

# **ESSENTIALS IN CYTOPATHOLOGY**

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# Glandular Lesions of the Uterine Cervix

Cytopathology  
with Histologic Correlates

 Springer

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# Foreword

I am delighted to contribute the foreword to this book written by two colleagues who are not only good friends but also outstanding diagnostic pathologists who have assisted me greatly over the years. I also consider it highly appropriate that a book on cytopathology of the uterine cervix be coauthored by two members of the cytopathology laboratories of the Massachusetts General Hospital, Harvard Medical School, given the very significant role the unit played in the acceptance of cytopathology as a discipline in the United States. Some readers may not know that when cytopathology was entering the field of anatomic pathology as a subdiscipline, it received much initial opposition from many traditional diagnostic pathologists, including the then chief of pathology of the Massachusetts General Hospital (MGH), Dr. Tracy Mallory. That they might have some reservations about the “new kid on the block” was perhaps not surprising, and we should not cast any aspersions on that distinguished pathologist or others who felt as he did. Nonetheless, it has been to the great benefit of medicine, and more importantly the populace at large, that others felt differently, including the pioneering gynecologic oncologist Dr. Joe V. Meigs. As Dr. Wilbur has recounted elsewhere, he was approached by an MGH internist, Dr. Maurice Fremont-Smith, after the latter visited the laboratory of Dr. Papanicolaou in New York, and he was intrigued by what he saw. Dr. Meigs was of an

innovative disposition, saw the potential benefit of the technique quicker than many, and recruited the pioneering cyto-technologist Ruth M. Graham to help implement cytopathology in practice in Boston. The first cytology laboratory at this hospital was accordingly established in the gynecology service of the MGH (then and now known as the Vincent Memorial Hospital) in 1942 and was the first such cytology laboratory established in this country after that of Dr. Papanicolaou himself. The work of the early investigators at the MGH was noted by the American Medical Association when, in 1944, they honored them with a certificate of merit because of their work (the honor being shared with Cornell Medical Center). The elegant diploma still is displayed in the cytology laboratories of this institution. Further note might be made of the fact that Ruth Graham and her staff published the first textbook of cytology in 1950. As will be evident from these remarks, Dr. Tambouret and Dr. Wilbur are part of a great tradition, and I can certainly, based on my own personal knowledge of their expertise, simply note that they are upholding this noble tradition in a most outstanding manner on a daily basis and by their efforts both nationally and internationally. Cytology only transitioned to pathology at this institution in the mid-1950s, and has resided there from that time, Dr. Wilbur serving as director of the unit for a number of years beginning in 2001 until, voluntarily, he passed on the torch. He remains fully active in the unit, signing out on a regular basis, as does Dr. Tambouret, and both are mainstays of the general gynecologic pathology diagnostic histopathology service.

That this text covers glandular lesions of the uterine cervix is itself noteworthy, inasmuch as the early pioneers focused largely on squamous lesions. It is only since the mid- to late 1970s that progressively greater attention has been focused on the numerous challenges provided by endocervical glandular lesions in both cytopathology and histopathology. Although of course getting coverage in various texts and other sources on occasion, glandular lesions get overwhelmed from the coverage viewpoint by the more common squamous

abnormalities, and it is timely to see a work focused only on the endocervical cell. In my own practice, I see countless problematic endocervical glandular proliferations, many of which Dr. Tambouret and Dr. Wilbur assist me with, and it is not unusual for them, quite appropriately, to me wish to correlate biopsy findings with those in cytologic preparations. Considering the two can be of great benefit in arriving at the correct diagnosis. The initial evaluation of endocervical abnormalities of most patients does begin with cytologic material, and it is the first point in the chain that we all hope leads to good clinical care. Accordingly, it is obviously crucial that such specimens are appropriately evaluated so that significant lesions are not delayed in further evaluation, and from a contrary perspective, lesions of benign nature do not lead to mismanagement and undue patient anxiety. The practice of cytopathology is a visual discipline, albeit impacted of course by the eye of experience and some awareness of the clinical background including the patient age, among other things. Much as words may help in elaboration of potential pitfalls, the proverbial “picture speaks a thousand words,” and accordingly, this work is liberally presented with high-quality illustrations. All who practice the discipline of cytopathology will, I am sure, find this a most instructive volume to have available, given the knowledge and experience of the writers. I am delighted to have the opportunity to make these remarks concerning this fine work.

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Robert H. Young  
Robert E. Scully

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# Preface

The evaluation of glandular lesions in cervical cytology specimens can be vexing, even to the most experienced cytologist. The mere identification that a glandular lesion is present can be subtle during the screening process, and once a potential abnormality is detected, accurate classification can be even more challenging. Compared to the more prevalent squamous lesions, glandular lesions in cervical cytology specimens were not well recognized or fully classified until late. Endocervical adenocarcinoma in situ (AIS) was not fully described in the histopathology literature until 1953 [1], and it was not codified as a discrete cytologic entity until the second edition of the Bethesda Manual (TBS2) in 2001 [2]. Prior to that AIS was grouped under the descriptor of “atypical glandular cells of undetermined significance, favor neoplasia.” In the 1990s, a number of detailed publications that appeared defined the morphologic characteristics of AIS and showed that when applied correctly, these criteria were actually predictive when histologic specimens were obtained [3–5]. Extensive study of glandular lesions followed upon the publication of TBS2 such that a variety of conditions affecting glandular cells of the gynecologic tract became better recognized and the morphologic criteria for each became better defined.

It is fair to say that there has been an increased awareness that, although the test is not perfect, glandular lesions can

indeed be reliably identified in cervical cytology specimens. As with any newly emerging discipline, the ability to detect glandular lesions has had other effects. Patients now expect that, just like squamous neoplasia, glandular neoplasia can be perfectly identified when present. Many lawsuits alleging malpractice have involved this very subject. The unfortunate truth is that the Pap test is not as sensitive for endocervical as it is for squamous neoplasias. The anatomy of endocervical cell location and the plethora of reactive mimics make accurate detection difficult from both sampling and interpretation viewpoints, respectively. That being said, there is always room for improvement and that is the idea behind the present monograph.

At the Massachusetts General Hospital, we are fortunate to have access to the material from very active gynecologic oncology, colposcopy, and general screening services. In addition, there are a large number of outside consultation cases that are received for review by our subspecialty experts in gynecologic practice, both clinical and pathologic. In the writing of the text and collection of the illustrations, we have attempted to identify the key issues in the cytology of glandular lesions, to present the important demography and clinical features associated with them, and finally to describe and to illustrate the pertinent morphology of these lesions.

The monograph begins with a background discussion and illustration of the normal histology and cytology associated with glandular epithelia in the gynecologic tract. It then describes the prototypical endocervical and endometrial neoplasia spectrums. In addition, illustrations of malignant mimickers, namely metastatic adenocarcinomas, which can have appearances very similar to primary lesions will be presented, with the discussion focusing on the features that should help the observer to make a correct final interpretation. The latter morphologic chapters focus on the many mimickers of glandular neoplasia. Entities such as the large number of metaplastic processes, reactive endocervical cells caused by irritants such as polyps, intrauterine devices, prior biopsies, infectious disease, and many more will be detailed. These

benign entities are common and can actually be the underlying cause of many cases of interpretations of “atypical glandular cells (AGC).” It has been a “rule of thumb” for many years that the majority of cases of AGC will turn out to be either benign/reactive or unusual presentations of squamous intraepithelial lesions, with only a small minority actually representing true glandular neoplasias. Hence recognition and correct classification of these presentations as benign can lead to significant improvements in cervical cytology specificity and can help to avoid costly and stressful follow-up clinical investigations. Therefore accuracy in both directions, detection and false negativity, as well as classification and false positivity, are addressed by this monograph.

Aids to interpretation have become very important in histopathologic applications. When applied to cytologic preparations, the use of immunohistochemistry for markers associated with high risk HPV-associated neoplastic transformation and with types of differentiation has greatly aided again, both detection and classification. The principles behind their use and illustrations to aid in proper interpretation are presented in order to bring the reader up to speed with this newly emerging functionality.

Finally, the management of glandular lesions may seem like the clinicians’ domain. But it is extremely important for laboratory professionals to be aware of the published guidelines. These lesions are rare in the general screening population and the cytologist, because of their diagnostic role, may be in the best position to advise and guide the clinician trying to determine the best course of action. Therefore the newest management algorithms are presented to assist the cytologist in this important advisory role. In addition, appropriate quality assurance practices, such as prevalence monitoring, cytology–histology correlation, and HPV testing use are included as these will be important to the laboratorian.

We certainly hope that this monograph meets the needs of the cytology community and that the format and content is displayed in a manner that allows for easy access, adaptability to clinical situations, and ease of information transfer. It has

been our pleasure to “put down on paper” these subjects that we have studied and struggled over for the better parts of our careers. We hope that the knowledge and experience that we have gained will be useful to the reader.

Boston, MA  
2014

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