CYTOPATHOLOGY *of* FEMALE GENITAL TRACT NEOPLASMS

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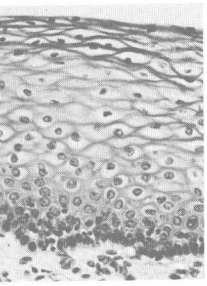

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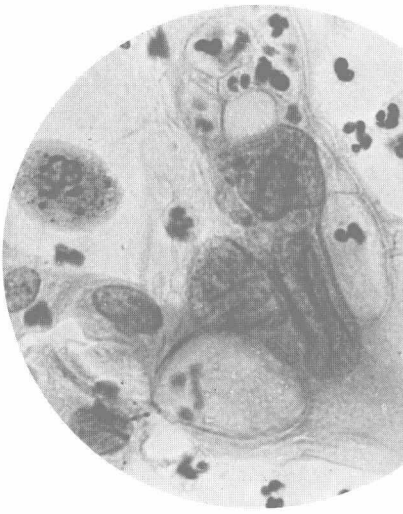

by

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To my ELSIE
who gave inspiration in the past
and strength for the future
D.N.T.

Preface

ALMOST EVERY BOOK serves a useful purpose, whether it be for the satisfaction of the author or the gratification of the reader. In compiling this volume, we have attained the former by recording certain ideas and concepts in the field of cytology that we believe are valuable. The book has ample references but does not pretend to be a compendium of all available information. The field of cytology has become so broad in such a short time that its full context could not be covered in a single or even in several volumes. Investigators have so extended the range of cytologic interpretation that, for example, one is seldom content merely to suggest the probability of the existence of cancer. Indeed, a cancer diagnosis is often so refined that it not only delineates the specific cell type but indicates whether a malignant lesion is in situ or invasive. In addition, the modern cytologist usually understands and applies practically, where feasible, the principles of chromosome analysis, cytochemistry, electron microscopy, labeling studies, microspectrophotometry, computer analysis, mensuration by automated means, Coulter counter and hormonocytologic studies. It is our purpose to supply the reader with practical information directed primarily to the cytologic diagnosis of gynecologic cancer. Comparison of these findings with cytologic observations suggesting or simulating malignant neoplasia is included in chapters dealing primarily with changes due to inflammation, repair, degeneration and radiation. Sections dealing with microspectrophotometric and computer application are intended to bridge the gap between what is now research and what might be tomorrow's reality. Chromosome studies, labeling and electron microscopy are similarly considered. Despite future advances, the cytotechnologist will always play an important role in cytodiagnosis. No matter how advanced, machines do not have a "brain" but reflect primarily the imagination and intelligence of the user. For example, despite the automation of chemical, hematologic, coagulation and other routine clinical laboratory procedures, there is still a serious shortage of medical technologists.

We hope that technology students, graduate technologists, resident physicians, pathologists, gynecologists and other physicians and scien-

tists interested in the cytologic diagnosis of female genital tract neoplasms will find this book valuable, both as a means of improving the precision of their diagnoses and as a reference source.

Acknowledgments

There are many people to whom we are indebted for their varied contributions to this book. Very special thanks go to all the cytotechnologists who through the years have given their time and energies to make this work possible. Mrs. Marjorie Laslie Holt, CT (ASCP), spent many dedicated hours maintaining special files so that we could extract cases of particular interest. Mrs. Mary Jane Fields Henderson, CT (ASCP), formerly our chief technologist, helped create a dynamic cytology section in a new medical school.

The following people participated in various research projects, the data from which is included throughout the book: Mrs. Sara Whitehouse Elam, CT (ASCP); Miss Elaine Kington; Mrs. Sandra Langenback, CT (ASCP); Mrs. Sandra Moore Mills; Earl Nelson, M.D.; Eula Jean Noble, CT (ASCP); William Offutt, M.D.; Charles Stephens, M.D.; and Carl Watson, M.D. The contribution of each was invaluable.

Our clinical colleagues, especially those from the Department of Obstetrics and Gynecology, have faithfully supported and encouraged our cytology program. Dr. John W. Greene, chairman of the Department of Obstetrics and Gynecology, and Dr. John W. Roddick, Jr., have been our closest allies.

Our secretarial staff, Mrs. Ted Herbert, Miss Shirley Calvert and Mrs. Phillip Lykins, have provided us with patient assistance.

We would be remiss if we forgot to express our gratitude to Year Book Medical Publishers for their patience and understanding.

Within the Department of Pathology, all of our colleagues have offered many constructive criticisms. To our special critic, Herbert Braunstein, M.D., we cannot find proper words to express our heartfelt thanks. In no way is he responsible for imperfections that may be detected. Finally, we want to thank W. B. "Pete" Stewart, M.D., our department chairman, for his encouragement and for creating available time to pursue this project.

D.N.T.
L.D.D.

Table of Contents

1. **History** 1

2. **Diagnostic Value of Cervico-Vaginal Cytology** 4

   Incidence of Positive Cytologic Diagnoses in Initial Screening 4

   Incidence of Positive Cytologic Diagnoses in Subsequent Screenings 5

   Effect of Vaginal Cytologic Examination on the Pattern of Invasive Cervical Carcinoma 6

   Prevalence of Dysplasia in Initially Screened and Rescreened Populations 7

   The Role of Cytodiagnosis in Adenocarcinoma of the Cervix and Endometrium 7

   Cytology During Pregnancy 8

   Teenage Cytology 9

3. **Collection Methods** 13

   General Principles 13

   Who Should Take the Cytologic Specimen? 15

   Vaginal Pool, Cervical Scraping, and Endocervical Aspiration Smears—Relative Value in the Detection of Malignancy 16

   The Irrigation Smear 18

   The Tampon Method to Obtain Cytologic Material 19

   Value of Various Techniques to Diagnose Ovarian Malignancy . . . 20

   Various Techniques in the Diagnosis of Miscellaneous Gynecologic Malignancies 20

4. **Fixation and Reporting of the Cytosmear** 23

   Methods of Fixation 23

   Methods of Reporting 25

5. **The Cell.** *By* JEPTHA R. HOSTETLER, PH.D., *Department of Anatomy, Ohio State University* 30

Cellular Constituents 31

6. Other Investigative Techniques Used in the Study of the Cell 42

Quantitative Cytochemical Analysis of Premalignant and Malignant Uterine Disorders 42

Cytogenetic Studies of Premalignant and Malignant Uterine Disorders 43

Fluorescence Microscopy 46

Phase and Interference Microscopy 47

Electron Microscopy 48

Vaginal Fluid Enzyme Analysis 48

7. Embryogenesis of the Female Reproductive System.
By HAROLD H. TRAURIG, PH.D., *Associate Professor of Anatomy, University of Kentucky Medical School* 51

Early Development 51

Specific Development of the Uterus, Cervix and Vagina 55

8. The Cervix Uteri: Anatomic and Cytologic Considerations 58

Gross Description 58

Microscopic Description 59

9. Squamous Dysplasia 73

Dysplasia Not Associated With Pregnancy or Postirradiation 77

Dysplasia Associated With Pregnancy 81

10. The Cytopathology of Squamous Carcinoma In Situ of the Cervix Uteri 86

The Concept 86

Characteristics of Cells Seen in Carcinoma In Situ 87

Specific Cell Types Seen in Carcinoma In Situ 94

Cytologic Characteristics of Associated Non-neoplastic Elements . . . 103

Cellular Patterns in Carcinoma In Situ of the Cervix Uteri 106

Cytologic Findings in Developmental Carcinoma In Situ of the Cervix 110

Correlated Cytohistologic Patterns Observed in Carcinoma In Situ of the Cervix 111

Varieties of Histologic Patterns Constituting In Situ Cancer (With Cytologic Correlation) 112

Practical Diagnostic Features for the Cytologic Diagnosis of Carcinoma In Situ of the Cervix 116

11. The Cytopathology of Invasive Squamous Carcinoma of the Cervix . . . 118

Introduction and Definition 118
Clinical Features 119
Cytologic Characteristics of Associated Non-neoplastic Elements . . . 119
Number of Malignant Cells and the Cancer Trend 120
The Malignant Cells of Invasive Squamous Cancer 121
Practical Diagnostic Features for the Cytologic Diagnosis of Invasive Squamous Cervical Cancer 128

12. The Cytopathology of Microinvasive Squamous Carcinoma of the Cervix 130

Introduction and Definition 130
Clinical Features 132
Cytologic Characteristics of Associated Non-neoplastic Elements . . . 133
Cellular Patterns Seen in Microinvasive Cancer of the Cervix—Percentage Distribution of Malignant Cell Types 134
General Spectrum of Neoplastic and Non-neoplastic Cellular Constituents from Smears of Microinvasive Cancer 140
Correlated Cytohistologic Patterns Observed in Microinvasive Cancer of the Cervix 140
Vascular Involvement 141
Practical Diagnostic Features for the Cytologic Diagnosis of Microinvasive Carcinoma of the Cervix 142

13. Cytopathology of Cervical Adenocarcinoma 144

General Clinical and Pathologic Characteristics 144
In Situ and Microinvasive Endocervical Adenocarcinoma—General Concepts 145
Non-neoplastic Cellular Characteristics of Cervical Adenocarcinoma 147
Neoplastic Cellular Characteristics of Cervical Adenocarcinoma . . . 148
Cellular Characteristics of Low-Grade Cervical Adenocarcinoma . . . 151
Cellular Characteristics of High-Grade (Undifferentiated) Cervical Adenocarcinoma 154
Cellular Patterns of Adenoacanthoma 156
Cellular Patterns of Mesonephric Adenocarcinoma (Gartner Duct Origin) 158

14. Uterine Corpus: Anatomic and Cytologic Considerations 161

Gross Description 161
Microscopic Considerations 161
Cytologic Considerations 166

15. The Cytopathology of Endometrial Adenocarcinoma **171**
Introduction 171
Clinical Correlates 171
Gross Morphologic Aspects of Endometrial Cancer 172
Histologic Features of Adenocarcinoma of the Corpus Uteri 172
Cytologic Features of Adenocarcinoma of the Corpus Uteri 175
Characteristics of Malignant Cells Seen in Endometrial Adenocarcinoma 177
Differential Cytodiagnosis of Endometrial Adenocarcinoma 180

16. The Cytopathology of Nonuterine Metastatic Neoplasms **189**
Nonuterine Carcinomas 189
Other Neoplasms 191

17. The Cytopathology of Sarcomas of the Female Genital Tract **193**
Leiomyosarcoma 193
Endometrial Stromal Sarcoma 195
Mixed Mesodermal Tumor 195
Sarcoma Botryoides 196
Carcinosarcoma of the Uterus 198

18. The Cytopathology of Primary Vaginal and Vulvar Neoplasms **202**
Primary Vaginal Neoplasms 202
Primary Vulvar Neoplasms 204

19. The Cytopathology of Recurrent Carcinoma **206**
Cytopathology of Recurrent Squamous Cancer Following Radiation Therapy 206
Cytopathology of Vaginal Squamous Cancer Following Surgical Therapy for Carcinoma In Situ of the Cervix 215

20. The Cytopathology of Certain Benign Findings That May Be Confused with Malignancy **221**
Cells With Multinucleation 221
Cells of Elongated Appearance 227
Cells of Large Size 232
Cells With Prominent Nucleoli 236
Notes on Hyperchromasia Associated With Blood and Cytology Following Cauterization 238

Index **241**

CHAPTER 1

History

THE USE OF CYTOLOGIC study to diagnose malignancy dates back to the 19th century. Most of the earlier workers concentrated on microscopic examination of sputum. In 1847, Pouchet[16] examined vaginal secretions while studying the problem of whether spontaneous ovulation occurs in animals and man. He observed epithelial plaques in the vagina during menstruation and also noted gross changes in vaginal secretions. It is not certain whether actual microscopic examination was done on the secretions as he did not detail his methodology. As late as 1869,[11] the value of vaginal cytology in the diagnosis of gynecologic malignancy was denied. The major interest in gynecologic cellular examination continued to be the study of hormonal changes, earlier in the guinea pig and rat, and later in humans.[10] Papanicolaou[15] discussed the potential value of vaginal smears as an aid in the diagnosis of uterine cancer with Dr. James Ewing in 1925. Because of limitations in both cytologic and histopathologic knowledge, he did not realize fully that asymptomatic cervical cancer could be diagnosed by such means. In fact, Broders[2] did not coin the term carcinoma in situ until 1932, although the condition had been described years earlier. On April 11, 1928, Dr. Aurel A. Babes[1] published a monumental communication in *La Presse Médicale* entitled, "Diagnosis of Cancer of the Uterine Cervix by Smears." His material was collected by a platinum loop, fixed in methyl alcohol and stained with the Giemsa method. He detailed and illustrated characteristics of malignant cells, indicated the existence of carcinoma in situ and stated that the diagnosis of cervical cancer could be made at an early stage by the smear technique. His work had been first presented to the Society of Gynecology of Bucharest on January 23, 1927, and again on April 10, 1927. Almost simultaneously, Papanicolaou,[8] at the Third Race Betterment Conference held January 2–6, 1928, at Battle Creek, Michigan, reported independently the occurrence of malignant cells as seen by cytology. His paper entitled "New Cancer Diagnosis" described his technique, which utilized a small pipette to remove vaginal fluid, and indicated cytologic characteristics of malig-

nant cells. His foresight was reflected by the following quote:

"We have a better understanding of the situation in a cancer case, and we may have some help in analyzing the cancer problem in the future. In fact, I think this work will be carried a little further, and that analogous methods may be applied in the recognition of cancers in other organs. I think that some such method can be, and will be, developed in the future."

Thirteen years later, in collaboration with H. F. Traut, he published "Diagnostic Value of Vaginal Smears in Carcinoma of the Uterus."[13] They not only described cellular changes in invasive cervical carcinoma and endometrial adenocarcinoma but indicated the possibility of a positive cytodiagnosis in early stages of those diseases. A further contribution in 1943[14] recorded two instances of early carcinoma of the cervix and endometrium detected initially by cytologic means. That same year they published a 48-page monograph, entitled "Diagnosis of Uterine Cancer by the Vaginal Smear," that included twelve color plates.[15] The readers will be interested in an excellent biography of the late Dr. Papanicolaou by Leopold G. Koss.[7]

Through support by the American Cancer Society and the United States Public Health Service, expansion and corroboration of the value of cytology in the early diagnosis of uterine malignancy, primarily cervical, was established. The mass survey projects started in 1952 eventually revealed the high incidence of unsuspected cervical cancer, further establishing a role of cytology in medicine.[5, 6] In the course of such studies, up to 83% of white women and 69% of Negro women from a select area had a vaginal cytologic examination.[6] For the most part, vaginal cytologic diagnosis still was in embryonic stages in the early 1950's. This was the natural result of a technique requiring time and experience to master, both for the technologist and cytopathologist, as well as a necessary period in which the practicing physician gained understanding of and confidence in the method. Schools of cytotechnology were established and registry examinations were first administered in 1957 by the American Society of Clinical Pathologists. Cytology became part of the American Board of Pathology examination in 1962. Many workers promoted cytology through a plethora of articles in the 1950's and 1960's. *Acta Cytologica*, a journal devoted to cytology, published its first issue in 1956. The sum total of the above efforts has saved tens of thousands of lives annually. As an important bonus, cytology has led to the most intense study to date on the genesis of early cancer.

Despite the now unquestioned merit of the vaginal smear in the early diagnosis of cervical cancer, it is discouraging that only about 15% of all women over the age of 20 in the United States had a Papanicolaou smear examined in 1963.[4, 17] Thus, there remains a vast reservoir of women with cervical cancer who may die because a simple, inexpen-

sive technique has not been applied. We feel that the smear examination is an integral part of an adequate physical examination. Indeed, it has been suggested that, in our insurance-conscious population, a cytologic examination is the cheapest insurance available.[3]

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CHAPTER 2

Diagnostic Value of Cervicovaginal Cytology

THE USE OF VAGINAL cytology is predicated on the premise that lesions diagnosed by this method actually are early stages in the genesis of malignancy. The logical result of their ablation would be to prevent progression to later stages of cervical or endometrial cancer. More specifically, there is much corroborative evidence to indicate that carcinoma in situ of the cervix, a term coined by Broders in 1932[3, 26] but described earlier under a variety of names, is a precursor of invasive cancer.[26, 29] The evidence has been of a statistical or morphologic nature; the latter will be discussed in a subsequent chapter. Because of the recognized importance of diagnosing cervical cancer early, the present discussion stresses the value of vaginal cytology. This will be approached from the viewpoint of:

1. Incidence of positive cytologic diagnoses in initial screening.
2. Incidence of positive cytologic diagnoses in subsequent screenings.
3. Effect of the above on the incidence of invasive cervical cancer.
4. Prevalence of dysplasia in initially and rescreened populations.
5. The role of cytodiagnosis in adenocarcinoma of the cervix and endometrium.
6. Cytology during pregnancy.
7. Teenage cytology.

Since the pick-up rate for cervical cancer is dependent on such factors as socioeconomic status, race, age, parity and religion, the statistical data of any series must be interpreted with care, acknowledging potential peculiarities or circumstances surrounding a particular locale.

Incidence of Positive Cytologic Diagnoses in Initial Screening

Large collected series are heavily weighted by cases from community surveys. They give a good cross-section of a particular population, being influenced primarily by the population distribution related to socioeco-

nomic status. Other series may be quite selective. For example, Papanicolaou's[39] first series of 3,014 women resulted in the diagnosis of 7 cases of in situ carcinoma (0.23%) and of 120 cases of invasive carcinoma (4%). The high per cent of invasive lesions was the result of a select group of women attending that cancer diagnostic clinic. By contrast, analysis of initial screenings, gleaned mainly from community or area surveys,[9, 18, 31, 36, 51, 55, 58] reveals that slightly over 1% will be found to have cervical carcinoma, of which the invasive lesions outnumber in situ carcinomas (0.577% vs. 0.487%). To emphasize the strong modifying factor of the socioeconomic status of those examined, Ludin, *et al.*,[35] observed that the annual incidence rates for cervical cancer were 54.3 per 100,000 whites. Others[50] have noted surprisingly similar results. Caucasians living in a low socioeconomic area also have a similarly high incidence of cervical cancer. This has been our experience in studying cervical cancer among women living in severely depressed economic areas of Appalachia. For example, our ratio of cervical carcinoma to endometrial carcinoma is about 7.5:1. Because of neglect prevalent among those of low socioeconomic levels, cervical neoplasia in whites, when compared with Negroes, ordinarily will be found in earlier stages of genesis when discovered initially.[35, 50] In contrast, a large series from a private clinic revealed that 90% of cervical squamous carcinomas were in situ.[15] In addition, the factors of early marriage (and coitus) and multiparity, usually paralleling a low socioeconomic status, will be found associated with those women having more cervical cancer than a control population.[1, 8, 11, 12, 20, 21, 47, 53]

Incidence of Positive Cytologic Diagnoses in Subsequent Screenings

Marshall[36] noted in the course of an active screening program over a 6-year period (1958–1963) that the total number of cases of cervical carcinoma confirmed by biopsy dropped from 0.71% to 0.15%. The incidence drop was attributed to a progressive screening-out process in which approximately 60% of the women were screened at least twice. The decline in the incidence of invasive cervical carcinoma was striking, opposed to a fairly stable rate for those of in situ nature. Sprunt and Berton[50] found 2.8 cervical carcinomas per 1,000 white women among 73,422 screened for the first time, and a corresponding 5.6 per 1,000 nonwhite women among 34,785 screened. Of the total of 108,207 women, 0.38% had invasive cervical cancer and 0.38% had carcinoma in situ. The second screening resulted in 0.2 cervical cancers per 1,000 white women among 20,783 screened, and 0.6 per 1,000 nonwhite women among 11,955 screenings. Of the total of 32,738 women, 0.25% had invasive cervical cancer and 0.04% had carcinoma in situ. They

believed that the incidence drop with a rescreening is the result of the natural history of the cancer. Christopherson, *et al.*[9] observed an initial incidence of 2.8 per 1,000 women with invasive cervical carcinoma and 3.7 women per 1,000 with carcinoma in situ among 66,043 screened. By the third annual screening of 9,518 women, only 0.11 per 1,000 had invasive cervical cancer and 0.53 per 1,000 had carcinoma in situ. They believed "that repeated examinations at yearly intervals would virtually eliminate cervical cancer as a major cause of death in our female population." Others[15] recording similar findings feel that repeat annual smears "weed out" cases of invasive cervical carcinoma from the test population. Bryans, *et al.*[4] saw an almost tenfold increase in invasive cervical carcinoma among those not previously screened when compared with those who had annual smear studies.

Effect of Vaginal Cytologic Examination on the Pattern of Invasive Cervical Carcinoma

The above studies have been unanimous with respect to the efficacy of cytologic screening to diagnose cervical carcinoma. In a population that has been screened adequately, and especially rescreened, as indicated, the subsequent pick-up rate of cervical carcinoma has been reduced, often dramatically. That is true mainly of invasive carcinoma, but also to a lesser degree for carcinoma in situ. Regarding the occurrence of invasive cervical carcinoma in a screened population, certain important facts emerge.[2, 4, 22, 52] The result of an active screening program is a progressive decrease in the number of women with invasive cervical cancers. The invasive cancers that have been cytologically identified in these circumstances generally are found in earlier stages.[31, 35, 52] For example, Stevenson, *et al*,[52] noted that the incidence of stage I and II carcinomas increased from 56% to 75% over a 12-year period, whereas stage III and IV lesions decreased from 44% to 25% during that same period.

However, the sum total of the value of screening programs should be reflected in mortality statistics of a screened community. Christopherson[6] noted a gradual decline in reported mortality statistics from cervical cancer in Jefferson County, Kentucky. The drop was not precipitous, but there are some factors possibly accounting for that finding. First, a few cases may have been women who were relatively long survivors of a disease diagnosed in the early days of cytologic experience. Second, and most likely of greater importance, are the women who had not been screened in the population. Many of them may have been indigent, as that group is often the most difficult to get to co-operate and is the one most likely to get cervical carcinoma. Added factors

may be false negative diagnoses in the face of invasive carcinoma, and a transient population.

Prevalence of Dysplasia in Initially Screened and Rescreened Populations

The prevalence of dysplasia is variable, having been reported from 0.13% to 3.8% of selected series. Reagan[40] believes that it occurs in 0.8% of all women, although he found 6.2% of a group of pregnant patients from a charity clinic to have that abnormality.[43] Among 2,417 pregnant women seen at our institution, 26 (1.1%) had dysplasia. Despite that finding, the lesion does seem to be distinctly more frequent among pregnant females. The variable incidences are undoubtedly reflective of the population screened, for, if a series contains a large number of pregnant women, the incidence may be overwhelmingly high.[43] In common with in situ carcinoma, dysplasia has a high incidence in the lower socioeconomic groups, being at least twice that of a routinely screened population in Christopherson's studies.[7,9] In contrast, if a predominately older group of women is screened, there will be a lower incidence of dysplasia, a reflection of the mean age of 34 years at detection of that lesion.[41]

Of populations rescreened, dysplasia has been discovered with equal or slightly decreased frequency as the original screening. In contrast, squamous cell epithelioma in situ has demonstrated a more marked decrease in incidence.[9,18] What is the significance of such a finding? Possibly, it is a reflection of ablation of a precursor to in situ cancer and the subsequent occurrence of a constant number of new cases with dysplasia, most remaining static but a few progressing to cancer.

The Role of Cytodiagnosis in Adenocarcinoma of the Cervix and Endometrium

It is axiomatic in cytology that the accuracy and pick-up rate, in general, is inversely proportional to the distance that abnormal cells have to travel before collection. For example, cytodetection of pulmonary neoplasms is considerably poorer than is that of the cervix, as the latter site lends ready anatomic availability. When contrasting cytodetection of cervical and endometrial adenocarcinoma, it is readily apparent that the former area yields a much higher incidence of symptomatic and asymptomatic lesions. In fact, Koss and Durfee identified only one case of endometrial carcinoma in screening 5,000 asymptomatic patients.[34] There are several reasons why cervical and vaginal smears fail to reveal endometrial cancer.[23] The endometrial cancer cells travel a modest distance and may degenerate; cervical stenosis is not uncommon in the