Chapter 2

Non-Neoplastic Findings

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Negative for Intraepithelial Lesion or Malignancy

(when there is no cellular evidence of neoplasia, state this in the General Categorization and/or in the Interpretation/Result section of the report—whether or not there are organisms or other non-neoplastic findings)

Organisms:

- Trichomonas vaginalis
- Fungal organisms morphologically consistent with Candida spp.
- Shift in flora suggestive of bacterial vaginosis
- Bacteria morphologically consistent with Actinomyces spp.
- Cellular changes consistent with herpes simplex virus

Other Non-Neoplastic Findings

(optional to report; list not inclusive):

- Reactive cellular changes associated with:
  - inflammation (includes typical repair)
  - radiation
  - intrauterine contraceptive device (IUD)
- Glandular cells status post hysterectomy
- Atrophy

Background

In previous versions of The Bethesda System (TBS), infections and reactive cellular changes were reported under the categorical heading of “Benign Cellular Changes” (BCC); but under the General Categorization section, BCC was separate from “Within normal limits” (WNL). There-
fore, some clinicians viewed BCC as something other than WNL and felt obligated to do more than routine screening for women with a BCC designation. To emphasize the ‘negative’ nature of an interpretation of reactive changes, the 2001 Bethesda System collapses the BCC and WNL categories into a single category: “Negative for Intraepithelial Lesion or Malignancy” (NILM). This term is used both as the general categorization and/or as the interpretation in the report.

The category of “Infections” has been changed to “Organisms” because the presence of some organisms reflects colonization rather than clinical infection. Although not the main focus of cervical screening, providing such information may be clinically relevant in certain circumstances. Clinicians and laboratories should communicate with one another about their expectations for reporting organisms. In the absence of specific communication regarding this issue, the organisms listed should generally be reported if identified.

Cervical cytology is a screening test primarily for detection of squamous cell carcinoma of the cervix and its precursors. Criteria for reactive cellular changes are not always well defined, and consequently the interpretation may lack reproducibility.1–6 Except for organisms discussed above, reporting non-neoplastic findings is optional and at the discretion of the laboratory. However, reasons for continuing to report non-neoplastic findings in a cervical cytology report include:

1. Utility as a triage tool and as documentation for laboratory regulations regarding referral for hierarchical review.
2. Fostering a discipline in applying cytomorphologic criteria during screening and sign-out.
3. Documentation of morphologic findings to explain differences in interpretation on review.7
4. Facilitation of clinical–cytologic correlation. For example, the cytomorphologic finding of hyperkeratosis and parakeratosis may correlate with the colposcopist’s assessment of the uterine cervix.
5. Documentation of reactive cellular changes in the report to spot trends in a series of cervical cytology specimens from one woman. Studies have reported a slight increase in the incidence of squamous intraepithelial lesion (SIL) in cases interpreted as reactive compared to those interpreted as within normal limits.8,9 Reporting non-neoplastic findings may facilitate future studies to identify specific morphologic findings that better correlate with risk.

Note that the list of non-neoplastic findings in Bethesda 2001 is not comprehensive. In addition, the interpretive categories do not necessarily correspond to regulatory requirements for hierarchical supervisory review;
within the parameters of government regulation, it is up to the laboratory to specify findings that trigger such review.

**Negative for Intraepithelial Lesion or Malignancy (NILM)**

Specimens for which no epithelial abnormality is identified are reported as “Negative for intraepithelial lesion or malignancy” (NILM). If non-neoplastic findings are reported, NILM should still be included as an interpretation or as the General Categorization to avoid ambiguity.

**Organisms**

*Trichomonas vaginalis* (Figs. 2.1-2.3)

**Criteria**

Pear-shaped, oval, or round cyanophilic organism ranging in size from 15 to 30 μm (Fig. 2.1).
Nucleus is pale, vesicular, and eccentrically located.
Eosinophilic cytoplasmic granules are often evident.
Flagella are usually not seen.
Leptothrix may be seen in association with *T. vaginalis* (Fig. 2.2).

**Liquid-Based Preparations**

Organisms tend to be smaller due to rounding.
Occasional kite-shaped forms may be seen.
Nuclei and cytoplasmic eosinophilic granules are often better visualized.
Flagella may be preserved and identified in liquid-based preparations (LBP) (Fig. 2.3).
Trichomonas vaginalis (conventional preparation, CP). Pear-shaped organism with eccentrically located nucleus and eosinophilic cytoplasmic granules.

Trichomonas vaginalis in association with Leptothrix (CP). Leptothrix may be seen in association with T. vaginalis; this finding alone is not sufficient, but suggests the presence of trichomonads.
Figure 2.3. *Trichomonas vaginalis* (liquid-based preparation, LBP). 32-year-old woman with vaginal discharge. The organism’s nucleus, cytoplasmic granules, and flagella may be better visualized on LBPs. Note the kite shape and flagella (bottom right insert).
Fungal Organisms Morphologically Consistent with *Candida* species (Figs. 2.4–2.6)

**Criteria**

Budding yeasts (3–7 μm); pseudohyphae are eosinophilic to gray-brown on the Papanicolaou stain.

Pseudohyphae, formed by elongated budding, show constrictions along their length (Fig. 2.4).

Fragmented leukocyte nuclei and rouleau formation of squamous epithelial cells “speared” by hyphae may be seen.

**Liquid-Based Preparations**

“Spearing” of epithelial cells is more common in LBPs and can be seen at low power even if the pseudohyphae are not prominent (“shish kebab” effect) (Fig. 2.5).

*Note:* *Candida (Torulopsis) glabrata* consists of small, uniform, round budding yeast forms surrounded by clear halos on Papanicolaou stain. Unlike other *Candida* species, it does not form pseudohyphae in vivo or in culture (Fig. 2.6).

*Figure 2.4.* Fungal organisms morphologically consistent with *Candida* spp. (CP). Note pseudohyphae.
2. Non-Neoplastic Findings

**Figure 2.5.** Fungal organisms morphologically consistent with *Candida* spp. (LBP). 45-year-old woman. Note “spearing” of squamous cells, a feature that is readily appreciated at low power, even when the pseudohyphae are not prominent. Follow up was NILM.

**Figure 2.6.** Fungal organisms morphologically consistent with *Candida* spp. (*Torulopsis* glabrata) (CP). Routine screening of 63-year-old woman. Note clear halos surrounding the yeast forms (*left*). Bacteria, not pseudohyphae, are also seen in the background.
Shift in Flora Suggestive of Bacterial Vaginosis (Figs. 2.7-2.8)

Criteria

Filmy background of small coccobacilli is evident (Fig. 2.7). Individual squamous cells may be covered by a layer of bacteria that obscures the cell membrane, forming so-called clue cells (Fig. 2.8). There is a conspicuous absence of lactobacilli (Fig. 2.9).

Liquid-Based Preparations

Squamous cells are covered with coccobacilli; however, the background is clean (Fig. 2.8).

![Figure 2.7](image)

**Figure 2.7.** Shift in flora suggestive of bacterial vaginosis (CP). Note the clue cell and filmy background due to the coccobacilli.
2. Non-Neoplastic Findings

**Figure 2.8.** Shift in flora suggestive of bacterial vaginosis (LBP). 25-year-old woman. Note clue cell and the relatively clean background compared to that in CPs (Fig. 2.7).

**Figure 2.9.** Lactobacilli (*left*, LBP; *bottom right insert*, CP). They are typically seen on the cell surfaces in LBP and not dispersed in the background as in CP. Compare to coccobacilli in Figs. 2.7 and 2.8.
Bacteria Morphologically Consistent with Actinomyces (Figs. 2.10, 2.11)

Criteria

Tangled clumps of filamentous organisms, often with acute angle branching, are recognizable as “cotton ball” clusters on low power (Fig. 2.10). Filaments sometimes have a radial distribution or have an irregular “woolly body” appearance (Fig. 2.11). Masses of leukocytes adherent to microcolonies of the organism, with swollen filaments or “clubs” at the periphery, may be identified. An acute inflammatory response with polymorphonuclear leukocytes is often present.

Cellular Changes Consistent with Herpes Simplex Virus (Fig. 2.12)

Criteria

Nuclei have a “ground-glass” appearance due to intranuclear viral particles and enhancement of the nuclear envelope caused by peripheral margination of chromatin. Dense eosinophilic intranuclear inclusions surrounded by a halo or clear zone are variably present. Large multinucleated epithelial cells with molded nuclei are characteristic but may not always be present; mononucleate cells with the nuclear features described above may be the only finding.

Explanatory Notes

Occasionally degenerated fragments of cytoplasm or macrophages can be mistaken for trichomonads, particularly in liquid-based preparations. Therefore, at least one of the following—good nuclear detail, eosinophilic cytoplasmic granules, or flagella—should be present to make an interpretation of *Trichomonas*. When *Leptothrix* is seen, one should search for the possible presence of trichomonads. *Lactobacillus* spp. constitute a major component of the normal vaginal flora (see Fig. 2.9). Predominance of coccobacilli represents a shift in vaginal flora from lactobacilli to a polymicrobial process involving several types of obligate and facultative anaerobic bacteria, including but not limited to *Gardnerella vaginalis* and *Mobiluncus* spp. This shift in flora, with or without accompanying clue cells, is not sufficient for the
2. Non-Neoplastic Findings

**FIGURE 2.10.** Bacteria morphologically consistent with *Actinomyces* (CP). 41-year-old woman. Low power shows “cotton ball” appearance of tangled clumps of filamentous organisms. An acute inflammatory response is also apparent. ([*•*] Bethesda Interobserver Reproducibility Project (BIRP) image (see xvii Introduction).)

**FIGURE 2.11.** Bacteria morphologically consistent with *Actinomyces* (CP). Thin filamentous bacilli are seen longitudinally and on end under high magnification.
The presence of *Actinomyces* species in cervical cytology is associated with intrauterine contraceptive device (IUD) usage. Detection of *Actinomyces* in cervical cytology specimens along with clinical evidence of pelvic infection can help alert clinicians to the possibility of a pelvic actinomycotic abscess.16

Because of the controversy regarding the sensitivity and reproducibility of a cytologic finding of *Chlamydia* and the availability of more specific detection methods such as culture, enzyme-linked immunoassay, and polymerase chain reaction (PCR), the interpretation of *Chlamydia* spp. is not included in TBS.17,18
Other Non-Neoplastic Findings

Reactive Cellular Changes

Definition

Reactive cellular changes that are benign in nature, associated with inflammation, radiation, an IUD, or other nonspecific causes.

Reactive Cellular Changes Associated with Inflammation (Includes Typical Repair) (Figs. 2.13–2.22)

Criteria

Nuclear enlargement (one and one-half to two times the area of a normal intermediate squamous cell nucleus or more) (Figs. 2.13, 2.14, 2.21). Endocervical cells may show greater nuclear enlargement (Figs. 2.17, 2.18).

Occasional binucleation or multinucleation may be observed. Nuclear outlines are smooth, round, and uniform. Nuclei may appear vesicular and hypochromatic (Figs. 2.13, 2.14). Mild hyperchromasia may be present, but the chromatin structure and distribution remain uniformly finely granular.

Prominent single or multiple nucleoli may be present. Cytoplasm may show polychromasia, vacuolization, or perinuclear halos but without peripheral thickening (Fig. 2.14). Similar changes may be seen in squamous metaplastic cells (Fig. 2.15); cytoplasmic processes (spider cells) may also be seen (Fig. 2.16).

In typical repair, any of the above cellular changes may be seen; however, cells occur in flat, monolayer sheets with distinct cytoplasmic outlines (in contrast to the syncytial appearance of some high-grade lesions and cancers), streaming nuclear polarity, and typical mitotic figures. Single cells with nuclear changes are not usually seen (Figs. 2.17–2.20).

Liquid-Based Preparations (Figs. 2.21, 2.22)

Reparative groups are more rounded, with less streaming (Fig. 2.22). Nucleoli may be more prominent.
[**] Figure 2.13. Reactive squamous cells (CP). Mild nuclear enlargement without any significant chromatin abnormalities. (Reprinted with permission from Kurman, RJ (ed.), Blaustein's Pathology of the Female Genital Tract, Fourth Edition, Springer-Verlag New York, © 1994.)

[**] Figure 2.14. Reactive squamous cells (CP). 26-year-old woman, day 14 of menstrual cycle with mild vaginal discharge. Squamous cells show mild nuclear enlargement, perinuclear halos, and cytoplasmic polychromasia resulting in a “moth-eaten” appearance. Trichomonads are seen in the background. Follow up was NILM.
2. Non-Neoplastic Findings

**FIGURE 2.15.** Squamous metaplastic cells (CP). Metaplastic cells have a higher nuclear/cytoplasmic (N:C) ratio than mature cells, but nuclear membranes are smooth and chromatin is finely granular and evenly distributed. Small round nucleoli can be seen.

**[+] FIGURE 2.16.** Squamous metaplastic cells (CP). Routine screening from 27-year-old woman, day 8 of menstrual cycle. Note the “spidery” cytoplasmic processes, a feature that may be seen in conventional smears. Follow up was NILM.
**Figure 2.17.** Reactive endocervical cells (LBP). 32-year-old woman. Variation in nuclear size, prominent nucleoli, and rare intracytoplasmic polymorphonuclear leukocytes are seen; features of endocervical repair. Follow up was NILM.

**Figure 2.18.** Reactive endocervical cells (CP). A 22-year-old woman status post loop electrosurgical excision procedure (LEEP) 6 months earlier for cervical intraepithelial neoplasia (CIN). Endocervical cells show variable increase in nuclear size, prominent nucleoli, and fine chromatin. Concurrent biopsy was benign.
2. Non-Neoplastic Findings

[*] **Figure 2.19.** Reactive squamous cells, repair (CP). A 67-year-old woman with uterine prolapse. Flat, monolayer sheet of reparative cells with distinct cytoplasmic borders, streaming nuclear polarity, and a prominent nucleolus in almost every cell. Reactive group of endocervical cells at top center.

[*] **Figure 2.20.** Reactive squamous cells (CP). Typical repair—squamous cells in a flat, monolayer sheet with maintenance of nuclear polarity.
FIGURE 2.21. Reactive squamous cells (LBP). Routine screen of 32-year-old woman. Although there is nuclear enlargement in the cells on the right side, the smooth nuclear contours and finely distributed chromatin favor reactive change over ASC-US.

FIGURE 2.22. Repair (LBP). 32-year-old woman. Changes are similar to those seen on CPs, but cell streaming may be less apparent due to rounding of cell clusters. Note the intracytoplasmic polymorphonuclear leukocytes, another feature seen in repair. Compare to Figures 2.19 and 2.20.
Reactive Cellular Changes Associated with Radiation (Fig. 2.23)

Criteria

Cell size is markedly increased without a substantial increase in the nuclear to cytoplasmic ratio.
Bizarre cell shapes may occur.
Enlarged nuclei may show degenerative changes including nuclear pallor, wrinkling or smudging of the chromatin, and nuclear vacuolization.
Nuclei may vary in size, with some cell groups having both enlarged and normal-sized nuclei; binucleation or multinucleation is common. Mild nuclear hyperchromasia may be present.
Prominent single or multiple nucleoli may be seen if coexisting repair is present.
Cytoplasmic vacuolization and/or cytoplasmic polychromatic staining may be seen.

Figure 2.23. Reactive cellular changes associated with radiation (CP). A 40-year-old woman with history of squamous cell carcinoma of the cervix who completed radiation therapy 8 weeks earlier. Cells with enlarged nuclei, abundant vacuolated polychromatic cytoplasm, mild nuclear hyperchromasia without coarse chromatin, and prominent nucleoli. Note multinucleation (upper right corner insert).
Reactive Cellular Changes Associated with Intrauterine Contraceptive Device (Figs. 2.24, 2.25)

Criteria

Glandular cells may be present singly or in clusters, usually of 5 to 15 cells, amid a clean background (Fig. 2.24). The amount of cytoplasm varies, and frequently large vacuoles may displace the nucleus, creating a signet-ring appearance (Fig. 2.24). Occasional single epithelial cells with increased nuclear size and high nuclear/cytoplasmic ratio may be present (Fig. 2.25). Nuclear degeneration frequently is evident. Nucleoli may be prominent. Calcifications resembling psammoma bodies are variably present.

Glandular Cells Status Post hysterectomy (Fig. 2.26)

Criteria

Benign-appearing endocervical-type glandular cells that cannot be differentiated from those sampled from the endocervix. Goblet cell or mucinous metaplasia may be seen. Round to cuboidal cells may resemble endometrial-type cells.

Figure 2.24. Reactive cellular changes associated with intrauterine contraceptive device (IUD) (CP). Note small cluster of glandular cells with cytoplasmic vacuoles displacing nuclei.
**Figure 2.25.** Reactive cellular changes associated with IUD (CP). Epithelial cells with a high nuclear/cytoplasmic ratio may mimic high-grade squamous intraepithelial lesion (HSIL) (left); however, the morphologic spectrum of abnormalities usually present with squamous intraepithelial lesions is absent. Presence of nucleoli in isolated cells with a high N/C ratio (right) is not typical of HSIL.

**Figure 2.26.** Glandular cells status posthysterectomy (CP). Vaginal smear from a 49-year-old woman status posthysterectomy for squamous cell cancer of the cervix, showing benign-appearing endocervical cells.
Atrophy With or Without Inflammation
(Figs. 2.27–2.32)

Criteria

Flat, monolayer sheets of parabasal-like cells with preserved nuclear polarity (Fig. 2.28).
Dispersed parabasal-type cells may predominate.
Generalized nuclear enlargement, up to three to five times the area of an intermediate cell nucleus, may occur with a slight increase in nuclear/cytoplasmic ratio.
Intermediate cells tend to be normochromatic, but parabasal-type cells may have mild hyperchromasia and tend to have more elongated nuclei.
Chromatin is uniformly distributed.
Autolysis may result in naked nuclei.
An abundant inflammatory exudate and basophilic granular background that resembles tumor diathesis may be present (Fig. 2.29).
Globular collections of basophilic amorphous material (blue blobs) reflect either degenerated parabasal cells or inspissated mucus.
Degenerated orangeophilic or eosinophilic parabasal cells with nuclear pyknosis resembling “parakeratotic” cells may be present (Fig. 2.31).
Histiocytes varying in size and shape, and containing multiple, round to epithelioid nuclei and foamy or dense cytoplasm, may be seen (Fig. 2.30).

Liquid-Based Preparations

Liquid-based preparations have less nuclear enlargement than conventional smears due to immediate fixation.
Naked nuclei from autolysis may be reduced in number.
Granular background material tends to clump rather than be dispersed, yielding a “cleaner” background (Fig. 2.31); however, the clumps may “cling” to the cells and make it difficult to visualize individual cells (Fig. 2.32).
2. Non-Neoplastic Findings

**Figure 2.27.** Atrophy (histology, H&E).

**Figure 2.28.** Atrophy (CP). Note flat, monolayer sheet of parabasal-type cells, with preserved nuclear polarity. Atrophic cells may have nucleoli (lower right insert).
**FIGURE 2.29.** Atrophy with inflammation ("atrophic vaginitis") (CP). Note granular debris in background, degenerating parabasal cells, and polymorphonuclear leukocytes.

**FIGURE 2.30.** Atrophy with multinucleated giant cells (CP). Multinucleated histiocytic giant cells are a nonspecific finding and are often seen in postmenopausal and postpartum specimens.
2. Non-Neoplastic Findings

[*] Figure 2.31. Atrophy (LBP). Note more dissociation of parabasal cells and degenerated parabasal cells in a relatively clean background.

[*] Figure 2.32. Atrophy with inflammation (atrophic vaginitis) (LBP). In LBP, the granular debris is clumped and adheres to cell clusters in a pattern that may mimic “clinging tumor diathesis” (see Fig. 5.39). Attention to cellular features is crucial.
Other Non-Neoplastic Findings Not Specifically Listed in 2001 Bethesda Terminology

Tubal Metaplasia (Figs. 2.33–2.35)

Criteria

Columnar endocervical cells that may occur in small groups or pseudo-stratified, often crowded groups (Fig. 2.34).
Nuclei are round to oval and may be enlarged, pleomorphic, and often hyperchromatic.
Chromatin is evenly distributed and nucleoli are usually not seen.
Nuclear to cytoplasmic ratio can be high.
The cytoplasm may show discrete vacuoles or goblet cell change (Fig. 2.35).
Presence of cilia and/or terminal bars is characteristic, but single ciliated cells in isolation are not sufficient for the designation.

[*] Figure 2.33. Tubal metaplasia (histology, H&E).
2. Non-Neoplastic Findings

**Figure 2.34.** Tubal metaplasia (CP). Note terminal bar and cilia at left edge.

**Figure 2.35.** Tubal metaplasia (CP). There are ciliated columnar endocervical cells, and a goblet cell is also seen in the center.
Keratotic Cellular Changes ("Typical Parakeratosis") (Figs. 2.36, 2.37)

Criteria

Miniature superficial squamous cells with dense orangeophilic or eosinophilic cytoplasm.

Cells may be seen in isolation, in sheets, or in whorls; cell shape may be round, oval, polygonal, or spindle shaped.

Nuclei are small and dense (pyknotic).

If atypical nuclear or cellular changes are present, consider atypical squamous cell (ASC) interpretation.

Keratotic Cellular Changes ("Hyperkeratosis") (Fig. 2.38)

Criteria

Anucleate but otherwise unremarkable mature polygonal squamous cells, often associated with mature squamous cells with keratohyaline granules.

Empty spaces or "ghost nuclei" may be seen.

[†] Figure 2.36. Keratotic cellular changes, “typical parakeratosis” (CP). On the left side, note the “squamous pearl” formation in this specimen from a 49-year-old woman being followed up after treatment for SIL. On the right side is a small cluster of miniature squamous cells. Both are examples of “typical parakeratosis” with small bland nuclei.
[*] **FIGURE 2.37.** Keratotic cellular changes, “typical parakeratosis” (left, CP; right, LBP). On the left is an orangeophilic cluster, and on the right are more eosinophilic squamous cells with small, opaque nuclei. Human papillomavirus (HPV) testing, performed for other reasons on the liquid-based specimen, was negative.

Lymphocytic (Follicular) Cervicitis
(Figs. 2.39, 2.40)

Criteria

Polymorphous populations of lymphocytes with or without tingible body macrophages are seen in clusters or streaming out in mucus (Fig. 2.39).

Liquid-Based Preparations

Lymphoid cells may appear in clusters and more scattered single cells can be seen in the background (Fig. 2.40).

Explanatory Notes

Reactive changes are included in the 2001 Bethesda System under NILM. Recognizing such changes is important for defining the boundary between NILM and epithelial abnormalities. In general, round nuclear contours and even chromatin distribution favor a non-neoplastic process. However, exuberant reactive changes in mature squamous cells may raise the differential of “low-grade squamous intraepithelial lesion” (LSIL) or even cancer if reparative features are present (see following paragraph on repair), and an interpretation of “atypical squamous cells of undetermined significance” (ASC-US) or “atypical squamous cells, cannot exclude high grade SIL” (ASC-H) may be considered. Reactive nuclear enlargement in squamous metaplastic cells may mimic “high-grade SIL” (HSIL).

Squamous metaplastic cells in LBPs, in particular, often demonstrate an increased nuclear/cytoplasmic (N:C) ratio due to rounding up of cells, which may raise the differential of an HSIL. In addition, overlapping nuclei in a binucleated cell may give the impression of hyperchromasia (see Fig. 4.21). An N:C ratio of less than 50%, smooth nuclear contours, and even distribution of chromatin all favor benign squamous metaplasia. A higher N:C ratio in conjunction with hyperchromasia and/or nuclear contour irregularities such as notching or grooving should prompt consideration of HSIL or an ASC-H designation. Note that with degeneration, nuclei may become wrinkled and hyperchromatic and therefore difficult to differentiate from HSIL; in such cases, an interpretation of ASC-H may be appropriate (see Fig. 4.12).
2. Non-Neoplastic Findings

**FIGURE 2.39.** Lymphocytic (follicular) cervicitis (CP). Abundant lymphoid cells with a tingible body macrophage located centrally.

**FIGURE 2.40.** Lymphocytic (follicular) cervicitis (LBP). Note polymorphous population of lymphoid cells and tingible body macrophages; cells may clump on LBPs.
Reparative changes ("typical repair") may involve mature squamous, squamous metaplastic, or columnar epithelium. The increased nuclear size and prominent nucleoli characteristic of repair may raise concern for the presence of a more significant lesion. However, in a reparative process, cells typically occur in monolayer sheets with nuclei oriented in the same direction, imparting a streaming look to the epithelial fragments. In addition, there is a paucity of single cells with nuclear changes. If marked anisonucleosis, irregularities in chromatin distribution, or variation in size and shape of nucleoli are present, so-called "atypical repair," the changes should be categorized as "atypical glandular cells" or "atypical squamous cells."

Acute radiation-induced changes, consisting of degenerated blood, bizarre cell forms, and cellular debris, generally resolve within six months following therapy. However, in some patients, chronic radiation-induced cellular changes may persist indefinitely. These chronic changes can include cytomegaly, nuclear enlargement without nuclear/cytoplasmic ratio alteration, mild hyperchromasia, engulfed neutrophils, and persistent polychromatic cytoplasmic staining. Certain chemotherapeutic agents may produce changes in cervical epithelial cells similar to those seen with acute and chronic radiation effects.

The reactive glandular cell clusters occasionally seen in women with IUDs may represent either endometrial or endocervical columnar cells exfoliated as a result of chronic irritation by the device. Such cells may persist for several months after removal of the IUD. Cells may be shed in two patterns: as three-dimensional clusters or singly. The three-dimensional glandular clusters with vacuolated cytoplasm and nuclear changes may closely resemble clusters of cells derived from adenocarcinoma of the endometrium, fallopian tube, or ovary (see Fig. 6.5). Single cells with higher nuclear/cytoplasmic ratio may mimic a high-grade SIL; however, the morphologic spectrum of abnormalities usually present with true precursor lesions is absent. In general, the diagnosis of adenocarcinoma should be made only with caution in the presence of an IUD. If there is any doubt as to the significance of the cellular abnormalities, the cytopathologist should consider recommending removal of the IUD followed by repeat cervical cytology sampling.

On occasion, benign-appearing glandular cells may be seen posthysterectomy.20 There are a number of explanations for this phenomenon, including development of adenosis after traumatic stimulation of stromal mesenchymal cells,21,22 mucinous or goblet cell metaplasia in response to atrophy,23 or prolapse of the remaining fallopian tube after simple hysterectomy. Most important is to exclude adenocarcinoma, particularly when the hysterectomy was performed for glandular neoplasia.

Atrophy is a normal aging phenomenon with a wide spectrum of cel-
lular changes and variable amounts of inflammation. Note that air-drying, a common problem with smear preparations of this type of specimen, may artificially cause nuclear enlargement. Reporting of atrophic changes is variable and nonreproducible. However, atypical cellular changes associated with atrophy or atrophy with inflammation may warrant an interpretation of atypical squamous cells (ASC) (see Figs. 4.17, 4.18).

Multinucleated histiocytes are frequently observed in cervical cytology specimens and can be associated with chronic inflammatory processes and as part of granulation tissue along with occasional fibroblasts and poorly preserved epithelial cells. They may be numerous in specimens from post-menopausal women in the absence of inflammation, and can also be seen postpartum.

Tubal metaplasia of endocervical cells is also a normal phenomenon that includes several cell types (ciliated cells, peg cells, goblet cells). It is important to recognize that enlarged and/or crowded nuclei and nuclear stratification may lead to an interpretation of atypical endocervical glandular cells unless terminal bars and cilia are identified (see Figs. 6.13–6.16).

Normally, the cervix is a nonkeratinizing, stratified squamous epithelium. Keratotic changes may occur as a reactive phenomenon or in association with human papillomavirus (HPV)-induced cell changes. “Keratosis,” “hyperkeratosis,” “parakeratosis,” and “dyskeratosis” are descriptive terms for such changes, but have been used inconsistently in the past, sometimes to convey benignity but in other cases to indicate a dysplastic change. These terms are not specifically listed in Bethesda terminology due to lack of consensus definitions; they are included parenthetically for clarification only. Although some cytologists may choose to include such terms to describe a morphologic feature, they do not constitute a report interpretation and should not be used alone to report results.

The Bethesda classification and interpretation of such keratotic changes depend on the cytoplasmic and nuclear alterations present. Miniature squamous cells with small pyknotic nuclei and orangeophilic to eosinophilic cytoplasm (“parakeratosis”) is a non-neoplastic reactive cellular change. However, single cells or cell clusters that demonstrate pleomorphism of cell size or shape, that is, caudate or elongate cells, and/or increased nuclear size and chromasia (“atypical parakeratosis” or “dyskeratosis”), represent an epithelial cell abnormality. Such findings should be categorized as atypical squamous cells (ASC) or as a squamous intraepithelial lesion (SIL), depending on the degree of cellular abnormality identified (see Figs. 4.3, 4.17, 5.8, 5.23, 5.24).

Anucleate, but otherwise unremarkable mature, squamous cells (“hyperkeratosis”) is a non-neoplastic change. Inadvertent contamination of the
specimen with vulvar material may also introduce anucleate squamous cells on the cervical cytology specimen. When extensive hyperkeratosis is seen an underlying neoplastic or nonneoplastic process may be present. Thick plaques of pleomorphic anucleate squamous cells with irregular contours may rarely be the only clue to an underlying squamous cell carcinoma.

Lymphocytic cervicitis (follicular cervicitis) is an uncommon form of chronic cervicitis that results in the formation of mature lymphoid follicles in the subepithelium of the uterine cervix.

**Sample Reports**

**Example 1:**
*Specimen Adequacy:*
Satisfactory for evaluation; endocervical/transformation zone component present.

*Interpretation:*
Negative for intraepithelial lesion or malignancy.

**Example 2:**
*Specimen Adequacy:*
Satisfactory for evaluation; endocervical/transformation zone component present; partially obscuring inflammation present.

*Interpretation:*
Negative for intraepithelial lesion or malignancy.
*Trichomonas vaginalis* identified.
Reactive squamous cells associated with inflammation.

**Example 3:**
*Specimen Adequacy:*
Satisfactory for evaluation; endocervical/transformation zone component absent.

*Interpretation:*
Negative for intraepithelial lesion or malignancy.
Reactive cellular changes associated with radiation.

**Example 4:**
*Specimen Adequacy:*
Satisfactory for evaluation; endocervical/transformation zone component cannot be assessed because of severe atrophy.

*Interpretation:*
Negative for intraepithelial lesion or malignancy.
Fungal organisms morphologically consistent with *Candida* species.
Atrophy.

Bethesda System 2001 Workshop
Forum Group Moderators:

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References


The Bethesda System for Reporting Cervical Cytology
Definitions, Criteria, and Explanatory Notes
Solomon, D.; Nayar, R. (Eds.)
2004, XXIII, 191 p. 174 illus. in color., Softcover