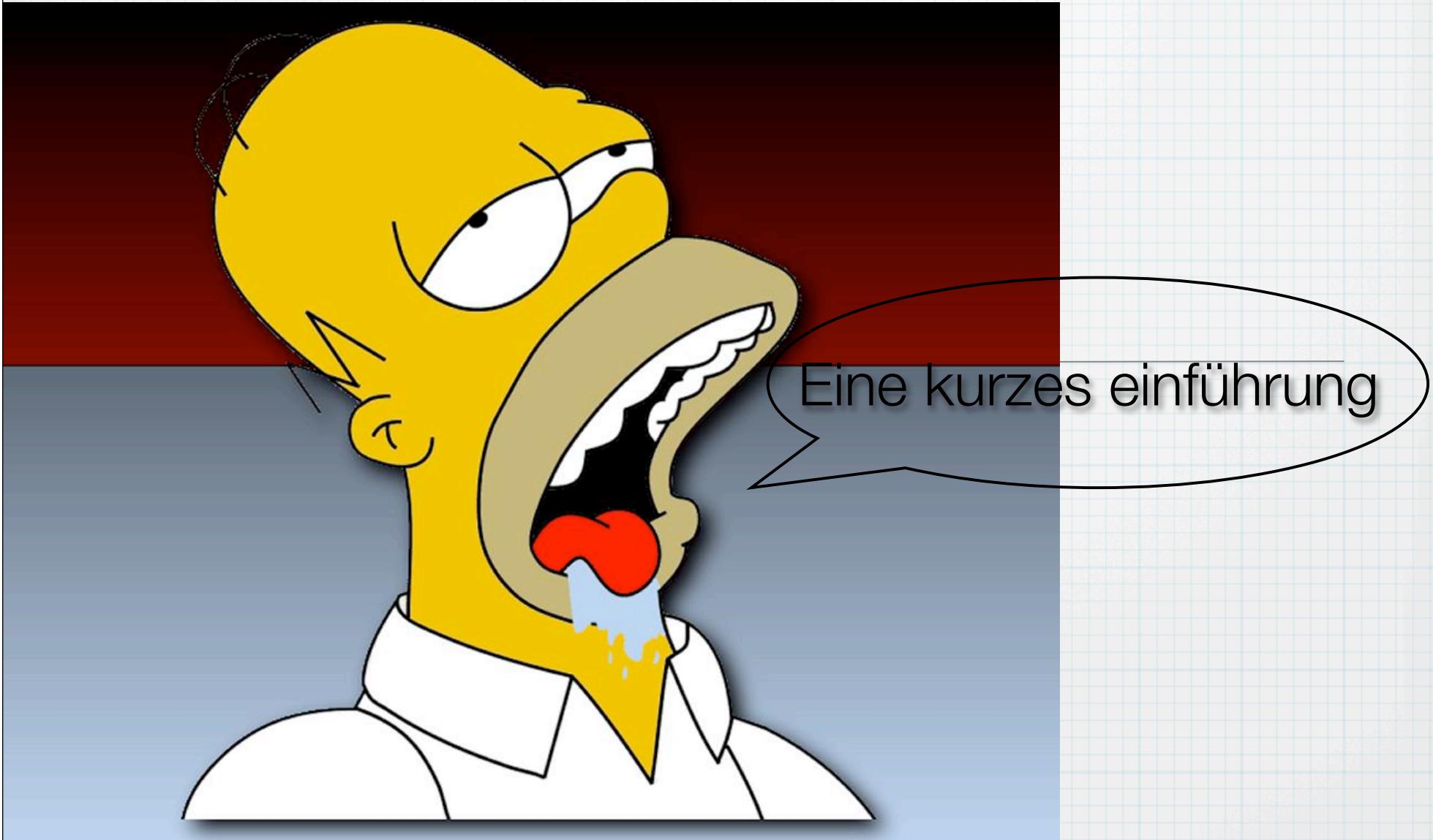


# Neuroendokrine lungetumorer



# Neuroendokrine lungetumorer



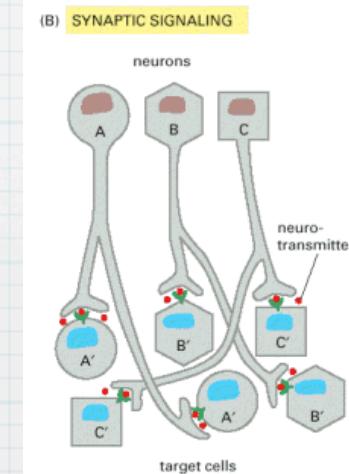
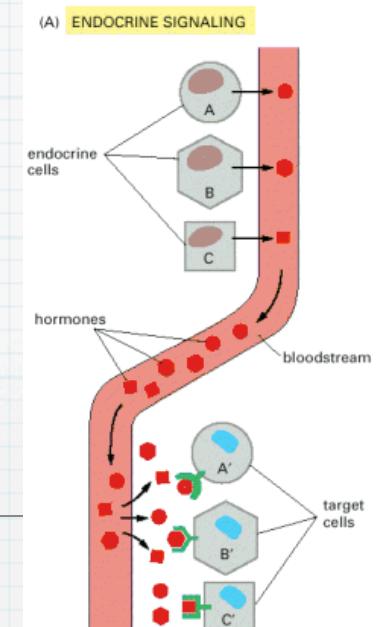
René Théophile Hyacinthe Laennec (1781–1826)

# Neuroendokrine lungetumorer

## Det neuroendokrine system

### Det endokrine system

Består af endokrine celler, endokrine væv og endokrine kirtler, som syntetiserer hormoner, der secerneres til blodet, og derved når fjerntliggende målceller



### Nervesystemet

Kommunikerer via signalmolekyler (neurotransmittere), der formidler kontakten mellem nerveceller og andre målceller

# Neuroendokrine lungetumorer

## Det neuroendokrine system

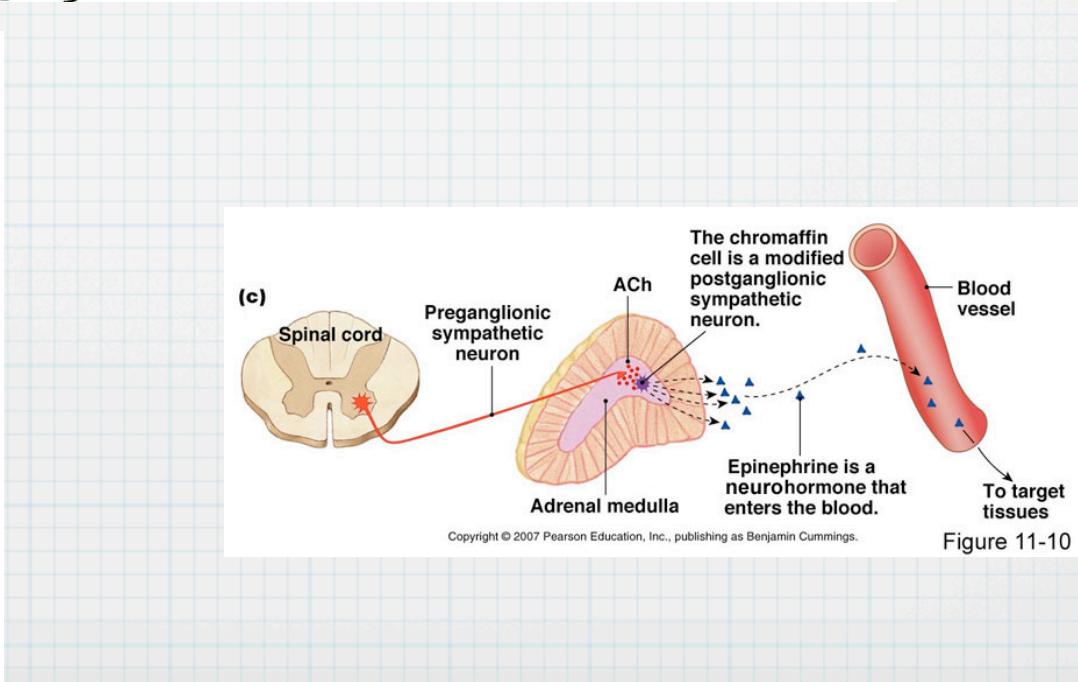
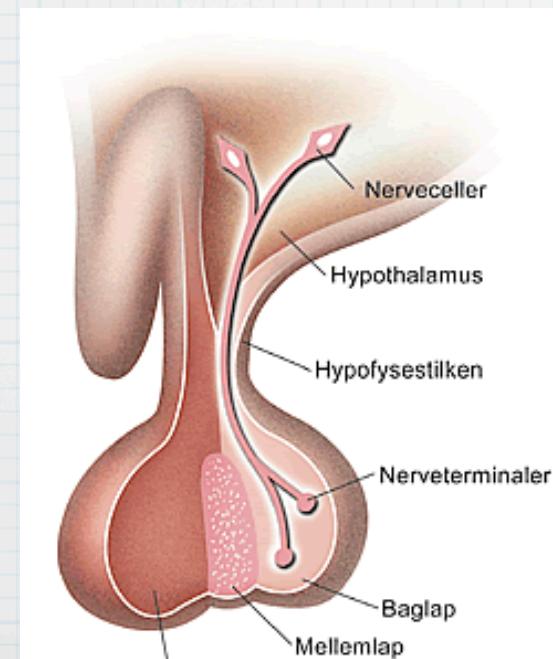
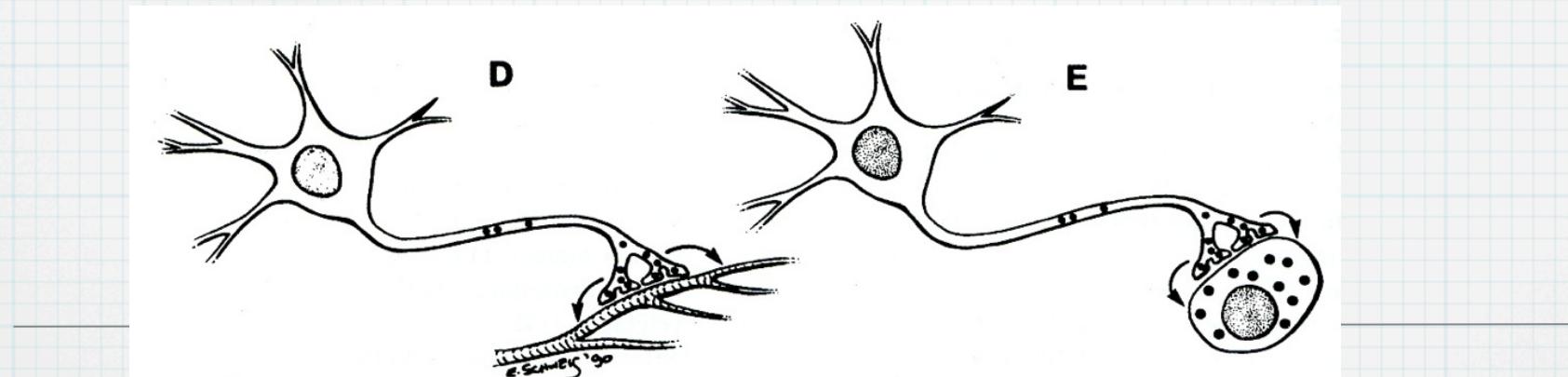


Figure 11-10

# Neuroendokrine lungetumorer

## Det neuroendokrine system

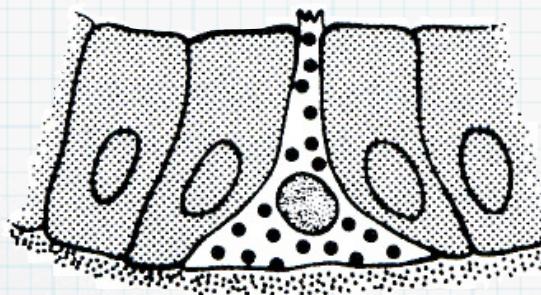
### Neuroendocrine Cells

- Pearse (1969) described APUD (**Amine Precursor Uptake** and **Decarboxylation**) cells that produced polypeptide hormones and biogenic amines identical to those found in neurons → neuroendocrine cell
- Definition of neuroendocrine cells (Langley 1994):
  - Production of a neurotransmitter, neuromodulator or neuropeptide hormone
  - Presence of dense-core secretory granules from which the hormones are released by exocytosis in response to an external stimulus
  - Absence of axons and synapses

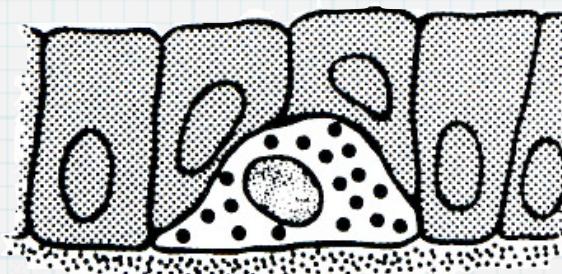
# Neuroendokrine lungetumorer

Det neuroendokrine system

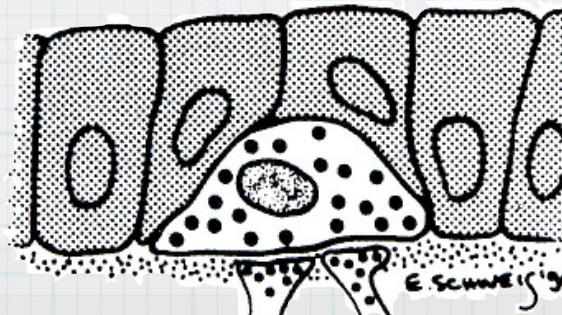
A



B

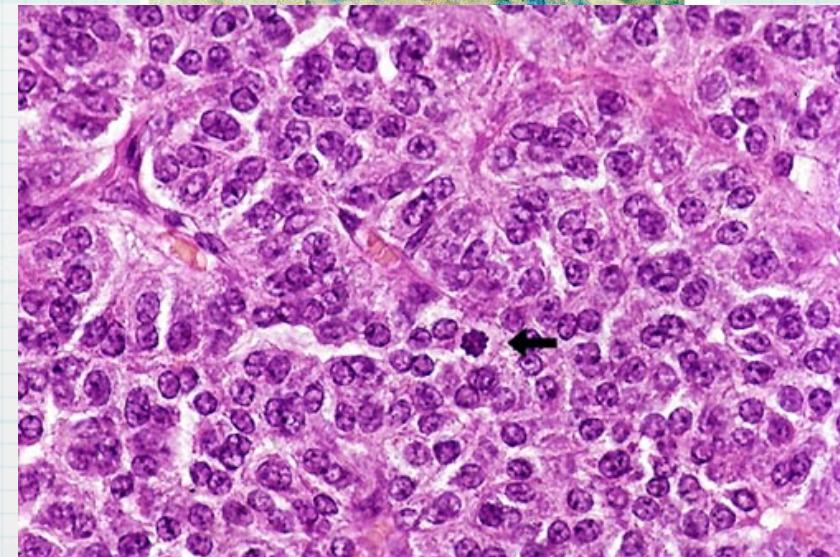
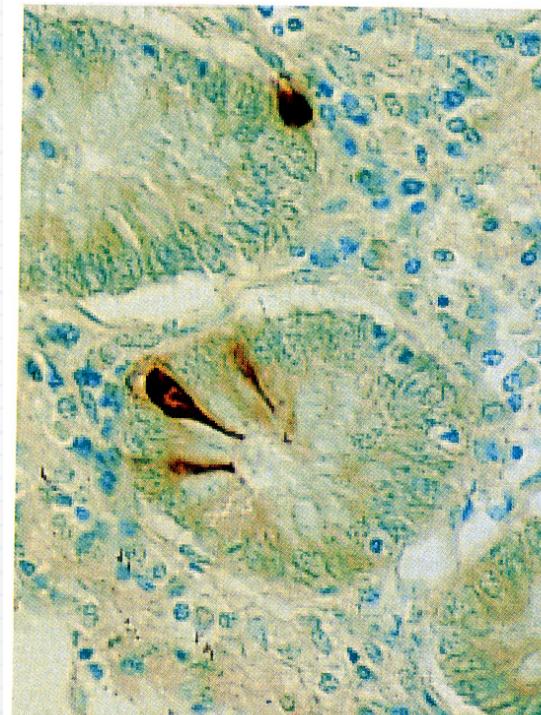
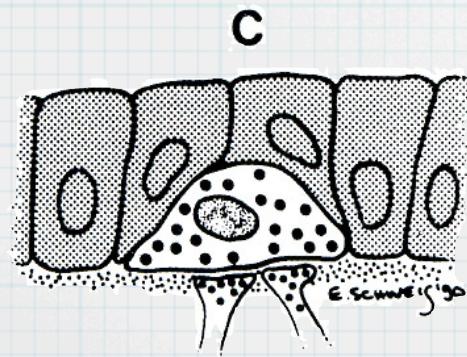
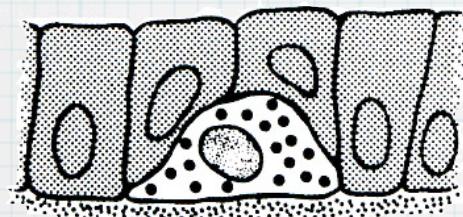
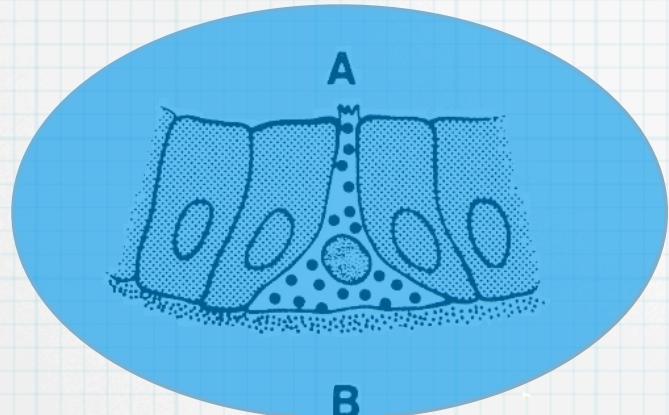


C



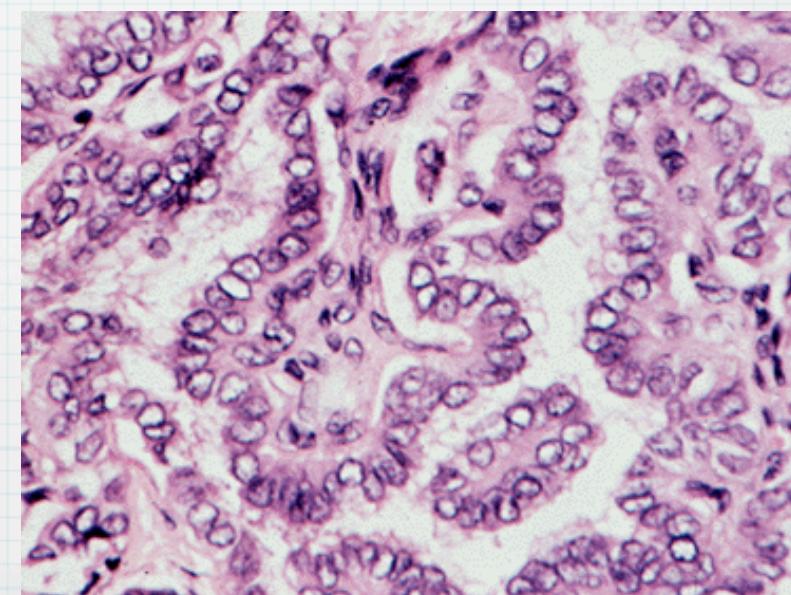
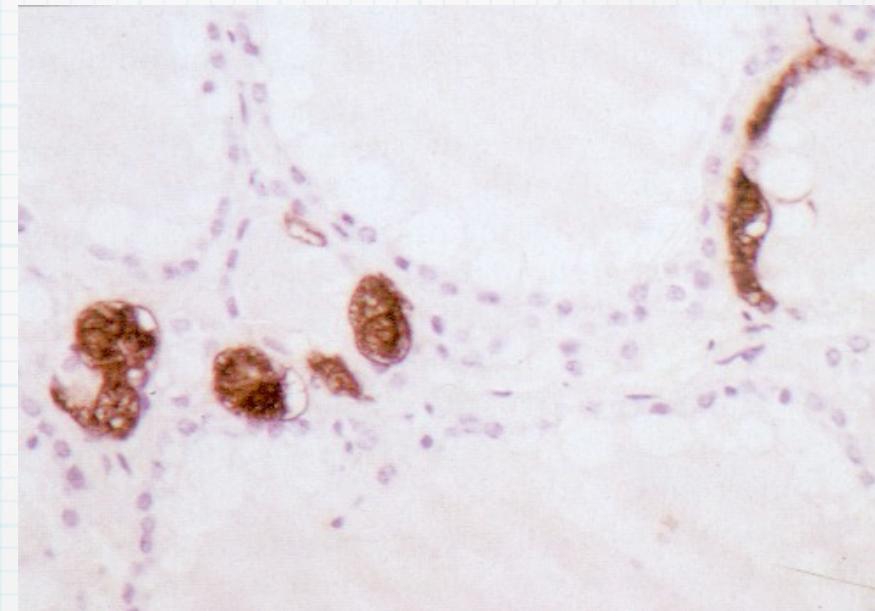
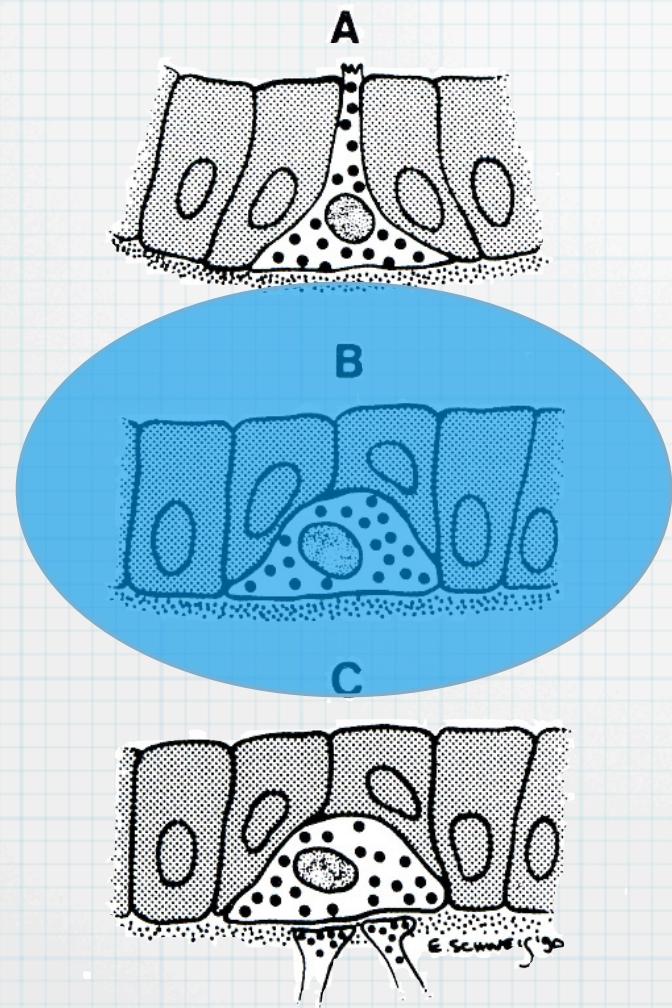
# Neuroendokrine lungetumorer

Det neuroendokrine system



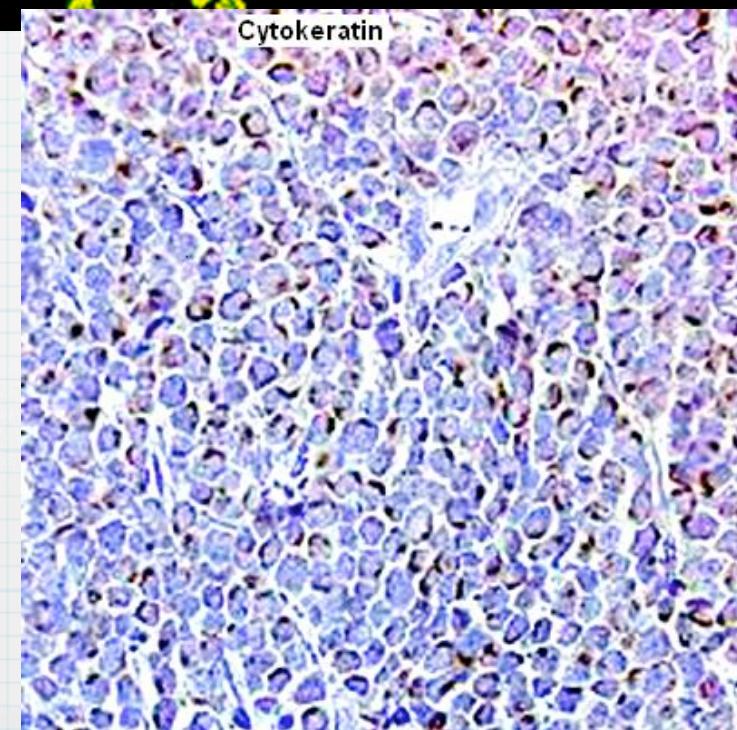
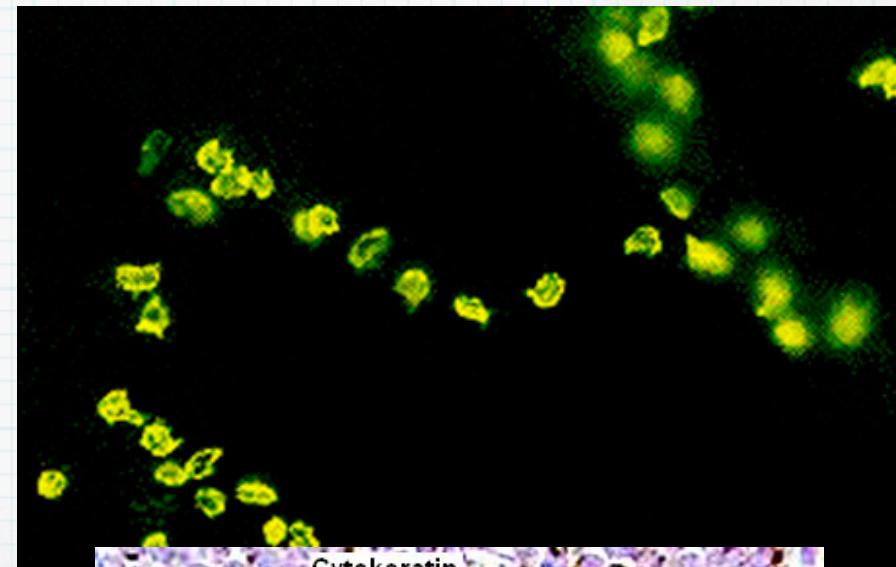
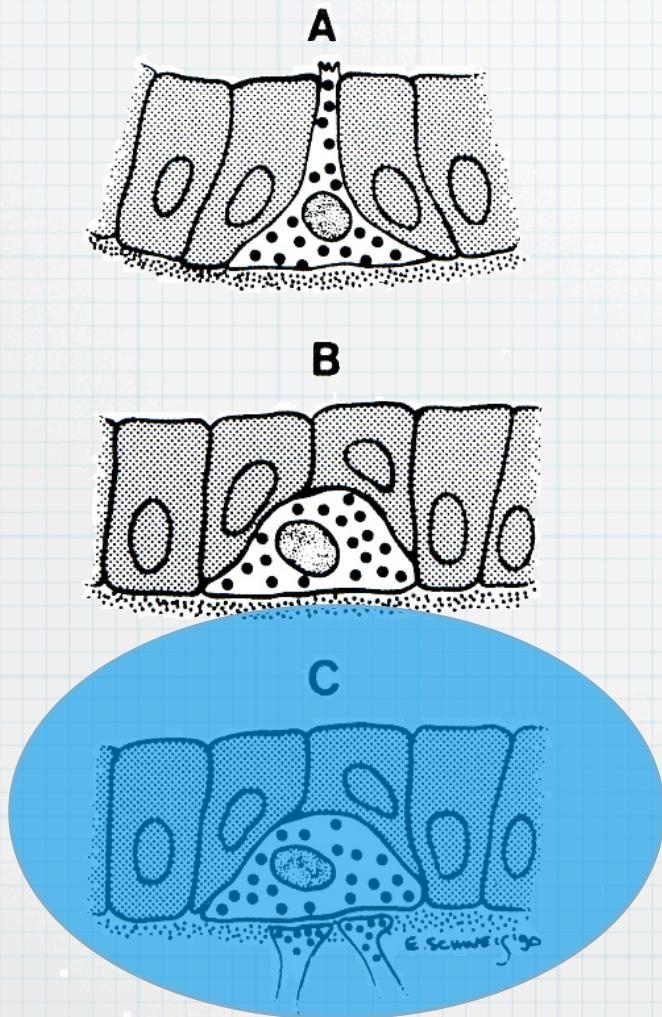
# Neuroendokrine tumorer

Det neuroendokrine system



# Neuroendokrine lungetumorer

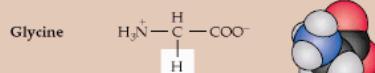
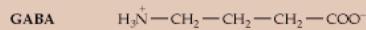
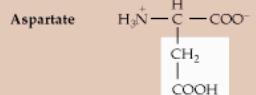
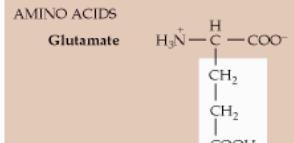
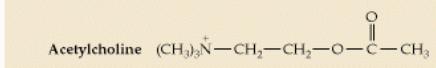
Det neuroendokrine system



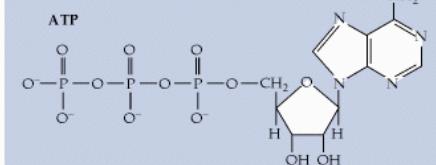
# Neuroendokrine lungetumorer

## Det neuroendokrine system

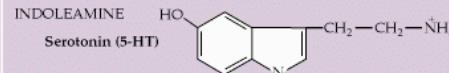
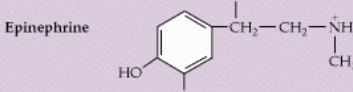
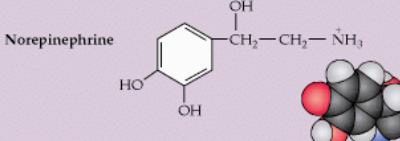
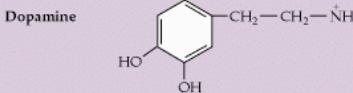
### SMALL-MOLECULE NEUROTRANSMITTERS



### PURINES



### BIOGENIC AMINES

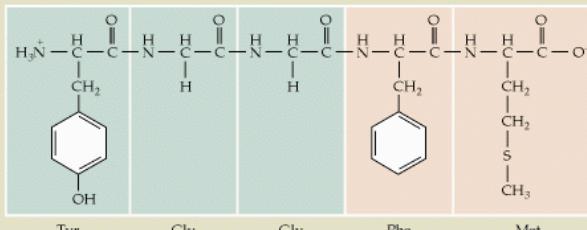


### IMIDAZOLEAMINE



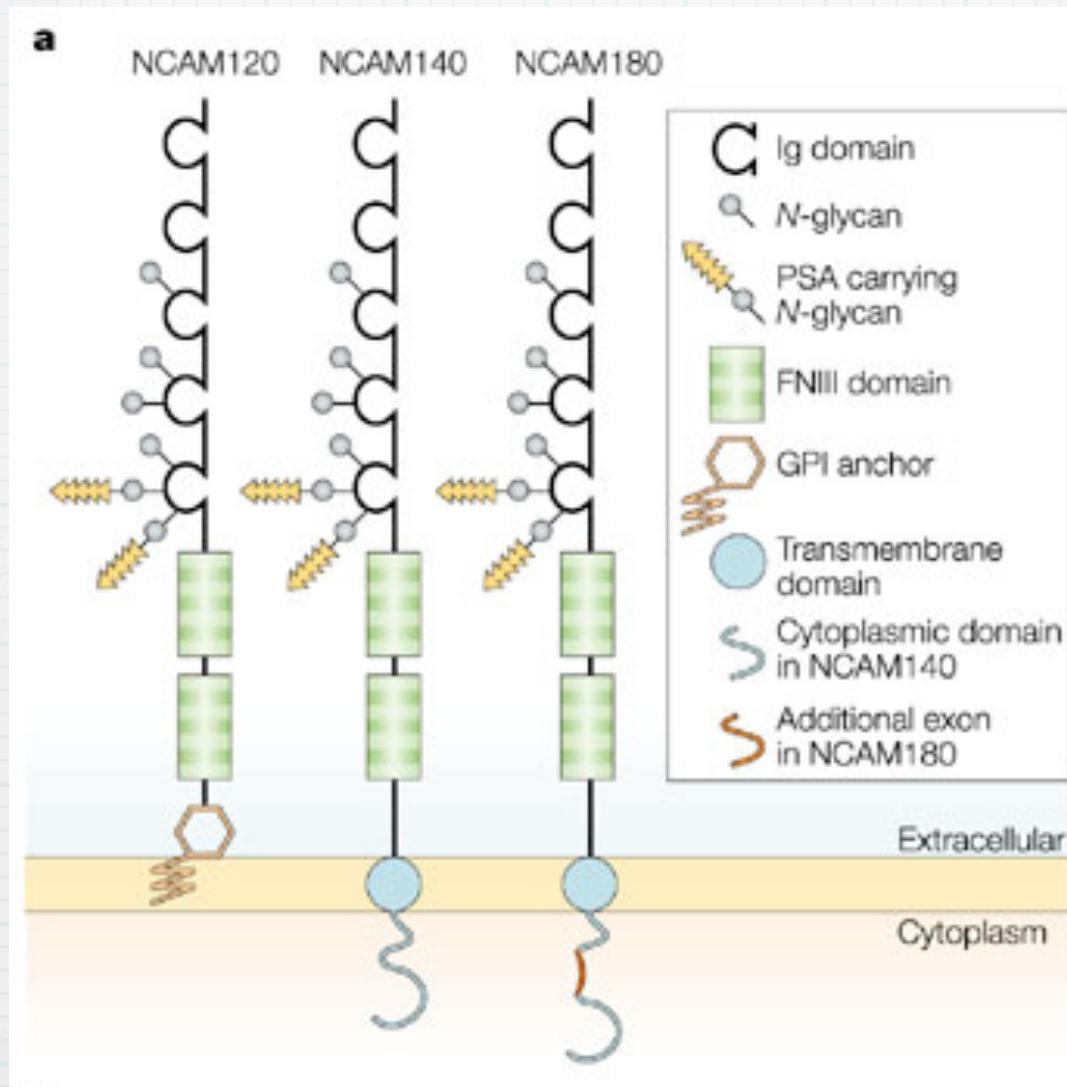
### PEPTIDE NEUROTRANSMITTERS (more than 100 peptides, usually 3–30 amino acids long)

Example: Methionine enkephalin (Tyr-Gly-Gly-Phe-Met)



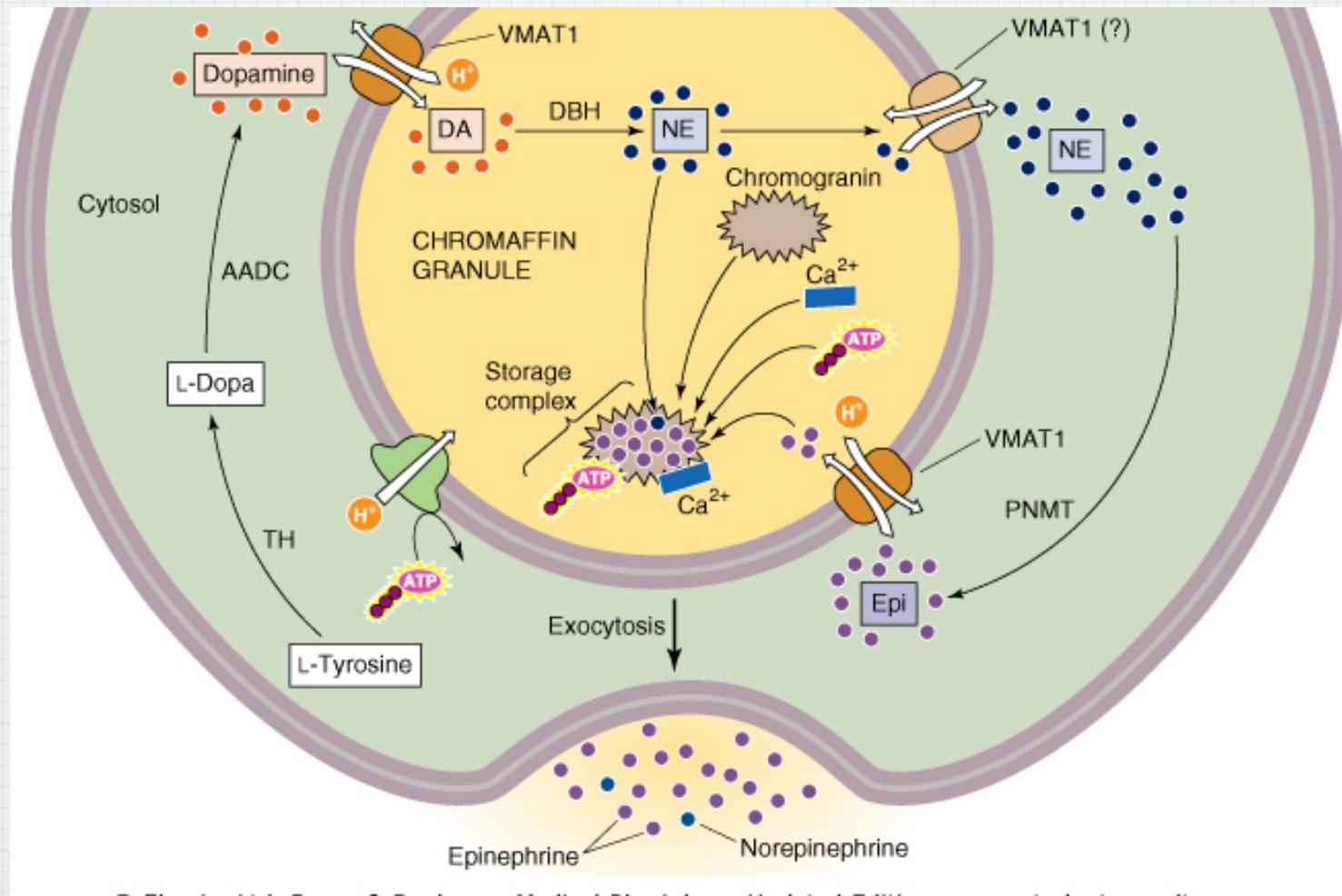
# Neuroendokrine lungetumorer

## Det neuroendokrine system



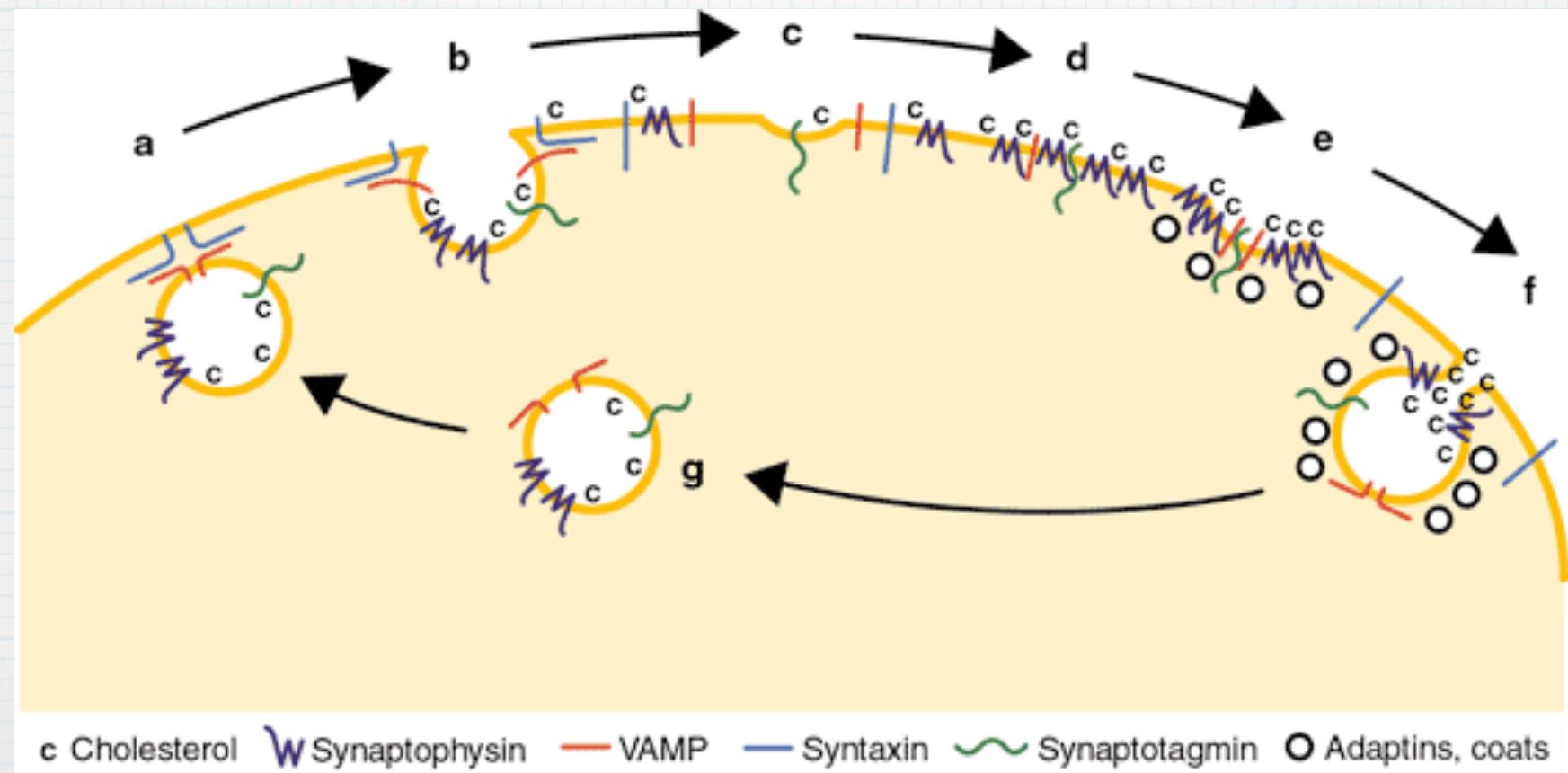
# Neuroendokrine lungetumorer

## Det neuroendokrine system



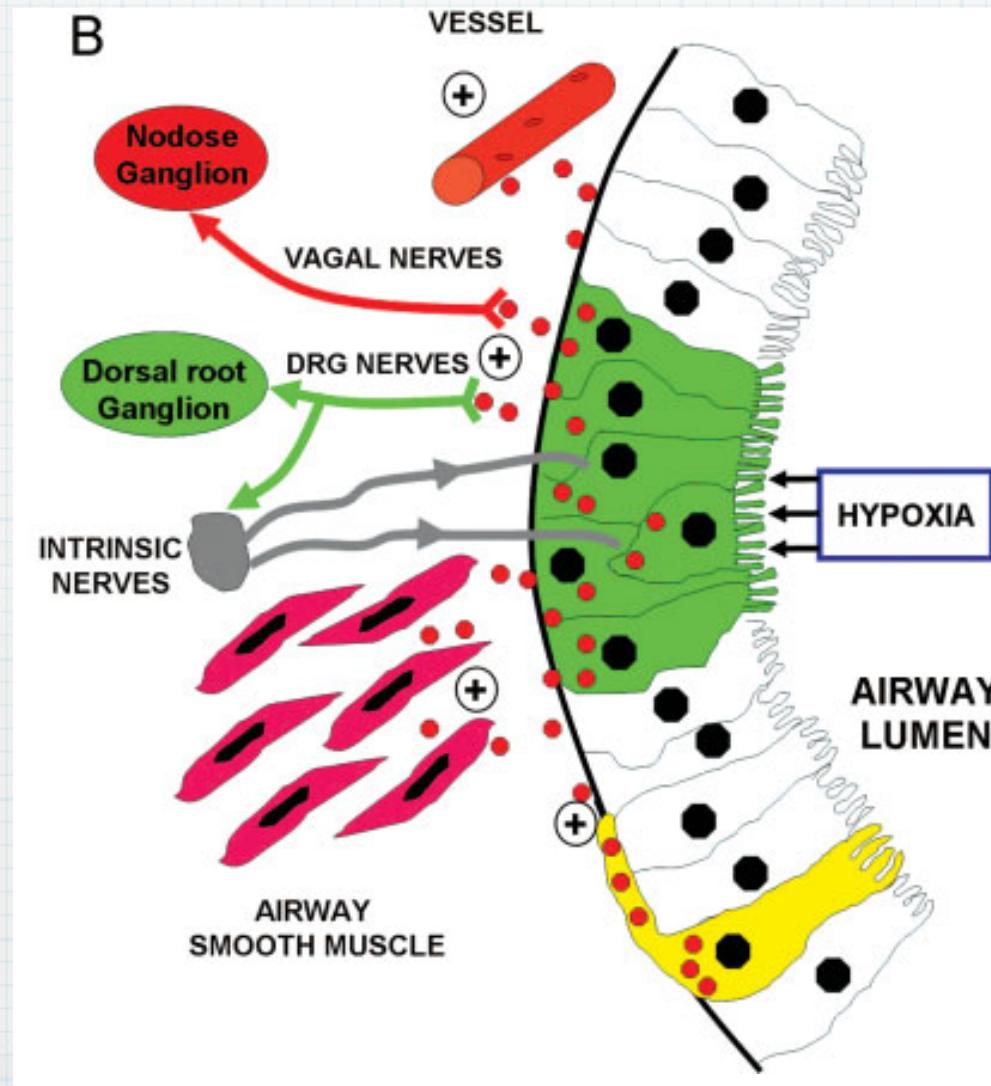
# Neuroendokrine lungetumorer

## Det neuroendokrine system



# Neuroendokrine lungetumorer

## Det neuroendokrine system, lunger



# Neuroendokrine lungetumorer



<b>Malignant epithelial tumours</b>			<b>Mesenchymal tumours</b>	
Squamous cell carcinoma	8070/3		Epithelioid haemangioendothelioma	9133/1
Papillary	8052/3		Angiosarcoma	9120/3
Clear cell	8084/3		Pleuropulmonary blastoma	8973/3
Small cell	8073/3		Chondroma	9220/0
Basaloid	8083/3		Congenital peribronchial myofibroblastic tumour	8827/1
Small cell carcinoma	8041/3		Diffuse pulmonary lymphangiomatosis	
Combined small cell carcinoma	8045/3		Inflammatory myofibroblastic tumour	8825/1
Adenocarcinoma	8140/3		Lymphangioleiomyomatosis	9174/1
Adenocarcinoma, mixed subtype	8255/3		Synovial sarcoma	9040/3
Acinar adenocarcinoma	8550/3		Monophasic	9041/3
Papillary adenocarcinoma	8260/3		Biphasic	9043/3
Bronchioloalveolar carcinoma	8250/3		Pulmonary artery sarcoma	8800/3
Nonmucinous	8252/3		Pulmonary vein sarcoma	8800/3
Mucinous	8253/3			
Mixed nonmucinous and mucinous or indeterminate	8254/3			
Solid adenocarcinoma with mucus production	8230/3			
Fetal adenocarcinoma	8333/3			
Mucinous ("colloid") carcinoma	8480/3			
Mucinous cystadenocarcinoma	8470/3			
Signet ring adenocarcinoma	8490/3			
Clear cell adenocarcinoma	8310/3			
Large cell carcinoma	8012/3			
Large cell neuroendocrine carcinoma	8013/3			
Combined large cell neuroendocrine carcinoma	8013/3			
Basaloid carcinoma	8123/3			
Lymphoepithelioma-like carcinoma	8082/3			
Clear cell carcinoma	8310/3			
Large cell carcinoma with rhabdoid phenotype	8014/3			
Adenosquamous carcinoma	8560/3			
Sarcomatoid carcinoma	8033/3			
Pleomorphic carcinoma	8022/3			
Spindle cell carcinoma	8032/3			
Giant cell carcinoma	8031/3			
Carcinosarcoma	8980/3			
Pulmonary blastoma	8972/3			
Carcinoid tumour	8240/3			
Typical carcinoid	8240/3			
Atypical carcinoid	8249/3			
Salivary gland tumours				
Mucoepidermoid carcinoma	8430/3			
Adenoid cystic carcinoma	8200/3			
Epithelial-myoepithelial carcinoma	8562/3			
Preinvasive lesions				
Squamous carcinoma <i>in situ</i>	8070/2			
Atypical adenomatous hyperplasia				
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia				
<b>Metastatic tumours</b>				

# Neuroendokrine lungetumorer

- Adenocarcinom (22%)
- Planocellulært carcinom (21%)
- Storcellet carcinom (3%)
- Småcellet carcinom (15%)
- Blandede former
- Andre
  - Carcinoid, atypisk carcinoid og storcellet neuroendokrint carcinom

# Neuroendokrine lungetumorer

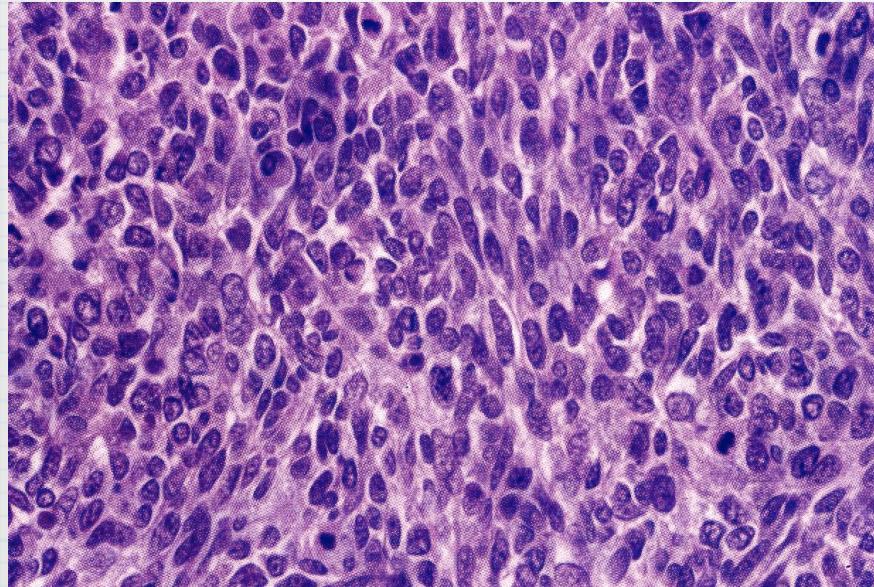
**TABLE 1.** Immunoreactivity for Neuroendocrine Markers in Different Subtypes of NSCLC

NSCLC Cell Type	Chomogranin (Ch)	Synaptophysin (SNP)	N-CAM (CD56)
Adenocarcinoma	1 (0.4%)	23 (11.2%)	11 (5.1%)
Squamous cell carcinoma	1 (0.4%)	10 (4.3%)	29 (12.4%)
Non-small cell carcinoma nos	0 (0%)	3 (12%)	2 (7.4%)
Large cell carcinoma	0 (0%)	3 (9.3%)	2 (6.2%)
Others	0 (0%)	0 (0%)	0 (0%)

# Neuroendokrine lungetumorer

- Adenocarcinom (22%)
- Planocellulært carcinom (21%)
- Storcellet carcinom (3%)
- **Småcellet carcinom (15%)**
  - Blandede former
  - Andre
    - Carcinoid, atypisk carcinoid og storcellet neuroendokrint carcinom

*Centrale men Hurtigt spredende  
Lavt differentierede  
Kompakt vækstmønster  
Kernedominerede*



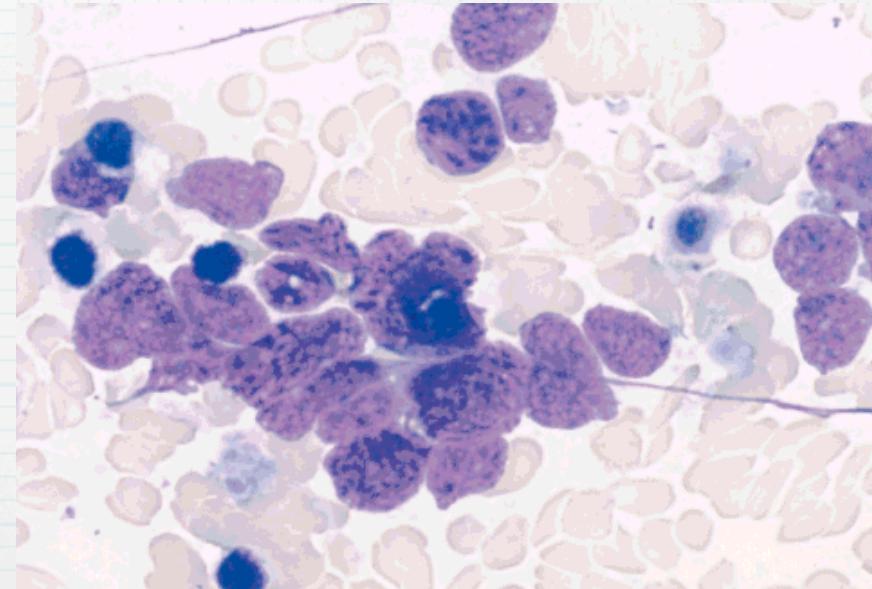
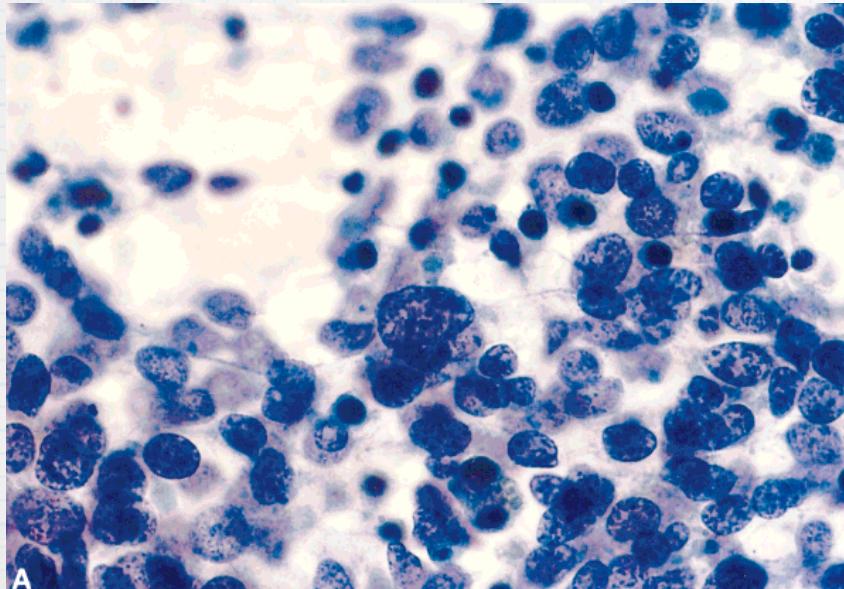
## Small cell carcinoma

Small size (generally less than the diameter of 3 small resting lymphocytes)

1. Scant cytoplasm
2. Nuclei: finely granular nuclear chromatin, absent or faint nucleoli
3. High mitotic rate (11 or greater per  $2 \text{ mm}^2$  (10 HPF), median of 80 per  $2 \text{ mm}^2$  (10 HPF)
4. Frequent necrosis often in large zones

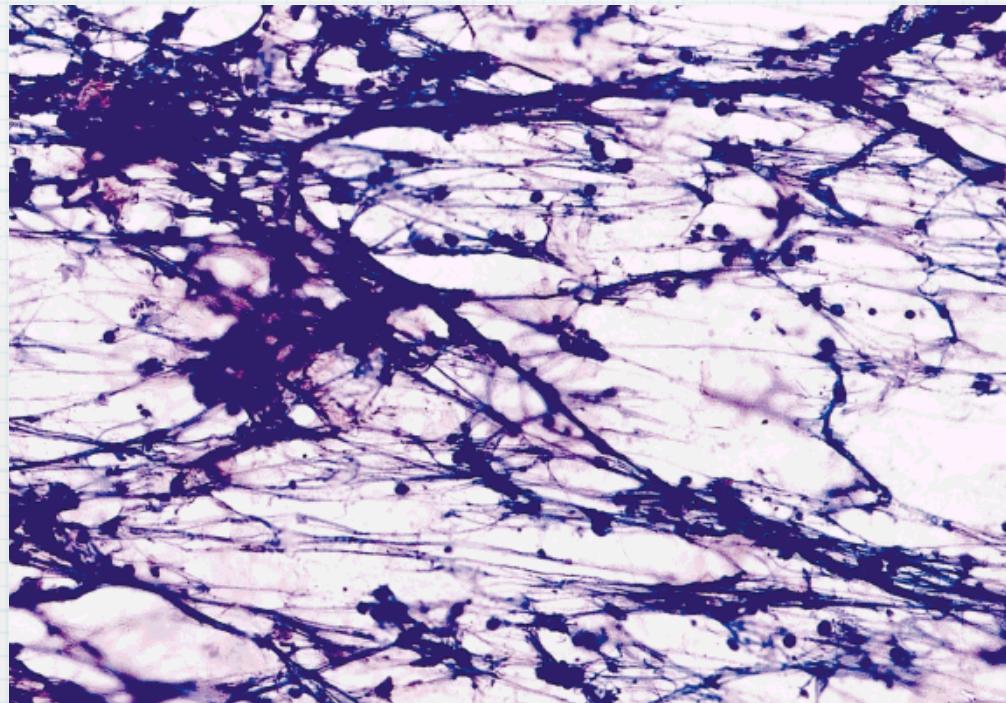
# Neuroendokrine lungetumorer

- Adenocarcinom (22%)
- Planocellulært carcinom (21%)
- Storcellet carcinom (3%)
- Småcellet carcinom (15%)
  - Blandede former
  - Andre
    - Carcinoid, atypisk carcinoid og storcellet neuroendokrint carcinom



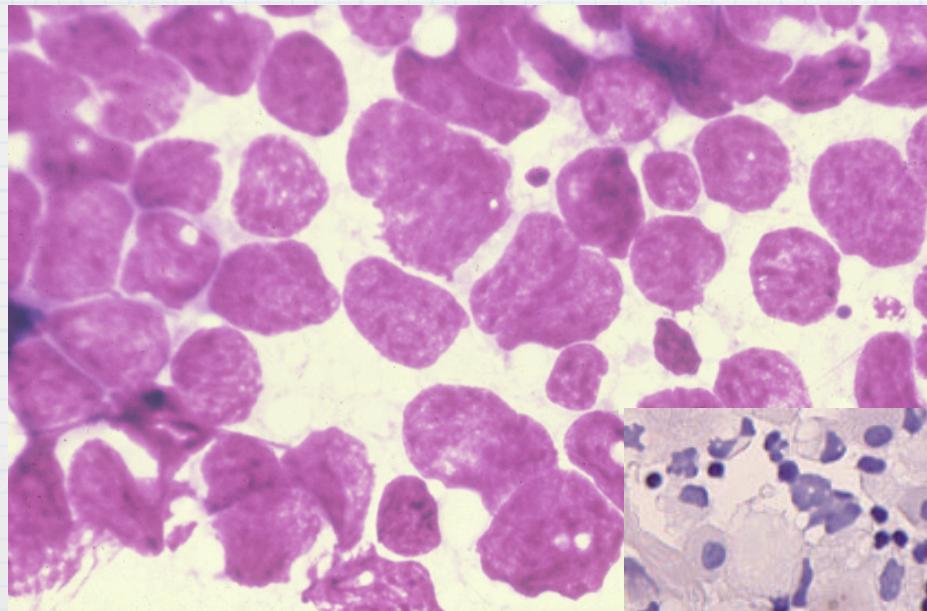
# Neuroendokrine lungetumorer

- Adenocarcinom (22%)
- Planocellulært carcinom (21%)
- Storcellet carcinom (3%)
- Småcellet carcinom (15%)
  - Blandede former
  - Andre
    - Carcinoid, atypisk carcinoid og storcellet neuroendokrint carcinom

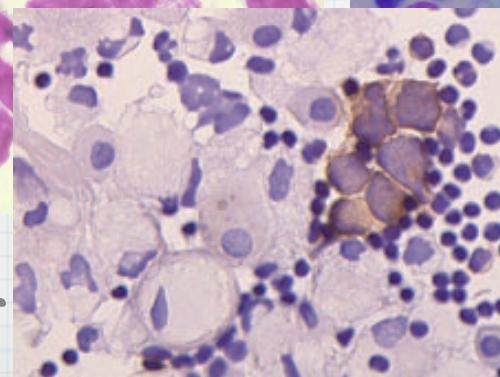


# Neuroendokrine lungetumorer

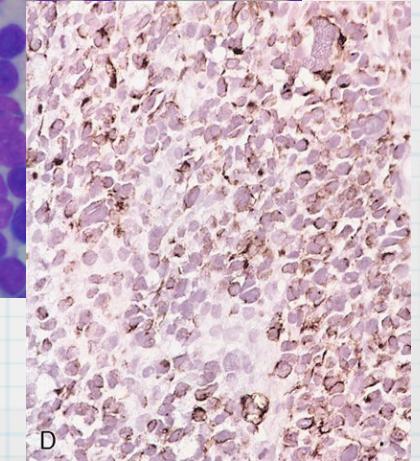
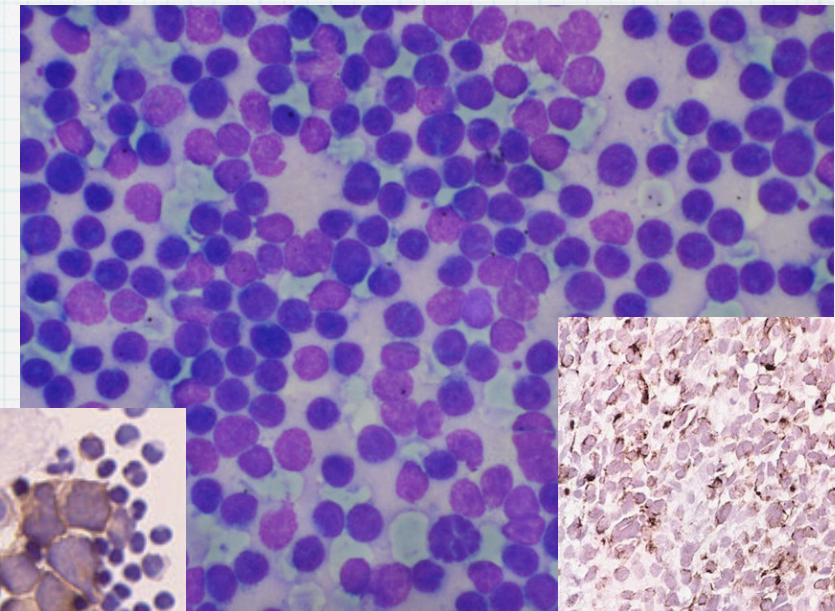
- Adenocarcinom (22%)
- Planocellulært carcinom (21%)
- Storcellet carcinom (3%)
- Småcellet carcinom (15%)
  - Blandede former
  - Andre
    - Carcinoid, atypisk carcinoid og storcellet neuroendokrint carcinom



Cytokeratin+, CD56+

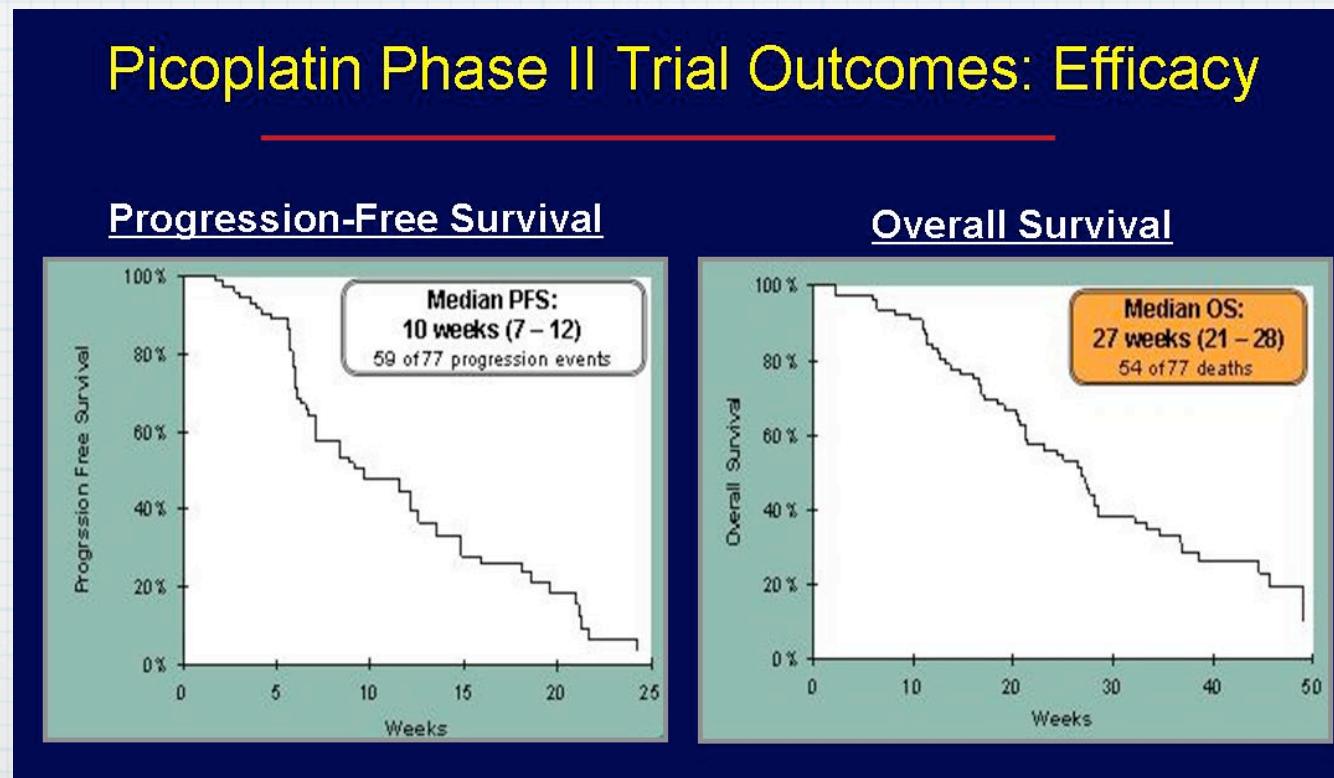


CD45+



# Neuroendokrine lungetumorer

- Adenocarcinom (22%)
- Planocellulært carcinom (21%)
- Storcellet carcinom (3%)
- Småcellet carcinom (15%)
  - Blandede former
  - Andre
    - Carcinoid, atypisk carcinoid og storcellet neuroendokrint carcinom

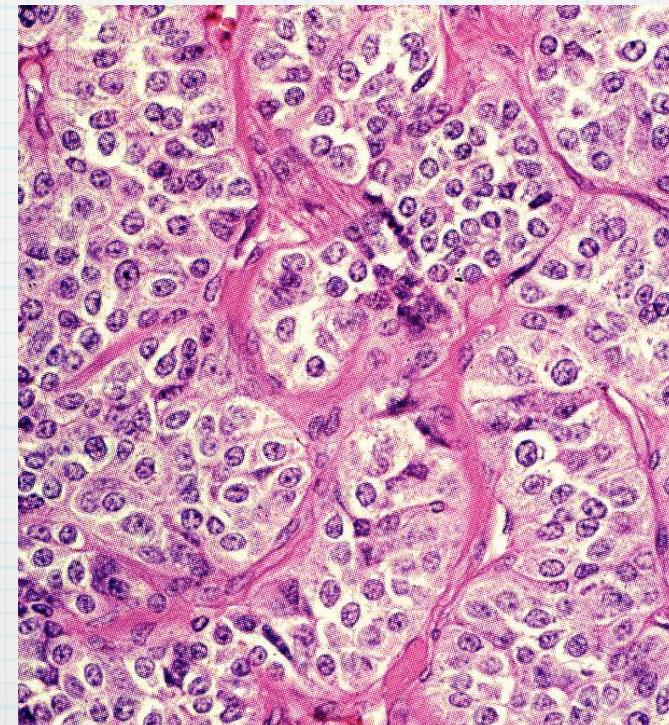


# Neuroendokrine lungetumorer

- Adenocarcinom (30%)
- Planocellulært carcinom (35%)
- Storcellet carcinom (9%)
- Småcellet carcinom (25%)
- Blandede former

- Andre

- **Carcinoid**, atypisk carcinoid og storcellet neuroendokint carcinom

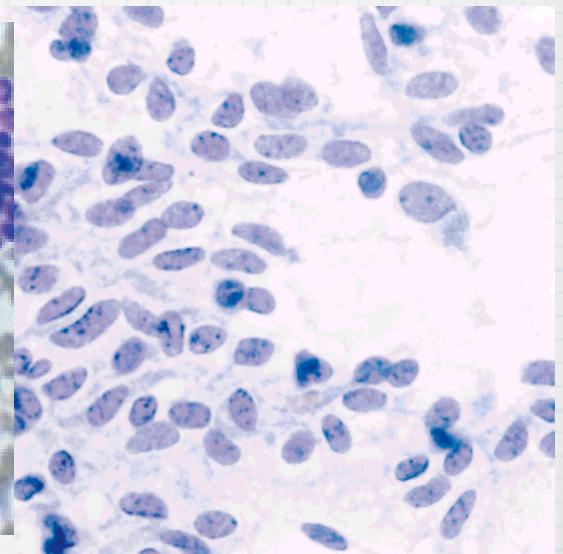
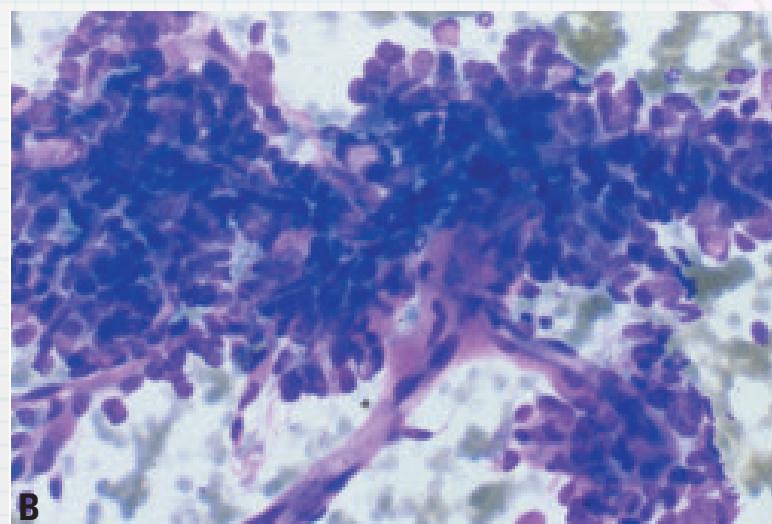
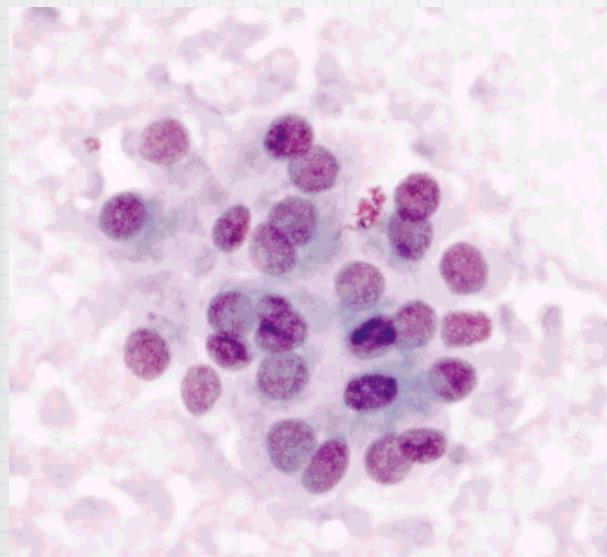


# Neuroendokrine lungetumorer

- Adenocarcinom (30%)
- Planocellulært carcinom (35%)
- Storcellet carcinom (9%)
- Småcellet carcinom (25%)
- Blandede former

- Andre

- **Carcinoid**, atypisk carcinoid og storcellet neuroendokint carcinom

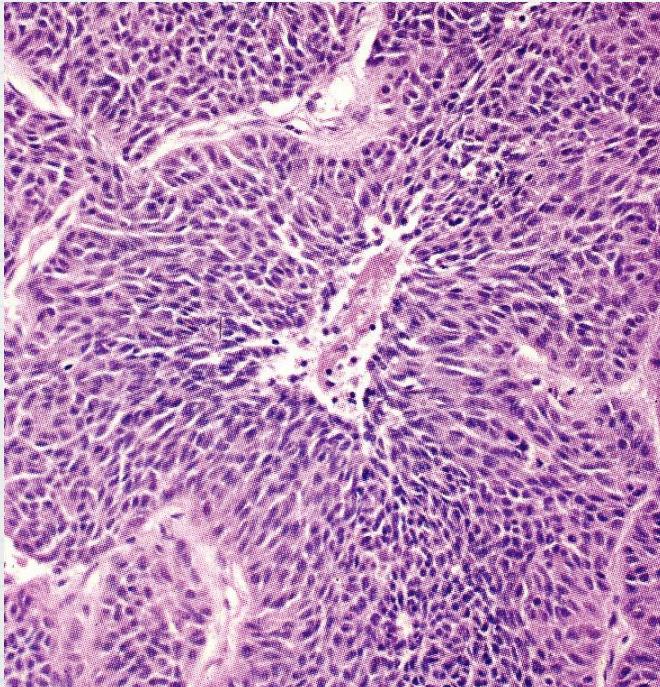


# Neuroendokrine lungetumorer

- Adenocarcinom (30%)
- Planocellulært carcinom (35%)
- Storcellet carcinom (9%)
- Småcellet carcinom (25%)
- Blandede former

- Andre

- **Carcinoid, atypisk carcinoid og storcellet neuroendokrint carcinom**



**Typical carcinoid**

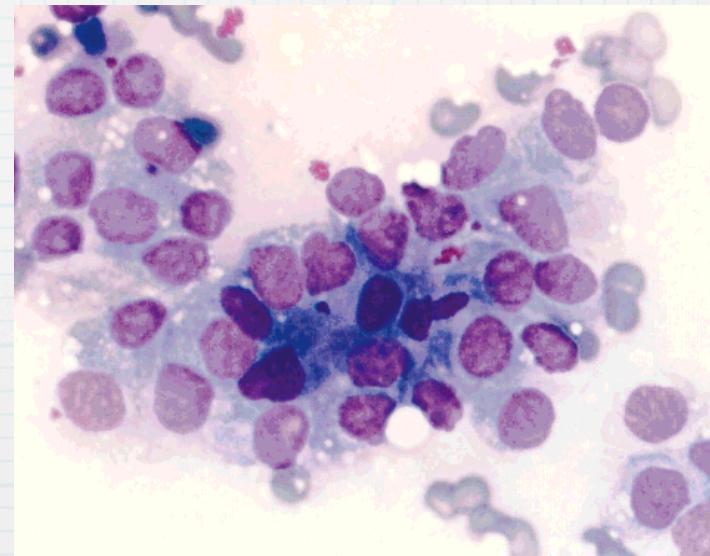
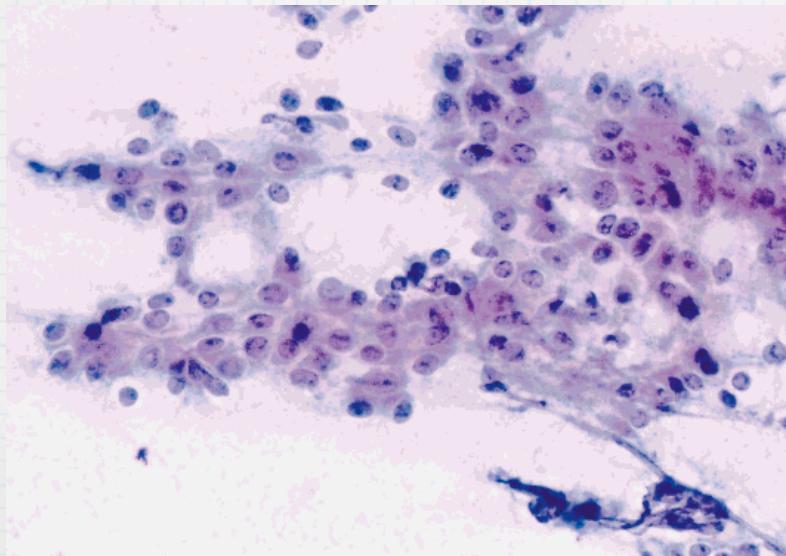
A tumour with carcinoid morphology and less than 2 mitoses per  $2\text{ mm}^2$  (10 HPF), lacking necrosis and 0.5 cm or larger

**Atypical carcinoid**

A tumour with carcinoid morphology with 2-10 mitoses per  $2\text{ mm}^2$  (10 HPF) OR necrosis (often punctate)

# Neuroendokrine lungetumorer

- Adenocarcinom (30%)
- Planocellulært carcinom (35%)
- Storcellet carcinom (9%)
- Småcellet carcinom (25%)
- Blandede former
- Andre
  - Carcinoid, **atypisk carcinoid** og storcellet neuroendokrint carcinom



# Neuroendokrine lungetumorer

- Adenocarcinom (30%)
- Planocellulært carcinom (35%)
- Storcellet carcinom (9%)
- Småcellet carcinom (25%)
- Blandede former

- Andre

- **Carcinoid, atypisk carcinoid og storcellet neuroendokrint carcinom**

## What Are the Key Statistics About Lung Carcinoid Tumor?

Less than 1% of all lung tumors are lung carcinoid tumors. Most lung carcinoids are small. They vary from 0.5 cm (slightly smaller than  $\frac{1}{4}$  inch) to 2 cm (a little over  $\frac{3}{4}$  inch) at the time of diagnosis. Patients with carcinoids larger than 3 cm (almost  $1\frac{1}{4}$  inch), atypical carcinoids, or carcinoids that have spread to lymph nodes have a worse outlook for chances of survival (prognosis).

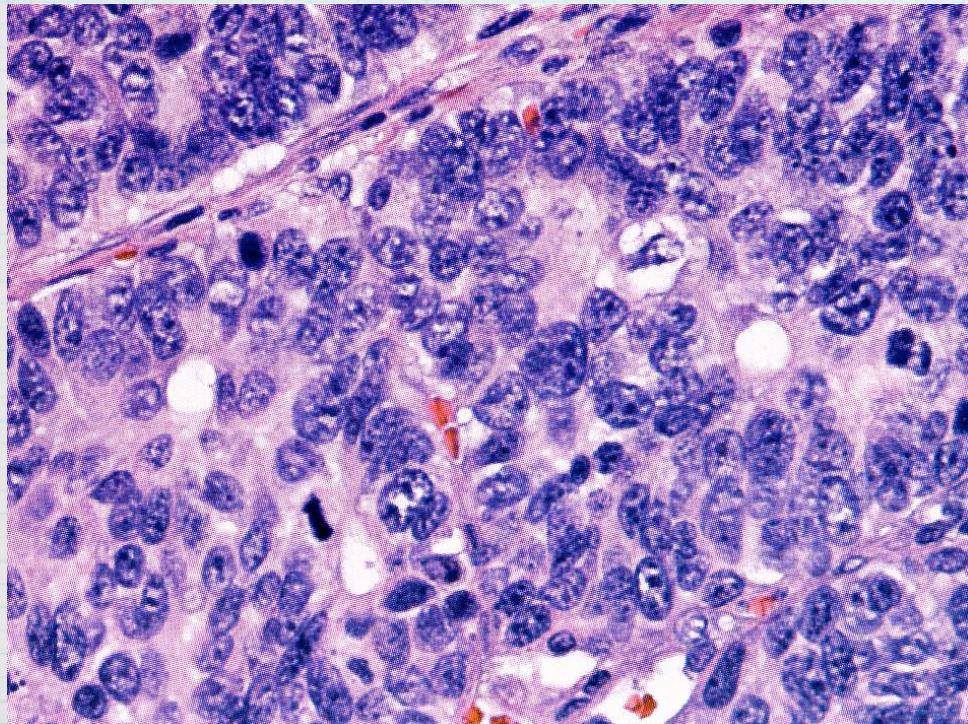
The 5-year survival rates for patients with typical and atypical lung carcinoids are around 95% and 70%, respectively. The ranges reflect different survival rates quoted by several medical journal articles. For both types of carcinoids, the 10-year survival rates are about 10% lower than the 5-year rates. The 5-year survival rate for patients whose carcinoid tumors have not spread (metastasized) to their lymph nodes is 85%. For those patients with lymph node metastasis, the 5-year survival rate is 70%. These numbers will be higher for patients with typical carcinoids and lower for those with atypical carcinoids.

# Neuroendokrine lungetumorer

- Adenocarcinom (30%)
- Planocellulært carcinom (35%)
- Storcellet carcinom (9%)
- Småcellet carcinom (25%)
- Blandede former

- Andre

- Carcinoid, atypisk carcinoid og storcellet neuroendokint carcinom

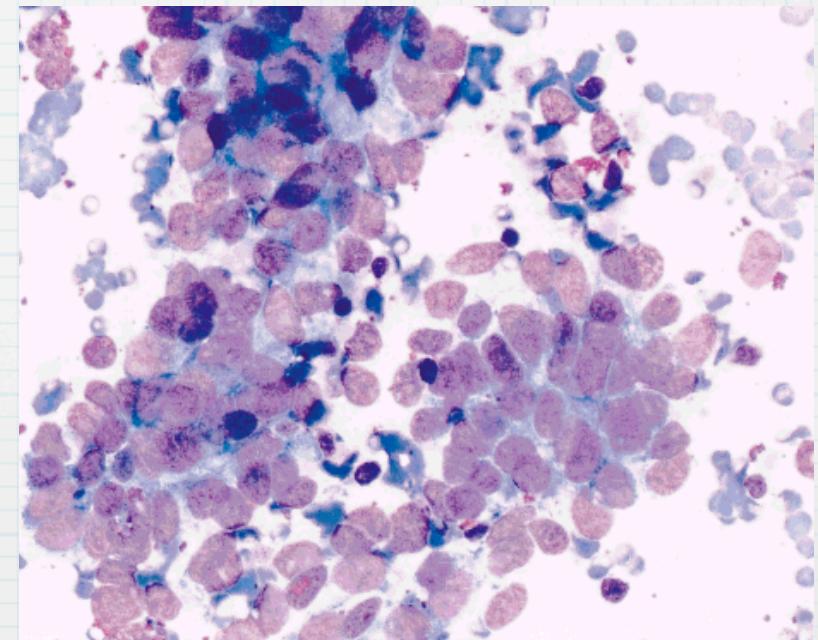
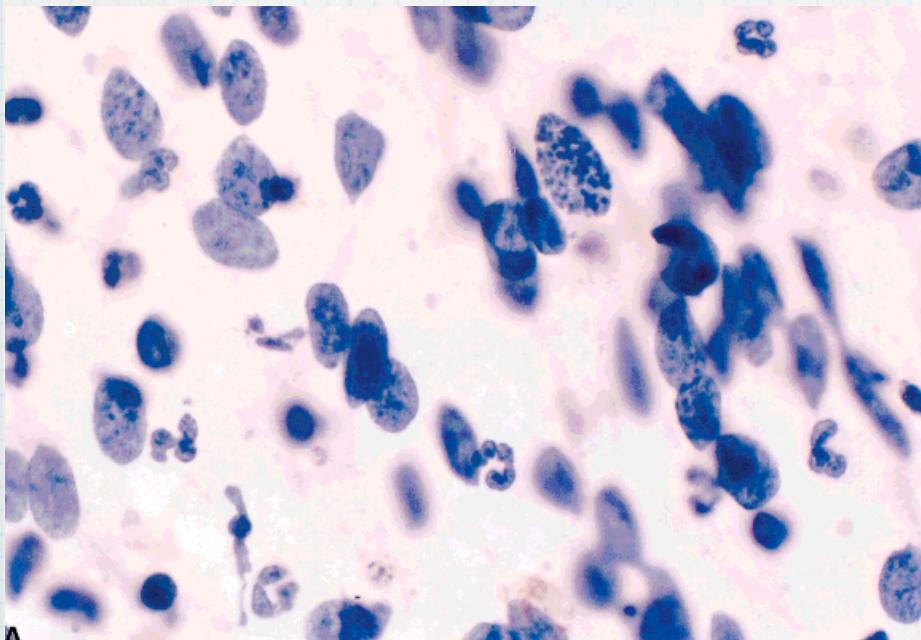


#### Large cell neuroendocrine carcinoma

1. A tumour with a neuroendocrine morphology (organoid nesting, palisading, rosettes, trabeculae)
2. High mitotic rate: 11 or greater per  $2\text{ mm}^2$  (10 HPF), median of 70 per  $2\text{ mm}^2$  (10 HPF)
3. Necrosis (often large zones)
4. Cytologic features of a non-small cell carcinoma (NSCLC): large cell size, low nuclear to cytoplasmic ratio, vesicular, coarse or fine chromatin, and/or frequent nucleoli. Some tumours have fine nuclear chromatin and lack nucleoli, but qualify as NSCLC because of large cell size and abundant cytoplasm.
5. Positive immunohistochemical staining for one or more NE markers (other than neuron specific enolase) and/or NE granules by electron microscopy.

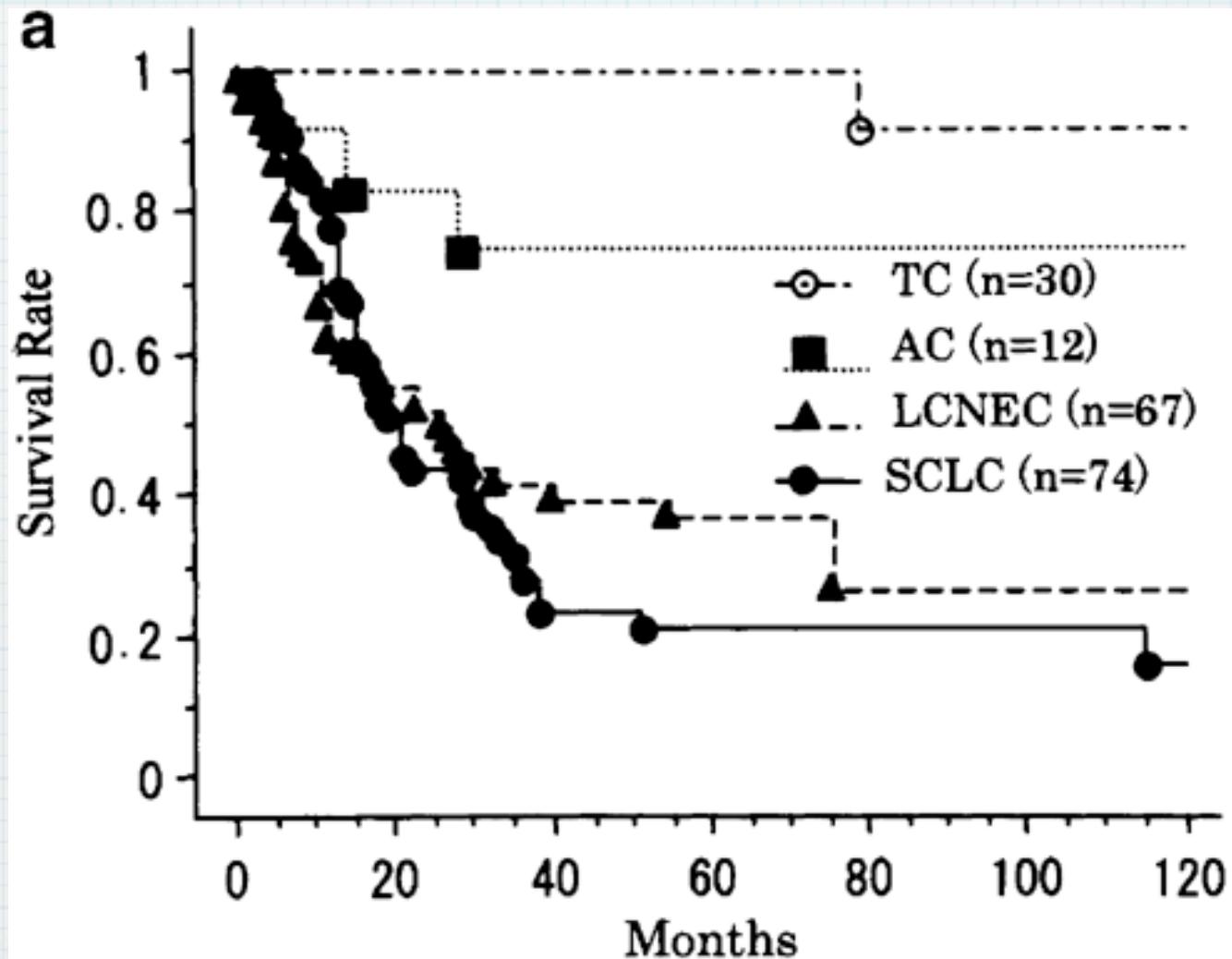
# Neuroendokrine lungetumorer

- Adenocarcinom (30%)
- Planocellulært carcinom (35%)
- Storcellet carcinom (9%)
- Småcellet carcinom (25%)
- Blandede former
- Andre
  - Carcinoid, atypisk carcinoid og storcellet neuroendokint carcinom



lunge

# Neuroendokrine lungetumorer



# Neuroendokrine lungetumorer



# Neuroendokrine lungetumorer



# Neuroendokrine lungetumorer

## Distinguishing Carcinoid Tumor From Small Cell Carcinoma of the Lung

Correlating Cytologic Features and Performance in the College of American  
Pathologists Non-Gynecologic Cytology Program

*Objective.*—To correlate the cytologic features of individual cases of carcinoid tumor of the lung in fine-needle aspiration specimens in the College of American Pathologists Non-Gynecologic Cytology Program with the frequency of misclassification as small cell carcinoma.

# Neuroendokrine lungetumorer

## Distinguishing Carcinoid Tumor From Small Cell Carcinoma of the Lung

Correlating Cytologic Features and Performance in the College of American Pathologists Non-Gynecologic Cytology Program

*Design.*—We reviewed 1100 interpretations from 26 different cases of carcinoid tumor in lung fine-needle aspiration specimens in the College of American Pathologists Non-Gynecologic Cytology Program and correlated the cytologic features with the performance in the program.

# Neuroendokrine lungetumorer

## Distinguishing Carcinoid Tumor From Small Cell Carcinoma of the Lung

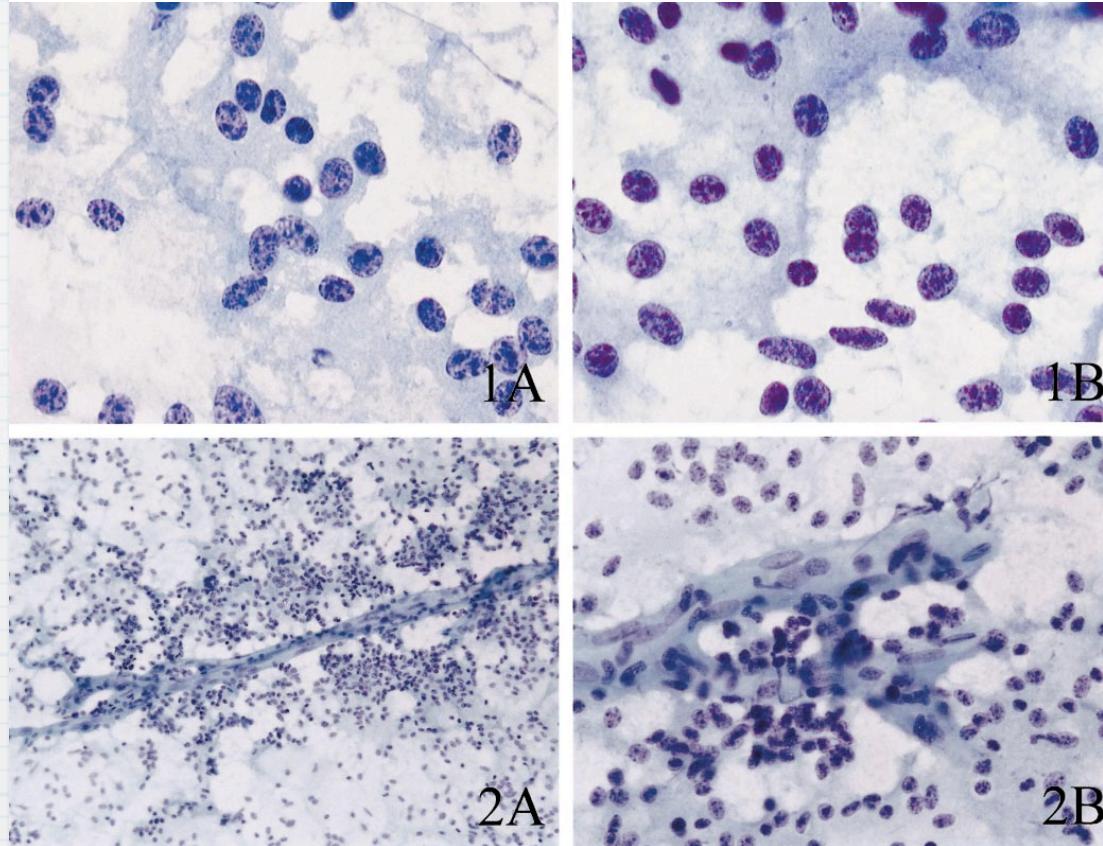
Correlating Cytologic Features and Performance in the College of American Pathologists Non-Gynecologic Cytology Program

mor cells attached to the endothelial cell core. In contrast, cases that were frequently misclassified had 1 of 6 patterns that were not seen in cases that were rarely misclassified. These 6 patterns were: (1) poorly preserved and pale-staining cells with fine chromatin and a suggestion of molding (5 cases); (2) numerous large, well-preserved, spindle-shaped cells (2 cases); (3) numerous cells varying markedly in both size and shape (both round and spindle-shaped cells), with a common finding of degenerated, smudgy, small round and spindle-shaped cells (9 cases); (4) hypocellular specimens (8 cases); (5) obscuration of cells by blood (2 cases); and (6) tumor cells present predominantly in groups, with few isolated cells (8 cases). In none of these cases were mitoses or true necrosis identified.

# Neuroendokrine lungetumorer

## Distinguishing Carcinoid Tumor From Small Cell Carcinoma of the Lung

Correlating Cytologic Features and Performance in the College of American Pathologists Non-Gynecologic Cytology Program



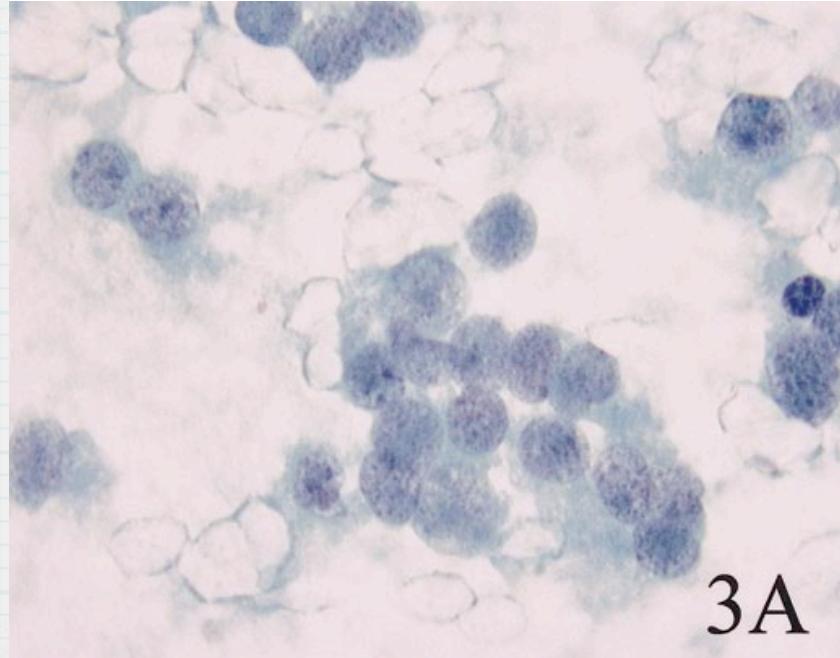
**Figure 1.** Carcinoid tumor aspirates that were infrequently misclassified. Aspirates consisted of monotonous groups of well-preserved round cells (A) or a mixture of round and spindle cells (B) (Papanicolaou stain, original magnification  $\times 1000$ ).

**Figure 2.** Carcinoid tumor aspirates that were infrequently misclassified showing prominent streaming vascular patterns (Papanicolaou stain, original magnifications  $\times 100$  [A] and  $\times 400$  [B]).

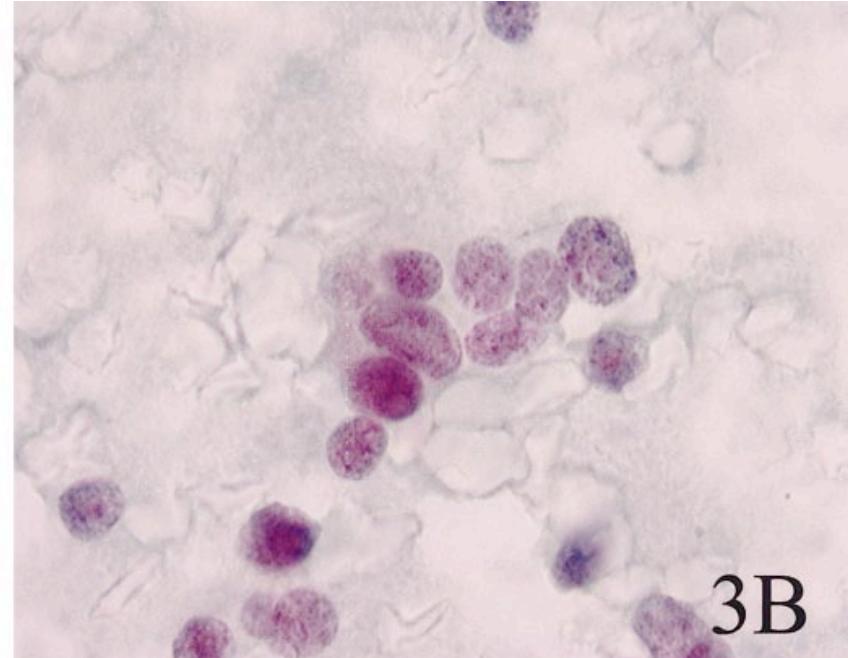
# Neuroendokrine lungetumorer

## Distinguishing Carcinoid Tumor From Small Cell Carcinoma of the Lung

Correlating Cytologic Features and Performance in the College of American Pathologists Non-Gynecologic Cytology Program



3A



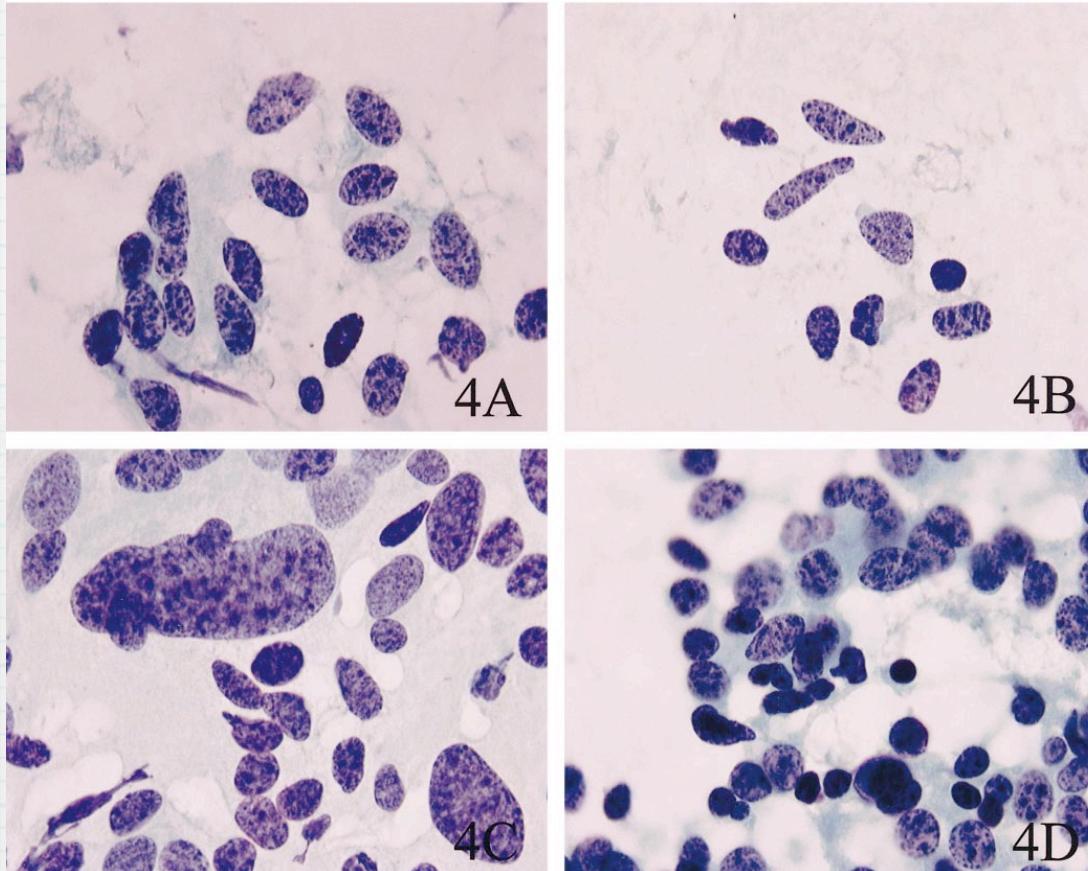
3B

**Figure 3.** Carcinoid tumor aspirates frequently misclassified as small cell carcinoma. Cells are poorly preserved and stained, have fine chromatin, and give a suggestion of molding (Papanicolaou stain, original magnification  $\times 1000$ ).

# Neuroendokrine lungetumorer

## Distinguishing Carcinoid Tumor From Small Cell Carcinoma of the Lung

Correlating Cytologic Features and Performance in the College of American Pathologists Non-Gynecologic Cytology Program



**Figure 4.** Carcinoid tumor aspirates that were frequently misclassified as small cell carcinoma. Aspirates consisted of a variety of appearances. Some areas showed numerous large, well-preserved, spindle-shaped cells (A), whereas others showed smaller round and spindled cells with degeneration and dark, smudgy chromatin. Occasional large, irregular nuclei with degenerative changes were noted (B, C, D) (Papanicolaou stain, original magnification  $\times 1000$ ).

# Neuroendokrine lungetumorer

## Distinguishing Small Cell Carcinoma From Non-Small Cell Carcinoma of the Lung

Correlating Cytologic Features and Performance in the College of American Pathologists Non-Gynecologic Cytology Program

***Objective.***—To correlate the cytologic features of individual cases of small cell carcinoma of the lung in fine-needle aspiration specimens from the College of American Pathologists Non-Gynecologic Peer Comparison Cytology Program with the frequency of misclassification as non-small cell carcinoma.

# Neuroendokrine lungetumorer

## Distinguishing Small Cell Carcinoma From Non-Small Cell Carcinoma of the Lung

Correlating Cytologic Features and Performance in the College of American Pathologists Non-Gynecologic Cytology Program

*Design.*—We reviewed 1185 interpretations of 23 different cases of small cell carcinoma in lung fine-needle aspiration specimens and correlated the cytologic features noted in these cases with performance in the program.

# Neuroendokrine lungetumorer

## Distinguishing Small Cell Carcinoma From Non-Small Cell Carcinoma of the Lung

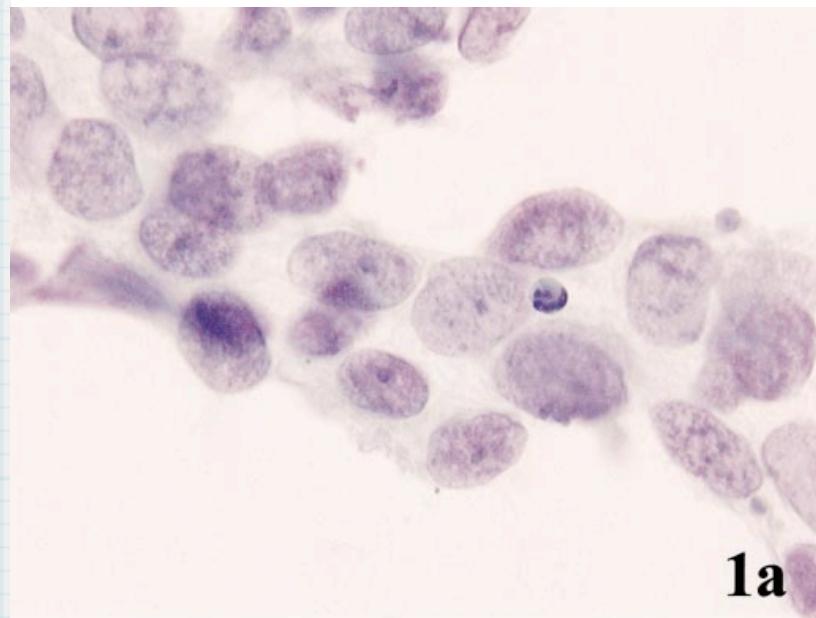
Correlating Cytologic Features and Performance in the College of American Pathologists Non-Gynecologic Cytology Program

of 11 cases that were frequently misclassified as non-small cell carcinoma had cells with either increased cytoplasm (4 cases), cytoplasmic globules (so-called paranuclear blue bodies) (3 cases), or apparent intracytoplasmic lumina (3 cases). These features were not identified in cases that were

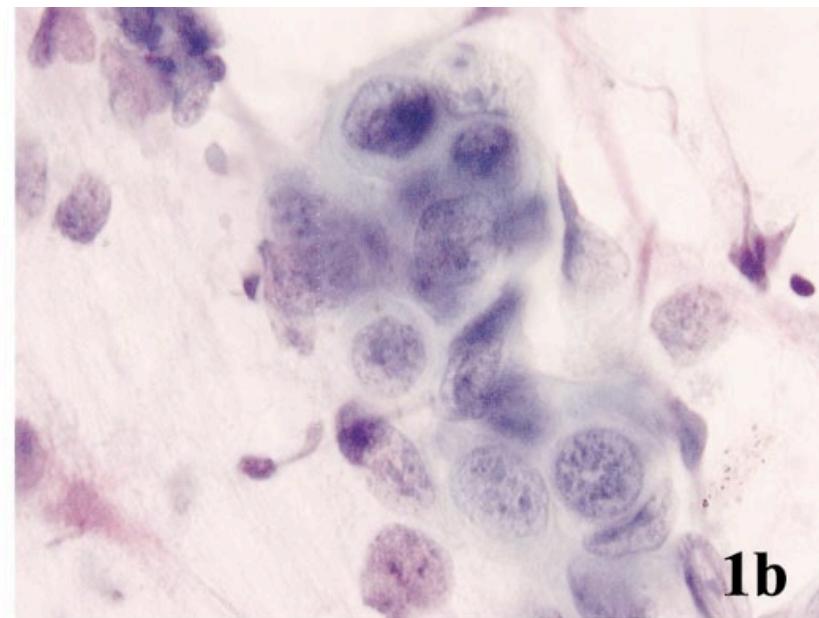
# Neuroendokrine lungetumorer

## Distinguishing Small Cell Carcinoma From Non-Small Cell Carcinoma of the Lung

Correlating Cytologic Features and Performance in the College of American Pathologists Non-Gynecologic Cytology Program



1a



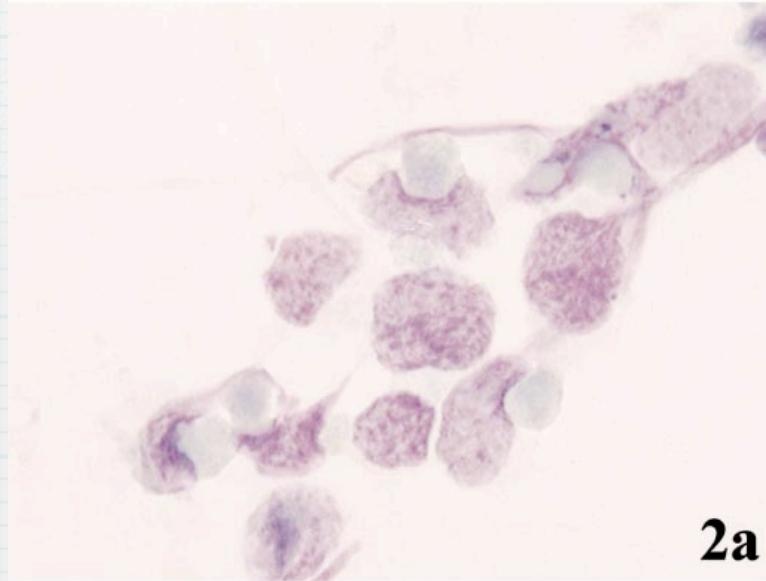
1b

**Figure 1.** Cells showing increased cytoplasm from cases of small cell carcinoma that were frequently mistaken for non-small cell carcinoma (Papanicolaou stain, original magnification  $\times 1000$ ).

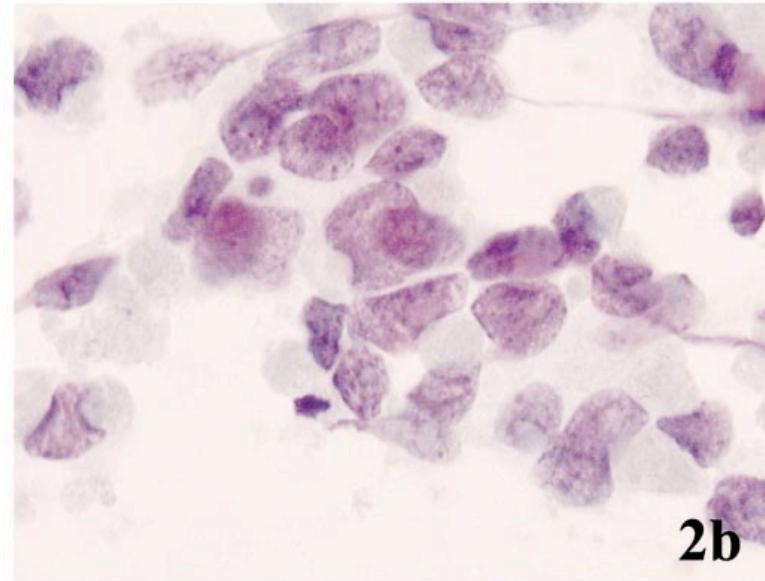
# Neuroendokrine lungetumorer

## Distinguishing Small Cell Carcinoma From Non-Small Cell Carcinoma of the Lung

Correlating Cytologic Features and Performance in the College of American Pathologists Non-Gynecologic Cytology Program



2a



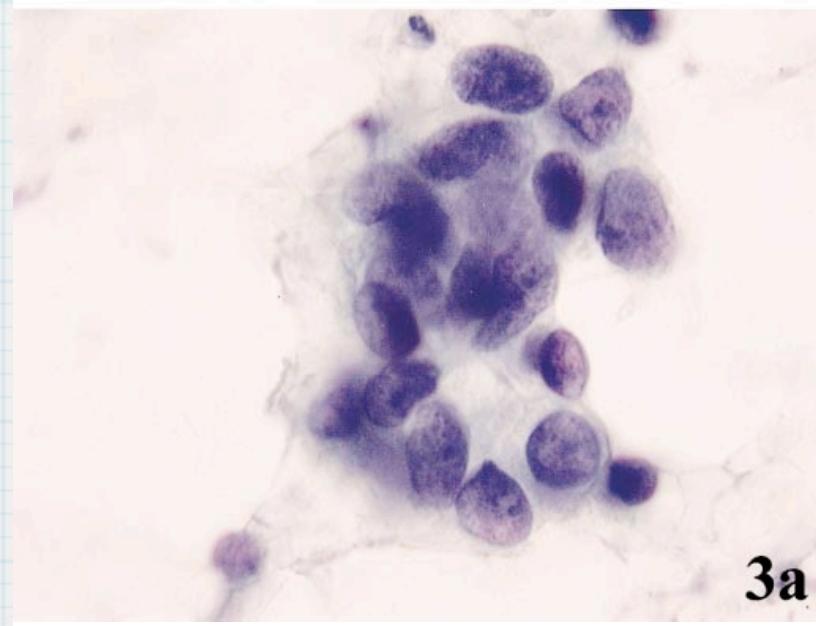
2b

**Figure 2.** Cells from cases of small cell carcinoma frequently show cytoplasmic globules (so-called paranuclear blue bodies) (Papanicolaou stain, original magnification  $\times 1000$ ).

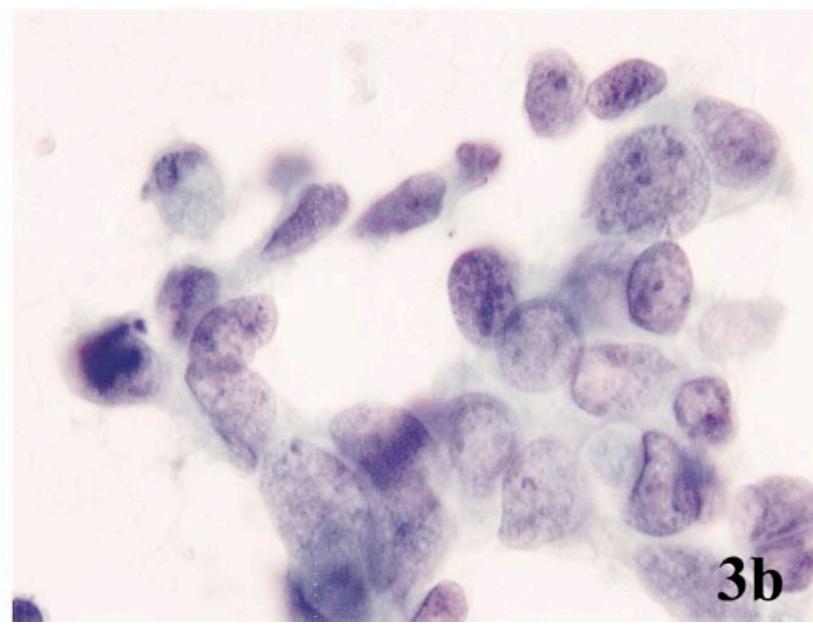
# Neuroendokrine lungetumorer

## Distinguishing Small Cell Carcinoma From Non-Small Cell Carcinoma of the Lung

Correlating Cytologic Features and Performance in the College of American Pathologists Non-Gynecologic Cytology Program



3a



3b

**Figure 3.** Cells with pseudoglandular group conformations with apparent ill-formed lumen (a) and intracytoplasmic vacuole (b) (Papanicolaou stain, original magnification  $\times 1000$ ).

# Neuroendokrine lungetumorer

	cd56	ck5/6	p63	tf1	ck7
planocellulært carcinom	-	+	+	-	-
Adenokarcinom	-	-	-	+	+
Småcellet carcinom	+	-	-	+	-

Slut

