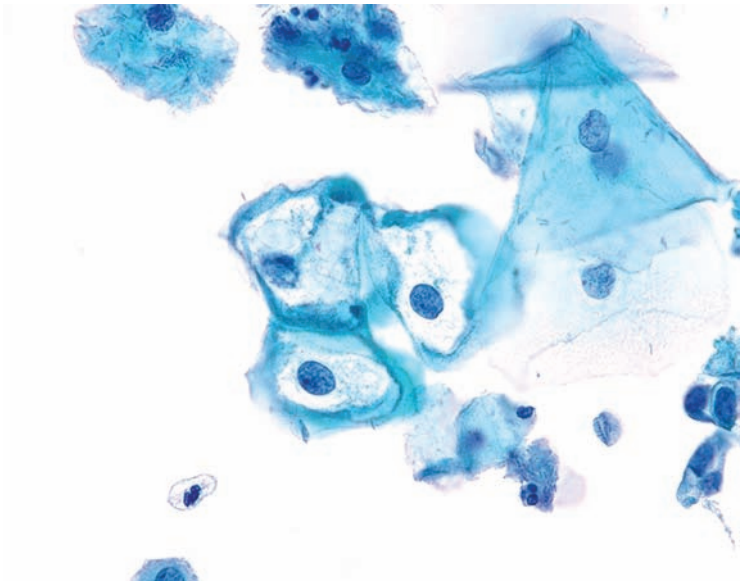


Figure 5.5 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; High Power). When nuclei are only slightly larger than the normal intermediate cells in the image, and their chromatin only slightly darker, the decision to keep the case in the atypical squamous cells of uncertain significance (ASC-US) category may be entertained. Although these are classic koilocytes, if only a few cells are on the slide, it may be more prudent to call the case "ASC-US" and reflexively order an HPV test to determine the presence of an oncogenic type.

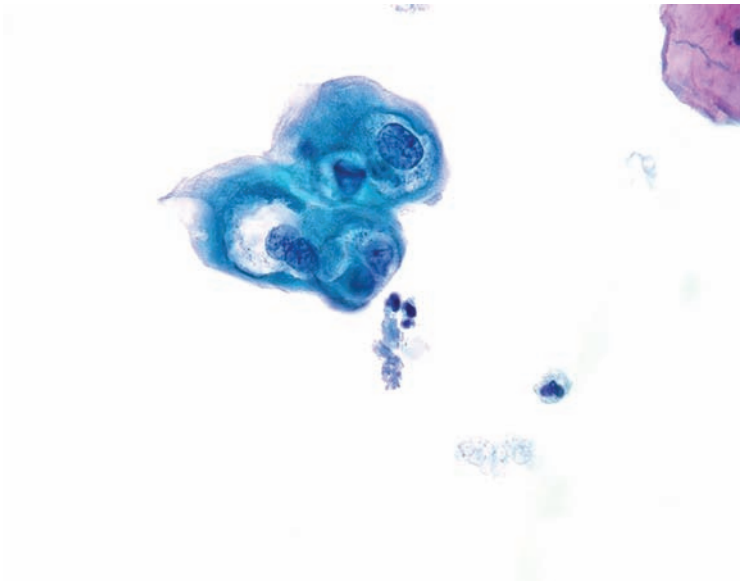


Figure 5.6 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; High Power). In contrast to Figure 5.5, these nuclei are a bit larger, and vary in size and shape within the group. They are clearly from a low-grade infection.

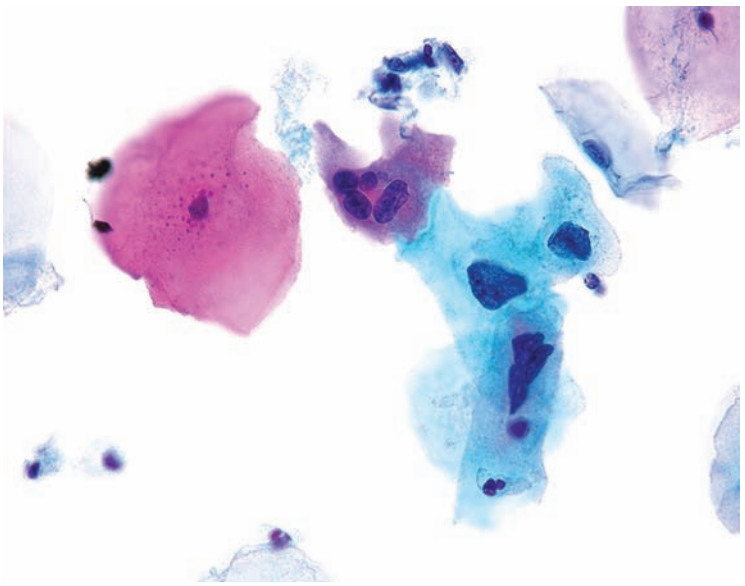


Figure 5.7 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; High Power). The distinction between low- and high-grade lesion is sometimes blurred. In this group, koilocytes are absent, and nuclear shapes are bizarre. Hyperchromasia does not appear to be from degeneration. Depending on the rest of the sample, the interpretation of HSIL may be justified.

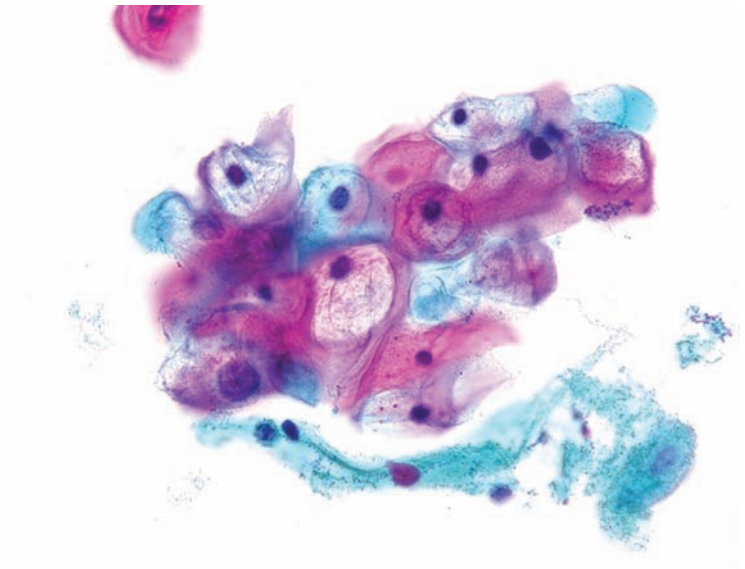


Figure 5.8 — Low-Grade Squamous Intraepithelial Lesion (LSIL) Versus Progesterone Effect (Liquid Based; High Power). Although most of the cells have large cytoplasmic vacuoles, many of the nuclei are very small and eccentric. Such changes have been referred to as "navicular" cells, or more recently, "pseudokoilocytes." Examination of the rest of the slide, as well as clinical history, may be helpful. If these are the only cellular changes, then the ASC-US category with reflex HPV testing is the better classification.

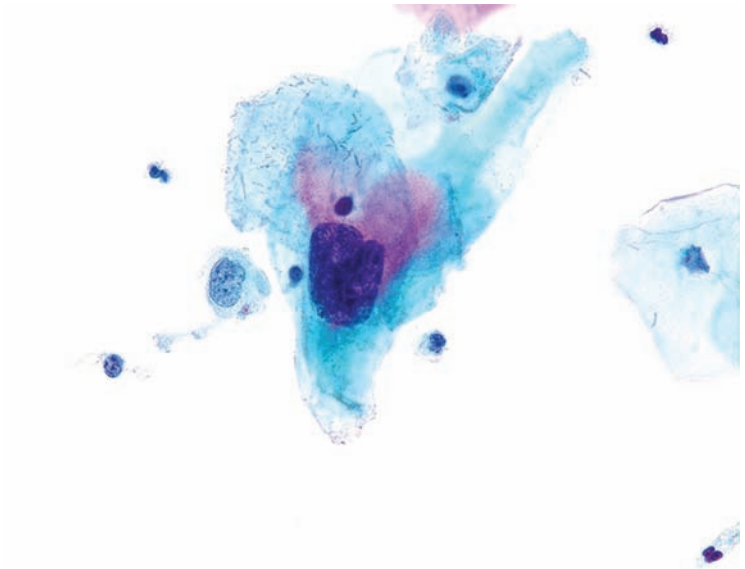


Figure 5.9 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; High Power). Cells with low-grade dysplasia have nuclei that are three to four times the size of normal intermediate squamous cells. The individual cell in this image possesses a large nucleus meeting this criterion. Additionally, the nucleus is much darker than the adjacent cells and also has irregular nuclear borders. However, a single atypical cell is generally insufficient for a diagnosis of LSIL.

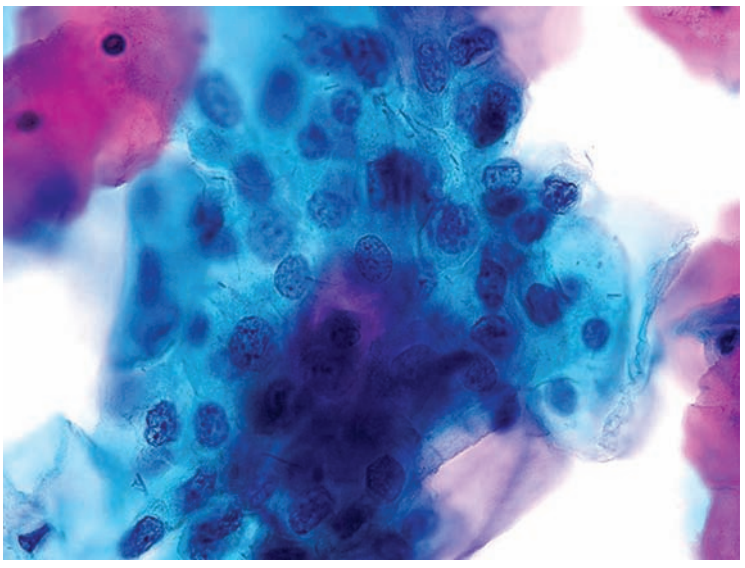


Figure 5.10 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; High Power). These cells have enlarged nuclei and irregular nuclear borders. There is also nuclear pleomorphism and a jumbled architecture, as compared to the organized "school of fish" pattern seen in reactive atypia. While these cells lack cytoplasmic halos and are not koilocytes, it is not uncommon to see fragments such as these in low-grade dysplasia.

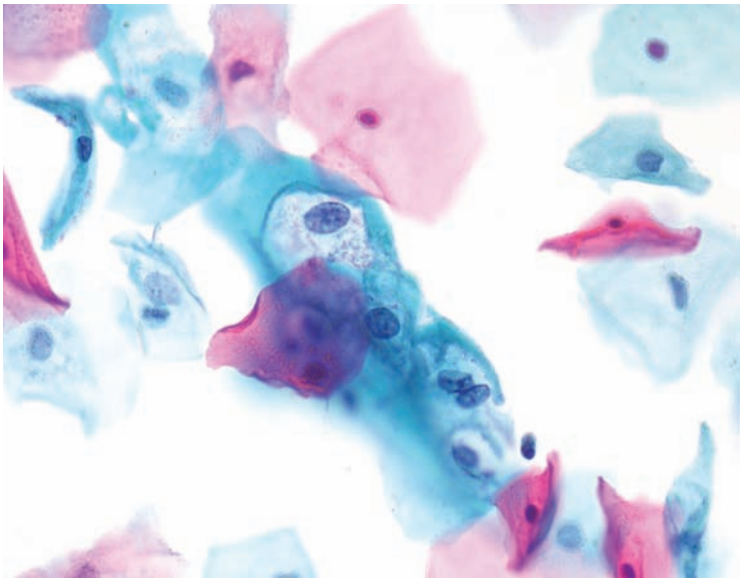


Figure 5.11 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; High Power). The koilocytes seen here have only slightly enlarged nuclei with relatively smooth borders. However, other features of low-grade dysplasia are present, such as polygonally shaped perinuclear halos and binucleation. Molecular assays for high-risk HPV may be negative, as low-risk subtypes can also result in koilocyte formation.

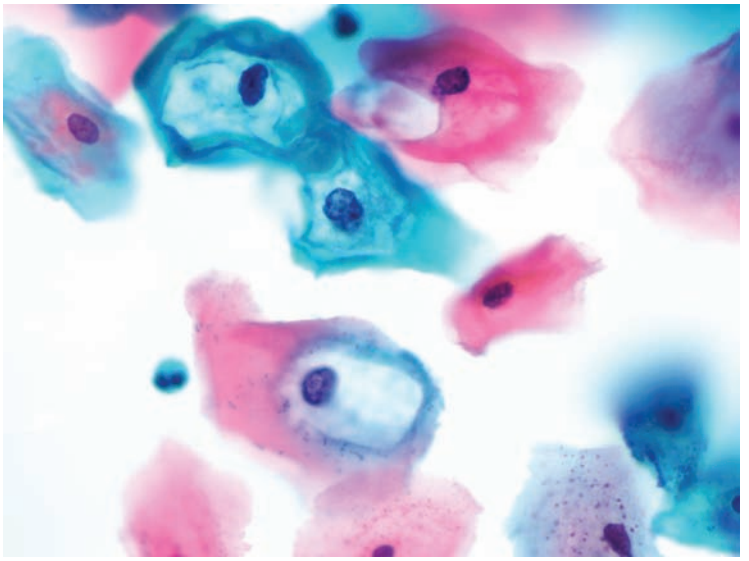


Figure 5.12 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; High Power). The perinuclear halo is a cytopathic effect of HPV. It is thought that the viral E4 protein binds keratins in the cytoplasm, resulting in disruption of the cytoplasmic structure.

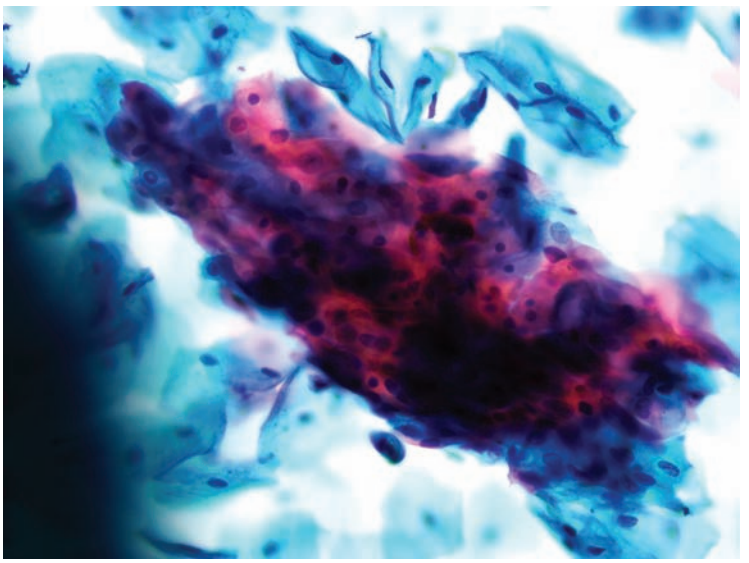


Figure 5.13 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; Medium Power). This fragment contains a large number of atypical cells, none of which is a classic koilocyte. However, there is dramatic nuclear pleomorphism, and some nuclei meet the size criterion for LSIL. The presence of cells with orangeophilic cytoplasm suggests that this is a dysplastic process arising in an area of parakeratosis. Parakeratosis may be benign, and benign-appearing parakeratosis may be associated with, and mask, an underlying dysplasia.

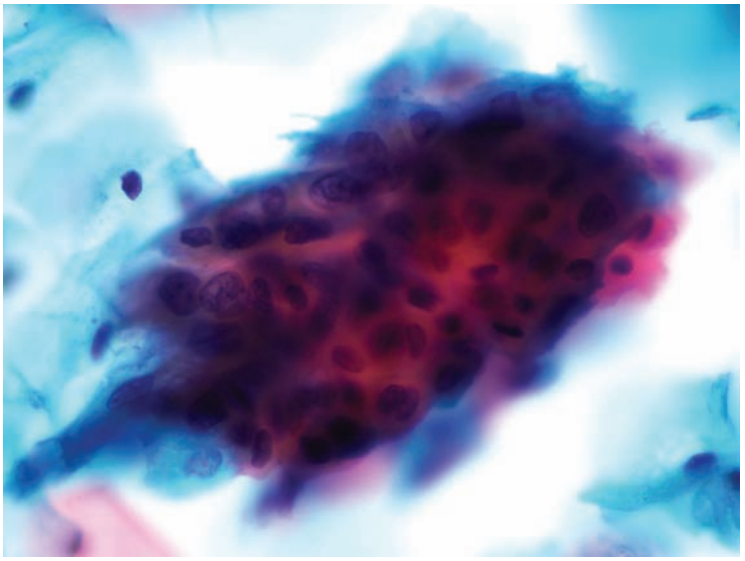


Figure 5.14 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; Medium Power). This fragment is similar to the fragment in the previous figure, but the nuclear enlargement and pleomorphism are more striking. This lesion should not be classified as HSIL because the dysplastic cells maintain abundant cytoplasm.

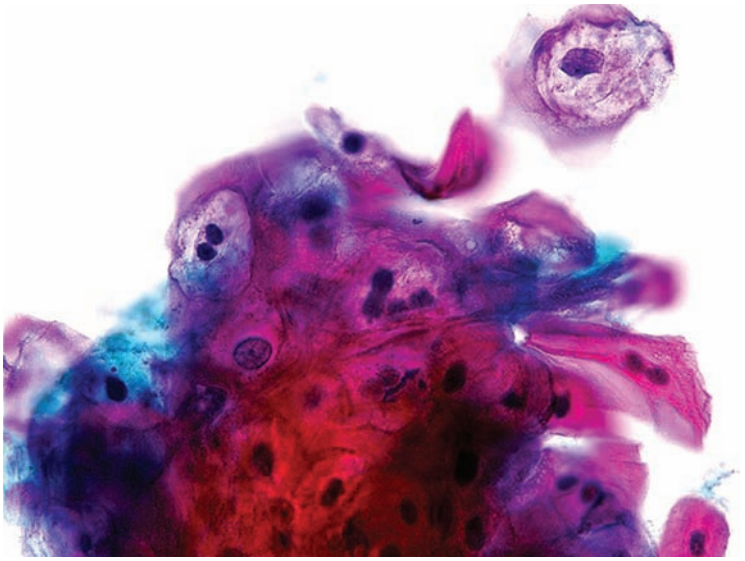


Figure 5.15 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; Medium Power). In contrast to the previous two figures, koilocytes with halos are present in this fragment. There are multiple binucleate cells (some with figure "8" shapes); other cells contain enlarged nuclei with irregular borders. Similar to the previous two fragments is the striking cytoplasmic orangeophilia.

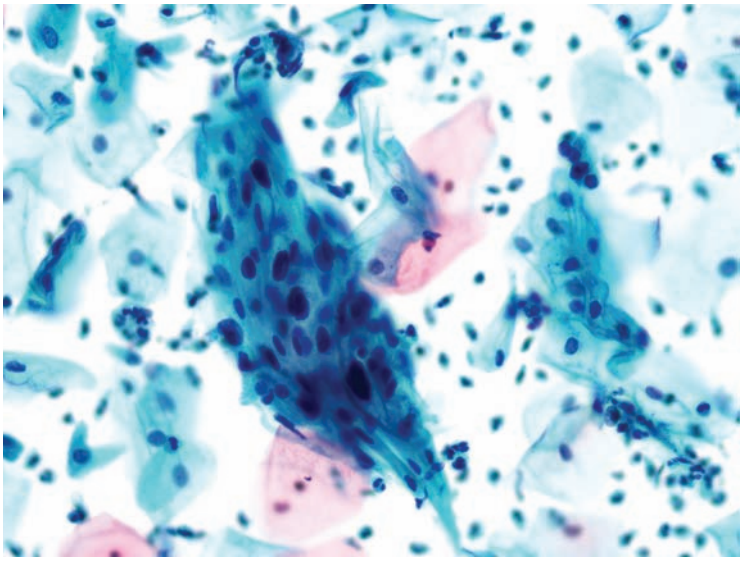


Figure 5.16 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; Medium Power). This fragment lacks koilocytes but there is patchy nuclear enlargement. Furthermore, some nuclei are dark and have irregular borders. If no other atypical cells are found, one may entertain a diagnosis of ASC-US rather than LSIL. The background is busy and contains inflammatory cells, but nucleoli seen in reactive atypia are not found in the atypical cells. Careful examination is required to exclude single cells that may be suspicious for HSIL.

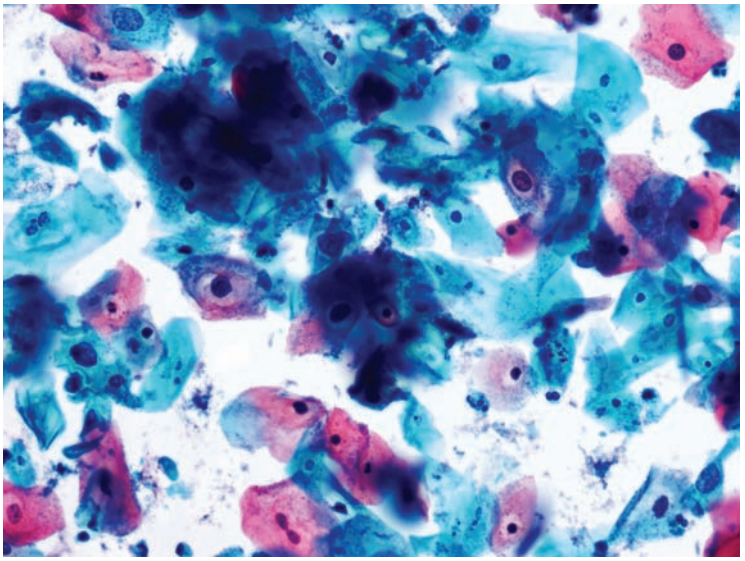


Figure 5.17 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Liquid Based; Medium Power). The presence of bacteria partially obscures the field and some cells contain halos that are not convincing of true koilocytes. However, one cell (left center) has a polygonally shaped halo and an irregular, enlarged nucleus. There are several atypical cells in the background with enlarged nuclei, some with irregular nuclear borders. While this field alone may be insufficient for an LSIL diagnosis, these findings are suggestive of an HPV infection.

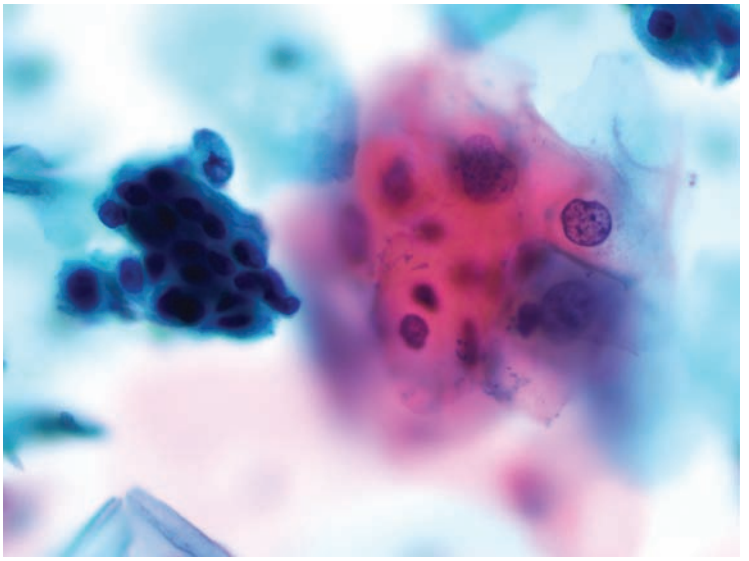


Figure 5.18 — Low-Grade Squamous Intraepithelial Lesion (LSIL), Cannot Exclude High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; Medium Power). Koilocytes are not found in this field, but the fragment on the right has cells with enlarged nuclei and irregular nuclear borders. These cells have abundant cytoplasm and in sufficient quantity merit a diagnosis of LSIL. The fragment on the left contains cells with enlarged, dark nuclei, high nuclear-to-cytoplasmic (N/C) ratios, and some nuclear border irregularities. While the fragment on the left alone may represent atypical squamous metaplasia, in the presence of other indications of HPV infection LSIL, the possibility of HSIL may be difficult to exclude.

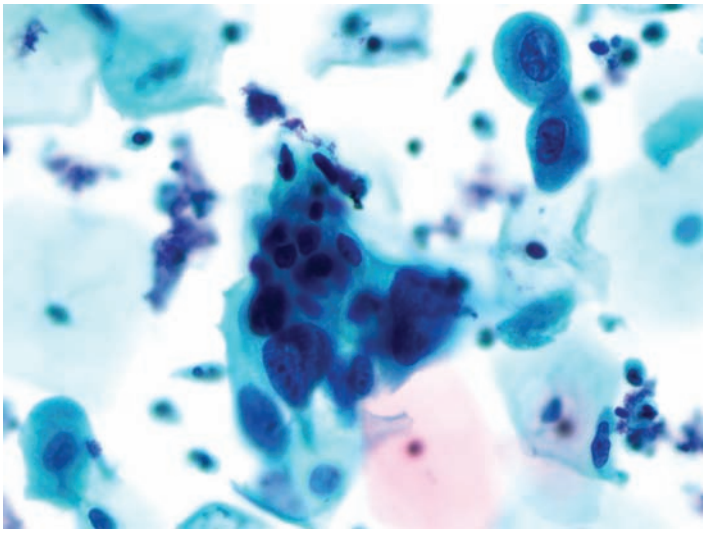


Figure 5.19 — Low-Grade Squamous Intraepithelial Lesion (LSIL), Cannot Exclude High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; Medium Power). This fragment contains highly pleomorphic atypical cells that demonstrate hyperchromasia and nuclear border irregularities. The largest nuclei are enlarged far beyond the needed 3:1 ratio as compared to normal intermediate squamous cells. Several cells have increased N/C ratios and HSIL cannot be excluded.

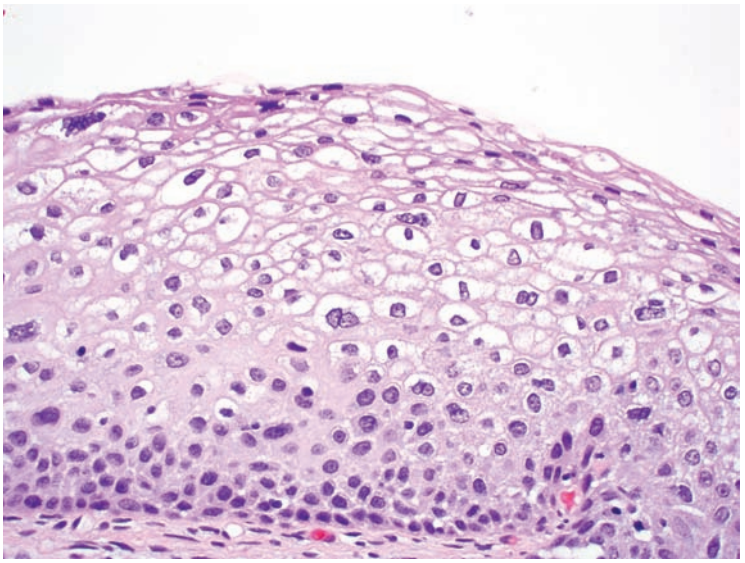


Figure 5.20 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Biopsy) (Hematoxylin and Eosin [H&E] Stain; High Power). The squamous epithelium is not significantly thickened. Many of the cells show cytoplasmic clearing without significant nuclear abnormalities (cytoplasmic clearing in isolation is nonspecific and not diagnostic of LSIL without significant nuclear abnormalities). Some cells do show subtle features of LSIL with combined nuclear enlargement, irregular chromatin distribution, and irregular nuclear membranes. However, a rare cell (*upper left-hand corner*) exhibits marked changes of LSIL (including nuclear enlargement with hyperchromasia, cytoplasmic clearing, and irregular nuclear membranes), which imparts a "raisinoid" appearance characteristic of fully developed LSIL. Cells with classic koilocytic atypia (cytoplasmic clearing with significant nuclear abnormalities) in LSIL are usually found in the superficial layers of the squamous epithelium. In contrast, high-grade squamous intraepithelial lesion (see Chapter 6) typically shows a loss of maturation of the lower two thirds (CIN2) or full thickness (CIN3) of the epithelium.

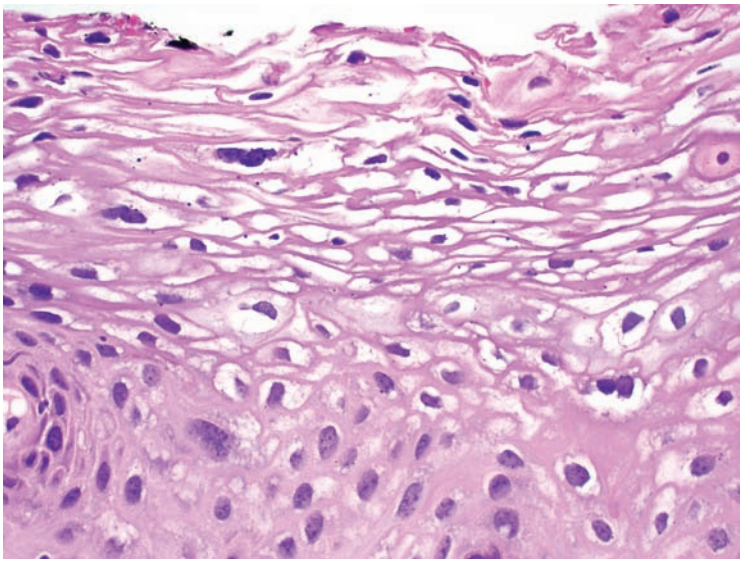


Figure 5.21 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Biopsy) (H&E Stain; High Power). This case shows the "basket weave" pattern of LSIL, which is due to the combined cytoplasmic clearing and hypereosinophilic and thickened cytoplasmic membranes. Occasional binucleated cells are noted. Binucleation alone does not qualify for a diagnosis of LSIL, but the combination of this finding with the subtle nuclear atypia and cytoplasmic clearing in this case is sufficient for that diagnosis.

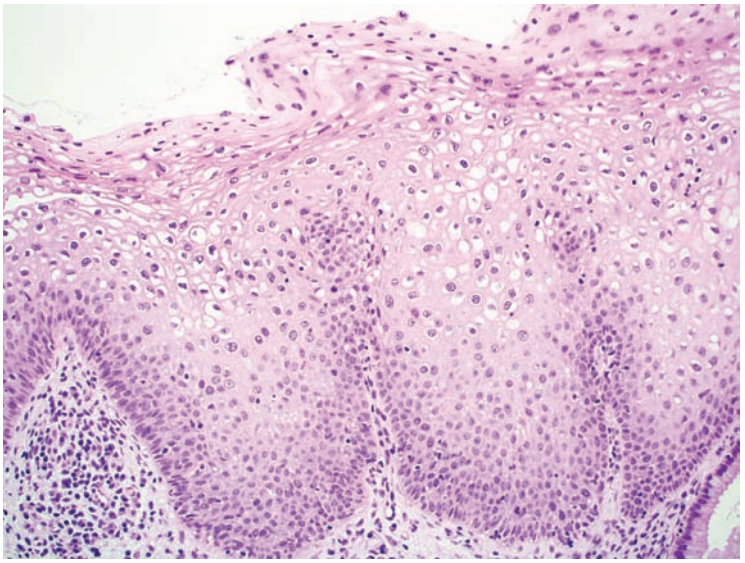


Figure 5.22a — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Biopsy) (H&E Stain; Intermediate Power). This example shows slight thickening of the squamous epithelium, a mild increase in cellularity, nuclear enlargement, and irregular nuclear membranes. Although this case exhibits some degree of variation in nuclear size, shape, and chromatin pattern, this example is more uniform than other LSILs. Furthermore, a mild expansion of the parabasal region is present; however, this finding is typically confined to the lower third of the epithelium and, therefore, insufficient for a diagnosis of high-grade squamous intraepithelial lesion (HSIL; CIN2), particularly as the squamous epithelium exhibits maturation.

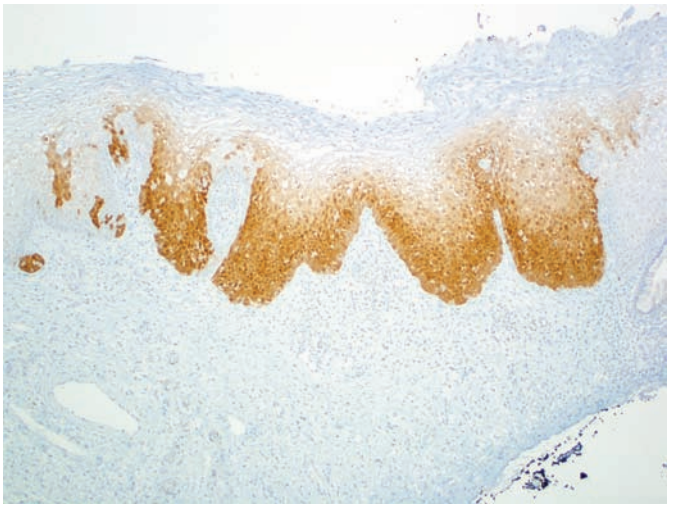


Figure 5.22b — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Biopsy) (p16 Immunohistochemical Stain; Intermediate Power). A diffuse pattern of p16 expression is present; however, this finding without diagnostic histologic alterations does not equate with a diagnosis of HSIL. Although essentially all HSILs show diffuse p16 expression, a subset of LSIL can also diffusely stain for p16. LSILs with diffuse p16 expression often show a pattern of staining that is not of full thickness in contrast to HSIL (CIN3). Using diffuse expression of p16 to favor a diagnosis of HSIL for ambiguous squamous intraepithelial lesions, in which the differential diagnosis is LSIL versus HSIL (CIN2), is recommended. Nevertheless, this case would not be diagnosed as HSIL as the morphologic features are insufficient. Furthermore, it is not recommended to perform p16 immunohistochemistry for cases where the histologic features are sufficient for an LSIL diagnosis.

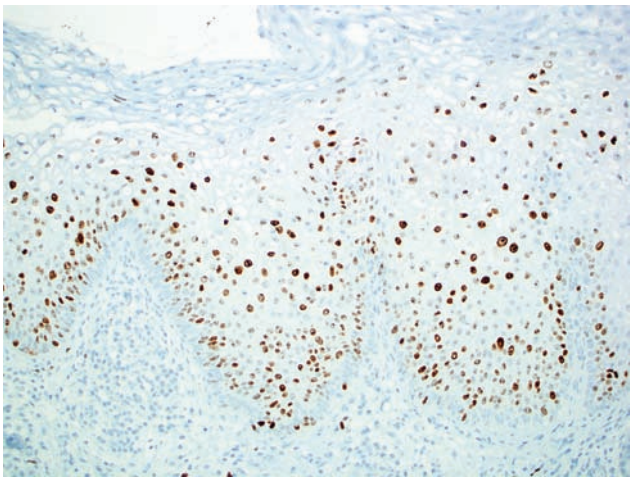


Figure 5.22c — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Biopsy) (Ki-67 Immunohistochemical Stain; Intermediate Power). Increased proliferative activity is noted in the lower half of the epithelium. Other cases of LSIL may have most of the proliferative activity in the upper half of the epithelium or superficial layers. Although Ki-67 cannot be used for grading a squamous intraepithelial lesion, HSIL tends to have a higher Ki-67 index compared with LSIL.

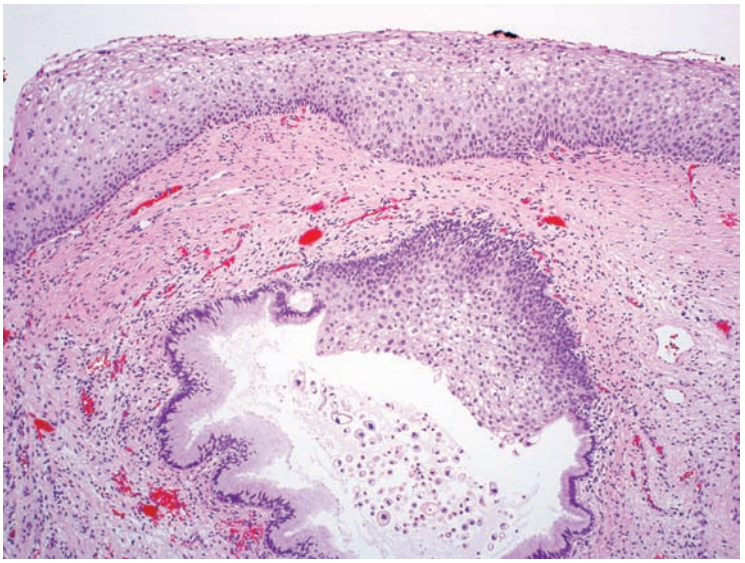


Figure 5.23 — Low-Grade Squamous Intraepithelial Lesion (LSIL) (Biopsy) (H&E Stain; Intermediate Power). LSIL is present in the overlying surface mucosa, which partially extends into an underlying endocervical gland. Although involvement of endocervical gland is more common with high-grade squamous intraepithelial lesion, this finding can also occur in LSIL.

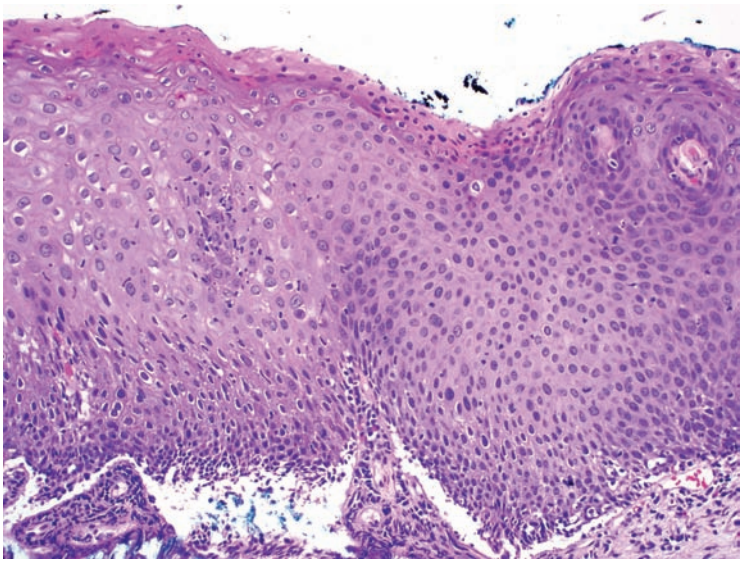


Figure 5.24 — Low-Grade Squamous Intraepithelial Lesion (LSIL) Adjacent to High-Grade Squamous Intraepithelial Lesion (HSIL) (CIN2) (Loop Electrosurgical Excision Procedure [LEEP]) (H&E Stain; Intermediate Power). Although LSIL is not thought to directly "progress" to HSIL and carcinoma, LSIL and HSIL can be found together in surgical specimens, given their shared pathogenesis with HPV. Note that the LSIL (*left half of photograph*) in this case shows typical cytologic features, whereas the adjacent HSIL (*right half*) shows loss of maturation without the koilocytic atypia of LSIL.

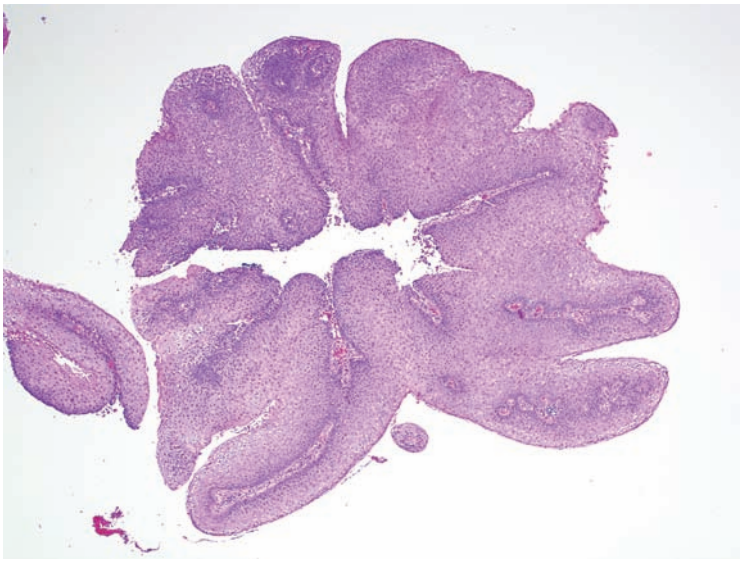


Figure 5.25a — Cervical Condyloma Acuminatum (Excision; H&E Stain; Low Power). The exophytic verrucous architecture is typical of condyloma. The large papillae consist of fibrovascular cores lined by thickened squamous epithelium with a smooth luminal surface (H&E stain, low-power magnification).

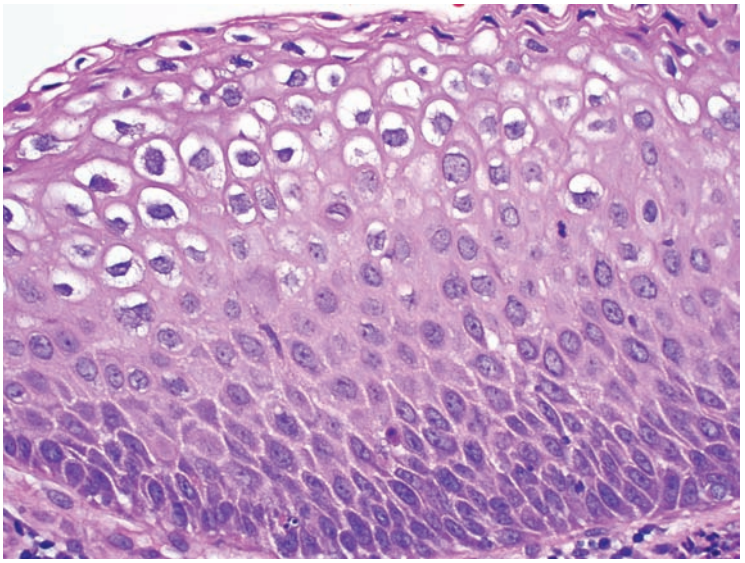


Figure 5.25b — Cervical Condyloma Acuminatum (Excision) (H&E Stain; High Power). The squamous epithelium shows maturation with koilocytic atypia in the superficial layers. The koilocytic change in cervical condyloma is usually more frequent or extensive and better developed than in its vulvar counterpart. Note that the cytologic appearance is essentially identical to LSIL.

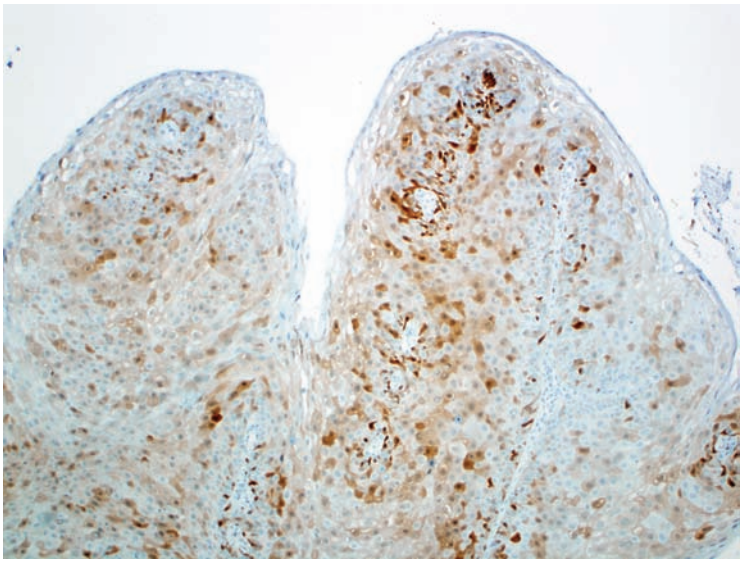


Figure 5.25c — Cervical Condyloma Acuminatum (Excision) (p16 Immunohistochemical Stain; Intermediate Power). The lesion has a patchy pattern of p16 expression, which is consistent with a non–high-risk form of HPV (condyloma acuminatum typically contains low-risk HPV, either type 6 or 11).

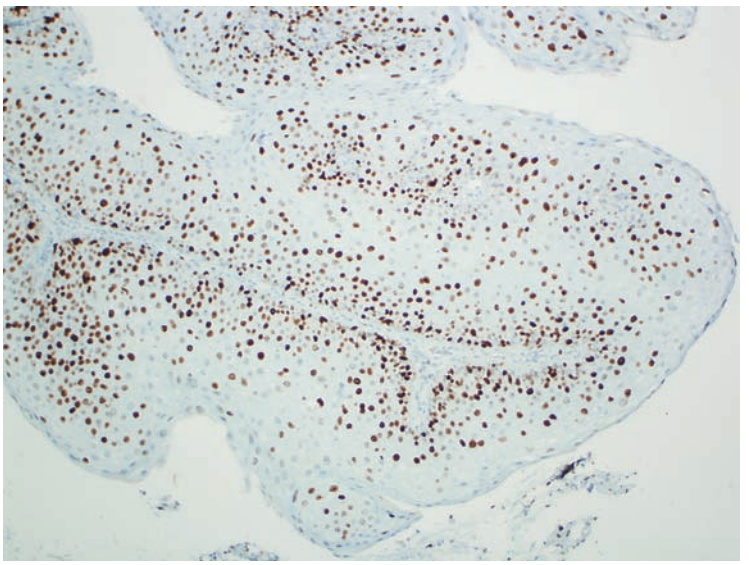


Figure 5.25d — Cervical Condyloma Acuminatum (Excision) (Ki-67 Immunohistochemical Stain; Intermediate Power). Proliferative activity is mostly within the parabasal layers, but a substantial amount of staining is present within the upper half of the epithelium. Some condylomas and LSILs can have a high Ki-67 index.

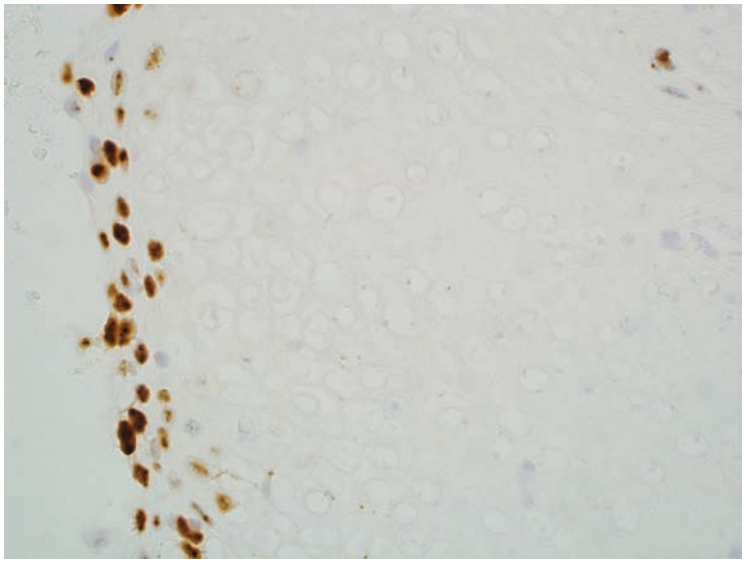


Figure 5.25e — Cervical Condyloma Acuminatum (Excision) (In Situ Hybridization for HPV 6/11; High Power). HPV (either type 6 or 11) is detected in the superficial layers of the squamous epithelium. Furthermore, note that the pattern of staining within each positive nucleus is a diffuse rather than punctate pattern, which is frequently found in condylomas. The superficial layers are the compartment of the squamous epithelium that is most commonly positive by in situ hybridization.

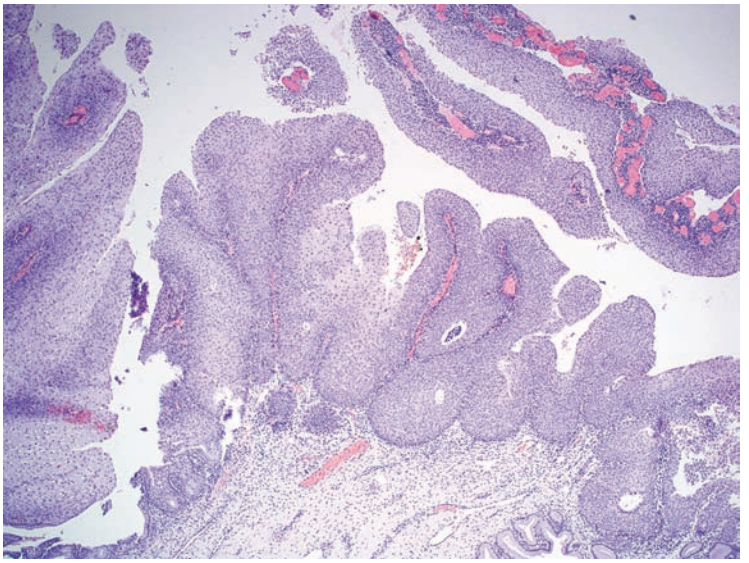


Figure 5.26a — Cervical Papillary Immature Metaplasia (Immature Condyloma) (Hysterectomy) (H&E Stain; Low Power). The lesion is noninvasive and has an exophytic verrucous configuration. The morphologic features are similar to those of condyloma acuminatum.

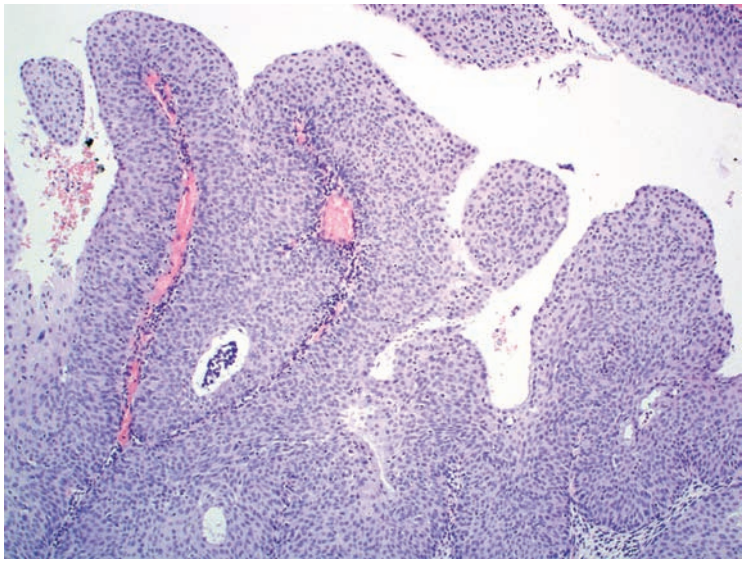


Figure 5.26b — Cervical Papillary Immature Metaplasia (Immature Condyloma) (Hysterectomy) (H&E Stain; Intermediate Power). The slightly increased N/C ratio in this architectural setting can simulate papillary squamous cell carcinoma.

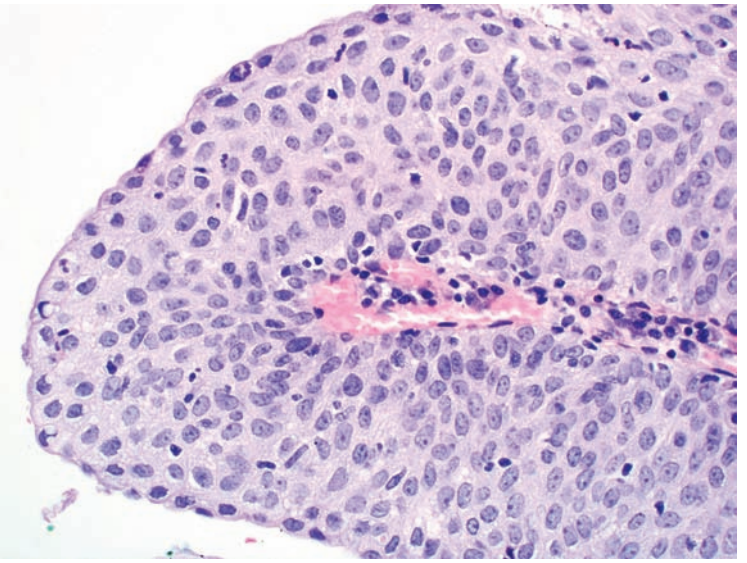


Figure 5.26c — Cervical Papillary Immature Metaplasia (Immature Condyloma) (Hysterectomy) (H&E Stain; High Power). Even though the cytologic appearance is somewhat immature, the nuclei of the squamous epithelium are bland and uniform and lack hyperchromasia and mitotic activity. Immunohistochemical stains for p16 would not show a diffuse pattern of staining as this kind of lesion is associated with low-risk HPV, either type 6 or 11, as opposed to high-risk HPV. Polymerase chain reaction performed on this case revealed the presence of HPV 6.

6

High-Grade Squamous Intraepithelial Lesion

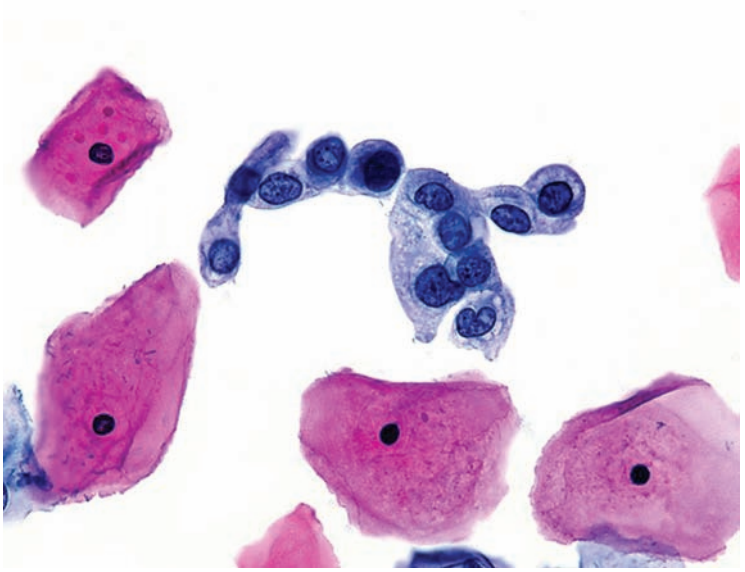


Figure 6.1 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). Although the cytoplasm is vacuolated, the nuclei have coarse chromatin more consistent with squamous origin than glandular. Inconspicuous nucleoli and thickened irregular nuclear outlines add to the interpretation.

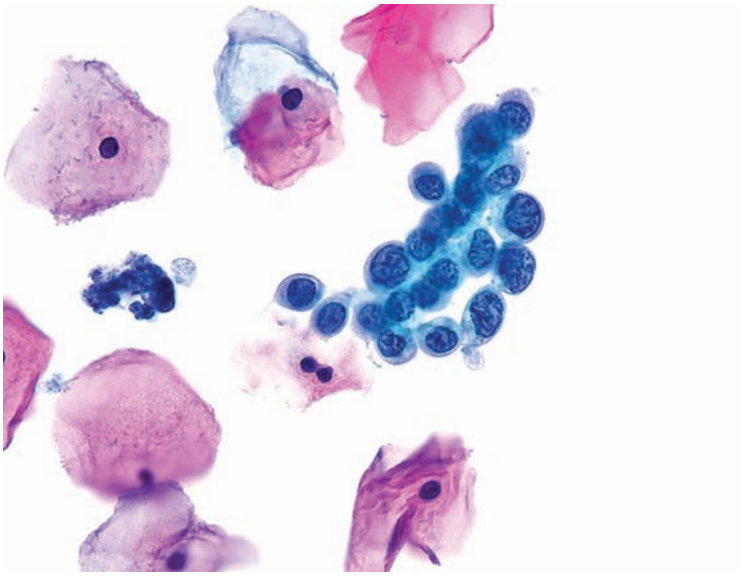


Figure 6.2 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; Medium Power). Cells of a high-grade squamous lesion are the most primitive of all the squamous lesions of the cervix, including invasive carcinomas. Nuclear-to-cytoplasmic (N/C) ratios are almost 1:1, and chromatin is dark and coarse. Nuclear shapes are generally round but irregular, and nuclear membranes thickened, reflecting the coarse chromatin. Cell size also displays little variation.

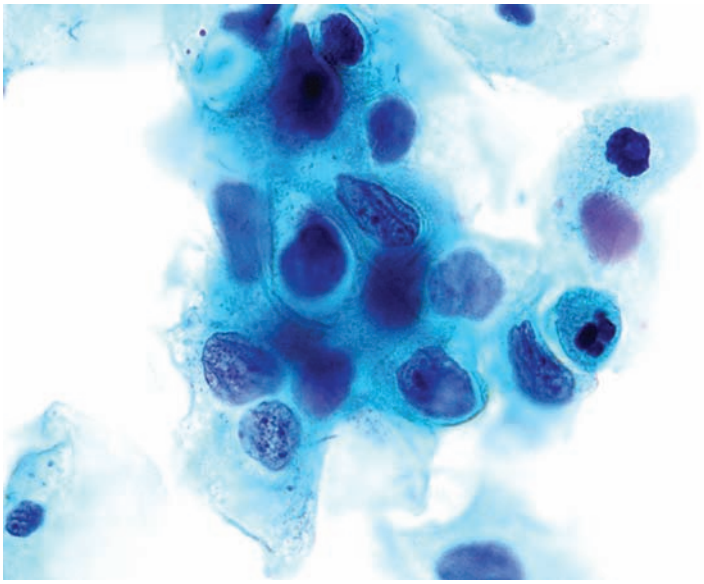


Figure 6.3 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). Some high-grade lesions have lower N/C ratios than the cells in Figure 6.2. Their large nuclear size indicates their high-grade status. The mitotic figure adds to the diagnosis.

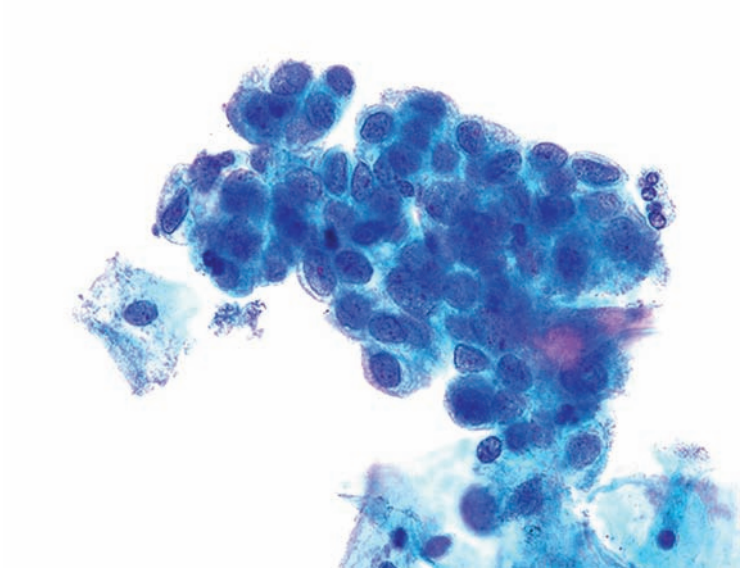


Figure 6.4 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; Medium Power). Liquid-based Paps can sometimes present cell groups that are layered. Only careful focusing through the cells will reveal their features. Even in this two-dimensional photograph, some of the cells are clearly high grade because of their high N/C ratios and coarse chromatin.

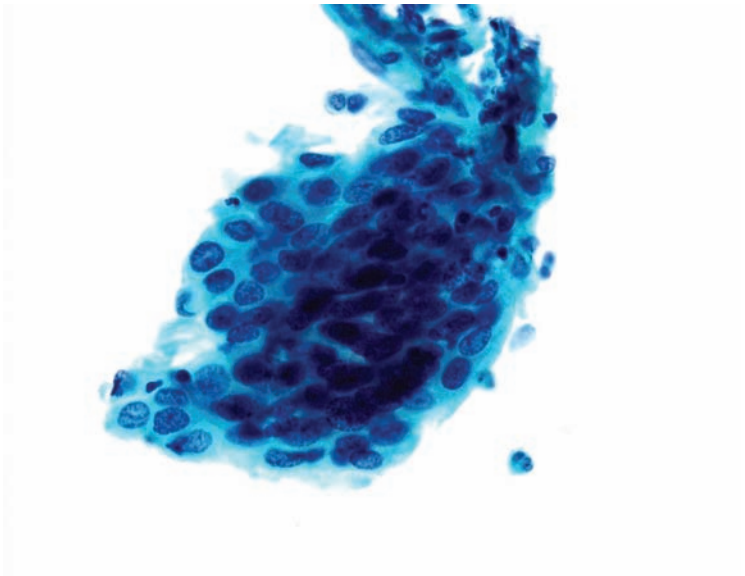


Figure 6.5 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). A hyperchromatic crowded group (HCG) represents HSIL with gland involvement. The individual cells along the left edge of the group display features characteristic of HSIL, including high N/C ratios, thick nuclear membranes, and coarse chromatin. The smooth border of cytoplasm along the right edge of the group indicates the luminal aspect of the lesion within an endocervical gland.

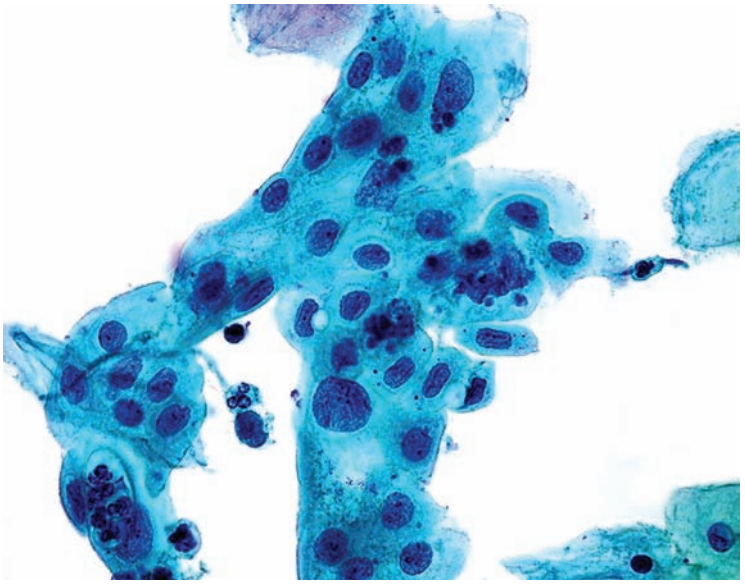


Figure 6.6 — High-Grade Squamous Intraepithelial Lesion (HSIL), Rule Out Squamous Cell Carcinoma (Liquid Based; High Power). Most of the cells in this fragment have low N/C ratios, but a few others have greatly enlarged nuclei, N/C ratio greater than 0.7:1.0, and coarse, dark chromatin. The lesion is most likely a CIN2 (HSIL).

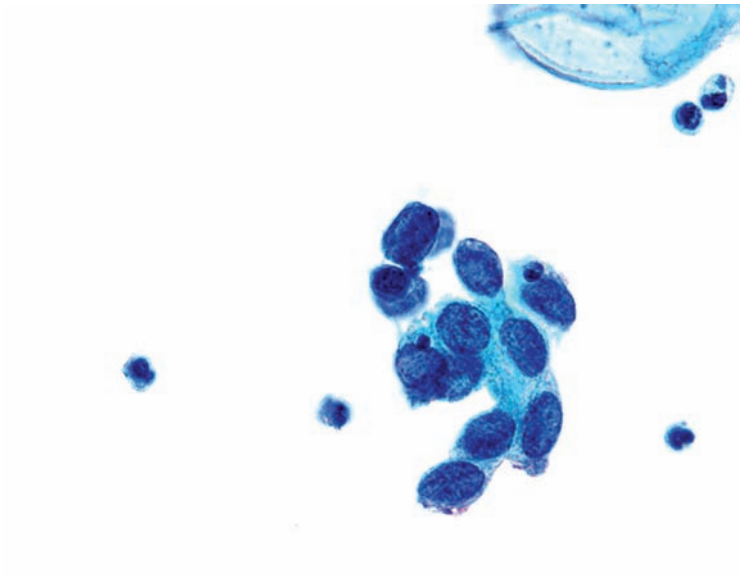


Figure 6.7 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). Syncytial groups from a high-grade squamous lesion originate at the squamocolumnar junction, giving the cells their frothy cytoplasm. Because of rapid cell division, the cytoplasm lags behind the nuclei in dividing, so that many cell boundaries are lost. Although it is tempting to call them glandular in origin, these cells have the hyperchromasia and coarse chromatin of a squamous lesion.

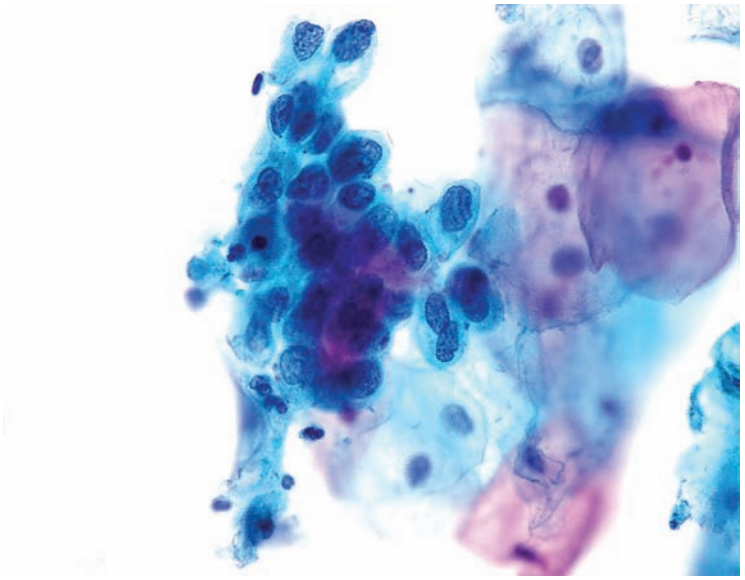


Figure 6.8 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). A syncytial group of high-grade squamous cells has variably sized and shaped nuclei with coarse chromatin. N/C ratios are greater than 0.5:1.0, placing the fragment in the HSIL category. Mitotic figures add to the diagnosis but are not mandatory as they are in histopathology.

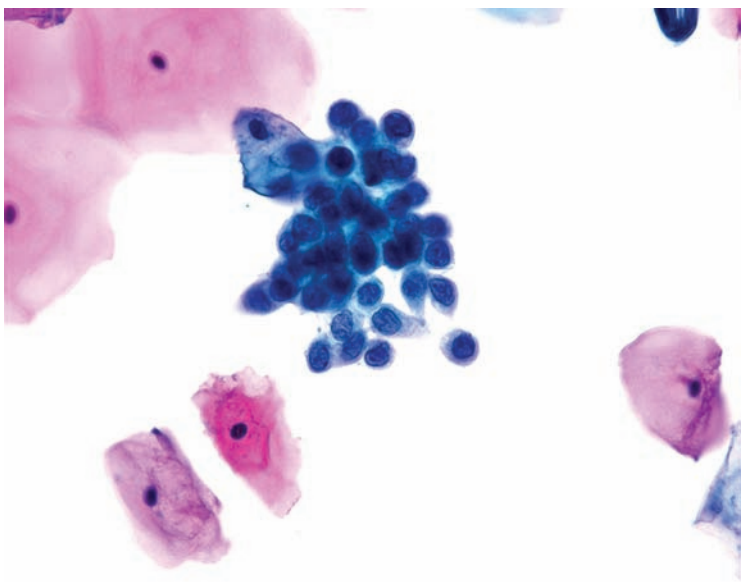


Figure 6.9 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; Medium Power). The monotony of all cell features is the hallmark of an HSIL derived from a CIN3 or carcinoma in situ (CIS). Perhaps, the most variation is seen in nuclear contours.

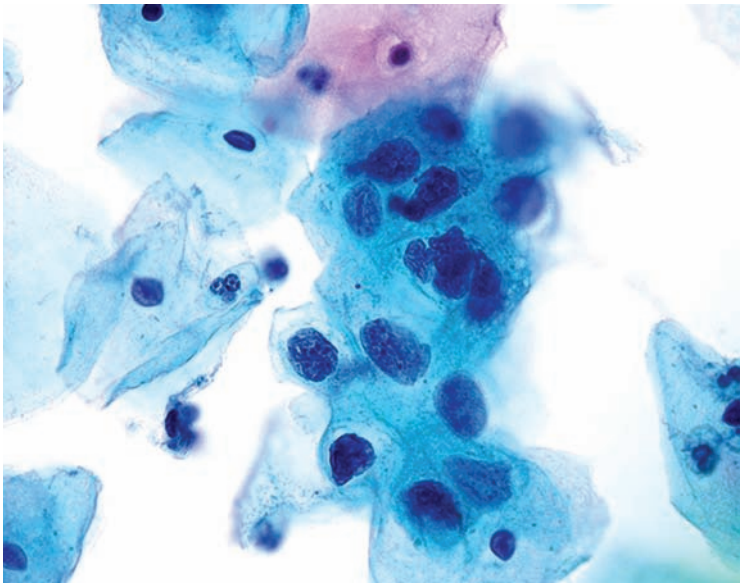


Figure 6.10 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). Not all HSIL cells have very high N/C ratios. These cells are variable in nuclear size and shape, unlike those in Figures 6.6 to 6.9, but all are greatly enlarged when compared with an intermediate nucleus. The hyperchromasia and coarse chromatin complete the picture.

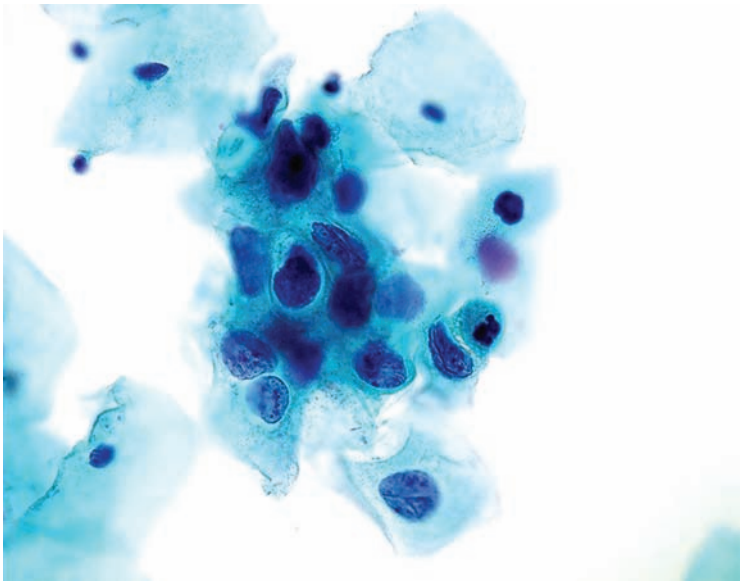


Figure 6.11 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). The nuclei are enlarged and have irregular borders. The chromatin is coarse and dark. While some cells at the edges appear to have more cytoplasm, the cells in the center of the fragment have elevated N/C ratios and would be diagnosed as atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion (ASC-H) if found singly in the smear. The squamous features in this fragment can be well appreciated, as the cells have sharp borders and intercellular bridges.

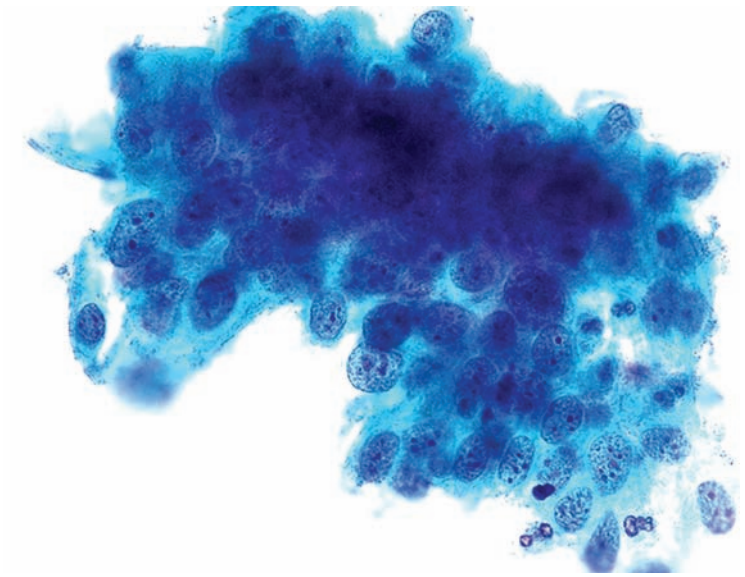


Figure 6.12 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). This fragment contains cells that appear similar to those in the previous figure, but the cell number is increased. While sharp cell borders can be appreciated in some areas, overlapping nuclei in other areas give the appearance of a syncytium, which is a common form taken by HSIL. The coarse chromatin and absence of nucleoli exclude the possibility that these represent reactive endocervical cells. From a low-power view, this fragment would appear as a hyperchromatic crowded group.

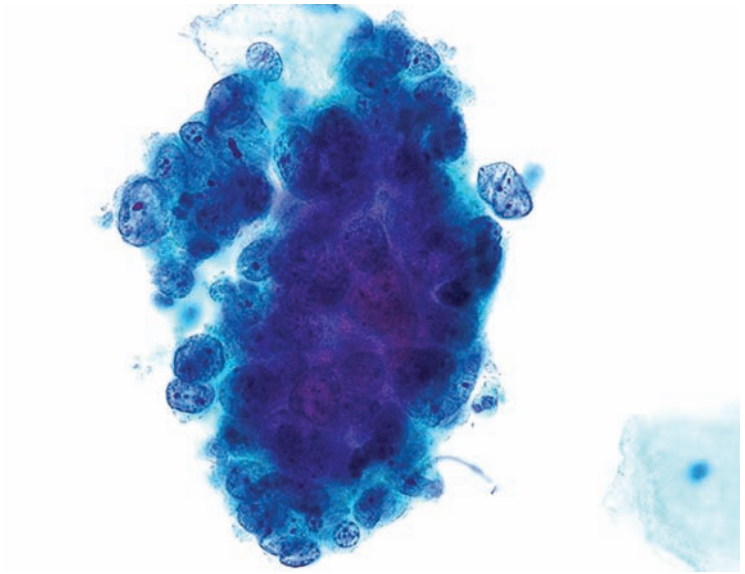


Figure 6.13 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). This fragment contains a syncytial arrangement that is similar to that seen in the previous figure. Although the coarse chromatin pattern sometimes gives the appearance of a single nucleolus, remember that nucleoli are associated with squamous cell carcinoma or reactive changes, and not HSIL. In such syncytial fragments, the edge may appear to be hobnailed, but the nuclei are too big to be normal endometrial cells (compare with the superficial cell in the corner). The nuclear pleomorphism is striking.

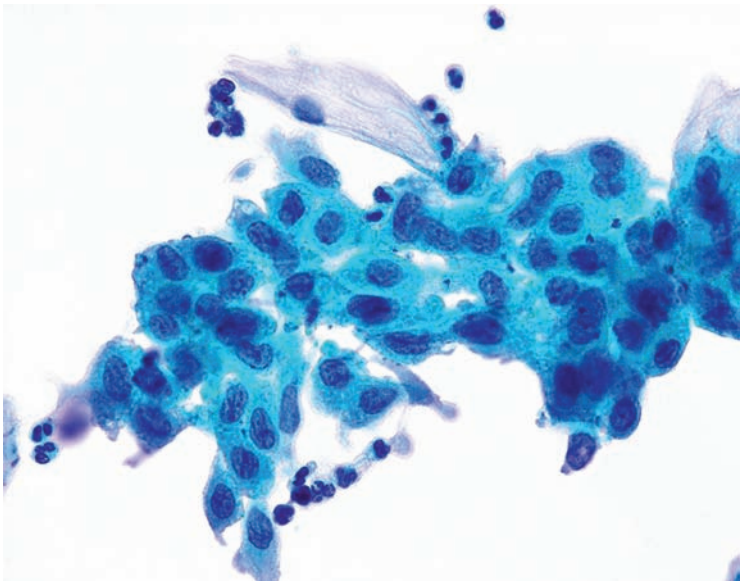


Figure 6.14 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). The presence of intercellular bridges and dense, sharp cytoplasm indicates that these cells have a squamous origin. Inflammatory cells are present, but this is not the "school of fish" appearance seen in repair. No nucleoli are present and there is an underlying disorganization. The nuclear borders are irregular and wrinkled, the N/C ratio is elevated, and the chromatin is dark and coarse. This fragment alone is diagnostic of HSIL and one would expect to see single atypical cells in the background.

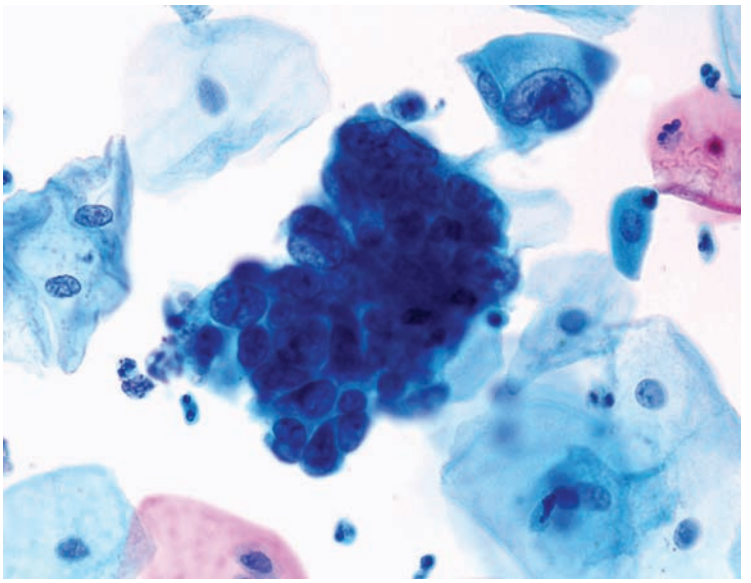


Figure 6.15 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). The nuclear pleomorphism demonstrated by the cells in this fragment is striking. Again, the majority of cells in the fragment have a syncytial appearance but sharp edges and greatly increased nuclear size are not compatible with normal endometrial cells. Compare the size to the intermediate squamous cells in the bottom right corner of the field.

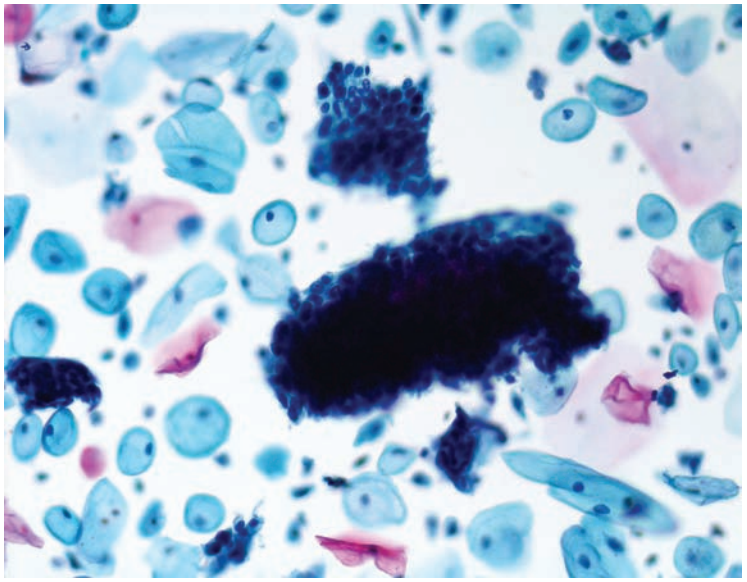


Figure 6.16 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; Intermediate Power). When viewed on lower power, HSIL appears as a hyperchromatic group and, thus, one must examine a good sample of HCGs present on a smear to exclude HSIL. The differential includes reactive endocervical cells, tubal metaplasia, and endometrial cells.

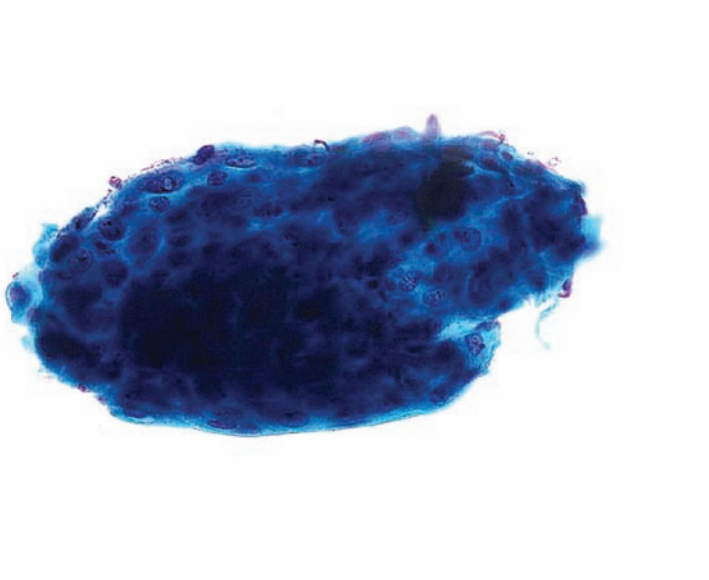


Figure 6.17 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). This group of cells initially appears benign as the nuclei appear in approximately the same size, but closer examination reveals the presence of coarse chromatin. Additionally, the syncytial appearance should raise the possibility of HSIL. The edges are smooth, whereas a hobnailed appearance would be more suggestive of endometrial cells.

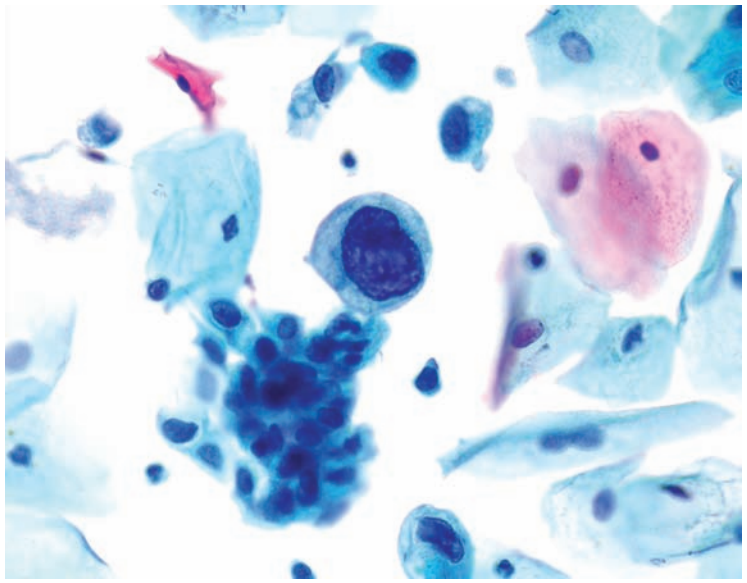


Figure 6.18 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). This single cell distracts from its surroundings due to its huge nucleus. The cell is well preserved and there is no reason to suggest that its atypical features are due to degeneration: hyperchromasia, irregular nuclear borders, and high N/C ratio. Many HSIL lesions do not have strikingly increased nuclear size but rather have increased N/C ratio. In this instance, a single atypical cell is not sufficient for a diagnosis of HSIL, but signals the need to closely examine the entire slide. While other cells in the background look benign compared to this dramatically atypical cell, are the smaller single cells with increased N/C ratio also cells from the lesion? Is the fragment of cells adjacent to the large atypical cell also atypical in its own right?

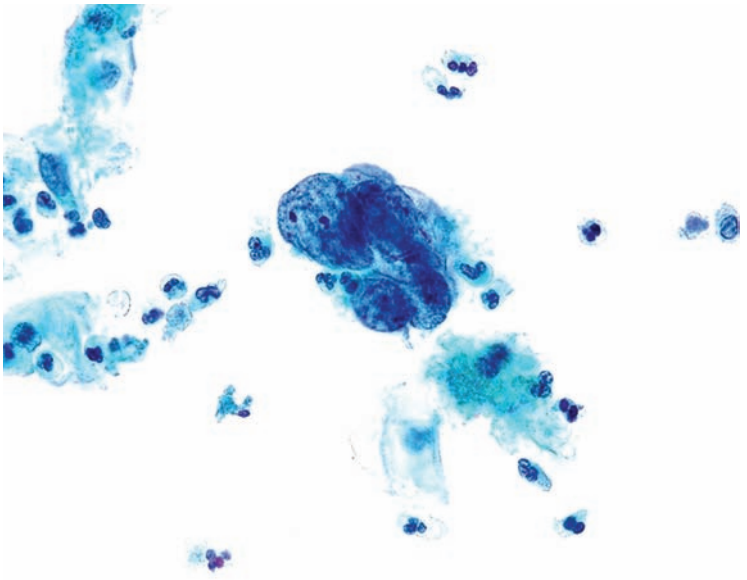


Figure 6.19 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). The lack of cytoplasm in this atypical cell group may suggest degenerative changes, but the nuclei appear intact and have coarse, dark chromatin. These highly atypical cells should create worry that squamous cell carcinoma may be present; furthermore, the neutrophils and granular debris in the background suggest the possibility of tumor diathesis.

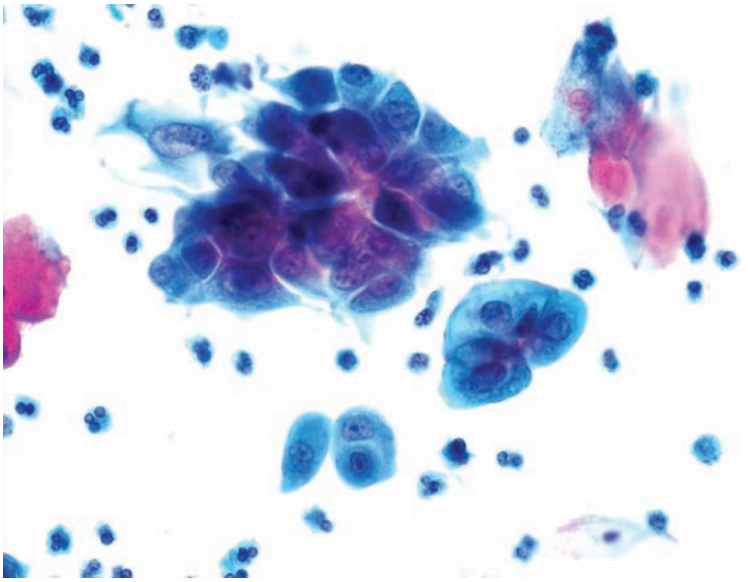


Figure 6.20 — High-Grade Squamous Intraepithelial Lesion (HSIL) Versus Reactive Endocervical Cells (Liquid Based; High Power). The mosaic tile appearance of cells in this fragment can be seen in squamous metaplastic cells or endocervical cells standing en face. The neutrophils in the background suggest the possibility of a reactive process. The nuclei are enlarged and slightly pleomorphic, but the N/C ratios are not as increased as in previous examples of HSIL. Most importantly, nucleoli seen in a reactive process are not readily identifiable, though some coarse chromatin is seen. Although this fragment is not diagnostic of HSIL, there is enough atypia to merit an ASC-H diagnosis.

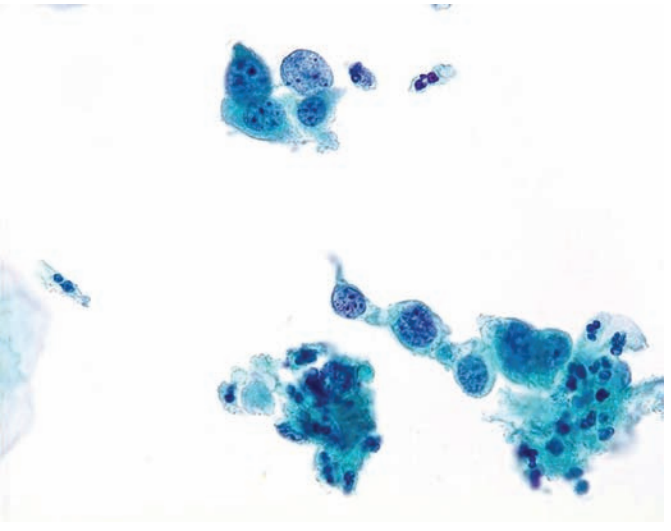


Figure 6.21 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). Several cells with coarse chromatin and a high N/C ratio are singly present; if present in enough numbers throughout the slide, this would be diagnostic of HSIL. The presence of granular debris and neutrophils suggests the possibility of tumor diathesis, though it is nothing more than a suggestion in this field.

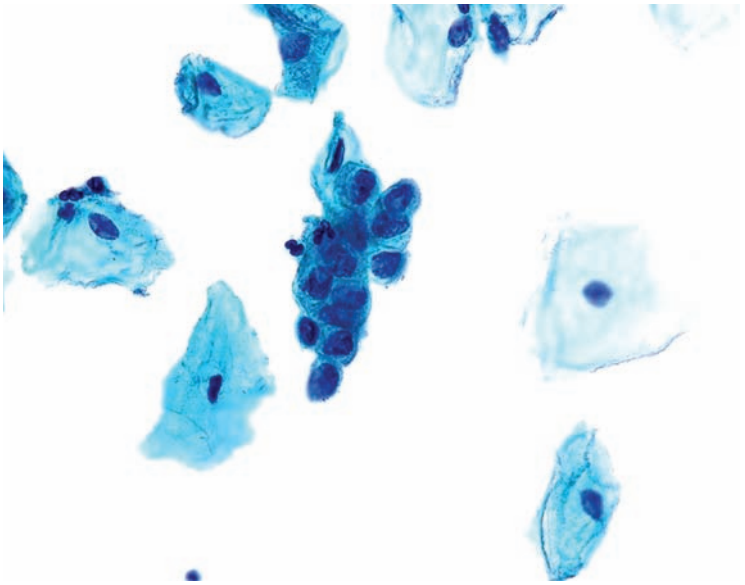


Figure 6.22 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). The nuclei of HSIL are often homogeneously dark and do not necessarily contain coarse chromatin. Furthermore, the nuclear size is only slightly larger than that of an intermediate squamous cell (compared to adjacent cells). The primary diagnostic feature in this instance is the greatly increased N/C ratio, which results from the dramatic decrease in the amount of cytoplasm.

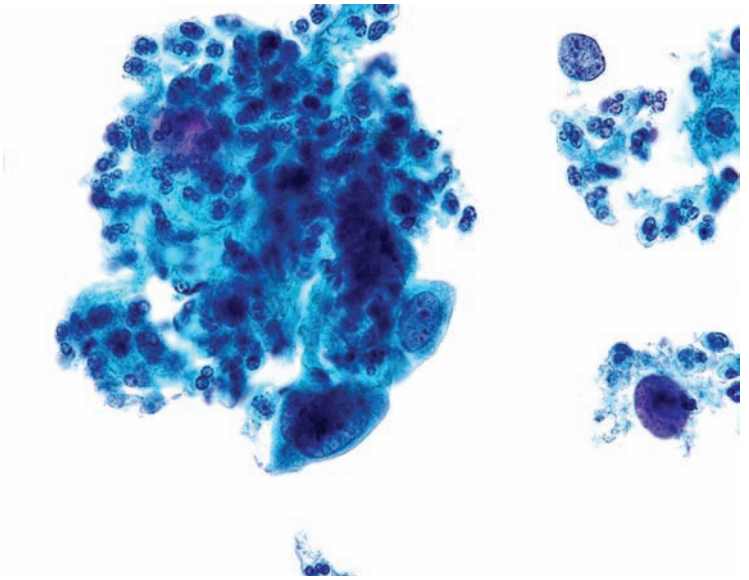


Figure 6.23 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; High Power). The field is obscured by inflammatory cells, but large atypical cells are seen at the edge. Compared to the neutrophils, the nuclei are tremendously increased. There is only a thin rim of cytoplasm and the chromatin is coarse. These cells are well preserved, and there is no question that these cells are beyond an ASC-H diagnosis; the only question is whether they arise from a squamous cell carcinoma, which requires further examination of the smear.

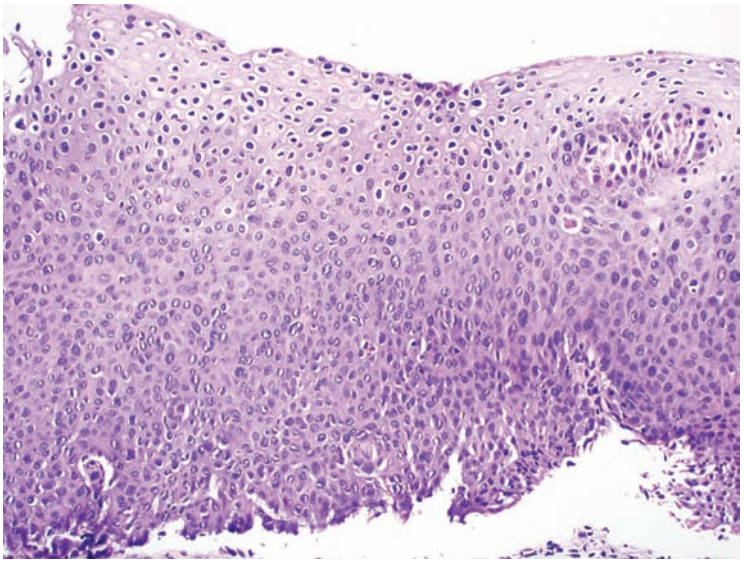


Figure 6.24 — High-Grade Squamous Intraepithelial Lesion (HSIL; CIN2) (Biopsy) (Hematoxylin and Eosin [H&E] Stain; Intermediate Power). In contrast to low-grade squamous intraepithelial lesion (LSIL) having koilocytic atypia in the superficial layers of the squamous epithelium without the loss of maturation in the deeper layers (see Chapter 5), HSIL typically shows immaturity of the lower two thirds (CIN2) or full thickness (CIN3) of the epithelium. In this example (CIN2), the lower two thirds of the epithelium show nuclear enlargement, coarse chromatin, and an increased N/C ratio. Other cases may have mitotic figures in the upper half of the epithelium. Despite the presence of koilocytic atypia in the superficial layers in this case, the specimen is still diagnosed as HSIL based on the degree of immaturity in the lower layers. Note the overall basaloid appearance compared with typical cases of LSIL.

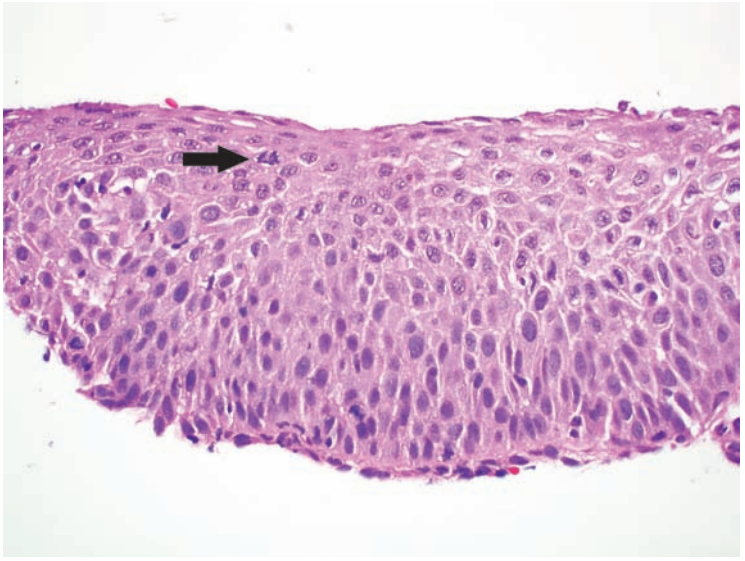


Figure 6.25a — High-Grade Squamous Intraepithelial Lesion (HSIL; CIN2) (Biopsy) (H&E Stain; High Power). This example shows metaplastic-like features. Overall, it has a more eosinophilic appearance compared to other cases of HSIL (CIN2). The subtle degree of atypia and deceptive loss of maturation in the lower two thirds of the epithelium can result in a misdiagnosis of squamous metaplasia. Particularly, a number of cells exhibit a higher N/C ratio, slightly greater nuclear size, and mildly coarser chromatin compared to most cases of metaplasia. In addition, note the mitotic figure (*arrow*) in the upper half of the epithelium.

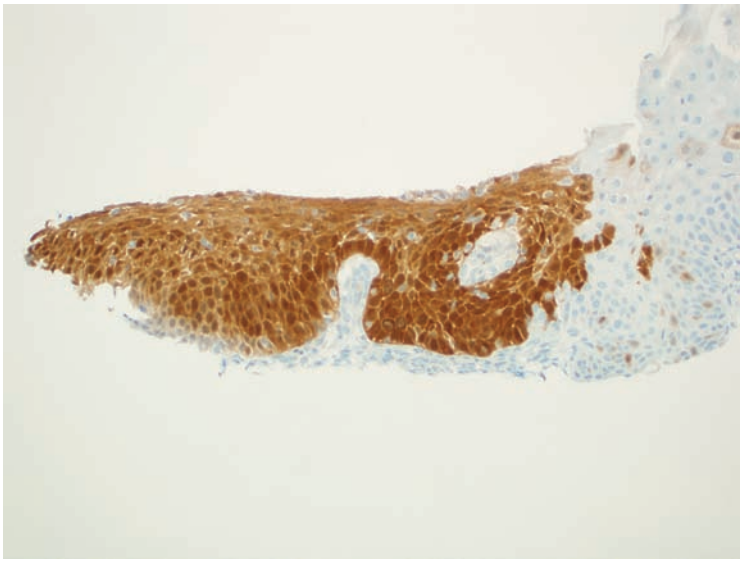
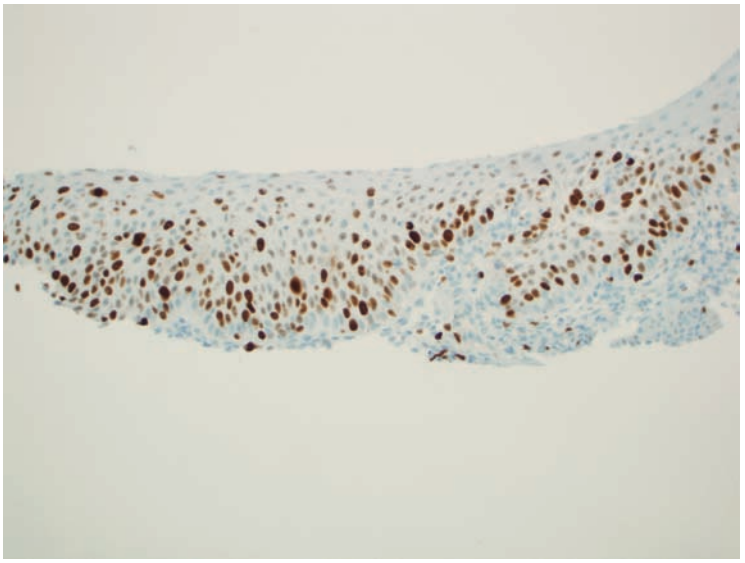


Figure 6.25b — High-Grade Squamous Intraepithelial Lesion (HSIL; CIN2) (Biopsy) (p16 Immunohistochemical Stain; Intermediate Power). p16 is diffusely expressed consistent with high-risk human papillomavirus (HPV). Within the lesion, note that staining for p16 is complete within both the horizontal and vertical dimensions.

Figure 6.25c — High-Grade Squamous Intraepithelial Lesion (HSIL; CIN2) (Biopsy) (Ki-67 Immunohistochemical Stain; Intermediate Power). Increased proliferative activity occurs within the lower and upper halves of the squamous epithelium. These combined morphological and immunohistochemical (p16/Ki-67) findings support a diagnosis of HSIL. Immunostaining for Ki-67 is not necessary for diagnosing HSIL if the morphology and p16 result are concordant. According to the CAP-LAST consensus guidelines, the routine addition of Ki-67 to p16 immunohistochemistry is not recommended; however, for cases in which p16 immunohistochemistry is inconclusive or technically inadequate, use of Ki-67 may be considered. Specifically, when the differential diagnosis concerns HSIL versus atrophy/transitional cell metaplasia or immature squamous metaplasia, a Ki-67 stain can be useful if the p16 stain is difficult to assess. It is, nonetheless, important to recognize that interpreting a Ki-67 stain in tangentially oriented tissue or attenuated mucosa may be problematic.



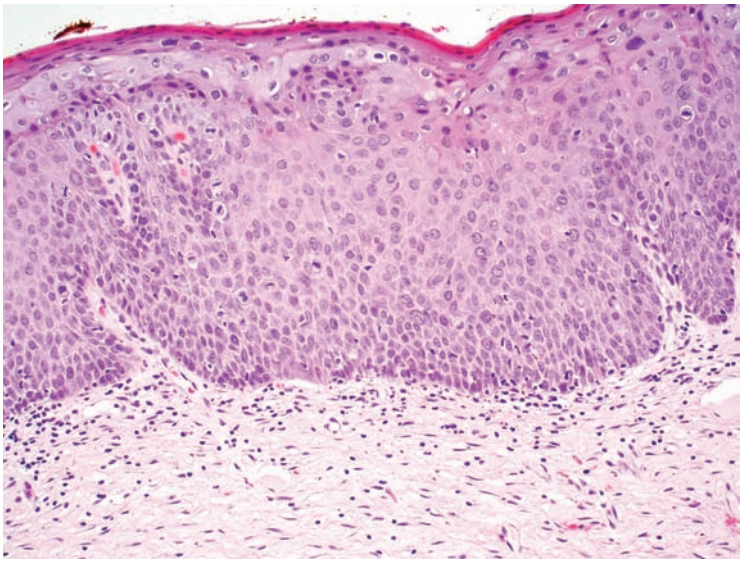


Figure 6.26 — High-Grade Squamous Intraepithelial Lesion (HSIL; CIN2) (Biopsy) (H&E Stain; Intermediate Power). This is another example with a metaplastic-like appearance. In this case, a substantial degree of parakeratosis is present, which can occur in squamous intraepithelial lesions. In other cervical biopsies with prominent parakeratosis, subtle HSILs of this type with a metaplastic-like appearance may be overlooked if the underlying lesional squamous epithelium is not fully represented in a superficial biopsy.

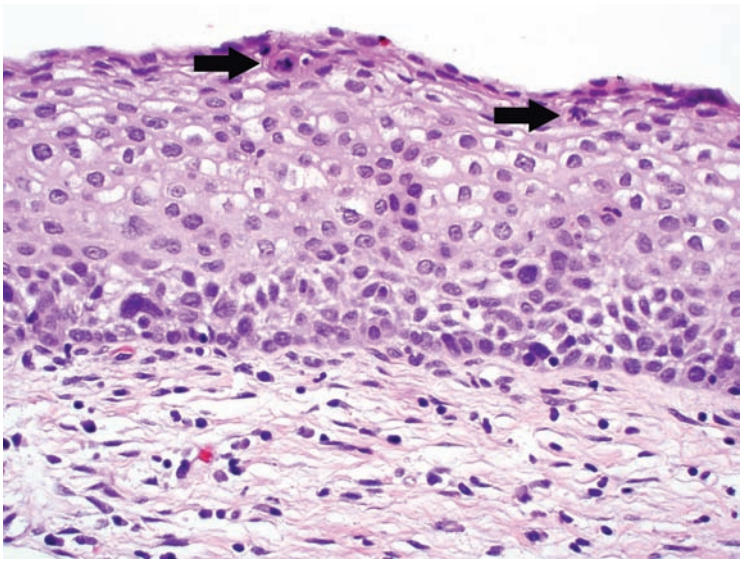


Figure 6.27a — Squamous Intraepithelial Lesion, Favor High-Grade Squamous Intraepithelial Lesion (HSIL; CIN2) (Biopsy) (H&E Stain; High Power). The differential diagnosis in this case is between low-grade squamous intraepithelial lesion (LSIL; CIN1) and HSIL (CIN2), and the overlapping histologic features make definitive classification problematic. The degree of immaturity, however, is slightly greater than what would be expected for LSIL. Furthermore, structures suspicious for mitotic figures (*arrows*) are noted in the upper half of the squamous epithelium. Mitotic figures that may be present in the lower half of the epithelium in other cases, particularly when close to the parabasal layer, are a noncontributory finding as it can be seen in reactive or reparative settings. Nonetheless, mitotic figures in the upper half of the epithelium are helpful because that feature is usually associated with HSIL.

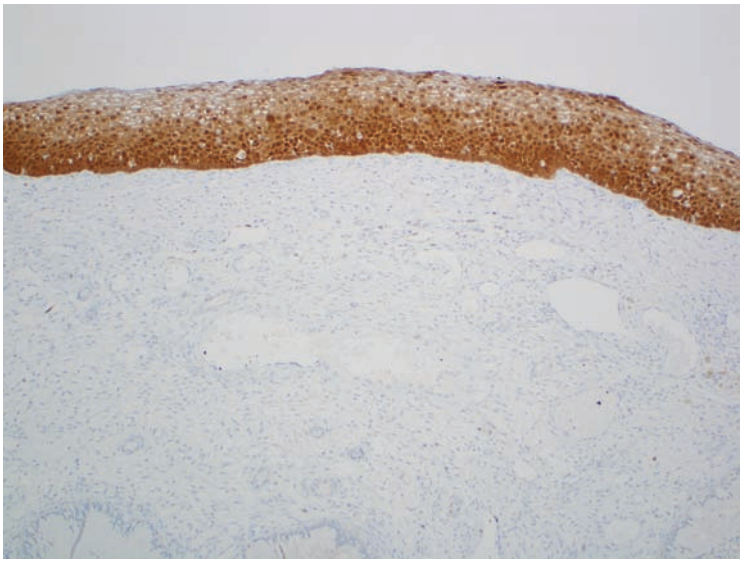


Figure 6.27b — Squamous Intraepithelial Lesion, Favor High-Grade Squamous Intraepithelial Lesion (HSIL; CIN2) (Biopsy) (p16 Immunohistochemical Stain; Intermediate Power). Diffuse expression of p16 is present. Although diffuse staining for p16 can be seen in a subset of LSILs, using diffuse expression of p16 to favor a diagnosis of HSIL for ambiguous squamous intraepithelial lesions, in which the differential diagnosis is LSIL versus HSIL (CIN2), is recommended.

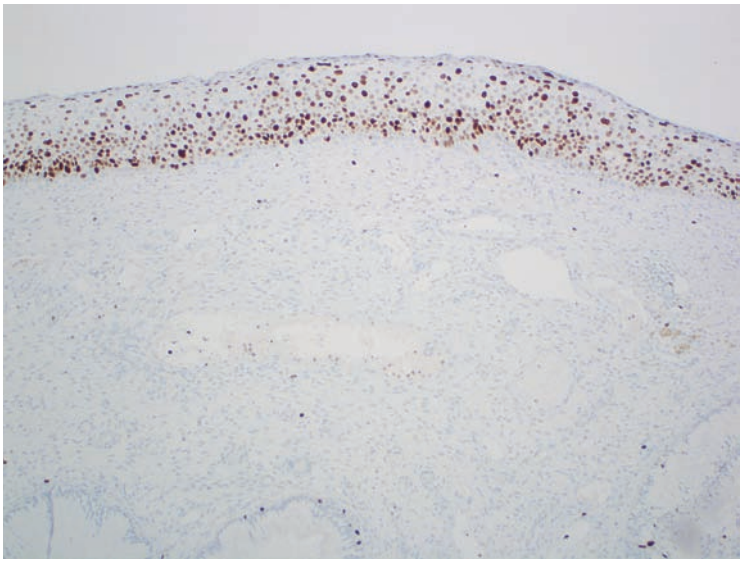


Figure 6.27c — Squamous Intraepithelial Lesion, Favor High-Grade Squamous Intraepithelial Lesion (HSIL; CIN2) (Biopsy) (Ki-67 Immunohistochemical Stain; Intermediate Power). Both the upper and lower layers of the epithelium show increased proliferative activity. This degree of proliferation, in isolation, is nonspecific and does not distinguish LSIL from HSIL. Unequivocal distinction between LSIL and HSIL is not possible in this case, and some degree of interobserver disagreement among gynecologic pathologists would probably occur; however, the combined morphological and p16 immunohistochemical findings favor a diagnosis of HSIL (CIN2). Moreover, immunostaining for Ki-67 is not necessary for diagnosing HSIL if the morphology and p16 result are concordant. According to the CAP-LAST consensus guidelines, the routine addition of Ki-67 to p16 immunohistochemistry is not recommended; however, for cases in which p16 immunohistochemistry is inconclusive or technically inadequate, use of Ki-67 may be considered. Specifically, when the differential diagnosis concerns HSIL versus atrophy/transitional cell metaplasia or immature squamous metaplasia, a Ki-67 stain can be useful if the p16 stain is difficult to assess. It is, nonetheless, important to recognize that interpreting a Ki-67 stain in tangentially oriented tissue or attenuated mucosa may be problematic.

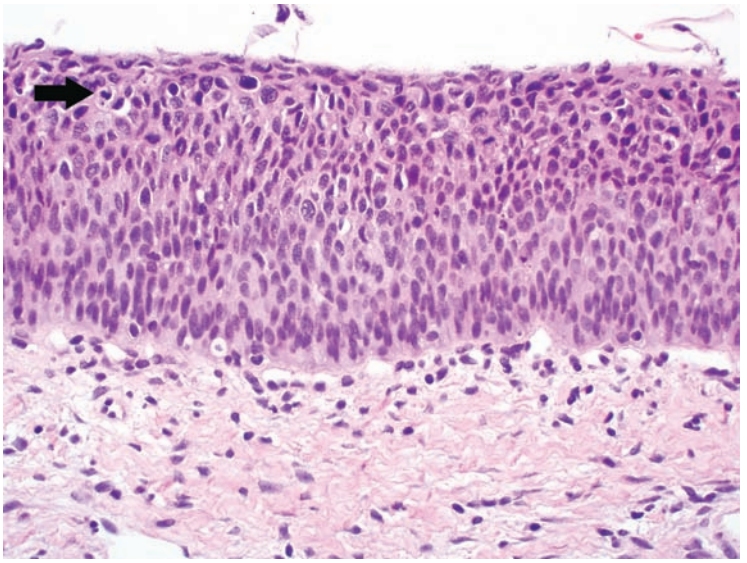
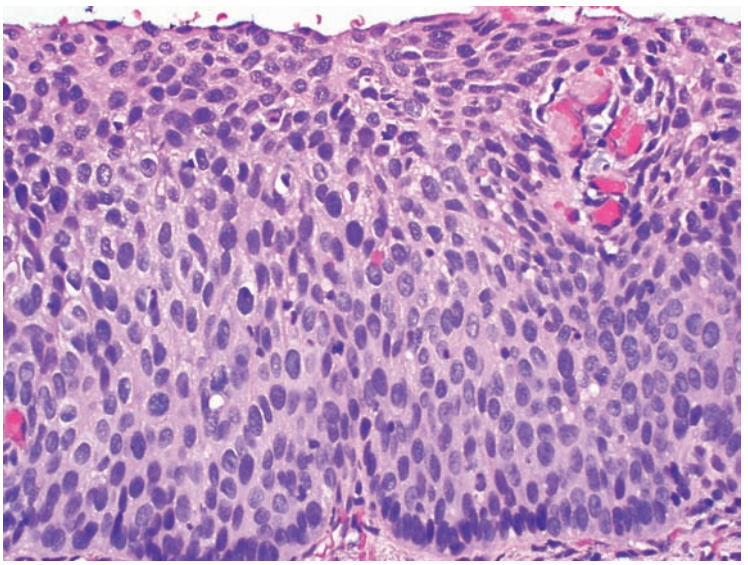


Figure 6.28 — High-Grade Squamous Intraepithelial Lesion (HSIL; CIN3) (Biopsy) (H&E Stain; High Power). Full-thickness loss of maturation is present. Although the nuclei in this case are small and somewhat uniform, the degree of immaturity and increased N/C ratio are diagnostic of HSIL. Note the presence of a mitotic figure in the upper half of the epithelium (*arrow*).

Figure 6.29 — High-Grade Squamous Intraepithelial Lesion (HSIL; CIN3) (Biopsy) (H&E Stain; High Power). Note the thicker squamous epithelium compared with Figure 6.28. Furthermore, compared with that case, this example of HSIL shows nuclei that are much larger, but the cells have a lower N/C ratio. Nonetheless, the degree of nuclear enlargement, immaturity, and hyperchromasia are diagnostic of HSIL.



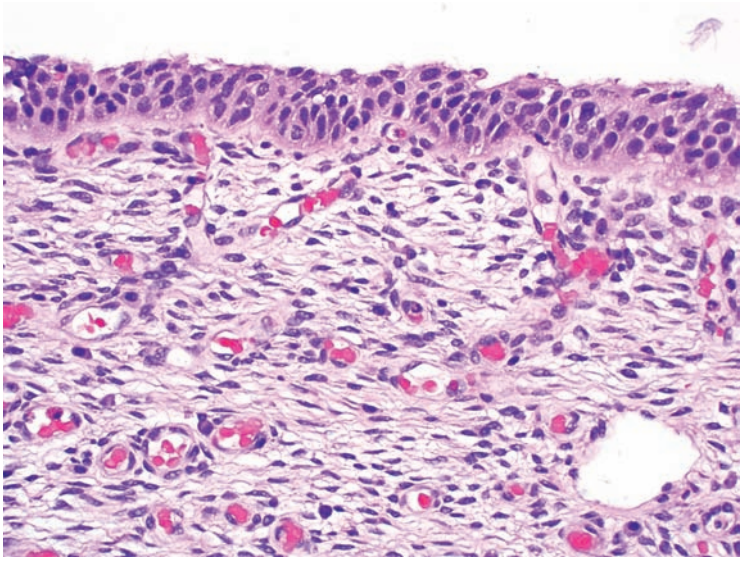


Figure 6.30a — Attenuated High-Grade Squamous Intraepithelial Lesion (HSIL) (Biopsy) (H&E Stain; High Power). The HSIL in this example is thin. At low-power magnification, this pattern of HSIL can be missed because of its thin nature. On high-power examination, the differential diagnosis concerns immature squamous metaplasia versus HSIL. Even though there is no significant nuclear enlargement in this case, the N/C ratio is increased, and the chromatin is somewhat coarse.

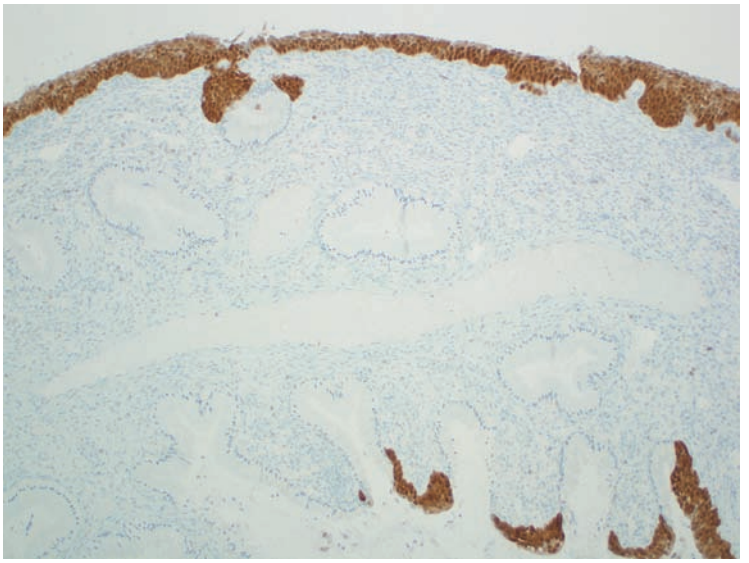


Figure 6.30b — Attenuated High-Grade Squamous Intraepithelial Lesion (HSIL) (Biopsy) (p16 Immunohistochemical Stain; Intermediate Power). p16 is diffusely expressed, which argues against a diagnosis of metaplasia.

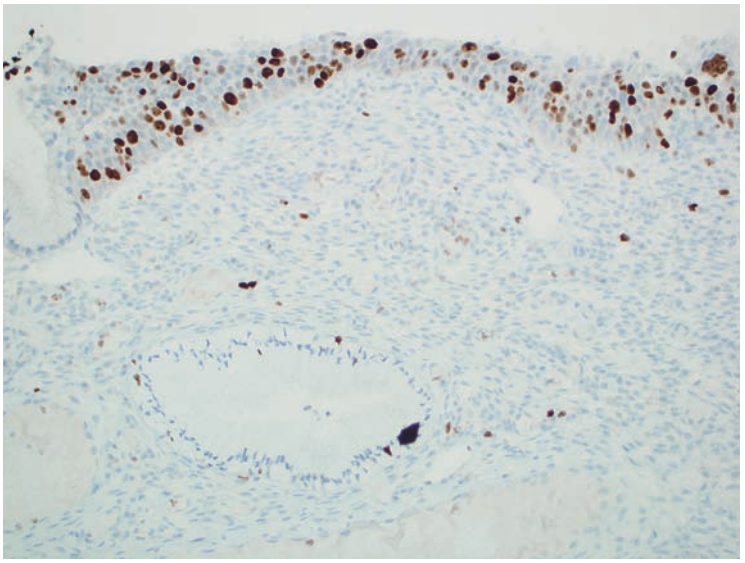


Figure 6.30c — Attenuated High-Grade Squamous Intraepithelial Lesion (HSIL) (Biopsy) (Ki-67 Immunohistochemical Stain; Intermediate Power). Although the Ki-67 index is difficult to determine, given the thin nature of the lesion, there is increased proliferation in the upper half of the epithelium. These combined histological and immunohistochemical (p16/Ki-67) findings support a diagnosis of HSIL, but in the opinion of some gynecologic pathologists the thin nature of the lesion precludes distinguishing CIN2 from CIN3. Furthermore, immunostaining for Ki-67 is not necessary for diagnosing HSIL if the morphology and p16 result are concordant. According to the CAP-LAST consensus guidelines, the routine addition of Ki-67 to p16 immunohistochemistry is not recommended; however, for cases in which p16 immunohistochemistry is inconclusive or technically inadequate, use of Ki-67 may be considered. Specifically, when the differential diagnosis concerns HSIL versus atrophy/transitional cell metaplasia or immature squamous metaplasia, a Ki-67 stain can be useful if the p16 stain is difficult to assess. It is, nonetheless, important to recognize that interpreting a Ki-67 stain in tangentially oriented tissue or attenuated mucosa may be problematic.

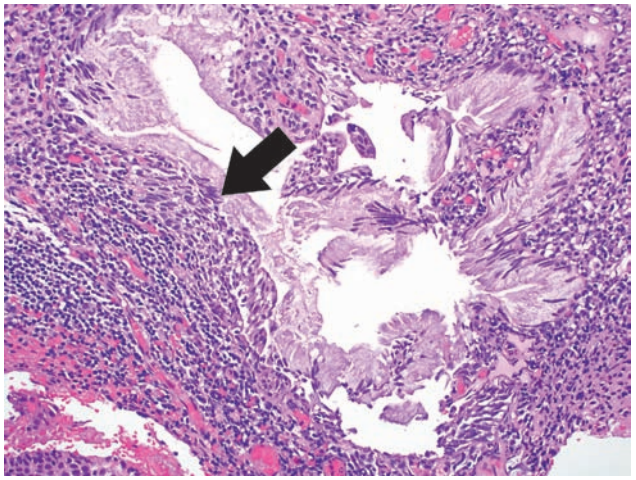


Figure 6.31a — High-Grade Squamous Intraepithelial Lesion (HSIL) With Thermal Injury (Loop Electrosurgical Excision Procedure [LEEP]) (H&E Stain; High Power). The HSIL (*arrow*) that extends into the endocervical gland in this case is focal, small, and involved by cautery artifact. This focus is near a tissue edge, a location frequently showing thermal injury in LEEP specimens. Note the elongated nuclei and streaming effect typical of thermal injury. Because of the small and focal nature of the lesion, presence of cautery artifact, and adjacent florid inflammation within stroma, recognition of such foci of HSIL may be problematic, especially when present at a tissue edge or margin.

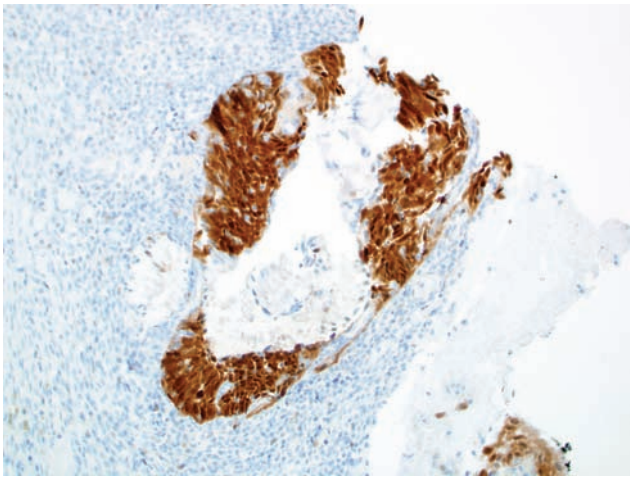
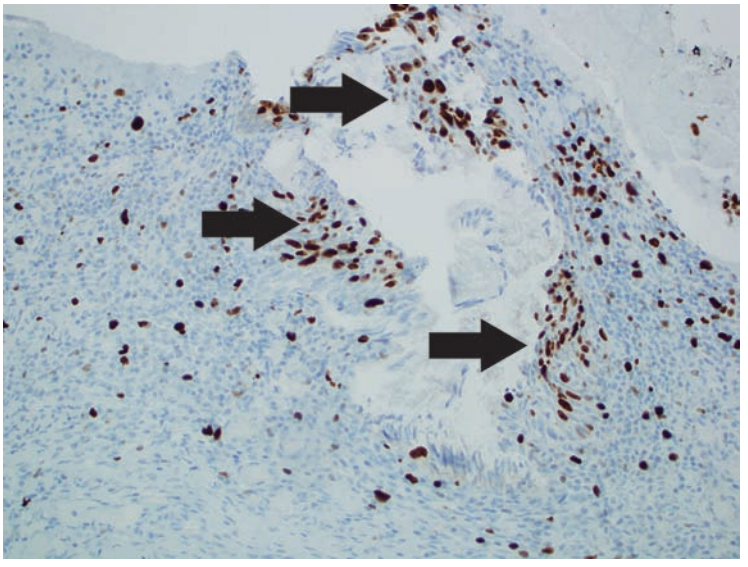


Figure 6.31b — High-Grade Squamous Intraepithelial Lesion (HSIL) With Thermal Injury (LEEP) (p16 Immunohistochemical Stain; Intermediate Power). Diffuse expression of p16 is present within the lesion. Other foci of HSIL, which were not seen on the H&E level, are present in this level used for immunohistochemistry.

Figure 6.31c — High-Grade Squamous Intraepithelial Lesion (HSIL) With Thermal Injury (LEEP) (Ki-67 Immunohistochemical Stain; Intermediate Power). The presence of numerous inflammatory cells makes assessing the Ki-67 index difficult, but increased proliferation is noted within the lesion (*arrows*). Other foci of HSIL, which were not seen on the H&E level, are present in this level used for immunohistochemistry. The combined p16 and Ki-67 immunohistochemical findings support a diagnosis of HSIL for the cauterized focus seen on the H&E slide. In suspicious cauterized foci in LEEP specimens, performing immunohistochemical stains for p16 and Ki-67 can highlight foci of HSIL. This can be very useful for cases in which the margin status is in question due to thermal injury. Immunostaining for Ki-67 is not necessary for diagnosing HSIL if the morphology and p16 result are concordant. According to the CAP-LAST consensus guidelines, the routine addition of Ki-67 to p16 immunohistochemistry is not recommended; however, for cases in which p16 immunohistochemistry is inconclusive or technically inadequate, use of Ki-67 may be considered. Specifically, when the differential diagnosis concerns HSIL versus atrophy/transitional cell metaplasia or immature squamous metaplasia, a Ki-67 stain can be useful if the p16 stain is difficult to assess. It is, nonetheless, important to recognize that interpreting a Ki-67 stain in tangentially oriented tissue or attenuated mucosa may be problematic.



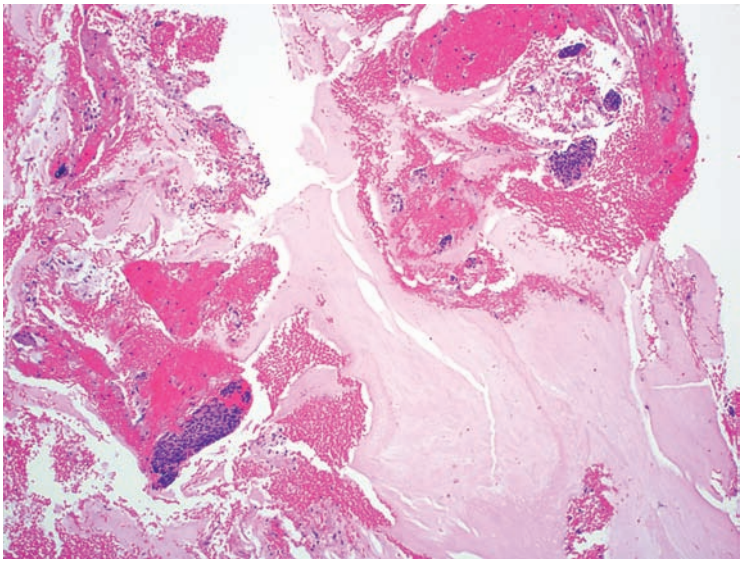


Figure 6.32a — High-Grade Squamous Intraepithelial Lesion (HSIL) (Endocervical Curettage) (H&E Stain; Intermediate Power). Detached and unoriented fragments of cellular squamous epithelium are present. At lower power magnification, the differential diagnosis includes immature squamous metaplasia and HSIL.

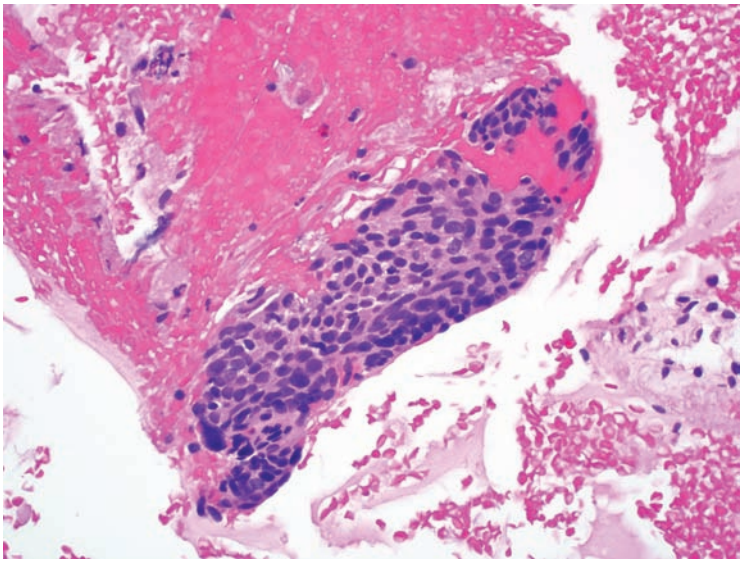


Figure 6.32b — High-Grade Squamous Intraepithelial Lesion (HSIL) (Endocervical Curettage) (H&E Stain; High Power). On higher power magnification, these fragments have an increased N/C ratio, hyperchromasia, and focal nuclear enlargement.

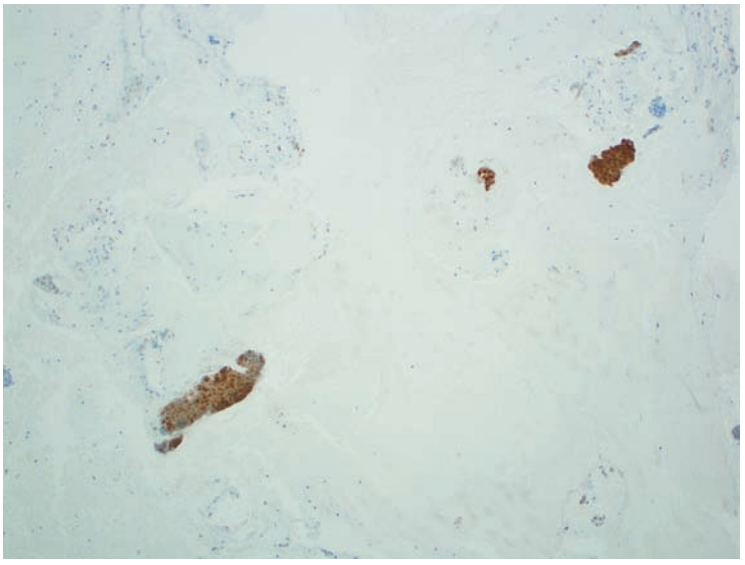


Figure 6.32c — High-Grade Squamous Intraepithelial Lesion (HSIL) (Endocervical Curettage) (p16 Immunohistochemical Stain; Intermediate Power). An immunohistochemical stain for p16 shows diffuse staining, confirming the diagnosis of HSIL. In endocervical curettage specimens, it is not uncommon for HSIL to have this configuration and small size. Because of the latter finding, fragments of HSIL can be overlooked on low-power magnification.

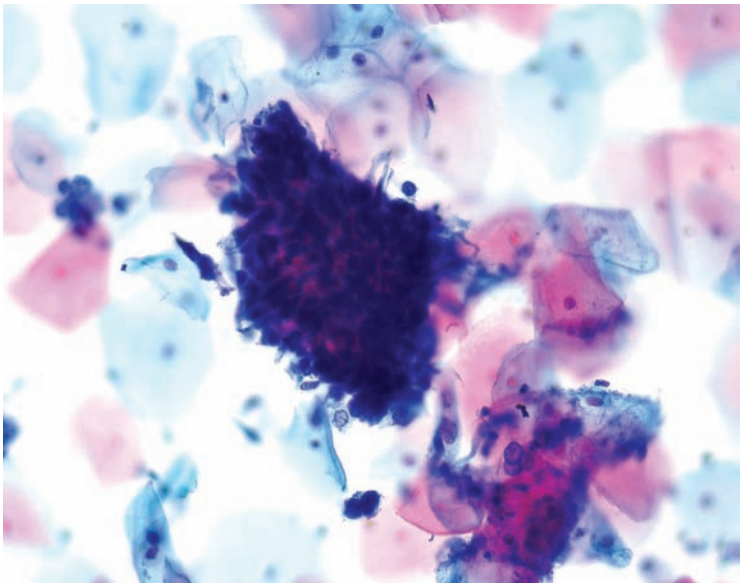


Figure 6.33 — High-Grade Squamous Intraepithelial Lesion (HSIL) With Possible Glandular Involvement (Liquid Based; Intermediate Power). This group is hyperchromatic and crowded, making interpretation difficult. There are single cells adjacent to the fragment with hyperchromasia and high N/C ratios, suggesting the presence of HSIL. The fragment edges are more interpretable and appear jagged, not smooth or hobnailed. This could represent HSIL arising in an area of squamous metaplasia, HSIL with glandular involvement, or even possibly adenocarcinoma in situ (AIS). Because interpretation is limited by cellular density in this fragment and also because AIS can result in definitive treatment without intervening biopsy and/or curettage, one option is to diagnose this fragment as HSIL with atypical glandular cells (AGC).

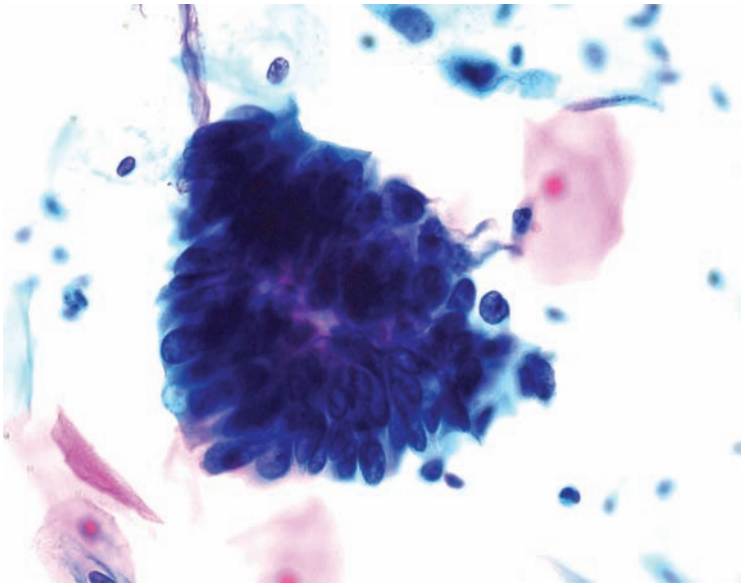


Figure 6.34 — High-Grade Squamous Intraepithelial Lesion (HSIL) With Glandular Involvement (Liquid Based; High Power). This HCG could represent an adenocarcinoma in situ (AIS), or it could simply be involvement of an endocervical gland neck by the HSIL. Adenocarcinoma in situ and HSIL commonly occur together.

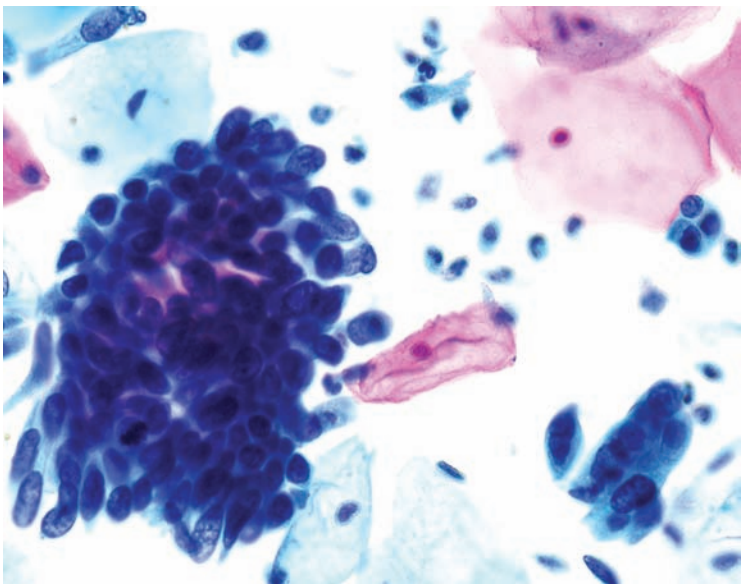


Figure 6.35 — High-Grade Squamous Intraepithelial Lesion (HSIL) With Glandular Involvement (Liquid Based; Medium Power). Although not so tightly packed as the cells in Figure 6.34, this HCG could also represent involvement of endocervical glands. This aspect of interpretation has no meaning for staging, although noting possible glandular involvement will help correlation with the results of cervical curettage and/or biopsy, especially if no lesion is found but the glandular component is undersampled.

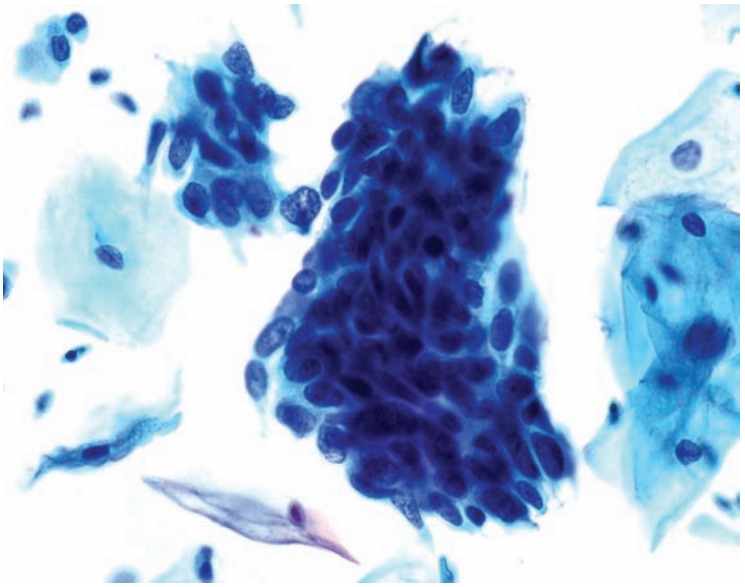


Figure 6.36 — High-Grade Squamous Intraepithelial Lesion (HSIL) (Liquid Based; Medium Power). This HCG appears to have been plucked from a gland neck. The cells are clearly from an HSIL rather than resembling endocervical cells.

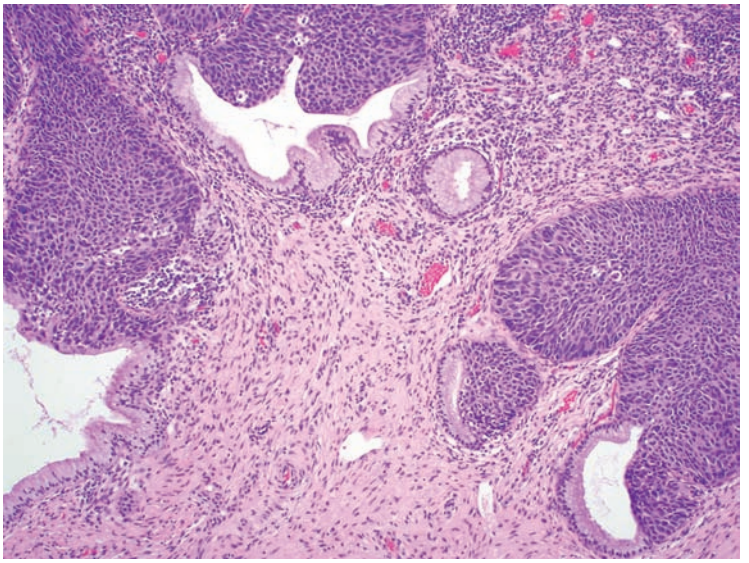


Figure 6.37 — High-Grade Squamous Intraepithelial Lesion (HSIL) With Extension Into Endocervical Glands (Cold Knife Cone Biopsy) (H&E Stain; Intermediate Power). It is not uncommon for HSIL to extend into endocervical glands. However, it is important to not mistake this finding for superficially invasive squamous cell carcinoma (microinvasion). In this example, residual endocervical glandular epithelium is present, and the HSIL conforms to the shape of the underlying glands. These features provide a clue to the noninvasive nature of this lesion. In other cases, it may be difficult to identify these findings. In that situation, obtaining deeper H&E levels may be of help.

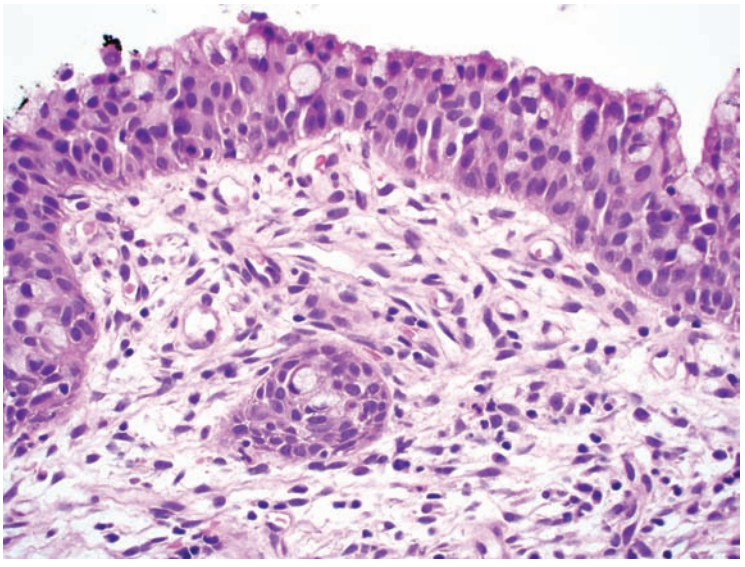


Figure 6.38a — Stratified Mucin-Producing Intraepithelial Lesion ("SMILE") (Biopsy) (H&E Stain; High Power). The lesion is immature and shows some features of high-grade squamous intraepithelial lesion (HSIL), but it also displays a degree of mucinous differentiation. Note the subtle atypia, with some cells showing an increased N/C ratio, minimal hyperchromasia, and slight nuclear enlargement. The nest of epithelium within the stroma represents a tangential section of involvement of an underlying endocervical gland rather than invasive carcinoma.

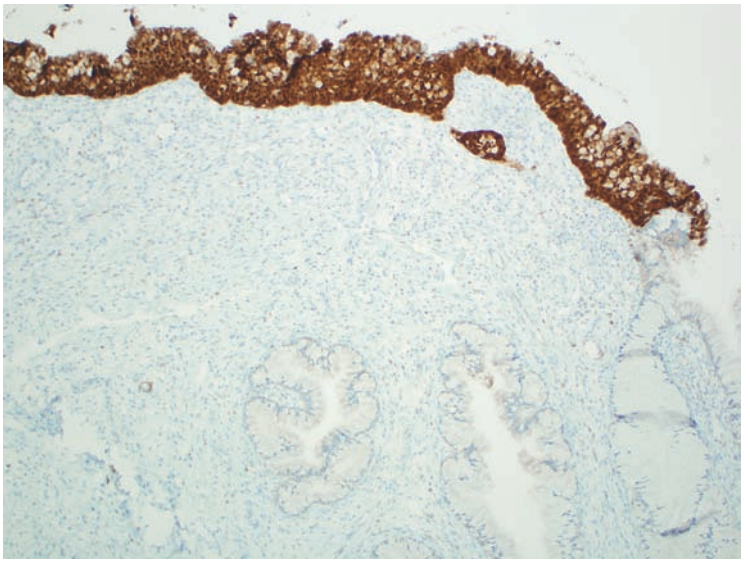


Figure 6.38b — Stratified Mucin-Producing Intraepithelial Lesion ("SMILE") (Biopsy) (p16 Immunohistochemical Stain; Intermediate Power). Diffuse strong expression of p16 is present within the lesion. SMILE is considered a hybrid form of a high-grade intraepithelial lesion with features intermediate between HSIL and endocervical adenocarcinoma in situ (AIS). Alternatively, it can be viewed as adenosquamous carcinoma in situ. For clinical management, SMILE should be regarded as a variant of AIS.

7

Atypical Squamous Cells of Uncertain Significance

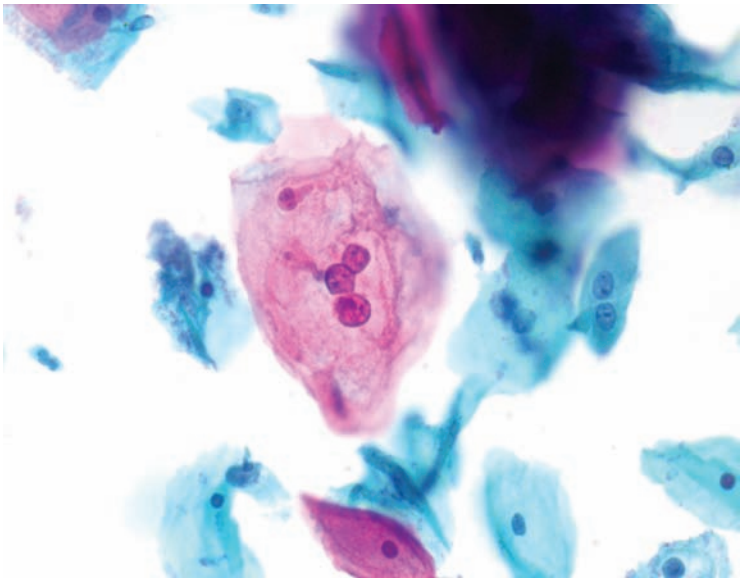


Figure 7.1a — Atypical Squamous Cells of Uncertain Significance (ASC-US) (Liquid Based; Medium Power). A diagnosis of ASC-US may apply to cells with enlarged nuclei, but do not qualify for a diagnosis of low-grade squamous intraepithelial lesion (LSIL); in such situations, the changes may simply be reactive. In other situations, some cells may meet the criteria for LSIL but are not present in sufficient quantity for an unequivocal diagnosis. In this field, the keratinized cells in the center are noteworthy because of the three enlarged nuclei with increased chromasia. Compare with all the other nuclei in the image.

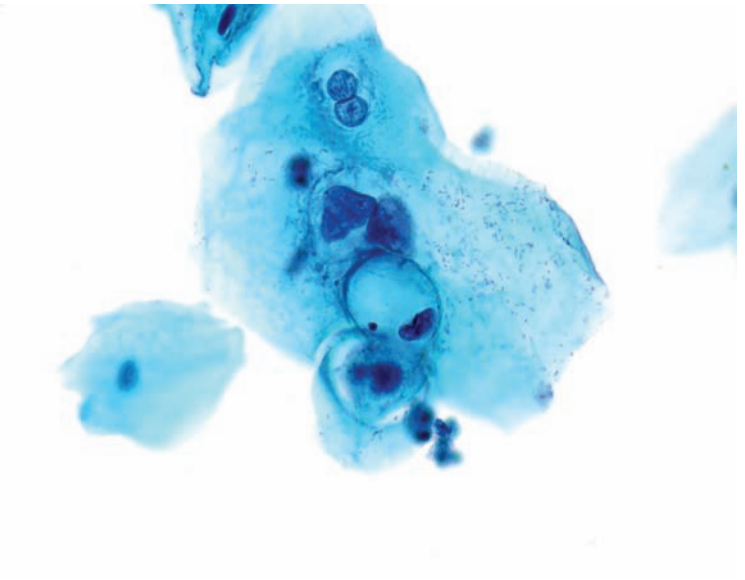


Figure 7.1b — Atypical Squamous Cells of Uncertain Significance (ASC-US) (Liquid Based; Medium Power). This cell appears to have two twin nuclei, each twin surrounded by a small halo. The halo is not typical of a koilocyte, but other cells on the smear may be more convincing of LSIL. One set of nuclei has irregular borders, more typical of dysplasia than a reactive change.

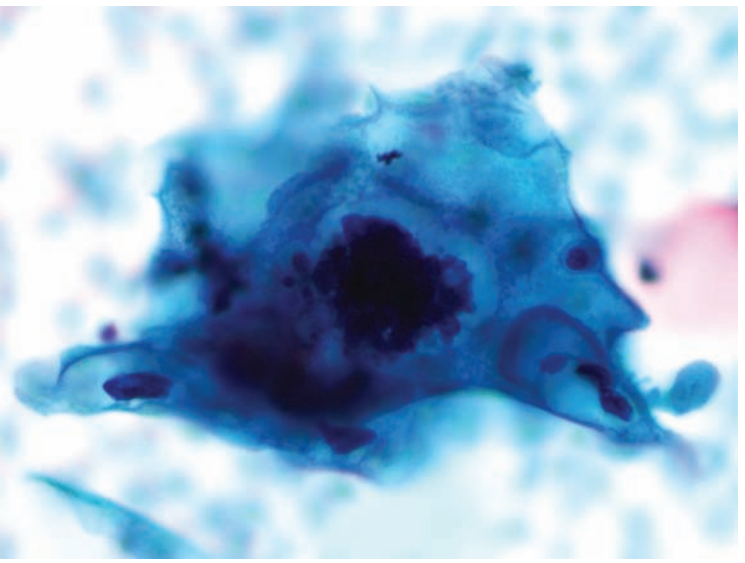


Figure 7.1c — Atypical Squamous Cells of Uncertain Significance (ASC-US) (Liquid Based; High Power). It is unclear what the cellular changes in this cell represent and, thus, a diagnosis of ASC-US may be appropriate. There appear to be small halos surrounding dark nuclei with irregular chromatin, but these findings could just be secondary to degeneration.

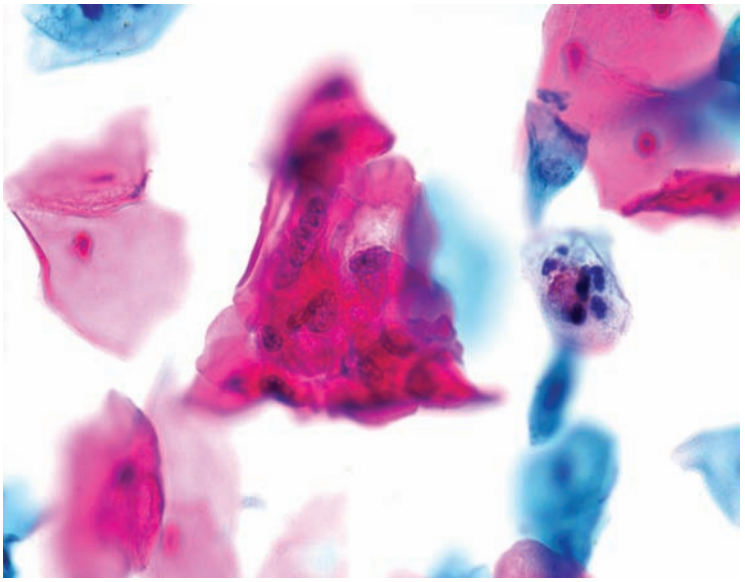


Figure 7.2 — Atypical Squamous Cells of Uncertain Significance (ASC-US) (Liquid Based; Medium Power). Aggregates of large epithelial cells are difficult to fully appreciate on SurePath slides because the groups retain their three-dimensional (3-D) quality. A careful focus through the groups (impossible on a static 2-D photograph) is necessary to fully appreciate any abnormal cells. This fragment displays increased nuclear size and koilocyte formation, placing the interpretation in the ASC-US or LSIL category, depending on the rest of the cells on the slide.

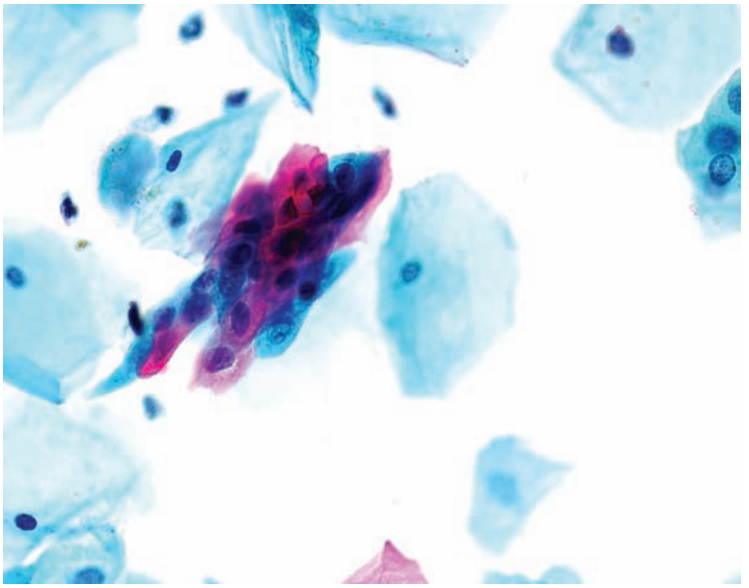


Figure 7.3 — Atypical Squamous Cells of Uncertain Significance (ASC-US) (Liquid Based; Medium Power). In contrast to the large squamous cells in Figure 7.2, the cells in this cluster are metaplastic cells. Nuclear-to-cytoplasmic (N/C) ratios are increased, chromatin is dark and coarsely granular, and nuclear outlines are irregular. These features indicate an atypical parakeratosis, often associated with high-grade squamous intraepithelial lesion (HSIL). Depending on the rest of the slide, the category could remain ASC-US, upgraded to atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion (ASC-H), or even HSIL if similar single cells were abundant.

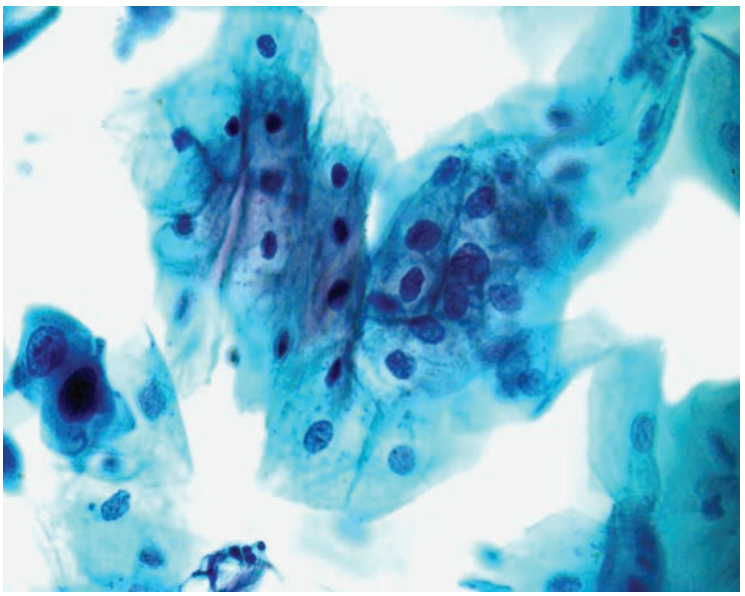


Figure 7.4 — Atypical Squamous Cells of Uncertain Significance (ASC-US) (Liquid Based; Medium Power). This photograph contains three kinds of nonkeratinized squamous cells: to the far left are metaplastic endocervical cells with high N/C ratios, thickened nuclear membranes, and open chromatin. To the left of the center are normal intermediate cells, and to the right of the center are intermediate cells with enlarged nuclei and slightly irregular nuclear membranes. Compare with the two benign intermediate nuclei at the bottom of the central groups.

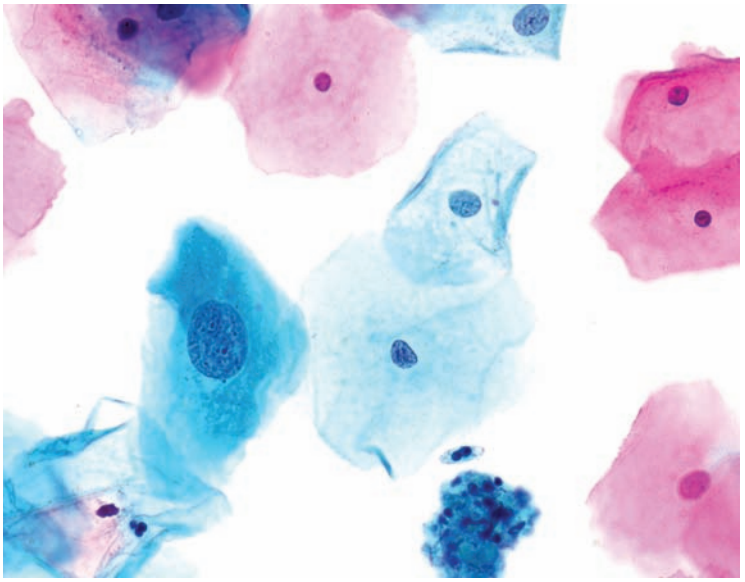


Figure 7.5 — Atypical Squamous Cells of Uncertain Significance (ASC-US) (Liquid Based; High Power). This cell on the left of the center could be considered a prototypical ASC-US example. Compared with the two intermediate cell nuclei in the center, our prototype has an enlarged uniformly shaped oval nucleus, granular but evenly distributed chromatin, and a barely discernible chromocenter. No cytoplasmic alterations are appreciated.

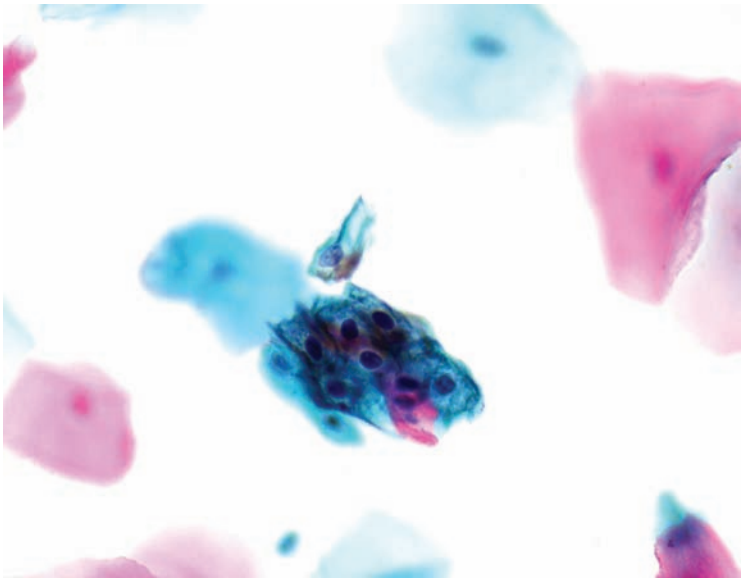


Figure 7.6 — Atypical Squamous Cells of Uncertain Significance (ASC-US) (Liquid Based; Medium Power). The center group of metaplastic cells demonstrates perinuclear halos, with raisinoid nuclei. These changes of human papillomavirus (HPV) affect not only large intermediate cells but also smaller metaplastic ones. Compare this group with the fragment of atypical parakeratosis in Figure 7.3 to appreciate the differences in nuclear changes.

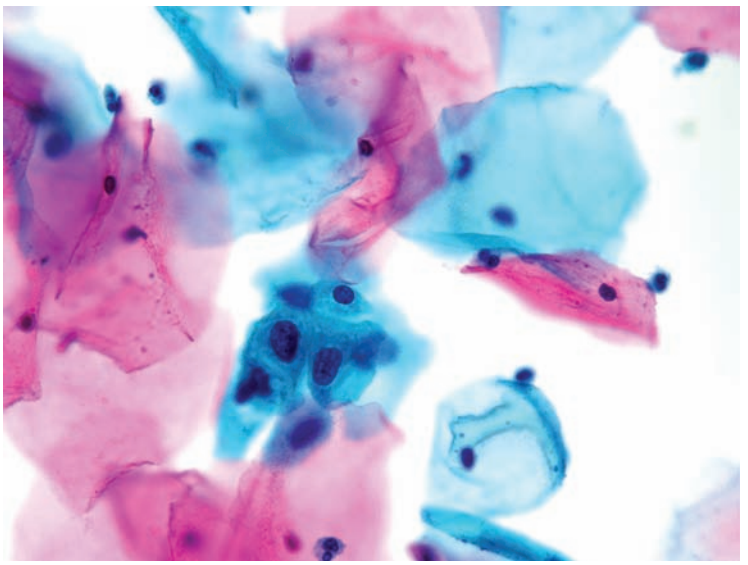


Figure 7.7 — Atypical Squamous Cells of Uncertain Significance (ASC-US) (Liquid Based; High Power). Although the nuclear chromatin is dark and the nuclear shapes are irregular, these atypical cells have relatively low N/C ratios, taking them out of the HSIL category. A careful search of the slide is imperative to find worse cells.

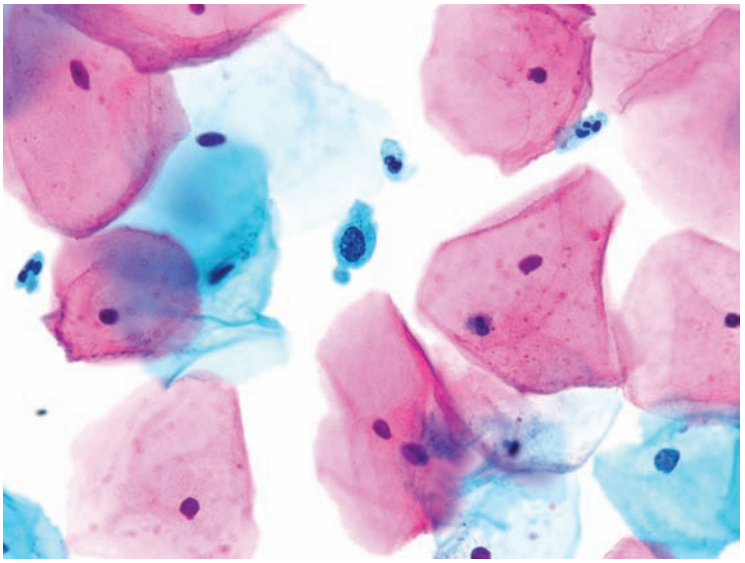


Figure 7.8 — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; High Power). Often dubbed "skip-a-cyte" (D. Wilbur) or "litigation cell" (W. J. Frable), rare cells such as this can hide among the thousands of benign cells on a slide. Once seen, a meticulous search for similar cells is mandatory. Depending on the overall quantity or worse criteria, the final category for the slide may either remain as ASC-H or be upgraded to HSIL.

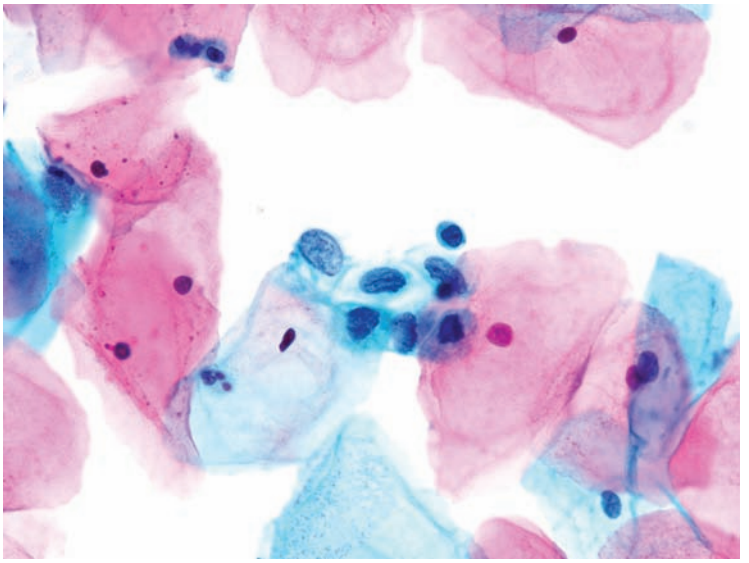


Figure 7.9 — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; High Power). Not every cell will have all the usual features to appropriately classify it. Here, the largest abnormal cell has the palest chromatin of the seven atypical cells in the center of the field. Yet, it qualifies as originating in a high-grade lesion. The final slide category will depend on the quantity as well as quality of the abnormal cells.

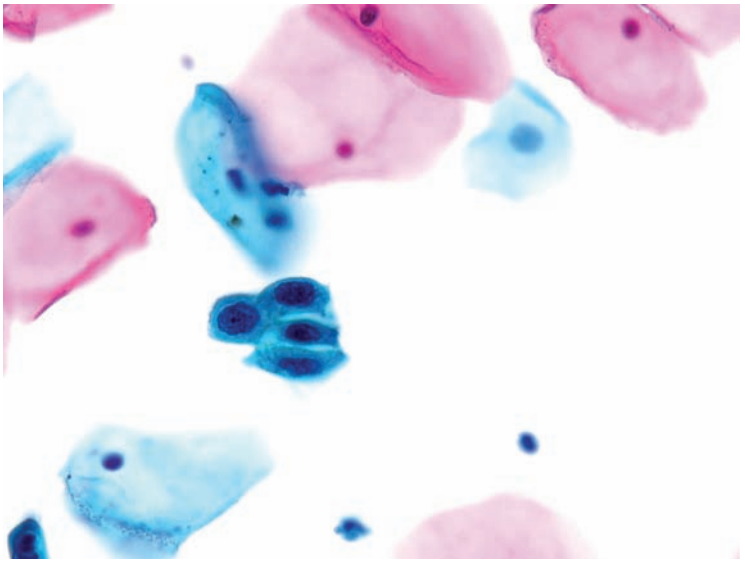


Figure 7.10 — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; High Power). If the slide contains single cells with the features seen in this group, then the interpretation of the sample should be HSIL. However, most pathologists will do so only with single cells, and a convincing number, not just cohesive clusters.

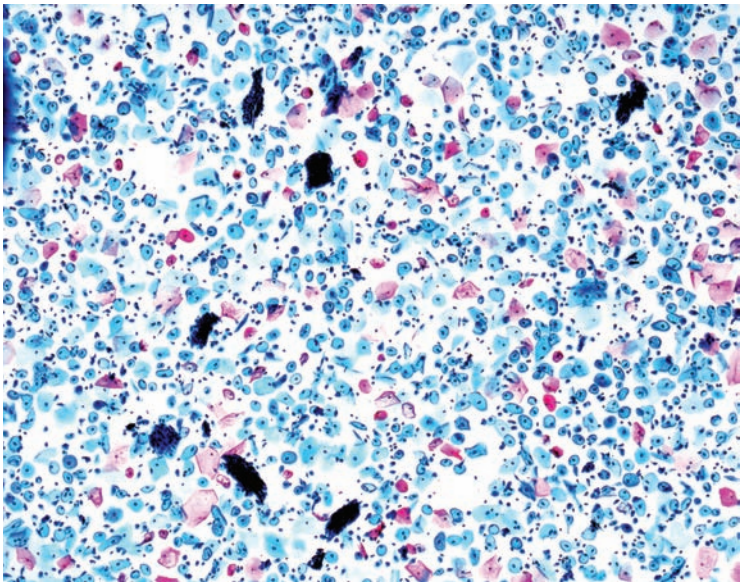


Figure 7.11 — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; Low Power). All that can be appreciated at this magnification is the adequate cellularity and the dark tissue fragments. Hyperchromatic crowded groups (HCGs) may originate in benign or neoplastic tissue, and be from exocervix, endocervix, or endometrium, usually the lower uterine segment. Careful examination on high power is necessary to determine the source of the cells and any abnormalities.

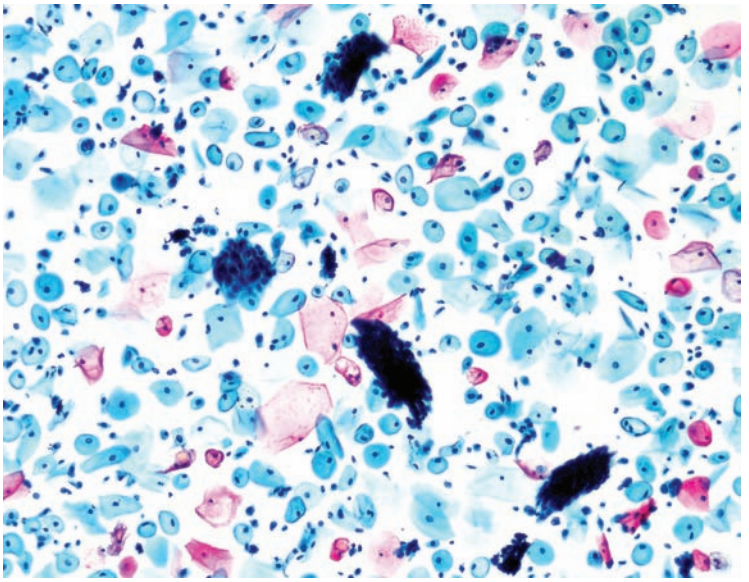


Figure 7.12 — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; Low Power). Closer examination of the slide in Figure 7.11 reveals an atrophic population of squamous cells, along with the HCGs. The density of the cells within the HCGs varies, depending on the size of the individual cells and the N/C ratios. Therefore, the denser the group and the lesser the cytoplasm, the more suspect the group becomes. However, *every* group must be carefully examined on high power to avoid missing any abnormality.

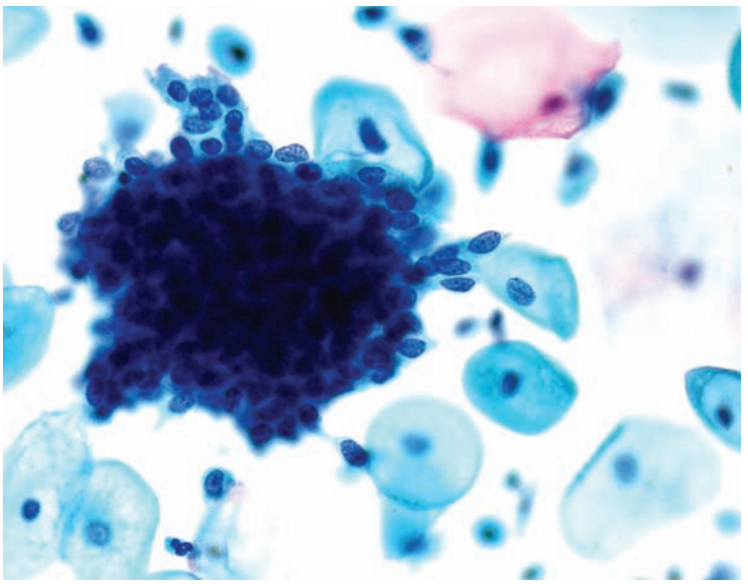


Figure 7.13 — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; High Power). On higher power, the individual cells in the HCG are more evident. Nuclear-to-cytoplasmic ratios are definitely high, nuclear chromatin is coarse, and nuclear shapes are variable and irregular. An interpretation of HSIL would have been appropriate. Clinical management following ASC-H and HSIL Pap results is the same, however.

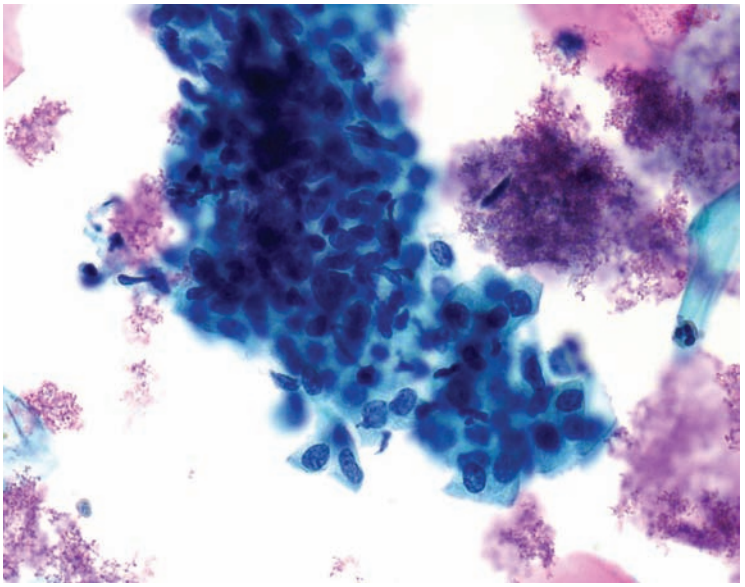


Figure 7.14 — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; Medium Power). Uniformity of the cells in the group may be misleading, convincing the observer that the cells are benign. Careful examination reveals that the N/C ratios are high, and while the chromatin is not extremely dark, it is coarse, and nuclear sizes and shapes vary. This fragment no doubt originated at the transformation zone, which is why it resembles metaplastic endocervical cells. Lysed blood in the background is ominous unless the patient is currently menstruating.

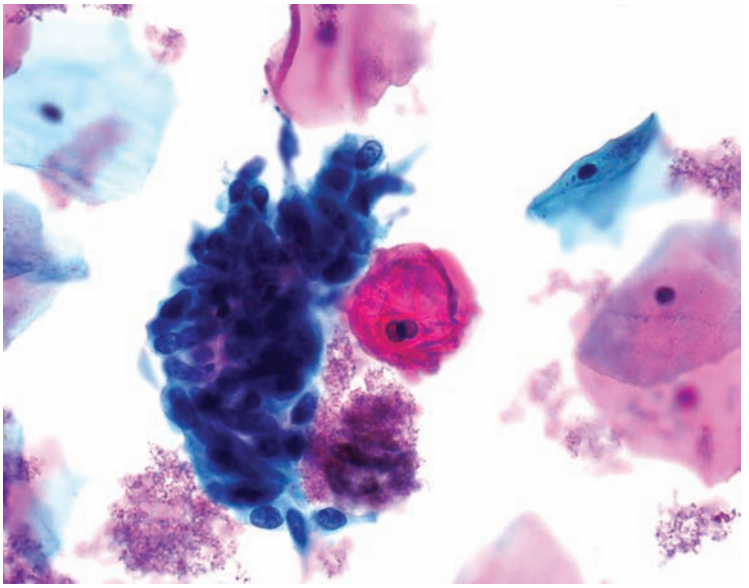


Figure 7.15 — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; High Power). An HCG may have "tails" of cytoplasm on the cells, suggesting its origin in an adenocarcinoma in situ (AIS). However, the architectural disorganization is not consistent with AIS, but more suggestive of an HSIL, which is what the lesion was proved to be on biopsy.

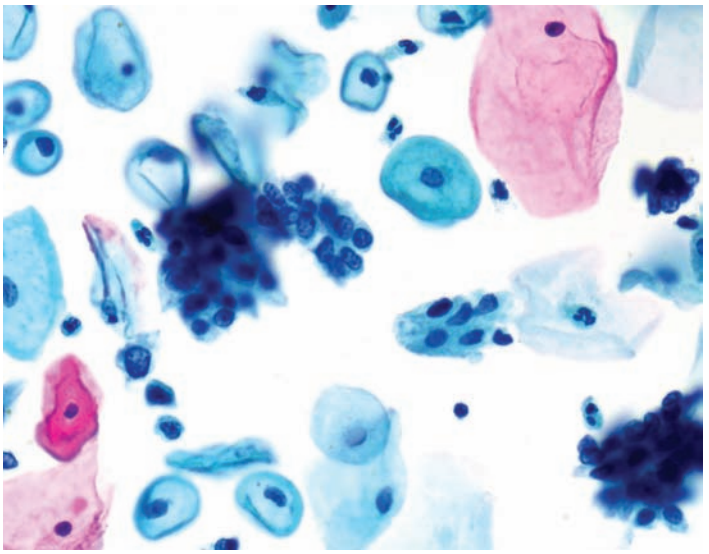


Figure 7.16 — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; Medium Power). Individual cells, HCGs, and tissue fragments all demonstrate the same features: high N/C ratios, nuclear hyperchromasia, and irregular nuclear outlines. An interpretation of HSIL could be appropriate for this slide.

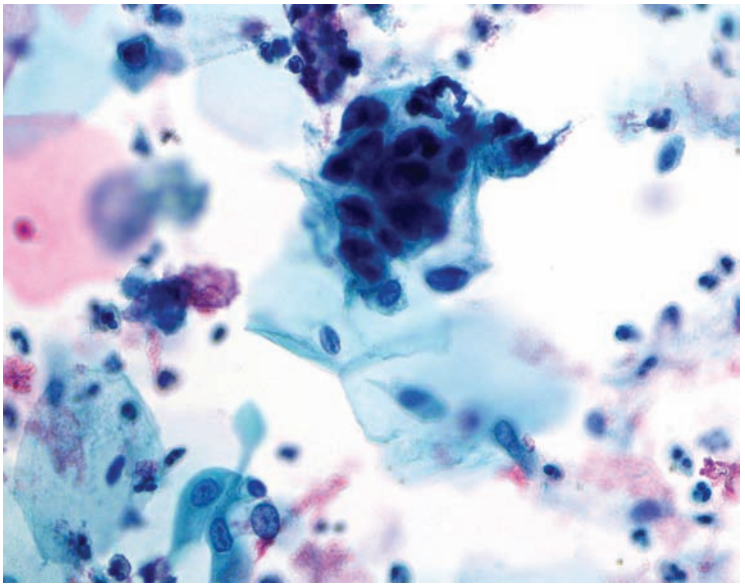


Figure 7.17 — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; High Power). Three-dimensional tissue fragments are problematic, but deserve careful examination as they may be "where the money is!" Loss of polarity, hyperchromasia, and scant cytoplasm are all evident features even if the nuclear detail is obscured. These features are enough to place the sample in the category that warrants immediate follow-up for the patient.

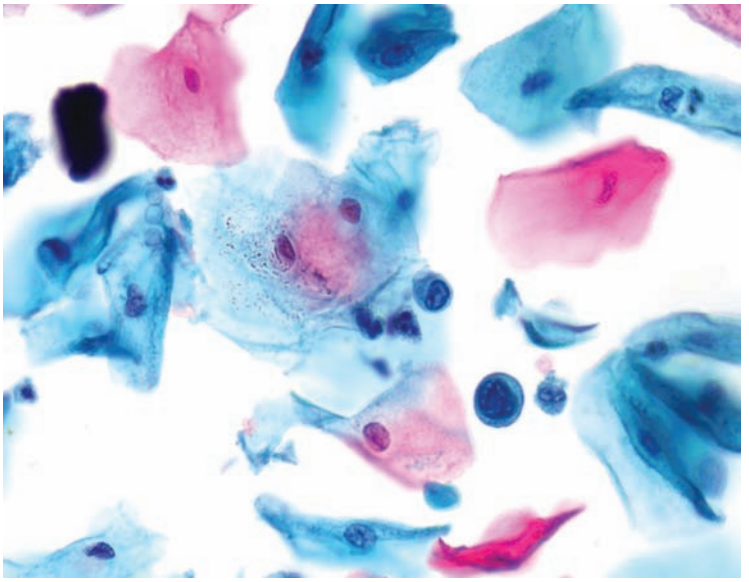


Figure 7.18 — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; High Power). Even by itself, the single enlarged metaplastic cell is strongly suggestive of HSIL. From this field, no signs of invasion are present. In fact, Pap test slides are not reliable indicators of invasive disease, and staging is clearly impossible. However, cytologic changes reflect the grade of neoplasia, and based even on this single cell, the patient can be considered to be at high risk of cervical cancer.

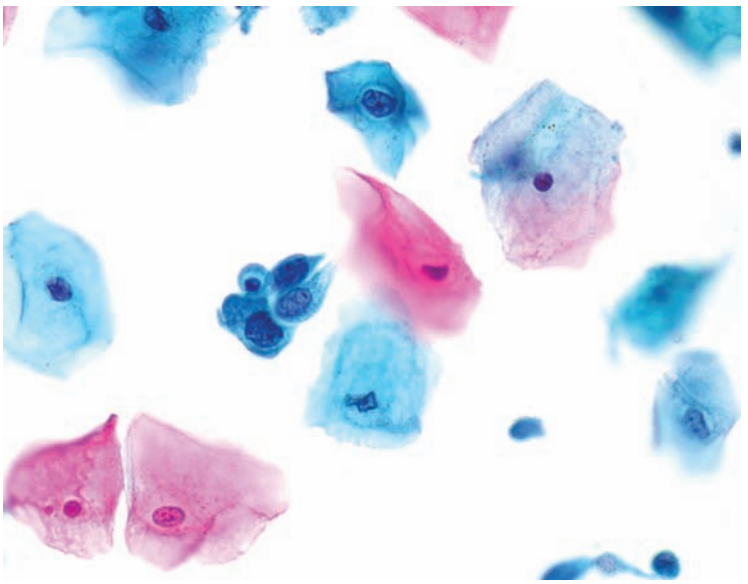


Figure 7.19 — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; Medium Power). A cell group similar to other ASC-H groups fulfills the purpose of the Pap test—getting the patient to the proper management strategy. Hence, whether this slide was interpreted as ASC-H, or HSIL, or matched the subsequent diagnosis of cancer, the patient received the appropriate follow-up and her disease was detected.

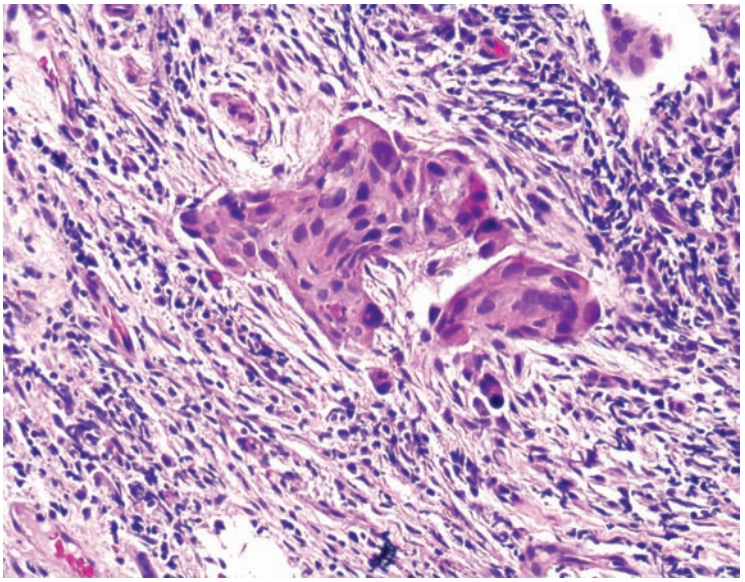


Figure 7.20 — Squamous Cell Carcinoma (Hematoxylin and Eosin [H&E] Stain; High Power) (Follow-up for Figures 7.18 and 7.19). Invasive cervical squamous cell carcinoma, histologic section (biopsy): The invasive nests are irregularly shaped and vary in size. The nuclei are enlarged with coarse chromatin. Abundant eosinophilic cytoplasm is present. The stroma is altered and shows desmoplasia and chronic inflammation.

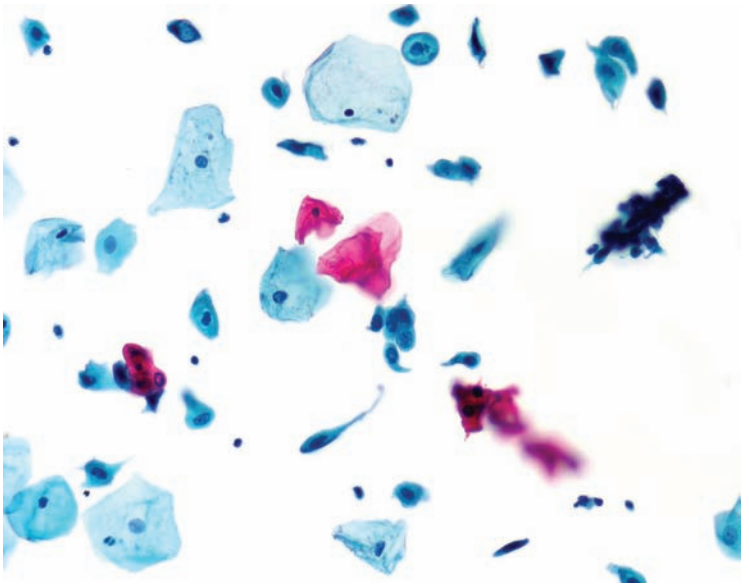


Figure 7.21 — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; Medium Power). One of the characteristic features of invasive squamous cell carcinoma (SqCCa) is variation: in cell size, shape, N/C ratios, and especially keratinization of cytoplasm. In contrast, HSIL is most often monotonous in its features. The "job" of the cytologist is not to match the grade of disease, but indicate the need of the patient to undergo a diagnostic procedure. Furthermore, the clean background of the slide does not suggest invasion, another impossible task for the cytologist. The presence or absence of invasion and depth can only be determined by adequate biopsy.

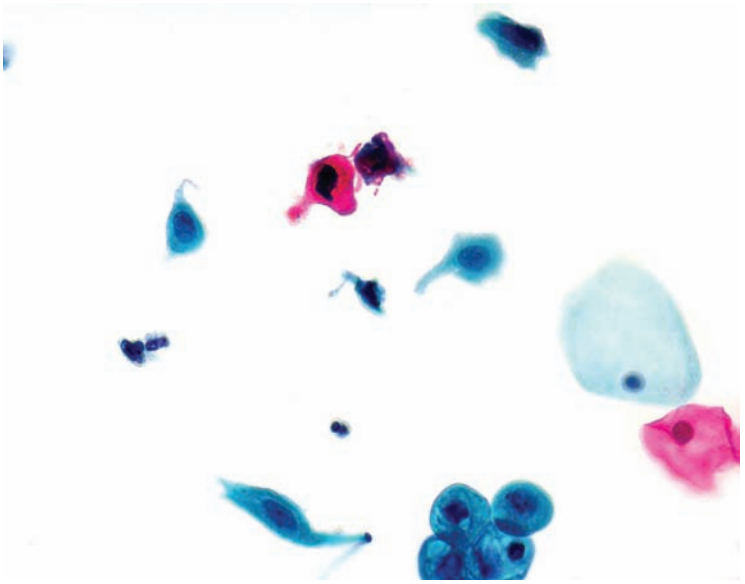


Figure 7.22 — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; High Power). Highly abnormal cells vary in size, keratinization, nuclear shape, and chromasia. This is a departure from the typical HSIL cells that are virtually identical to each other. Especially when keratinized cells have cytoplasmic tails, an invasive lesion may be suspected, even if all other criteria are not present. However, a prudent interpretation is either ASC-H or HSIL. Patient management will be the same.

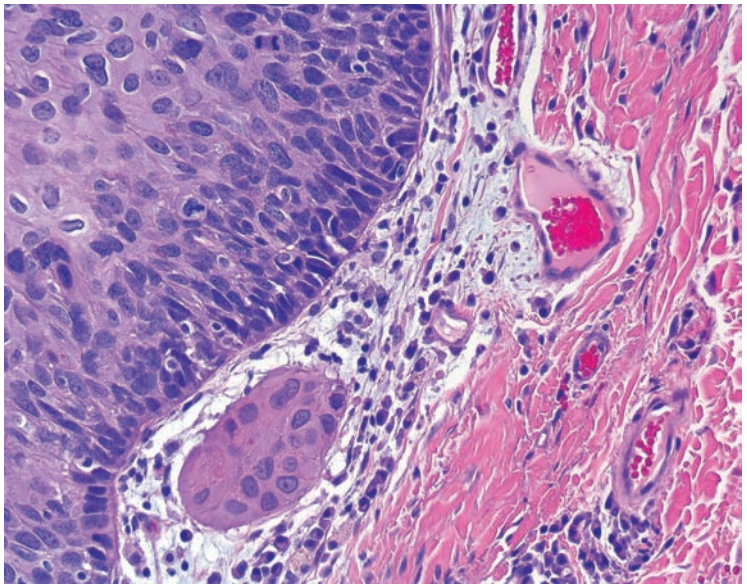


Figure 7.23 — Superficially Invasive Squamous Cell Carcinoma (Microinvasive Squamous Cell Carcinoma) (H&E Stain; High Power) (Follow-up for Figures 7.21 and 7.22). Superficially invasive cervical squamous cell carcinoma, histologic section (biopsy): High-grade squamous intraepithelial lesion (HSIL) is present at the left side of the photograph. Note the circumscribed epithelial–stromal border and polarized arrangement of epithelial cells at the base of the epithelium. Just below the center of the photograph, a nest of invasive carcinoma is present within inflamed stroma. The nest of carcinoma exhibits nuclear features similar to that of the HSIL; however, the former displays "reverse maturation," in which the N/C ratio with abundant eosinophilic cytoplasm is lower in contrast to that of the base of the HSIL.

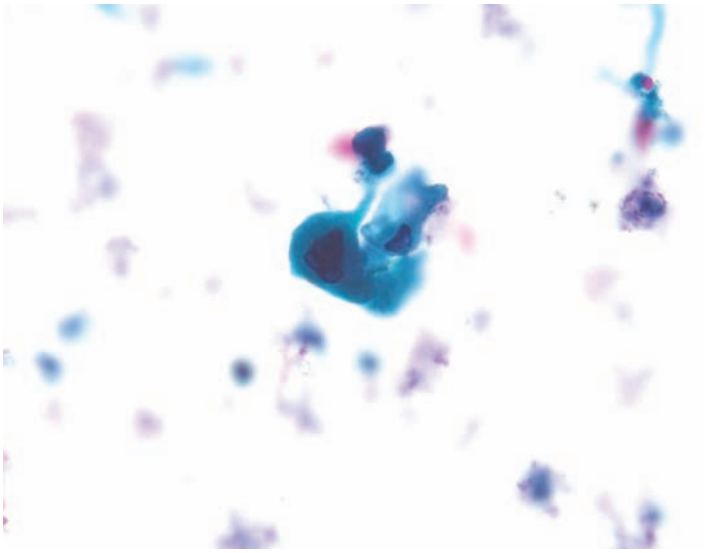


Figure 7.24a — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; High Power). These few cells have dense cytoplasm and "coal black" nuclei. The nuclei are enlarged and the N/C ratios are increased. There is an irregular cytoplasmic projection arising from the larger cell. Although these few cells alone may result in an ASC-H diagnosis, this patient had squamous cell carcinoma on follow-up. The isolated tumor cells ("litigation cells") often seen in ASC-H usually lack the pyknotic nuclei and have less cytoplasm; on follow-up, these findings are most often associated with HSIL. The cells in the current field, arising in squamous cell carcinoma, paradoxically have an increased amount of cytoplasm.

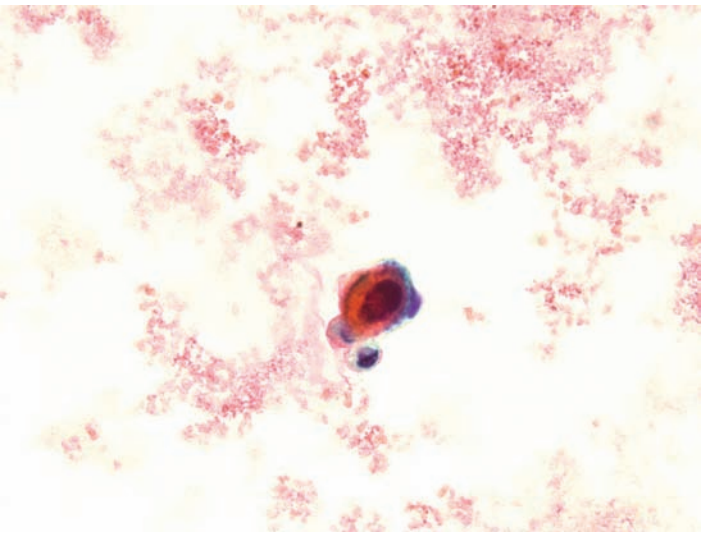


Figure 7.24b — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; High Power). The cells seen here are poorly preserved, but contain troubling features. The N/C ratios are increased, there is a pattern of atypical keratinization (compare the cytoplasmic colors), and the nuclei are dark and irregular. This patient had squamous cell carcinoma on follow-up. Similar to the last figure, the features seen here are not typical of the usual "litigation cells" seen in ASC-H because they arise from a squamous cell carcinoma. However, if these are the only atypical cells seen, the diagnosis is best left as ASC-H.

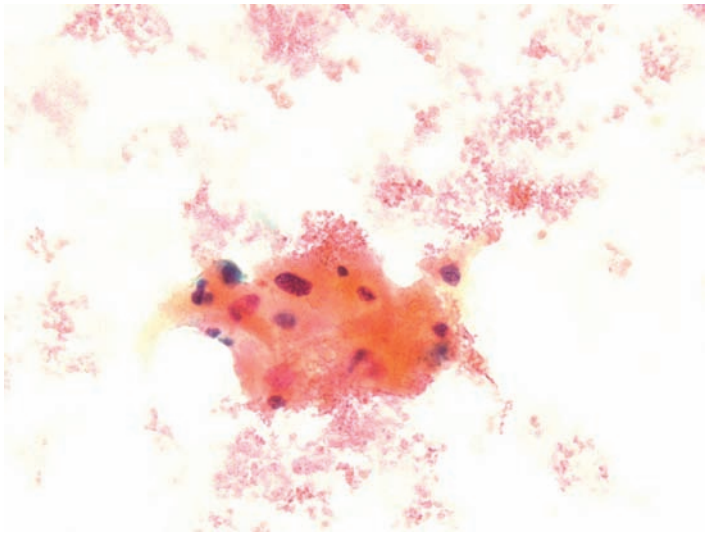


Figure 7.24c — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; High Power). This fragment qualifies as atypical parakeratosis based on nuclear pleomorphism and the irregular nuclear borders. However, some features are suggestive of squamous cell carcinoma, which was found on this patient's follow-up biopsy. The cytoplasm is very dense and has irregular extensions. The nuclei have become entombed in this dense keratin and have begun to lose their dark staining quality. Malignant keratin, such as this fragment, may be difficult to distinguish from degenerative changes. In most instances, additional findings will be seen on other fields to allow for a diagnosis of squamous cell carcinoma.

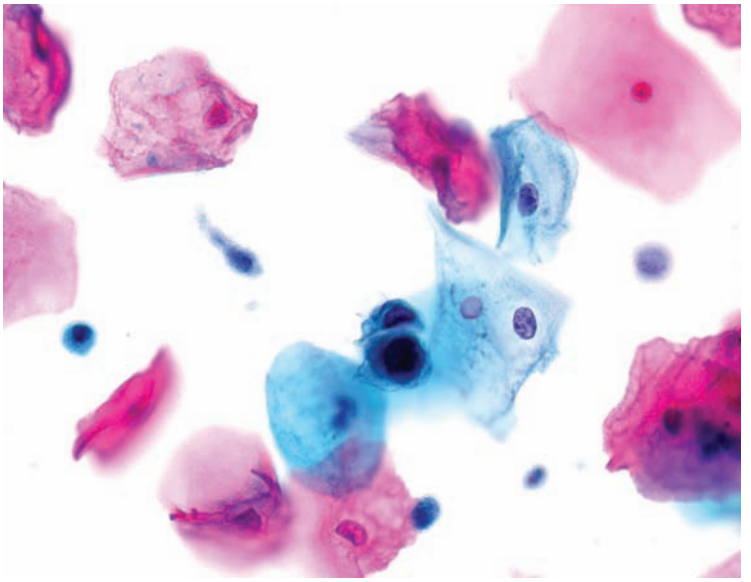


Figure 7.24d — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; High Power). These two cells appear very different from the benign squamous cells in the background. The cytoplasm lacks the typical dense quality of squamous cells, but, in fact, this patient was found to have squamous cell carcinoma on subsequent biopsy. The nuclei are very dark and enlarged, and, if found alone, these cells should merit a diagnosis of ASC-H.

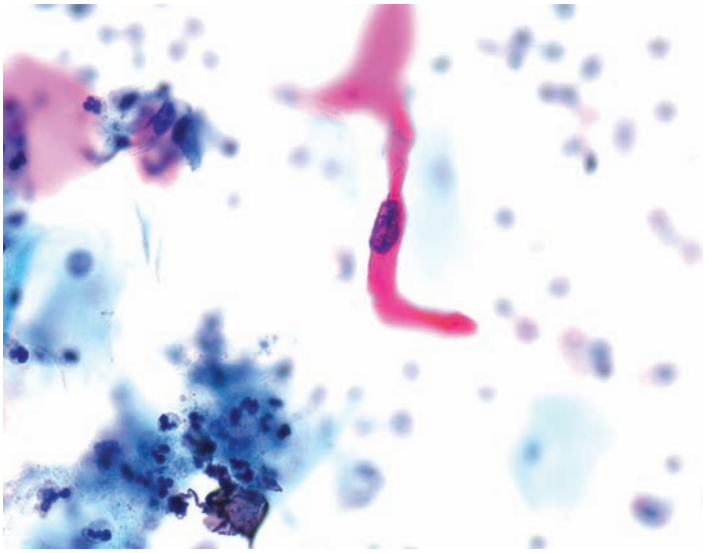


Figure 7.25a — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; High Power). This "snake cell" is typically only found in squamous cell carcinomas, but the presence of a single "snake cell" might best be diagnosed as ASC-H. Note the dense keratin and irregular cytoplasmic projections; the nucleus is hyperchromatic and enlarged (compared to adjacent neutrophils). Typically, these cells are part of a constellation of findings seen in squamous cell carcinoma.

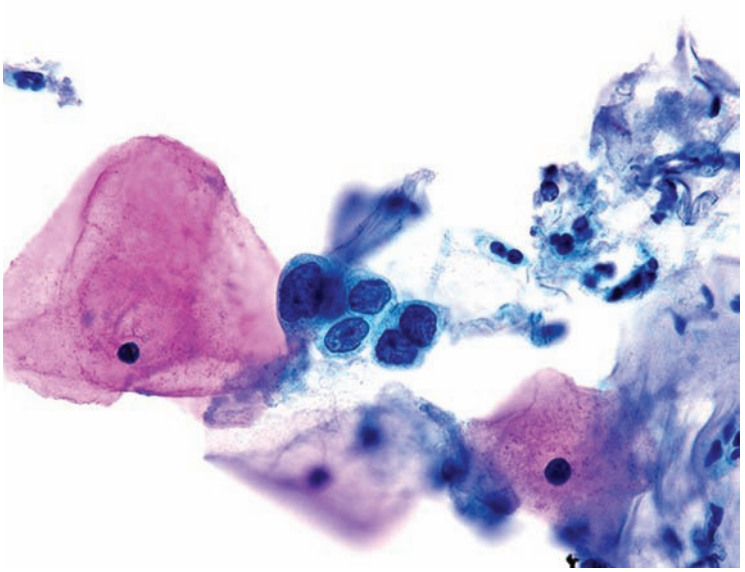


Figure 7.25b — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Liquid Based; High Power). These cells have enlarged nuclei with irregular borders and hyperchromasia, and the N/C ratios are very high. These cells are similar to previous examples of "litigation cells," except that they demonstrate an even greater extent of atypia. This patient had squamous cell carcinoma on subsequent biopsy.

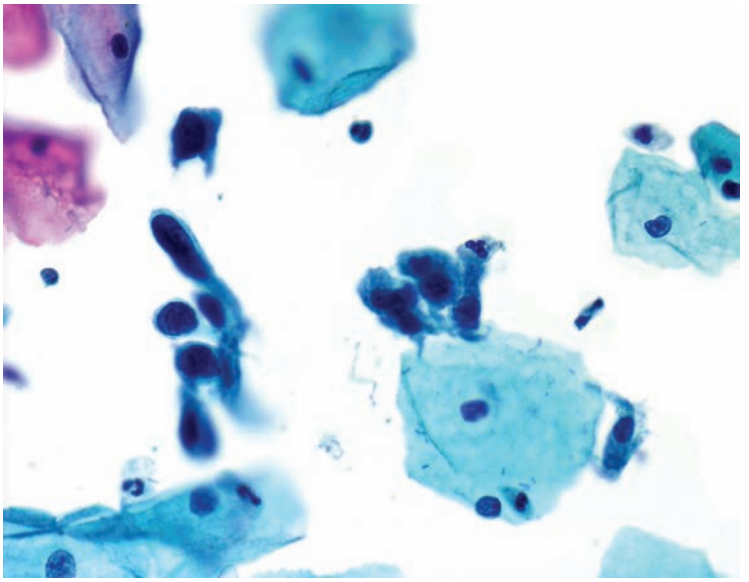


Figure 7.26a — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Conventional; High Power). Similar to the previous figure, these atypical cells are hyperchromatic and have pleomorphic, enlarged nuclei. There is very little cytoplasm. Although one cell has a cytoplasmic extension, the cytoplasm is not as dense as that seen in "snake cells." The follow-up biopsy for this patient demonstrated HSIL.

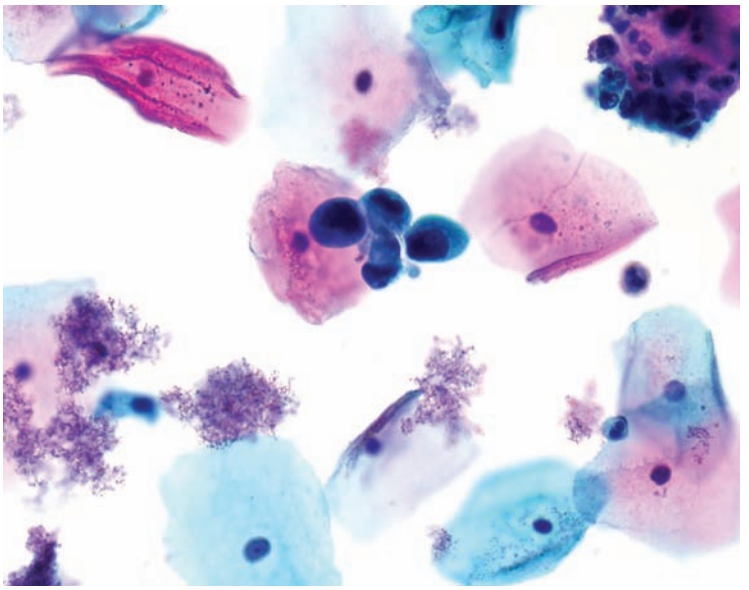


Figure 7.26b — Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H) (Conventional; High Power). These cells have very dark nuclei and slightly more cytoplasm than those seen in the previous figure. Overall, the cells are small, but the nuclei are enlarged and dark (compare the adjacent benign squamous cells). This patient had HSIL proven by a subsequent biopsy.

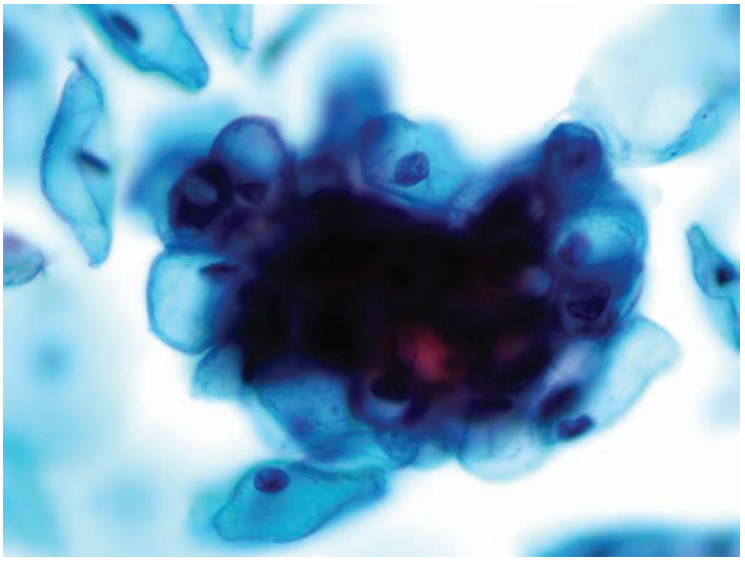


Figure 7.27 — Pseudokoilocytes (Liquid Based; High Power). Occasionally, reactive cells may have enlarged nuclei and perinuclear clearing that mimic the morphology of a koilocyte. Note that, although these cells have slight nuclear irregularities, there is minimal hyperchromasia and abundant cytoplasm. Because of the enlarged nuclei, this group may stand out and be appropriately identified as ASC-US. However, in this case, the associated HPV test was negative, strongly implying that these changes are reactive and not secondary to HPV infection.

8

Squamous Cell Carcinoma

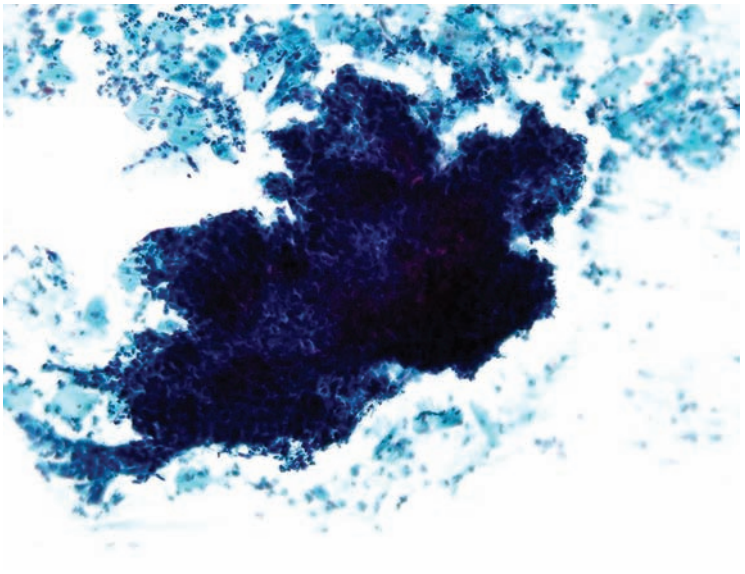


Figure 8.1 — Squamous Cell Carcinoma (Conventional; Low Power). An unusually large fragment of a hyperchromatic crowded group (HCG) is suggestive of malignancy. Further examination using higher magnification is necessary.

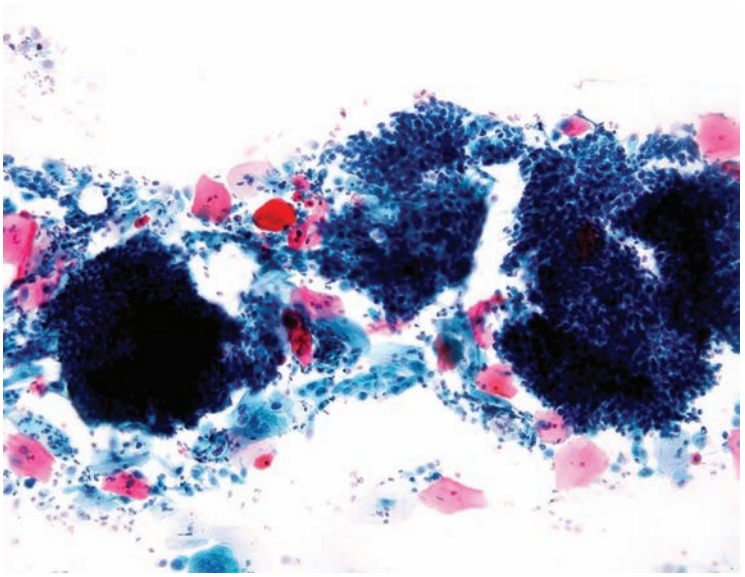


Figure 8.2 — Squamous Cell Carcinoma (Conventional; Low Power). In addition to large dense fragments of tissue, bright orange cells indicate a partially keratinizing lesion. The density of the fragments is attributable to cells with high nuclear-to-cytoplasmic (N/C) ratios and hyperchromatic nuclei.

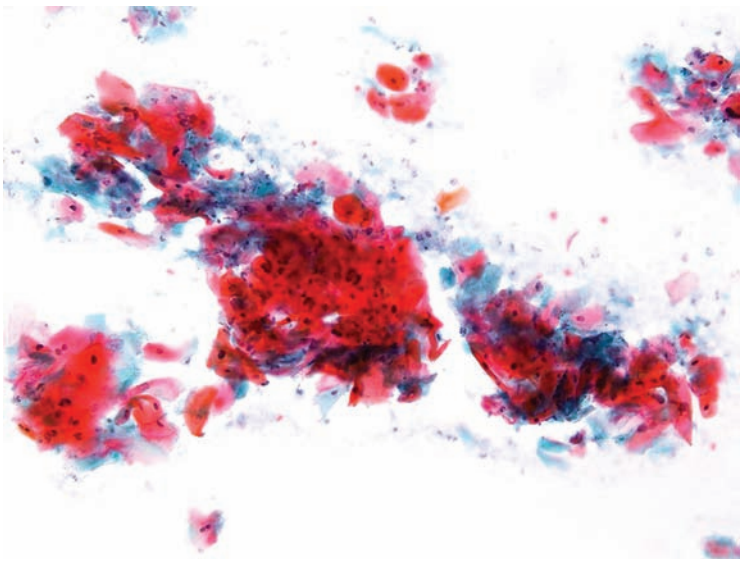


Figure 8.3 — Squamous Cell Carcinoma (Conventional; Low Power). The Pap stain is designed to exhibit keratinized eosinophilic cytoplasm. The nuclei appear small in this photograph, not indicative of a malignant lesion. Further examination of the slide is warranted to rule out carcinoma.

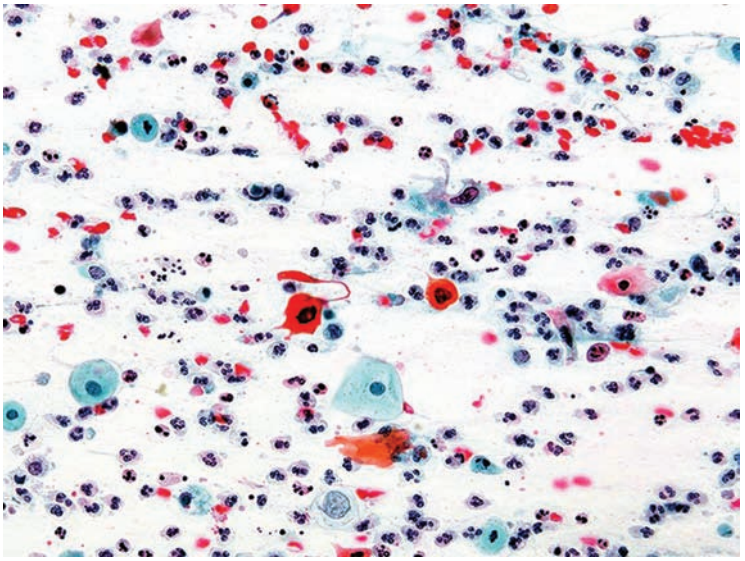


Figure 8.4 — Squamous Cell Carcinoma (Conventional; Medium Power). This is a classic picture of a conventional smear with malignant squamous cells. Some are keratinized with aberrant cytoplasmic tails, some resemble cells from a high-grade squamous intraepithelial lesion (HSIL), and some are apoptotic bodies, a reflection of the usual necrosis that accompanies squamous cell carcinoma. The polymorphic collection of cells is classic for squamous cell carcinoma. Even a high grade, poorly differentiated adenocarcinoma will not display so much variation from cell to cell, and of course, no keratinization. Tumor diathesis is prominent in the smear background with serum and acute inflammatory cells.

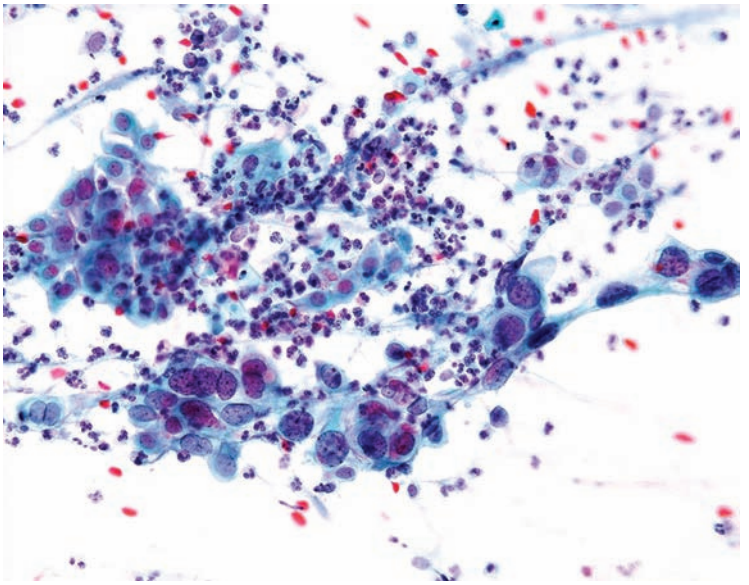


Figure 8.5 — Squamous Cell Carcinoma (Conventional; Medium Power). In contrast to Figure 8.4, these cells display no keratinization and more monotony of cell features. Distinction from an endocervical adenocarcinoma can be difficult, especially because the malignant cells are accompanied by benign cells from the endocervix. One noteworthy feature is the absence of prominent nucleoli, which would undoubtedly be present if this were an adenocarcinoma.

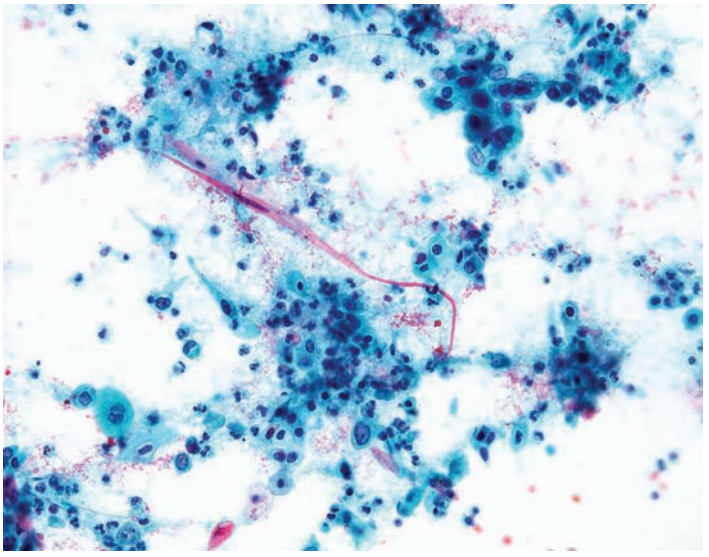


Figure 8.6 — Squamous Cell Carcinoma (Conventional; Medium Power). Elongated fiber cells were the hallmark of invasive squamous carcinoma when this was a common lesion. Hyperchromatic nuclei and cytoplasm are very elongated. Usually seen in clumps, their source is unclear, whether from the surface of the lesion or the depths at the breach of the basement membrane. The term comes from the cell's resemblance to fibroblasts.

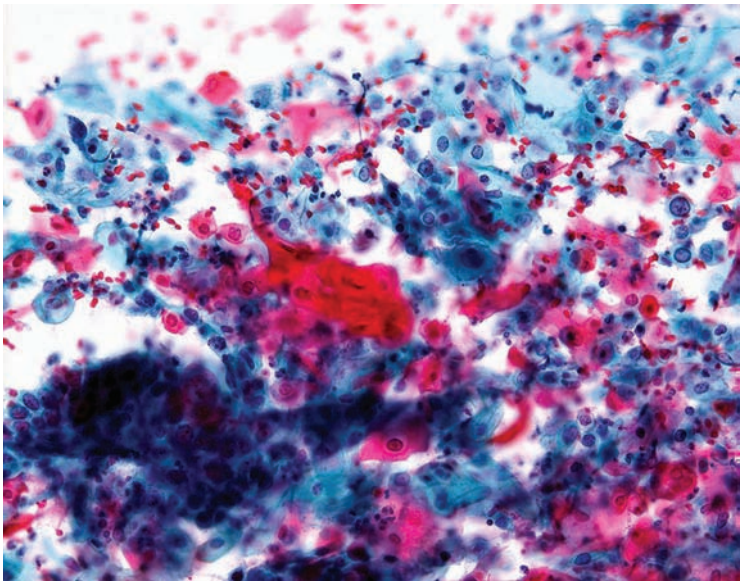


Figure 8.7 — Squamous Cell Carcinoma (Liquid Based; Medium Power). The enormous cellularity of this sample is testimony to the friability of the lesion. The keratinized fragment and individual cells are no doubt from the surface, with the less well differentiated cells closer to the basement membrane.

Figure 8.8 — Squamous Cell Carcinoma (Liquid Based; Medium Power). The cell in the center is not keratinized, but the sharp cytoplasmic outline, the opacity of the cytoplasm, the high N/C ratio, and the overall large size of the cell place it in a malignant squamous carcinoma category. The inexperienced observer may be tempted to classify it as a cell from a high-grade squamous intraepithelial lesion (HSIL), but it is way too large. Careful examination of the entire slide will no doubt discover other malignant cells.

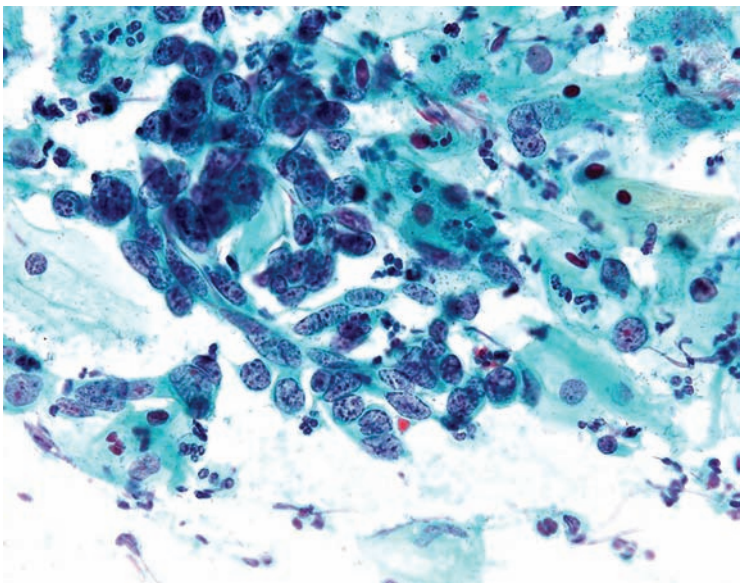


Figure 8.9 — Squamous Cell Carcinoma (Liquid Based; Medium Power). Non-keratinizing squamous carcinoma is usually considered poorly differentiated, and may be difficult to distinguish from poorly differentiated adenocarcinoma of the cervix. Some morphologic features can be of help: discrete cytoplasmic borders, coarse chromatin, inconspicuous nucleoli, and lack of attempted gland formation speak in favor of squamous origin.

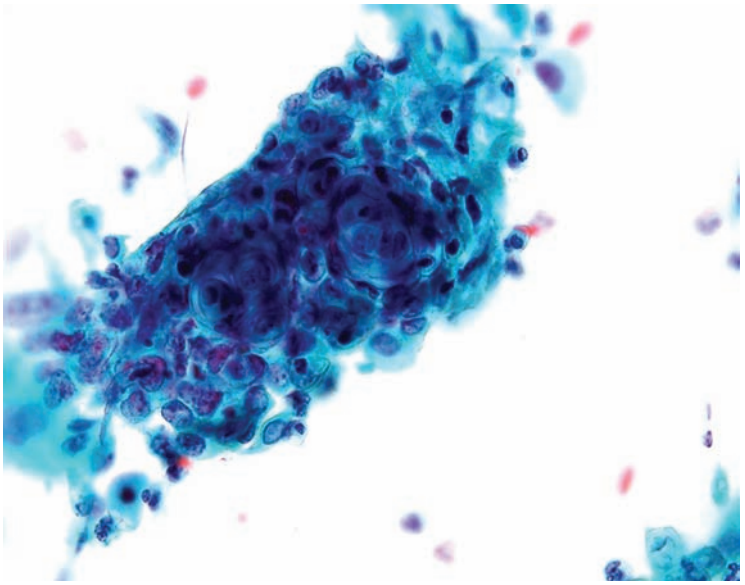


Figure 8.10 — Squamous Cell Carcinoma (Liquid Based; High Power). Even though this is not a keratinized fragment, the characteristics of squamous epithelium are evident. The pearl formation in the center of the group is represented by the concentric layering of squamous cells, more obvious when examined microscopically. Other cells have distinct cell borders and opaque cytoplasm. Cell within cell formation (cannibalism) is also present. All of these are the same characteristics that are used in histopathology, and are applicable to cytopathology when tissue fragments are being considered.

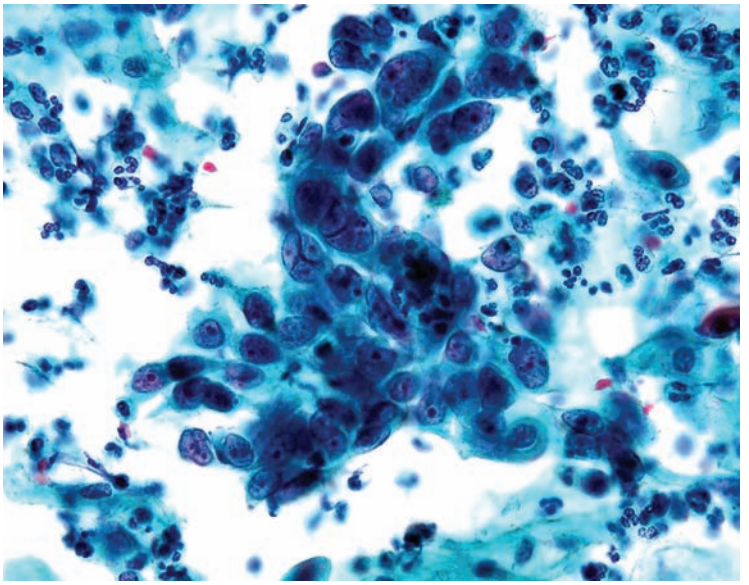


Figure 8.11 — Squamous Cell Carcinoma (Liquid Based; Medium Power). Cells within this tissue fragment contain prominent nucleoli and have finely granular chromatin, two features usually attributable to adenocarcinoma. In favor of squamous differentiation are the distinct cell boundaries and opaque cytoplasm. When deciding upon cell of origin for a malignant tumor, cytoplasmic features trump nuclear features.

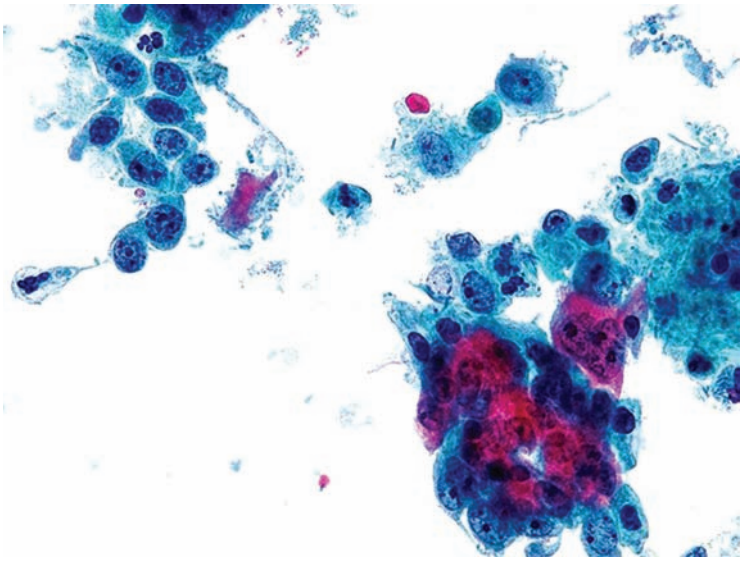


Figure 8.12 — Squamous Cell Carcinoma (Liquid Based; Medium Power). Malignant cells from a poorly differentiated carcinoma may have characteristics of both squamous and glandular origin as in the cells in this photo. As the Pap test is a screening test, it is inconsequential to definitely identify the tissue of origin. The next step is a diagnostic excisional procedure regardless of the Pap interpretation.

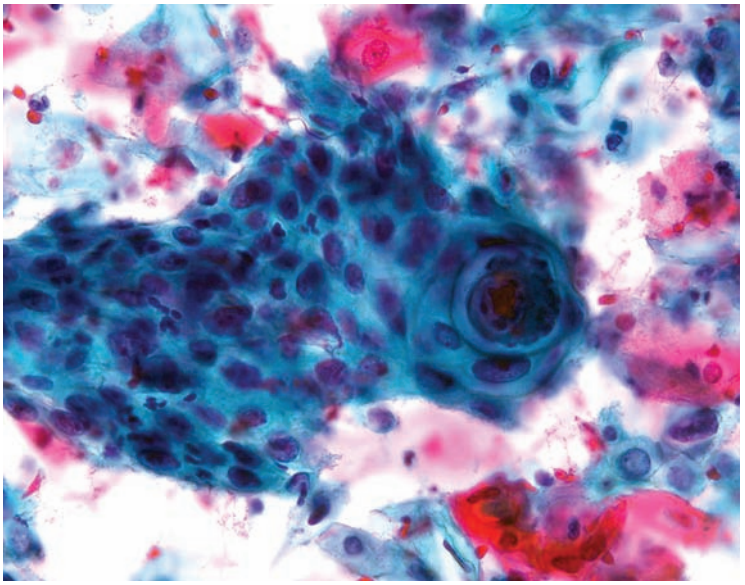


Figure 8.13 — Squamous Cell Carcinoma (Conventional; Medium Power). Keratinized and non-keratinized cells are features of a well-differentiated squamous carcinoma. Cytoplasm is opaque and nucleoli are indistinct. Pearl formation is evident in the larger fragment.

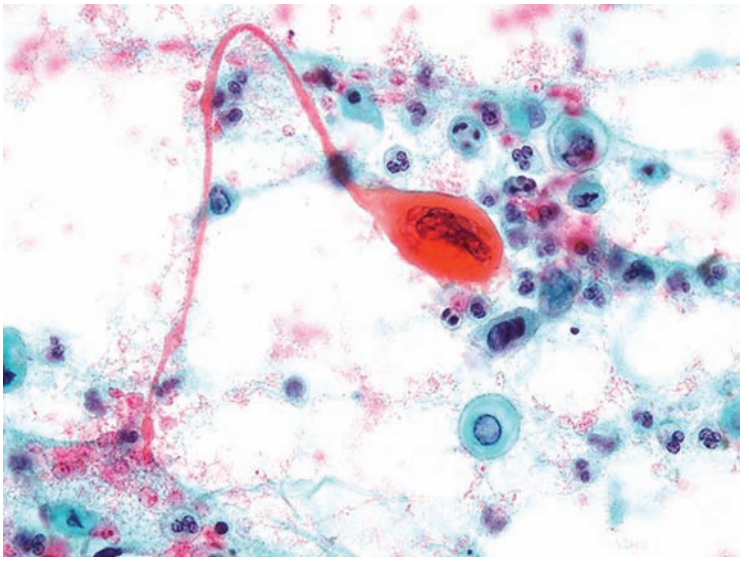


Figure 8.14 — Squamous Cell Carcinoma (Conventional; High Power). The classic tadpole cell is the sine qua non of squamous carcinoma. Attenuated keratinized cytoplasm and an enlarged hyperchromatic nucleus are the defining cellular features.

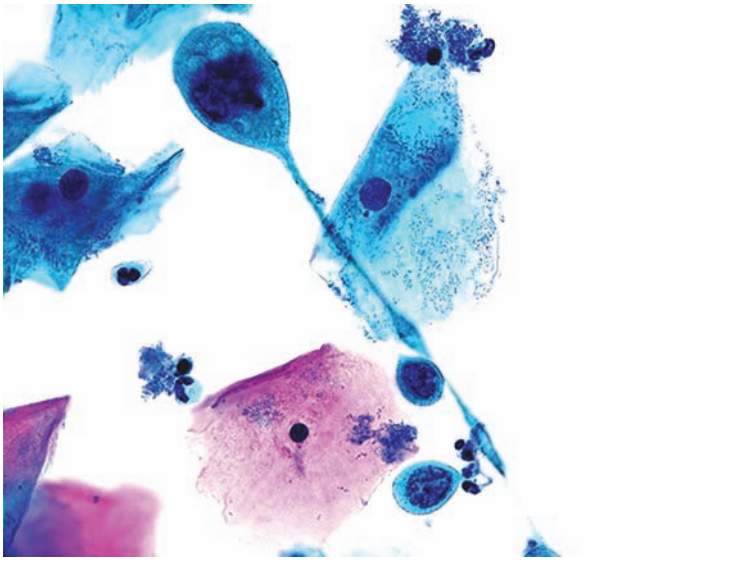


Figure 8.15 — Squamous Cell Carcinoma (Liquid Based; Medium Power). Even if the cells are not keratinized, aberrant cytoplasmic extensions and hyperchromatic nuclei indicate an invasive squamous lesion. The accompanying cells are consistent with a high-grade squamous intraepithelial lesion (HSIL).

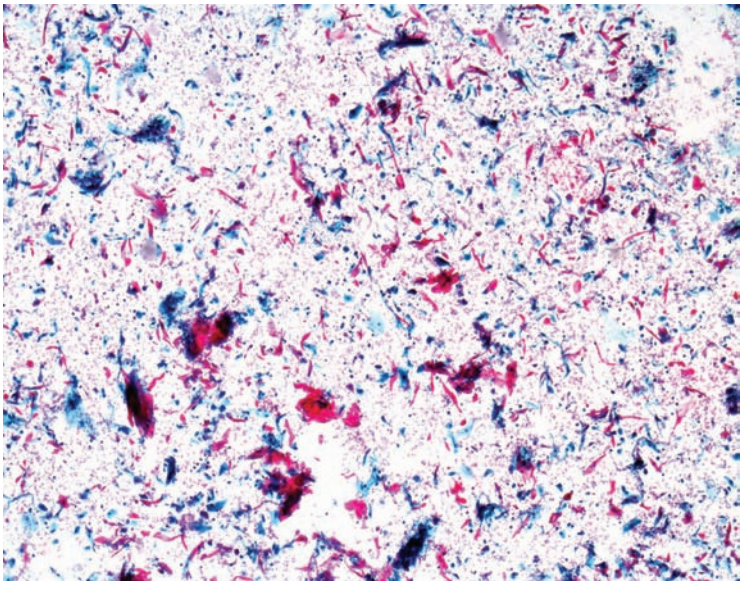


Figure 8.16 — Squamous Cell Carcinoma (Liquid Based; Very Low Power). In contrast to a normal cellular liquid-based Pap, the slender shape of many of the keratinized cells is apparent even on initial inspection. This is a characteristic of squamous cell carcinoma, even if classically malignant cells are absent.

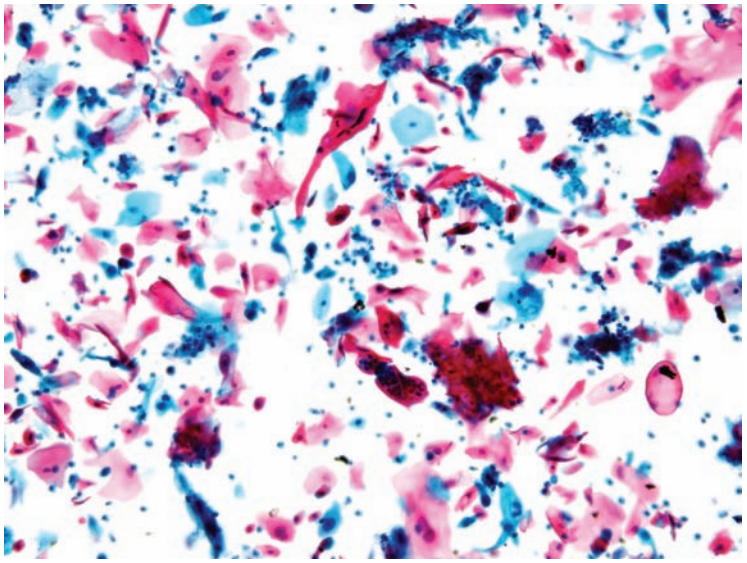


Figure 8.17 — Squamous Cell Carcinoma (Liquid Based; Low Power). Higher magnification of Figure 8.16 reveals anucleate squames with aberrant shapes as well as nucleated abnormal cells. No lesion other than keratinizing squamous cell carcinoma will present with this pattern.

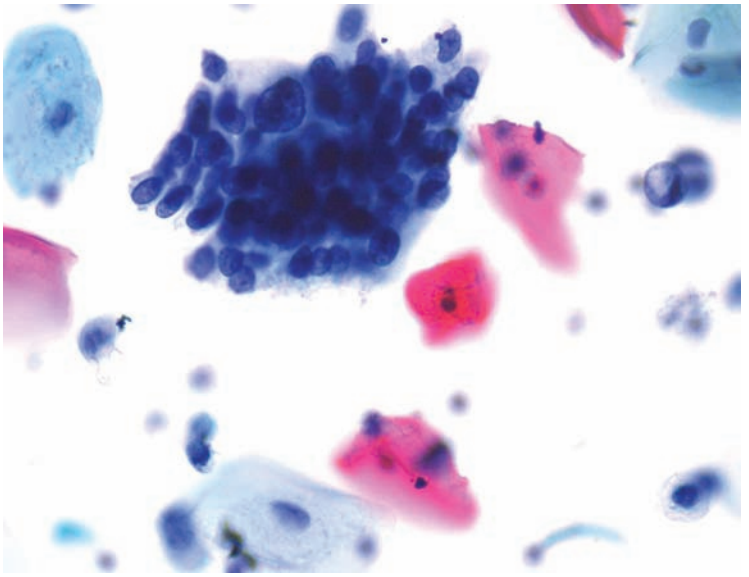


Figure 8.18a — Squamous Cell Carcinoma (Liquid Based; Medium Power). Even if the cells are not keratinized, aberrant cytoplasmic extensions, nuclear pleomorphism, and hyperchromatic nuclei indicate an invasive squamous lesion. The accompanying cells are consistent with an HSIL.

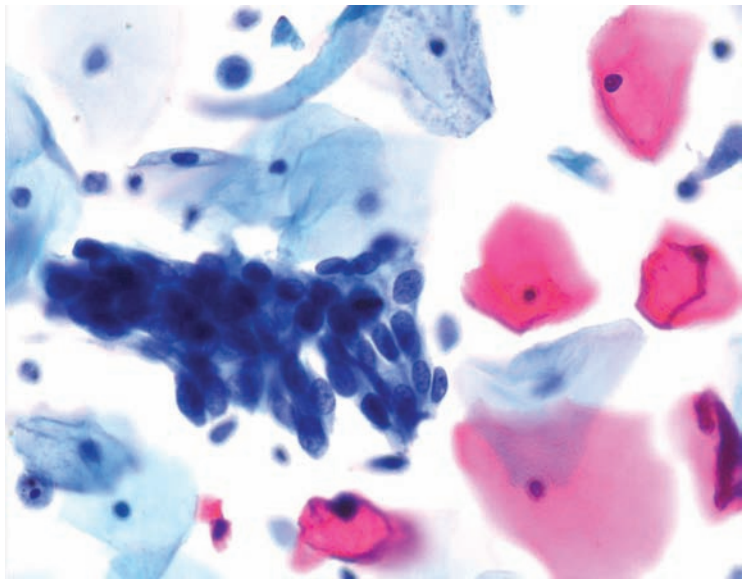


Figure 8.18b — Squamous Cell Carcinoma (Liquid Based; Medium Power). These cells are from the same specimen as Figure 8.18a, but lack the pleomorphism and appear bland, although hyperchromasia and a syncytial formation are present. These fragments are consistent with an HSIL, even though the follow-up is squamous cell carcinoma.

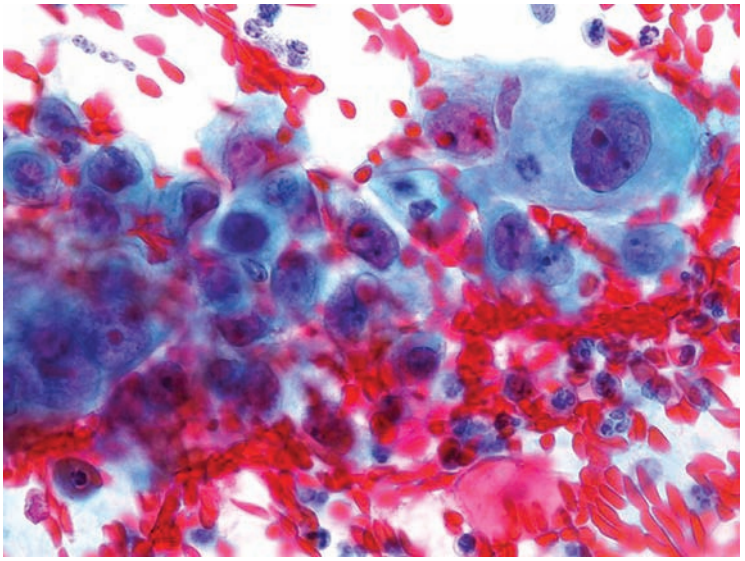


Figure 8.19 — Squamous Cell Carcinoma (Conventional; High Power). Some squamous cell carcinomas are non-keratinizing with opaque cytoplasm and distinct cell borders. Although the nuclei may have features suggestive of adenocarcinoma, for example, prominent red nucleoli, the cytoplasmic quality places the lesion in the squamous category.

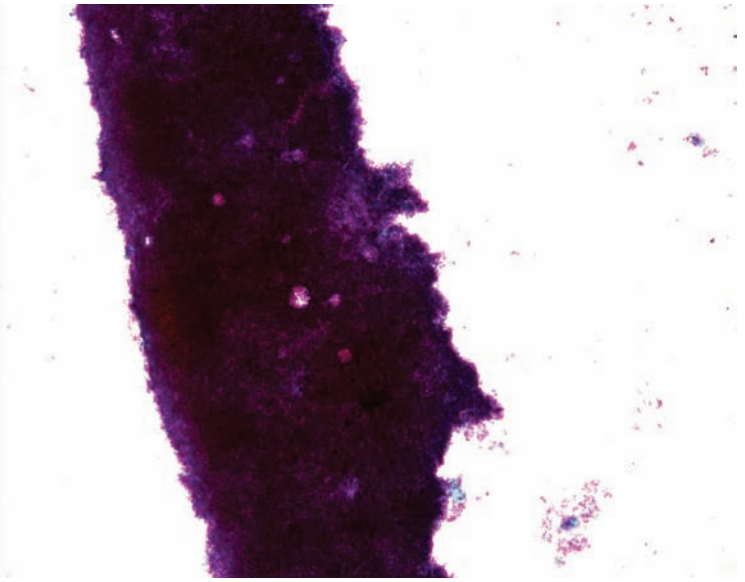


Figure 8.20a — Squamous Cell Carcinoma (Liquid Based; Very Low Power). The edge of a bloody ThinPrep™ will create a halo of red cell membranes. The center of the filter area will contain only rare cells, necrotic debris, or tissue fragments. Preprocessing with glacial acetic acid will rid the sample of the blood and preserve the diagnostic material for slide transfer.

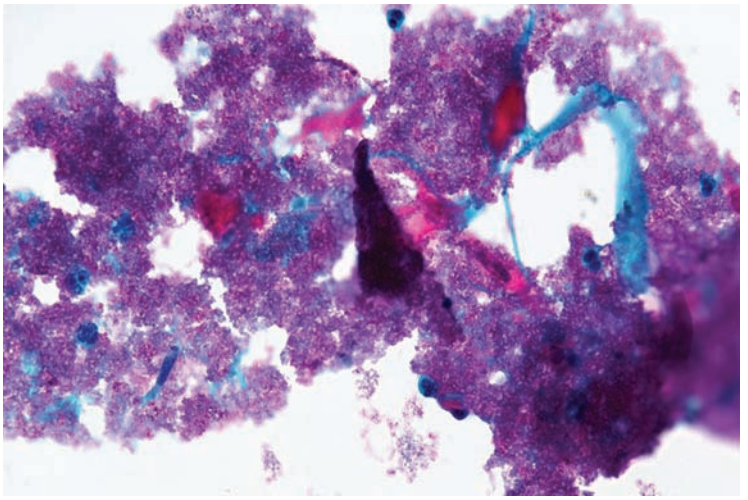


Figure 8.20b — Squamous Cell Carcinoma (Liquid Based; Intermediate Power). Careful examination of the specimen shown at low power in the previous figure may reveal the presence of highly atypical squamous cells embedded in the granular debris. Interpretation may be limited by the debris, as well. In this field, there are multiple fragments of irregularly shaped keratin, which alone should serve as a warning that squamous cell carcinoma may be present. Two fragments possess dark and irregularly shaped nuclei, confirming that the atypical keratin fragments are arising from a malignant process.

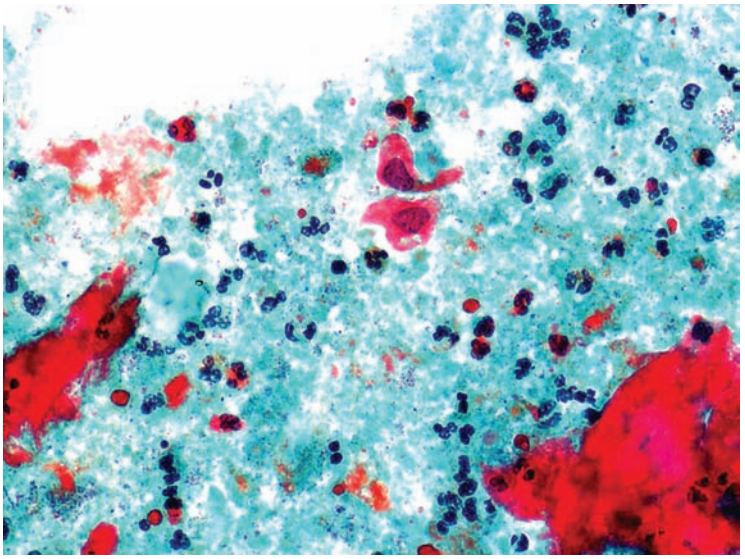


Figure 8.21 — Squamous Cell Carcinoma (Liquid Based; Medium Power). Bloody ThinPreps must be preprocessed with glacial acetic acid according to the manufacturer's instructions, else it will result in a very hypocellular sample. Even so, careful search will usually reveal highly abnormal tumor cells, in this case, from a squamous cell carcinoma. In addition to single cells, large fragments of anucleate keratin represent the surface of the malignant lesion.

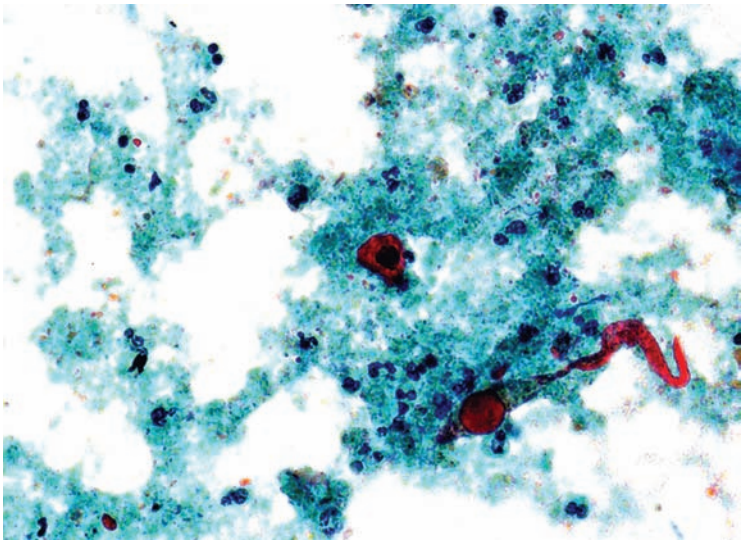


Figure 8.22 — Squamous Cell Carcinoma (Liquid Based; Medium Power). Another bloody ThinPrep with only occasional tumor cells in a background of fibrinated blood and necrotic debris. A second slide prepared after reprocessing the vial with glacial acetic acid would lyse the blood, allowing the heavier cellular material to be successfully captured on the filter membrane, ready for transfer to the slide.

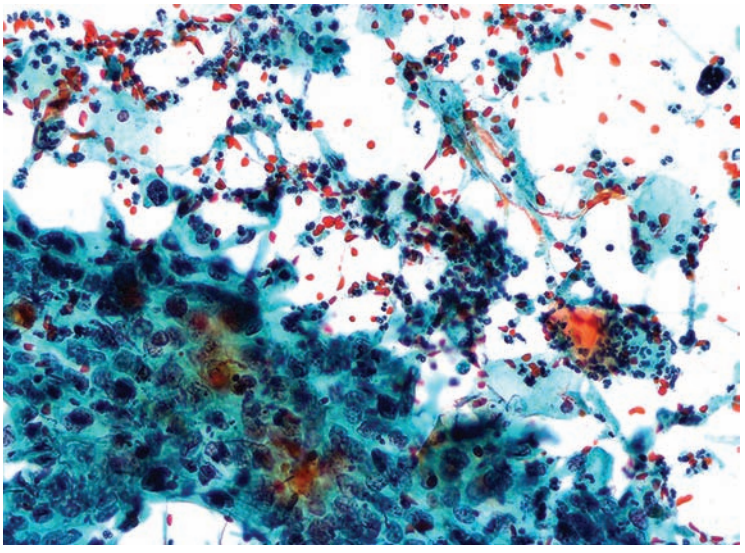


Figure 8.23 — Squamous Cell Carcinoma (Conventional; Medium Power). A non-keratinizing squamous cell carcinoma may be difficult to categorize. Careful search of the sample for diagnostic squamous or glandular features will usually place the sample in the correct category. Regardless, biopsy is needed and will usually settle the question.

Figure 8.24 — Squamous Cell Carcinoma (Liquid Based; High Power). Although benign processes can produce keratinaceous fragments and debris, keratinizing squamous cell carcinoma often produces irregularly shaped, dense fragments. These fragments on their own are not diagnostic of dysplasia or malignancy but should raise awareness of these possibilities.

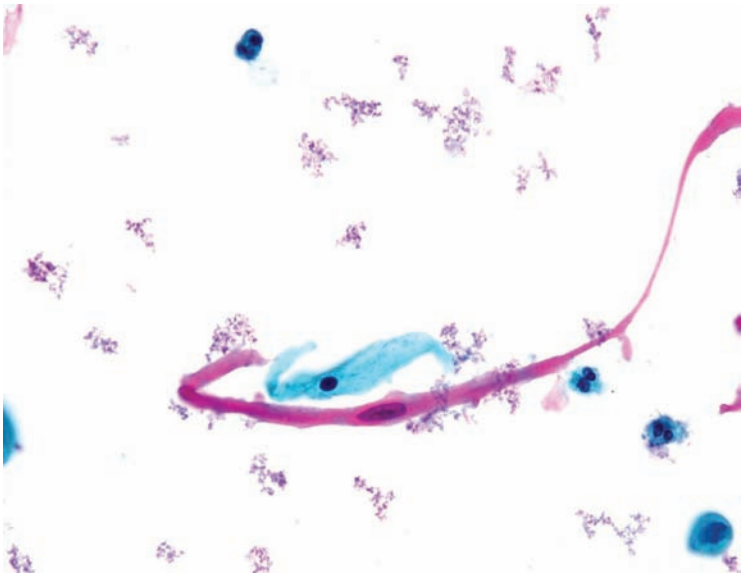


Figure 8.25a — Squamous Cell Carcinoma (Liquid Based; High Power). One feature seen almost exclusively in squamous cell carcinomas is the presence of extremely long, thin cells with atypical nuclear features, sometimes known as "snake cells." Although not diagnostic of squamous cell carcinoma in themselves, they are usually accompanied by other findings suggestive of malignancy.

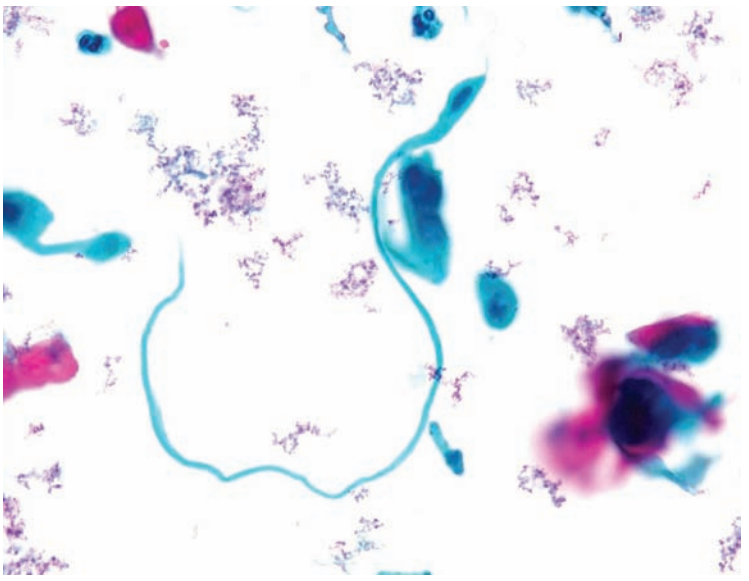


Figure 8.25b — Squamous Cell Carcinoma (Liquid Based; Intermediate Power). This field contains both an irregular "snake cell" as seen in the previous figure, as well as several dense irregular fragments of keratin throughout the field, similar to that seen in Figure 8.24. The nuclei in these fragments are barely perceptible, as they have degenerated within their tombs of keratin.

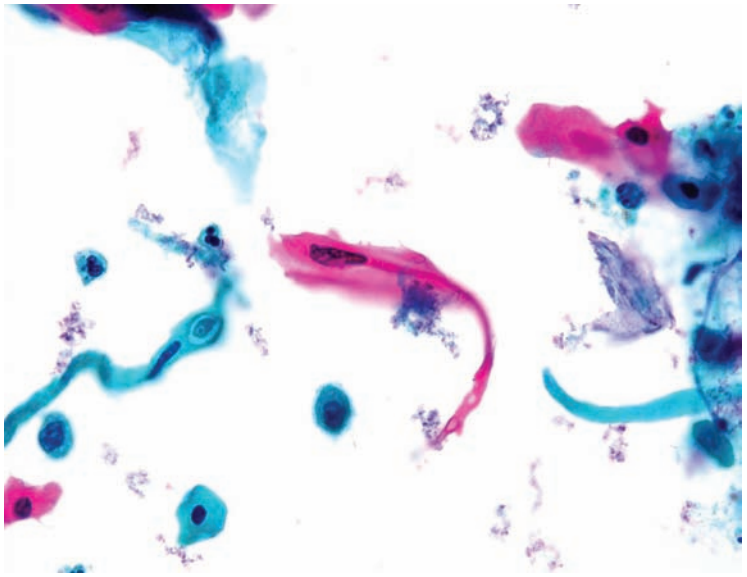


Figure 8.25c — Squamous Cell Carcinoma (Liquid Based; Intermediate Power). This field shows the many faces of squamous cell carcinoma and is a stark contrast from the findings in HSIL. The "snake cells" are fatter than those in the previous two figures. Scattered single cells have smaller N/C ratios than the single cells seen in HSIL or atypical squamous cells, cannot exclude HSIL (ASC-H), but the nuclei are coal black and the cells have extremely dense cytoplasm with irregular extensions.

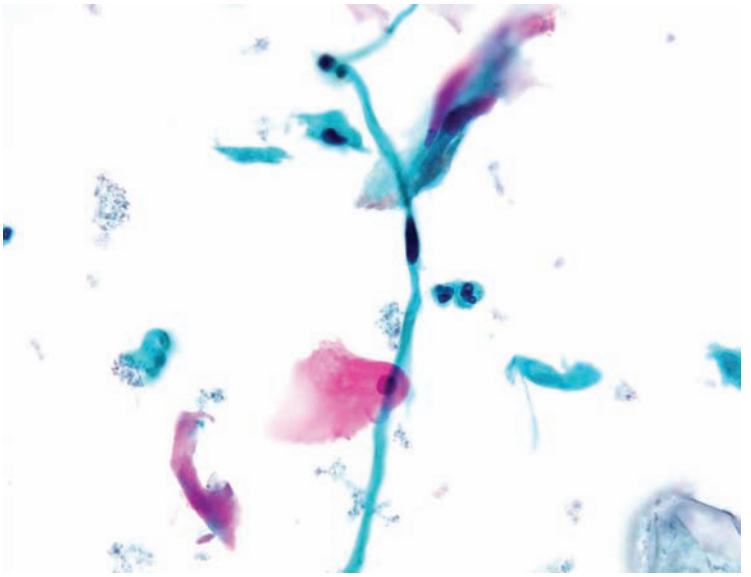


Figure 8.25d — Squamous Cell Carcinoma (Liquid Based; Intermediate Power). If examined carelessly, one may initially mistake the long and slender process of this "snake cell" for a contaminating fiber or other element. The coal-black nuclei reveal this fragment to be a highly atypical squamous cell.

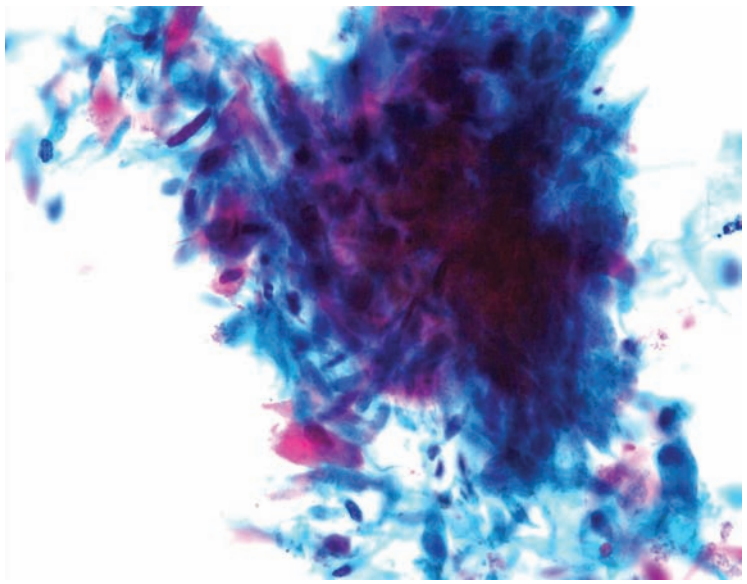


Figure 8.26a — Squamous Cell Carcinoma (Liquid Based; High Power). Malignant cells producing abundant keratin may be difficult to decipher at first glance. The alternating pink and blue colors are typical in keratinizing squamous cell carcinoma, and atypical nuclei are readily identifiable at the fragment edge. These atypical nuclei are dark and pleomorphic, and some contain irregular nuclear borders. The nuclei in the middle of the fragment seem to fade away and are more difficult to interpret, although they still provide a sense of dysplasia.

Figure 8.26b — Squamous Cell Carcinoma (Liquid Based; High Power). The nuclei in this fragment are fading away, but the denseness of the cytoplasm and irregular shape of the fragments are a strong clue that malignancy is present. Similar to the previous figure, alternating colors of pink and blue are suggestive of malignancy. Although other fields may contain clearly malignant cells, lesions that produce abundant keratin may produce smears that contain predominantly anucleate cells with highly atypical keratin.

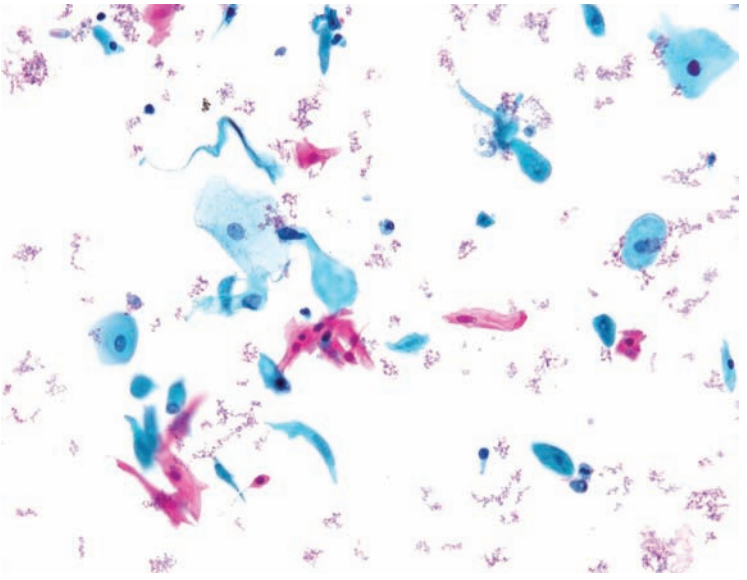


Figure 8.27a — Squamous Cell Carcinoma (Liquid Based; Low Power). At low power, the cells in this field appear deceptively bland although many of them are malignant. A "snake cell" is identifiable, as are fragments of atypical dense keratin. The center of the field contains cells suggestive of atypical parakeratosis; however, their cytoplasm is dense and forms irregular extensions, a feature of malignancy.

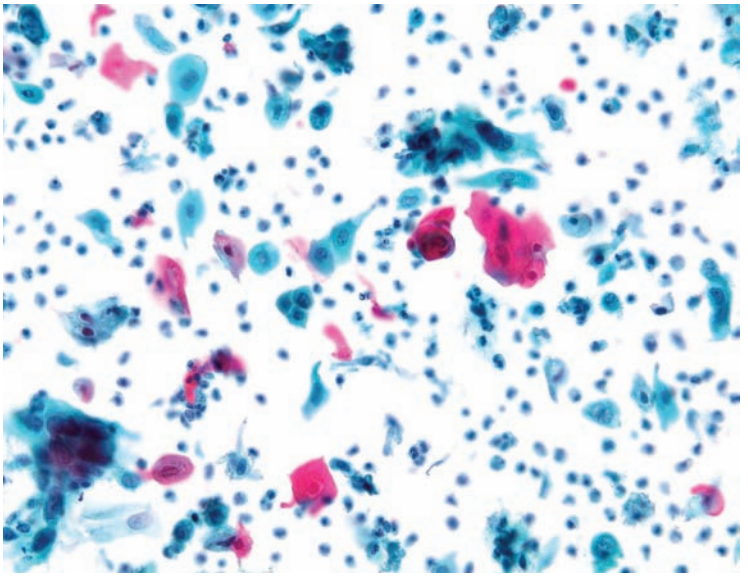


Figure 8.27b — Squamous Cell Carcinoma (Liquid Based; Low Power). This field contains a mixture of squamous metaplasia, inflammatory cells, and a few groups of cells with enlarged nuclei, irregular nuclear borders, and high N/C ratios. The center of the field contains an atypical squamous pearl (note the faint yet pleomorphic nuclei present in the pearl). Adjacent to the pearl are pleomorphic cells with low N/C ratios but dense cytoplasm with irregular extensions. Although this specimen may only reach a diagnosis of HSIL, overall these findings should point to squamous cell carcinoma.

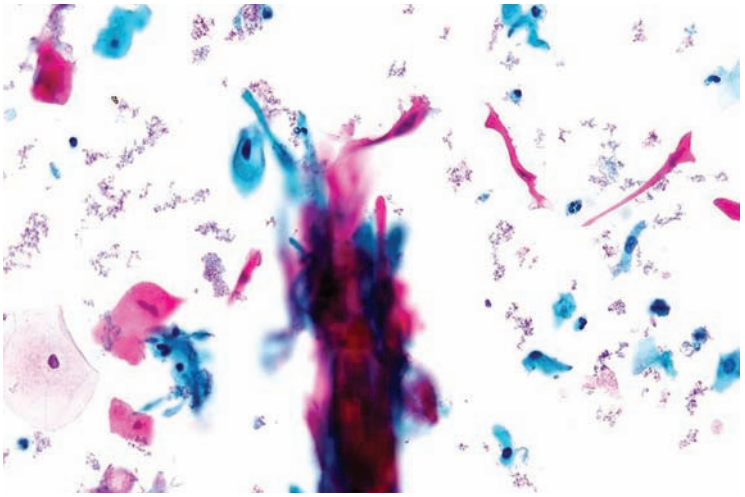


Figure 8.28a — Squamous Cell Carcinoma (Liquid Based; Intermediate Power). The center fragment, although partially out of focus, contains alternating dense blue and pink keratin with highly irregular shapes, only found in squamous cell carcinoma. If there was any doubt, "snake cells" appear to sprout from the top of the fragment. Other atypical cells are present in the background, as well as some fragments of dense irregular keratin.

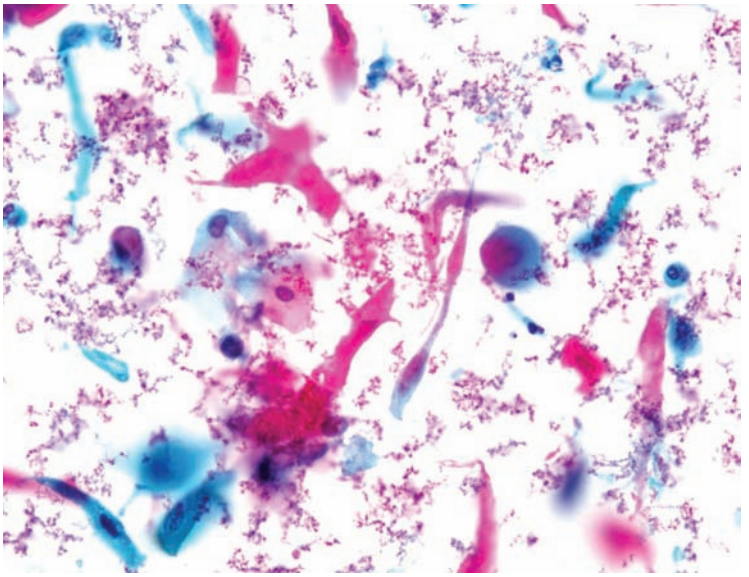


Figure 8.28b — Squamous Cell Carcinoma (Liquid Based; Intermediate Power). The abundant keratin production by some squamous cell carcinomas may result in poor staining quality due to poor stain penetration and/or stain consumption. Note the highly irregular cellular shapes; in many cells the nuclei are absent or have faded away, though the few that are present are highly atypical.

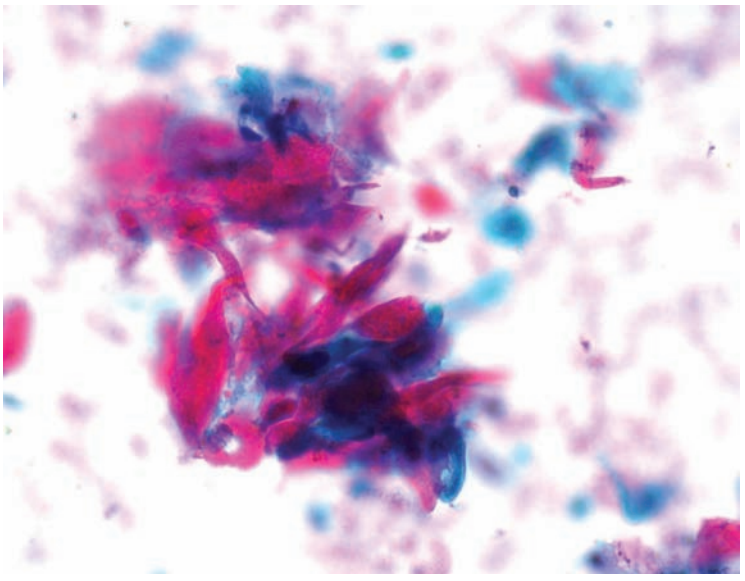


Figure 8.29a — Squamous Cell Carcinoma (Liquid Based; High Power). This is another example of atypical keratin fragments being the primary diagnostic feature in a field. The only well-preserved nucleus in the field is dark and atypical, but the cells with dense cytoplasms of alternating colors are strongly suggestive of squamous cell carcinoma.

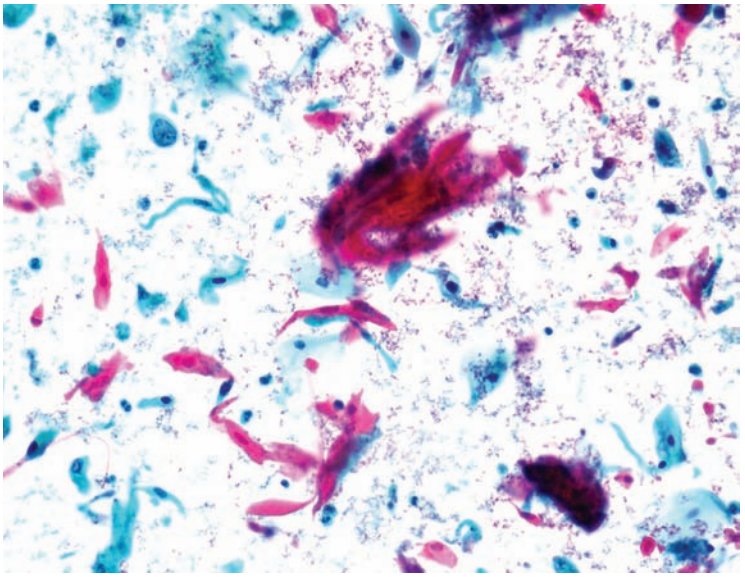


Figure 8.29b Squamous Cell Carcinoma (Liquid Based; Intermediate Power). This field is busy but demonstrates findings of a squamous cell carcinoma. The cell with the largest nucleus (top left corner) does not demonstrate much hyperchromasia and thus does not immediately stand out. Several "snake cells" are present along with other anucleate fragments of atypical keratin. Neutrophils are not a specific feature of squamous cell carcinoma, but are often associated with necrotic areas, which are sometimes present.

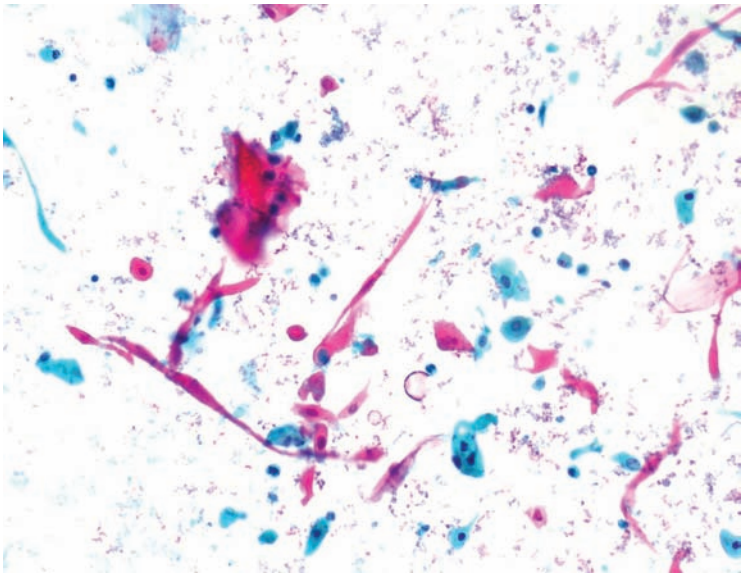


Figure 8.29c — Squamous Cell Carcinoma (Liquid Based; Intermediate Power). Similar to the previous figure, this field is busy and to a certain extent deceptively bland. HSILs contain hyperchromatic groups and the primary challenge is determining the origin of those groups. In keratinizing squamous cell carcinoma, nuclei are often absent and when present appear pyknotic.

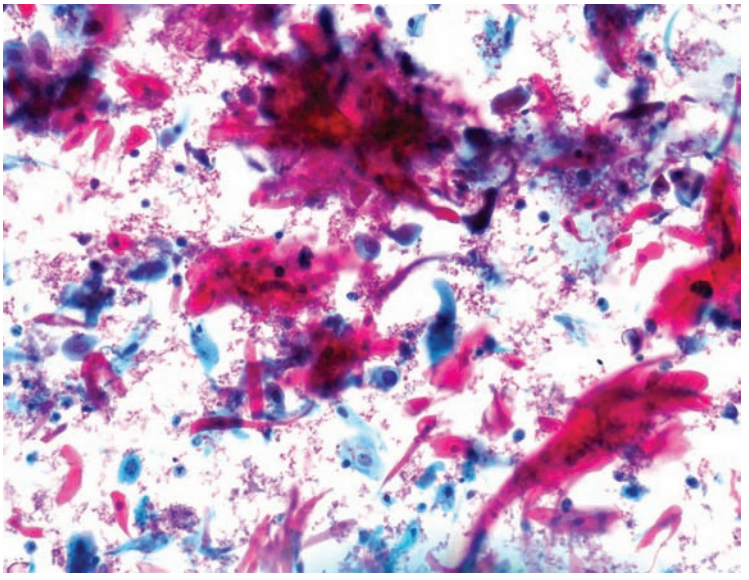


Figure 8.29d — Squamous Cell Carcinoma (Liquid Based; Intermediate Power). This field contains abundant atypical keratin fragments and malignant keratinized squamous cells. Most elements in this field are malignant—study them individually to appreciate their significance in a scant specimen.

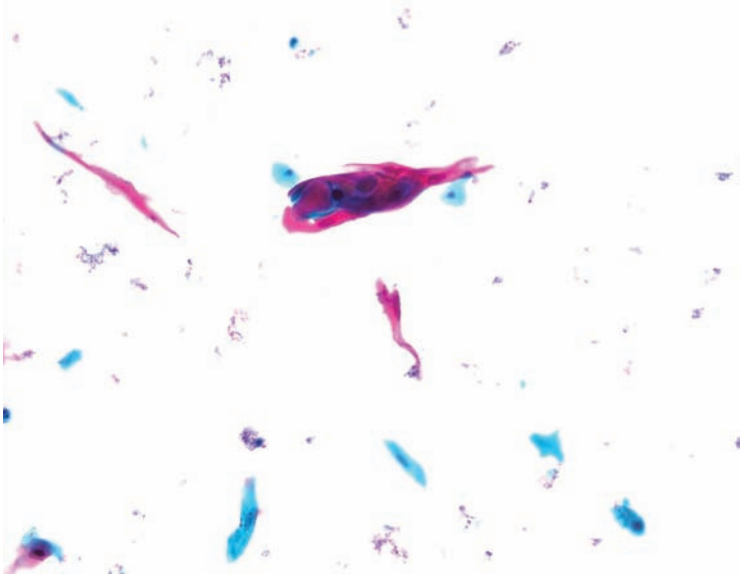


Figure 8.30a — Squamous Cell Carcinoma (Liquid Based; Intermediate Power). This fragment contains alternating cytoplasmic colors and one gets the sense of a squamous pearl on the fragment's left-hand side. The scattered cells surrounding the fragment, nucleate and anucleate, are also atypical, having dense cytoplasm and bizarre shapes.

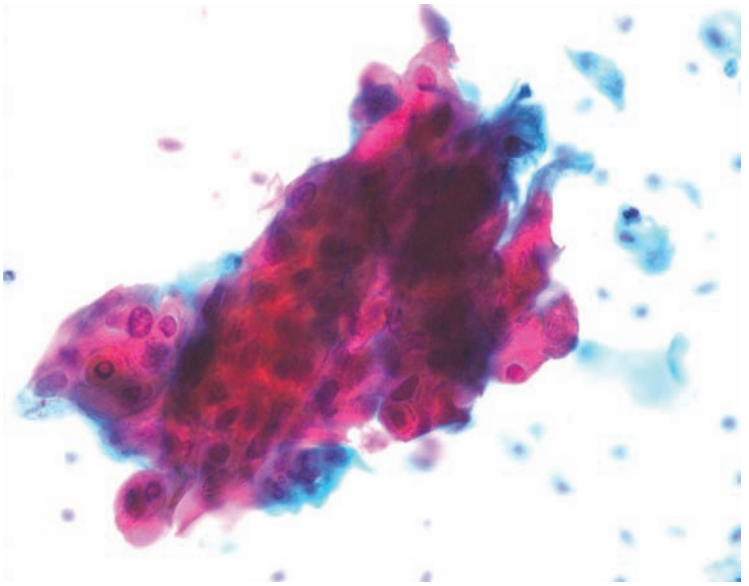


Figure 8.30b — Squamous Cell Carcinoma (Liquid Based; High Power). This fragment of keratinizing squamous cell carcinoma demonstrates several entombed nuclei that now have a targetoid appearance and the eosinophilia in a large portion of the fragment has a "Halloween orange" appearance.

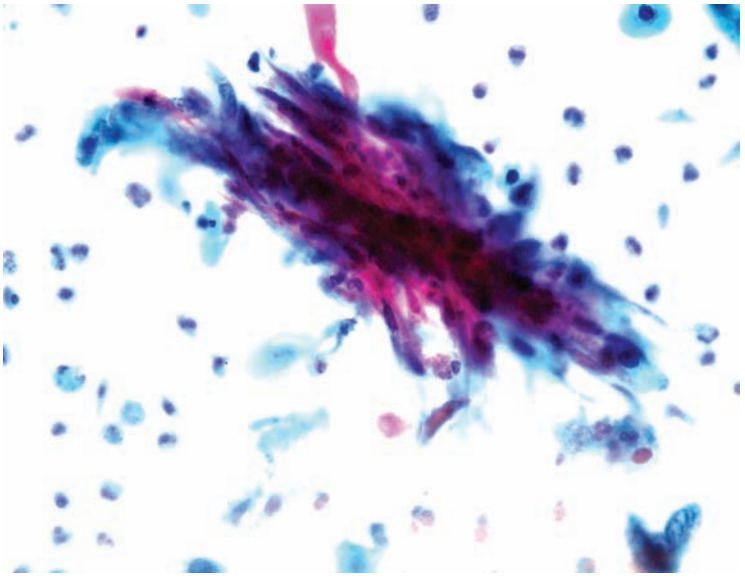


Figure 8.30c — Squamous Cell Carcinoma (Liquid Based; Intermediate Power). This fragment has a lamellated appearance; poor stain penetration and associated neutrophils make initial interpretation difficult. However, highly atypical nuclei are present and are especially apparent at the frayed edges.

Figure 8.30d — Squamous Cell Carcinoma (Liquid Based; Intermediate Power). This field demonstrates the dense cytoplasm and irregular cell shapes found in squamous cell carcinoma. Again, the atypical "stretched taffy" shapes are more striking than the degenerated atypical nuclei.

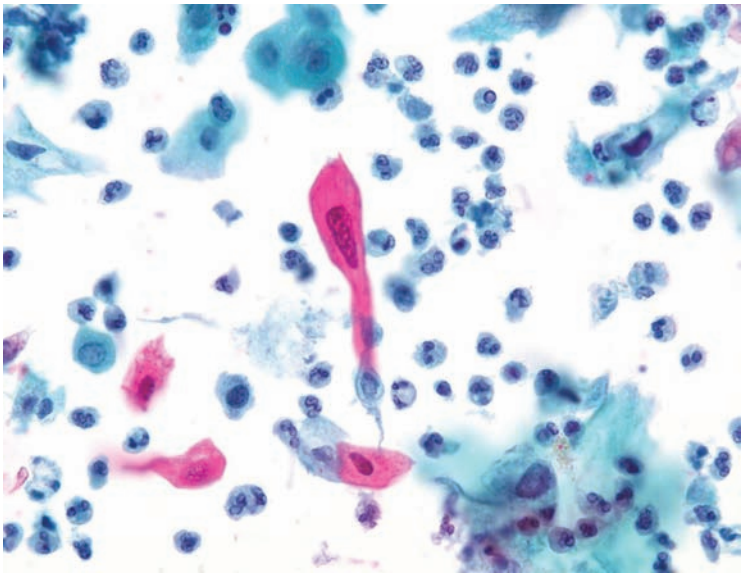


Figure 8.31a — Squamous Cell Carcinoma (Liquid Based; High Power). This cell appears large at high power, but the nucleus is not significantly large. At low power, these eosinophilic and dyskeratotic cells might appear to represent atypical parakeratosis. However, the prominent cytoplasmic extension strongly suggests the possibility of squamous cell carcinoma.

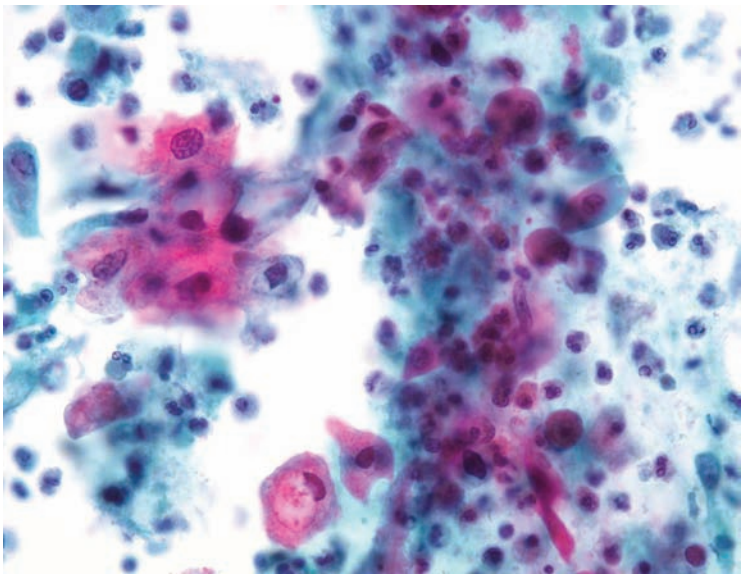


Figure 8.31b — Squamous Cell Carcinoma (Liquid Based; Intermediate Power). Necrosis, abundant neutrophils, and cellular degeneration can lead to poor staining quality and an obscured field. A documented history of cervical dysplasia and abnormal Pap tests are not necessarily seen in patients with squamous cell carcinoma, because noncompliant patients are at greatest risk of cancer, which generally requires years to develop.

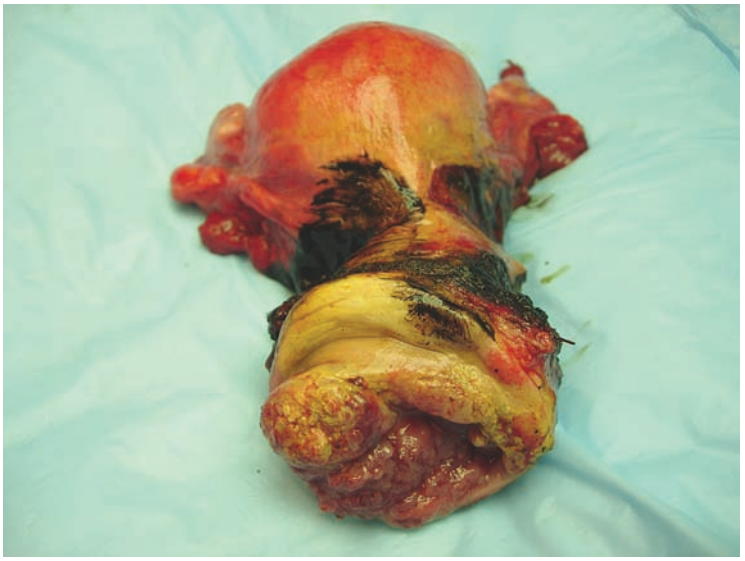


Figure 8.32 — Cervical Squamous Cell Carcinoma, Gross Specimen (Hysterectomy). The cervix is enlarged and has an exophytic heterogeneous mass protruding from the cervical os. The parametria and vaginal cuff margins should be inked so that margin status can be determined microscopically. Unlike other gynecologic specimens, cervical cancers are staged clinically rather than surgically. It is important to note that surgical specimens will not be received from all patients with cervical carcinoma. Surgery is typically reserved for patients with early-stage disease.

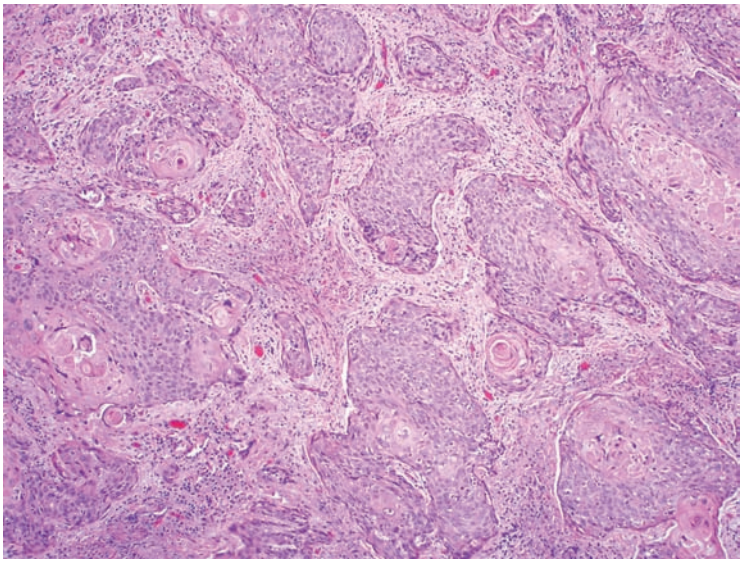


Figure 8.33 — Invasive Cervical Squamous Cell Carcinoma (Hysterectomy) (Hematoxylin and Eosin [H&E] Stain; Intermediate Power). The carcinoma is characterized by an infiltrating pattern with nests of atypical squamous epithelium arranged in a haphazard fashion. The nests have irregular contours and vary in size and shape. They are markedly crowded and separated by desmoplastic stroma. Note the presence of abrupt keratinization at the periphery of multiple nests. In other problematic cases in which it may be difficult determining whether a lesion in question represents invasive carcinoma versus high-grade squamous intraepithelial lesion with florid extension into endocervical glands, this finding of "reverse maturation" is a helpful clue to the diagnosis of invasive squamous cell carcinoma.

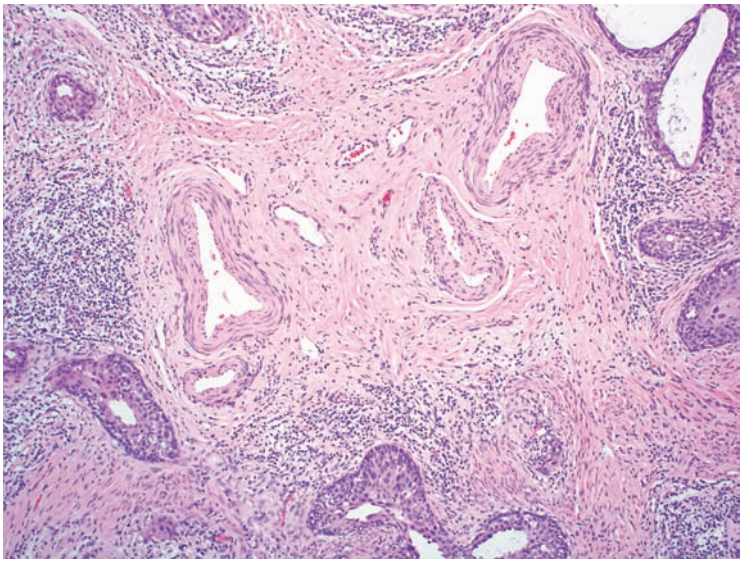


Figure 8.34 — Invasive Cervical Squamous Cell Carcinoma (Hysterectomy) (H&E Stain; Intermediate Power). The invasive nests are in close proximity to large thick-walled blood vessels. This finding can provide a helpful clue when determining whether a problematic case represents invasive carcinoma versus high-grade squamous intraepithelial lesion with florid extension into endocervical glands. Also, note that some of the nests of carcinoma display cystic change, which occurs on occasion. If the underlying squamous nature of the carcinoma is not appreciated in other cases, then this finding may cause misclassification as adenocarcinoma.

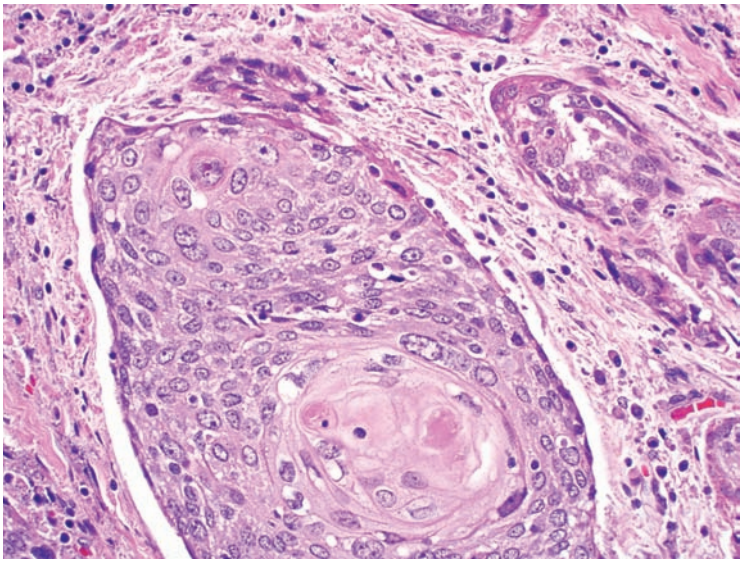


Figure 8.35a — Invasive Cervical Squamous Cell Carcinoma (Hysterectomy) (H&E Stain; High Power). A standardized histologic grading system for cervical squamous cell carcinoma has not been established, and the interobserver reproducibility of grade will likely be poor. Nonetheless, tumors are typically graded as well, moderately, and poorly differentiated for reporting purposes. Tumors that are well differentiated are easily identifiable as being of squamous lineage. In this example, the cells are polygonal with well-developed cell borders, abundant pink cytoplasm with a low N/C ratio, and some degree of keratinization. The nuclei are round with vesicular chromatin, and only small nucleoli are barely evident.

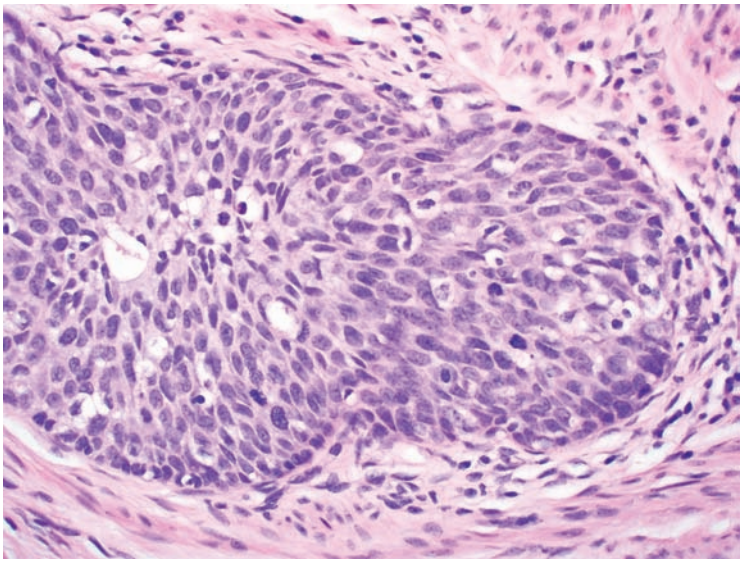


Figure 8.35b — Invasive Cervical Squamous Cell Carcinoma (Hysterectomy) (H&E Stain; High Power). In moderately to poorly differentiated tumors, as in this case, the squamous cell type is not as easy to appreciate as in well-differentiated tumors. The N/C ratio is higher, and the chromatin is coarser. The overall morphology imparts a basaloid appearance with a suggestion of peripheral palisading. Note occasional small cystic spaces, which can falsely lead to an interpretation of adenocarcinoma or adenosquamous carcinoma; however, true glandular lumens are not present.

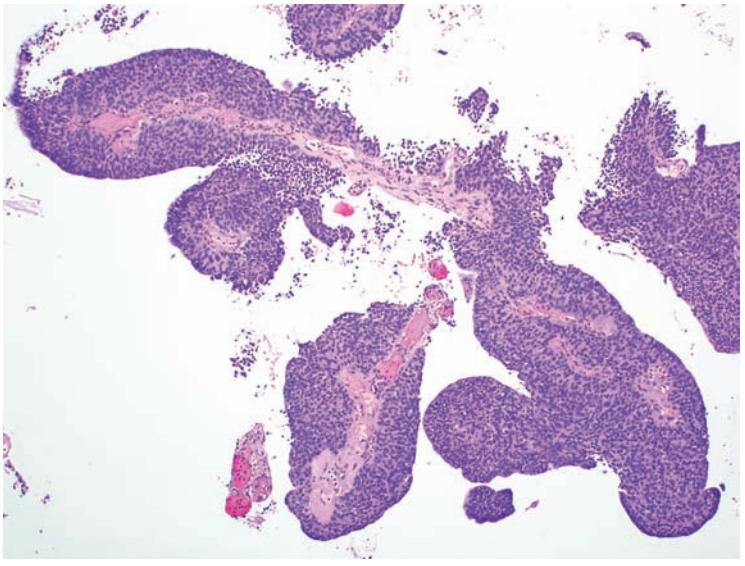


Figure 8.36a — Papillary Cervical Squamous Cell Carcinoma (Biopsy) (H&E Stain; Intermediate Power). The tumor is exophytic and displays large, broad papillae, which consist of fibrovascular cores lined by thick squamous epithelium with smooth luminal borders.

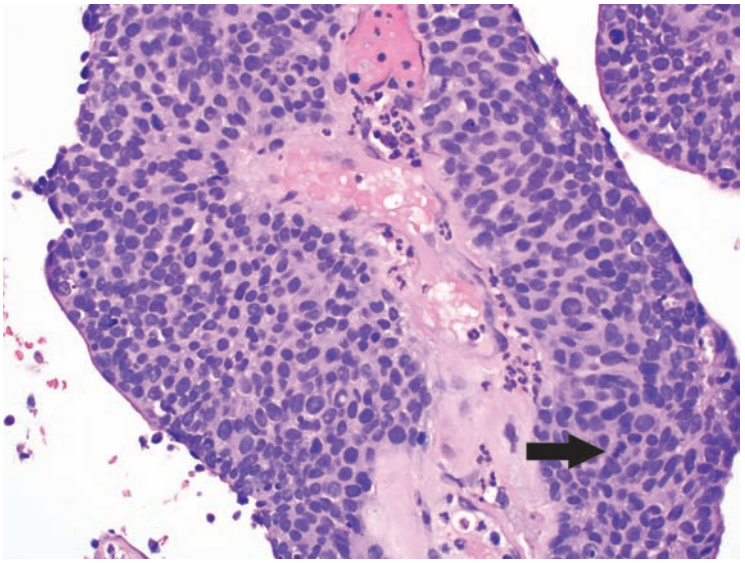


Figure 8.36b — Papillary Cervical Squamous Cell Carcinoma (Biopsy) (H&E Stain; High Power). The squamous epithelium is stratified and shows full thickness of immaturity. The cells have a high N/C ratio with a basaloid appearance. The nuclei are round and have coarse chromatin. A mitotic figure (*arrow*) is present. The histologic appearance resembles a "papillary" form of high-grade squamous intraepithelial lesion (HSIL); however, proliferations of this type with exophytic papillary architecture exceed the morphologic features allowable for HSIL and are characteristic of papillary squamous cell carcinoma.

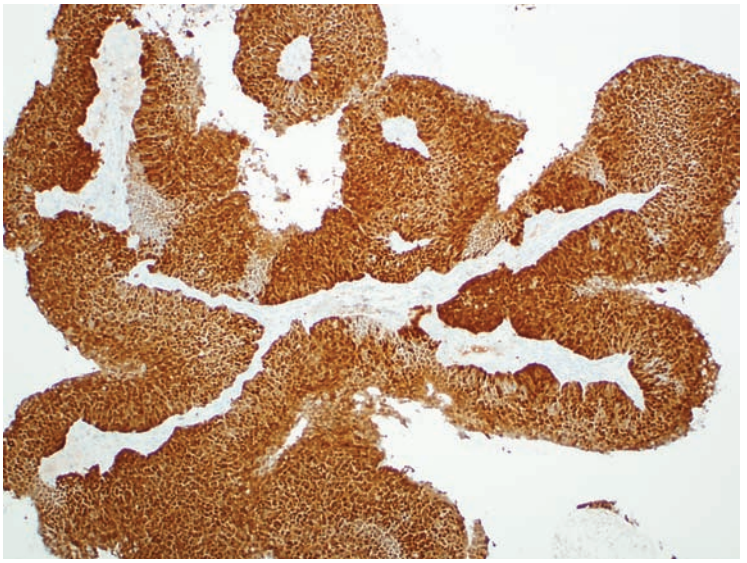


Figure 8.36c — Papillary Cervical Squamous Cell Carcinoma (Biopsy) (p16 Immunohistochemical Stain, Intermediate Power). The tumor exhibits diffuse expression of p16. Essentially, all cervical squamous cell carcinomas, whether conventional type or the papillary variant, should have this pattern of staining for p16.

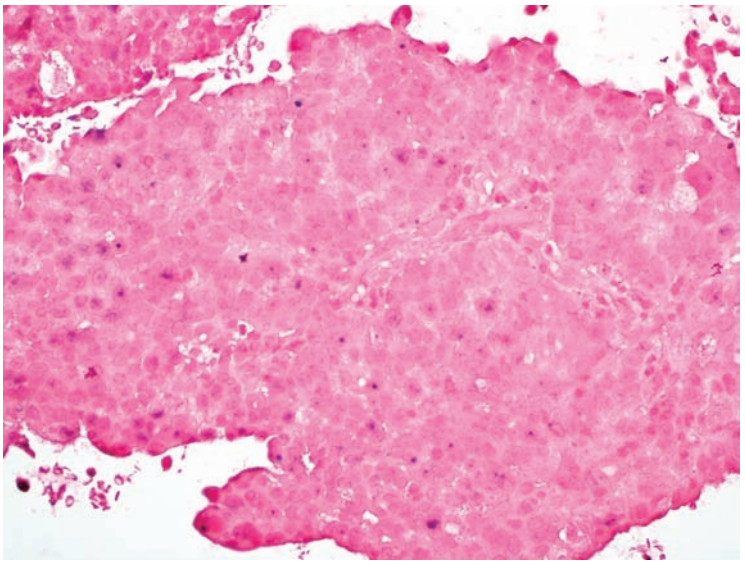


Figure 8.36d — Papillary Cervical Squamous Cell Carcinoma (Biopsy) (In Situ Hybridization for High-Risk Human Papillomavirus [Ventana INFORM HPV III Family 16 Probe, HPV Genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 66], High Power). Fine punctate nuclear signals are present, consistent with HPV. Almost all cervical squamous cell carcinomas are high-risk HPV related. However, the sensitivity of in situ hybridization for HPV is not 100%, and a "negative" result does not exclude the presence of HPV. Such "negative" results can occur because of either low-viral copy below the detection limit of in situ hybridization, technical failure, or an HPV type not covered by the probes used. Even though it may not be possible to diagnose invasion in a biopsy specimen because of the exophytic nature of the papillary lesion without underlying stroma, papillary lesions of this type are frequently associated with stromal invasion in hysterectomy specimens. Thus, it is reasonable to diagnose an exophytic papillary lesion of this type as carcinoma. However, it should be noted that rare cases of papillary squamous cell carcinoma may be entirely exophytic without invasion of underlying cervical stroma. Such cases have variably been referred to as papillary squamous cell carcinoma in situ.

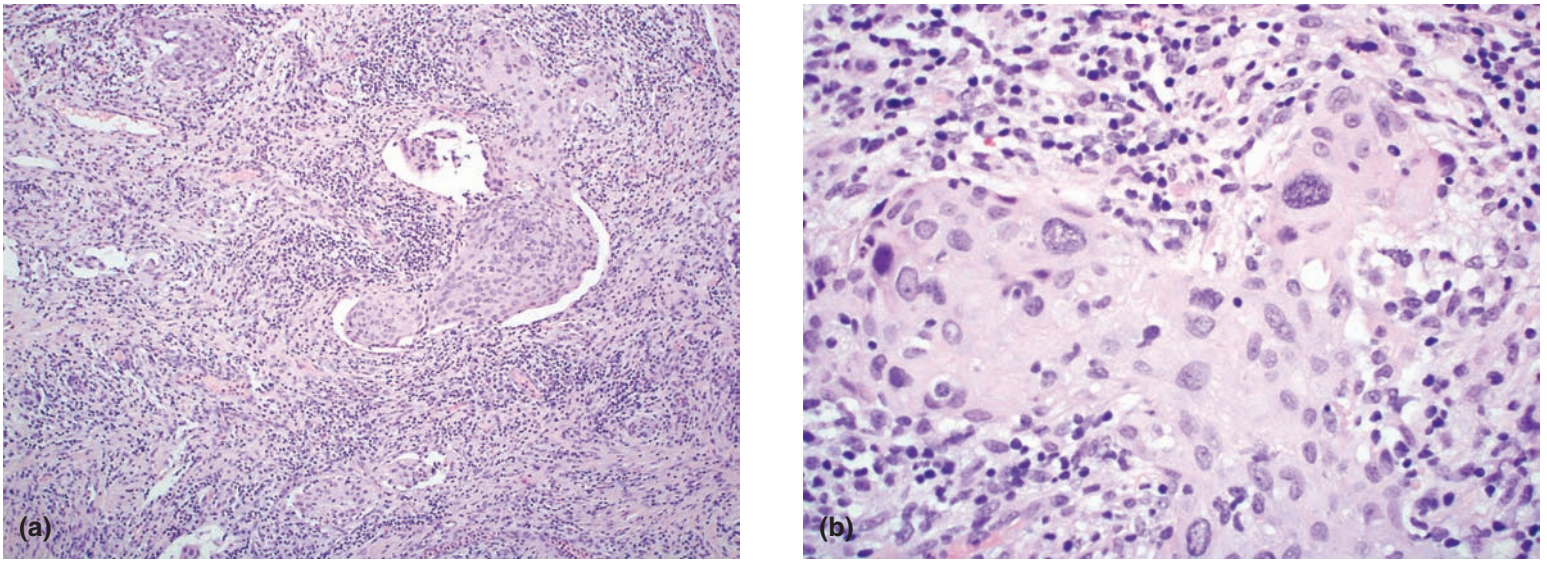


Figure 8.37 — Superficially Invasive Cervical Squamous Cell Carcinoma (Microinvasion) (Cold Knife Cone Biopsy; H&E Stain; (a) Intermediate and (b) High Power). Nests of atypical squamous epithelium are present within an altered stroma containing desmoplasia and inflammation. They vary in size and shape. A larger nest is present in the center and upper right although two smaller ones are noted in the upper left-hand corner and lower center of the photograph (a). The nests are irregularly shaped and haphazardly arranged. The cells of the carcinomatous nests are polygonal with abundant pink cytoplasm producing a low N/C ratio. The nuclei are large and pleomorphic and have coarse chromatin. This type of "reverse maturation" is a helpful clue when there is a question of whether or not stromal invasion is present. When stromal invasion is present, the term superficially invasive or microinvasion should only be used for cases that have negative margins. This designation is reserved for cases that have stromal invasion of less than or equal to 3 mm in depth and less than or equal to 7 mm in horizontal spread [width] (FIGO stage IA1).

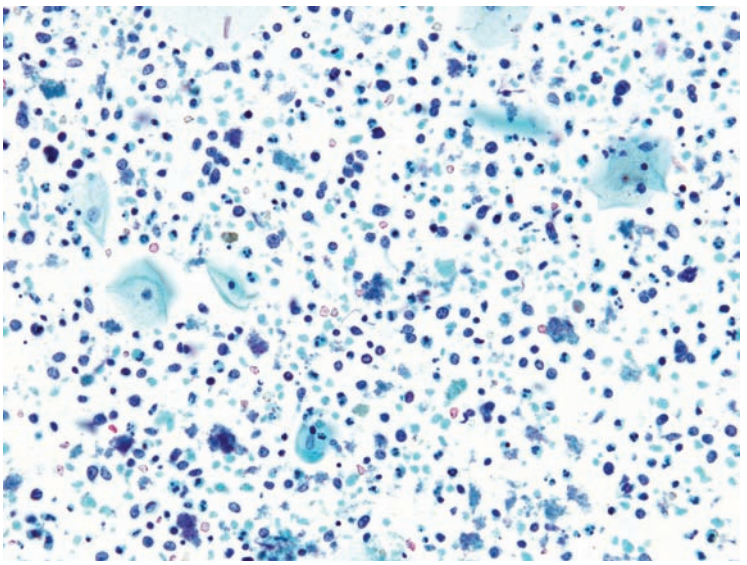


Figure 8.38a — Small Cell Carcinoma (Liquid Based; Low Power). In liquid-based preparations, small cell carcinomas lose some of the morphologic features that are often seen in conventional smear preparations. Cells are more dispersed, molding and necrosis are less prominent, and the "crush artifact" absent. In these low power fields, the cells are predominantly discohesive and demonstrate a single cell pattern. As a result, they could easily be mistaken for lymphocytes. However, they appear much larger than bystander neutrophils and even the "salt and pepper" chromatin pattern is identifiable at this power. Numerous blue blobs are present and dispersed away from the tumor cells; in this case, the blue blobs are necrotic tumor cells.

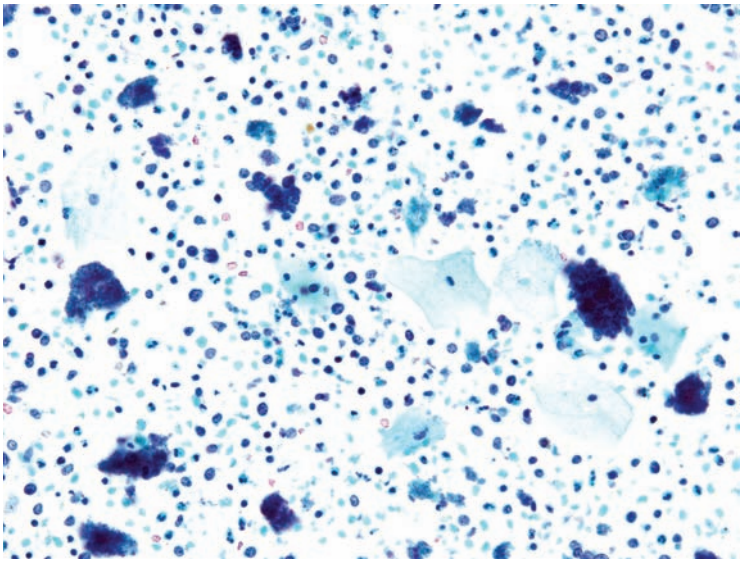


Figure 8.38b — Small Cell Carcinoma (Liquid Based; Low Power). More fragments are visible in this field, some of which contain intermixed or predominantly necrotic debris. The fragments are dark and may give the impression of endometrial cells due to the hobnailed pattern present at the fragment edges and minimal cytoplasm. If mistaken for lymphocytes, follicular cervicitis may enter the differential, but tingible macrophages are not seen.

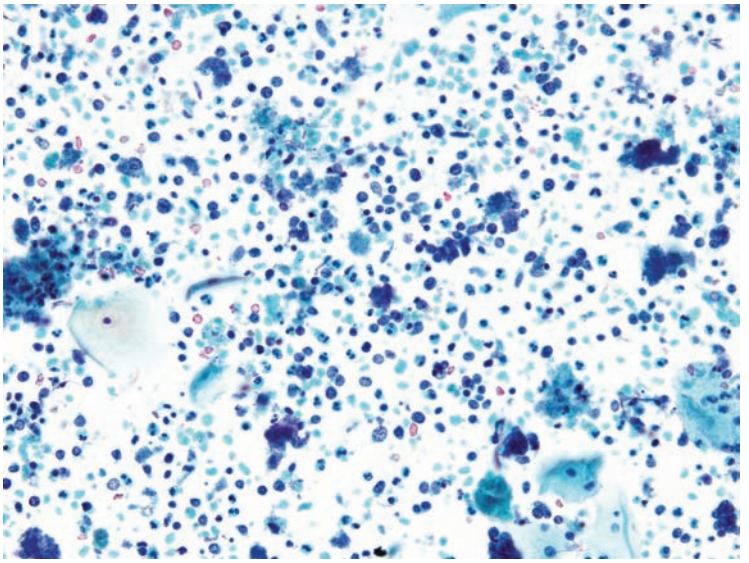


Figure 8.38c — Small Cell Carcinoma (Liquid Based; Low Power). This field contains areas in which the necrotic debris has taken on a lighter blue color, similar to that of the necrotic blobs in the background. Neutrophils are occasionally associated.

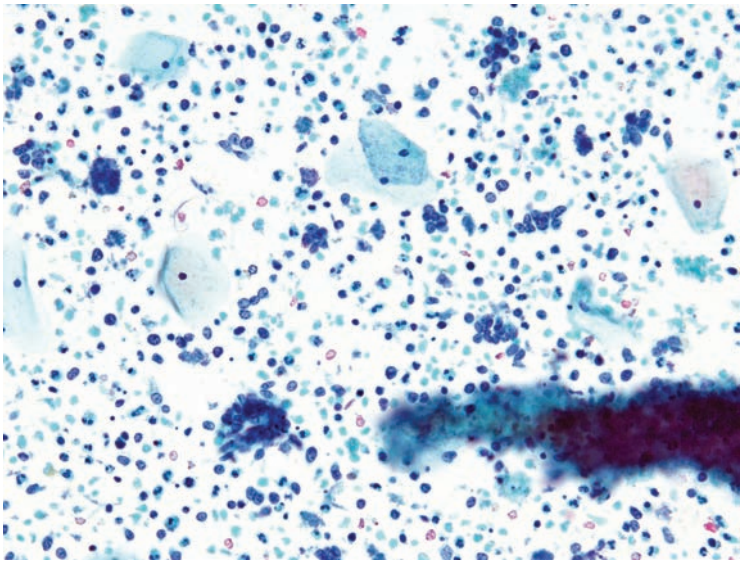


Figure 8.38d — Small Cell Carcinoma (Liquid Based; Low Power). Small clusters of cells are present in this field, where the tumor cells appear to be gently touching each other rather than molding together.

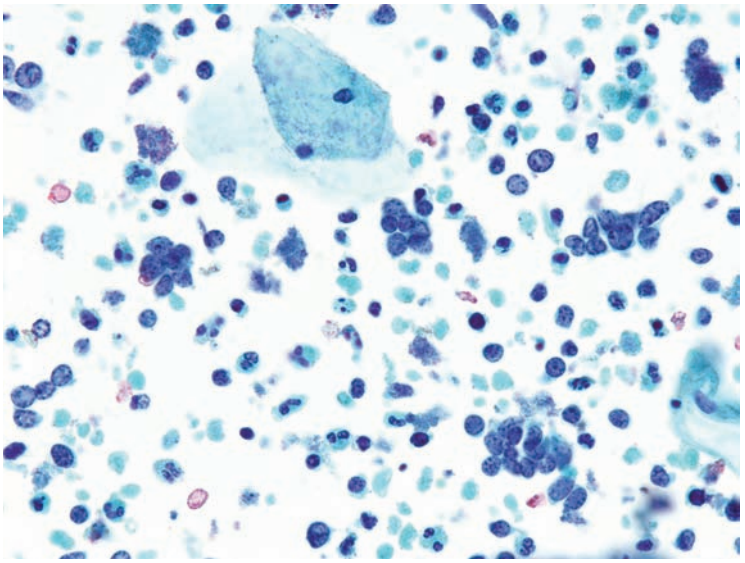


Figure 8.39a — Small Cell Carcinoma (Liquid Based; High Power). At higher power, the neuroendocrine chromatin pattern of the tumor cells is more apparent. The cells are loosely associated and molding is not prominent. It is easier to compare the size to adjacent neutrophils. The cytoplasmic rim often seen in lymphocytes is absent.

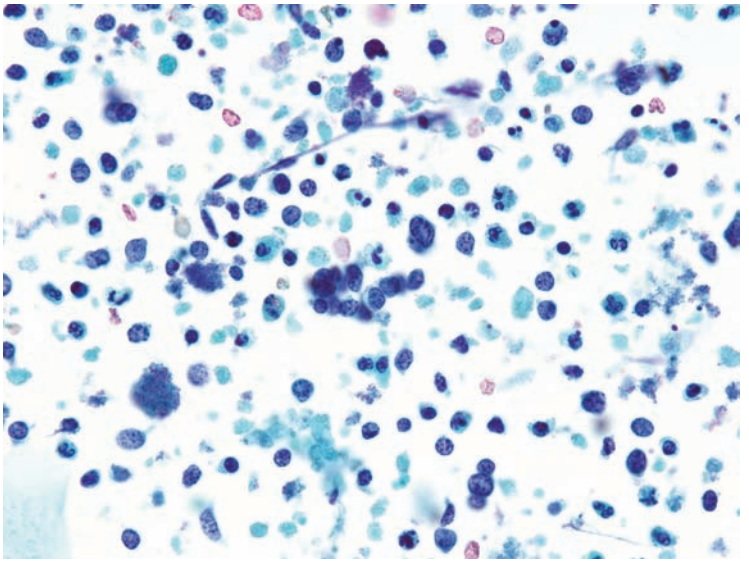


Figure 8.39b — Small Cell Carcinoma (Liquid Based; High Power). The blue blobs, which represent necrotic tumor cells, are loosely associated in one area. They have not completely degenerated into debris, but appear much smaller than the individual intact tumor cells. Athough the tumor cells are small, slight pleomorphism can be seen.

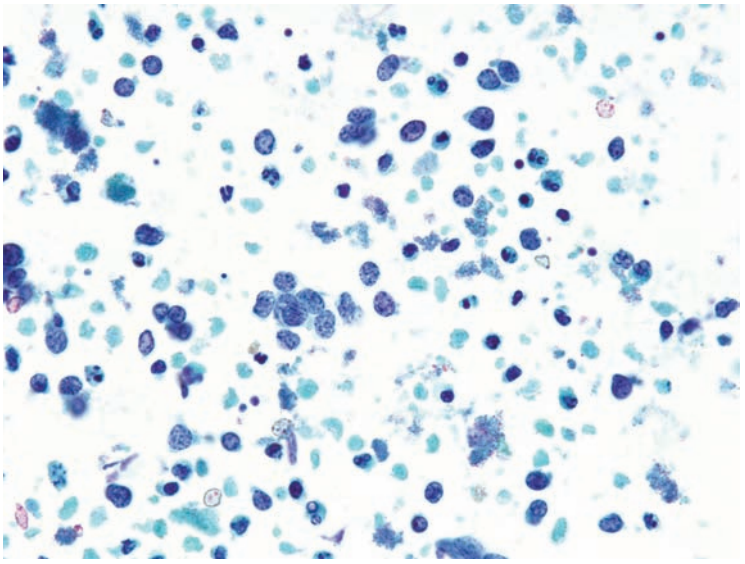


Figure 8.39c — Small Cell Carcinoma (Liquid Based; High Power). The speckled chromatin of the tumor cells is well appreciated in this field. There are no normal squamous epithelial components in this field, suggesting that the lesion is highly cellular.

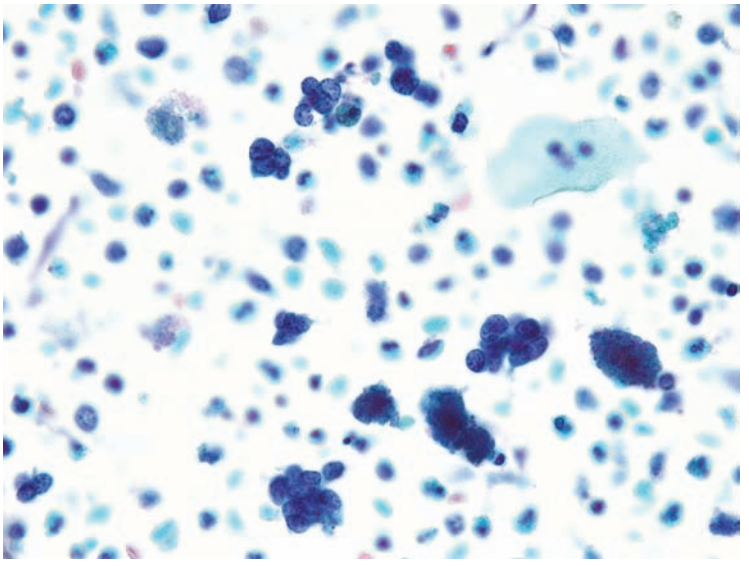


Figure 8.39d — Small Cell Carcimoma (Liquid Based; High Power). The tumor cells in this field appear more hyperchromatic, but also demonstrate some overlapping and molding, thus appearing similar to what is typically seen in conventional smear preparations.

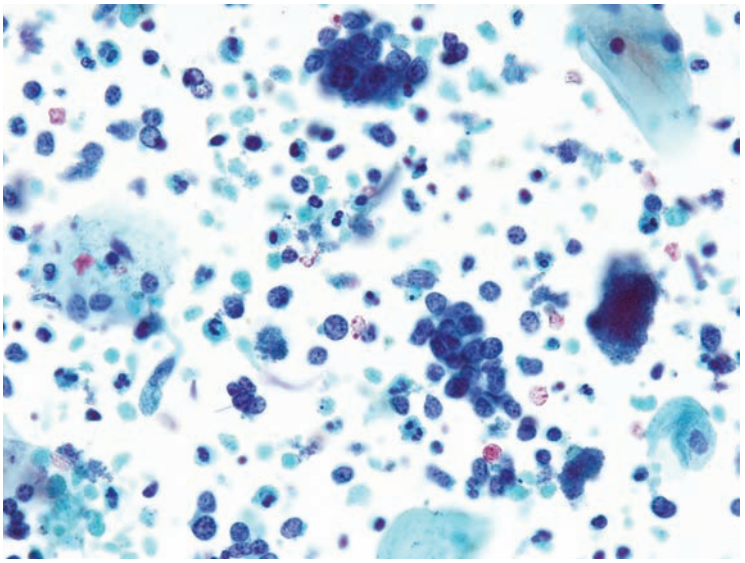


Figure 8.40a — Small Cell Carcinoma (Liquid Based; High Power). Although some molding is evident, the cells appear to overlap more than mold together. In addition to the increased size compared to adjacent neutrophils and the slight pleomorphism present, even some single cells demonstrate slight nuclear membrane irregularities, helping differentiate them from lymphocytes.

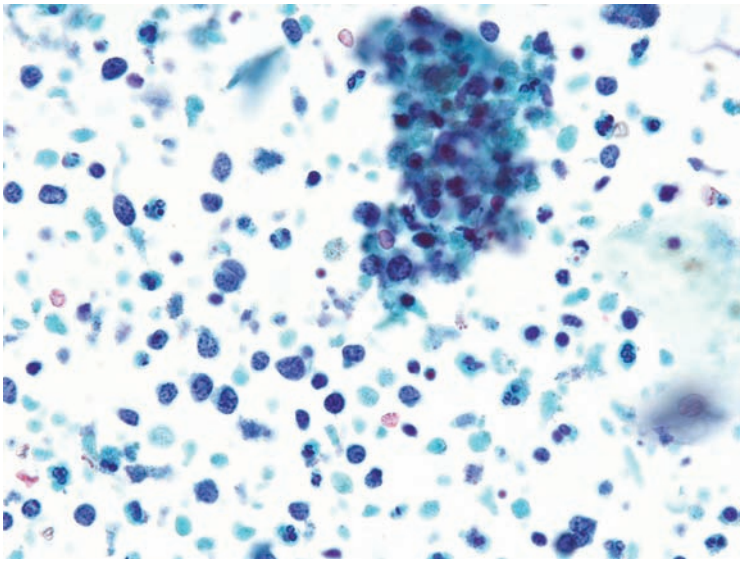


Figure 8.40b — Small Cell Carcimoma (Liquid Based; High Power). The large fragment of cells in the upper corner of the field show the more typical checkerboard pattern in which viable tumor cells alternate with necrotic cells. In liquid-based preparations, these cohesive clusters are not usually seen and thus are not as identifiable as in H&E sections.

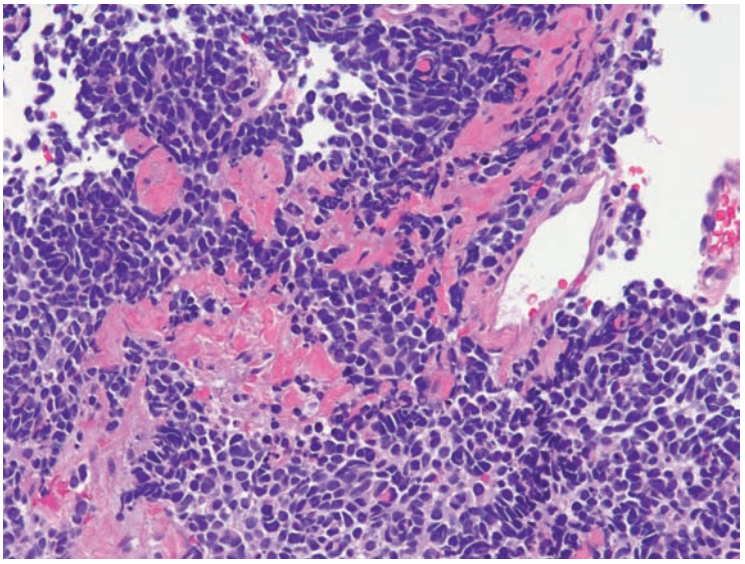


Figure 8.41a — Small Cell Carcinoma (Biopsy) (H&E Stain; High Power). Small cell carcinoma of the cervix on histologic section demonstrates high cellularity, minimal to absent cytoplasm, and nuclear molding. In this field, high mitotic activity, crush artifact, and necrosis are not apparent. Small cell carcinoma of the cervix is extremely rare and comprises less than 1% of all cervical carcinomas. Small cell carcinoma is aggressive and treated with surgery, which may be combined with chemotherapy and/or radiation therapy.

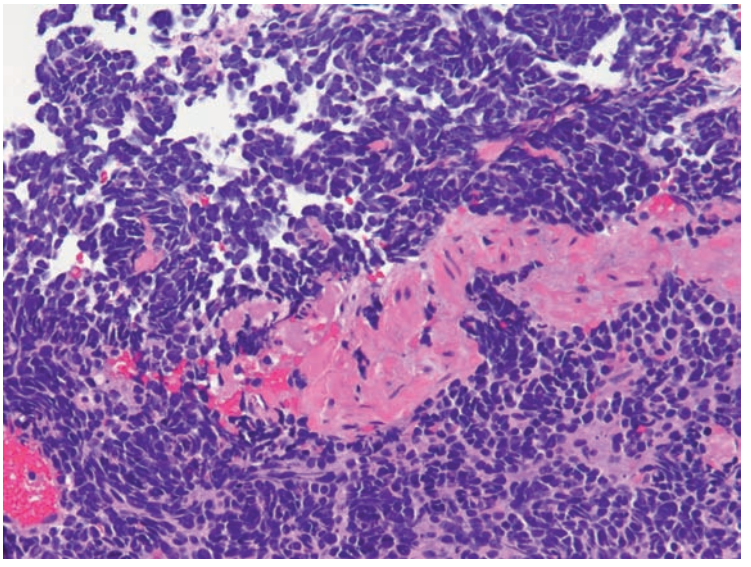


Figure 8.41b — Small Cell Carcinoma (Biopsy) (H&E Stain; High Power). In this field, crush artifact and molding are more prominent than in the previous figure. As small cell carcinoma of the cervix is so uncommon, its etiology is not completely understood. However, it is associated with HPV, often HPV type 18.

9

Atypical Glandular Cells

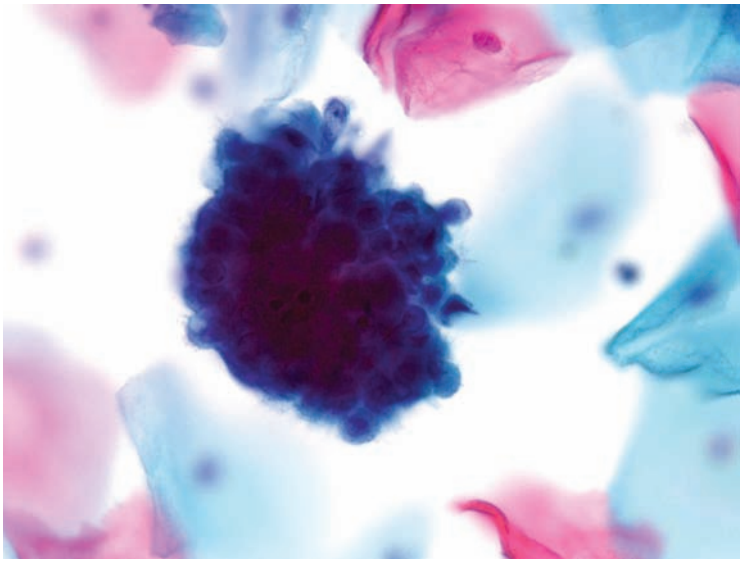


Figure 9.1 — Atypical Glandular Cells (Liquid Based; High Power). A very dense cluster of tiny cells can barely be visualized. Compare the cells at the upper right edge of the group with the nucleus of the nearby pink squamous cell. Being the same size places our unknown cells in the category of endometrial cells. Clinical history, including patient's age and last menstrual period, is essential to decide if the presence of these cells is physiological or abnormal as they are not morphologically atypical. On follow-up, the patient was diagnosed with endometrial atypical hyperplasia.

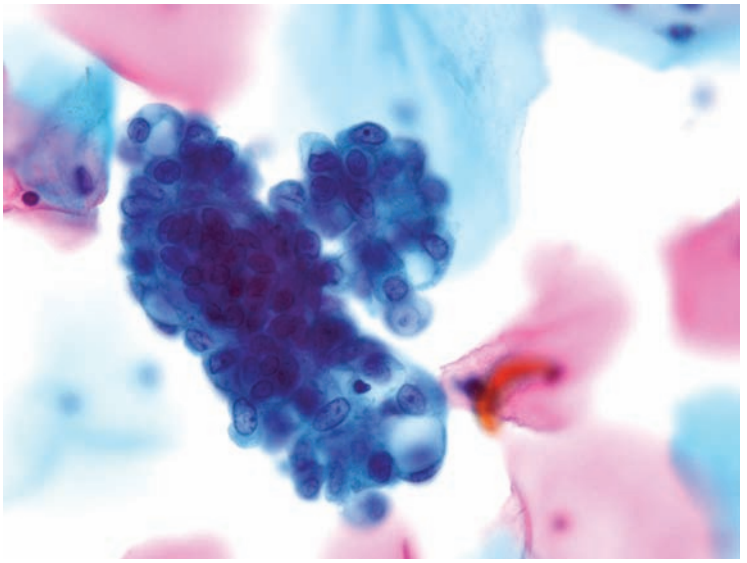


Figure 9.2 — Atypical Glandular Cells (Liquid Based; High Power). Compared with the cells in Figure 9.1, these two cell clusters have easily visible differences, specifically the great visibility of cell details in this photograph, larger cell and nuclear sizes, and cytoplasmic vacuoles of cells around the edges of the groups. The larger group has dense cells in the middle, the stroma of the endometrium. As in Figure 9.1, in order to pass judgment on the significance of these cells, the patient's clinical history is essential. If physiological, they are normal. If seen in a perimenopausal or menopausal patient, they are abnormal, most likely representing a hyperplasia, as indeed was present on biopsy.

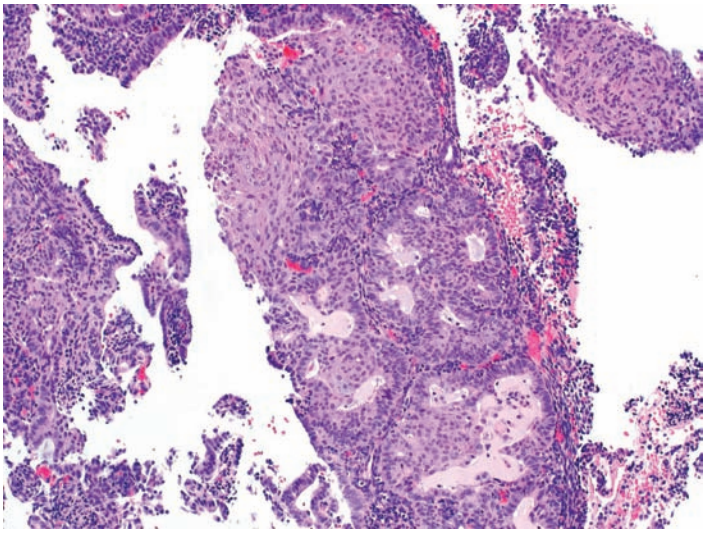


Figure 9.3a — Endometrial Complex Atypical Hyperplasia (Endometrial Biopsy) (Hematoxylin and Eosin [H&E] Stain; Intermediate Power). The glands are crowded with an increase in the gland-to-stroma ratio. These glands are filled with squamous morular metaplasia, and the lumens are mostly situated at the periphery of the glands. Note that desmoplastic stroma is not present, and glandular confluence or papillary architecture is absent. Thus, the findings are insufficient for a diagnosis of FIGO grade 1 endometrioid carcinoma.

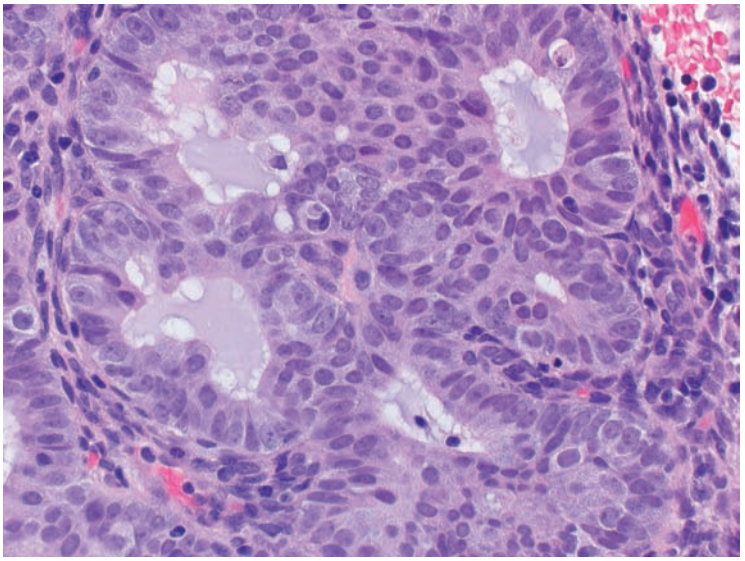


Figure 9.3b — Endometrial Complex Atypical Hyperplasia (H&E Stain; High Power). Although loss of nuclear polarization (which is commonly seen in other cases of atypical hyperplasia) is not seen in this case, the atypical glandular cells exhibit nuclear enlargement, round nuclei (as opposed to columnar), some degree of chromatin pallor, prominent nuclei, and cytoplasmic pallor. Note that other non-atypical glandular cells are admixed with the atypical ones. In general, the diagnosis of atypical hyperplasia is not highly reproducible among pathologists. Therefore, when the diagnosis of atypia is considered for a case of endometrial hyperplasia, subjecting the case to consensus agreement among colleague pathologists is suggested.

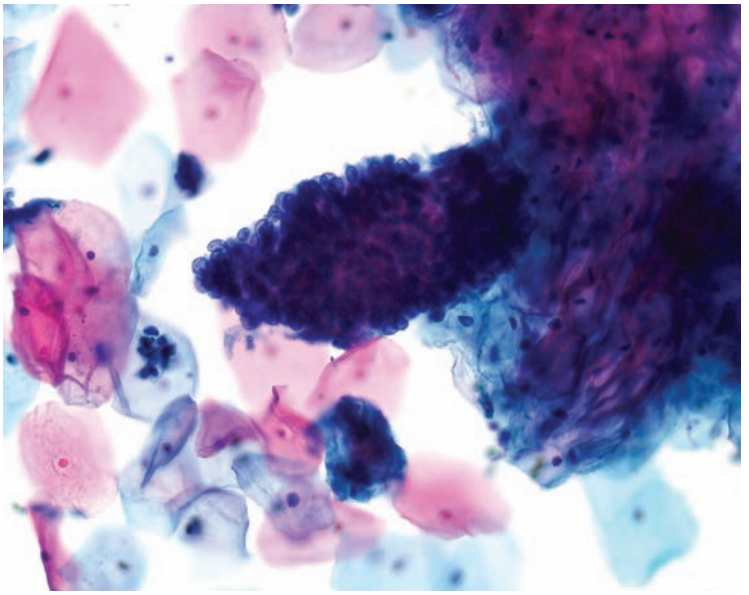


Figure 9.4 — Atypical Glandular Cells (Liquid Based; Medium Power). A large fragment of tissue is similar in density to those in Figure 9.1. Higher power inspection is needed in order to identify the cell of origin, as they could be endometrial, endocervical, or originating in a high-grade squamous intraepithelial lesion (HSIL). On follow-up, the patient was diagnosed with HSIL involving endocervical glands.

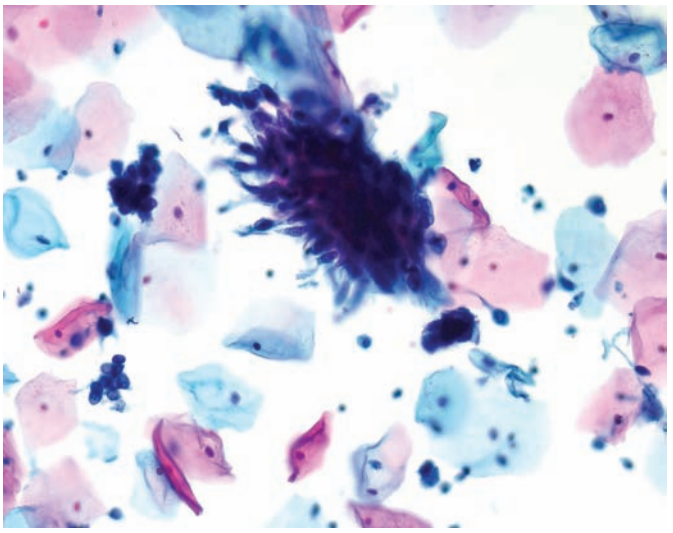


Figure 9.5 — Atypical Glandular Cells (Liquid Based; Medium Power). The borders of this tissue fragment are not smooth, but resemble a rag mop, with irregular thin projecting cells. Higher magnification is needed to identify the cells. Although the tissue diagnosis is HSIL with gland involvement, the configuration of the group could suggest an endocervical adenocarcinoma in situ (AIS). On follow-up, the patient was diagnosed with HSIL involving endocervical glands.

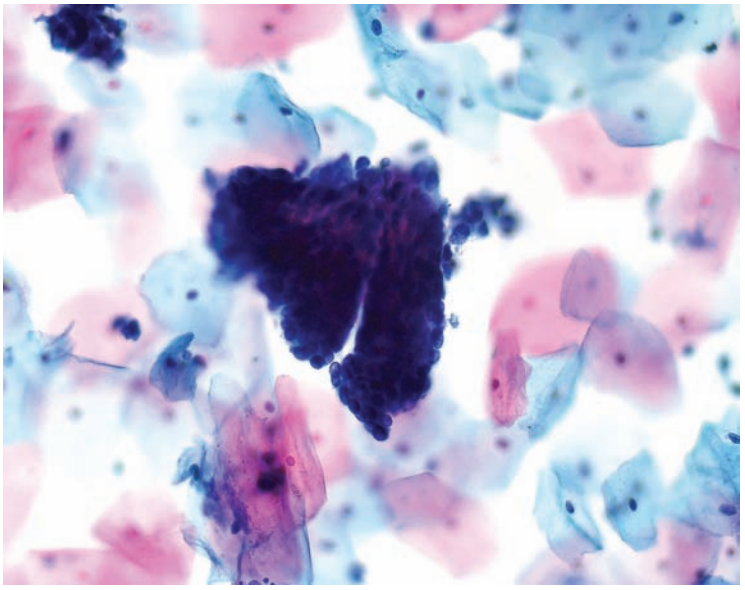


Figure 9.6 — Atypical Glandular Cells (Liquid Based; Medium Power). The origin of this large fragment in endocervical glands is easy to imagine, as the borders of the fragment are smooth. Certain cell identification is possible only on higher power. On follow-up, the patient was diagnosed with HSIL involving endocervical glands.

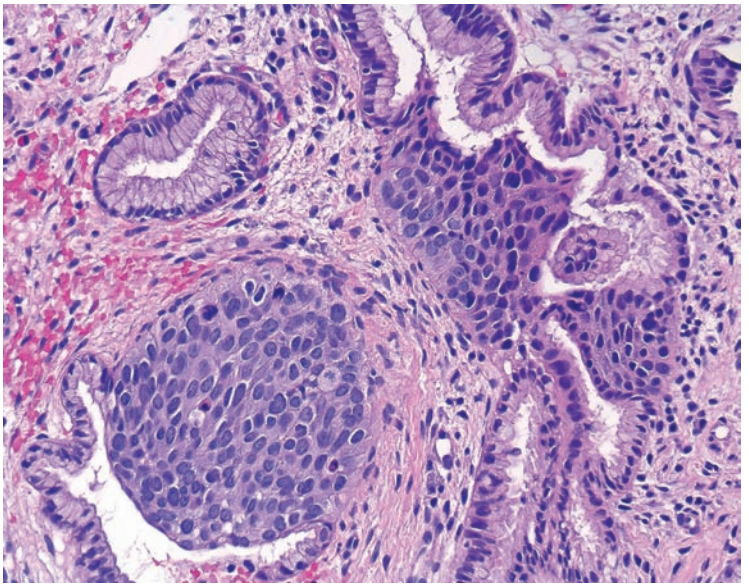


Figure 9.7 — High-Grade Squamous Intraepithelial Lesion (HSIL) With Extension Into Endocervical Glands (Cervical Biopsy) (H&E Stain; High Power). High-grade squamous intraepithelial lesion is present within endocervical glands. Note that it is within the intraepithelial compartment of the gland and that stromal invasion is absent. The differential diagnosis in this case could potentially include immature squamous metaplasia. However, the histologic features are consistent with a diagnosis of HSIL (in particular, the degree of loss of maturation, nuclear enlargement, increased nuclear-to-cytoplasmic (N/C) ratio, hyperchromasia, and mitotic figures). If needed, immunohistochemistry for p16 be performed to confirm this impression.

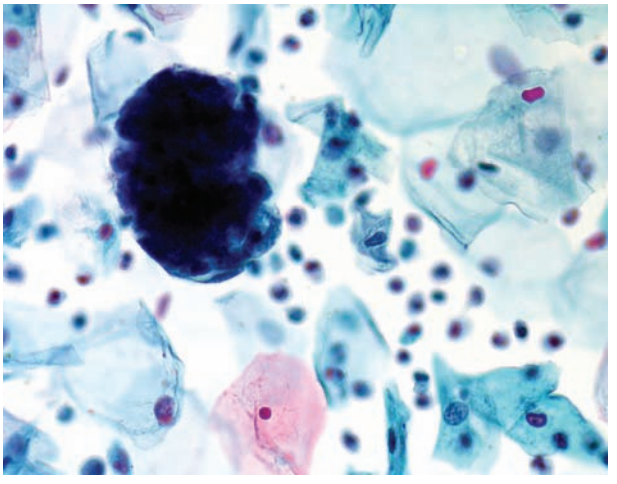


Figure 9.8 — Atypical Glandular Cells (Liquid Based; High Power). A three-dimensional ball of epithelial cells is too thick to visualize, except along the edge of the group. Glandular cells are evidenced by the vacuolated cytoplasm, but their organ of origin is not obvious. History and physical or radiologic examination are important to make the diagnosis other than "malignant cells present." On follow-up, the patient was diagnosed with a malignant mixed Müllerian tumor (MMMT).

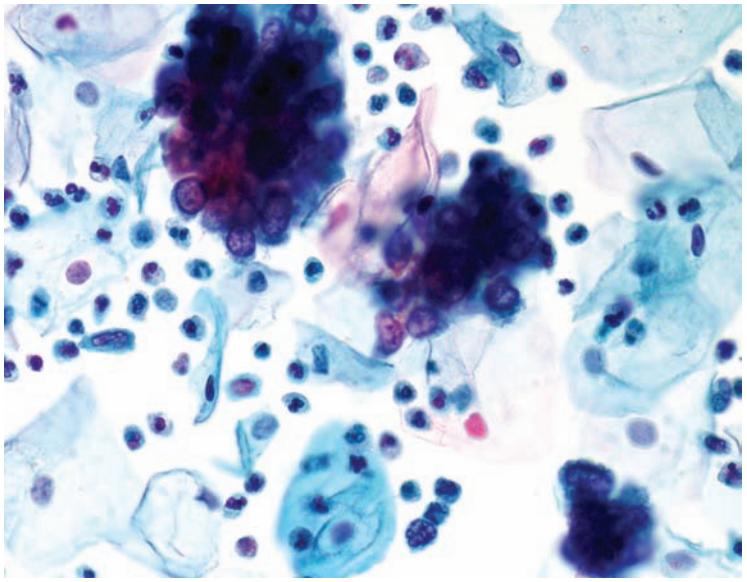


Figure 9.9 — Atypical Glandular Cells (Liquid Based; High Power). Groups of cells from the same patient, as displayed in Figure 9.8, are easier to visualize, although their origin is still obscure. They could be endometrial or ovarian. A diagnosis of "atypical glandular cells, favor neoplastic" would suffice without the clinical history. On follow-up, the patient was diagnosed with a malignant mixed Müllerian tumor (MMMT).

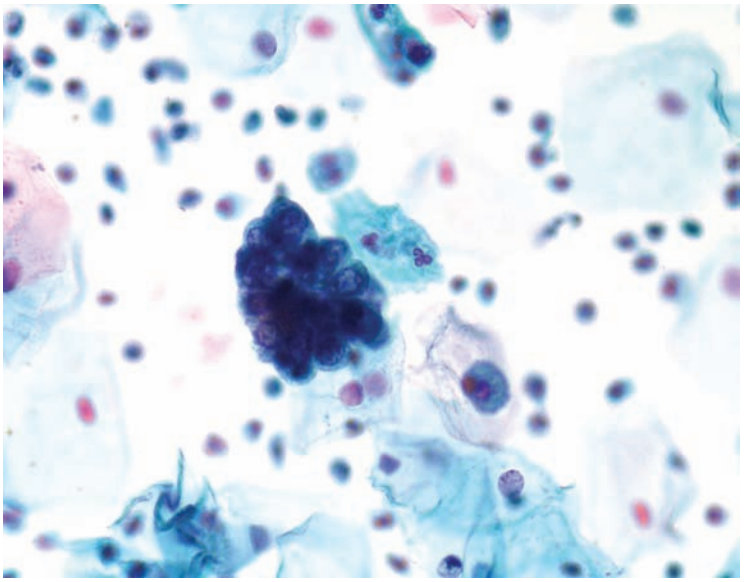


Figure 9.10 — Atypical Glandular Cells (Liquid Based; High Power). This group of cells is highly atypical due to the increased N/C ratio, dark chromatin, irregular nuclear borders, and three-dimensional arrangement. The cells in the fragment appear to be forming a gland, and the hobnailed appearance along the fragment border is suggestive of an endometrial origin. On follow-up, the patient was diagnosed with a malignant mixed Müllerian tumor (MMMT).

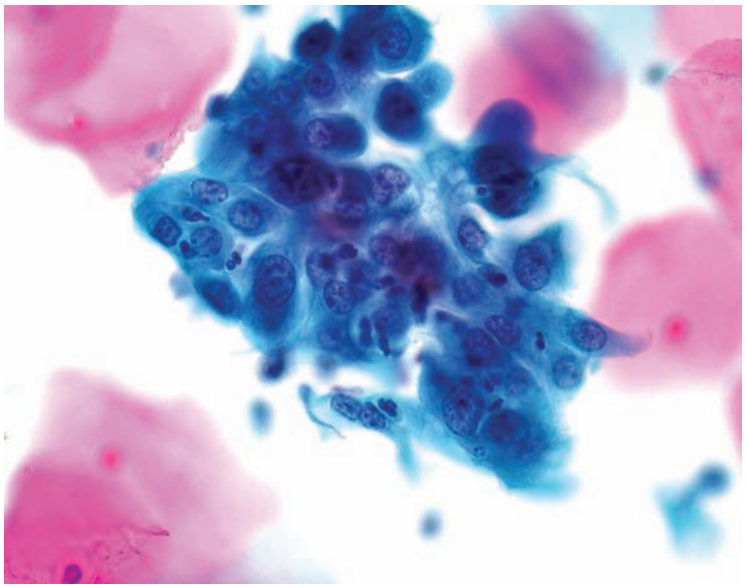


Figure 9.11 — Atypical Glandular Cells (Liquid Based; High Power). Loosely attached glandular cells demonstrate enlarged nuclei, conspicuous nucleoli, and opaque cytoplasm with defined cytoplasmic boundaries. Neutrophils are peppered within the group. The cell size is compatible with endocervical origin, and the reactive changes are consistent with a polyp.

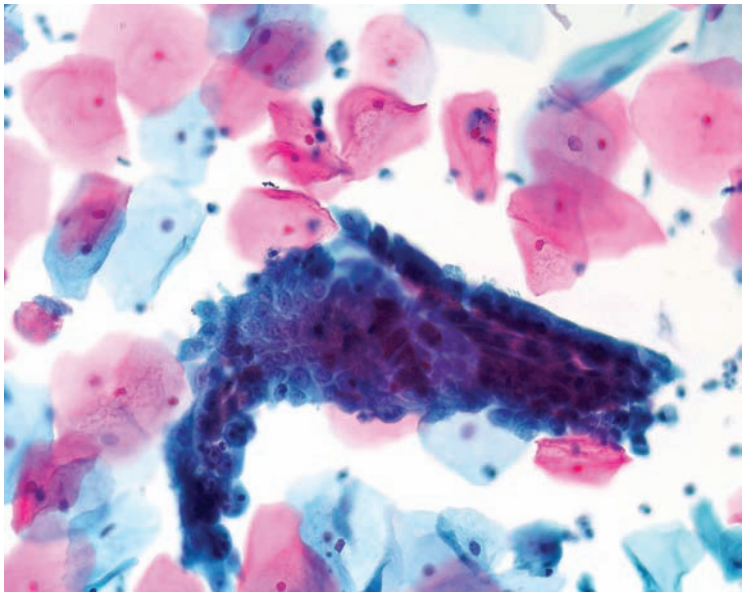


Figure 9.12 — Atypical Glandular Cells (Liquid Based; Medium Power). This large fragment of glandular tissues appears well organized, including the straight luminal edge at the upper portion of the fragment. The nuclei appear uniformly small and the cytoplasm is scant. An endocervical polyp was found on follow-up.

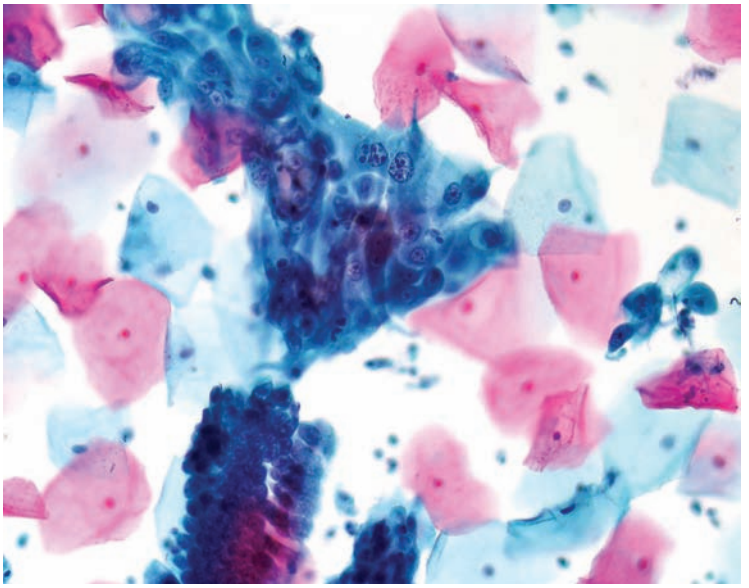


Figure 9.13 — Atypical Glandular Cells (Liquid Based; Medium Power). The tissue fragment in the upper half of the figure displays the same characteristics as the cells in Figure 9.11. The fragment in the lower half of the photo is composed of smaller endocervical cells identified by a very uniform mucosal seam along the right portion of the fragment. The latter fragment is probably from normal endocervical tissue, whereas the inflamed tissue is typical of the surface of an irritated polyp.

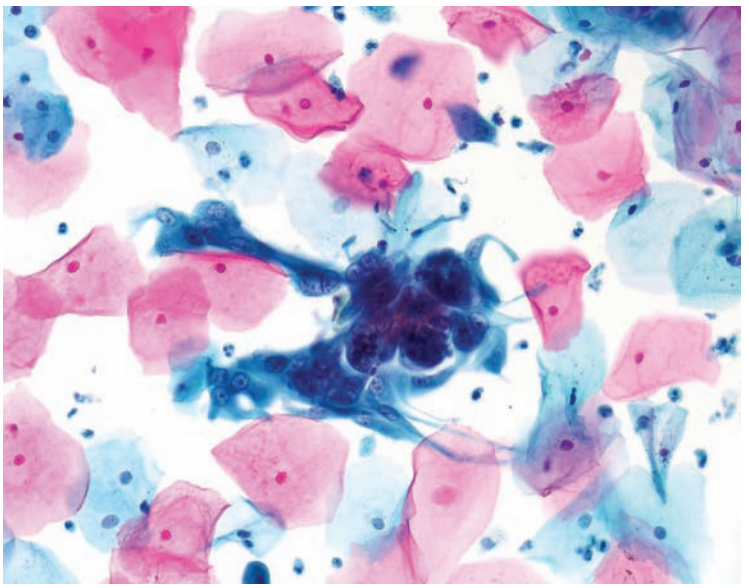


Figure 9.14 — Atypical Glandular Cells (Liquid Based; Medium Power). The surface of a polyp can become atypical because of irritation, and acquire the features of atypical repair. These changes may mimic a glandular neoplasm, but attention to the fine nuclear chromatin and attenuated tails of cytoplasm will assure that this lesion is benign. An endocervical polyp was found on follow-up.

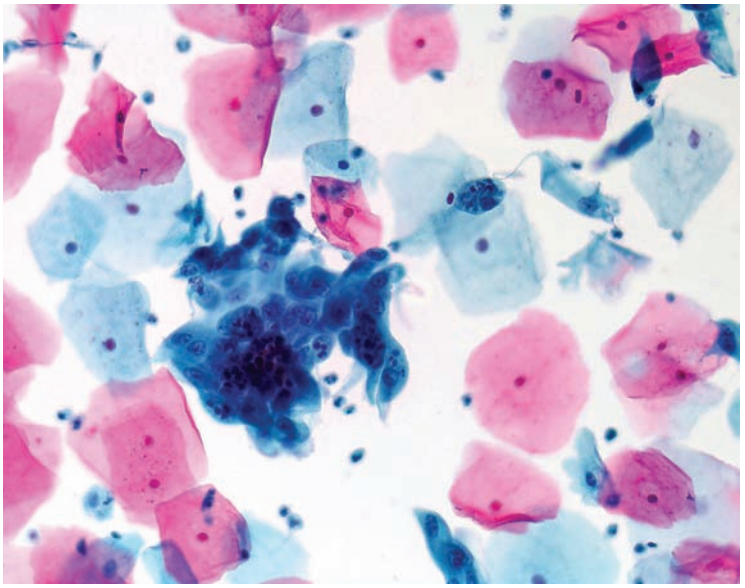


Figure 9.15 — Atypical Glandular Cells (Liquid Based; Medium Power). This fragment has acquired a metaplastic appearance because of the very opaque cytoplasm and well-defined cell boundaries. The prominent nucleoli reflect the reactive nature of these cells, as well as the neutrophils embedded in the cytoplasm. An endocervical polyp was found on follow-up.

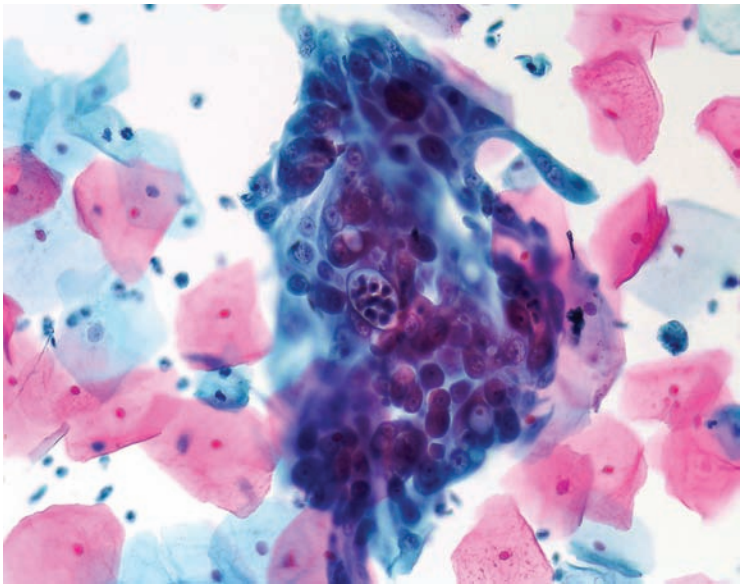


Figure 9.16 — Atypical Glandular Cells (Liquid Based; Medium Power). However agitated these cells appear, they should not be interpreted as neoplastic. Close examination of the thin nuclear membranes and fine chromatin are convincing factors for a benign process. The vacuoles containing neutrophils might mislead the observer to consider an endometrial carcinoma, but the opaque cytoplasm is consistent with a squamous origin. The entire picture is that of atypical repair, classic for the surface of an endocervical polyp.

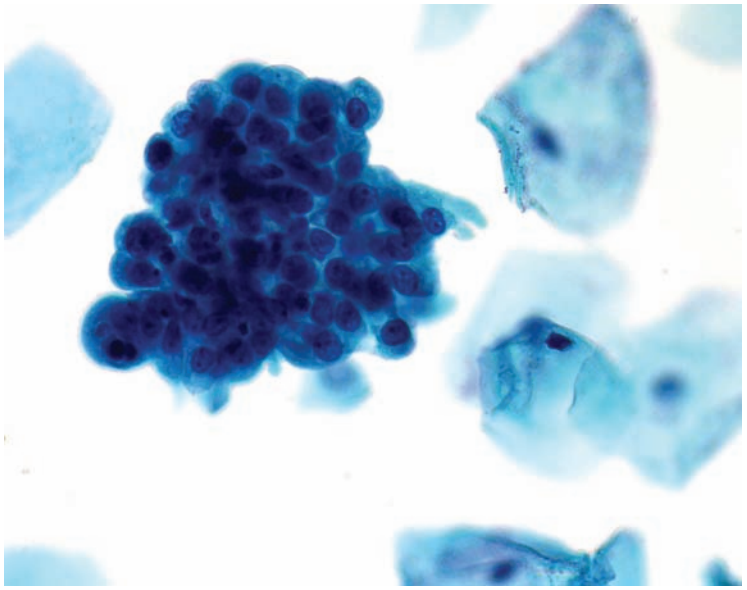


Figure 9.17 — Atypical Glandular Cells (Liquid Based; High Power). Areas of polyps not exposed to vaginal irritation will retain their normal endocervical morphology, that is, low columnar or cuboidal shape with slightly opaque cytoplasm, indicating a metaplastic transformation. Nuclear shapes are round and size is uniform.

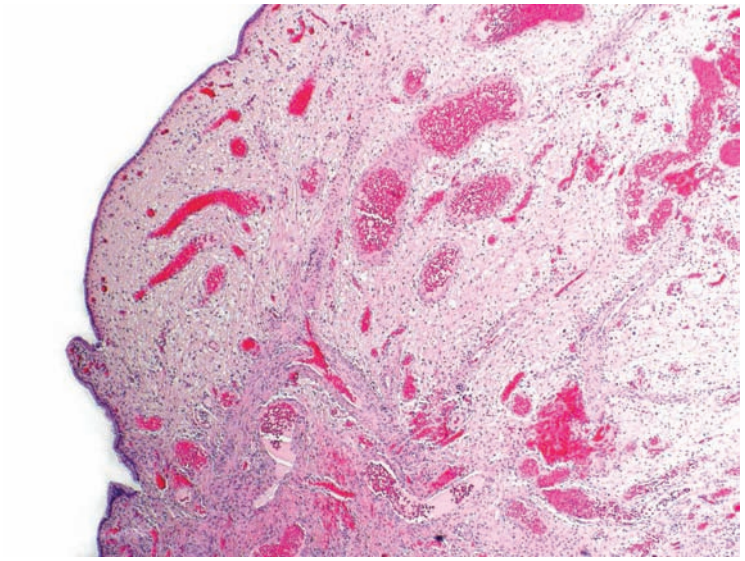


Figure 9.18a — Endocervical Polyp (Polypectomy) (H&E Stain; Low Power). The lesion is polypoid and lined by mucinous epithelium. Abundant stroma is present, which is hypocellular and myofibroblastic. Numerous large thick-walled vessels are seen.

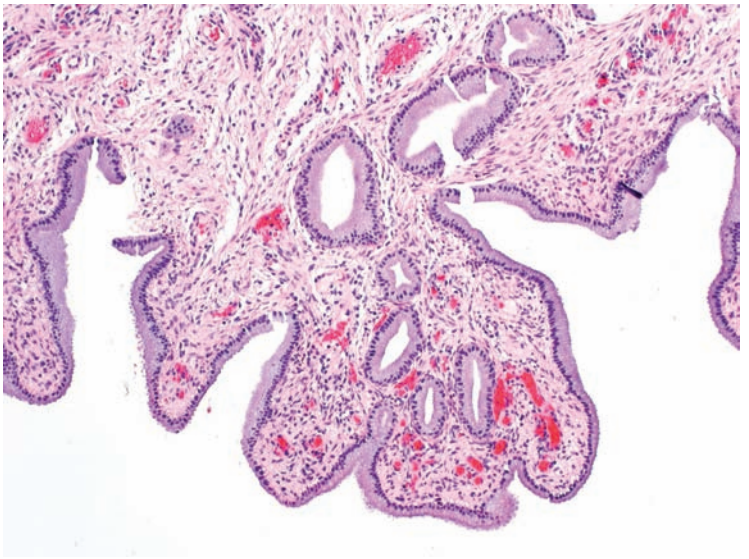


Figure 9.18b — Endocervical Polyp (Polypectomy) (H&E Stain; High Power). The glandular epithelium is non-stratified and composed of columnar mucinous cells. The nuclei are small, round, uniform, and basally situated. Atypia, mitotic activity, and apoptotic bodies are all absent. The appearance of the glands and stroma is virtually identical to normal endocervical mucosa.

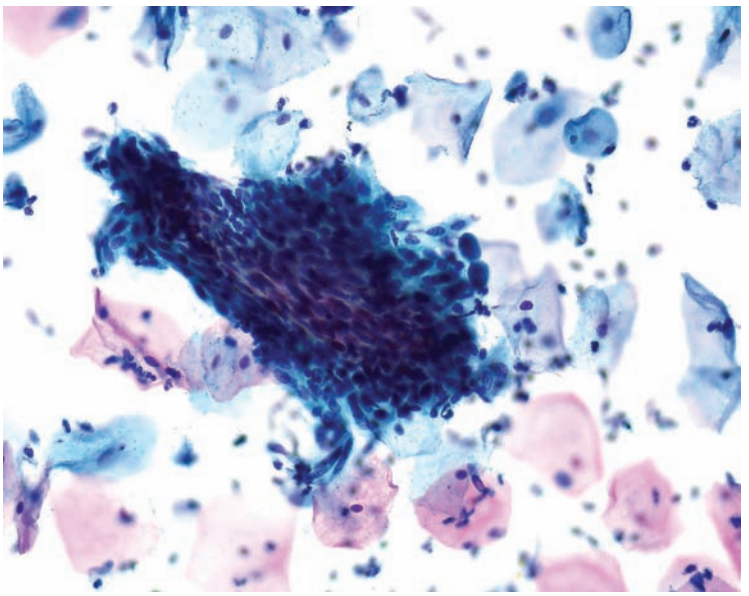


Figure 9.19 — Atypical Glandular Cells (Liquid Based; Medium Power). This thick fragment of glandular type tissue might be a benign hyperchromatic crowded group or a lesion from the endocervix. Higher magnification is necessary to see the individual cells. The patient was diagnosed with AIS on follow-up biopsy.

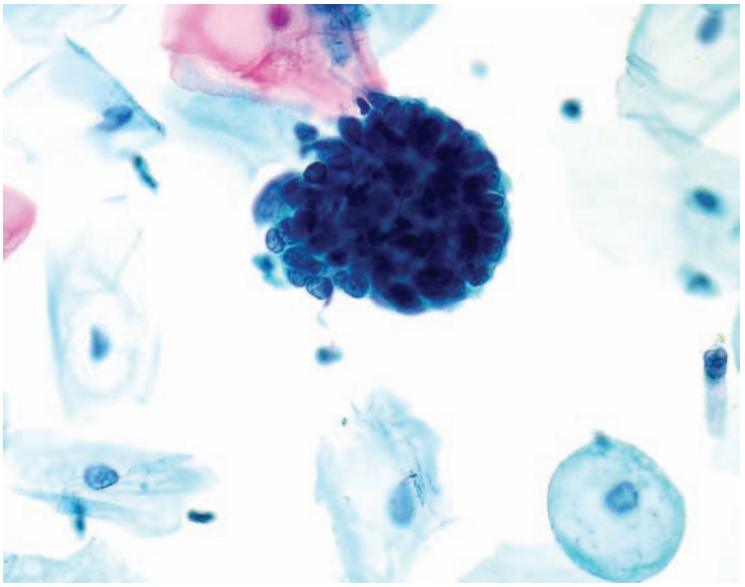


Figure 9.20 — Atypical Glandular Cells (Liquid Based; High Power). Along the edge of this hyperchromatic crowded group are cells with visible criteria of neoplasia, that is, high N/C ratios and grainy chromatin. Tiny chromocenters are present and should not be interpreted as the nucleoli of reactive endocervical cells. The patient was diagnosed with AIS on follow-up biopsy.

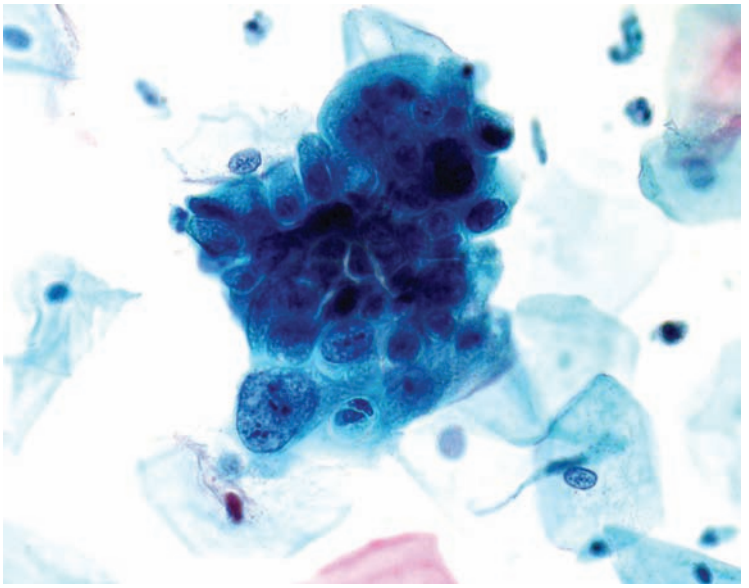


Figure 9.21 — Atypical Glandular Cells (Liquid Based; High Power). Anisonucleosis is the predominant feature of this tissue fragment, which is more likely from the glandular portion of the lesion than from the squamous. The lesional cells are bordered by benign columnar cells, which have distinct terminal bars, and perhaps cilia. AIS and HSIL frequently coexist, a reflection of mutual vulnerability to human papillomavirus (HPV) infection. The patient was diagnosed with AIS on follow-up biopsy.

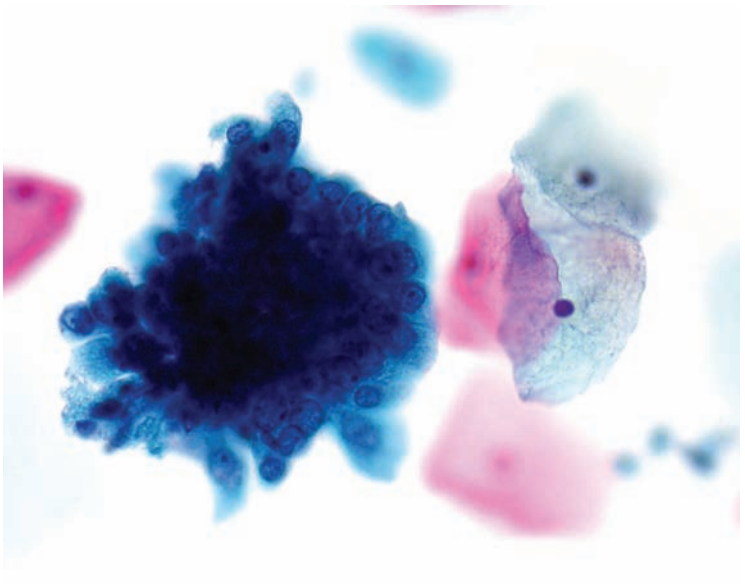


Figure 9.22 — Atypical Glandular Cells (Liquid Based; High Power). This hyperchromatic crowded group may mimic a neoplasm, unless the edge of the group is examined carefully. The amount of cytoplasm is abundant, and the basal location of the nuclei along the right side of the fragment indicates an orderly growth. Follow-up curettage demonstrated endocervical microglandular hyperplasia.

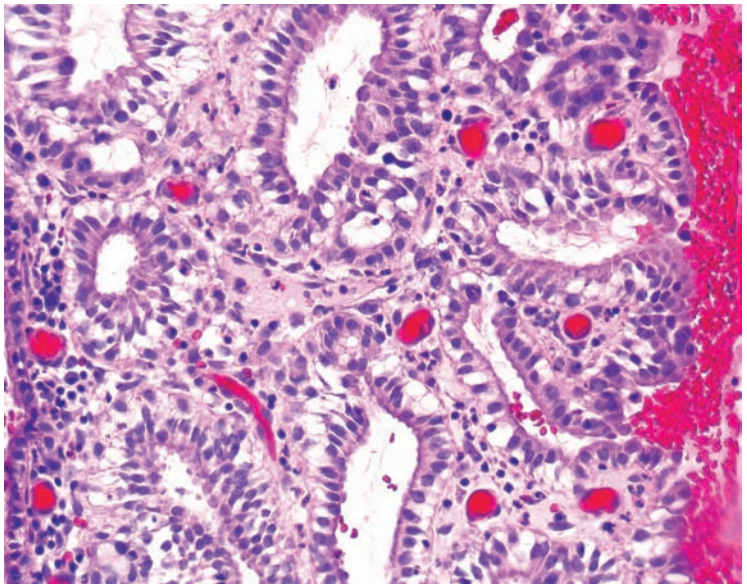


Figure 9.23 — Endocervical Microglandular Hyperplasia (Curettage) (H&E Stain; High Power). The glands are of relatively small caliber, round, and crowded. They are lined by non-stratified columnar cells with mucinous cytoplasm. The nuclei are small, round, and uniform and do not exhibit atypia or mitotic activity. Note prominent subnuclear vacuoles. The stroma is edematous and contains mixed acute and chronic inflammation. These are all typical features of microglandular hyperplasia. However, it should be remembered that some endometrial carcinomas can have an endocervical microglandular hyperplasia-like appearance.

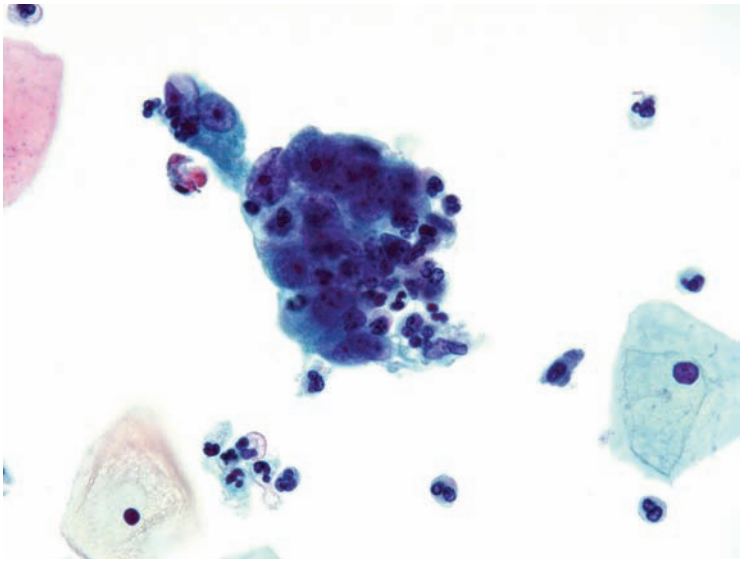


Figure 9.24 — Atypical Glandular Cells (Liquid Based; High Power). The cells in this group have enlarged nuclei with coarse, dark chromatin and prominent nucleoli. Their cytoplasm is foamy and the eccentrically placed nuclei suggest a glandular origin. Associated neutrophils suggest the possibility that these are endometrial cells and thus the primary concern is for an endometrial malignancy. However, this smear comes from a pregnant patient, and the markedly atypical changes are benign pregnancy-related changes known as the Arias-Stella reaction (phenomenon).

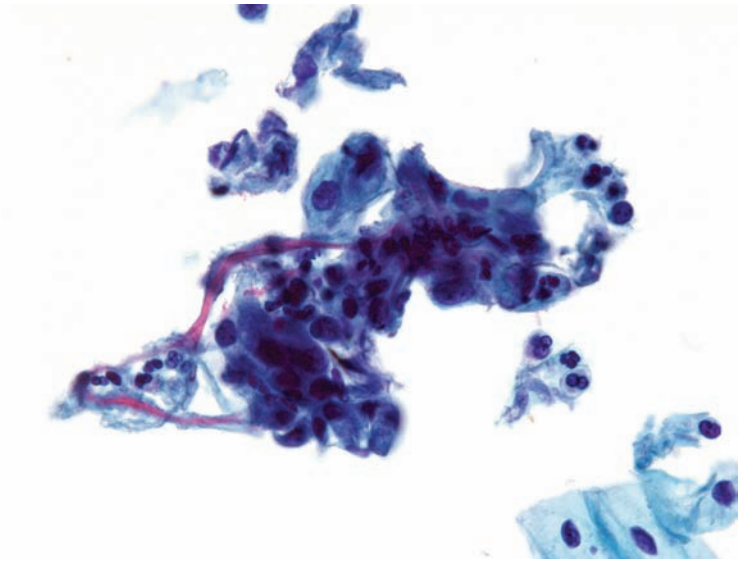


Figure 9.25 — Atypical Glandular Cells (Liquid Based; Medium Power). This is a second example of an Arias-Stella reaction. Without an appropriate history, these atypical changes are often misdiagnosed as atypical glandular cells or as a squamous intraepithelial lesion. The changes were initially described by Dr. Javier Arias-Stella, a Peruvian pathologist, in cases previously thought to represent an early form of endometrial carcinoma.

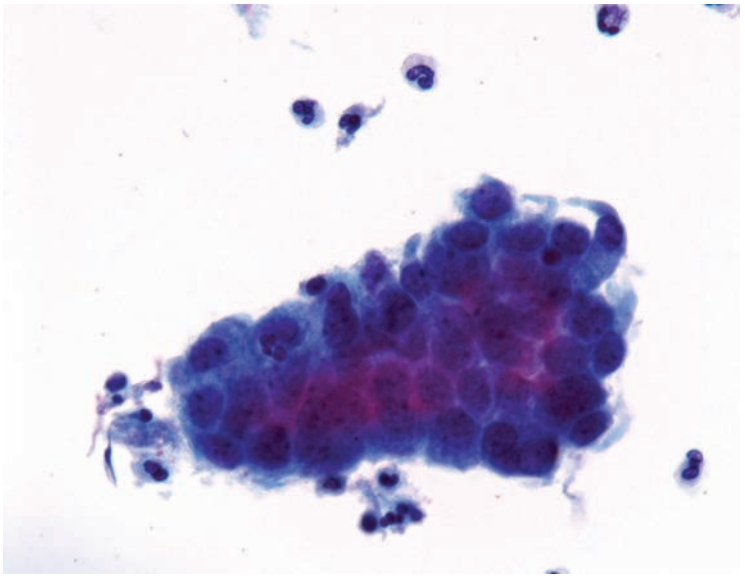


Figure 9.26 — Atypical Glandular Cells (Liquid Based; Medium Power). Nuclear enlargement is a common feature of the Arias-Stella reaction, as demonstrated by the cells in this fragment. Although the atypical features are prominent, there is an underlying orderliness to the fragment. Although Arias-Stella changes were initially described in the endometrium, it has since been shown that they can also occur in the endocervix.

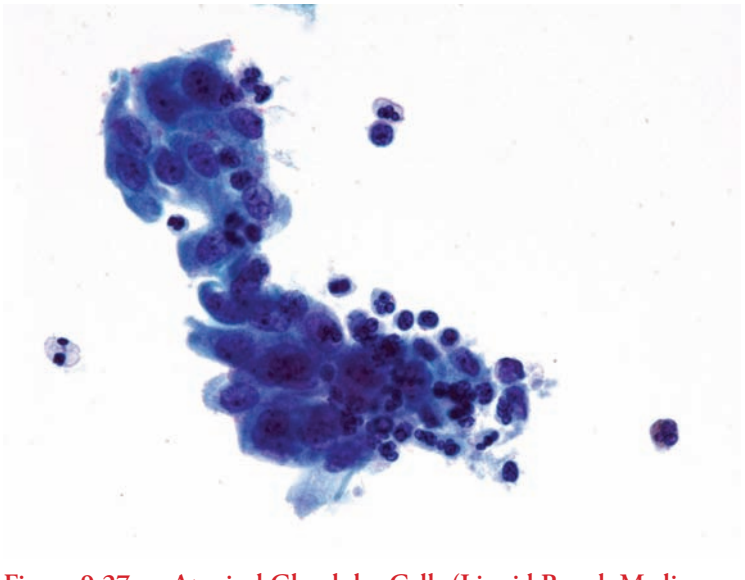


Figure 9.27 — Atypical Glandular Cells (Liquid Based; Medium Power). The atypical cells are hyperchromatic, contain coarse chromatin, and have enlarged nuclei. However, the nuclei do not typically overlap in the Arias-Stella reaction. Because this fragment is less intact than in the previous example, the architecture appears more disorganized.

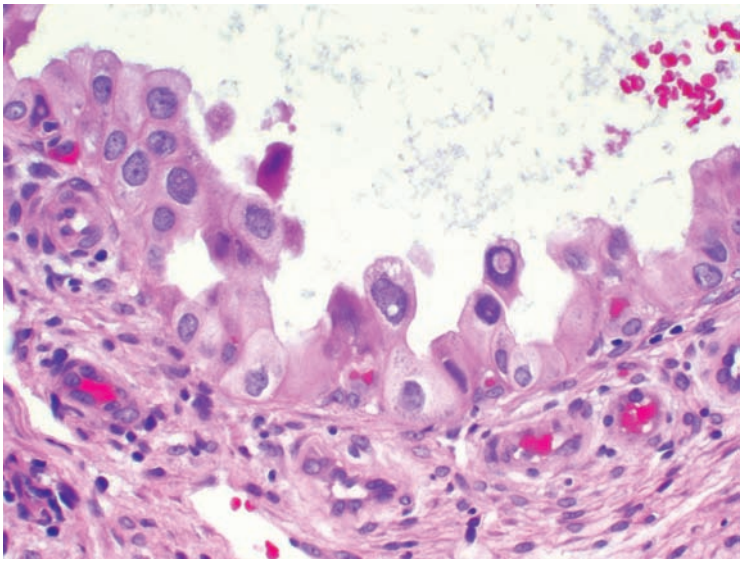


Figure 9.28 — Endocervical Arias-Stella Reaction (Polypectomy) (H&E Stain; High Power). The endocervical glandular epithelium exhibits nuclear enlargement, intranuclear inclusions, abundant pale or clear cytoplasm, and hobnail shapes. Other cases may have cells with darker chromatin with a "smudgy" appearance. The differential diagnosis can include clear cell carcinoma; however, the combination of the aforementioned morphologic appearance, lack of other features of clear cell carcinoma (glandular confluence, papillary/tubulocystic/solid patterns, mitotic figures, hyalinized stroma, and/or stromal invasion), and the presence of progestin therapy or young age is consistent with Arias-Stella reaction.

10

Adenocarcinoma

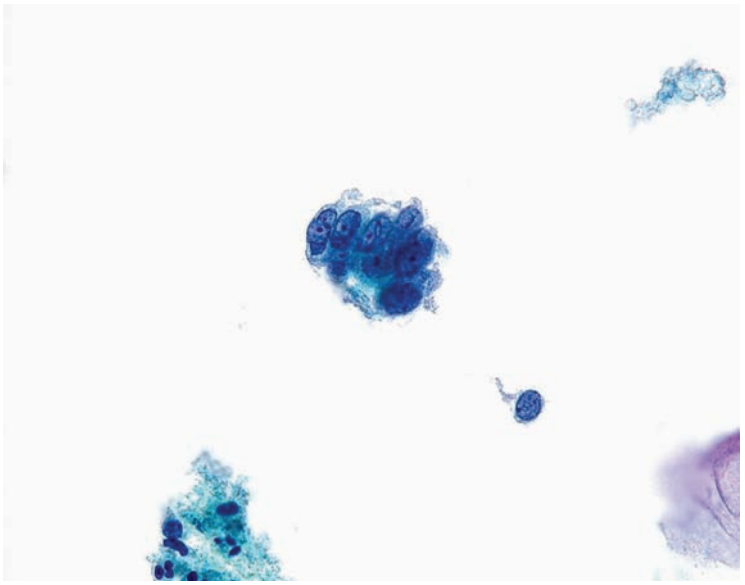


Figure 10.1 — Adenocarcinoma In Situ (AIS) (Liquid Based; High Power). Cells from the endocervix retain their columnar shapes, but the nuclei are larger than normal size, occupying more than half of the length of each cell. Nucleoli are inconspicuous, blending in with the darkened nuclear chromatin. The nucleus of the lone cell off the center is the size of a normal endocervical nucleus. The clean background supports the "in situ" designation.

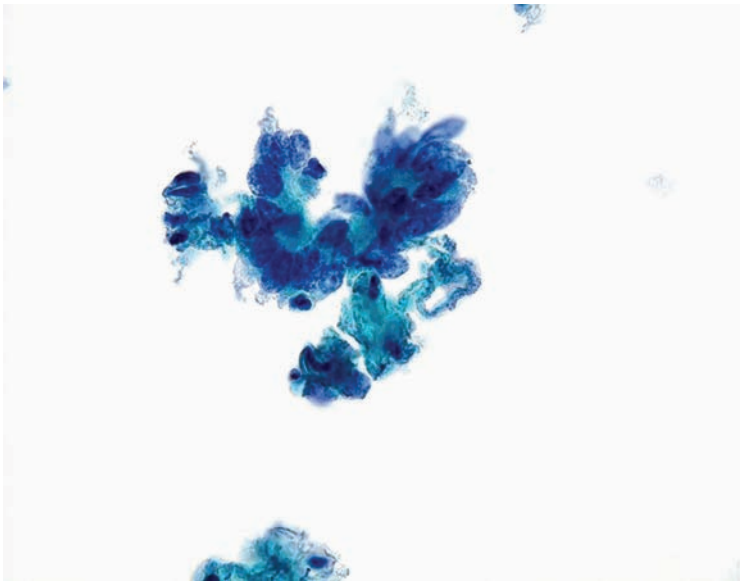


Figure 10.2 — Adenocarcinoma In Situ (AIS) (Liquid Based; High Power). Three-dimensional groups of cells are radially arranged, forming four pseudo-rosettes, an attempt at gland formation. Nuclei protrude from the edges of the glands, the characteristic "feathering" of AIS. Except for the center of the "glands," there is almost no cytoplasm visible around the nuclei.

Figure 10.3 — Adenocarcinoma In Situ (AIS) (Liquid Based; High Power). Pseudo-glands display feathering and minimal cytoplasm except for the center of the glands. Nuclear shapes vary and darkened nuclear chromatin obscures the tiny nucleoli. The background is clean of blood and necrotic debris, consistent with the AIS interpretation.

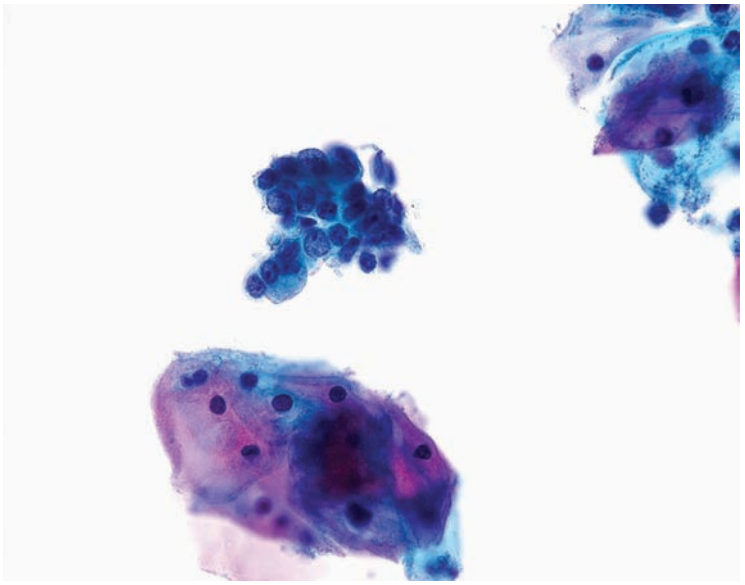


Figure 10.4 — Normal Endocervical Cells (Liquid Based; High Power). In contrast to the glandular cells in Figures 10.1–10.3, these glandular cells have smaller nuclei, are round in shape, and are about the same size as the nuclei of the intermediate squamous cells. Cytoplasm occupies two thirds of the cellular column.

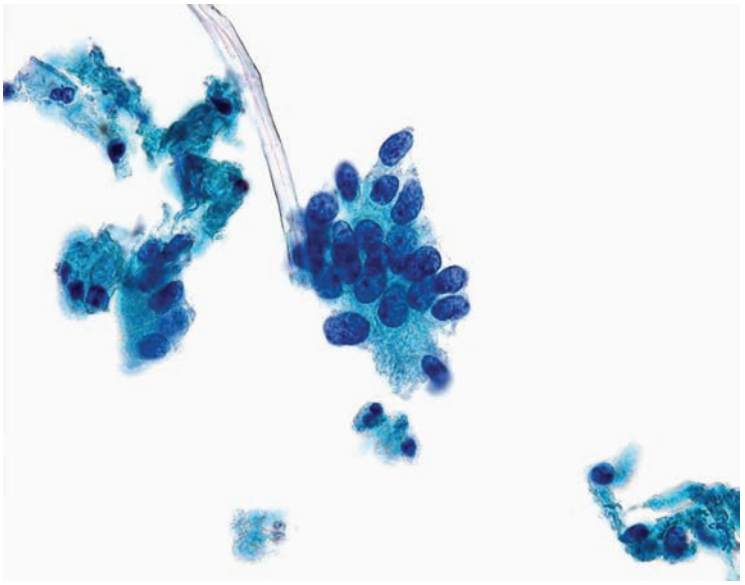


Figure 10.5 — Adenocarcinoma In Situ (AIS) With Normal Endocervical Cells (Liquid Based; High Power). Cells to the far left of the photograph are normal endocervical cells, with small nuclei and abundant cytoplasm. In contrast, the glandular group in the center is composed of cells with elongated hyperchromatic nuclei that often protrude from the outer edges of the group (feathering). The size of the AIS nuclei is three to five times the size of the normal nuclei. Cytoplasmic borders are not defined in the AIS group, whereas they are defined in the normal group.

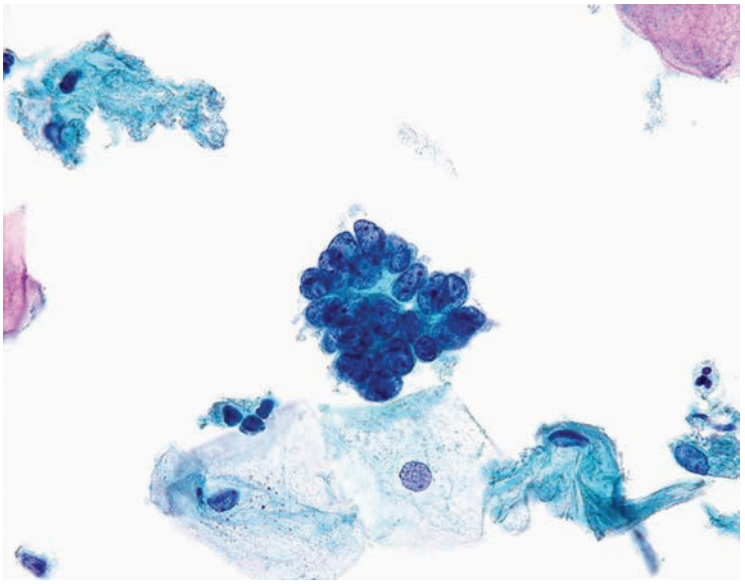


Figure 10.6 — Adenocarcinoma In Situ (AIS) (Liquid Based; High Power). A classic group of cells from an endocervical AIS forming a pseudo-gland, complete with wisps of cytoplasmic tails and protruding nuclei, the characteristic feathering of an AIS. Compare the chromatin quality and density of the intermediate squamous nuclei below the AIS group with those from the neoplasm. Crowding of the AIS nuclei and irregular nuclear shapes complete the features.

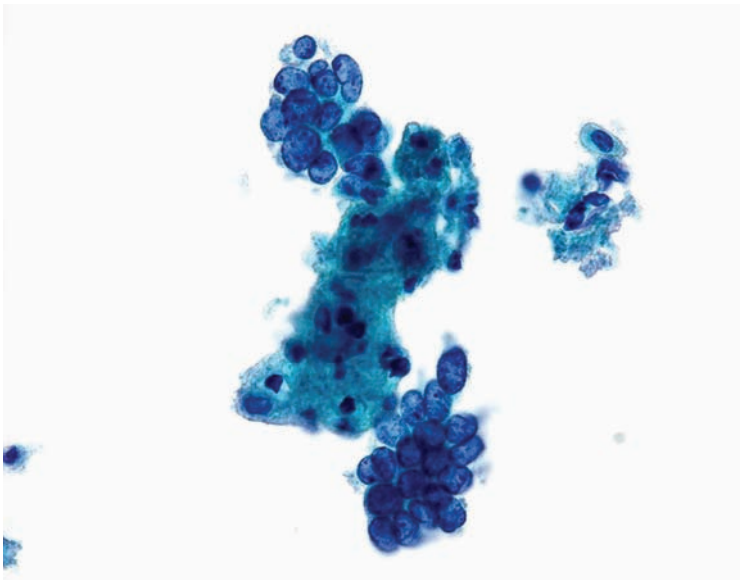


Figure 10.7 — Adenocarcinoma In Situ (AIS) (Liquid Based; High Power). Two groups of AIS cells demonstrate the crowding of cells from this neoplasm, so-called hyperchromatic crowded groups (HCGs). HCGs are not always neoplastic, but they deserve careful scrutiny, for when they are from a neoplasm, they should not be ignored. Compare with Figure 10.8.

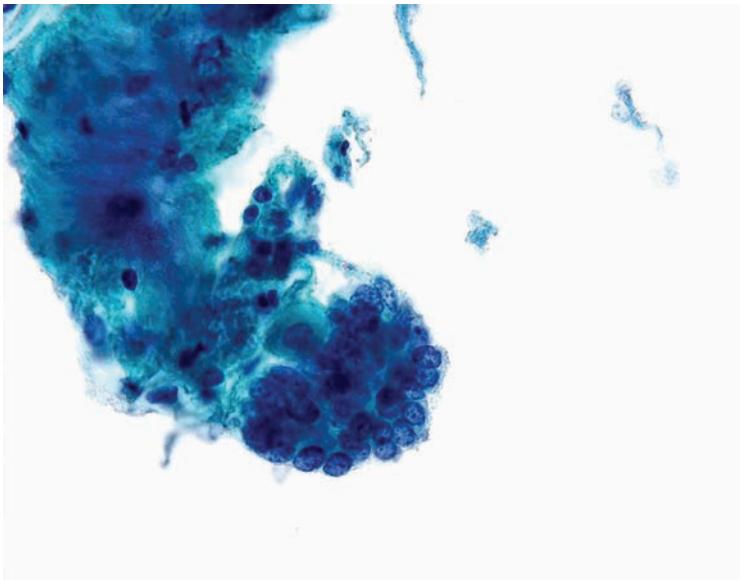


Figure 10.8 — Normal Endocervical Cells (Liquid Based; High Power). This hyperchromatic crowded group (HCG) may look similar on scanning power to those HCGs in Figure 10.7. However, the nuclear size, nuclear-to-cytoplasmic (N/C) ratios, and architecture of the groups are quite different. Every HCG in a sample deserves to be inspected carefully with high-power magnification, and not assumed to be benign simply because others in the sample are deemed benign. This is the most common pitfall in cases of adenocarcinoma in situ that eventuates in litigation.

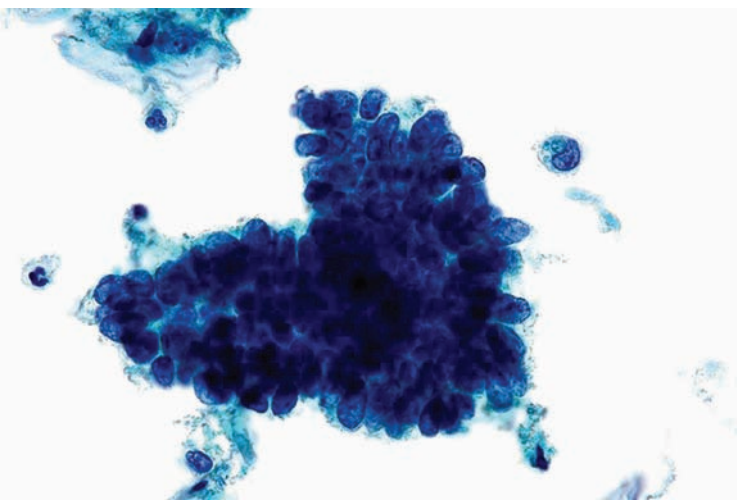


Figure 10.9 — Adenocarcinoma In Situ (AIS) (Liquid Based; High Power). A large HCG with feathered edges ("bird tail" appearance) and almost no visible cytoplasm. Nuclei in the center of group may be very difficult to visualize, but the edges of the group offer the opportunity to see the chromatin density and texture, and the variation in nuclear shape.

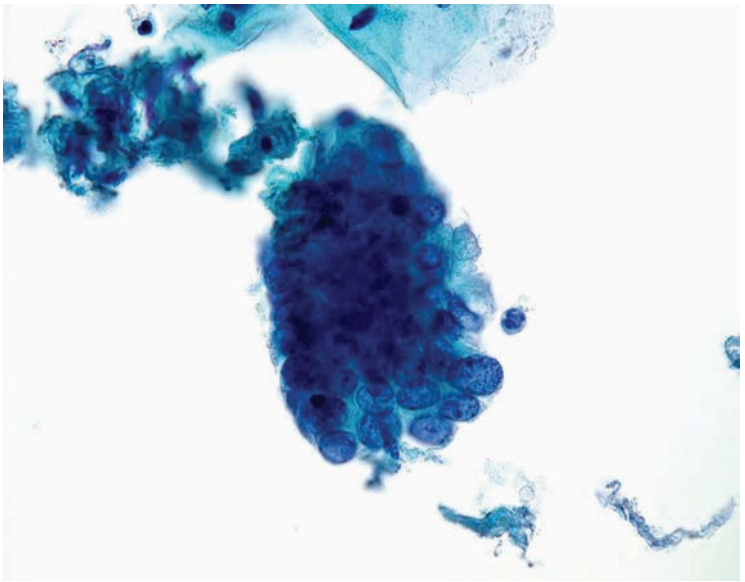


Figure 10.10 — Adenocarcinoma In Situ (AIS) (Liquid Based; High Power). A large epithelial group has a smooth left edge and could be interpreted as being formed due to gland involvement by high-grade squamous intraepithelial lesion (HSIL). The nuclei vary in size and shape, chromatin is dark and homogeneous, and nucleoli are invisible or inconspicuous. Regardless of the interpretation, AIS versus HSIL, the patient needs immediate follow-up according to current guidelines. Many patients with AIS also have HSIL concurrently, as both lesions are caused by human papillomavirus (HPV).

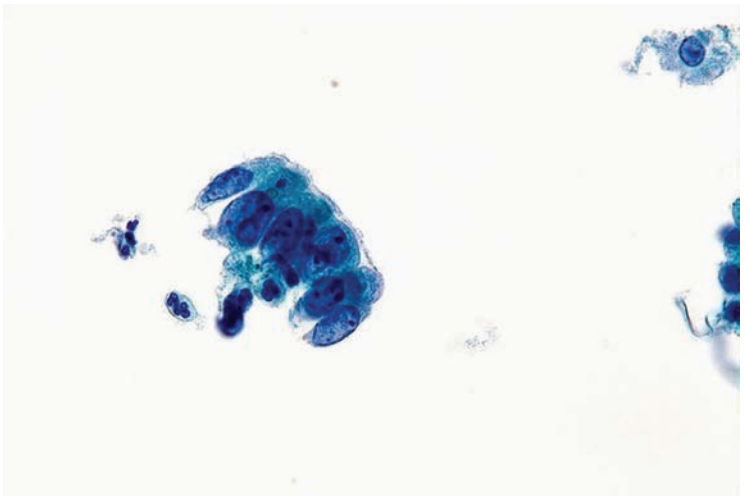


Figure 10.11 — Atypical Glandular Cells (Liquid Based; High Power). The nuclei in this flat strip of endocervical cells are enlarged and reduce the N/C ratio to the same degree as do the AIS cells. However, the nuclear shape is very smooth and the size uniform. The cytoplasmic edge of the fragment is sharp and there may be cilia attached to the cytoplasm, in which case, they could be normal cells from the lower uterine segment. Careful search of the sample is warranted for more severe atypia. Follow-up revealed AIS.

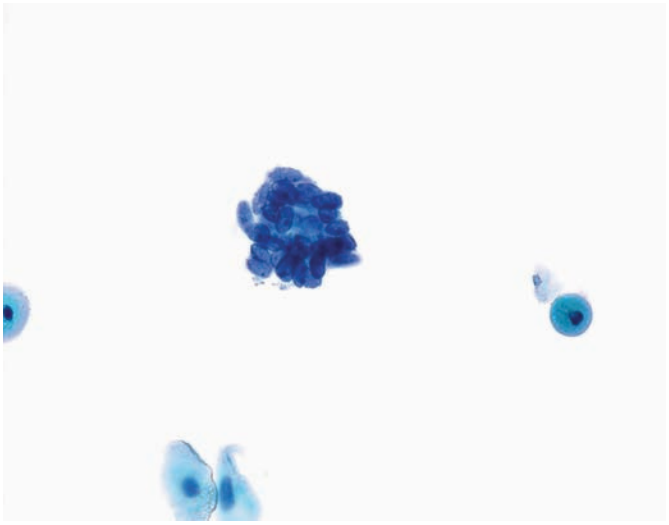


Figure 10.12 — Atypical Glandular Cells (Liquid Based; High Power). This tight cluster of essentially naked nuclei may be either from the endocervix, as a result of normal cell death, or from the endometrium. Parabasal cells on either side of the photograph suggest that the patient is menopausal, but clinical history is necessary to establish the possible origin and significance of these cells. Follow-up revealed AIS.

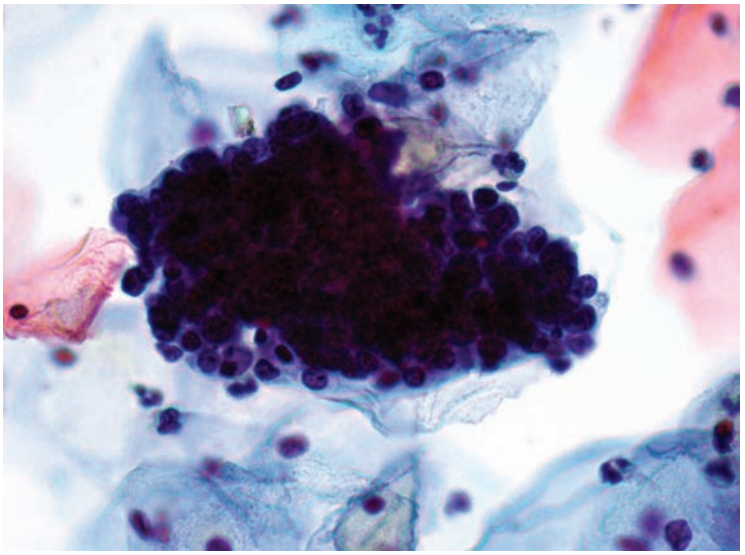


Figure 10.13 — Atypical Glandular Cells (Liquid Based; High Power). An HCG composed of very small cells with almost no cytoplasm is always problematic. Taken alone, its origin may not be verified. However, clinical correlation as well as careful search of the remainder of the sample will usually settle the question. The patient was eventually diagnosed with squamous carcinoma of the cervix, and was not menstruating at the time this sample was obtained.

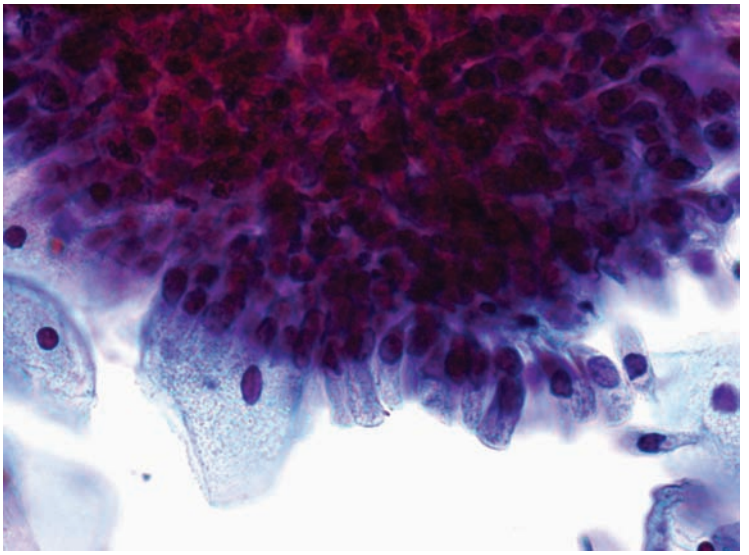


Figure 10.14 — Atypical Glandular Cells (Liquid Based; High Power). Another HCG from the same patient sample as in Figure 10.13. The edge of this group is very orderly, consistent with normal endocervical cells. However, careful examination of the deeper areas of the group disclosed disorganization and atypical cells with high N/C ratios. The ultimate squamous lesion was initially thought to be neuroendocrine, but immunohistochemistry on the hysterectomy tissue was negative for neuroendocrine differentiation, and positive for squamous origin and HPV infection.

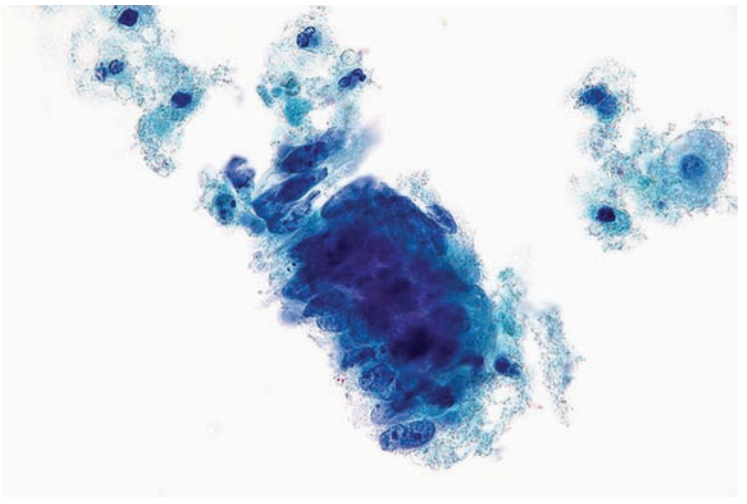


Figure 10.15 — Adenocarcinoma In Situ Suspicious for Invasion (Liquid Based; High Power). The classic feature of invasion in a liquid-based Pap test is "clinging diathesis." The cell group has elongated nuclei that feather off the left edge of the group. However, because of the lysed blood clinging to the cells, an invasive lesion should be suspected.

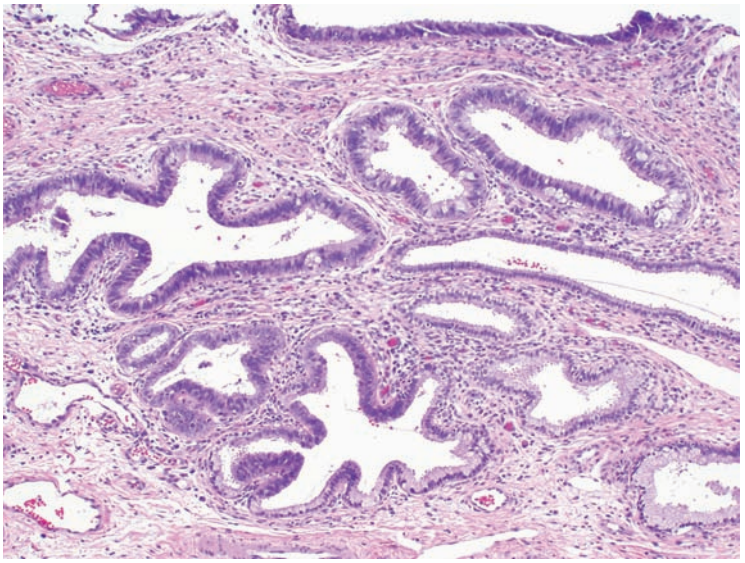


Figure 10.16a — Endocervical Adenocarcinoma In Situ (Loop Electrosurgical Excision Procedure [LEEP]) (Hematoxylin and Eosin [H&E] Stain; Intermediate Power). The glandular architecture is preserved, but the glandular epithelium has been replaced by neoplastic cells, which stain darkly at this level of magnification. Note the sharp transition between lesional and normal epithelium.

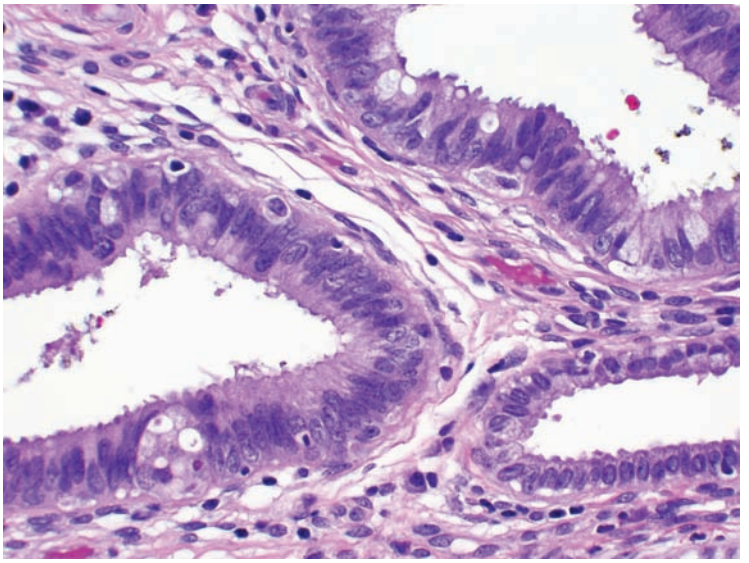


Figure 10.16b — Endocervical Adenocarcinoma In Situ (LEEP) (H&E Stain; High Power). The neoplastic cells are columnar and have oval to columnar hyperchromatic nuclei. There is loss of mucin, which results in a relatively increased N/C ratio. This finding produces the darkly staining glands seen at lower power magnification. A normal gland is in the lower right-hand corner of the photograph.

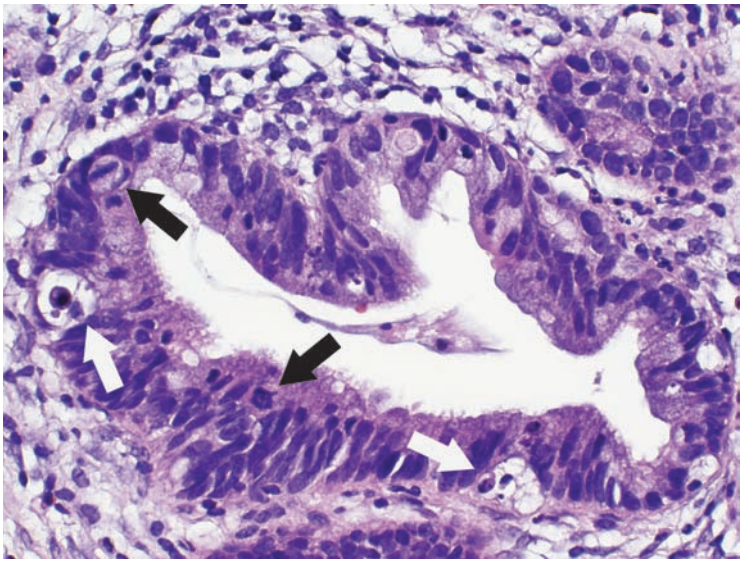


Figure 10.16c — Endocervical Adenocarcinoma In Situ, Histologic Section (LEEP) (H&E Stain; High Power). In this example, the glands have features similar to Figure 10.16b. Note the presence of mitotic figures (black arrows) and basal apoptotic bodies (white arrows), which are common in endocervical adenocarcinoma in situ.

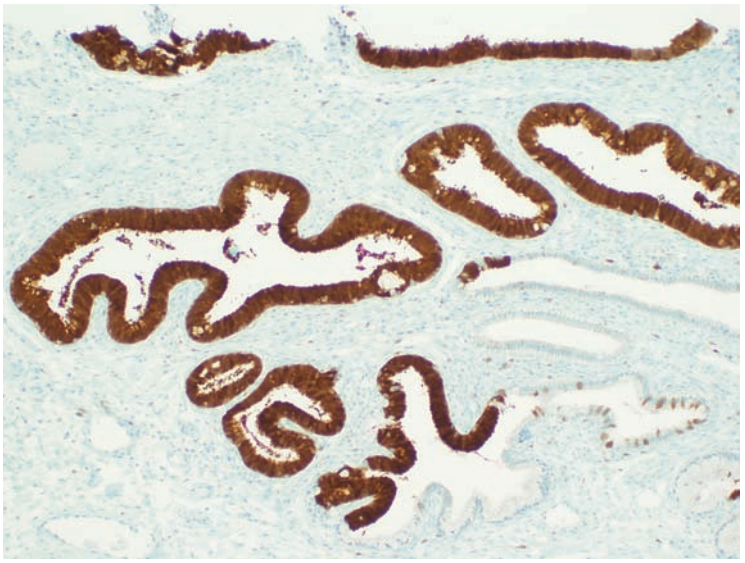


Figure 10.16d — Endocervical Adenocarcinoma In Situ, Histologic Section (LEEP) (p16 Immunohistochemical Stain; Intermediate Power). Diffuse expression of p16 is present within the neoplastic epithelium, consistent with high-risk HPV. The adjacent normal glands have no to focal staining for contrast. Endocervical adenocarcinoma in situ is etiologically related to high-risk HPV. See Figure 10.16a for corresponding H&E photograph.

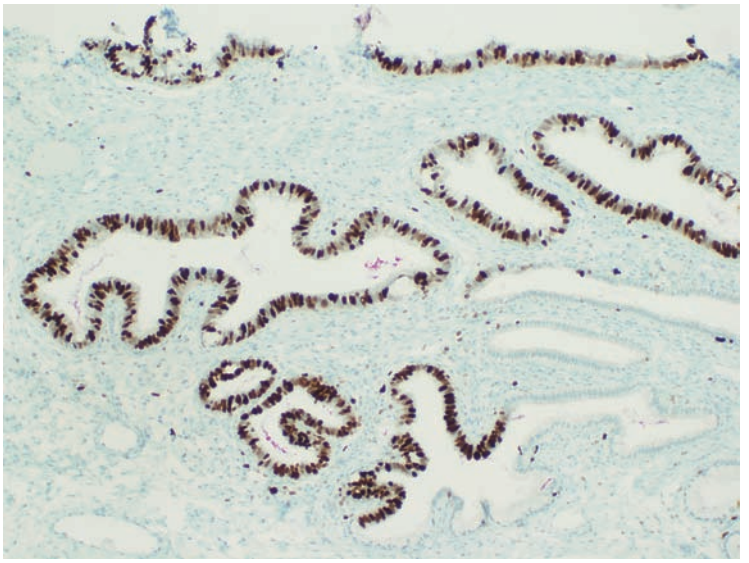


Figure 10.16e — Endocervical Adenocarcinoma In Situ, Histologic Section (LEEP) (Ki-67 Immunohistochemical Stain; Intermediate Power). The neoplastic epithelium shows a high proliferation index. The adjacent normal glands, in contrast, have a low index. Immunohistochemical stains for estrogen receptor (ER) and progesterone receptor (PR) typically show loss of expression. See Figure 10.16a for corresponding H&E photograph.

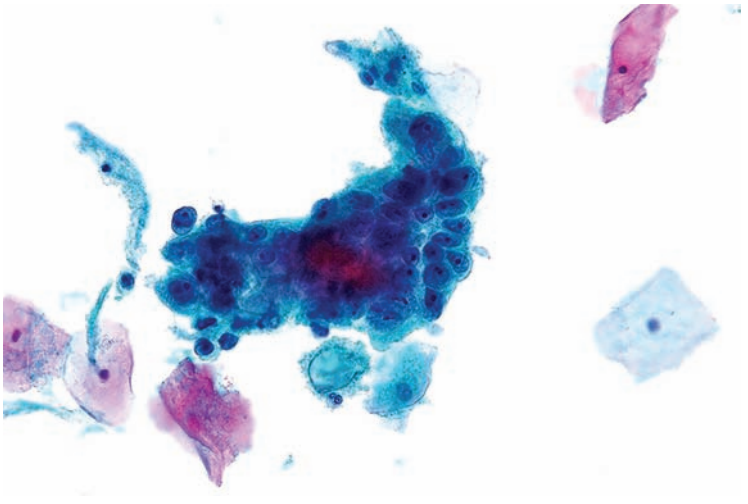


Figure 10.17 — Endocervical Adenocarcinoma (Liquid Based; Medium Power). In contrast to the nuclei in Figure 10.15, those in this malignant tissue fragment are generally round; nucleoli are prominent, single, and central; and chromatin is deceptively pale and uniform. Clinging diathesis is suggested by the hazy outline of the group at this magnification.

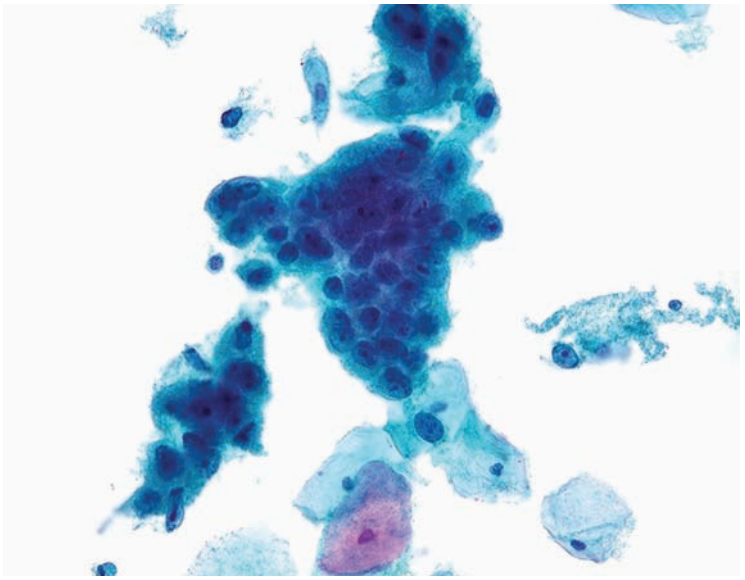


Figure 10.18 — Endocervical Adenocarcinoma (Liquid Based; Medium Power). At first glance, this group could be mistaken for reactive endocervical cells. However, the variation in N/C ratios and overlapping nuclei indicate architectural disorder. At the upper left corner, a benign endocervical cell will provide the comparative size of the nuclei and N/C ratio.

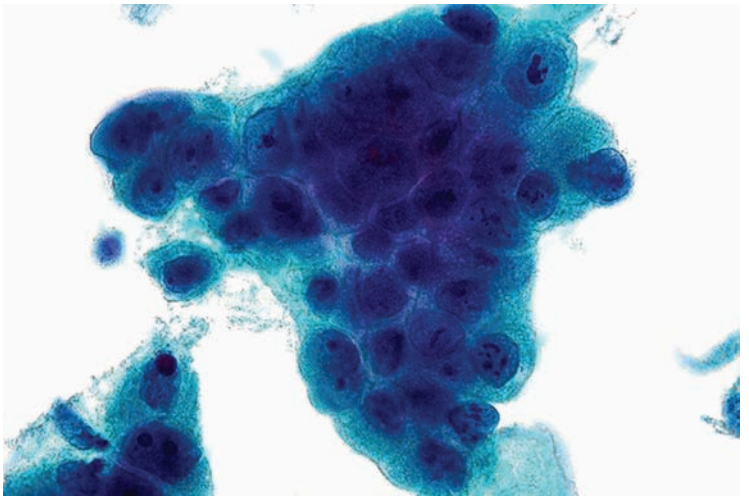


Figure 10.19 — Endocervical Adenocarcinoma (Liquid Based; High Power). The same fragment as in Figure 10.18 confirms the loss of polarity, variation in N/C ratios, and an abnormal mitotic figure. Clinging diathesis completes the criteria for invasive adenocarcinoma.

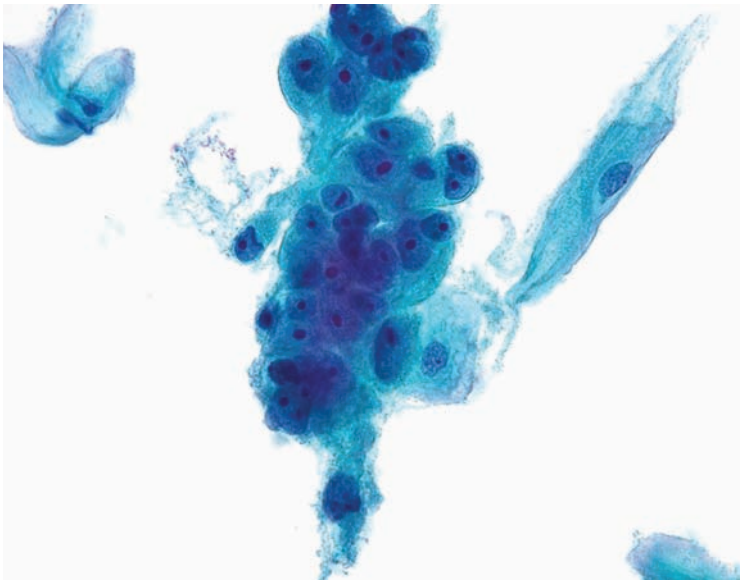


Figure 10.20 — Endocervical Adenocarcinoma, High Grade (Liquid Based; High Power). A true tissue fragment of glandular type cells consists of enlarged cells with high N/C ratios, homogeneous nuclear chromatin, and prominent nucleoli. Nuclear shapes are variable as is nuclear size. On either side of the fragment are two smaller glandular cells, most likely also from the endocervix. The nucleus of the nearby intermediate cell performs as a reliable size marker. Note the clinging diathesis attached to the tumor fragment.

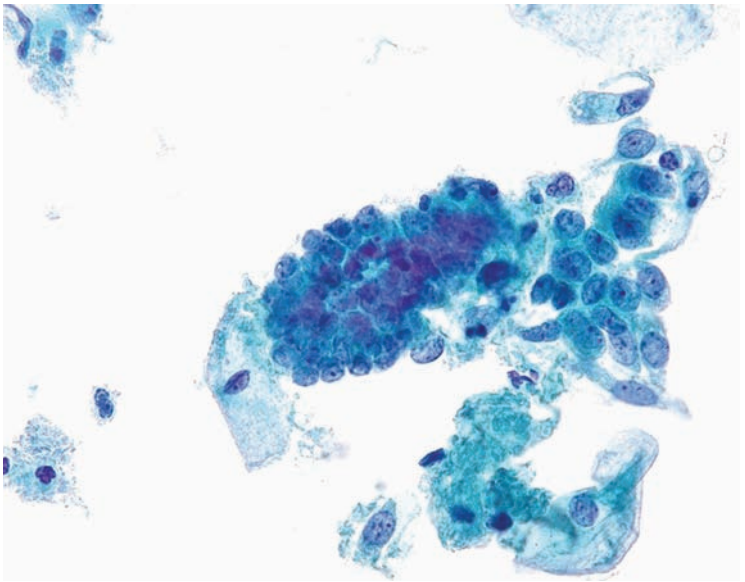


Figure 10.21 — Endocervical Adenocarcinoma, Low Grade (Liquid Based; Medium Power). The central fragment of tissue is noteworthy due to the nuclear crowding and lack of cellular borders. Otherwise, the nuclear size is comparable to the benign endocervical cells adjacent to the right side of the tumor fragment. However, chromatin density and texture differ between the benign and malignant cells, as does the N/C ratios. Clinging diathesis completes the malignant features.

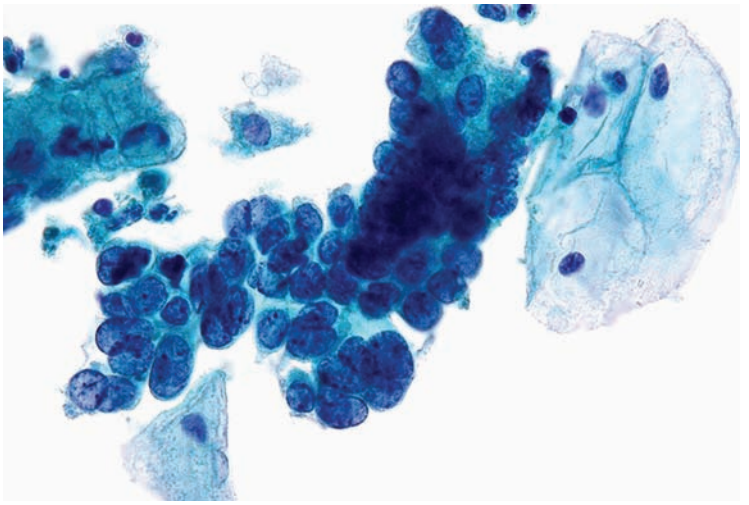


Figure 10.22 — Endocervical Adenocarcinoma, Low-Grade Versus Adenocarcinoma In Situ (AIS) (Liquid Based; High Power). The neoplastic cells have all of the features of AIS, especially in the central portion of the photograph, where gland formation can be appreciated. In the left half of the figure, tumor cells vary greatly in size, nuclear overlap is common, and architecture is disorganized. The chromatin quality of both cell populations is similar and nucleoli are inconspicuous or absent. Normal endocervical cells may be seen in the upper left corner of the figure.

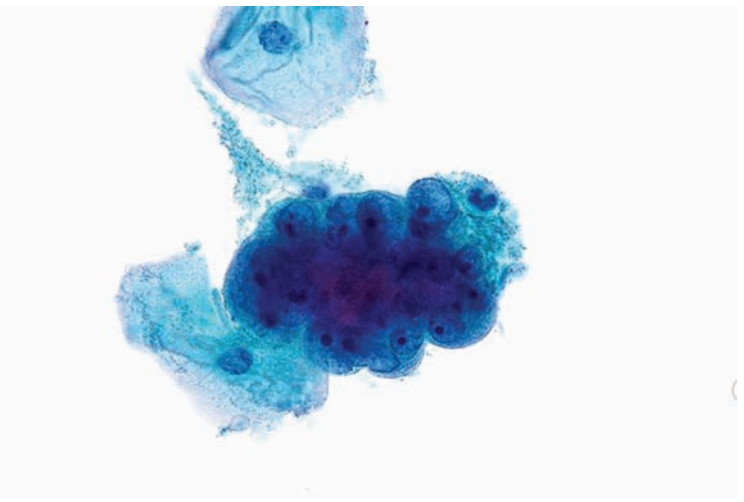


Figure 10.23 — Endocervical Adenocarcinoma, High-Grade (Liquid Based; High Power). Glandular cells are enlarged with high N/C ratios, round nuclei, very prominent nucleoli, sharp cytoplasmic borders, and opaque cytoplasm. These features, in contrast to low-grade adenocarcinoma, are typical of the high-grade variant.

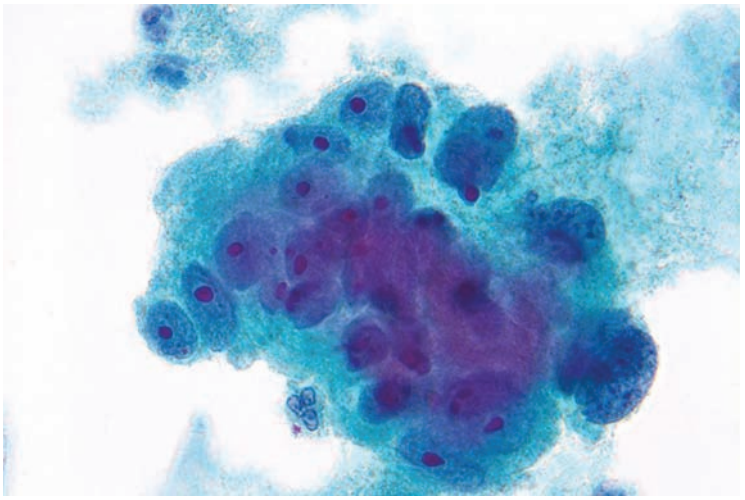


Figure 10.24 — Endocervical Adenocarcinoma, High-Grade (Liquid Based; High Power). Unlike the group of adenocarcinoma cells in Figure 10.23, these cells are not visibly separated by cytoplasmic borders. Cytoplasmic quality is more granular than opaque, perhaps a sign of impending cellular death. Nuclei are very large (compared to neutrophils at the lower edge of the group), and vary in size and shape; nucleoli are large, round, singular, and central. Proteinaceous debris is present in the background.

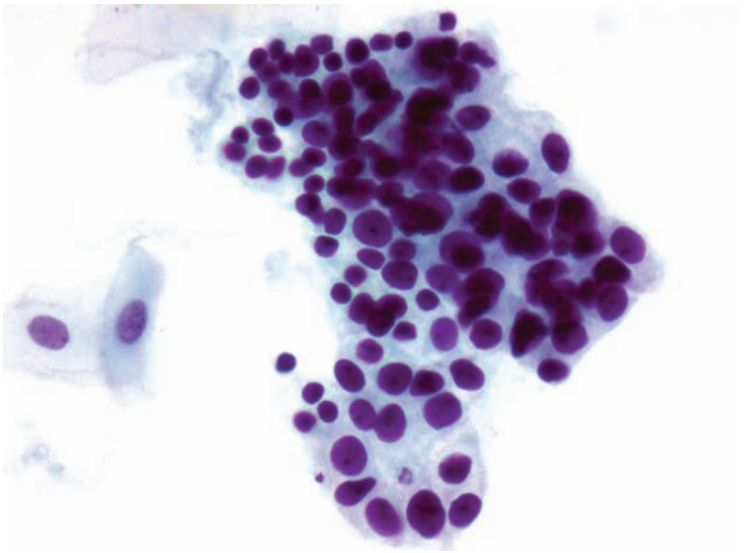


Figure 10.25 — Adenocarcinoma In Situ (AIS) Preceding Adenocarcinoma (Liquid Based; High Power). Within this tissue fragment, nuclei are more hyperchromatic than those in the two intermediate cells to the left. The architecture is a valid attempt at acinar formation, albeit with glands of variable size. Eighteen months later, the patient was diagnosed with endocervical adenocarcinoma.

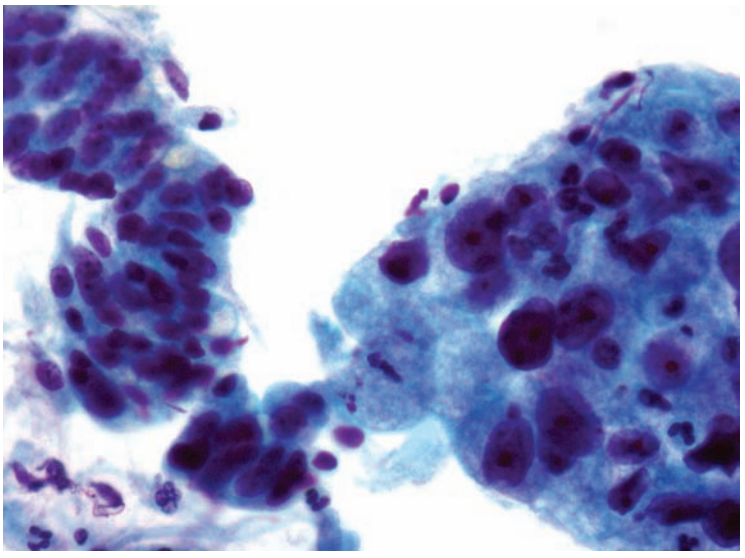


Figure 10.26 — Adenocarcinoma (Liquid Based; High Power). The epithelial strip on the left displays all the characteristics of AIS, that is, tall nuclei, high N/C ratios, feathering, and gland formation. The fragment on the right is pleomorphic, disorganized, composed of cells with large round nuclei containing nucleoli, and variable N/C ratios, consistent with adenocarcinoma. The two lesions may exist side by side, as they are here. Note that the background is clean implying early invasion, if any.

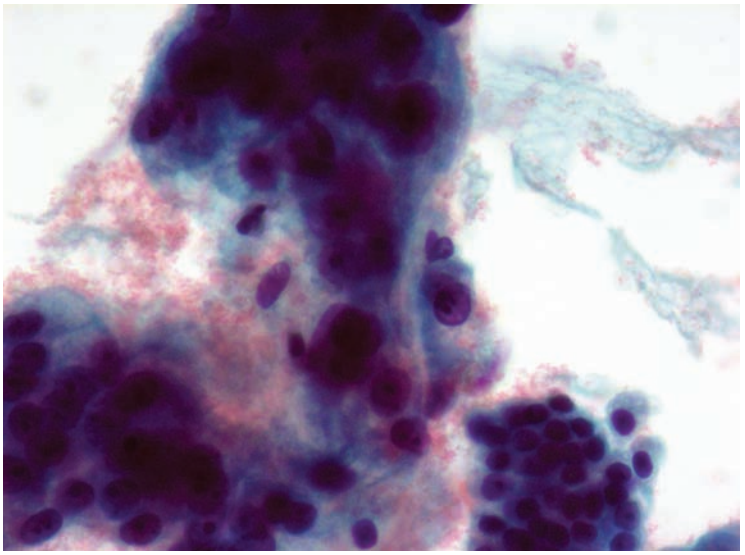


Figure 10.27 — Adenocarcinoma (Liquid Based; High Power). In a background of fibrinated red blood cells and fibrin (clinging diathesis), a large fragment of adenocarcinoma is accompanied by normal endocervical cells on the lower right.

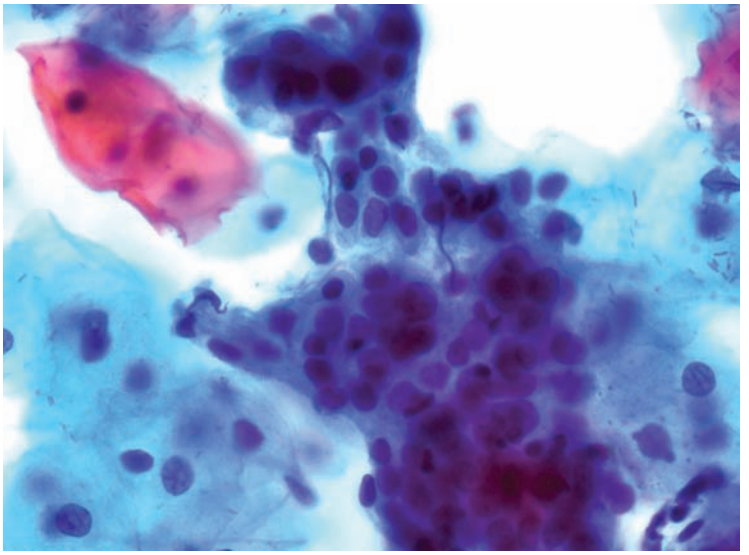


Figure 10.28 — Adenocarcinoma In Situ (AIS) Preceding Adenocarcinoma (Liquid Based; High Power). Although nuclei are bland, their oval shape and acinar arrangement are abnormal. This patient developed invasive adenocarcinoma 3 years after this Pap was obtained.

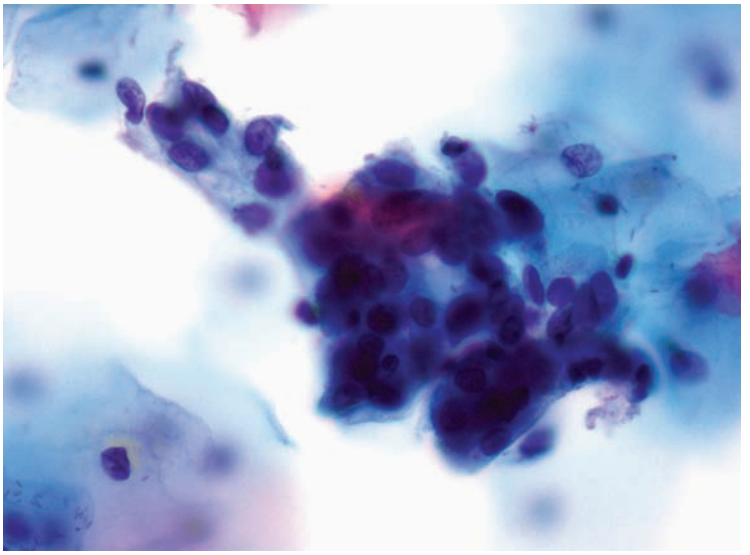
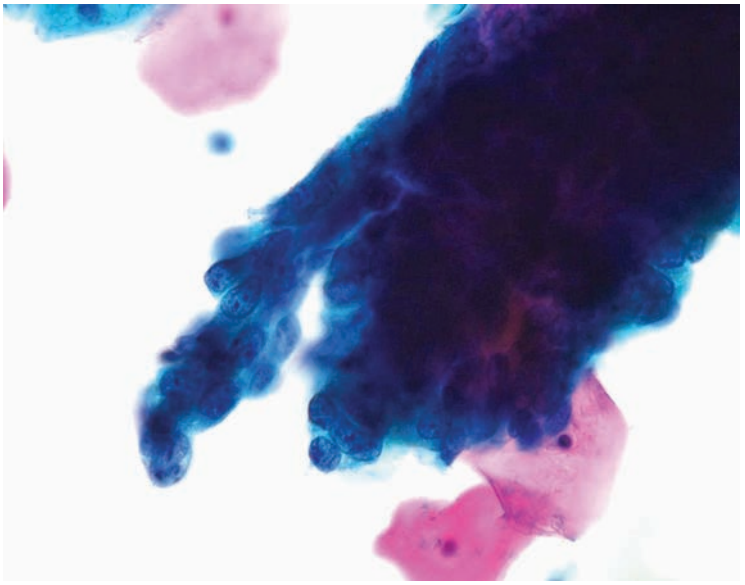
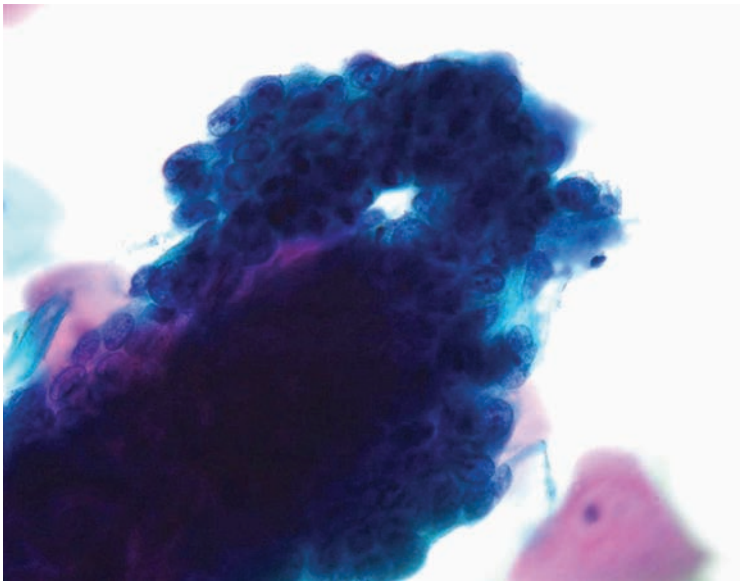


Figure 10.29 — Adenocarcinoma In Situ (AIS) Preceding Adenocarcinoma (Liquid Based; High Power). The disorganization of these glandular cells is apparent, made more difficult to visualize by the layering often found in a liquid-based Pap. Gland formation is evident, although not so well defined as in Figure 10.28, from the same sample.





Figures 10.30 and 10.31 — Adenocarcinoma (Liquid Based; High Power). Both figures are the opposite ends of the same fragment. Very large tissue fragments as crowded as this are neoplastic until proven otherwise. Two-dimensional images are problematic, but cells along the edges of the fragments display the large nuclei, high N/C ratios, nuclear crowding, and architectural disarray. Search of the sample will usually provide groups or single cells that are easier to appreciate for their characteristic features.

Figure 10.32 — Adenocarcinoma (Liquid Based; Low Power). Halo edge from a bloody ThinPrep—although blood from menses can appear like this, closer inspection will reveal a necrotic tumor. Compare this pattern with that in the chapter on squamous cell carcinoma (Chapter 8). The cellular features will differ between cell types, but the pattern is "cancer until proven otherwise."

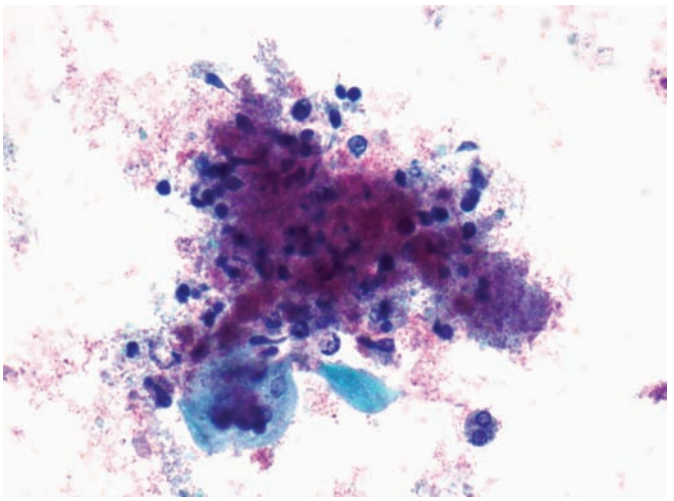


Figure 10.33 — Adenocarcinoma (Liquid Based; High Power). Surfaces of invasive tumors are often mostly necrotic debris and inflammatory cells. Occasionally, an intact epithelial cell may be seen, as the one at the lower portion of this photo. The patient had a combined tumor with glandular and squamous features, the latter of which became apparent only after the lesion matured and invaded. This large cell is more likely from the squamous component of her tumor because of the tail of opaque cytoplasm.

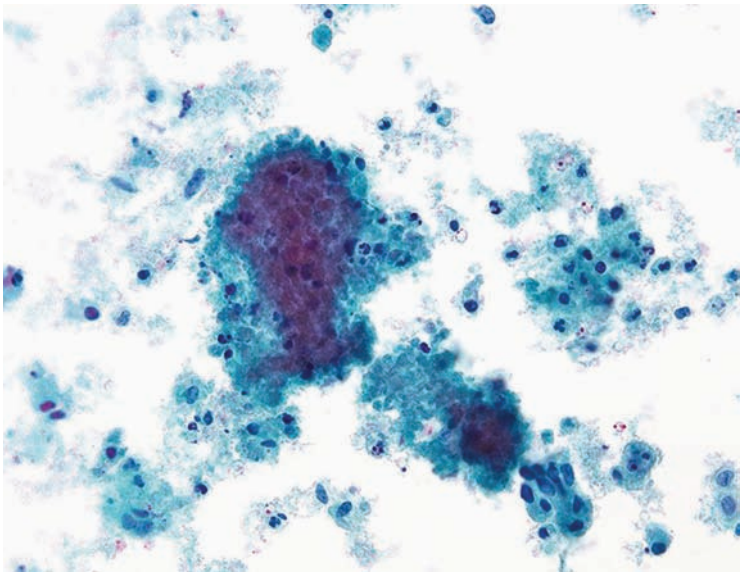


Figure 10.34 — Adenocarcinoma (Liquid Based; Medium Power). Necrotic surfaces from invasive tumors do not reveal the cell of origin. Careful search of the rest of the sample usually finds intact cells from the cancer. The pattern—fibrinated blood and necrotic debris—indicates an invasive lesion.

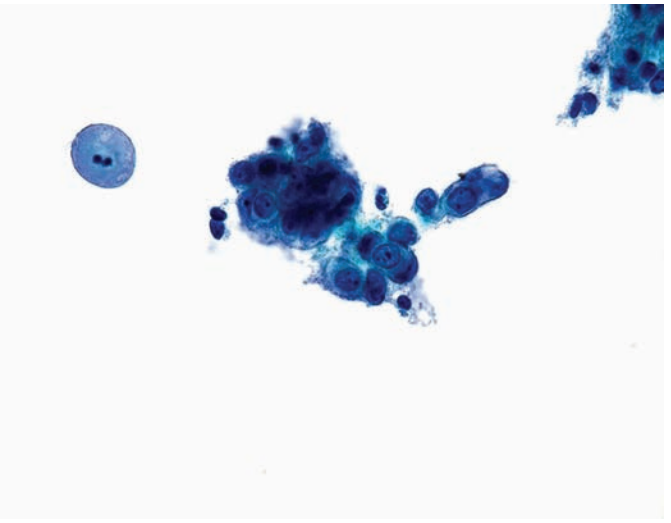


Figure 10.35 — Adenocarcinoma (Liquid Based; High Power). Identifying these cells as malignant is not difficult, but deciding their site of origin will depend on clinical presentation, correlation with imaging studies, and immunohistochemical tests on subsequent tissue obtained. The role of the cytologist is simply to direct the next step in management.

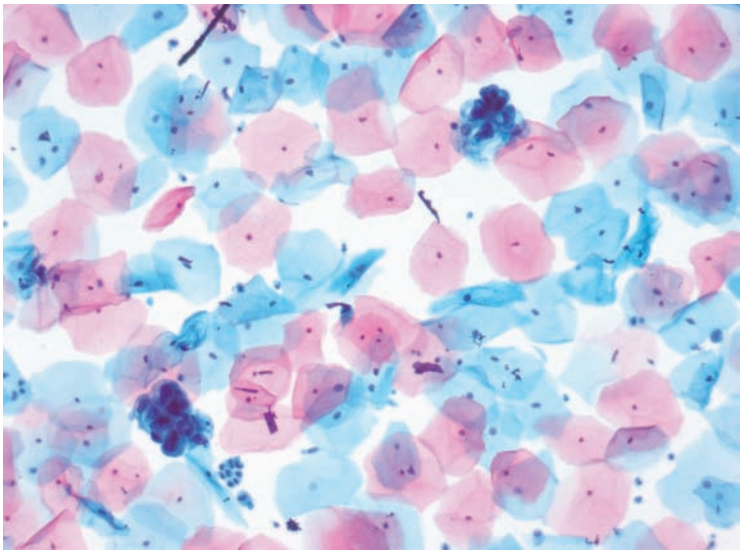


Figure 10.36 — Adenocarcinoma (Liquid Based; Low Power). The background is clean, but these two glandular groups are clearly abnormal. Previous cytologic "rules" would have classified this picture as a metastatic lesion. However, this patient was diagnosed with an endometrioid carcinoma of her uterus.

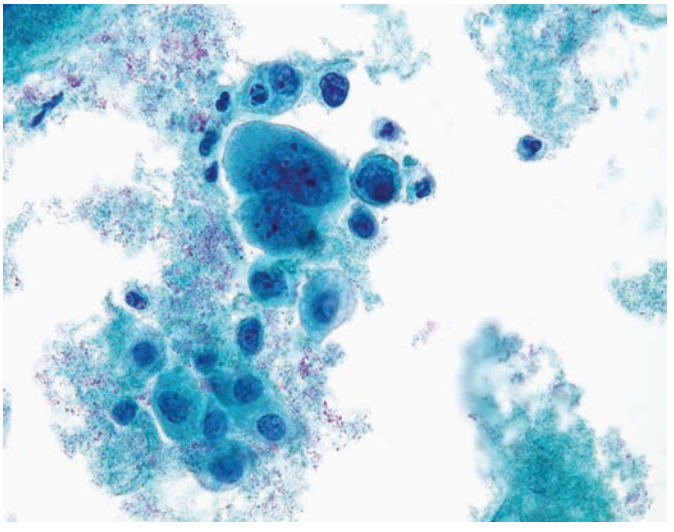


Figure 10.37a — Adenocarcinoma (Liquid Based; High Power). Within the tumor diathesis in a liquid-based preparation, both normal metaplastic cells and greatly enlarged malignant cells are seen. Their opaque cytoplasm may suggest squamous origin, but the nuclear chromatin is very pale, consistent with an adenocarcinoma. An interpretation of "poorly differentiated adenocarcinoma" is appropriate, with no indication of the source of cancer.

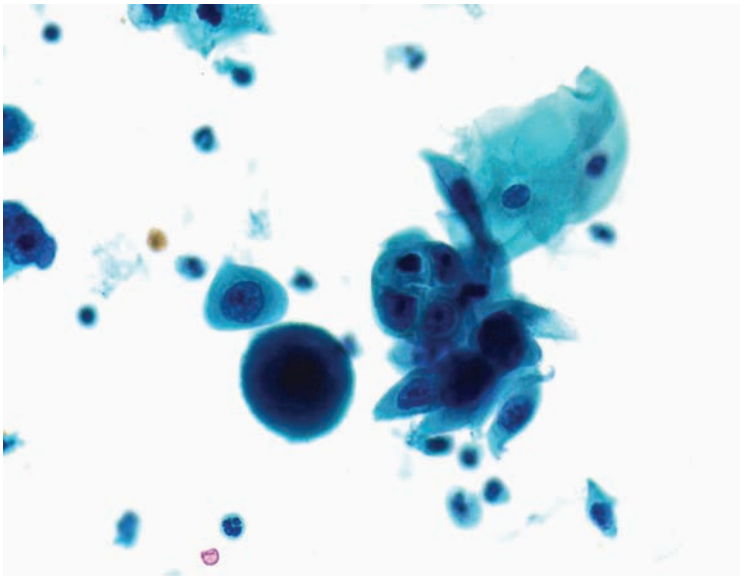


Figure 10.37b — Adenocarcinoma (Liquid Based; High Power). The atypical cells shown here demonstrate some features of squamous differentiation. The cytoplasm appears dense, and a small gap is seen between some cell junctions, creating a tile-like appearance seen in squamous metaplasia. A few cells have dark pyknotic nuclei, a feature of squamous cell carcinoma. The presence of cells with a more columnar appearance at the edges suggests the possibility of a glandular lesion. High-grade squamous intraepithelial lesion involving glands shows squamous dysplasia with glandular-like areas; however, the coarse chromatin and nuclear pleomorphism seen here are not compatible with HSIL.

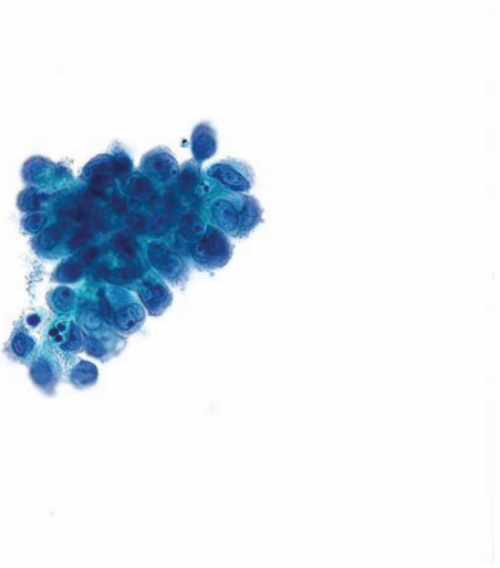


Figure 10.38 — Adenocarcinoma (Liquid Based; Medium Power). In contrast to Figures 10.37a and b, this group of cells is clearly glandular, including occasional cytoplasmic vacuoles, pale chromatin, and well-defined nucleoli. This sample can be categorized as a "well differentiated adenocarcinoma."

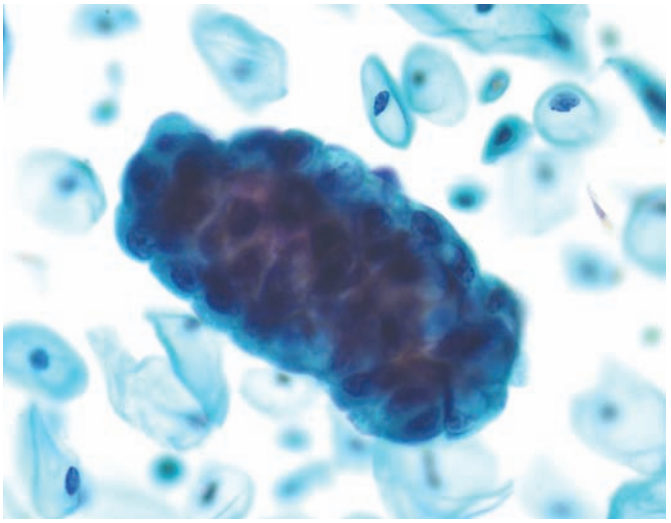


Figure 10.39 — Adenocarcinoma (Liquid Based; High Power). A true tissue fragment, spontaneously exfoliated, will have smooth outlines and a three-dimensional appearance. The individual cells may appear relatively normal, but the configuration of the group is abnormal and indicates a low-grade adenocarcinoma. Once again, the clean background is deceptive, but not unexpected in a low-grade lesion.

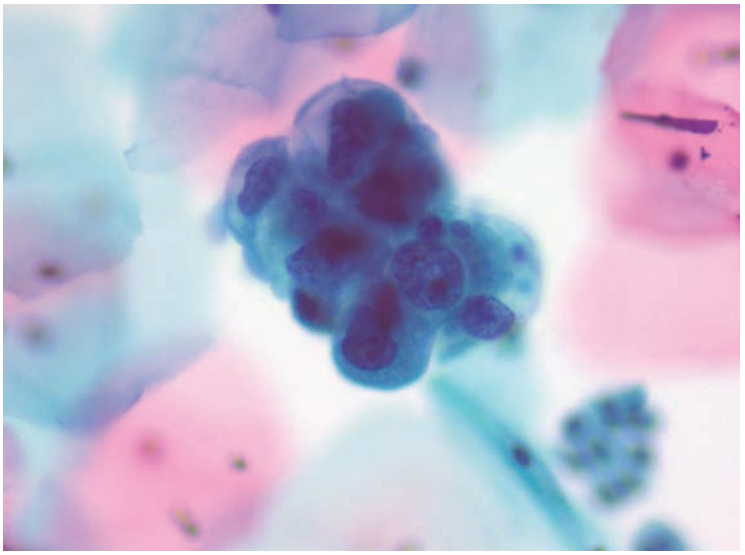


Figure 10.40 — Adenocarcinoma (Liquid Based; High Power). This true tissue fragment is similar to that in Figure 10.39, except that the individual cells are more atypical. Despite the large nuclear size and prominent nucleoli, the histologic diagnosis was FIGO 1, endometrioid carcinoma of the uterus.

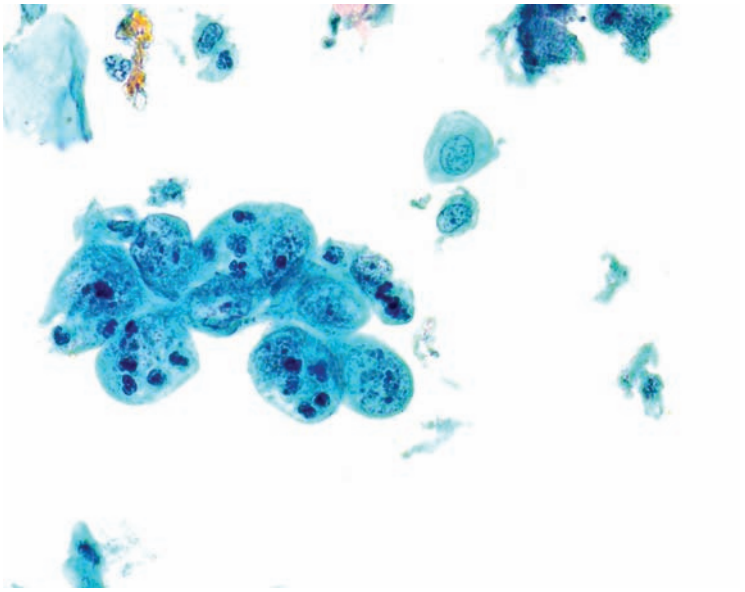


Figure 10.41 — Adenocarcinoma (Liquid Based; High Power). The characteristic neutrophils within the vacuoles of endometrial adenocarcinoma are strong indicators of the origin of the malignant cells. Their absence does not necessarily negate the endometrial source.

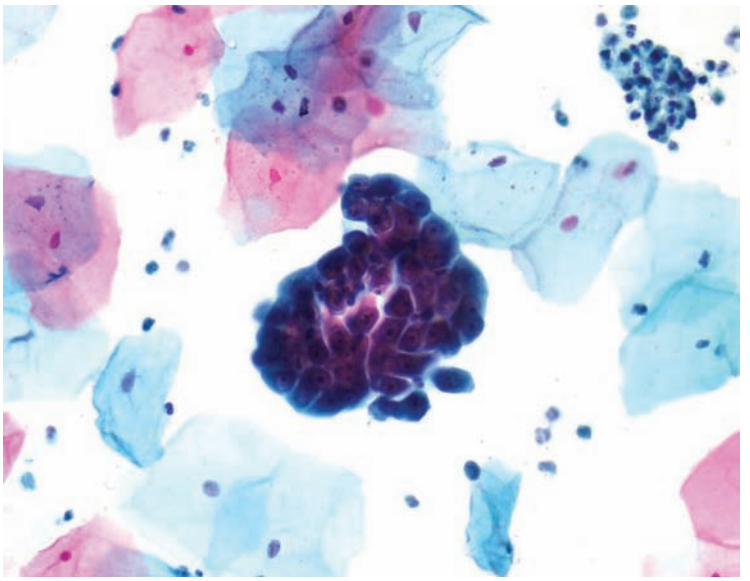


Figure 10.42 — Adenocarcinoma (Liquid Based; Medium Power). Glandular groups in a Pap test must be compared with normal endocervical cells from the same sample. These cells were determined to be carcinoma, but the clean background suggested a lesion metastatic from outside the uterus. In this case, the origin was a low-grade endometrial cancer without muscle invasion, hence the "clean background." Liquid-based preparations also tend to present a clean background more so than the conventional Pap smear.

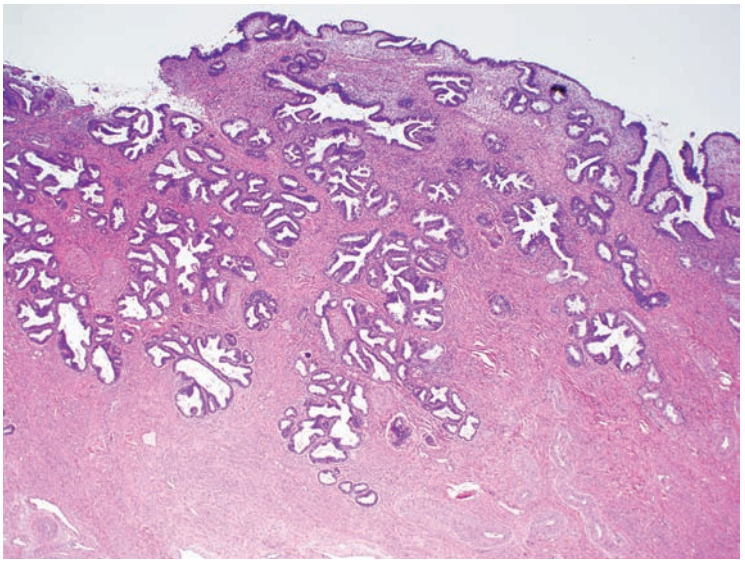


Figure 10.43a — Invasive Well-Differentiated Endocervical Adenocarcinoma of Usual Type (Hysterectomy) (H&E Stain; Low Power). This is an example of an adenocarcinoma in situ-like (AIS-like) pattern of invasion because the architectural features mimic AIS. The distinction between the upper limit of AIS and the earliest form of stromal invasion is difficult because uniformly accepted criteria have not been developed and the interobserver reproducibility between gynecologic pathologists is variable. Furthermore, invasive endocervical adenocarcinomas often do not show stromal alterations. However, in this example, the combination of the depth of the lesion, extent of proliferation, degree of glandular crowding, slightly haphazard arrangement of glands, and focal proximity of glands near thick-walled vessels (*best seen at the left center*) is interpreted as invasive adenocarcinoma. This type of pattern of invasion frequently has admixed AIS in the background, which may be difficult to appreciate in this example. However, the surface mucosa replaced with neoplastic epithelium in the upper right-hand corner of the photograph likely represents AIS.

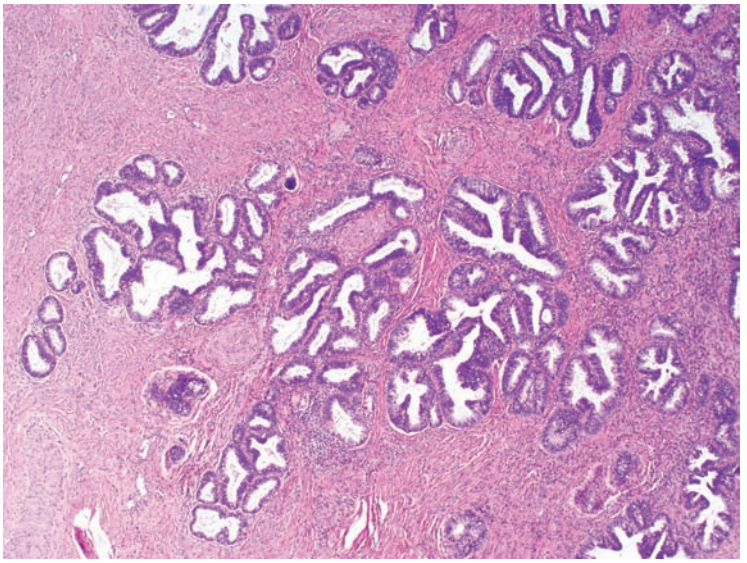


Figure 10.43b — Invasive Well-Differentiated Endocervical Adenocarcinoma of Usual Type (Hysterectomy) (H&E Stain; Intermediate Power). In the center of the photograph, glands are in close proximity to and encircle a thick-walled vessel. In cases where the differential diagnosis concerns AIS versus invasive adenocarcinoma, this finding is a helpful clue for invasion.

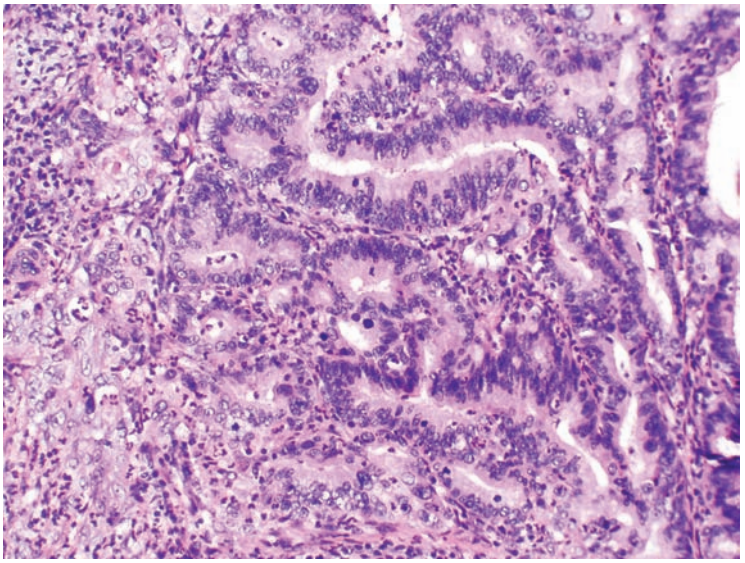


Figure 10.43c — Invasive Well-Differentiated Endocervical Adenocarcinoma of Usual Type (Hysterectomy) (H&E Stain; High Power). The cytologic features are essentially identical to those of AIS. Numerous mitotic figures are present. Immunohistochemical stains typically show diffuse expression of p16 and usually exhibit loss of ER and PR expression. This combined morphologic and immunohistochemical profile is characteristic of usual-type endocervical adenocarcinomas, which are caused by high-risk HPV. In general, the vast majority of endocervical adenocarcinomas are related to high-risk HPV, whereas only a minority are unrelated to HPV. The latter have cytologic features different from those of the usual type. Endocervical adenocarcinoma in situ is the precursor of invasive endocervical adenocarcinoma of usual type. Although a grading system for endocervical adenocarcinoma has not been standardized, cases such as the one illustrated here are considered well differentiated because of the absence of solid patterns and lack of nuclear pleomorphism.

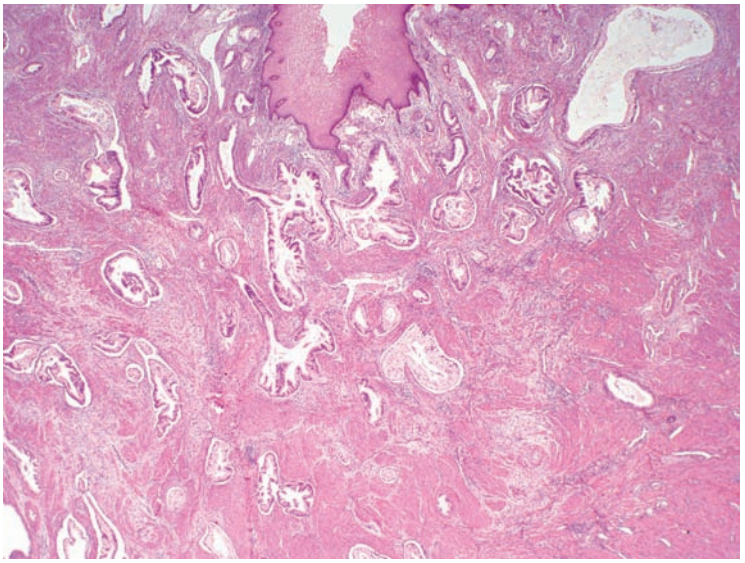


Figure 10.44a — Minimal Deviation Adenocarcinoma (Adenoma Malignum) (Hysterectomy) (H&E Stain; Low Power). Recognizing minimal deviation adenocarcinoma is problematic because an obviously invasive growth pattern is not always readily apparent at low-power magnification and other endocervical glandular pseudoneoplastic mimics, such as lobular endocervical glandular hyperplasia, can have architectural overlap with minimal deviation adenocarcinoma. However, the combination of depth of the lesion, variation in size and shape of the glands (including irregular glandular contours), and haphazard growth pattern (in combination with the cytologic features) in this example is interpreted as stromal invasion. Furthermore, other cases on higher power magnification can have some degree of altered stroma surrounding the neoplastic glands. It is important to note that there is no formally recognized in situ component for minimal deviation adenocarcinoma.

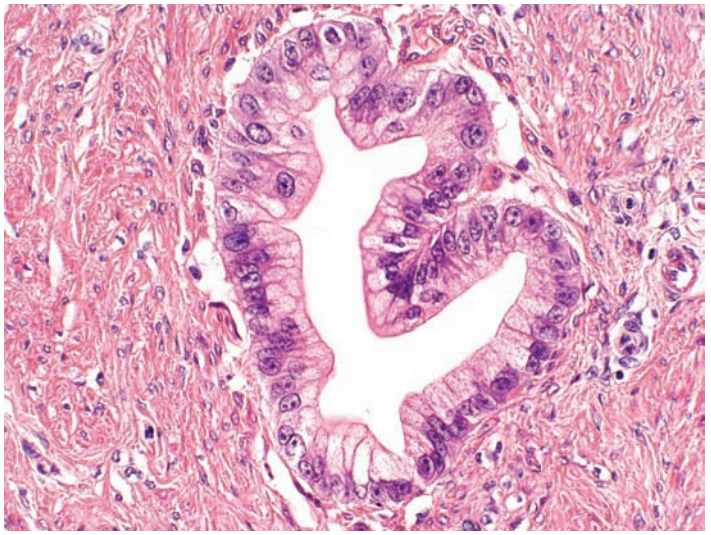


Figure 10.44b — Minimal Deviation Adenocarcinoma (Adenoma Malignum) (Hysterectomy) (H&E Stain; High Power). These cytologic features are typical of minimal deviation adenocarcinoma. The neoplastic glands have columnar cells with abundant mucinous cytoplasm. The nuclei are slightly enlarged, round, and basally located with pale chromatin and evident nucleoli. Although the cytologic appearance is not overtly pleomorphic, it is in contrast with the bland nuclear features of benign endocervical glandular proliferations. Other HPV-unrelated endocervical adenocarcinomas, such as the so-called gastric variant, have cytologic features that overlap with those of minimal deviation adenocarcinoma (in the 2014 WHO Classification for Gynecologic Tumors, minimal deviation adenocarcinoma is included in the family of gastric-type adenocarcinomas). Note that the cytologic appearance of minimal deviation adenocarcinoma is distinct from that of the HPV-related endocervical adenocarcinomas of usual type. In contrast to the majority of endocervical adenocarcinomas, which are related to high-risk HPV, a minority of endocervical adenocarcinomas, particularly minimal deviation adenocarcinoma, are unrelated to HPV. Thus, the latter will not have diffuse expression of p16. However, the Ki-67 proliferation index is usually slightly elevated, and expression of ER and PR is typically lost.

Figure 10.45b — Endometrial Endometrioid Carcinoma (Liquid Based; High Power). While the presence of inflammatory cells is often associated with reactive or infectious processes, in this case, a striking number of neutrophils (polymorphonuclear leukocytes) is present inside an endometrial cell. Such endometrial cells are called a "bag of polys," and this finding suggests the possibility of an endometrial adenocarcinoma. Occasionally, reactive endocervical cells may contain neutrophils, but, in this case, the nucleus has a coarse chromatin pattern, indicating malignancy.

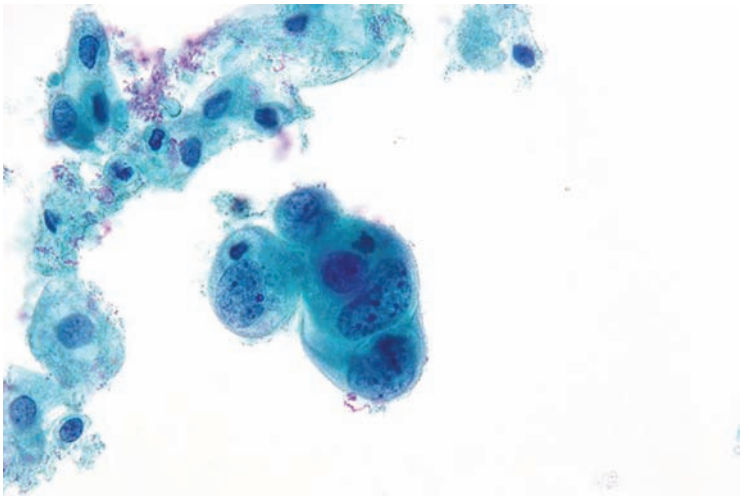
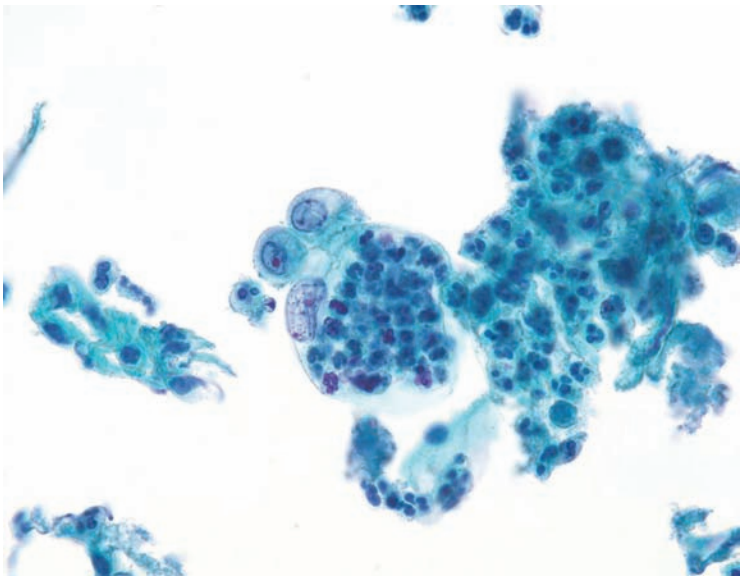


Figure 10.45a — Endometrial Endometrioid Carcinoma (Liquid Based; High Power). The cells in the center of the field should catch your attention. They are larger than the cells at the edges and have nuclei four to five times the size of the bystander cells. The chromatin pattern is coarse, a worrisome feature not typically found in reactive or dysplastic lesions on a Pap test. The eccentrically placed nuclei are suggestive of a glandular origin. The malignant cells have ingested neutrophils, which are more indicative of an endometrial origin. Tumor diathesis can be seen as granular debris "clinging" to the adjacent cells.



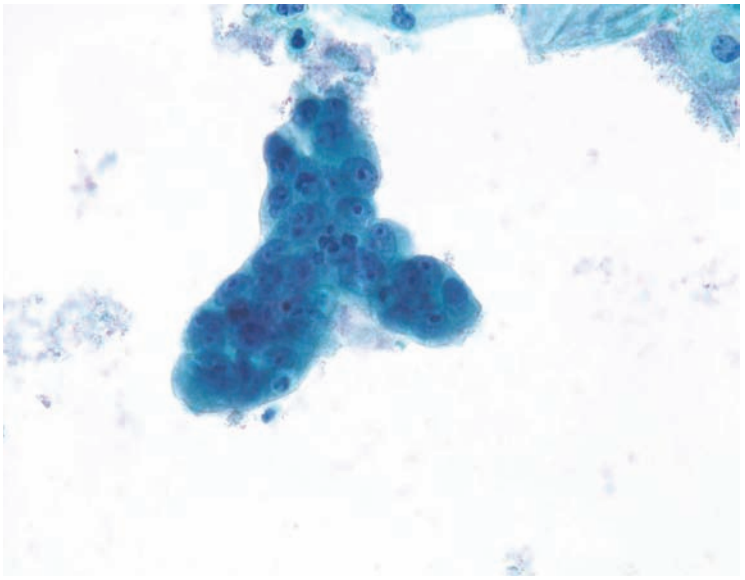


Figure 10.45c — Endometrial Endometrioid Carcinoma (Liquid Based; Medium Power). Endometrial adenocarcinomas may demonstrate prominent nucleoli. In this case, the fragment forms an irregular branching shape, a contrast from the tightly clustered balls formed by benign endometrial cells. Neutrophils are also seen inside the endometrial cells.

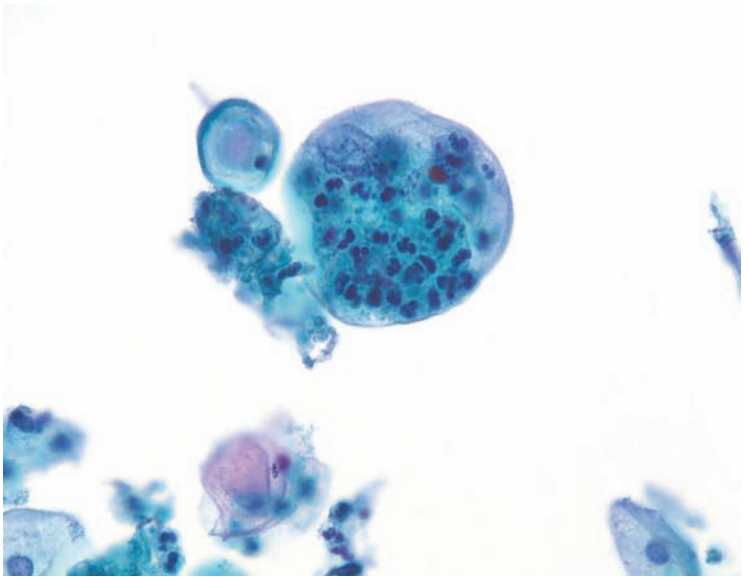


Figure 10.45d — Endometrial Endometrioid Carcinoma (Liquid Based; High Power). This is another example of a "bag of polys" and represents endometrial adenocarcinoma. The neutrophils almost make the nucleus difficult to identify.

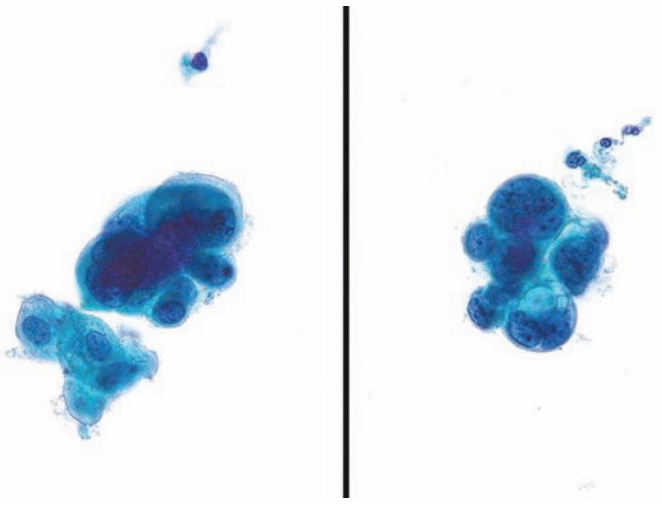


Figure 10.45e — Endometrial Endometrioid Carcinoma (Liquid Based; Medium Power). Vacuolization is another feature found in endometrial carcinoma (right panel). However, vacuolization alone can also be found in the absence of malignancy, such as the case in which an intrauterine device (IUD) is present. Although the nuclei in these clusters have dramatic size differences and coarse chromatin patterns, the nuclear borders remain relatively smooth and the overall shape of the nuclei remains round. This "rounding up" of the nuclei in endometrial adenocarcinomas is a common finding.

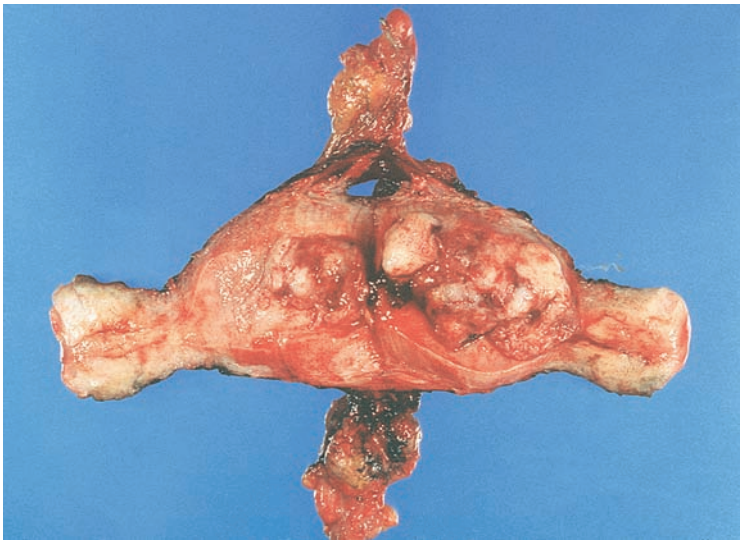


Figure 10.45f — Endometrial Endometrioid Carcinoma, Gross Specimen (Hysterectomy). The specimen has been "bivalved" and shows an endometrial cavity filled with a polypoid mass. The tumor is heterogeneous in appearance with variable admixtures of tan-red areas and an irregular tumor surface. The gross appearances of the different histologic types of endometrial carcinoma are nonspecific. At the time of gross examination, it is important to measure the tumor; document the depth of invasion into the myometrium; and determine whether or not there is involvement of the cervix, uterine serosa, ovaries, or fallopian tubes.

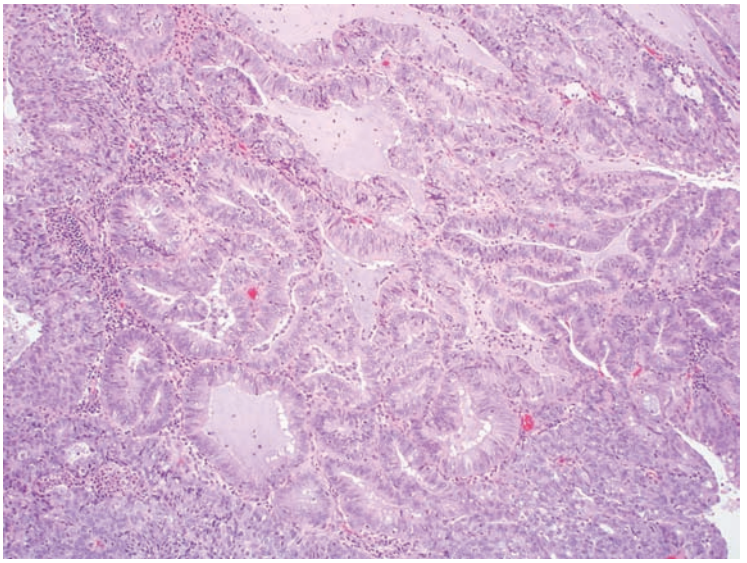


Figure 10.46a — Endometrial FIGO Grade 1 Endometrioid Carcinoma (Biopsy) (H&E Stain; Intermediate Power). The tumor shows glandular confluence. Other cases can exhibit papillary or villoglandular architecture. Grading of endometrioid carcinomas, in general, is based on the extent of solid growth and degree of nuclear atypia.

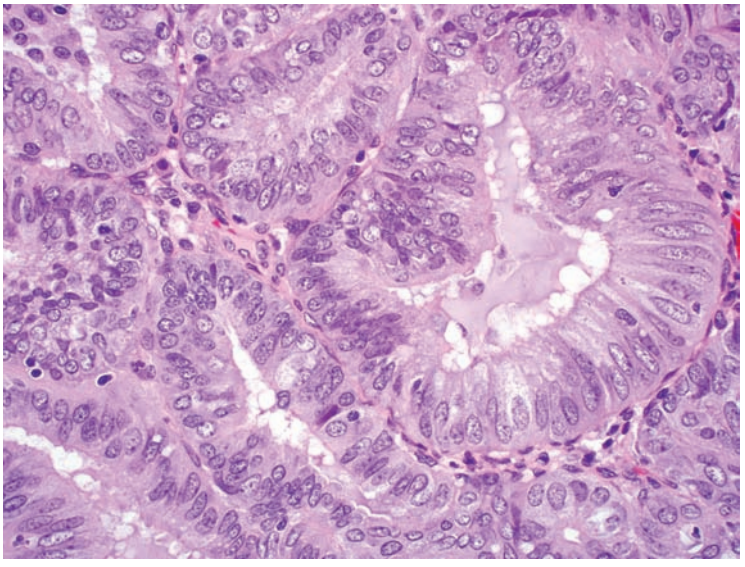


Figure 10.46b — Endometrial FIGO Grade 1 Endometrioid Carcinoma (Biopsy) (H&E Stain; High Power). The glands resemble the proliferative phase endometrium, but nuclear atypia is present. The cells are columnar with oval to columnar nuclei. They contain abundant pink cytoplasm with flat luminal borders. The nuclei show loss of polarization with nuclei being found at various levels throughout the cells instead of being restricted to the base of the cells. Some degree of nuclear pallor is present, while other cases may have more hyperchromatic nuclei or prominent nucleoli. Note that there is almost no intervening stroma between the glands.

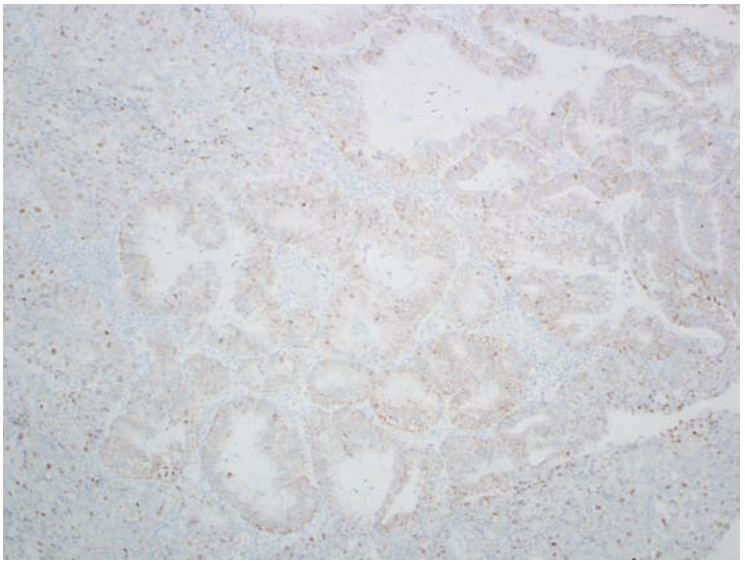


Figure 10.46c — Endometrial FIGO Grade 1 Endometrioid Carcinoma, Histologic Section (Biopsy) (p53 Immunohistochemical Stain; Intermediate Power). The tumor cells exhibit only focal nuclear staining for p53, which correlates with a wild-type *TP53* gene. A minority of endometrioid carcinomas can have a *TP53* gene mutation (and an abnormal immunohistochemical expression pattern), but those tend to be high-grade endometrioid carcinomas.

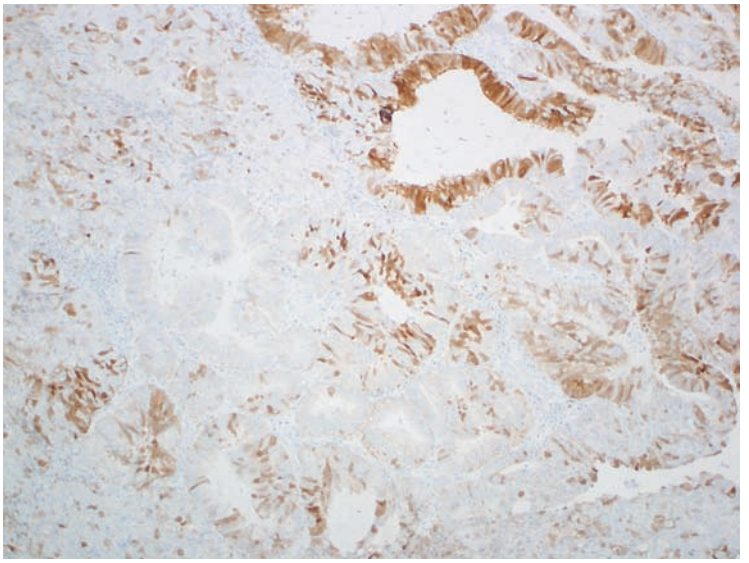


Figure 10.46d — Endometrial FIGO Grade 1 Endometrioid Carcinoma (Biopsy) (p16 Immunohistochemical Stain; Intermediate Power). Patchy expression of p16 is observed. The vast majority of endometrial carcinomas are of endometrioid histologic type. Endometrioid carcinomas are usually positive for ER and PR, although expression can be lost in the higher grade tumors. When distinguishing endometrioid from serous carcinoma, including a panel of immunohistochemical markers for p53 and p16 is helpful because most endometrioid carcinomas do not have abnormal expression patterns of p53, and diffuse expression of p16 would be highly unusual for an endometrioid carcinoma.

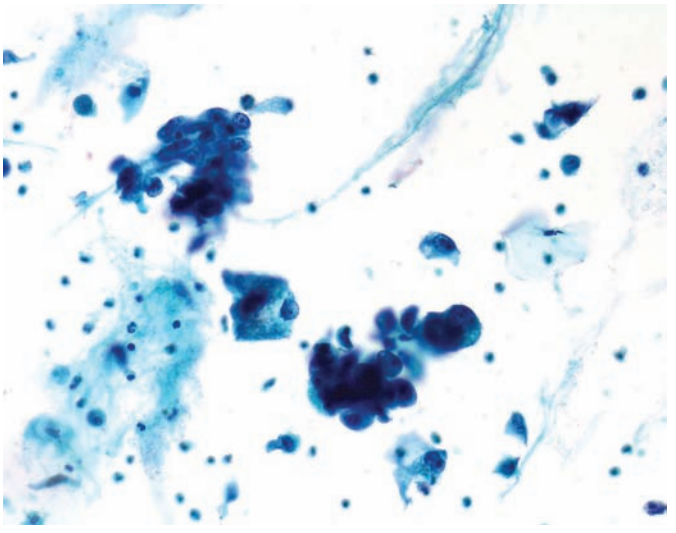


Figure 10.47a — Endometrial Serous Carcinoma (Liquid Based; Low Power). Although definitive classification of a serous versus endometrioid uterine carcinoma is not possible on a Pap test, serous carcinomas tend to be identified more readily owing to their ability to generate more cellularity, necrosis, and atypical features. The cells here are pleomorphic and are surprisingly large in this low-power field (compared to the tiny neutrophils in the background). Stripped (bare) nuclei and psammoma bodies are other features occasionally present.

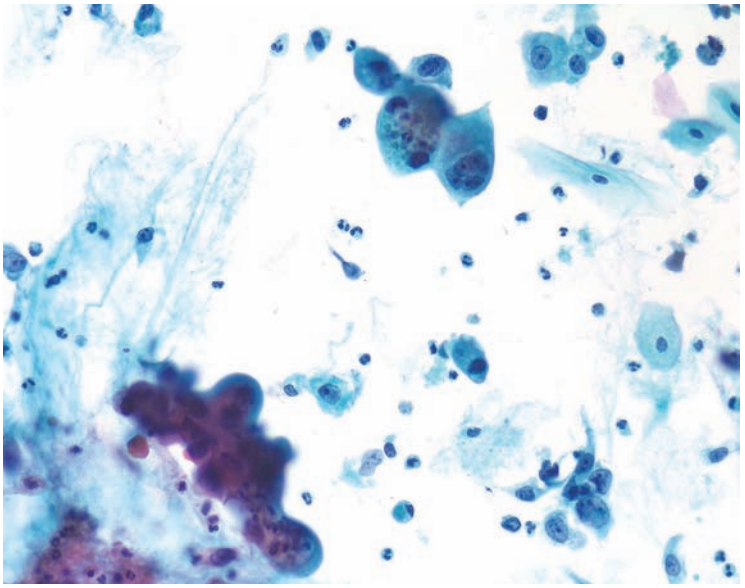


Figure 10.47b — Endometrial Serous Carcinoma (Liquid Based; Medium Power). Serous carcinoma cells also contain ingested neutrophils, as seen here. Again, the malignant cells are pleomorphic and large in size (compared to background neutrophils). In this case, a giant multinucleated tumor cell is seen (top center). Many cells are entangled in a web of fibrinous debris.

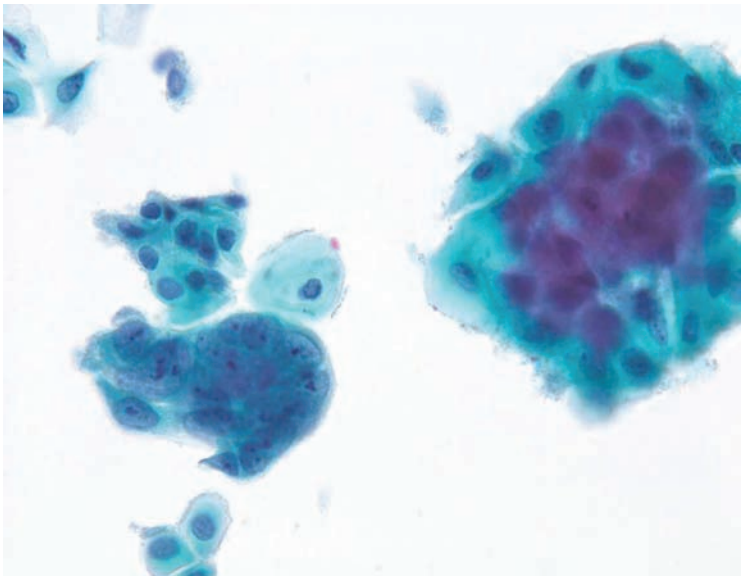


Figure 10.47c — Endometrial Serous Carcinoma (Liquid Based; Medium Power). These atypical cells were found in a patient who was subsequently diagnosed with an endometrial serous carcinoma. The cells are not as strikingly atypical as found in the previous two figures, though their clumpy coarse chromatin indicates a malignancy. Neutrophils are not present here, but the smooth borders and foamy cytoplasm are more suggestive of an adenocarcinoma. While it is helpful to suggest an endometrial versus endocervical source when possible, subclassification of endometrial adenocarcinomas is not expected. The absence of high-risk HPV would be strongly suggestive of an endometrial adenocarcinoma, given the association of HPV with endocervical adenocarcinomas.

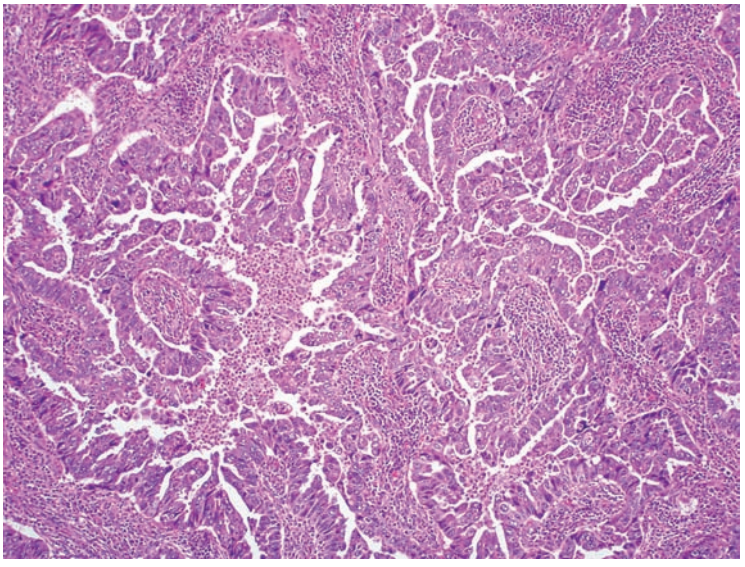


Figure 10.47d — Endometrial Serous Carcinoma (Biopsy) (H&E Stain; Intermediate Power). The tumor is composed of medium-size papillae with thick fibrovascular cores and detached small epithelial clusters producing irregular slit–slit spaces within the neoplastic epithelium. Necrotic and inflammatory debris is present within large epithelial-lined spaces. This case is predominantly papillary, but other cases can show glandular-rich patterns mimicking endometrioid carcinoma. Furthermore, other histologic types of endometrial carcinoma can have a papillary architecture. A papillary growth pattern, therefore, is not specific for serous carcinoma, and a predominantly glandular pattern does not exclude the possibility of serous carcinoma.

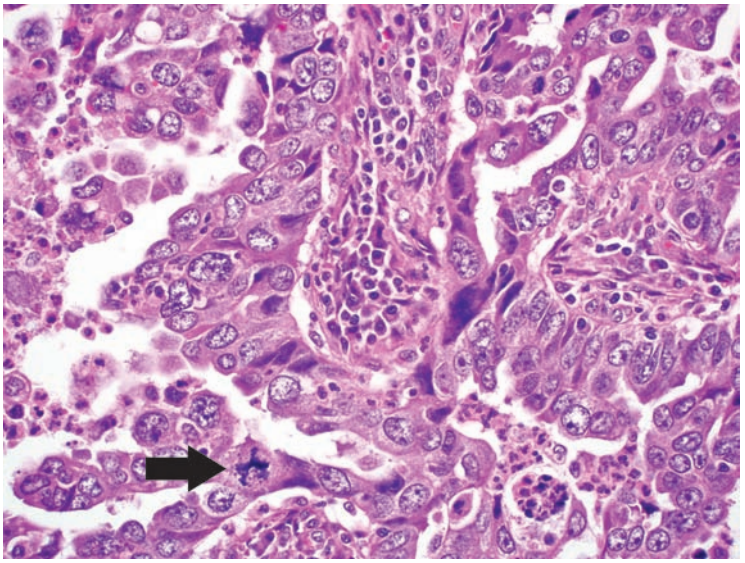


Figure 10.47e — Endometrial Serous Carcinoma (Biopsy) (H&E Stain; High Power). The neoplastic epithelium is stratified and contains cuboidal to round cells with a moderate amount of pink cytoplasm. The nuclei are pleomorphic and have vesicular chromatin with occasionally prominent nuclei. A few nuclei are hyperchromatic. An abnormal mitotic figure (*arrow*) is also seen. In contrast to endometrioid carcinoma, serous carcinoma has much higher grade nuclei and a greater degree of mitotic activity.

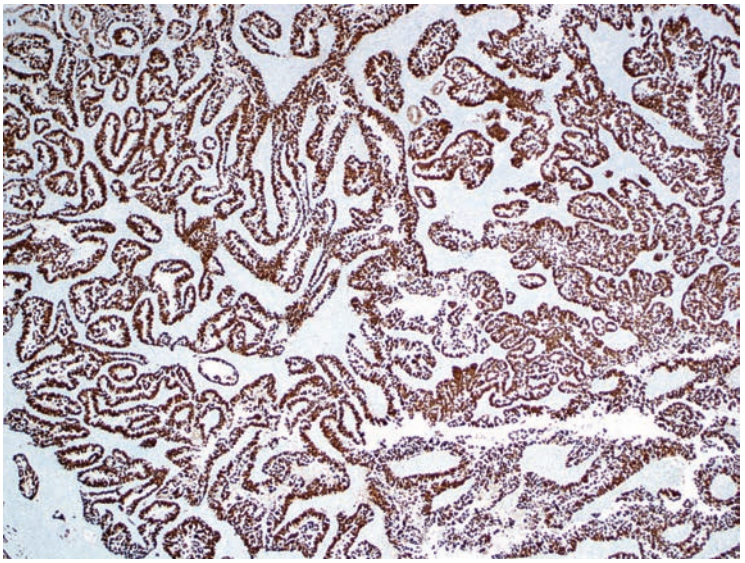


Figure 10.47f — Endometrial Serous Carcinoma (Biopsy) (p53 Immunohistochemical Stain; Intermediate Power). The tumor displays diffuse strong staining for p53. This pattern, particularly when strong and more than 75% of tumor cells are positive, is characteristic of serous carcinoma. This pattern correlates with a *TP53* mutation, which is typical of serous carcinoma. The majority of serous carcinomas show this p53 expression pattern. A minority of cases will show another pattern of staining that has complete loss of expression (ie, 0% labeling index). That pattern also correlates with another type of *TP53* mutation that can occur in serous carcinoma. The "null" pattern should not be considered "negative" because it is an abnormal expression pattern. True negative patterns, which are those that correlate with a wild-type *TP53* gene, will have rare weakly staining cells scattered throughout the tumor. Furthermore, focal or patchy patterns generally do not correlate with a *TP53* mutation.

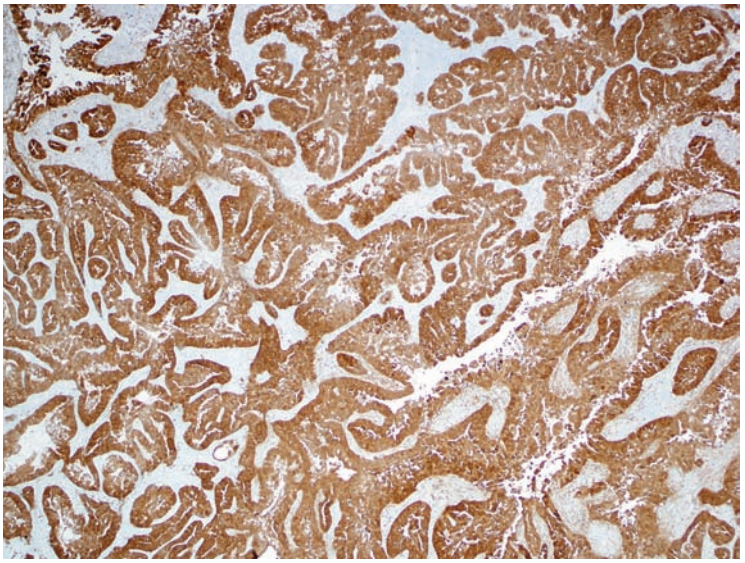


Figure 10.47g — Endometrial Serous Carcinoma (Biopsy) (p16 Immunohistochemical Stain; Intermediate Power). Diffuse expression of p16 is present. Virtually, all endometrial serous carcinomas have this pattern (in which usually 90%–100% of tumor cells are positive), and negative, focal, or patchy patterns of expression argue against a diagnosis of endometrial serous carcinoma. Unlike cervical adenocarcinomas that show p16 overexpression because of disturbed molecular pathways resulting from high-risk HPV infection, the molecular pathway producing p16 overexpression in serous carcinoma is independent of an HPV-related process. Only a minority of endometrial carcinomas are of serous histologic type. In contrast to endometrioid carcinoma, serous carcinoma exhibits a higher Ki-67 index, although there can be overlap between these two tumors. Endometrial serous carcinoma frequently shows loss of expression of ER and PR, but a substantial proportion of cases can retain expression for these hormone receptors. In general, the immunohistochemical level of ER and PR expression in serous carcinoma is less than that of endometrioid carcinoma. The immunohistochemical profiles (p53/p16/ER/PR/Ki-67) of serous and endometrioid carcinomas are different; however, ER, PR, and Ki-67 are not as discriminatory for this differential diagnosis as are p53 and p16. Thus, if all five markers are performed on a given case, more diagnostic value should be placed on p53 and p16.

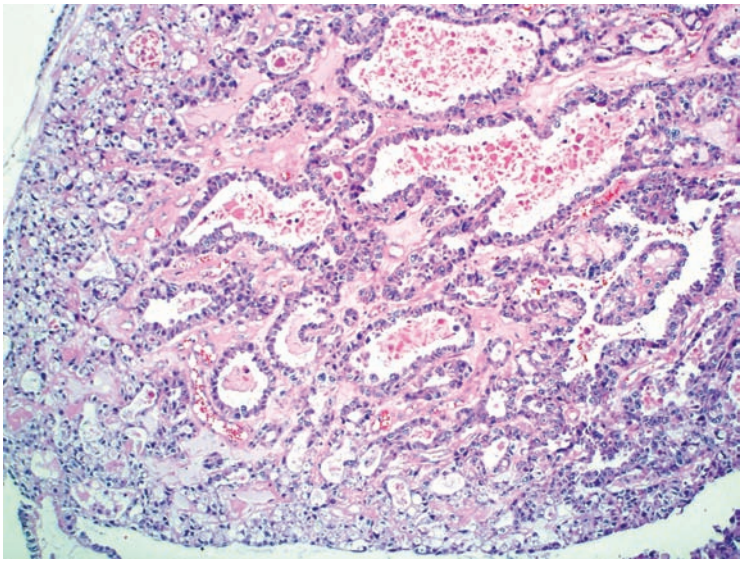


Figure 10.48a — Endometrial Clear Cell Carcinoma (Biopsy) (H&E Stain; Intermediate Power). This example shows the tubulocystic pattern of clear cell carcinoma, which is characterized by tubules that range from those that are of small caliber to ones that are cystically dilated. The glands are lined by a non-stratified layer of neoplastic epithelium. Note that the glands are not confluent, which is not necessary for diagnosing clear cell carcinoma. They are separated from one another by partially hyalinized stroma. Dense hyalinized stroma, which is characteristic of clear cell carcinoma, may be more prominent in other cases. Other clear cell carcinomas can show different architectural patterns, including papillary, glandular (non-tubulocystic type), and solid. Cases will frequently show an admixture of patterns.

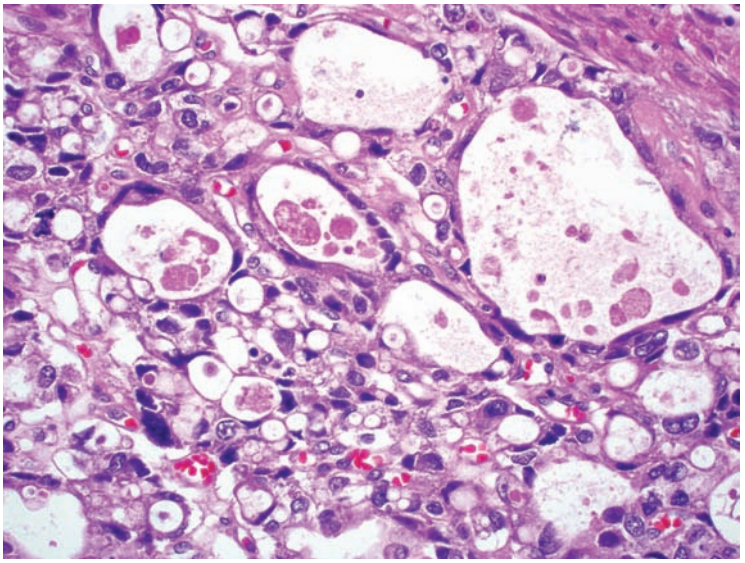


Figure 10.48b — Endometrial Clear Cell Carcinoma (Biopsy) (H&E Stain; High Power). A variety of cell shapes can be seen in clear cell carcinoma. Here, a single layer of flat cells are depicted. Note that the thin tubules do not have stratified epithelium, and their cells have oval to elongated hyperchromatic nuclei. Other cells in this example have cytoplasmic droplets of mucin producing a "targetoid" appearance.

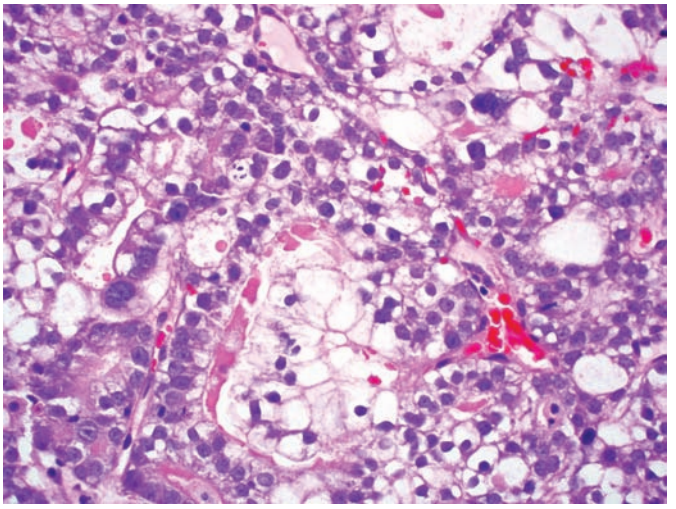


Figure 10.48c — Endometrial Clear Cell Carcinoma (Biopsy) (H&E Stain; High Power). Other cases may show different cell shapes. In this case, cuboidal cells with clear cytoplasm are seen. The nuclei have a slight degree of pleomorphism. Most are medium sized and round with fine chromatin and centrally placed small- to medium-sized nucleoli. Some nuclei are hyperchromatic. Occasional hyaline globules are present, which are somewhat typical of clear cell carcinoma. Other cases can have hobnail and columnar cells. Many cases will have a mixture of the different cell shapes. It is important to recognize that not all clear cell carcinomas have clear cytoplasm. Some cases can have pink cytoplasm, particularly the oxyphilic variant of clear cell carcinoma. Therefore, clear cell carcinoma is diagnosed based on a combination of architectural patterns and cell shapes and not the color of the cytoplasm (clear).

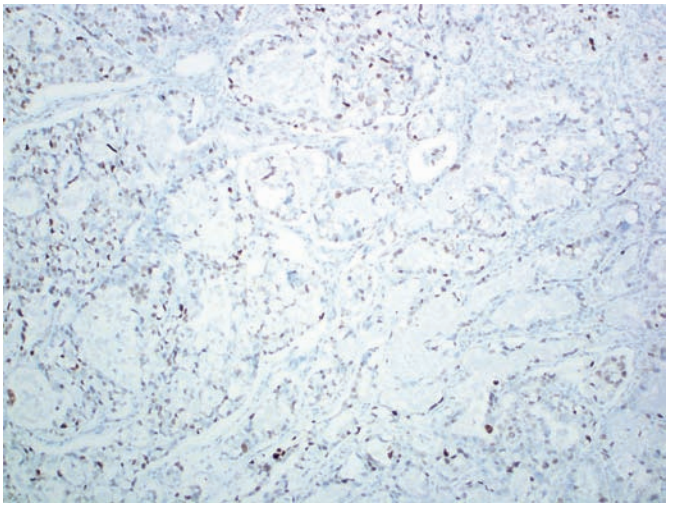


Figure 10.48d — Endometrial Clear Cell Carcinoma (Biopsy) (p53 Immunohistochemical Stain; Intermediate Power). Focal staining for p53 is present. Most clear cell carcinomas do not have a *TP53* mutation; thus, abnormal expression patterns (although seen infrequently) are not typical of clear cell carcinoma.

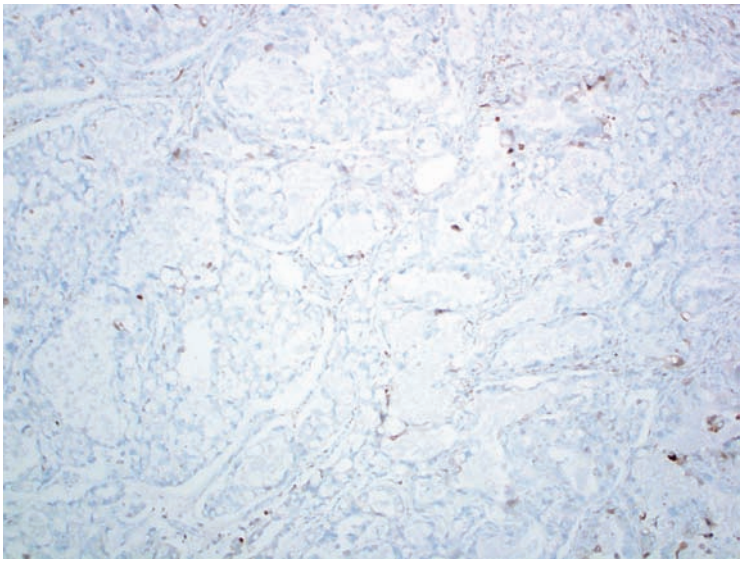


Figure 10.48e — Endometrial Clear Cell Carcinoma (Biopsy) (p16 Immunohistochemical Stain; Intermediate Power). The tumor shows focal expression of p16. The pattern of staining is generally variable in clear cell carcinoma, and a diffuse pattern can be seen on occasion.

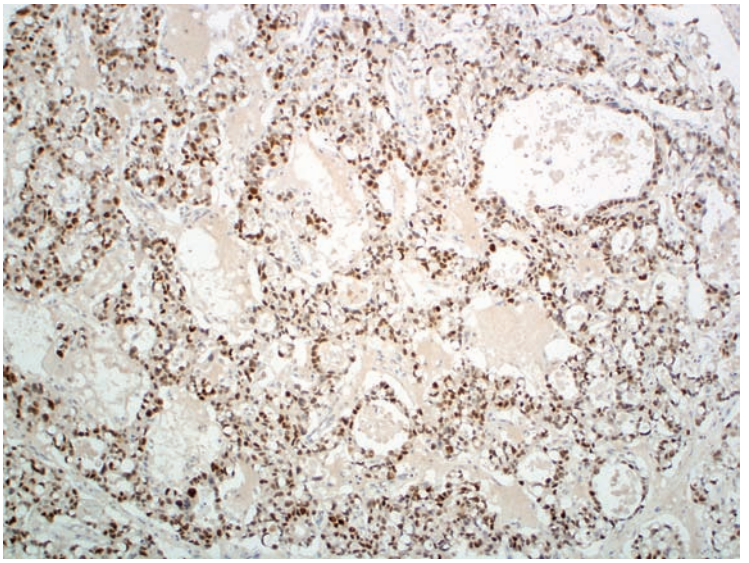


Figure 10.48f — Endometrial Clear Cell Carcinoma (Biopsy) (Hepatocyte Nuclear Factor 1-Beta Immunohistochemical Stain; Intermediate Power). Diffuse nuclear staining for hepatocyte nuclear factor 1-beta is seen. This marker is frequently expressed in clear cell carcinoma and is relatively specific among endometrial carcinomas. However, one cannot always rely on using this marker to establish a diagnosis of clear cell carcinoma because some such cases can be negative and other carcinomas (including endometrioid and serous carcinomas) occasionally can be positive. It is worthwhile noting that secretory endometrium and Arias-Stella reaction can also show expression of hepatocyte nuclear factor 1-beta. Only a minority of endometrial carcinomas are of clear cell histologic type. Clear cell carcinoma is not a highly reproducible diagnosis among gynecologic pathologists, particularly as endometrioid carcinomas and unclassified high-grade endometrial adenocarcinomas can have clear cell-like appearances that overlap with clear cell carcinoma.

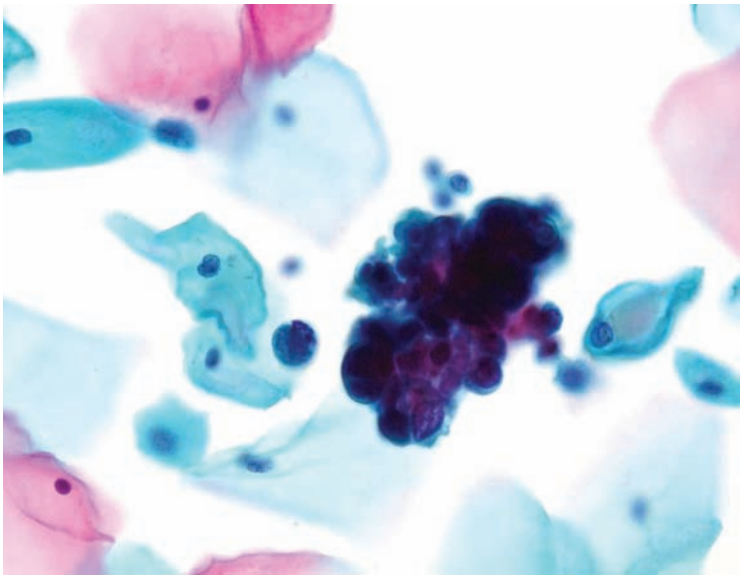


Figure 10.49 — Endometrial Malignant Mixed Müllerian Tumor (MMMT; Carcinosarcoma) (Liquid Based; Medium Power). These cells are markedly atypical, with hyperchromasia, high N/C ratios, nucleomegaly, and marked pleomorphism. Some cells have highly irregular nuclear borders. These cells are obviously malignant and best resemble an adenocarcinoma. In this case, the patient had an endometrial MMMT, which may be represented by either or both components (carcinoma and sarcoma). In this case, the sarcomatous features are not obvious.

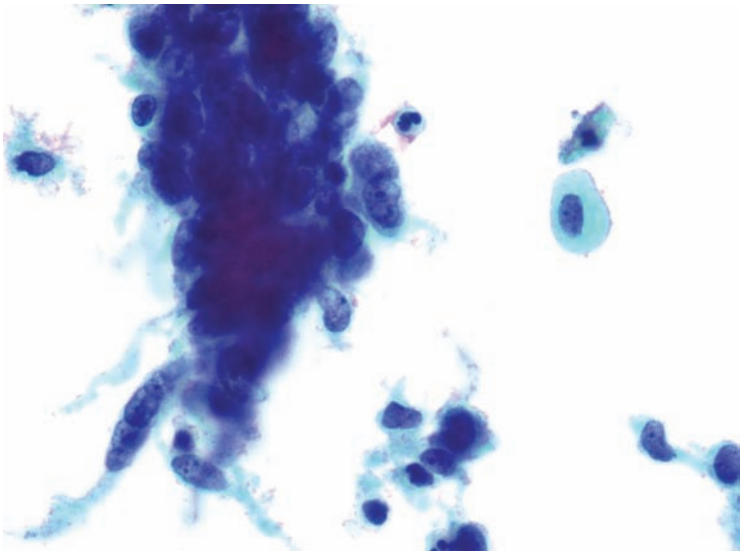


Figure 10.50 — Endometrial Malignant Mixed Müllerian Tumor (MMMT; Carcinosarcoma) (Liquid Based; High Power). A closer look at the composition of this fragment reveals the sarcomatous features, especially the variability in nuclear size and shape, as well as the jagged cytoplasmic tails.

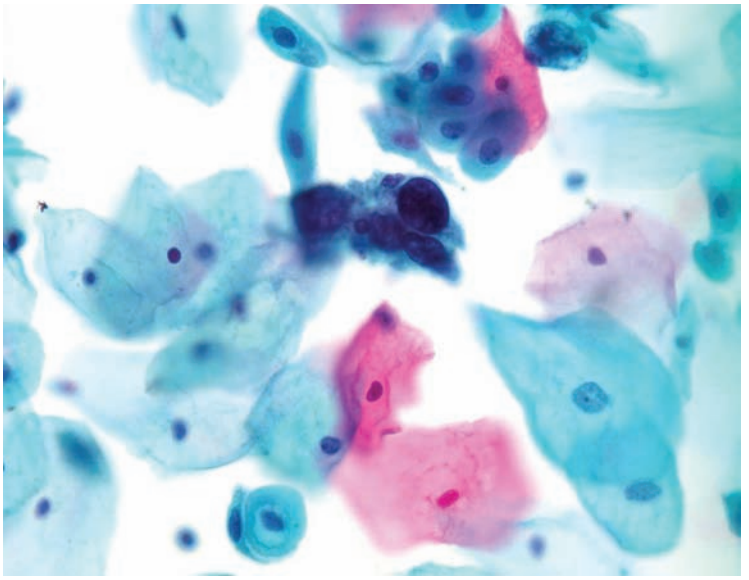


Figure 10.51 — Endometrial Malignant Mixed Müllerian Tumor (MMMT; Carcinosarcoma) (Liquid Based; Medium Power). These atypical cells are also from a patient with an endometrial MMMT; sarcomatous features are not identified here. However, the sarcomatous component may appear more epithelioid and therefore a definitive diagnosis of MMMT is not usually possible or necessary. MMMT found initially on a Pap test may be diagnosed as a carcinoma of unknown origin or differentiation; the possibility of a malignancy from outside the gynecologic tract may also be considered. Ultimately, further investigation will yield diagnostic tissue.

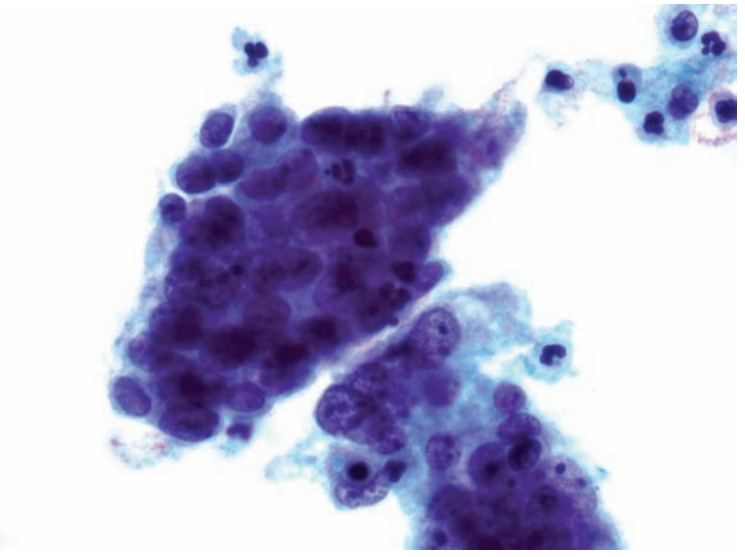


Figure 10.52 — Endometrial Malignant Mixed Müllerian Tumor (MMMT; Carcinosarcoma) (Liquid Based; High Power). The obvious features of malignancy associated with neutrophils suggest an endometrial primary, and adenocarcinoma is likely the primary consideration. The marked nuclear pleomorphism and crowding are beyond those typically found in an endometrioid endometrial adenocarcinoma and, thus, a serous carcinoma, or possibly extension or metastasis from a secondary site, may be considered. In this case, the patient was subsequently diagnosed with an endometrial MMMT, which may not be considered unless an overtly sarcomatous component is present.

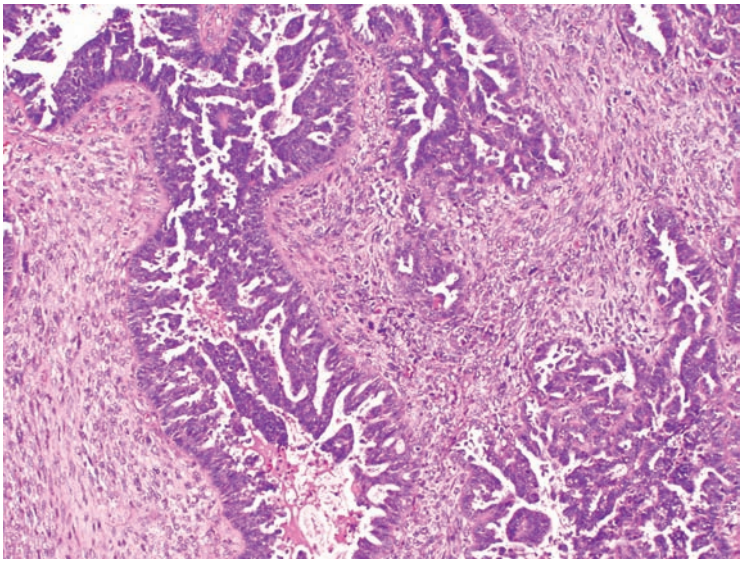


Figure 10.53a — Endometrial Malignant Mixed Müllerian Tumor (MMMT; Carcinosarcoma) (Hysterectomy; H&E Stain; Intermediate Power). MMMT classically shows an intimate admixture of malignant epithelial and mesenchymal components. In this case, the epithelium is stratified and markedly complex, whereas the mesenchymal component is cellular.

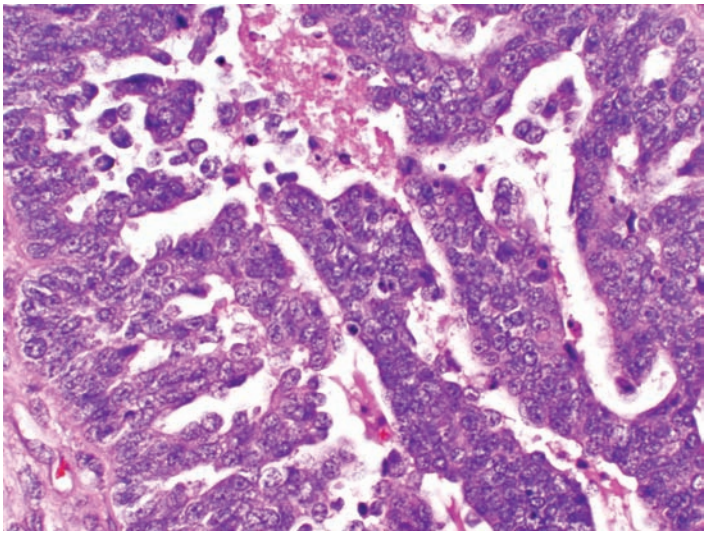


Figure 10.53b — Endometrial Malignant Mixed Müllerian Tumor (MMMT; Carcinosarcoma) (Hysterectomy; H&E Stain; High Power). The epithelial component can consist of any type of Müllerian carcinoma. Frequently, it is composed of serous carcinoma or unclassified high-grade adenocarcinoma. Some may consist of endometrioid carcinoma. Although the histologic features are suggestive of serous carcinoma in this example, the morphologic findings are somewhat nonspecific, and definitive distinction between serous carcinoma and unclassified high-grade adenocarcinoma would be best accomplished with the aid of immunohistochemical stains.

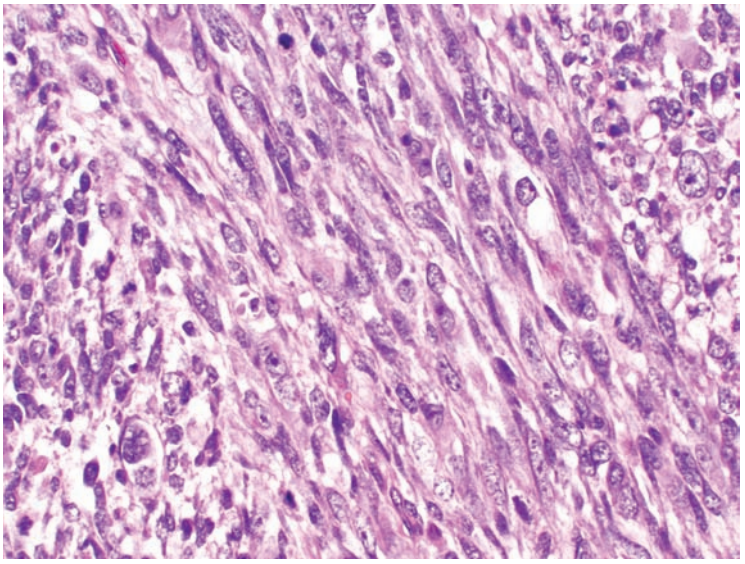


Figure 10.53c — Endometrial Malignant Mixed Müllerian Tumor (MMMT; Carcinosarcoma) (Hysterectomy; H&E Stain; High Power). The sarcoma component of MMMT can consist of almost any histologic type and may be either homologous or heterologous. Homologous types are those commonly seen in the uterus, like leiomyosarcoma or "high-grade endometrial stromal sarcoma." Heterologous types are those usually not seen in the uterus, such as rhabdomyosarcoma, chondrosarcoma, and osteosarcoma. The most common type of sarcoma component in MMMT is rhabdomyosarcoma. Routinely, specification of the histologic types of the carcinoma and sarcoma components is not necessary for reporting purposes. Small endometrial biopsies that have limited tissue can be potentially misclassified as either a pure carcinoma or sarcoma if both components are not present. It is noteworthy that the proportion of either component in MMMT can vary, and in some cases, one component may nearly overgrow the other. Although it has been debated whether endometrial MMMT is truly a carcinosarcoma as opposed to a very poorly differentiated carcinoma, many gynecologic pathologists accept the latter scenario.

11

Metastatic and Unusual Malignancies

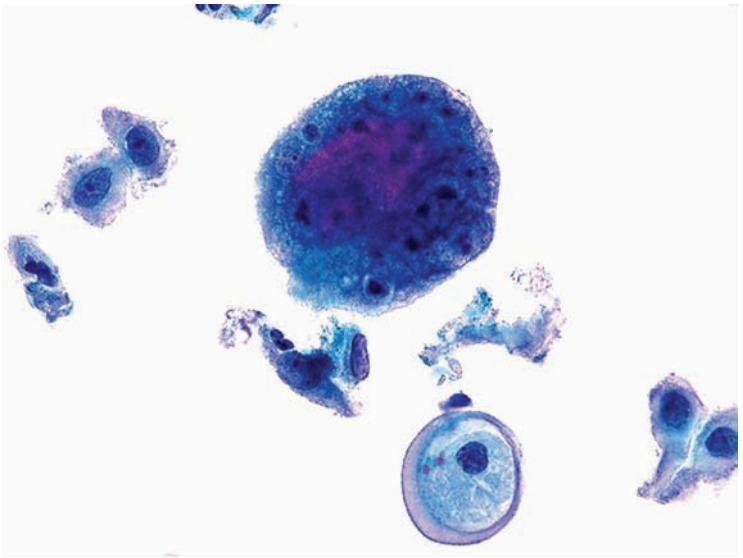


Figure 11.1 — Metastatic Breast Carcinoma (Liquid Based; High Power). A morula of malignant cells is an unusual finding from a Pap test. If this were in a serous cavity fluid, breast cancer would be high on the list of possible sources. Complete clinical history is important. Even if the history is not helpful, a generic category of "metastatic adenocarcinoma, differential includes breast and ovary" will suffice.

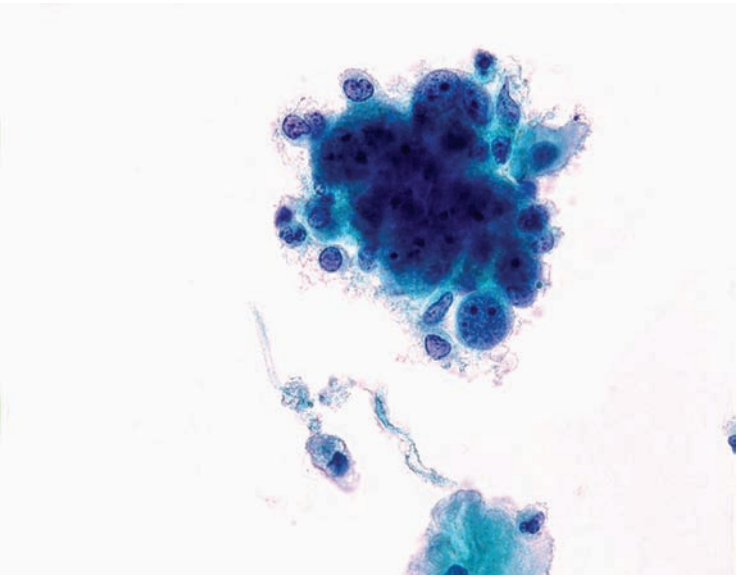


Figure 11.2 — Metastatic Breast Carcinoma (Liquid Based; High Power). A patient with a history of breast cancer may have two issues to consider with unexpected findings in a Pap test: metastatic breast cancer, or endometrial cancer, induced by tamoxifen. The background of lysed red cells and macrophages (possible stromal cells?) raises the possibility of endometrial cancer. However, the morphology of the cells is more consistent with breast origin. Another generic category is adequate when in doubt, for example, "adenocarcinoma, consider breast and endometrium as sources."

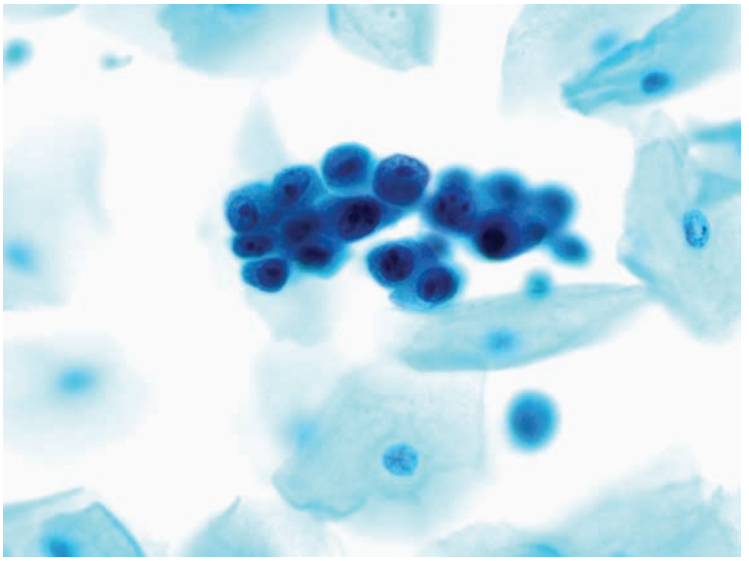


Figure 11.3 — Metastatic Adenocarcinoma (Gastrointestinal Origin) (Liquid Based; High Power). Without knowing the patient's history, these could be considered from the endocervix. The clean background speaks in favor of a metastatic lesion. Clinical correlation is necessary to define the source, as well as physical examination and tissue for immunohistochemical (IHC) studies.

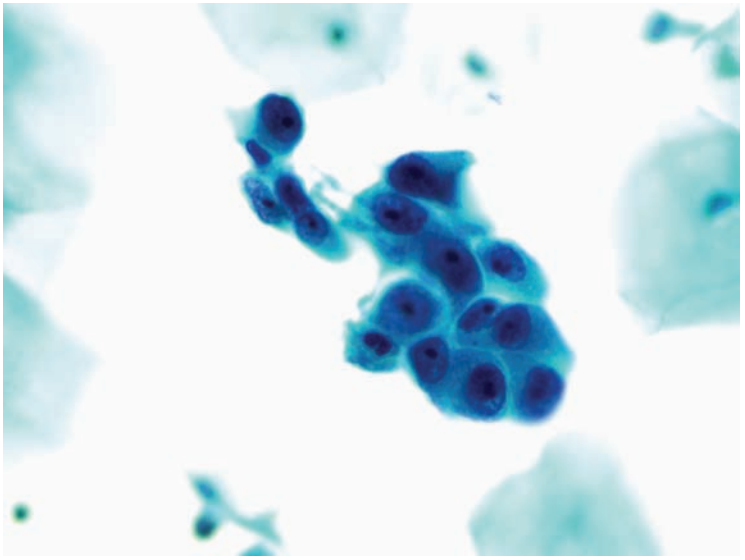


Figure 11.4 — Metastatic Ovarian Carcinoma (Liquid Based; High Power). This is an unusual presentation of an ovarian lesion in a Pap. The distinct cell boundaries might suggest squamous origin. However, serous ovarian carcinomas may have very distinct cytoplasmic outlines. The round nuclei, open chromatin, and prominent central nucleoli are more characteristic of a glandular carcinoma. The clean background is another feature in favor of metastases.

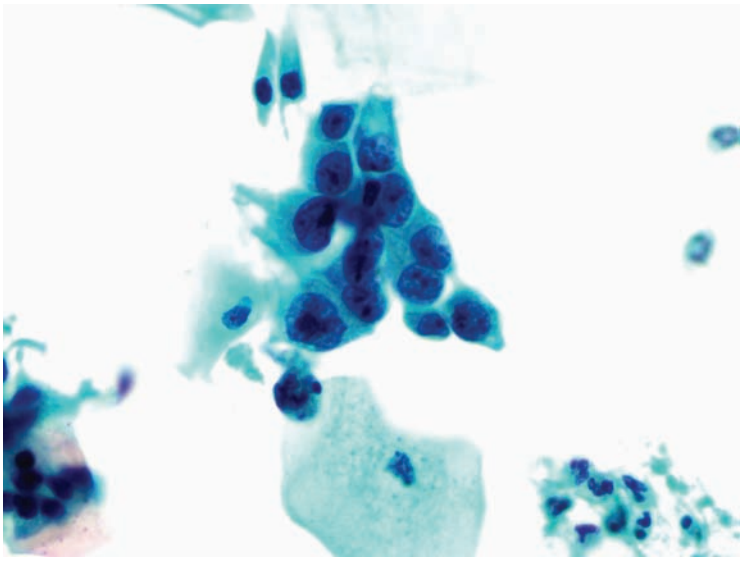


Figure 11.5 — Metastatic Ovarian Carcinoma (Liquid Based; High Power). Cells similar to those in Figure 11.4 are definitely glandular in origin; compare with the two benign endocervical cells directly above the malignant group. A primary endocervical adenocarcinoma must be considered, especially if there is abundant inflammatory debris in the background. Biopsy with IHC, in addition to radiographic or physical findings, will, no doubt, clarify the source of the malignancy.

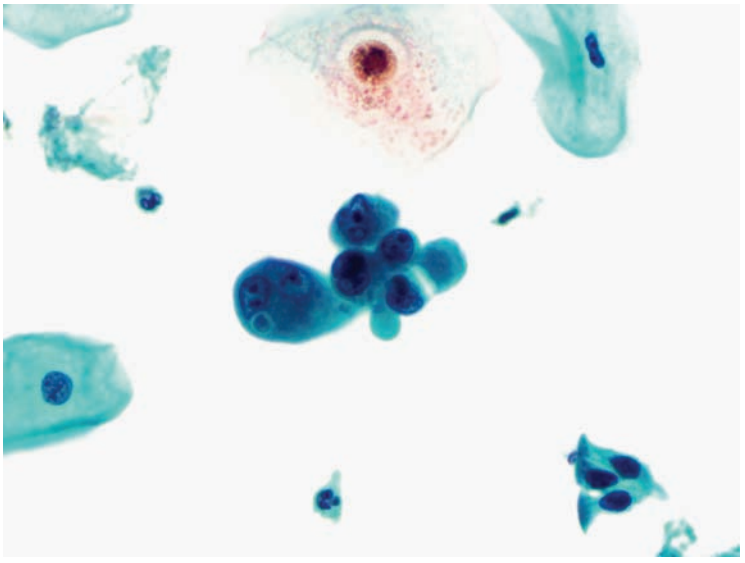


Figure 11.6 — Metastatic Ovarian Carcinoma (Liquid Based; High Power). Malignant glandular cells in a clean background can be from many origins. However, a few clues are helpful. The "window" between the two smaller cells suggests Müllerian origin, as does the "hobnail" outline of the group.

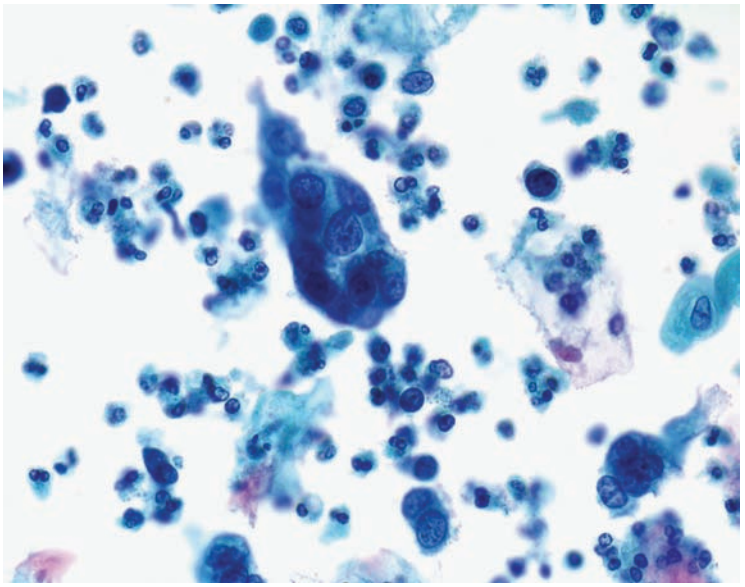


Figure 11.7 — Metastatic Ovarian Carcinoma (Liquid Based; Medium Power). A glandular fragment in an inflammatory background may be from a benign polyp or from a neoplasm, either primary or metastatic. The cells in this group are not nearly as ugly as those in Figures 11.5 and 11.6. A descriptive diagnosis with a list of possible origins is prudent.

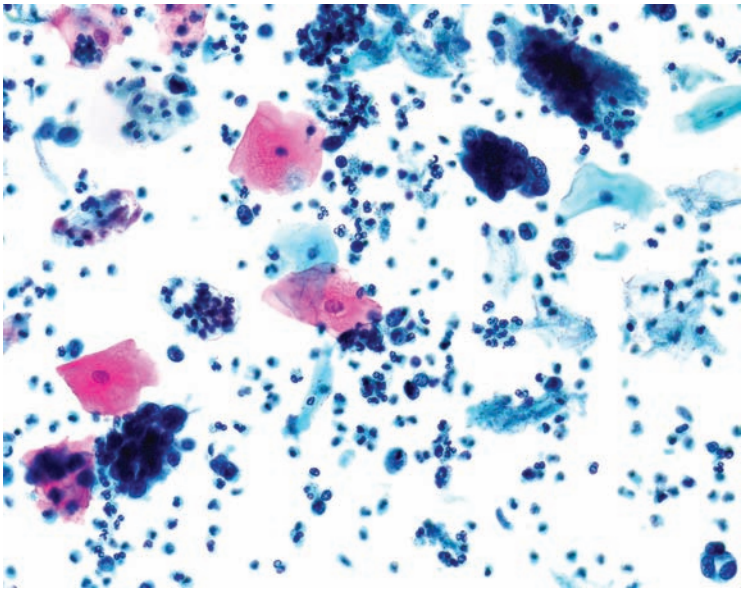


Figure 11.8 — Metastatic Ovarian Carcinoma (Liquid Based; Low Power). This pattern is full of red herrings: intense inflammatory background, single cells with high nuclear-to-cytoplasmic (N/C) ratios, and multiple hyperchromatic crowded groups (HCGs). These are all features of a possible lesion local to the cervix. Higher power is needed to appreciate that the HCGs are malignant. This is a rare pattern for metastatic disease, because there are usually very few malignant groups in that circumstance.

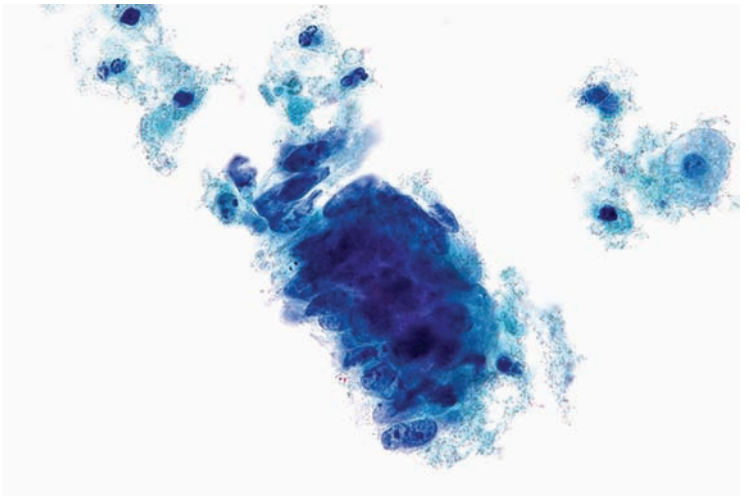


Figure 11.9 — Metastatic Colonic Adenocarcinoma (Liquid Based; High Power). Three adenocarcinomas will present with a palisade of tall cells: endometrioid cancer, either from the endocervix or endometrium; endocervical adenocarcinoma in situ; and colonic adenocarcinoma. The large size of the nuclei favors colon primary. However, the lysed blood may signify a uterine primary. Clinical correlation is important.

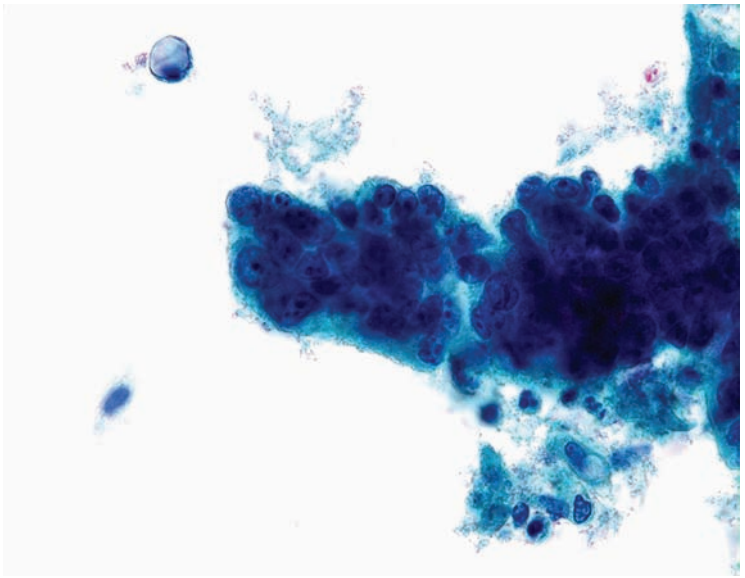


Figure 11.10 — Metastatic Colonic Adenocarcinoma (Liquid Based; High Power). Poorly differentiated adenocarcinoma accompanied by lysed blood and cell debris is consistent with a uterine primary, *or* direct extension from a colorectal primary. The pathway into the vagina may be through lymphatics or a fistulous tract. Consider the latter, especially if the fecal material is recognized in the Pap sample.

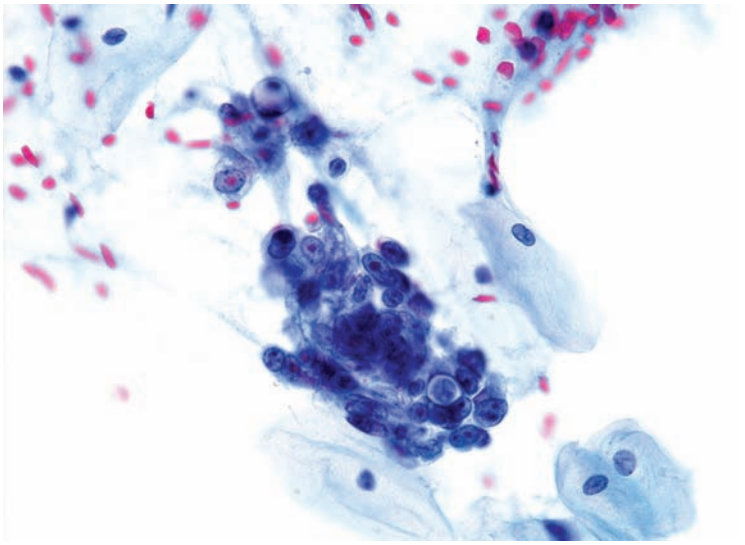


Figure 11.11 — Metastatic Lobular Breast Carcinoma (Liquid Based; Medium Power). Some tumors carry their own "markers," such as the cytoplasmic microtubules in lobular breast cancer. However, if they are only cytoplasmic vacuoles, the cells could be signet ring cells from gastrointestinal (GI) or bladder primary sites. Clinical history is vitally important.

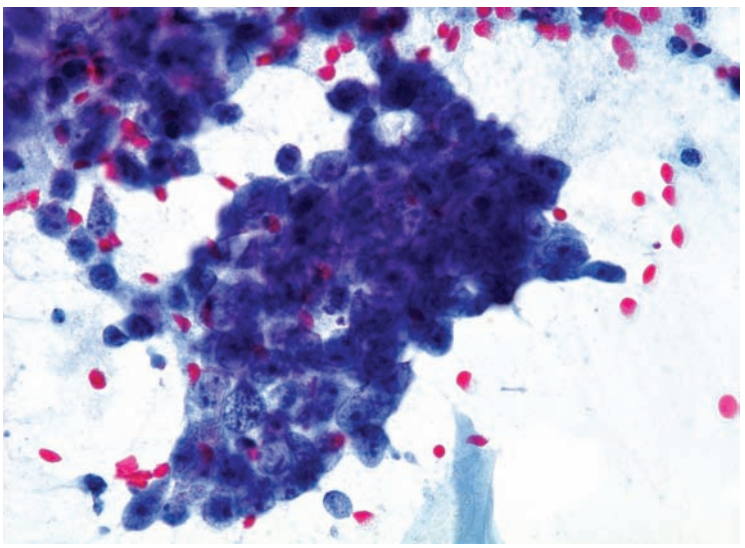


Figure 11.12 — Metastatic Lobular Breast Carcinoma (Liquid Based; High Power). This is an unusually large tissue fragment to be a metastasis to the cervicovaginal tract unless it is from a drop metastasis into the pouch of Douglas that directly extended into the vagina. Clinical history, biopsy, and IHC are necessary to define the origin of the cancer.

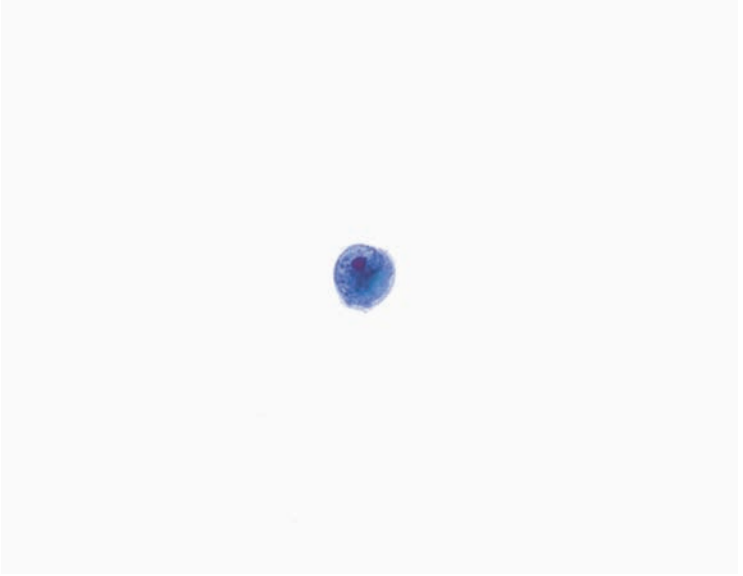


Figure 11.13a — Metastatic Lobular Breast Carcinoma (Liquid Based; High Power). While no other cells are present in this field for comparison, consider the features of this cell and how dissimilar it is to components usually found in a Pap smear. There is a thin rim of foamy cytoplasm, the chromatin pattern is somewhat coarse, and there is a very prominent nucleolus. Metastasis from lobular breast carcinoma may present with rare malignant cells and can be difficult to detect in a Pap sample.

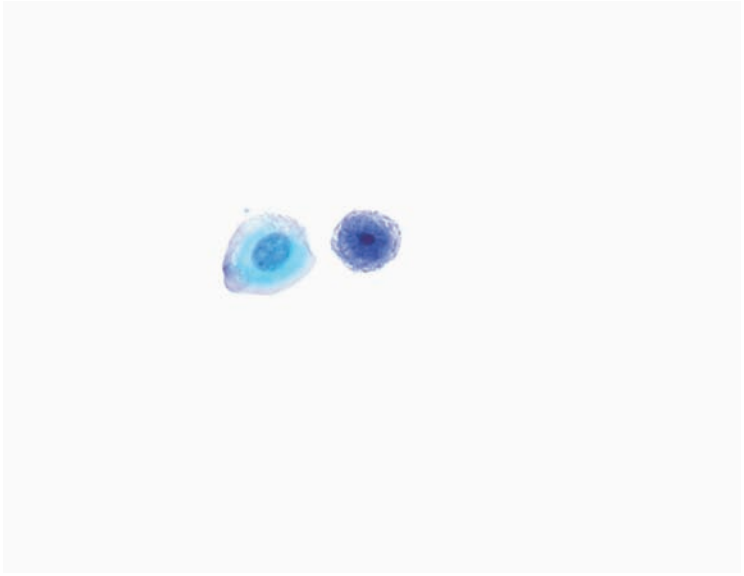


Figure 11.13b — Metastatic Lobular Breast Carcinoma (Liquid Based; High Power). Adjacent to this squamous cell, one now has a sense of the malignant cell's large nucleus. Its nucleus is almost as large as the entire squamous cell. Another differential diagnosis would be an intrauterine device (IUD) cell.

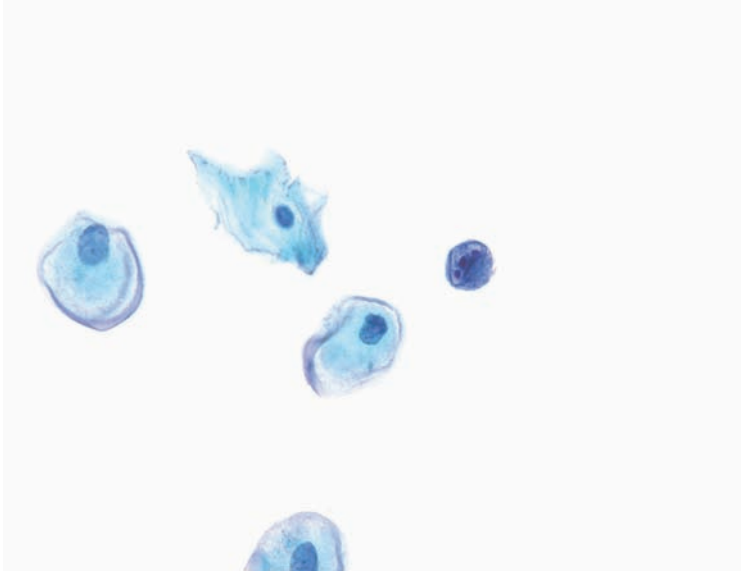


Figure 11.13c — Metastatic Lobular Breast Carcinoma (Liquid Based; High Power). This field contains another individual malignant cell. The cytoplasm is foamy, suggesting its glandular origin, and the delicate cytoplasm may initially suggest the possibility of degenerative changes. The nucleus, however, appears intact and contains three enlarged nucleoli. Because the malignant cells may be singly dispersed throughout the smear, they may be easily overlooked. The presence of such foreign-appearing cells in a Pap smear requires a review of the patient's history.

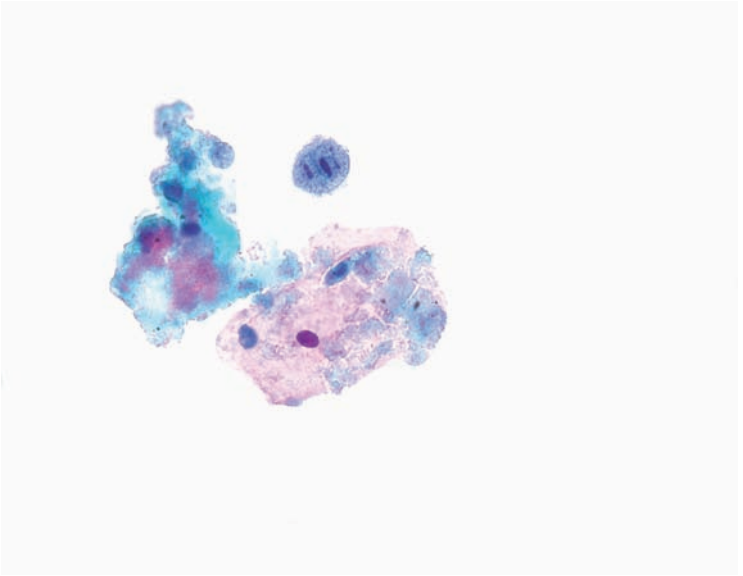


Figure 11.13d — Metastatic Lobular Breast Carcinoma (Liquid Based; High Power). Comparing this malignant cell to those in the previous fields, it is easy to see their morphologic similarities. However, this field alone does not give one the impression of overt malignancy. This carcinoma cell has an indistinct nucleus and the chromatin appears to merge with the foamy cytoplasm. The prominent and irregular nucleolus is the most recognizable feature. However, especially when adjacent to areas of degenerated cells and debris, this malignant cell could easily be overlooked.

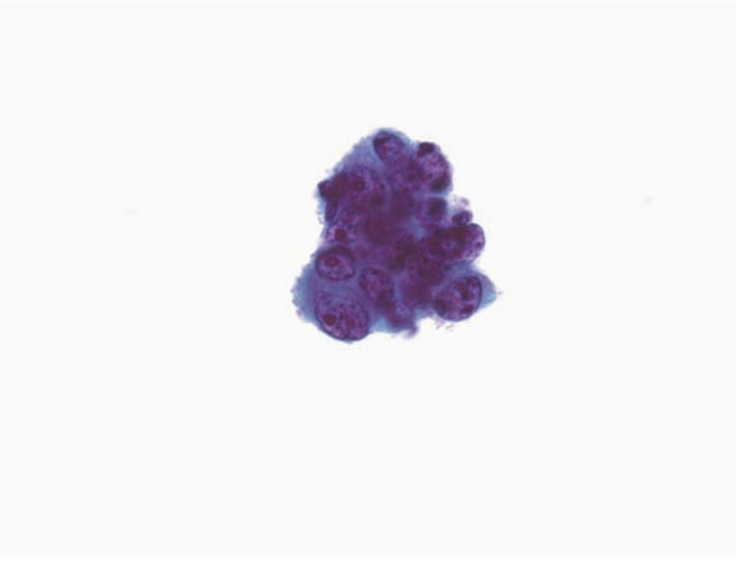


Figure 11.14a — Metastatic Rectal Adenocarcinoma (Liquid Based; High Power). Although these cells do not have the columnar appearance of some intestinal adenocarcinomas, some cytomorphologic features are distinctive for an adenocarcinoma. The cytoplasm is amphophilic and foamy, and there are prominent nucleoli. Other features of malignancy include pleomorphic nuclei, coarse chromatin, and irregular nuclear borders. There is no definitive glandular formation, but the nuclei overlap as a syncytial group.

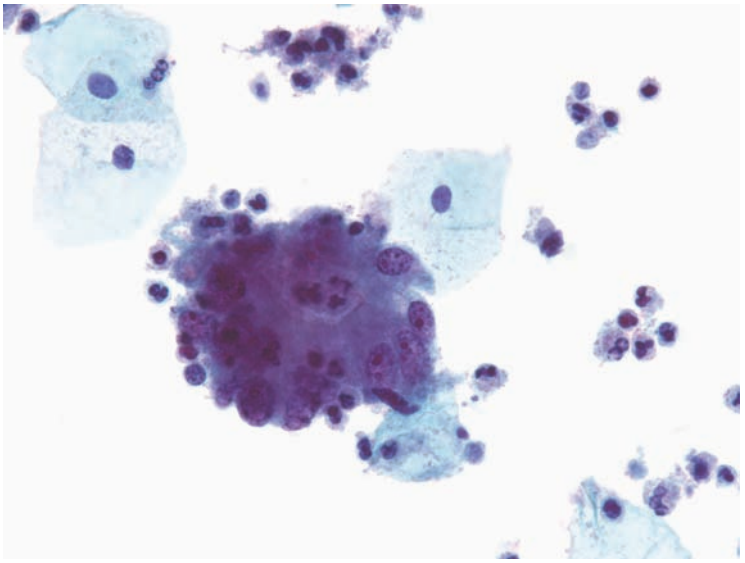


Figure 11.14b — Metastatic Rectal Adenocarcinoma (Liquid Based; High Power). Here the nuclei of the malignant cells are similar to those seen in the previous figure, and while the cellular borders remain indistinct, there is definite gland formation containing luminal neutrophils, and the nuclei are eccentrically placed, giving the cells a columnar appearance. The edges of the tissue fragment, as well as adjacent areas, are associated with necrotic debris and neutrophils, a common finding in metastases from the colon and rectum. Necrosis and debris are generally associated with invasive primary malignancies of the cervix, whereas a clean background is associated with metastatic malignancies. Metastatic colonic and rectal adenocarcinomas are an exception to this generalization.

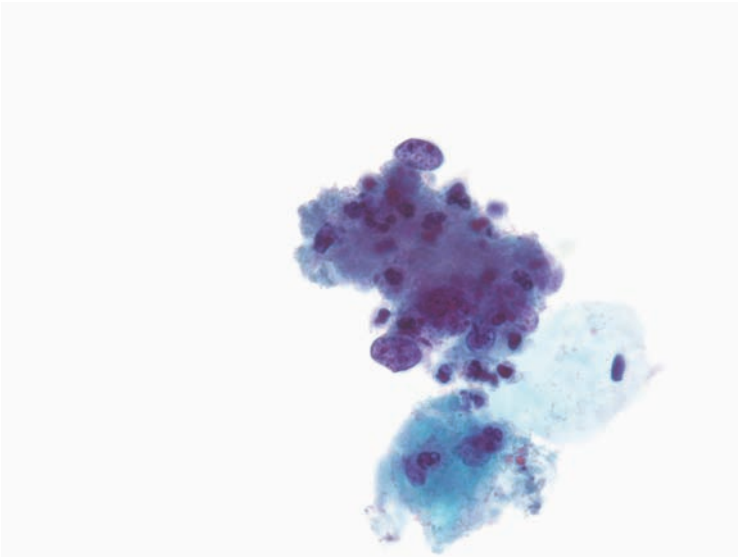


Figure 11.14c — Metastatic Rectal Adenocarcinoma (Liquid Based; High Power). This field contains predominantly necrotic debris with intact nuclei that are no longer associated with cytoplasm. However, the nuclear features are similar to those seen in the previous two figures.

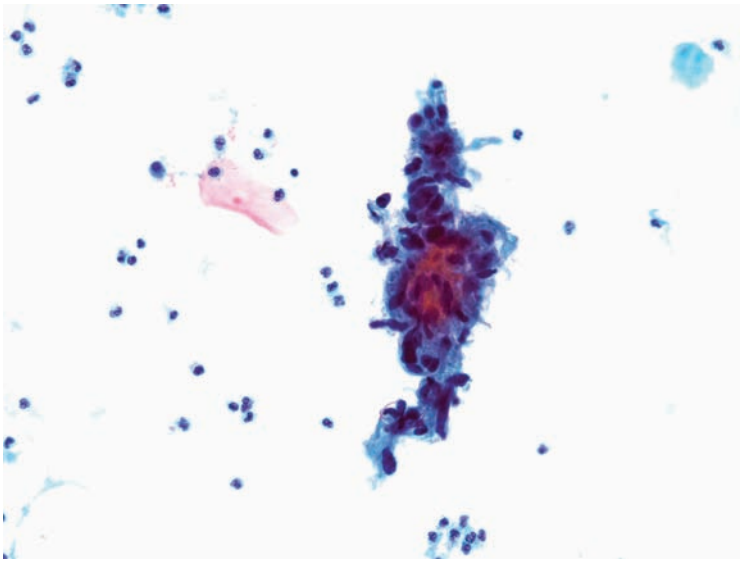


Figure 11.15a — Leiomyosarcoma (Liquid Based; Intermediate Power). This fragment of cells contains nuclei with predominantly spindled shapes. The nuclei also have dark chromatin and highly irregular shapes. Primary sarcomas of the gynecologic tract usually involve the uterus (leiomyosarcoma or endometrial stromal sarcoma) and, although uncommon, they are more common than metastatic sarcomas of the gynecologic tract.

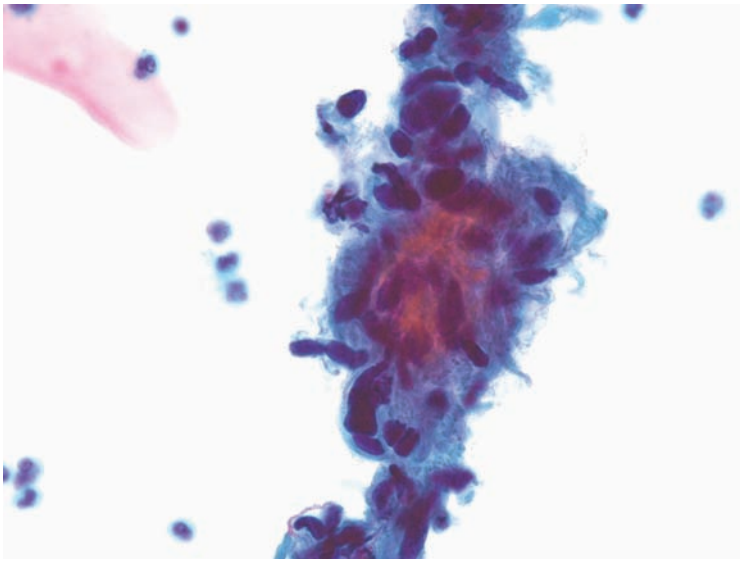


Figure 11.15b — Leiomyosarcoma (Liquid Based; High Power). The striking pleomorphism and irregular shapes of the nuclei can be better appreciated at high power. The differential for malignant spindle cell lesions in a Pap smear includes sarcomatoid carcinoma and a sarcomatoid component of a malignant mixed Müllerian tumor (MMMT). Homologous components include uterine stromal sarcoma and leiomyosarcoma. Occasionally, MMMT may arise in the ovary and be found as a metastasis in a Pap test.

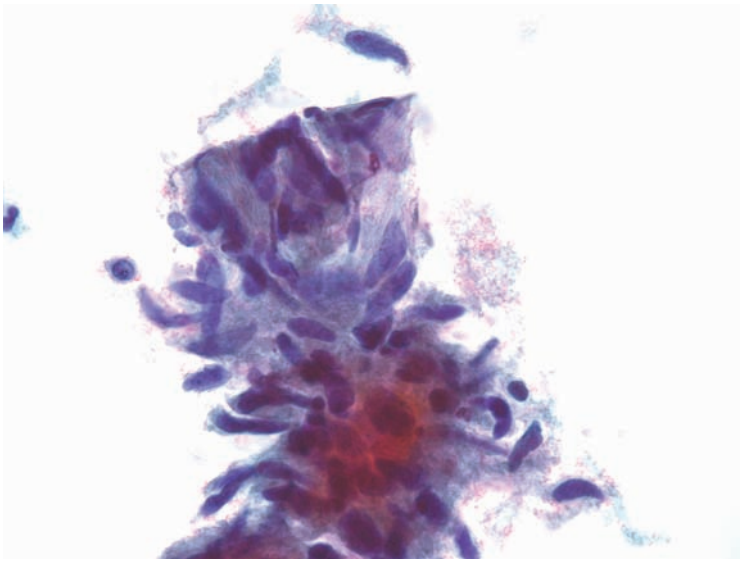


Figure 11.16a — Leiomyosarcoma (Liquid Based; High Power). Although the nuclei assume a plump spindle shape, the ends are generally blunt giving a "cigar shape." However, nuclear indentation is prominent in this field and many of the nuclei have the appearance of a canoe. Epithelioid nuclei can also sometimes be seen (lower center of the field).

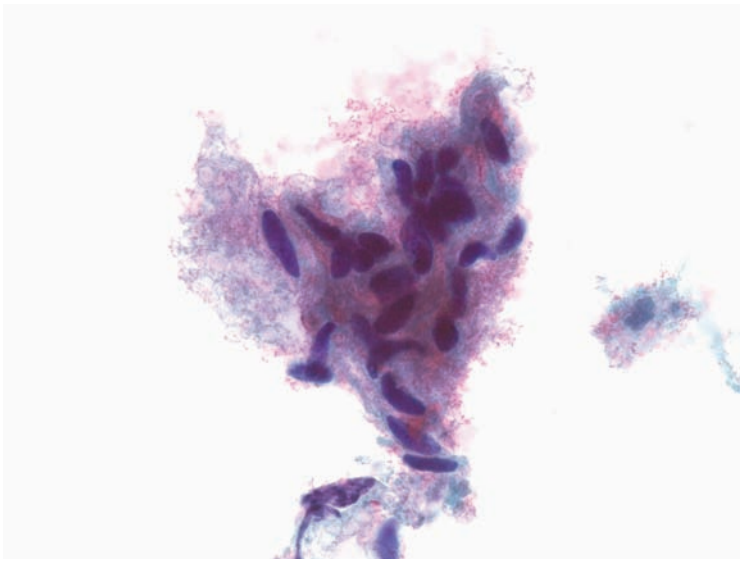


Figure 11.16b — Leiomyosarcoma (Liquid Based; High Power). The cell cytoplasm is indistinct and delicate, making the nuclei the most apparent feature in this fragment. Determining the specific type of neoplasm in a Pap smear is not possible, but the presence of highly atypical spindle cells suggests a malignant process. One possible diagnosis could be "markedly atypical spindle cells" with a differential diagnosis that includes sarcoma and sarcomatoid carcinoma. Clinical follow-up will yield tissue for histopathologic and immunohistochemical analysis.

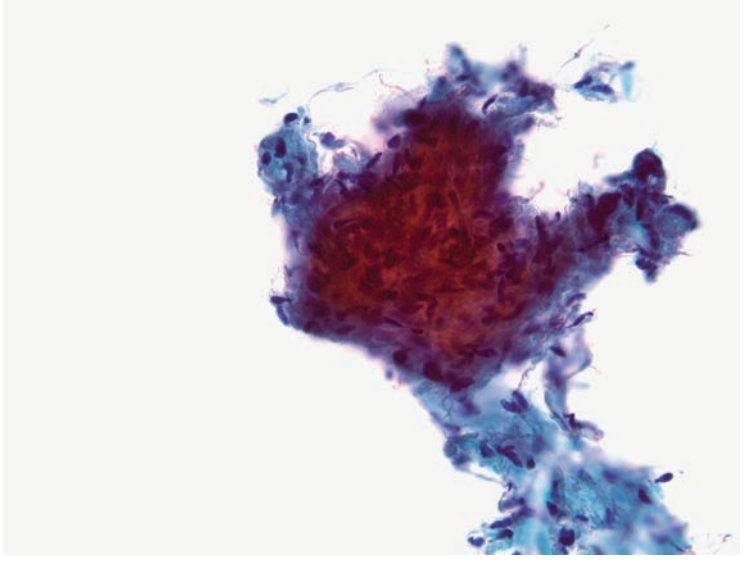


Figure 11.16c — Leiomyosarcoma (Liquid Based; Intermediate Power). At lower power, the malignant features in this particular fragment are less obvious. The center of the fragment is poorly stained, making interpretation difficult. The edges of the fragment contain nuclei with a stringy appearance, though they remain hyperchromatic. The differential here may include fibroinflammatory tissue, though comparison with adjacent inflammatory cells should demonstrate the extent to which the nuclei in this fragment are enlarged. However, given the rarity of sarcomas in a Pap smear, the possibility of a more common process should be considered, such as granulation tissue or granulomatous inflammation. Radiologic data and patient history should prove useful.

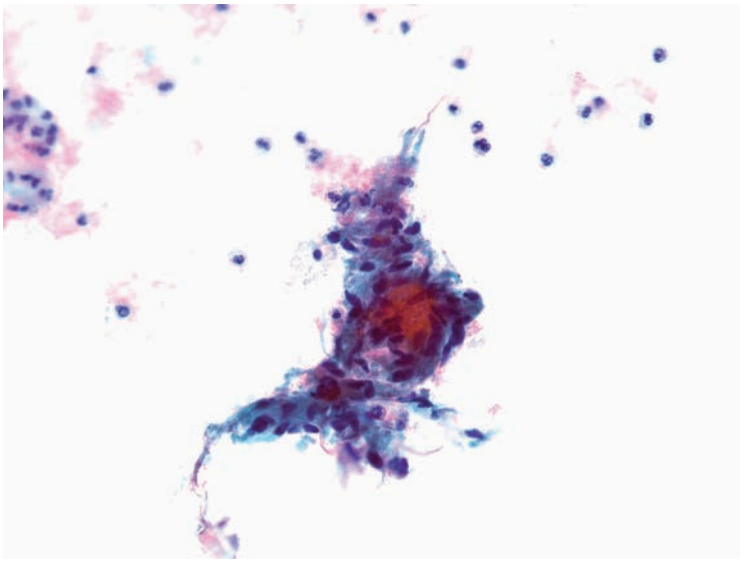


Figure 11.16d — Leiomyosarcoma (Liquid Based; Intermediate Power). Once the leiomyosarcoma presents itself on a Pap test, the tumor is often necrotic and friable. Thus, the fragments are more delicate and appear less cohesive than typical soft tissue neoplasms. This feature also contributes to the increased cellularity found in the Pap test.

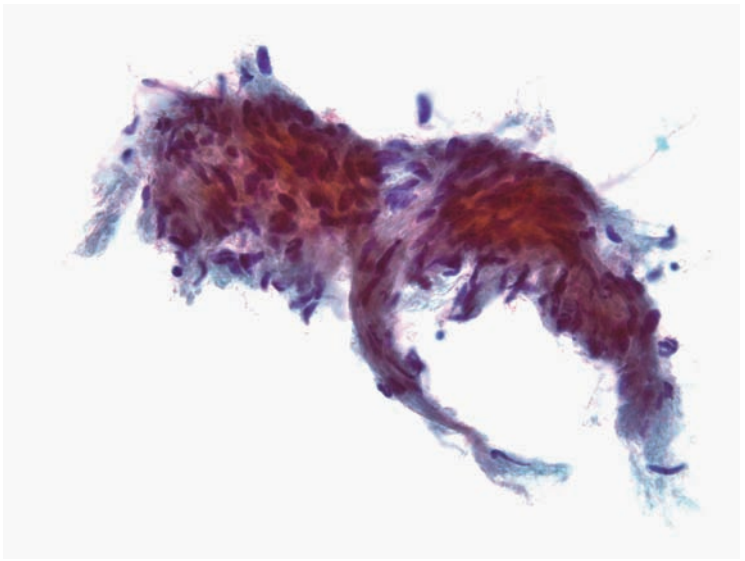


Figure 11.16e — Leiomyosarcoma (Liquid Based; Intermediate Power). This fragment demonstrates spindle cell morphology in the center, more epithelioid cells in the fragment "wings," and wispy cytoplasm, which appears to fade away at the fragment edges.

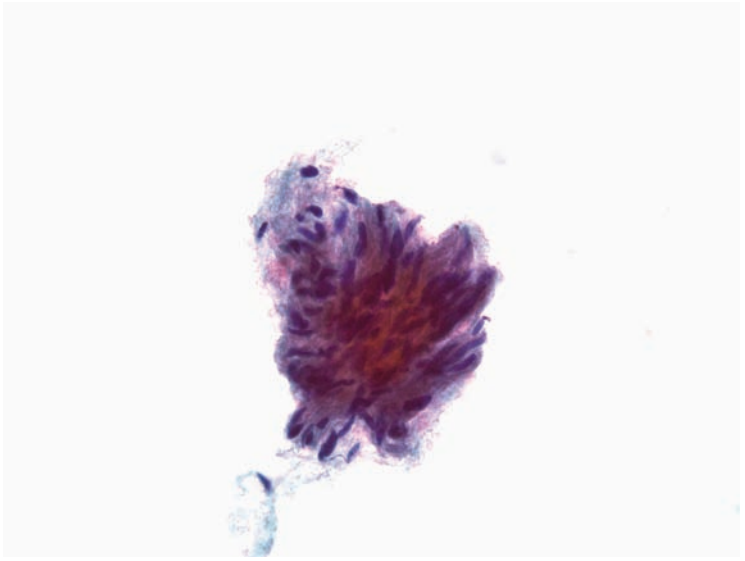


Figure 11.16f — Leiomyosarcoma (Liquid Based; Intermediate Power). This fragment contains predominantly cells with "cigar shape" nuclei, which is the classical appearance of smooth muscle neoplasms. One can also imagine a fascicular pattern in this fragment, with the right edge containing nuclei streaming within the plane of the field, and the top left corner containing nuclei that are "standing up" and streaming into the face of the viewer.

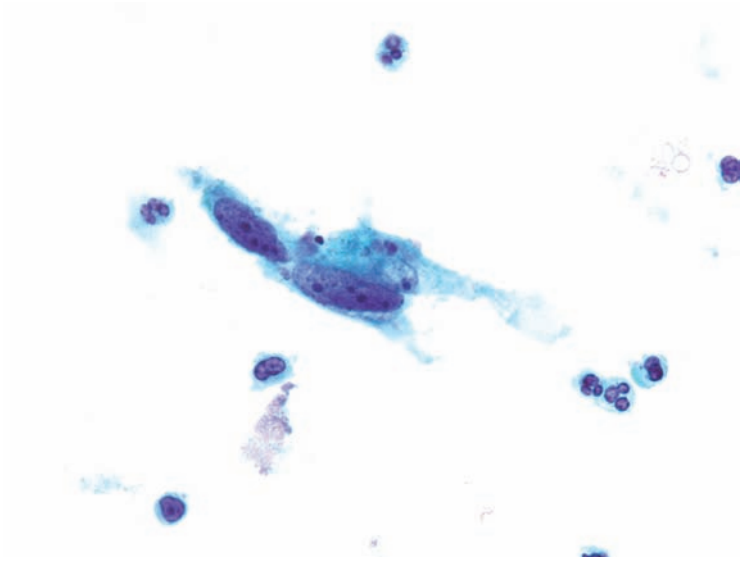


Figure 11.17a — Leiomyosarcoma (Liquid Based; High Power). If viewed at high power and stained appropriately, nucleoli can sometimes be observed in leiomyosarcomas. These nuclei also have blunt ends and do not have prominent indentations seen in previous figures.

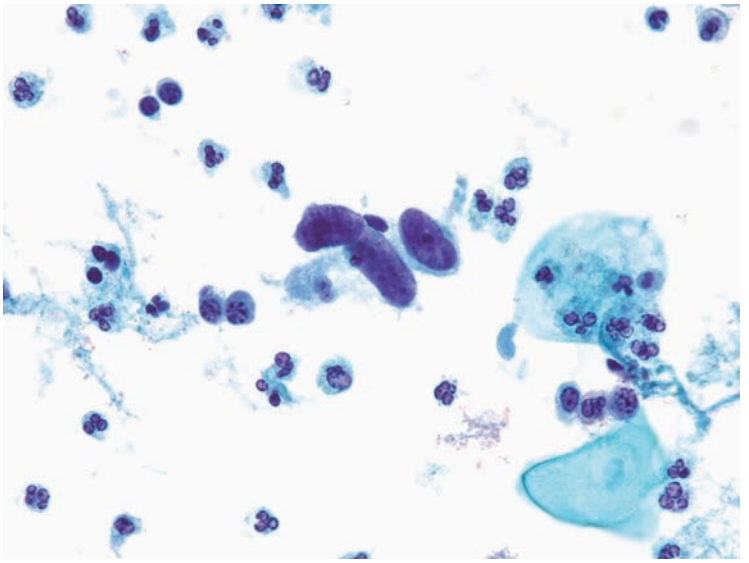


Figure 11.17b — Leiomyosarcoma (Liquid Based; High Power). The cell on the right contains a prominent nucleolus, though hyperchromasia makes the chromatin pattern difficult to identify in these three cells. The cytoplasm is indistinct, but the nuclei are quite large (compare to the adjacent inflammatory cells).

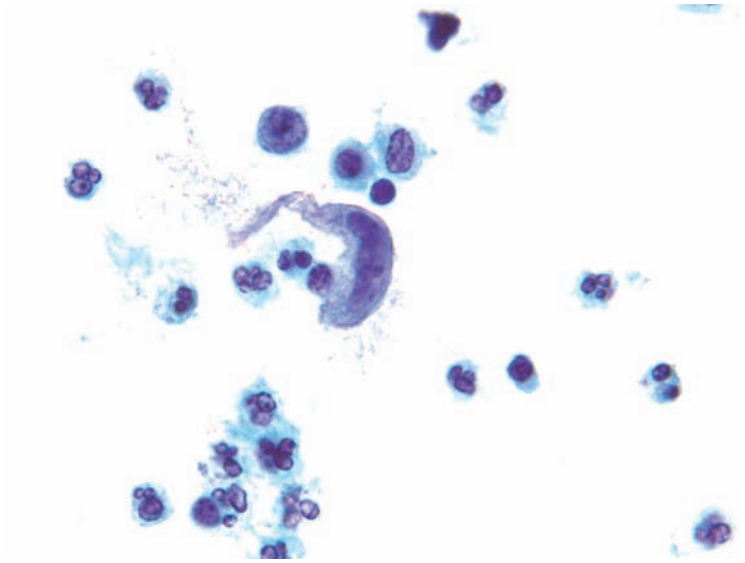


Figure 11.17c — Leiomyosarcoma (Liquid Based; High Power). This canoe-shaped nucleus also contains a nucleolus, though it is difficult to discern from the background chromatin. The cytoplasmic tail is also a feature of spindle cell neoplasms.

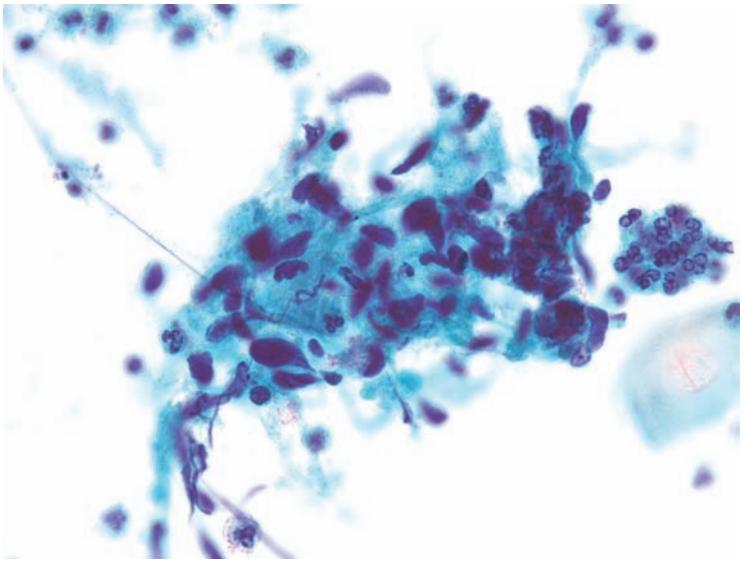


Figure 11.18a — Leiomyosarcoma (Liquid Based; High Power). This mixture of malignant cells and neutrophils gives one the initial impression of a granulation tissue, or granulomatous inflammation compounded by acute inflammation. However, the hyperchromasia and highly irregular-shaped nuclei instead suggest the possibility of malignancy. Note how the indistinct and wispy cytoplasm of the malignant cells mimics the debris that might be seen in an inflammatory process, such as an ulcer.

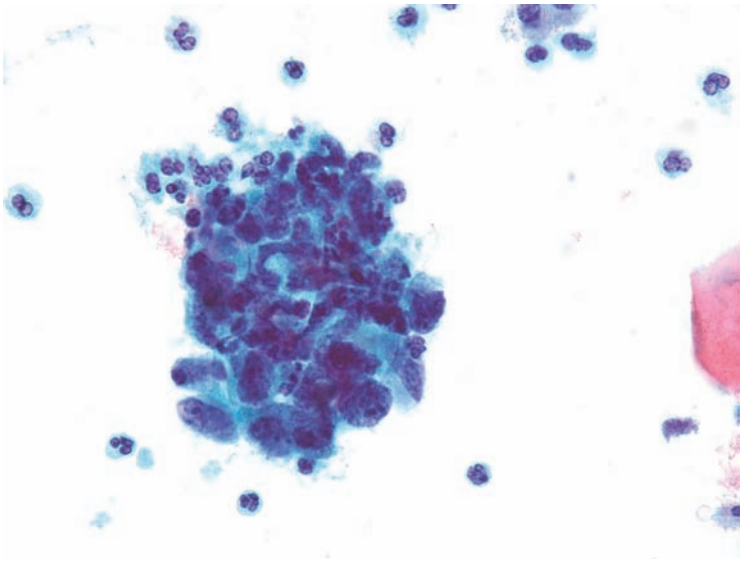


Figure 11.18b — Leiomyosarcoma (Liquid Based; High Power). There are no features in this fragment to suggest a sarcoma, though the hyperchromasia, pleomorphism, and irregular nuclear borders indicate a malignancy. Coupled with the delicate cytoplasm, this fragment alone is most suggestive of an adenocarcinoma, even though it is simply another field of leiomyosarcoma cells.

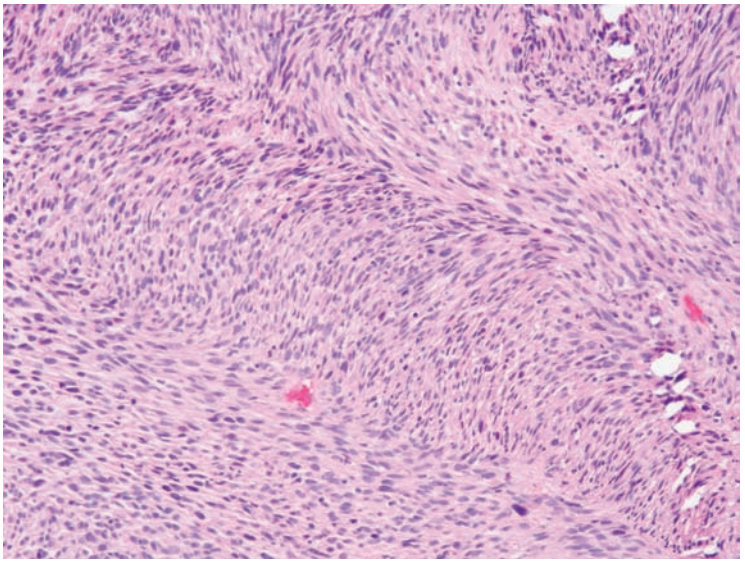


Figure 11.19a — Leiomyosarcoma (Biopsy) (Hematoxylin and Eosin [H&E] Stain; Intermediate Power). At intermediate power, the fascicular nature of this spindle cell neoplasm is apparent. Areas of perinuclear clearing, a feature seen in smooth muscle neoplasms, can be identified. The tumor is cellular, and the nuclei are uniformly atypical but do not exhibit overt pleomorphism. Neither mitotic figures nor necrotic areas are seen in this field. No normal elements are present.

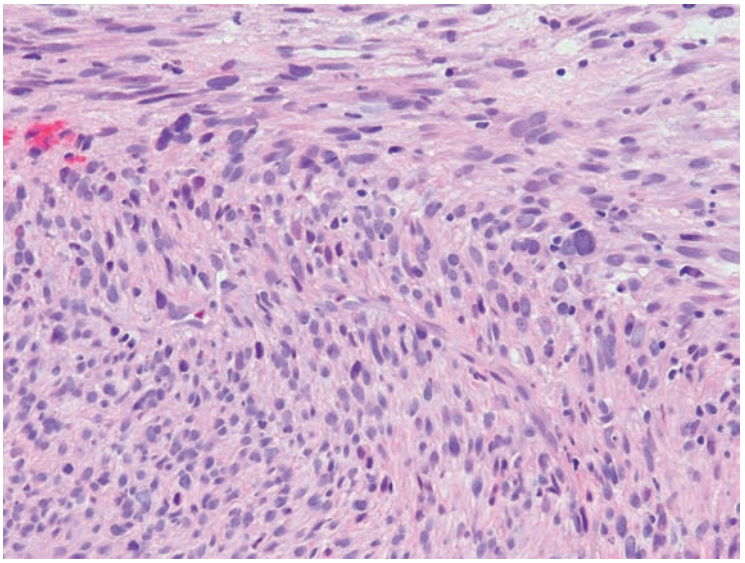


Figure 11.19b — Leiomyosarcoma (Biopsy) (H&E Stain; High Power). At high power, the nuclei morphologically correspond to those seen on the Pap smears. Both spindle-shaped and epithelioid cells are present, and small distinct nucleoli can be seen in some cells. Other features of malignancy (not pictured) include 10 or more mitotic figures per 10 high-power fields in the most mitotically active areas and coagulative tumor necrosis. However, benign smooth muscle neoplasms (leiomyomas) are rarely seen on Pap smears unless they ulcerate the cervix. Such lesions rarely produce the cellularity seen when a Pap smear is involved by a malignant smooth muscle neoplasm.

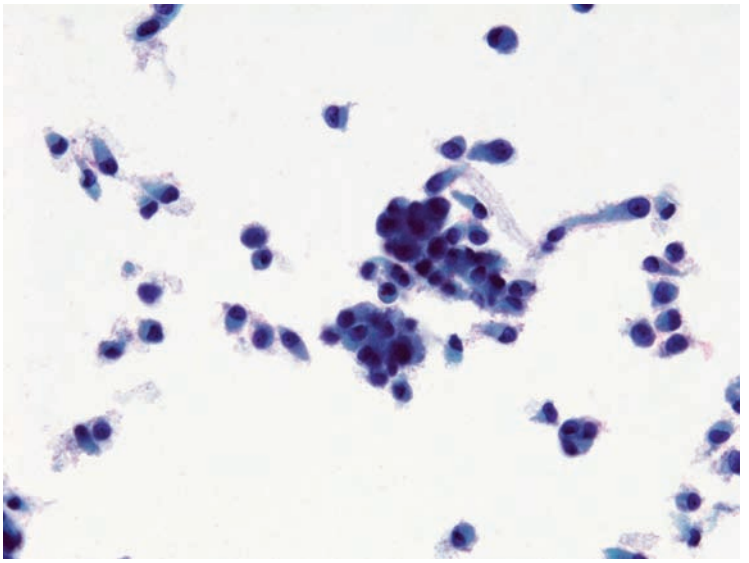


Figure 11.20a — Metastatic Urothelial Carcinoma (Liquid Based; Medium Power). The field contains almost entirely a monotonous population of atypical cells that appear foreign in a Pap test. While the hyperchromasia and dense cytoplasm are both reminiscent of a high-grade squamous intraepithelial lesion (HSIL) or squamous cell carcinoma, other features are peculiar, such as the dispersed pattern, eccentrically placed nuclei, and feathery cytoplasmic extensions, which are distinct from the dense irregular keratin-rich cytoplasmic extensions found in squamous cell carcinomas. "Clinging" tumor diathesis coats the surface of most cells, suggesting an invasive and thus malignant process.

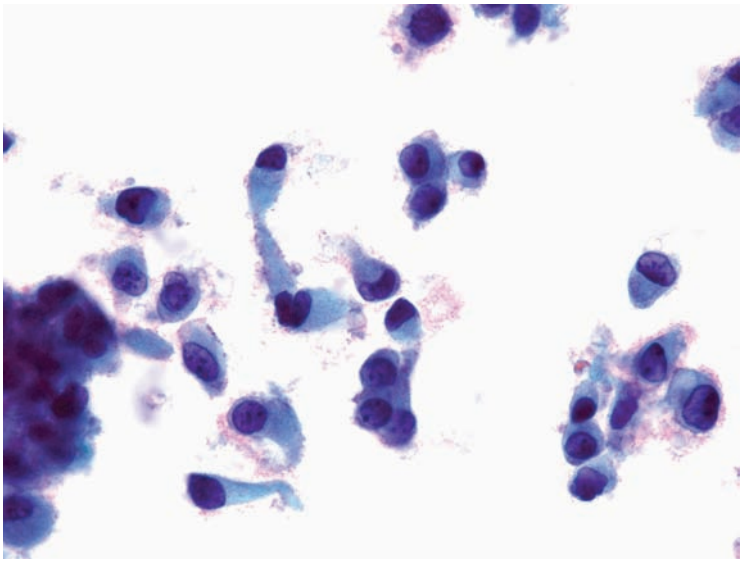


Figure 11.20b — Metastatic Urothelial Carcinoma (Liquid Based; High Power). At higher power, the "comet cell" morphology becomes more apparent and would be consistent with a urothelial origin. The cells are not unlike what one would find in a voided urine specimen containing high-grade urothelial carcinoma, demonstrating hyperchromasia, irregular nuclear borders, a coarse chromatin pattern, and an especially high N/C ratio in cells lacking the cytoplasmic extension. The dispersed (single cell) pattern would be unusual for a primary cervical malignancy, though the possibility of a non-urothelial origin (such as sarcoma or a metastatic poorly differentiated adenocarcinoma) exists. Although the plasmacytoid morphology can also be found in melanoma, the absence of a single prominent nucleolus and cytoplasmic pigment makes this less likely.

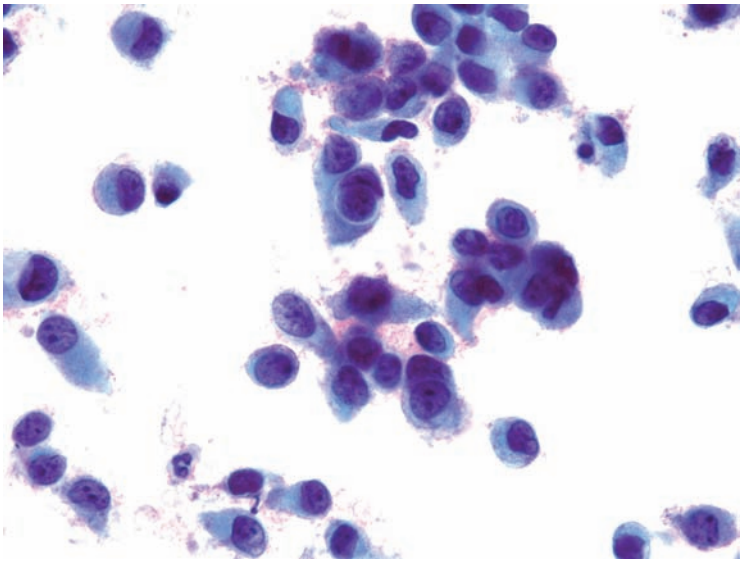


Figure 11.20c — Metastatic Urothelial Carcinoma (Liquid Based; High Power). Additional features of urothelial carcinoma can be found here, including a cell-in-cell pattern, in which two cells appear to be "hugging" each other. The field contains a bystander neutrophil, which demonstrates the greatly increased nuclear size found in the carcinoma cells. In most instances, patients have a documented primary tumor by the time a metastasis is found on a Pap test. However, due to their anatomic relationship and overlapping symptomology, urothelial carcinomas invading the gynecologic tract may be first thought to be a gynecologic tract primary. The presence of high-grade cells (perhaps called "HSIL") combined with a negative human papillomavirus (HPV) test may be the first clue.

12

Cervical Cancer Screening and Follow-up of Limited and Abnormal Screen Results

Dina R. Mody

The uniform Bethesda reporting terminology and our better understanding of human papillomavirus (HPV) biology, as it relates to cervical cancer carcinogenesis, have enabled the professional organizations around the world to formulate evidence-based screening guidelines for cervical cancer and management of women with abnormal screening results.

The Pap smear or test has been the mainstay of cervical cancer screening around the world and has resulted in a 70% drop in the rate of deaths from cervical cancer in those parts of the world that have implemented screening programs. Screening and management guidelines vary in different parts of the world, depending on whether it is a government-funded organized screening program with call and recall mechanisms, as in the United Kingdom, or an opportunistic program, as that in the United States. The screening guidelines in the United States are developed by the United States Preventive Services Task Force (USPSTF) and collaborating organizations, which include the American Cancer Society (ACS), the American Society of Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP), to mention a few (1–3). The management guidelines are developed by the professional organizations, with the ASCCP taking the lead with representation from other stakeholder organizations, such as the American College of Obstetrics and Gynecology (ACOG) (4–7).

This chapter provides a synopsis of the 2012 screening and management guidelines and the reasoning behind the various options. For a more detailed discussion, the references and website are provided (www.asccp.org).

ACCEPTABLE CANCER RISKS AND BASIS FOR RECOMMENDATIONS

It has become evident over the years that, irrespective of the screening methodology, computerized screening, and/or high-risk HPV testing, a zero error or zero cancer risk is unattainable. Because cervical cancer is rare in Western countries, high grade squamous intraepithelial lesion (HSIL) or higher is a reasonable proxy for invasive cancer in studies. Hence, if the risk of HSIL+ is greater than 10%, then immediate colposcopy is recommended. High-grade squamous intraepithelial lesion (HSIL) and atypical squamous cells, cannot rule out HSIL (ASC-H), are examples of diagnoses with the highest risk. If that risk is between 5% and 10%, then a 6- to 12-month return is used as the follow-up strategy. However, if the 5-year risk of HSIL+ is between 0.3% and 1%, then a 3-year return is the strategy. A 5-year return is recommended for the risk of HSIL+ of less than 0.3%. An example of this is a double-negative Pap and HPV co-test in women aged 30 years or older. Keep in mind that a zero-risk standard for HSIL+ at 5 years is unachievable in any of the screening scenarios (8).

CERVICAL CANCER SCREENING GUIDELINES IN THE UNITED STATES (2012)

It is recommended that screening for cervical cancer should begin at age 21 years irrespective of the age of onset of sexual intercourse. Cervical cancers are very rare (0.1% of cases) before the age of 20 years, and most women in this age-group have transient HPV infections, which are easily cleared. Women between the ages of 21 and 29 years are tested by cervical cytology alone every 3 years. Co-testing with HPV is not recommended in women younger than 30 years due to the higher prevalence of transient HPV infection in this age-group. Conventional Pap smears and Food and Drug Administration (FDA)-approved liquid-based technologies are used in the United States. More recently, the FDA approved the Roche Cobas HPV test for the 14 high-risk HPV types for use as a primary screen in women older than 25 years. This is based on the Athena trials (9–11). The interim guidance for screening incorporating the use of primary HPV screening has been published (12). Currently, primary HPV screening is one of the three options for women between ages 25 and 65 years.

Women between 30 and 65 years of age have the option of a Pap test every 3 years or a Pap test coupled with high-risk HPV co-testing using an FDA-approved or Clinical Laboratories Improvement Amendments (CLIA)-validated

Table 12.1 — Cervical Cancer Screening Guidelines in the United States

Age	Method	Interval	Comments
<21 y	• No Screening	N/A	• Cancers are very rare • Mostly transient HPV infections
21–29 y	• Cytology	• 3 y	• HPV co-testing not recommended
30–65 y	• Cytology + HPV co-testing or • Cytology alone	• 5 y if both negative or • Every 3 y for cytology alone	• h/o CIN2+ or AIS to continue screening for at least 20 y
25–65 y	• HPV testing	• 3 y	• Refer to Ref. 12
>65 y	• No screening	N/A	• Exceptions are h/o CIN2+ or AIS in past 20 y
Women with total hysterectomy	• No screening	N/A	• Exceptions as above
Vaccinated for HPV	Age specific, as above		

Abbreviations: AIS, adenocarcinoma in situ of cervix; CIN2+, cervical intraepithelial neoplasia 2, 3 and carcinoma; h/o, history of; HPV, high-risk human papillomavirus testing; N/A, not applicable.

HPV test. If both are negative, then these women can be tested at longer intervals (5 years). A third option of HPV testing is using the FDA-approved Cobas platform beginning at age 25 years. If HPV is negative, then routine screening every 3 years. If HPV is 16 or 18+, then immediate colposcopy and management per colposcopic findings. If non-16 or -18 types, then reflex to Pap. If Pap positive at the level of ASC-US or above, manage accordingly. If Pap is negative, rescreen at 1 year. Screening ends at age 65 years or when the woman has a hysterectomy for a benign disease. Exceptions to these screening intervals are women who are positive for human immunodeficiency virus (HIV), immunocompromised, or diethylstilbestrol (DES)-exposed in utero, or who have been previously treated for HSIL, in which case, they should not exit screening for 20 years after treatment for cervical dysplasia. Irrespective of the screening interval, annual well-women visits to the physicians are recommended. A synopsis of the screening recommendations is provided in Table 12.1. A synopsis of the first-line management of women with various abnormal screening results is listed in Table 12.2.

MANAGEMENT OF UNSATISFACTORY CYTOLOGY SCREENING RESULT

Scant squamous cellularity is the most frequent reason for an unsatisfactory diagnosis on liquid-based cytology. Triage using HPV alone is not recommended. However, if a woman older than 30 years has a positive HPV co-test, repeat cytology in 2 or 4 months or colposcopy is acceptable. If the HPV status is unknown or negative, then a repeat Pap test in 2 to 4 months is recommended. If the repeat is unsatisfactory, then colposcopy is recommended. If the repeat cytology is negative and HPV is positive, then co-testing in 1 year is recommended. If genotyping shows 16 or 18 positive, then immediate colposcopy is recommended. If both (cytology and HPV) are negative on the repeat test, then the patient returns to routine screening. If the Pap test is abnormal at the level of atypical squamous cells of uncertain significance (ASC-US) or above, then management is done per ASCCP guidelines.

An unsatisfactory diagnosis due to blood or obscuring inflammation, especially on a conventional Pap smear, carries a

Table 12.2 — Consensus Guidelines for Initial Management of Abnormal Cervical Cancer Screening Tests

Screen Result	Age (y)				Comments
	21–24	25–Menopause	Postmenopausal	65+	
ASC-US (see ASCCP algorithm for details)	Repeat cytology at 12 mo irrespective of HPV status However, if HPV(–) then routine cytology screening in 3 y	*Preferred:* HPV reflex or co-test. If (+) then colposcopy, if (–) repeat co-test at 3 y *or* *Option 2*: repeat cytology at 1 y if ASC-US or > then colposcopy	Same as general population (25–menopause)	ASC-US HPV(+) to colposcopy If HPV(–) then rescreen at 1 y (co-testing preferred)	In those 25 y and older HPV reflex testing preferred over repeat cytology at 1 y HPV(–) ASC-US screen in 3 y
LSIL	Repeat cytology at 12 and 24 mo If ASC-US or worse at 24 mo then colposcopy	(+) HPV or no HPV test then colposcopy. If HPV co-test (–), co-test at 1 y preferred or colposcopy acceptable	Colposcopy or HPV test or repeating cytology at 6 or 12 mo all acceptable. If HPV(–) or no CIN on colposcopy, repeat cytology in 12 mo	Same as postmenopausal	
ASC-H	Colposcopy	Colposcopy	Colposcopy	Colposcopy	Reflex HPV testing not recommended
HSIL	Colposcopy See and treat unacceptable	Colposcopy or immediate see and treat (LEEP) acceptable	Same as general population (25–Menopause)	Same as general population	See www.asccp.org for details of guidelines if no lesion is identified on colposcopy or biopsy
Atypical endocervical cells and AIS	Colposcopy and endocervical sampling	Colposcopy and endocervical sampling	Colposcopy and endocervical and endometrial sampling	Colposcopy and endocervical and endometrial sampling	Endometrial sampling if >35 y or at risk of endometrial cancer
Atypical endometrial cells	Endocervical and endometrial sampling Colposcopy acceptable	Endocervical and endometrial sampling Colposcopy acceptable	Endocervical and endometrial sampling Colposcopy acceptable	Endocervical and endometrial sampling Colposcopy acceptable	If ECC and EMB (–) then colposcopy if not done initially

Abbreviations: AIS, adenocarcinoma in situ; ASCCP, American Society of Colposcopy and Cervical Pathology; ASC-H, atypical squamous cells, cannot rule out HSIL; ASC-US, atypical squamous cells of uncertain significance; CIN, cervical intraepithelial neoplasia; ECC, endocervical curettage; EMB, endometrial biopsy; HPV, high-risk human papillomavirus testing; LEEP, loop electrosurgical excision procedure; LSIL, low-grade squamous intraepithelial lesion.

higher risk of disease, hence repeat in 2 to 4 months is required. Additionally, the avoidance of certain types of lubricant gels is recommended. If a woman has two consecutive unsatisfactory Pap tests, then colposcopy is recommended.

NEGATIVE CYTOLOGY WITH ABSENT OR INSUFFICIENT ENDOCERVICAL OR TRANSFORMATION ZONE COMPONENT

For 21- to 29-year-olds with negative cytology, routine screening is recommended. For women 30 years and older, if HPV co-test is negative, routine screening is recommended. If an HPV co-test is positive, then repeating both in 1 year, or HPV genotyping, is also acceptable. If HPV 16 or 18 is positive on HPV genotyping, then colposcopy is recommended. If positive for a non-16 or -18 HPV type, then repeat co-testing in 1 year is recommended.

ATYPICAL SQUAMOUS CELL OF UNDETERMINED SIGNIFICANCE

ASC-US is the most common abnormal category and accounts for between 4% and 5% of Pap tests in most laboratories based on College of American Pathologists (CAP) data (www.cap.org). An ASC-US diagnosis, based on the Kaiser data, carries a 6.9% risk of CIN2+ and a 0.2% risk of cancer based on 5 years of follow-up (13–15). If the ASC-US is HPV positive, then the risk of CIN2+ rises to 18% and CIN3+ to 6.8%. Based on this information, for women 25 years and older, reflex HPV testing is the preferred option. If positive, then triage to colposcopy is recommended. If HPV is negative, then risk of CIN3+ at 5 years is 0.45%. Hence, a 3-year screening interval follow-up is recommended. HPV genotyping is not recommended for ASC-US diagnoses. A second management option for ASC-US is to repeat the Pap test at 1 year and manage accordingly.

Because young women have a higher incidence of transient HPV infections, and risk of overtreatment can result in harm, a less aggressive strategy is followed for both ASC-US and low-grade squamous intraepithelial lesion (LSIL). For women aged 22 to 24 years with ASC-US, a repeat Pap test at 12 month intervals for 2 years is recommended. Colposcopy is not recommended. If the repeat test results in ASC-H or above, then colposcopy is recommended. If the result is ASC-US or worse on cytology at 24 months, then colposcopy is recommended. If two consecutive annual follow-up Pap tests are negative, then these women return to routine screening every 3 years.

Pregnant women are managed the same way as nonpregnant women. Deferring colposcopy to 6 weeks postpartum is acceptable. If, however, colposcopy is performed and no CIN is detected, then postpartum follow-up is recommended. Endocervical curettage (ECC) is contraindicated during pregnancy.

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION

A diagnosis of LSIL on a Pap test carries a 16% risk of CIN2+. For women with a diagnosis of LSIL with no HPV test or a positive HPV test due to co-testing, colposcopy is recommended. If, however, HPV is negative as part of co-testing in women older than 30 years, then repeat co-testing at 1 year is preferred. However, colposcopy is also acceptable in this situation. If repeat co-testing at 1 year is chosen and the result is HPV and cytology negative (a double negative), then repeat co-testing after 3 years is recommended.

In 21- to 24-year-olds, follow-up with a Pap test at 12 to 24 months is recommended. If ASC-H or worse is found on follow-up, then colposcopy is the choice of management. If the result is ASC-US or worse at 24 months, then colposcopy is recommended. The same applies to pregnant women. In pregnant women, colposcopy is preferred but ECC is unacceptable.

For postmenopausal women with LSIL, the options include HPV testing, repeat cytology at 6 and 12 months, and colposcopy. In the case of a negative HPV test or the absence of CIN on colposcopy, repeating cytology at 12 months is recommended. For details, visit www.ASCCP.org/guidelines.

MANAGEMENT FOR CYTOLOGIC DIAGNOSIS OF ATYPICAL SQUAMOUS CELLS, CANNOT RULE OUT HSIL

This is a high-risk category with a higher positive predictive value for CIN2+ than ASC-US or LSIL but lower than that for HSIL. Colposcopy is recommended irrespective of age, HPV status, or pregnancy. Endocervical sampling is contraindicated in pregnant women. Refer to ASCCP guidelines for further details.

MANAGEMENT OF HSIL

HSIL accounts for 0.2% to 0.3% of Pap test results reported for an average-risk population in most laboratories. It carries a 70% risk of CIN2+, 48% for CIN3+, and 8.2% for cancer over 5 years (13–15). Colposcopy is recommended for all age-groups. Triage using HPV status or repeat cytology is not recommended. Immediate loop electrosurgical excision procedure (LEEP), or "see and treat," is acceptable except in special populations, such as in women between 21 and 24 years of age. If HSIL is absent on colposcopy and biopsy, then observation for up to 24 months using cytology and colposcopy at 6 month intervals is acceptable. Visit www.asccp.org for further details.

ATYPICAL GLANDULAR CELLS AND ADENOCARCINOMA IN SITU

This is considered a high-risk category, especially if "AGC, favor neoplastic" or adenocarcinoma in situ (AIS) is indicated. Glandular and squamous lesions can coexist. Endometrial cancers are HPV negative. Cytologic follow-up or HPV triage is not recommended for this category. Colposcopy with endocervical sampling is recommended irrespective of the HPV result (Table 12.2). Pregnant women, or women who are 21 to 24 years old, are initially evaluated with colposcopy and endocervical sampling, with the exception of pregnant women in whom ECC is contraindicated but can be performed 6 weeks postpartum. Endometrial sampling is performed in women older than 35 years or in those who are at risk of endometrial cancer (eg, chronic anovulation). For a diagnosis of atypical endometrial cells, both endocervical and endometrial sampling are recommended. A diagnosis of atypical glandular cells (AGC), favor neoplastic, or AIS should proceed to diagnostic excision if the initial colposcopy and endocervical sampling do not show CIN2+ or AIS.

In summary, initial management is discussed in this chapter. For further details, visit www.asccp.org. Modifications that incorporate the recent approval of one HPV test (Roche Cobas) as a primary screen in the United States will likely be made in the near future. Other countries, such as England and Australia, have already begun to use limited HPV testing as a primary screen. While co-testing with HPV and Pap offers the best negative predictive value for CIN3+ over a 5-year period, financial constraints and Pap screening infrastructure determine the screening protocols for cervical cancer in different parts of the world.

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