

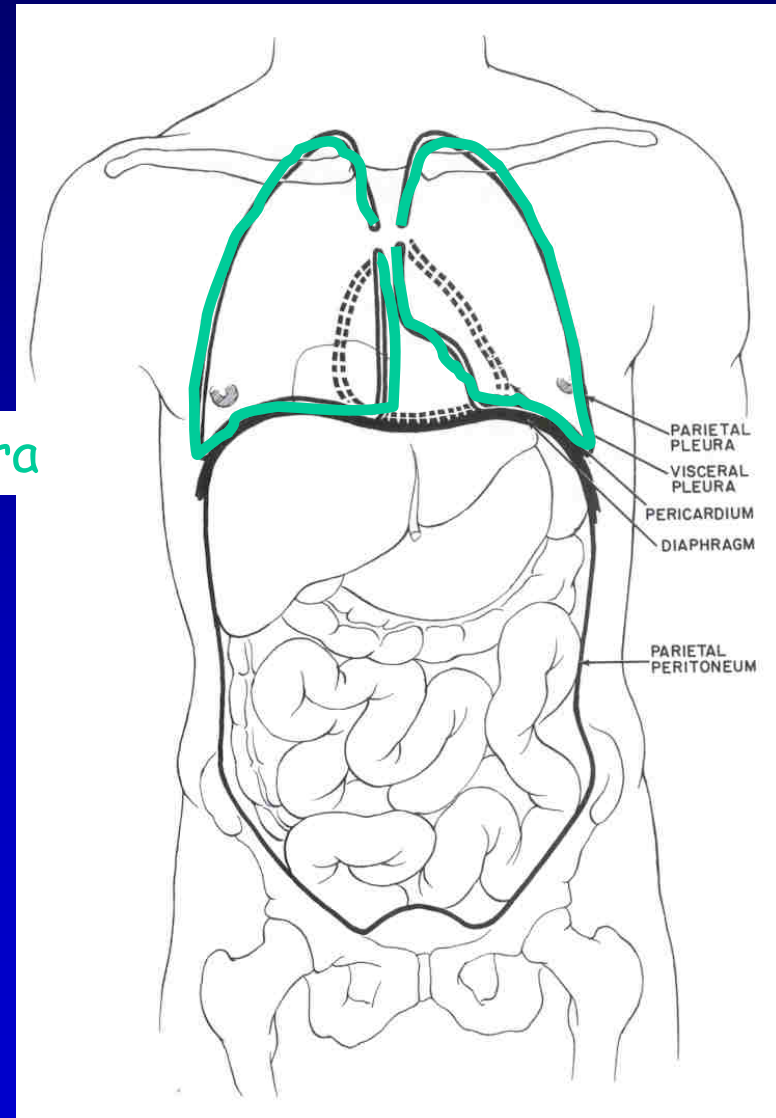
Cytology : first alert of mesothelioma?

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Introduction

3 cavities with the same
embryologic origin
the mesoderme

Pleura



Exudates

22%

45%

| Pleura | Peritoneum | Pericardium |
|-------------------------------|---------------------------|-----------------------|
| Infections (BK !) | Infections | Infections |
| Cancer | Cancer | Cancer |
| Embolism +/- infarction | Embolism +/- infarction | Myocardial infarction |
| Systemic diseases | | Systemic diseases |
| Gastrointestinal inflammation | Pancreatitis, peritonitis | |
| Post-myocardial infarction | | |
| Chylous | Chylous | Chylous |
| Traumatism | Traumatism | Traumatism |

Normal cells

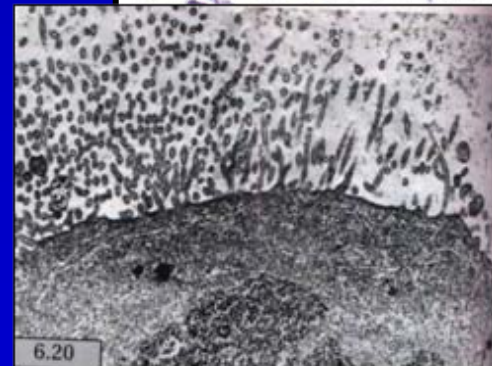
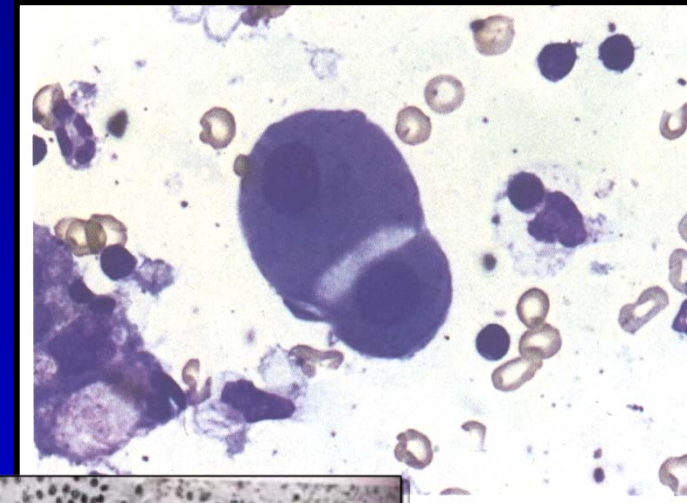
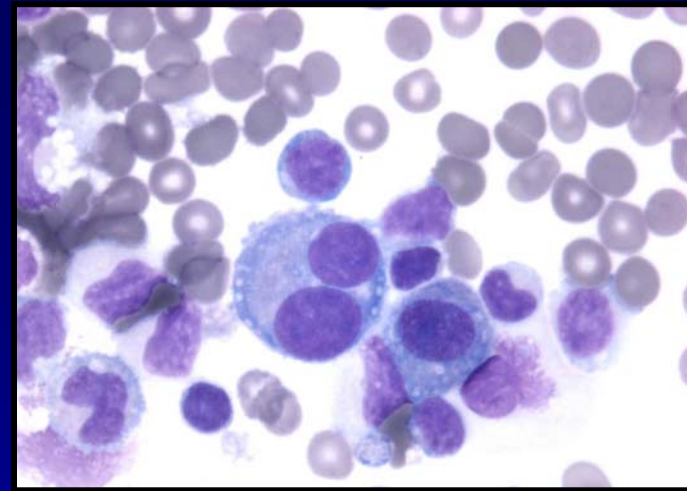
■ Mesothelial cells:

◆ Nuclei

- centrally or peripherally located, bi or plurinucleation
- fine chromatin pattern
- sometimes prominent nucleolus

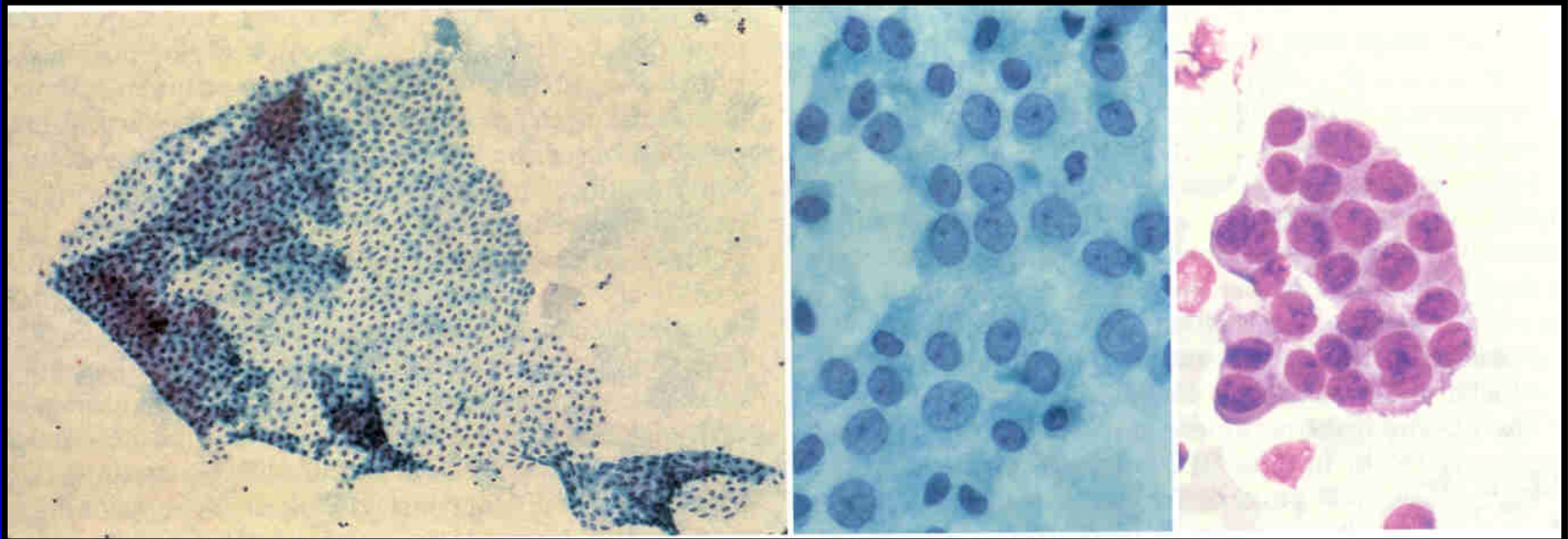
◆ Cytoplasm

- basophilic (MGG), amphophilic (Pap)
- irregular cell limits covered by microvilli
- sometimes vacuolated at the periphery
- intercellular windows



Normal cells

- Mesothelial cells:
 - ◆ In case of lavage, presence of monolayered cell sheets



Normal cells

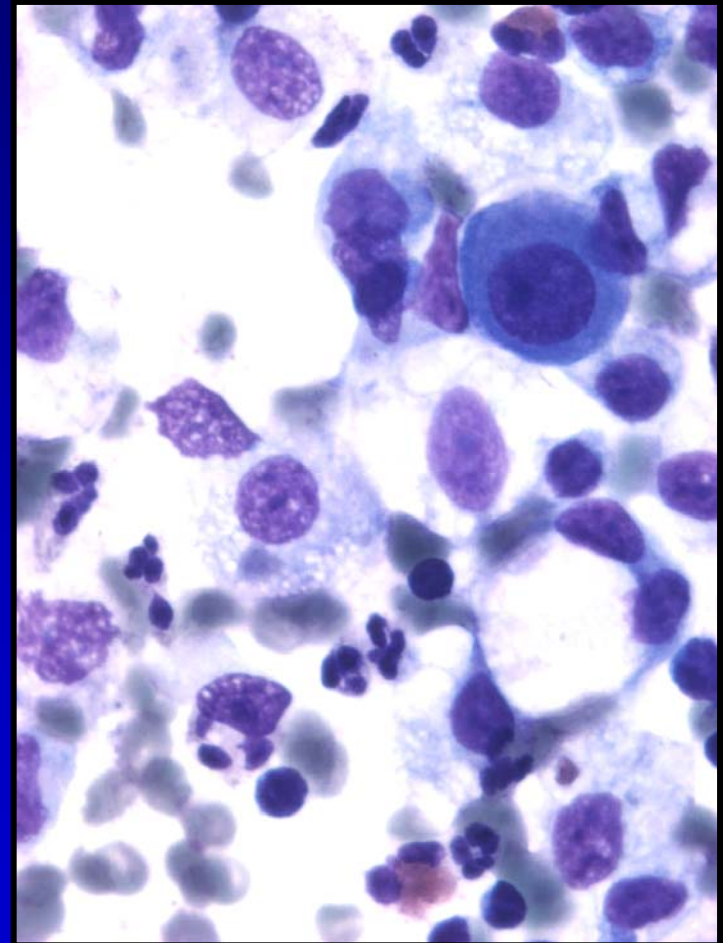
■ Macrophages:

◆ Nuclei

- Kidney-shaped or round, peripherally located
- Multinucleation

◆ Cytoplasm

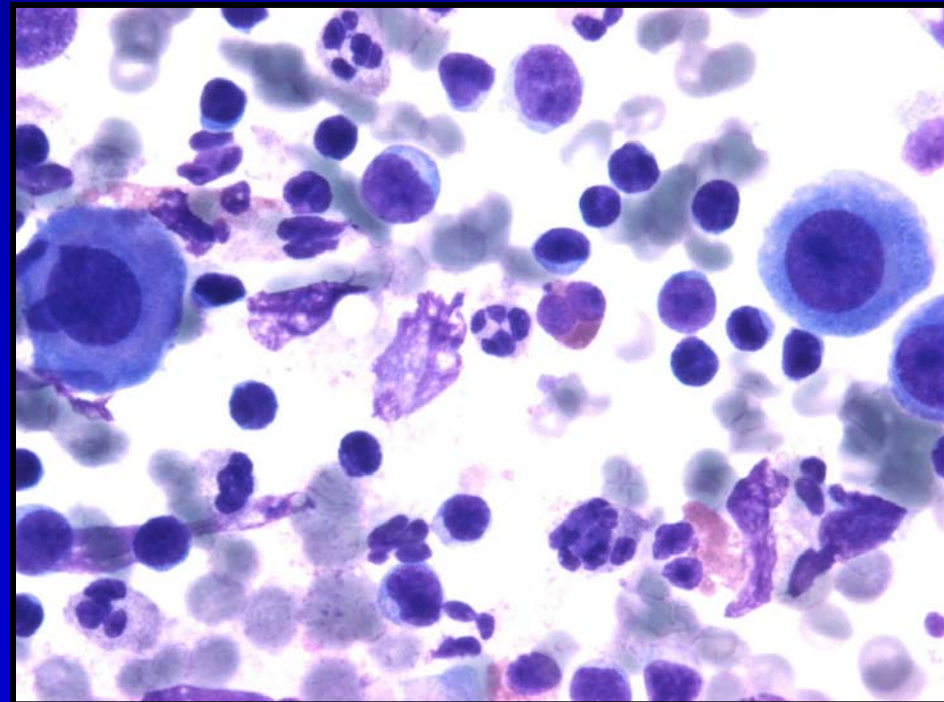
- Often microvacuolated
- Intracytoplasmic material such as hemosiderin, ...



Normal cells

■ Inflammatory cells:

- ◆ Lymphocytes
- ◆ Neutrophils
- ◆ Eosinophils



Malignant cytology

Introduction

- Serosal cytology has a much better sensitivity than a biopsy => important role
- Difficulties:
 - ◆ Differential diagnosis between a reactive mesothelial cell and a malignant cell
 - ◆ Differential diagnosis between different tumours metastatic to the pleura and a mesothelioma

Introduction

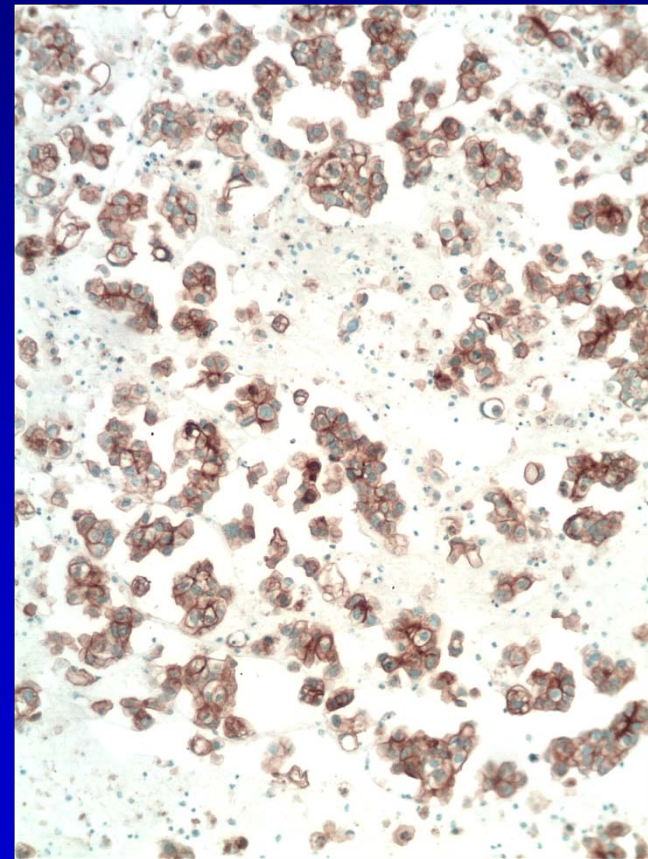
- A malignant effusion may be
 - ◆ either a **transsudate** due to the compression of lymphatics => no neoplastic cells present in the effusion
 - ◆ or an exudate due to
 - **metastatic spread** via lymphatics or blood vessels (i.e.: breast cancer)
 - **direct invasion** (i.e.: peripheral lung adenocarcinoma, mesothelioma)

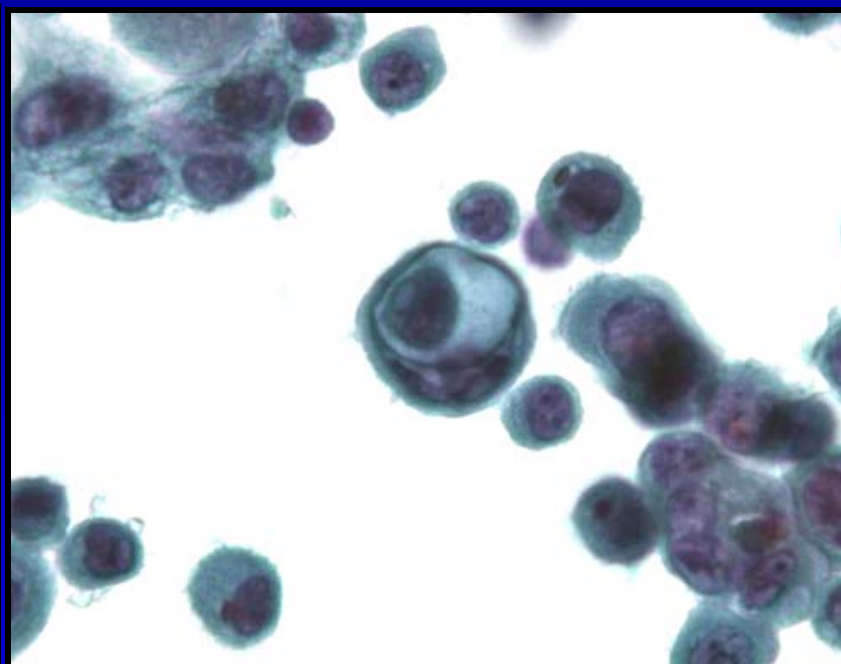
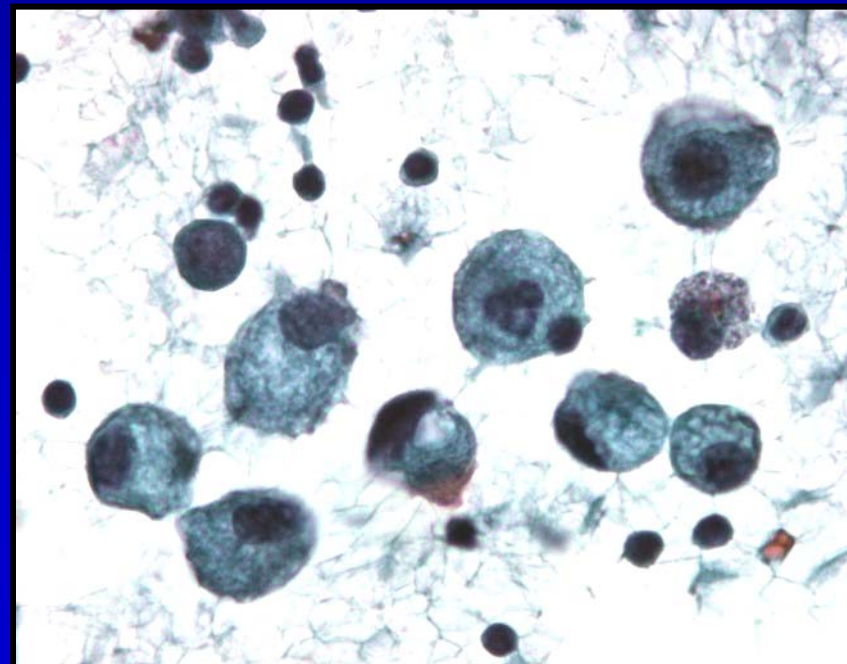
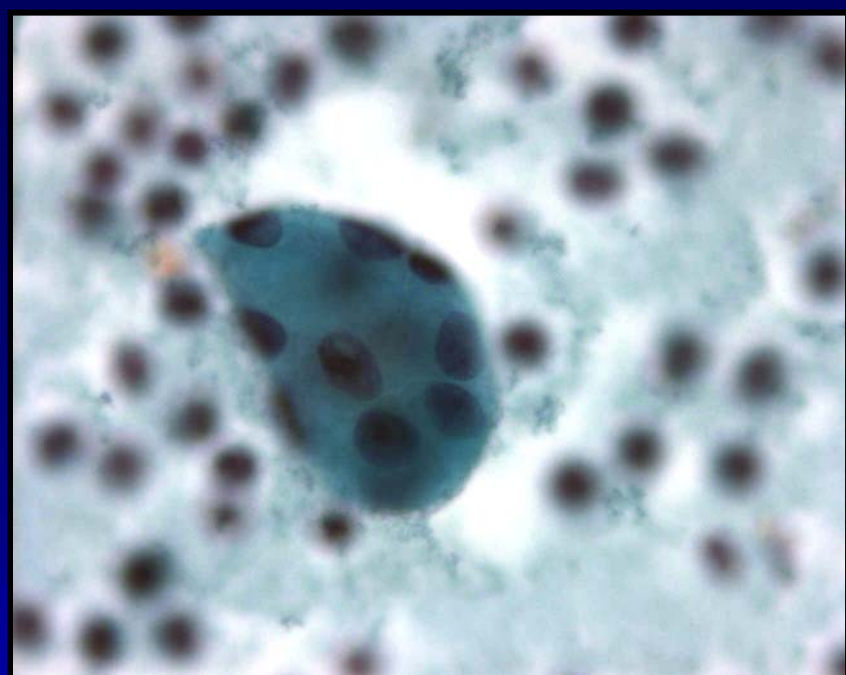
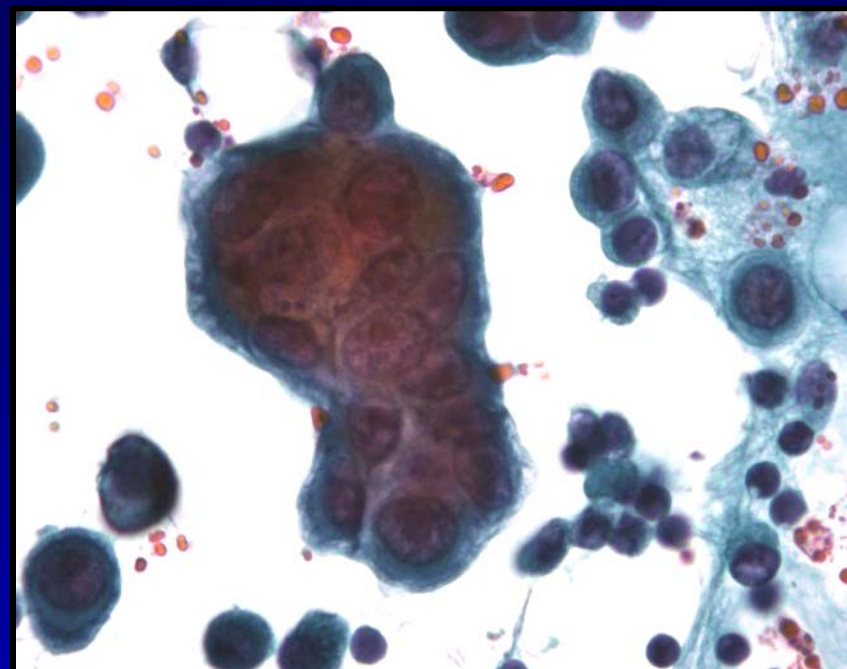
Cytologic criteria of malignancy

- Malignant effusion
 - ◆ Often hemorrhagic
 - ◆ Lymphocyte-rich without other inflammatory cells
 - ◆ Often numerous macrophages, not restricted to malignancy (i.e.: inflammation)

Cytologic criteria of malignancy

- On low magnification:
 - ◆ Presence of three-dimensional clusters with nuclear crowding
 - ◆ Presence of isolated atypical cells
- On high magnification:
 - ◆ Always compare cell size to normal mesothelial cells
 - ◆ Round cells, because of the liquid environment
 - ◆ Nuclear abnormalities





Frequency of metastatic tumours

| Primary site | Pleura % | Peritoneum% |
|--------------|----------|-------------|
| Breast | 51 | 7 |
| Lung | 16 | 26 |
| Ovary | 10 | |
| Stomach | | 40 |
| Undetermined | 8.5 | 7 |

Pleural effusion

| Men | % | Women | % |
|--------------|----|--------------|----|
| Lung | 50 | Breast | 40 |
| Lymphoma | 15 | Lung | 17 |
| Other | 14 | Gyn tract | 15 |
| Undetermined | 10 | Undetermined | 7 |
| GI tract | 9 | Other | 5 |
| Mesothelioma | 4 | GI tract | 4 |
| | | Mesothelioma | 2 |

Difficulties

- Definition of a malignant effusion in case of mesothelioma
- DD reactive mesothelial cell versus mesothelioma
- Definition of a malignant effusion in case of a metastatic carcinoma
- DD reactive mesothelial cell versus carcinomatous cell
- DD epithelioid mesothelioma versus adenocarcinoma

Malignant mesothelioma

- By definition, a tumour arising from the surface serosal cells lining the pleural, the peritoneal and the pericardial cavities
- Pleural mesothelioma is the commonest (90%)
- 90% of patients with pleural mesothelioma present with pleuritic pain associated with recurrent, unilateral, bloody pleural effusions which usually contain neoplastic cells

Malignant mesothelioma

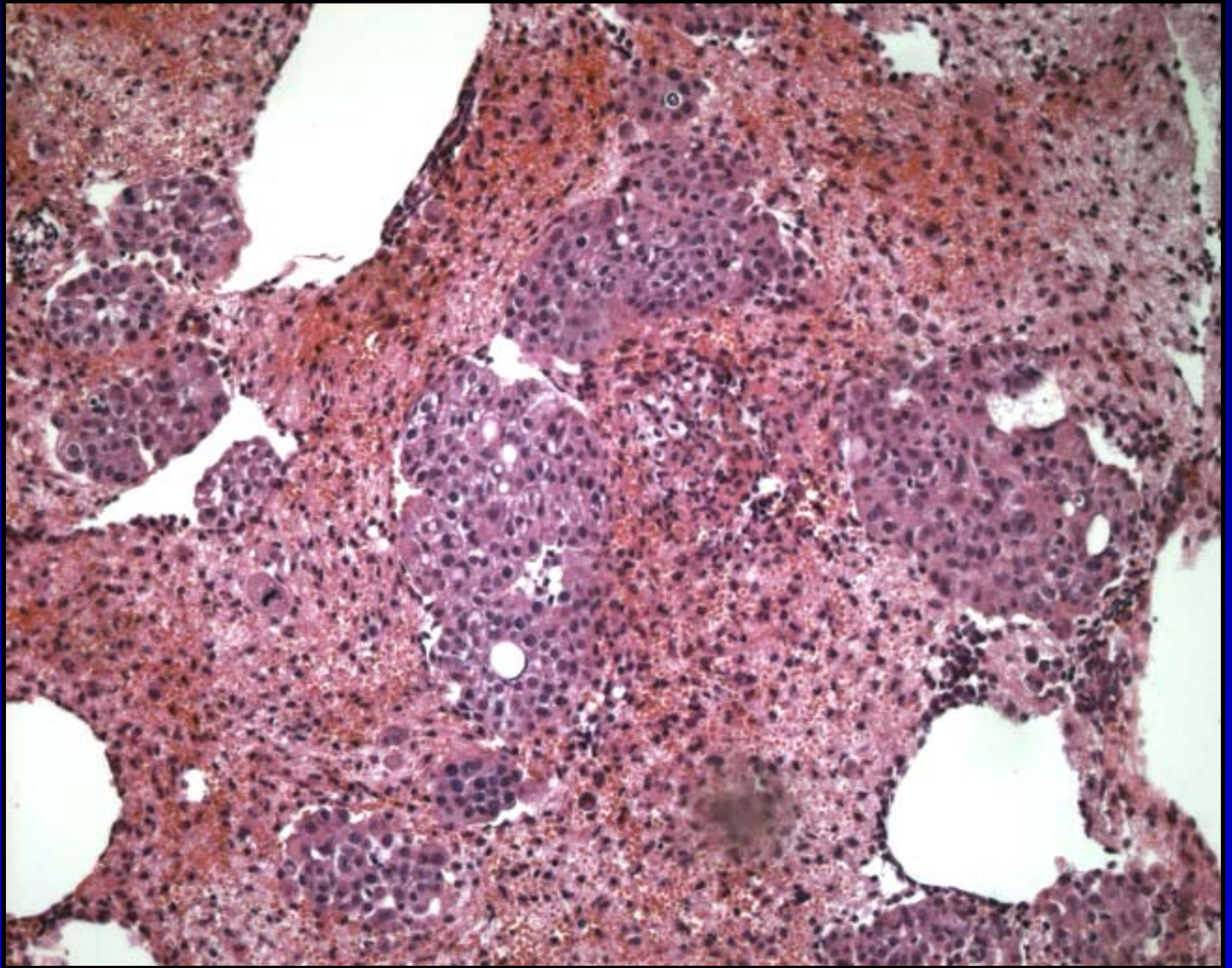
■ Cytology

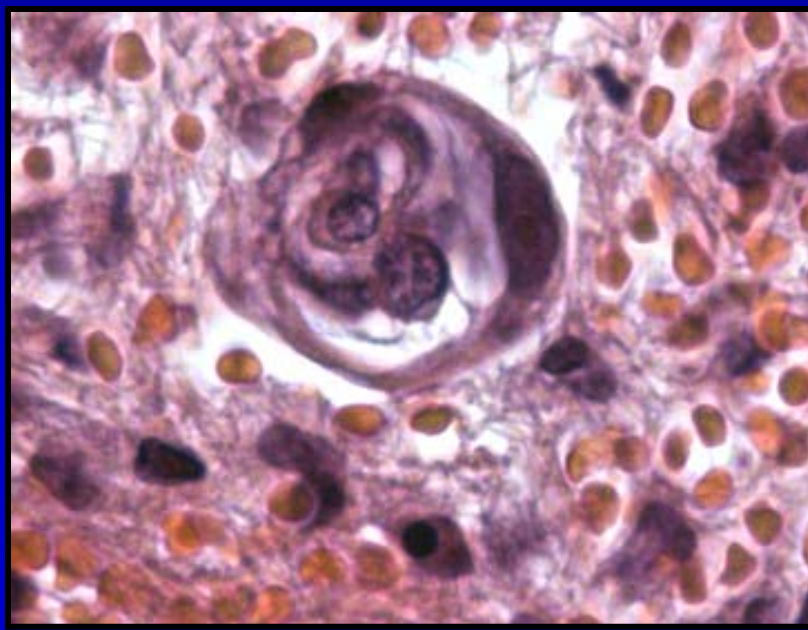
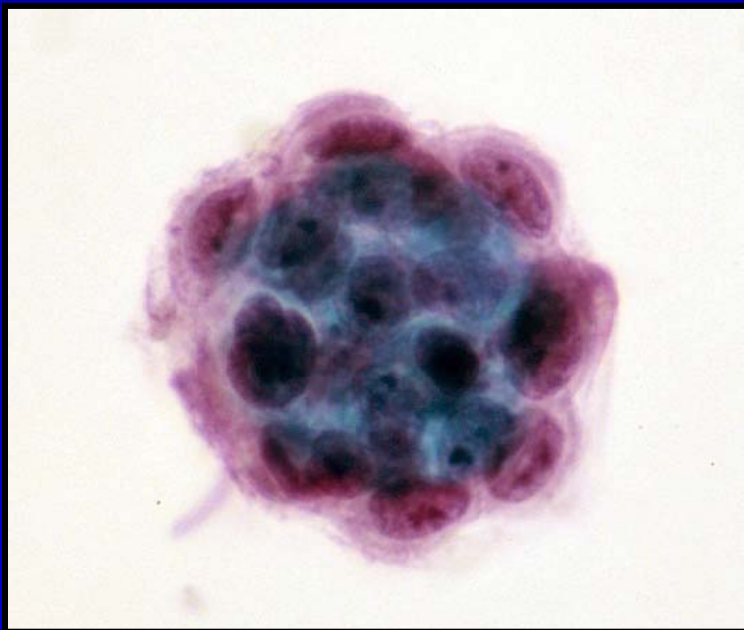
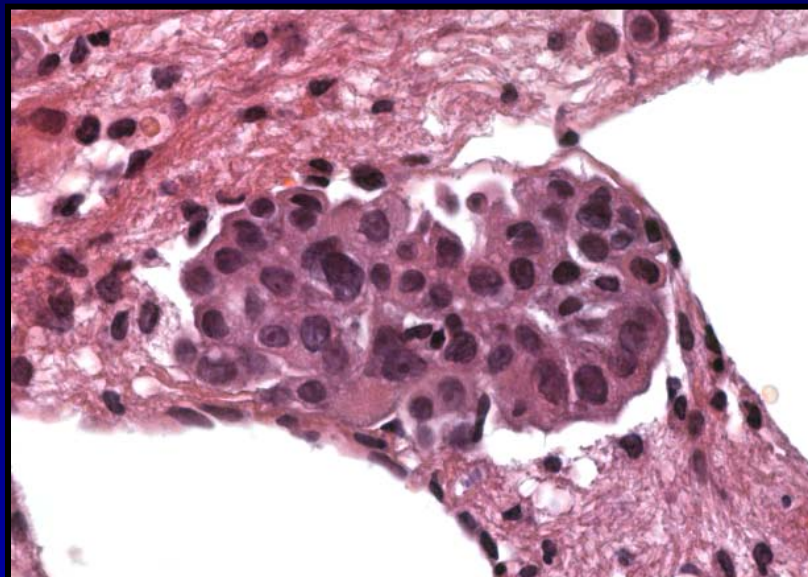
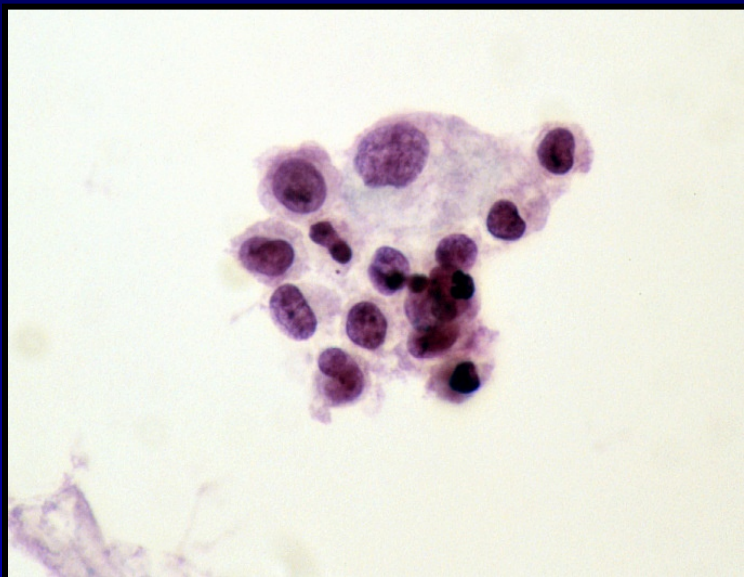
- ◆ On cytology, the different subtypes can not be identified because in a liquid environment cells tend to round up
- ◆ Epitheloid mesothelioma is the most frequent subtype (59%)
- ◆ Desmoplastic and sarcomatoid mesothelioma are less often associated with an effusion

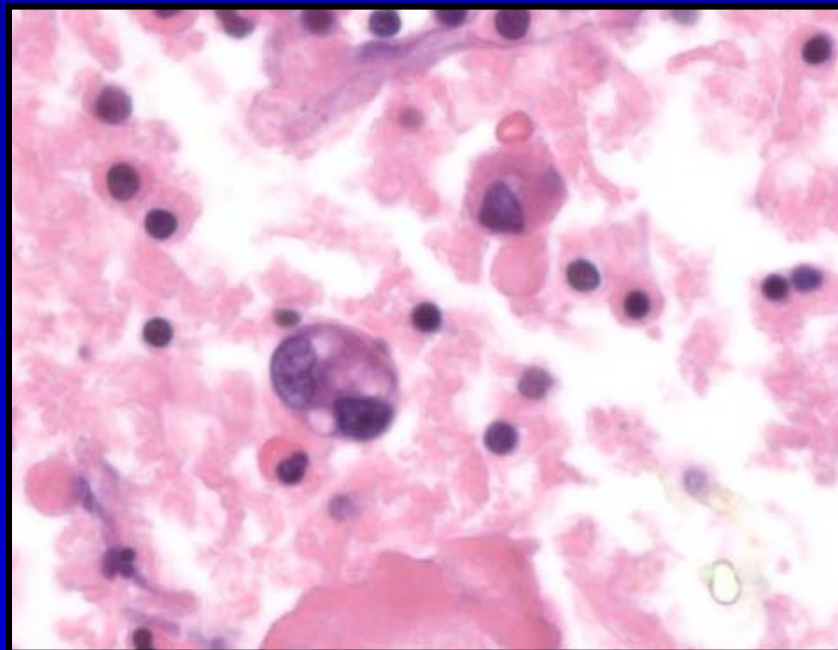
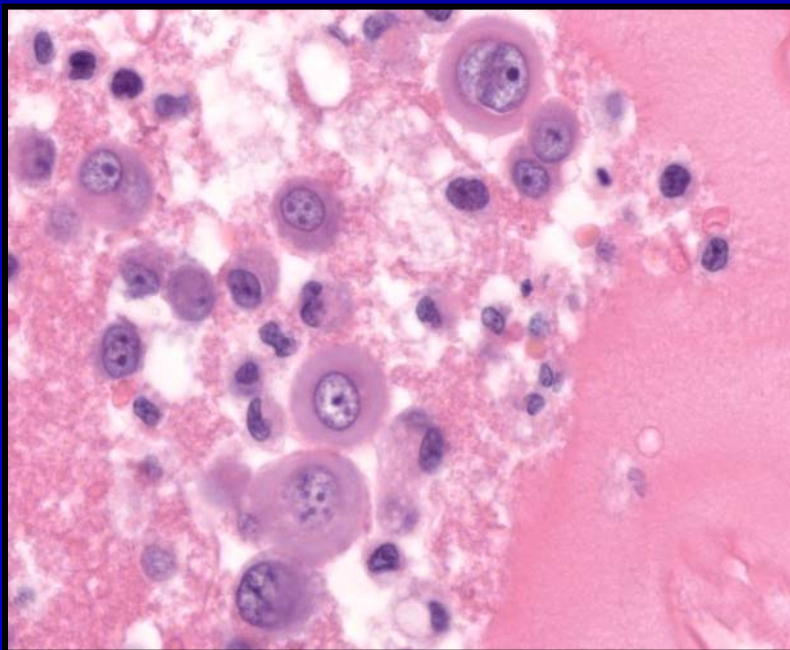
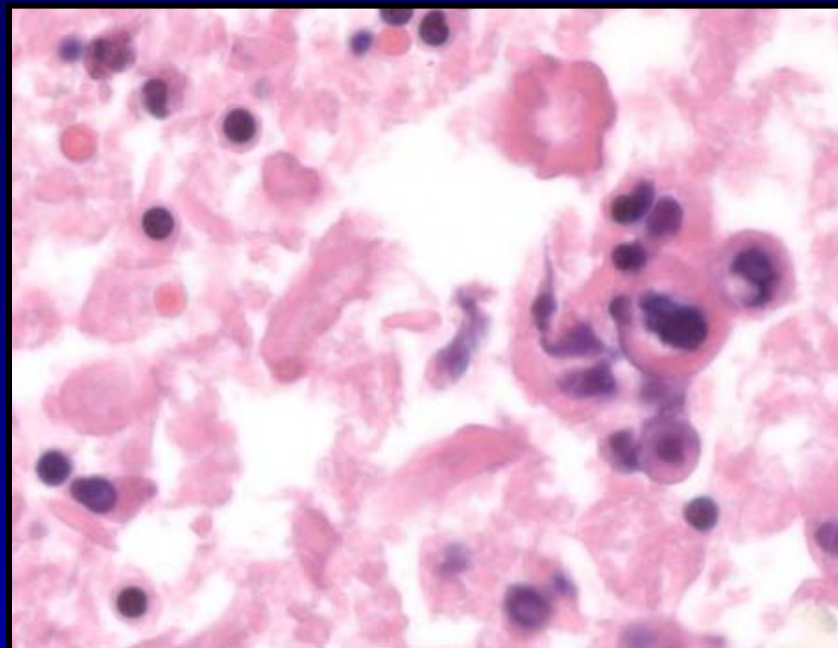
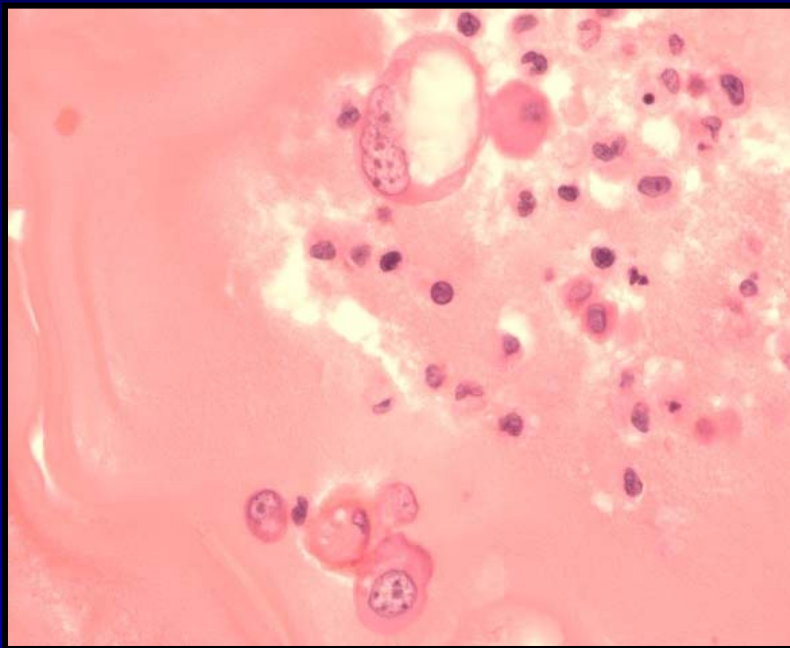
Malignant mesothelioma

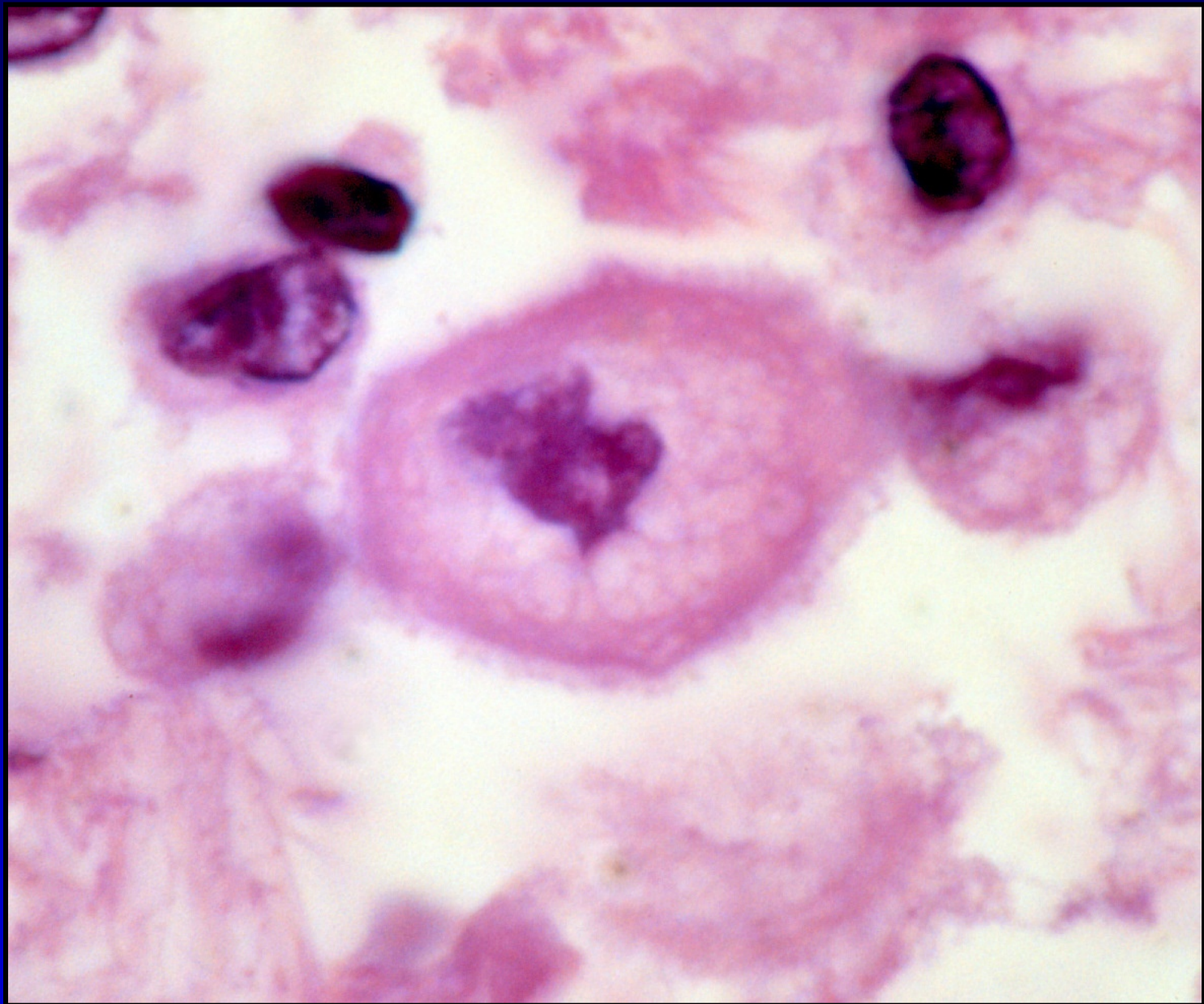
■ Cytologic criteria:

- ◆ Hemorrhagic and very cellular effusion
- ◆ All the cells belong to the same family with a mesothelial morphology
- ◆ Nuclear atypia and frequent multinucleation
- ◆ Macronucleoli
- ◆ Cluster formation (three-dimensional) with knobby outlines (scalloped borders)
- ◆ Cell in cell arrangements
- ◆ Fuzzy cell border
- ◆ Intercellular windows
- ◆ Cytoplasmic vacuoles, peripheral blebs





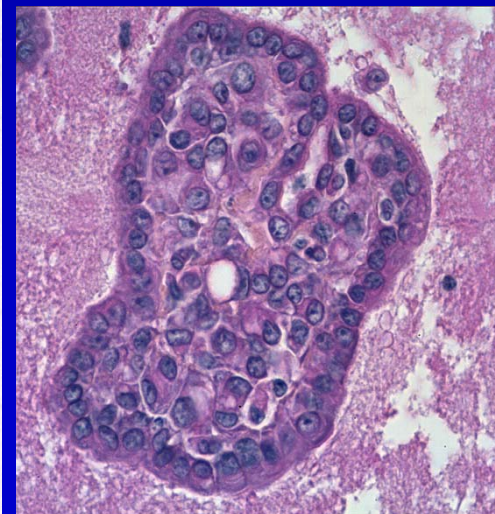
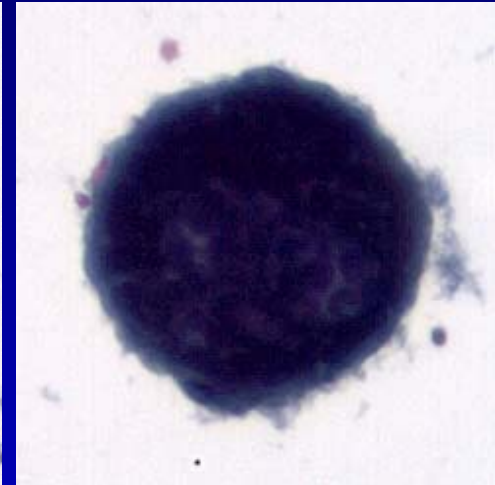
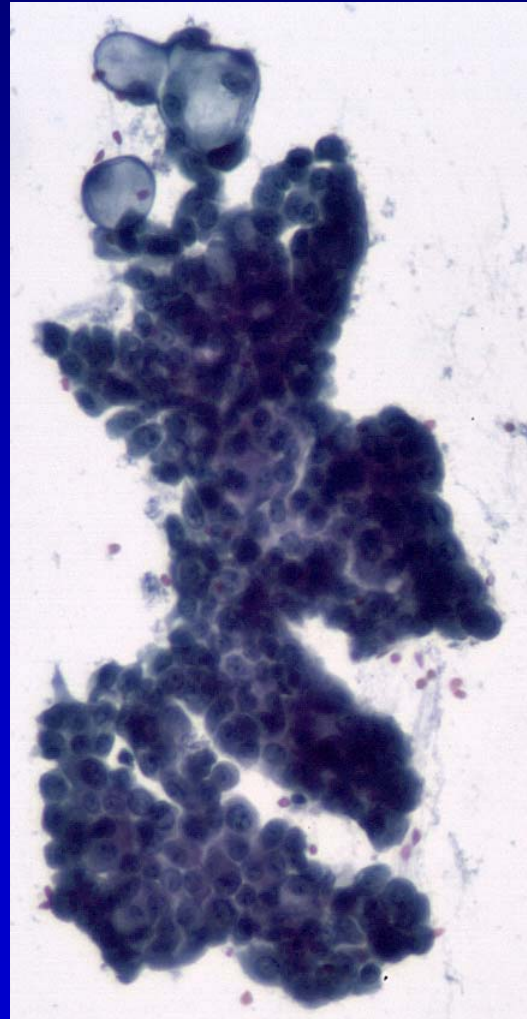
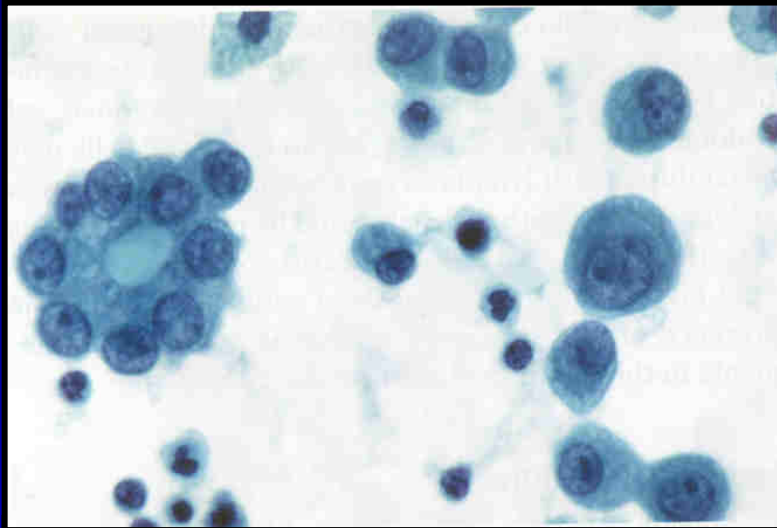




Reactive mesothelial cell versus mesothelioma

| Reactive mesothelial cells | Mesothelioma |
|--|--|
| Moderately cellular specimens | Hypercellular specimens |
| Mainly mono-layered sheets | Two-dimensional sheets and three-dimensional cell groups |
| Cell groups (relatively smaller) with knobbly outlines | Cell groups (relatively larger) with knobbly outlines |
| Intercellular windows present | Intercellular windows present |
| No acinus formation | No acinus formation |
| Mild size variability | Greater variation in size |
| Giant mesothelial cells and multinucleate cells usually absent | May be present |
| Peripheral cytoplasmic blebs and microvilli may be present, but not very prominent | Usually prominent |
| Nuclear features of malignancy—pleomorphic and enlarged nuclei, prominent nucleoli, and atypical mitoses—are not prominent | May be present |

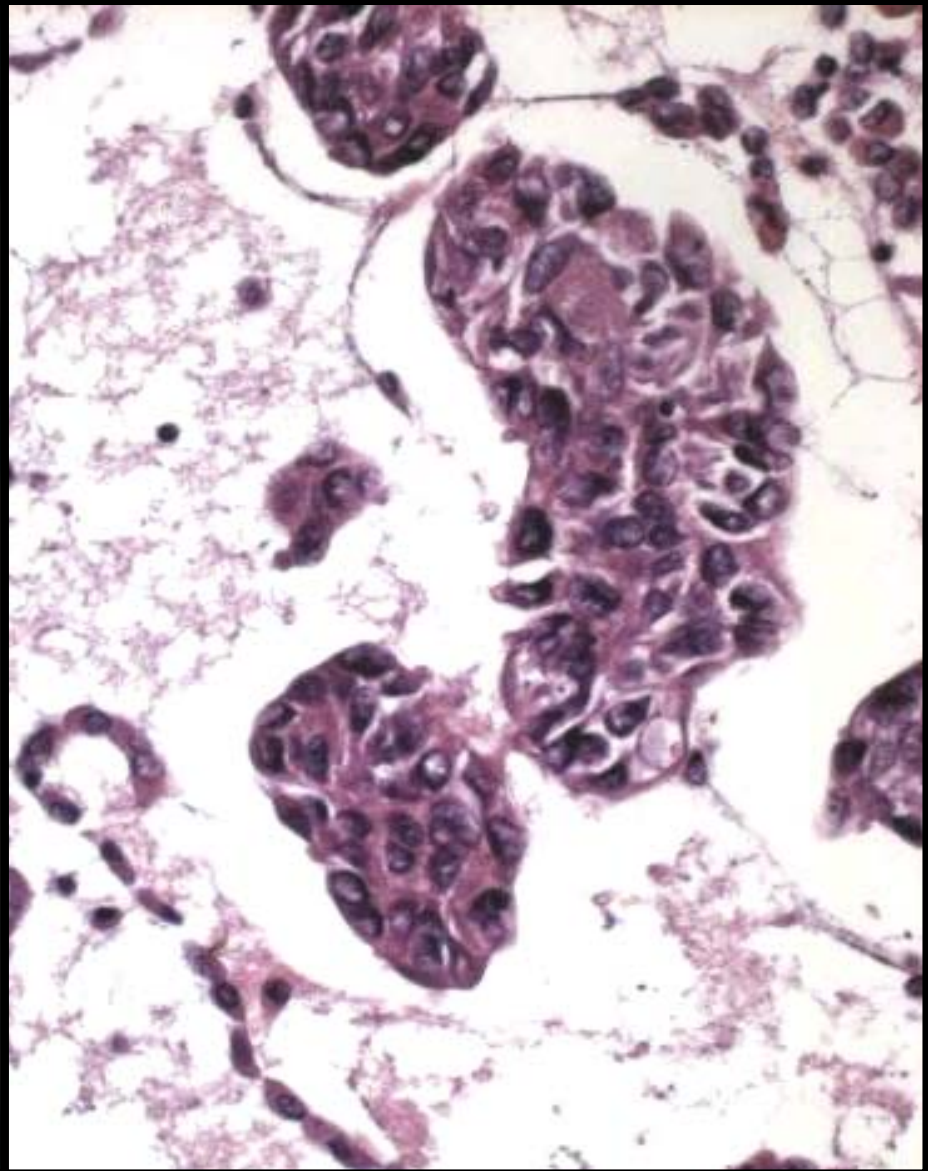
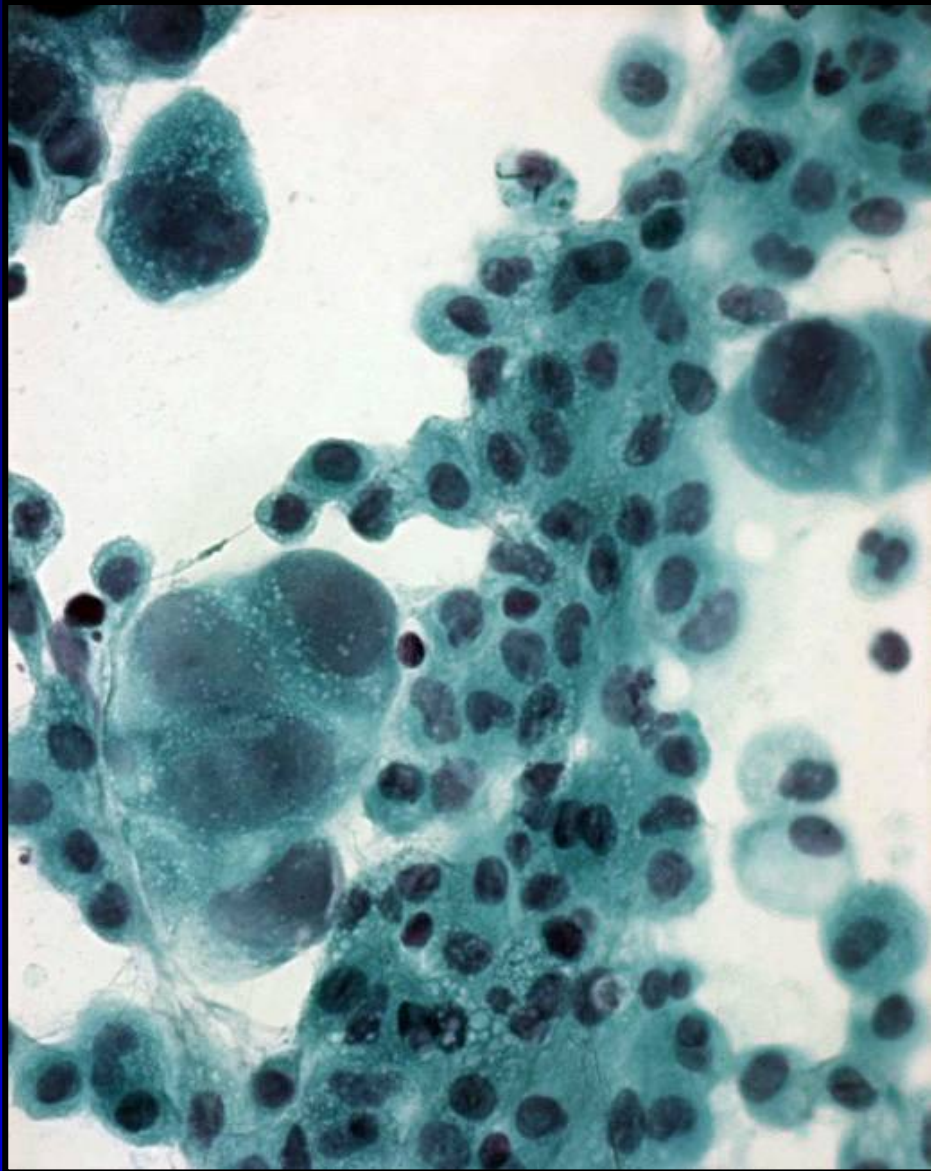
Reactive mesothelial cell versus mesothelioma



Carcinoma

■ Cytology:

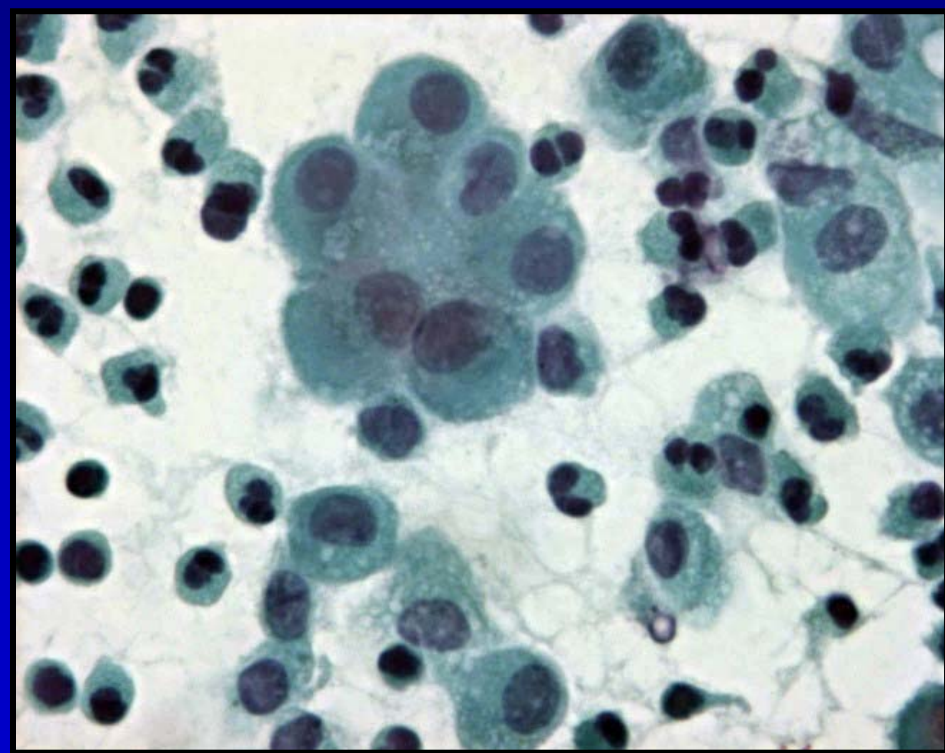
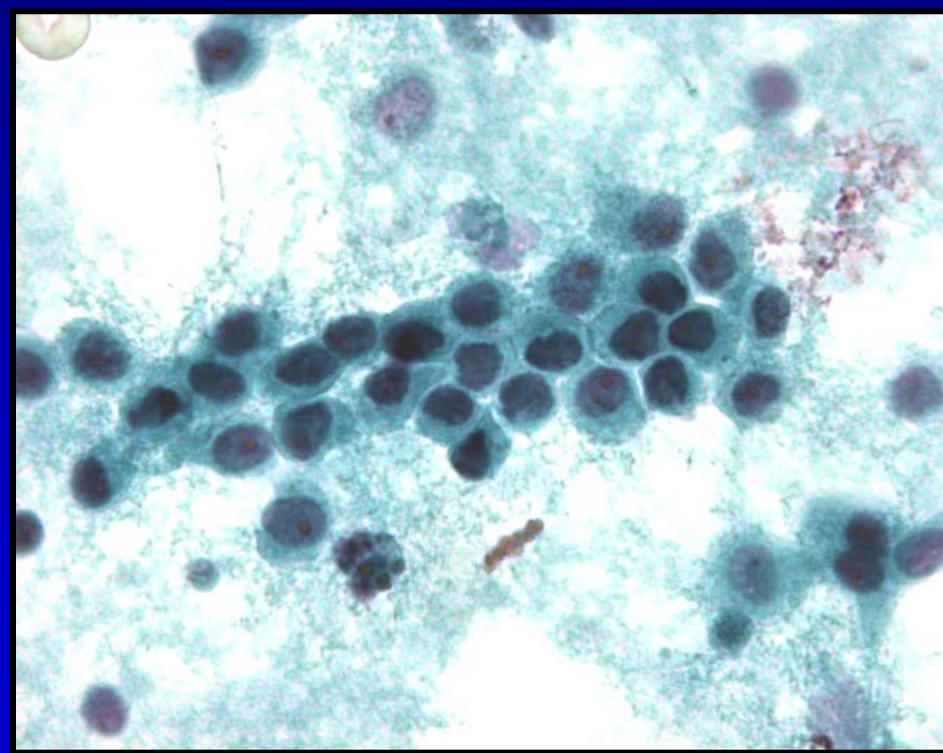
- ◆ Two distinct cell populations : reactive mesothelial and carcinomatous cells
- ◆ Macrophages, inflammatory cells and variable blood contamination
- ◆ Mesothelial cells and macrophages may be in groups



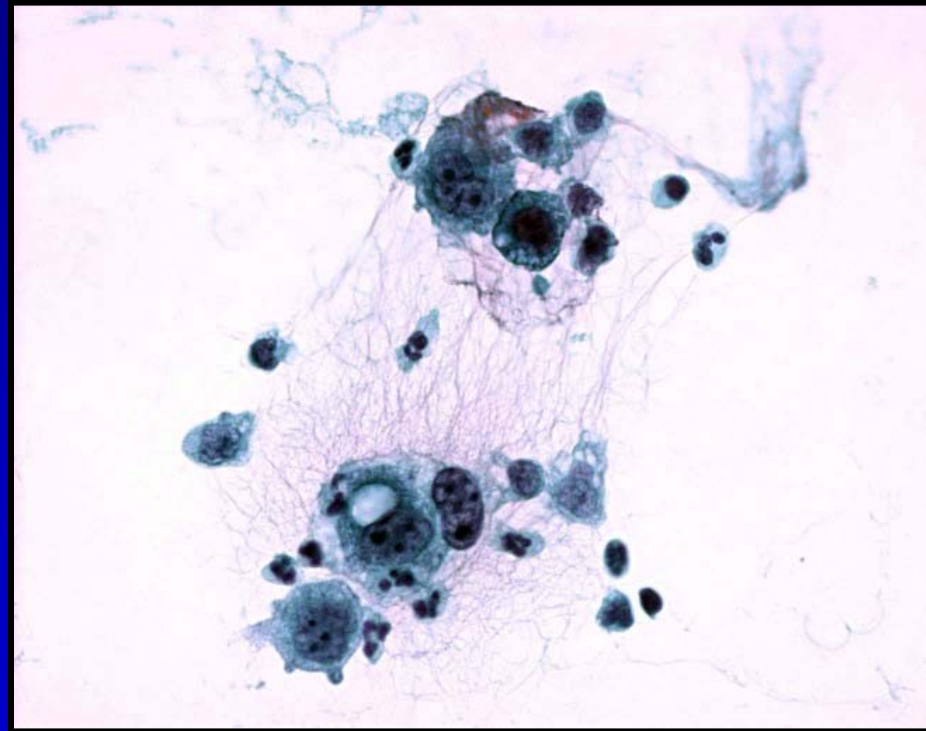
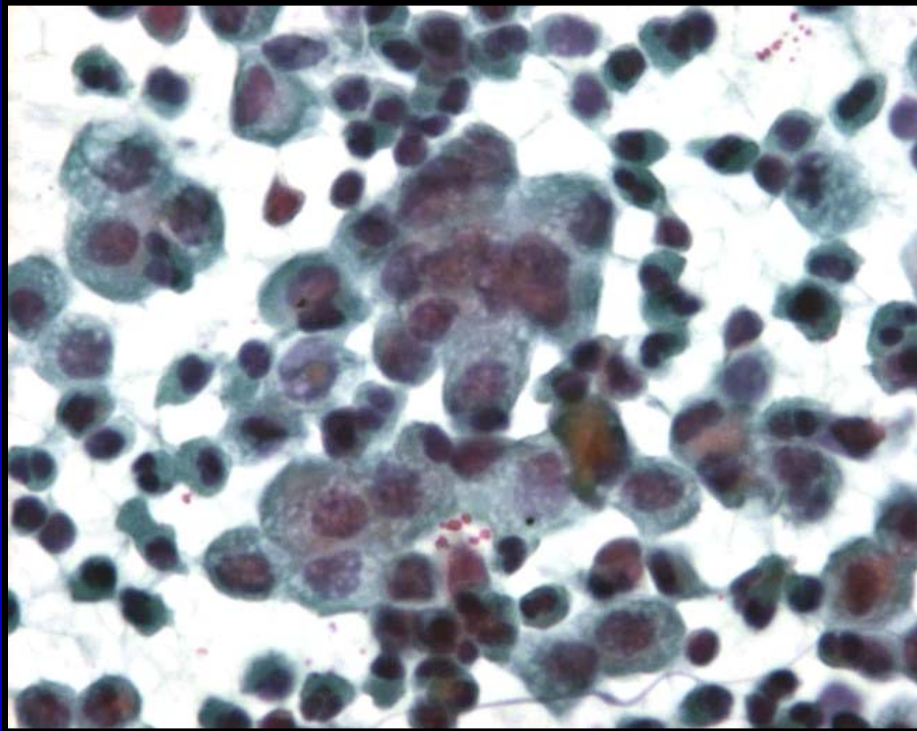
DD reactive mesothelial versus carcinomatous cell

- Higher N/C ratio
- Proeminent nucleoli
- Irregular nuclear contour
- Well defined cytoplasmic border
- Three-dimensional groups
- Cell in cell arrangement

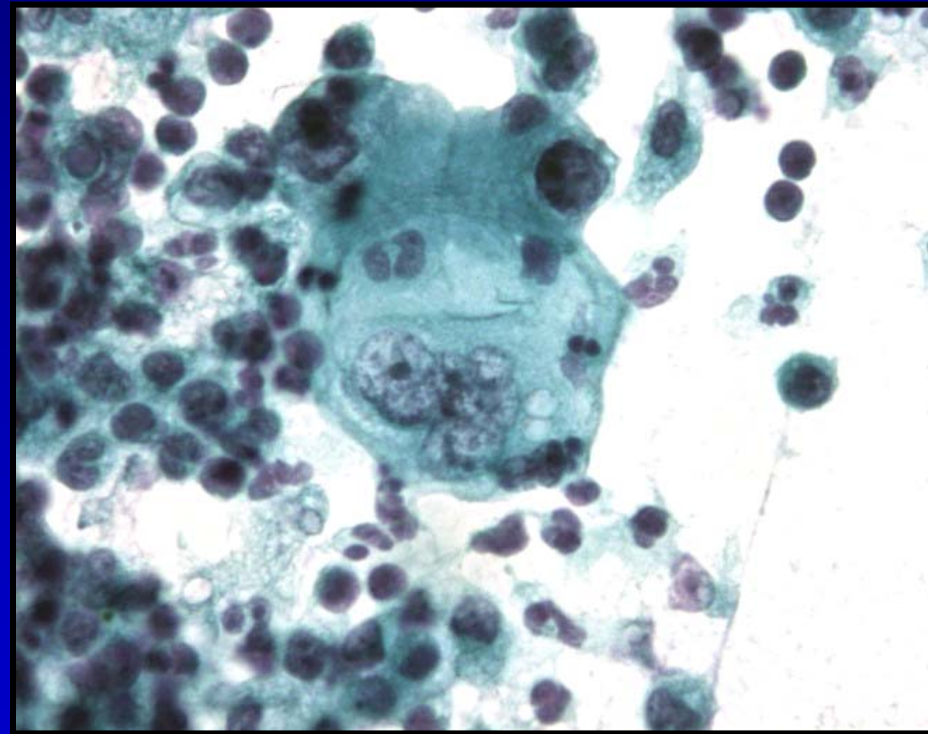
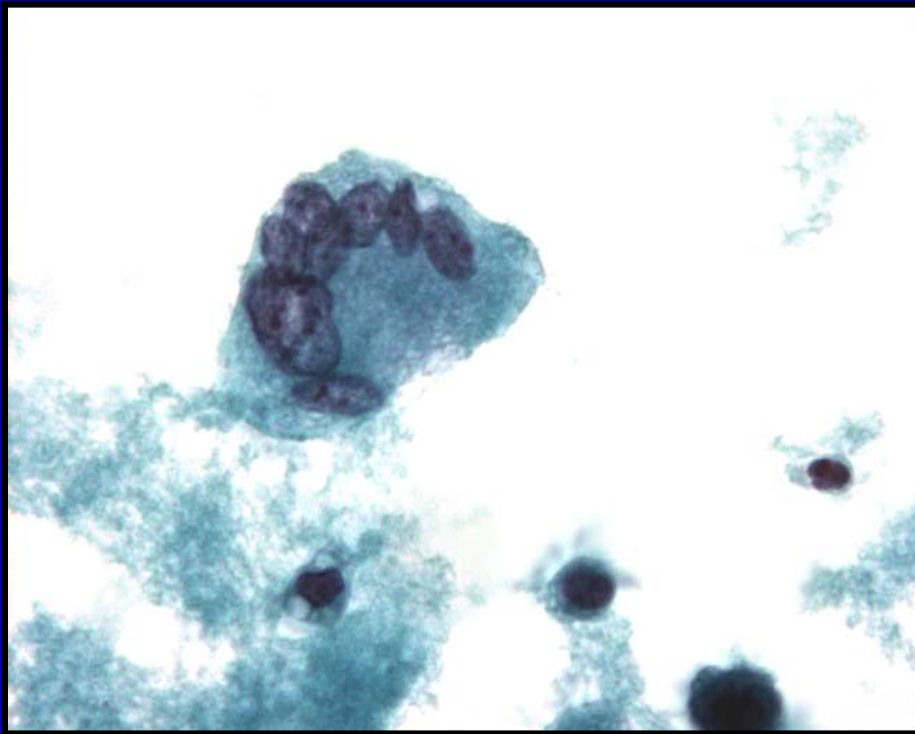
DD reactive mesothelial versus carcinomatous cell



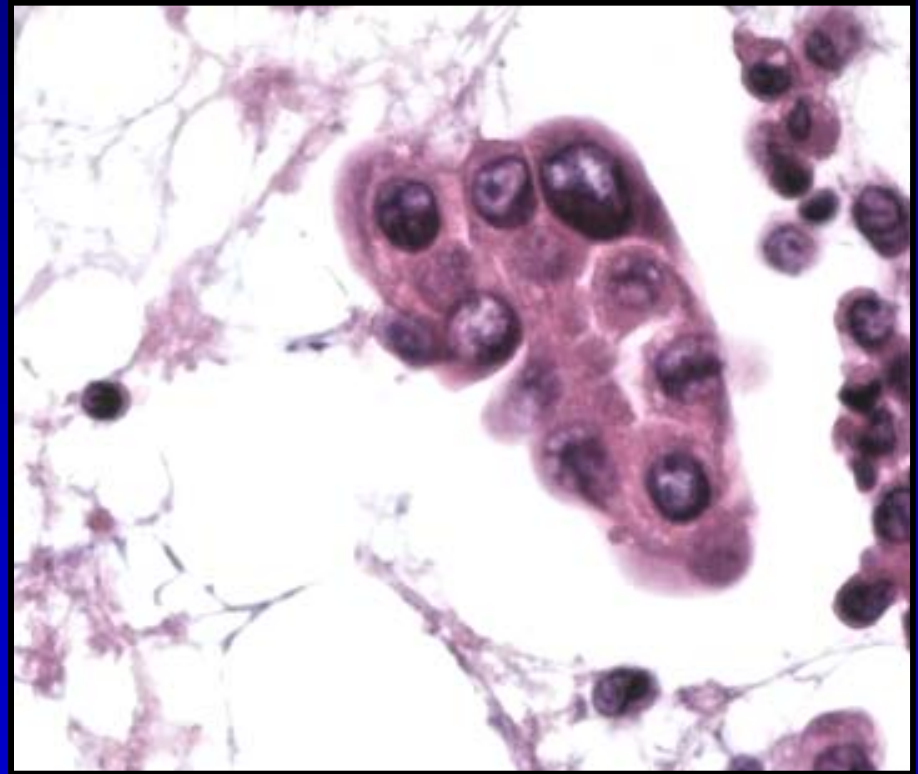
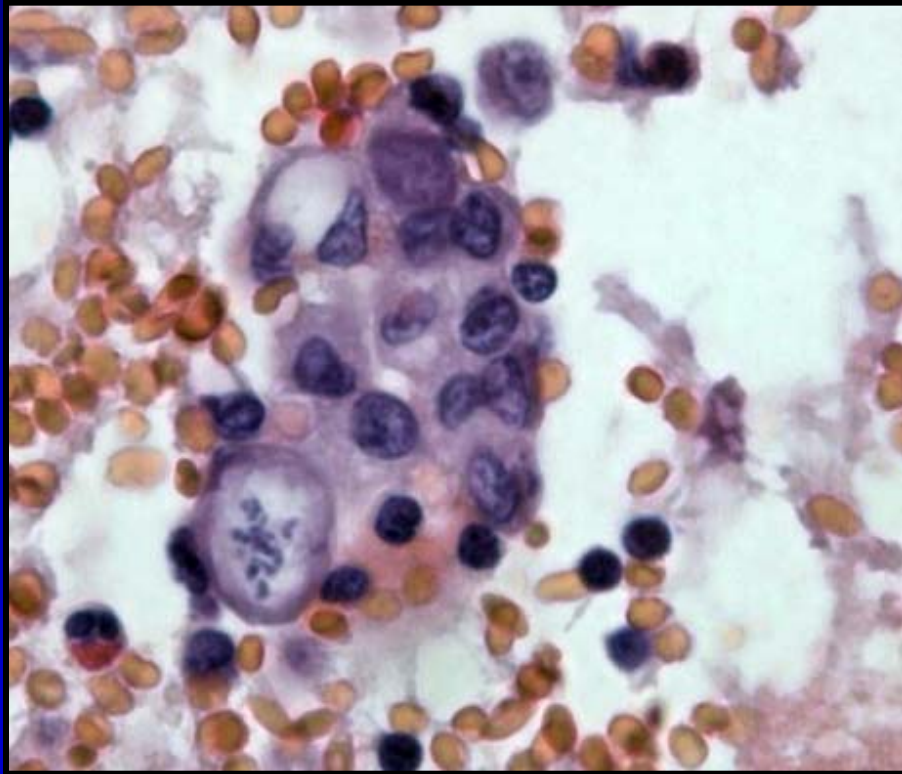
DD reactive mesothelial versus carcinomatous cell



DD reactive mesothelial versus carcinomatous cell



DD reactive mesothelial versus carcinomatous cell



DD epithelioid mesothelioma versus adenocarcinoma

- Very difficult based on morphology alone
 - Need for an immunohistochemical panel including epithelial and mesothelial markers
- => paraffin embedded cell block is mandatory

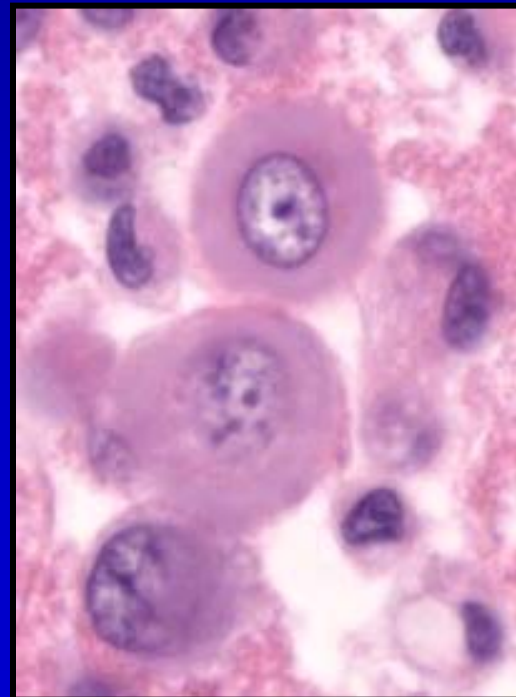
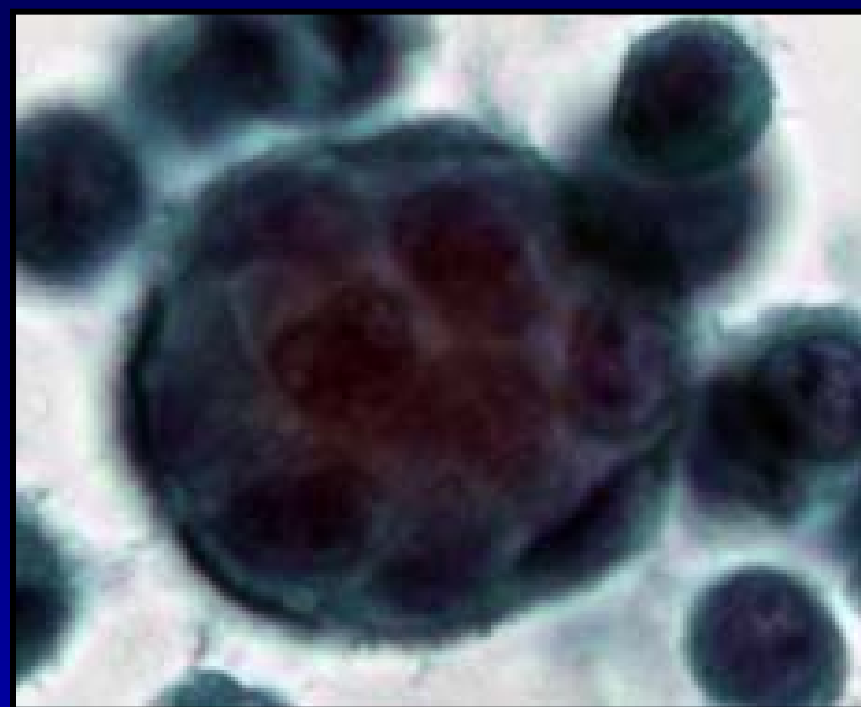
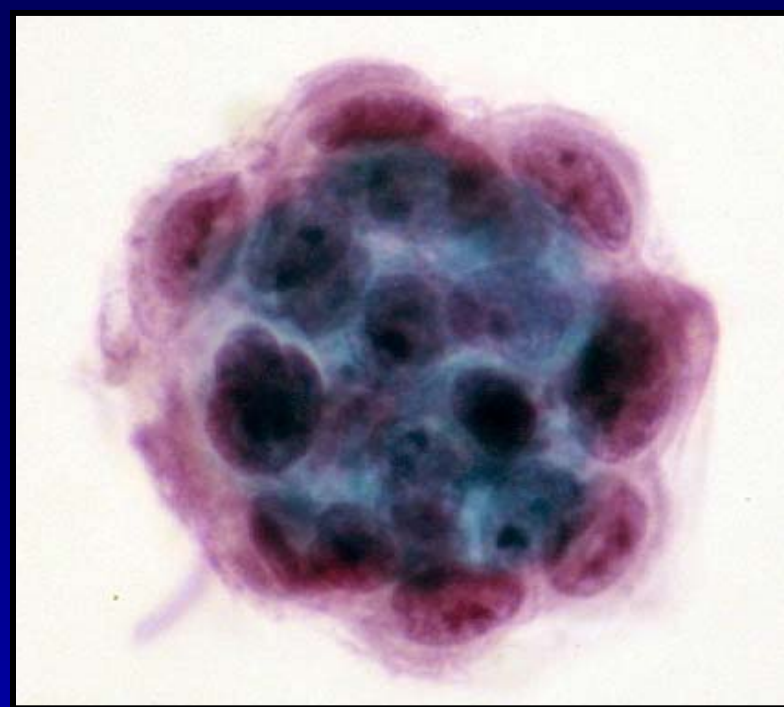
MM versus ADC

■ MM

- ◆ High cellularity
- ◆ One cell population
- ◆ Three-dimensional cell groups with scalloped borders
- ◆ Acinus formation usually absent
- ◆ Centrally located nuclei
- ◆ True papillary aggregates
- ◆ Intercellular windows present
- ◆ Peripheral cytoplasmic blebs with microvilli present

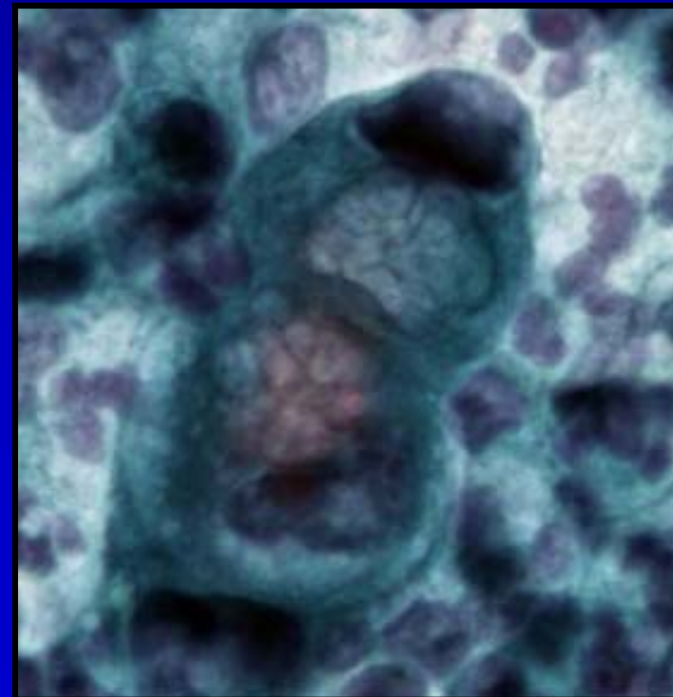
■ ADC

- ◆ High cellularity
- ◆ Double cell population
- ◆ Three-dimensional cell groups with smooth contours
- ◆ Usually present
- ◆ Peripherally located nuclei
- ◆ No true papillae
- ◆ Absent
- ◆ Absent



M
M

A
D
C



Accuracy of diagnosis

- Sensitivity of conventional cytology for malignant cell detection in effusion fluids is reported around 58% with a 97% specificity
- In case of known primary, positive diagnosis is possible in 50 to 60% of cases
- Sometimes the effusion is the first symptom => cytology may help in identifying the primary
- Important for treatment options

Conclusion

- Effusions remain a difficult field in cytological diagnosis
- Immunocytochemical stainings are mandatory for a definite diagnosis
- Do not hesitate to perform them
 - ◆ in case of a suspicious fluid
 - ◆ if there is a clinical history of cancer (in particular for breast carcinoma)
- Paraffin embedded cell blocks are the best material to perform immunos
- In case of a cytology suggestive of a mesothelioma, ask for a biopsy for confirmation
- If a clear-cut diagnosis can not be made, do not hesitate to ask for a new specimen