Endometrial Cytology with Tissue Correlations
ESSENTIALS IN CYTOPATHOLOGY SERIES

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Endometrial Cytology
with Tissue Correlations
The authors wish to dedicate this work to our loved ones and to our beloved mentors, who encouraged us in our pursuit of gynecological pathology and cytopathology, and who inspired us to create this work. Special mention is given to Dr. Liang-Che Tao, whose seminal publications, heartfelt support, and brilliant invention both inspired and encouraged us to gain a further understanding of the art of endometrial cytopathology. Also, especial thanks must be extended to Dr. David G. Bostwick, whose innovative views on the practice of anatomic pathology and cytopathology have helped to move this field forward and to make this effort possible.
Foreword

Although only 2 cm separate the cervical mucosa from the lining of the uterine cavity, the endometrium has not been screened for neoplasms to the same extent as has the uterine cervix. As a result, endometrial cancers are now the most common malignancies of the female reproductive organs in the United States. Two factors have long been blamed as the reason to bypass cytological examination of endometrial tissue in favor of biopsy: inadequate material to reliably categorize the sample, and inadequate experience by cytopathologists to accurately triage the patient for further management. Maksem and his colleagues provide convincing evidence, both by data and by superb micrographs, that good material can be harvested and experience can be acquired to direct clinicians in managing their patients. In an era in which cost containment is essential, the ability to adequately sample a potentially malignant tissue in an office setting without sedation or anesthesia is a bonus. The Editorial Board of the EIC Series predicts that this volume will become a seminal work. We look forward to reading about your experience with this long-neglected frontier in cytopathology.

*Dorothy L. Rosenthal, M.D., F.I.A.C.*
The subspecialty of cytopathology is 60 years old and has become established as a solid and reliable discipline in medicine. As expected, cytopathology literature has expanded in a remarkably short period of time, from a few textbooks prior to the 1980’s to a current and substantial library of texts and journals devoted exclusively to cytomorphology. Essentials in Cytopathology does not presume to replace any of the distinguished textbooks in cytopathology. Instead, the series will publish generously illustrated and user-friendly guides for both pathologists and clinicians.

Building on the amazing success of The Bethesda System for Reporting Cervical Cytology, now in its second edition, the Series will utilize a similar format, including minimal text, tabular criteria, and superb illustrations based on real-life specimens. Essentials in Cytopathology will, at times, deviate from the classic organization of pathology texts. The logic of decision trees, elimination of unlikely choices, and narrowing of differential diagnosis via a pragmatic approach based on morphologic criteria will be some of the strategies used to illustrate principles and practice in cytopathology.

Most of the authors for Essentials in Cytopathology are faculty members in The Johns Hopkins University School of Medicine, Department of Pathology, Division of Cytopathology. They bring to each volume the legacy of John K. Frost and the collective experience of a preeminent cytopathology service. The archives at Hopkins are meticulously catalogued and form the framework for text and illustrations. Authors from other institutions have been selected on the basis of their national reputations, experience, and enthusiasm for cytopathology. They bring to the series complementary
viewpoints and enlarge the scope of materials contained in the photographs.

The editor and authors are indebted to our students, past and future, who challenge and motivate us to become the best that we possibly can be. We share that experience with you through these pages, and hope that you will learn from them as we have from those who have come before us. We would be remiss if we did not pay tribute to our professional colleagues, the cytotechnologists and preparatory technicians who lovingly care for the specimens that our clinical colleagues send to us.

And finally, we cannot emphasize enough throughout these volumes the importance of collaboration with the patient care team. Every specimen comes to us as a question begging an answer. Without input from the clinicians, complete patient history, results of imaging studies and other ancillary tests, we cannot perform optimally. It is our responsibility to educate our clinicians about their role in our interpretation, and for us to integrate as much information as we can gather into our final diagnosis, even if the answer at first seems obvious.

We hope you will find this series useful and welcome your feedback as you place these handbooks by your microscopes, and into your book bags.

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Introduction

Direct cytological sampling and examination of the endometrium is not generally practiced, which is surprising as the endometrium is exceedingly easy to sample. Over the years, as we gained more experience with specimen acquisition, processing, and interpretation, we found endometrial cytology to be an effective method both for ensuring endometrial normalcy and for discovering and diagnosing malignant and premalignant states. In comparing endometrial cytology to biopsy, we found that, among samples obtained by individuals experienced in specimen collection, cytology outperforms outpatient biopsy in terms of tolerance of the procedure by the patient, adequacy of the sample among postmenopausal women, and detection of occult neoplasms.

By using the Tao brush (also known as the Indiana University Medical Center endometrial sampler) and devising a technical strategy to ensure the simultaneous creation of cell blocks and cytological samples from a single collection, we moved our appreciation of endometrial brush collection into an arena whose significance equals other methods of specimen collection and interpretation. Cytology performs equally as well as biopsy in detecting hyperplasia and carcinoma. If nothing else, by reliably identifying benign normal endometrial states, it serves to confidently exclude more than 70% of women from unnecessary follow-up testing.

Because the Tao brush samples only the superficial 2 mm of the endometrium, the method is not designed to detect endome-
trial polyps, leiomyomas, stromal tumors, and tumors of the uterine wall musculature. However, it is useful for detecting benign estrogen-excess states such as disordered proliferation and various degrees of benign hyperplasia and for separating these from neoplastic states such as endometrial intraepithelial neoplasm (EIN), endometrial gland dysplasia (EmGD), and cancer. Nonetheless, it cannot always subclassify benign hyperplastic states of the endometrium without the aid of cell blocks.

When endometrial brushing is combined with liquid fixation and with other techniques such as immunohistochemistry, cell block examination, hysteroscopy, or sonohysterography, endometrial benignancy can be confidently assured. In a woman with a patent cervix, endometrial brushing successfully collects material, even from late postmenopausal atrophic endometrium. It detects serious low-volume diseases such as endometrial intraepithelial carcinoma (serous surface carcinoma, or EIC) under conditions where suction biopsy may have missed or otherwise obviated the diagnosis.

This monograph focuses on the background, collection technique, and reliability of endometrial cytology. It overviews diagnostic criteria and diagnostic pitfalls encountered in practicing this art. Because endometrial cytology interpretation relies heavily on intuiting tissue patterns from cytology preparations, emphasis is placed on cytohistological correlations with cell block material, and, where effective as part of a diagnostic strategy, on ancillary immunohistochemical staining. The discussion moves from normal states, through otherwise benign changes induced by an altered hormonal milieu or surface irritants, into precancerous and malignant endometrial conditions. Finally, it covers fixative and slide preparation methods for the benefit of those who wish to repeat this work in their own practice.

**Suggested Reading**


Office-Based Endometrial Sampling

Outpatient biopsy has replaced dilatation and curettage for evaluating most endometrial disorders, including hyperplasia and cancer. The literature is replete with arguments that support its accuracy, convenience to the patient and physician, and cost containment benefits. The most common option for outpatient sampling is the suction biopsy device, best exemplified by the Unimar Pipelle. A meta-analysis of 142 published studies ranked the success of endometrial sampling methods in women with abnormal vaginal bleeding and showed that outpatient endometrial biopsy adequately samples the uterus from 24% to 97% of the time and detects from 67% to nearly 100% of endometrial cancers.

This work presents direct cytological sampling of the uterine cavity as another diagnostic tool available to clinicians and pathologists alike. As with suction biopsy, its purpose is the assurance of endometrial benignity and the detection of endometrial neoplasm. Cytological sampling of the endometrium is a gentle method that is less painful than suction biopsy. Our intention is to show that in experienced hands direct cytological sampling is at least as thorough and as accurate as suction biopsy.

Endometrial sampling is generally performed as a response to abnormal vaginal bleeding of endometrial origin. Abnormal vaginal bleeding may be caused by anything from a physiological event such as dysfunctional uterine bleeding resulting from endometrial atrophy, to a benign tumor such as a polyp or leiomyoma, or
neoplastic disease such as endometrial intraepithelial neoplasm (EIN) and cancer. Persistent postmenopausal bleeding in the setting of an endometrial stripe in excess of 4-mm thickness imposes a greater than 60-fold-increased risk for endometrial cancer, and some investigators report that combining suction curettage with endometrial cytology is the best strategy for examining outpatients with abnormal uterine bleeding.

Endometrial sampling may be used to screen or monitor selected “at-risk” populations. For example, because of an increase in the use of hormones as adjuvant therapy in both postmenopausal women and women with breast cancer, endometrial sampling has become a mainstay of therapeutic monitoring. It is also useful for monitoring women with premalignant endometrial changes who have been treated with hormones to assess their response to therapy.

Endometrial cytology is a reliable and well-tolerated method of detecting uterine pathology in tamoxifen-treated women. In one study of 687 tamoxifen-treated women, 189 had a double-layer endometrial thickness (i.e., stripe) of more than 8 mm. Of these, 150 underwent cytological endometrial sampling followed by hysteroscopy and curettage. The cytological and histological findings correlated well in 145 cases, leading investigators to recommend the combination of ultrasonography and brush cytology as a monitoring strategy for women treated with this drug.

When coupled to ultrasonography, liquid-based cytology, and cell block examination, endometrial cytology is at least as sensitive and specific as other office-based biopsy methods. The advantage of liquid-based processing is that it affords standardized and reproducible endometrial preparations, which in turn fosters the application of common diagnostic criteria among cytopathologists. For example, in a study of 162 endometrial samplings fixed in CytoLyt and processed with ThinPrep, nearly perfect interobserver diagnostic agreement was achieved.

A study of abnormal uterine bleeding using PreservCyt fixative and ThinPrep recorded a 96% overall specificity for endometrial cytology, a 78% positive predictive value and a 96% negative predictive value for atypical hyperplasia and adenocarcinoma, and a 15% unsatisfactory rate, about half that of endometrial biopsy (26%). Another study evaluated the accuracy of liquid-based endometrial cytology as compared to biopsy in 670 women