Diagnostic Categories and Atypia in Urine Cytology

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Outline

- Diagnostic categories
- Common sources of "Atypia" in urine cytology
- A practical approach to Dx of UC
  - *Focus on:*
    - Low grade urothelial neoplasms
    - High grade urothelial CA
    - Other neoplastic & non-neoplastic lesions included in the DDx
- Management of "atypical" and "suspicious" urines

Introduction

- Majority of UT malignancies are UC
  - **Urothelial carcinoma, 80-90%**
  - **Mixed Carcinoma- UC (5%)**
  - Squamous cell carcinoma (5%)
  - Adenocarcinoma (2%)
  - Small Cell Carcinoma (1%)
- The main function of urine cytology is to diagnose UC

Indications

1. Establish Dx in symptomatic patients-hematuria
   - Most common, low yield (5-10% malignancy)
2. Screen high risk patients (exposure to industrial chemicals, metals, etc.)
3. Follow-up patients with Hx of UC
4. Complementary to cystoscopy and biopsy: detect small and hidden lesions (diverticuli, ureters, renal pelvis)

- Urine cytology is the most reliable method for detecting urothelial CIS (> biopsies)

Diagnostic Accuracy of Urine Cytology

- *Number of Specimens*
  -Voided urine on 3 consecutive days
  - 50% accuracy (1 specimen)
  - 75-90% accuracy (3 specimens)
- *Patient Population*
  High risk and history of CA
- *Tumor Grade*
  - HG UC: > 90 %
  - LG UC: <50 %

Diagnostic Categories

- JH created a template similar to Gyn TBS:
  1. Negative
  2. AUC-US
  3. AUC-H
  4. LG neoplasm
  5. HG neoplasm
  6. Non-diagnostic

Rosenthal, cancer cytopath 2013

Diagnostic Categories

- JH created a template similar to Gyn TBS:
  1. Negative
  2. **AUC-US (26%)**
  3. **AUC-H (5%)**
  4. LG neoplasm
  5. HG neoplasm
  6. Non-diagnostic

1. **Negative for HGUC**
2. **Suspicious for HGUC**
3. **Positive for HGUC**

Rosenthal, cancer cytopath 2013

Should We Eliminate the "Atypical" Category?

- 10-20% of urines classified as "atypical"
- Considerable inter-observer variability among pathologists as what constitutes atypia
- Most urologists interpret "atypia" as negative or unhelpful

Arguments for Not Eliminating "Atypia"

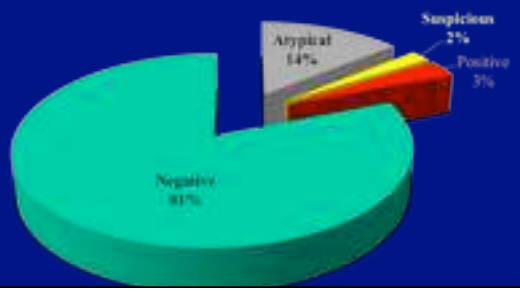
- Significant proportion of malignant cases would be missed if "atypia" was eliminated
  - Malignant rate on FU: 23-68%
- Ancillary studies such as FISH can be helpful in those cases
- Dr. Wojcik

Diagnostic Categories- CC

- Negative
- Atypical
  - R/O LGUC /PUNLMP
- Suspicious
  - for HG UC/ malignancy
- Positive
  - HG UC or other malignancies

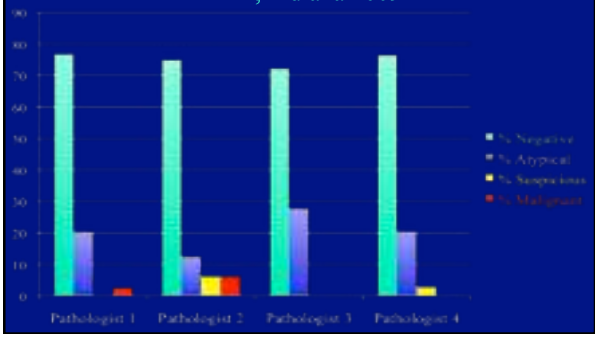
Total Urines at Cleveland Clinic

2008-2010 (17,800 cases)



Urine Dx's Categorized by Pathologist

BMH, Indiana 2009



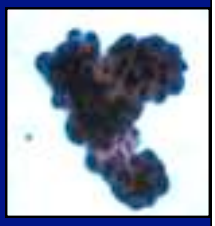
Atypia in Urine Cytology

Common Sources of "Atypia" in Urine Cytology

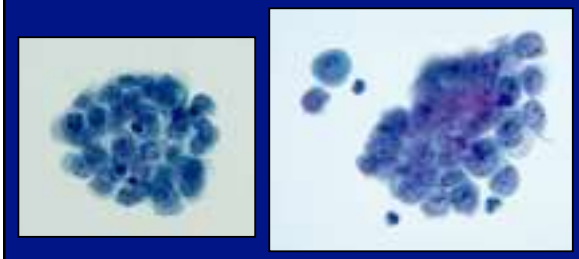
1. Papillary clusters in voided urine
2. Mild nuclear atypia
3. Degenerated large atypical nuclei
4. Coy cells

1. Clusters in voided urine

- Papillary clusters are not associated with increased risk of neoplasia
  - >3 clusters in ThinPrep→ high sensitivity, poor specificity
  (Deshpande & Mckee, Cancer Cytopathol, 2005)
- Should place less reliance on presence or shape of clusters
  - Exception- fibrovascular core
- More emphasis on nuclear features



Not Atypical



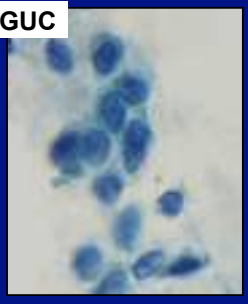
- Deep urothelial cells and instrumentation effect

2. Mild Nuclear Atypia

- Single cells with enlarged and irregular nuclei (no significant hyperchromasia)
- Most common and most frustrating: R/O LGUC

Mild Nuclear Atypia

LGUC

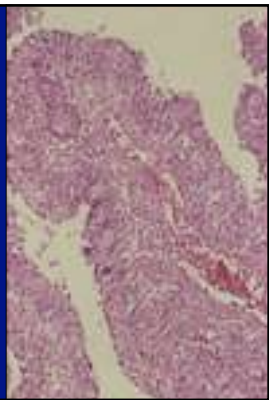


Benign

Few cells with enlarged slightly irregular nuclei.

Low Grade Urothelial CA

- Predominately papillary
- Capacity to invade (<20%)
- Rarely metastasizes
- Progression < 15%



Low Grade Urothelial CA [2]

- Cytologic diagnosis of LGUC is problematic
  - Minimal shedding of neoplastic cells
  - Subtle cytologic alterations, difficult to distinguish from reactive changes, i.e. stones, instrumentation
  - Cytologic overlap between PUNLMP and LGUC
    Whisnant, 2003: No discriminating cytologic features between PUNLMP and LGUC, in 86 specimens

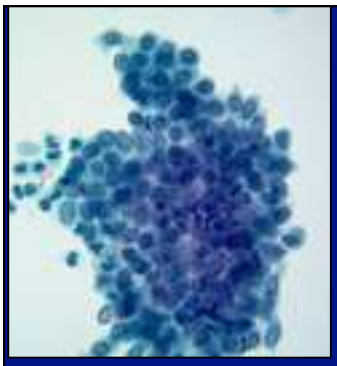
Cytology of LG Urothelial CA [3]

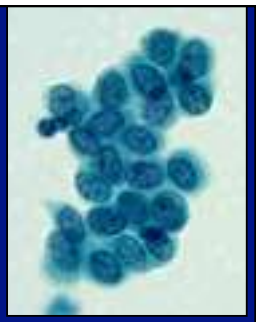
- Generalized disagreement about accuracy of cytologic Dx and which criteria are most useful
  - Wide range of sensitivities 0-73%
  - Overall sensitivity for LGUC 25-40%

LG Urothelial CA vs. Reactive changes[2]

Raab et al. Cancer 1994

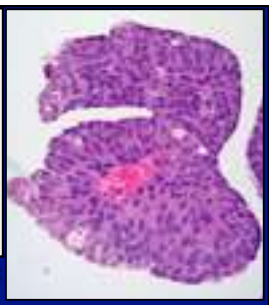
- 3 Key cytologic criteria useful for discriminating LGUC from reactive changes
  1. **↑ N/C ratio**
  2. **Irregular nuclear membrane**
  3. **Non-vacuolated (homogeneous) cytoplasm**
- All 3 features present in only ½ of cases
- At least 2 key criteria = Sensitivity 85%, Specificity 96%
- ?? Value in voided urine



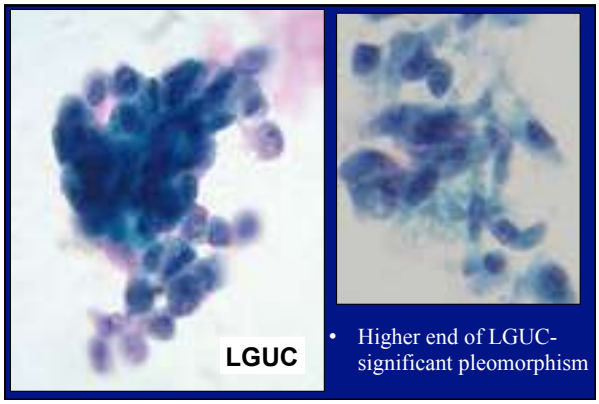


LGUC- washings and brushing

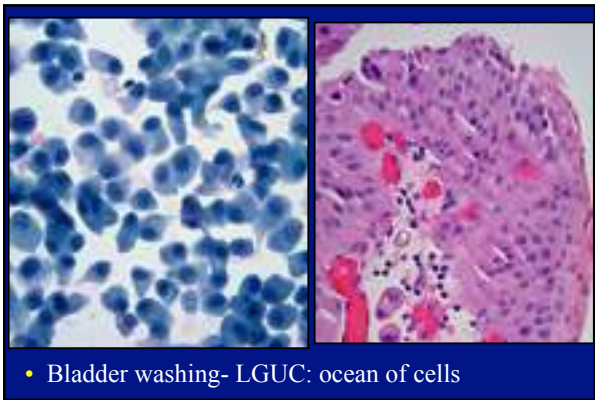
Washings and brushing- LGUC



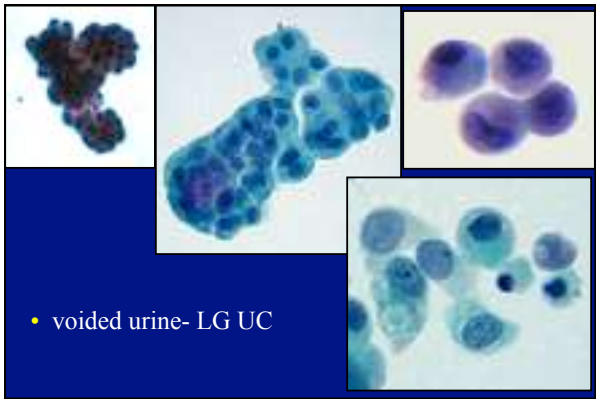
- Tight papillary clusters with extreme nuclear overlapping and protrusion from edges of clusters



- Higher end of LGUC- significant pleomorphism



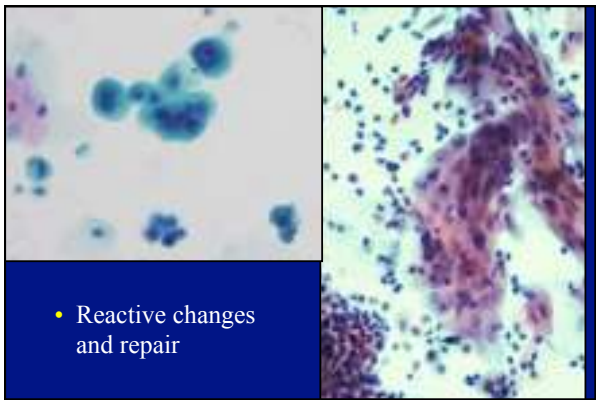
- Bladder washing- LGUC: ocean of cells



- voided urine- LG UC

Differential Diagnosis of LG Urothelial CA

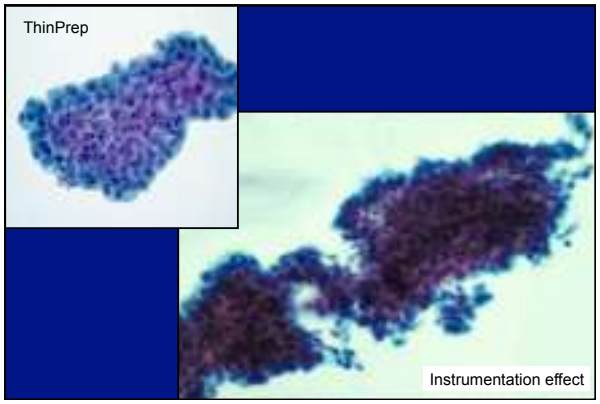
- Reactive/reparative changes
- Instrumentation effect
- Lithiasis
- Upper urinary tract sampling



- Reactive changes and repair

Instrumentation Effect

- Catheterized urine and bladder wash specimens
- Large pseudopapillary groups and 3D clusters
- Nuclear overlap and crowding
- Low N/C ratio
- Finely granular chromatin with even distribution
- Well defined cytoplasmic borders
- Nuclear palisading at periphery of clusters with abundant cytoplasm (cytoplasmic collar)



LG Urothelial CA vs. Instrumentation

• Cytologic criteria that showed statistical significance in descending order- bladder wash

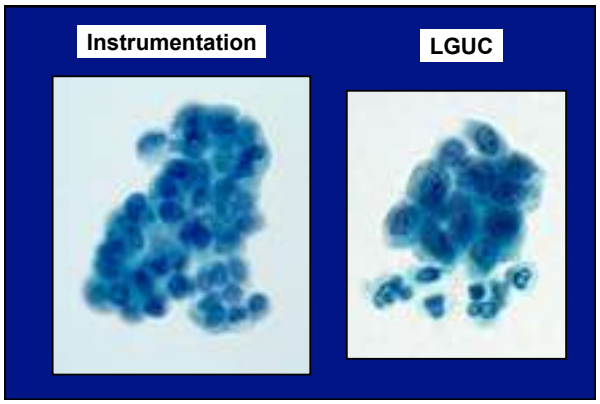
LGUC

- Homogeneous cytoplasm
- ↑ N/C ratio
- Eccentric nuclei
- Irregular nuclear membrane
- Haphazard overlap of nuclei
- Ragged border of clusters
- Nuclear hyperchromasia and enlargement
- Nuclear pleomorphism

Non-neoplastic

- Vacuolated cytoplasm
- Smooth border of cluster
- Cytoplasmic collar
- Abundant acute and chronic inflammation
- Mixture of small and large urothelial cells

Chu et al, 2002



How Long is Cytology Abnormal after Cystoscopy?

- Evaluated 48 patients
- Examined urine before, immediately after, 1, 2, 7, 14 and 28 days
- Instrumentation effect was transient, mostly disappearing within 1 day after cystoscopy

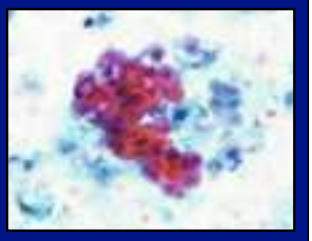
McVey et al. BJU INT, 2004

Lithiasis

- Papillary clusters common
- Smooth bordered clusters
- Centrally placed nuclei, smooth nuclear membranes, finely granular chromatin
- Hyperchromatic smudgy nuclei (degenerative changes)
- Multinucleated giant cells

Lithiasis [2]

- Inflammation & debris in background may be misinterpreted as tumor diathesis
- May be impossible to distinguish from PUNLMP or LGUC



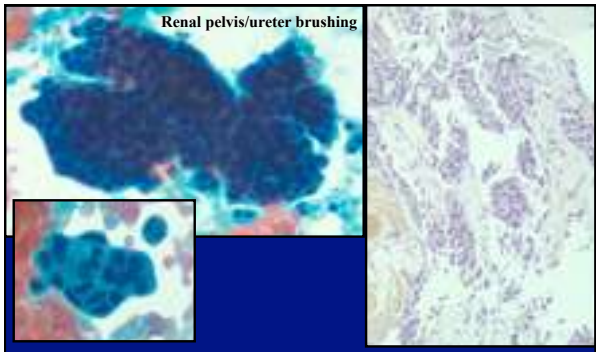
- Occasionally marked cytologic atypia, including nuclear pleomorphism, coarsely granular chromatin, mitotic figures → false-positive diagnosis of HGUC

Lithiasis [3]

- Important source of false positive Dx for LG and HG UC
- Clinical history not reliable: filling defect in upper UT→ stone vs. neoplasm
- Persistent atypical features (weeks)→ aggressively worked up for neoplasia

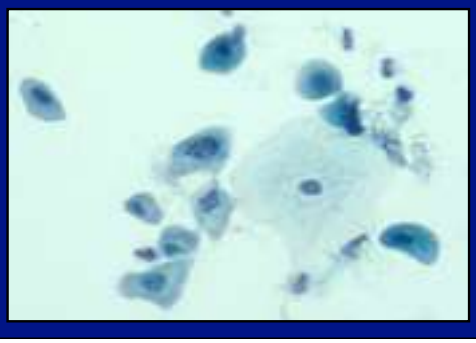
Upper Urinary Tract specimens

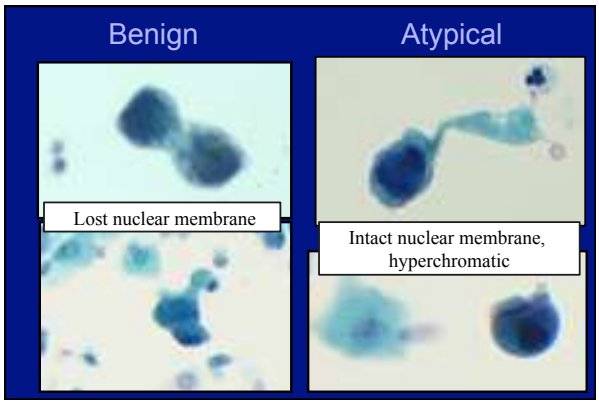
- Direct sampling of upper UT is effective in detecting HGUC, but poor for low grade lesions
- Normal upper UT epithelium shows more atypia than lower UT and occasionally more than LGUC
- High N/C ratio, enlarged nuclei, nuclear membrane irregularities
- Often present in papillary clusters
- **Almost impossible to distinguish low grade UC from upper tract benign changes**



- Negative cystoscopy, biopsy & followup

3. Degenerative Changes



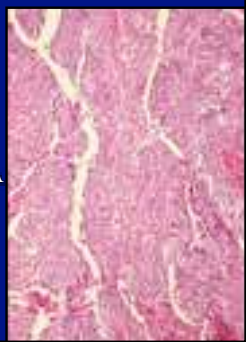


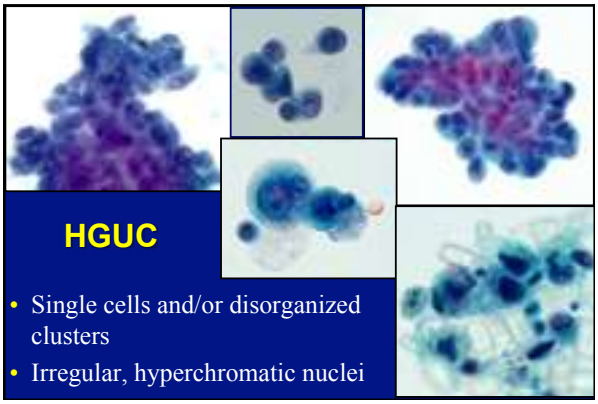
Differential Diagnosis

- High grade UC
- Human polyoma viral infection
- Therapy effect
- Stones and reactive changes

High Grade Urothelial CA

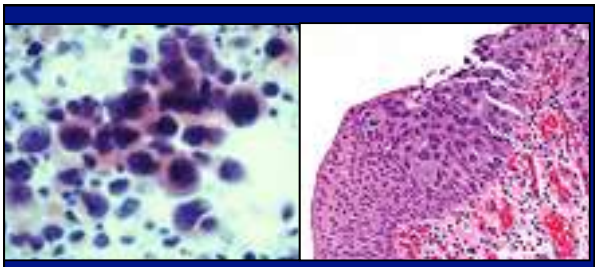
- Often invasive, 70% mortality
- 90% of pts dying of disease present initially with HGUC
- Cytology cannot reliably separate CIS from invasive CA
- High diagnostic accuracy of cytology
  - Sensitivity 80-90 %
  - Specificity > 95%





HGUC

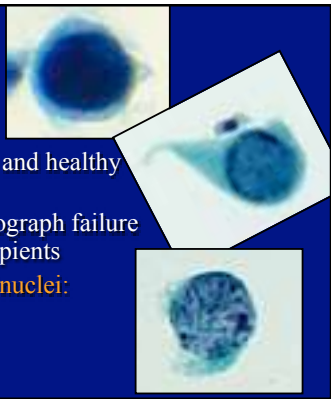
- Single cells and/or disorganized clusters
- Irregular, hyperchromatic nuclei



- Pleomorphic bizarre cells, enlarged eccentric nuclei, coarse dark chromatin

Human Polyomavirus

- DNA virus (Papova)
- Immunocompromised and healthy individuals
- Important cause of allograph failure in renal transplant recipients
- Decoy Cells- infected nuclei:
  - Smudgy
  - Washed out
  - Reticulated

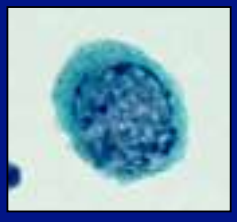


Polyoma Virus

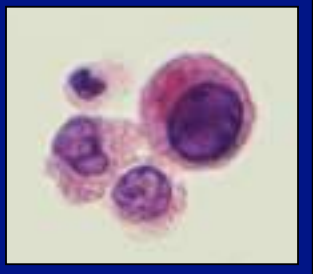
- Diff DX is degenerated HG UC

	Polyoma virus	HG UC
Architecture	Single cells	Single cells & clusters
Nuclear membrane	Smooth, round	Marked irregularity
Chromatin	Uniform, smudgy, reticulated	Coarsely granular

Polyoma



HGUC



Therapy Effect

- ***Cytoxan & Busulfan***
  - Systemic treatment of non urothelial malignancies
  - Hemorrhagic cystitis
  - Severe cytologic atypia may be indistinguishable from CA
  - Atypia more bizarre than usual HGUC
  - Atypia often has degenerative features

Therapy Effect [2]

Photo from Murphy WM. Urinary Cytopathology. ASCP Press,2000

Thiotepa & Mitomycin C

Intravesical Rx of sup UC

Repair-like changes

BCG Vaccine

Treatment of CIS

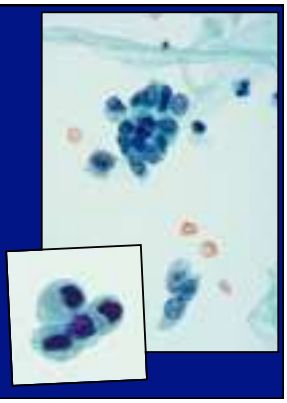
Granulomas, mild atypia

Radiation Change

Extreme cytomegaly, multinucleation, but low N/C ratio

4. Coy Cells

- Suspicious finding
- Opposite of "decoy cells"
  - Often sparse in number
  - Been compared to "litigation cells" on Paps
  - Small cells with hyperchromatic irregular nuclei
  - India ink/coal black nuclei



Suspicious for HGUC

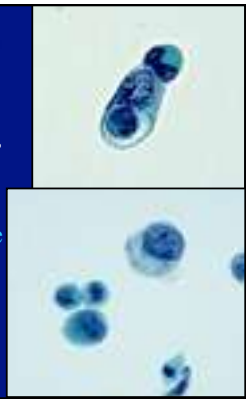
- Studied 58 pts for features predictive of HGUC
- 4 features were recognized:
  - Marked hyperchromasia- obscuring nuclear detail
  - Irregular nuclear borders
  - Increased N/C ratio
  - Anisonucleosis, striking: often > 3:1 ratio

(VandenBussche, 2013)

Suspicious for HGUC[2]

- Hyperchromasia by far the strongest predictor for HGUC, even in absence of other features
- These features were predictive of HGUC in surveillance pts but not hematuria pts- stone atypia

(VandenBussche, 2013)



Management of Suspicious Urine Cytology

- Differs from "atypical" specimens (regarded as neg)
- Patients with persistent suspicious cytology or recurrent hematuria need further evaluation and follow up
- Patients with suspicious cytology and negative initial evaluation should have repeat urine cytology at 6-8 weeks

Dogs Sniff Out Cancer

- *Willis et al, British Medical Journal 2004:*
  - Dogs correctly identified urine from cancer patients: 41% success rate vs. 14% chance alone (Pathologist sensitivity for Dx of LGUC 25-40%)
  - Suggested that tumor-related volatile compounds are present in urine imparting a characteristic odor

Summary

- Urine cytology best applied to HGUC
- Cytology less helpful for detecting and monitoring LG neoplasms
  - Not major limitation
  - LG neoplasms rarely aggressive and can be readily detected by cystoscopy

"Atypical" Urine Cytology

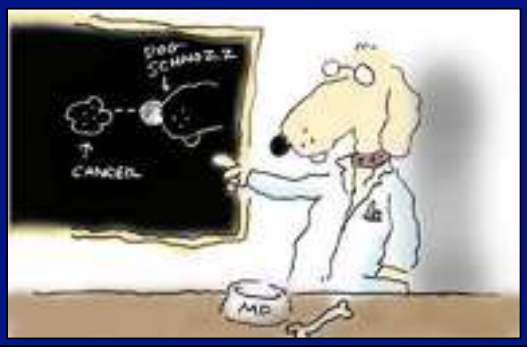
- Do not make "atypia" a waste basket diagnosis
- May qualify "atypical" to R/O LG neoplasm
- *"Atypical"* diagnoses should not be used for reactive/reparative changes → Negative
- Don't use "suspicious" terminology to rule out LG neoplasms

Sub-classifying Atypical Urinary Cytology

- Cell clusters in voided urine→ Negative
- Increased NC ratio without nuclear membrane irregularity→ Negative
- Increased NC ratio with nuclear membrane irregularity→ Atypical, R/O LGUC
- Poorly preserved cells/ smudgy nuclei
  - Nuclear membrane not intact→ Negative
  - Nuclear membrane intact and irregular → Atypical or Susp. for HGUC
- Enlarged, hyperchromatic, irregular nuclei→ Susp.

Modified from Renshaw 2009

Is there a doctor -or dog- in the house?



Potential Pitfalls

- *False Negative Diagnosis*
  - Low grade UC
  - Inadequate specimens
  - Degenerated malignant cells

Potential Pitfalls [2]

- ***False Positive Diagnosis*** *(1.3-15 %)*
  - Instrumentation, stones, palpation
  - Chemo-Radiation therapy changes
  - Viral changes
  - Upper urinary tract specimens
  - Reactive/degenerative changes

Possible Additional Explanations of "False Positives"

- CIS sloughs easily in urine but maybe non-diagnostic on histology = False-FP
- Neoplasia may involve hidden inaccessible sites = False-FP
- Upper UT specimens (ureter, renal pelvis) are most difficult to interpret→ overcall = True FP

Management of "False Positive" Cytology

- Positive cytology should be confirmed histologically before definitive treatment
- Positive cytology requires close follow-up
- Malignancy is found on follow up of most patients with positive cytology and negative initial clinical evaluation