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E. Albert Reece, Robert L. Barbieri

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6 Pap Smear and Human Papilloma Virus Testing

Benjamin Piura and Ruthy Shaco-Levy

After breast cancer, cervical cancer is the second most common malignancy diagnosed in women worldwide. Approximately 500000 new cases of cervical cancer are diagnosed each year, and nearly 250000 women die of this disease each year worldwide.

Cervical cancer is the most common malignancy encountered in women in developing countries. The majority of these cases occur in countries with limited or no effective screening programs using the Papanicolaou (Pap) smear test[1] for detecting cervical cellular abnormalities, which places women at a greater risk for developing cervical cancer. In the United States, Finland, Sweden, Iceland, and other developed countries where Pap smear screening is widely used, rates of cervical cancer have noticeably dropped up to 50% over the past 20–30 years (see Evidence Box 6.1).

However, health disparities prevent more lives from being saved with Pap smear screening, even in developed countries. Indeed, despite the test's widespread availability in the United States, for example, more than 10000 new cases of cervical cancer are diagnosed each year, and almost 4000 women die each year unnecessarily from this preventable disease. About 50% of women with cervical cancer in the United States did not have a Pap smear test in the preceding 3 years, and an additional 10% had not been screened in the past 5 years.

Nevertheless, more than 50 million Pap smears are performed each year in the United States alone, and 7% (3.5 million) of these give abnormal test results. It has been estimated that women who never had a Pap smear have a 3.5% risk of developing cervical cancer, whereas the risk is reduced to 0.8% with Pap smear screening. Since infection with human papilloma virus (HPV) has been found in almost all cervical cancers, testing for the presence of high-risk HPV types in cervical samples has now become a part of routine clinical work-up in women with equivocal Pap smear test results.

[1] In 1928, George Papanicolaou began sampling vaginal cells, speculating that the presence of any atypical cells might predict the development of cervical cancer. It was only in 1943 when he and Herbert Traut published a monograph on the topic that the Papanicolaou (Pap) smear became the standard cervical cancer screening test. In 1947, Ayers introduced a specially designed wooden spatula (Ayer spatula) for the direct collection of cells from the uterine cervix.

Pap Smear Terminology

There are a number of outdated terminologies regarding Pap smear results (**Table 6.1**). The lack of a common terminology initially resulted in widespread confusion about what really constitutes an abnormal test result. This confusion necessitated further action. In December 1988, a National Cancer Institute workshop held in Bethesda, Maryland, provided for the first time a consensus, now known as the Bethesda System, on how to properly read Pap smears. The result was initial guidelines designed to decrease the variability among laboratories reporting the results.

The three most important contributions of this Bethesda System were:

1. Establishing a special category of abnormal squamous cells of undetermined significance (ASCUS)
2. Organizing the four grades of atypical squamous cells (mild, moderate, severe, and carcinoma in situ) of the old classifications into two distinctive groups: low-

Table 6.1 Historical Pap smear terminology

Papanicolaou	United States	United Kingdom
Normal	Normal	Normal
Inflammatory	Inflammatory	Inflammatory
Atypical cells	Mild atypia Moderate atypia	Mild dyskariosis Moderate dyskariosis
Carcinoma in situ	Severe atypia	Severe dyskariosis
Carcinoma	Carcinoma	Carcinoma

grade squamous intra-epithelial lesion (LSIL) (**Fig. 6.4**), and high-grade squamous intra-epithelial lesion (HSIL) (**Fig. 6.5**). LSIL (previously referred to as "mild atypia") is compatible with grade 1 cervical intraepithelial neoplasia (CIN 1) and HSIL (encompassing "moderate atypia," "severe atypia," and "carcinoma in situ") is compatible with grade 2 or 3 cervical intra-epithelial neoplasia (CIN 2, 3) and carcinoma in situ (CIS)

3. Establishing a new category of abnormal glandular cells of undetermined significance (AGCUS)

Key Terminology Changes in the 2001 Bethesda System

The Bethesda System was revised in 1991 and 2001. The 2001 Bethesda System (**Table 6.2**) reflects the most current knowledge about the biology of Pap test abnormalities and addresses new screening technologies such as the liquid-based, thin-layer Pap smear and HPV testing. It recommends dividing the category of atypical squamous cells (ASCs) into two subcategories: a) atypical squamous cells of undetermined significance (ASCUS), and b) atypical squamous cells that cannot exclude high-grade intra-epithelial lesion (ASC-H).

Overall, among all women with ASC, the risk of developing invasive cancer is low (0.1–0.2%). Nevertheless, the prevalence of CIN 2, 3 confirmed by biopsy among women with ASC is 7–12%, whereas the prevalence of CIN 2, 3 confirmed by biopsy among women with ASC-H ranges from 26% to 68%. Rates of high-risk HPV DNA positivity are 40–51% among women with ASCUS, whereas they are 74–88% among women with ASC-H. Consequently, ASC-H should be considered to represent equivocal HSIL and a productive HPV infection. Thus, the performance of HPV testing allows for clear statements regarding the meaning of an ASC interpretation.

The 2001 revisions to the Bethesda System also eliminated the category of AGCUS (atypical glandular cells of undetermined significance) and identified three subcategories of atypical glandular cells (AGCs):

- AGC not otherwise specified
- AGC favoring neoplasia
- adenocarcinoma in situ (AIS)

Table 6.2 The 2001 Bethesda System

Specimen adequacy
Satisfactory for evaluation (8000–12 000 well-visualized squamous cells for conventional smears and 5000 squamous cells for liquid-based preparations (*note presence/absence of endocervical/transformation zone component*—there should be at least 10 well-preserved endocervical or squamous metaplastic cells)
Unsatisfactory for evaluation (specimens with >75% of epithelial cells obscured)

Table 6.2 Continued

General categorization
Negative for intra-epithelial lesion or malignancy
Epithelial cell abnormality
Other
Interpretation/result
Negative for intra-epithelial lesion or malignancy
• **Organisms** – *Trichomonas vaginalis* – Fungal organisms morphologically consistent with *Candida* species – Shift in flora suggestive of bacterial vaginosis – Bacteria morphologically consistent with *Actinomyces* species – Cellular changes consistent with herpes simplex virus
• **Other non-neoplastic findings** Reactive cellular changes associated with: – inflammation (includes typical repair) – radiation – intrauterine contraceptive device Glandular cells status posthysterectomy Atrophy
Epithelial cell abnormalities
• **Squamous cell** – Atypical squamous cells (ASC) – of undetermined significance (ASC-US) – cannot exclude HSIL (ASC-H) (*5–10% of ASC cases overall*)
• **Low-grade squamous intra-epithelial lesion (LSIL)** (generally a transient infection with HPV) encompassing: human papilloma virus/mild dysplasia/cervical intra-epithelial neoplasia (CIN) 1
• **High-grade squamous intra-epithelial lesion (HSIL)** (more often associated with HPV persistence and higher risk of progression) encompassing: moderate and severe dysplasia, carcinoma in situ; CIN 2 and CIN 3
• **Invasive squamous cell carcinoma**
• **Glandular cell**
• **Atypical glandular cells (AGC)** (*specify endocervical, endometrial, or glandular cells not otherwise specified*)
• **Atypical glandular cells (AGC)** (*specify endocervical, endometrial, or glandular cells not otherwise specified*)
• **Endocervical adenocarcinoma in situ (AIS)**
• **Invasive adenocarcinoma**
Other
Endometrial cells in a woman ≥40 years of age

Reproduced with permission from Salomon D et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 2002; 287:2116.

Types of Pap Smear, Their Sensitivity, and Screening Guidelines

There are two main types of Pap smear: a conventional Pap smear, and liquid-based Pap smear.

Conventional Pap Smear

For a conventional Pap smear, the cell specimen on the collection instrument is spread across a glass slide and fixed to it by either spraying a fixative on the glass slide (**Fig. 6.1**) or placing it in a vial containing an ethanol fixative.

Ideally, samples for this type of a Pap smear should be obtained from three locations: (i) the endocervical canal (E), (ii) the exocervix (including the entire transformation zone) (C), and (iii) posterior vaginal pool (posterior fornix) (V). The samples can be smeared separately on three glass slides that are marked with the letters E, C, or V, respectively.

Some investigators, however, do not advocate collecting samples from the posterior vaginal pool. Nevertheless, for screening, all three samples can be smeared and mixed on one glass slide. The smear should be thick enough that it is not transparent.

Pap smears on a glass slide should be evaluated by a trained laboratory technician or cytopathologist, utilizing a regular light microscope (**Fig. 6.2**). In 1997, the US Food and Drug Administration (FDA) approved two systems for routine use as quality control (rescreening) devices. Although studies have shown that these systems can catch problems not detected on a microscopic evaluation of Pap smears, such technical triumphs have been overshadowed by conflicting opinions about their cost-effectiveness and accuracy among cytopathology professionals, clinicians, patients, and device manufacturers.

Liquid-Based, Thin-Layer (ThinPrep) Pap Smear

A ThinPrep Pap smear involves rinsing or dropping the collection instrument into a vial containing a liquid fixative (**Fig. 6.3**). The cells obtained are filtered, placed on a

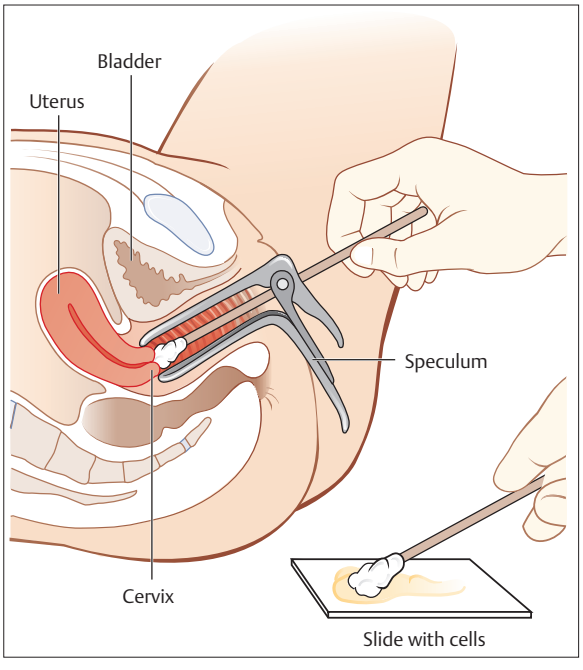

Fig. 6.1 The proper technique for obtaining a sample of cells for a Pap smear.

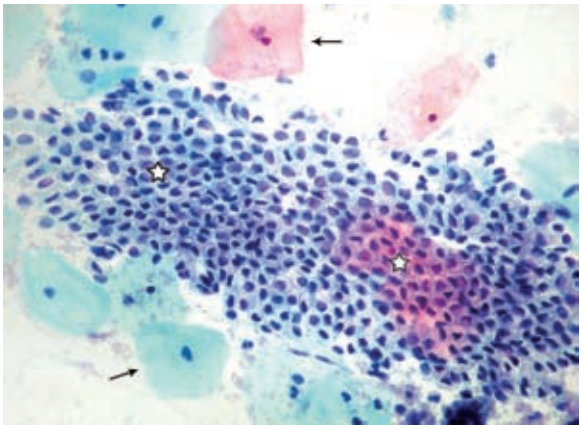

Fig. 6.2 The normal Pap smear. Benign superficial squamous cells (arrows) and endocervical cells (white stars) can be visualized by light microscopy.

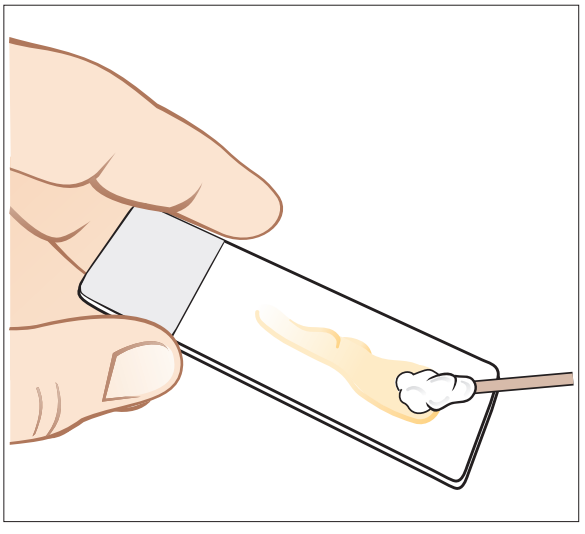

Fig. 6.3 A liquid-based Pap smear requires the collection instrument to be inserted into a vial containing a liquid fixative.