THE CYTOLOGIC DIAGNOSIS OF CANCER

GRAHAM

THE CYTOLOGIC DIAGNOSIS OF CANCER

RUTH M. GRAHAM

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To

GEORGE N. PAPANICOLAOU, M.D., Ph.D.

whose outstanding contributions in the field of exfoliative cytology have opened a new and productive approach to the early diagnosis of malignant disease

Preface to the Second Edition

WHEN THE FIRST EDITION was published, the cytologic diagnosis of cancer was a controversial subject. Many doubted that individual cancer cells could be recognized accurately. Today, the method is widely accepted, both here and abroad.

The purpose of this edition is exactly the same as the first. It is intended as a guide in cellular interpretation. The typical cells, either normal or malignant, are shown in a colored plate. Variations from the typical and additional examples follow the colored plate. At the end of the chapters on malignant cells, the accuracy of the laboratory in the diagnosis of that particular lesion is given. It appeared pertinent to state just how accurate the cytologic diagnosis is for each site. Also, the reader is entitled to know what results are obtained using the cellular criteria described.

The chapters on histiocytes in vaginal secretion and on adenocarcinoma of the uterine corpus have been rewritten. In teaching, it became evident that one of the most difficult cells for the student to identify accurately was the histiocyte, and that a more detailed description of its morphology was needed. The chapter on carcinoma of the uterine corpus was rewritten because the diagnosis of this carcinoma is not particularly good in most laboratories, and we are convinced that recognition of the single adenocarcinoma cell will substantially improve the accuracy. A new chapter on postradiation smears, both negative and positive, has been added. This is one of the most difficult interpretations in cytologic material, and obviously needed greater discussion.

Four subjects not discussed in the previous edition are treated in separate chapters: the cytologic picture of dysplasia of the uterine cervix, the cytology of esophageal cancer, the cytology of needle aspirations of solid masses, and the cellular aberrations present in pernicious anemia.

Cytologic prognosis of cancer of the cervix patients treated with radiation has only been lightly touched—not because we are less impressed with its value, but because an exhaustive treatment of prognosis did not appear to be pertinent to a book concerned primarily with diagnosis.

Three new chapters have been included: on the confirmation of unsuspected positive reports, on the reporting of smears, and finally and we hope, most importantly, on the identification of cells. It is suggested that the beginner in cytology refer to this chapter early in his study of the subject.

No discussion of cancer cells in the blood has been included. We do not regard this aspect of cytology as a diagnostic tool, but rather as an interesting aspect of research in cytology.

We have included the most common types of cytologic specimens. We have received specimens of breast secretion, colonic washings, scrapings from the oral cavity, and so forth, for cytologic examination; but we have not found that their application is routine. This impression is borne out by the bibliography, where references to these types of specimens are few.

Recently there has been interest in the fluorescent staining of cytologic specimens by acridine orange. We have included references to this method in the bibliography. We have not discussed this method in the text since we have not had any personal experience with it. We have used fluorescent microscopy in other techniques in research. Since we feel that the only accurate identification of a malignant cell is on distinct nuclear abnormalities, we felt the method has little to recommend it in replacing the standard Papanicolaou technique. It is, however, extremely useful for the identification of parasites and microorganisms.

The bibliography is extensive but not complete. It was chosen as fairly representative of the voluminous literature in the field of cytology. The number of publications in the field is startling. When I started in this field in 1942, there was one publication available, that of Papanicolaou and Traut published in the *American Journal of Obstetrics and Gynecology* in 1941.

I have done the photography for this edition. The photographs were taken on Kodak-Panatomic X film in a Zeiss Photomicroscope with 40× ocular and 10× objective and printed on F-2 paper. Miss Ildiko Sarkany has done the new drawings, which were occasionally retouched by the author. All photographs of exfoliated cells are at the *same* magnification unless otherwise indicated.

In the first edition, we included a list of the pathologic diagnoses for each figure of cancer cells. This was because the method was then controversial and we took care to point out that each case had been confirmed histologically. In this edition, it is probably sufficient to state that the malignant cells in every new photograph have been confirmed by histologic examination.

Many have contributed their help to this second edition. I would like to thank Dr. James W. Reagan for sending me examples of dysplasia from which the photograph illustrating this entity was taken. Dr. Alfred Glucksmann has kindly classified the invasive cancers of the cervix, thus allowing for the discussion of exfoliated cell types according to tumor type. Dr. Cyrus Rubin allowed me to photograph a slide of gastric secretion that contained parietal cells. I am grateful to Dr. Goryun Nigogosyan for the loan of the slides illustrating metaplasia in the lung and cancer of the esophagus.

Both my past and present laboratory staff have been of real help. Two of my former technicians, Mrs. Jean Johnson and Mrs. Hilda Rosbash, have made useful suggestions for improving this edition. My head technician, Miss June Stevens, has assisted in correcting the manuscript. Dr. Mercedes Sinats and Mrs. Josephine Chaffin have helped with the many technical details.

I am grateful to my secretary, Mrs. Dolores Williams, for her efficiency and continued cheerfulness during the preparation of the manuscript.

I would like to express my appreciation to the W. B. Saunders Company for their considerable patience during the many delays in the preparation of this edition.

Color plates for the first edition of this work were made possible by support from the American Cancer Society.

Without the constant support and encouragement of Dr. John Graham, this edition would have never become a reality.

Finally, I would like to thank my many students, who taught me much more than I taught them.

RUTH M. GRAHAM

Contents

Benign Cells of the Squamous Epithelium of Cervix and Vagina

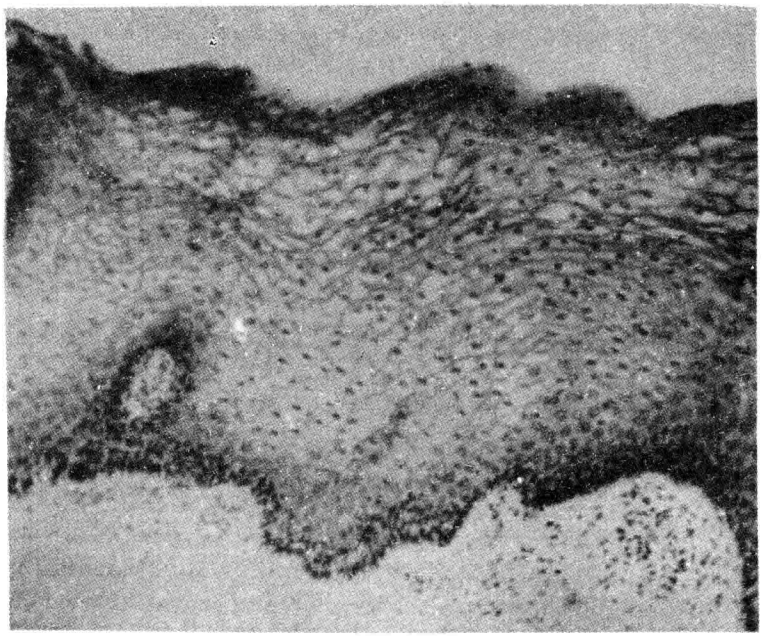


FIGURE 1

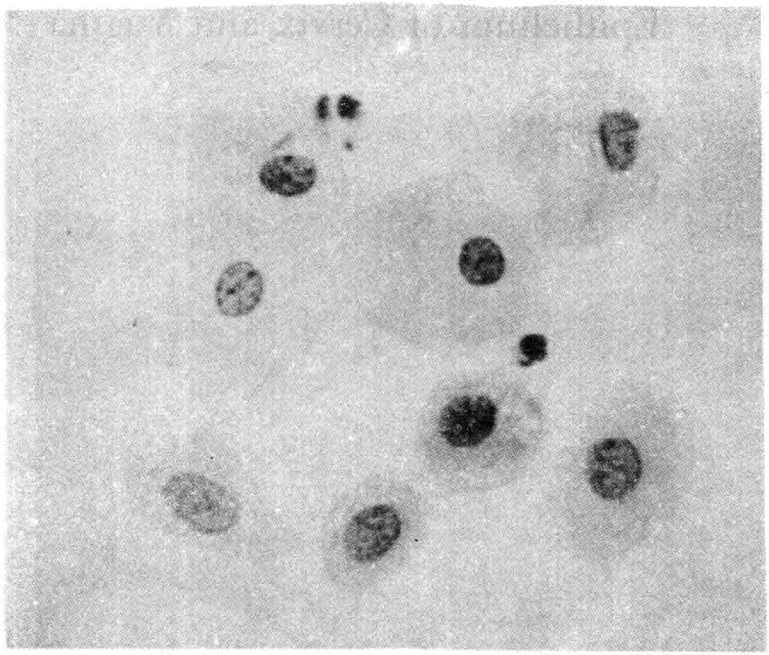
Histologic Section: Cervical Squamous Epithelium

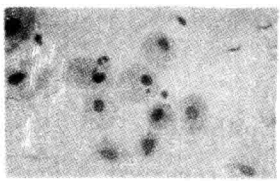
The squamous epithelium of the female genital tract is composed of four layers. Beginning at the basement membrane they are: germinal, basal or transitional, intermediate, and superficial. (See Figure 1.)

The maturation of cells from the germinal layer to the superficial layer is characterized by an increase in the amount of cytoplasm and a concomitant decrease in nuclear size. The *germinal cell* has a large nucleus and occasionally a scant cytoplasmic rim, but more often appears devoid of cytoplasm. As the germinal cell grows and pushes up to the adjacent layer, it acquires a definite though narrow rim of cytoplasm and may be identified as an *inner layer basal cell.* As maturation progresses, the cytoplasmic constituent of the cell continues to increase, and at this cellular level the nuclear size decreases. The *outer layer basal cell* has a cytoplasmic rim that is greater than the maximum diameter of the nucleus, and is oval or round.

At the level of the *intermediate cell,* the cells are no longer oval or round, but have definite corners. Again, the maturation progress is reflected in an increase in cytoplasm and some shrinkage in nuclear size. Complete shrinkage of the nuclear material to a contracted amorphous mass is evident in the *superficial cell.*

Description of Basal Epithelial Cells





Low Power: Discrete, round or oval squamous epithelial cells with centrally placed nuclei.

High Power:

A. CHARACTERISTICS OF NUCLEUS: *1.* The chromatin is finely granular. The individual particles are small. There may be two or three larger clumps of chromatin. The background is smoothly granular. *2.* The position of the nucleus is usually central. (See cells 6, 7 and 8.) If the nucleus is somewhat off center, as in cell 2, it is still surrounded by adequate cytoplasm on all sides. *3.* Variation in size is slight. Cells 5, 6 and 7 are inner layer basal cells and their nuclei are quite uniform. Cells 1 and 2 are more mature and their nuclei have contracted slightly.

B. CHARACTERISTICS OF CYTOPLASM: *1.* Definite cellular borders. *2.* Amount of cytoplasm: in outer layer basal cells, the distance from cellular wall to nuclear wall is *greater* than the maximum diameter of the nucleus. (See cells 1, 2, 3 and 8.) In inner layer basal cells, the distance from cellular wall to nuclear wall is *less* than the maximum diameter of the nucleus. (See cells 5, 6 and 7.) *3.* Density: greatest in inner layer basal, less in outer layer basal, and least in intermediate cell. Compare cells 7, 2 and 4. Staining reaction: cyanophilic in well preserved cells.

C. GENERAL CHARACTERISTICS: Round or oval cells containing a centrally placed vesicular nucleus. Amount and density of cytoplasm dependent on maturity of the cell. Inner layer basal cell: less cytoplasm, less transparency. Outer layer basal cell: more cytoplasm, more transparency.

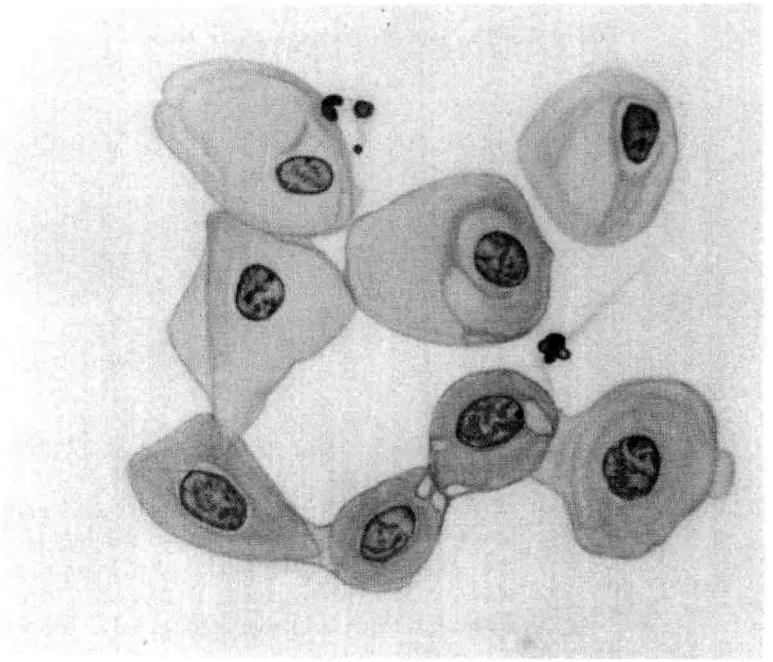
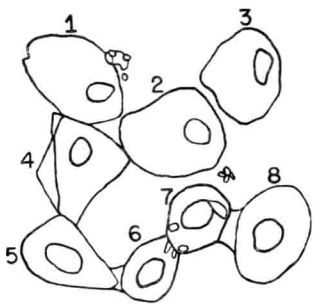


PLATE 1



Key to Basal Cell Plate

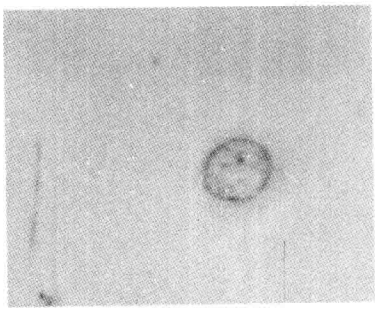
1. Outer layer basal cell: vesicular nucleus, thin transparent cytoplasm.
2. Outer layer basal cell: finely granular nucleus, unevenness in density of cytoplasm.
3. Outer layer basal cell: degenerate, partially pyknotic nucleus, perinuclear vacuole.
4. Intermediate cell: square shape and folding of transparent cytoplasm.
5. Inner layer basal cell: oval nucleus, cellular form slightly elongated.

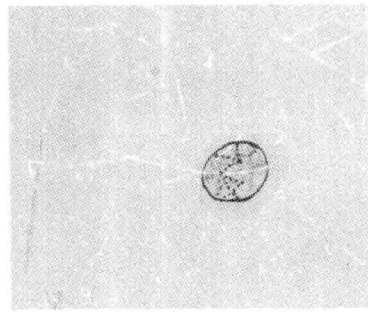
6 and 7. Inner layer basal cells: dense cytoplasm showing beginning of vacuolization, round vesicular nuclei.

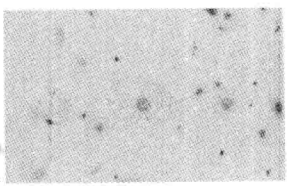
8. Outer layer basal cell: central nucleus containing finely divided chromatin.

FIGURE 2

Basal Cells: Narrow Cytoplasmic Rim



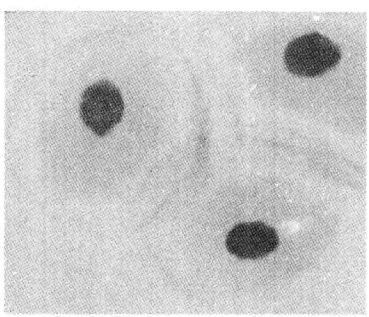


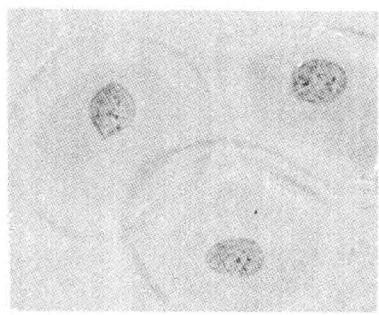


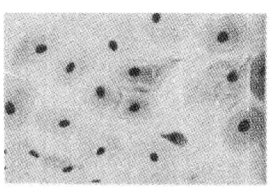
Low Power: Field of inner and outer layer basal cells. One large nucleus.
High Power: Inner layer basal cells may have the amount of cytoplasm illustrated in Plate 1, or they may have a narrow rim of cytoplasm as illustrated here. The nucleus has fine chromatin granules and threads distributed evenly. Nuclear and cytoplasmic borders are definite. Cell is round.

FIGURE 3

Basal Cells: Cytoplasmic Changes—Thick Cell Walls



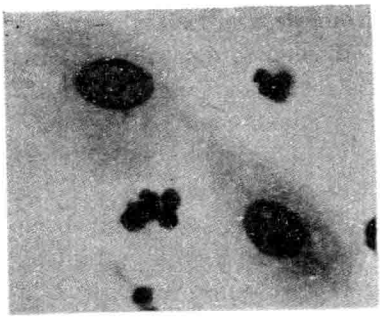


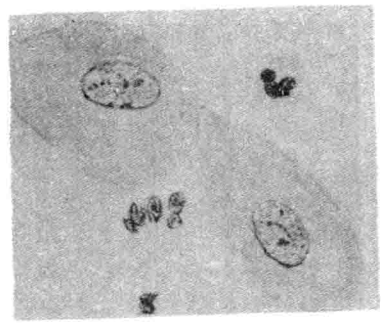


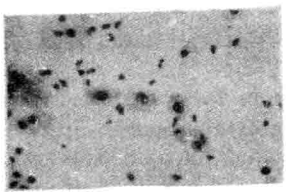
Low Power: Group of outer layer basal cells with thick cellular borders.
High Power: These cells are distinctive in that their cellular borders are much thicker than usual. The border stains a much deeper blue than the remaining cytoplasm. The central deposits around the nuclei are irregular and take a deep yellow stain. The significance of this change is not known.

FIGURE 4

Basal Cells: Cytoplasmic Changes—Fine Vacuolization





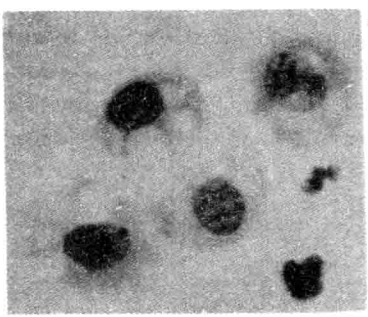


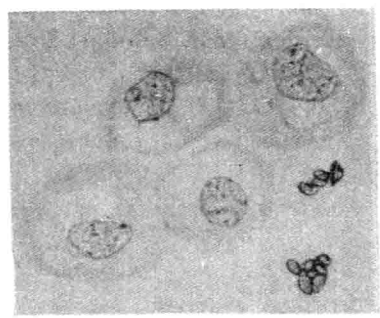
Low Power: Four outer layer basal cells in rather clean field of intermediate and superficial cells.

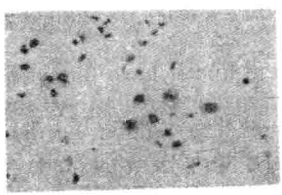
High Power: Two outer layer basal cells with fine vacuoles distributed throughout their cytoplasm. This is not a degenerative change, but probably indicates increased activity. The nuclei of these cells are well preserved and have a finely granular appearance. The cell border is sharp.

FIGURE 5

Basal Cells: Cytoplasmic Changes—Prominent Vacuolization





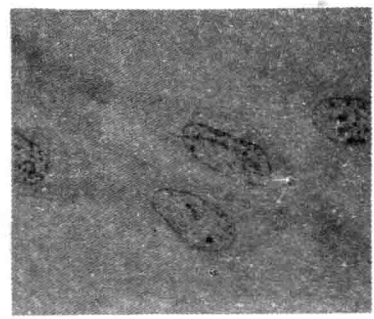


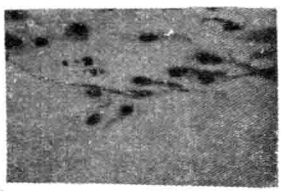
Low Power: Four inner layer basal cells with extensive vacuolization of cytoplasm.

High Power: The vacuoles of these cells vary from extremely fine spaces to the large vacuoles overlying the nucleus in the cells at the upper right. The nuclei are active, having larger clumps of chromatin than is usually seen. These cells and those above are examples of basal cells exhibiting the *sensitization response.*

FIGURE 6

Basal Cells: Cytoplasmic Changes—Change in Shape

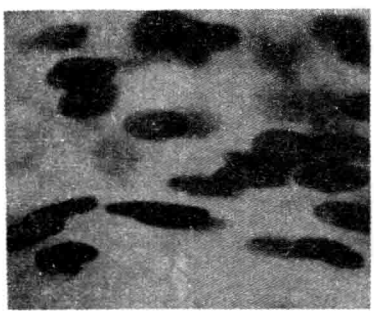


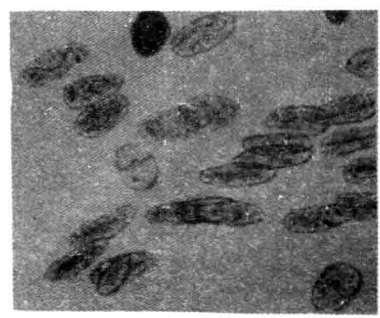


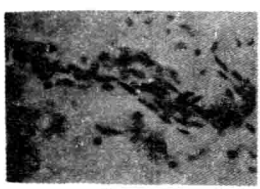
Low Power: Group of inner layer basal cells, all but one having elongated form.
High Power: The two inner layer basal cells are bizarre in shape. The long cytoplasmic projections of the upper cell stretch beyond the field. The lower cell is triangular. These cells are identified as inner layer basals because of the small amount of cytoplasm surrounding the finely granular nucleus.

FIGURE 7

Basal Cells: Cytoplasmic Change—Elongation



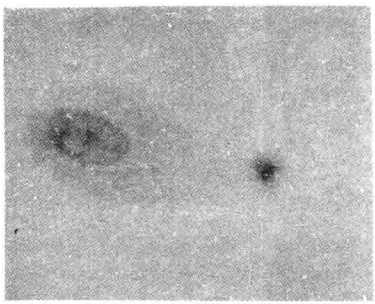


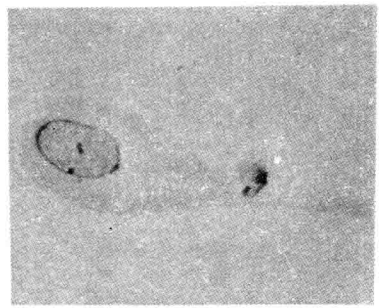


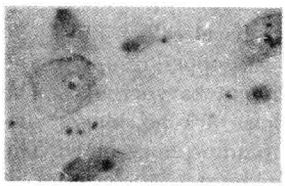
Low Power: Long, snake-like cluster of elongated nuclei.
High Power: The elongated nuclei have finely divided chromatin that is even in distribution and identifies the cells as benign. The cellular borders are not distinct, but the cytoplasm stretches out on either side of the nucleus. These are immature cells and probably originated from near the basement membrane in an atrophic epithelium.

FIGURE 8

Basal Cells: Cytoplasmic Changes—Aberrant Shape



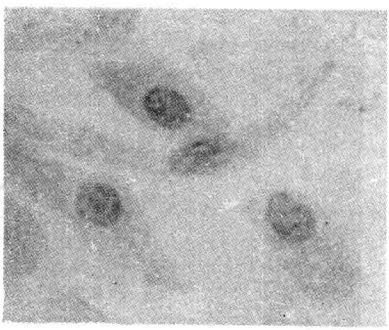


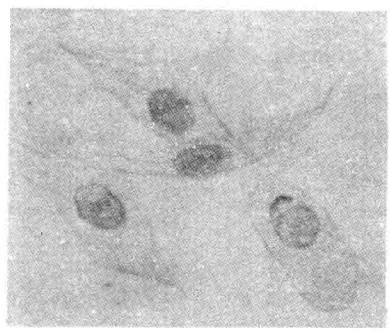


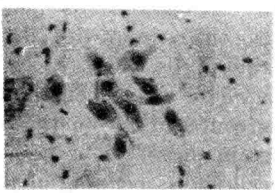
Low Power: Inner layer basal cell with extremely long tail of cytoplasm.
High Power: The nucleus of this cell is characteristic of a benign cell. The chromatin particles are of equal size and are distributed evenly throughout the nucleus. The only abnormality exhibited by this cell is the long cytoplasmic projection. It is identified as an inner layer basal because of the cytoplasmic-nuclear ratio. (See Plate 1.)

FIGURE 9

Basal Cells: Cytoplasmic Changes—Aberrant Shapes







Low Power: Group of epithelial cells with abnormally shaped cytoplasm.
High Power: The nuclei are round and of the same structure as the basal nuclei shown in Plate 1. These are called aberrant basal cells because of the abnormally elongated shape of their cytoplasm, which usually stains eosinophilic. Three of the four cells show tail projections coming from the cytoplasm.