RUTH M. GRAHAM

THIRD EDITION

THE CYTOLOGIC DIAGNOSIS OF CANCER

1972

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The Heyman Laboratory
Buffalo, N.Y.

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Preface to the Third Edition

It is gratifying to those of us who were pioneers in the cytologic field to see the present widespread adoption of the cytologic method in the early diagnosis of cancer. It is especially gratifying to know that the percentage of early lesions is increasing and the mortality rate declining in cancer of the uterine cervix and to believe that the cytologic diagnosis of cancer has contributed significantly to this effect.

The purpose of this edition is the same as in the previous two editions. It is intended as a guide to cellular interpretation. The typical cells, either normal or malignant, are shown in a color plate. Variations from the typical and additional examples follow the color plate. At the end of a chapter 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 by using the cellular criteria described.

It is suggested that the beginner in cytology refer to the chapter on identification of cells early in his study of the subject.

All illustrations are at the same magnification unless otherwise indicated. The microscopic fields were photographed at 450 × magnification, and enlarged to a constant size.

The chapter on cancer cells from the ovary as seen in vaginal secretion has been rewritten. Five new chapters on the normal and malignant cells seen in cul-de-sac aspirations have been added. During the period of time which elapsed between the second and third editions, it became increasingly evident that carcinoma of the ovary was becoming the most serious problem in gynecologic cancer. More women die in New York State every year from cancer of the ovary than from cancer of the cervix. These new chapters represent our attempt to apply the cytologic method to the early diagnosis of cancer of the ovary.

With the widespread use of oral contraceptives, it has become apparent that some of the women on these medications have cellular abnormalities. A discussion of these changes is found in a new chapter.

New data have been added on cytologic screening in the Buffalo area. I am grateful to the many clinicians who have sent material to the Heyman Laboratory, and especially grateful to them for taking the time to fill out the laboratory forms so completely. Without their constant cooperation, the data presented on prevalence rates in patients on contraceptive medication, in pregnancy, and in different age groups would not have been possible.

The new drawings for this edition have been done by Miss Lynn McDowell, presently at the Department of Medical Illustration, Memorial Hospital, New York City.

Many members of the staff have helped in the preparation of this edition. Mrs. Frances Jamieson, manager of the Heyman Laboratory, has directed the staff in the compilation of data with accuracy and efficiency. Mrs. Myrna Hottum collected and analyzed the data related to rescreening of women. Mrs. Dolores Williams, as for the second edition, has been a most efficient secretary.

I would like particularly to thank Mr. John L. Dusseau, Editor of W. B. Saunders Company, for his help and patience.

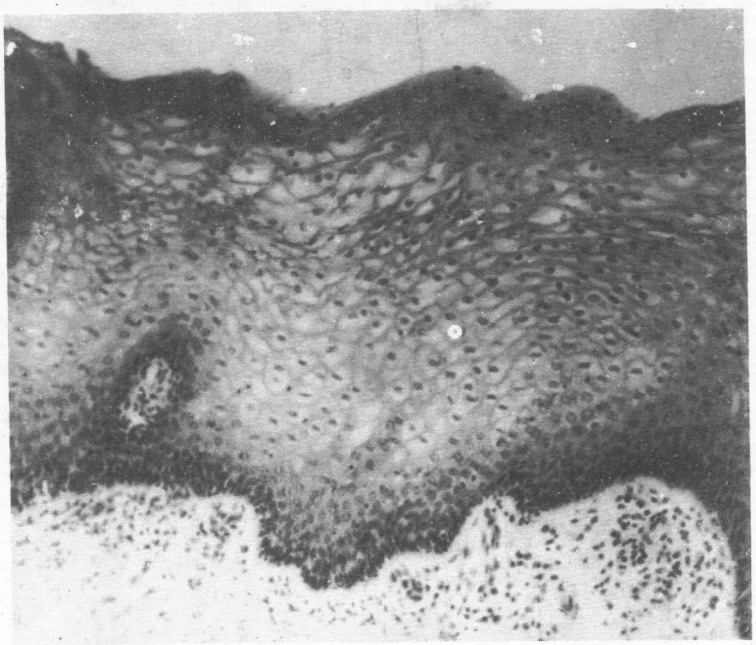
The additional material on carcinoma of the ovary presented in this edition required the active cooperation of an interested clinician. I must thank the late Dr. John B. Graham for supplying me with this clinical material.

RUTH M. GRAHAM

Contents

Chapter 1
Benign Cells of the Squamous Epithelium of Cervix and Vagina

FIGURE 1–1



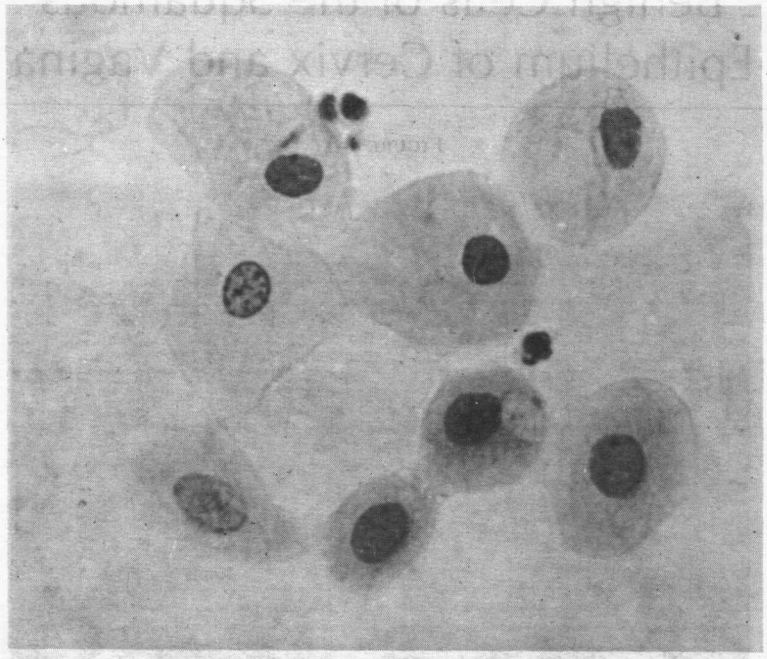
HISTOLOGIC SECTION: CERVICAL SQUAMOUS EPITHELIUM

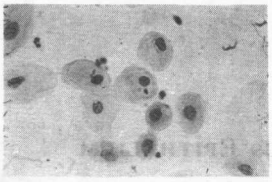
The squamous epithelium of the female genital tract is composed of four layers. Beginning at the basement membrane they are: germinal, basal or transitional, intermediate, and superficial. (See Figure 1–1.)

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.* Define 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.

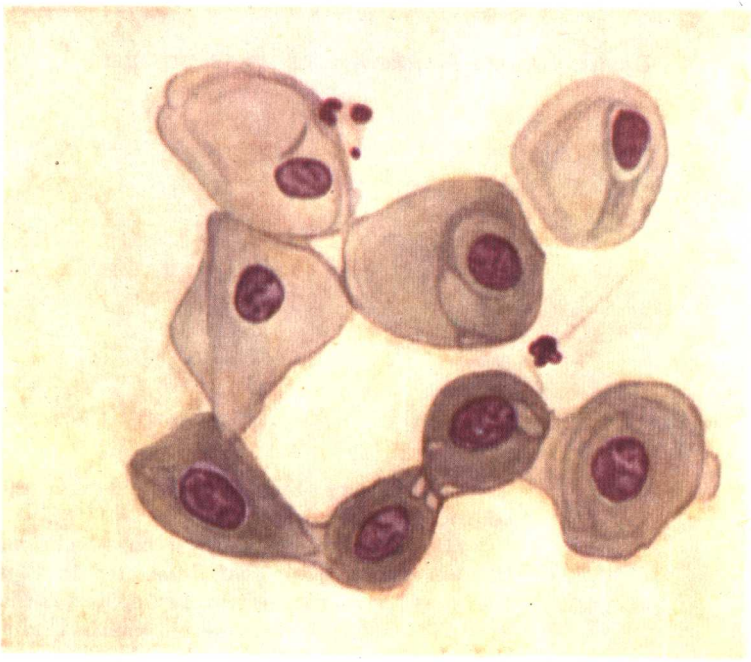
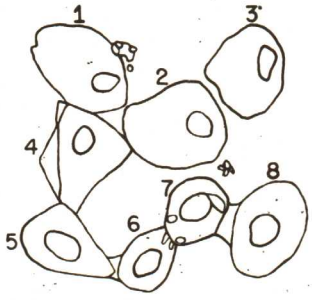


PLATE 1



KEY TO BASAL CELL PLATE

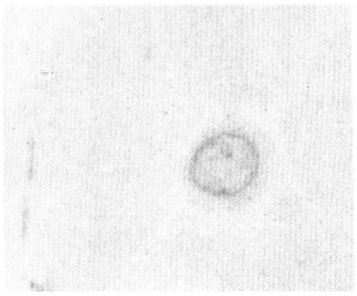
1. Outer layer basal cell: vesicular nucleus, thin transparent cytoplasm.
2. Outer layer basal cell: finely granular nucleus, unevenness in density of cytoplasm.
3. Outer layer basal cell: degenerate, partially pyknotic nucleus, perinuclear vacuole.
4. Intermediate cell: square shape and folding of transparent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

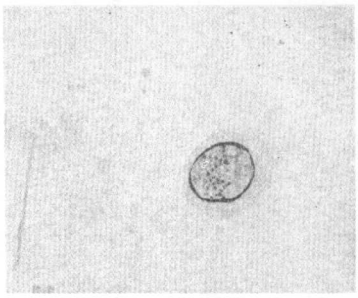
6 and 7. Inner layer basal cells: dense cytoplasm showing beginning of vacuolization, round vesicular nuclei.

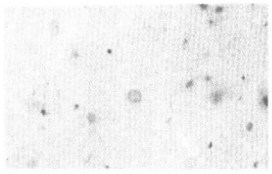
8. Outer layer basal cell: central nucleus containing finely divided chromatin.

FIGURE 1–2

BASAL CELLS: NARROW CYTOPLASMIC RIM





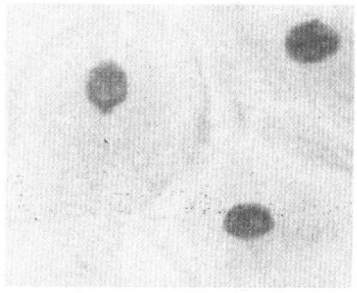


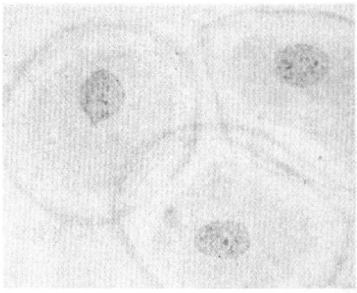
Low Power: Field of inner and outer layer basal cells. One large nucleus.

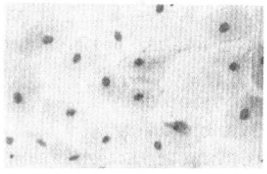
High Power: Inner layer basal cells may have the amount of cytoplasm illustrated in Plate 1, or they may have a narrow rim of cytoplasm as illustrated here. The nucleus has fine chromatin granules and threads distributed evenly. Nuclear and cytoplasmic borders are definite. Cell is round.

FIGURE 1–3

BASAL CELLS: CYTOPLASMIC CHANGES—THICK CELL WALLS





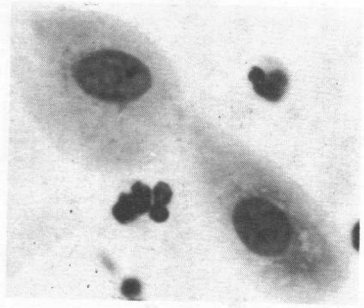


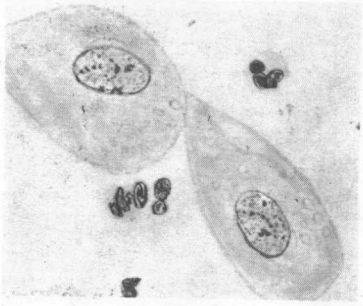
Low Power: Group of outer layer basal cells with thick cellular borders.

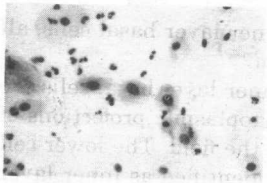
High Power: These cells are distinctive in that their cellular borders are much thicker than usual. The border stains a much deeper blue than the remaining cytoplasm. The central deposits around the nuclei are irregular and take a deep yellow stain. The significance of this change is not known.

FIGURE 1–4

BASAL CELLS: CYTOPLASMIC CHANGES—FINE VACUOLIZATION





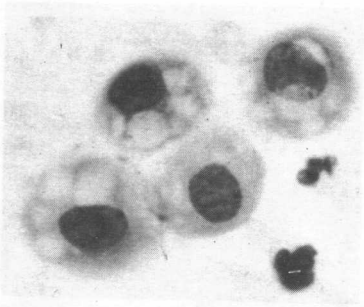


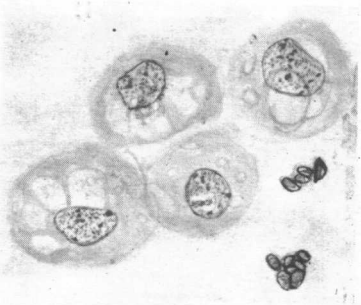
Low Power: Four outer layer basal cells in rather clean field of intermediate and superficial cells.

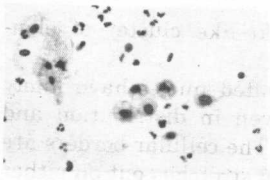
High Power: Two outer layer basal cells with vacuoles distributed throughout their cytoplasm. This is not a degenerative change, but probably indicates increased activity. The nuclei of these cells are well preserved and have a finely granular appearance. The cell border is sharp.

FIGURE 1–5

BASAL CELLS: CYTOPLASMIC CHANGES—PROMINENT VACUOLIZATION





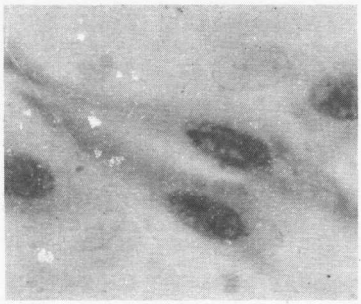


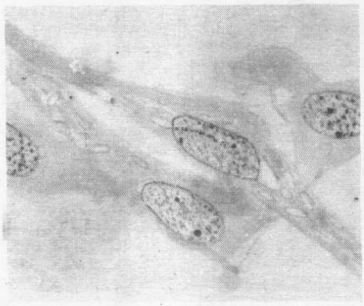
Low Power: Four inner layer basal cells with extensive vacuolization of cytoplasm.

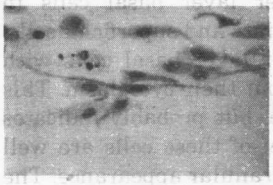
High Power: The vacuoles of these cells vary from extremely fine spaces to the large vacuoles overlying the nucleus in the cells at the upper right. The nuclei are active, having larger clumps of chromatin than are usually seen. These cells and those above are examples of basal cells exhibiting the *sensitization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

FIGURE 1–6

BASAL CELLS: CYTOPLASMIC CHANGES—CHANGE IN SHAPE





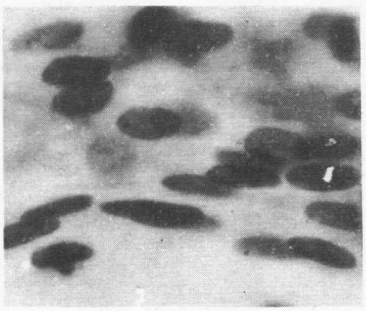


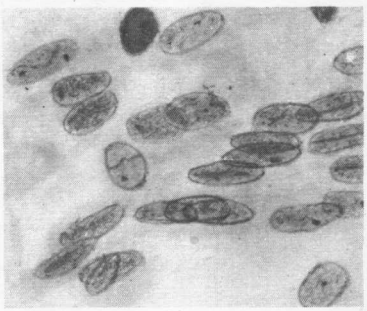
Low Power: Group of inner layer basal cells, all but one having elongated form.

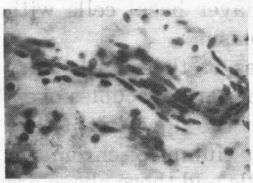
High Power: The two inner layer basal cells are bizarre in shape. The long cytoplasmic projections of the upper cell stretch beyond the field. The lower cell is triangular. These cells are identified as inner layer basals because of the small amount of cytoplasm surrounding the finely granular nucleus.

FIGURE 1–7

BASAL CELLS: CYTOPLASMIC CHANGE—ELONGATION





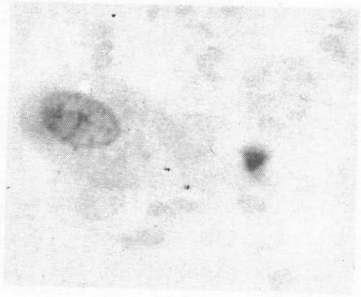


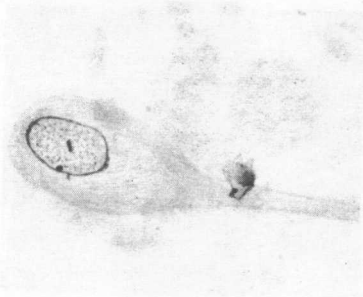
Low Power: Long, snake-like cluster of elongated nuclei.

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 1–8

BASAL CELLS: CYTOPLASMIC CHANGES – ABERRANT SHAPE



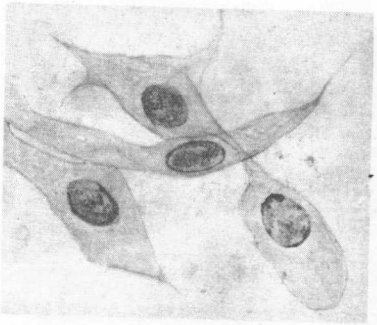


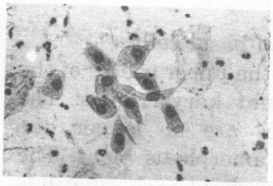
Low Power: Inner layer basal cell with extremely long tail of cytoplasm.

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 1–9

BASAL CELLS: CYTOPLASMIC CHANGES – ABERRANT SHAPES



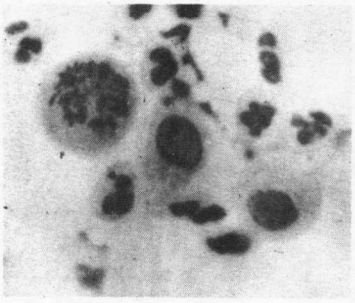


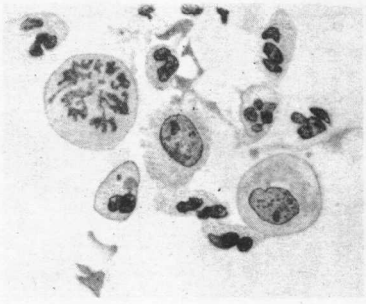
Low Power: Group of epithelial cells with abnormally shaped cytoplasm.

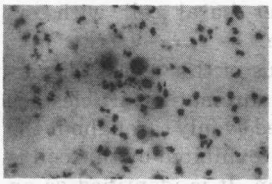
High Power: The nuclei are round and of the same structure as the basal nuclei shown in Plate 1. These are called aberrant basal cells because of the abnormally elongated shape of their cytoplasm, which usually stains eosinophilic. Three of the four cells show tail projections coming from the cytoplasm.

FIGURE 1–10

BASAL CELLS: MITOTIC FIGURE





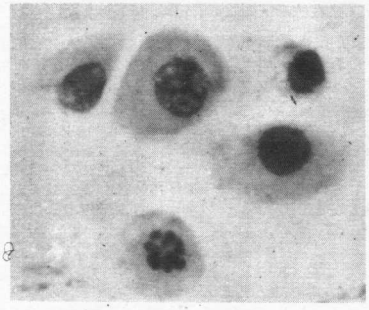


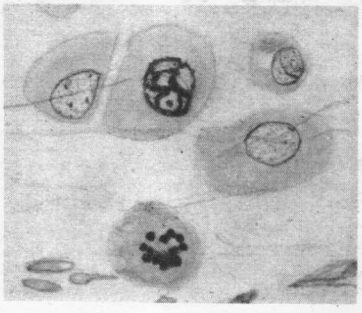
Low Power: Leukocytes and inner layer basal cells.

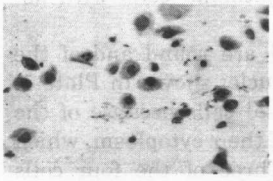
High Power: The cell in the upper left is in division, and has no nuclear wall. The chromatin material has condensed to form the chromosomes, which are fine long and short strands arranged radially. A mitotic figure must be distinguished from karyorrhexis; see Figure 1–11 below, in which the nuclear wall also disappears but the chromatin material is in heavy clumps.

FIGURE 1–11

BASAL CELLS: NUCLEAR CHANGES – DEGENERATION





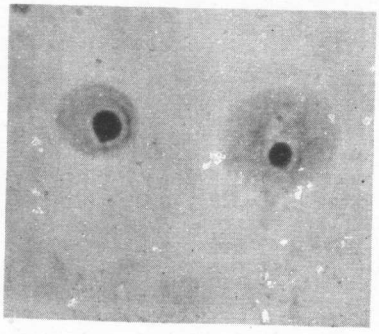


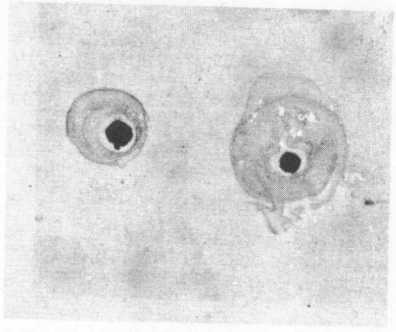
Low Power: Clean field of basal cells.

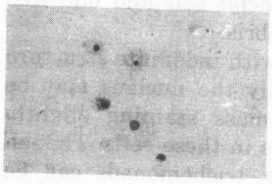
High Power: The cell at the upper center of the field is an example of incipient karyorrhexis. The individual chromatin particles are no longer discrete but have coalesced into amorphous blobs. The lower cell has lost its nuclear border; the chromatin is in large clumps – an example of karyorrhexis. Other basal cells in the field show normal nuclear structure.

FIGURE 1-12

BASAL CELLS: NUCLEAR CHANGES—PYKNOSIS





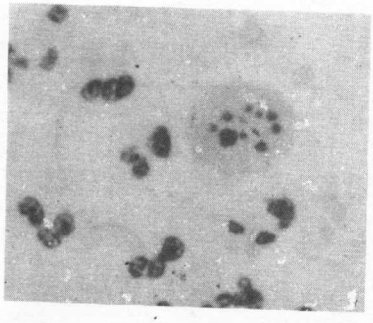


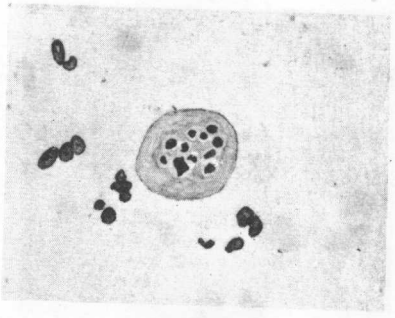
Low Power: Several epithelial cells with small dark nuclei.

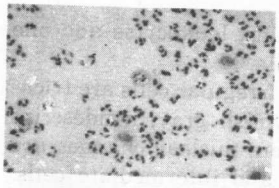
High Power: The chromatin of these nuclei has condensed until no structure can be observed. The condensation leaves a perinuclear vacuole formerly occupied by the whole nucleus. We identify these cells as basal, instead of superficial, because of their small size and round appearance. Cytoplasm of cell on the right presents an irregular border, another sign of degeneration.

FIGURE 1-13

BASAL CELLS: NUCLEAR CHANGES—KARYORRHEXIS







Low Power: Inner layer basal cells with indefinite nuclear patterns.

High Power: The chromatin of the nucleus has separated into many individual clumps, which appear as dense black particles. The nuclear border has disappeared. This particular pattern of the nucleus is seen as the last stage of disintegration. It should be distinguished from the metaphase of mitosis, where chromatin particles are much finer and more numerous.