ESSENTIALS OF ANATOMIC PATHOLOGY

THIRD EDITION

Edited by

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Preface to the Third Edition

It is our privilege to present the Third Edition of Essentials of Anatomic Pathology. This edition has been substantially revised to include the most current knowledge and understanding of pathologic processes and to provide contemporary, comprehensive, evidence-based practice information in a consistent and user-friendly outline format. It is our sincere hope that this new edition will serve the educational and reference needs of both trainees and practicing pathologists.

This work has been greatly expanded and enhanced with the addition of seven new chapters: Immunohistochemistry for the Surgical Pathologist, Tumors of Unknown Primary, Biomedical Informatics for Anatomic Pathology, Quality Assurance and Regulations for Anatomic Pathology, Molecular Pathology of Solid Tumors, and others. The addition of these chapters reflects the increased importance of these topics in the modern practice of pathology. The most recently published TNM staging classifications (2010 revision) by the American Joint Committee on Cancer (AJCC) and the World Health Organization (WHO) classification of tumors have been incorporated. This new edition includes 2083 full color photographs and 235 tables, making it an even more useful visual reference than previous editions. Additional emphasis has been placed on newly discovered biomarkers and histologic variants. A limited number of “Suggested Readings” rather than an exhaustive list of references are included with each chapter.

The text, authored by leading international experts, will serve as an evidence- and criterion-based reference that fully outlines the current scope of our specialty. This new edition details in a clear and concise manner the most important aspects of anatomic pathology, and the topics presented herein constitute the fundamentals and core base of knowledge that is required for the daily practice of surgical pathology. We hope that this updated edition will continue to serve as a frontline resource for trainees and practicing pathologists.

Our profound gratitude goes to all who have been involved in the development and production of this new edition. We are indebted to the contributing authors for sharing their knowledge and experiences with our readers and with us. We also express our appreciation to the excellent production staff at Springer Publishing whose efforts made this project possible. In particular, we would like to thank Ryan P. Christy from the Multimedia Education Division of the Department of Pathology at Indiana University, who edited the digital images for this book, and Tracey Bender, who provided superior editorial assistance. Finally, we thank our readers who have made many insightful suggestions that have enhanced the quality of this work. As always, we welcome the opinions of our readers to ensure greater usability in future editions.

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The past decade has witnessed remarkable progress in surgical pathology. The ability of contemporary surgical pathologists to reach a definite diagnosis has been enhanced greatly by innovative immunohistochemical techniques and biomarkers. The information that is useful for pathology practice may not be readily accessible in the daily signout. An up-to-date handbook that contains relevant information to establish an accurate diagnosis would be of practical value. Therefore, we have concentrated on diagnostic criteria and differential diagnosis to ensure an accurate diagnosis.

The purpose of Essentials of Anatomic Pathology is to provide a concise review of anatomic pathology for pathologists in training and practicing pathologists, integrating recent advances in diagnostic surgical pathology. This book is organized to allow easy reference for daily practice, and is intended to aid residents who are preparing for Anatomic Pathology Boards and in-service examinations. It will be a useful resource for medical students and for anyone interested in pathology.

Part I covers general anatomic pathology, including diagnostic molecular pathology, medical cytogenetics, human genetic disorders, microbiology for surgical pathologists, forensic pathology, and cytopathology. Part II is classified by organ system, and covers important diagnostic features of common medical diseases and tumors. The pertinent clinical information, salient diagnostic features, relevant ancillary data (for example, immunohistochemical profiles), main differential diagnoses of each disease, and most recent tumor staging information are presented in a consistently user-friendly format. We believe that this format will provide easy access to essential information necessary for sign-out. It is not meant as a substitute for lavishly illustrated, comprehensive textbooks, but to complement them as a practical aid. We hope that this text will materially aid in continuing efforts to recognize, understand, and accurately interpret the gross and light microscopic findings in anatomic pathology specimens.

We earnestly solicit constructive criticism from colleagues so that the utility of this text can be expanded and improved to its maximum potential.

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David G. Bostwick, MD
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Part I

General Pathology
# Cytopathology

Fadi W. Abdul-Karim, MD, Jennifer Brainard, MD, and Claire W. Michael, MD

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Part A

Gynecologic Cytology
THE 2001 BETHESDA SYSTEM

Specimen Type
♦ Indicate conventional smear (Pap smear) vs. liquid-based preparation vs. other

Specimen Adequacy
♦ Satisfactory for evaluation (describe presence or absence of endocervical/Transformation Zone component (TZ) and any other quality limiting factors, e.g., partially obscuring blood, inflammation, etc.)
♦ Unsatisfactory for evaluation (specify reason)
  – Specimen rejected/not processed (specify reason)
  – Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (specify reason)

General Categorization (Optional)
♦ Negative for intraepithelial lesion or malignancy
♦ Other: See “Interpretation/Result” (e.g., endometrial cells in a woman ≥40 years of age)
♦ Epithelial cell abnormality: See “Interpretation/Result” (specify “squamous” or “glandular” as appropriate)

Interpretation/Result
NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY
♦ When there is no cellular evidence of neoplasia, state this in the General Categorization above and/or in the “Interpretation/Result” section of the report, whether or not there are organisms or other nonneoplastic findings

Organisms
♦ Trichomonas vaginalis
♦ Fungal organisms morphologically consistent with Candida spp
♦ Shift in vaginal flora suggestive of bacterial vaginosis
♦ Bacteria morphologically consistent with Actinomyces spp
♦ Cellular changes associated with Herpes simplex virus (HSV)

Other Nonneoplastic Findings (Optional to Report; not Inclusive)
♦ Reactive cellular changes associated with
  – Inflammation (includes typical repair)
  – Radiation
  – Intrauterine contraceptive device (IUD)
♦ Glandular cells status post hysterectomy
♦ Atrophy

Other
♦ Endometrial cells (in a woman ≥40 years of age)
  – Specify if negative for squamous intraepithelial lesion

Epithelial Cell Abnormalities
Squamous Cell
♦ Atypical squamous cells
  – Of undetermined significance (ASC-US)
  – Cannot exclude HSIL (ASC-H)
♦ Low grade squamous intraepithelial lesion (LSIL)
  – Encompassing: HPV/mild dysplasia/CIN1
♦ High grade squamous intraepithelial lesion (HSIL)
  – Encompassing: moderate and severe dysplasia, CIS; CIN2 and CIN3
  – With features suspicious for invasion (if invasion is suspected)
♦ Squamous cell carcinoma

Glandular Cell
♦ Atypical
  – Endocervical cells (NOS or specify in comments)
  – Endometrial cells (NOS or specify in comments)
  – Glandular cells (NOS or specify in comments)
♦ Atypical endocervical glandular cells, favor neoplastic
♦ Endocervical adenocarcinoma in situ (AIS)
♦ Adenocarcinoma
  – Endocervical
  – Endometrial
  – Extrauterine
  – Not otherwise specified (NOS)

Other Malignant Neoplasms (Specify)

Ancillary Testing
♦ Provide a brief description of the test method(s) and report the result so that it is easily understood by the clinician

Automated Review
♦ If the case is examined by automated device, specify the device and result

Educational Notes and Suggestions (Optional)
♦ Suggestions should be concise and consistent with clinical followup guidelines published by professional organizations (references to relevant publications may be included)
**Adequate Pap Test (Figs. 1.1 and 1.2)**

- An adequate test has well-visualized and well-preserved squamous cells with an estimated minimum of 8–13,000 cells (conventional Pap) and >5,000 (liquid-based Pap). This minimum cell range should be an estimate aided by published diagrams of representations of microscopic fields with different parameters of microscope objectives/oculars/field number and number of cells.
- Describe presence or absence of endocervical/ transformation component and any other quality indicators immediately after

Satisfactory and Unsatisfactory terms. The list of quality indicators might include: absence of pertinent clinical information (such as LMP, age, etc.), air drying, or poor preservation of cellular material, excessive blood/mucous/exudates, thick cell groups, scant cellularity, and excessive cytolysis.

- Any specimen with abnormal cells is by definition satisfactory for evaluation.

**Endocervical/Transformation Zone Component (Figs. 1.3 and 1.4)**

- At least 10 well-preserved endocervical and/or squamous metaplastic cells should be observed to report that a transformation zone component (TZ) is present. In a negative Pap test, its absence does not necessarily mean that the patient requires early repeat testing especially if the patient has a negative Pap.

---

**Fig. 1.1.** Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy. Superficial squamous cells, metaplastic cells, and intermediate squamous cells. *LBP* liquid-based preparation.

**Fig. 1.2.** Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy. Superficial, intermediate, and metaplastic squamous cells. *LBP* liquid-based preparation.

**Fig. 1.3.** Satisfactory for evaluation. Endocervical-transformation zone component present. Normal endocervical cells. *CP* Conventional preparation.

**Fig. 1.4.** Satisfactory for evaluation. Endocervical transformation zone component present. Immature and mature metaplastic cells. *CP* Conventional preparation.
history. However, attention to regular screening is suggested. If there is a history of abnormal Pap, incomplete visualization of cervix, immunocompromised status, or poor screening history, repeat in 6 months is suggested.

**Unsatisfactory Specimen (Fig. 1.5)**

- Clarify laboratory’s role in processing/evaluation of specimen in the report
- Suggested wording to clarify report
  - Rejected Pap
    - (a) Specimen rejected (not processed) because of the following: specimen not labeled, slide broken, etc
  - Fully evaluated unsatisfactory Pap
    - (a) Specimen processed and examined, but is unsatisfactory for evaluation of epithelial abnormality because of obscuring blood, inflammation (>75% of the cells are obscured), etc
- Additional comments or recommendations are suggested, as appropriate: An excessively bloody or inflamed Pap test may mask the screener’s ability to detect an underlying abnormality and a repeat examination/evaluation is suggested

**ORGANISMS**

**Trichomonas vaginalis (Figs. 1.6 and 1.7)**

- Approximately 25% of women are carriers of *Trichomonas vaginalis*. *Trichomonas vaginalis* often coexist with *leptothrix* and other coccoid bacteria. The organisms are small, "pear or kite-shaped," and faintly stained with small, oval, eccentric pale nuclei and red cytoplasmic granules. Rare flagella may be observed in LBP. Cannonball cells with agglomeration of neutrophils onto squamous cells maybe observed. The squamous cells may show vacuolization, polychromasia, and “moth eaten” appearance. Granular debris and inflammation is usually present in the background.

**Candida albicans (Figs. 1.8 and 1.9)**

- Approximately 10% of females are carriers of *Candida* organisms. The incidence of *Candida* infection increases with pregnancy, oral contraceptive use, and diabetes. The organisms
are yeast forms with long pseudohyphae. “Spearing” of epithelial cells by the pseudohyphae may be observed. Inflammatory cells are generally present in the background. Torulopsis glabrata lack the pseudohyphae observed in Candida, but the two organisms may be difficult to separate on Pap test.

**Bacterial Vaginosis (Fig. 1.10)**

- Bacterial vaginosis occurs in 10–30% of the general population. Patients have exponentially more anaerobes per ml of vaginal fluid than normal. The etiologic agents for bacterial vaginosis include Gardnerella vaginalis, anaerobic lactobacilli, and Bacteroides and Mobiluncus species. G. vaginalis (haemophilus-corynebacterium-vaginalis) may be cultured in 30–50% of asymptomatic women.

- A combination of Pap test, wet prep, and other tests including vaginal PH and “Whiff” test on KOH preparation, which is positive in symptomatic women, can establish the diagnosis. The organisms are gram variable bacilli, including numerous coccobacilli, curved bacilli, or mixed organisms imparting a “filmy” appearance to the preparation. Lactobacilli are absent. “Clue cells” refer to the presence of squamous cells covered by adherent, small, and uniformly spaced coccobacilli. This finding is neither specific nor sufficient for the diagnosis of bacterial vaginosis.

**Actinomyces (Fig. 1.11)**

- Actinomyces organisms are gram positive filamentous bacteria. They are associated with the use of IUD and vaginal pessaries. Actinomyces organisms are recognized by the presence of isolated tangled aggregates of long basophilic filamentous structures with a radiating pattern.
Herpes Simplex Virus (Fig. 1.12)
- 80% of exposed females develop Herpes simplex virus (HSV) infection following exposure and the recurrence rate is 60%. Herpetic infection is characterized by the presence of multinucleation, molding of nuclei, ground-glass nuclei, margination of chromatin, and eosinophilic intranuclear inclusions. Type I and type II (genital) herpes, or primary or secondary infections cannot be distinguished cytologically.

Chlamydia trachomatis
- Intracytoplasmic vacuoles containing eosinophilic dots (elementary particles) are not specific for C. trachomatis, as they probably represent mucinous or other vacuoles. C. trachomatis may be associated with follicular cervicitis. The Pap test has no role in the diagnosis of this infection.

Döderlein Bacilli (Lactobacillus acidophilus)
- Döderlein bacilli represent a heterogeneous group of bacilli whose function is to maintain an acid vaginal pH (3.5–4.5). They are the only species of bacteria that are capable of causing cytolysis or dissolution of cytoplasm of intermediate squamous cells by hydrolyzing intracytoplasmic glycogen, and they result in cytolysis of intermediate squamous cells.

Entamoeba histolytica
- Entamoeba histolytica organisms are large trophozoites with large nuclei and a dot-like central karyosome. Their cytoplasm is vacuolated and contains ingested RBCs.

Cytomegalovirus
- Cytomegalovirus infection in immunocompetent women is usually transient and asymptomatic. The infected cells are enlarged with a solitary basophilic intranuclear inclusion surrounded by a halo. Intracytoplasmic small granular inclusions may also be observed.

CONTAMINANTS

- Alternaria. Alternaria are air-borne contaminant fungi that have short yellow brown conidiospores and transversely and longitudinally septate macroconidia (snow shoe-like).
- Pollen
- Vegetable cells. Vegetable cells have dense cell walls and structureless nuclei. They may be observed in patients with rectovaginal fistulas along with goblet cells, inflammation, and necrotic debris.
- Graphite-pencil markings
- Lubricant jelly. Not recommended for gynecologic examination prior to Pap smear.
- Cotton, cardboard, and tampon fibers
- Trichome. “Octopus-like” or star-shaped structure derived from leaves of arrow-wood plant.
Typical Repair (Figs. 1.15 and 1.16)
- Typical repair is characterized by the presence of cohesive sheets of cells with rare or absence of isolated cells.

Ferning. Represents arborizing palm leaf-like pattern of cervical mucus that occurs at ovulation.

"Corn flakes." A refractile brown cell artifact representing air-trapping between the superficial squamous cell nuclei and the cover slip. It can be resolved by reprocessing.

Sperm. Sperm may be identified in the Pap test a few days after intercourse. In HIV-infected patients, the presence of sperm is indicative of unprotected intercourse.

Reactive Changes (Figs. 1.13 and 1.14)

Fig. 1.13. Reactive cellular changes associated with inflammation. Sheet of cells with slightly enlarged uniform nuclei and abundant cytoplasm. Polymorphonuclear leukocytes are present in the sheet. Elsewhere in this slide fungal organisms consistent with Candida species were observed. LBP liquid-based preparation.

Fig. 1.14. Reactive cellular changes associated with inflammation. Sheet of squamous cells with distinct borders, abundant cytoplasm, enlarged uniformly round nuclei and nucleoli. Isolated atypical cells are not observed. CP Conventional preparation.

Fig. 1.15. Reactive cellular changes associated with inflammation. Typical repair characterized by a sheet of cells with distinct borders, abundant cytoplasm, and slightly enlarged nuclei with uniform chromatin pattern and nucleoli. CP Conventional preparation.

Fig. 1.16. Reactive cellular changes associated with inflammation. Typical repair. LBP liquid-based preparation.
and regular. The cells have a delicate, cyanophilic cytoplasm without differentiation

No tumor diathesis is present

**Differential Diagnosis**

- The differential diagnosis of typical repair includes, among others, squamous cell carcinoma (SCC) and acantholytic cells in pemphigus vulgaris
- SCC presents as discohesive abnormal cells. The tumor cells have an irregular chromatin distribution and multiple irregular nucleoli. A tumor diathesis is present
- Acantholytic cells in pemphigus vulgaris are usually observed in vaginal smears. Isolated single cells are present: referred to as tombstone cells – Tzank cells. Correlation with clinical history is essential for accurate interpretation of cells derived from pemphigus vulgaris

**Radiation Effect (Figs. 1.17 and 1.18)**

- Radiated cells manifest cellular enlargement (macrocytosis), and nuclear enlargement, but the N/C ratio remains normal. The cells show nuclear and cytoplasmic vacuoles and large perinuclear halos. Cellular chromat in is finely granular or degenerative ("smudged"). Karyorrhexis and karyopyknosis are observed
- Binucleation and multinucleation, and micro- and macronucleoli are typical of radiated cells. Large bizarre cells with polychromasia, cytoplasmic vacuolization, peripheral cytoplasmic projections (pseudopodia), and cytophagocytosis including intracytoplasmic neutrophils are observed

**IUD-Associated Change (Fig. 1.19)**

- Small clusters of hypersecretory endocervical cells are observed. The cells have abundant cytoplasm with distinct cell borders. Large cytoplasmic vacuoles (bubble-gum cytoplasm) are observed

The nuclei are large, uniform and may contain prominent nucleoli. Inflammatory/reparative squamous changes may be present. The background is generally clean or inflammatory

- Actinomycotic colonies and calcified debris may be observed in the background

**Differential Diagnosis**

- The differential diagnosis of IUD is mainly endometrial adenocarcinoma
- Adenocarcinoma of endometrium, unlike IUD-associated changes occurs in older patients (postmenopausal). Generally endometrial adenocarcinoma is characterized by the presence of many abnormal cells with associated tumor diathesis. Cells derived from adenocarcinoma have an irregular chromatin pattern and prominent nucleoli