

# Urine CYTOLOGY

The 25<sup>th</sup> Congress of the International Academy of  
Pathology / Arab Division

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# Outline

- **Introduction**
- **Specimens & processing**
- **Reporting and adequacy**
- **Accuracy**
- **Normal elements**
- **Benign**
- **Ancillary tests**

# Introduction

- **Bladder cancer is the ninth most common cancer worldwide**
- **The age standardized incidence for north Africa is  $>5.3$  and  $<9.2$  /100,000 population**
- **The incidence is higher in Sudan and Saudi Arabia**
- **Egypt and Sudan also have a higher proportion of squamous cell carcinoma due to *Schistosoma hematobium***

# Introduction

- **At this point, there is no routine, effective bladder cancer screening test.**
- **However, urine cytology (consult) can be used as a surveillance tool for:**
  - **populations at high risk**
  - **symptomatic patients**
  - **patients with known prior urothelial malignancy.**
- **Urine cytology is feared because of low predictive values**
- **The low efficiency of urine cytology is inherent in the features of the urothelial lesions**

# CLINICAL INDICATIONS OF URINE CYTOLOGY

- **Hematuria**
- **Follow up for patients treated for UC**
- **Patients at high risk for bladder cancer**

# URINE SPECIMEN TYPES

Specimen Type	Advantages	Disadvantages
Voided urine	Noninvasive	Low cellularity
	No instrumentation artifact	Vaginal contamination
Catheterized	High cellularity	Poor preservation
		Invasive
Bladder washing	Instrumentation artifact	Poor preservation
	High cellularity	Invasive
Upper tract washing	Good cell preservation	Instrumentation artifact
	High cellularity	Invasive
Brush cytology	Good preservation	Instrumentation artifact
	Selective sampling	Invasive
Ileal loop	Selective sampling	Air drying possible (if direct smear)
	Permits screening for recurrent bladder cancer	Low cellularity
		Poor preservation

# PROCESSING

- **Fresh (1-12 hours), otherwise need fixation**
- **Refrigeration if more**
- **Fixation with equal volume of alcohol (50-70% ethanol).**
- **Cytocentrifugation, LBC, Cell block, smears**
- **Papanicolaou stain (H&E)**

# ADEQUACY

- **No standards**
- **Unsatisfactory specimen:**
  - **Vaginal cells only**
  - **Obscuring inflammation or lubricant**
  - **Blood only**
  - **Marked degeneration**



# ACCURACY

- **URINE:**

- Sensitivity: 25-75% for all grades
- Sensitivity increases when suspicious & with more than one specimen (3X)
- Grade dependent
- Post treatment (RT & CT), less detection (FISH)
- Specificity is high (95-100%)
- False +ve: stones, CT, Polyoma V
- LG papillary vs HG & CIS

# ACCURACY

- **BLADDER WASHINGS:**
  - **Sensitivity: 66-77%**
  - **More false positive than urine**
  - **Ureter and pelvic washings 70-80% sensitivity**

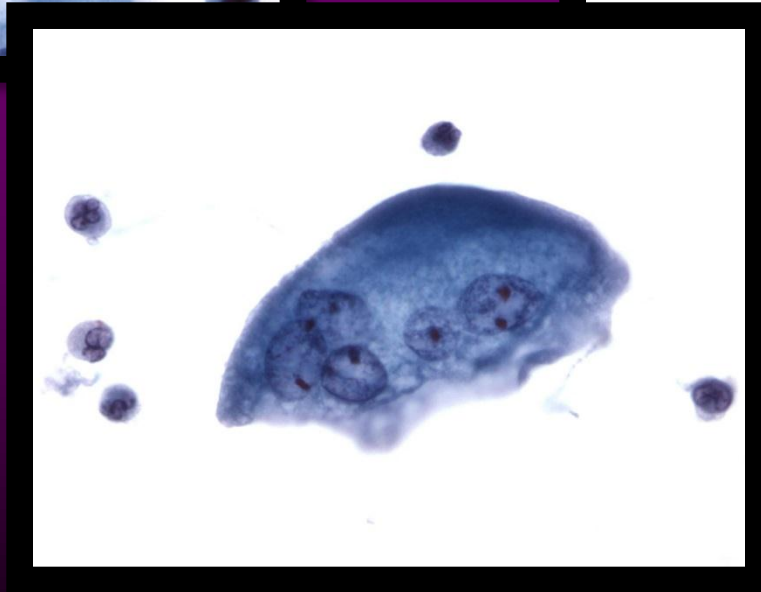
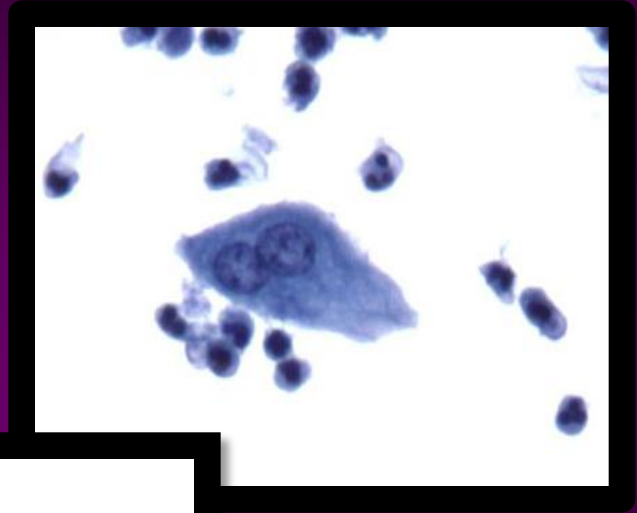
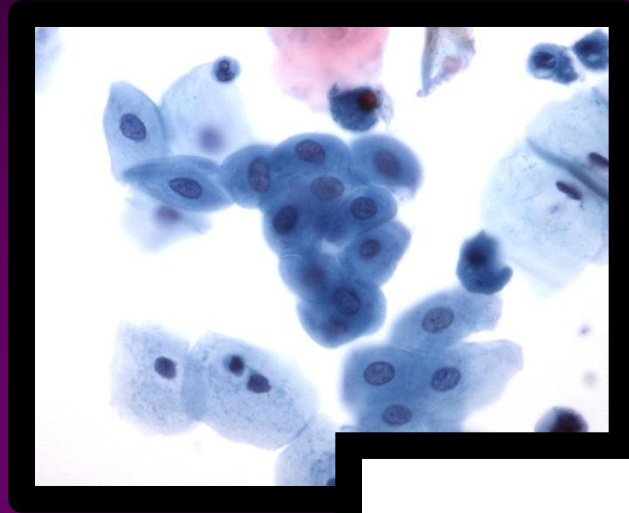
# CONVENTIONAL WISDOM

*“Low grade urothelial carcinoma are usually missed by the cytologist but seen by the urologist; while high grade carcinoma are easily identified by the cytologist but difficult to locate by the urologist”*

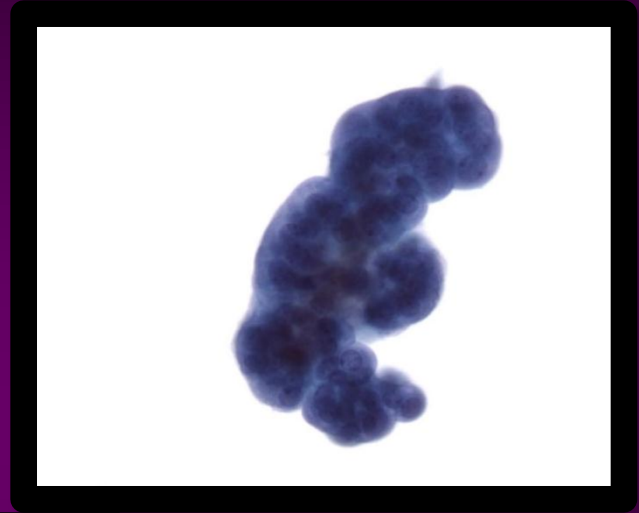
# NORMAL ELEMENTS:

- **Urothelial cells:**
  - **intermediate and superficial (umbrella) cells (voided urine)**
  - **intermediate, superficial, and basal cells (catheterized urine, washings)**
- **Squamous cells**
- **Seminal vesicle epithelial cells (rare)**
- **Degenerated intestinal epithelial cells (ileal conduit specimens)**

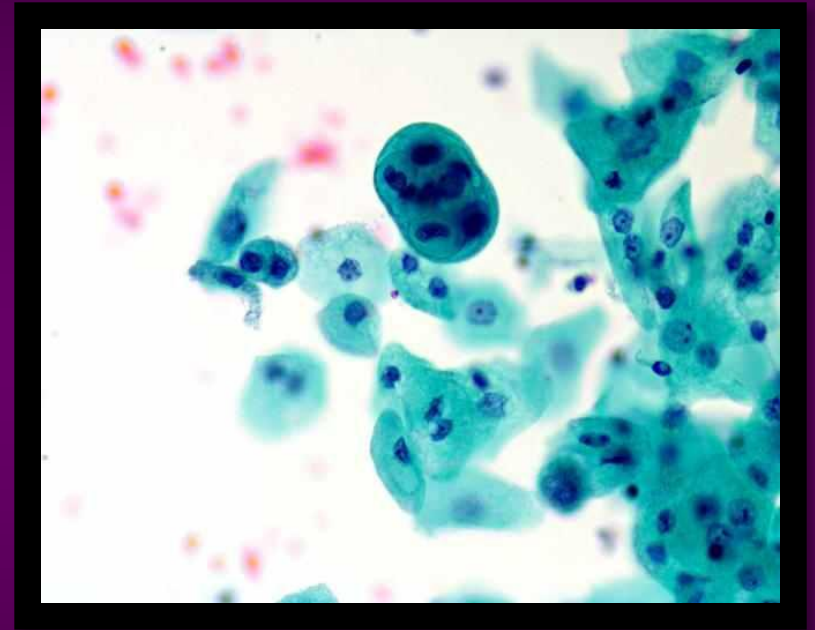
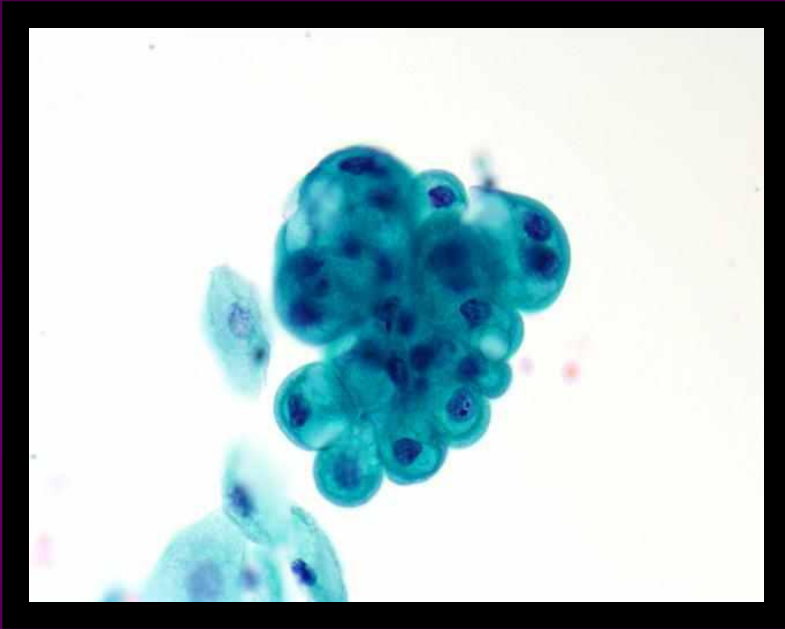
# UMBRELLA CELLS



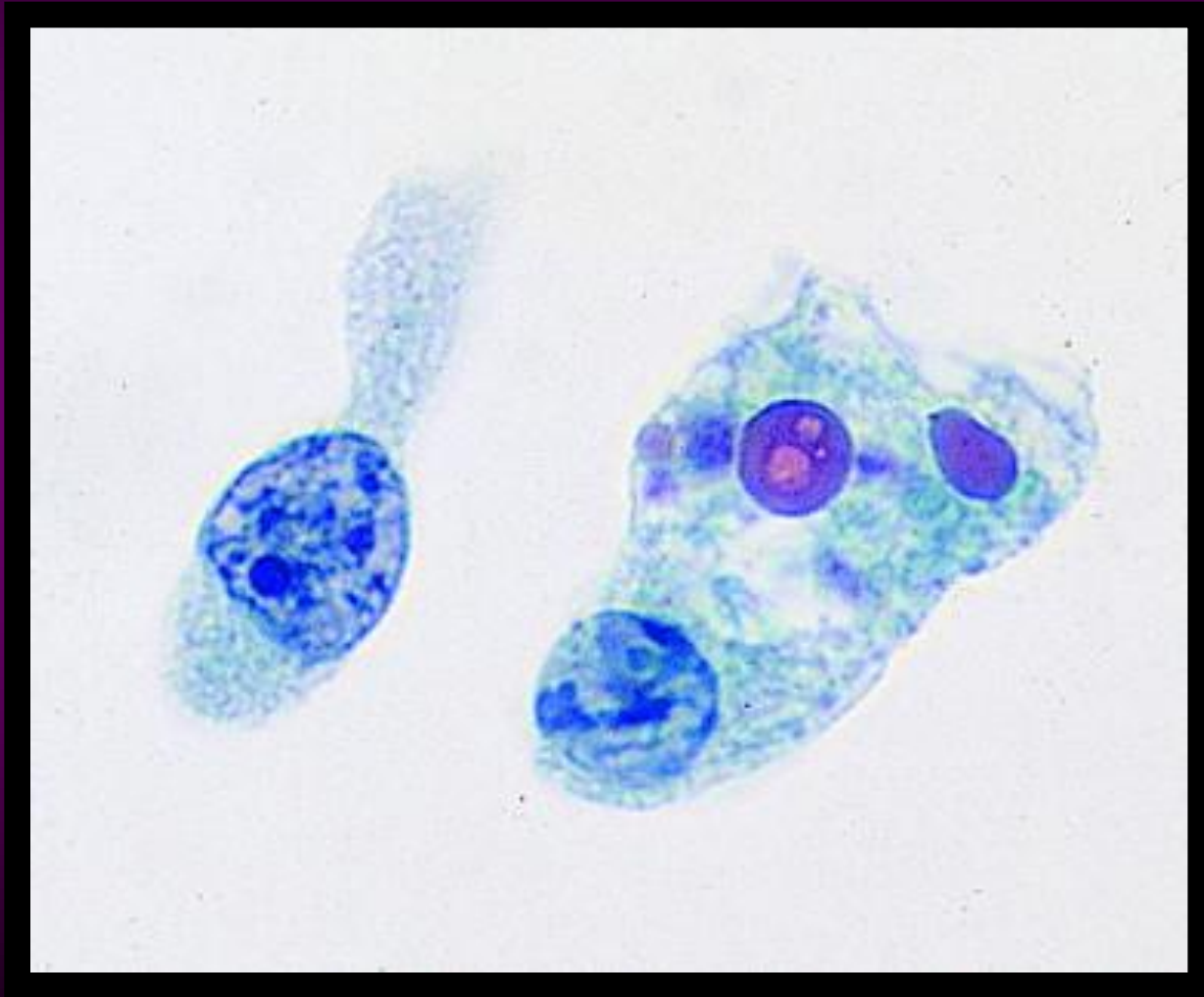
# NORMAL URINE



# Normal

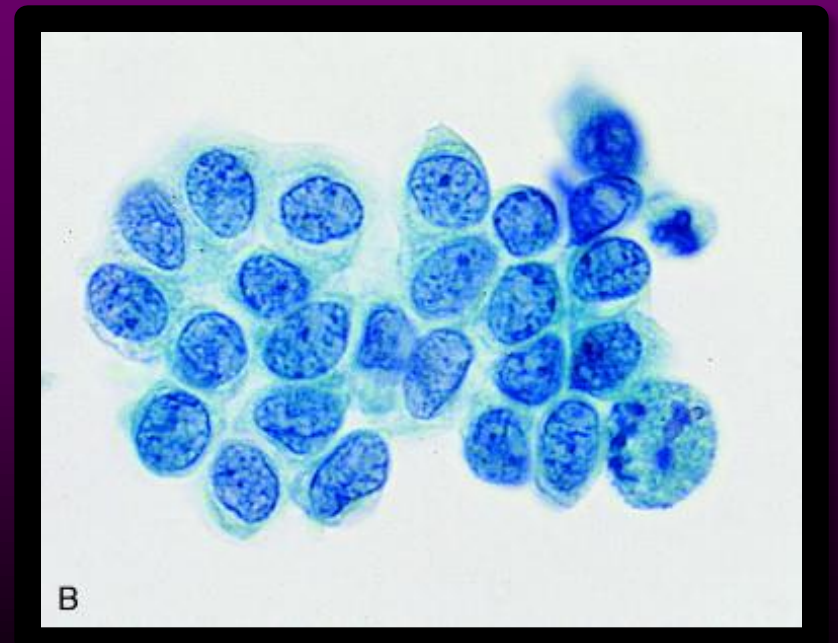
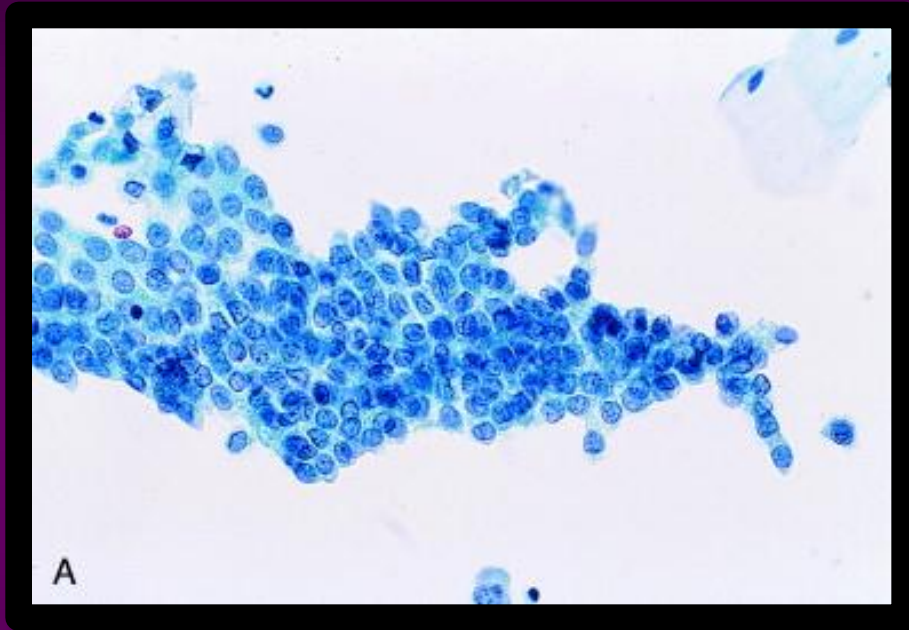


# DEGENERATED UROTHELIAL CELLS (MELAMED-WOLINSKA BODIES)

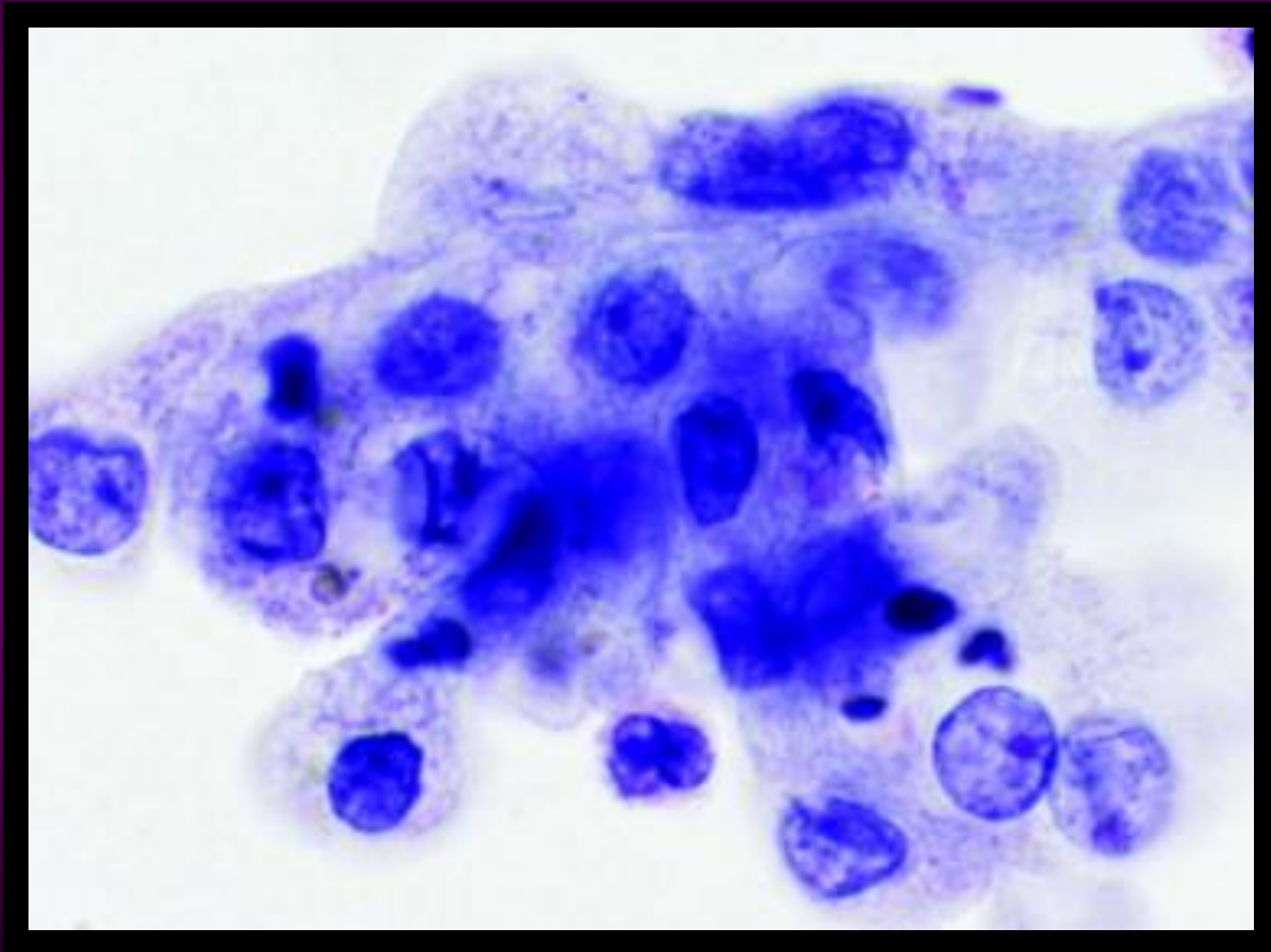




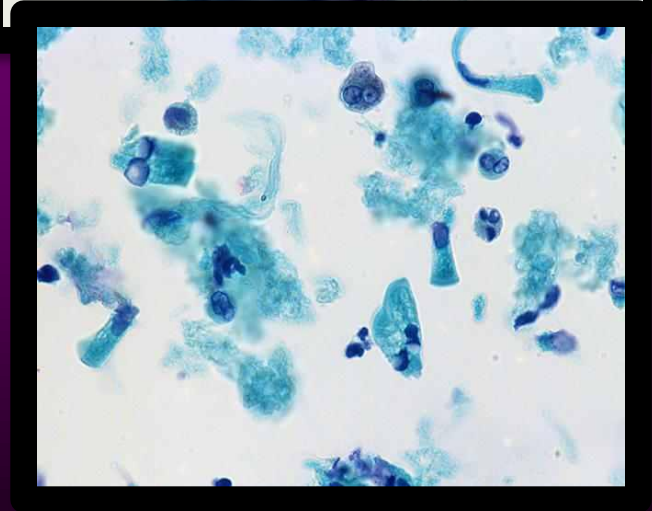
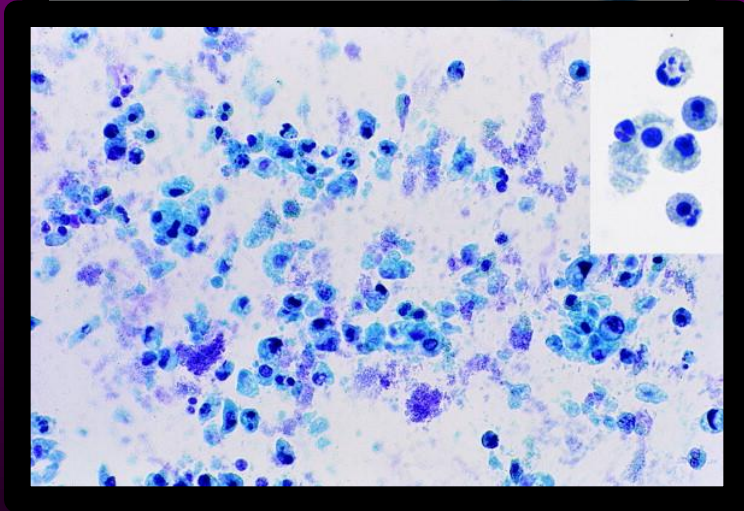
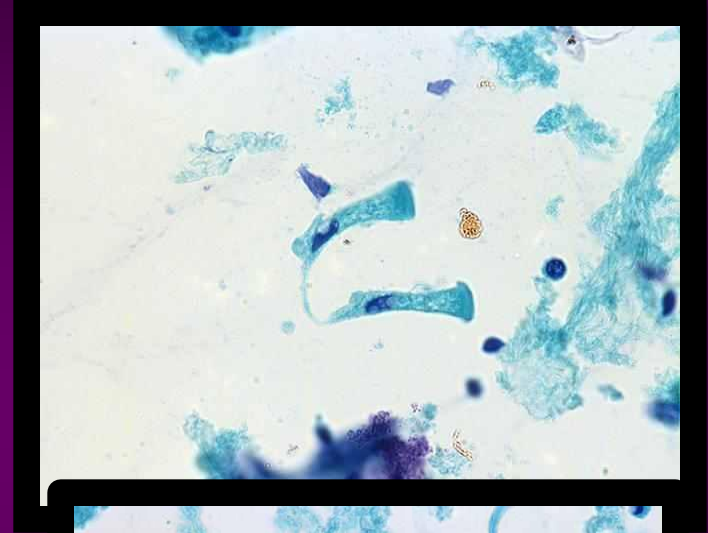
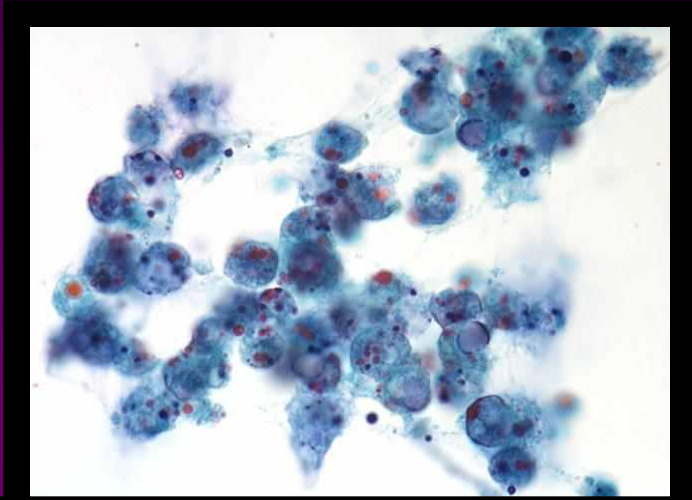
# BASAL CELLS



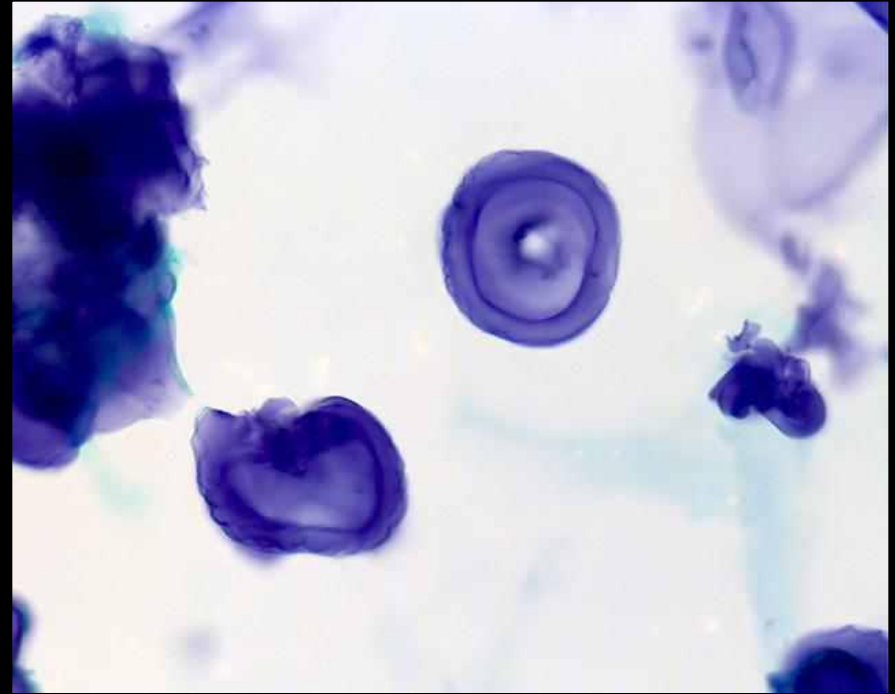
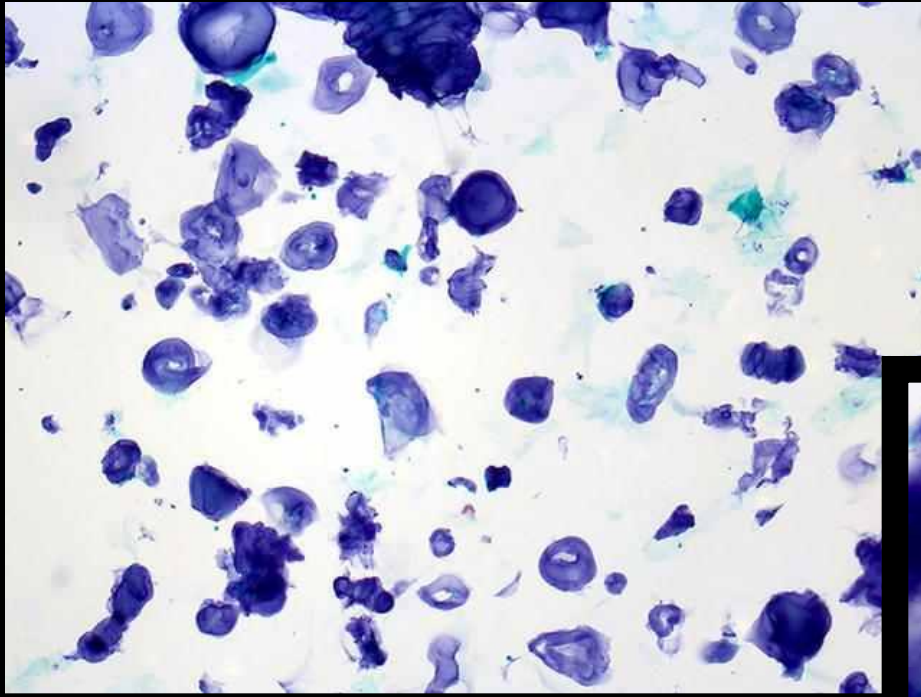
# SEMINAL VESICLE EP CELLS



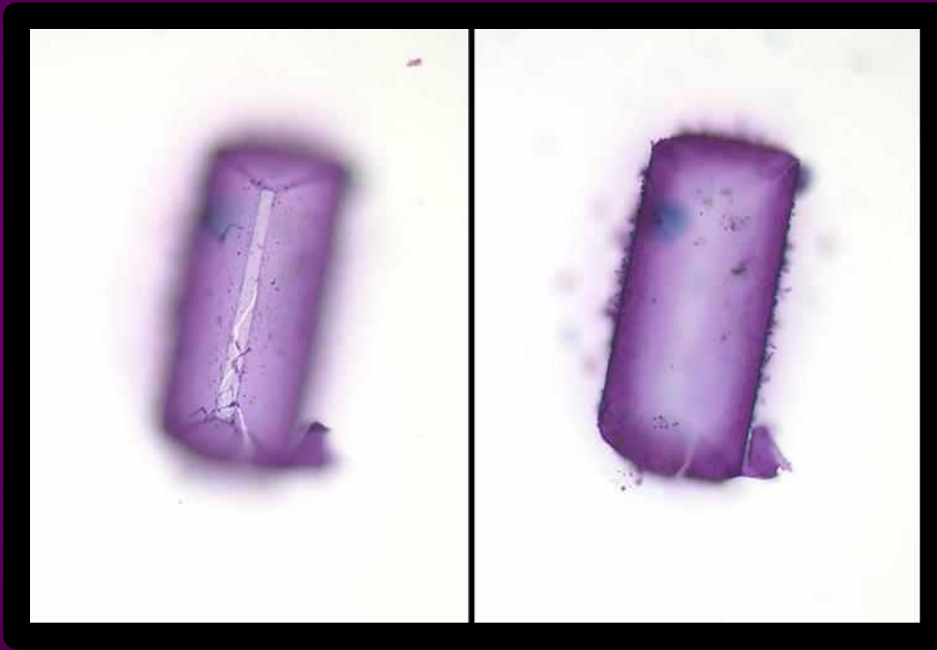
# ILEAL LOOP



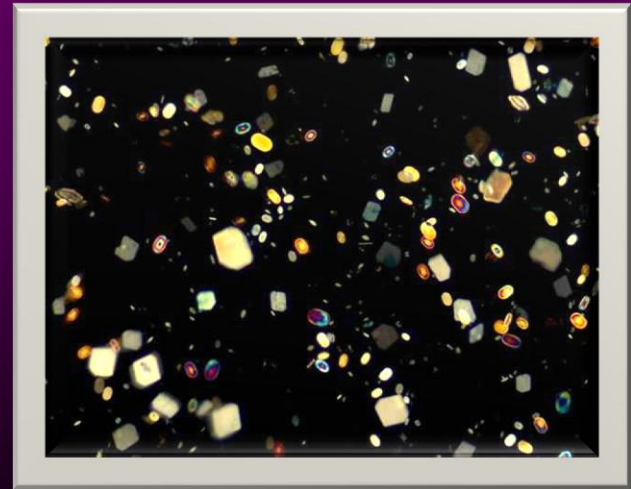
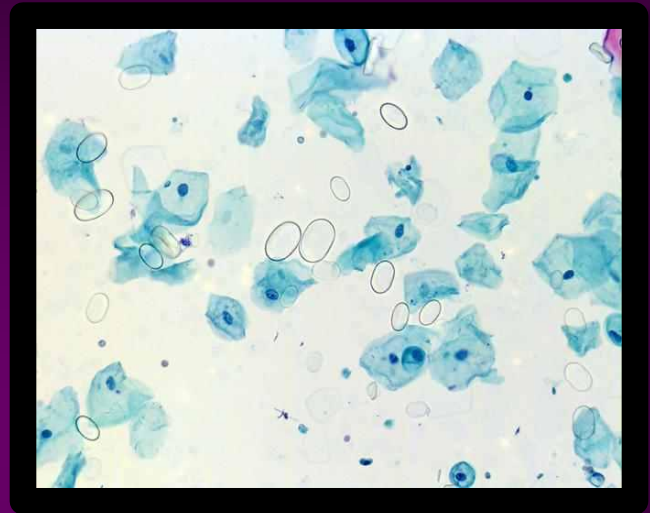
# Lubricant



# Triple phosphate crystals

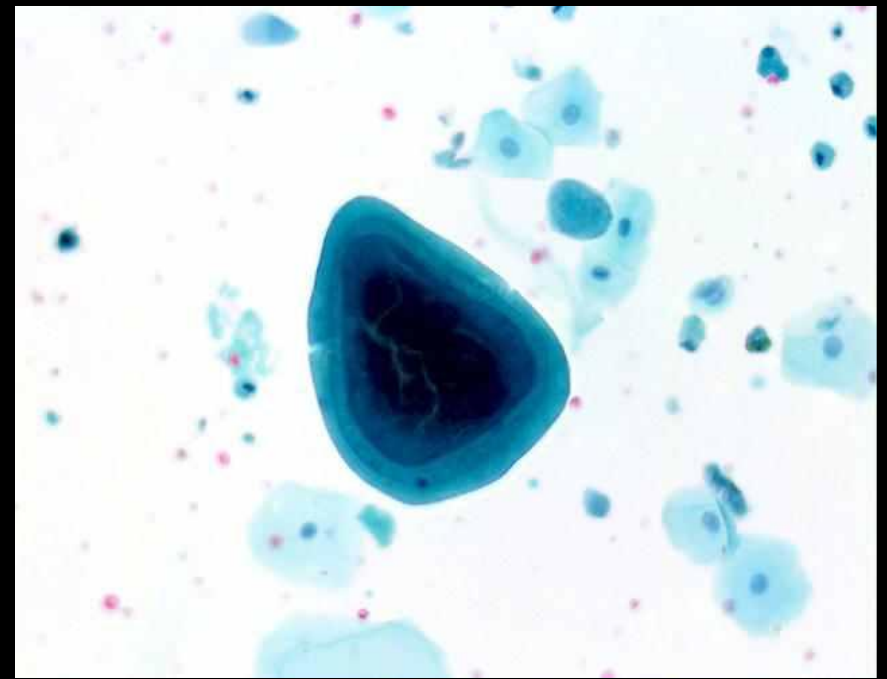
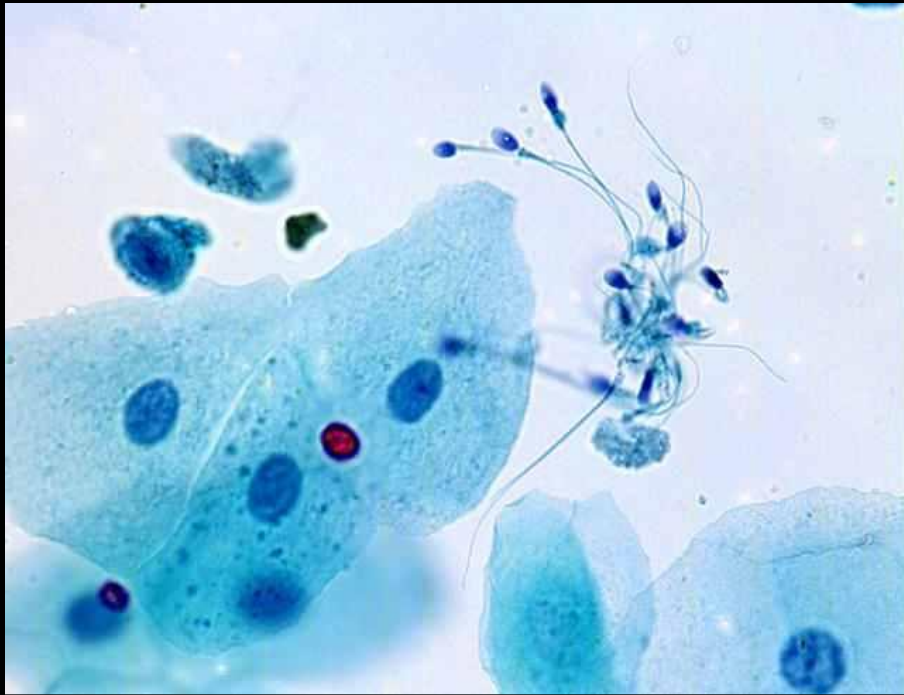


# Urate crystals



# Sperms

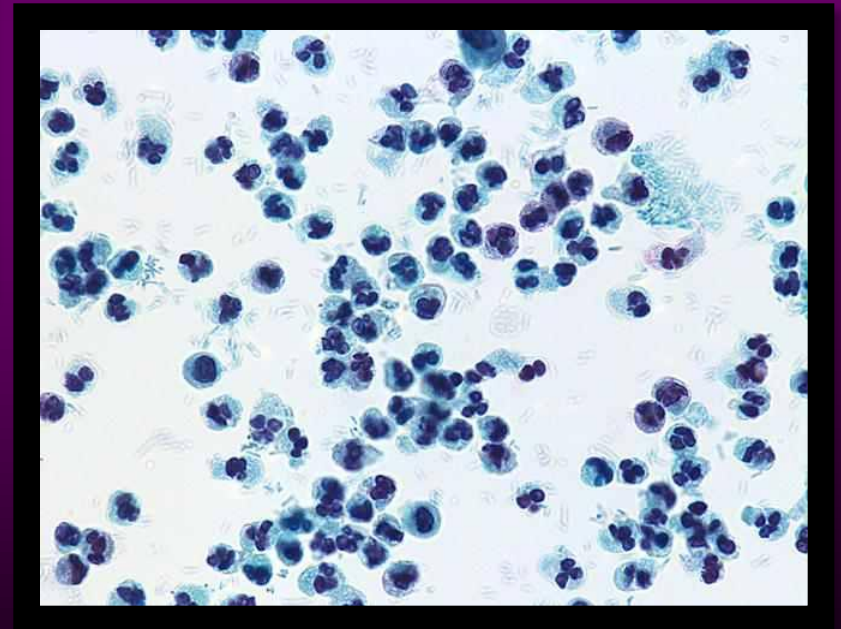
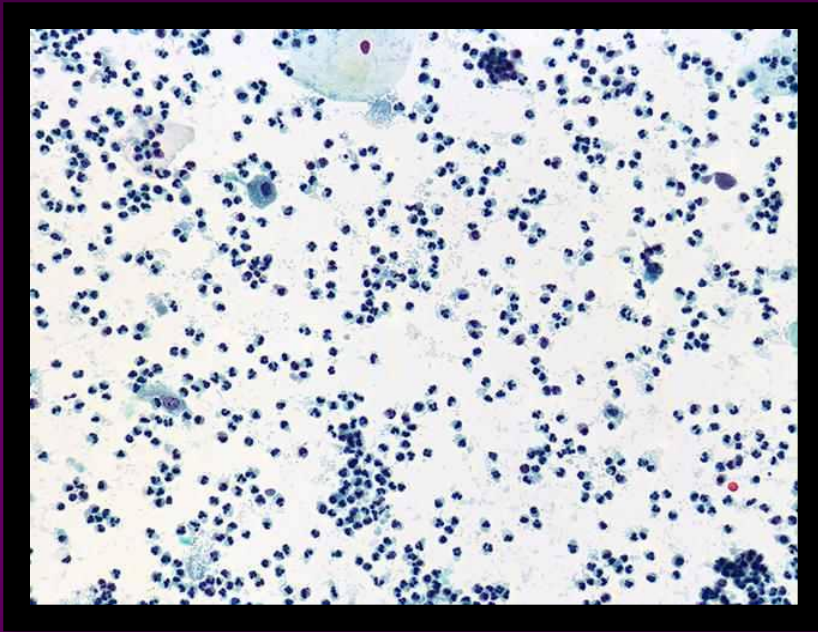
# Corpora amylacea



# INFECTIONS

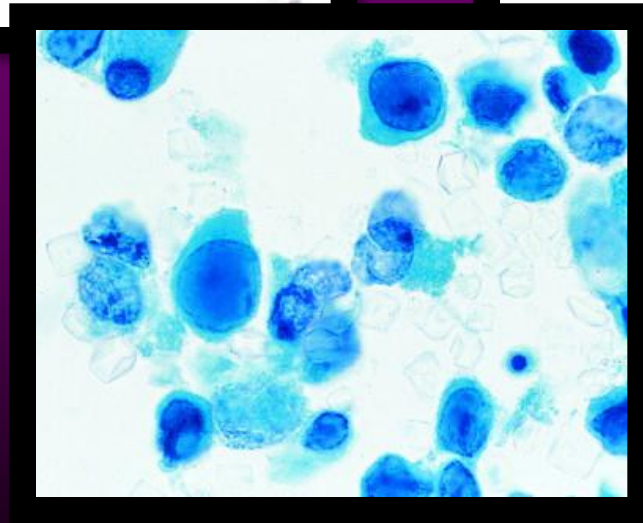
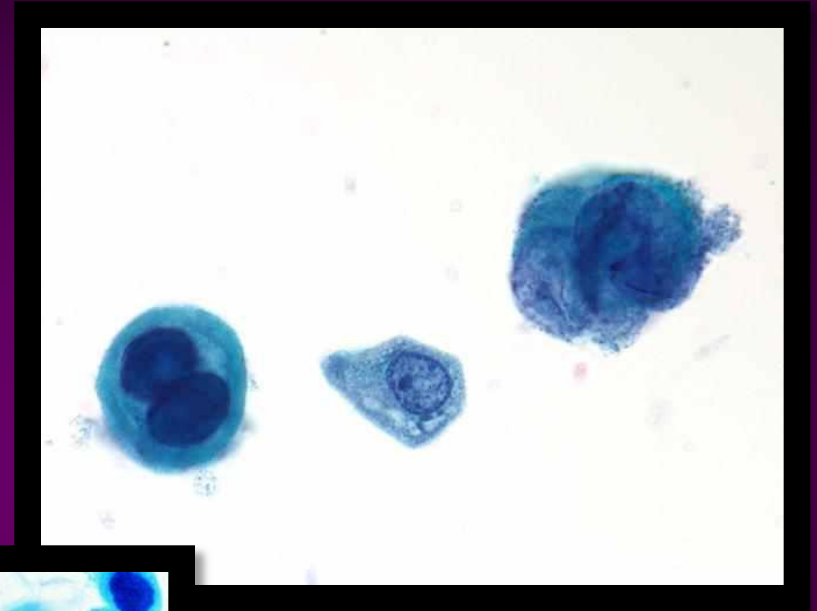
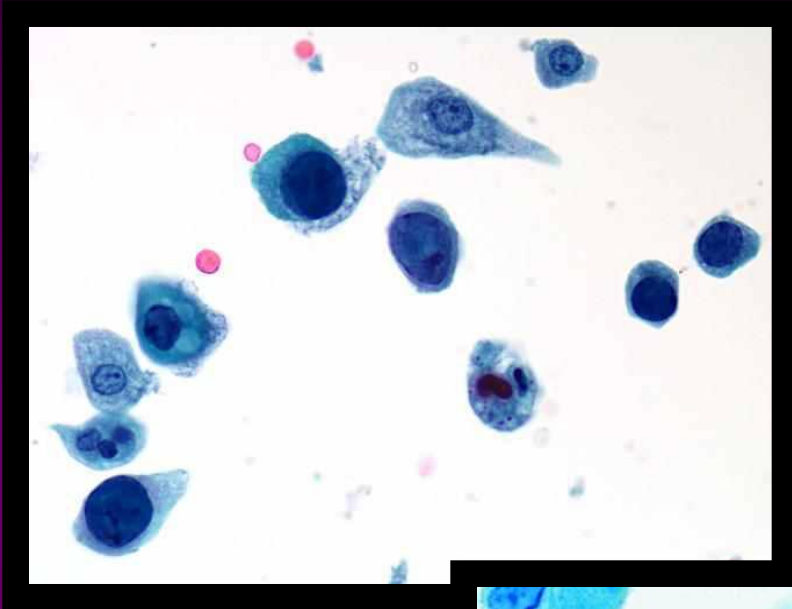
- Bacteria, including malakoplakia
- Fungi (especially *Candida*)
- Herpes simplex virus
- Cytomegalovirus (CMV)
- *Trichomonas vaginalis*
- Polyomavirus
- Human papillomavirus (HPV)

# Acute cystitis

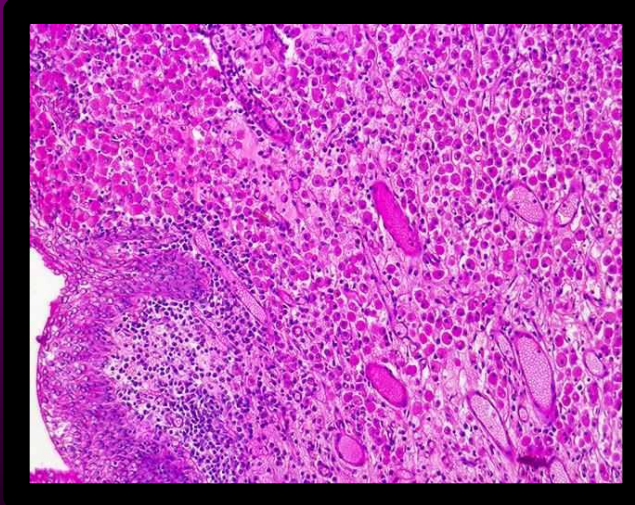
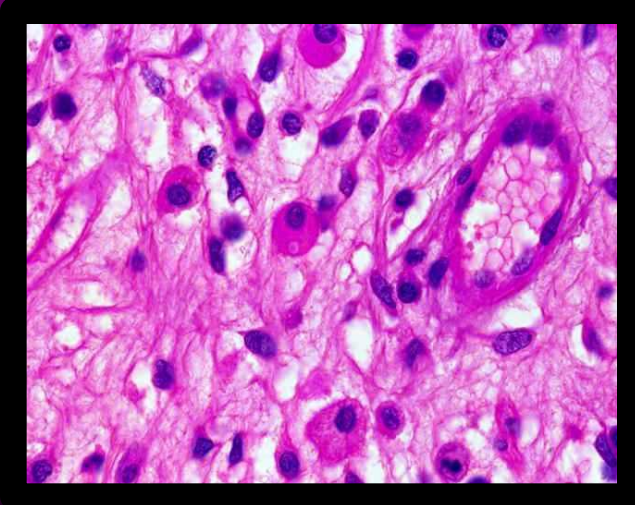
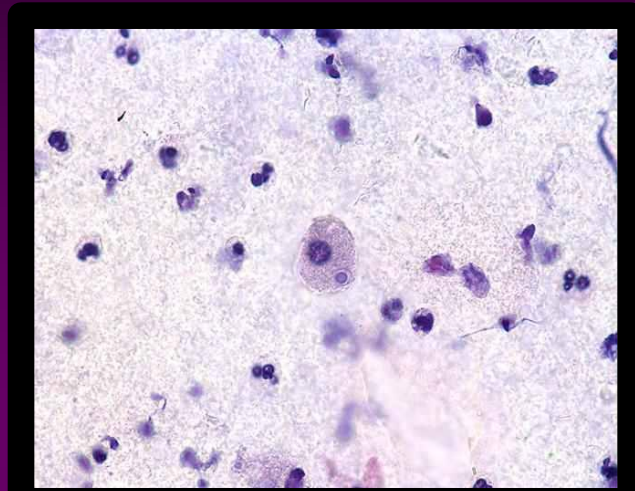
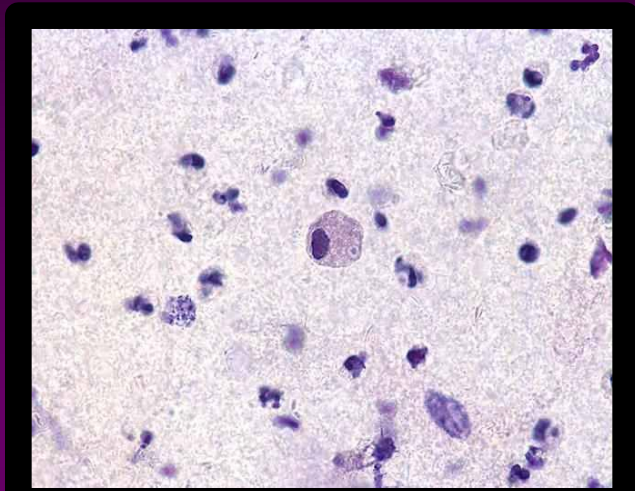




# BK virus “Polyoma”



# Malakoplakia “MG bodies”



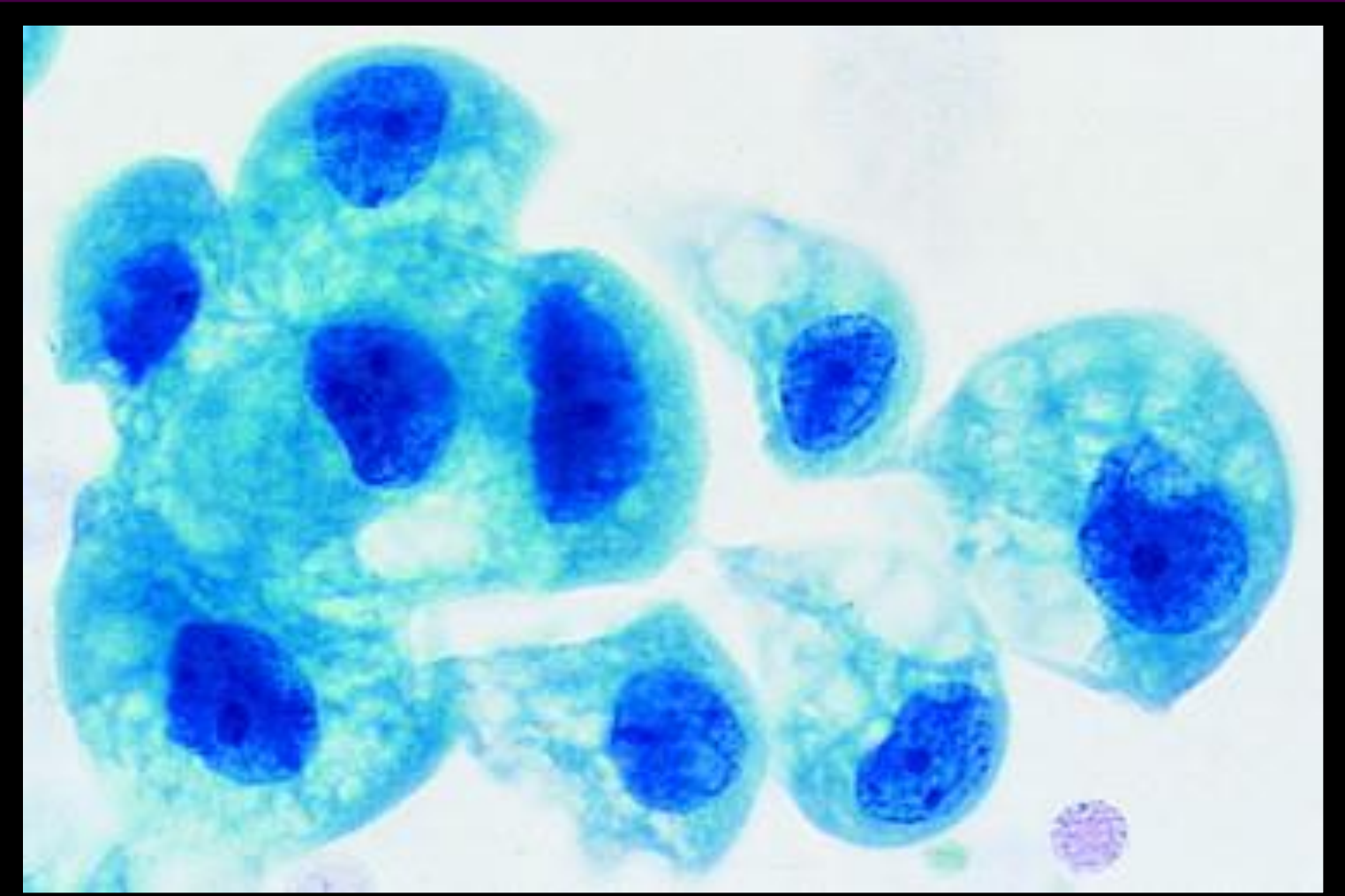
# **NONINFECTIOUS FINDINGS AND CONDITIONS:**

- **Crystals**
- **Casts**
- **Nonspecific reactive urothelial cell changes**
- **Chemotherapy effect**
- **Radiation therapy effect**
- **Urothelial atypia associated with urinary calculi**

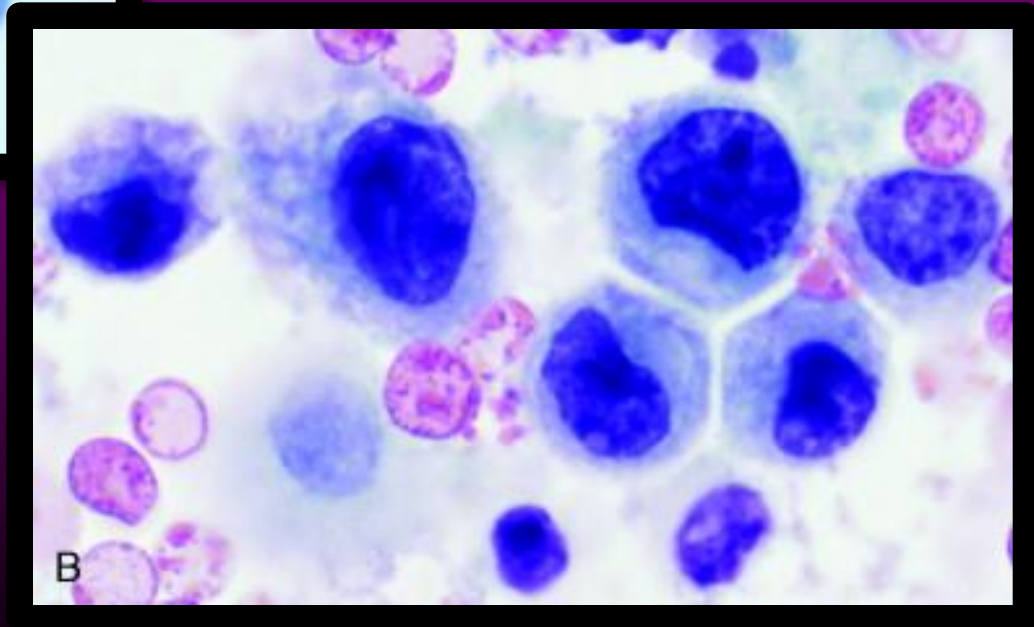
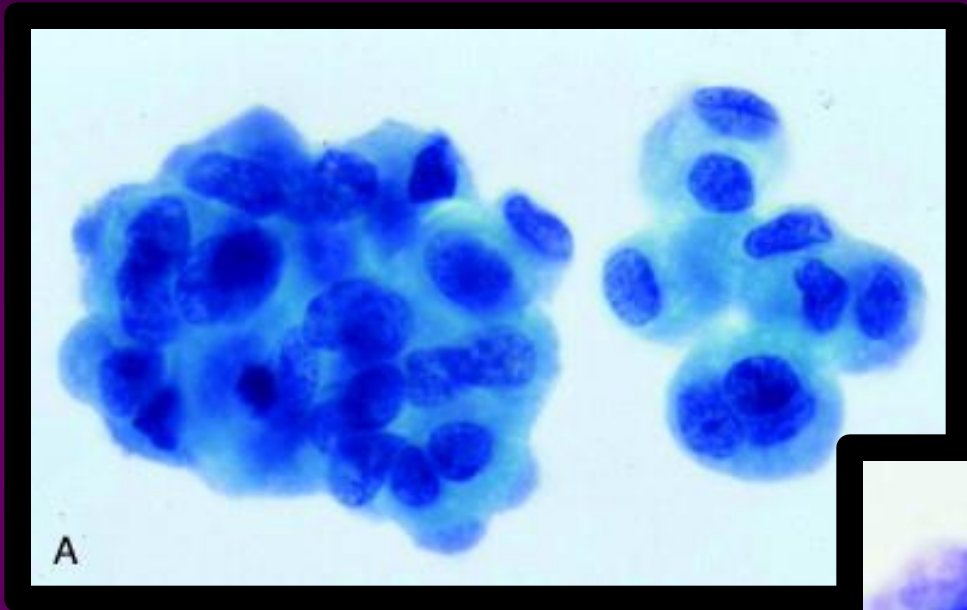
# **CYTOMORPHOLOGY OF NONSPECIFIC REACTIVE CHANGES:**

- **Enlarged nuclei**
- **Prominent nucleoli**
- **Coarsely vacuolated cytoplasm**

# REACTIVE UC (CATHETERIZED URINE):



# STONE ATYPIA: BE VERY CAREFUL



# UROTHELIAL NEOPLASMS

**CURRENT WORLD HEALTH ORGANIZATION AND INTERNATIONAL SOCIETY OF UROLOGIC PATHOLOGISTS CLASSIFICATION SYSTEM**

**FOR UROTHELIAL NEOPLASMS:**

- **Flat lesions:**
  - **Dysplasia ??????????**
  - **Carcinoma in situ**
- **Papillary lesions**
  - **Papilloma**
  - **PUNLMP**
  - **Low-grade UC**
  - **High-grade UC**



	Papilloma	Papillary neoplasm of low malignant potential	Low-grade papillary carcinoma	High-grade papillary carcinoma
Architecture				
Papillae	Delicate	Delicate; occasionally fused	Fused, branching, and delicate	Fused, branching, and delicate
Organization of cells	Identical to normal	Polarity identical to normal; any thickness; cohesive	Predominantly ordered, yet minimal crowding and minimal loss of polarity; any thickness; Cohesive	Predominantly disordered with frequent loss of polarity; any thickness; often dyscohesive
Cytology				
Nuclear size	Identical to normal	May be uniformly enlarged	Enlarged with variation in size	Enlarged with variation in size
Nuclear shape	Identical to normal	Elongated, round-oval, uniform	Round-oval; slight variation in shape and contour	Moderate-marked pleomorphism
Nuclear chromatin	Fine	Fine	Mild variation within and between cells	Moderate-marked variation both within and between cells with hyperchromasia
Nucleoli	Absent	Absent to inconspicuous	Usually inconspicuous*	Multiple prominent nucleoli may be present
Mitoses	Absent	Rare, basal	Occasional, at any level	Usually frequent, at any level
Umbrella cells	Uniformly present	Present	Usually present	May be absent

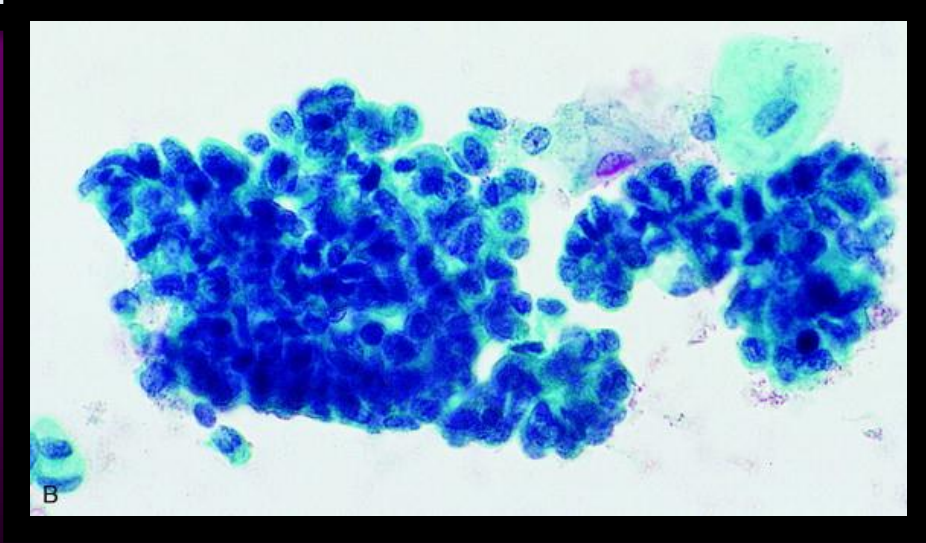
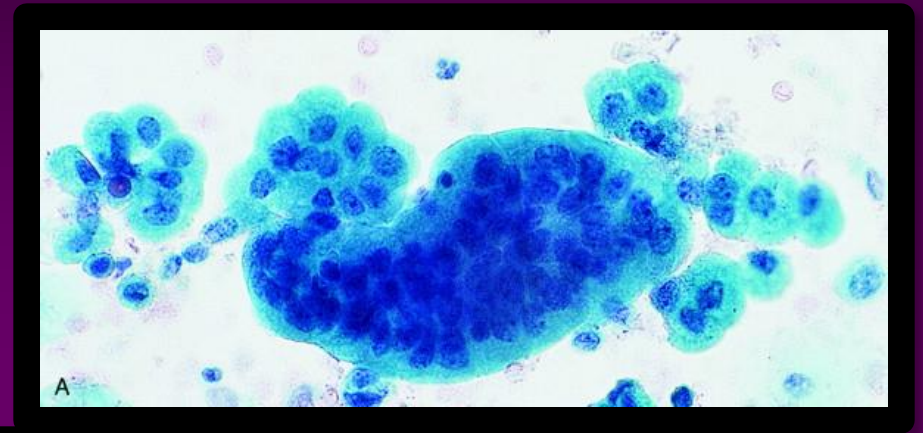
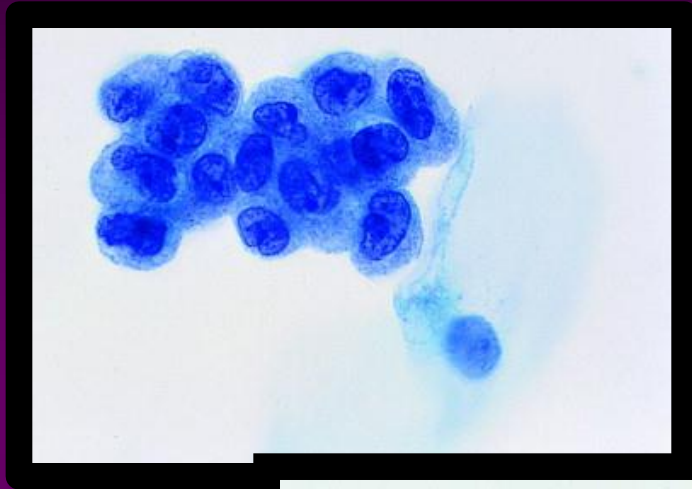
\* If present, small and regular and not accompanied by other features of high-grade carcinoma.

**LOW GRADE  
UROTHELIAL  
CARCINOMA**

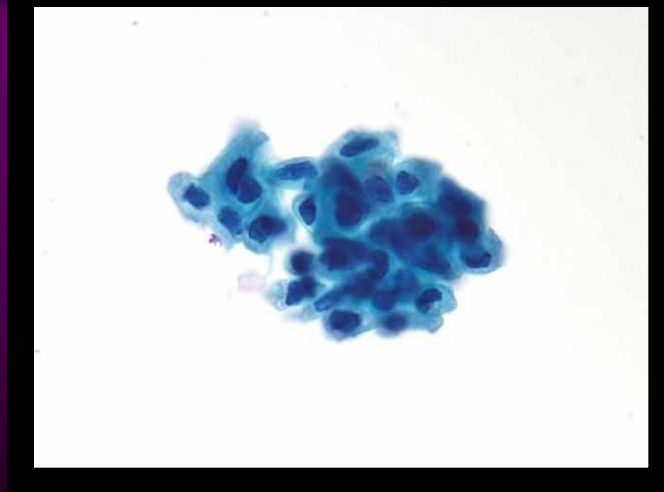
# **CYTOLOGIC CRITERIA FOR DIAGNOSING LOW-GRADE LESIONS:**

- **Cytoplasmic homogeneity**
- **High nuclear-to-cytoplasmic ratio**
- **Irregular nuclear membranes**

# LOW-GRADE UC



# LOW-GRADE UC

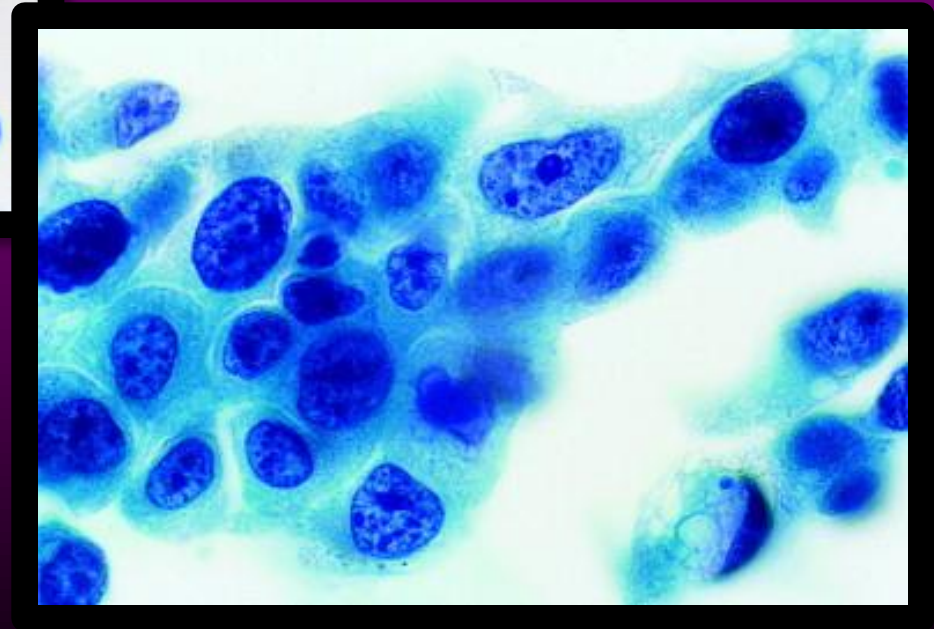
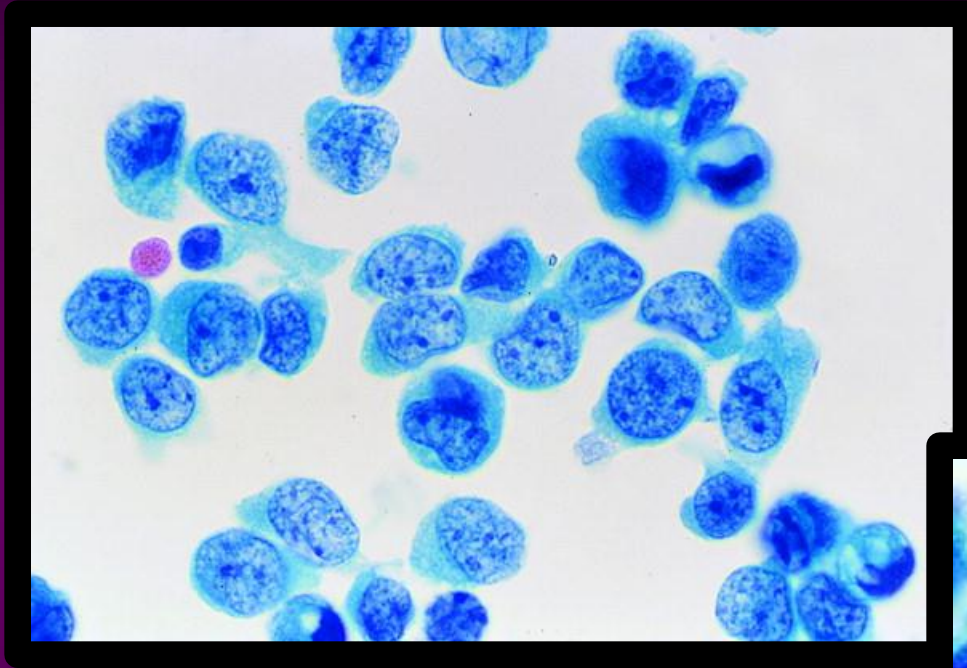


# HIGH GRADE UROTHELIAL CARCINOMA

# **CYTOMORPHOLOGY OF CARCINOMA IN SITU AND HIGH-GRADE UROTHELIAL CANCER:**

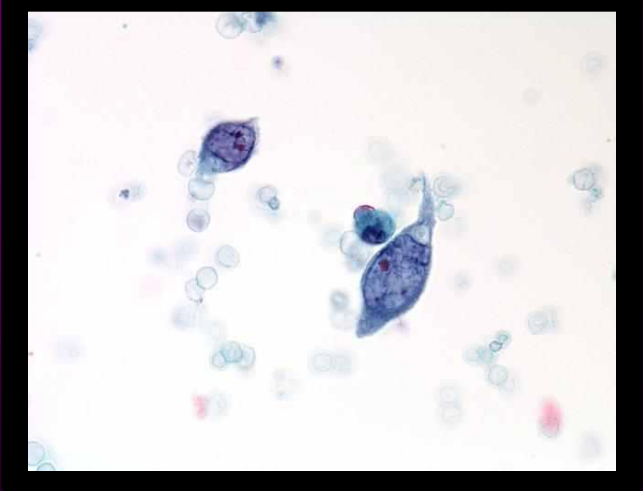
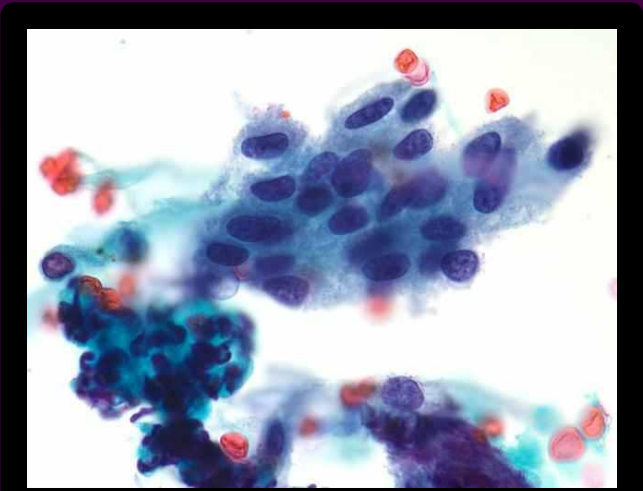
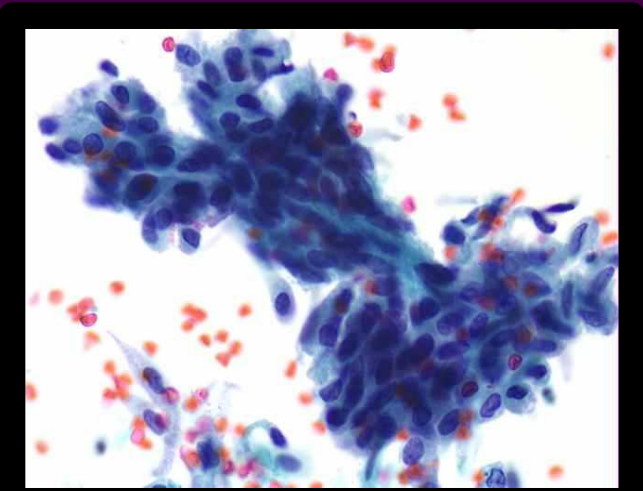
- **High nuclear-to-cytoplasmic ratio**
- **Marked nuclear hyperchromasia**
- **Coarsely granular chromatin**
- **Irregular nuclear outline**
- **Large nucleoli (some cases)**

# HIGH GRADE UC

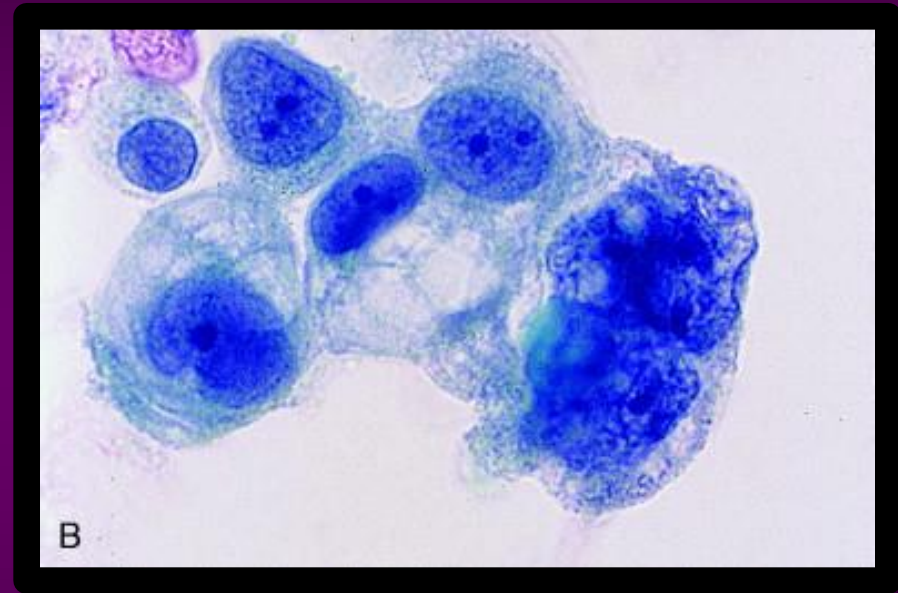
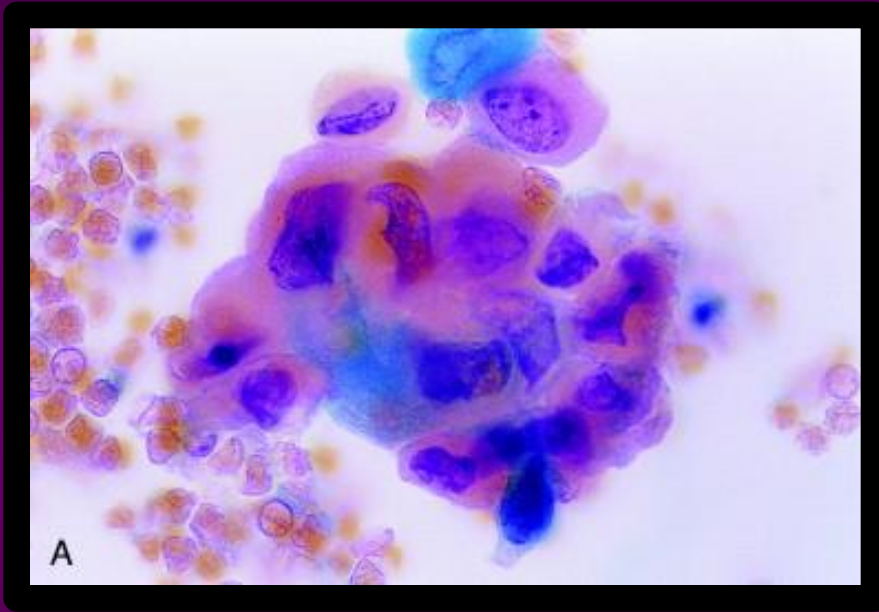




# High grade urothelial carcinoma



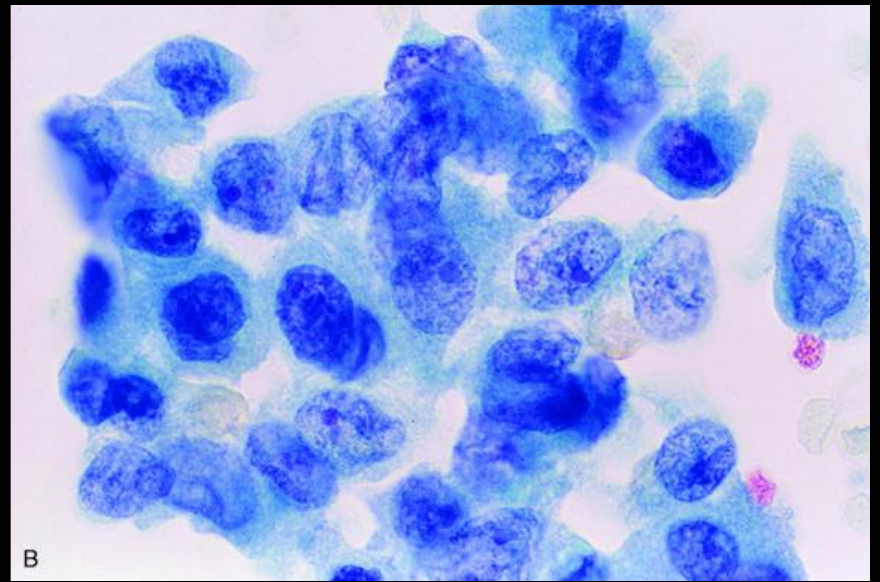
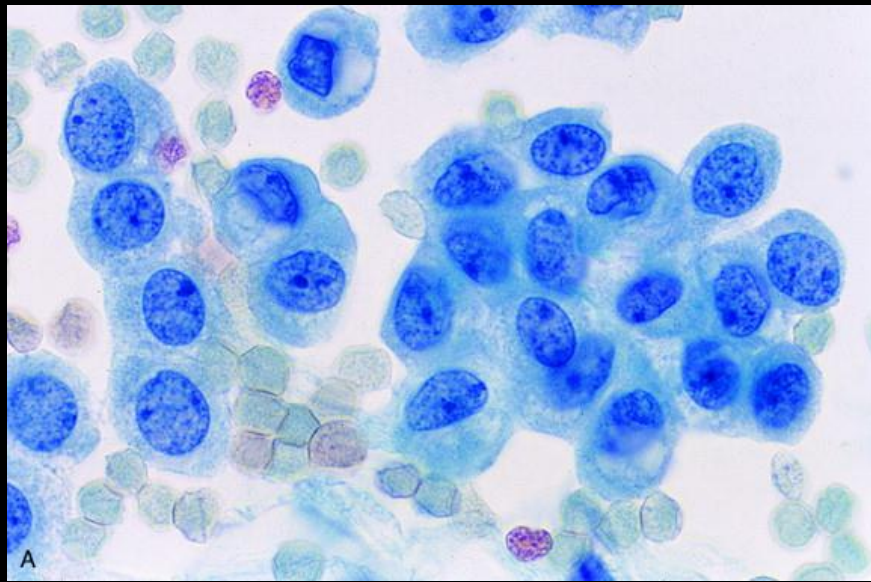
# VARIANTS: SQUAMOUS                      GLANDULAR DIFFERENTIATION



# **DIFFERENTIAL DIAGNOSIS OF CARCINOMA IN SITU AND HIGH-GRADE UROTHELIAL CARCINOMA:**

- **Polyomavirus**
- **Stone atypia**
- **Normal upper tract washings or brushings**
- **Treatment effect**
- **Nonspecific reactive changes**

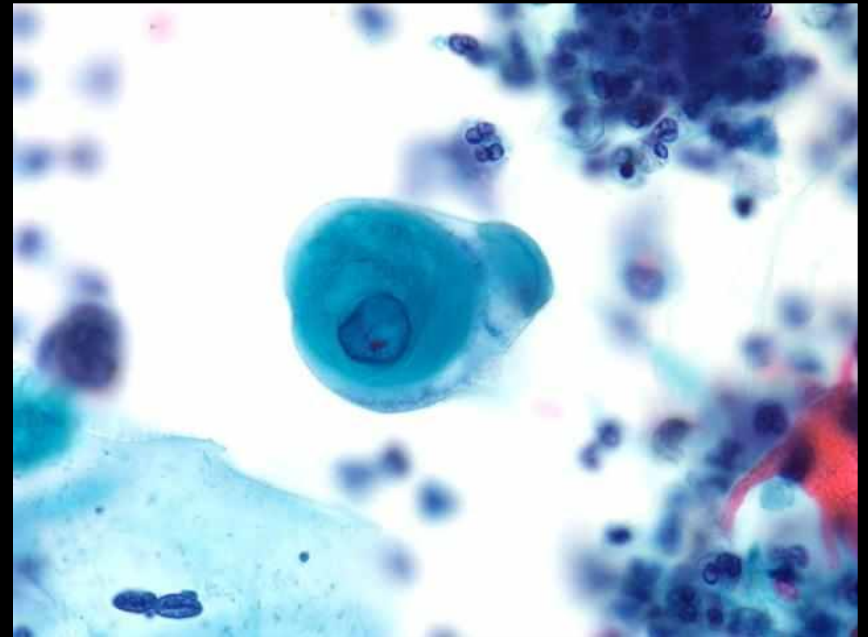
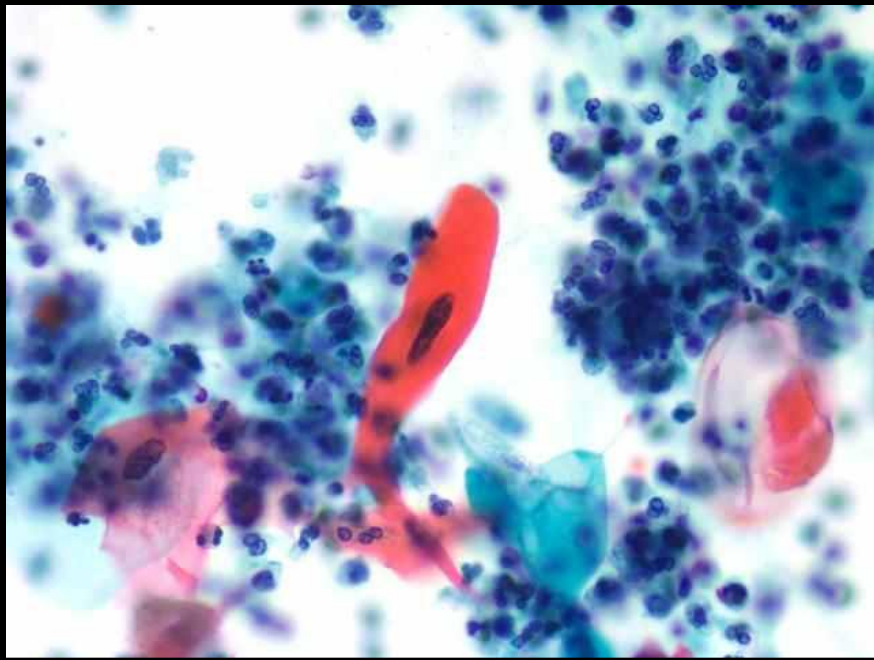
# BILATERAL URETERAL WASHINGS



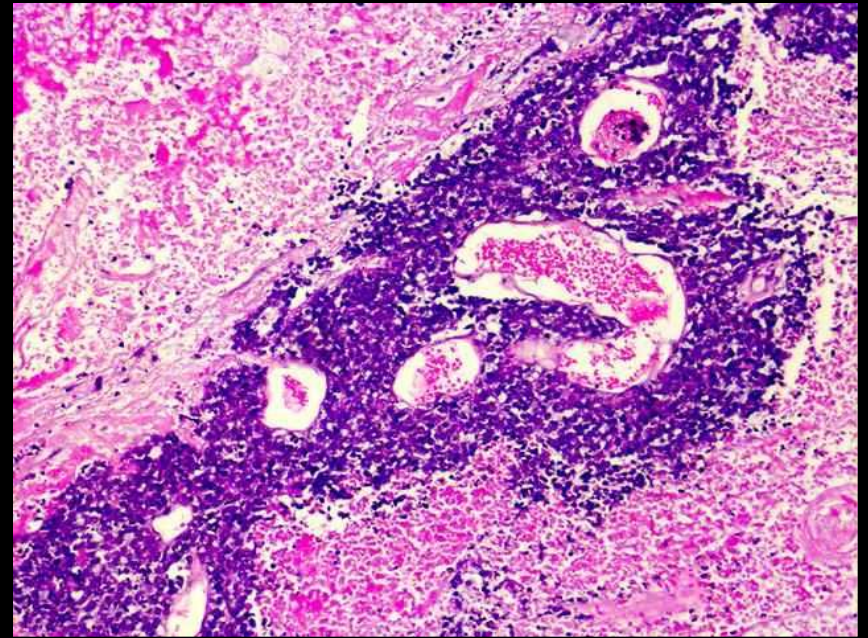
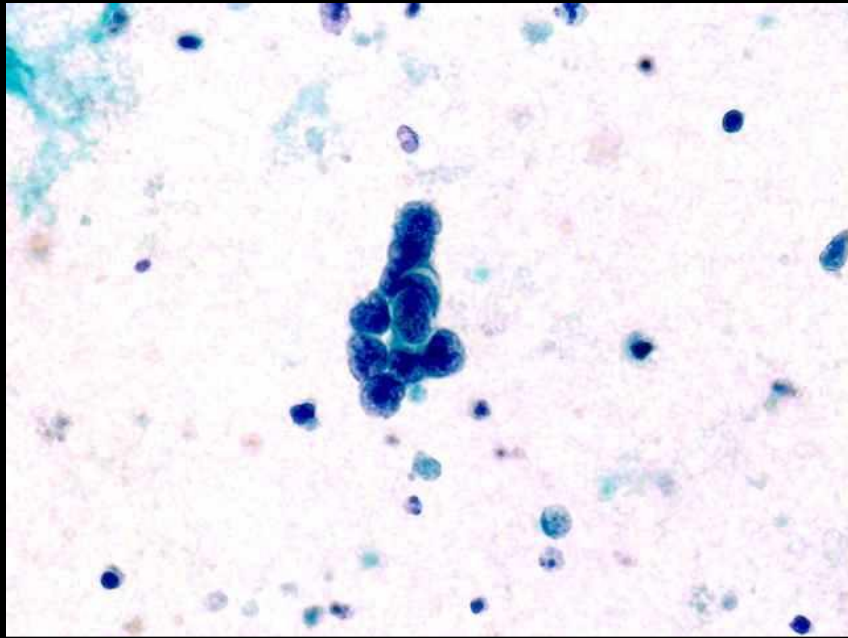
# **CYTOMORPHOLOGY OF SQUAMOUS CELL CARCINOMA:**

- **Cytoplasmic keratinization**
- **Pearls**
- **Bridges**
- **Angulated hyperchromatic nuclei**

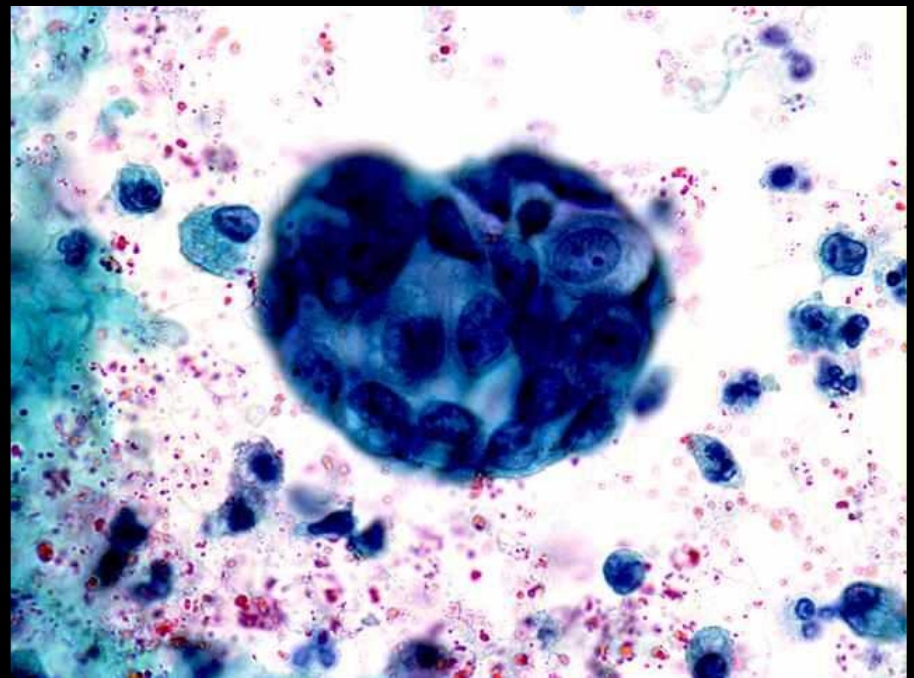
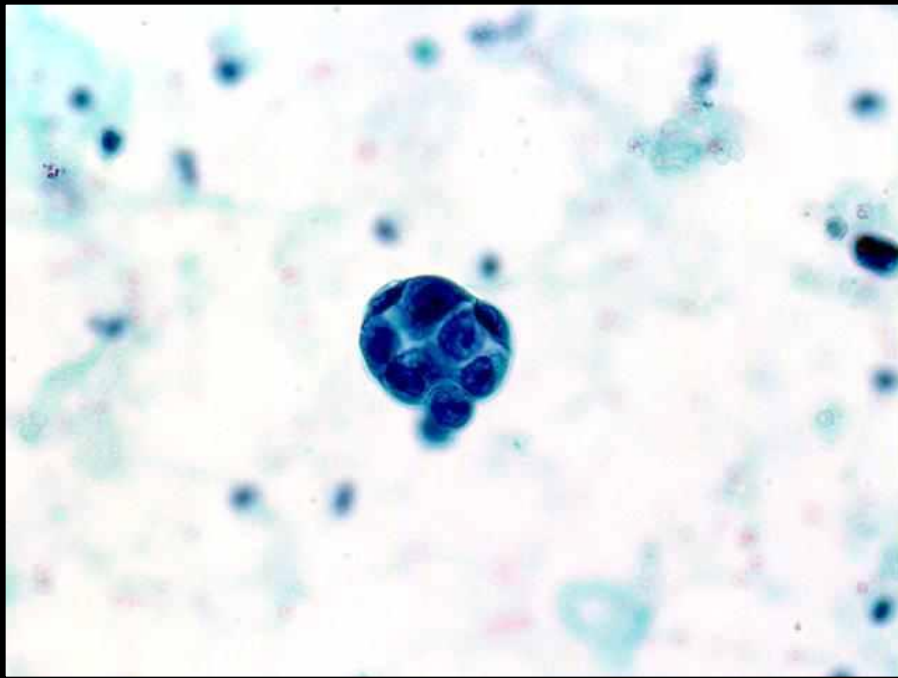
# SQUAMOUS CELL CARCINOMA



# SMALL CELL CARCINOMA

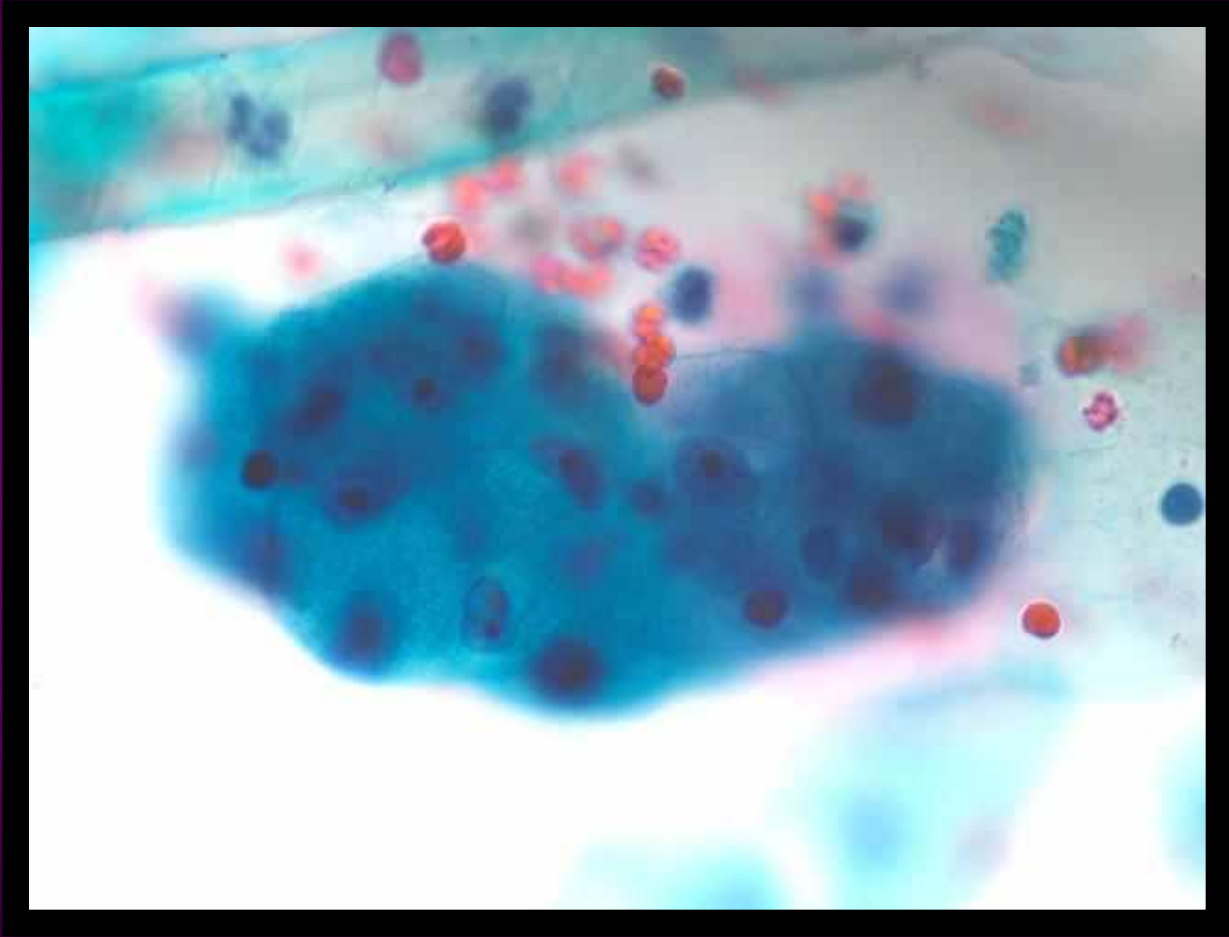


# ADENOCARCINOMA

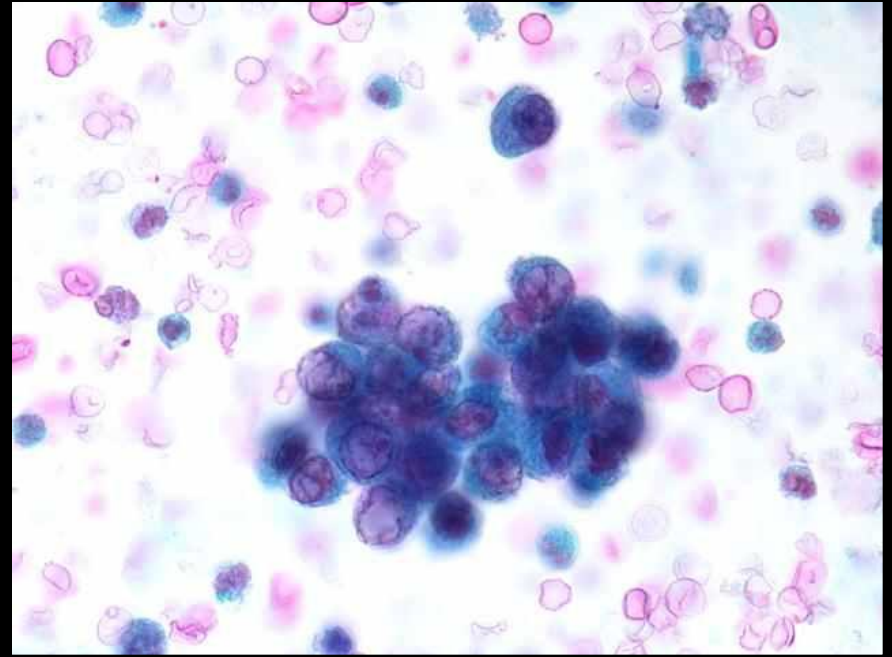
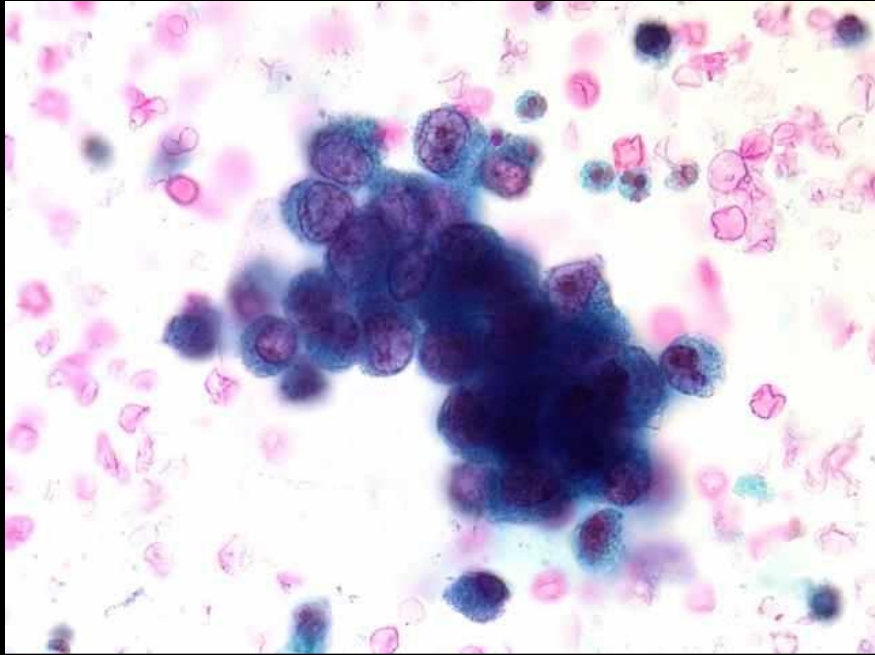




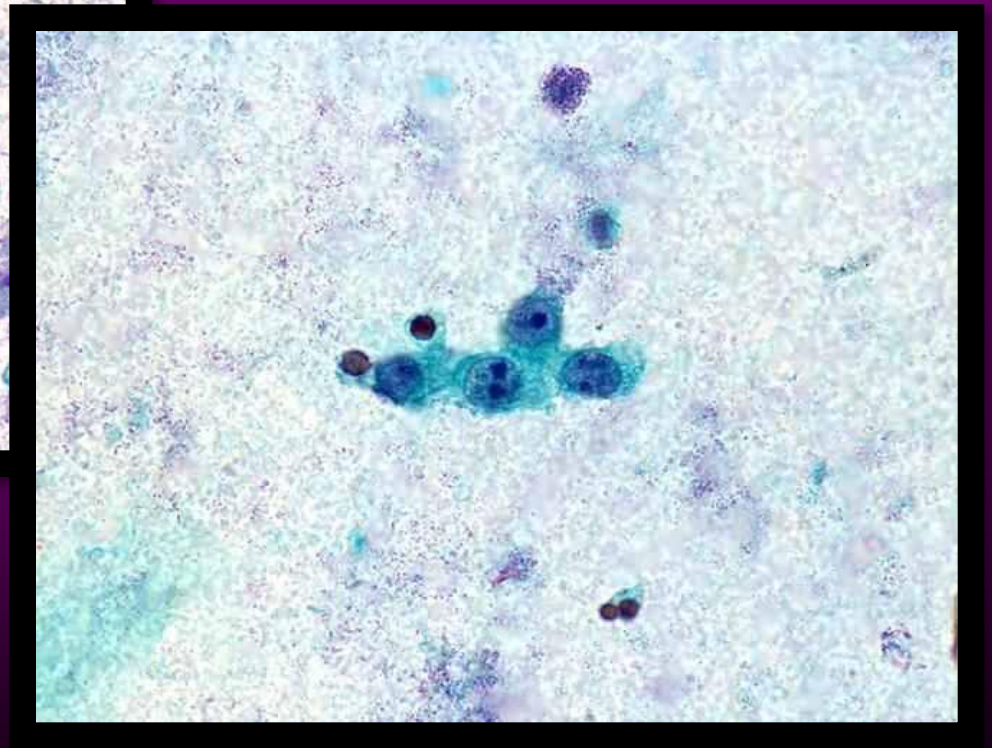
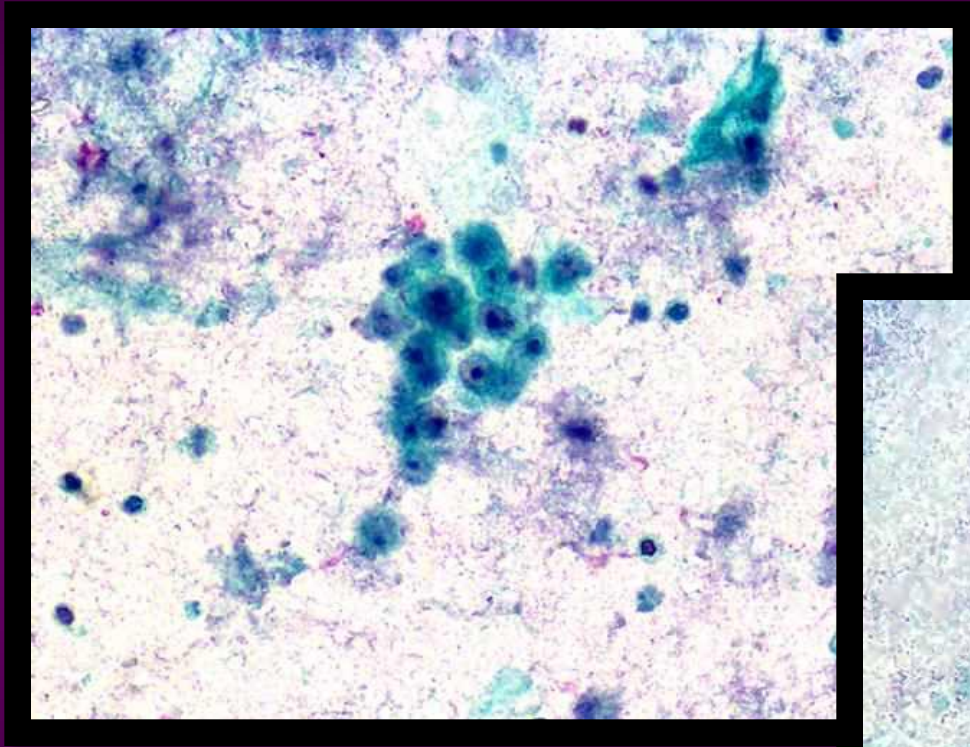
# RENAL CELL CARCINOMA



# PROSTATE CARCINOMA



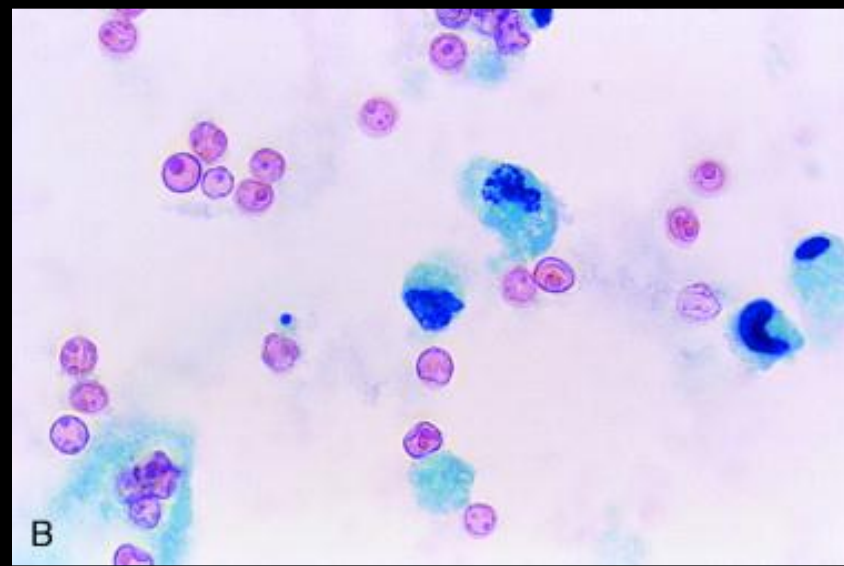
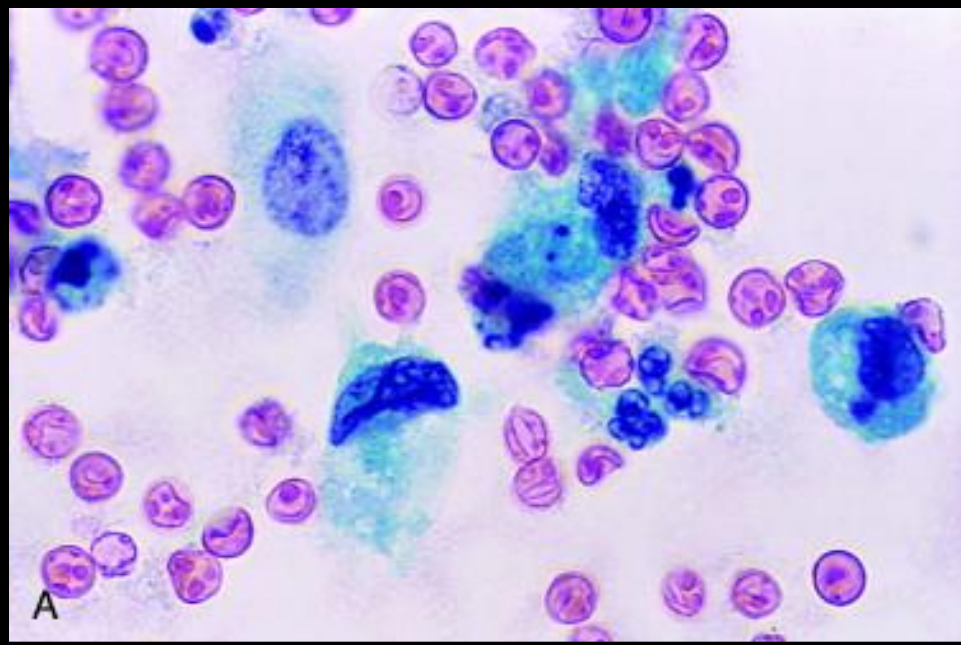
# Metastatic breast carcinoma



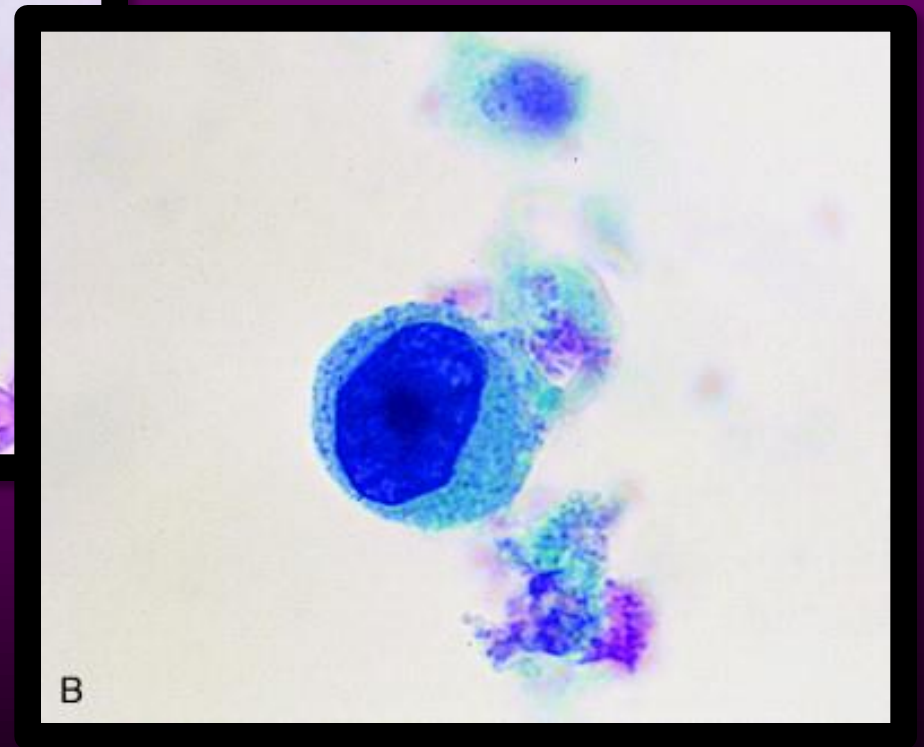
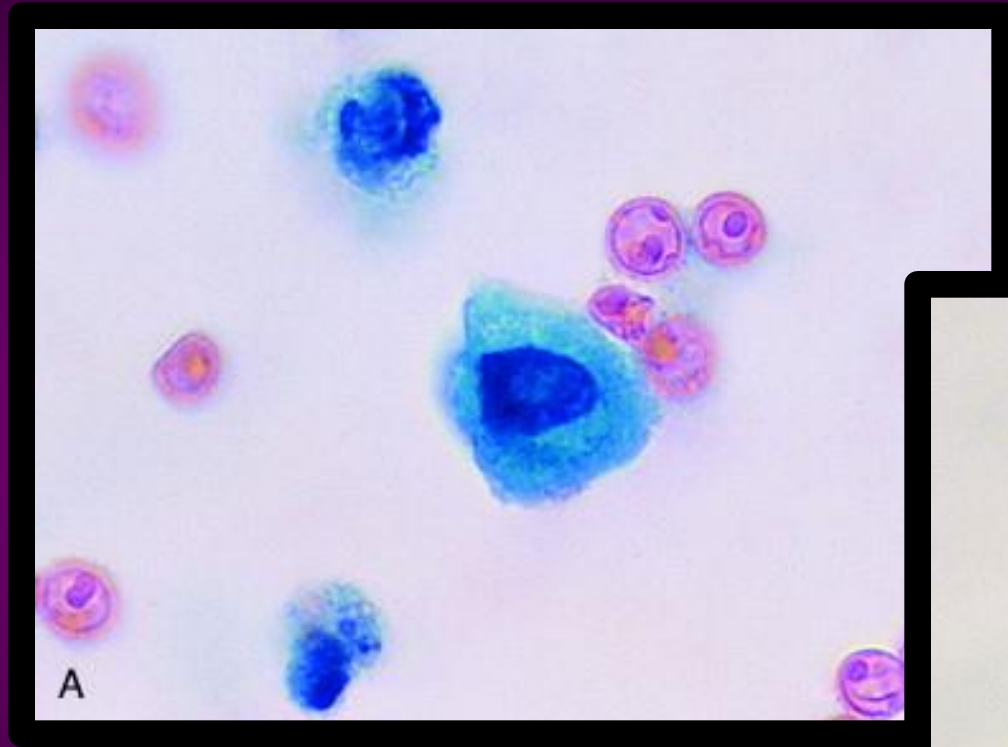
# **COMMON PATTERNS OF ATYPICAL URINE SPECIMENS:**

- **Cell clusters in voided urine: diagnose as negative**
- **Cytologic or architectural criteria for a low-grade lesion: diagnose as negative**
- **Rare small highly atypical cells: diagnose as suspicious**
- **Degenerated atypical cells with intact nuclear outlines: diagnose as suspicious**
- **Rare mildly atypical cells: try to diagnose as negative**

# HIGH GRADE CELLS HIDDEN “COY CELLS”



# DEGENERATED HIGH GRADE CELLS



# **ANCILLARY TESTING OF CYTOLOGICAL SAMPLES**

**Less specific**

**More sensitive**

**Used in conjunction with  
cytology**

# ANCILLARY TECHNIQUES:

- **DNA aneuploidy (flow cytometry, image analysis)**
- **Bard bladder tumor antigen (BTA)<sup>TM</sup> test**
- **Nuclear matrix protein NMP22 test**
- **Telomerase assays**
- **Microsatellite instability assays**
- **Hyaluronidase and hyaluronic acid**



# ANCILLARY TECHNIQUES:

- **Growth factors**
  - **acidic fibroblast growth factor (FGF)**
  - **basic FGF**
  - **autocrine motility factor**
  - **epidermal growth factor**
  - **transforming growth factor- $\beta$**
- **Cell adhesion molecules**
- **Fibrinogen degradation products**
- **Tumor-associated and blood group antigens**
- **FISH**

# **UroVysion™ test**

- **Multicolored FISH test**
- **Detects aneuploidy in Chr 3,7,17 and loss of 9p21 (p16)**
- **FDA approved for monitoring patients with h/o TCC and for detection in patients with hematuria.**

# UroVysion™ test

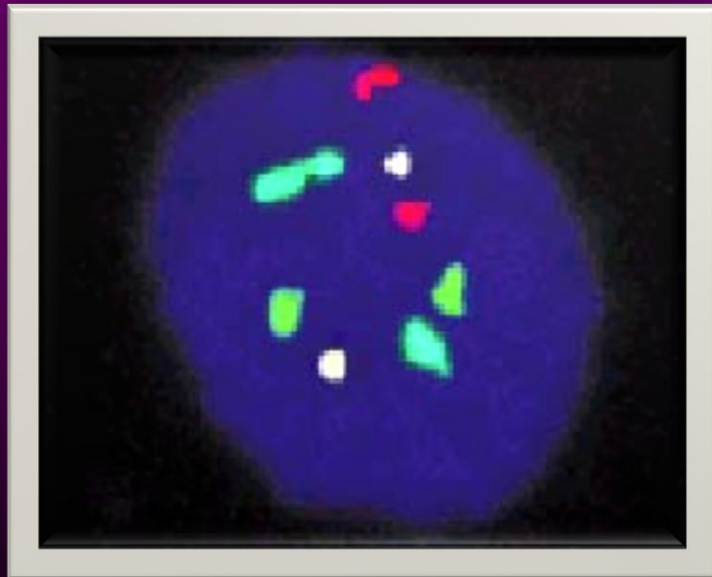
- **Normal UroVysion™ test**

CEP 3 = red

CEP 7 = green

CEP 17 = aqua

LSI 9p21 = gold



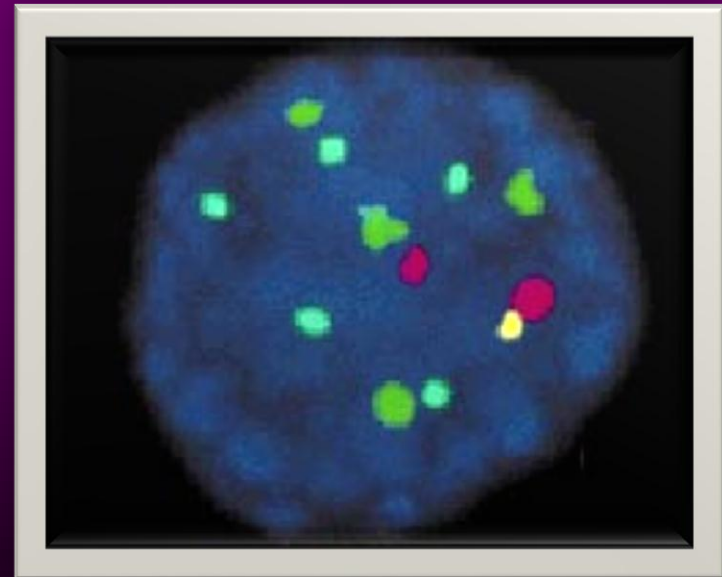
- **Abnormal UroVysion™ test**

Chr 3 = 2 copies

Chr 7 = 4 copies

Chr 17 = 4 copies

9p21 = 1 copy



# SUMMARY:

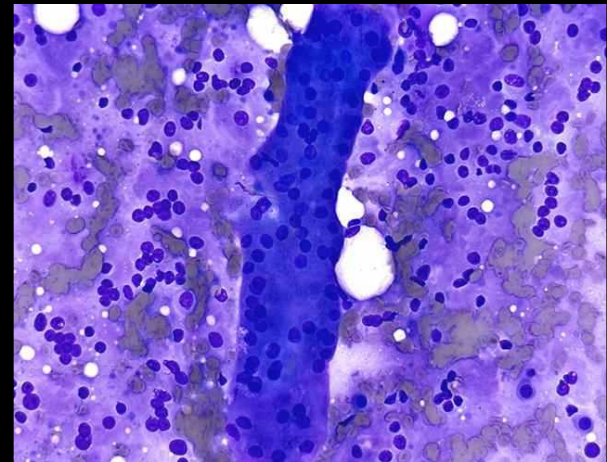
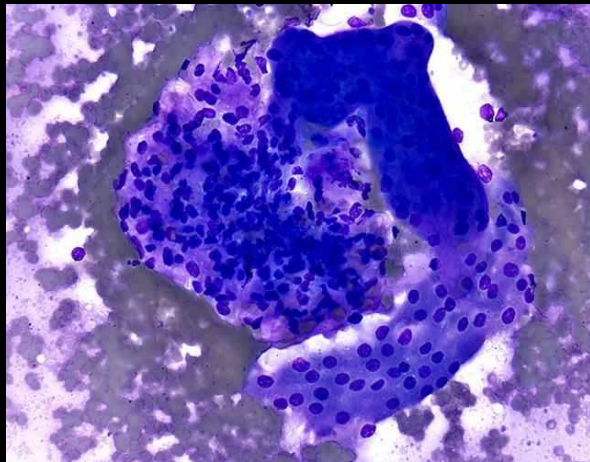
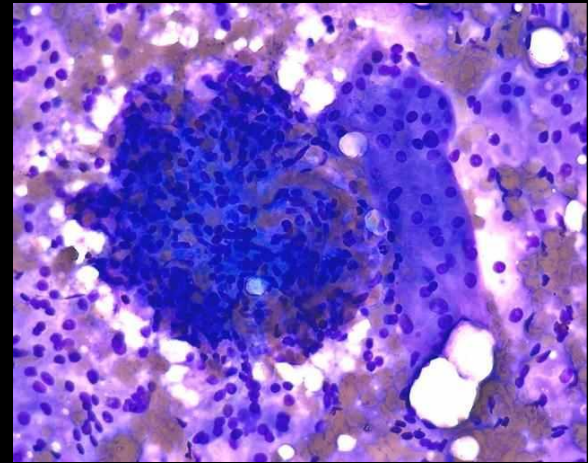
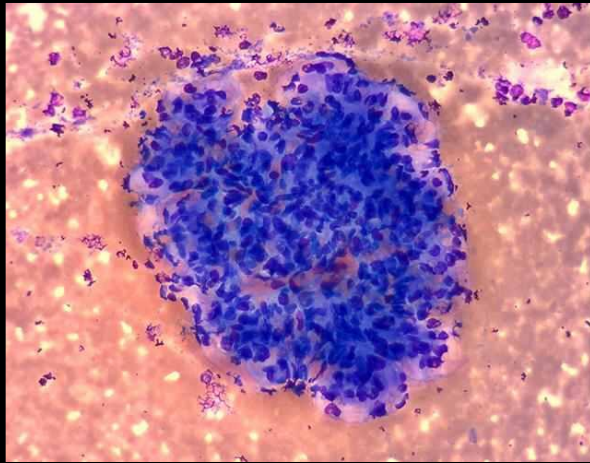
- **Most urine samples for hematuria are negative**
- **The value of urine cytology for high grade lesions are undisputed**
- **Criteria for low grade lesions lack specificity**
- **Urothelial clusters per se are of limited value to diagnose low grade lesions**

# SUMMARY:

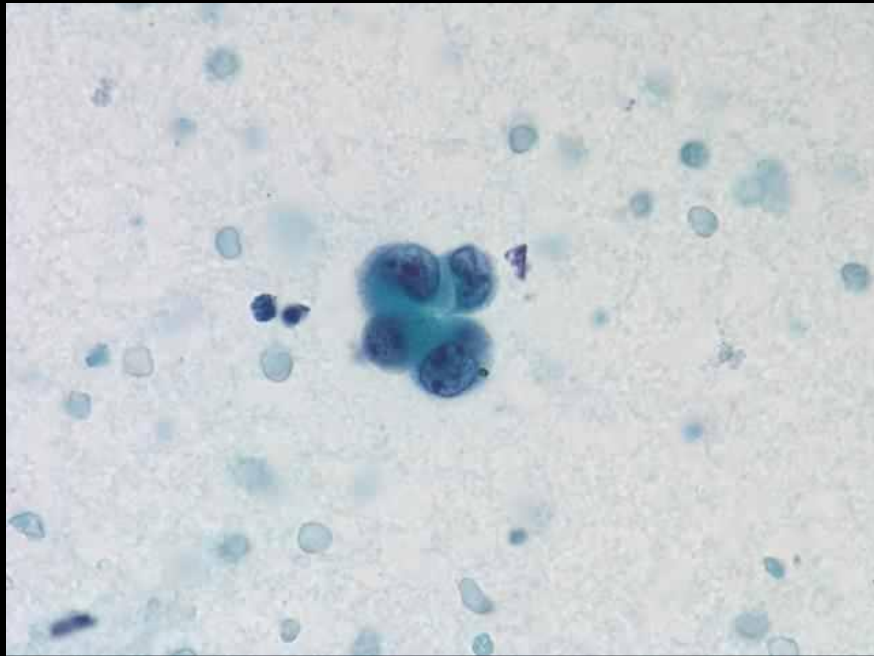
- The term *DYSPLASIA* should be avoided in cytology
- Upper tract lesions: be very conservative
- Separation of high risk from low risk patterns maybe of value to decrease atypical diagnosis
- FISH test (UroVysion™) is a promising adjunct to detect UC

**THANK  
YOU**

# Normal kidney on FNA: glomerulus and renal tubules

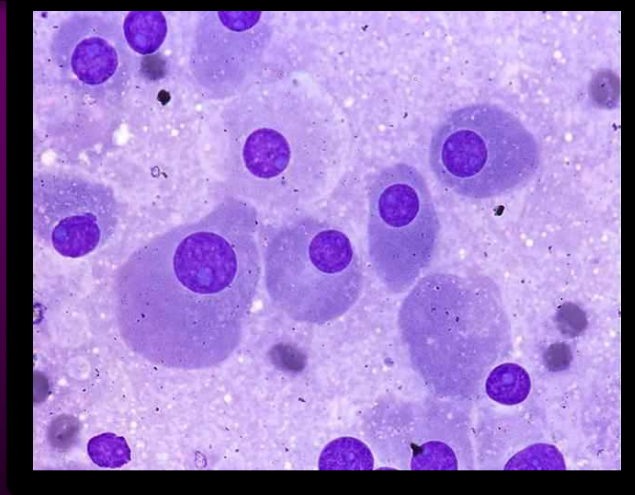
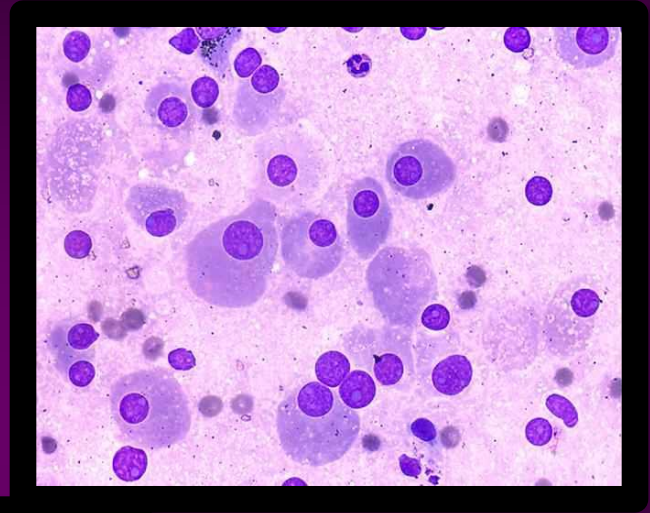
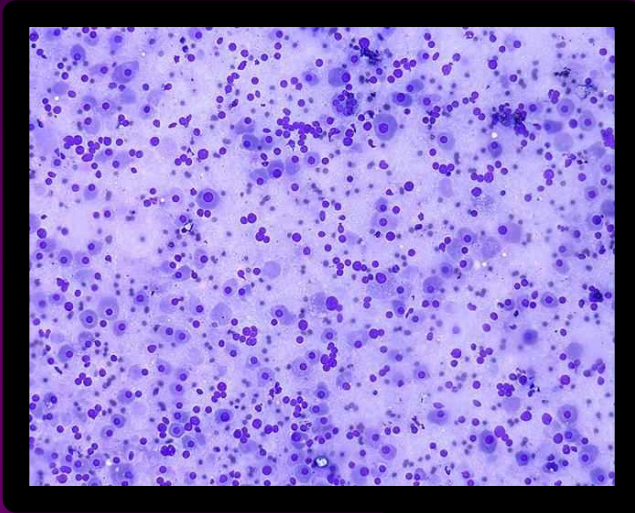


# Benign renal cysts (FNA)

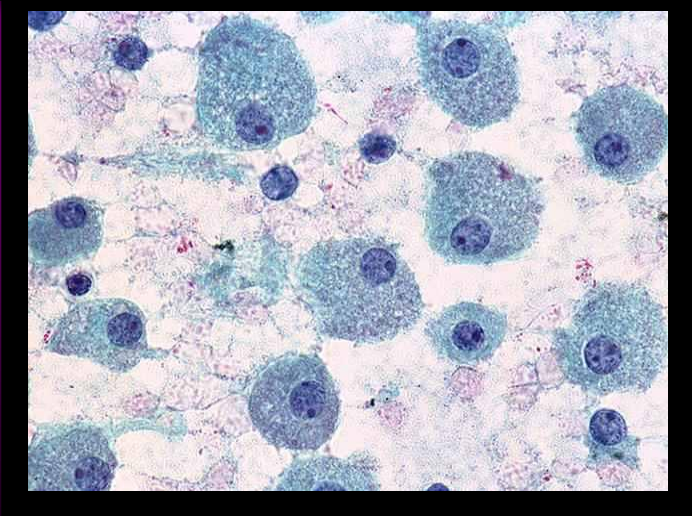
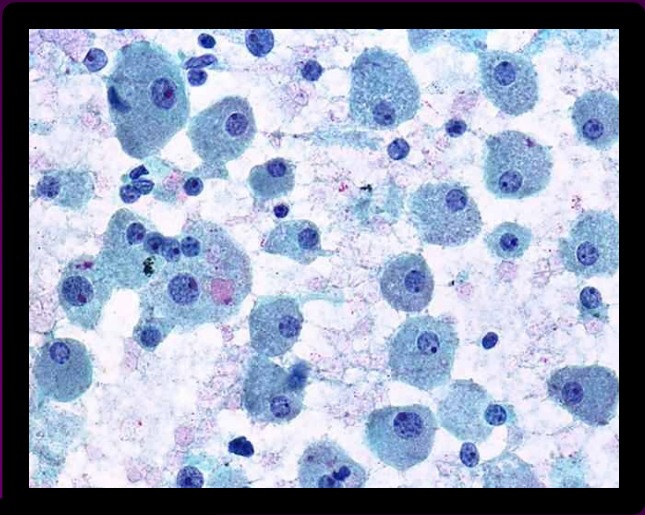
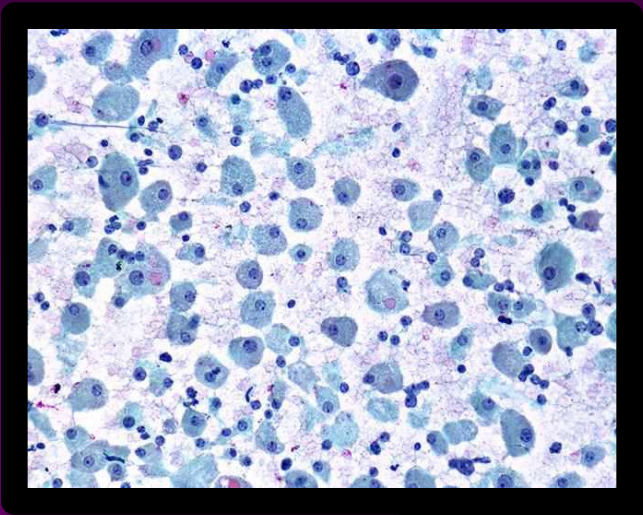




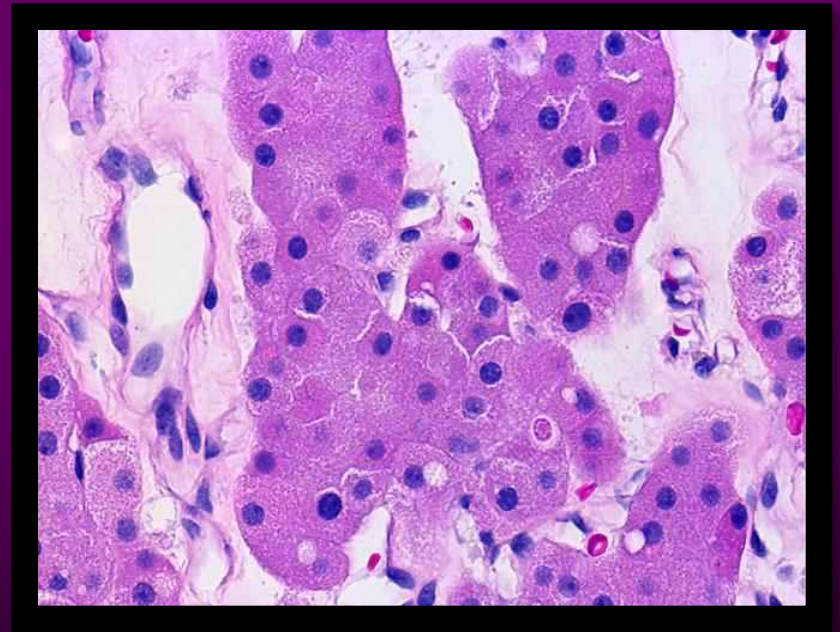
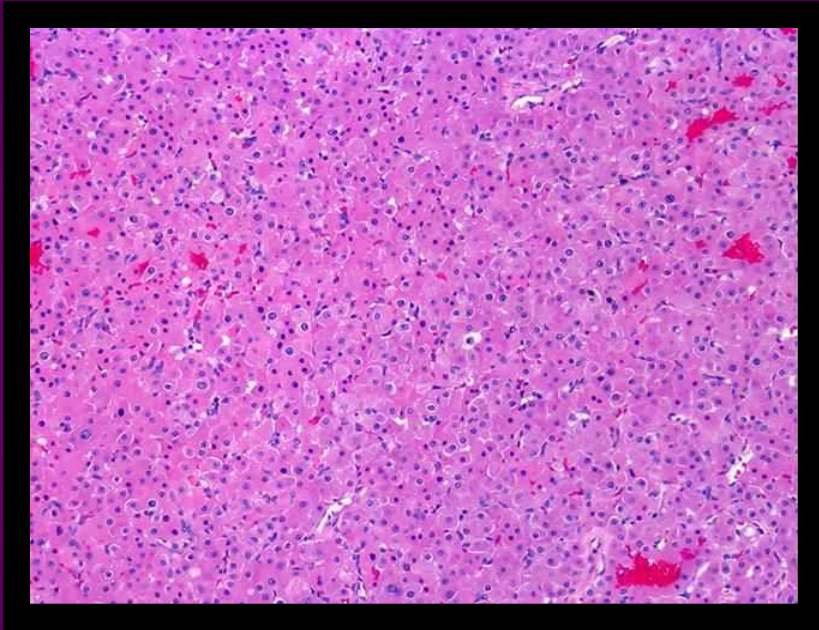
# Oncocytoma



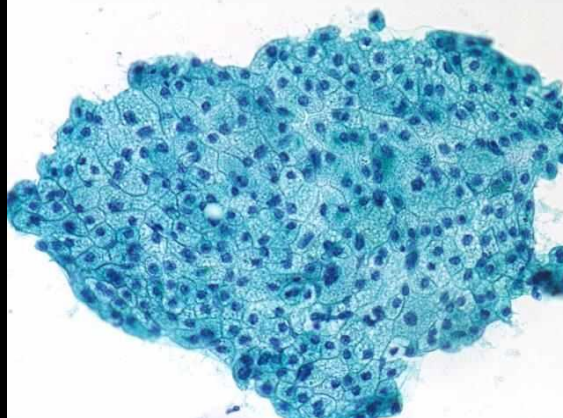
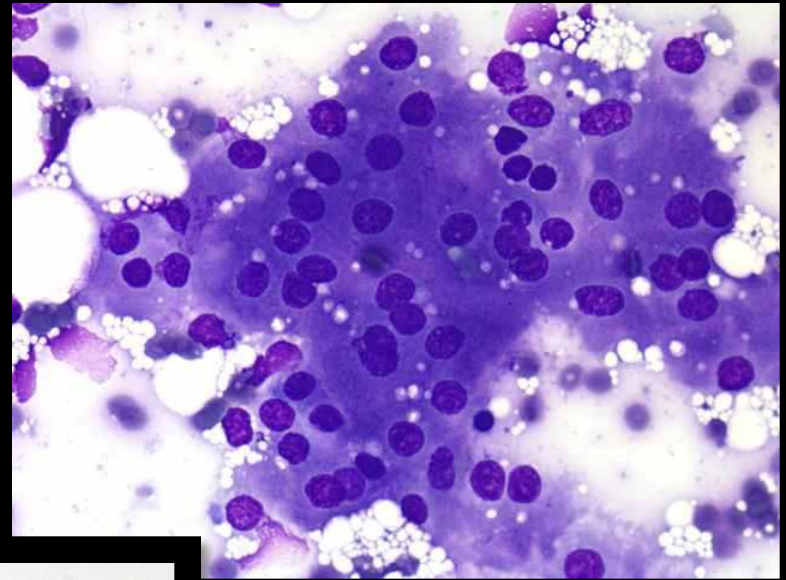
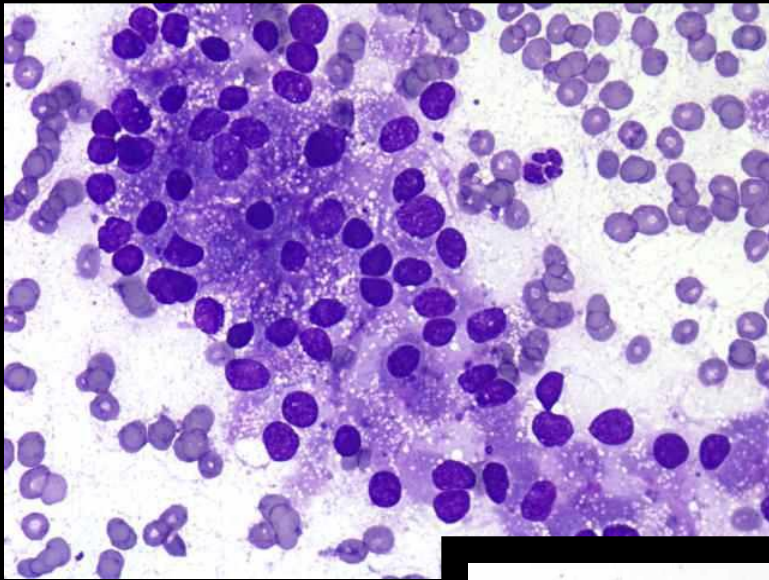
# Oncocytoma



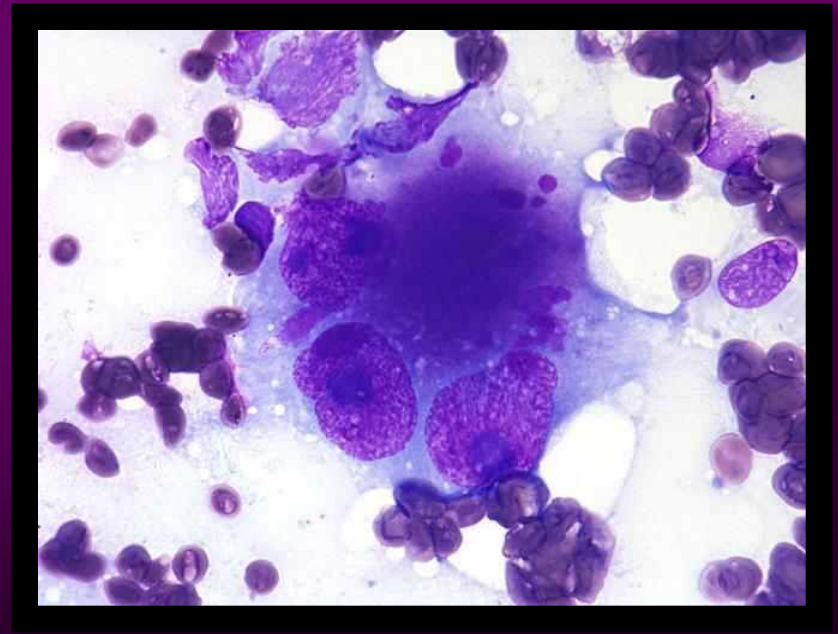
# Oncocytoma



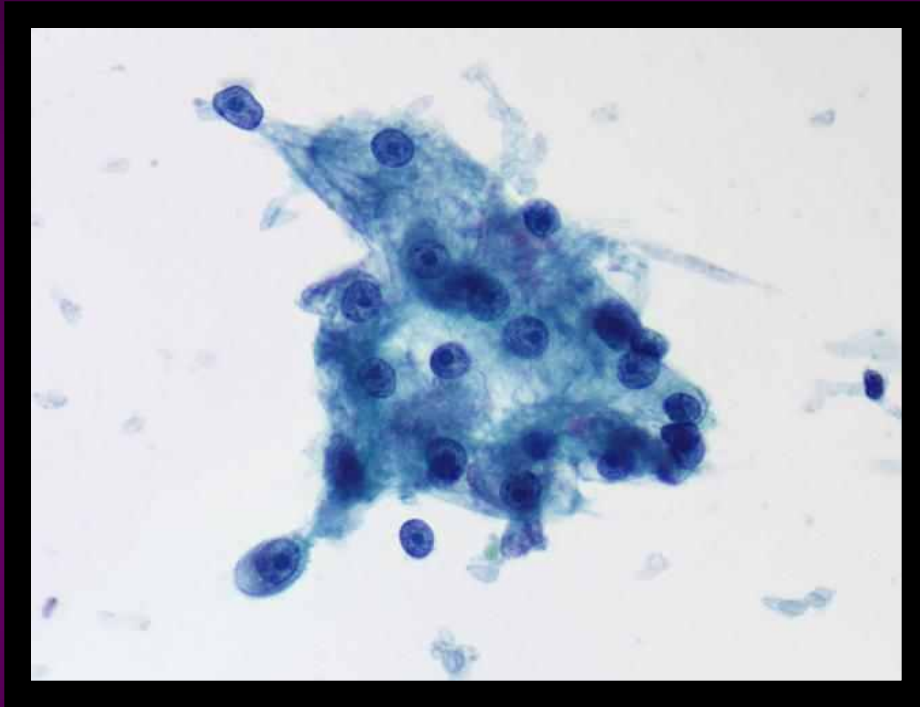
# Renal cell carcinoma



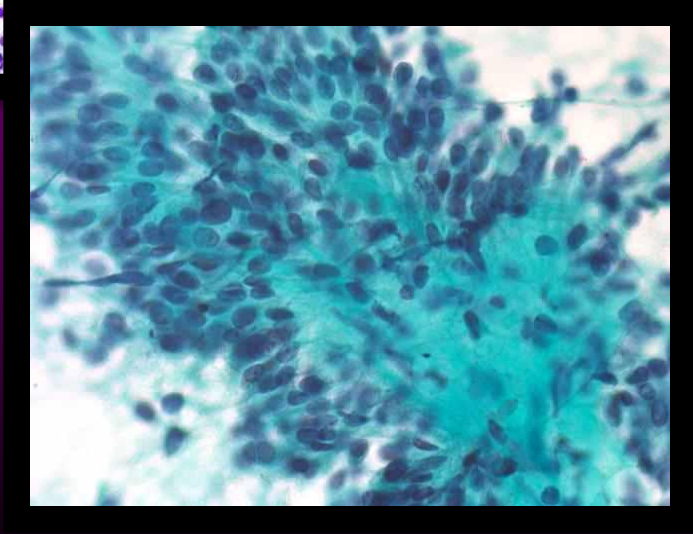
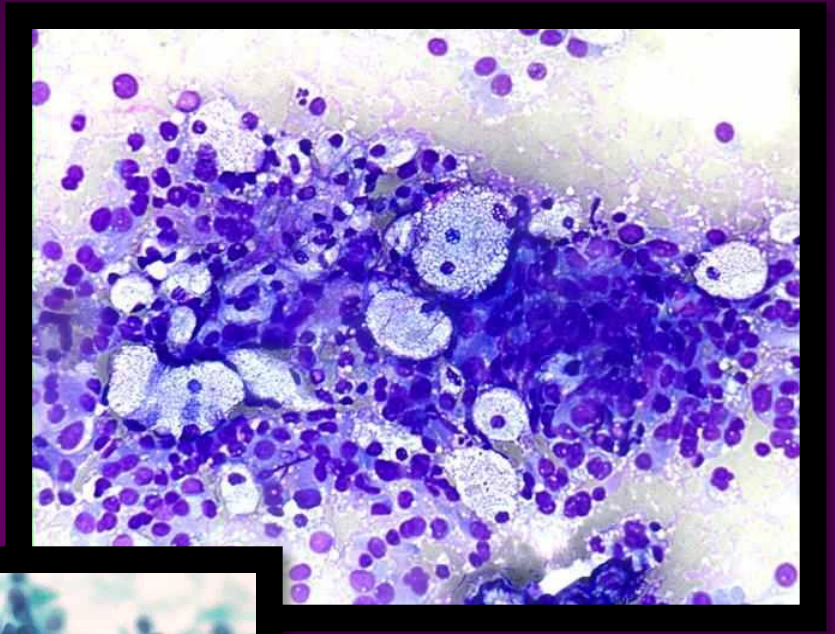
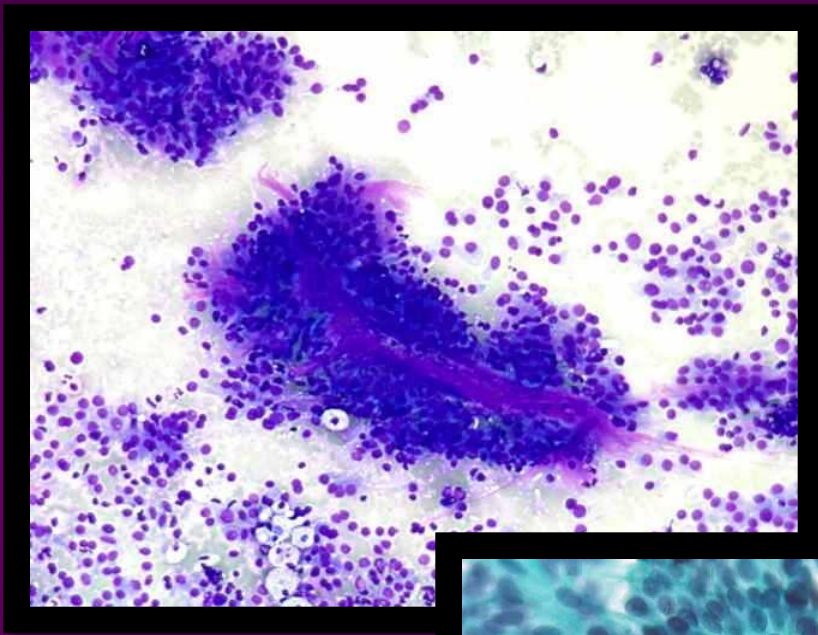
# RCC, High Fuhrman grade



# RCC, High Fuhrman grade



# RCC, papillary type



# Urothelial carcinoma of renal pelvis on FNA

