Benign Changes and Mimics of Malignant and Premalignant Epithelial Lesions

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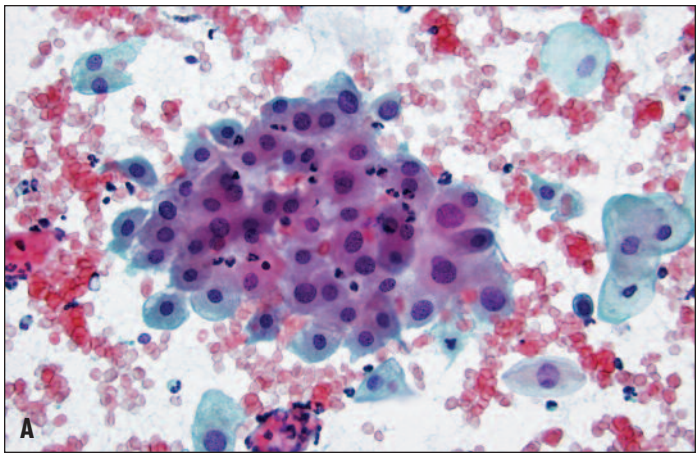
General Features

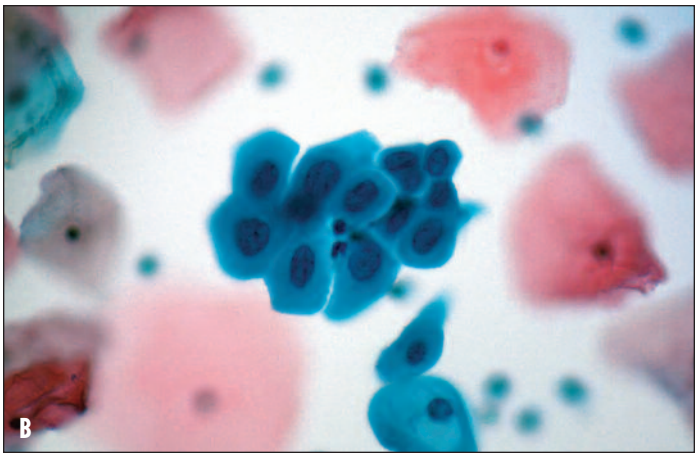
The recognition of benign changes, organisms, and artifacts in cervical/vaginal cytologic samples is important for all cytology practitioners. Many benign conditions observed in Pap slides are notorious for their ability to mimic malignant and premalignant epithelial lesions. Awareness of these entities and recognition of their unique cytomorphology are important to avoid misdiagnosis and, especially, overdiagnosis. The observation of various organisms may be useful in the treatment of diseases related to their presence. Recognition of various artifacts is also important for proper interpretation. The cytomorphology of common and uncommon benign conditions is discussed in this chapter, with emphasis on the features that are most useful in distinguishing them from malignant and premalignant epithelial lesions.

Benign Inflammatory Conditions

Figure 4-1. Reactive and inflammatory epithelial cell changes.

Inflammatory epithelial cell changes include nonspecific reactive features such as nuclear enlargement, prominent nucleoli, fine and evenly distributed chromatin, binucleation and multinucleation, and smooth nuclear borders (A through D). These changes may be seen in either squamous or endocervical cells. A benign finding that may be confused with low-grade squamous intraepithelial lesion (LSIL) is that of small perinuclear vacuoles, which are distinguished from koilocytes by their small diameter, lack of a sharp "cookie-cutter" edge, and absence of associated dysplastic nuclear changes (see Figure 7-17). These shallow vacuoles can also be found with specific infections, such as *Candida* and *Trichomonas* (E and F). Degenerative change (eg, dark clumpy or smudgy chromatin, karyopyknosis, karyorrhexis) is common in association with these processes (H). Distinction from dysplasia is sometimes difficult. However, dysplasia is associated with greater nuclear enlargement (greater than three times the size of a normal intermediate nucleus); darker, more coarsely granular, irregularly distributed chromatin; and frequent irregularity of the nuclear borders (I). Background inflammation is predominantly acute in nature, but remember that an acute inflammatory background can be seen with dysplasia as well.





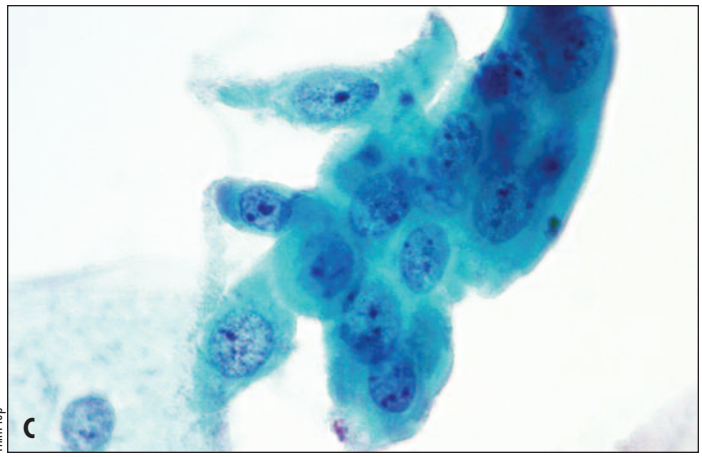


Figure 4-1 continued.

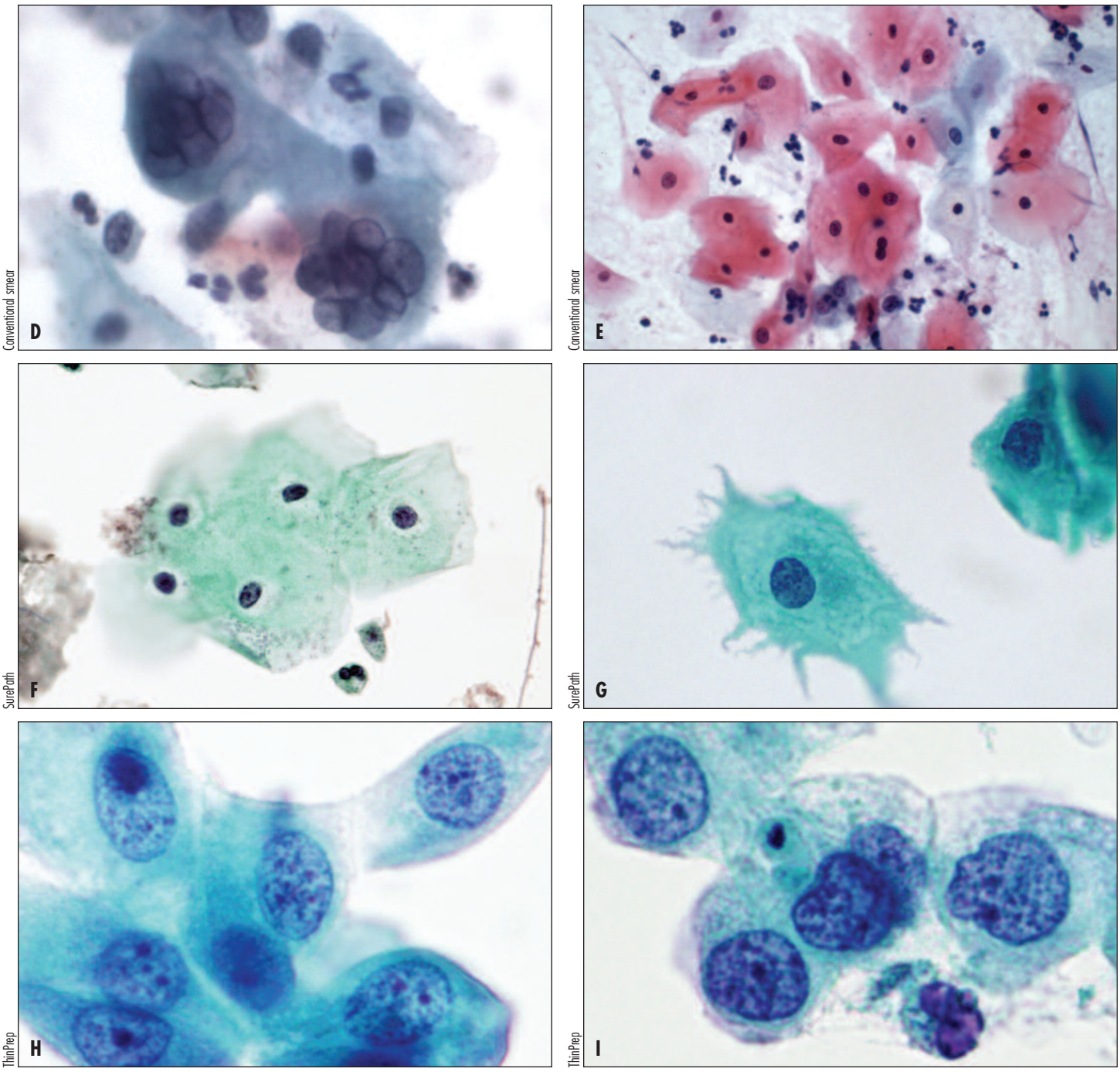


Figure 4-2. Parabasal and squamous metaplastic cells.

These two cell types are morphologically similar, and their presence in Pap specimens reflects sampling from a relatively thin, immature, squamous mucosal surface predisposed to conditions (eg, infection, irritation, erosion, ulceration) that lead to reactive/reparative and degenerative changes. Parabasal-like cells often dominate during the postpartum and postmenopausal periods and are also seen in some cyclic women taking Depo-Provera or other progestational drugs (C). These cells reflect the lack of maturation of the squamous epithelium due to low estrogen levels. Squamous metaplasia occurs at the transformation zone of cyclic women and may yield large numbers of immature squamous cells. Reactive/reparative change (prominent nucleoli, mild hyperchromasia, nuclear enlargement, mitotic activity) and degenerative changes (dark clumpy or smudgy chromatin) in these small squamous cells are sometimes confused with dysplasia or carcinoma (E and H). Cytologic features that support an accurate benign interpretation include nuclear uniformity, smooth nuclear borders, polarity in cell groups, and finely granular and evenly distributed chromatin (see Figure 7-19). In conventional Pap smears, these cells most often appear in two-dimensional sheets (D), but they can form more rounded groups in liquid-based preparations (F).

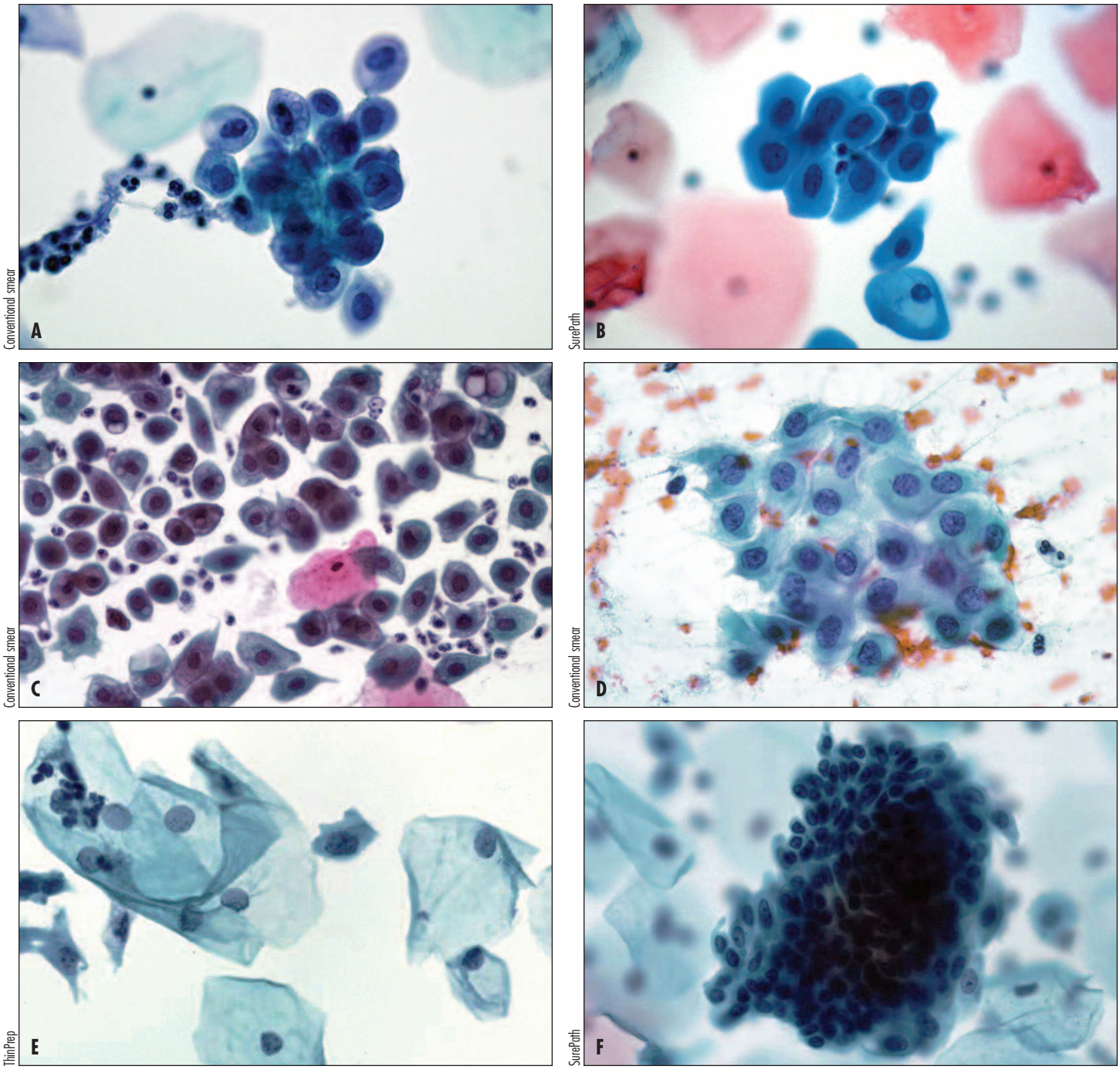
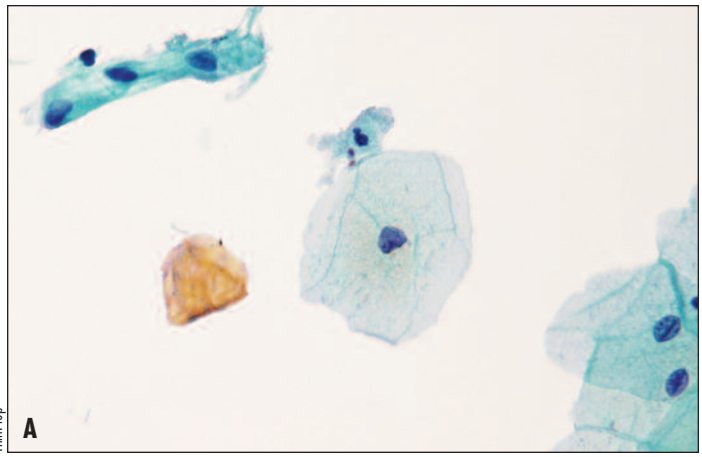
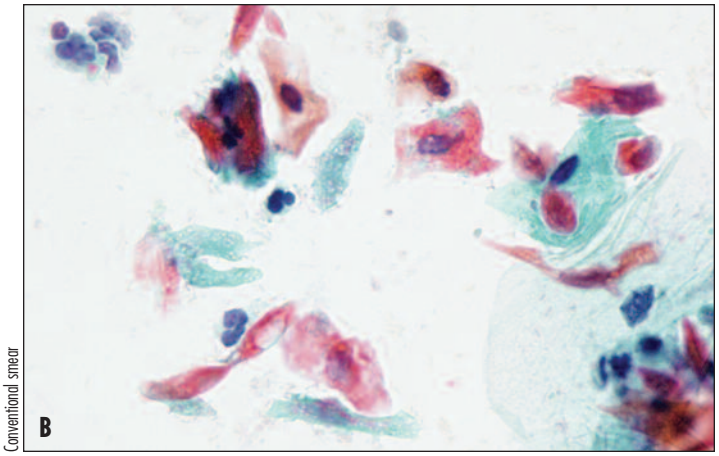


Figure 4-3. Anucleated squamous cells.

Anucleated squamous cells (ANSC) are indicative of superficial epithelial keratosis and, when present in small numbers, may represent contamination from skin and can be ignored, as this does not represent a significant clinical finding (A). ANSC, especially in larger numbers, may represent keratosis involving the cervix or vagina, where the cause is chronic irritation due to an infection or uterine prolapse. ANSC may also overlie squamous intraepithelial lesions and even, on occasion, squamous cell carcinoma (B). Therefore, careful review of the slide for an underlying epithelial lesion is warranted whenever abundant ANSC are present, especially when in large plaque-like aggregates (C).





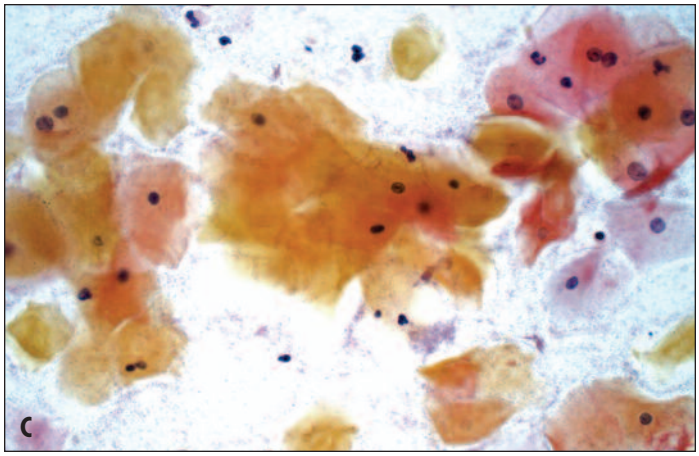
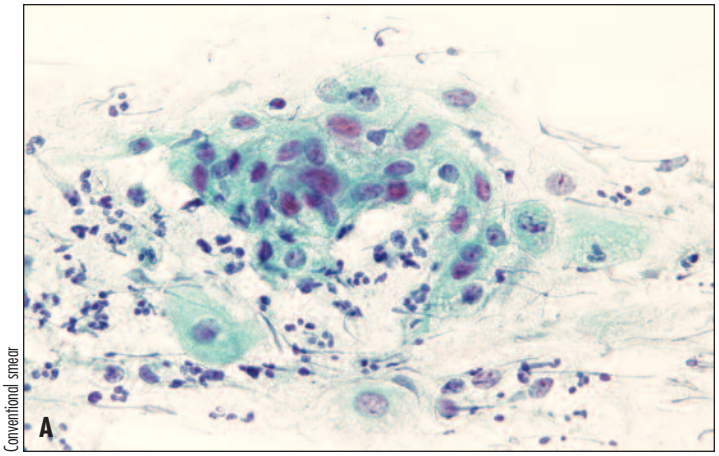
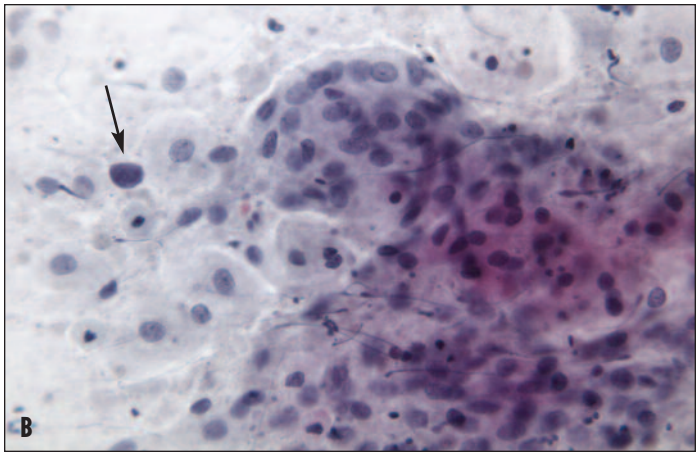


Figure 4-4. Atrophic vaginitis.

Atrophic vaginitis (AV) is usually observed in postmenopausal women or, uncommonly, in postpartum patients. Pap slides with AV show variable inflammation, marked background necrosis (simulating a tumor diathesis), and degeneration of the small, parabasal squamous cells. "Blue blobs," which are degenerating parabasal cells, resemble large, abnormal, bare nuclei (B, arrow). These findings can be confused with malignancy, especially when the atrophic changes include background necrosis or a degenerative pseudo-parakeratotic change (F, G, and H). Close examination of the viable cells and noting the absence of significant atypia in these cells help to avoid overinterpretation. In benign atrophy, there is most often a spectrum of atrophy ranging from obvious benign changes to the more atypical groups. Occasionally a diagnosis of atypical squamous cells of undetermined significance (ASC-US) or atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H) is warranted (see Figure 5-8), in which case follow-up testing for high-risk human papillomavirus (HPV) and/or colposcopy would be warranted, according to the latest American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines.





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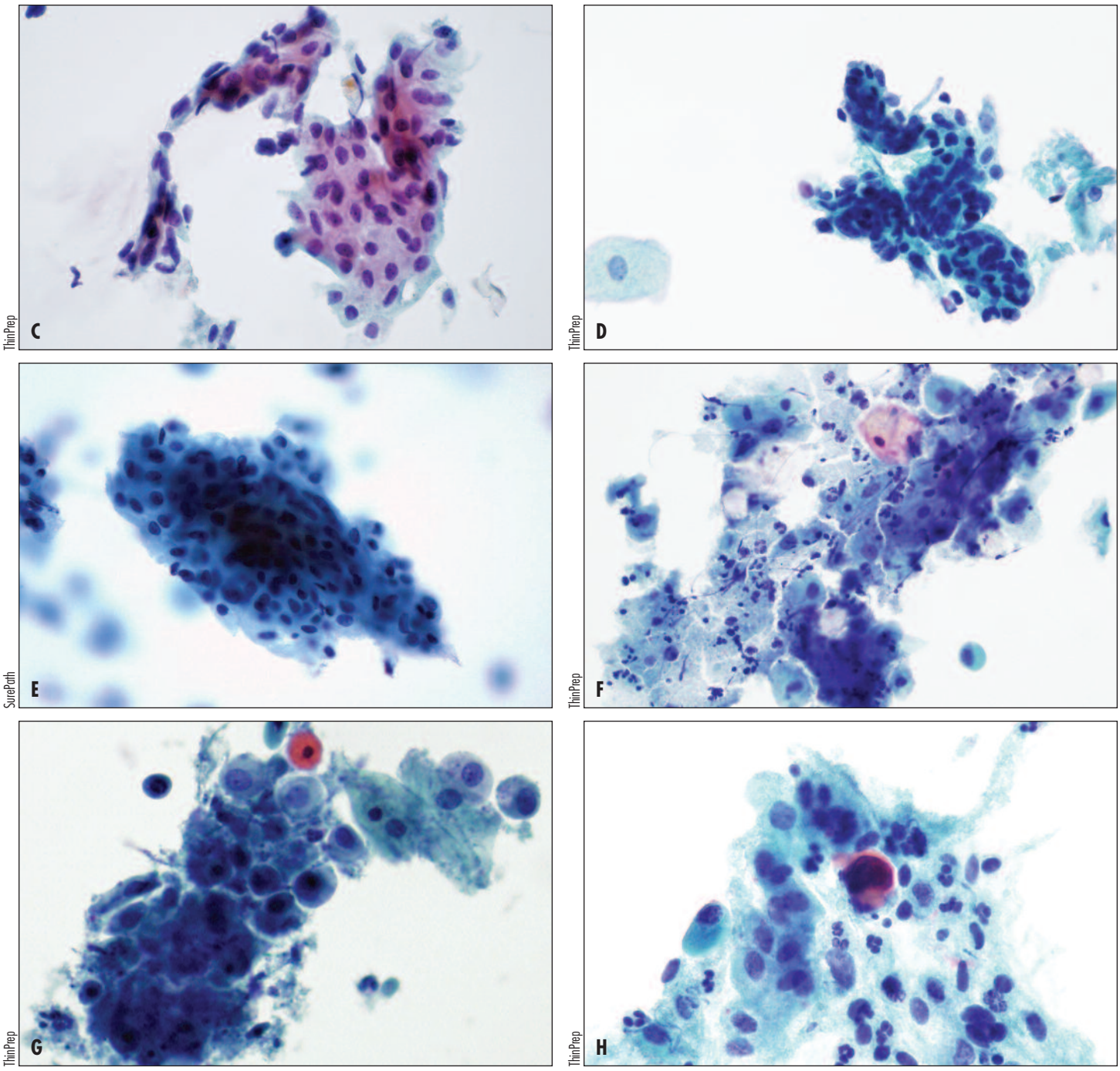

Figure 4-5. Degenerative changes in benign cells.

Degenerative changes include cytoplasmic and nuclear vacuolization, cellular and nuclear enlargement, chromatin clumping, karyopyknosis (very dense chromatin that lacks detail), karyorrhexis (the breaking up of nuclear chromatin following rupture of the nuclear membrane), and karyolysis (dissolution of the nuclear chromatin) (A, B, and C). The degenerative finding that is perhaps most worrisome for cancer or dysplasia is chromatin clumping. However, degenerative chromatin clumps are more smoothly contoured and regular in size, shape, and distribution than are those found in dysplasia or carcinoma (D and E). Exercise caution when evaluating for dysplasia or malignancy in groups of cells showing obvious degenerative changes.

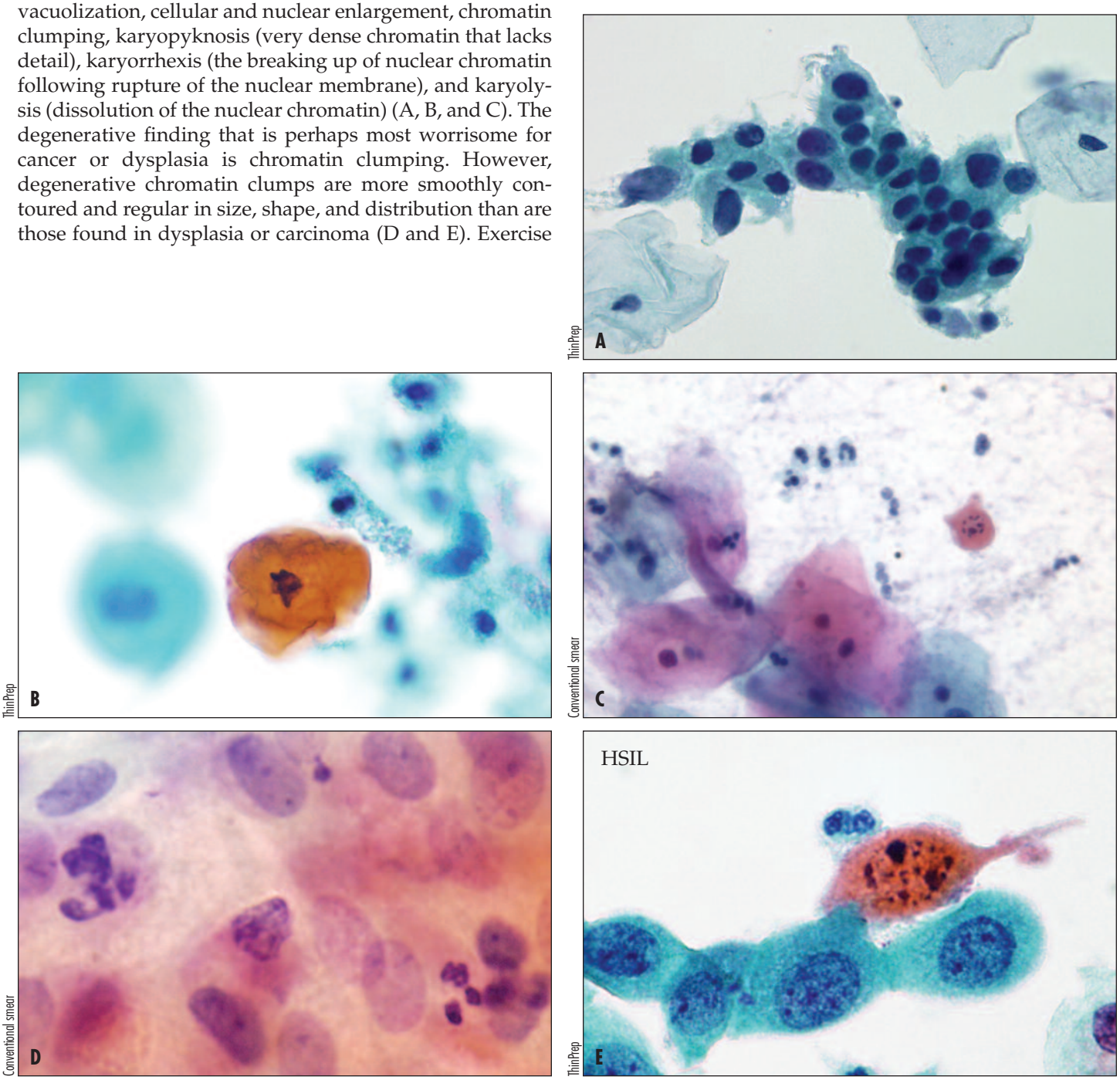

Figure 4-6. Chronic follicular cervicitis.

Chronic follicular (ie, germinal center) cervicitis (CFC) is limited to the cervical submucosa. Therefore, Pap slides may show evidence of CFC only when there is erosion or ulceration of the overlying mucosa or if the mucosa is very thin, as in markedly atrophic squamous conditions. CFC is characterized by focal collections of polymorphous lymphocytes with scattered intermixed tingible body macrophages. The differential diagnosis can include HSIL, small cell carcinoma and lymphoma/leukemia. Most helpful for interpretation is the appreciation of the characteristic dark, clumped chromatin of the small mature lymphocytes and the recognition of the larger, phagocytic tingible body macrophages (A, arrow). In HSIL, the chromatin is not as coarsely granular, and cells are overall larger and more pleomorphic, with some cells showing obvious squamous differentiation. In HSIL, abnormal epithelial clusters are also usually present elsewhere on the slide. Pap slides involved with a small cell malignancy (eg, primary or metastatic small cell carcinoma, leukemia/lymphoma) are typically dominated by the malignant cells and show a tumor diathesis and significant nuclear abnormalities. In contrast, CFC is a focal and minor component of the slide and is not associated with necrosis or a diathesis. When lymphoma or leukemia presents in Pap slides, there is usually a history of such, as primary lymphoma of the cervicovaginal area is extremely rare. With regard to CFC, there are differences between conventional smears and liquid-based preparations. In conventional smears, CFC presents as dispersed cells in localized areas (A and B), whereas in liquid-based preparations, the cells of CFC usually form loose clusters, with scattered isolated small lymphocytes present in the slide background (C, D, and E).