

# **Modern Uterine Cytopathology**

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*Moving to the Molecular Smear*

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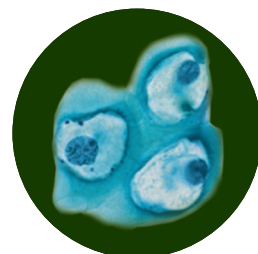
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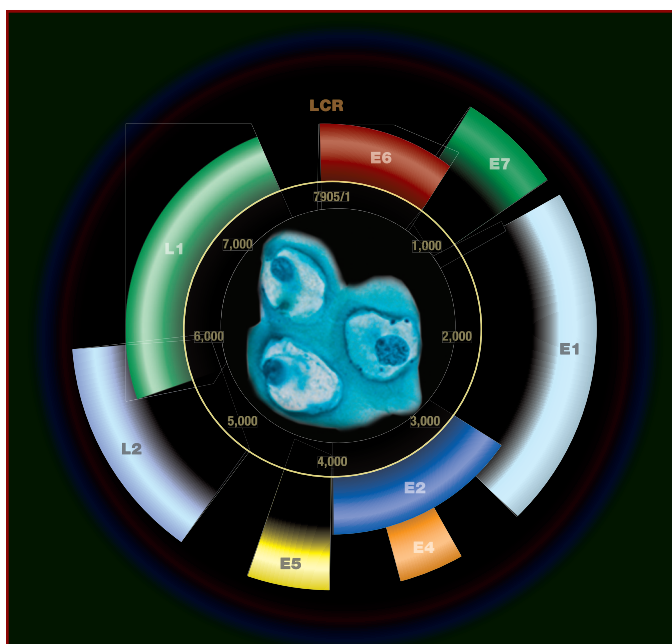
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# Preface

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The last century was the golden age of cytopathology for the prevention of intraepithelial and invasive neoplasia of the uterine cervix. Cytology produced a decrease of more than 80% of cervical mortality in areas where opportunistic or organized screening programs were implemented. Cytopathology was also important in the discovery of the etiologic agent of cervical cancer.

We are now in a new century. The principal etiologic agent, the human papillomavirus, has been identified, and prophylactic vaccines are now available. Newly recognized biomarkers linked to the cell cycle may help to reach more sensitive and specific diagnoses of precancerous and cancerous lesions of the uterine cervix. Additional new approaches such as liquid-based cytology and computer-assisted screening have become available. Sensitive testing technologies for the detection of papillomaviruses are now applicable in nonspecialist laboratories. Longer screening intervals and better management of risk in women may be possible. Therefore screening strategies need to be reevaluated and updated in the context of this new scientific environment.

Cytomorphology will remain an important technique for cervical cancer screening in the next twenty years, while gradually being replaced by molecular approaches in the context of prophylactic HPV vaccines that will help to further decrease the morbidity of cervical intraepithelial lesions and invasive carcinoma. Knowledge centered on cytomorphology alone will not be sufficient for students who wish to enter the field of cytopathology now. Real knowledge of molecular biology is mandatory. We have designed our book to be a reference guide that bridges the gap between cytomorphology, molecular biology, and molecular technologies.

But the real revolution took place back in 1976 when cervical intraepithelial lesions were linked for the first time to human papillomaviruses. The intervening 30 years have witnessed increasing understanding of cervical cancer. Claiming that cytology will remain forever the invincible screening tool for prevention of cervical cancer is untenable in face of that discovery. The Pap smear will inevitably be replaced by the “molecular smear,”

ie, by molecular technologies. Meanwhile cervical cytology remains a crucial part of cervical screening.

We hope that *Modern Uterine Cytology: Moving to the Molecular Smear* will be an important tool of use to everyone wanting to learn more about the interplay of cytology and molecular technologies in diagnosis. *Modern Uterine Cytopathology* will allow all those involved in the study of cervical cancer (cytologists, cytopathologists, pathologists, cytotechnicians, biologists, virologists, and epidemiologists) to get a global theoretical and practical vision of cell morphology, the classification of lesions (The Bethesda System), quality assurance in cervical cytology, the human papillomavirus and other infections, cervical carcinogenesis, the epidemiology and prevention strategies of cervical lesions; the HPV vaccines; and the new technologies for the study of cell morphology (liquid-based cytology and automatic screeners) with emphasis on recent developments in the detection of HPV and cell biomarkers. The principles of specialized techniques are fully described without cumbersome details of procedures. The necessary establishment of a quality assurance program for HPV testing and a safety program in the cytopathology laboratory are also discussed. Appendices were added: One illustrates a series of algorithms for the management of women with cytological abnormalities elaborated by the American Society for Colposcopy and Cervical Pathology (ASCCP); another reports on technical tips and special procedures; the third provides a current marketplace of suppliers. A glossary contains more than 400 definitions.

For over half a century cytology achieved great reductions in mortality due to cancer of the cervix in all countries where screening encompassed a majority of women, whether in an organized screening program (North European countries) or in a random manner (North America). It was practiced by well trained and dedicated cytotechnologists and cytopathologists in a simple way, using only unsophisticated means: Glass slides, coverslips, stains, and microscopes. Every cell on the cell spread was examined by the human eye and a diagnosis was reached based on past experience.

In order to be effective cytology has to be available as nearly as possible to every woman. Even in the best of circumstances, conventional cytology suffered from drawbacks, most importantly a false-negative rate that has been estimated to vary between 5% and 50%. Only the regularly repeated examination can obviate this problem.

The development of liquid-based cytology was intended to remedy the sometimes high rate of inadequate cell samples and to lessen the rate of false-negative results. Efforts to automate cytology, started by George Wied and others, met with very limited success. Wied's TYCAS system was highly proficient in diagnosing individual cases, but could not be applied as a screening tool because it was too slow and too expensive. Cytology became a challenge to the industry because it, with anatomic pathology, remained a non-automated laboratory procedure.

Electronic robots are beginning to screen slides, some of which will no longer be examined by human eyes. Typing for papillomaviruses can be automated, but only indicates infection, and at most an increased risk to develop a lesion. More specific markers for early neoplastic changes within cells are being developed and will probably be automated.

The emergence of vaccines will further limit the scope of cytology. Eventually only unvaccinated populations will be screened, and sooner or later the usefulness of gynecologic cytology will be considerably reduced, marking the end of applicability for the extraordinarily successful pap smear technique.

However we do not have a crystal ball to show us unequivocally where cytology is going. We should consider the sociologic impact of the new technologies. These new strategies will be mostly related to molecular approaches in the context of extensive vaccination programs against HPV, the main cause of cervical cancer. This development raises many questions. Is it possible to estimate

when this evolution will definitively take place? What is going to happen to cytopathologists and cytotechnologists within the next twenty years? How long are we going to continue to teach and train cytopathologists and cytotechnologists? How are women going to react about giving up cervical smear as a screening tool of cervical cancer? Will they embrace a recognition that cervical cancer is an STD issue? How can they be prepared to accept new technologies and screening protocols? Old habits are difficult to break, not only for the public, but also for the medical profession.

This new book is designed to be a practical reference guide to the complex domain of cervical cytopathology taking into account the developments of the last 30 years, but it cannot—and does not try to—answer many of those questions. *Modern Uterine Cytopathology: Moving To the Molecular Smear* instead focuses on the needs of working cytology and allied professionals.

We are most fortunate to have the collaboration of some of the world's premier experts in the field of historical perspectives on cytology and cytology automation; rare lesions of the uterus; epidemiology and prevention of cervical cancers; biomarkers in screening of cervical cancer; human papillomavirus vaccines; and new technologies on liquid-based cytology and computer assisted screeners. The Author/Editors are deeply indebted to all contributors who generously gave their time, enthusiasm, and invaluable help to make this text possible.

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