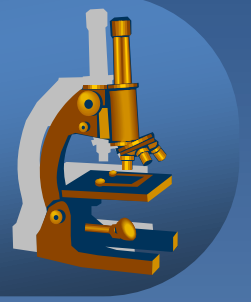
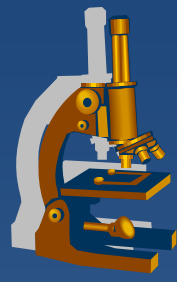
Systemic Pathology



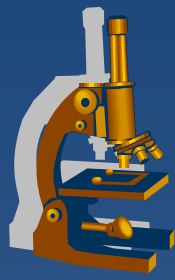
Hepatobiliary, pancreas,diabetes mellitus, endocrine system

Morphology of hepatic injury



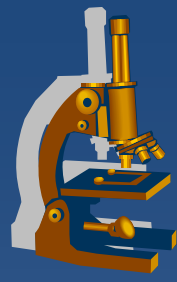
- hepatocyte degeneration and/or pathologic intracellular accumulation (i. e. fatty liver, pigment, …)
- hepatocyte necrosis, apoptosis
- inflammation
- regeneration
- fibrosis

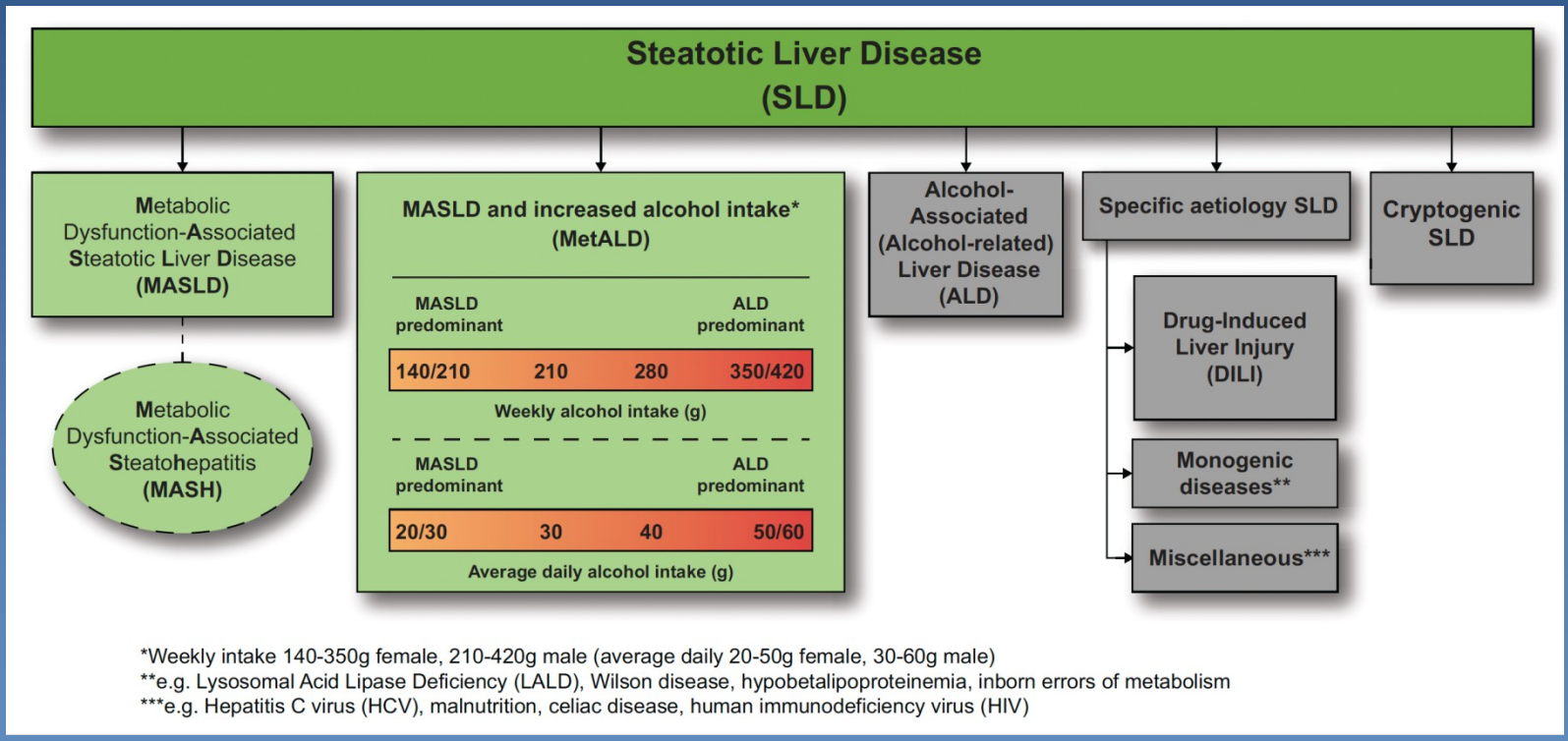
Fatty liver disease - steatosis



- gross:
  - *enlarged, paler, in extreme cases yellow, softer consistency*
- micro:
  - *small or confluent droplets in cytoplasm*
- causes:
  - *alcohol*
  - *other toxins (drugs, organic substances)*
  - *diabetes mellitus + metabolic syndrome*
  - *excessive fat intake*
  - *infection (hepatitis C, …)*
  - *hypoxia*

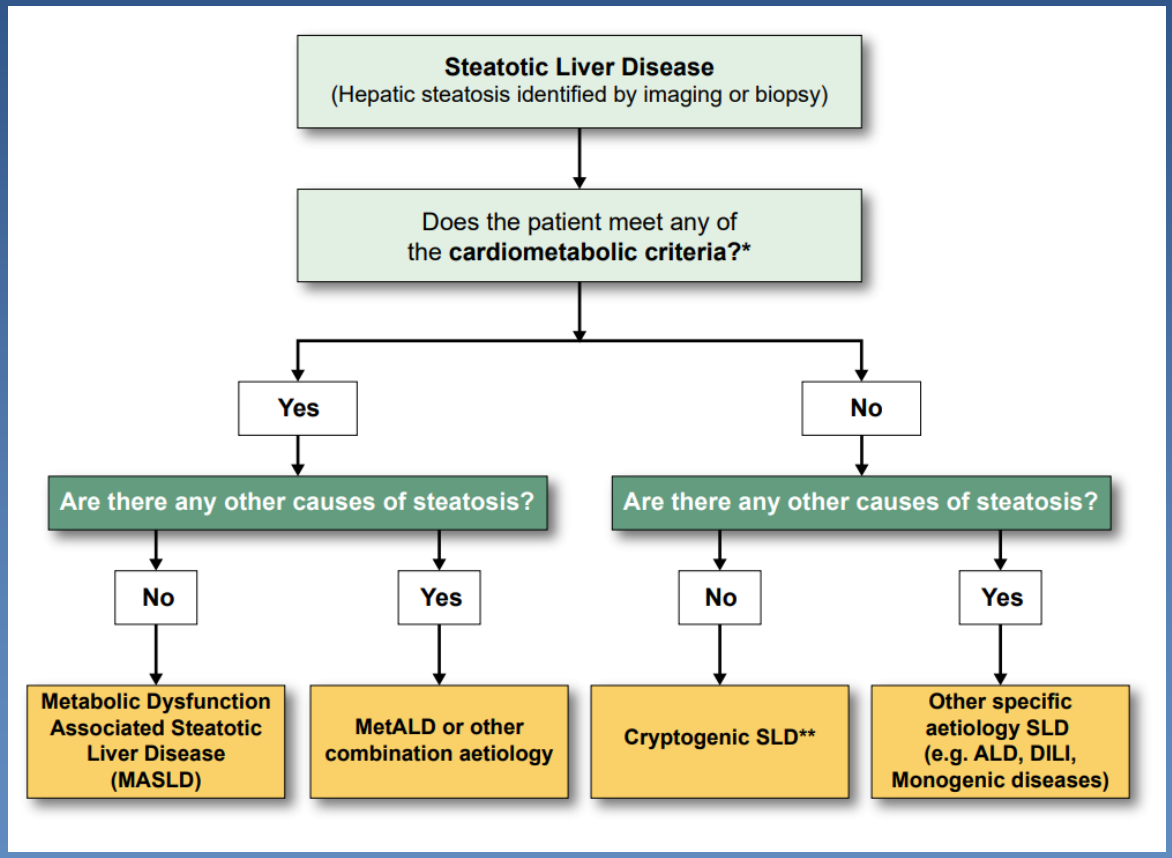
AASLD (Amer. Assoc. for Study of Liver Diseases



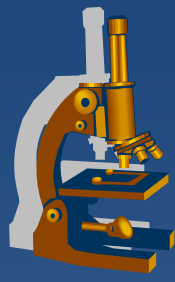


*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease, human immunodeficiency virus (HIV)

AASLD (Amer. Assoc. for Study of Liver Diseases



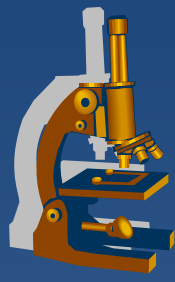
AASLD (Amer. Assoc. for Study of Liver Diseases



***Cardiometabolic criteria**

Adult Criteria	Pediatric Criteria
At least 1 out of 5:	**At least 1 out of 5:**
☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted equivalent	☐ BMI ≥ 85th percentile for age/sex [BMI z score ≥ +1] **OR** WC > 95th percentile **OR** ethnicity adjusted equivalent
☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes	☐ Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] **OR** serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol [140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** already diagnosed/treated type 2 diabetes **OR** treatment for type 2 diabetes
☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment	☐ Blood pressure age < 13y, BP ≥ 95th percentile **OR** ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg **OR** specific antihypertensive drug treatment
☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment	☐ Plasma triglycerides < 10y, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] **OR** lipid lowering treatment
☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment	☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] **OR** lipid lowering treatment

Fatty liver - steatosis

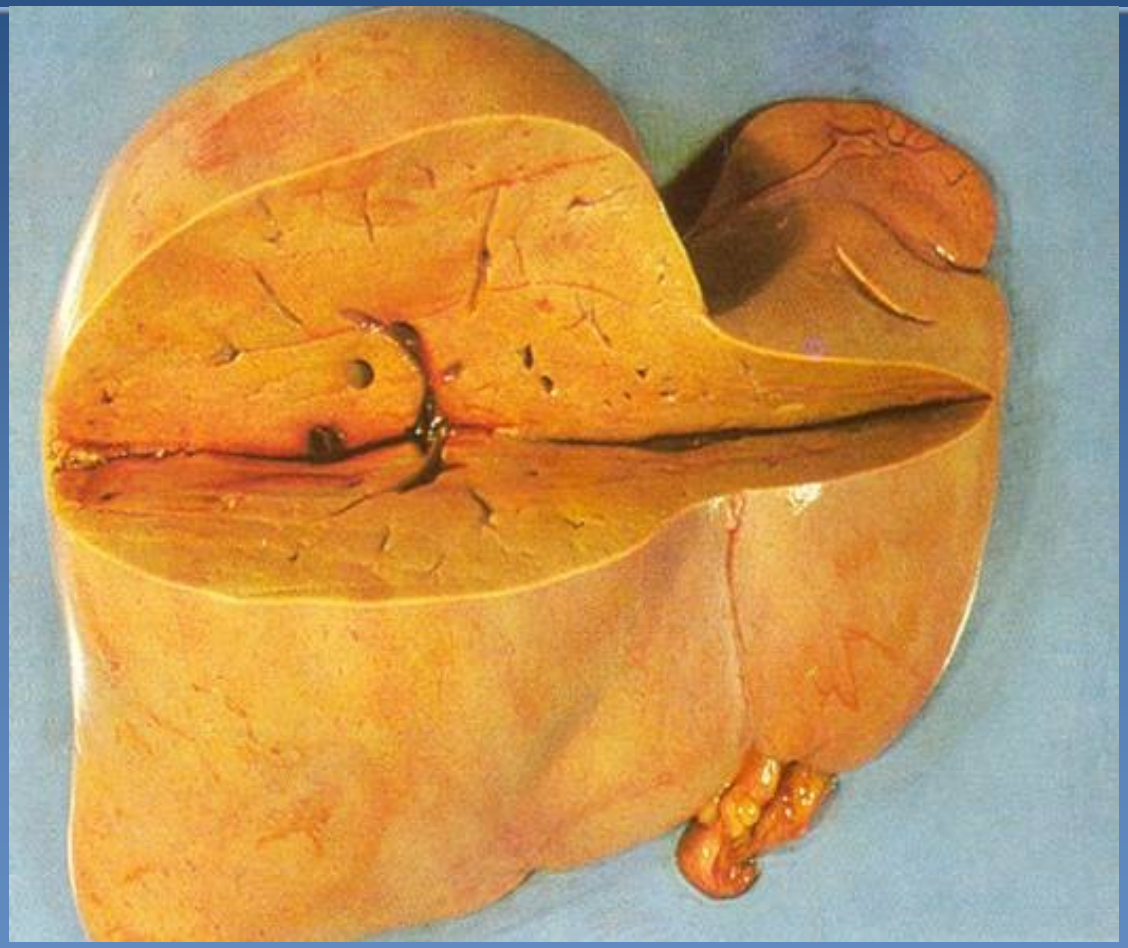


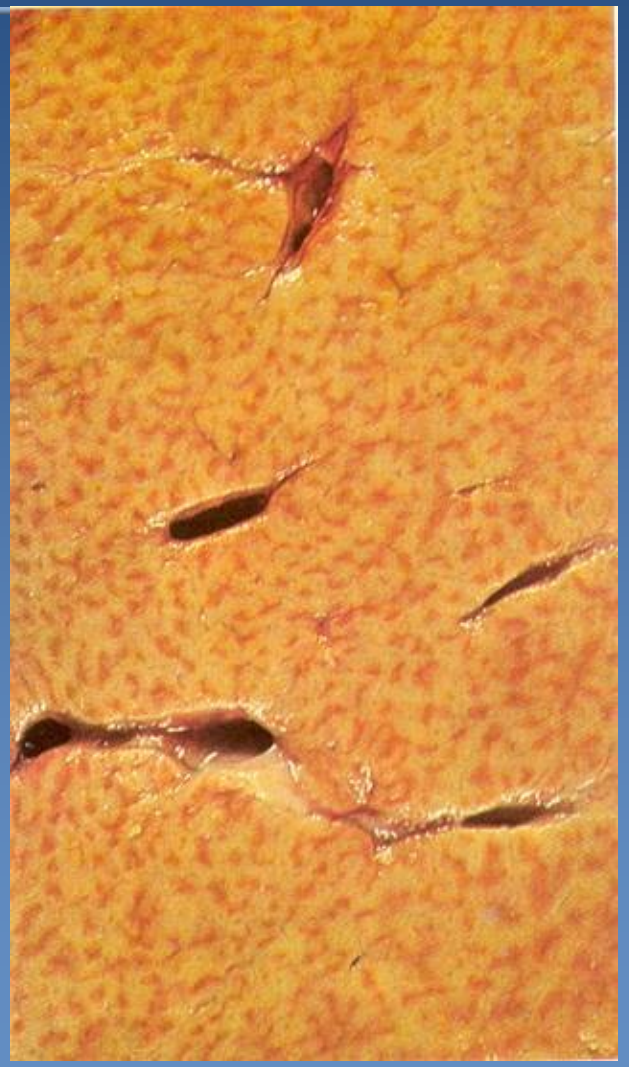
= pathological accumulation of lipids in form of intracytoplasmatic vesicles

- without inflammatory reaction reversible process
- with inflammation (steatohepatitis) – possible progression to cirrhosis

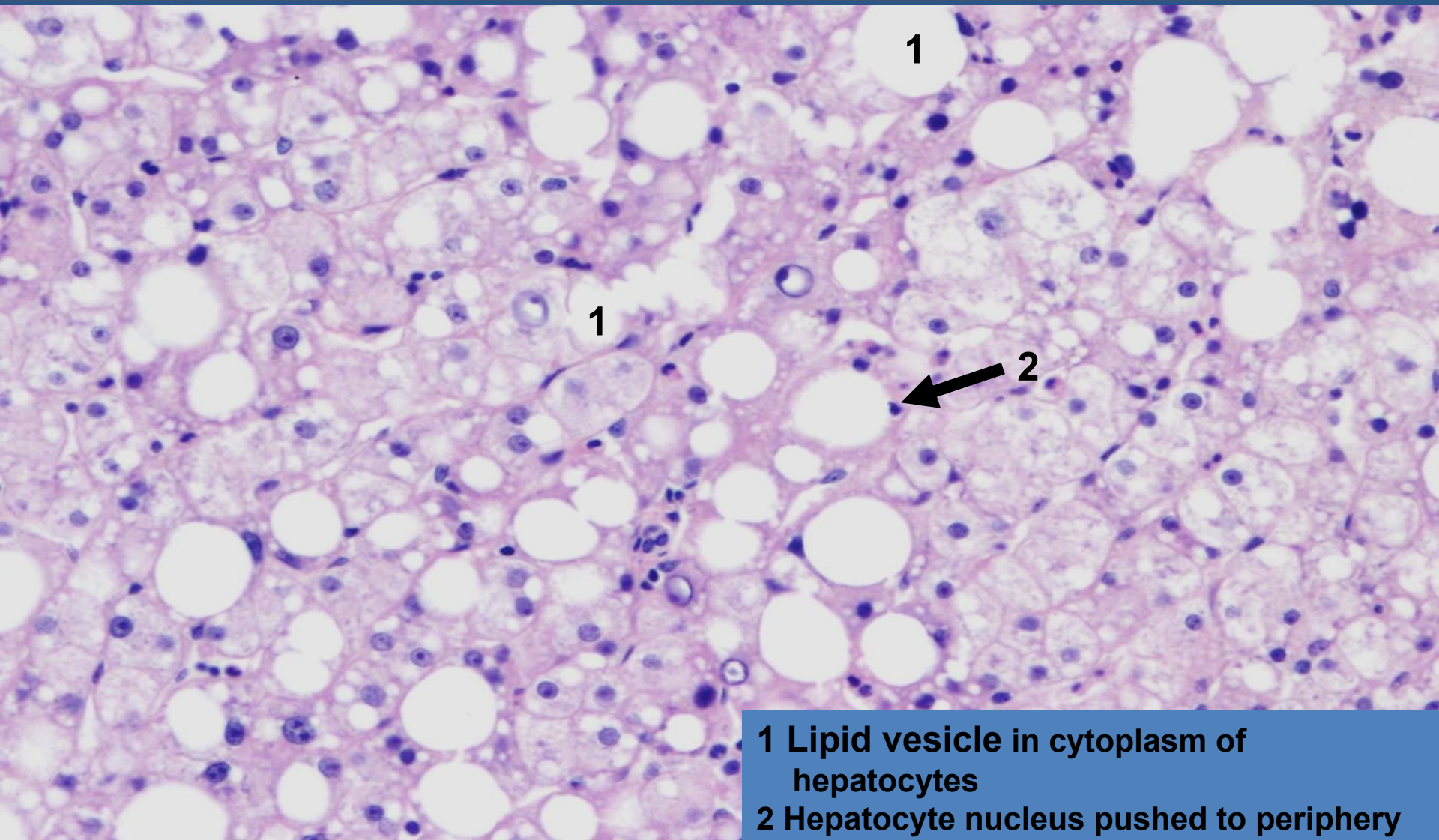
- microvesicular x macrovesicular
  - ⇨ ***vesicle < or > than hepatocyte nucleus***
  - ⇨ ***variable distribution (diffuse, zonal, focal), may help to the etiological diagnosis***

Fatty liver disease - steatosis



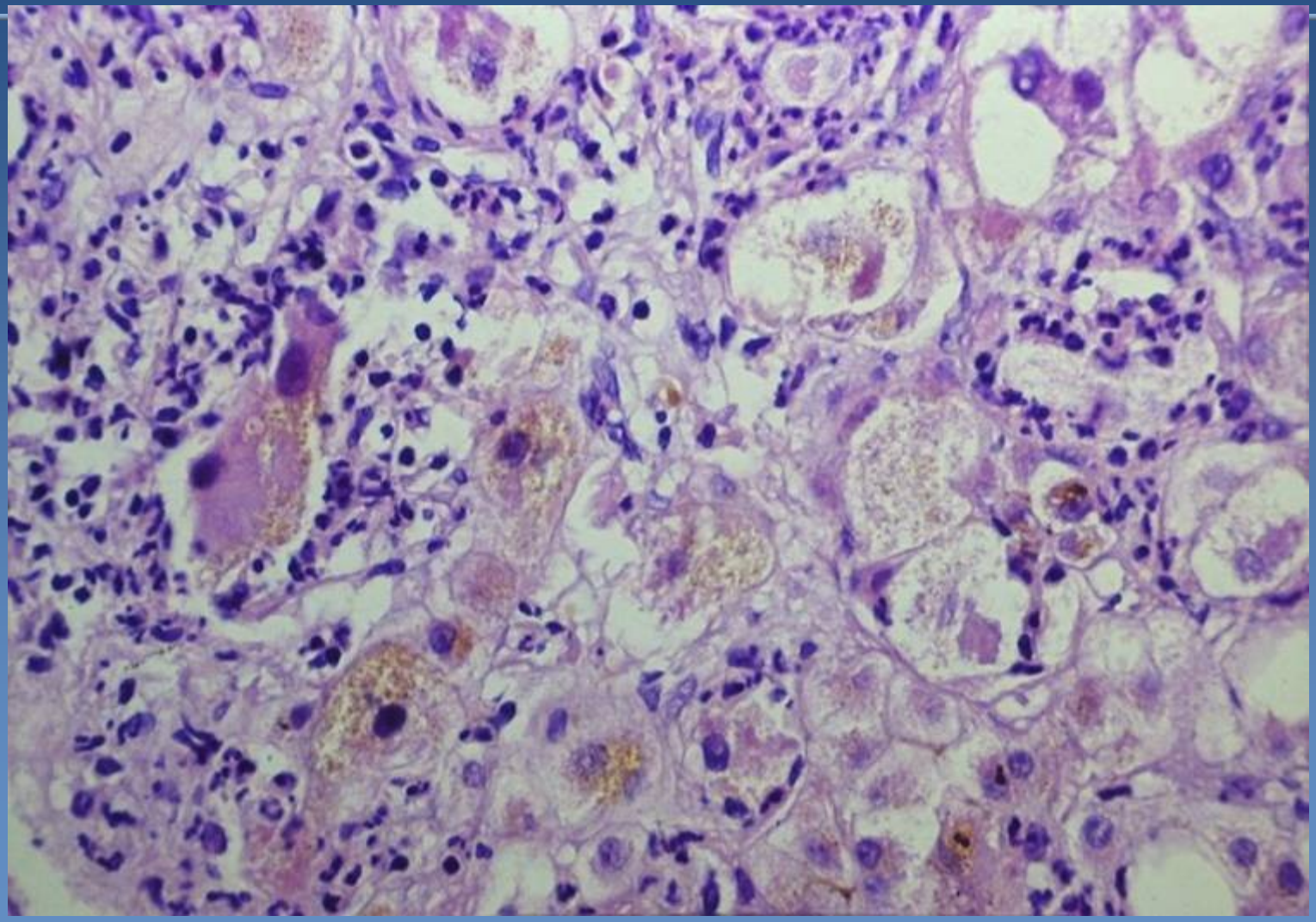


Alcoholic fatty liver

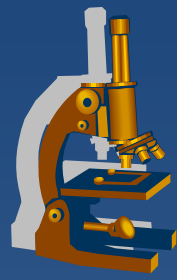


1 Lipid vesicle in cytoplasm of hepatocytes
2 Hepatocyte nucleus pushed to periphery

Alcoholic hepatitis *: steatohepatitis, cholestasis, Mallory hyaline*



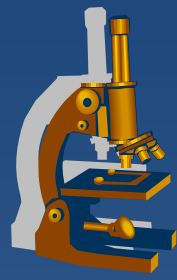
Cholestasis



- Causes:
  - ⇨ *hepatocellular dysfunction (inborn, acquired)*
  - ⇨ *biliary obstruction (intra-, extrahepatic)*

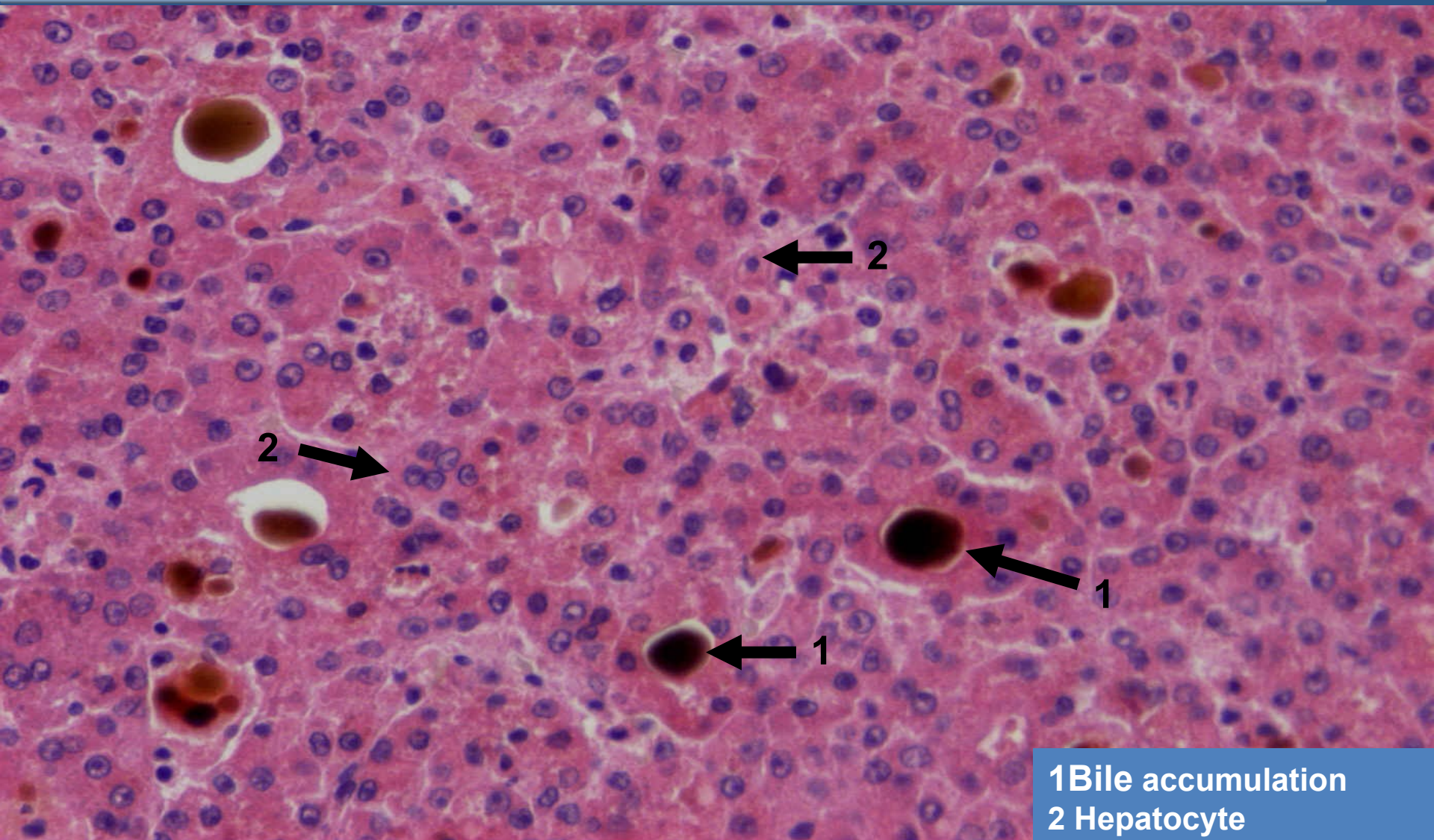
- Signs:
  - ⇨ *pruritus - itching(↑ serum bile acids)*
  - ⇨ *hyperlipidemia → skin xanthomas (focal cholesterol accumulation)*
  - ⇨ *malabsorption → ↓ fat soluble vitamins (A; D; K)*
  - ⇨ *↑ ALP (serum alkaline phophatase)*

Cholestasis
MORPHOLOGY



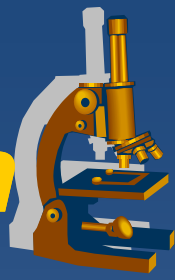
- Gross:
  - ⇨ ***green-brown (olive) discoloration***
- Micro:
  - ⇨ ***bile pigment accumulation in hepatocytes / canaliculi („bile plugs“)***
  - ⇨ ***edema, periductal neutrophilic infiltrates in portal spaces***
  - ⇨ ***chronic obstruction → portal fibrosis → biliary cirrhosis***

Cholestasis in HCC



1Bile accumulation
2 Hepatocyte

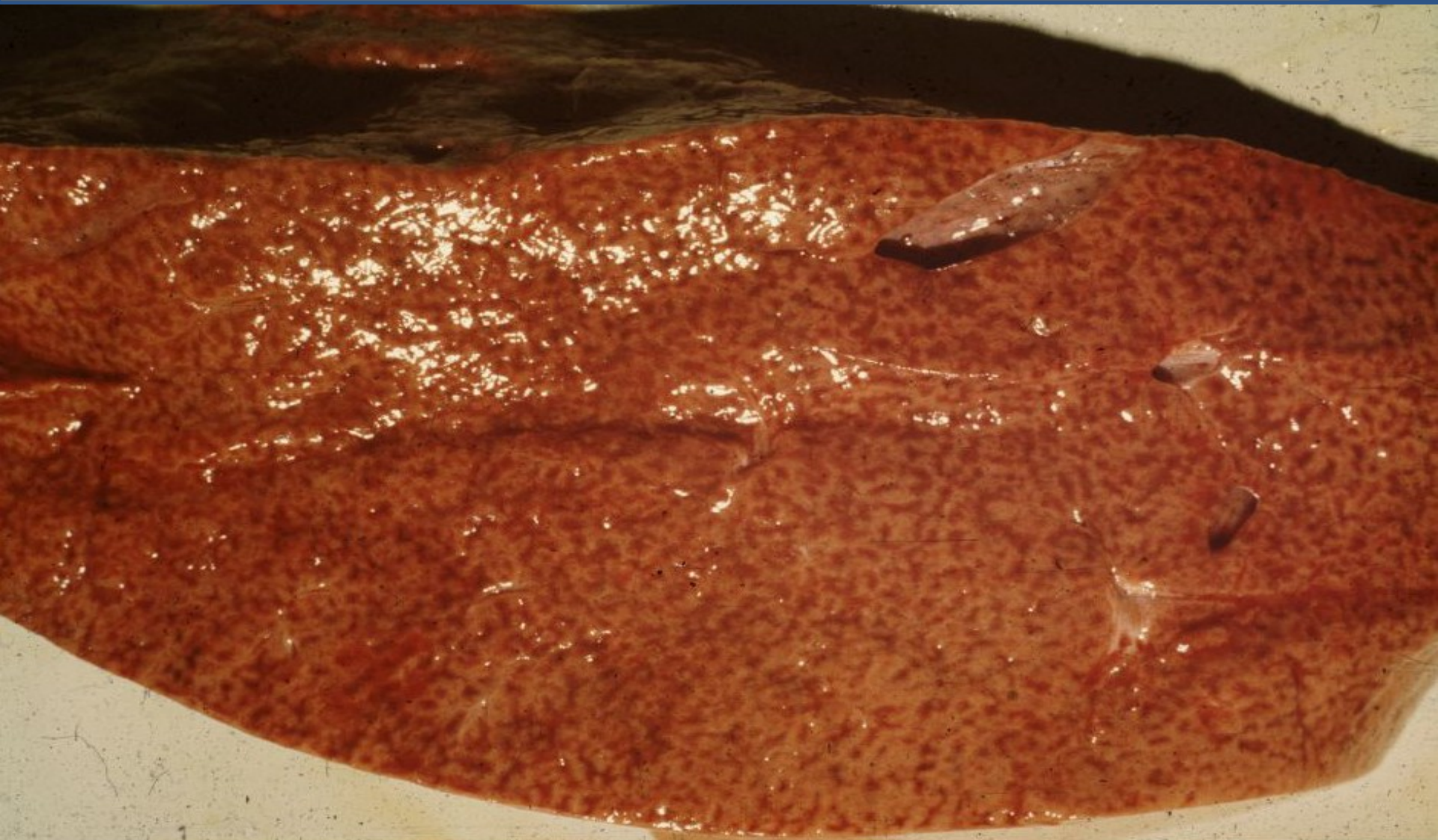
Hepatic venous congestion



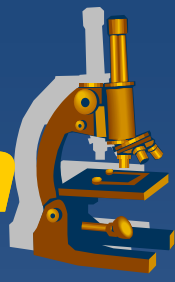
- GROSS:
  - ⇨ *enlarged, heavy liver*
  - ⇨ *dark – reddish brown color*
  - ⇨ *cardiac fibrosis (induration)*
  - ⇨ *combination with chronic hypoxemic steatosis – nutmeg liver*

Hepatic venous congestion

("nutmeg" liver)

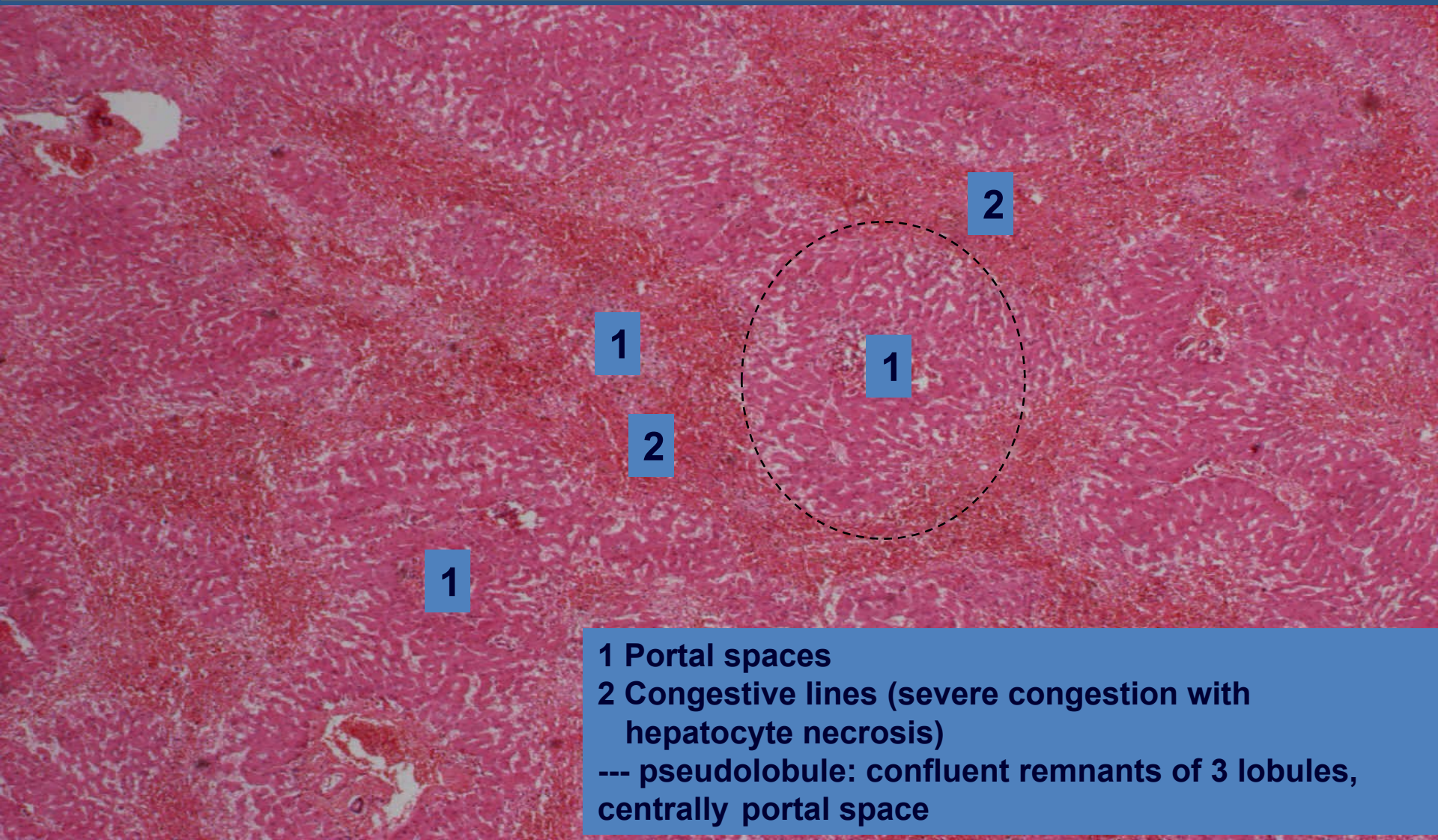


Hepatic venous congestion



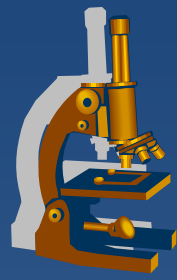
- MICRO:
  - ⇨ *central veins and sinusoidal dilatation*
  - ⇨ *centrolobular hepatocytic atrophy, necrosis*
  - ⇨ *„lines“ of congestion*

Hepatic venous congestion



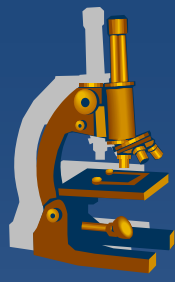
1 Portal spaces
2 Congestive lines (severe congestion with hepatocyte necrosis)
--- pseudolobule: confluent remnants of 3 lobules, centrally portal space

Hepatitis



- **infectious**
  - ⇨ *acute, chronic*
  - ⇨ *viral*
    - most common
    - primary hepatotropic - hepatitis viruses
    - systemic – EBV, CMV, HSV, yellow fever, enteroviruses, …
  - ⇨ *bacterial*
    - pyogennic bacteria, TBC, salmonella – typhoid fever, leptospirosis,…
  - ⇨ *parasitic*
    - ecchinococcus, schistosoma, …
  - ⇨ *protozoal*
    - amebiasis

Hepatitis

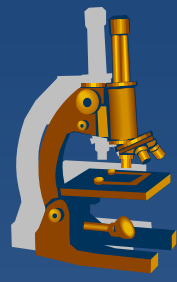


Non-infectious

(acute, chronic)

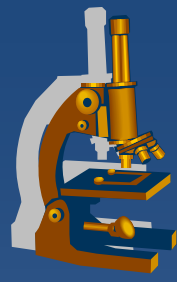
- ⇨ ***autoimmune*** *(AIH)*
- ⇨ ***metabolic***
  - hemochromatosis, NASH
- ⇨ ***toxic/drug induced***
- ⇨ ***cryptogenic***

Chronic hepatitis



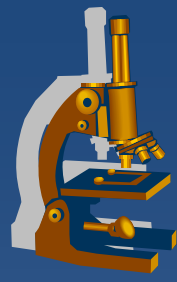
- Asymptomatic / clinical symptoms
- Laboratory signs of progressive/relapsing liver disease (> 6 months, 12 months in HCV)
- Etiology:
  - ⇨ ***Viruses***
    - HBV, HBV+HDV, HCV
  - ⇨ ***AIH***
  - ⇨ ***metabolic (inborn, NASH)***
  - ⇨ ***toxic/ drug induced (alcoholic)***
  - ⇨ ***cryptogenic***

Chronic hepatitis - pathology



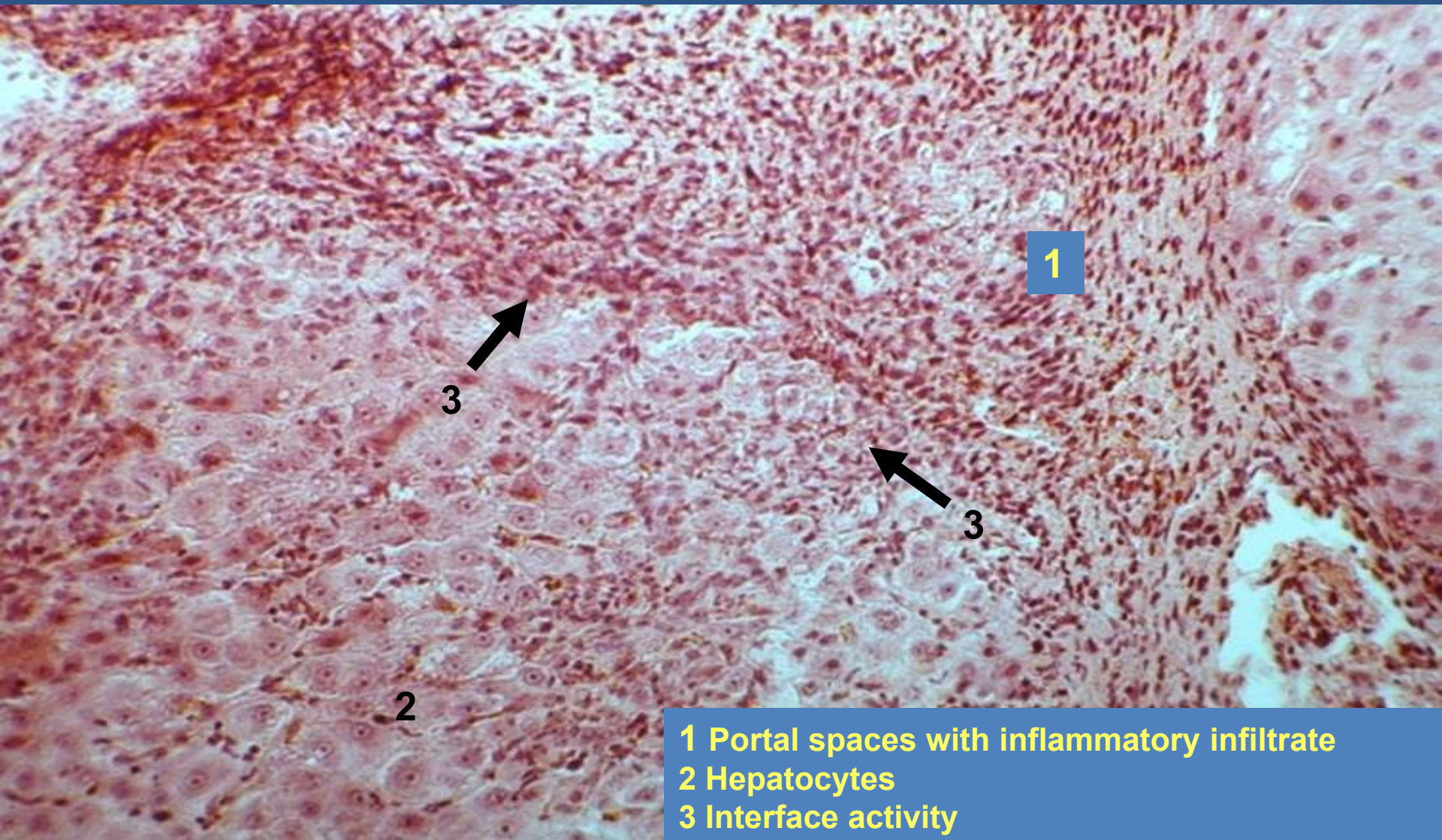
- Gross:
  - ⇨ ***non-charakteristic, commonly enlarged liver of firmer consistency***
- Micro:
  - ⇨***Disease activity: grade of necroinflammatory changes in portal spaces and lobules (interface activity; type, grade and localisation of necrosis; grade of inflammatory infiltrate)***

Chronic hepatitis - pathology



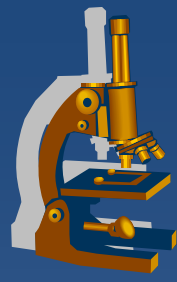
- Disease stage:
  - ⇨***stage*** *of fibrosis and architectural changes (portal fibrotic expansion, bridging fibrosis, nodularity → cirrhosis)*

Chronic hepatitis



1 Portal spaces with inflammatory infiltrate
2 Hepatocytes
3 Interface activity

NASH: non-alcoholic steatohepatitis



- **Spreading silent epidemics:**

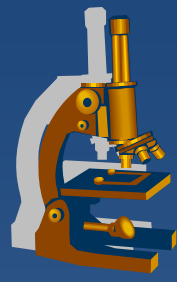
Patients with metabolic syndrome:

„male-type“ obesity (intraabdominal fat accumulation – waist size)

hyperlipidemia

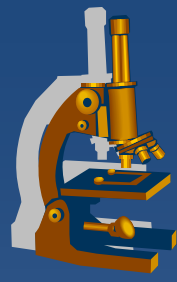
DM of II type, hyperglycaemia

Liver fibrosis



- Response to inflammation
- Mostly irreversible
  - ⇨ ***(under favorable conditions reversible to some extent)***
- Deposition of collagen
  - ⇨ → ***effects on hepatic metabolism and blood flow***
- Begins around portal tracts or central veins → spreads → links other regions (bridging fibrosis)
- Basic lobular architecture partially preserved

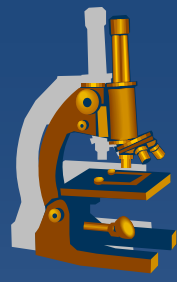
Advanced liver disease (cirrhosis)



- Complete loss of original architecture
  - ⇨ ***Regenerating groups of hepatocytes surrounded by fibrotic scar tissue***
  - ⇨ ***Reorganisation of vascular architectecture***
  - ⇨ ***Intrahepatic biliary trackt changes, incl. ductular hyperplasia***

- Due to continued parenchymal injury and fibrosis
- Advanced stage of liver disease, may be partially reversible

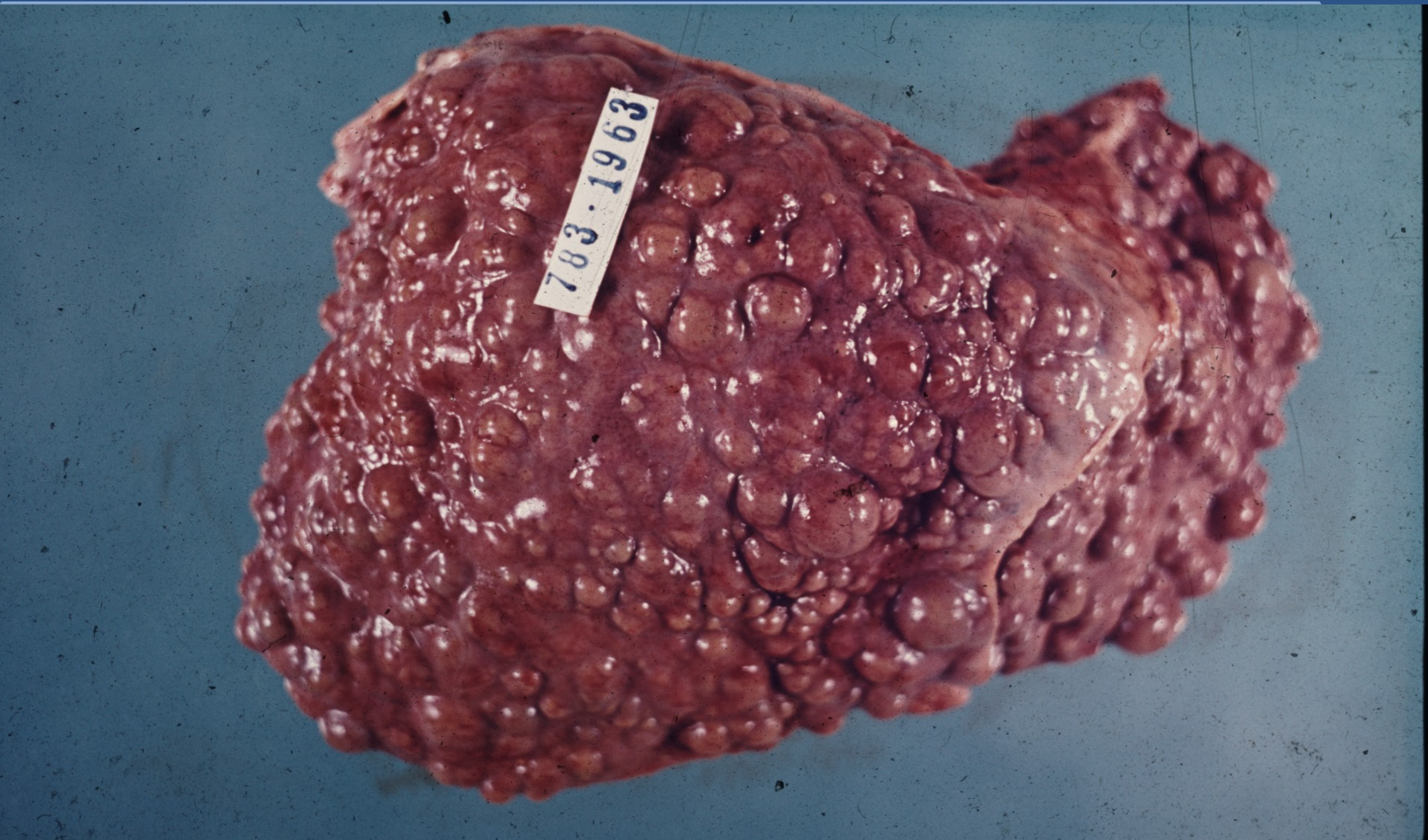
Advanced liver disease (cirrhosis)



- Etiology:
  - ⇨ ***massive acute necrosis***
  - ⇨ ***chronic hepatitis***
  - ⇨ ***biliary diseases:***
    - inborn (atresia)
    - acquired:
      - autoimmune (primary biliary cirrhosis, prim. sclerosing cholangitis), secondary biliary cirrhosis (chronic obstruction)
  - ⇨ ***cryptogenic cirrhosis***

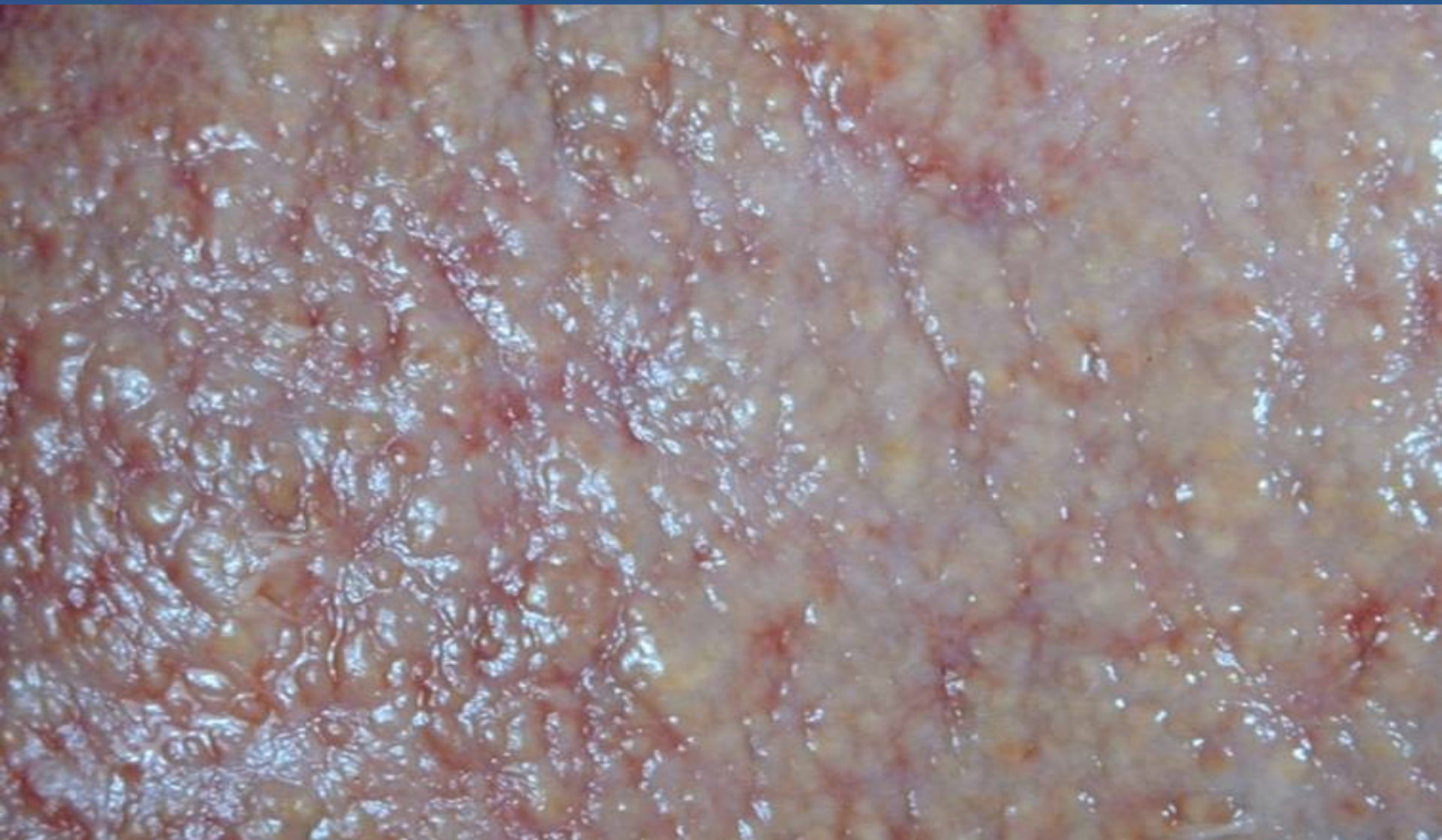
- Gross: liver usually diminished in size
  - ⇨ ***micronodular***
  - ⇨ ***macronodular***

Cirrhosis - macronodular

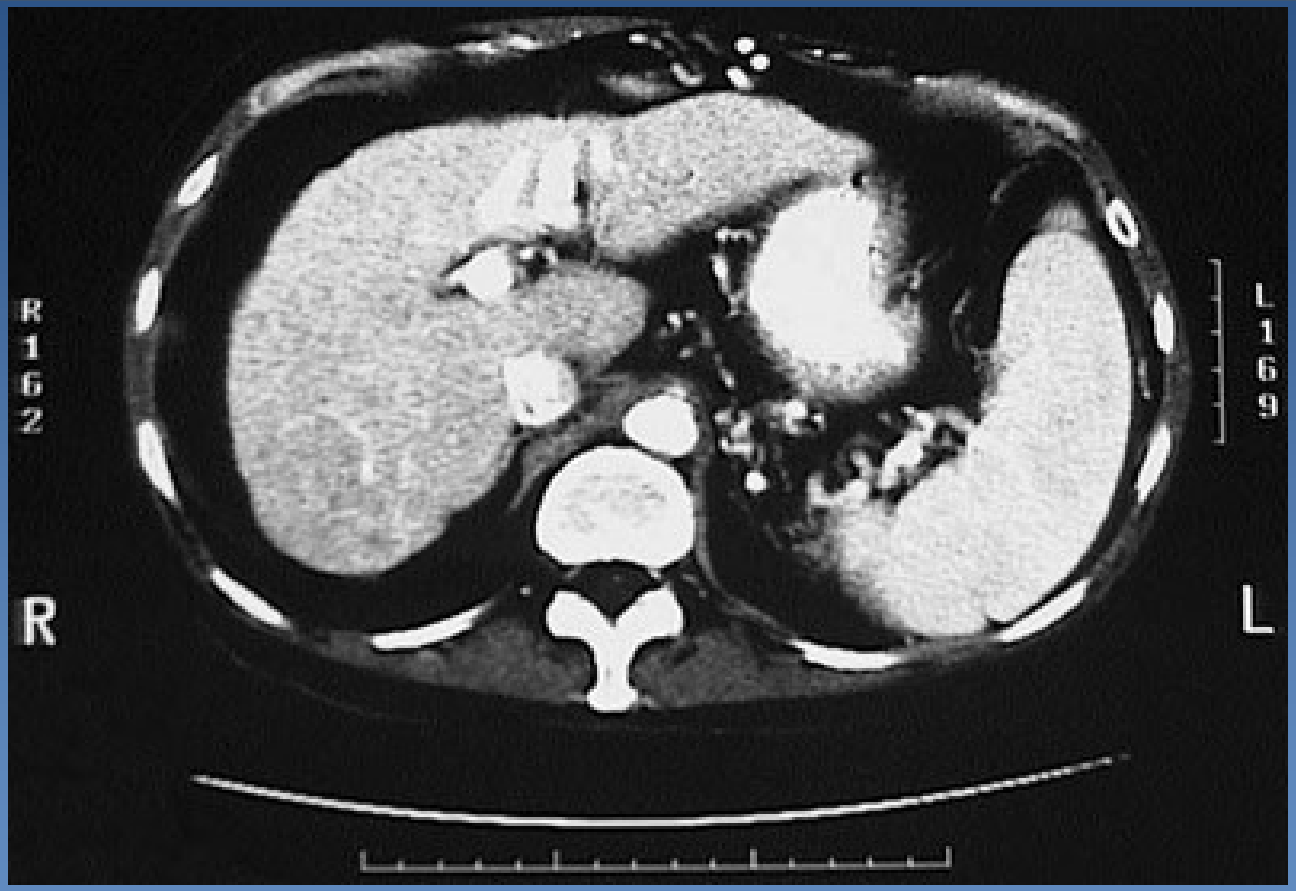


Cirrhosis - micronodular

Advanced liver disease (cirrhosis)

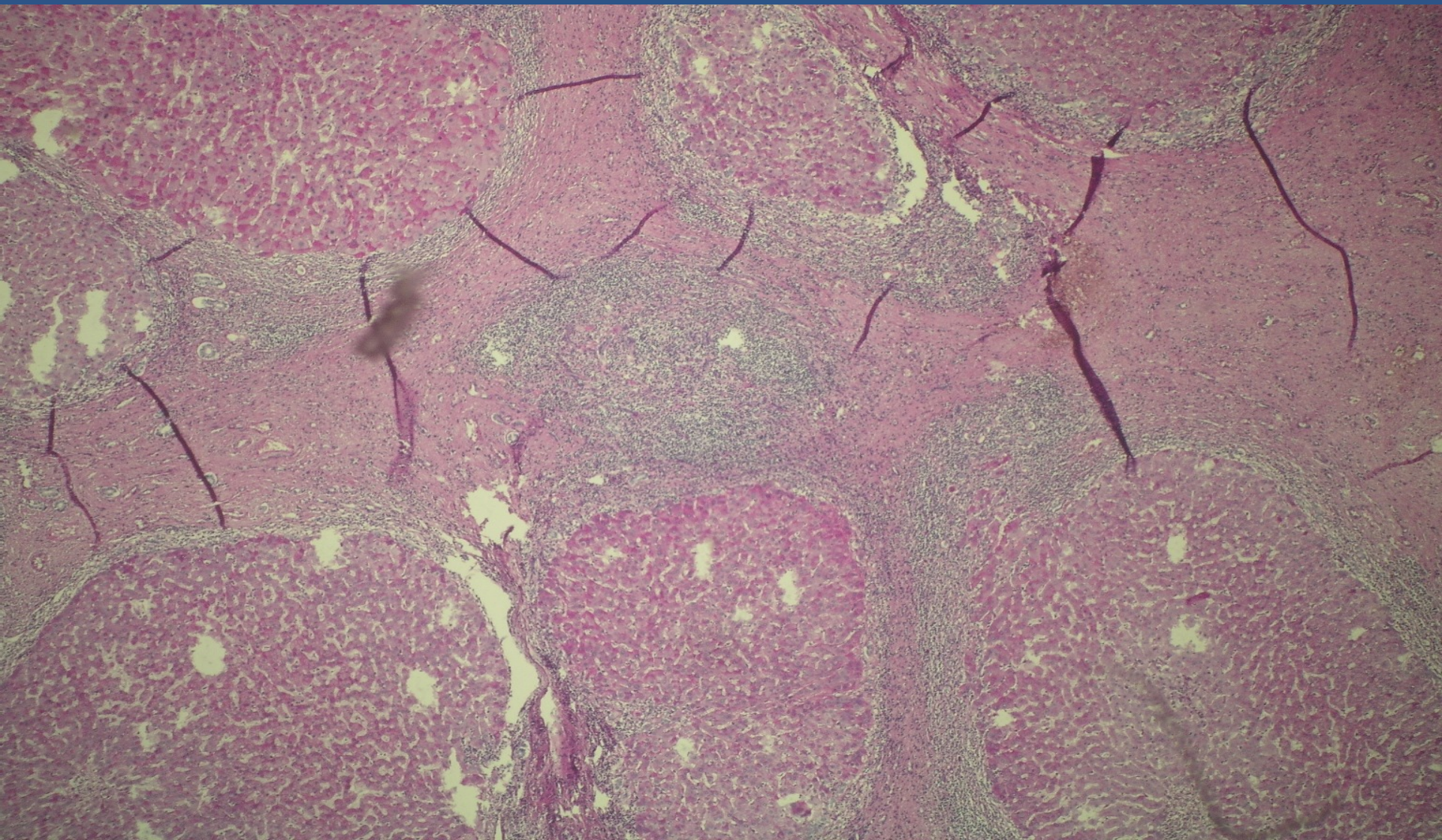


Advanced liver disease (cirrhosis)

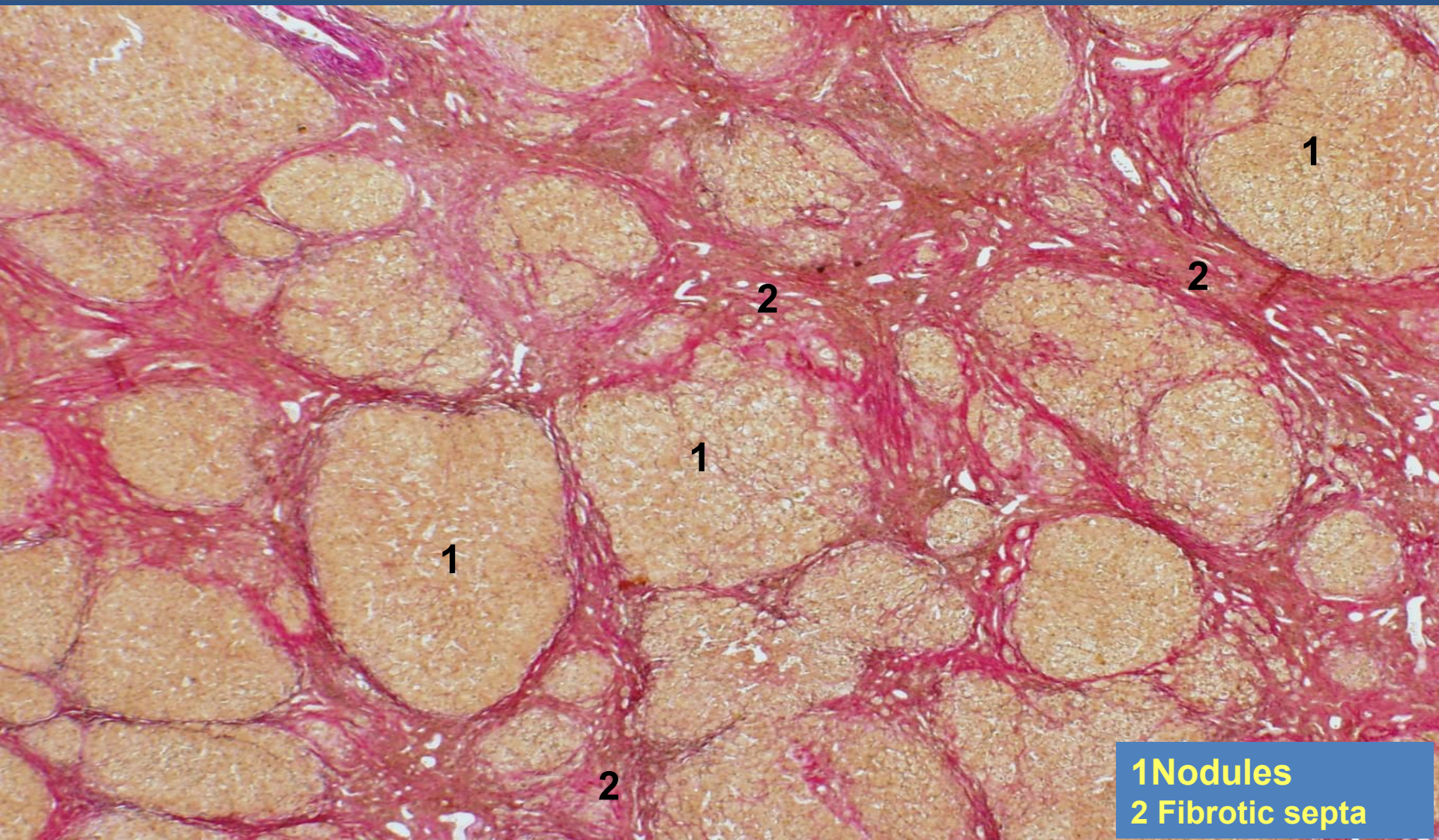


CT scan with contrast of the abdomen in transverse view demonstrates a **small liver with cirrhosis.** The spleen is enlarged from portal hypertension

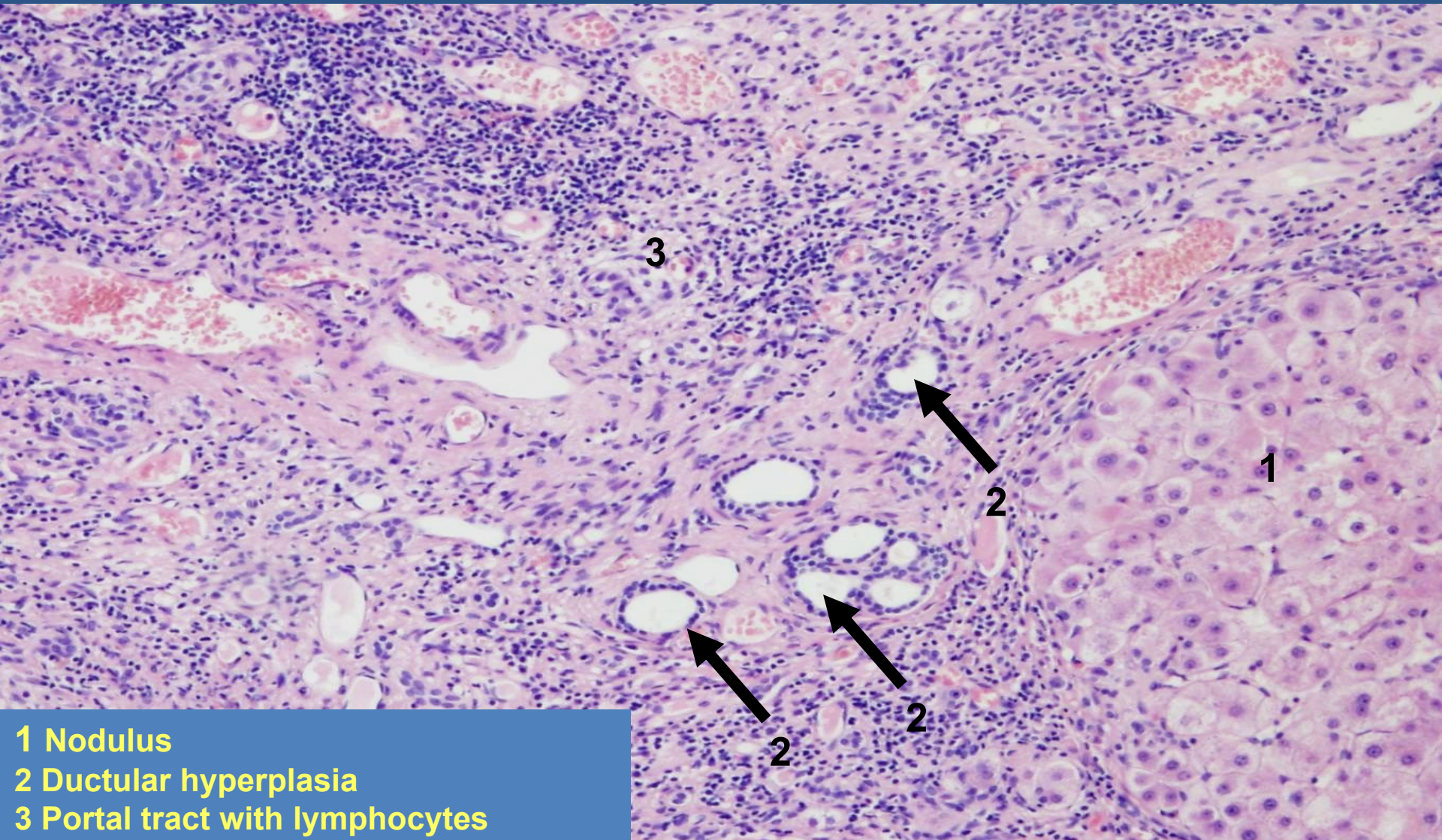
Advanced liver disease (cirrhosis)



Cirrhosis – fibrotic septa
(Van Gieson staining)

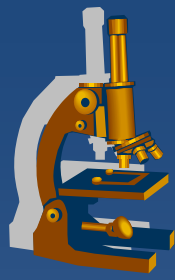


Cirrhosis - ductules



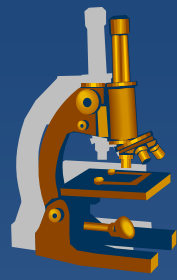
1 Nodulus
2 Ductular hyperplasia
3 Portal tract with lymphocytes

Complications of cirrhosis



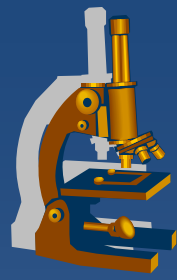
- Insufficiency of liver functions:
  - ⇨ ↓ *synthesis (proteins incl. clotting factors etc.)*
  - ⇨ ↓ *detoxication – hepatic coma*
  - ⇨ ↓ *Kupffer cells function*
- Portal hypertension:
  - ⇨ *splenomegaly, intestinal venous congestion (! infarsation, inflammation)*
  - ⇨ *ascites (! peritonitis)*
  - ⇨ *portocaval anastomoses (oesophageal varices)*
- Carcinoma
  - ⇨ *mostly hepatocellular*

Focal lesions and tumors



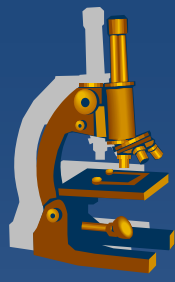
- **Tumor-like lesions**
- **Benign tumors**
- **Malignant tumors:**
  - ⇨ *primary, secondary*

Tumor-like lesions



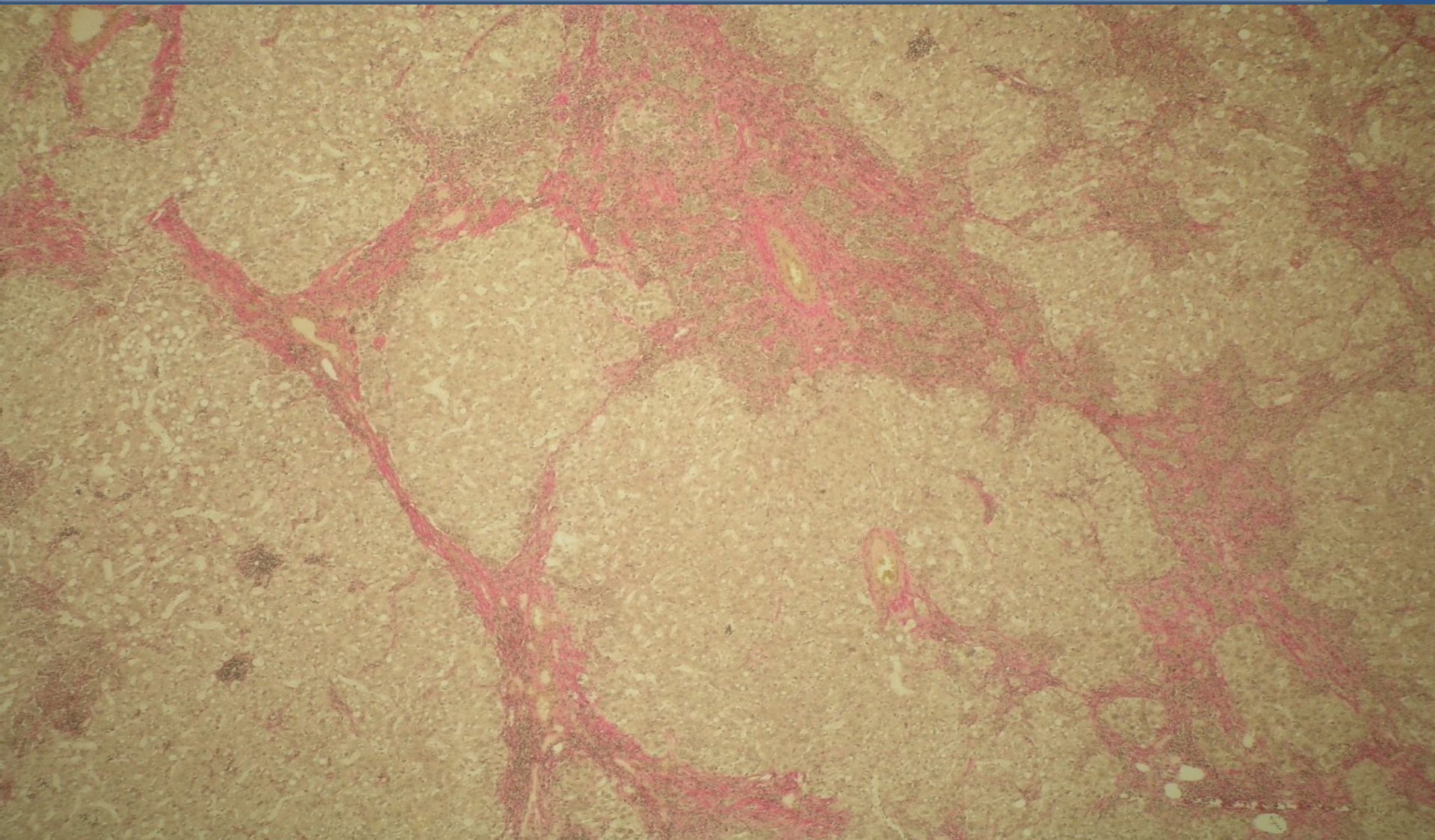
- Focal nodular hyperplasia
- Nodular regeneratory hyperplasia (lack of fibrosis)
- Cysts
- Biliary hamartoma (von Meyenburg complex)

Focal nodular hyperplasia

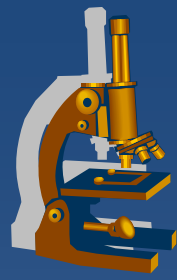


- Localized benign hepatocellular nodules with central stellate fibrous scar
- Single or multiple
- More common in females, oral contraceptives – estrogenes
- Diff. dg. x tumors

FNH – fibrotic scar



Benign tumors



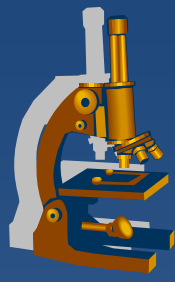
Adenoma

- hepatocellular
  - ⇨ ***lack of portal tracts, regular trabeculae***
- cholangiocellular
  - ⇨ ***biliary , accumulation of regular ducts, lack of bile production, less than 1cm, subcapsular***
- cystadenoma
  - ⇨ ***mucinous, rare***

Haemangioma

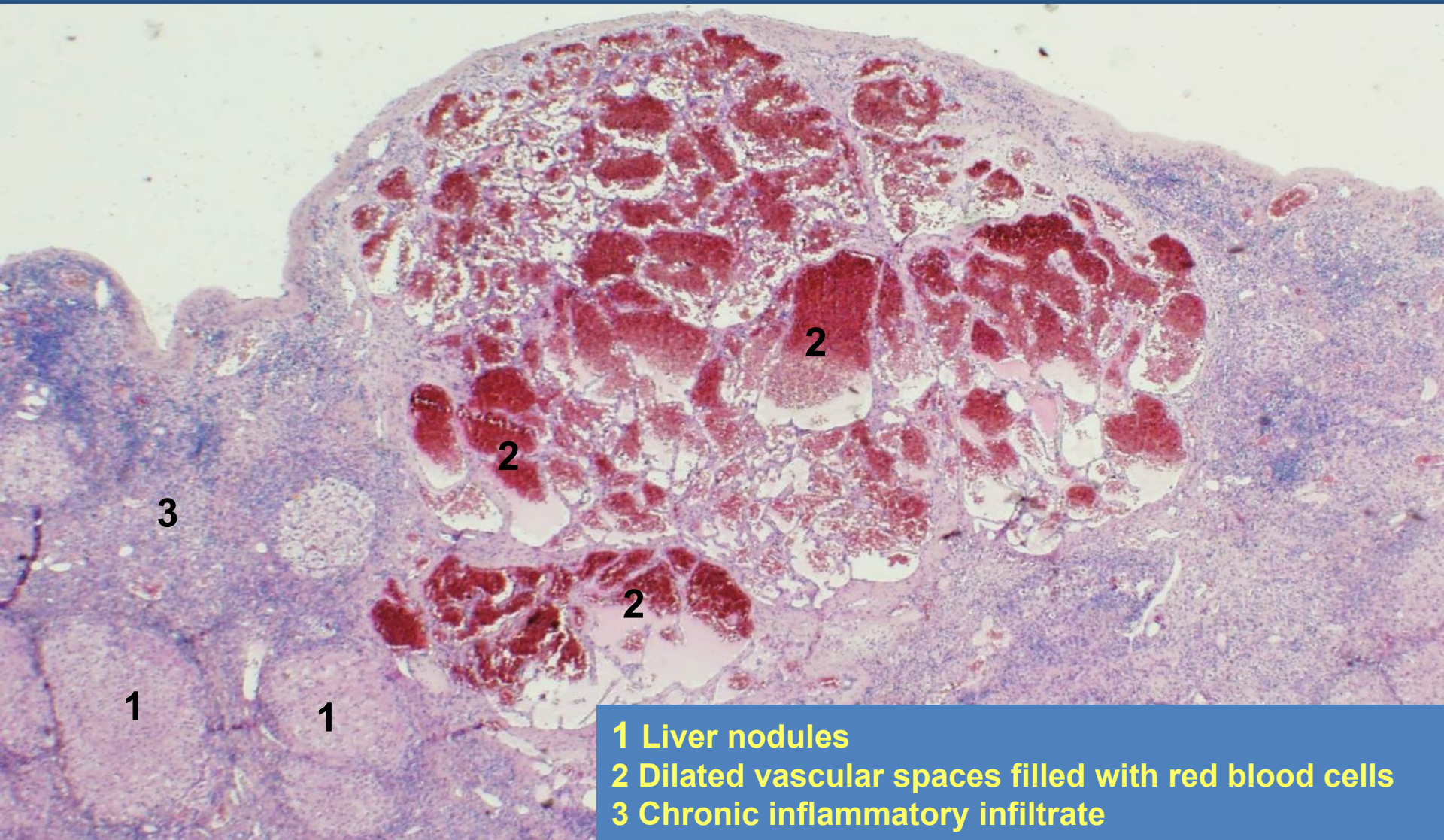
- cavernous

Cavernous haemangioma



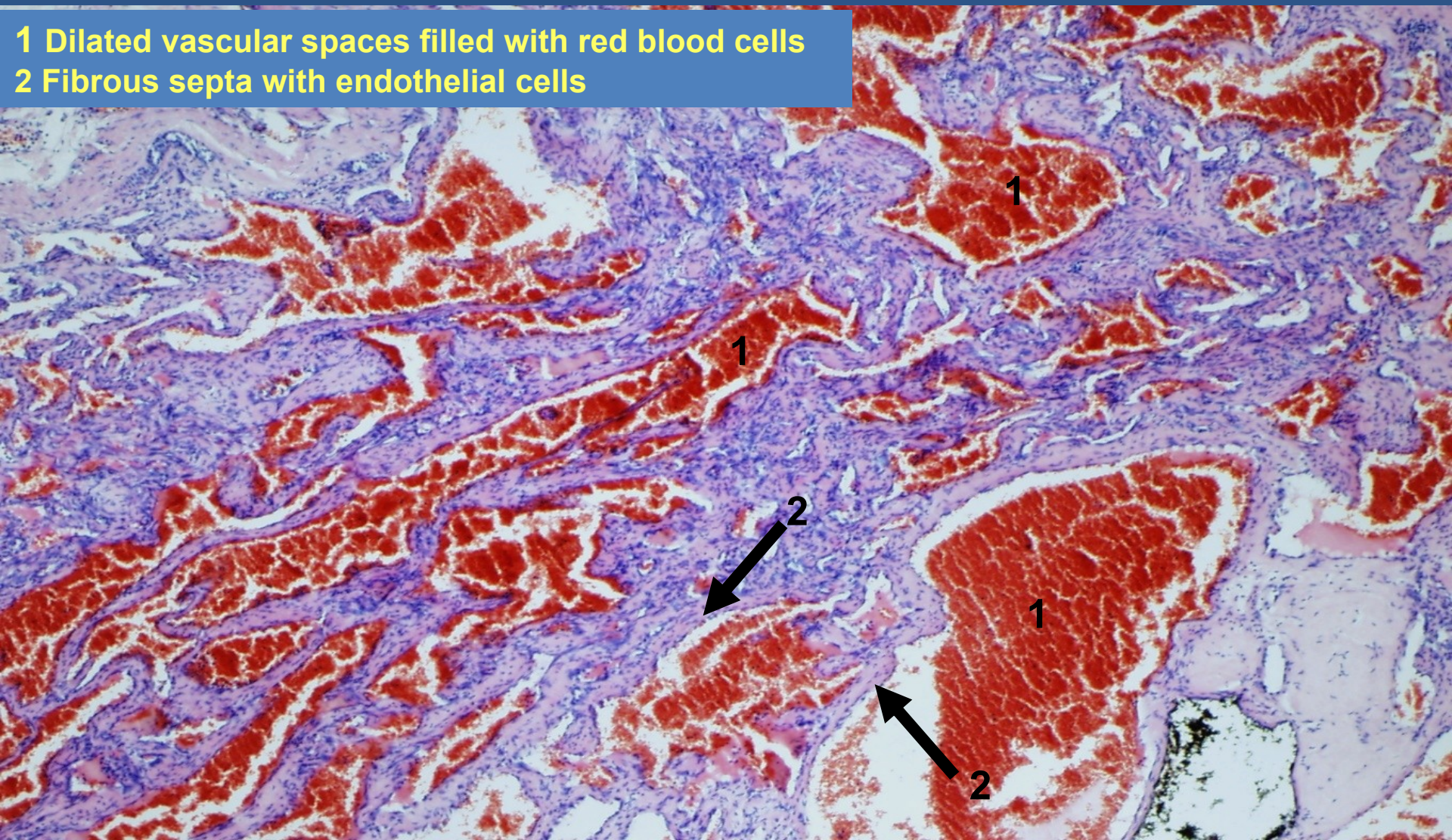
- hamartoma, commonly multiple
- 2 mm – 15 cm
- risk of rupture + bleeding, consumption coagulopathy
- common regressive changes – atypical US, CT, dif. dg. x malignancy
- dark spongiotic demarcated focus
- fibrous septa + vascular spaces

Cavernous haemangioma
(in micronodular liver cirrhosis)

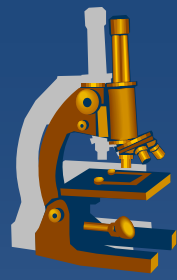


1 Liver nodules
2 Dilated vascular spaces filled with red blood cells
3 Chronic inflammatory infiltrate

Cavernous haemangioma

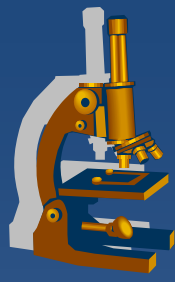


Malignant tumors



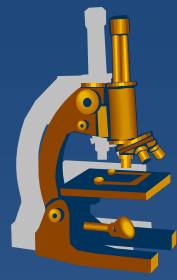
- Primary
  - ***Hepatocellular carcinoma (90%)***
  - ***Cholangiocarcinoma***
  - ***Hepatoblastoma***
    - children
  - ***Angiosarcoma***
    - associated with vinyl chloride, arsenic, or Thorotrast exposure

Malignant tumors



- **Secondary**
  - ***Metastatic carcinomas***
    - most common liver malignancy (GIT, lung, breast, kidney,…)
  - ***Direct spread of adjacent malignant tumors***
    - gall bladder, pancreas
  - ***Other metastasing tumors***
    - melanoma, sarcomas etc.
  - ***Haemopoetic neoplasms***
    - leukemia infiltrates, lymphomas

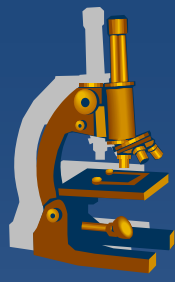
Preneoplastic changes



- **Liver cell dysplasia**
  - ⇨ *low grade, high grade*
  - ⇨ *usually in cirrhosis*
  - ⇨ *small foci or nodules, microcellular – smaller cells with less cytoplasm + bigger nuclei*

Diff. dg. x well diff. HCC

Hepatocellular carcinoma

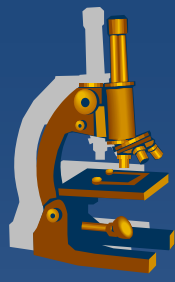


- World-wide 5th most common malignancy in males, 8th in females
- Possible primary prevention
- Different incidence due to geography / cause

  High-income countries: now lower incidence, usually in cirrhosis (alcohol), ↑ (NASH, HCV)

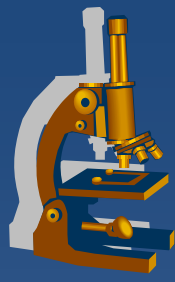
  Eastern Asia (HBV) + Africa (aflatoxin) – 80% of cases

Hepatocellular carcinoma



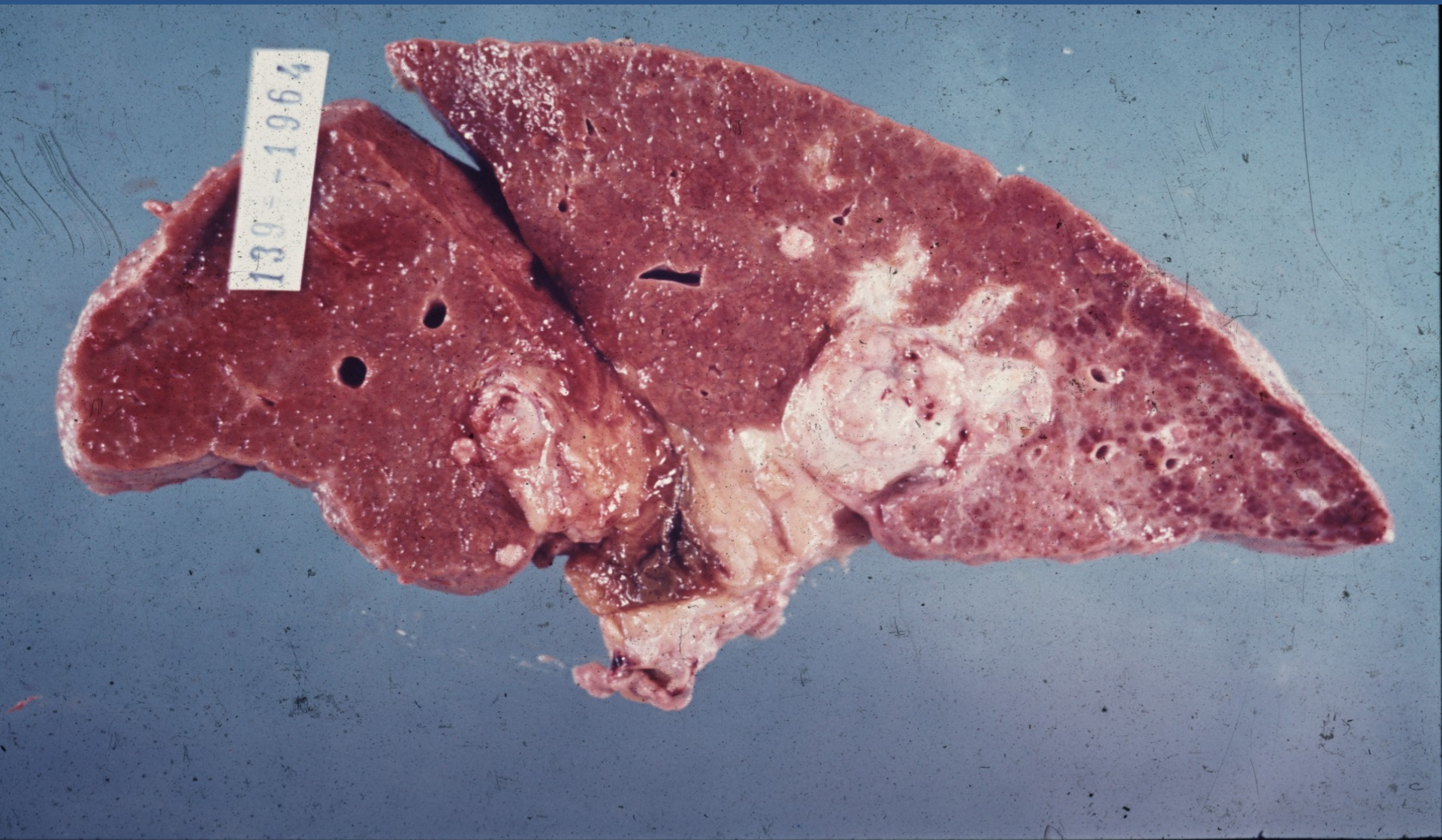
- Single or more nodules different from adjacent tissue
  - ⇨ ***multifocal start or intrahepatic metastases***
- Micro
  - ⇨ ***trabecular, acinar +/- pseudoglandular, solid***
  - ⇨ ***enlarged nuclei + nucleoli, ↑ mitotic activity, atypias; eosinophilic – pale cytoplasm***
- Possible steatosis, bile production

Hepatocellular carcinoma



- angioinvasion
  - ⇨ ***mostly venous***
- metastases
  - ⇨ ***lung, bones, LN***
- small solitary (→3) focus
  - ⇨ ***excision, transplantation***
- large, multiple
  - ⇨ ***ablation, bad prognosis***
- secondary prevention
  - ⇨***regular check-up of cirrhotic patients***

Hepatocellular carcinoma



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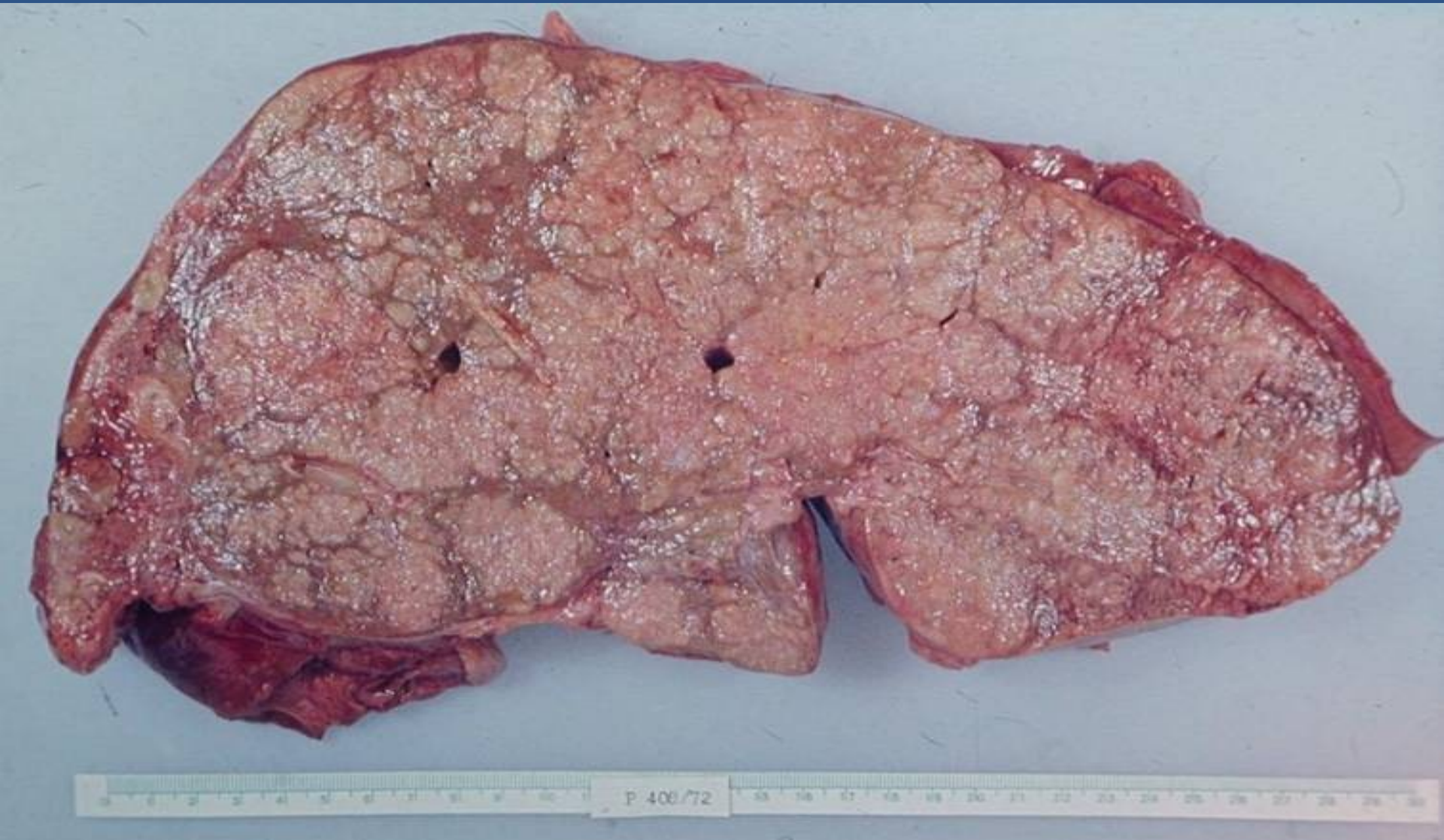

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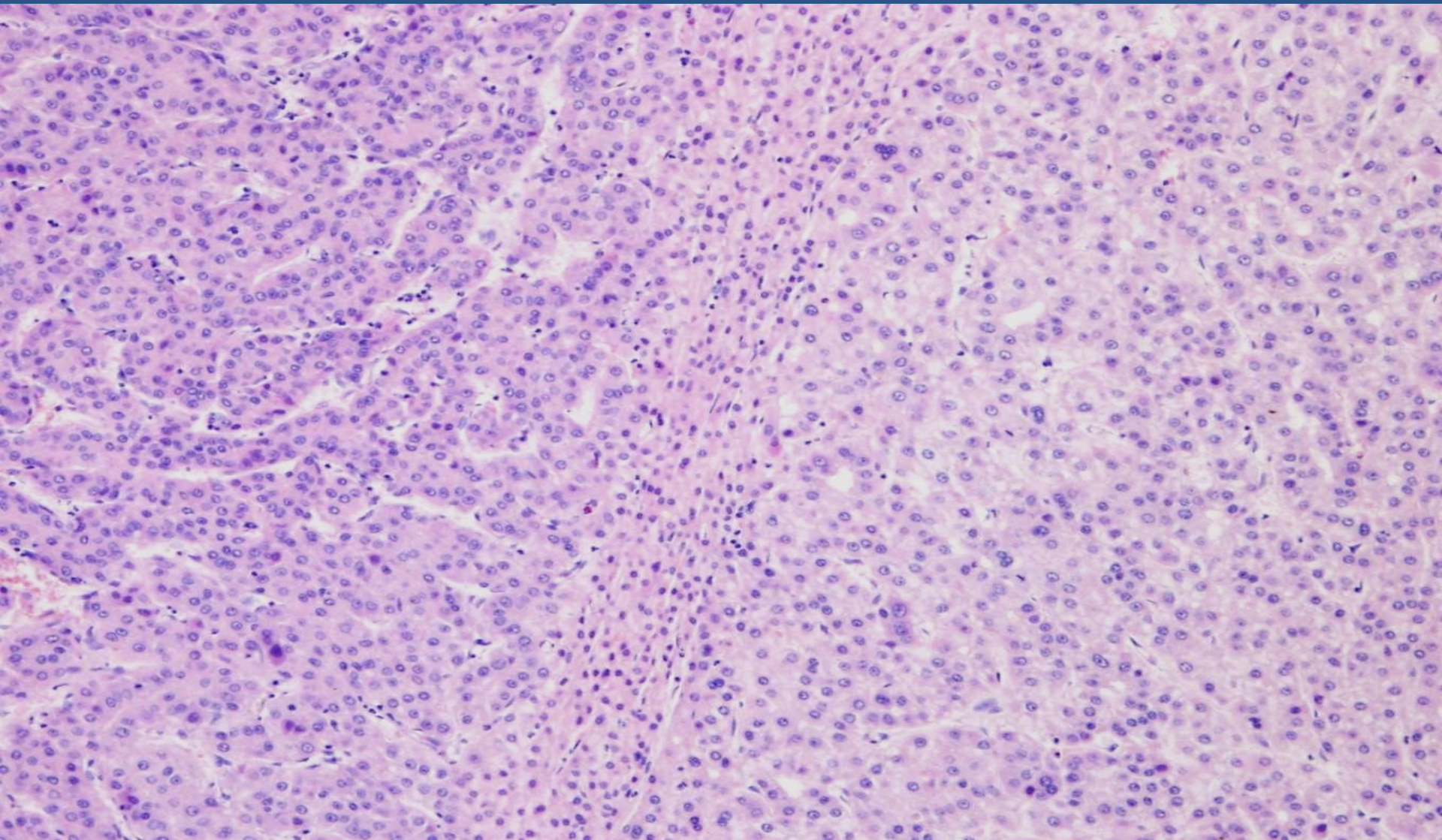

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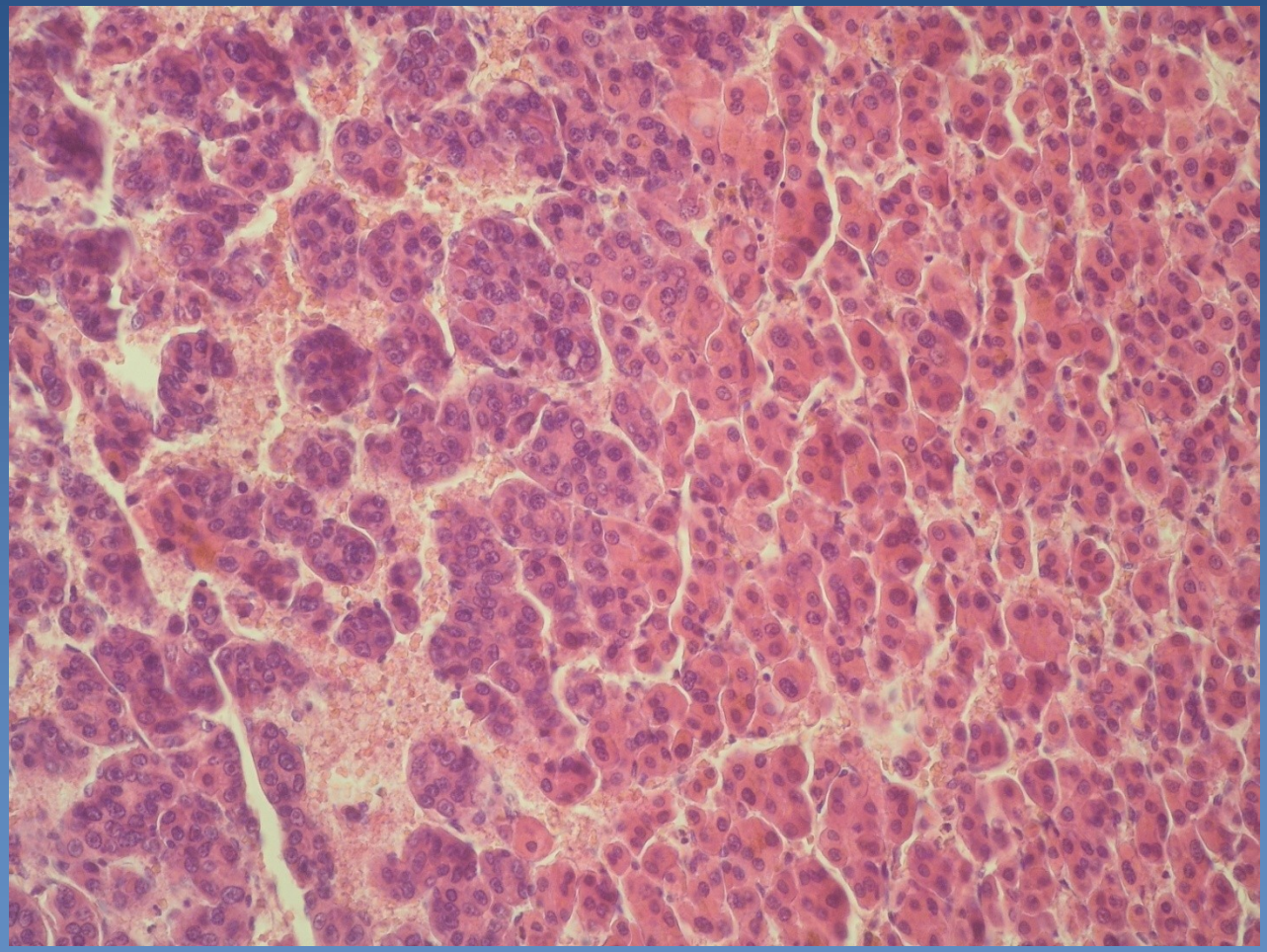
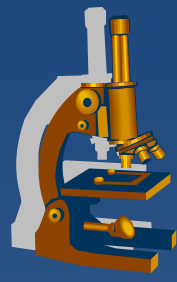
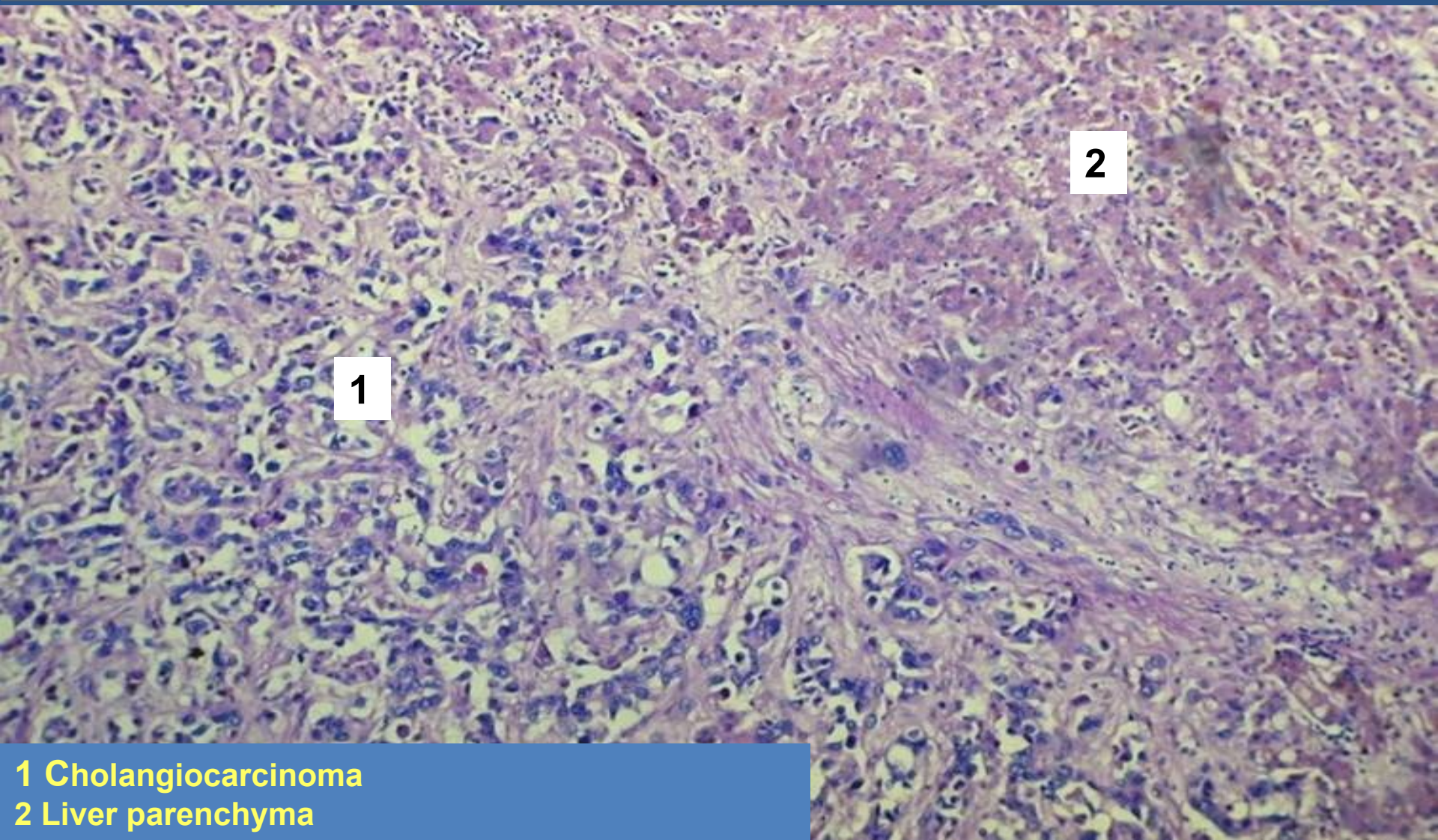


Cholangiocarcinoma



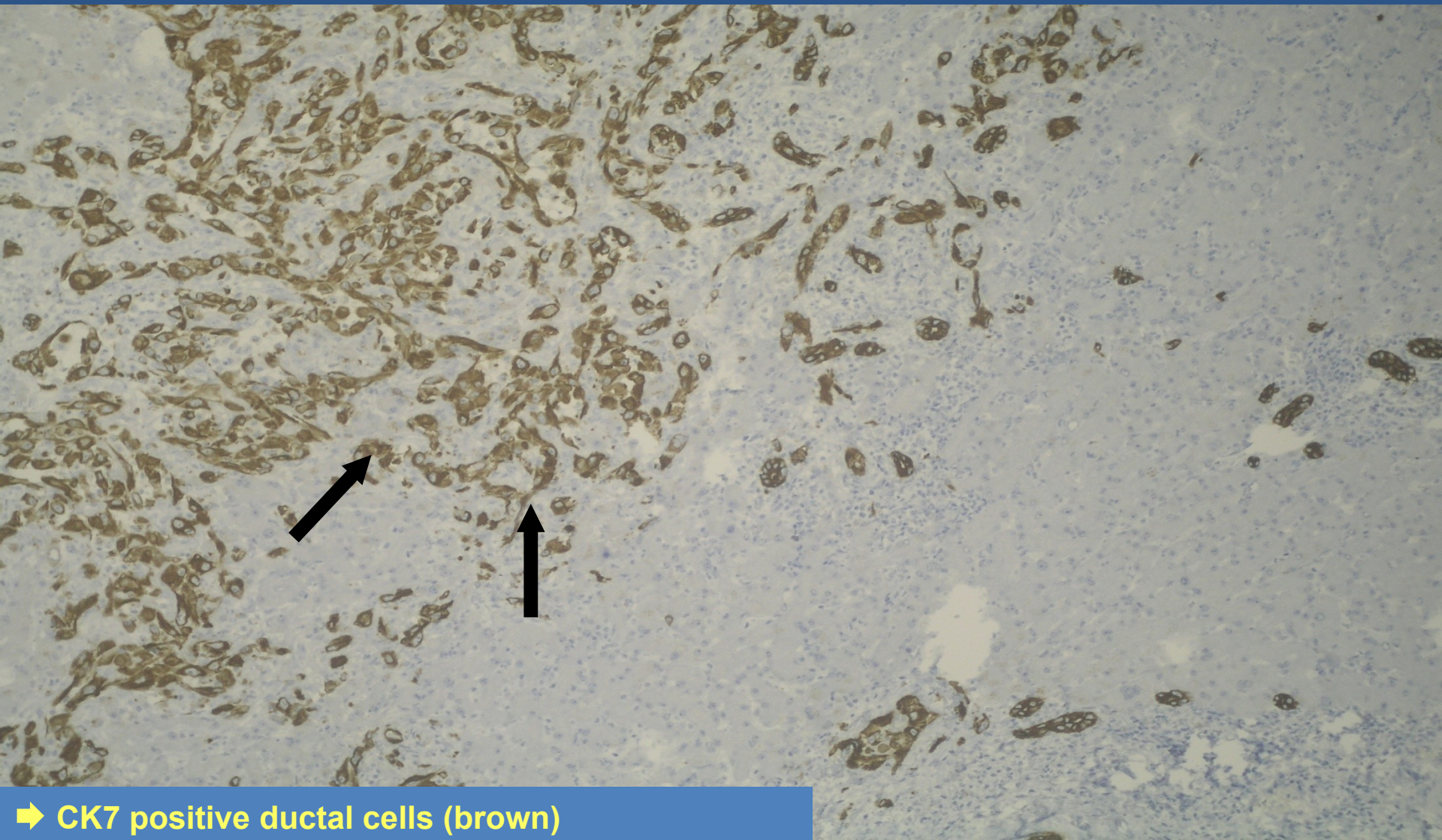
- From intrahepatic biliary ducts
- ↑ risk in PSC, HCV cirrhosis, …
- mucin secterion, no bilirubin pigment
- irregular ducts, strands of cells
- diff. dg. x metastatic or direct spread – gallbladder, pancreas, colorectal ca
- mostly bad prognosis

Cholangiocarcinoma



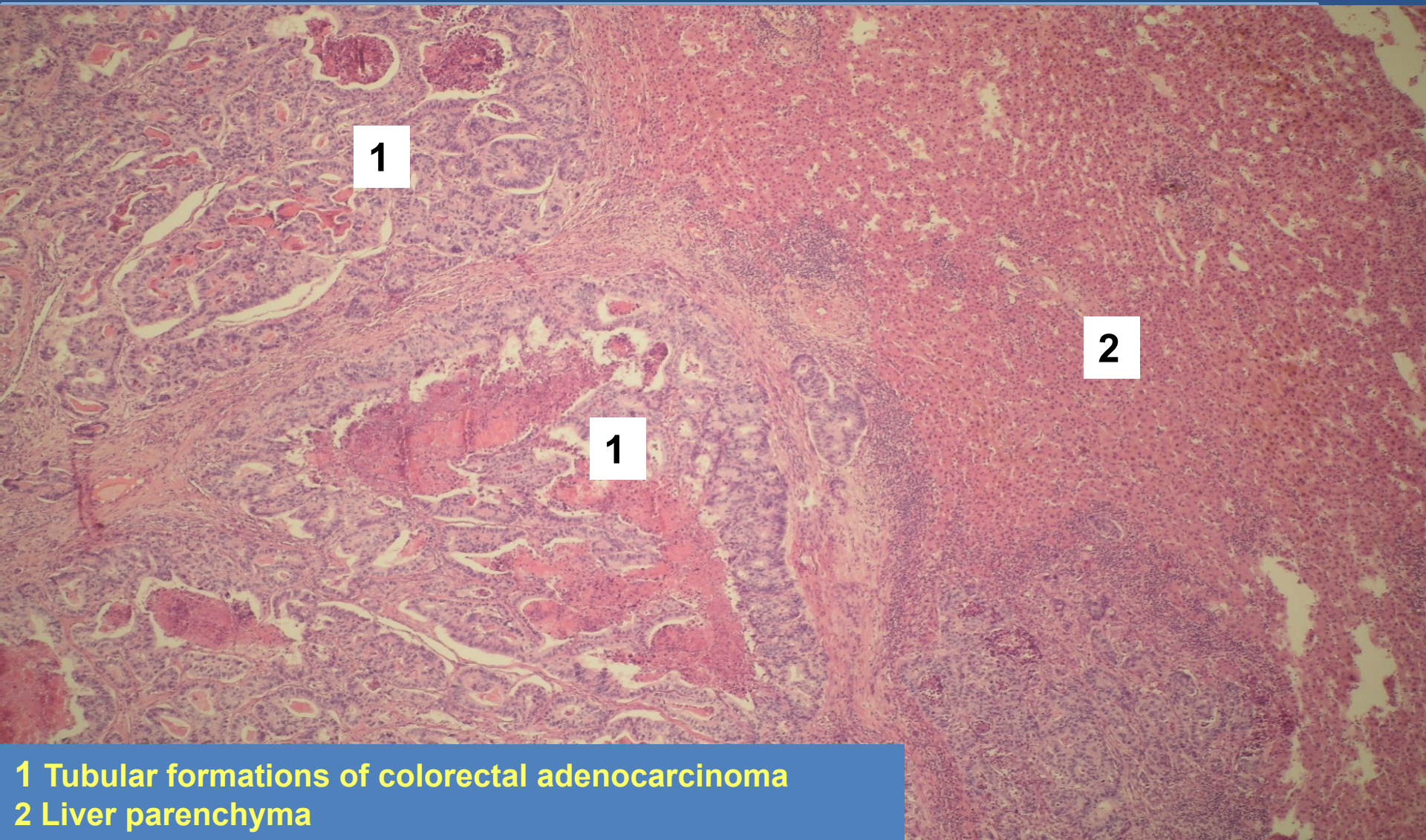
1 Cholangiocarcinoma
2 Liver parenchyma

Cholangiocarcinoma
(IHC CK7)



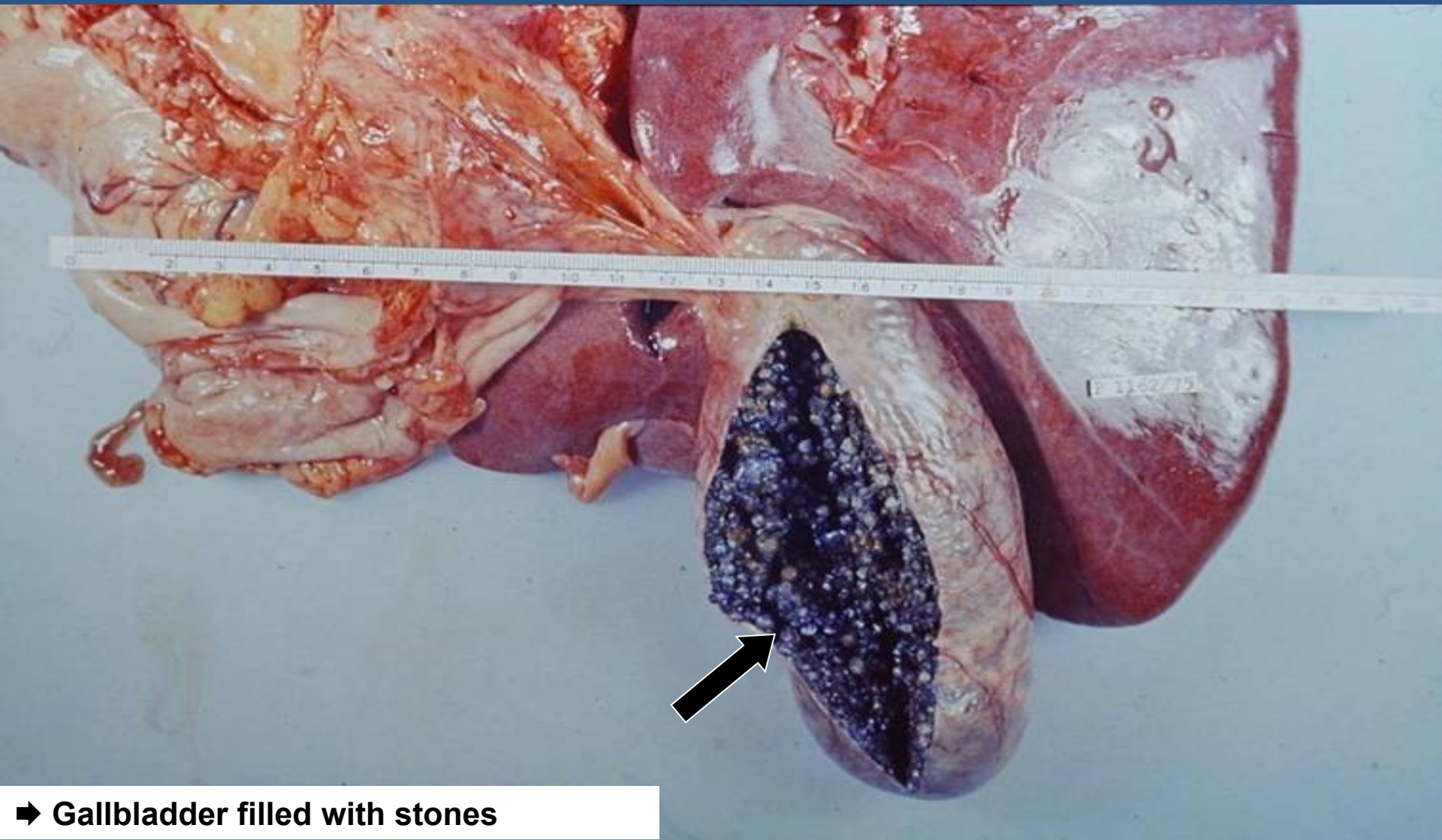
➡ CK7 positive ductal cells (brown)

Colorectal ca metastasis



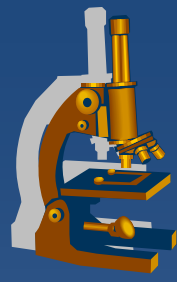
1 Tubular formations of colorectal adenocarcinoma
2 Liver parenchyma

Cholecystolithiasis



➡ Gallbladder filled with stones

Cholecystitis

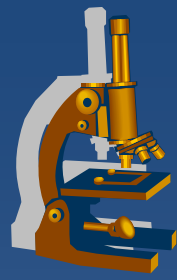


- **Acute calculous**
  - ⇨ ***Obstruction of GB neck or cystic duct***
  - ⇨ ***Local pain radiating to right shoulder***
  - ⇨ ***Fever, nausea, leukocytosis***
  - ⇨ ***Potential surgical emergency***

empyema of gallbladder

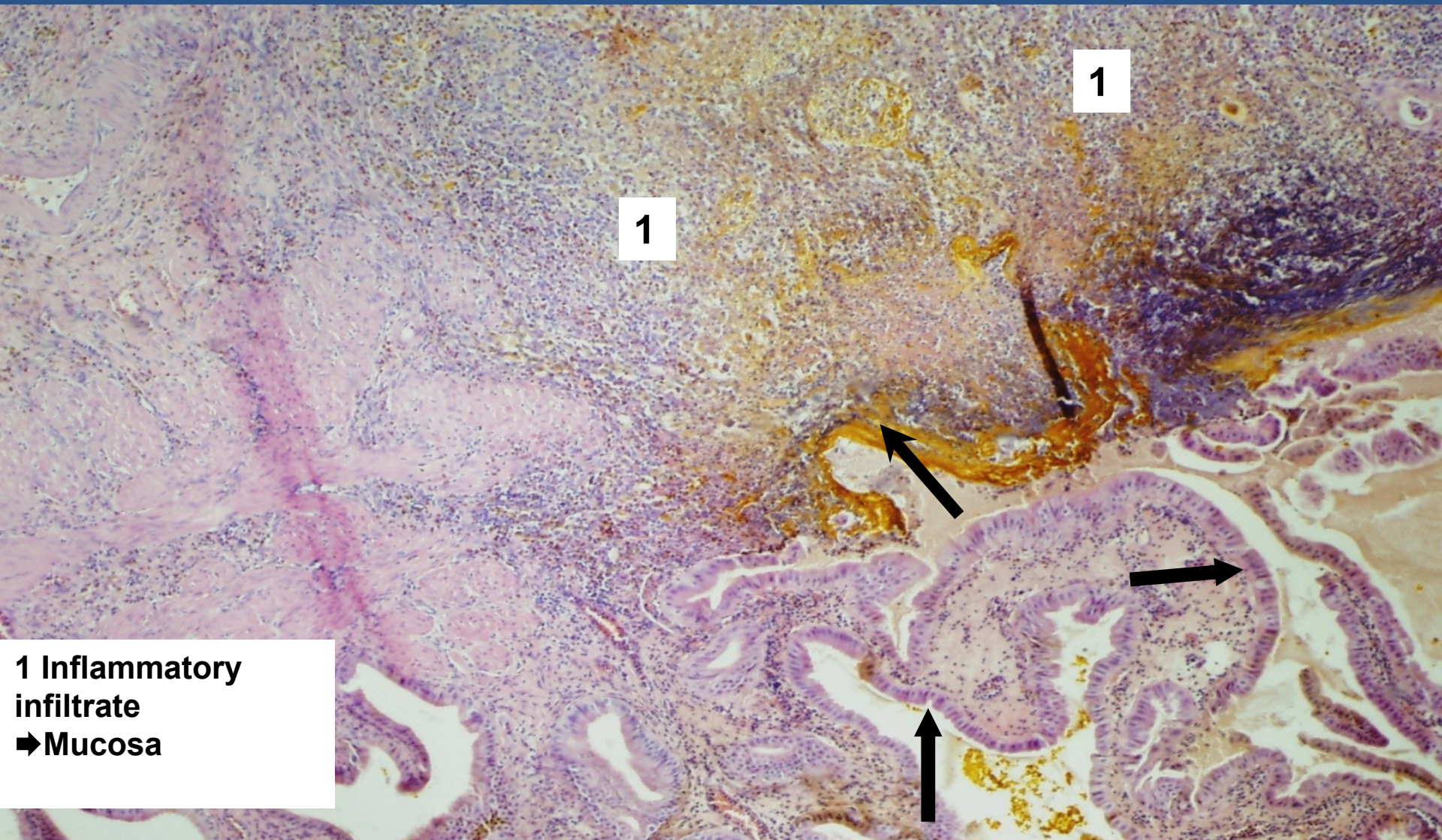
gangrenous cholecystitis

Cholecystitis



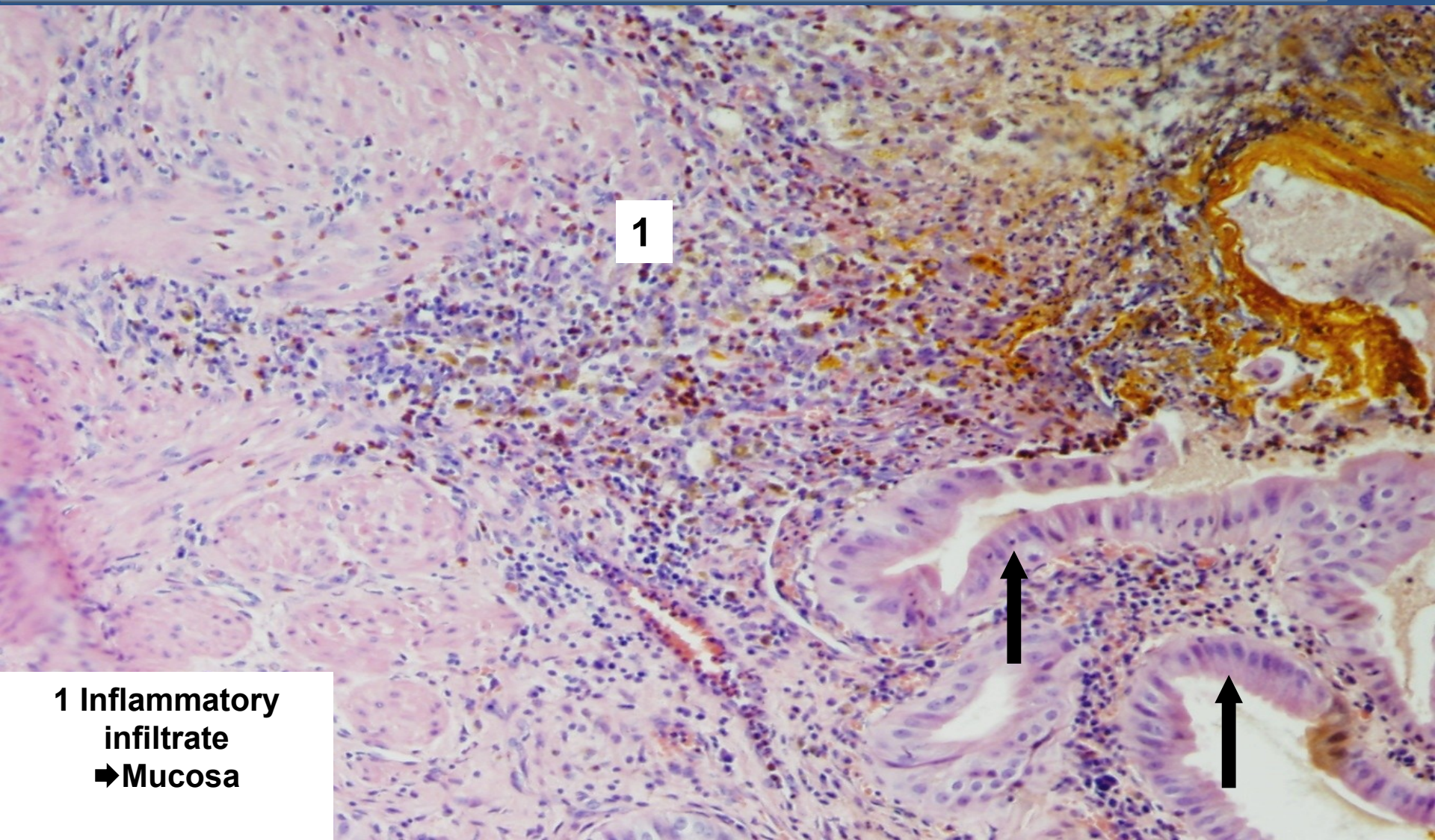
- **Acute acalculous**
  - ⇨ *less common, ischemic (postoperative, trauma, burns, sepsis,…)*
- Chronic
  - ⇨ *Recurrent attacks of pain*
  - ⇨ *Nausea and vomiting*
  - ⇨ *Associated with fatty meals*

Cholecystitis



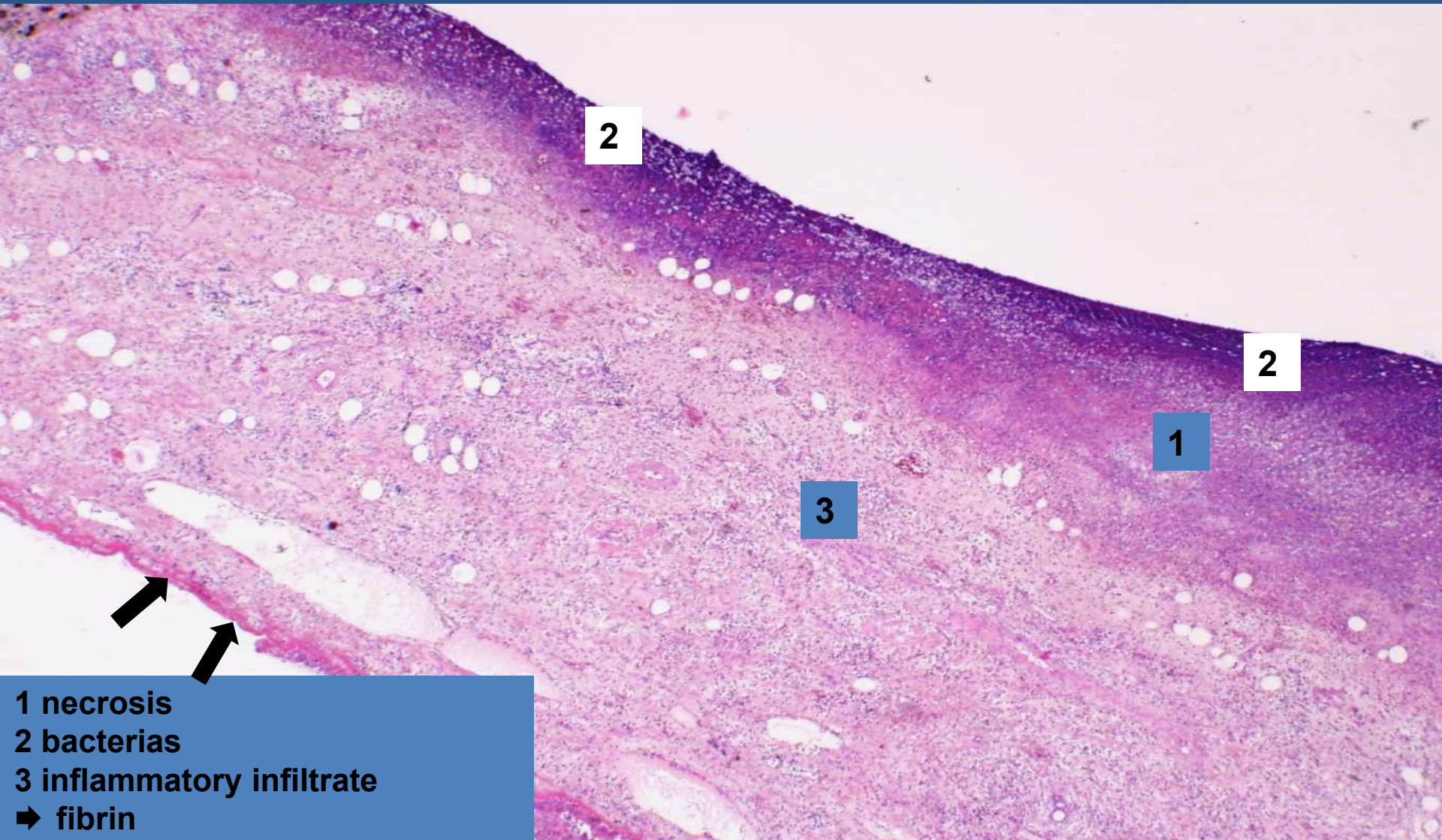
1 Inflammatory infiltrate
➡Mucosa

Cholecystitis



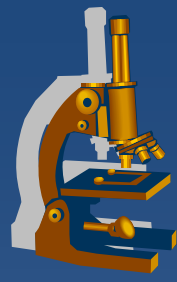
1 Inflammatory infiltrate
➡Mucosa

Gangrenous cholecystitis



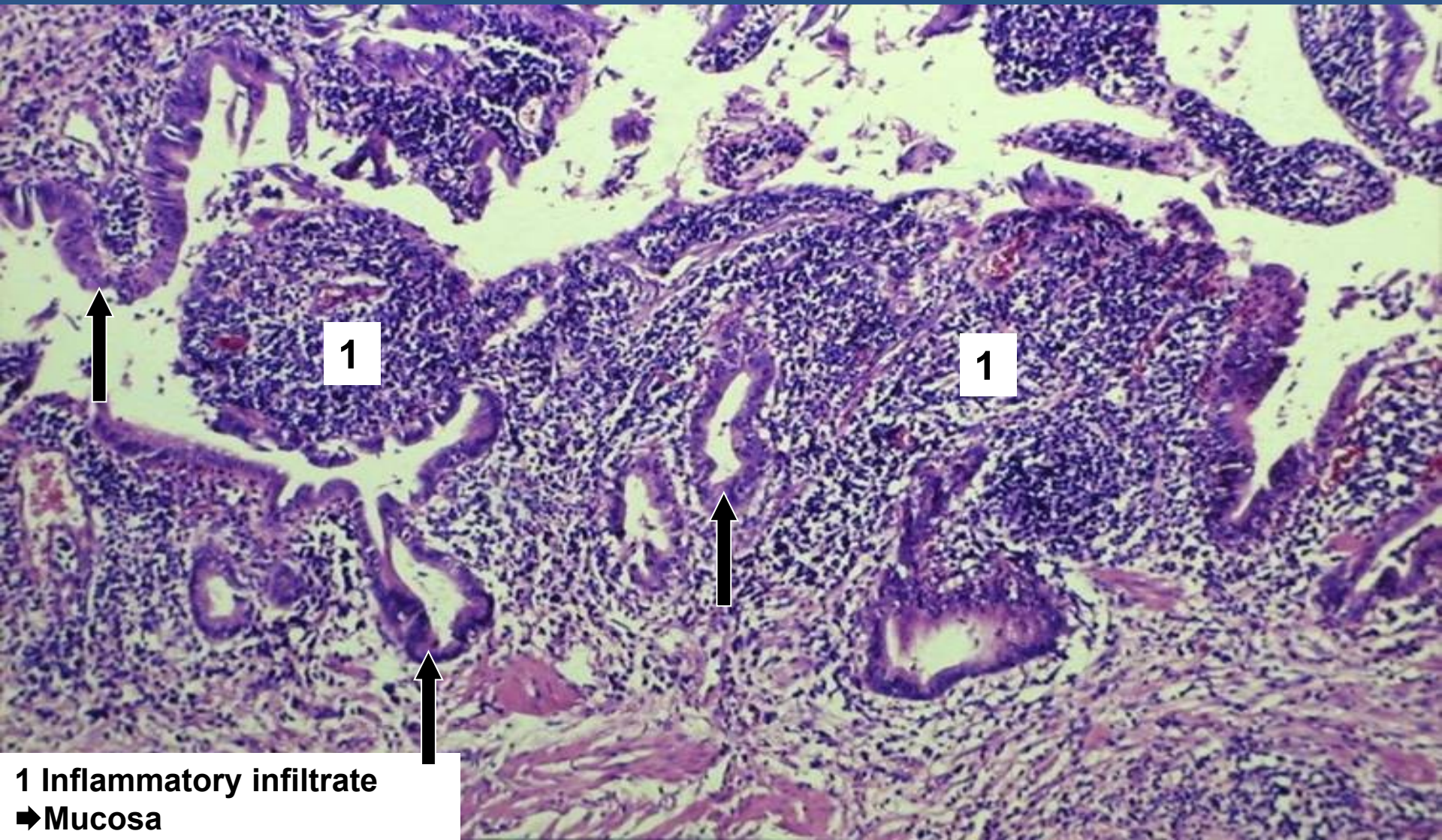
1 necrosis
2 bacterias
3 inflammatory infiltrate
➡ fibrin

Chronic cholecystitis



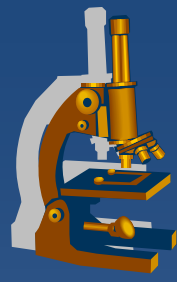
- Fibroproduction
  - ⇨ ***thickening of the wall, adhesion, diff. dg. x ca***
- Chronic inflammation
- Reactive epithelial atypias and metaplasia
  Possible dysplasia
  - ⇨ ↑ ***ca risk***
- Dystrophic calcification
- Gallbladder hydrops

Chronic cholecystitis



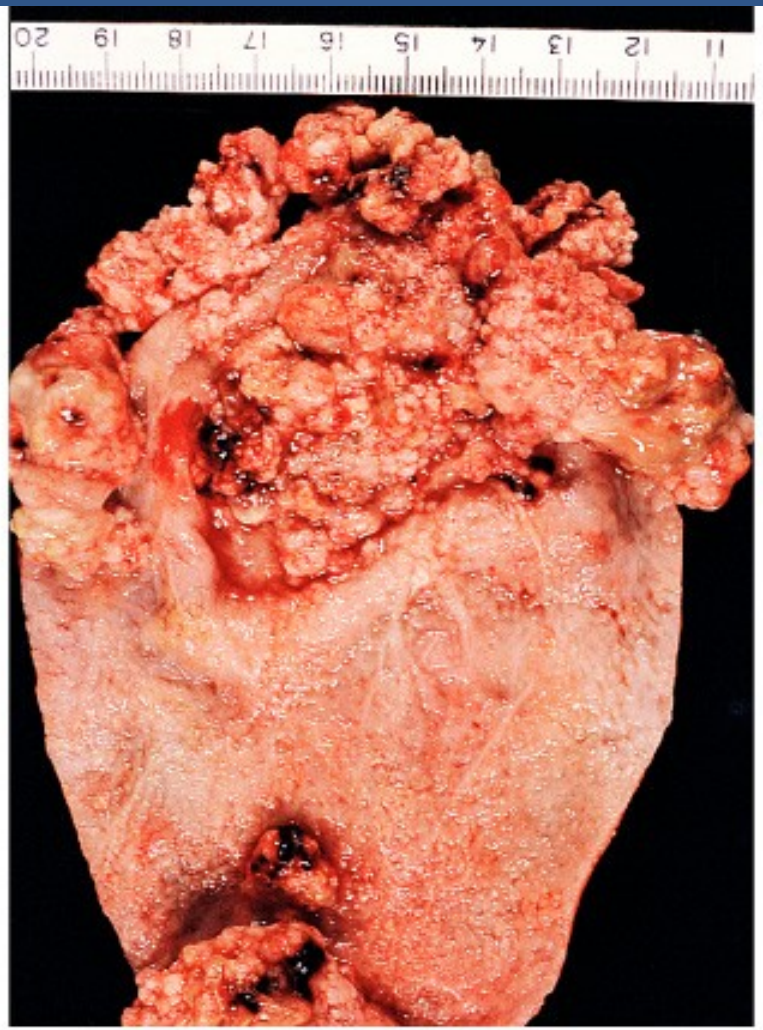
1 Inflammatory infiltrate
➡Mucosa

Gallbladder carcinoma



- Seventh decade
- F>M
- Discovered at late stage, usually accidental
- Adenocarcinoma, other types
- Local extension into liver, cystic duct, portal LN
- Mean 5 yrs survival 1%
  - ⇨ ***better prognosis if accidental finding in CHCE in incipient stage***

Gallbladder carcinoma



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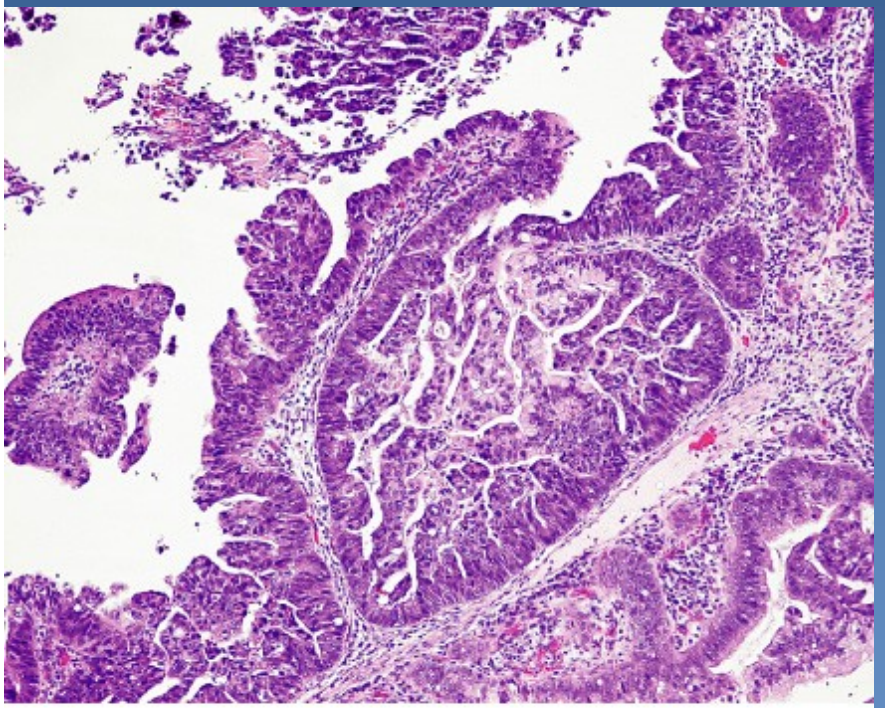

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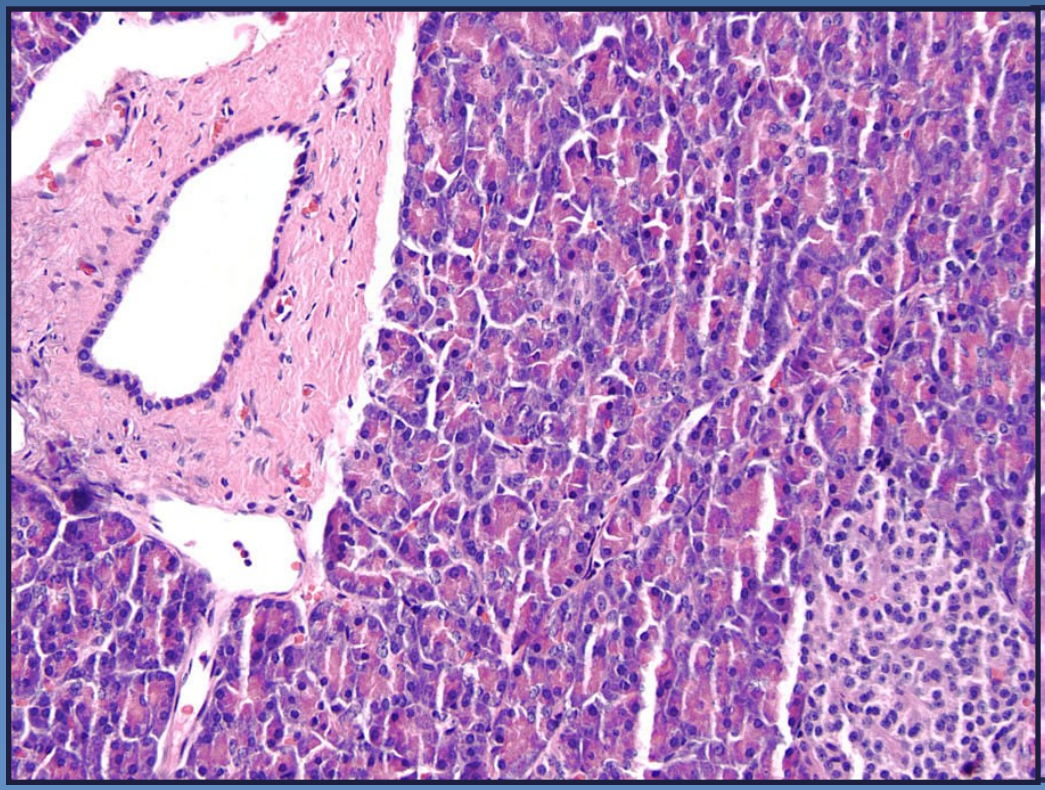
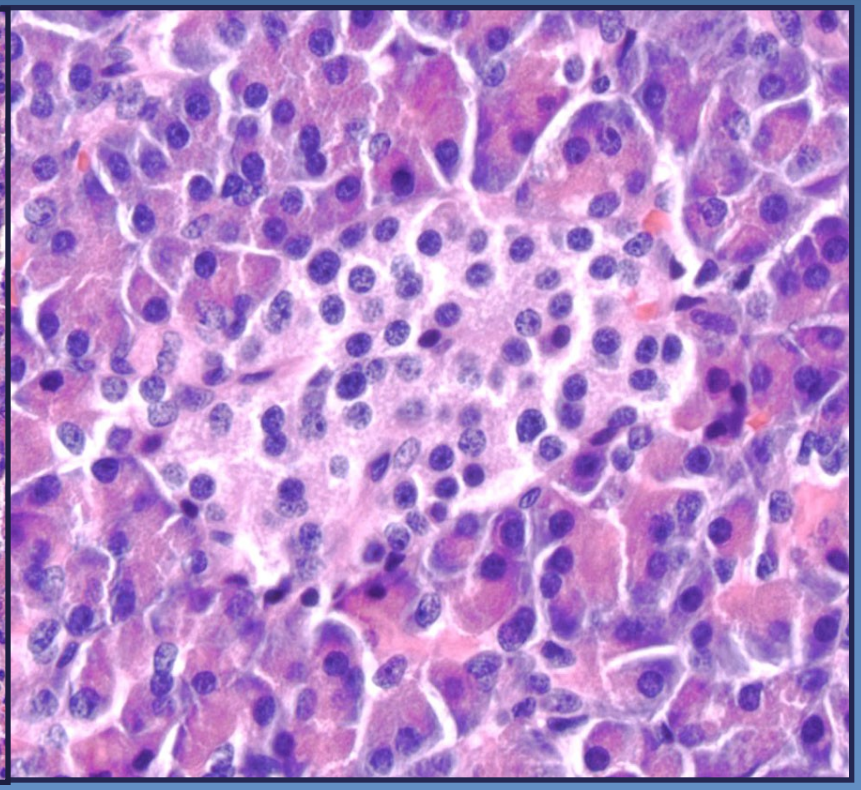
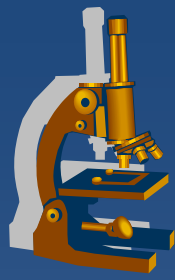
Pathology of pancreas

- Exocrine
- Endocrine



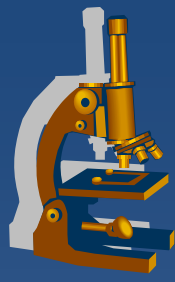


Acute pancreatitis



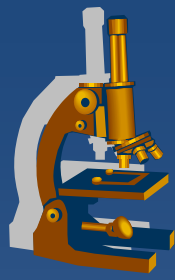
- etiological factors:
  - ⇨ ***Metabolic***
    - Alcohol
    - Hyperlipoproteinemia (type I and V)
    - Hypercalcemia (hyperparatyreoidismus)
    - Drugs
    - Genetics
  - ⇨ ***Mechanic***
    - Obstruction (lithiasis), spasms
    - Iatrogenic damage (ERCP, perioperative)
  - ⇨ ***Vascular, ischemic***
    - Shock, trombosis, embolia
    - Vasculitis – polyarteriitis nodosa
  - ⇨ ***Infections***
    - mumps
    - Coxsackieviruses
    - Mycoplasma pneumoniae

Acute pancreatitis



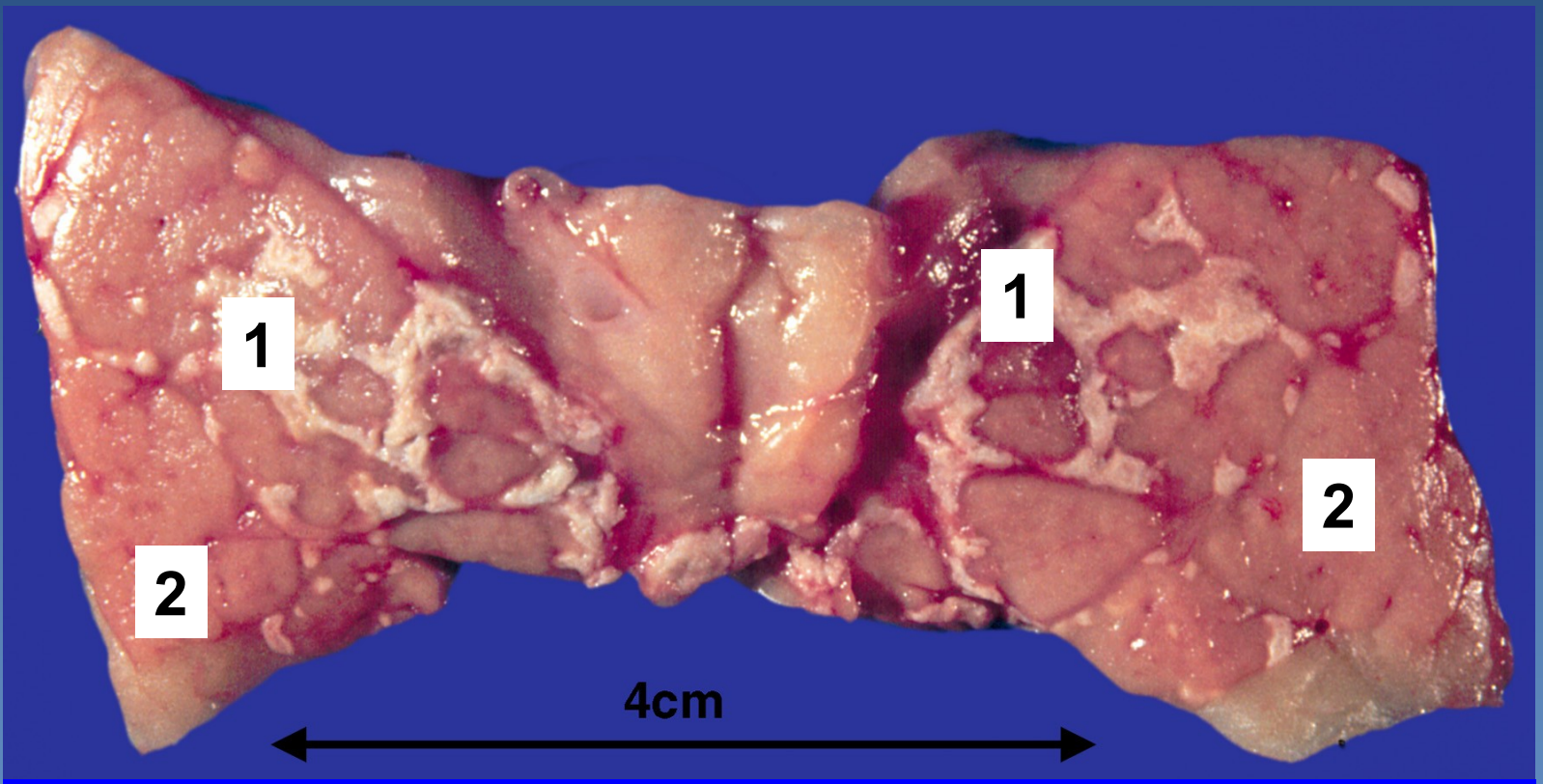
- clinical features:
  - ⇨ ***severe abdominal (epigastric) pain, nausea and vomitting – acute abdomen***
  - ⇨ ***DIC***
  - ⇨ ***shock, multiorgan failure, ARDS, renal failure***
  - ⇨ ***elevation of serum amylases, lipases, hypocalcaemia***
  - ⇨ ***infective complications***
  - ⇨ ***pseudocysts***

Acute pancreatitis



- Morphology:
  - ***serous and haemorrhagic exsudate in the peritoneal cavity***
  - ***swollen pancreas***
  - ***necroses, colliquation, haemorrhages***
  - ***Balzer´s fat necroses***

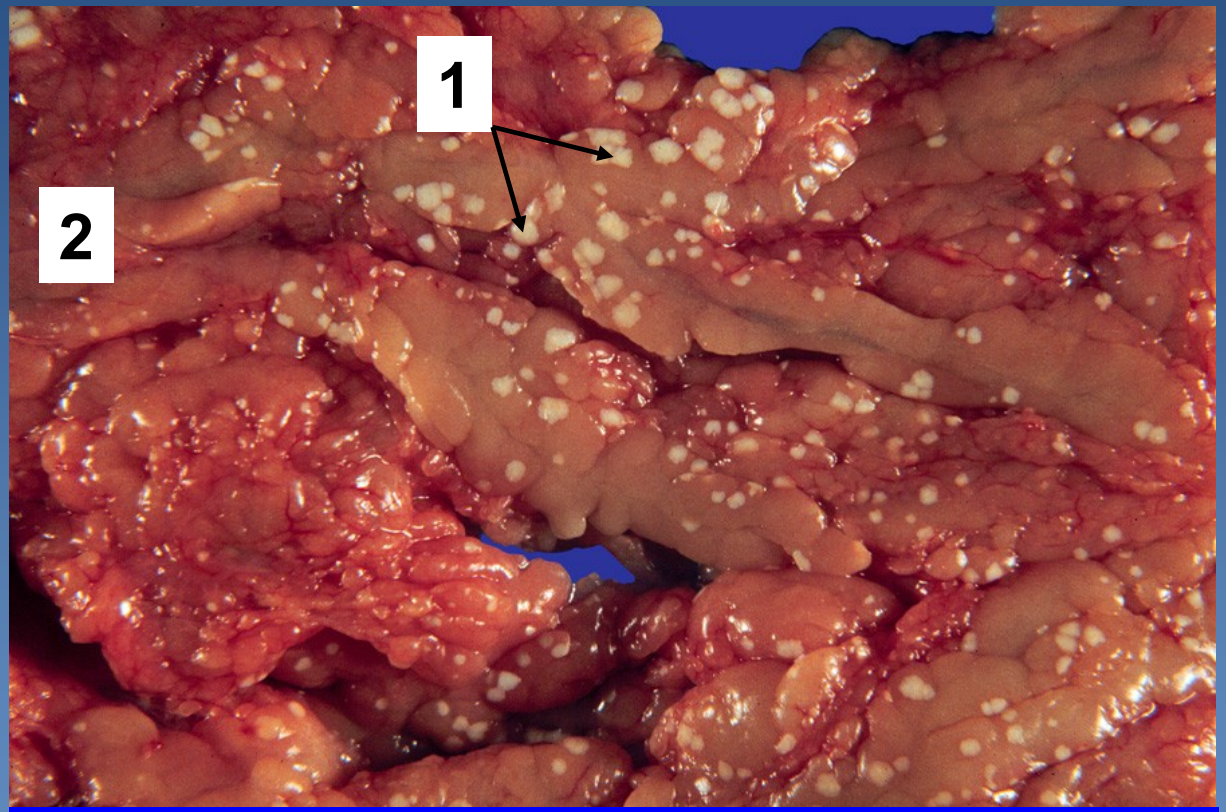
Acute pancreatitis



1. Fatty necroses with haemorrhagic rim

2. Adjacent pancreatic parenchyma

Balzer´s fat necroses

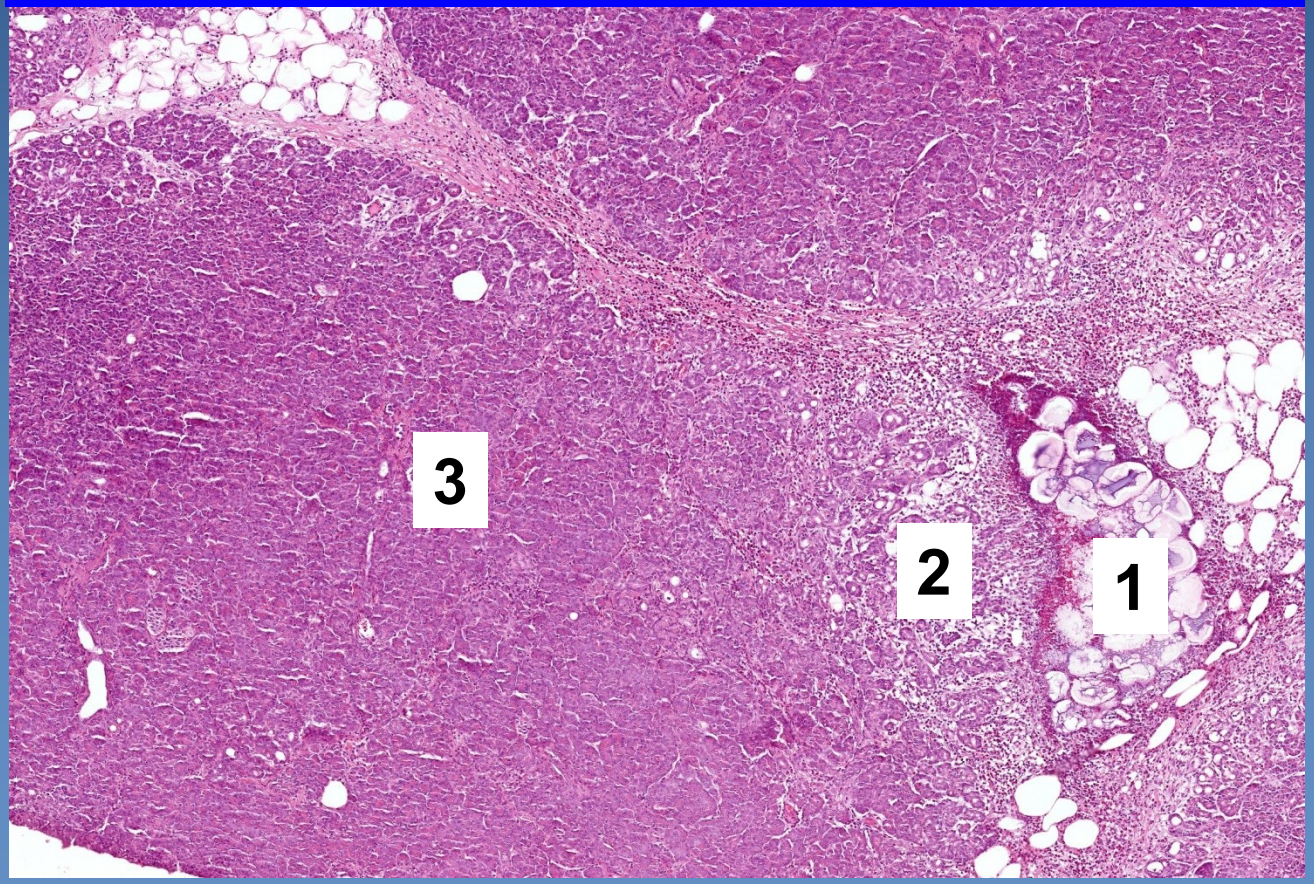


1. Balzer´s fat necrosis in the omentum

2. Surrounding fatty tissue

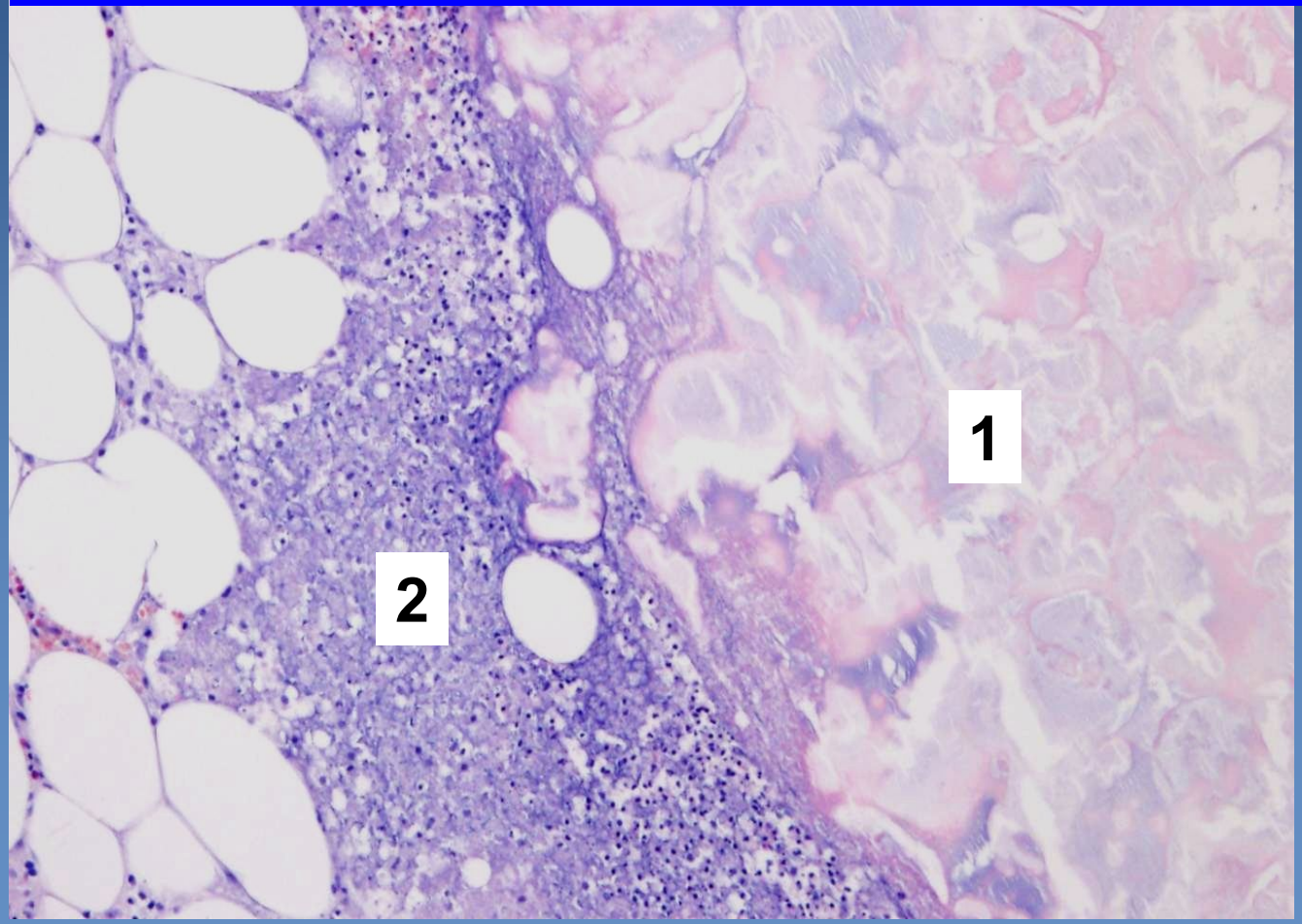
Acute pancreatitis

1. *Necrosis*
2. *Demarcation/leucocytes*
3. *Adjacent pancreatic tissue*

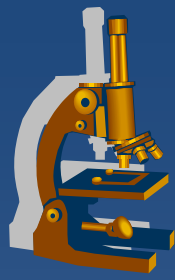


Acute pancreatitis

1. Necrosis
2. Demarcation/leucocytes

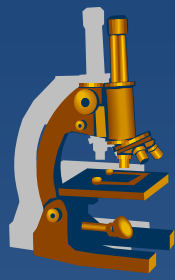


Chronic pancreatitis



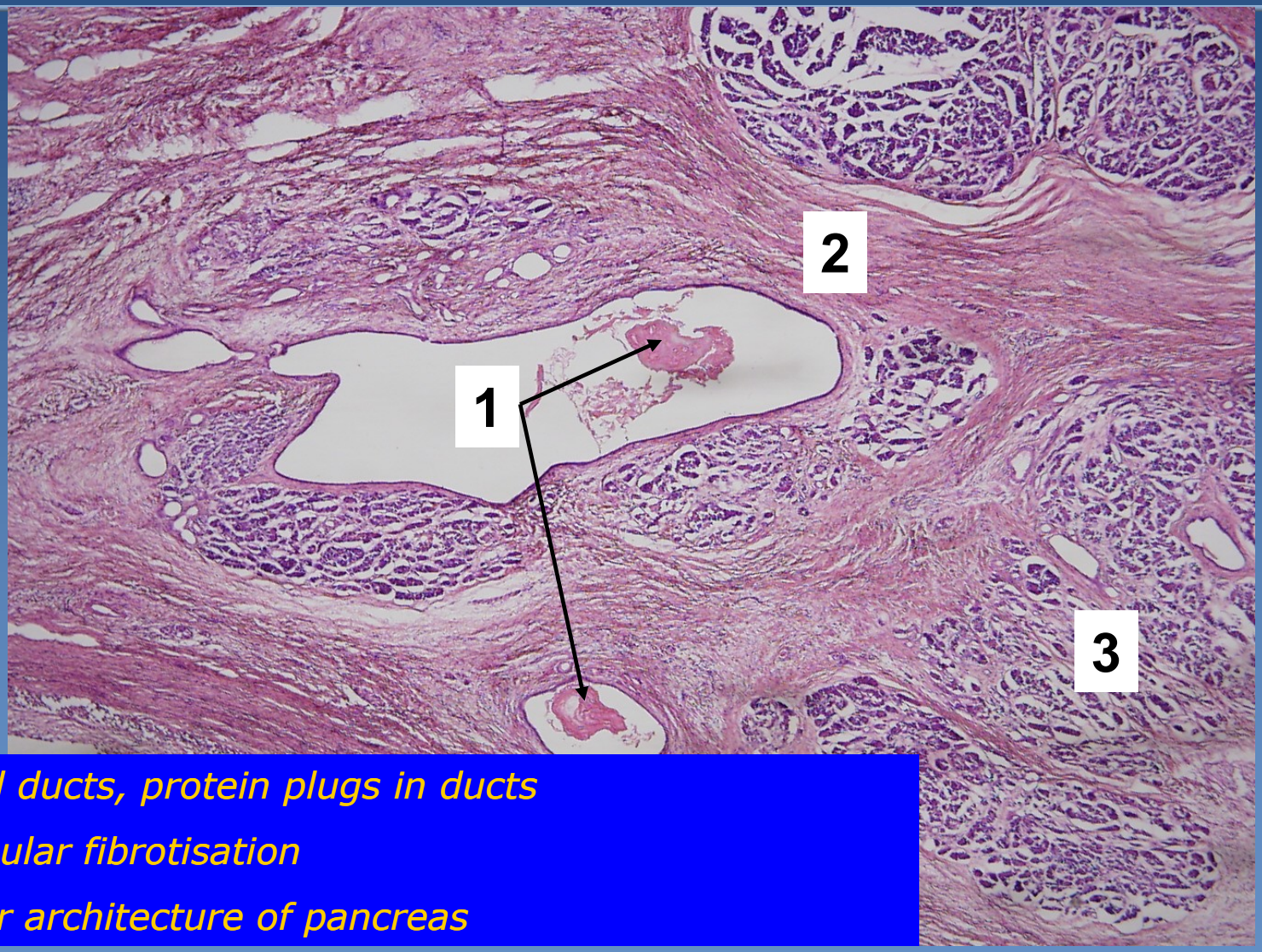
- TIGAR-O classification (2001):
  - ⇨ ***T**oxic/metabolic (alcohol, uremia, drugs)*
  - ⇨ ***I**diopathic*
  - ⇨ ***G**enetic (hereditary)*
  - ⇨ ***A**utoimmune*
  - ⇨ ***R**ecurrent acute*
  - ⇨ ***O**bstructive*

Alcoholic pancreatitis



- histologic features:
  - *chronic calcifying pancreatitis*
  - *fibrotisation of pancreas, mostly perilobular*
  - *autodigestive necroses and postmalatic pseudocysts*
  - *dilated and irregular ducts*
  - *protein plugs in ducts, calcifications*
  - *hyperplasia and metaplasia of ductal epithelium*
  - *increased risk of pancreatic cancer in chronic pancreatitis*

Alcoholic pancreatitis

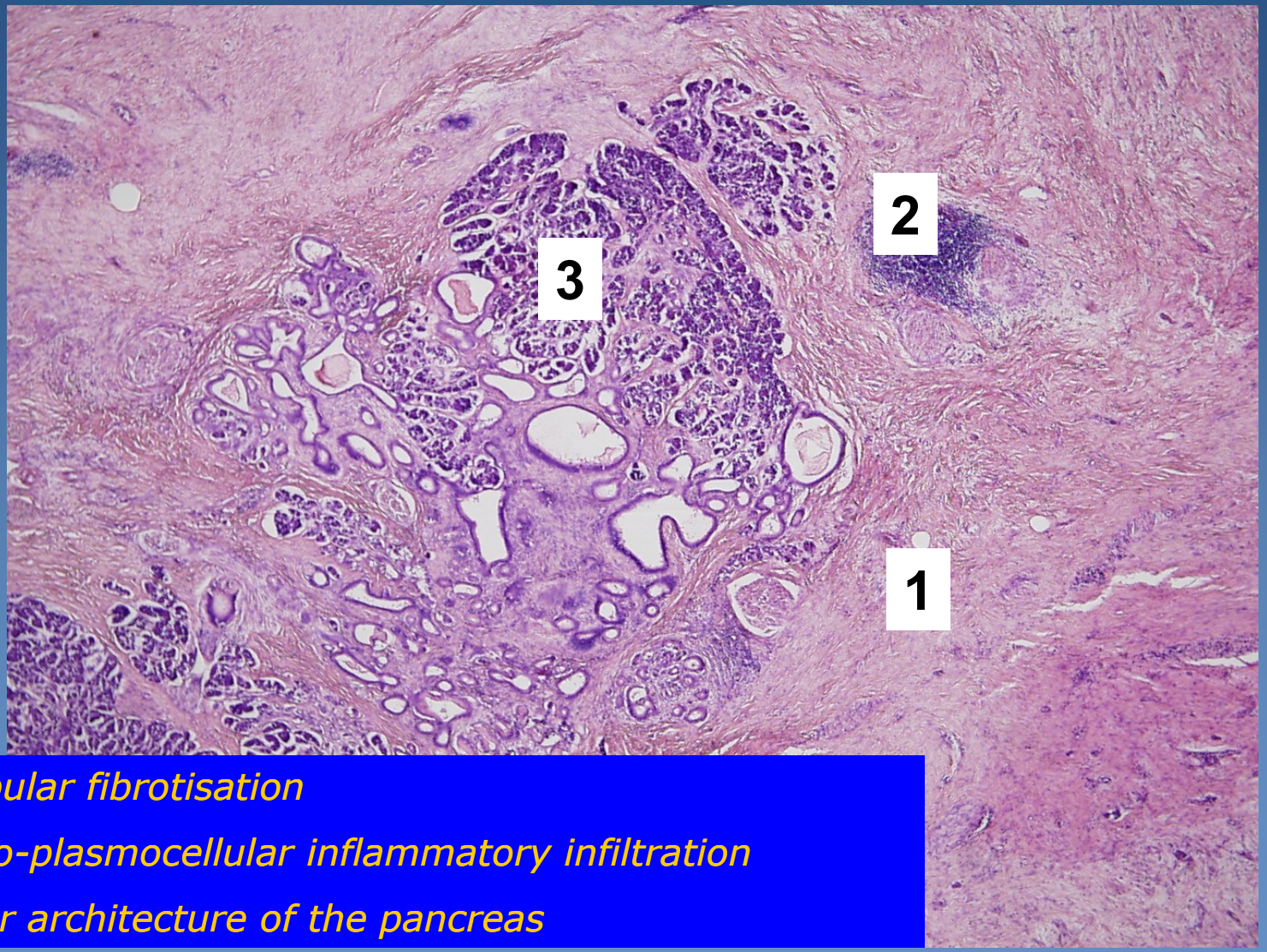


1. Dilated ducts, protein plugs in ducts

2. Perilobular fibrotisation

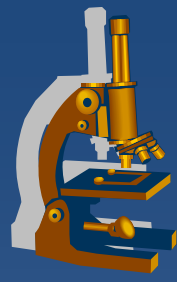
3. Lobular architecture of pancreas

Alcoholic pancreatitis



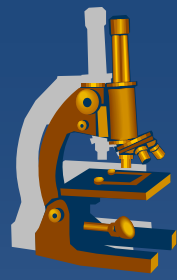
1. Perilobular fibrotisation
2. lympho-plasmocellular inflammatory infiltration
3. Lobular architecture of the pancreas

Autoimmune pancreatitis



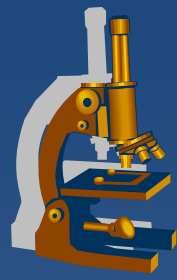
- **adults affected**
  - ⇨ *rare in 2nd and 3rd decade*
- **M>F**
- **clinical and radiological features mimic pancreatic cancer**
- **associated with other autoimmune disorders**

Obstructive pancreatitis



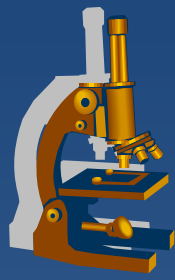
- Obstructive pancreatitis – histological features:
  - ⇨ *diffuse perilobular and intralobular fibrosis*
  - ⇨ *dilated ducts without obstruction, irregularities or signs of destruction of ductal epithelium*
  - ⇨ *no protein plugs or calcifications in ducts*
  - ⇨ *hyperplasia of ductal epithelium*
  - ⇨ *necroses and pseudocysts absent*

Tumours of the pancreas



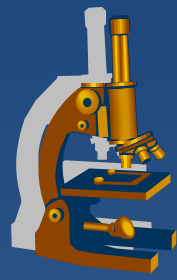
- epithelial
- non-epithelial
- secondary - metastatic

Epithelial tumours



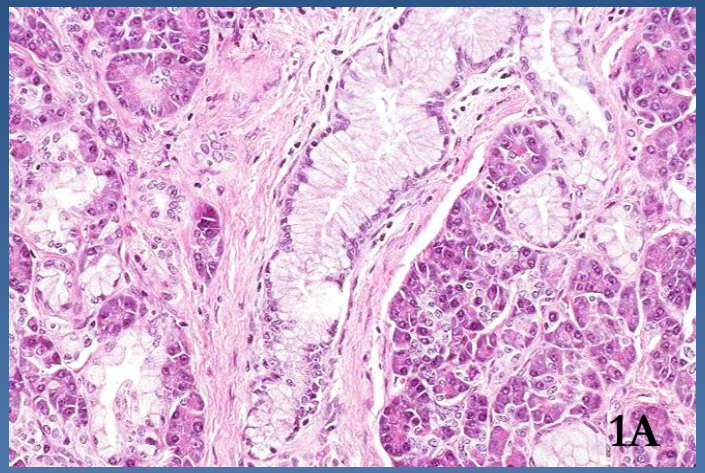
- *classified according to biological behavior:*
  - **benign:**
    - serous cystadenoma
    - acinar cell cystadenoma
  - **Premalignant lesion:**
    - pancreatic intraepithelial neoplasia grade 3 (PanIN-3)
    - mucinous cystic neoplasm with low- or intermediate grade dysplasia
    - mucinous cystic neoplasm with high grade dysplasia
    - intraductal papillary mucinous neoplasm with low- or intermediate grade dysplasia
    - intraductal papillary mucinous neoplasm with high grade dysplasia
    - intraductal tubulopapillary neoplasm
  - **malignant:**
    - **Ductal adenocarcinoma !! (PDAC)**
    - mucinous cystic neoplasm associated with invasive carcinoma
    - intraductal papillary mucinous neoplasm associated with invasive carcinoma
    - acinar cell carcinoma
    - acinar cell cystadenocarcinoma
    - serous cystadenocarcinoma
    - pancreatoblastoma
    - solid-pseudopapillary neoplasm
    - mixed acinar-ductal carcinoma
    - mixed acinar-neuroendocrine carcinoma
    - mixed acinar-neuroendocrine-ductal carcinoma
    - mixed neuroendocrine-ductal carcinoma

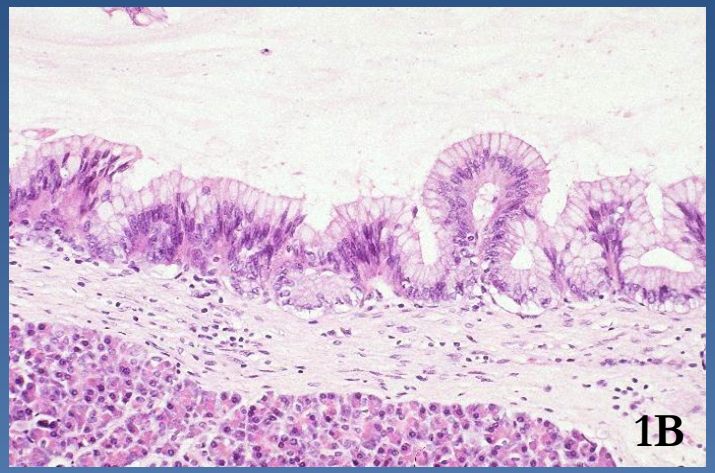
Precursor lesions of invasive pancreatic cancer

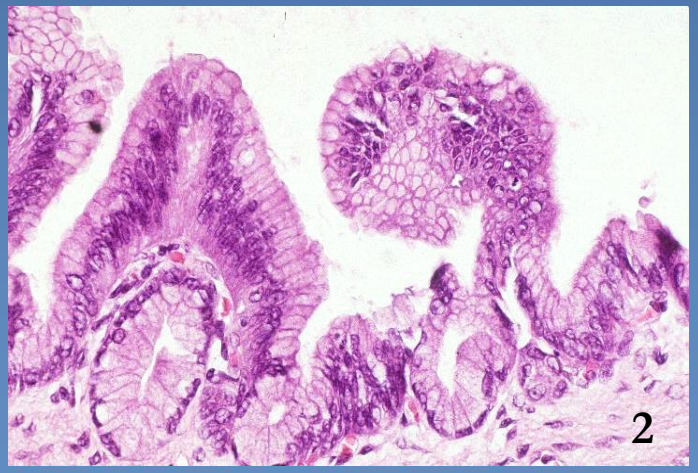


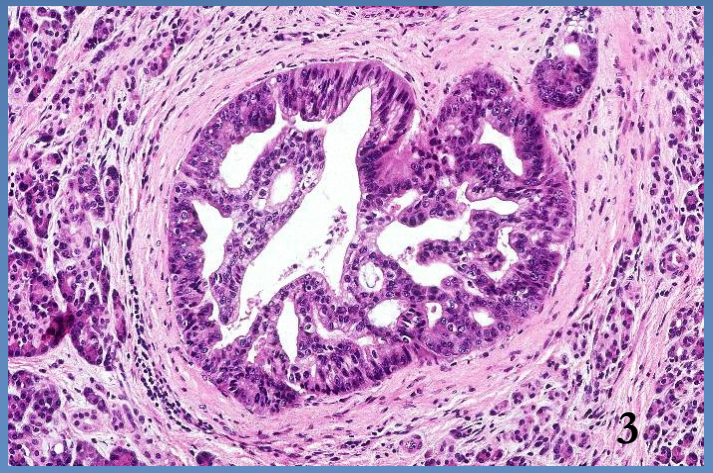
- **Pancreatic intraepithelial neoplasia (PanIN)**
  - ⇨ ***microscopic precursor of PDAC***
- Mucinous cystic neoplasm (MCN)
- Intraductal papillary mucinous neoplasm (IPMN)
  - ⇨ ***gross cystic precursor lesions***

Pancreatic intraepithelial neoplasia (PanIN)

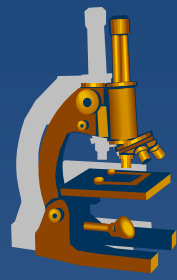






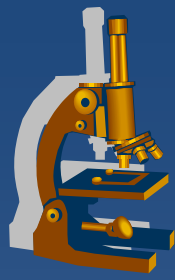


Ductal adenocarcinoma



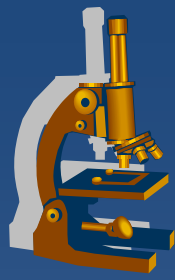
- *ductal adenocarcinoma* - 85-90% of all pancreatic neoplasias
- 5th most frequent cancer-related death
  - ⇨ *in GIT 2nd after colorectal cancer*
- risk factors:
  - ⇨ *higher age*
  - ⇨ *genetic factors*
  - ⇨ *environemntal factors:*
    - **smoking, high fat diet, obesity and low physical activity, chemicals**
  - ⇨ *chronic pancreatitis (both hereditary and sporadic); (CP)*
  - ⇨ *diabetes mellitus*
  - ⇨ *alcohol (indirectly, induces CP)*

Ductal adenocarcinoma



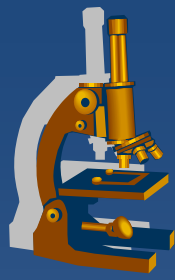
- Clinical features:
  - ***60-70 % in the pancreatic head***
  - ***abdominal and back pain***
  - ***weight loss***
  - ***icterus, pruritus, diabetes mellitus***
  - ***migratory thrombophlebitis***
  - ***symptoms related to liver metastasis and/or invasion of adjacent organs***

Ductal adenocarcinoma



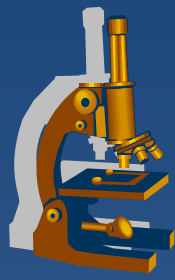
- biologiccal behavior
  - ⇨ ***lymphogennous metastasis (regional lymph nodes)***
  - ⇨ ***haematogennous metastasis (liver, lungs, bones)***
  - ⇨ ***carcinomatosis of peritoneum***
  - ⇨ ***perineural spreading***

Ductal adenocarcinoma



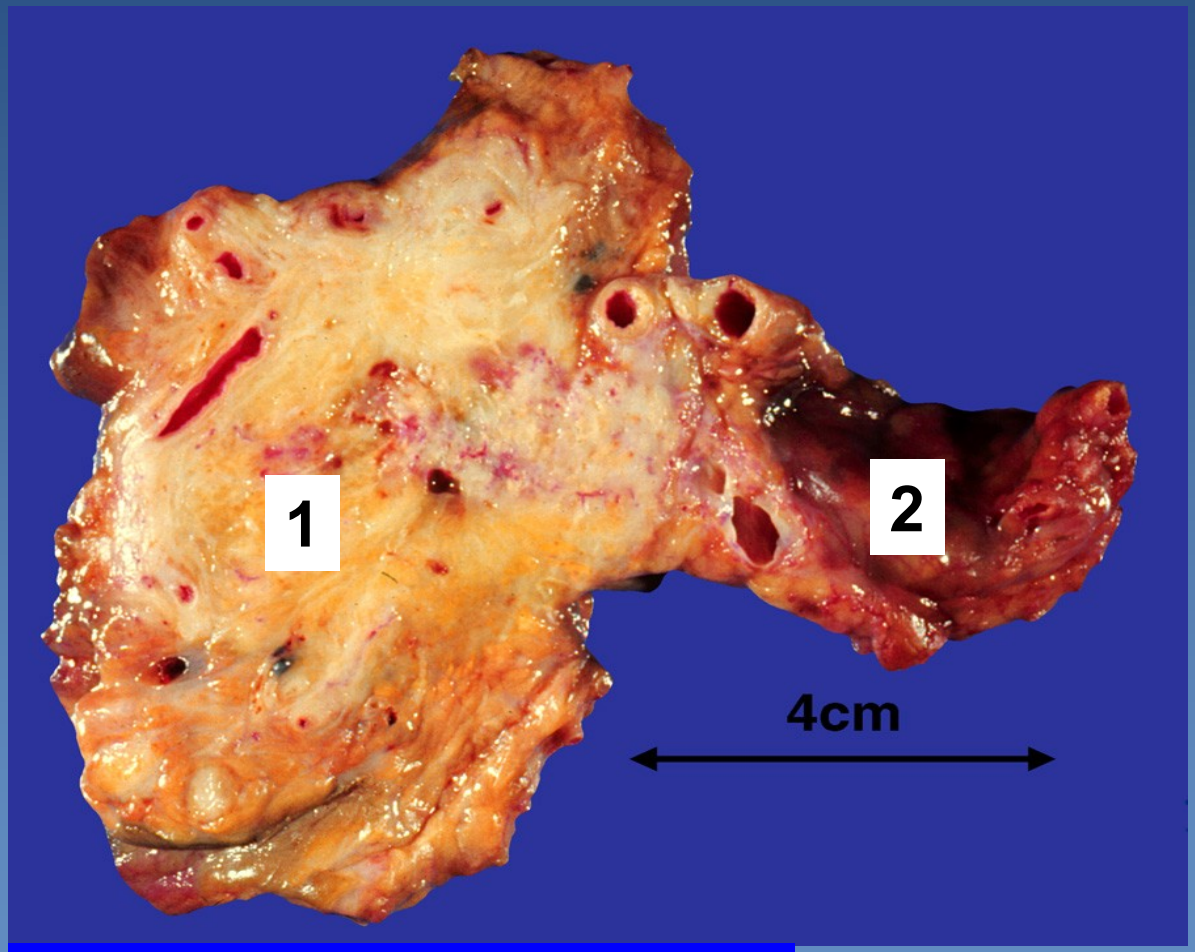
- Gross:
  - ⇨ *usually solid mass in the pancreatic head*
  - ⇨ *mean diameter 2-3 cm*
  - ⇨ *common bile duct and/or main pancreatic duct stenosis*
  - ⇨ *necrosis rare*
  - ⇨ *absence of calcifications and pseudocysts*

Ductal adenocarcinoma



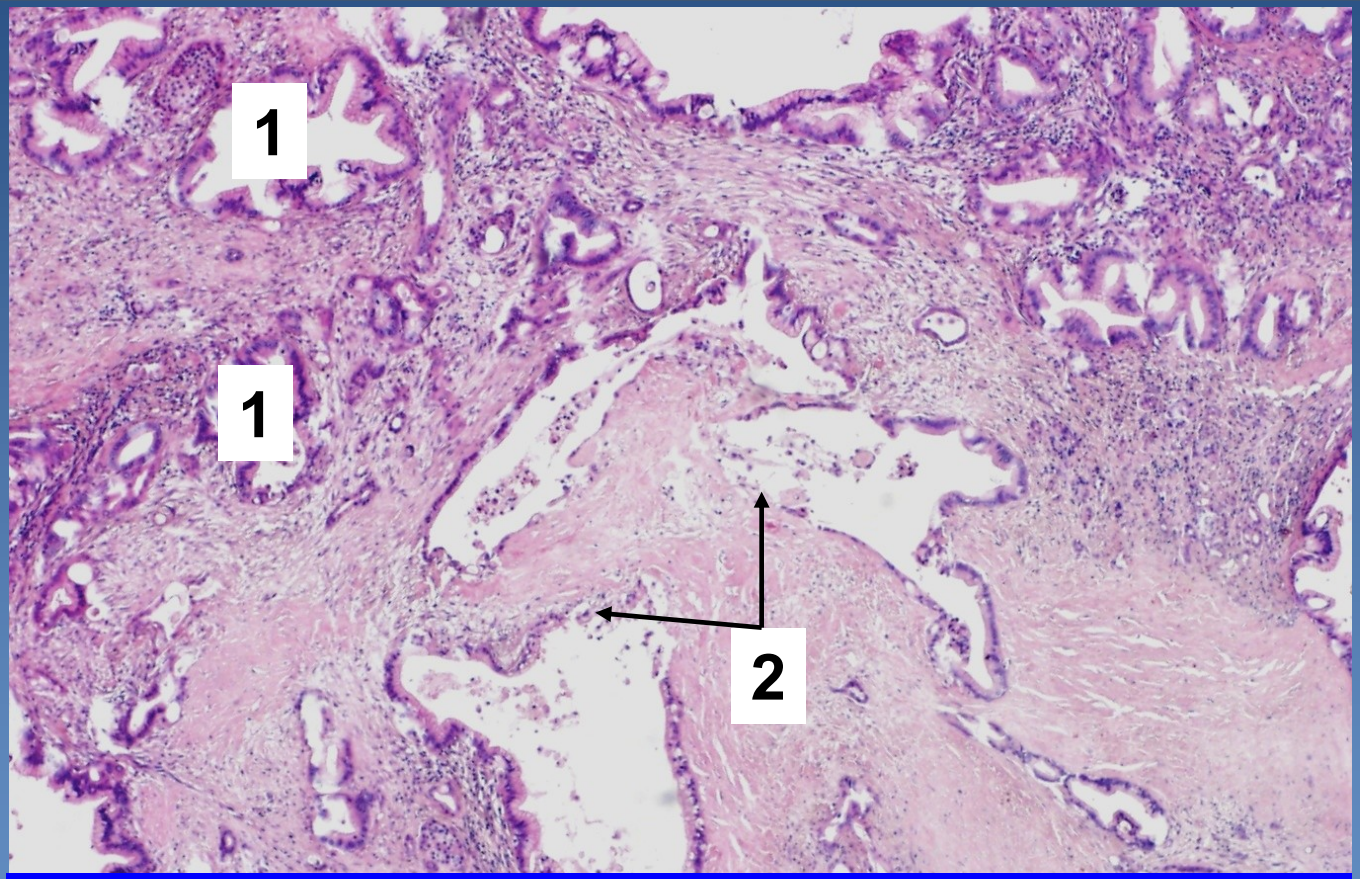
- Micro:
  - ⇨ ***grade of differentiation:***
    - grade 1: well differentiated
      - ductal and tubular formation in desmoplastic stroma, columnar mucin producing cell, distinct small nucleoli, low mitotic activity, low degree of pleomorphism/atypia
    - grade 2: moderately differentiated
      - ductal, tubular, microglandular, cribriform formation, desmoplasia, irregular mucin production, prominent nucleoli, higher pleomorhism
    - grade 3: poorly differentiated
      - irregular glandular structure, solid aggregates, squamoid foci, spindle cells, anaplastic, pleomorphic structures, mitotic activity

Ductal adenocarcinoma in the head of pancreas



1. Carcinoma of pancreatic head
2. Pancreatic body and tail

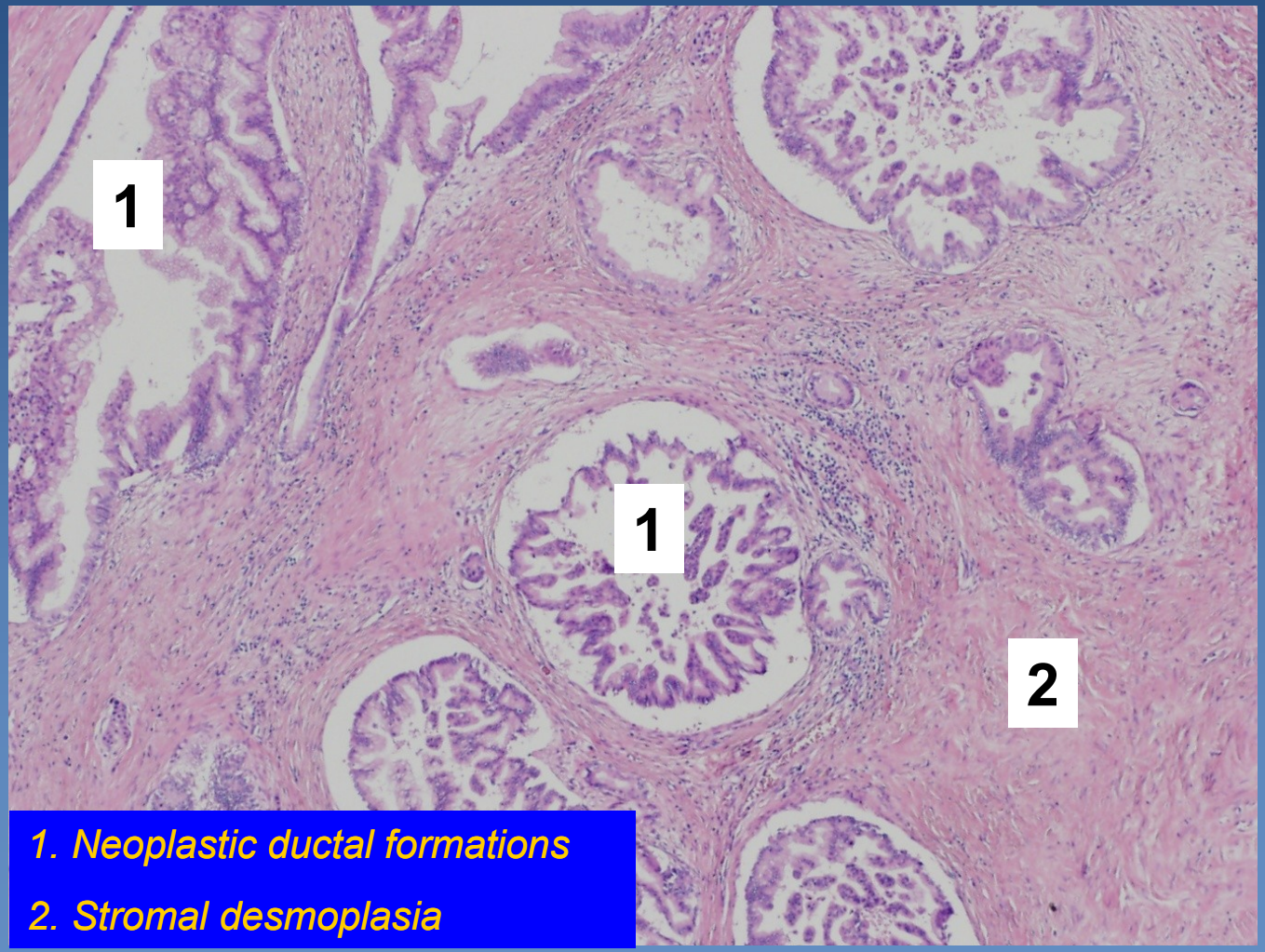
Ductal adenocarcinoma



1. Neoplastic ductal formations

2. Focal duct ruptures with macrophages and detritus intraluminally

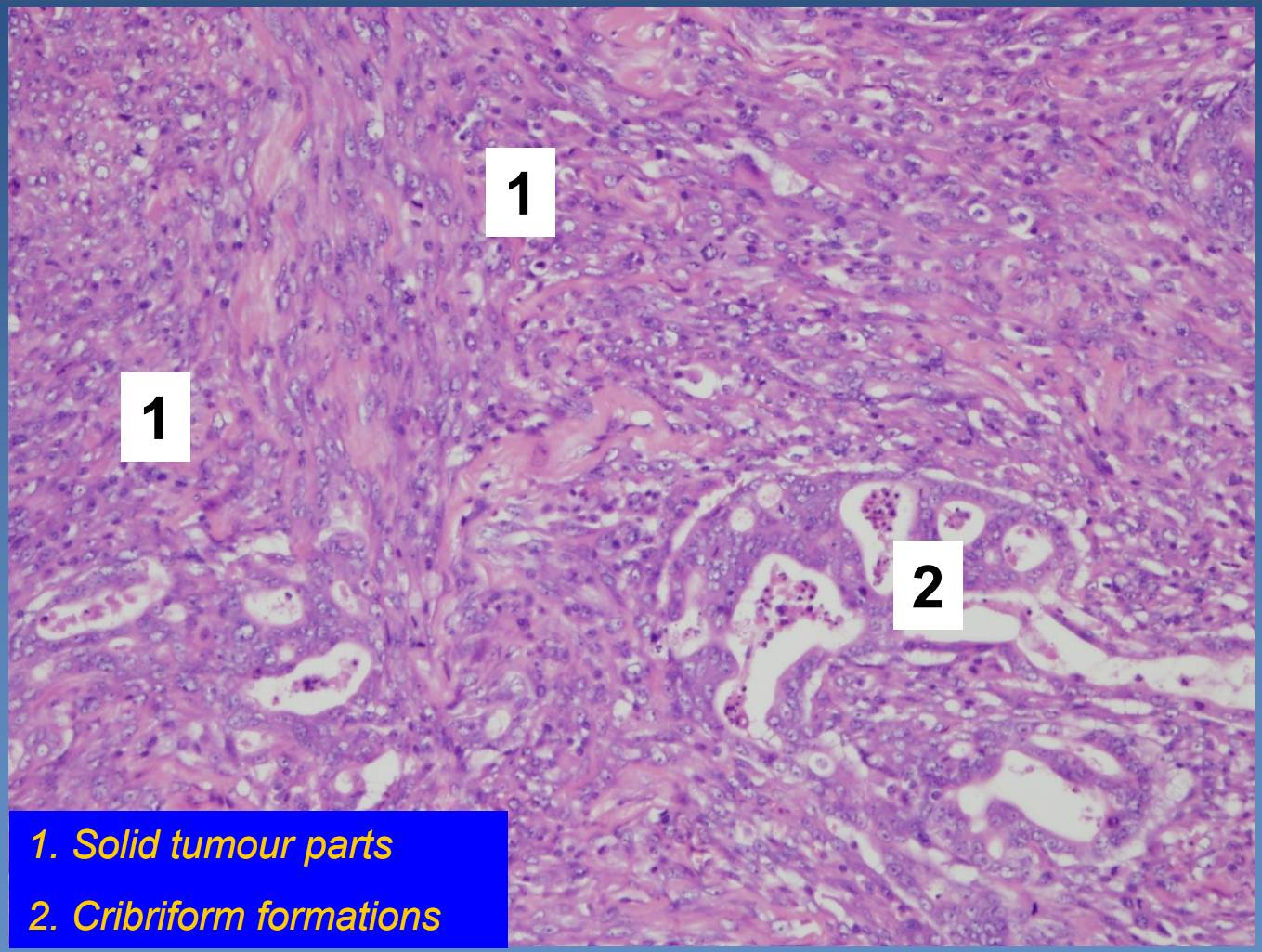
Ductal adenocarcinoma – well differentiated (G1)



1. Neoplastic ductal formations

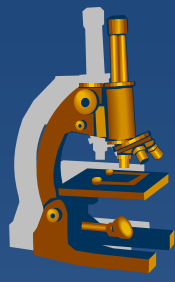
2. Stromal desmoplasia

Ductal adenocarcinoma– poorly differentiated (G3)



1. Solid tumour parts
2. Cribriform formations

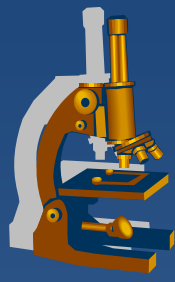
Differential diagnosis of ductal adenocarcinoma and chronic pancreatitis – clinical features



- Adenocarcinoma:
  - ⇨ *older patients*
    - rare under 40
  - ⇨ *no pancreatitis and alcoholism in medical history*
  - ⇨ *sudden painless icterus*

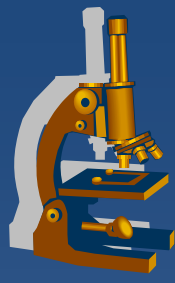
- Chronic pancreatitis:
  - ⇨ *often in younger patiens*
  - ⇨ *medical history:*
    - long term
      - recurrent acute pancreatitis
    - alcohol abuse
  - ⇨ *icterus after long term duration of disease*

Differential diagnosis of ductal adenocarcinoma and chronic pancreatitis – gross features



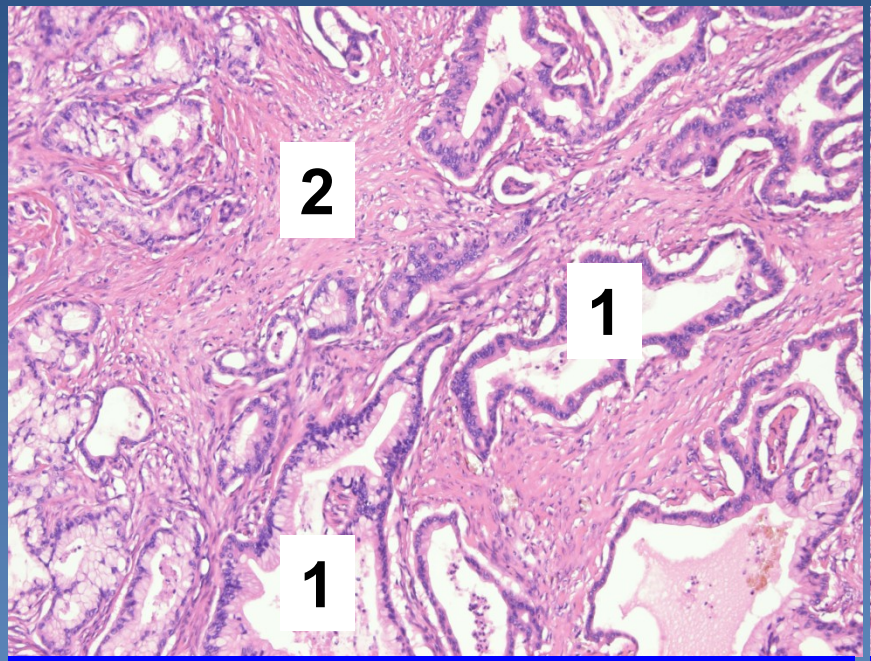
- Adenocarcinoma:
  - ⇨ *solid mass in the pancreatic head, mean diameter 2-3 cm*
  - ⇨ *common bile duct stenosis*
  - ⇨ *usually without necrosis, calcifications, pseudocysts*
- Chronic pancreatitis:
  - ⇨ *more diffuse*
  - ⇨ *Alternation of lobular parenchyma and areas of fibrosis*
  - ⇨ *protein plugs and calcifications in ducts*
  - ⇨ *extrapancreatic pseudocysts*

Differential diagnosis of ductal adenocarcinoma and chronic pancreatitis – microscopic features

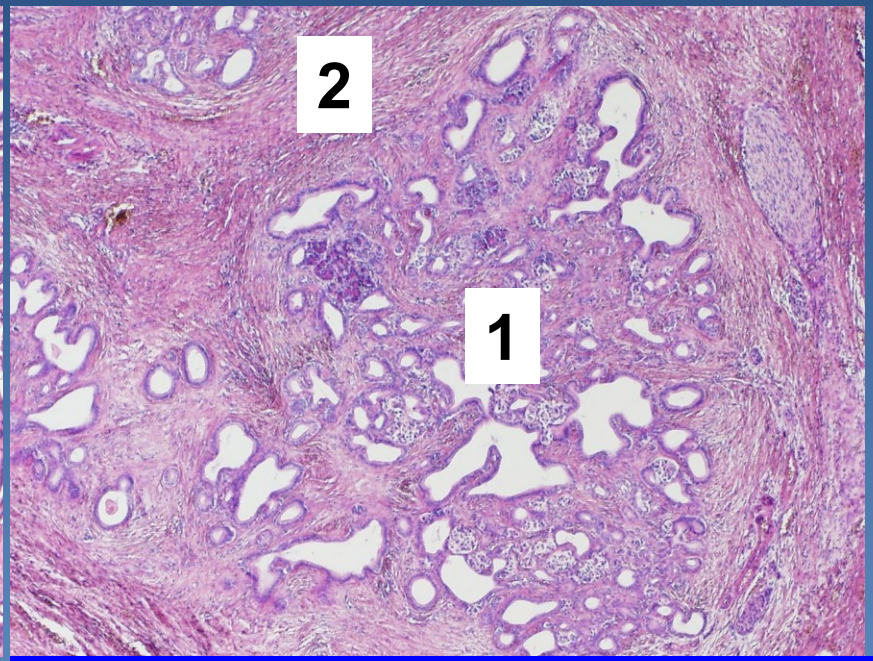


- Adenocarcinoma:
  - *haphazard distribution of irregular ductal structures*
  - *ducts perineurally, in extrapancreatic fatty tissue*
  - *hypercellular condensation of stroma around neoplastic ducts, stromal desmoplasia*
  - *enlarged nuclei, pleomorphism, hyperchromasia, mitoses, prominent nucleoli, loss of nuclear polarity*
  - *dense acidophilic cytoplasm, apical condensation of cytoplasm*
- Chronic pancreatitis
  - *(organoid) lobular arrangement*
  - *ducts intrapancreatically*
  - *smooth contours of the ducts, roud/oval lumens*
  - *dense hyalinized stroma*
  - *uniform nuclei, inconspicious nucleoli, no mitoses*
  - *cytoplasm normochromophilic, absence of apical condensation*

Differential diagnosis of ductal adenocarcinoma and chronic pancreatitis – microscopic features

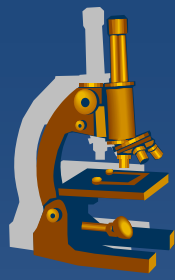


1. Haphazard distribution of irregular ducts
2. Stromal desmoplasia



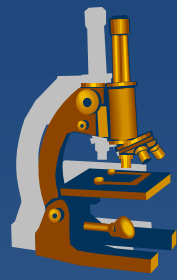
1. Lobular arrangement
2. Dense hyalinized stroma

Neuroendocrine neoplasms of the pancreas



- synonyms: pancreatic NETs, islet cell tumor, APUDoma
- 1 – 2 % of all pancreatic tumors
- 3rd-6th decade
- classification:
  - ⇨ *neuroendocrine tumour (NET)*
    - nonfunctional NET (NET G1, G2)
    - NET G1
    - NET G2
  - ⇨ *neuroendocrine carcinoma (NEC)*
    - large cell NEC
    - small cell NEC

Neuroendocrine neoplasms of pancreas



- Functional (hormonally active)
  - ***insulinoma***
  - ***glucagonoma***
  - ***somatostatinoma***
  - ***gastrinoma***
  - ***VIPoma***
  - ***serotonin producing NET***
  - ***others – with ectopic hormone production (ACTH, calcitonin,…)***
- Nonfunctional (with no association with hormonal syndrome)
- Pancreatic neuroendocrine microadenomas
  - *<0,5 cm*
  - ***usually clinically silent***

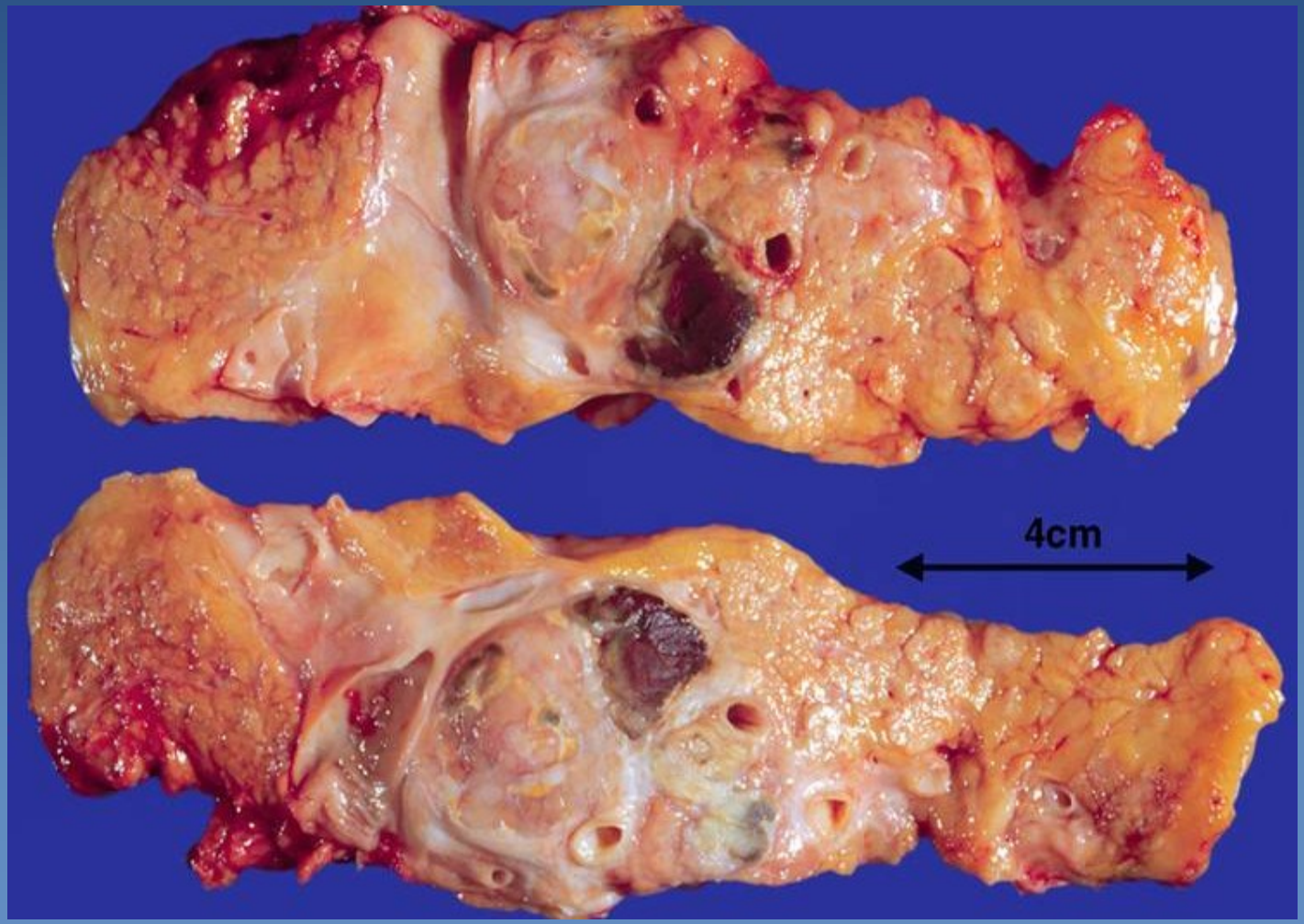
Neuroendocrine neoplasms of pancreas

- Gross:
  - ⇨ ***partially or totally circumscribed/encapsulated; usually solitary***
  - ⇨ ***white, yellow or pink-brown***
  - ⇨ ***haemorrhages, necrosis can occur; cystic tumors rare***

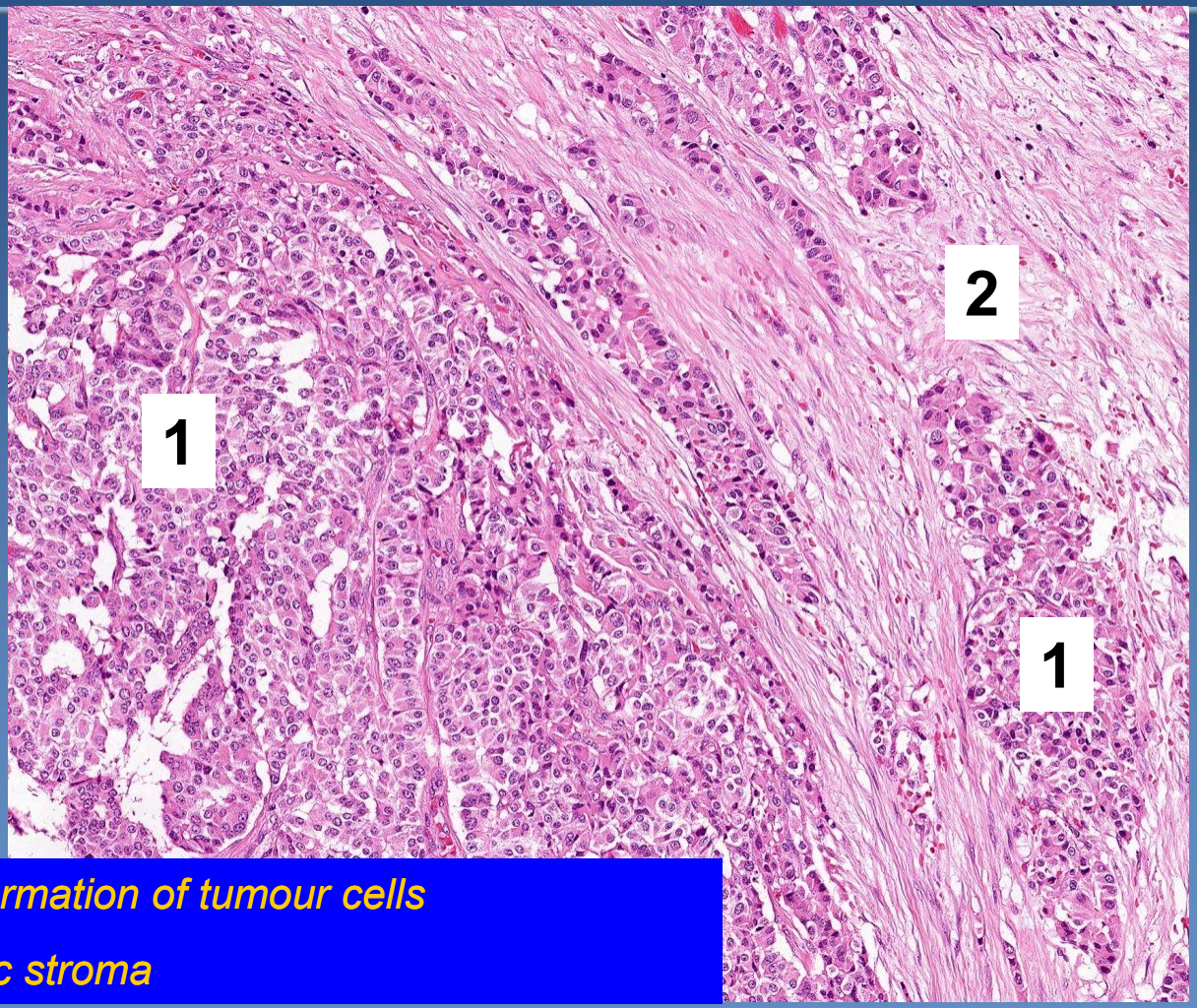
Neuroendocrine neoplasms of pancreas

- Micro:
  - ⇨ ***nesting, trabecular, glandular, acinar, tubuloacinar, pseudorosette,…arrangements of their cells***
  - ⇨***cells uniform, round, finely granular amphophilic to eosinophilic cytoplasm, coarsely clump chromatin („salt and pepper“)***
  - ⇨***Variable amount of stroma***
  - ⇨ ***IHC:***
    - CEA, synaptophysin, chromogranin, NSE, CD56
    - peptide hormones:
      - insulin, glucagon, serotonin, somatostatin, gastrin

Neuroendocrine neoplasms of pancreas

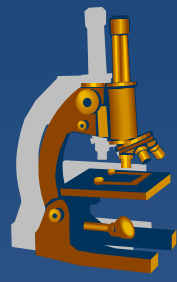


Neuroendocrine neoplasms of pancreas



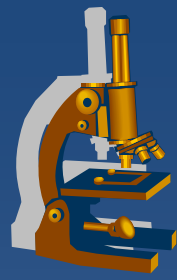
1. *Trabecular formation of tumour cells*
2. *Dense fibrotic stroma*

Diabetes mellitus



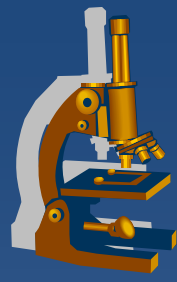
- Group of complex metabolic lesions
- Multifactorial etiology
- Common sign:
  - ⇨ ***glucose metabolism dysregulation → glucose intolerance - hyperglycaemia***
- Causes:
  - ⇨ ***insulin secretion disorders***
  - ⇨ ***disorders of insulin action / response to insulin***
  - ⇨ ***combination of both***

Diabetes mellitus



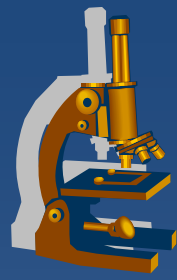
- Other metabolic disorders:
  - ⇨ ***lipolysis***
    - hyperlipidaemia (loss of weight), ketoacidosis
  - ⇨ ***hyperglycaemia***
    - osmotic diuresis (polyuria, dehydratation, thirst)
  - ⇨ ***diminished protein synthesis***

Diabetes mellitus - classification



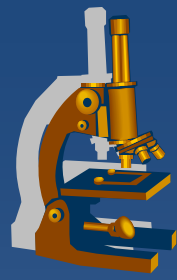
- **Primary DM:**
  - ⇨ ***DM type 1***
    - insulin-dependent
    - destruction of β-cells, autoimunne, idiopathic
  - ⇨ ***DM type 2***
    - non-insulin dependent
  - ⇨ ***Genetic defects of β-cells function***
    - MODY – maturity-onset diabetes of the young, etc.
- Now possible 5 DM types

Diabetes mellitus - classification



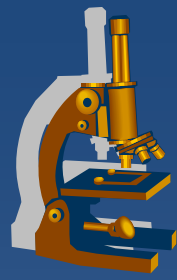
- **Secondary DM:**
  - ⇨ ***Exocrine pancreas defects***
    - (chron. pancreatitis, cystic fibrosis, hemochromatosis, tumor)
  - ⇨ ***Endocrinopathies***
    - (Cushing sy, hyperthyreosis, acromegaly, etc.)
  - ⇨ ***Infections***
    - (CMV, coxsackie B, congenital rubella)
  - ⇨ ***Drugs***
    - (glucocorticoids, proteases inhibitors, …)
- ***Gestational DM***

Diabetes mellitus



- Atypical glucose bond on proteins
  - ⇨ ***glycation → change of normal characteristics/functions, i.e. in vessels BM; monitoring - glycosylated hemoglobin HbA1c***
- Polyol pathways
  - ⇨ ***atypical metabolisation of glucose by reductases to sorbitol + fructose i.e. in kidneys, nerves, eye lens → oedema and cell damage***
- Free radicals formation
  - ⇨ ***oxidative stress***

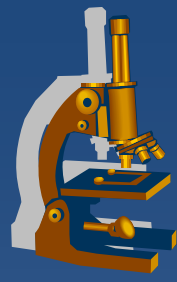
Diabetes mellitus - complications



Long-term consequences similar in all types:

- ⇨ ***microangiopathy (neuropathy, retinopathy)***
- ⇨ ***diabetic glomerulosclerosis***
- ⇨ ***accelerated atherosclerosis***
- ⇨ ***immune defect, mostly nonspecific (bacterias, fungi)***
- ⇨ ***diabetic ketoacidosis, hyperosmolar coma***
- ⇨ ***hypoglycaemia/coma due to insulin overdose***

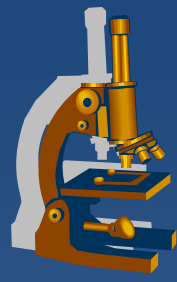
Diabetes mellitus – morphology



Pancreas

- DM type1
  - ⇨ ***more specific changes***
  - ⇨ ***insulinitis with lymfocytic infiltration of islets + ↓ of their size and number***
- DM type 2
  - ⇨ ***possible amyloid deposition or islet fibrotisation***

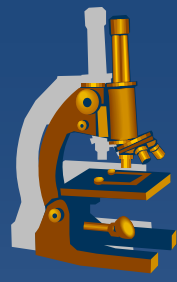
Diabetes mellitus – morphology



Large vessels

- AS, changes non-specific
- AS complications (MI, gangrene) sooner and more often
- accelerated hyaline arteriolosclerosis and hypertension → intracerebral haemorrhage, nephrosclerosis

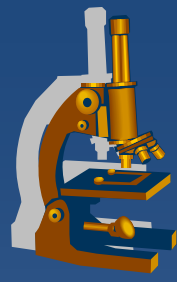
Diabetes mellitus – morphology



Small vessels

- Microangiopathy
  - ⇨ ***diffuse thickening of BM, but BM more leaky for proteins***
- Nephropathy
- Retinopathy
- Neuropathy

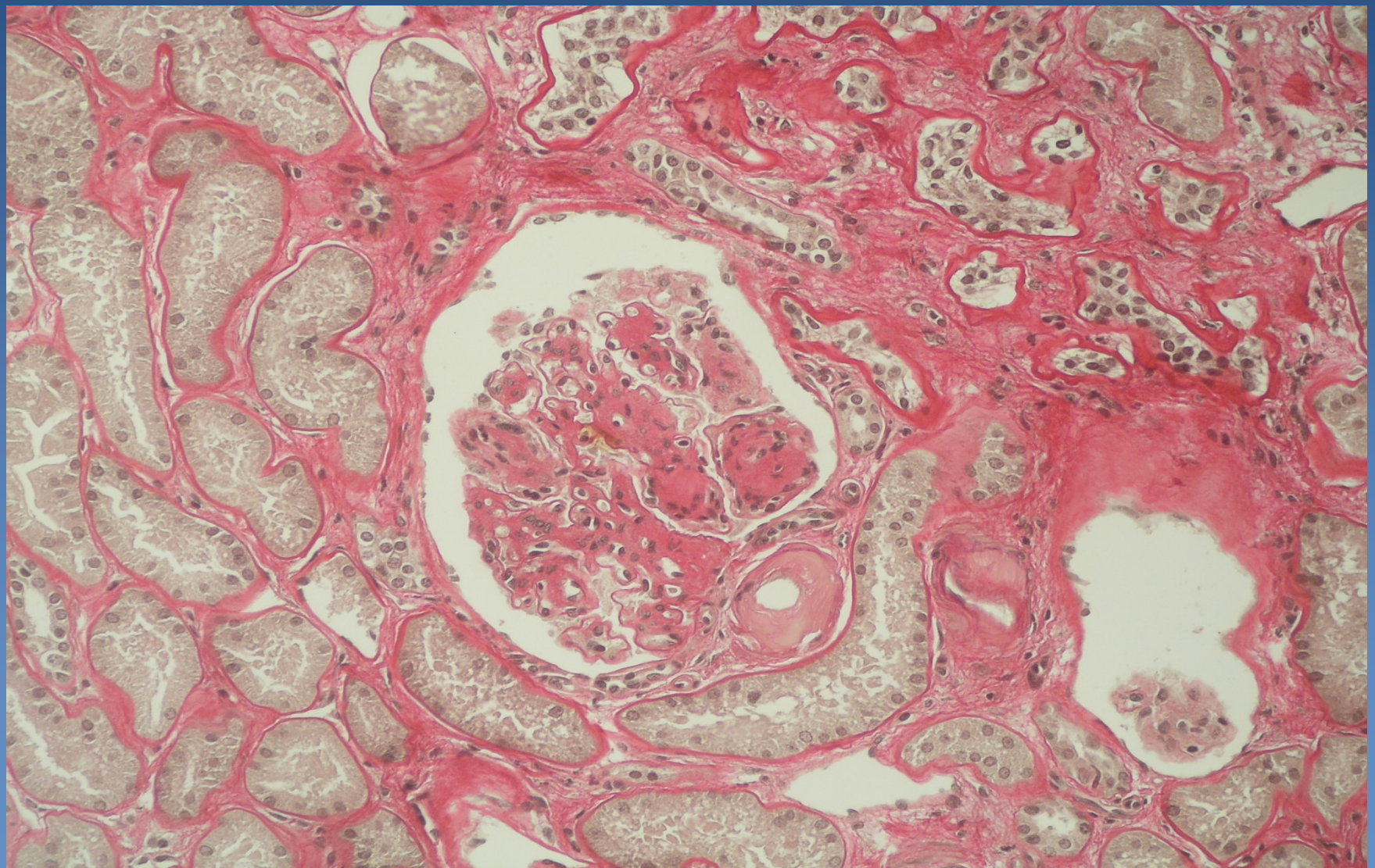
Diabetic nephropathy



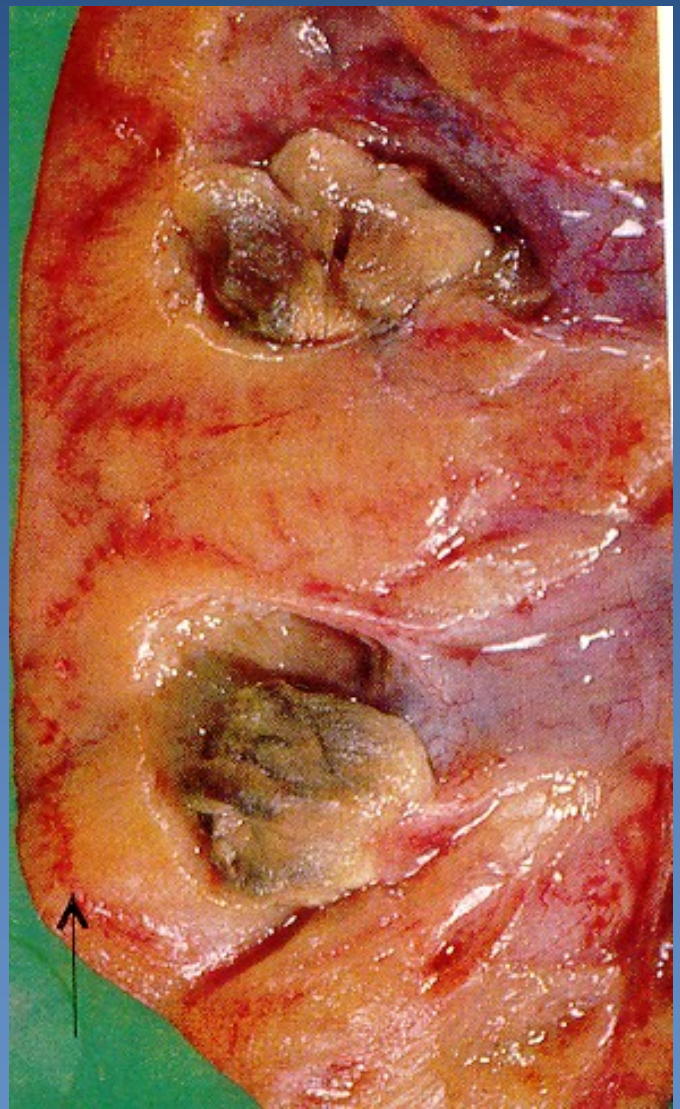
- Diabetic glomerulosclerosis
  - ⇨ ***diffuse x nodular***
- Renal vascular lesions
  - ⇨ ***arteriolosclerosis***
- Pyelonephritis incl. papillary necrosis

- Common progression to renal insufficiency

Glomerulosclerosis + arteriolosclerosis

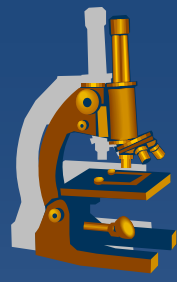


Papillary necrosis



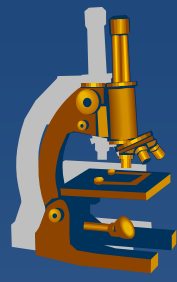
- Acute necrotizing papillitis in the setting of focal ischaemia

Diabetes mellitus – morphology



- Ocular lesions:
  - ⇨ ***retinopathy (neovascularization)***
  - ⇨ ***cataract formation (opaque lens)***
  - ⇨ ***glaucoma (intra-ocular hypertension)***

Diabetes mellitus – morphology

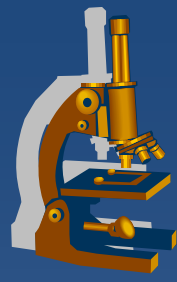


- Neuropathy

segmental demyelinization

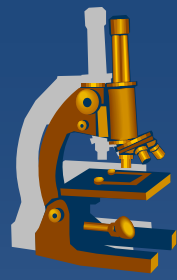
- ⇨ ***distal polyneuropathy***
  - mostly motoric + sensitive in lower extremities – incl. ↓ pain perception (→ ulceration)
- ⇨ ***autonomic neuropathy***
  - functional disorders of intestines, bladder, sexual

Diabetes mellitus – morphology



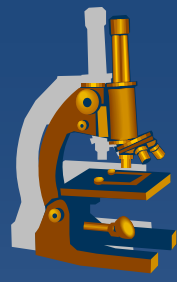
- Skin
  - ⇨ *increased susceptibility to infections incl. protracted mycotic i., gangrene*
  - ⇨ *granuloma annulare (foci of collagen degeneration + inflammatory infiltrate)*
  - ⇨ *necrobiosis lipoidica*

Diabetes mellitus – morphology



- Pregnancy
  - ⇨ ***pre-eclampsia***
  - ⇨ ***large babies (already in utero)***
  - ⇨ ***neonatal hypoglycaemia***

Metabolic syndrome

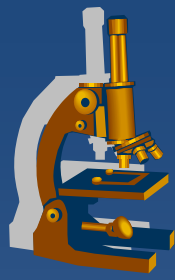


- abdominal obesity („male type“)
- insulin resistance
- hyperlipidemia + abnormal lipid spectrum

Consequences

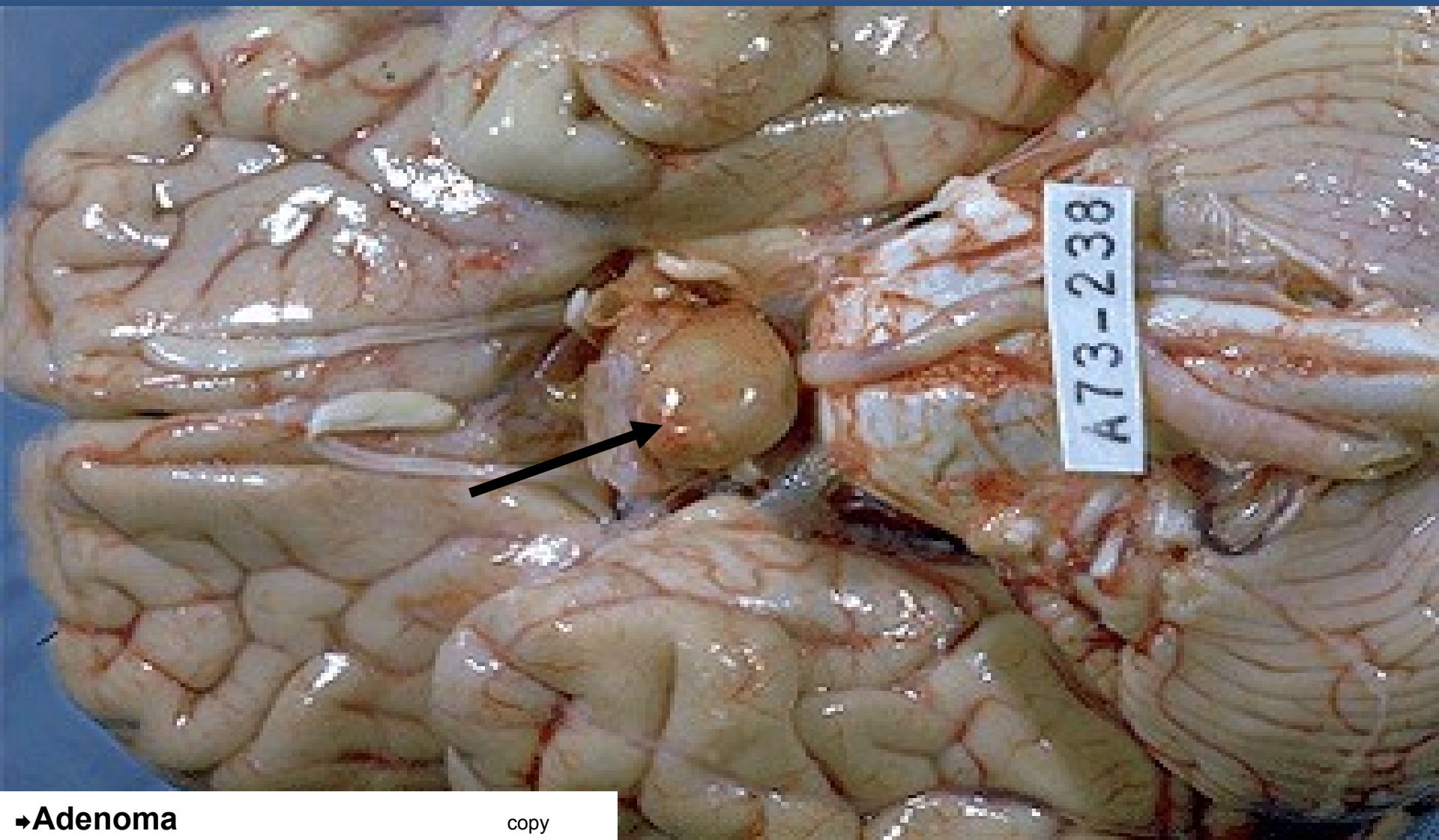
- cardiovascular lesions
- non-alcoholic steatohepatitis

Pathology of other endocrine organs (selected)



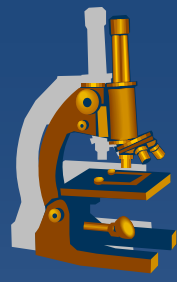
- Hyperfunction
- Hypofunction
- Neoplasia (+ event. functional changes)

Pituitary adenoma



➧**Adenoma**

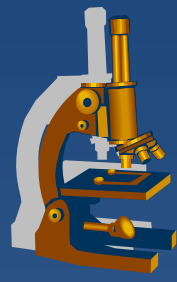
Thyroid gland



HYPERTHYROIDISM - thyrotoxicosis

- overproduction, ↑ release into the blood, extrathyroidal secretion
- hyperplasia
  - ⇨ ***Graves-Basedow disease, nodular goitre***
- hyperfunctional tumor
  - ⇨ ***adenoma, ca***
- incipient autoimmune thyroiditis
- endocrine axis dysregulation

Thyroid gland

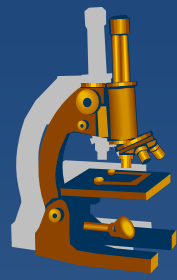


Thyrotoxicosis

hypermetabolic state + overactivity of sympathetic nervous system

- Exophthalmos
- Weight loss, diarrhoea, tremor, anxiety, insomnia
- Tachycardia, palpitations, arrhytmia - atrial fibrillation → thyrotoxic cardiomyopathy, hypertension
- Sweating, heat intolerance
- Osteoporosis
- Possible thyroid storm, heart failure

Thyroid gland



HYPOTHYROIDISM

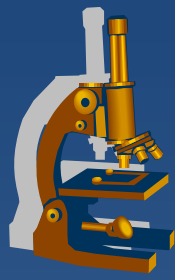
- congenital (cretinism),

⇨ ***geographic iodine deficiency (endemic cretinism), individual factors (hypoplasia, ectopy, genetic /metabolic defects)***

⇨ ***thyroid hormones necessary to fetal brain development → severe neurologic defects incl. mental retardation***

⇨ ***coarse facial features + hypomimia, protruding tongue, disorders of dentition + growth, sexual retardation***

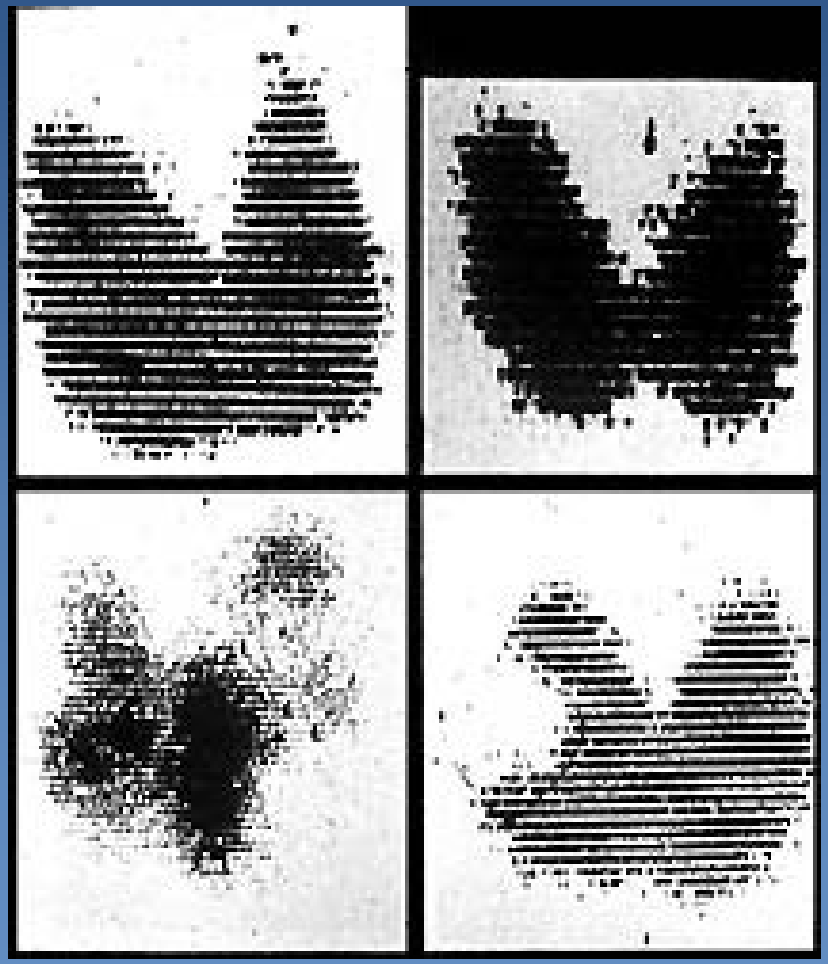
Thyroid gland



MYXEDEMA

- hypothyroidism developing in older child/adult
- **M:F 1:10**
- slowing of physical/mental activity
- accumulation of mucoid matrix substances in dermis, myocardium, vessels, …), hypercholesterolemia, AS acceleration
- cool skin, cold intolerance, constipation + overweight, fatigue, dyspnoea, decreased exercise capacity
- secondary oligo- amenorrhoea
- cardiovascular insufficiency

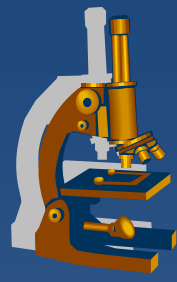
Thyroid gland - scintigraphy



radioactive iodine uptake

1. norm
2. diffuse hyperplasia
3. „hot“ nodule – usually adenoma
4. „ cold“ nodule - ca

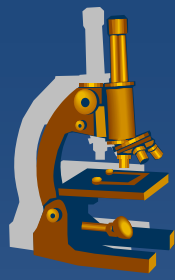
Thyroiditis



- Acute inflammations uncommon
  - ***purulent bacterial (abscess), tbc***
- Subacute granulomatous – giant cell thyroiditis (de Quervain‘s) ?viral
  - ⇨ ***painful enlargement, micro mixed inflammatory infiltrate + giant cell reaction***
- Chronic sclerosing t. (Riedel‘s)
  - ⇨***dense fibrotisatin, diff. dg. x ca***

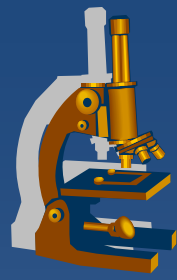
Chronic thyroiditis

Hashimoto's thyroiditis



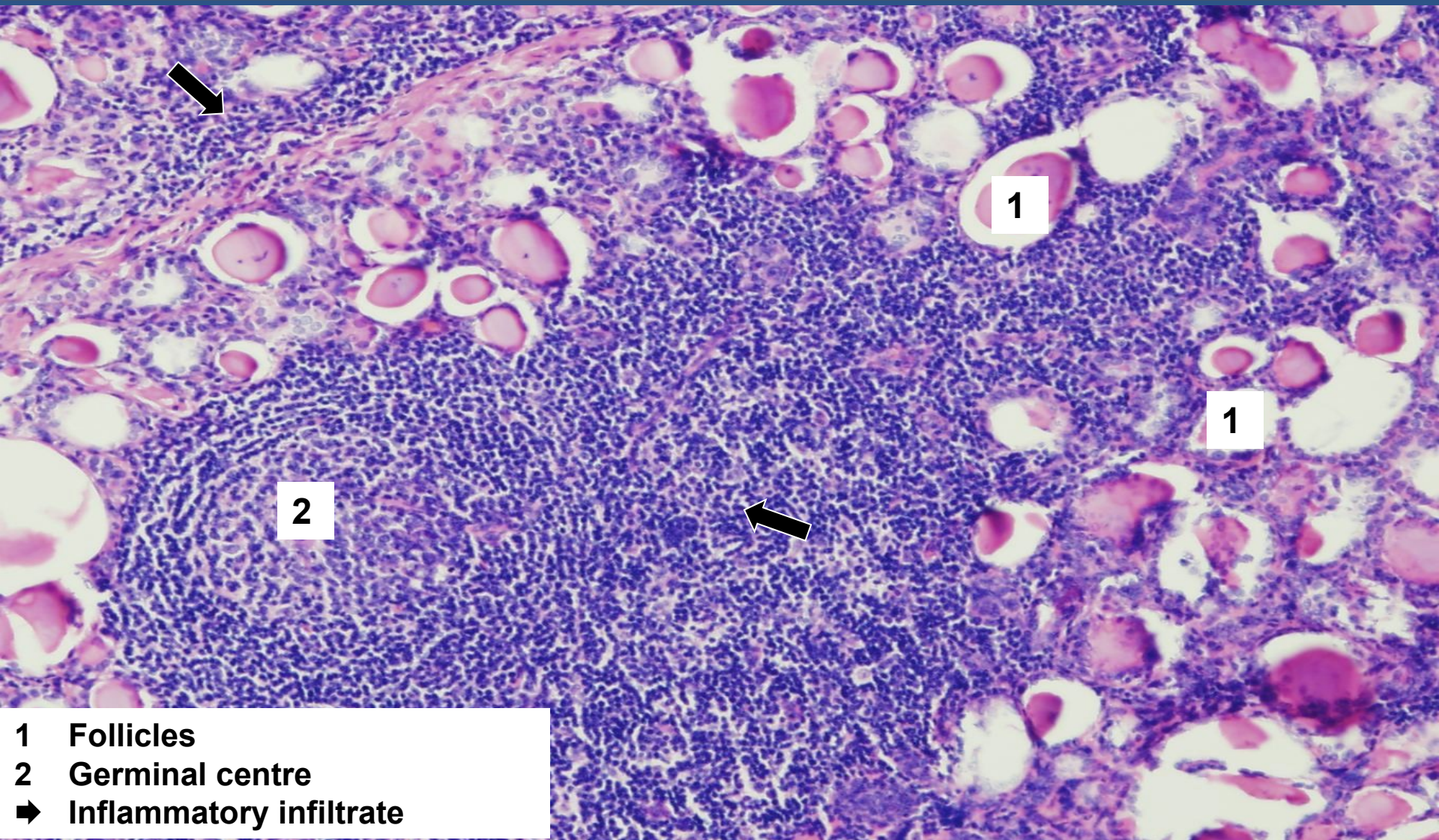
- organ-specific autoimmune inflammation
- variable auto-antibodies
  - ⇨ ***x peroxidase, thyroglobulin, etc.***
- early stage - enlargement + hyperfunction
- later hypofunction
- ↑ risk of other autoimmune diseases (DM, SLE,..)
- ↑ risk of malignancies
  - ⇨***MALT lymphomas, papillary thyroid carcinoma***

Hashimoto's thyroiditis



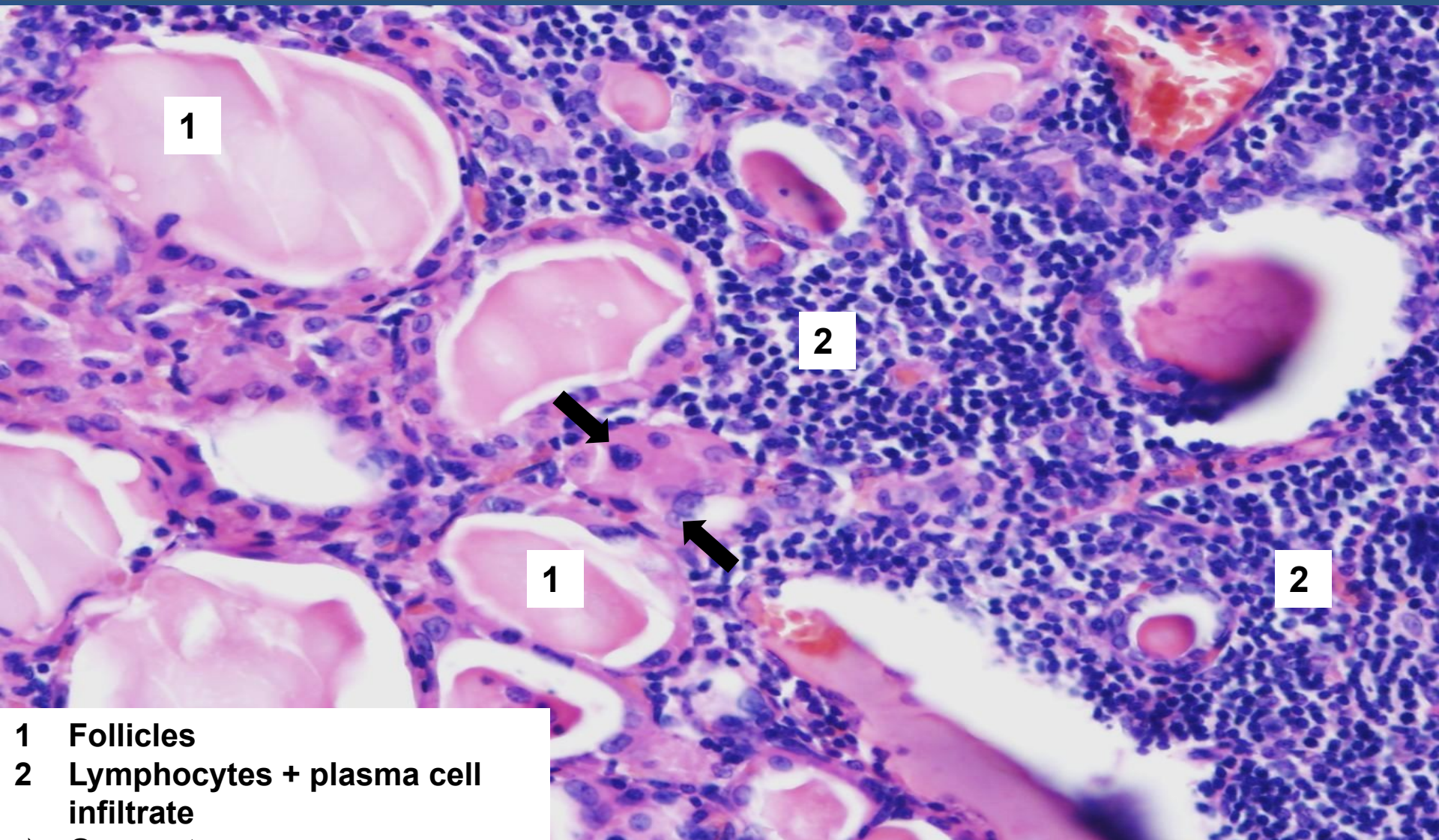
- Gross:
  - ⇨ ***non-homogennous, firm, small paler foci***
- Micro:
  - ⇨ ***dense lymphoplasmocellular infiltrate, incl. germinal centres***
  - ⇨ ***thyroid follicles atrophy, onkocytic transformation of follicular epithelium (Hürtle cells)***
    - eosinophilic cytoplasm, enlarged nucleus, distinctive nucleolus
  - ⇨ ***variable grade of fibrosis***

Hashimoto's thyroiditis



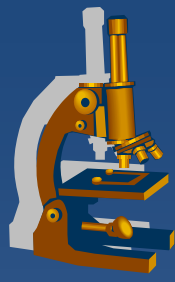
1 Follicles
2 Germinal centre
➡ Inflammatory infiltrate

Hashimoto's thyroiditis



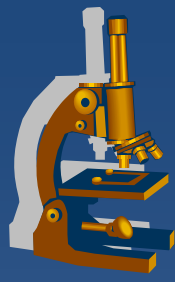
1 Follicles
2 Lymphocytes + plasma cell infiltrate

Thyroid gland hyperplasia



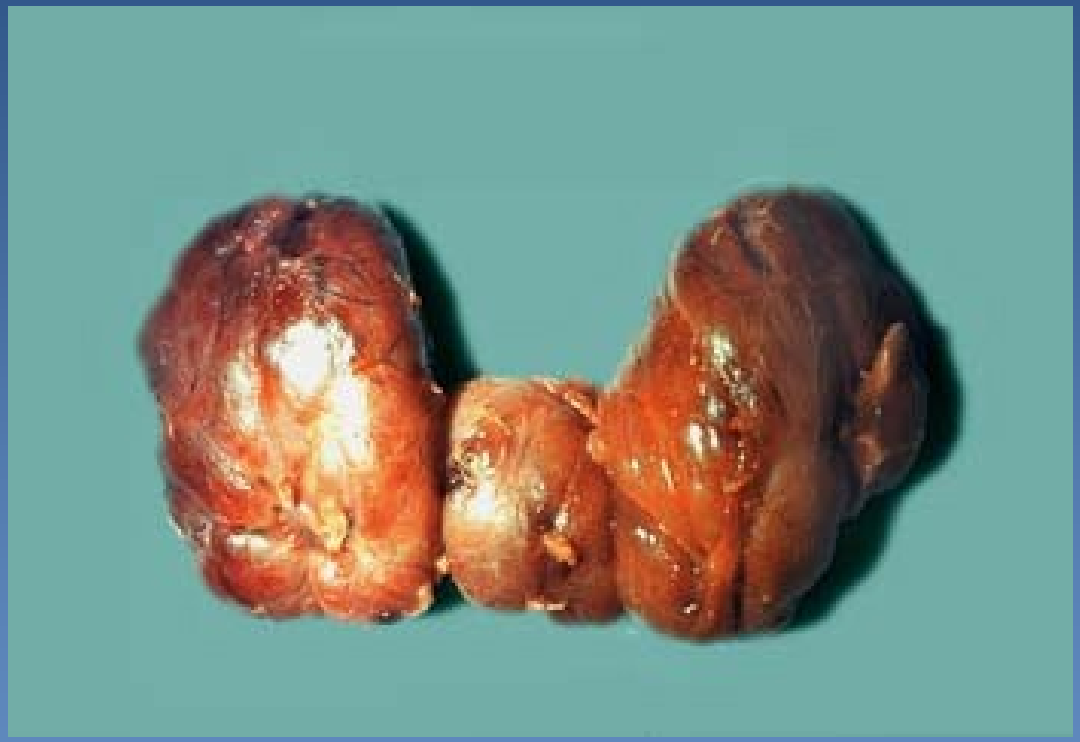
- Autoimmune Graves-Basedow disease
- Diffuse parenchymatous thyrotoxic goiter (> 60g) + exophthalmos
- IgG auto-antibody to the TSH receptor – LATS (long-acting thyroid stimulator)
- Adenomatoid nodules
  - ⇨ ***in the setting of nodular goiter, unencapsulated, diff. dg. x true adenoma may be difficult***

Thyroid gland hyperplasia

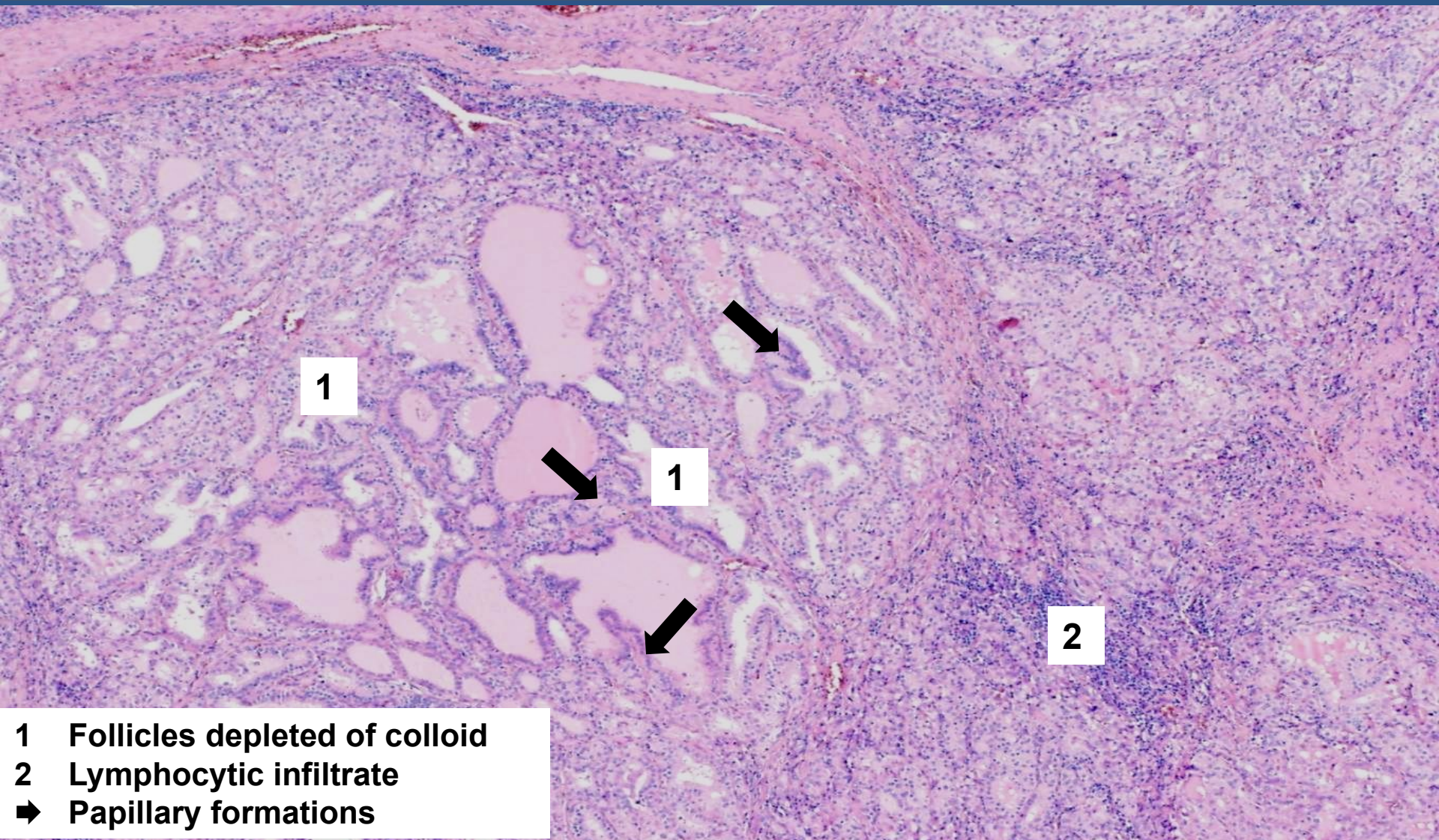


- Gross:
  - ⇨ ***symmetric diffuse enlargement, red-brown, „fleshy“***
- Micro:
  - ⇨ ***tall hyperplastic follicular cells, papillary formations, ↓ amount of colloid, numerous resorptive vacuoles, focal lymphocytic infiltration***

Thyroid hyperplasia

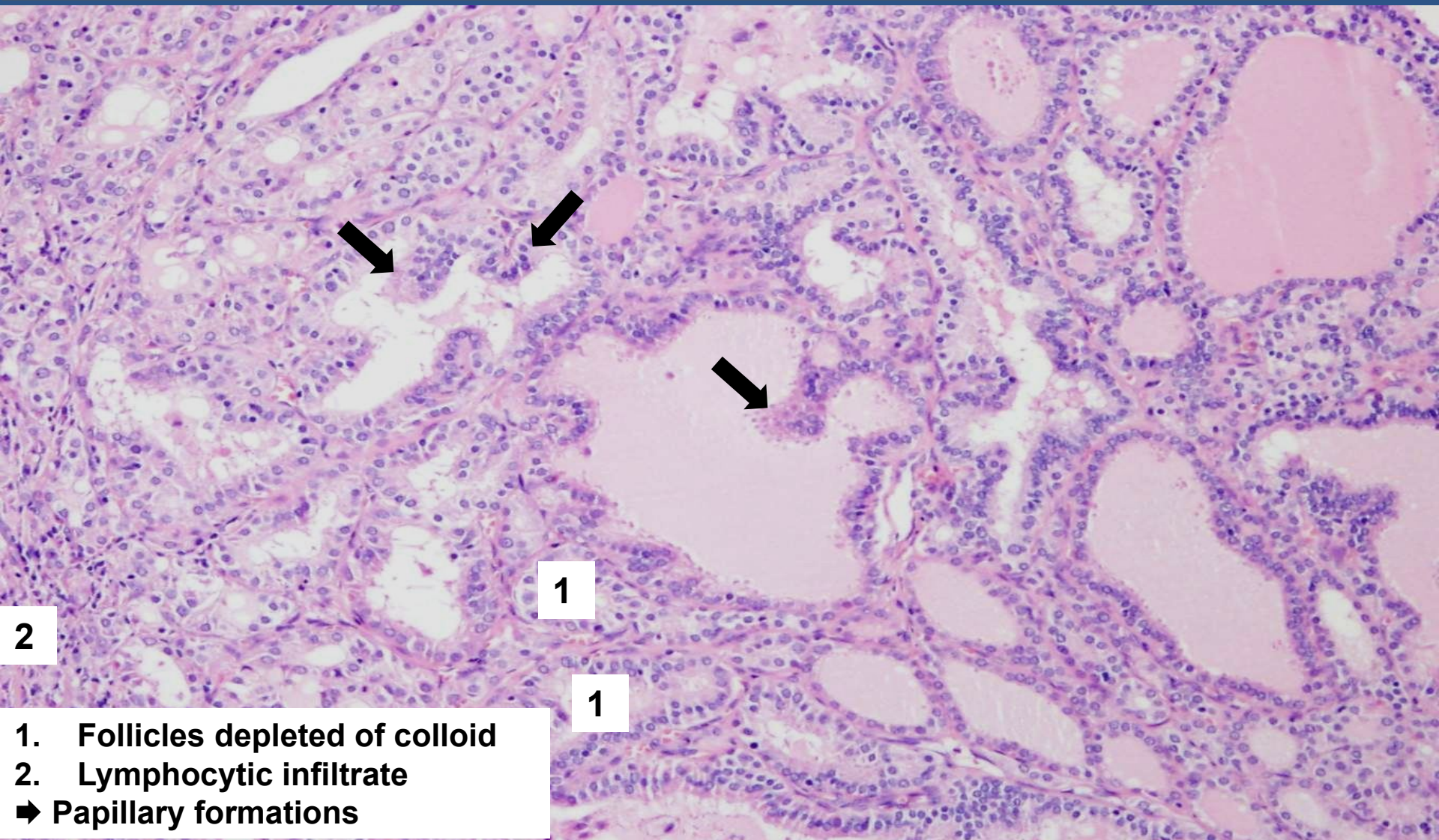


Thyroid hyperplasia



1 Follicles depleted of colloid
2 Lymphocytic infiltrate
➡ Papillary formations

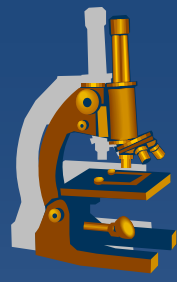
Thyroid hyperplasia



1. Follicles depleted of colloid
2. Lymphocytic infiltrate

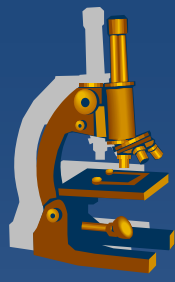
➡ Papillary formations

Nontoxic goitre



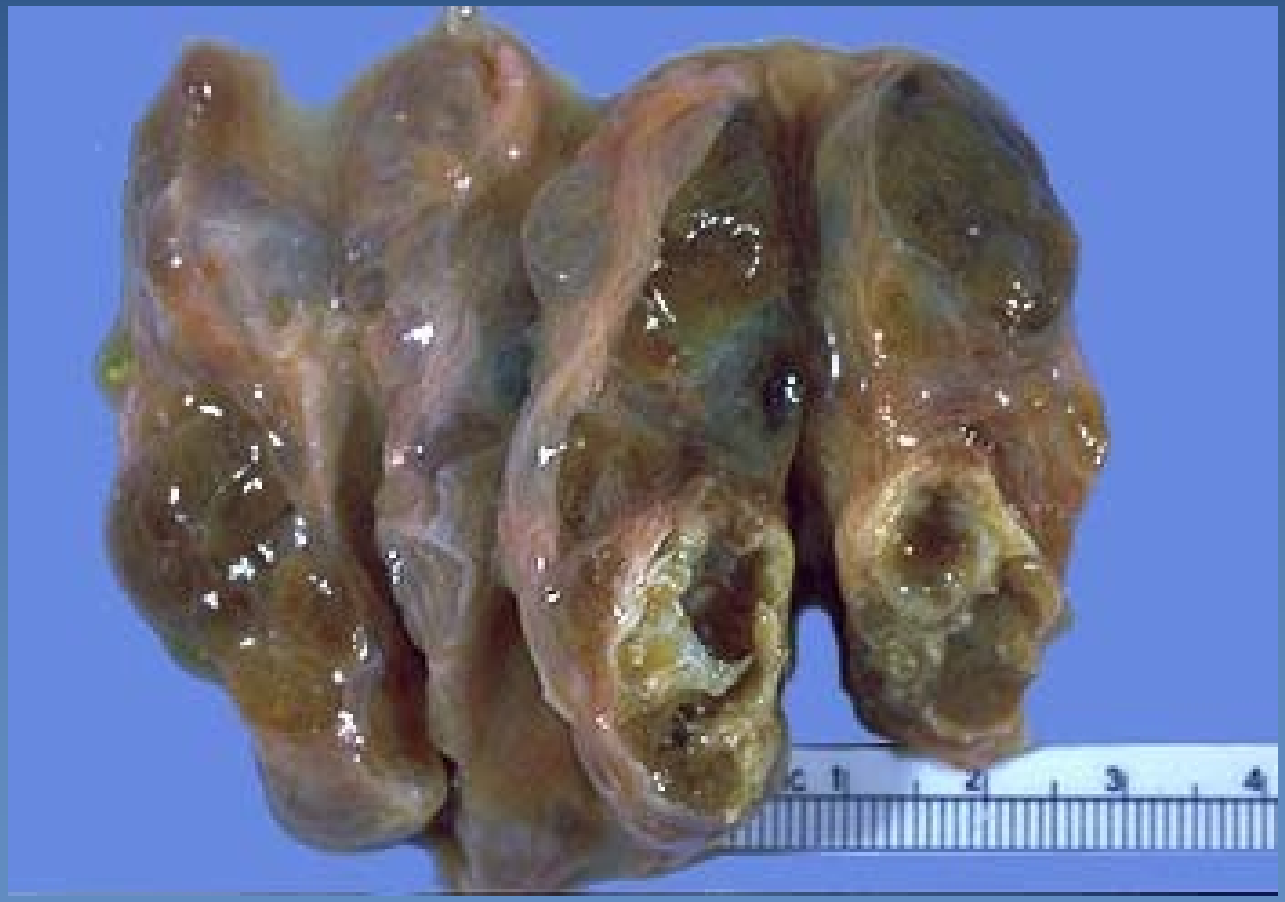
- Iodine defficiency, goitrogenes etc. → impaired synthesis of thyroid hormones → activation of hypothalamus-pituitary-thyroidal axis - ↑TSH
- Irregular activation, hyperplastic phase, colloid involution, reactive and regressive changes
- Nodular transformation – multinodular goitre
- Mostly euthyroid or low-level of hypothyroidism

Multinodular goitre

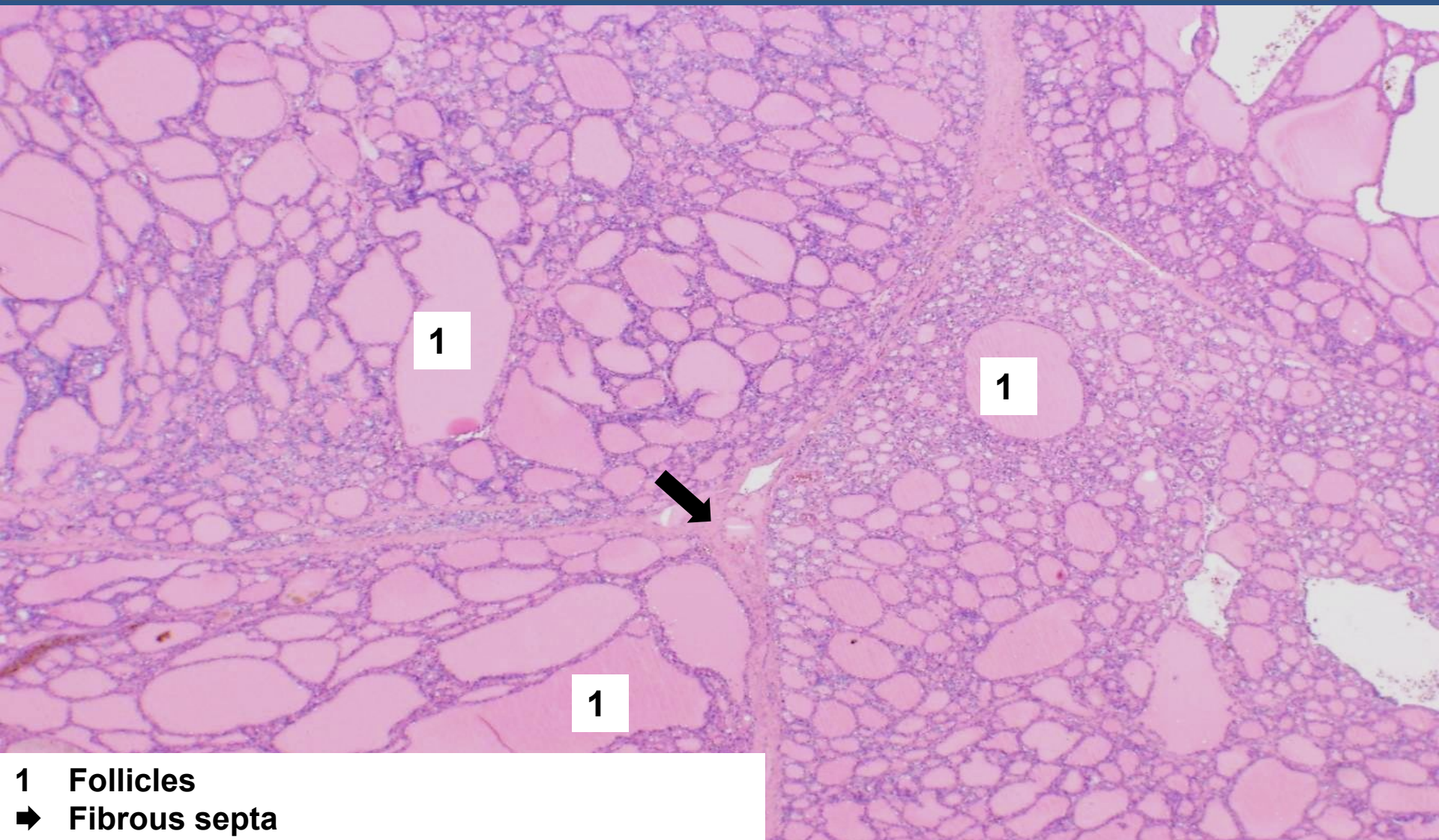


- Gross:
  - ⇨ *irregular nodules, granular, yellow-brown (colloid goitre)*
  - ⇨ *common regressive changes – haemorrhage, cysts, fibrosis, calcification*
- Micro:
  - ⇨ *dilated follicles filled with colloid, sparse resorptive vacuoles, flat epithelial cells*

Multinodular goitre



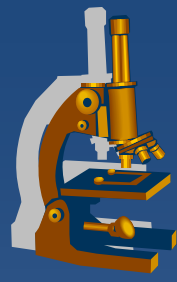
Multinodular goitre



1 Follicles

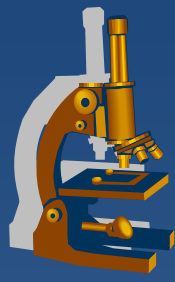
➡ Fibrous septa

Thyroid tumors



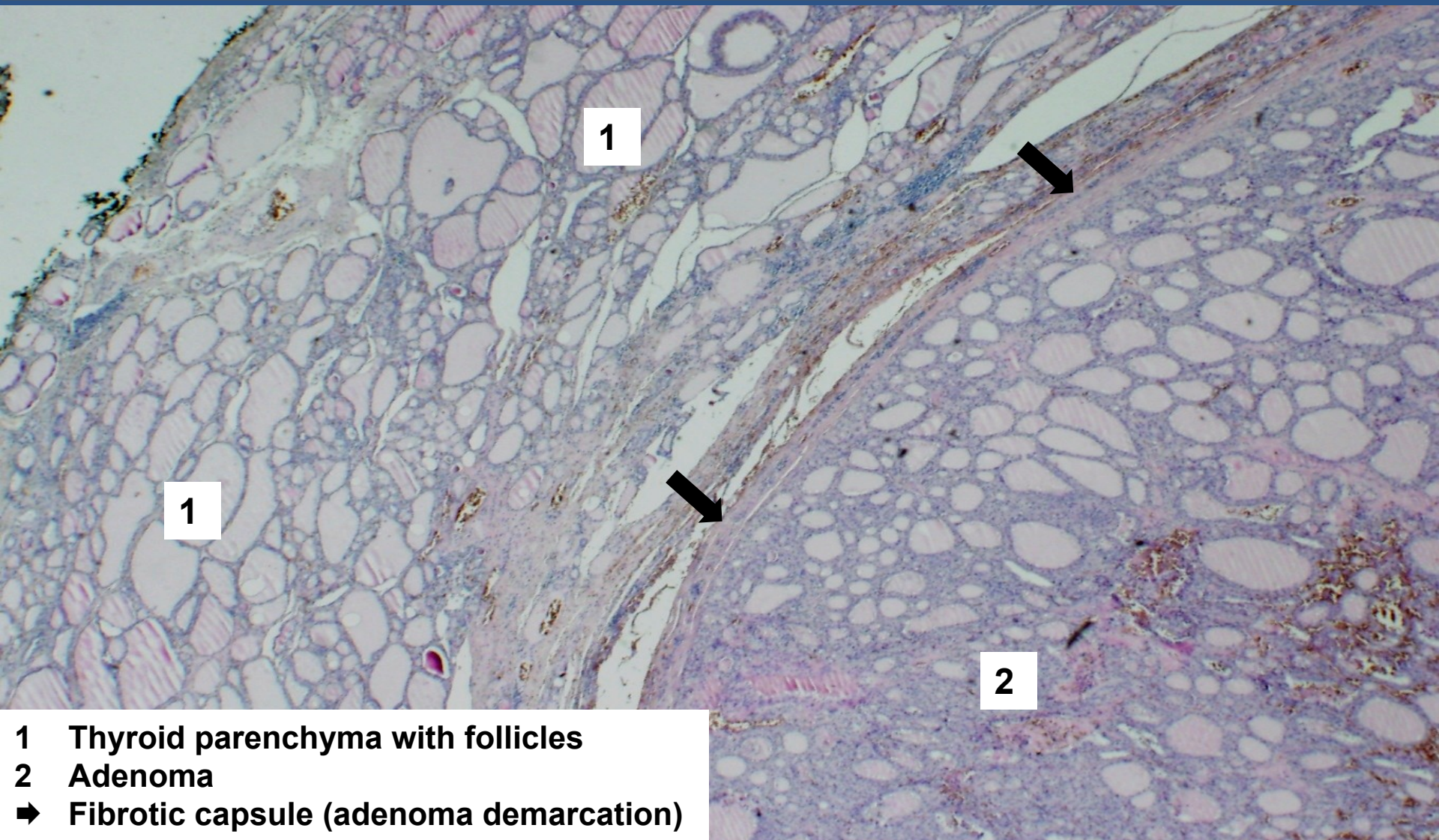
- Adenomas with variable structure
  - ⇨ ***follicular, oncocytic, etc.***
- Carcinomas
  - ⇨ ***papillary, follicular, medullary – parafollicular C-cells, anaplastic***
- Malignant lymphomas, secondary tu, etc.

Follicular adenoma



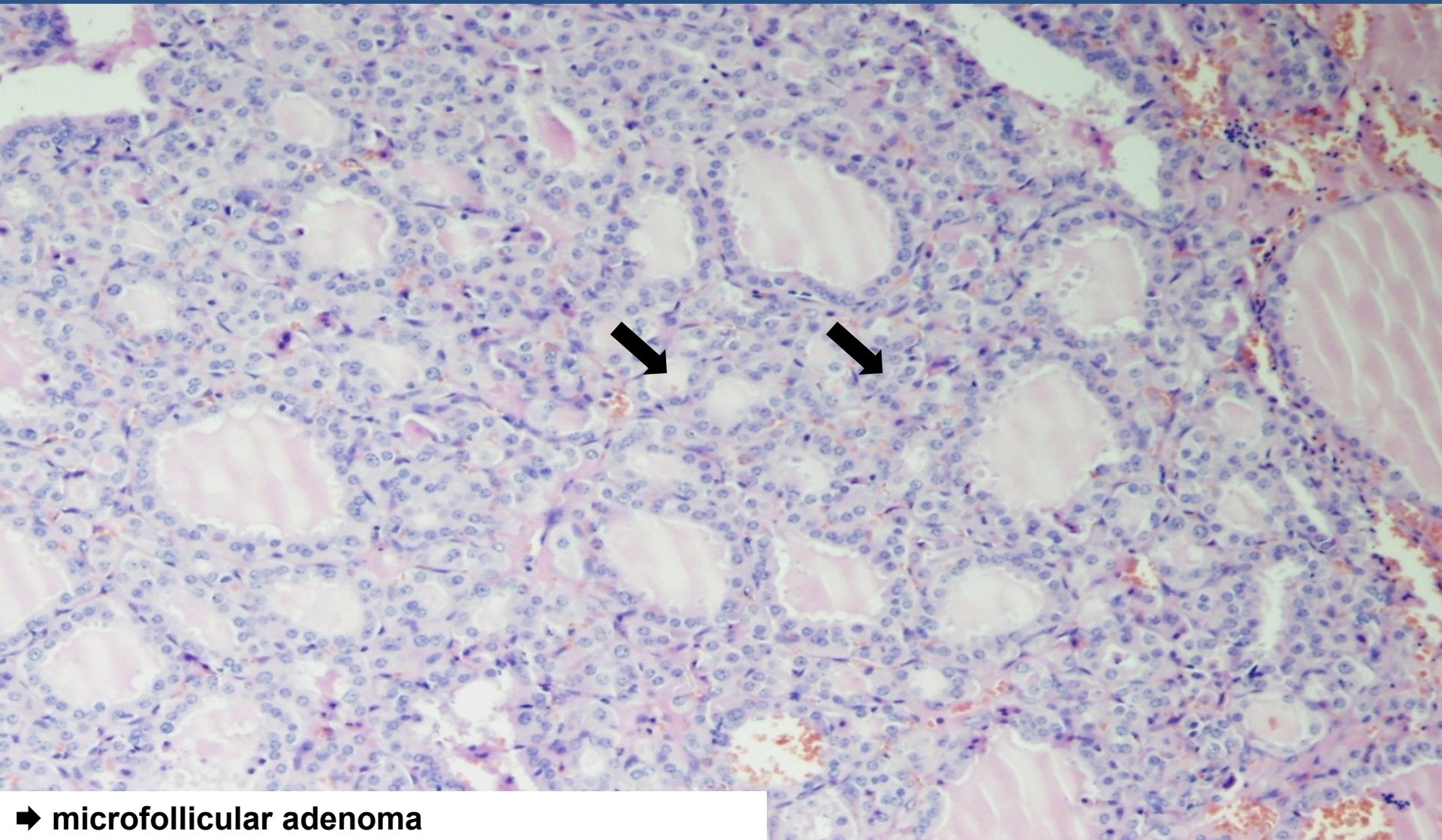
- Mostly solitary
- Encapsulated
- Pressure atrophy of adjacent parenchyma
- Diff. dg. x follicular carcinoma
  - ⇨ ***similar histologic structure, transcapsular invasion into surrounding thyroid tissue and/or angioinvasion necessary for ca diagnosis***
- Diagnosis possible only with complete biopsy
- Cytology – well differentiated follicular neoplasia

Follicular adenoma



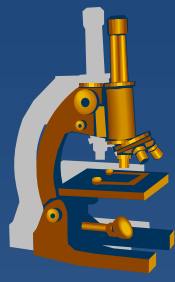
1 Thyroid parenchyma with follicles
2 Adenoma
➡ Fibrotic capsule (adenoma demarcation)

Follicular adenoma



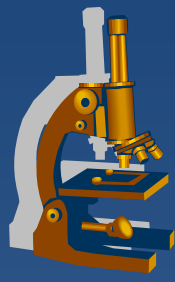
➡ microfollicular adenoma

Papillary adenocarcinoma



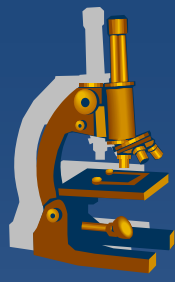
- Most common thyroid malignancy
- F 25-50 yrs, M less common, possible in children, adolescent
- ↑ incidence (better diagnostics)
- Solitary / multifocal
- Subtypes according histological structure
  - ⇨ ***papillary, follicular, diffuse sclerosing, etc.***
- Diagnosis based on cytologic morphology

Papillary adenocarcinoma



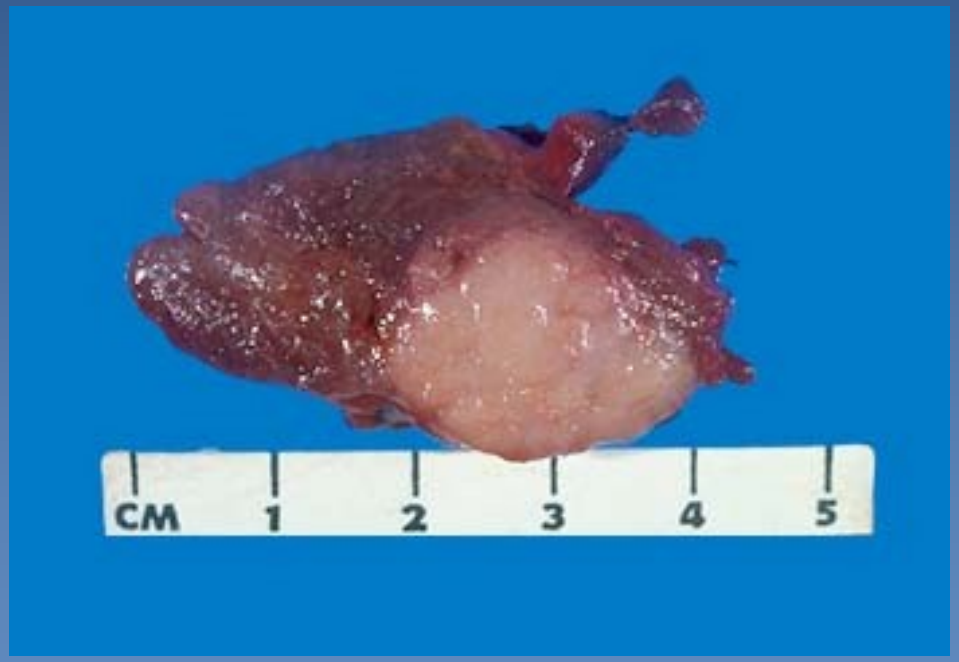
- Gross:
  - ⇨ ***pale focus***
- Micro:
  - ⇨ ***ground-glass nuclei***
    - clear nuclei, grooved nuclei, excentric nucleolus („Orphan Annie“), nuclear superposition
  - ⇨ ***papillary formations with disp. microcalcification***

Papillary adenocarcinoma

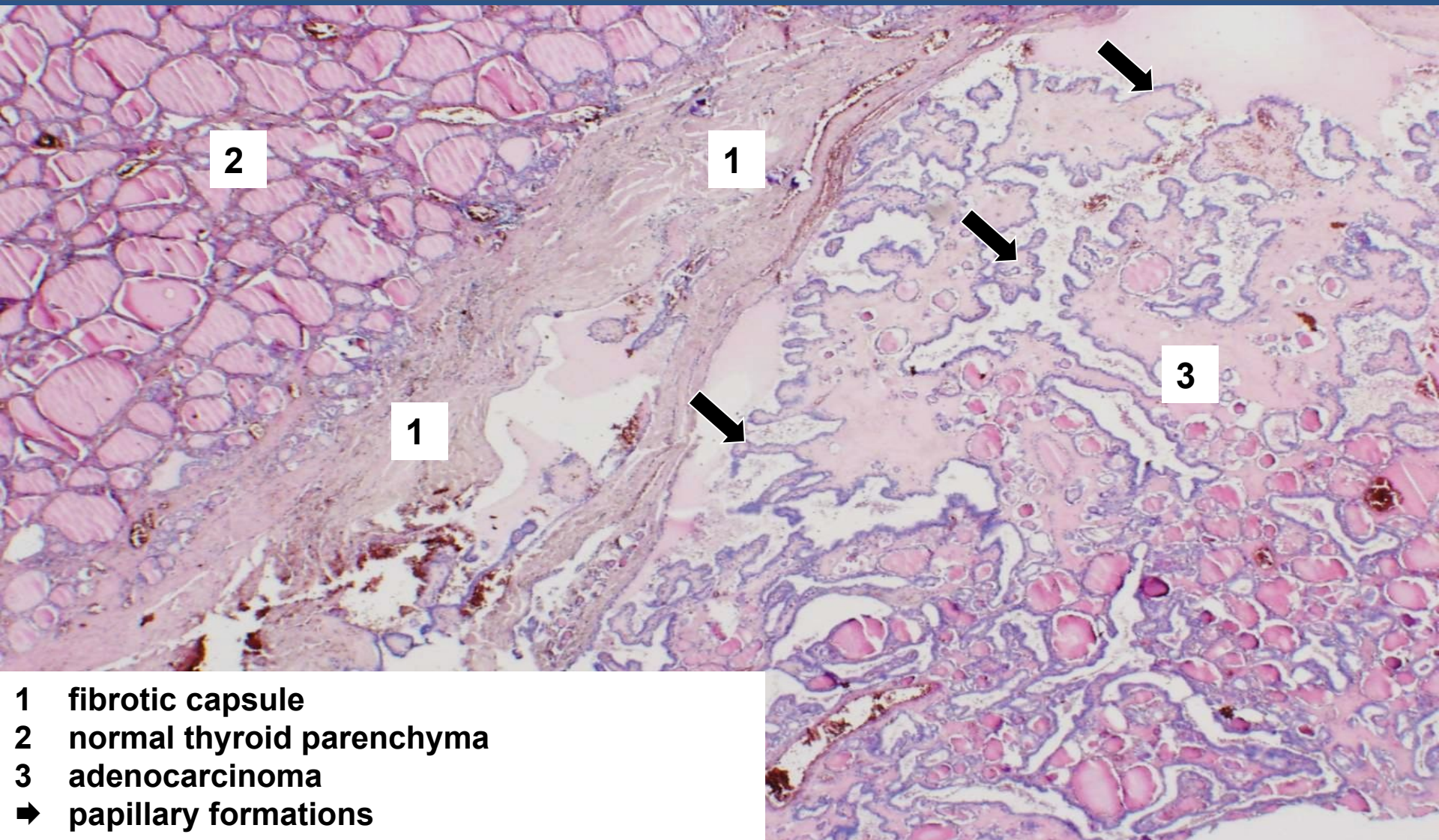


- Microcarcinoma
  - ⇨ ***incidental finding, < 1 cm, very good prognosis***
- Worse prognosis in males, older people, ca with extrathyroidal extension
- Metastases into regional LN, lungs

Papillary adenocarcinoma

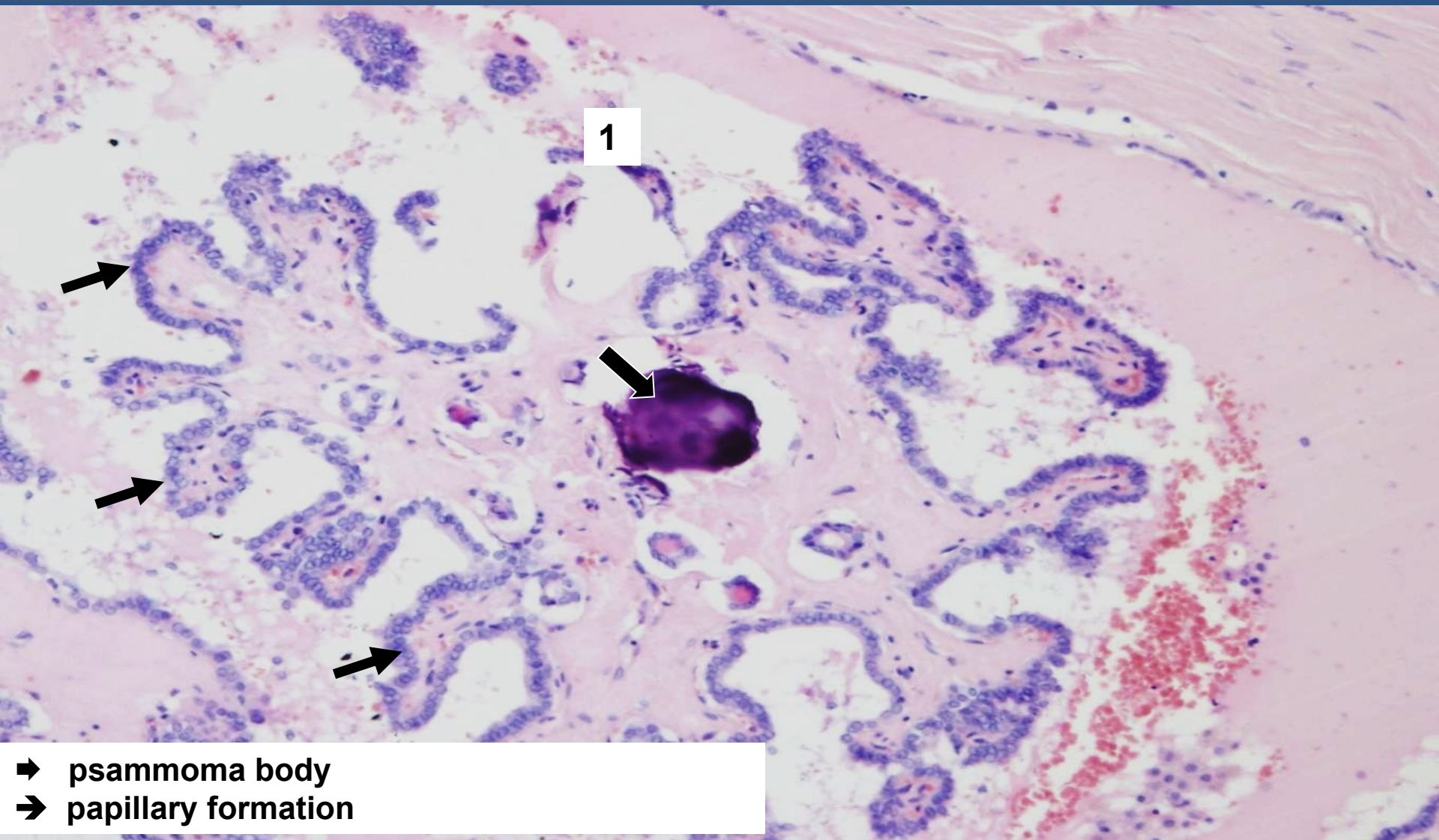


Papillary adenocarcinoma



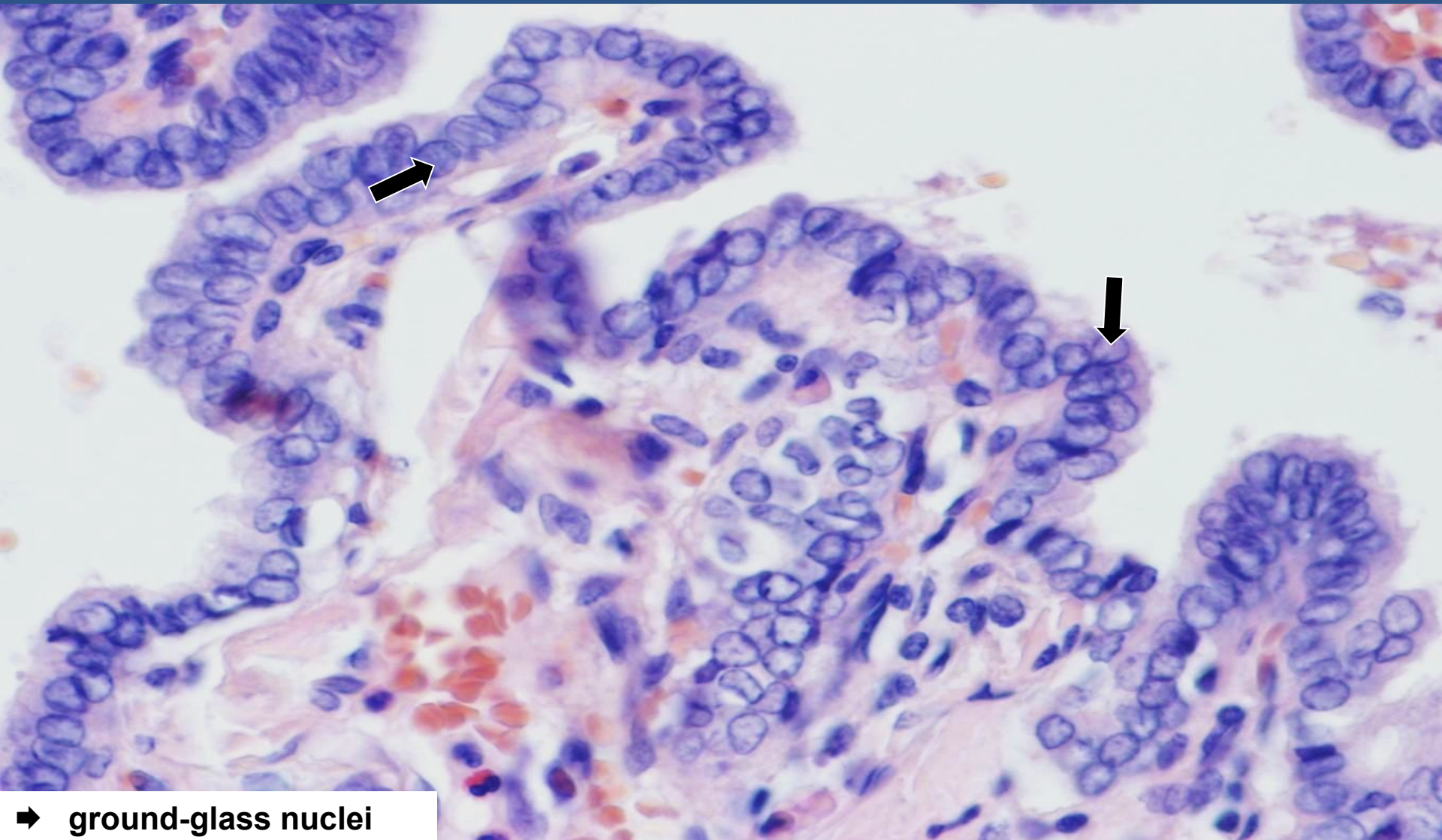
1 fibrotic capsule
2 normal thyroid parenchyma
3 adenocarcinoma
➡ papillary formations

Papillary adenocarcinoma



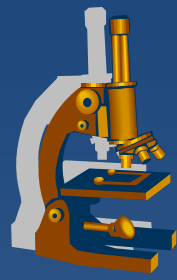
➡ psammoma body
➔ papillary formation

Papillary adenocarcinoma



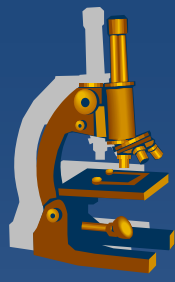
➡ ground-glass nuclei

Pathology of adrenals



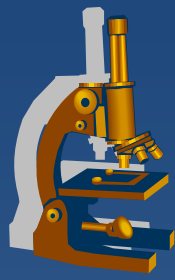
- Adrenal medulla pathology
  - ⇨ ***Hyperplasia (MEN sy)***
  - ⇨ ***Tumors***
    - Neuroblastoma
    - Ganglioneuroma
    - Pheochromocytoma

Pheochromocytoma



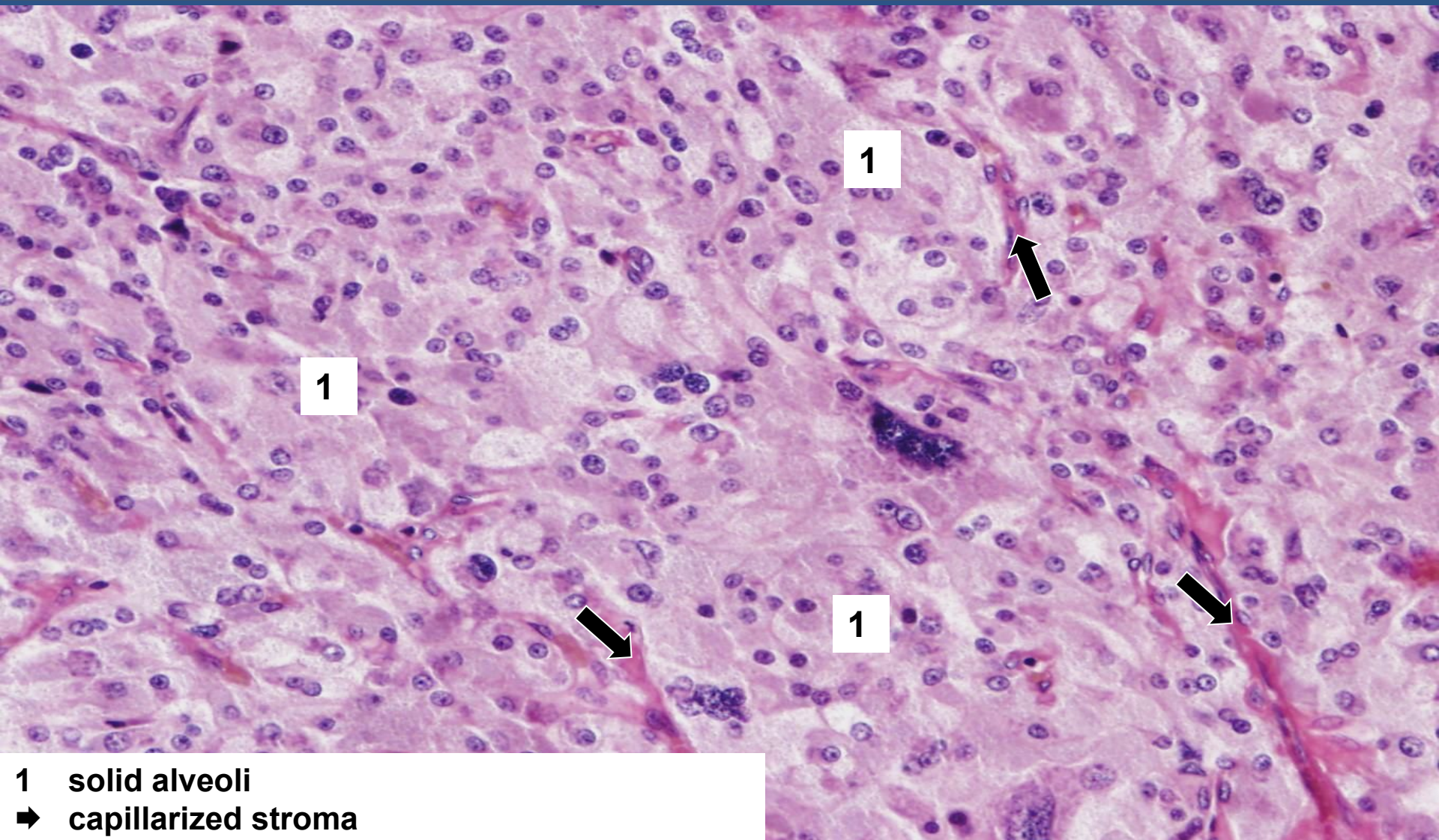
- Chromaffin cells of adrenal medulla (paraganglioma), extraadrenal site possible
- Catecholamines synthesis
- Hypertension (incl. paroxysmal), tachycardia, sweating, tremor, headache
- Risk of brain haemorrhage
- More common 4.-5. decade, possible in children
- 90% benign behaviour

Pheochromocytoma



- Gross:
  - ⇨ ***demarcated paler lesion of variable size (g-kg), possible regressive changes (haemorrhage, necrosis)***
- Micro:
  - ⇨ ***fine capillarized stroma***
  - ⇨ ***trabeculae, solid alveoli***
  - ⇨ ***large cells, granulated cytoplasm, neurosecretory granules***
  - ⇨ ***nuclear atypias are not a sign of malignancy***
- Definitive diagnosis of malignancy based exclusively on finding of metastases

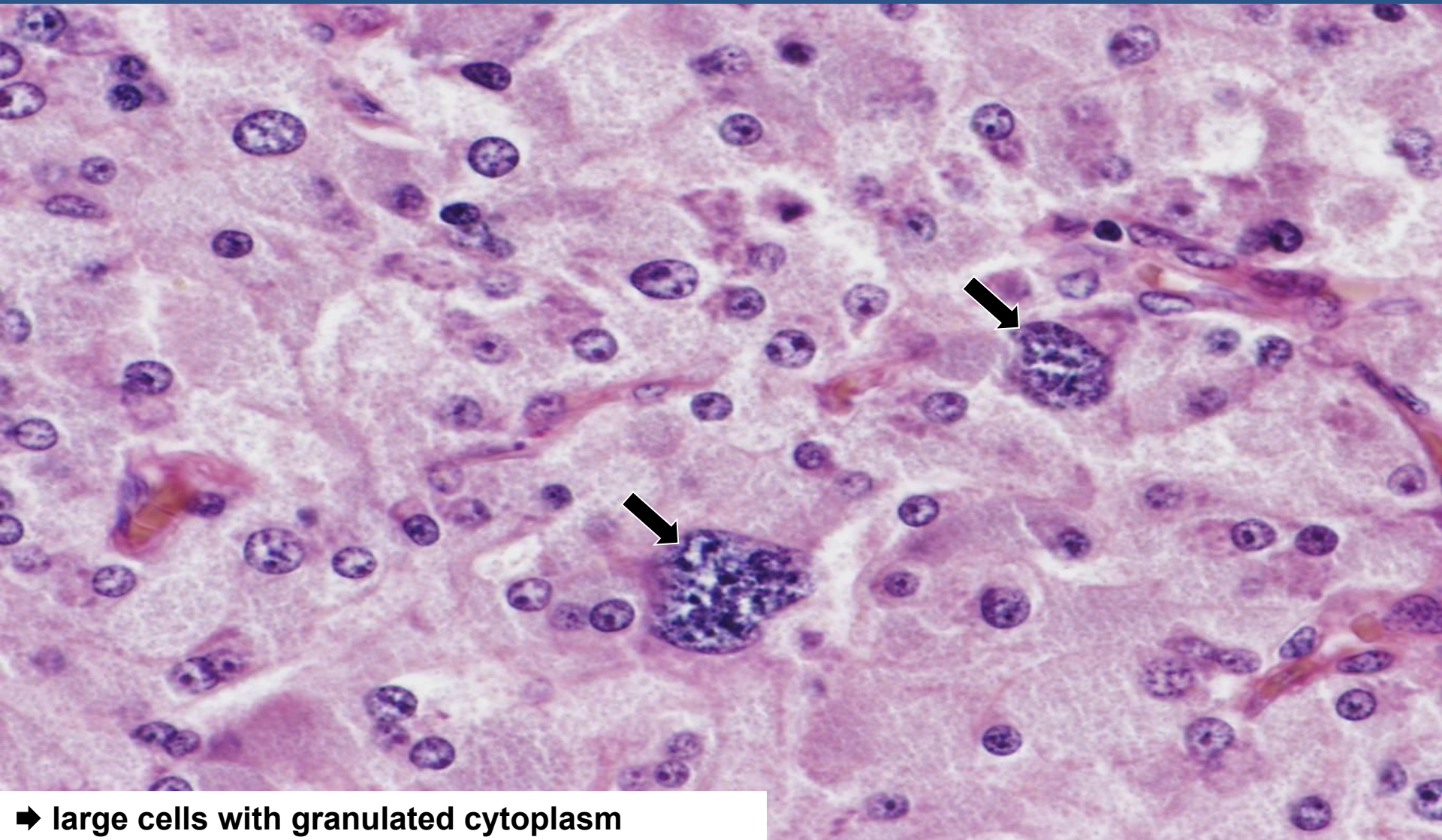
Pheochromocytoma



1 solid alveoli

➡ capillarized stroma

Pheochromocytoma



➡ large cells with granulated cytoplasm