Liver pathology (2)

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X = important, for exam
No sign = if you are interested

Liver Pathology (2)

- Toxic liver injury
- Alcoholic liver diseases
- Non alcoholic steatosis (NAFLD, NASH)
- Cirrhosis
- Diseases of the intrahepatic bile ducts
- Vascular diseases
- Liver diseases associated with pregnancy

Toxic liver injuries (1) X (the spectrum is very broad!!!)

- Intrinsic hepatotoxins
  - predictable, dosis dependence, zonal
  - Direkt, indirekt (cytotoxic, cholestatic)
  - Examples: CCl4, cloroform, mushroom poison etc
- Idiosyncratic drugs
  - Unpredictable, individual sensitivity
  - Altered drug metabolism, immunological mechanism

Toxic liver injuries (2) X

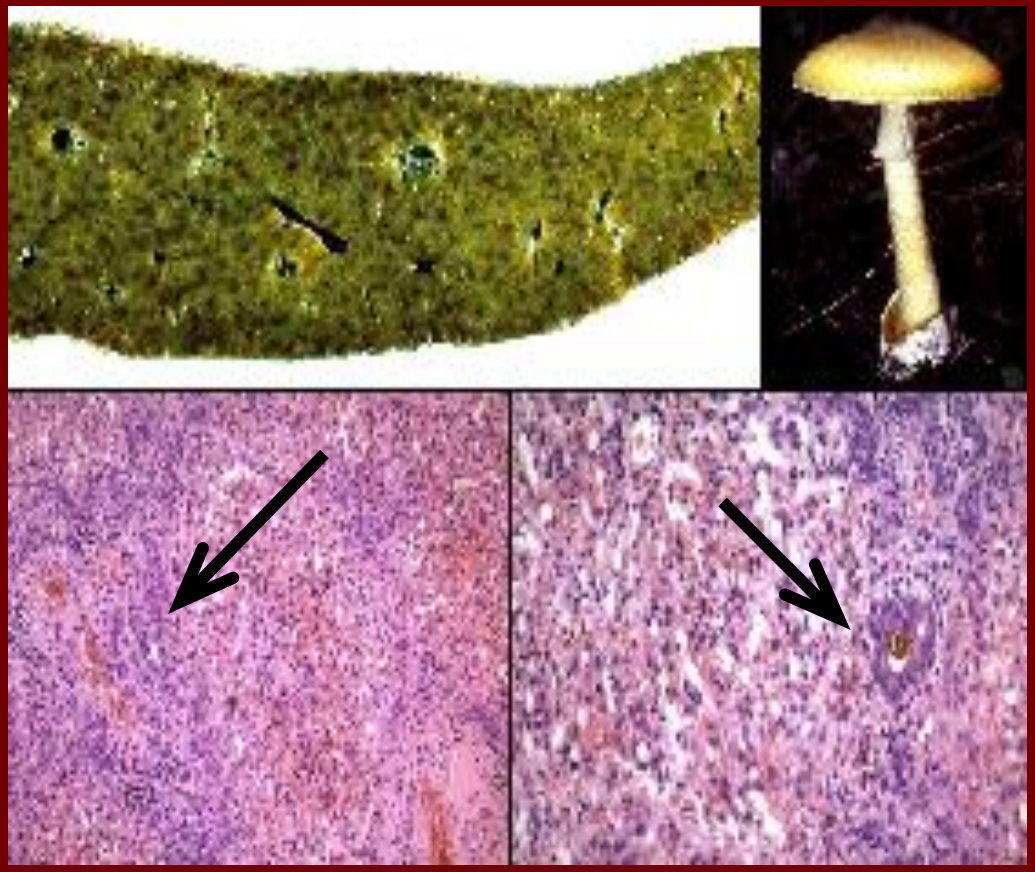
- Acute hepatotoxic effects
  - Cytotoxic, cholestatic, both
  - Ex: steatosis, necrotic, inflammatory (toxic hepatitis)
  - Mushroom poisoning (Amanita phalloides)
  - Acetaminophen (paracetamol), tetracyclins, anti-cancer drugs
  - Reye-syndrome (liver, brain mitochondrial alterations, microvesicular steatosis, often fatal, in children after taking aspirin)

Mushroom poisoning

Amanita phalloides

Extended necrosis

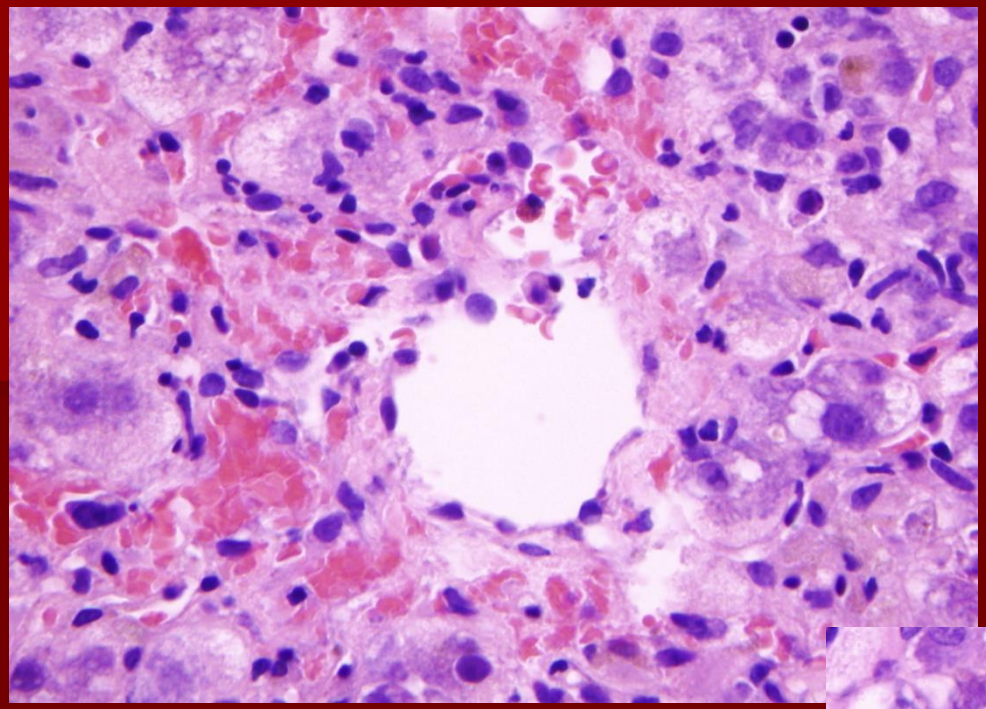
Regeneration from the bile canaliculi/stem cells

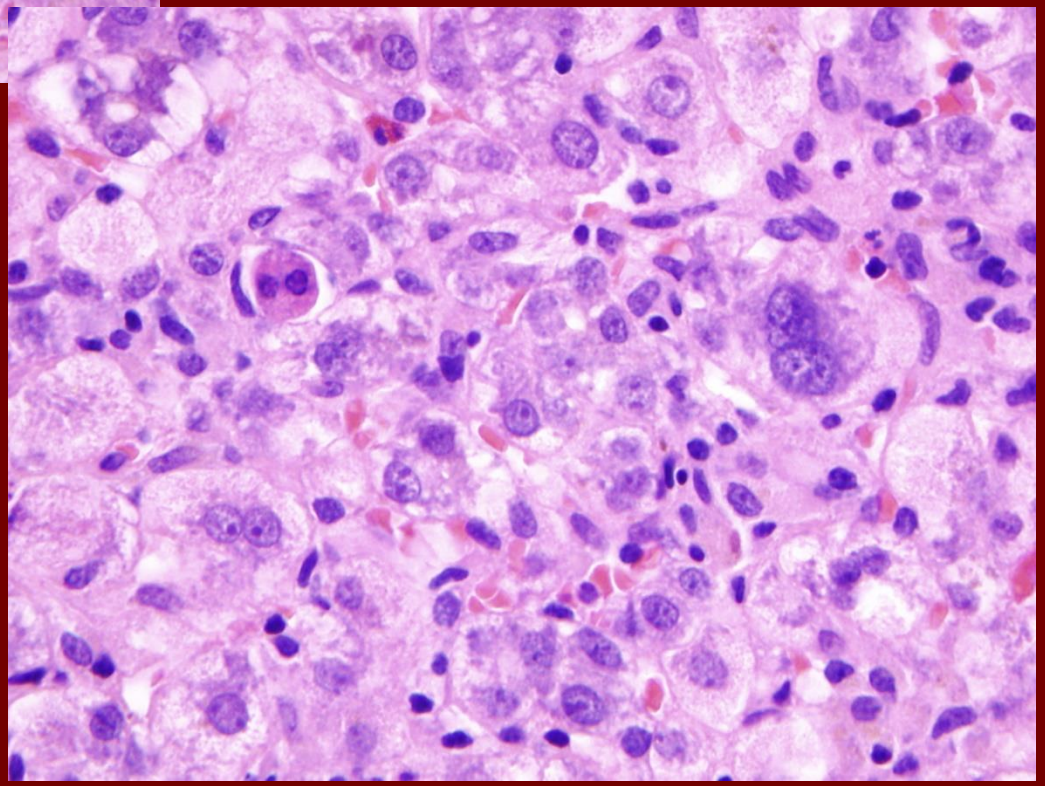


Toxic liver injuries (3) X

- *Chronic hepatotoxic injuries*
  - It can mimic all kind of liver alteration
  - CH, fibrosis, cirrhosis, steatosis, granuloma, tumor: adenoma (o.c., anabolic steroids), sarcoma (vinyl-chlorid, thorotrast)
  - INH, nitrofurantoin, methotrexat, sulfonamide etc
- *Adaptive changes*
  - Ground glass hepatocytes (P450, sER), increase of lysosomes (lipofuscin granules)

Toxic liver injury





Alcohol-related liver disease

(J.Hepatol. 2019. 70:521-530)

- 2.4 bilion people (m:1.5, f: 0.9)
- 2 million die of liver diseases each yr
- Alcohol use disorders as chronic and relapsing disease affects 1 in 10 individuals in Western world
- 50% of mortality with cirrhosis caused by alcohol
- Total per capita consumption of alcohol varies from continent to continent, from country.... (US: 10L/adult, France:12-13 L UK:11-12. Italy: 7-8L, Eastern Europe:11-13L, North Afriva/Middle East: 0-2L)
- Co-factors – influence progression and prognosis (fatty liver, metabolic syndrome, viral hepatitis, genetic factors – „lipid genes" etc)
- Higher risk of severe complications ≥210 g/w in men, ≥140 g/w in women

Alcoholic and non alcoholic liver disease

- ALD : alcoholic liver disease
- ASH : alcoholic steatohepatitis

- NAFLD : non alcoholic fatty liver disease
- NASH : non alcoholic steatohepatitis

Forms of alcohol-related liver diseases (1.)
(broad spectrum) XX

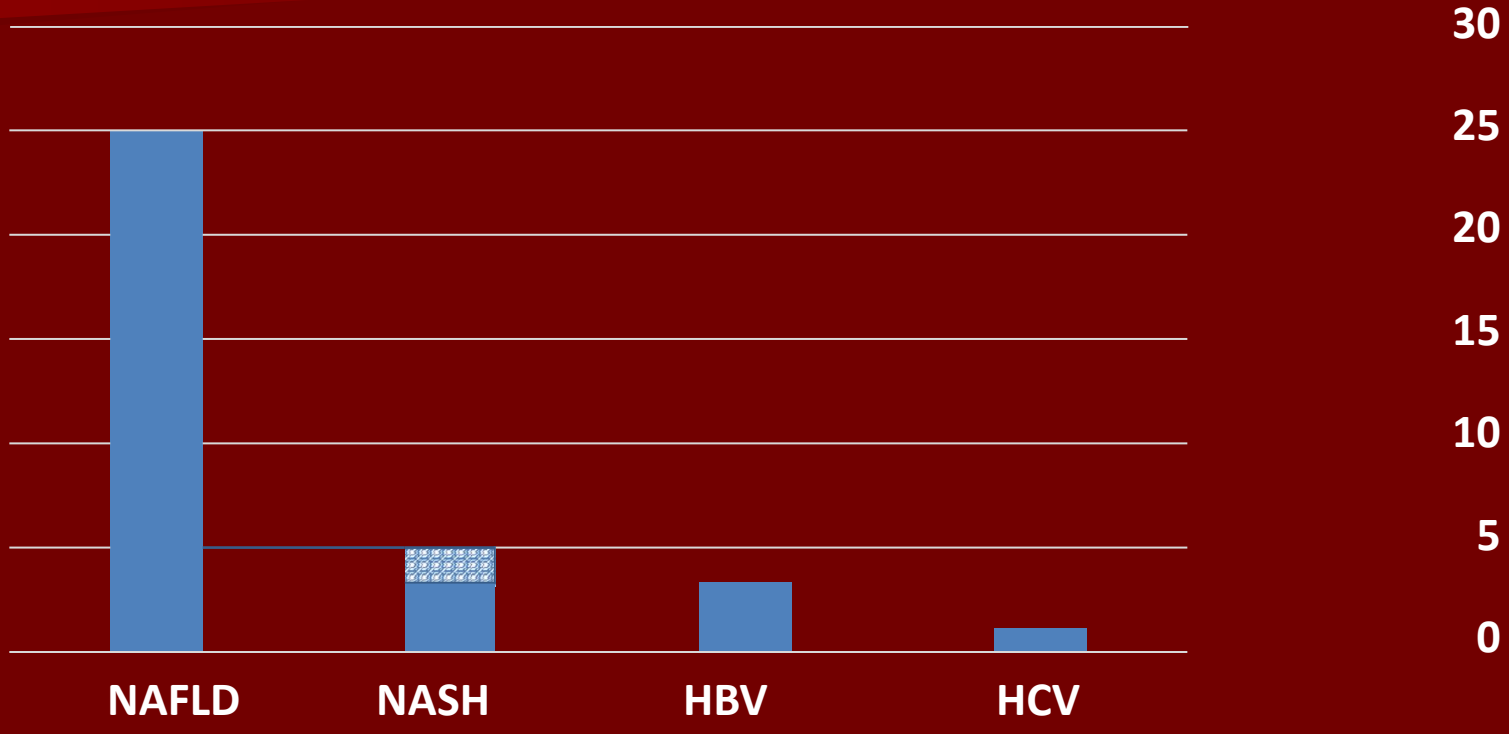
- *Alcoholic steatosis* (Fatty liver)
  - Most common
- *Alcoholic hepatitis*
- *Alcoholic cirrhosis*
  - with or without steatosis

Forms of alcohol-related liver diseases (2) X

- *Alcoholic steatosis* (Fatty liver)
  - Most common
- *Alcoholic hepatitis*
  - rapid onset of jaundice, malaise, anorexia, fever, abd.pain, leukocytosis, GOT incr ≥50 IU/ml, etc.
  - „acute-on-chronic" liver failure (hepatic and extrahepatic organ failure, mortality up to 30%), but, may be asymptomatic
  - Liver cell necrosis (mainly central), Mallory bodies (alcoholic hyalin), neutrophils, perivenular fibrosis
  - Appr. 3% progress to cirrhosis annually
  - 3 groups:
    - „definite alcoholic hepatitis", „probably alc.hep.", „possible alc.hep."
  - Grades („scorings"):
    - mild, moderate, severe
- *Alcoholic cirrhosis*
  - with or without steatosis

- NAFLD is the most prevalent chronic liver disorder worldwide
- Due to the increasing prevalence of metabolic syndrome and aging of the population, NAFLD prevalence and complications (including HCC) are projected to increase
- As many as 40 to 50% of HCC associated with NAFLD occur in non cirrhotic livers
- The most important risk factors for HCC in NAFLD are metabolic
- Lifestyle modifications are currently the most effective measures to reduce the risk of HCC in NAFLD

Global prevalence of major chronic liver disorders



GROUND KE. Av Sp Environm Med 1982;53:148; GRANT LM & LISKERMELMAN M. Ann Hepatol 2004;3:939; KLEINER DE, *et al.* Hepatology 2005;41:131321
WILLIAMS CD, *et al.* Gastroenterology 2011;140:12431; VERNON G, *et al.* Aliment Pharmacol Ther 2011;34:27485; RINELLA ME. Hepatology 2011;54:111820
CHALASANI N, *et al.* Gastroenterology 2012;142:1592609; RINELLA ME. JAMA 2015;313:226373; ESTES C, *et al.* Hepatology 2018;67:123133
YOUNOSSI Z, *et al.* Hepatology 2016;64:157786; WHO Global Hepatitis Report 2017

Etiology of NAFLD/NASH XX

Metabolic

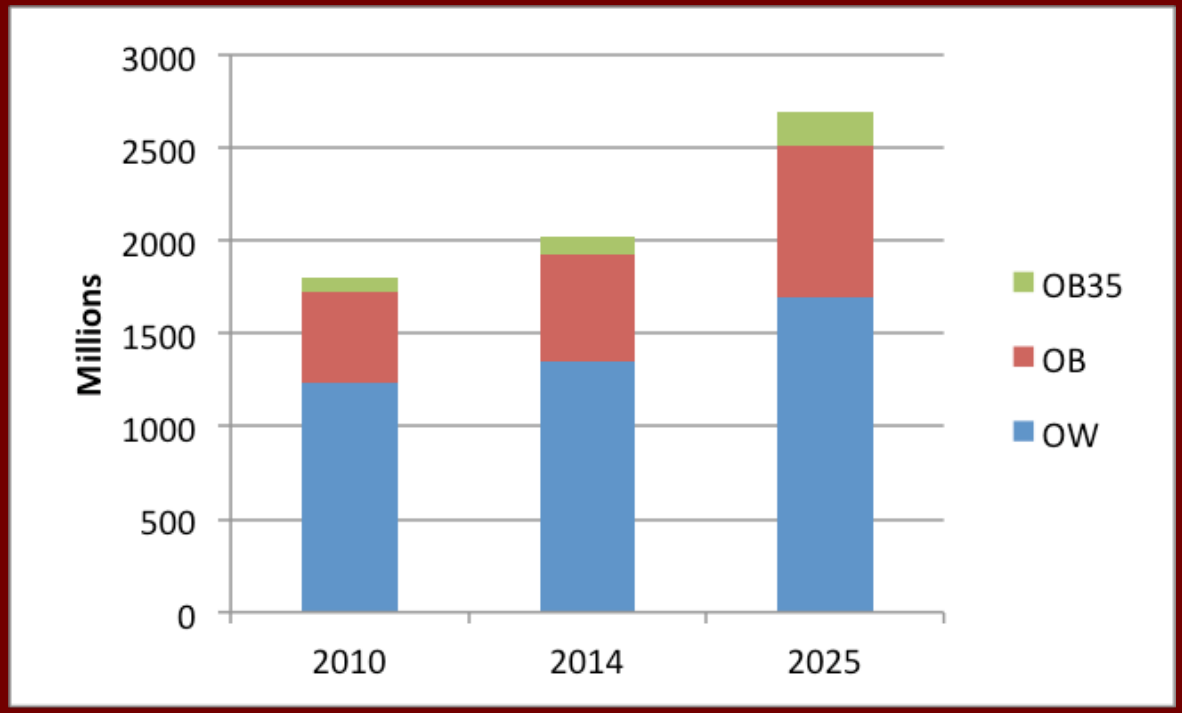
obesity, type 2 diabetes mellitus (T2DM), hyperlipidaemia, metabolic syndrome etc.)

Drugs (corticosteroids, synthetic estrogens etc)

Surgery (small bowel resection, jejunoileal bypass, etc.)

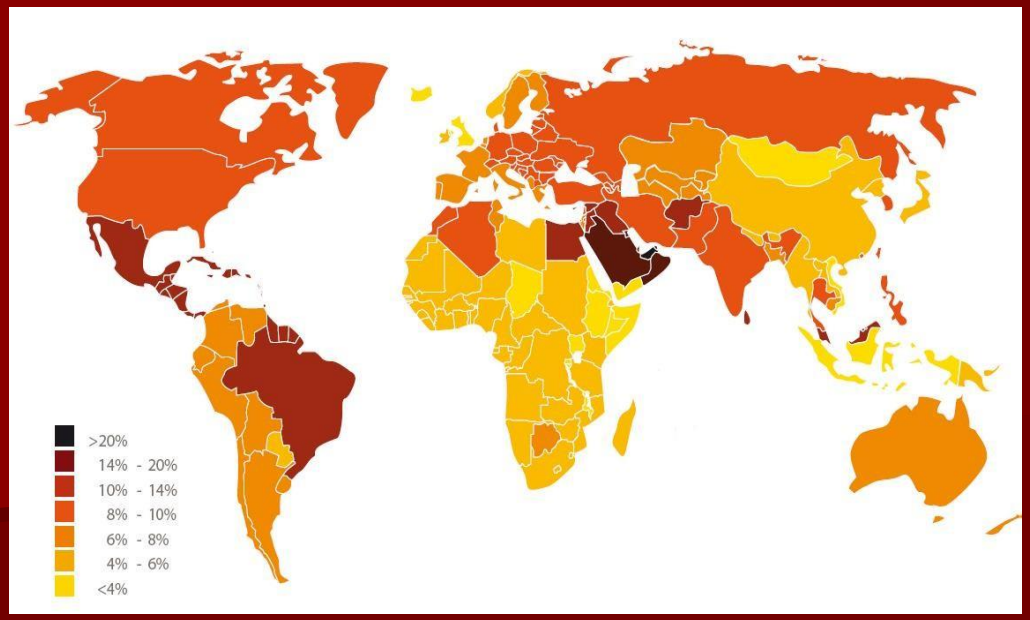
Other (a - β lipoproteinaemia, etc)

Trends for global overweight, obesity and severe obesity



http://blog.wcrf.org/wpcontent/uploads/2015/09/WOGraph.png

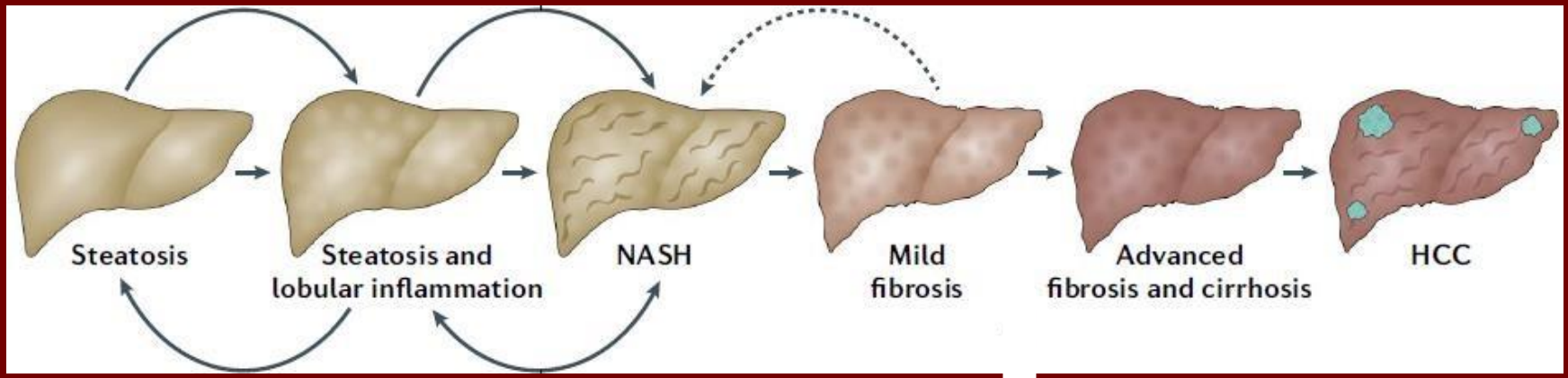
Diabetes in 2010



Diabetes in 2025

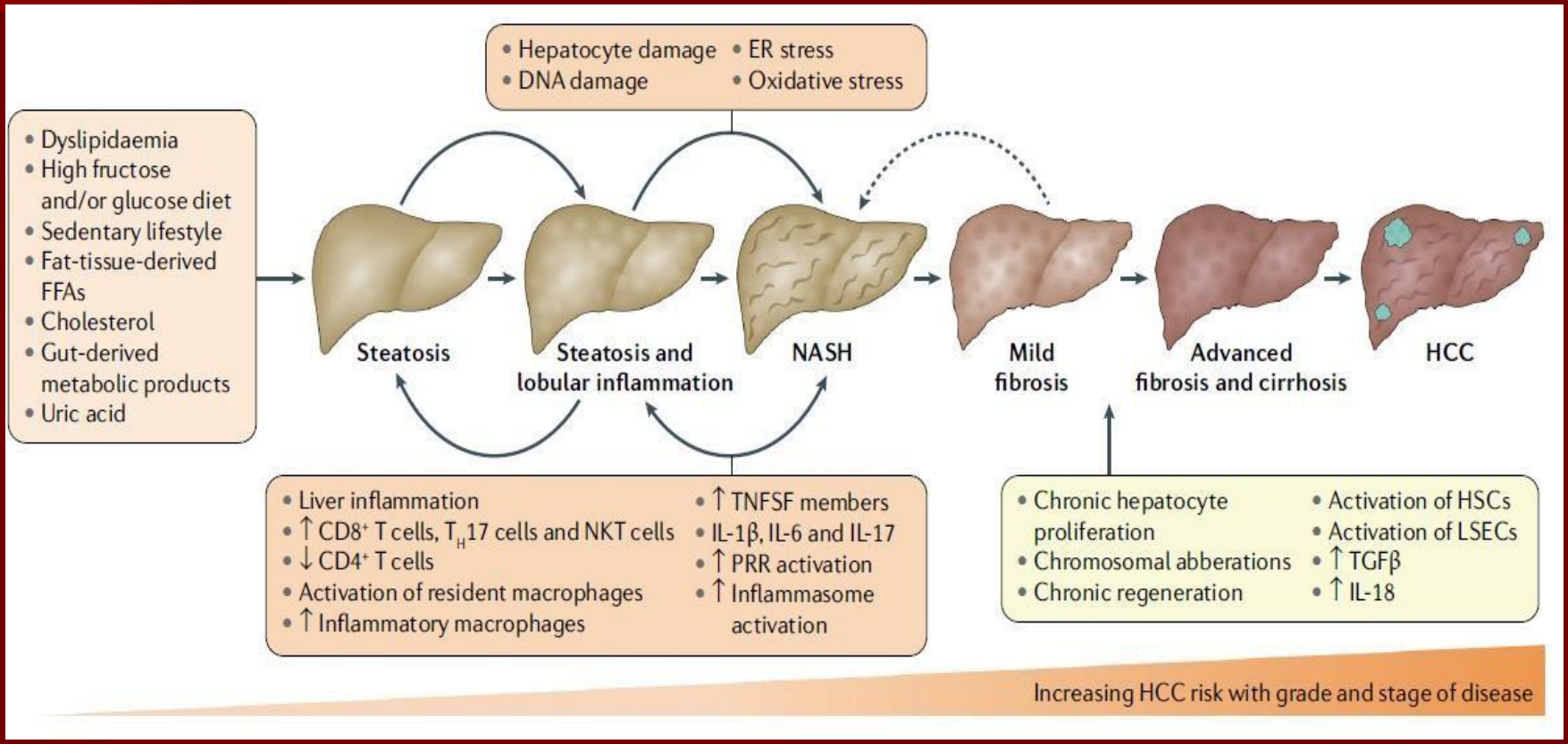
Source: www.who.org

Natural history of NAFLD X



Adapted from ANSTEE Q, et al. Nat Rev Gastroenterol Hepatol 2019;16:411428

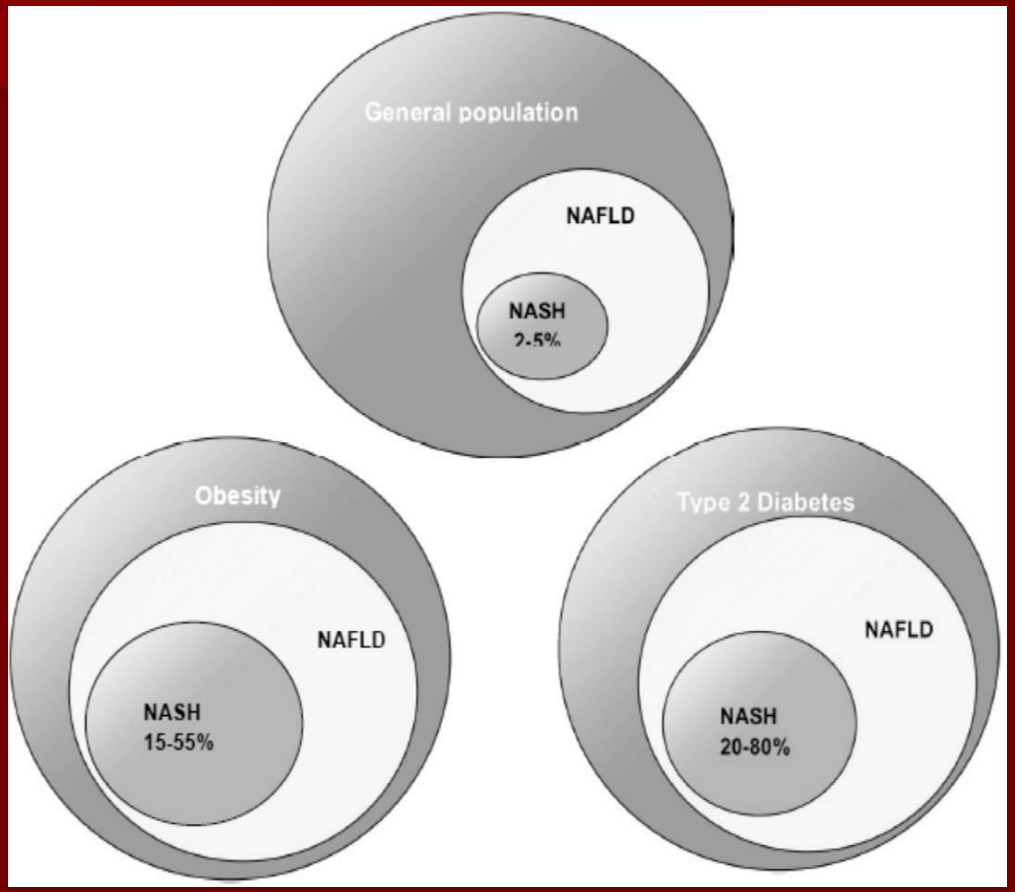
The risk of HCC progresses together with the progression of NAFLD grade and stage



ANSTEE Q, et al. Nat Rev Gastroenterol Hepatol 2019;16:411428

NAFLD The dimension of the problem

Obesity
1 billion persons overweight or obese around the world

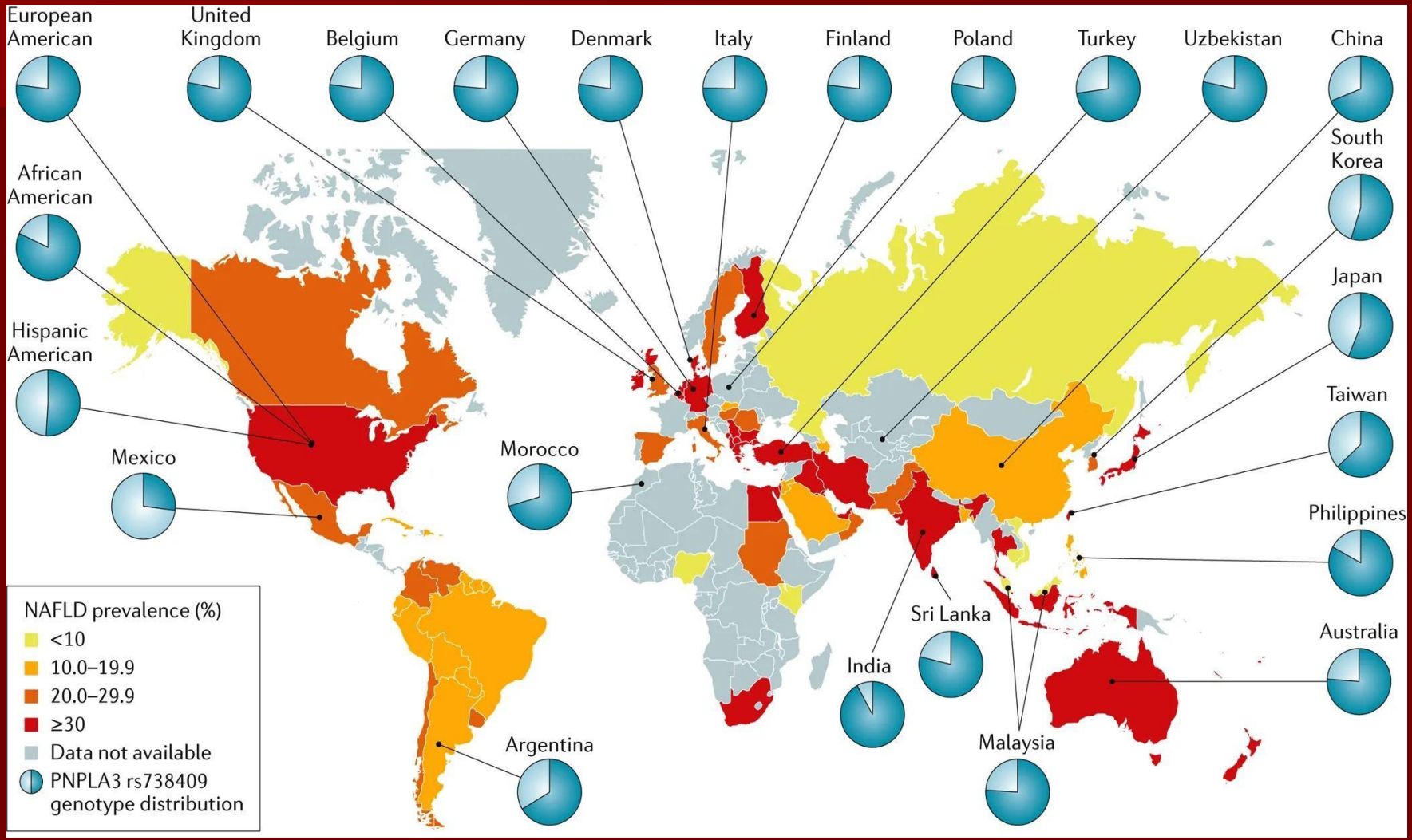


Hepatologists only see the most severe cases (the tip of iceberg), and have a scarce idea of the global extent of disease

Diabetes
> 380 milion cases
(550 in 2030)

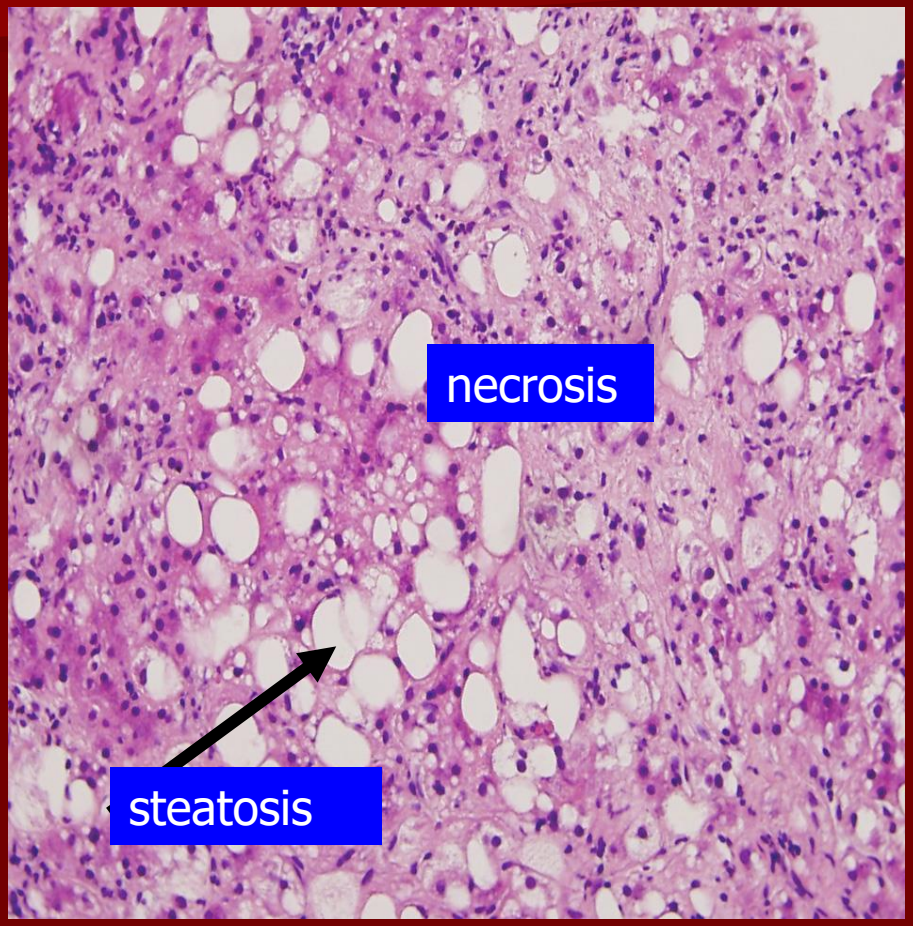
BHALA *et al*, Curr Pharma Des 2013;19:516976

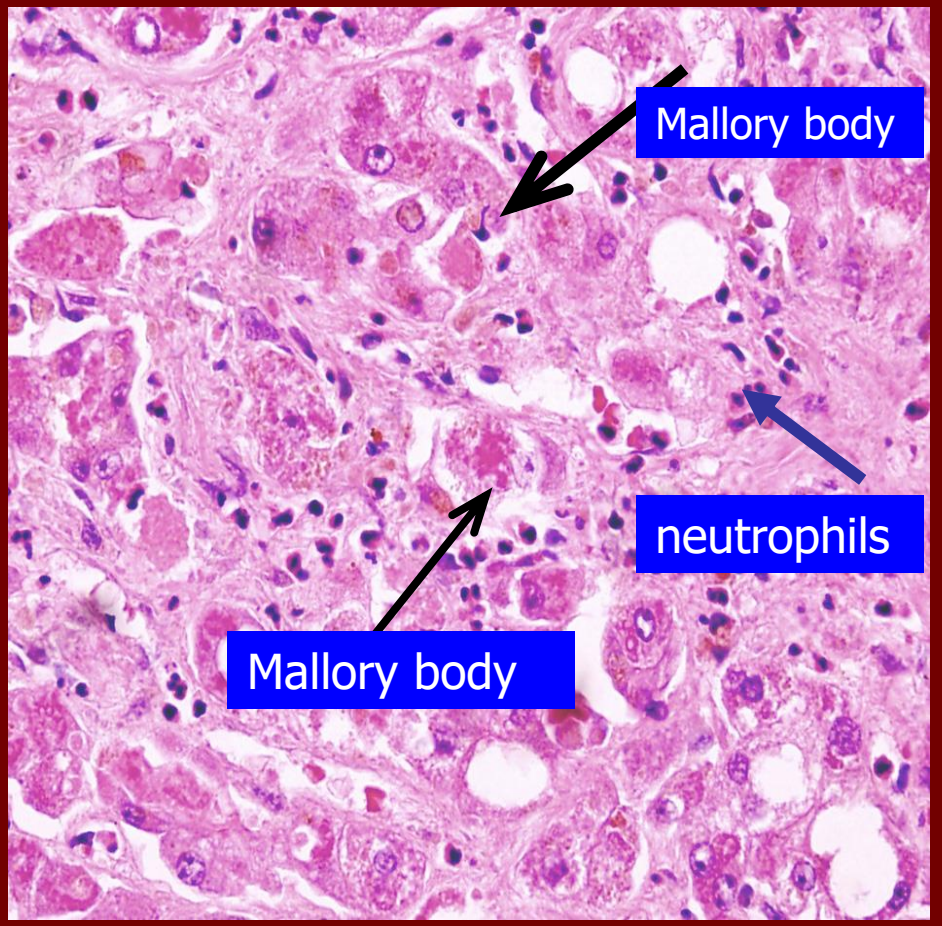
NAFLD affects one quarter of the global population



YOUNOSSI *et al,* Nat Rev Gastroenterol Hepatol 2017;15:1120

Histology of ASH/ NASH X





Histology and NAFLD

« Nonalcoholic fatty liver disease (NAFLD) includes a spectrum of histological changes that begin with simple fatty infiltration of the liver (NAFL), which may gradually progress to the development of chronic inflammation (NASH), fibrosis, and ultimately cirrhosis. …….. Currently, there are no clear criteria to identify this group of patients." *Draft Guidance from FDA, Dec 2018*

* If a diagnosis of NASH is required, then liver biopsy is necessary

- NAFLD clinical trials (eligibility and end-points)
- Comorbidities
- Suspicion of advanced liver disease

Definition of NASH (X)

Histology	Similar to ASH
	inflammation (lobular / portal)
	Mallory bodies (+ / -)
	fibrosis /cirrhosis

No alcohol abusus

No other liver disease

Obesity and diabetes as risk factors for NALD and NASH (J.Hepatol. 2019)

- T2DM is on rise
- 400 million with diabetes (in 2015), 90% T2DM (WHO)
- Diabetes-caused deaths 1,5 million in 2012
- diabetes begins to increase around puberty especially in children who are overweight
- The prevalence of NASH/NAFLD in T2DM over 60%
- T2DM accelerates the course of NAFLD, and is a predictor of advanced fibrosis and mortality

J.Hepatol.Hepatol 2019 70:531-544

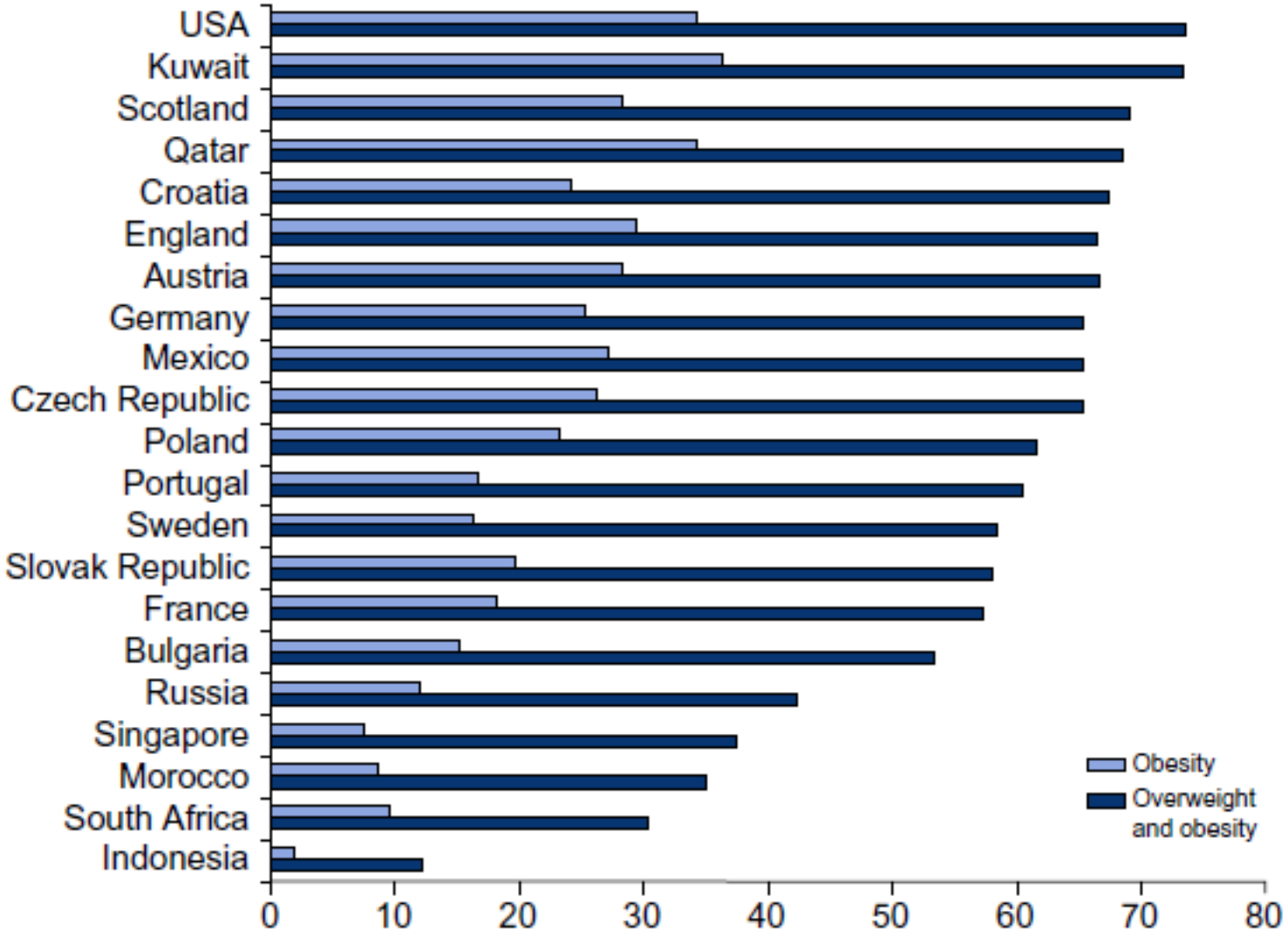


Fig. 1. Countries with the highest adult prevalence rate of overweight and obesity. (World Population: 7,505,257,673 and World Obesity Population: 774,000,000).[8,20]

Obesity and overweight in children
(WHO 2016, J.Hepatol 2019)

- 41 million children under 5 yrs overweight or obese
- 340 million between 5 – 19 yrs overweight or obese
- The numbers vary from country to country...

Joshi et al. J.Hepatol. 2017. 66:631-644, Nuzio et al. ClinRes.Hep.Gastroent. 2014. 38:277-283, Crespo et al. Metabolism 2016

NAFLD and NASH (X)

- NAFLD – global prevalence 25%
- NASH - global prevalence 3 – 5%
- Varies from country to country, with age, with ethnicity

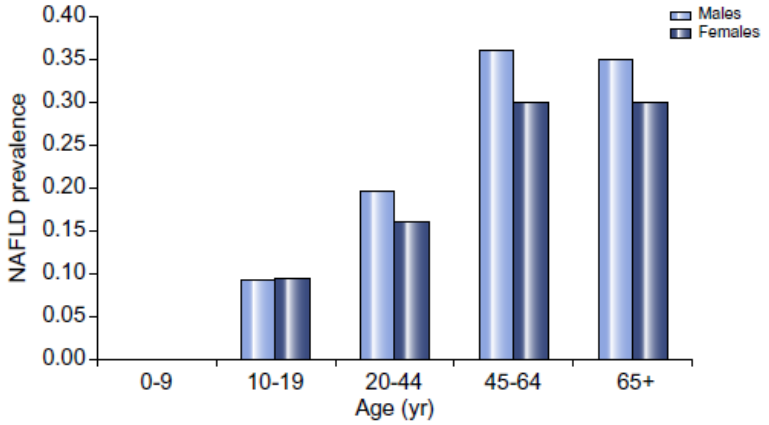


Fig. 2. Trends in the prevalence of NAFLD by age.[7,13] NAFLD, non-alcoholic fatty liver disease.

J.Hepat. 2019

Lean NAFLD

- BMI is lean
- But: may be
  - metabolic abnormality
  - congenital or acquired lipodytrophy
  - Genetic factors (PNPLA3 allele etc)
  - Congenital defects of metabolism (lysosomal acid lipase deficiancy)
  - Endocrine disorders (polycystic ovarian sy, hypothyreodism, growth hormon deficiency

Mortality in NAFLD

- Cardiovascular disease – 5-10 % in NAFLD
- Associated metabolic syndromes
- Cirrhosis
- HCC – 7 fold increase
- Transplantation

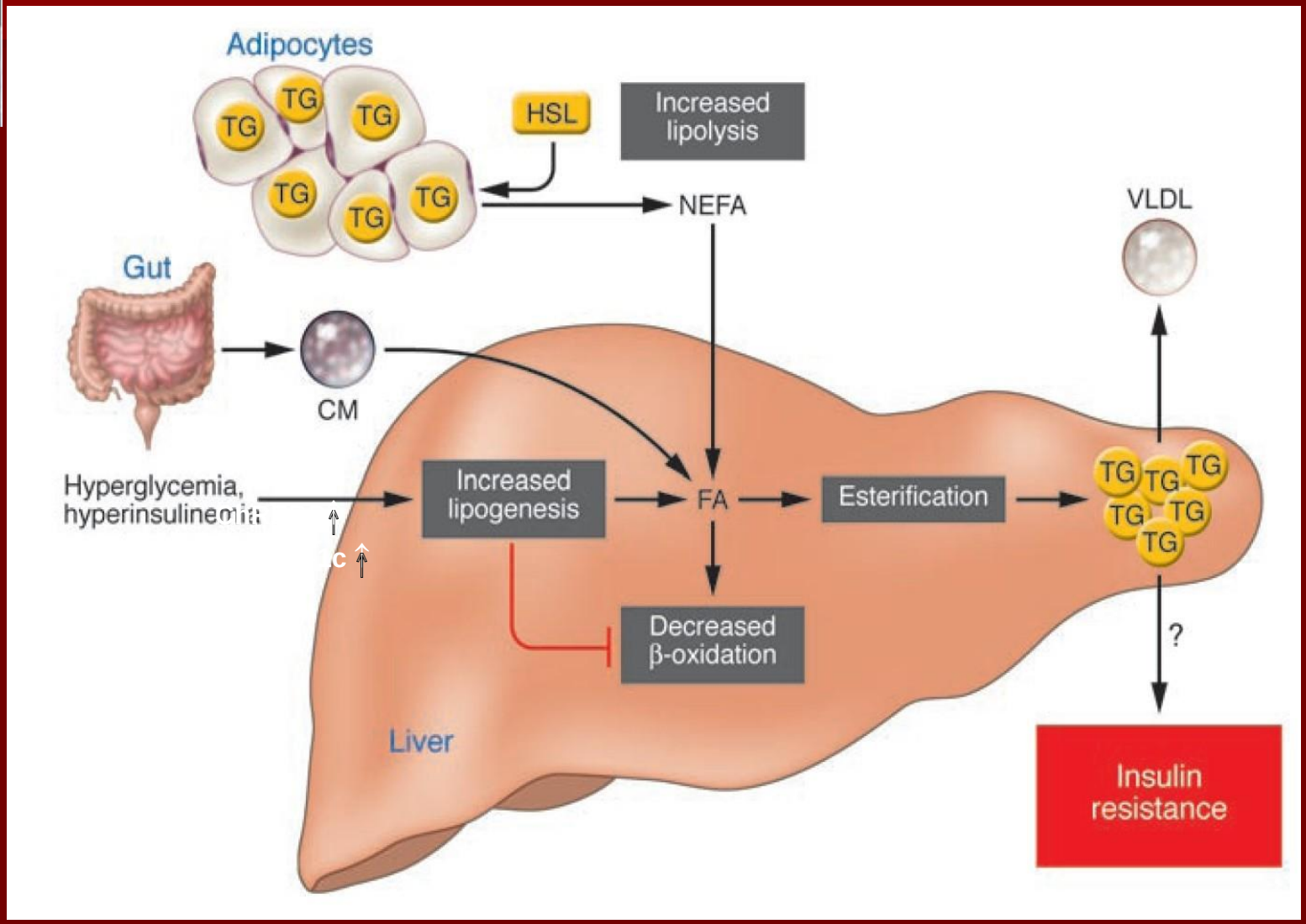
Prof Francesco Negro: Natural History of NASH and HCC

NAFLD is the most prevalent chronic liver disorder worldwide: 25% of the global population

- **Due to the increasing prevalence of metabolic syndrome and aging of the population, NAFLD prevalence and complications (including HCC) are projected to increase – 10-fold increase in past 10-15 years**
- **As many as 40 to 50% of HCC associated with NAFLD occur in non- cirrhotic livers**

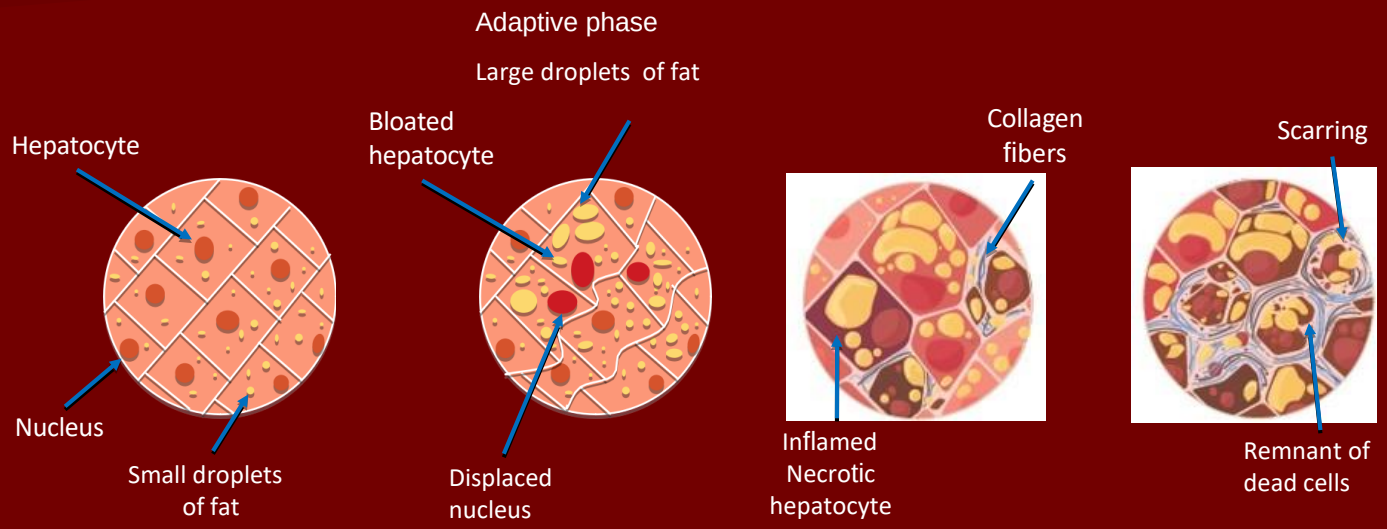
Prof Massimo Pinzani: PATHOPHYSIOLOGY OF NAFLD AND NASH

Metabolic Defects Leading to Steatosis



Postic and Girard, J

NASH Fibrosis: Stage-dependent Mechanisms



No evident necrosis

Defective Autophagy
LIPOTOXICITY
Oxidative Stress Genetic factors

Evident necrosis

Chronic Wound Healing Increase intestinal permeability Complex inflammatory networks Genetic factors

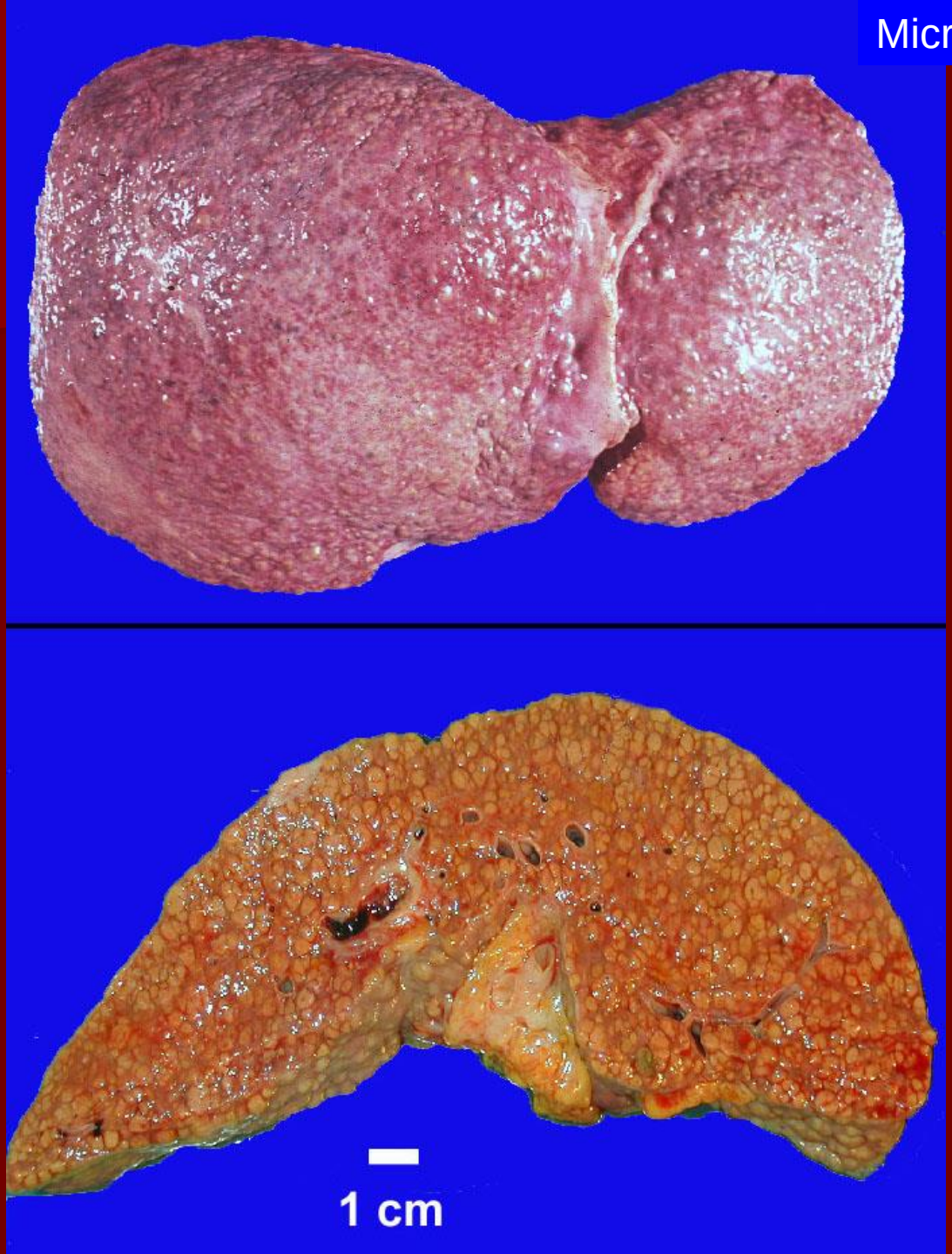
CIRRHOSIS (1) XX

- Cirrhosis is the end stage of chronic liver diseases characterized by destruction of normal hepatic architecture by fibrous septa, formation of regenerative nodules
  - (fibrotic septa, death/regeneration of hepatocytes, ductular reaction and varying degree of inflammation)

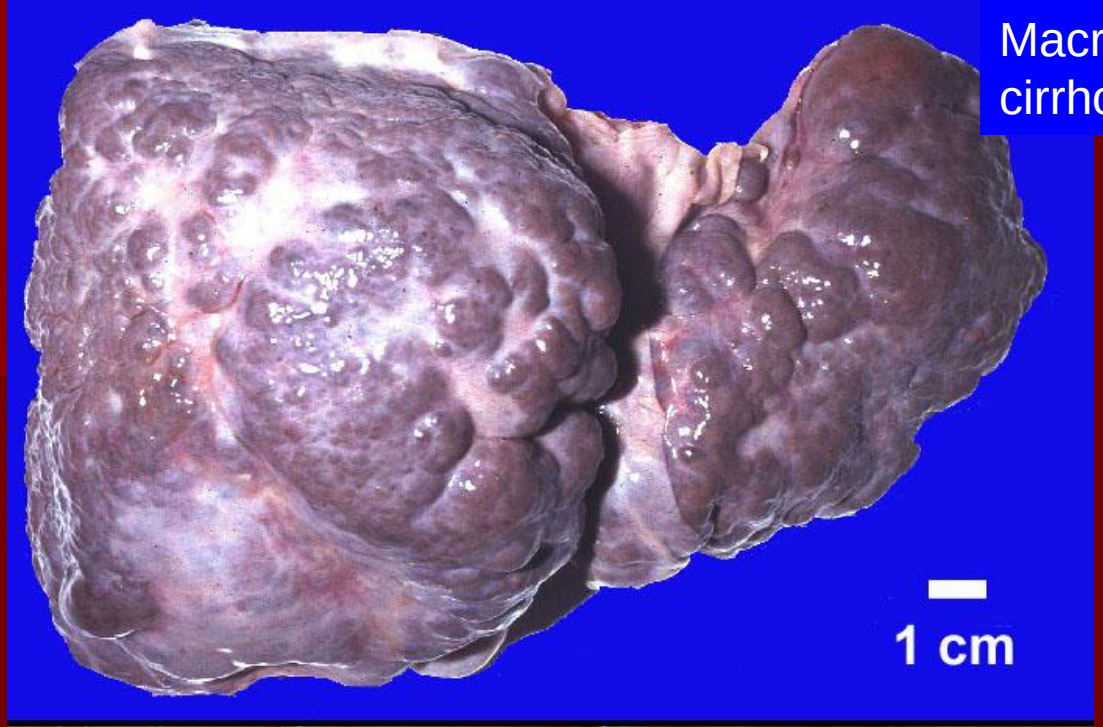
Classification of cirrhosis XX

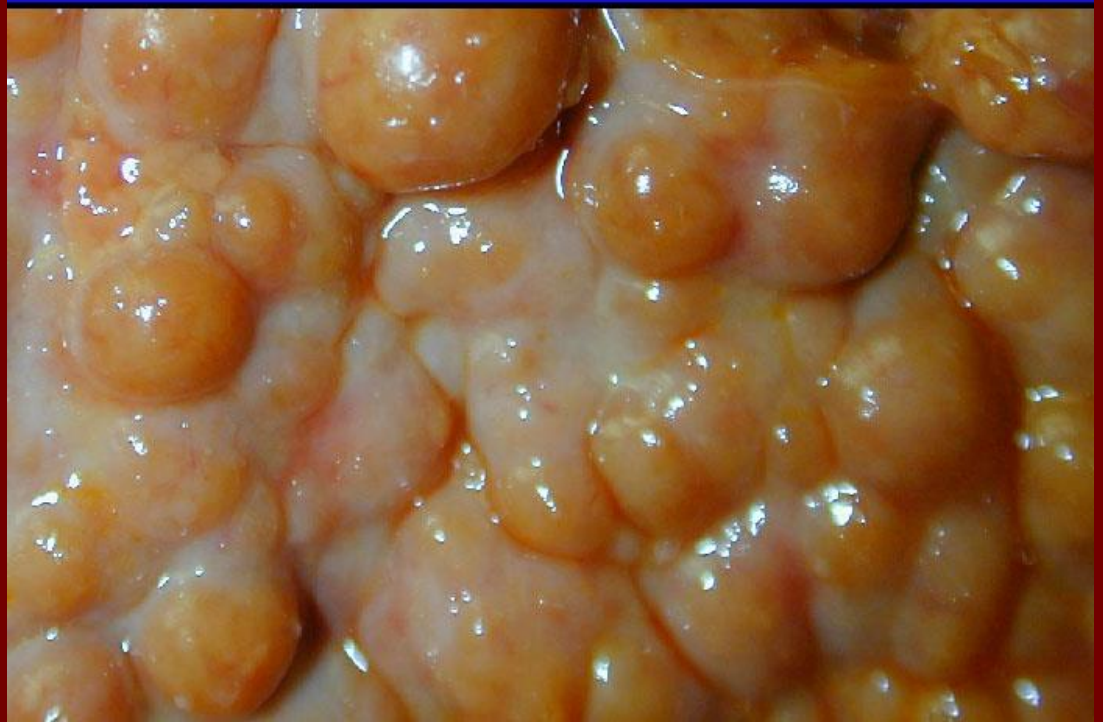
- *Morphological* (based on nodular pattern)
  - Micronodular (3 mm, Laennec, „portal, septal, nutritional”)
  - Macronodular („postnecrotic, posthepatitic, multilobular”)
  - mixed
- *Etiological*
  - Alcoholic, nutritional
  - Viral, postnecrotic, toxic, autoimmune
  - Metabolic (diabetes – NASH, Fe, Wilson, AAT, glycogenosis, tyrosinemia, Gaucher, Niemann-Pick etc)
  - Biliary (primary, secondary)
  - Other (infectious agents etc)

Micronodular cirrhosis

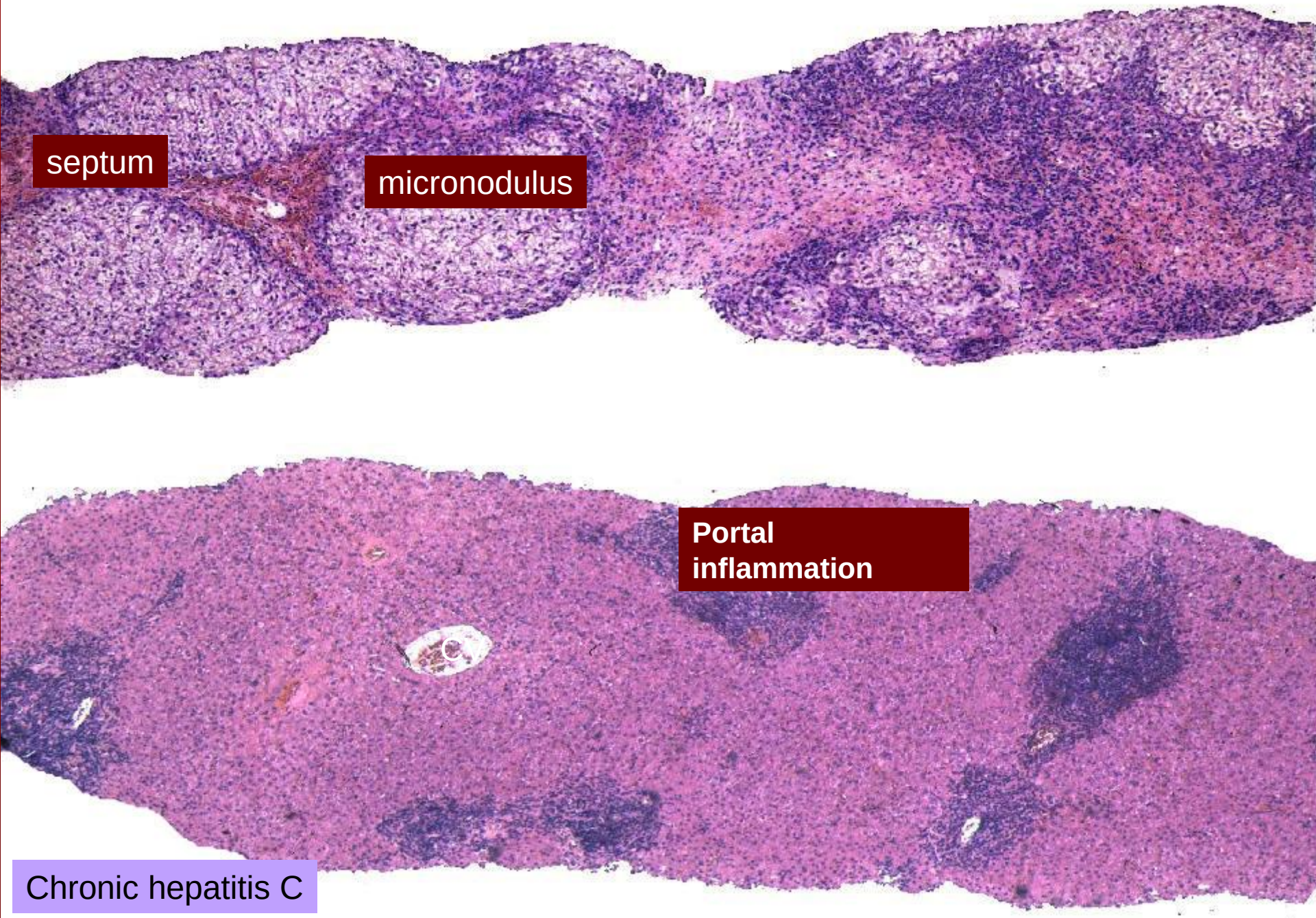


Macronodular/mixed cirrhosis

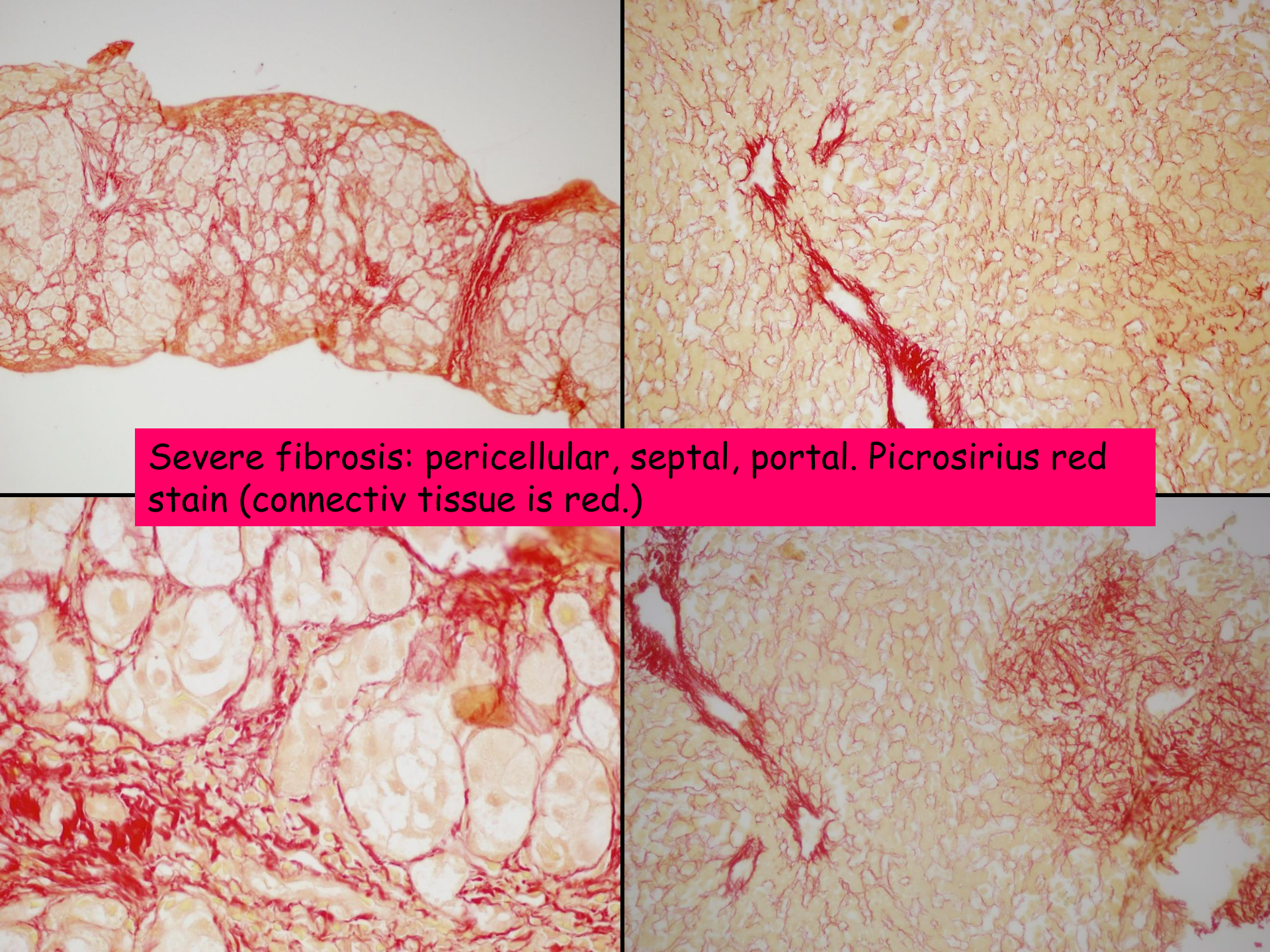




Micronodular cirrhosis. HE staining

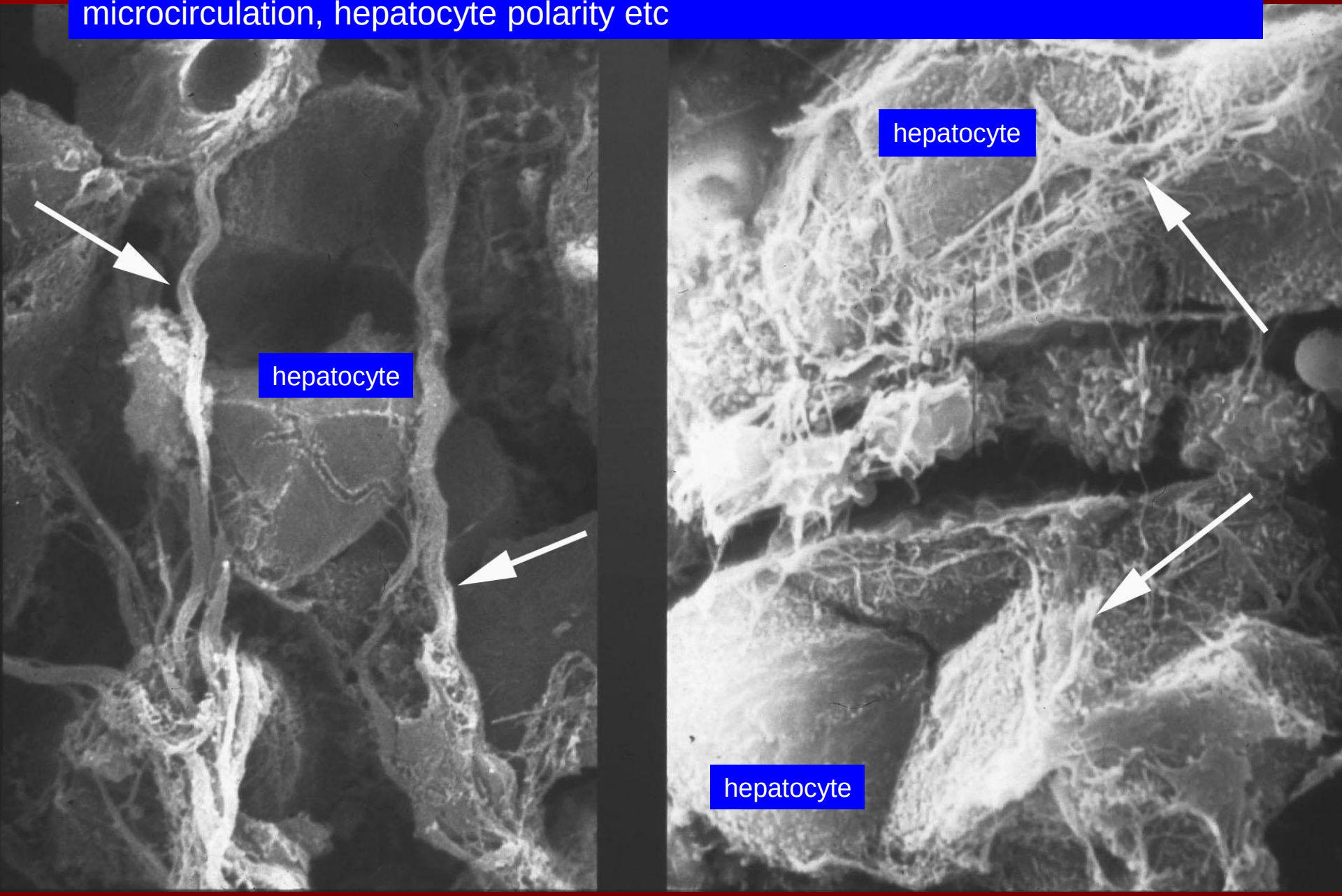


Chronic hepatitis C



Severe fibrosis: pericellular, septal, portal. Picrosirius red stain (connectiv tissue is red.)

Distorsion of the liver architecture, formation of septa and nodules. Change in microcirculation, hepatocyte polarity etc



Features and complication of cirrhosis (1) XX

- Liver insufficiency
  - Icterus
  - Hepatic encephalopathy (I-IV stadium)
  - Foetor hepaticus
  - Hepatorenal syndrom
  - Coagulation disturbances
  - Hypalbuminaemia
  - Endocrin alterations (feminisation, gynecomastia, testicular atrophy, impotencia, spider nevi, erythema plantare, palmare etc)

Features and complication of cirrhosis (2) XX

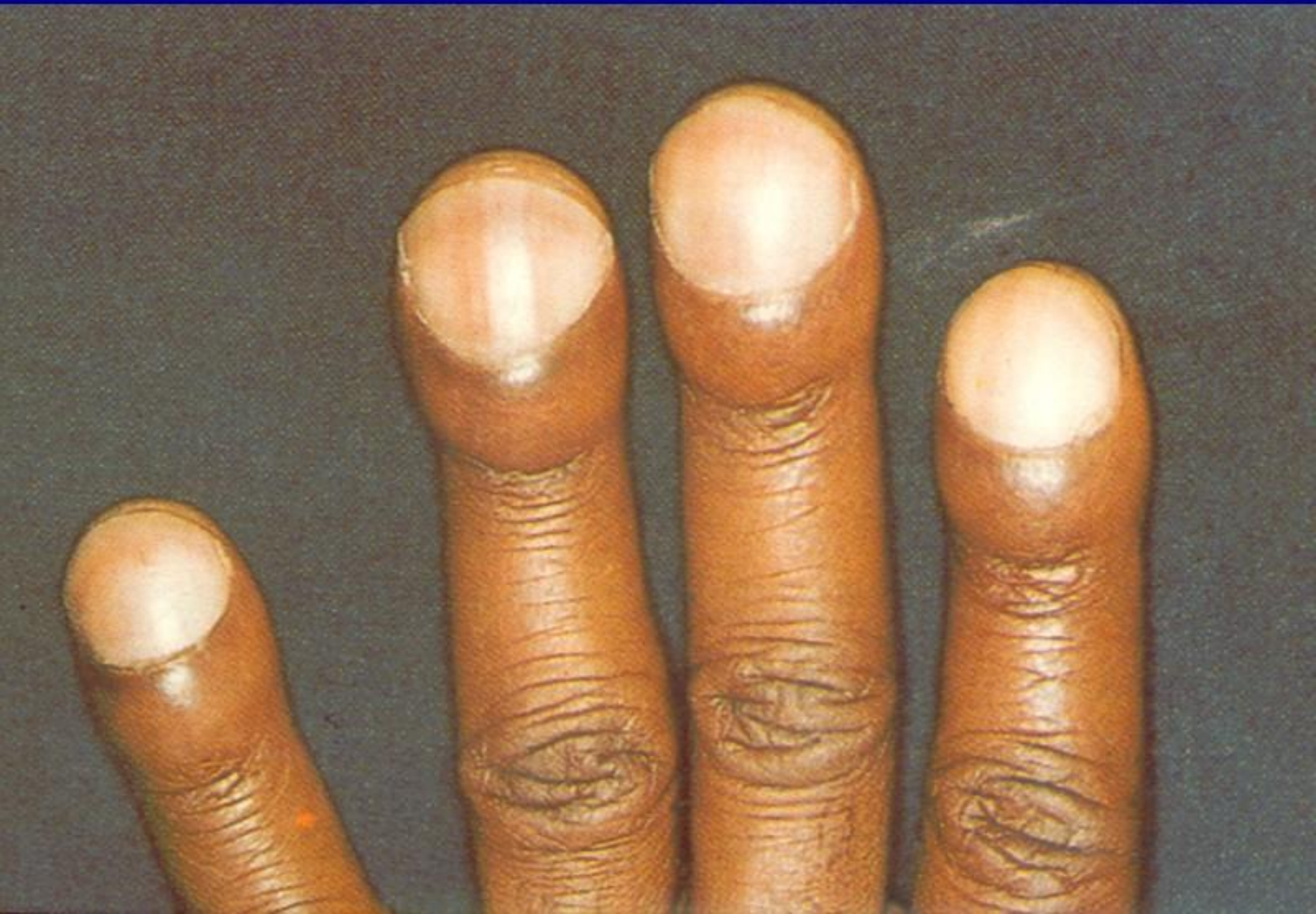
- Liver insufficiency (2)
  - Portal hypertension
    - Causes: prehepatic (v.portae thrombosis), intrahepatic (cirrhosis, PBC, Shistosomiasis), posthepatic (hepatic veins thrombosis – Budd-Chiari-syndrome, veno-occlusive disease)
    - Consequences
      - Ascites
      - Varices (esophageal, portosystemic shunt, anorectal, caput medusae)
      - Splenomegaly (hypersplenism)

Nemesánszky-Schaff-Szalay Hepatologia Oktató CD 2004 Falk

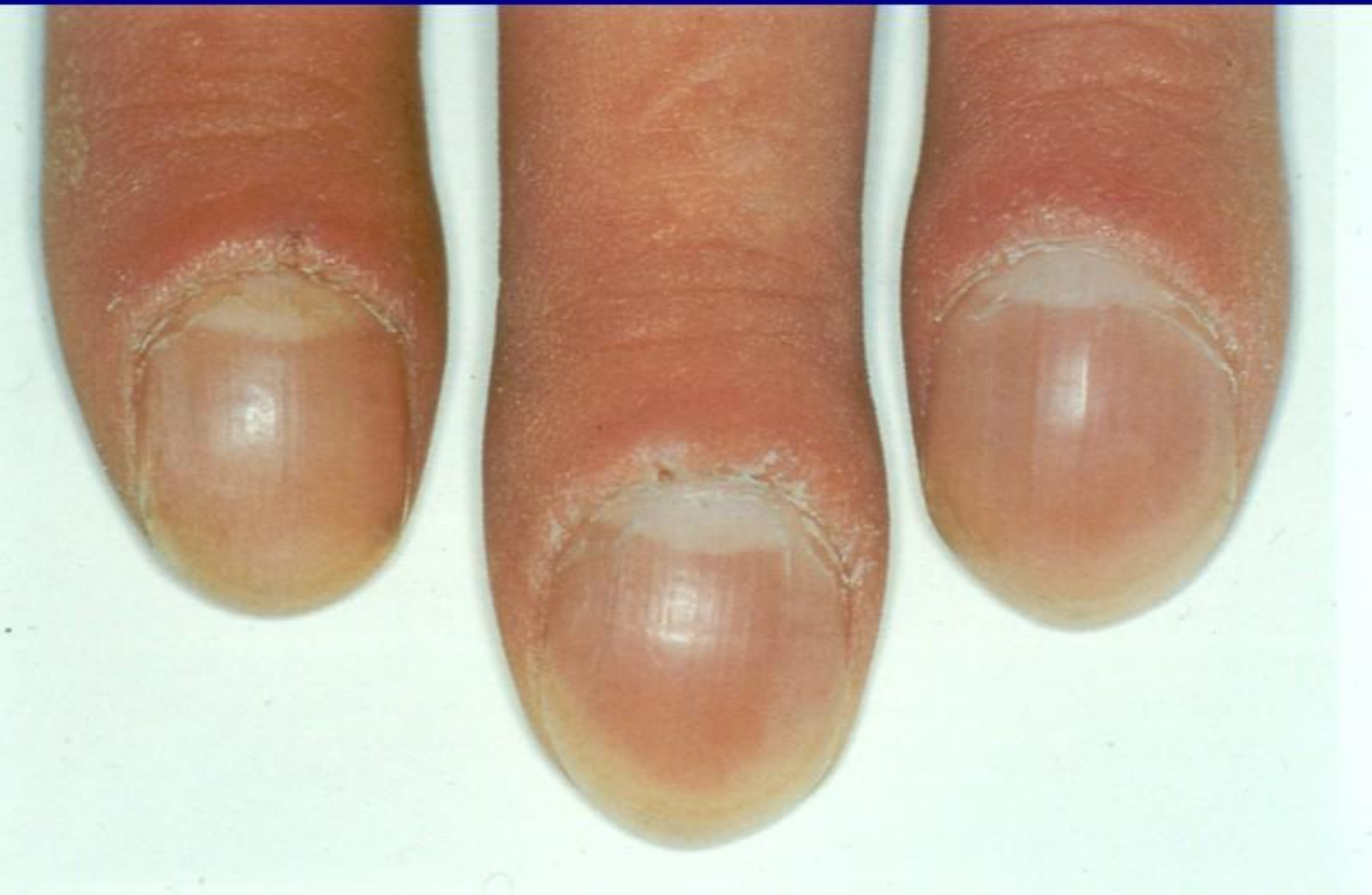
Nemesánszky-Schaff-Szalay Hepatologia Oktató CD 2004 Falk

Nemesánszky-Schaff-Szalay Hepatologia Oktató CD 2004 Falk

Clubbing of the nails

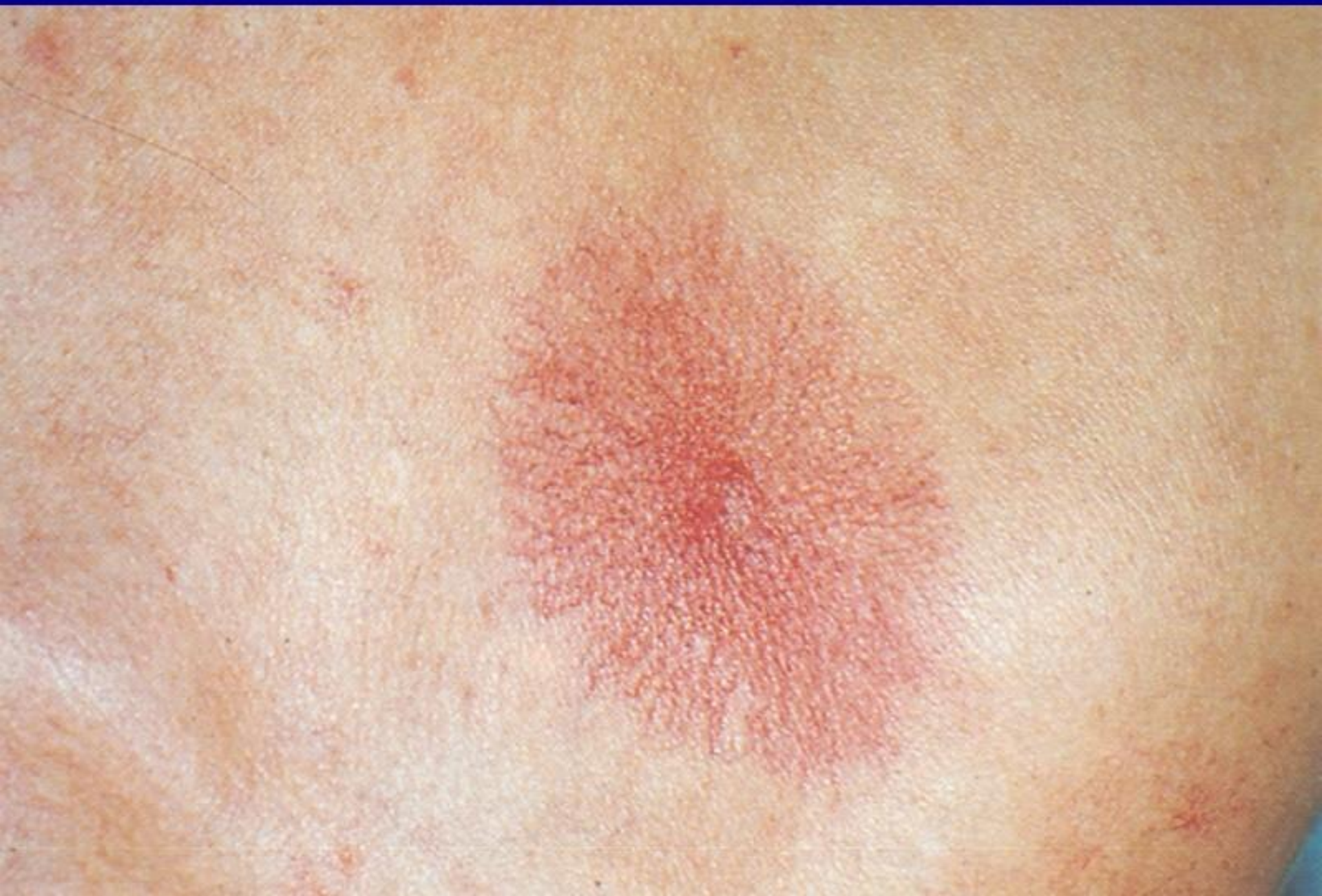


„Ground glass” nails



Nemesánszky-Schaff-Szalay Hepatologia Oktató CD 2004 Falk

Spider nevus



Causes of death in cirrhosis XX

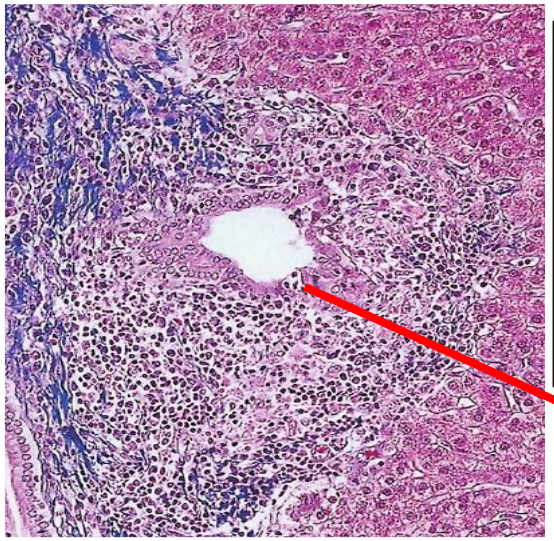
- Varix rupture (bleeding esophageal varices)
- Hepatic failure (encephalopathy)
- Intercurrent diseases

Diseases of intrahepatic biliary system XX

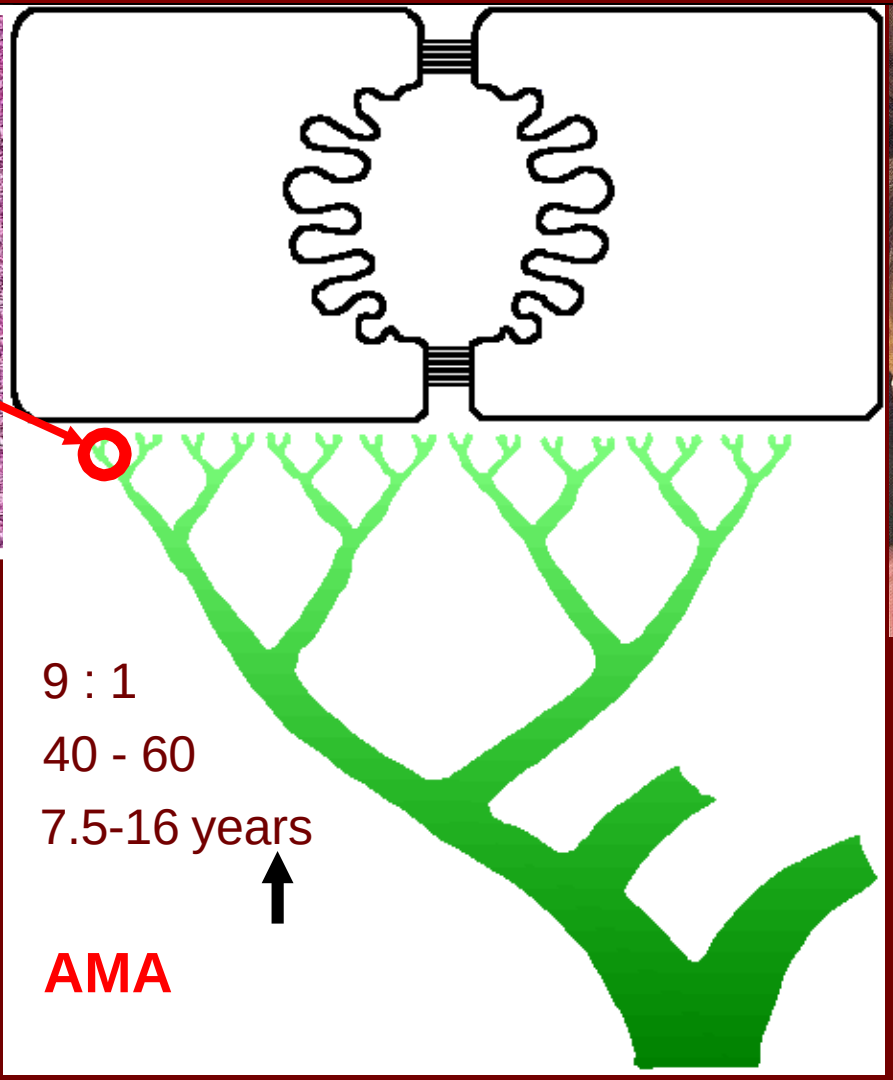
- Primary biliary „cirrhosis” - **cholangitis** (PBC)
  - Autoimmune, female predominance, ALP, AMA, seBi, hist:: non supp. cholangitis, ductular proliferation, bile duct loss, „cirrhosis”. 4 stadiums
- Secondary biliary cirrhosis
  - Following bile duct obstruction (stone, tumor, structure), bile duct dilatation, cholestasis
- Primary sclerosing cholangitis (PSC)
  - Autoimmune, male predominancy, colitis ulcerosa, medial/large bile duct narrowing , onion skin fibrosis

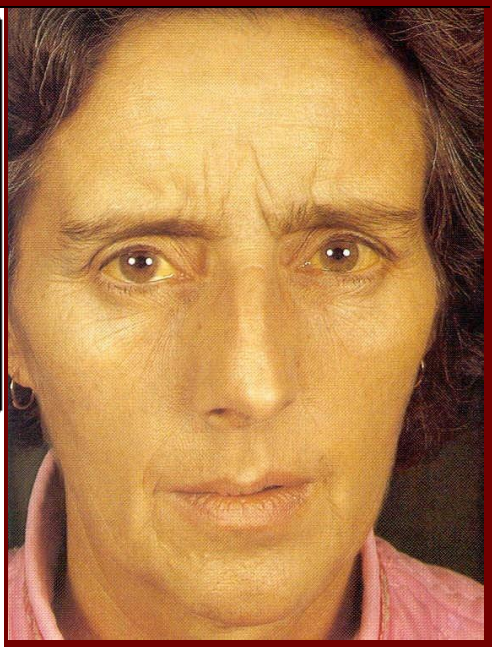
Primary biliary cholangitis* (PBC)

Characteristics



Florid, non-suppurative, destructive cholangitis





Sherlock and Summerfield, 1991

Women : Men **Age at diagnosis**

Survival without treatment

Cholestasis ALP, γGT

Autoantibodies

Symptoms

- Fatigue
- Pruritus
- Sicca syndrome
- …

Amsterdam UMC
University Medical Centers

* Beuers , Gershwin, …Poupon. J Hepatol 2015;63:1285

Primary biliary cholangitis:

Potential pathogenetic mechanisms

Immune-mediated bile duct injury

↓

Aggravation of bile duct injury by hydrophobic bile acids

↓

Cholestasis with retention of hydrophobic bile acids in liver

↓

Fibrosis, cirrhosis

↓

Liver failure

Genetic Predisposition

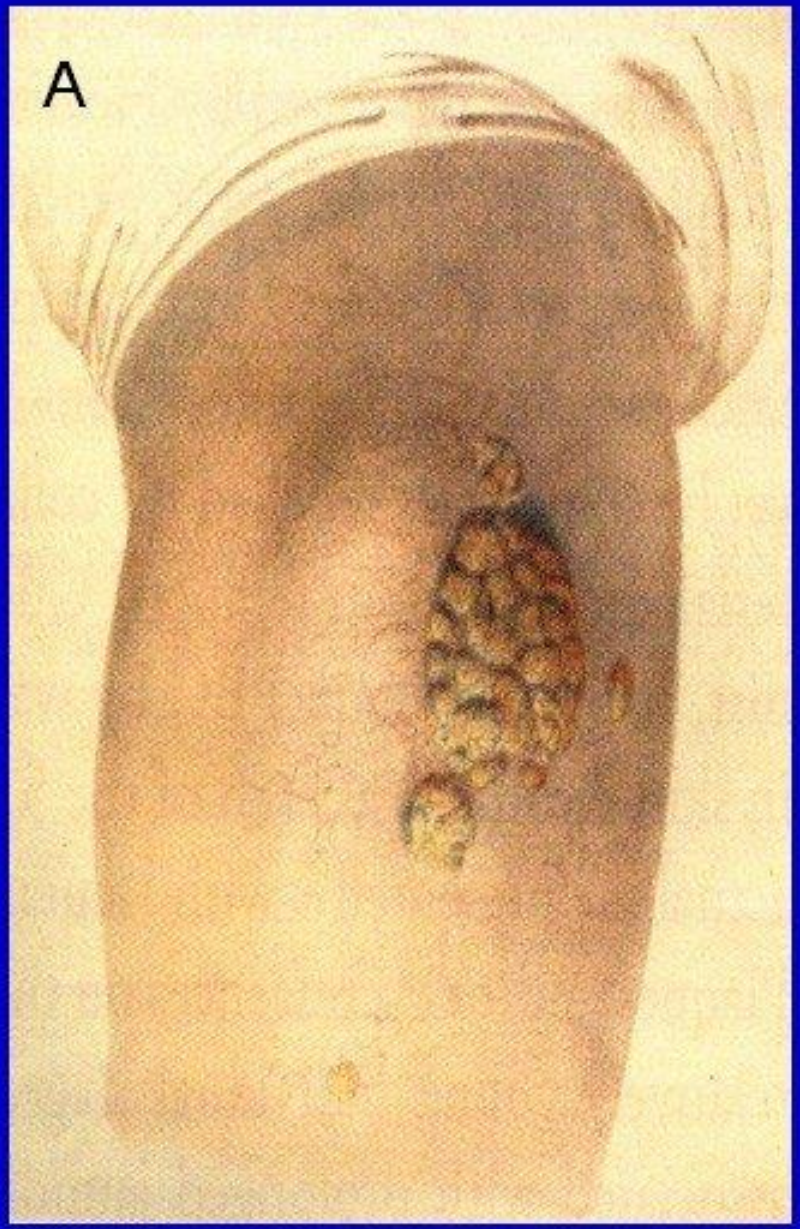
Environmental factors
(molecular mimicry)

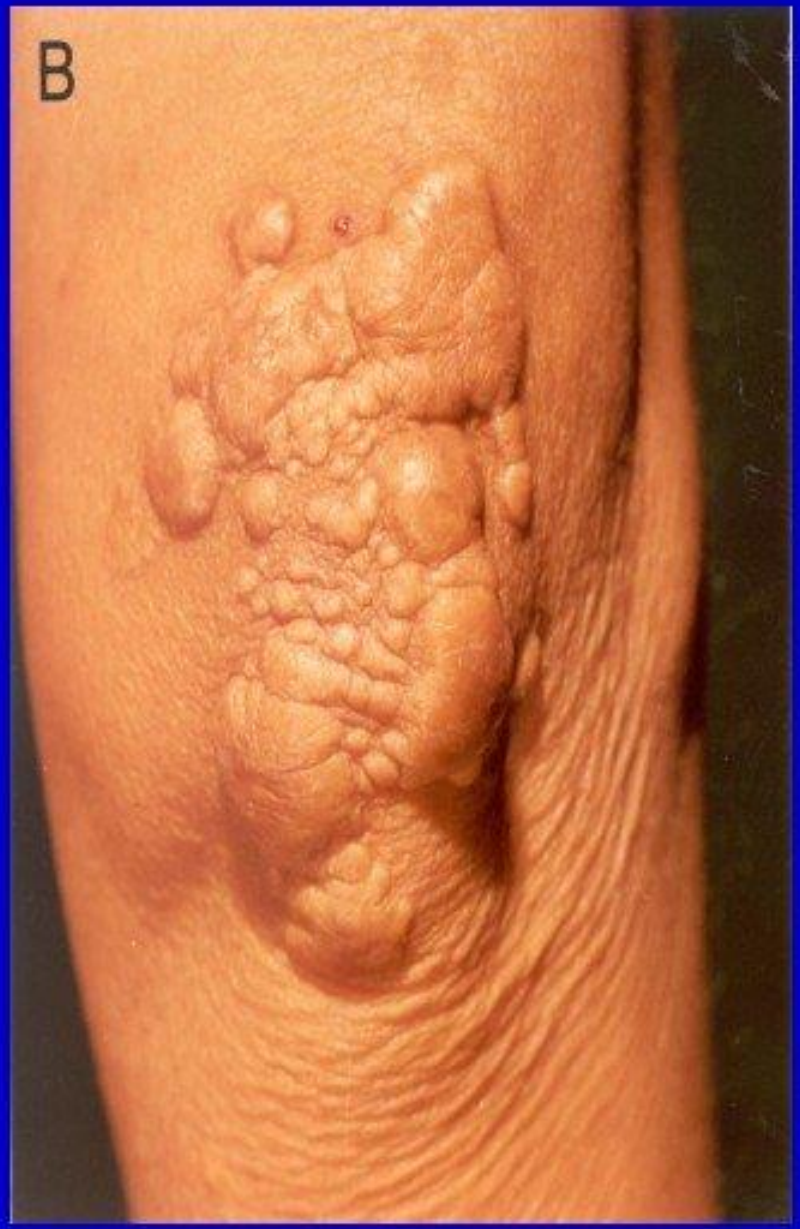
Cellular/humoral immune response

Beuers, Boyer, Paumgartner. Hepatology 1998;28:1449

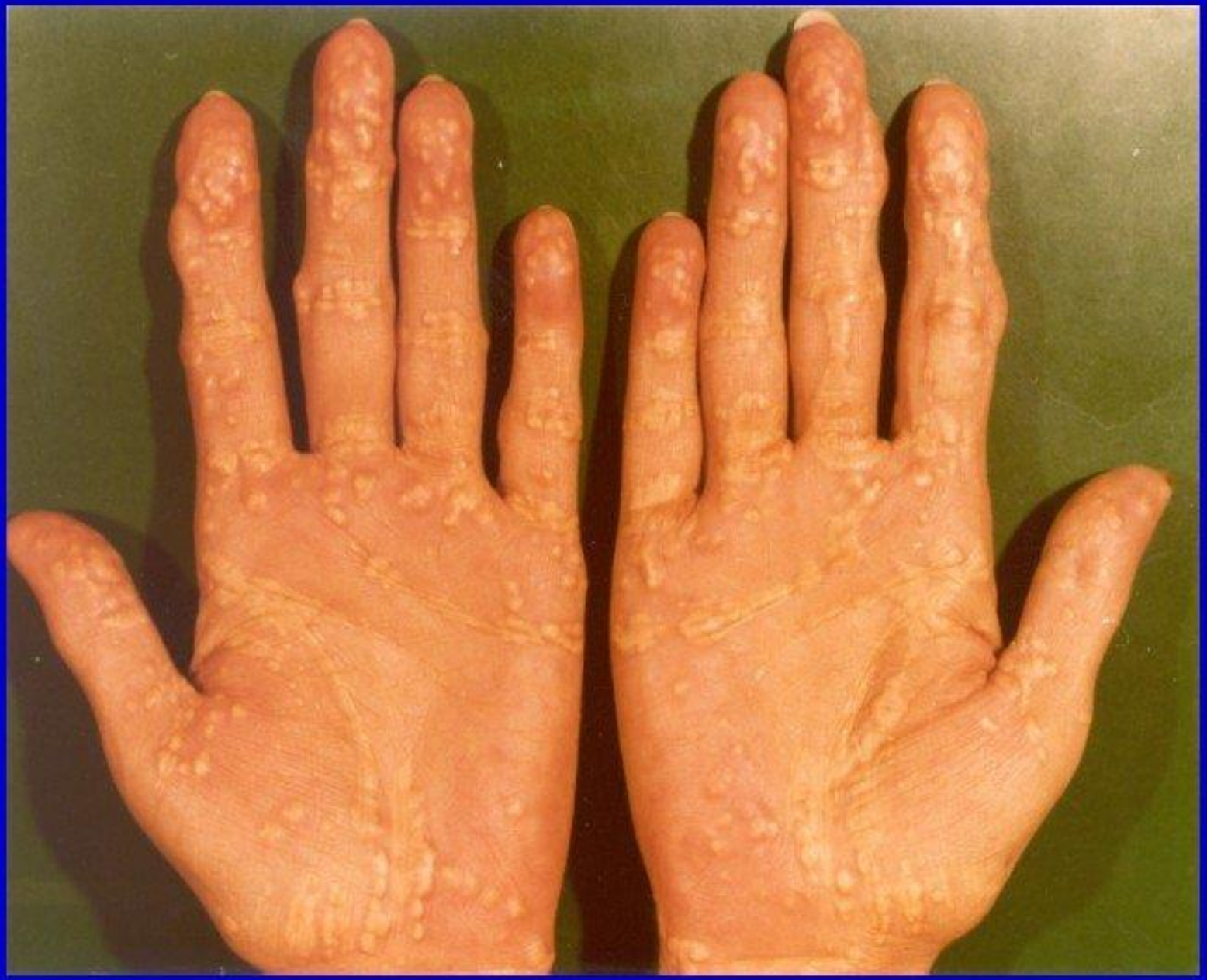
Amsterdam UMC
University Medical Centers

Xanthomák PBC-s beteg könyökén. A: Addison rajza (1851) B: Foto 1981

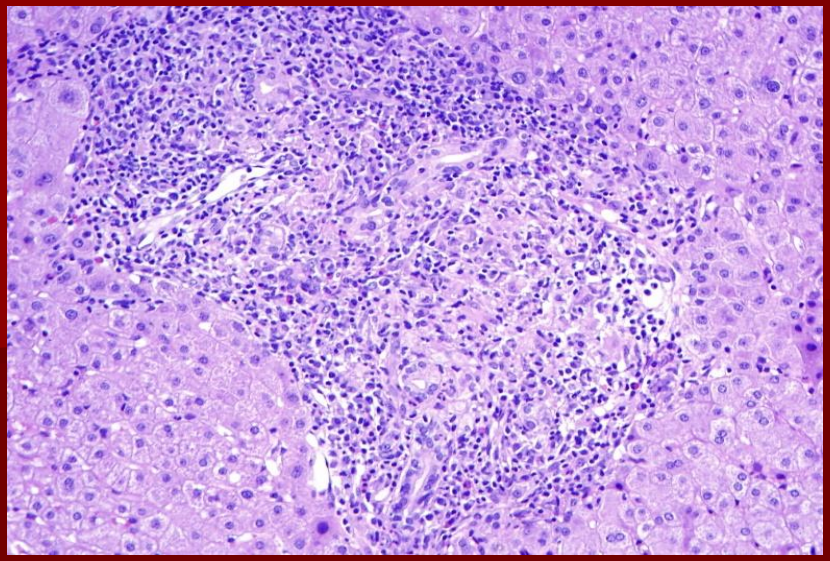


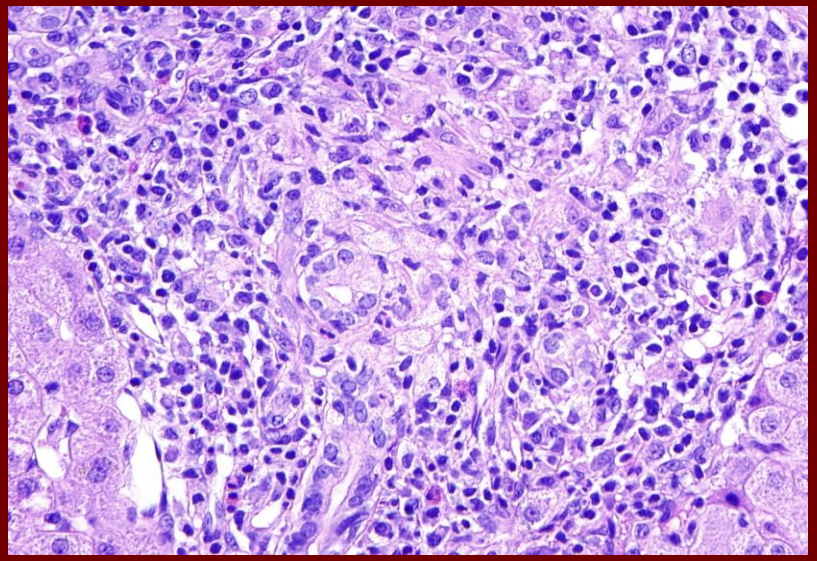


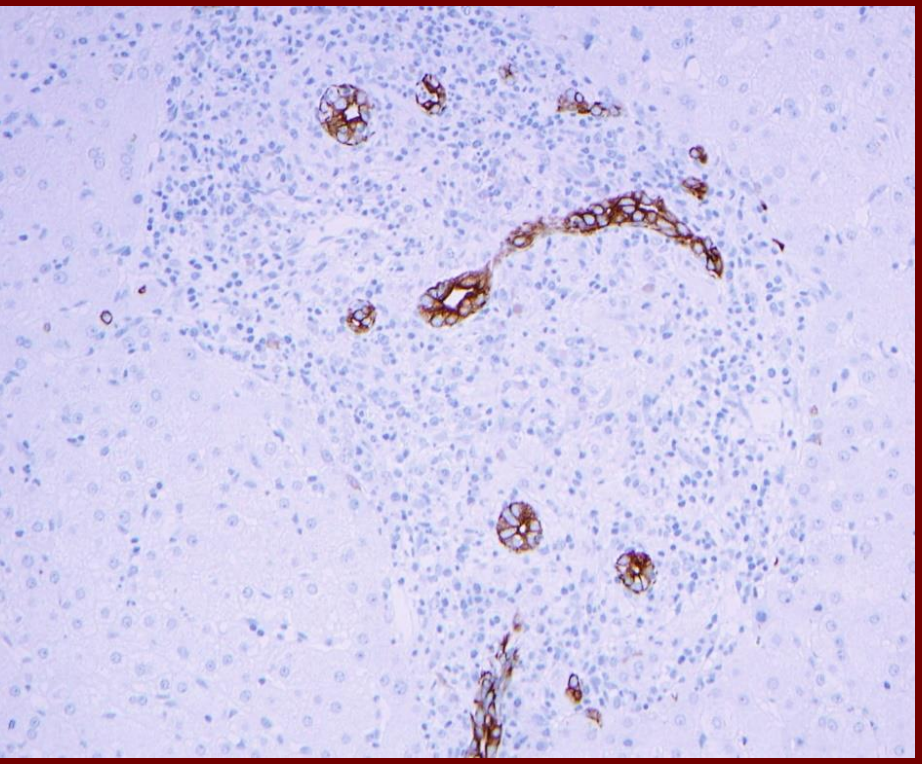
Xanthomatosis PBC-s beteg tenyerén

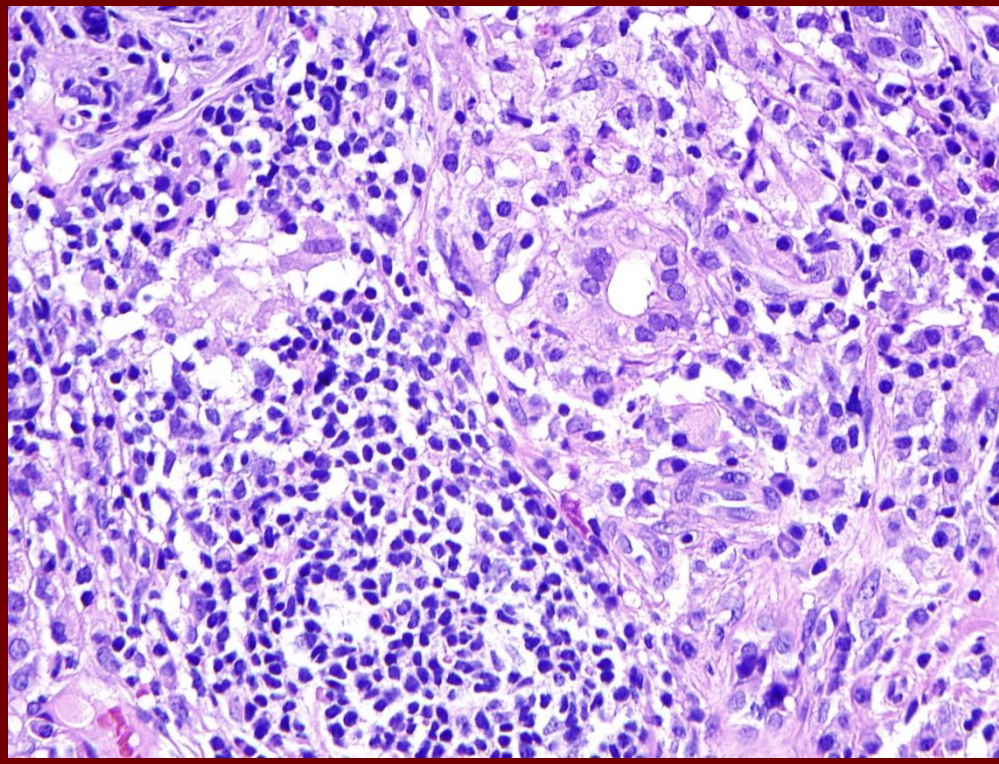


PBC

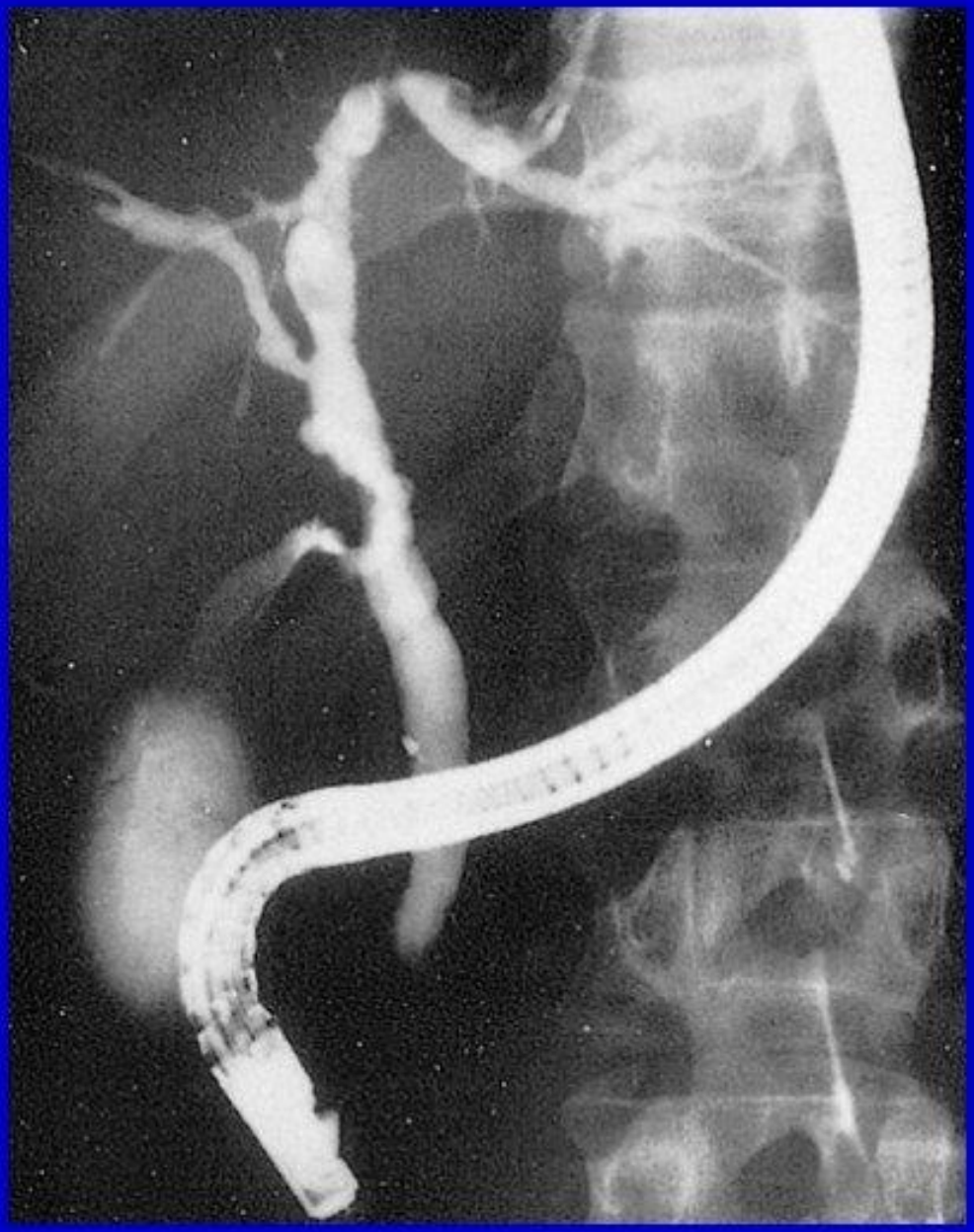








PSC ERCP KÉPE

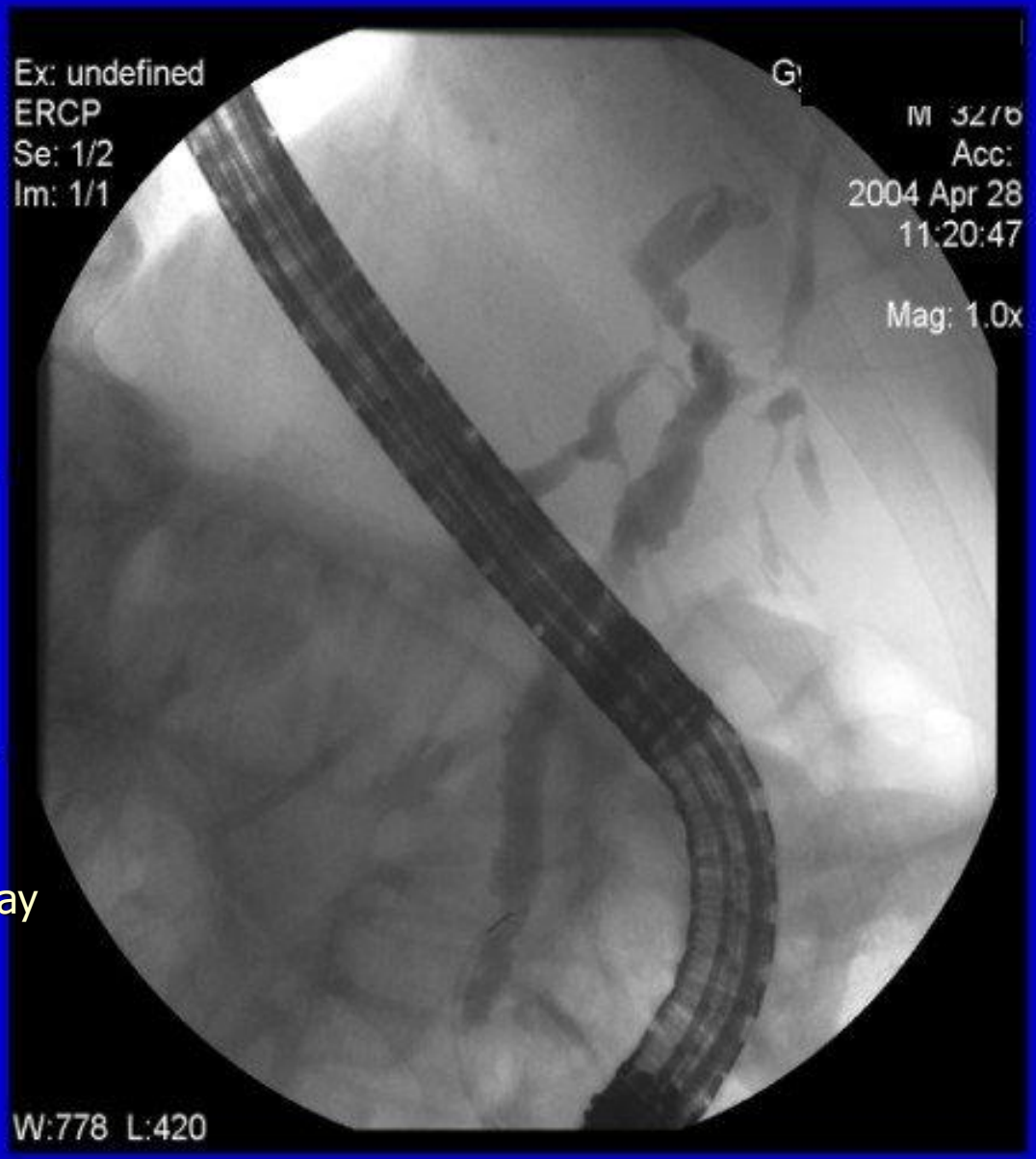


Szűkületek-tágulatok

Gyöngyfüzér-szerű kép

Nemesánszky-Schaff-Szalay
Hepatologia Oktató CD
2004 Falk

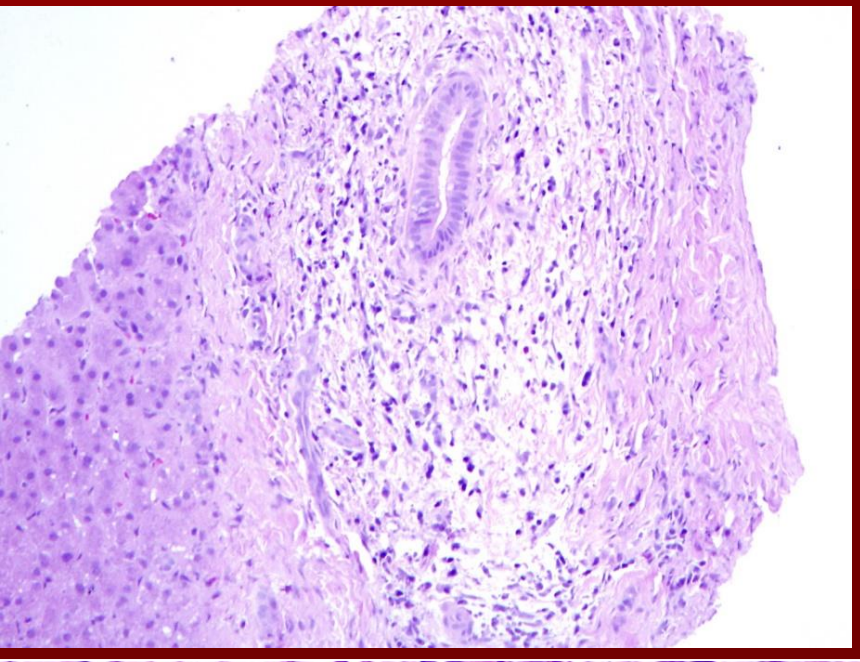
Primer sclerotisaló cholangitis ERCP

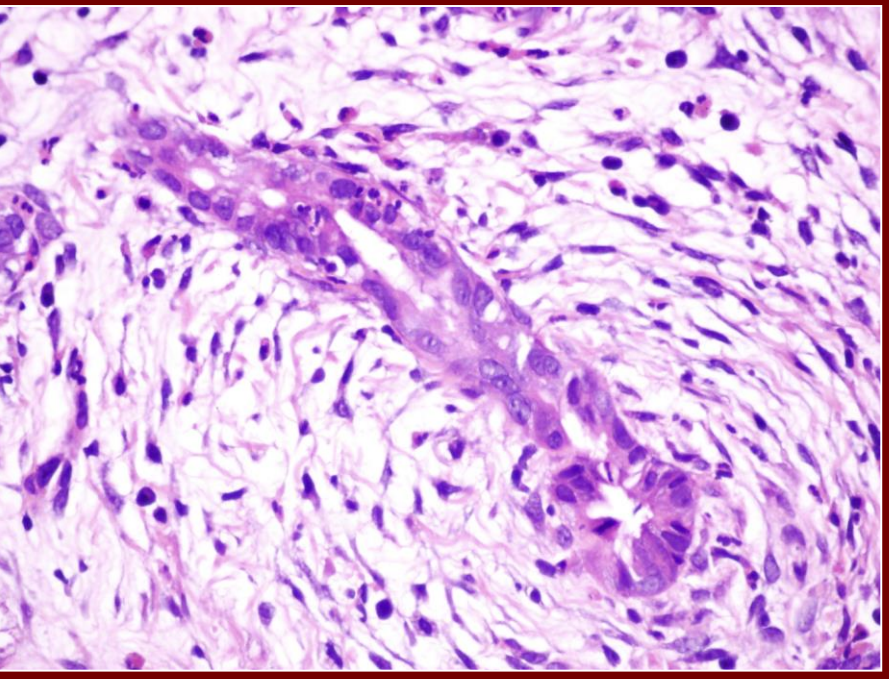


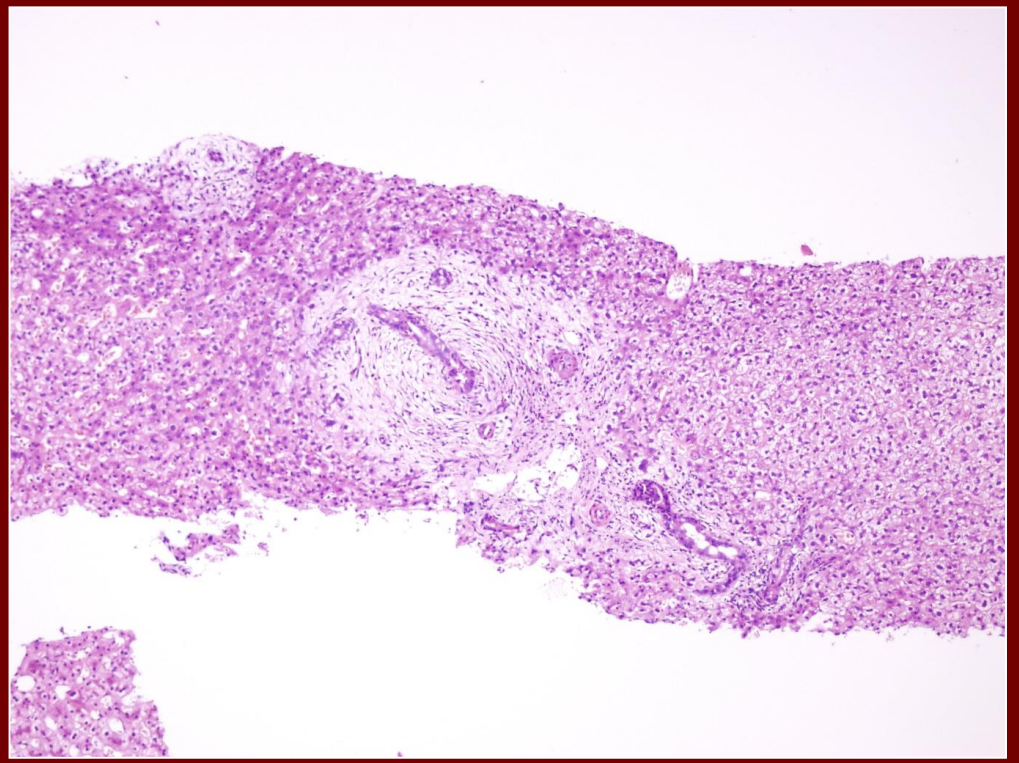
Szűkületek-tágulatok az epeutakon

Nemesánszky-Schaff-Szalay
Hepatologia Oktató CD
2004 Falk

Primary sclerosing cholangitis



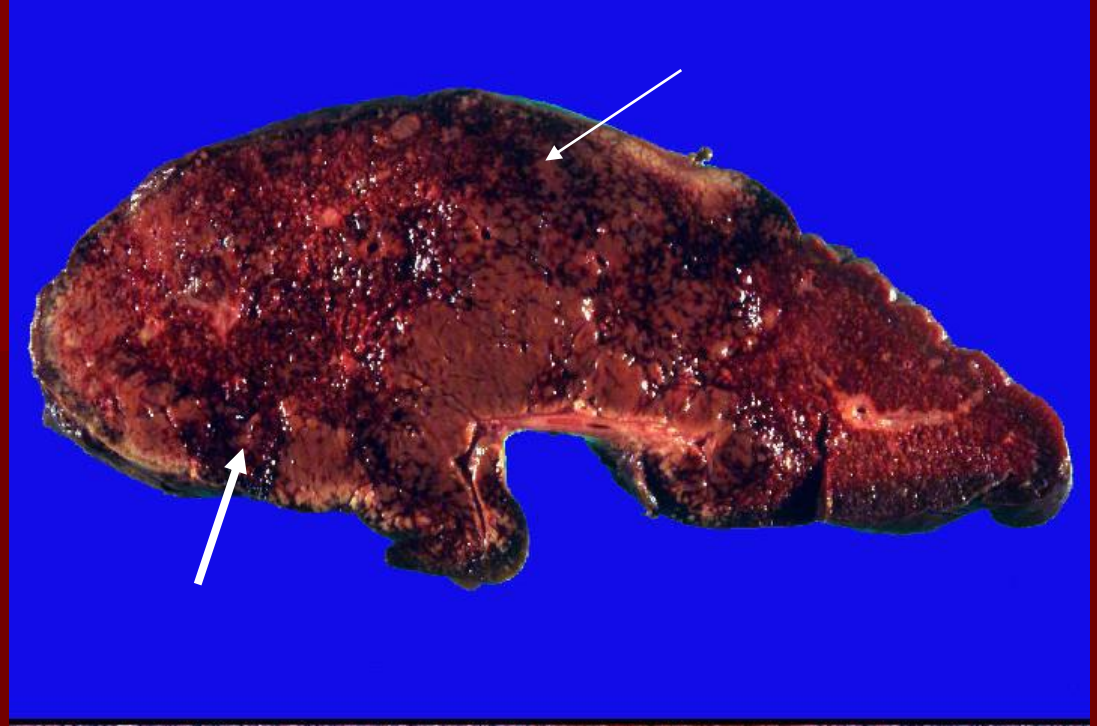


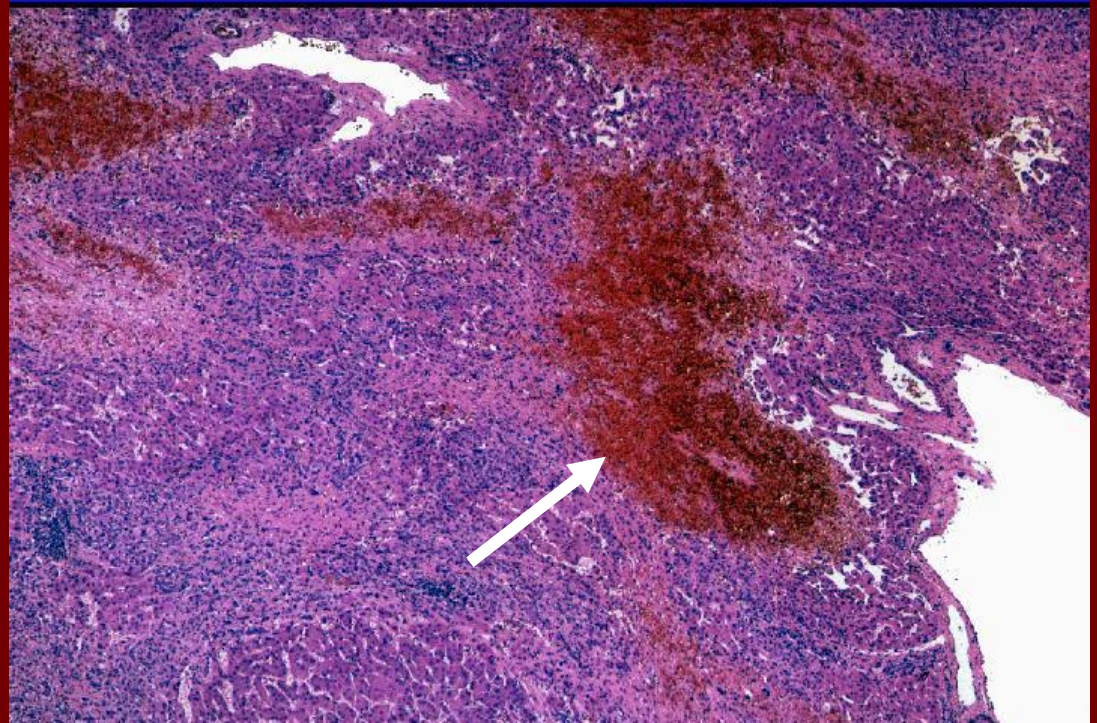


Vascular disorders

- Inflow
  - A.hepatica thromb., embolia – infarctus
  - V.portae obstruction, thrombosis (pylethrombosis) – portal hypertension, causes
- Trough
  - congestion, hepar moschatum, peliosis hepatis
- Outflow
  - Budd-Chiari syndrome
  - VOD

Budd-Chiari syndrome
(Extended hemorrhages in the liver parenchyma caused by thrombosis of hepatic veins)





Nemesánszky-Schaff-Szalay Hepatologia Oktató CD 2004 Falk

Liver alterations associated with pregnancy X

- Acute steatosis in pregnancy
  - rare, from mild to severe (could be fatal), 3.trimester, perinatal, microvesicular steatosis, pancreatitis (common)
- Intrahepatic cholestasis in pregnancy
  - 3. trimester, icterus, iching, cholestasis, ??
- Praeeclampsy, eclampsy
  - HELLP-syndrom (hemolysis, elevated liver enzymes, low platelets), pale liver with red foci, fibrin deposits in sinusoids, hemorrhages