

# Practical - 8 + 9

## MALIGNANCY + GYN MALIGNANCY

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# Malignancy

## Please note:

- The structure of the suspected atypical cell should always be compared to the structure of other similar, benign, cells which are present in the smears.
- The diagnosis is made on cells which show several criteria of malignancy.
- The nucleus is the most important part of the cells to show the malignant changes.
- Cytoplasm may show changes which could help in cell typing.

## Malignant morphological changes:

- Nuclear changes in malignancy
- Cytoplasmic changes in malignancy

# A- Nuclear changes in malignancy

## **1-Nuclear enlargement**

- There is increase in the nuclear size
- The abnormal nucleus should always be compared to the size of several other nuclei of similar but benign.
- Also should compare the nucleus of the cell to the size of the cytoplasm.
- Determination of Nuclear Cytoplasmic ratio = N/C ratio.

## **2-Nuclear size variation**

- Malignant cell vary in size

## **3-Nuclear shape variation** -Nuclear pleomorphism ( = nuclear variation in size and shape)

- Variation in the nuclear shape as a result of the rapid growth of the neoplastic cells that become crowded against each other.
- Molding of nucleus

## **4-Hyperchromasia**

- Hyperchromasia is often related directly to the quantity of DNA in the nucleus.
- Criteria is combined with irregularities of chromatin clumping and of the nuclear membrane.

## **5-Irregularity of chromatin pattern**

- The chromatin often forms irregular clumps variable in size and shape
- Multiple sharp points projections and uneven distribution

## **6-Changes in outline of the nucleus**

- The nuclear membrane in malignant cells are sharp, thick and well defined and is important in the diagnosis of malignancy.

## **7-Nucleoli changes**

- The nucleoli is part of the nucleus and it will respond to some stimuli resulting into changes corresponding to nuclear changes. The presence or absence of nucleoli is a feature associated with malignancy.

# **\*B-Cytoplasmic changes in malignancy**

- ✓ The amount of cytoplasm is important not only in the diagnosis of malignancy, but also in **typing the nature and the degree maturation of the neoplasm.**
- ✓ The cytoplasm of dysplastic and malignant cells usually does not enlarge in the same proportion as the nucleus.
- ✓ Increase in the N/C ratio is a good criterion of malignancy in the diagnosis of many tumors.

## **1-Cell shape**

- The outline of the cell is sharp, distinct and regular in some malignant cells
- Indistinct and heavy as in the case of thick, spherical malignant cells with scanty cytoplasm

## **2-Cell size**

- The difference in cytoplasmic size can also be the result of other factors, such as radiation, pregnancy, cellular degeneration
- Variation of cell size is important in malignancy of atypical cell

## **3-Cytoplasmic inclusions**

- The various significant types of inclusions and vacuolization must be differentiated from more common ingested debris and degenerative vacuoles.

## **4-Cellular arrangement in clusters**

- The benign secretory cells are arranged in honey comb, the loss of this typical honey comb cellular arrangement, giving way to the three dimension cluster formation is diagnostic criterion for malignancy.

### **\*Nuclear cytoplasmic ratio (N/C ratio)**

- The ratio between the size of nucleus to the whole size of the cell.
- It is always high in malignancy, as a result of the nuclear growth in a ratio more than a cell growth.

### **\*Staining affinity**

- The intensity of the staining and the color of the cell can be helpful in the diagnosis of the nature of neoplasm
- Abnormal amount of cytoplasm keratinization producing a glossy deep orange stain (as in the case of well differentiated squamous cell carcinoma).
- The cytoplasm is basophilic in the cells of immature or poorly differentiated carcinoma.

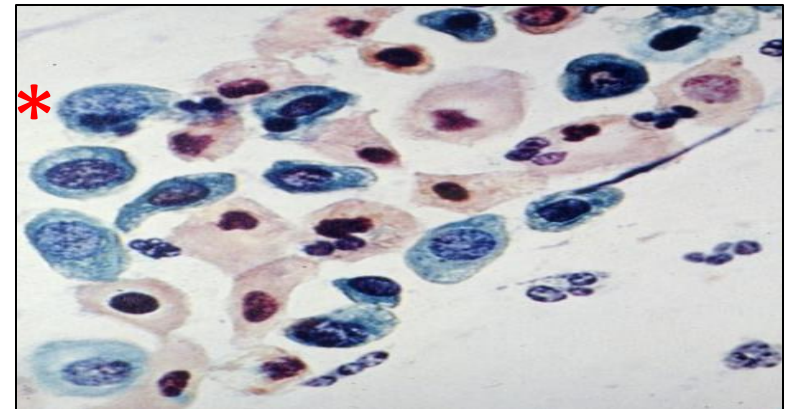
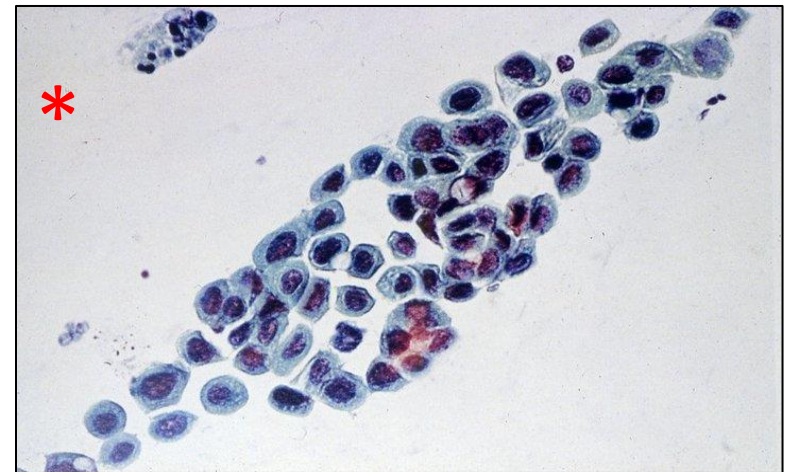
## Immature metaplastic squamous

- Small parabasal / basaloid –sized cells with optically dense cytoplasm, centrally placed nuclei and round cell borders.
- Often present singly but may form groups. Cytoplasm cyanophilic nuclei round or oval with finely granular chromatin and small nucleoli.
- When reactive nuclei become more prominent they show increasing chromatin granularity.
- Nuclear folds and finely serrated nuclear outlines are common.

## Squamous metaplastic

- Nuclei slightly larger than those of normal squamous intermediate cells,
- Smooth round or slightly irregular borders
- Well – dispersed chromatin,
- Dense cytoplasm with pulled out edges.

## ATYPICAL METAPLASIA



## **BORDERLINE CHANGES**

- Pronounced red coloration of both cytoplasm and nuclei
- Benign halos
- Nuclei not appreciably enlarged
- Possible bi-nucleation
- Nuclear border remains relatively smooth
- Chromatin distribution appears even but slightly granular
- Chromatin varies from smudged and hyperchromatic to finely granular
- Can be koilocytic or non-koilocytic

## **DYSPLASIA IS CHARACTERISED BY FOUR MAJOR PATHOLOGICAL MICROSCOPIC CHANGES:**

- Anisocytosis (cells of unequal size)
- Poikilocytosis (abnormally shaped cells)
- Hyperchromatism (excessive pigmentation)
- Presence of mitotic figures (an unusual number of cells which are currently dividing).



# 1- GYN MALIGNANCY

## TUMORS OF THE CERVIX TYPES:

### \*A) Squamous Cells:

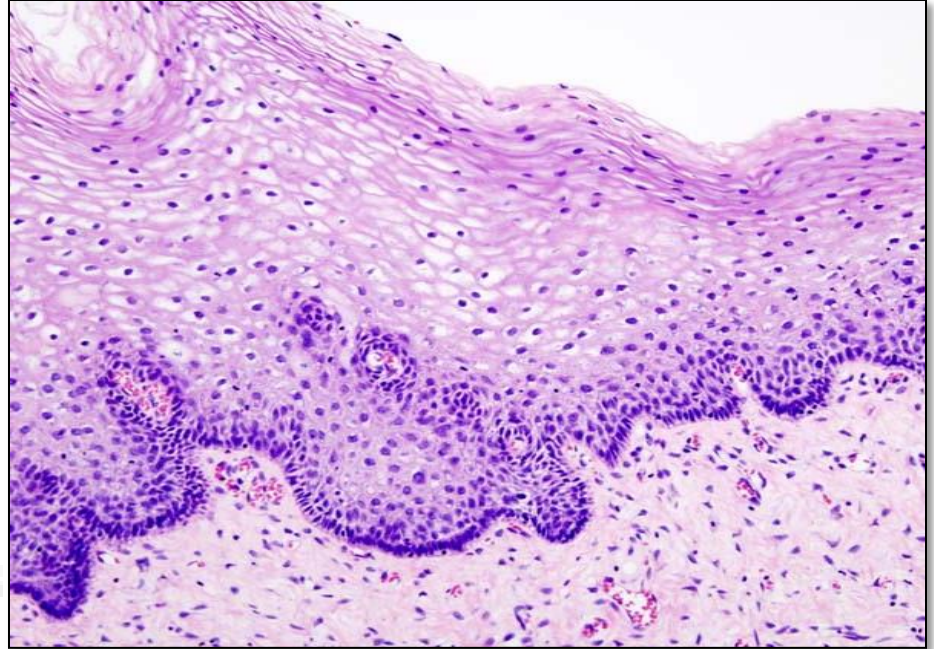
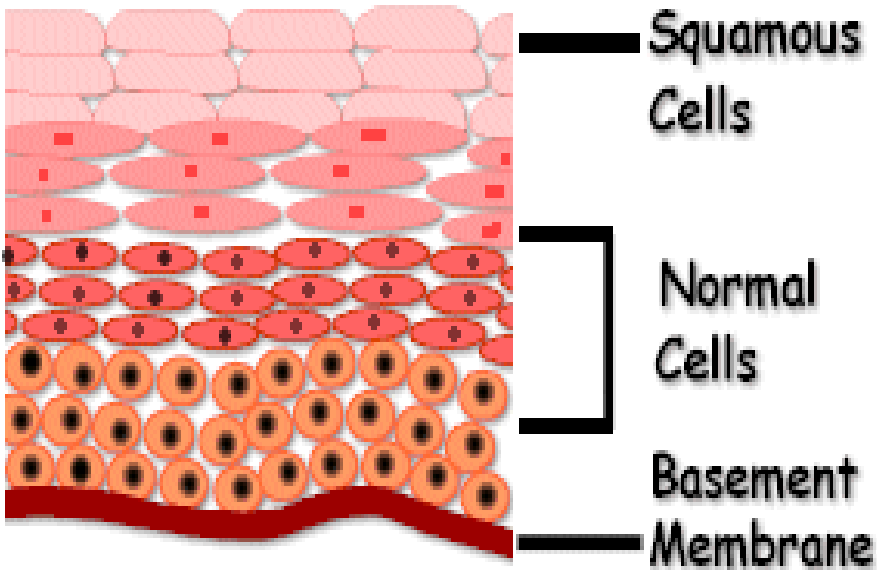
- Atypical Squamous Cells of Undetermined Significance (ASCUS).
- Cervical Intraepithelial Neoplasia (CIN)
- Squamous Cell Carcinoma = Carcinoma in Situ (CIS) = severe dysplasia.

### \*B) Glandular Cells:

- Atypical Glandular Cells of Undetermined Significance (AGUS).
- \*Adenocarcinoma which can arise from the endocervix, endometrium and extrauterine sites.



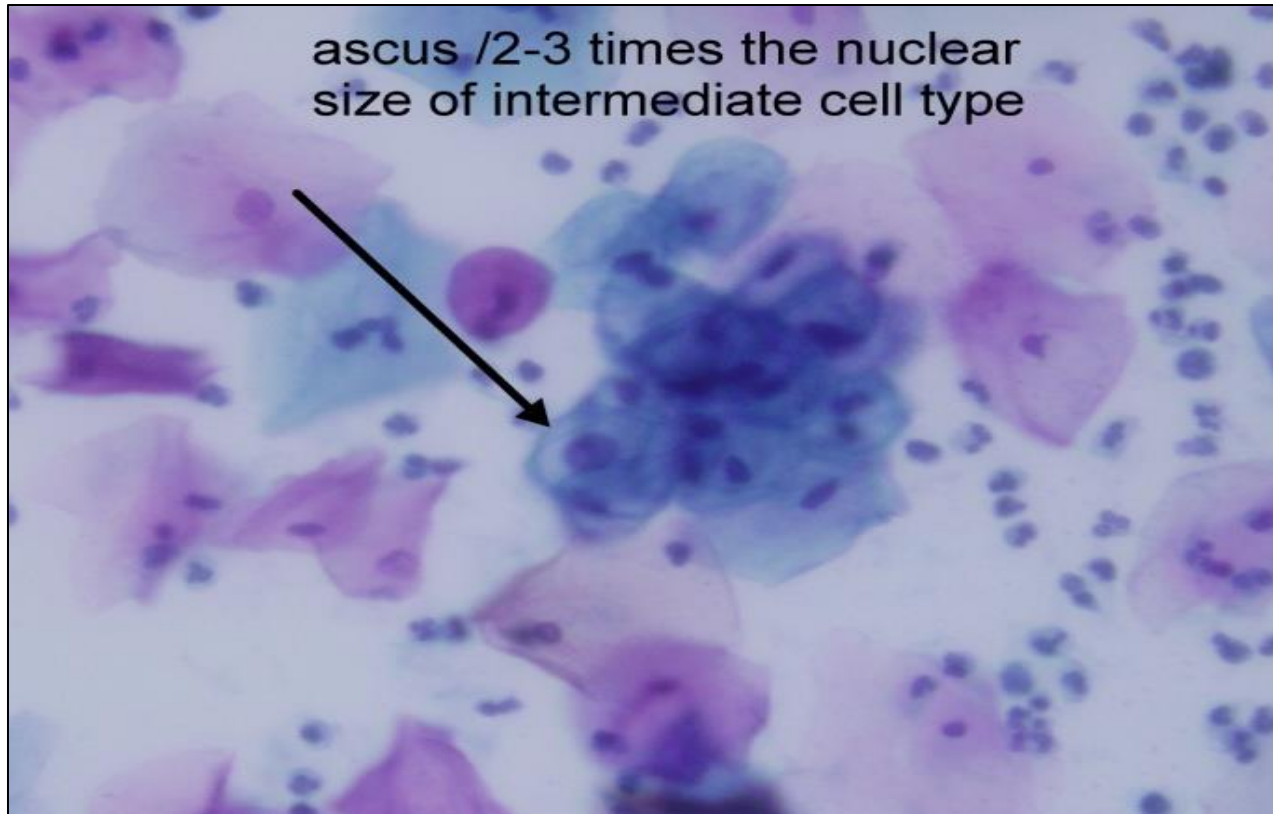
# Normal Cervix



The outside of the cervix and the vagina are covered by a layer of flat cells called squamous or skin-like cells. There are many of these cell layers before the first flattened layer of cells with a nuclei or center. Normally at the bottom of the cell layers are the round, younger cells. As the cells mature, they rise to the surface and become flat. The skin-like covering is separated from the underlying structures by a basement membrane. **This is an extremely important concept to remember as well as the Transition Zone area discussed on the Pap Smear Page.**

# 1- Squamous Cells

## Atypical Squamous Cells of Undetermined Significance (ASCUS)



Is the name given to squamous cells on a Pap smear or cervical cytology that do not have a normal appearance but are not clearly precancerous.

## \*Cervical Intraepithelial Neoplasia (CIN)

- It is the precancerous epithelial changes, and may precede the development of cancer by many years.
- CIN may progress to invasive carcinoma CIS

**Precancerous changes are graded as follows:**

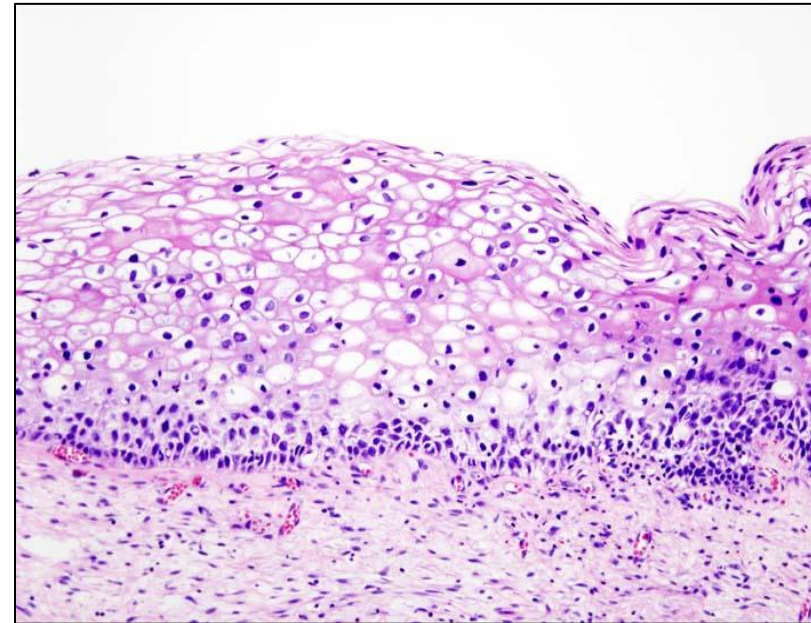
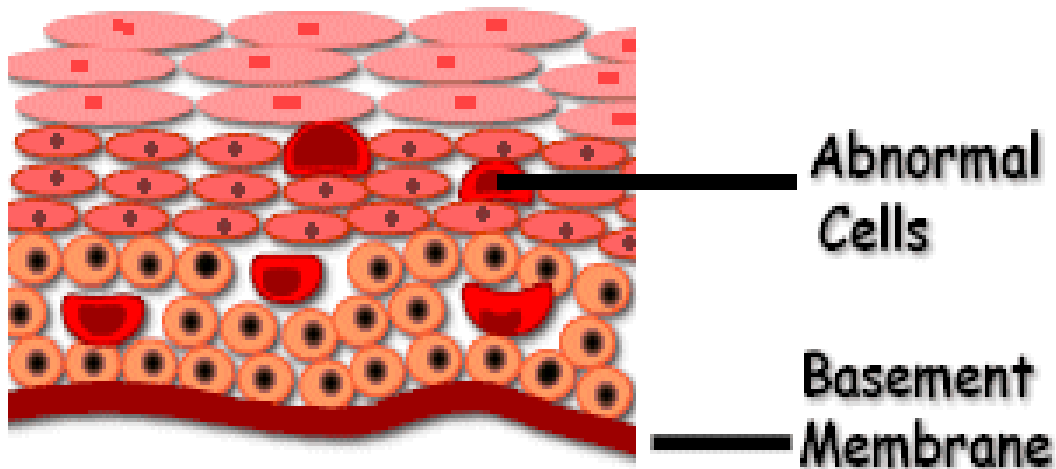
<b>Histology grade</b>	<b>Bethesda system (Cytology grade)</b>
CIN I : Mild dysplasia = Condyloma	Low-grade Squamous Intraepithelial Lesions (LSIL)
CIN II : Moderate dysplasia	
CIN III : Sever dysplasia and Carcinoma in Situ	High-grade Squamous Intraepithelial Lesions (HSIL)

# \*A- Histology grade

## 1- CIN 1 or Mild dysplasia

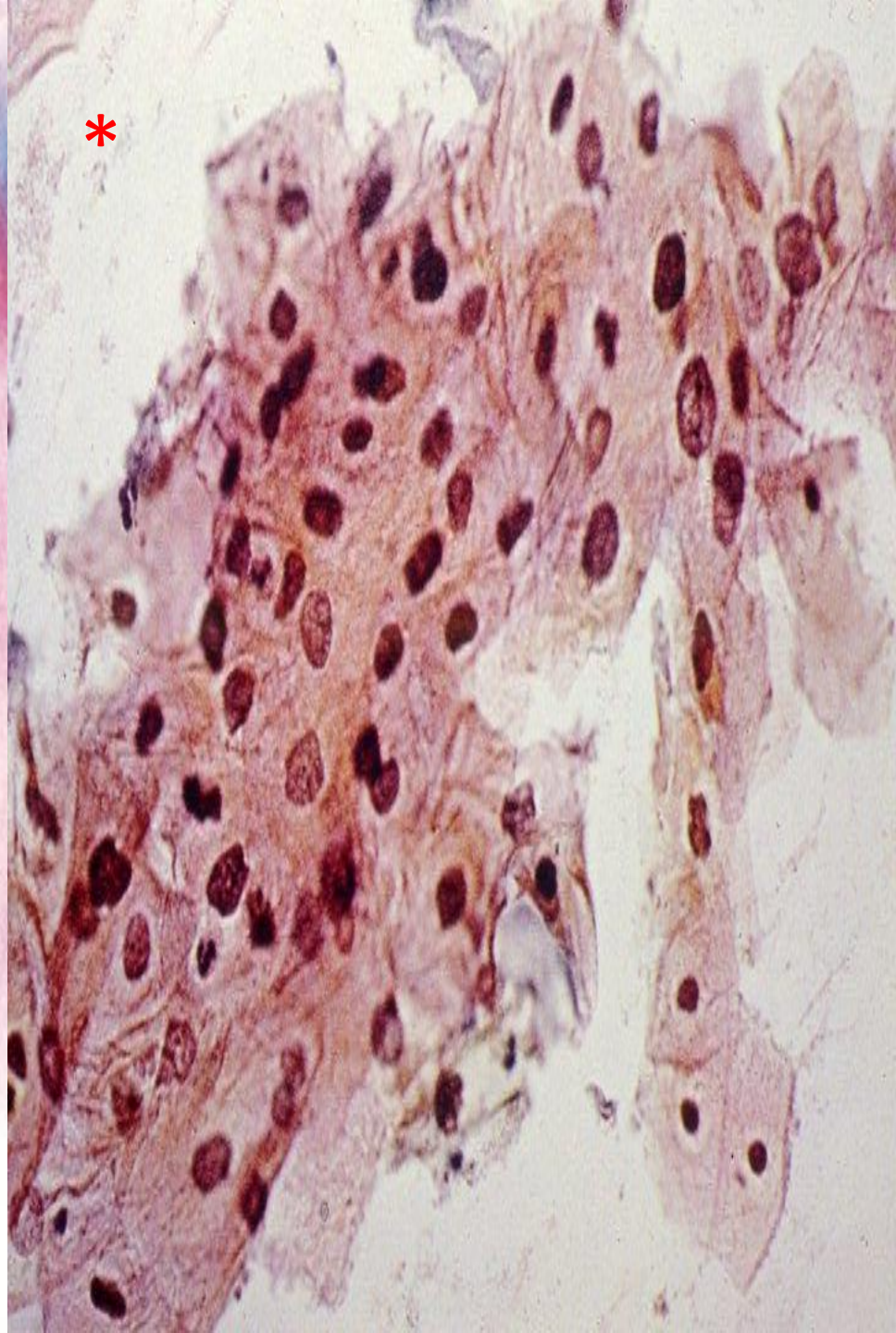
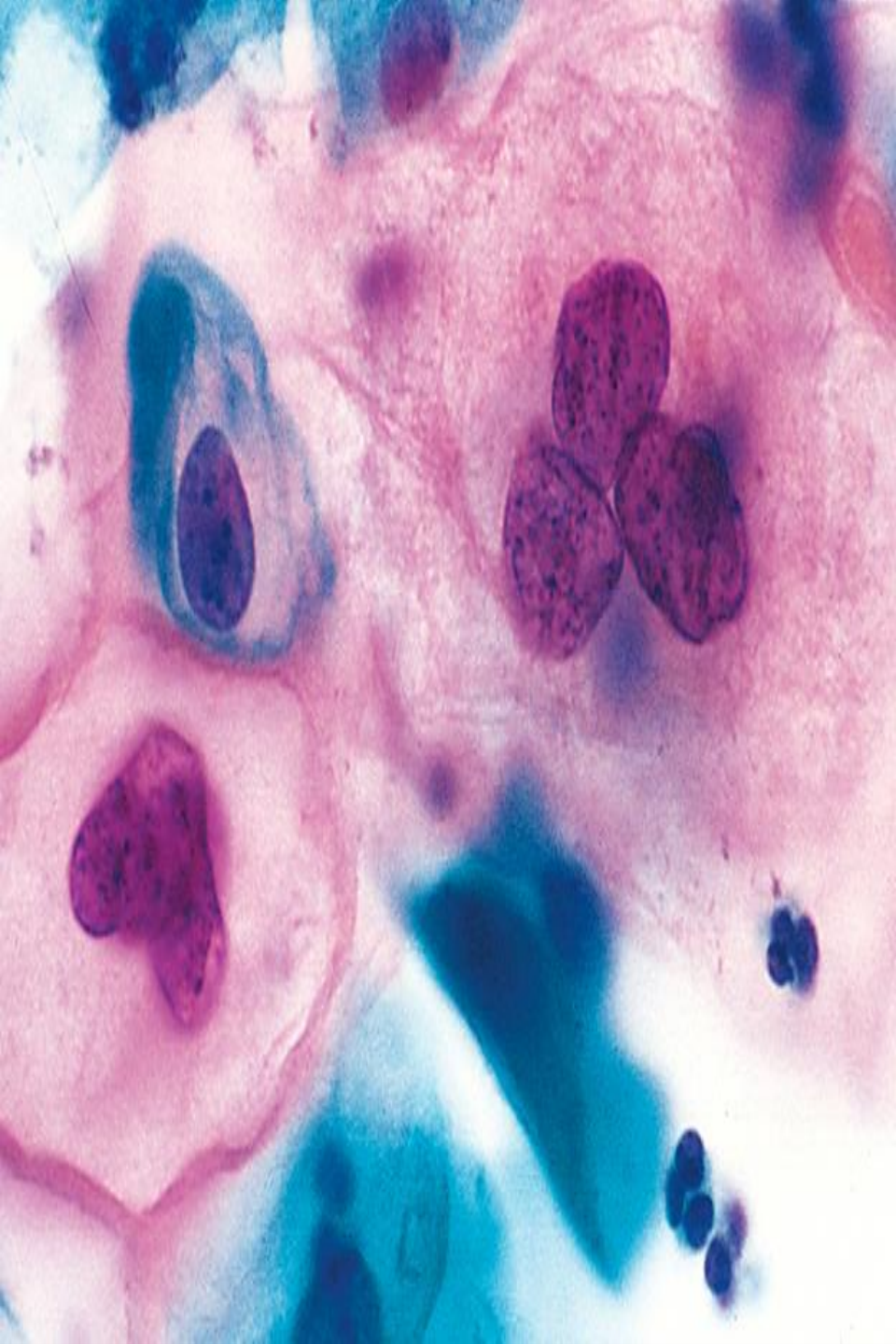
- The cells obtained show abnormality but are able to reach high degree of maturity to superficial level.

### Mild Dysplasia



In mild dysplasia (CIN I) only a few cells are abnormal. Mild cervical dysplasia sometimes goes away without treatment. However many doctors will treat it at this early stage to prevent it from progressing.

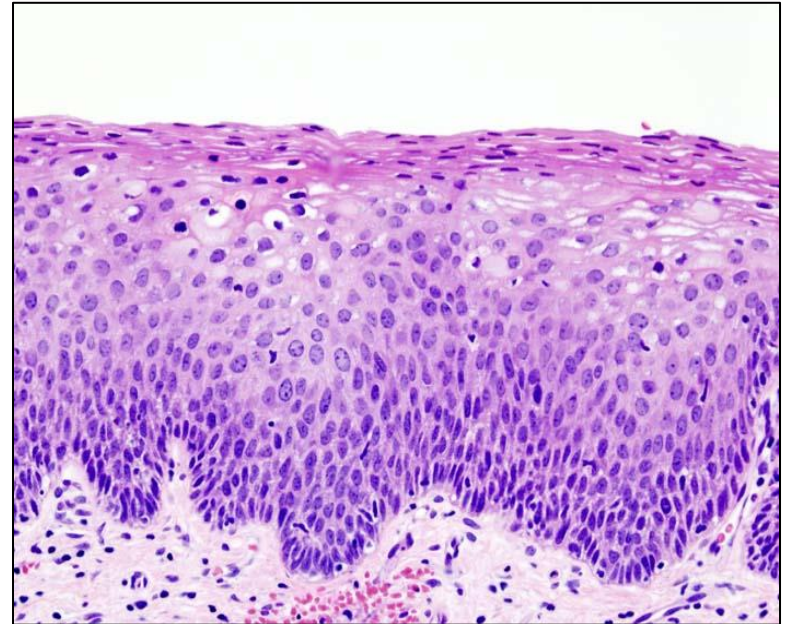
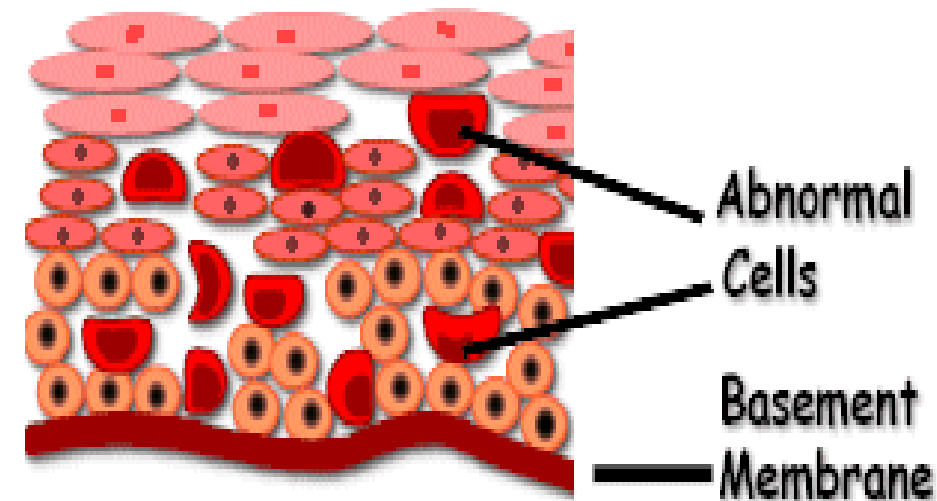




## \*2- CIN 2 or Moderate dysplasia

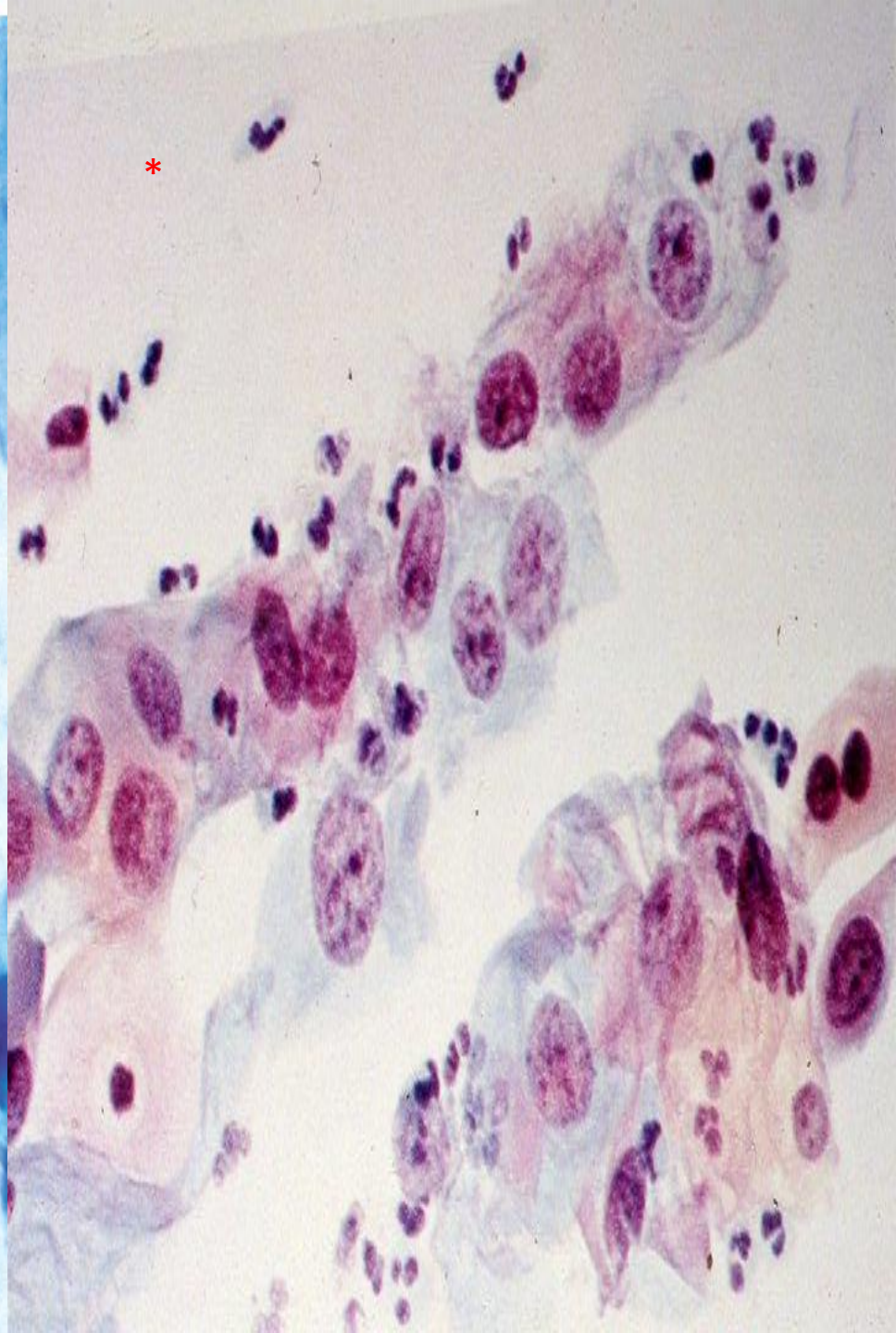
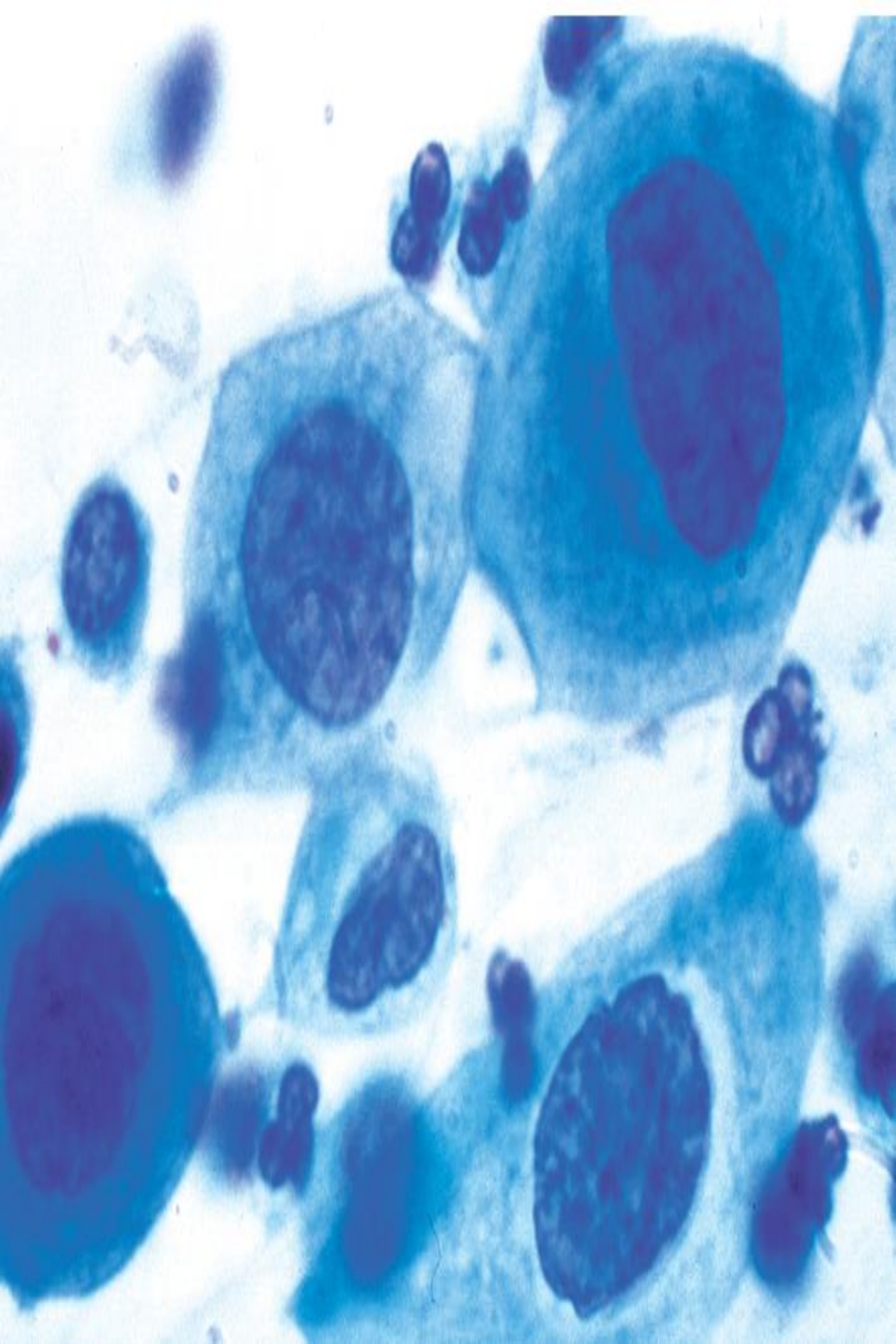
- Maturation does not progress beyond the inner intermediate or out parabasal level smear contains a large number of dyskaryotic intermediate and diskaryotic parabasal cell type.

### Moderate Dysplasia



In moderate dysplasia (CIN II) the abnormal cells involve about one-half of the thickness of the surface lining of the cervix.



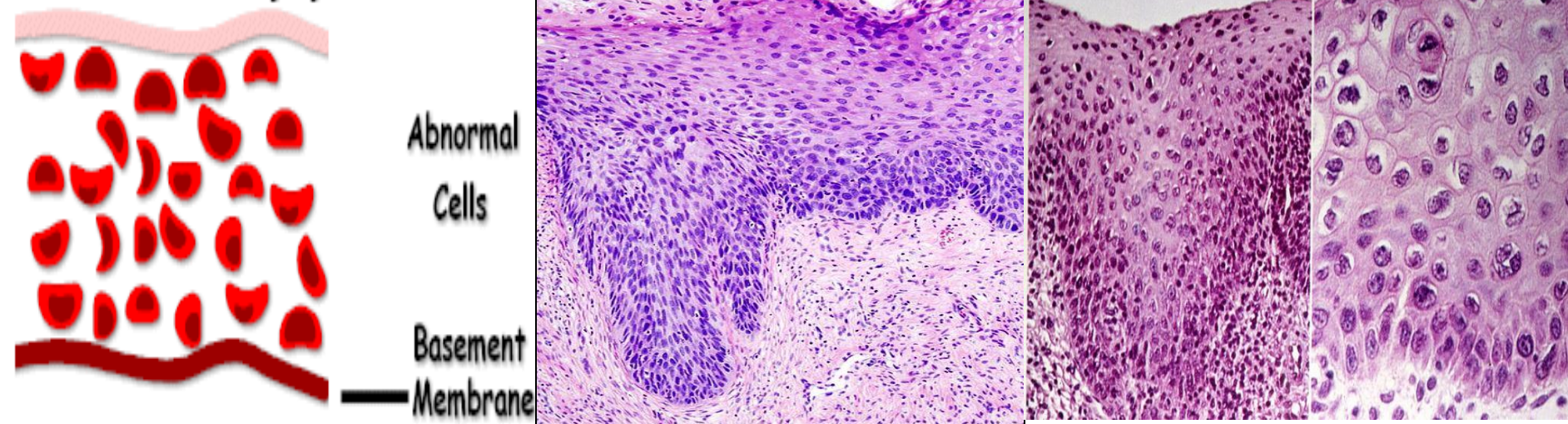




### \*3- CIN 3 or Carcinoma in situ

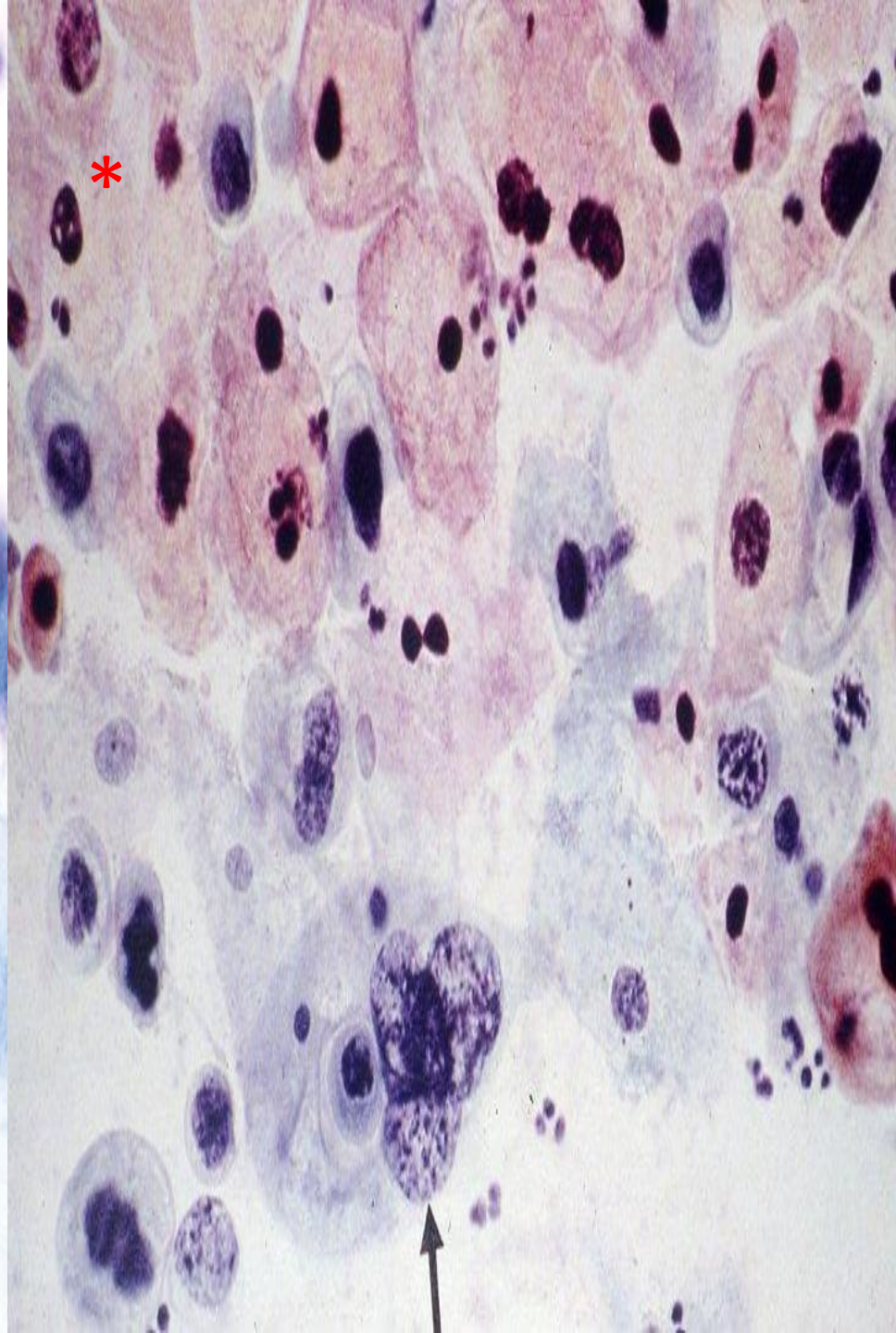
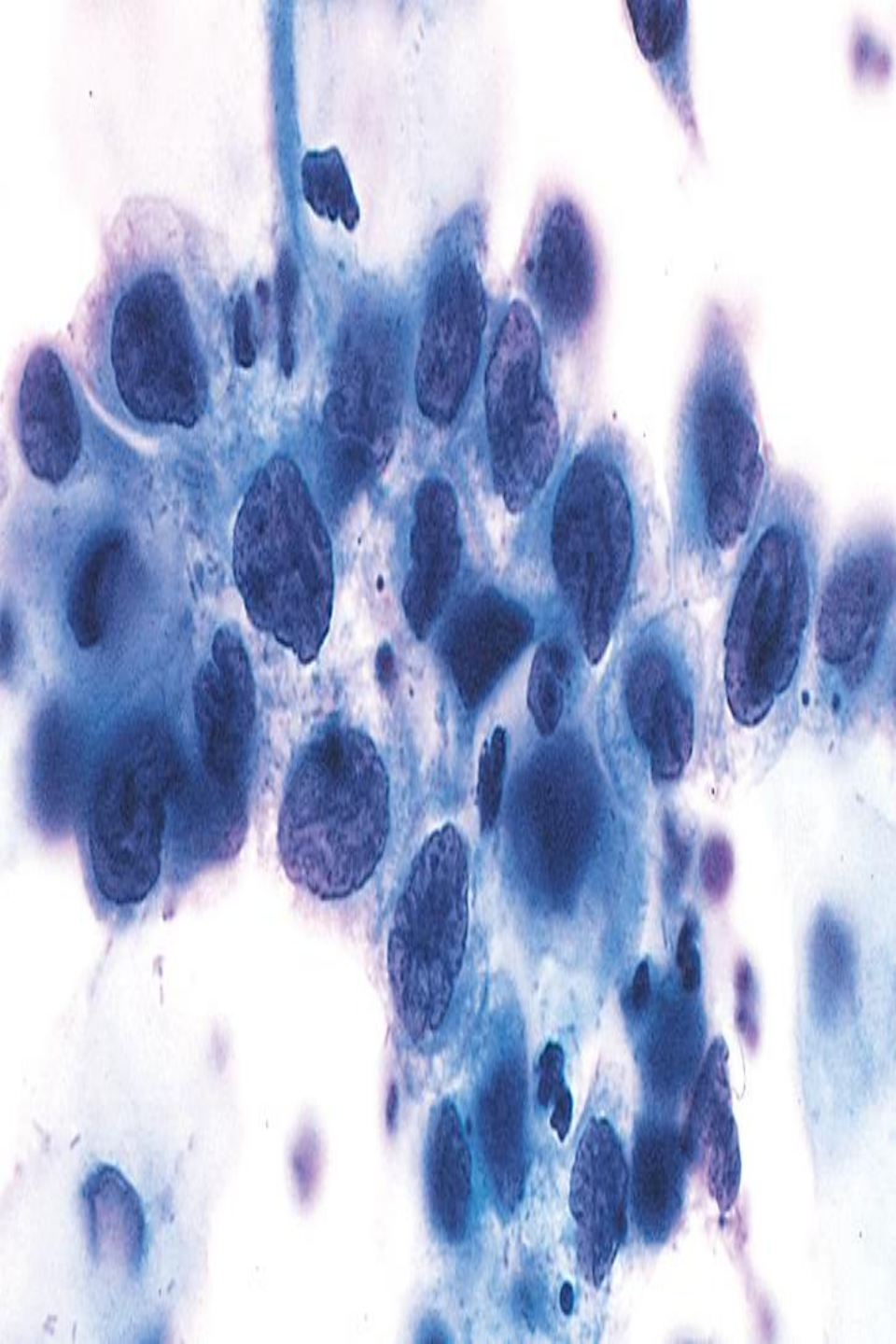
- Characterized by little or no maturation and the full thickness of the epithelium is made up of poor differentiation or undifferentiated malignant cells.

#### Severe Dysplasia



In severe dysplasia (CIN III), also called carcinoma-in-situ, the entire thickness of cells is abnormal, but the abnormal cells have not yet spread below the surface or basement membrane. Carcinoma-in-situ literally means "cancer in place". This severity of dysplasia **MUST BE TREATED** because it will most often develop into invasive cancer.



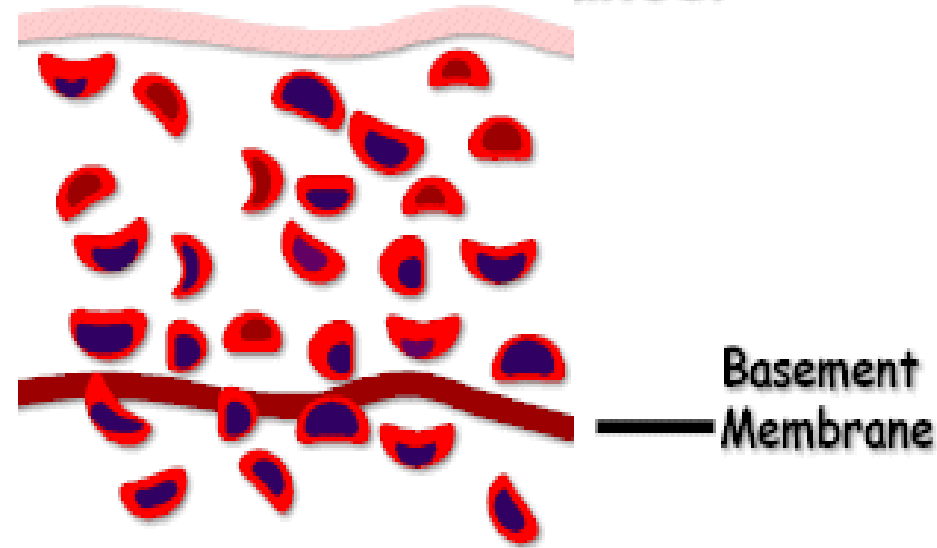




# \*Invasive Carcinoma In Situ (CIS)

- Maybe defined as malignant neoplasm that invades the underlying stroma of the cervical epithelium by infiltration or destruction of the basement membrane.

## Invasive Cancer

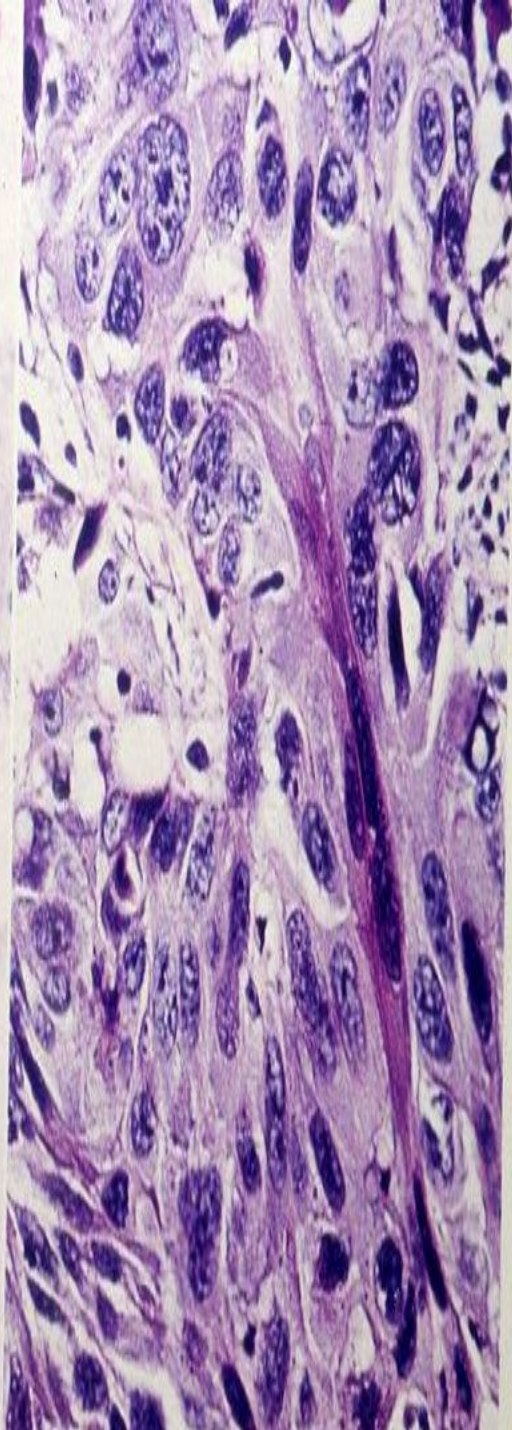
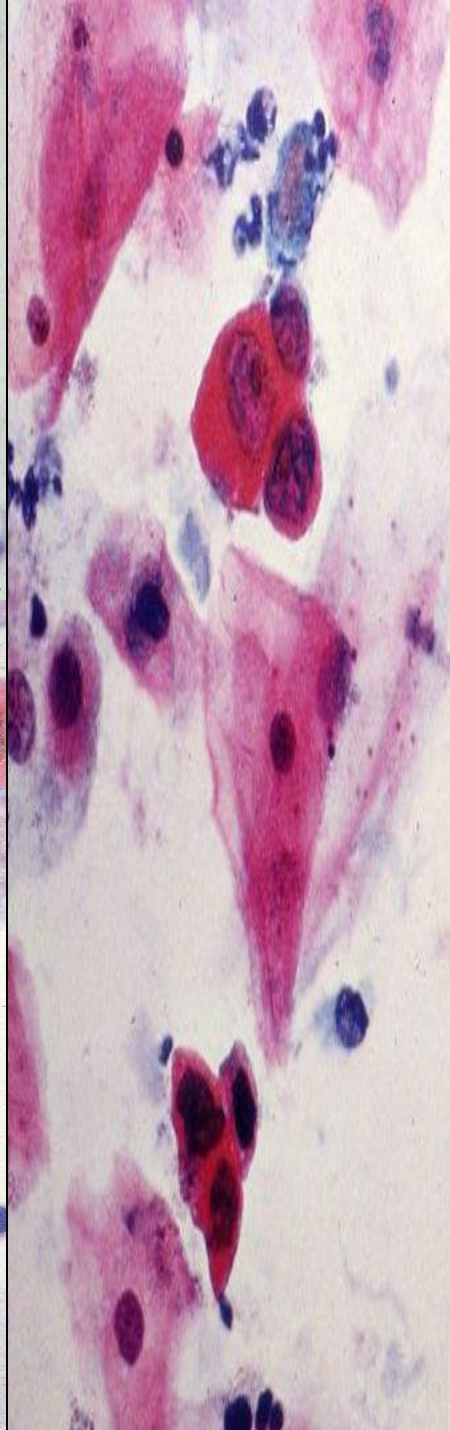
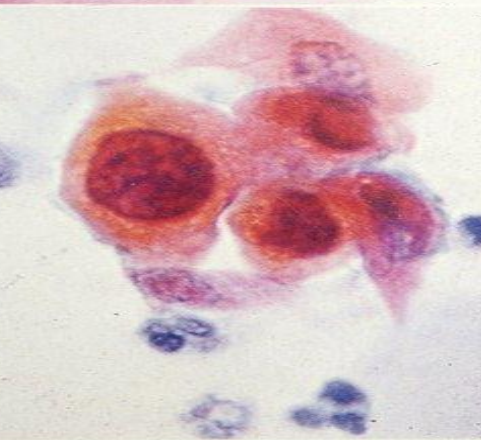
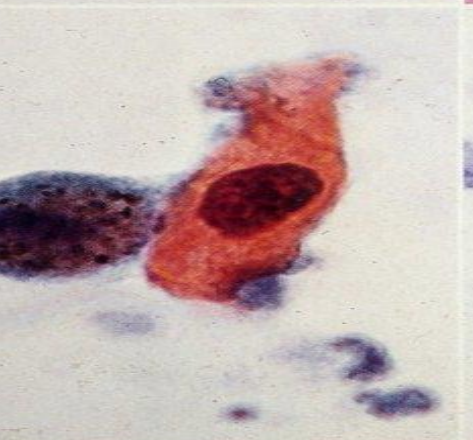
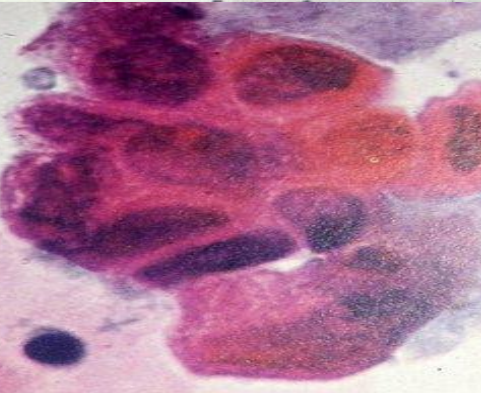
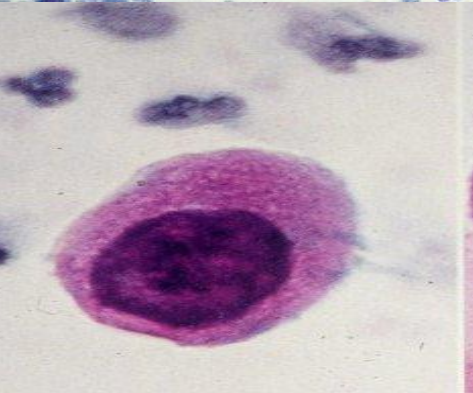
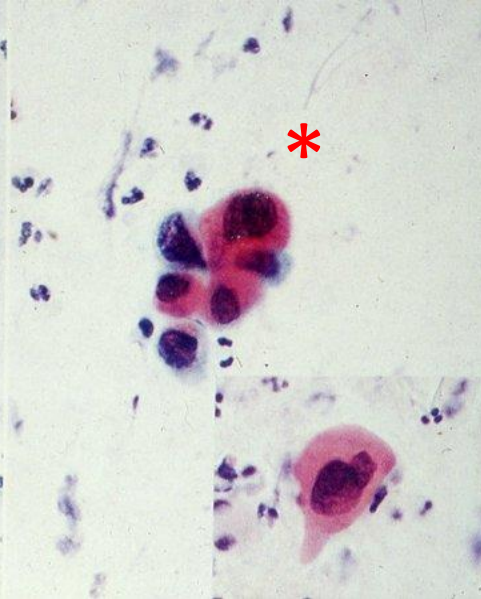


With invasive cancer, the cells are not only abnormal throughout the entire thickness from the top to the basement membrane, but **they invade the basement membrane**. The depth of invasion past the basement membrane is an important piece of information that will help make the decision on the proper treatment needed.

# \*A well differentiated invasive squamous carcinoma is contain keratinized of abnormal differentiated cells :

- Shapes: elongated cells and a caudate forms known as **tadpole cells**. Tadpole cells has a large head with malignant nucleus with tail.
- **Keratinized cytoplasm**, it takes up orange G and appear orange in color.
- Cell outline is clearly defined and cytoplasm is hard texture.
- Round cells are also seen, they are large with firm cytoplasm which is either eosinophilic or cyanophilic.
- Spindle shaped with irregular, long nucleus.
- Bizarre shape cell.





# B- Bethesda system (Cytology grade)

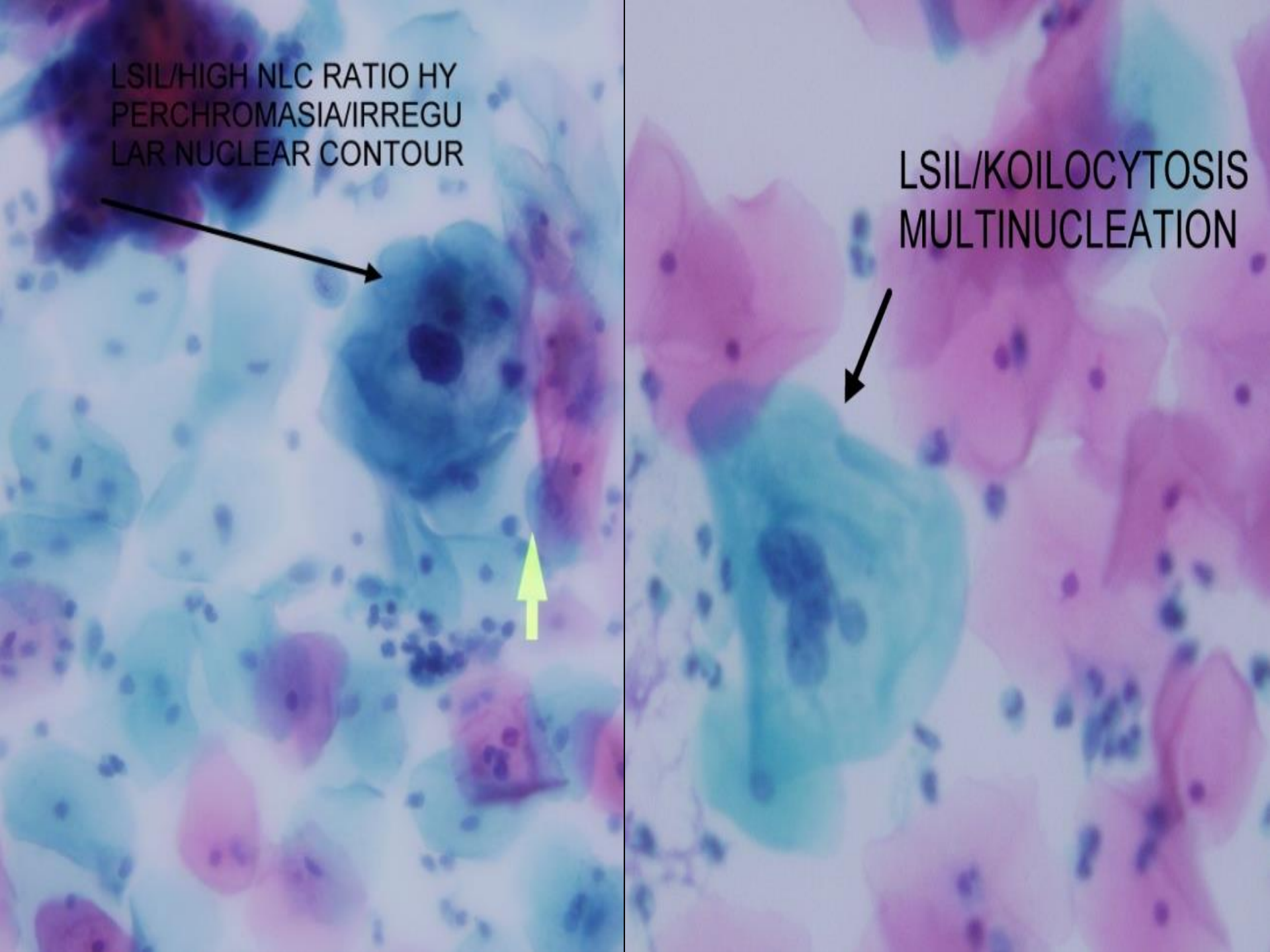
## 1- Low grade dyskaryosis (mild)

- Abnormal cells appear either singly or in sheets
- Enlarged nuclei with corresponding N/C ratio occupying less than half the area of the cell
- Irregularity of nuclear membrane and outline separate degenerative change from true abnormality
- Nuclear folding
- Abnormal chromatin pattern varying from coarse to finely stippled and extremely subtle
- Nuclear staining varies from hyperchromatic to hypochromatic
- May be scanty or abundant, single cells or groups



LSIL/HIGH NLC RATIO HY  
PERCHROMASIA/IRREGU  
LAR NUCLEAR CONTOUR

LSIL/KOILOCYTOSIS  
MULTINUCLEATION





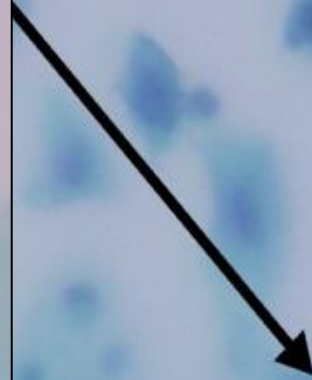
## 2- High grade dyskaryosis (moderate and severe)

- More isolated cells rather than streaks.
- Three dimensional groups allowing the depth of focus to be seen when focusing through each plane.
- Increased NCR ratio occupying between less than two thirds.
- Coarse chromatin distribution and pattern.
- Marked irregularities of the nuclear membrane.
- Nuclear hyperchromasia or hypochromasia.
- Multiple abnormal nucleoli.
- Small isolated cells stand out due to clean background.
- More dyskaryotic than more walnut like appearance.
- Clumping of the chromatin.
- Pleomorphism
- Mitotic figures often seen.
- Marked variation in the nuclei within the groups.

HSIL/HIGH N/C RATIO  
O WITH INCREASE H  
YPERCHROMASIA

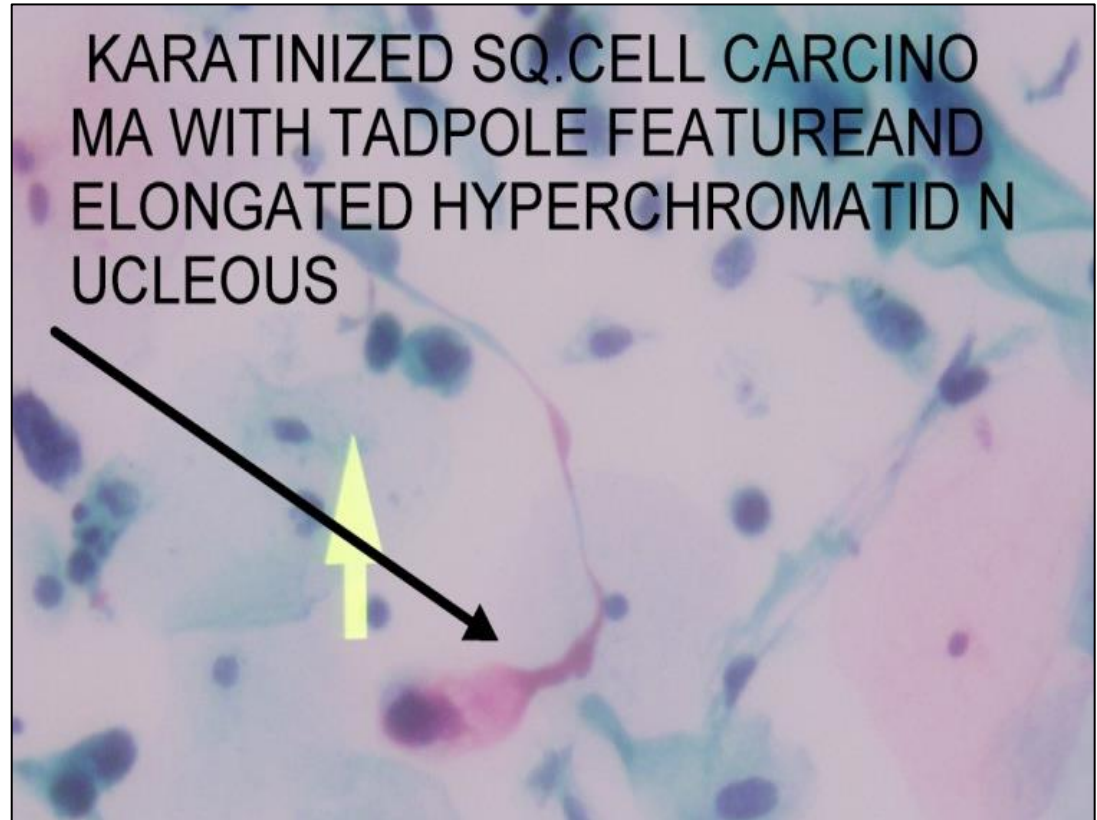


HSIL/HIGH N/C RATIO WITH  
NCREASE HYPERCHROMAS



# Additional for severe dyskaryosis

- Large cell
- Small cell
- Keratinizing
- Non-keratinizing
- Mixed  
(most common)



- Often single often groups
- Abundant cell population or scanty
- Architecturally abnormal crowded /  
super crowded groups

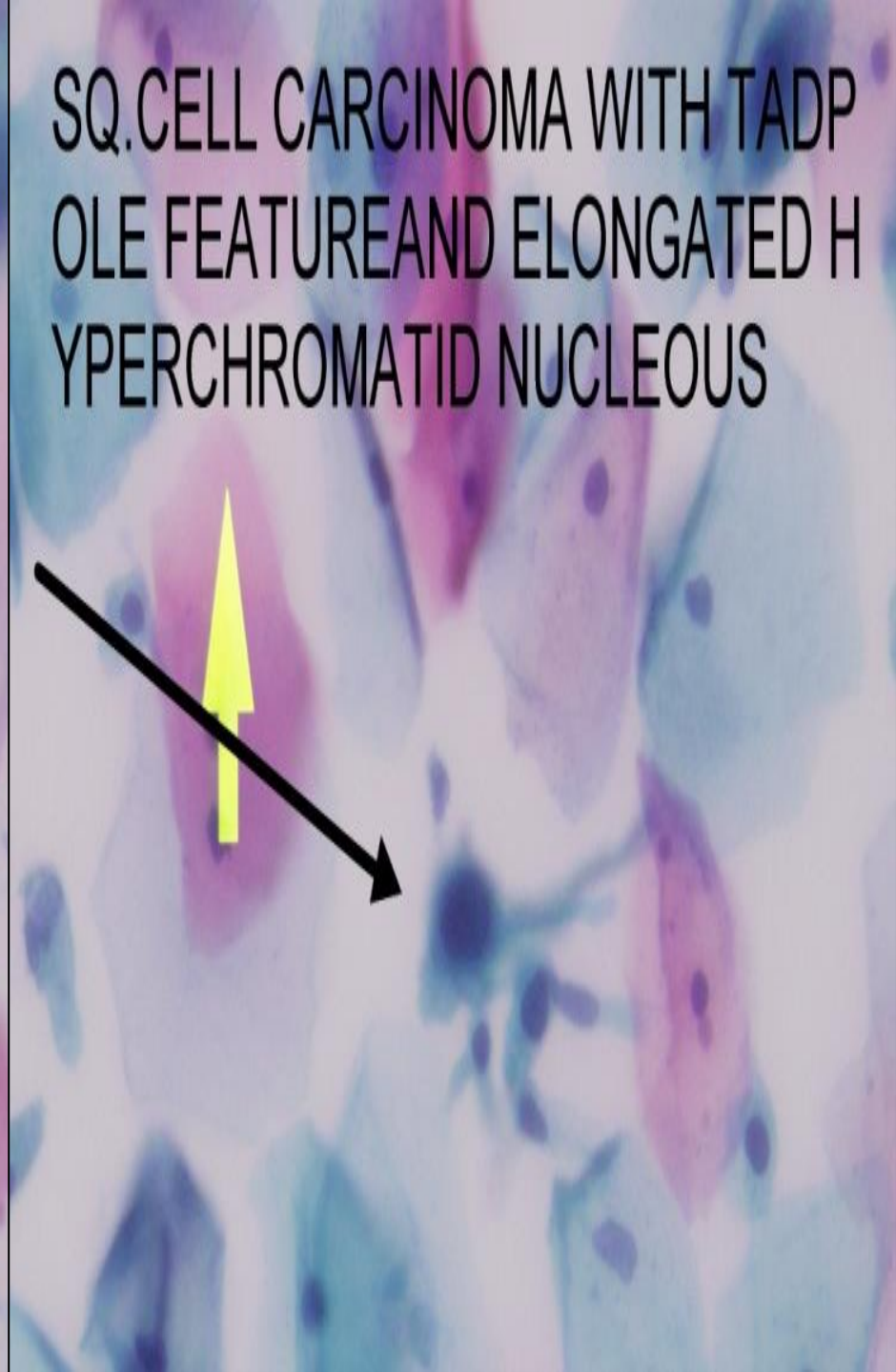
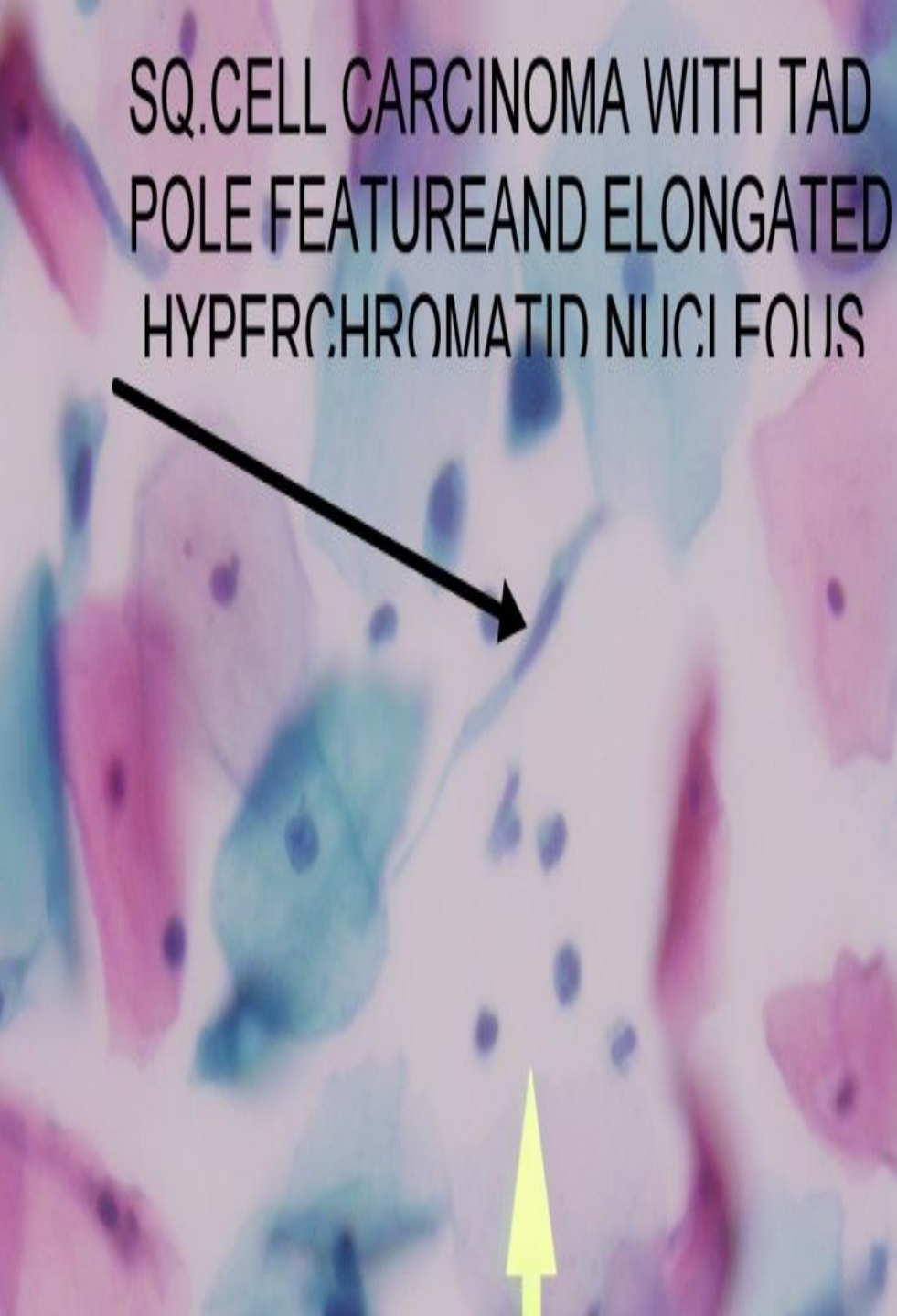
# \*Invasive

- Increased number of dyskaryotic cells
- Tumour diathesis present
- Nucleoli often more present
- Irregular parachromatin clearing or windowing
- Bizarre shapes
- Increased variation in the size and shape of the dyskaryotic cells
- Fiber cells
- Tadpole cells
- Keratinizing
- Tissue fragments
- Mitotic figures
- Abnormal chromatin with clumping and coarse aggregation



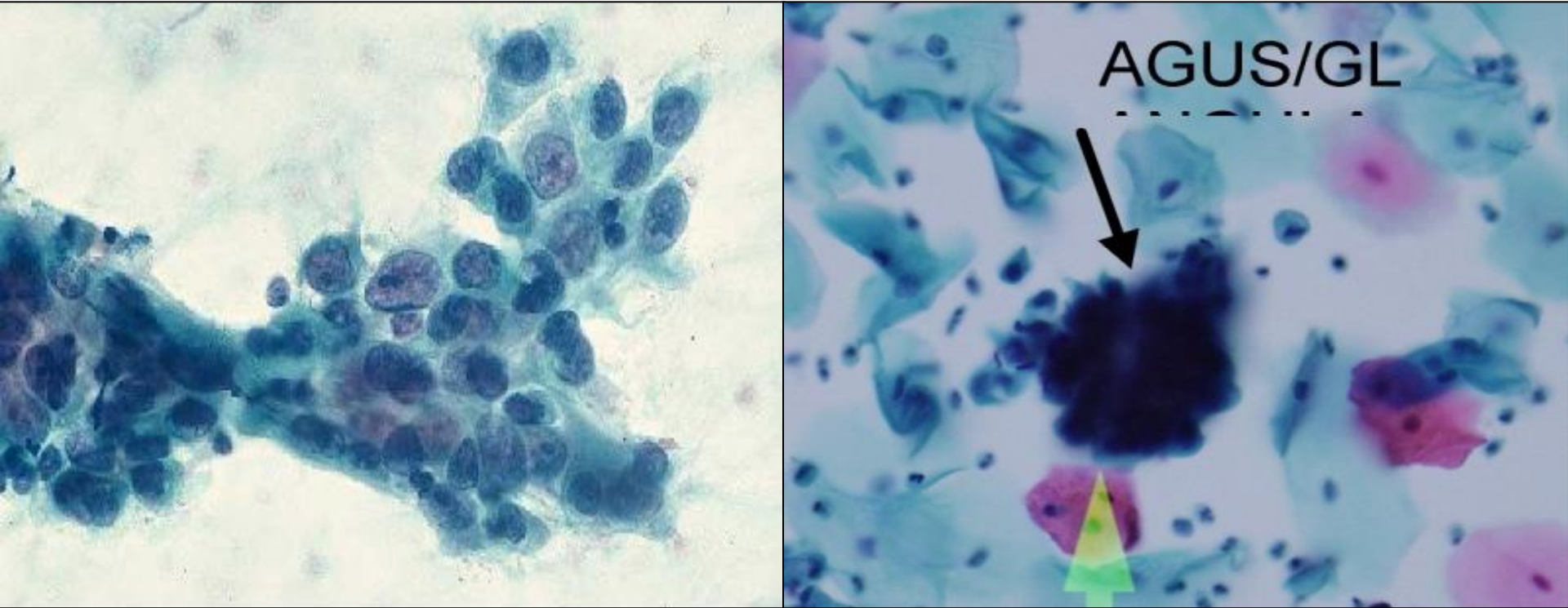
SQ.CELL CARCINOMA WITH TAD  
POLE FEATUREAND ELONGATED  
HYPERCHROMATID NUCLEI FOLIS

SQ.CELL CARCINOMA WITH TADP  
OLE FEATUREAND ELONGATED H  
YPERCHROMATID NUCLEOUS



## 2- Glandular Cells

### Atypical Glandular Cells of Undetermined Significance (AGUS)



Is the glandular cells on Papanicolaou smears that demonstrate nuclear atypia appearing to exceed reactive or reparative changes but lacking unequivocal features of adenocarcinoma. It is an unusual but important cytologic diagnosis.

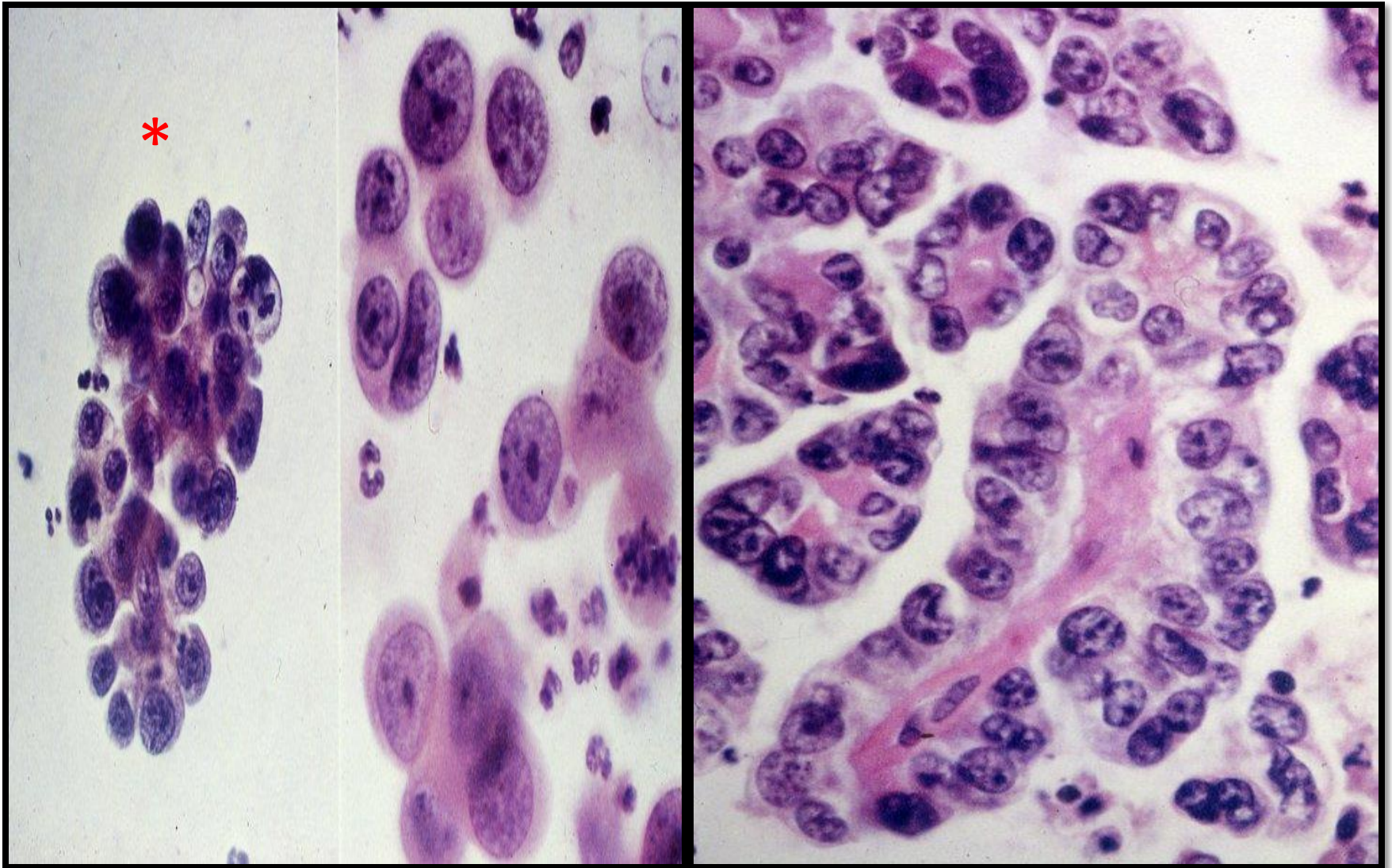
# \*Adinocarcinoma:

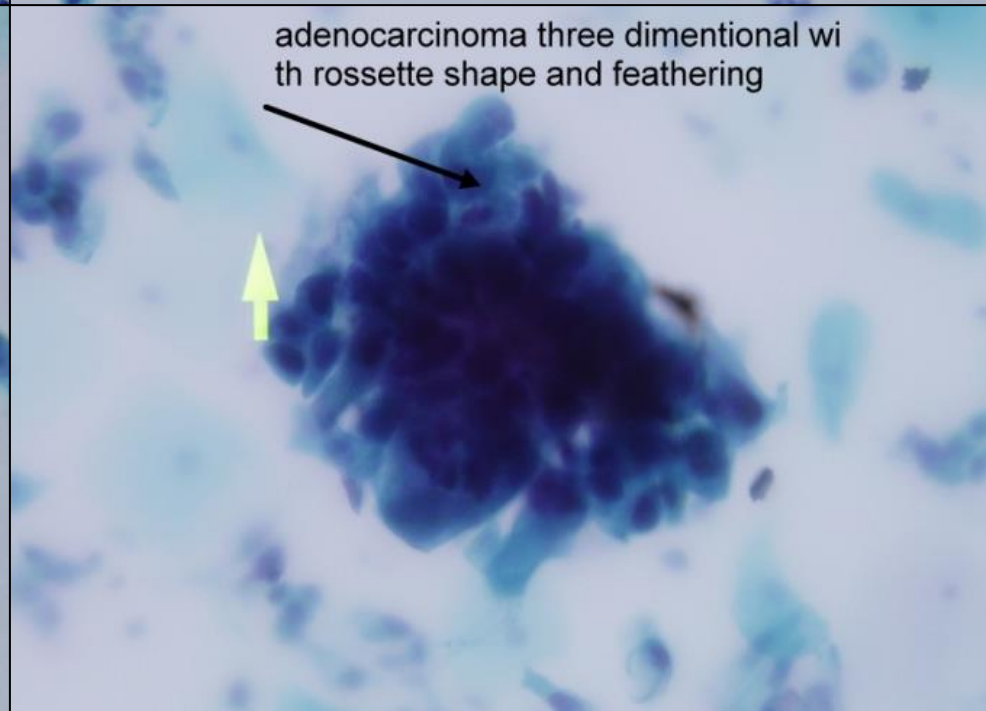
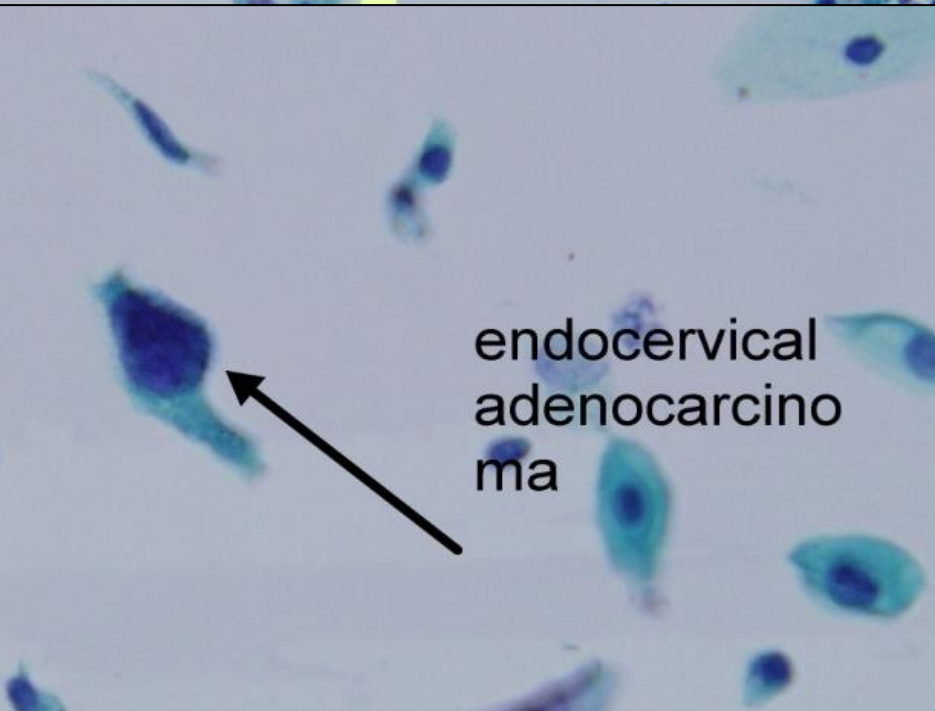
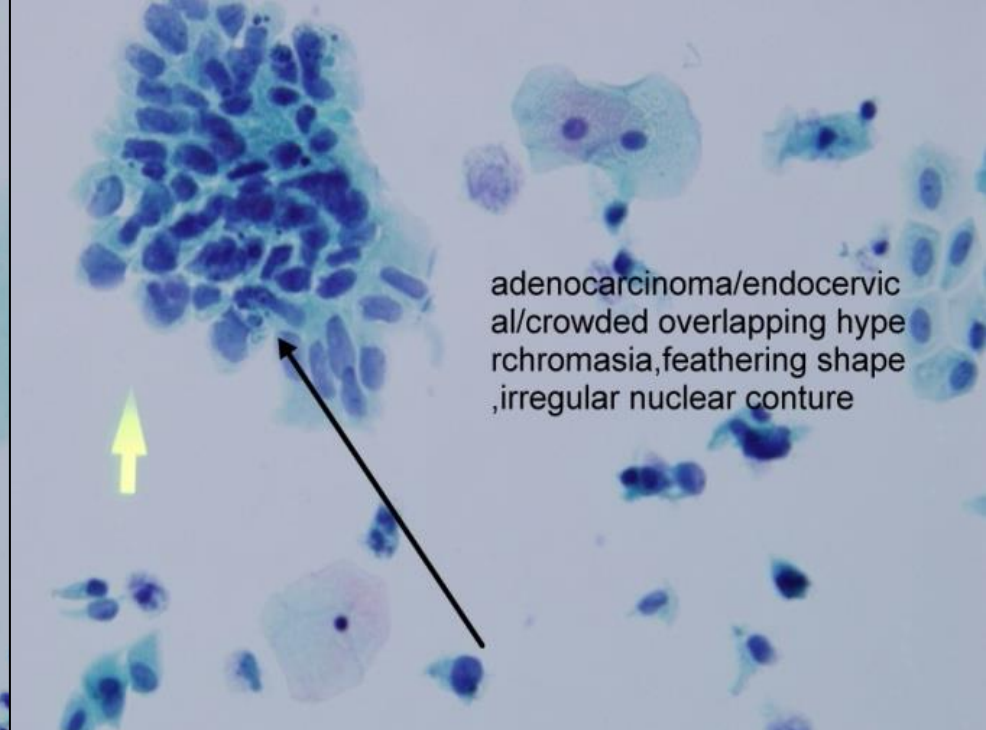
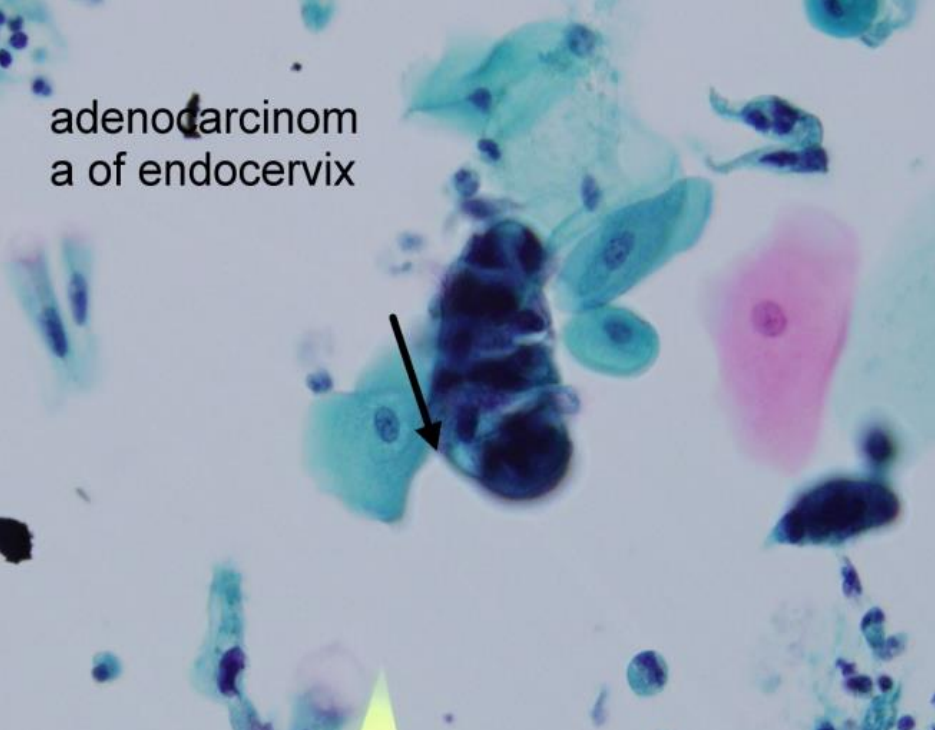
- This may be defined as a malignant neoplasm that originated from any secretory type of epithelium such as endocervical or endometrial glands.
- Pap smear, the malignant cells are in single or cluster formation. The cell outline is defined with vacuolated cytoplasm.
- Adinocarcinoma cells are seen in compact clumps, with pleomorphic nuclei and often with considerable cytoplasmic vacuolization.
- The nuclei are arranged on the outer edge of the group, giving scalloped appearance or of a raspberry.
- The enlargement of the nucleus gives an abnormal nuclear/cytoplasmic ratio.
- Chromatin pattern shows coarse clumping, with a tendency to condensation at the nuclear membrane, and prominent irregular, nucleoli are present.
- Adinocarcinoma cells have to be differentiated from histiocytes and normal bronchial epithelial.



Moderately differentiated Adenocarcinoma

Endometrial moderately diff. Adenocarcinoma





# \*Glandular abnormality (endocervical)

- More single cells
- Tumor diathesis
- Psuedostrification and hyperchromasia or hypochromasia
- Gland openings and rosettes
- Feathering present but not as pronounced
- Prominent macro-nucleoli
- More tow-dimensional than endometrial lesions
- Parachromatin clearing
- Nuclei become elongated and swollen with abnormal chromatin distribution.
- Nuclei become disorganized and lose respect for each other 's space
- Mitotic figure.
- Super crowding
- Greater depth of focus



# \*Glandular abnormality (endometrium)

- Vaculation of the cytoplasm
- Scalloped borders
- Parachromatin clearing often seen
- Enlarged nuclei crowded with overlapping borders
- Increase N/C ratio
- Prominent nucleolus
- Irregularities in nucleolus contour
- Signet ring appearance
- Bags of engulfed polymorphs
- Single cells often identified
- More three-dimensional than the endocervical cells
- Can appear in smaller numbers than the endocervical lesions
- Watery diathesis often apparent