Liver up-date - Lancaster 2007

Diseases of the bile ducts
Cholangiopathies

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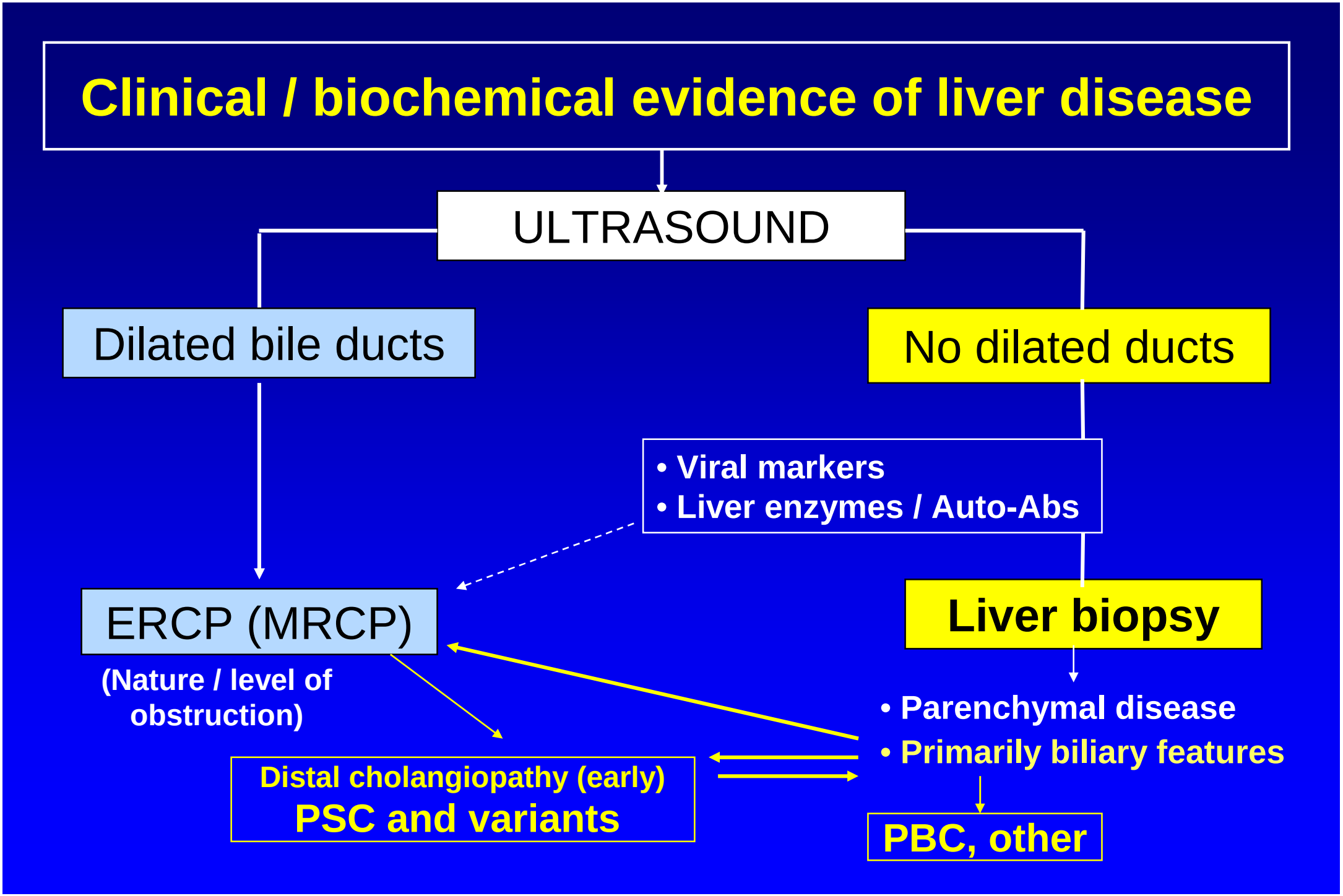
Primarily biliary disorders

- Generalities - liver biopsy indications
- Histological changes common to chronic biliary disorders
- Primary biliary cirrhosis
- ‘Primary’ sclerosing cholangitis
  - Overlap PSC / autoimmune hepatitis
- Acquired (secondary) sclerosing cholangitis


Clinical / biochemical evidence of liver disease
ULTRASOUND
Dilated bile ducts
No dilated ducts
• Viral markers
• Liver enzymes / Auto-Abs
ERCP (MRCP)
(Nature / level of obstruction)
Liver biopsy
• Parenchymal disease
• Primarily biliary features
Distal cholangiopathy (early)
PSC and variants
PBC, other

- **Cholestasis (for the clinician)**

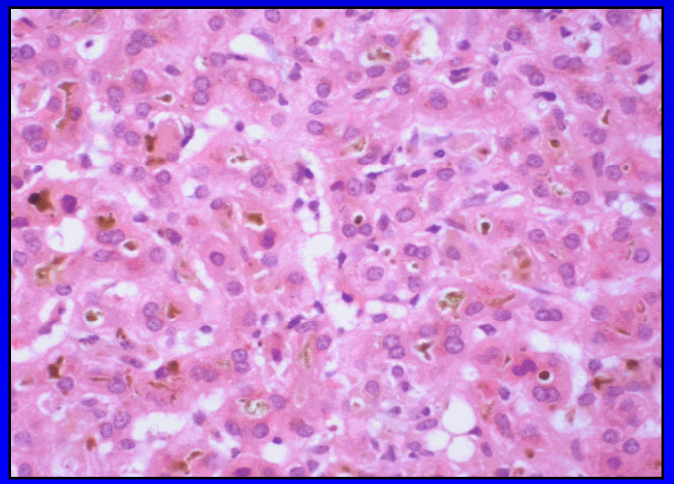
  = systemic retention of biliary solutes

  ⇨ raised Alkaline Phosphatase, γGT ± Bilirubin

≠

- **Cholestasis (for the pathologist)**

⇨ visible accumulation of bile in liver tissue ⟶



Cholestasis on biopsy specimens

- **[Biliary obstruction → now rarely biopsied**
  → imaging diagnosis]
- **Severe cholestasis**
  → generally intrahepatic
  - **Viral, autoimmune (recent acute onse or flare-up**
  - **Drug-induced / sepsis / TPN / pregnancy**

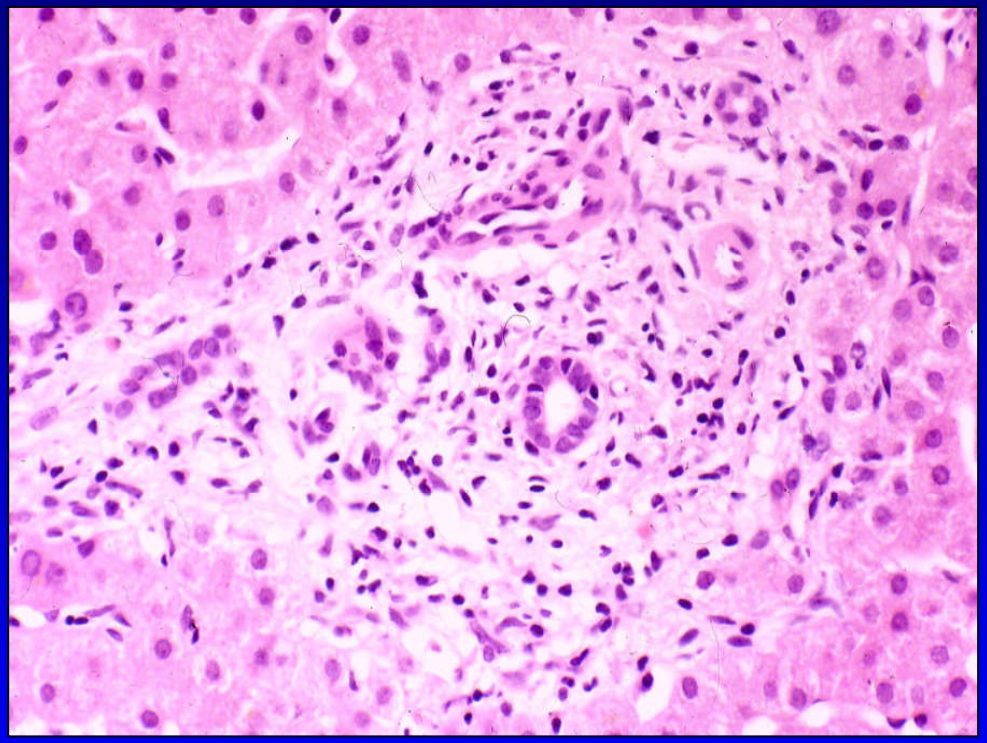
- **Primarily biliary disorders** (incomplete obstruction)
  e.g. primary biliary cirrhosis, sclerosing cholangitis
  ⇨ **no histological cholestasis** for the largest part of the clinical course

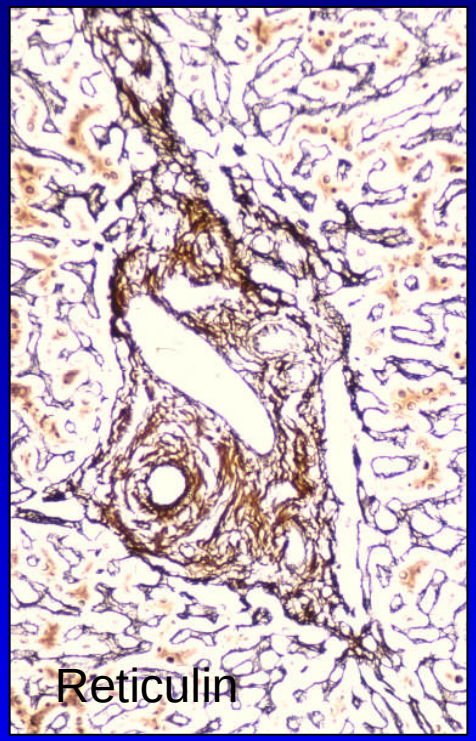
In absence of cholestasis

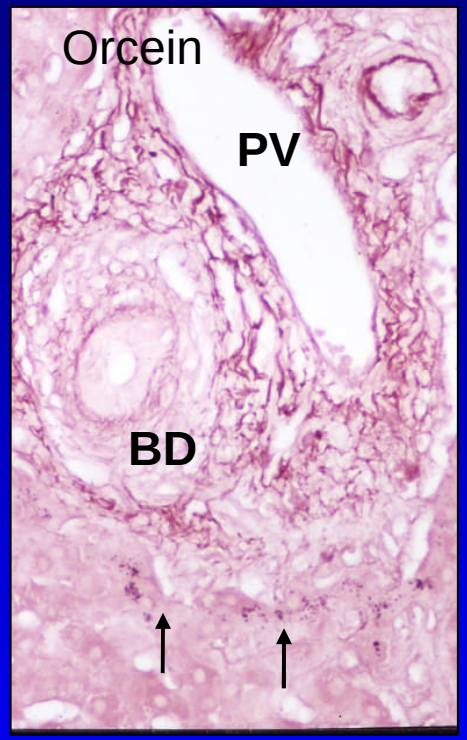
⇨ importance to recognize markers indicating a biliary disorder

- Biliary portal tract changes
- Biliary interface activity (cholate-stasis)
- Ductular reaction
- Ductopenia

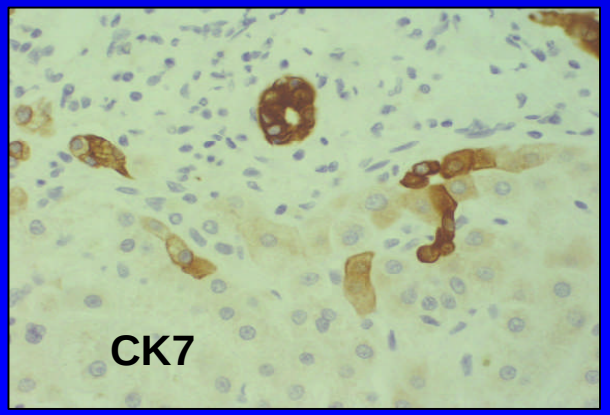
Primarily biliary disorders: early portal changes



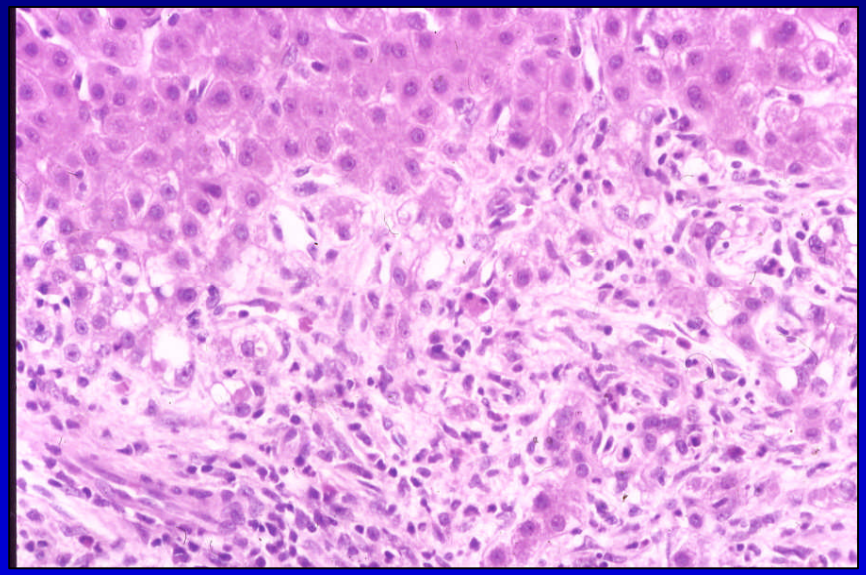


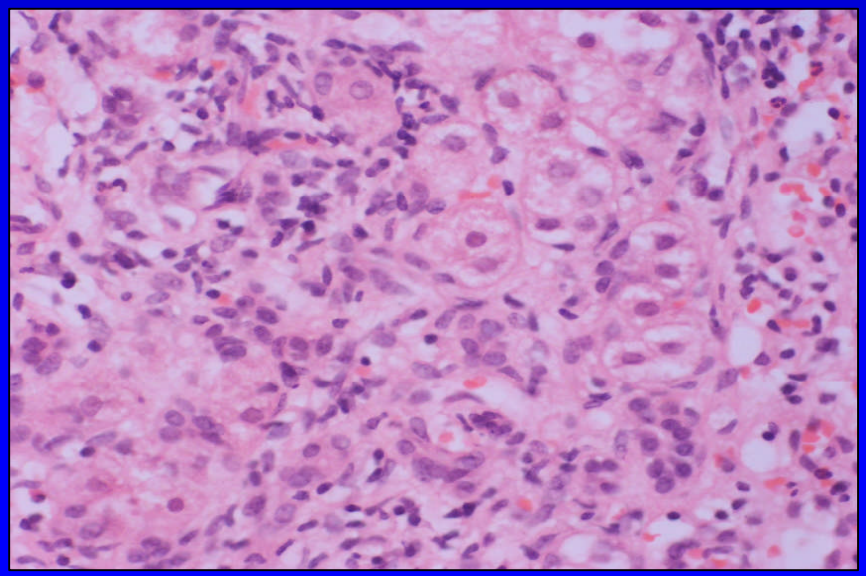


- Portal tract oedema - mild fibrosis
- Subtle ductular reaction (CK7)
- Light inflammation with minimal interface activity



Interface activity (piece meal necrosis)





Biliary (cholate-static)

PBC / PSC stage 2- 4

⇒ interference with bile flow (bile salt toxicity)

⇒ ursodeoxycholic acid

Hepatitic (lympho-plasmacytic)

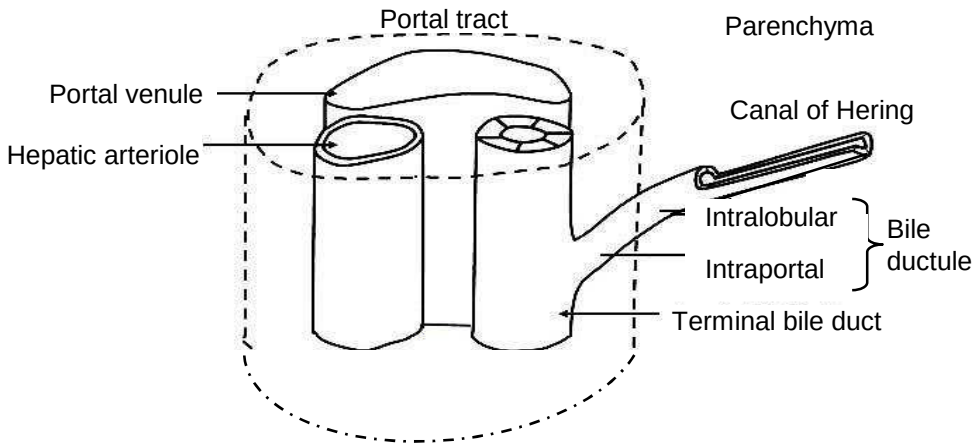
Autoimmune hepatitis

PBC / PSC stage 2

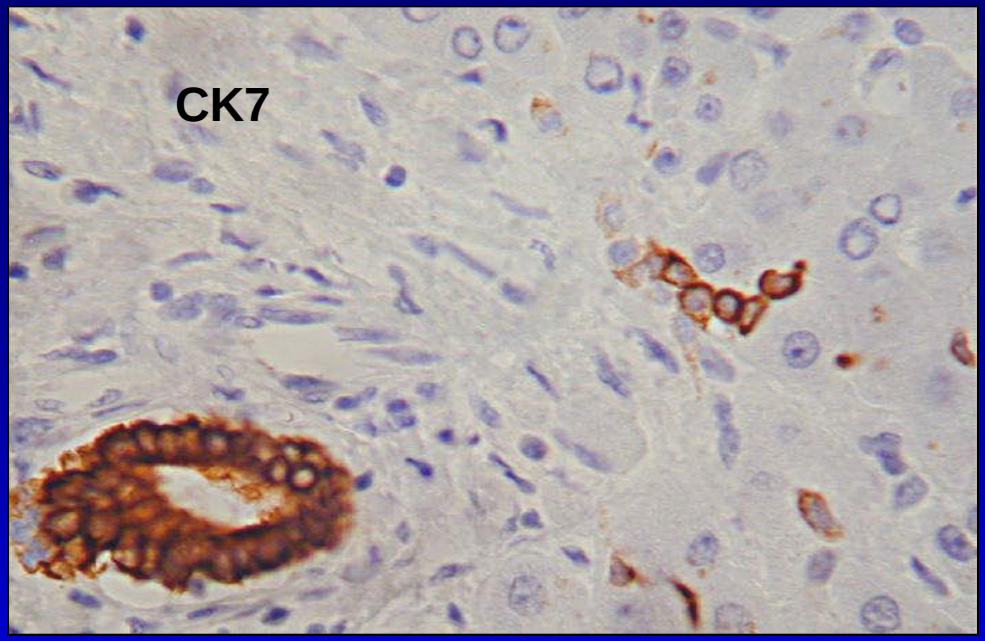
⇒ immune-mediated injury

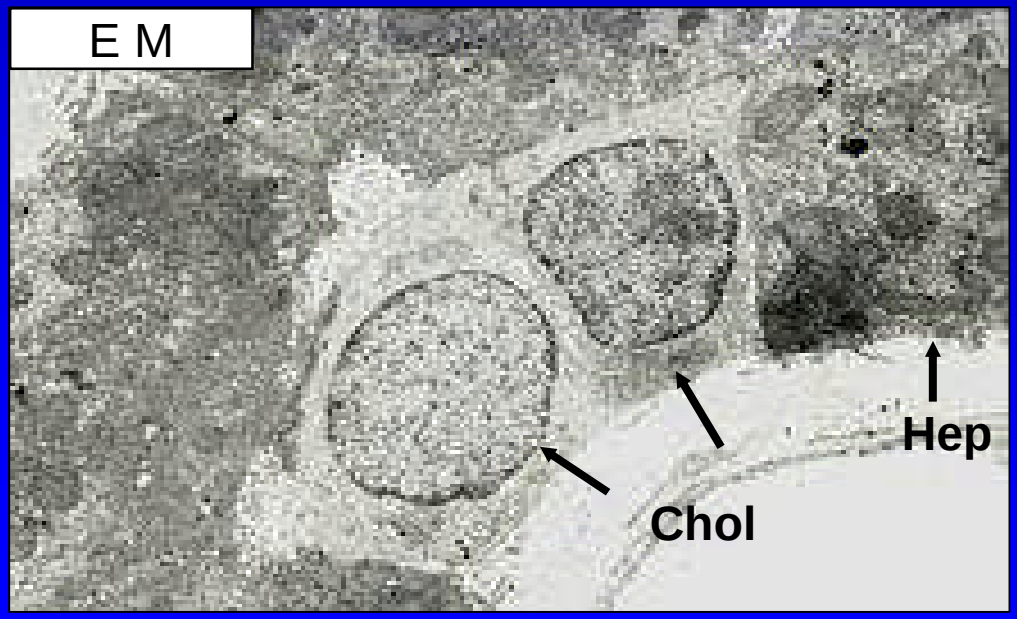
⇒ ? steroid responsive

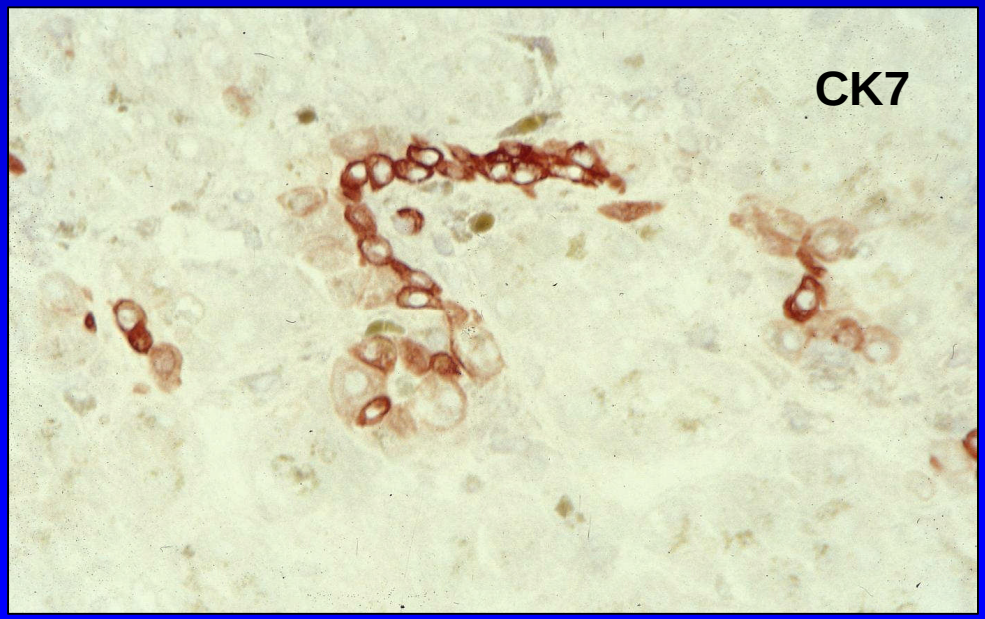
Ductule – canal of Hering



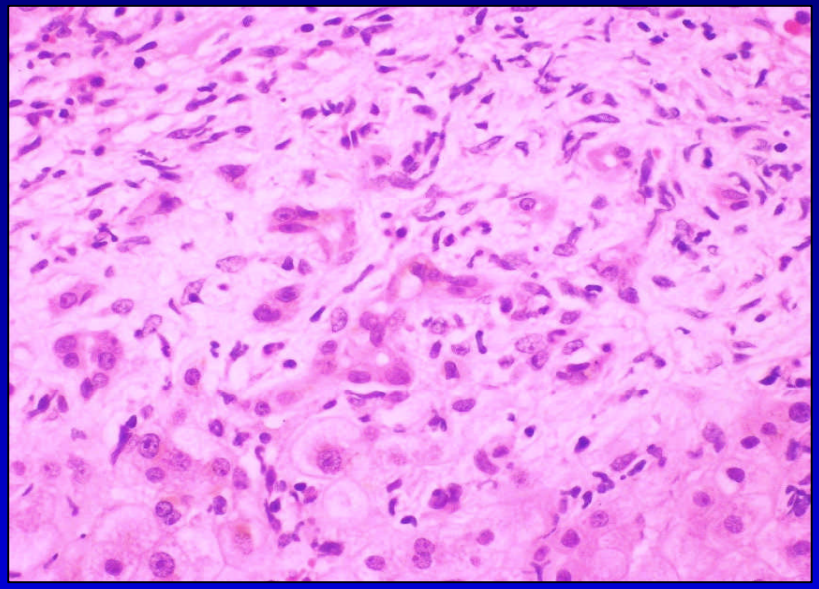
Normal

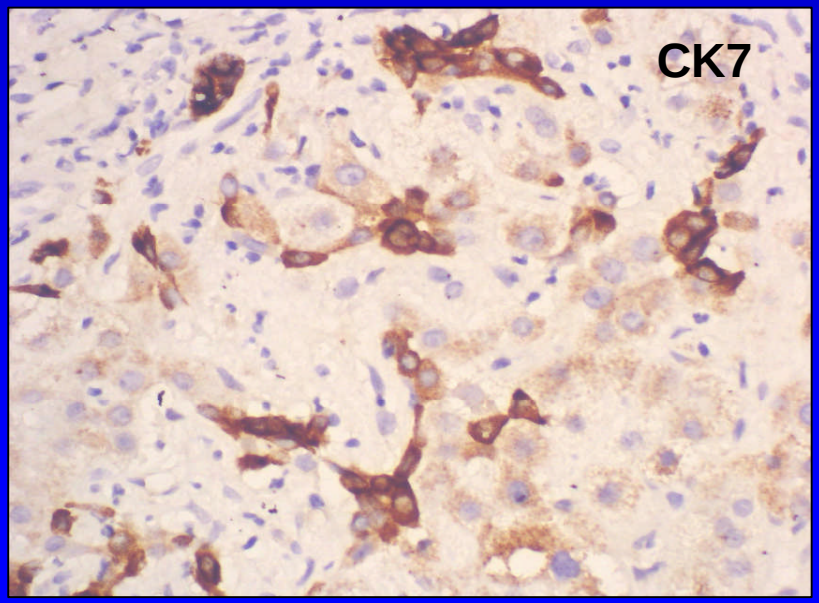






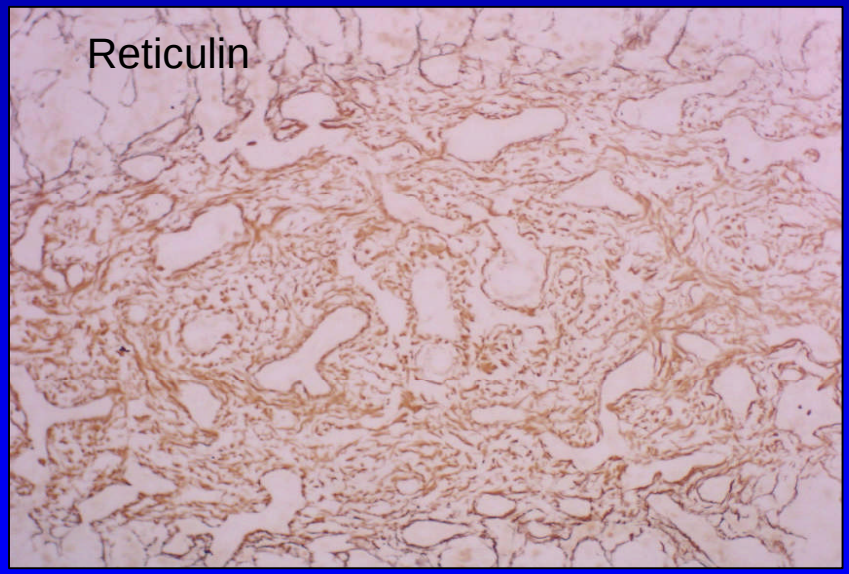
Ductular reaction





- **Role incompletely understood**
  ? By-pass mechanism for bile drainage
  ? Re-absorption of bile acids

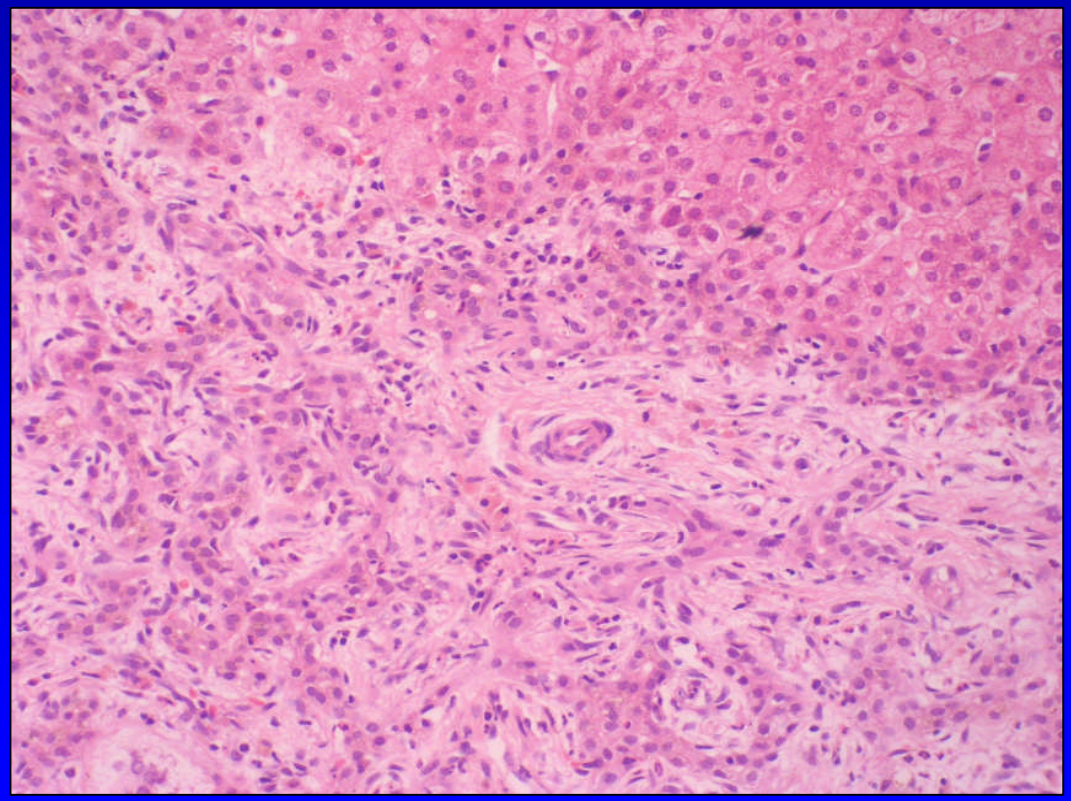
⇒ Basement membrane ⇒ fibroplasia

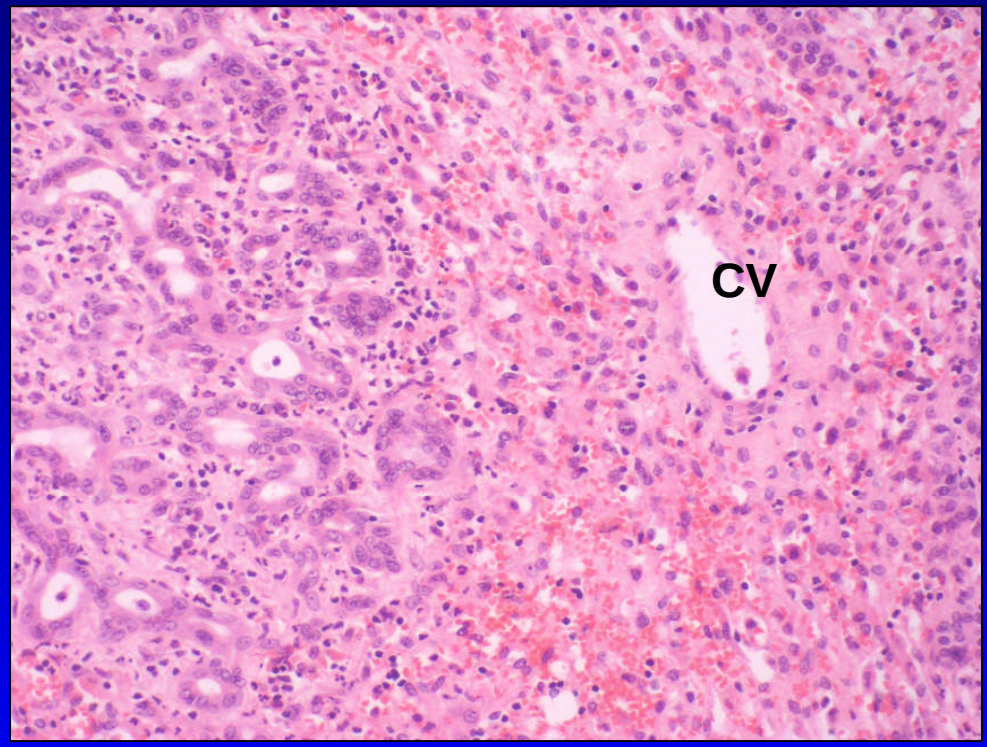


← Shift from hepatocellular to biliary phenotype demonstrated by CK7 immunostaining

Important to distinguish ductular reaction due to :

chronic cholangiopathy



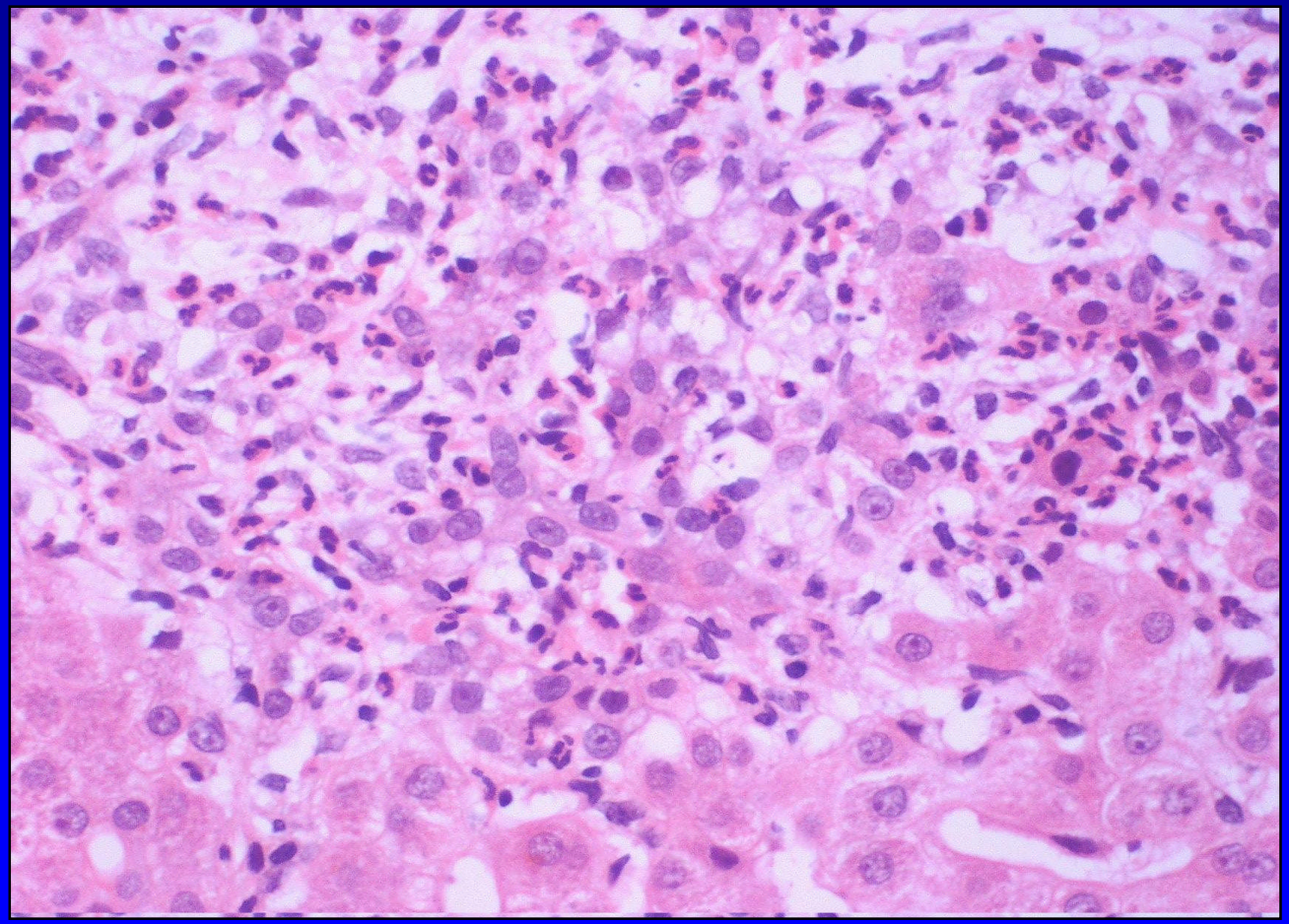


from that following confluent parenchymal necrosis and loss

Chronic biliary disorders : interface changes

- **Marked ductular reaction**
  + neutrophils

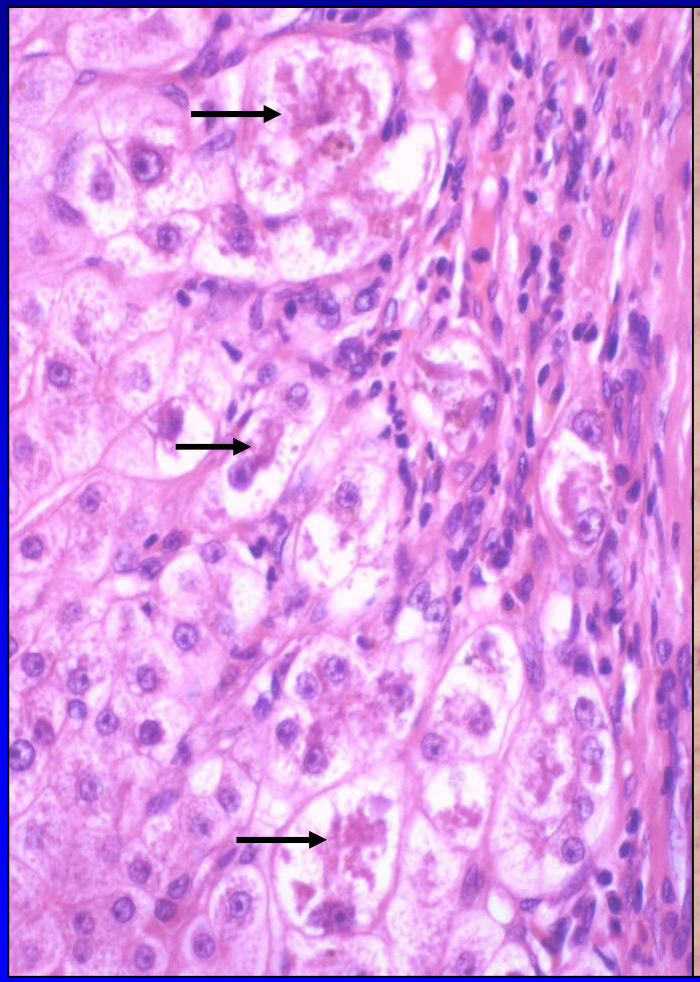
⇨ **Cholangiolitis**



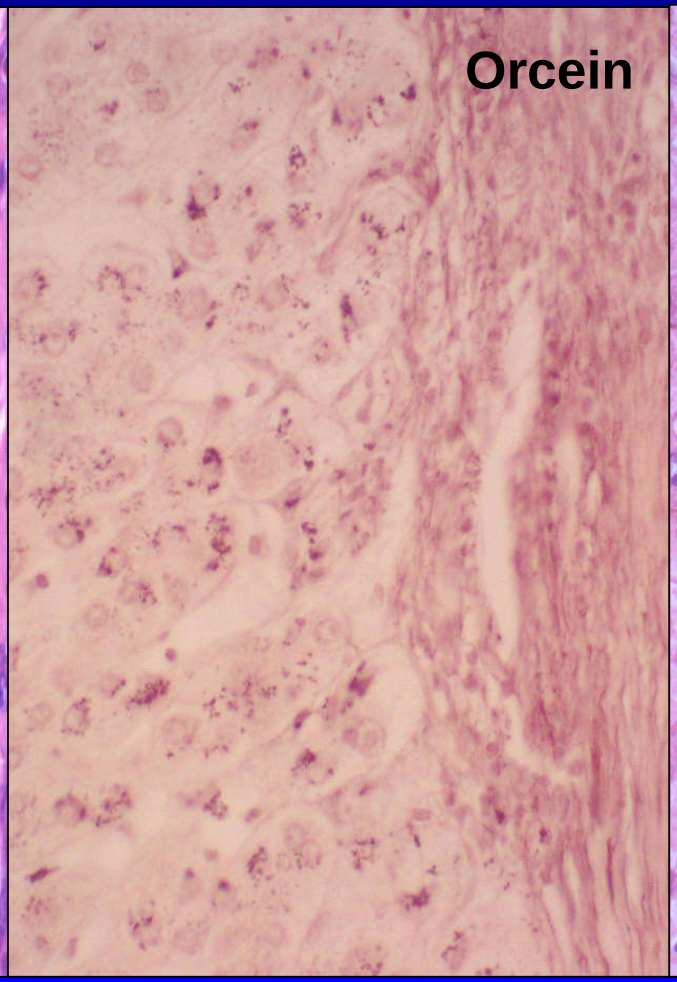
Chronic biliary disorders : late interface changes

Cholate stasis

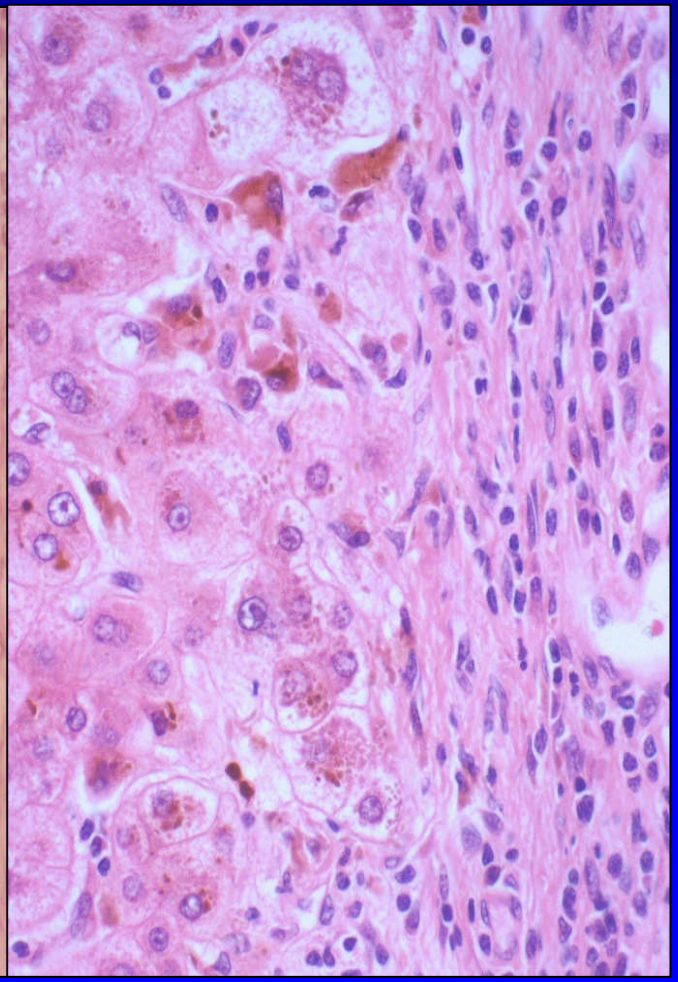
(Mallory bodies →)



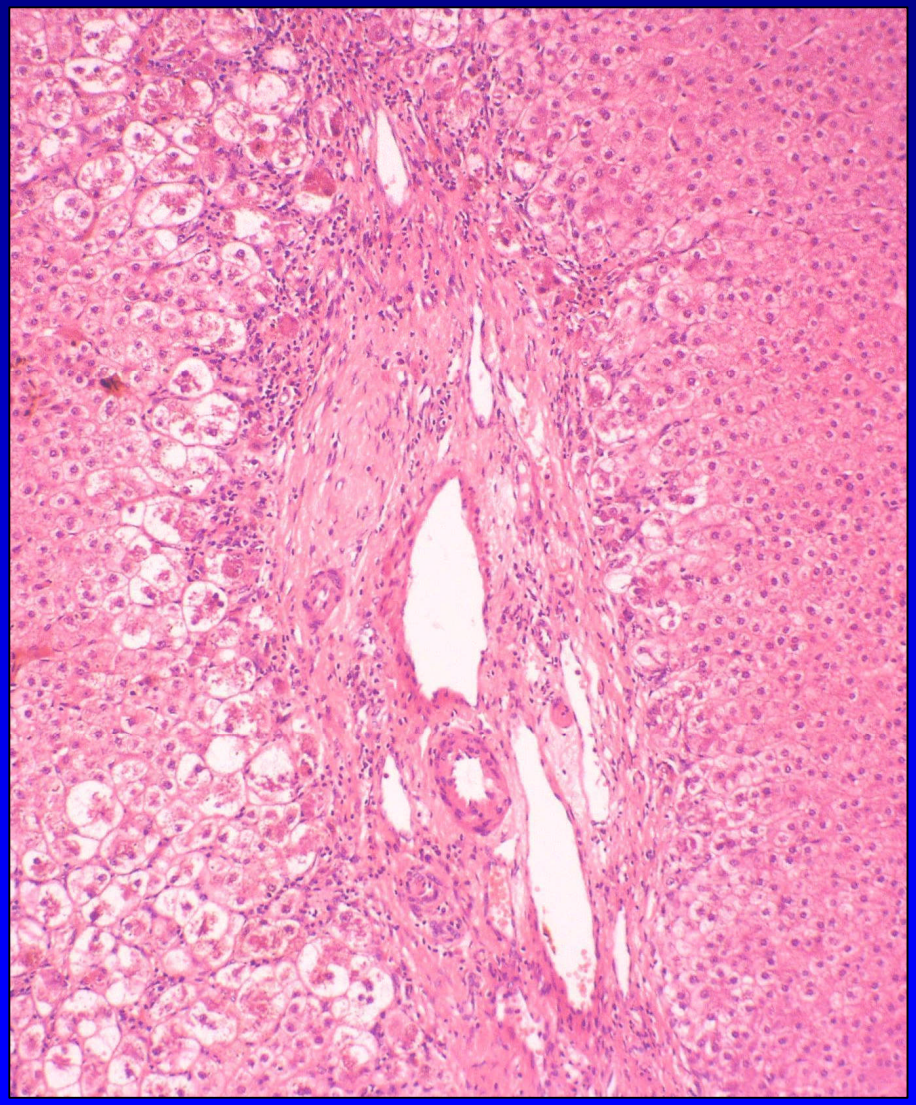
Cu-ass granules



Cholestasis



Bile duct loss or ductopenia

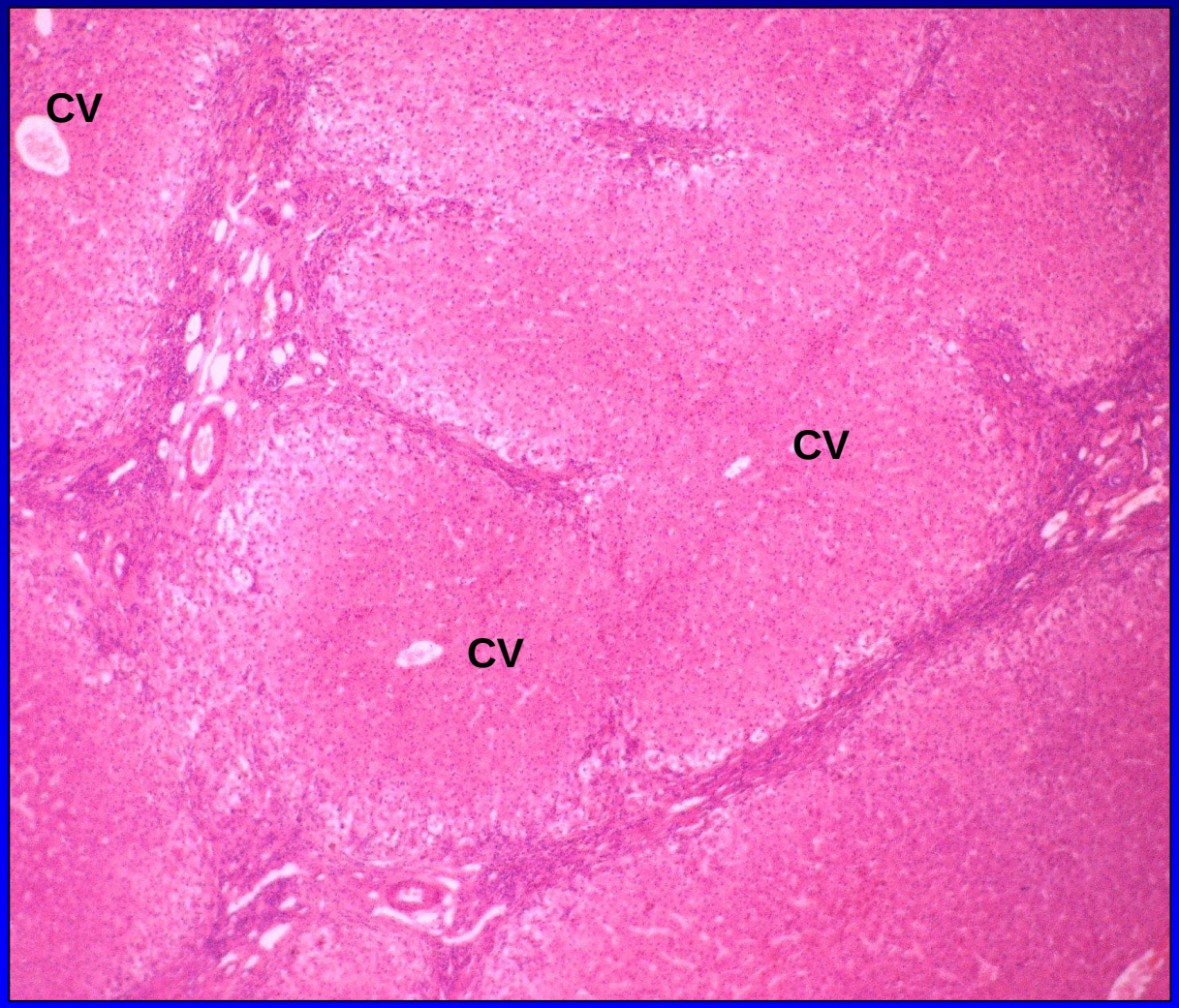


- Absence of identifiable bile duct

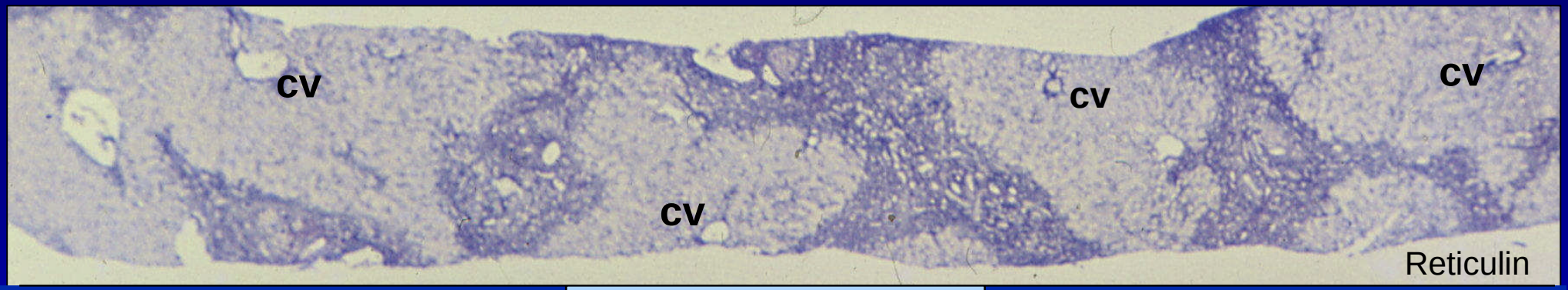
⇨ Hepatic arteries unaccompanied by ducts of matching size

⇨ Arbitrarily : 50 % out of 10 or more portal tracts devoid of ducts

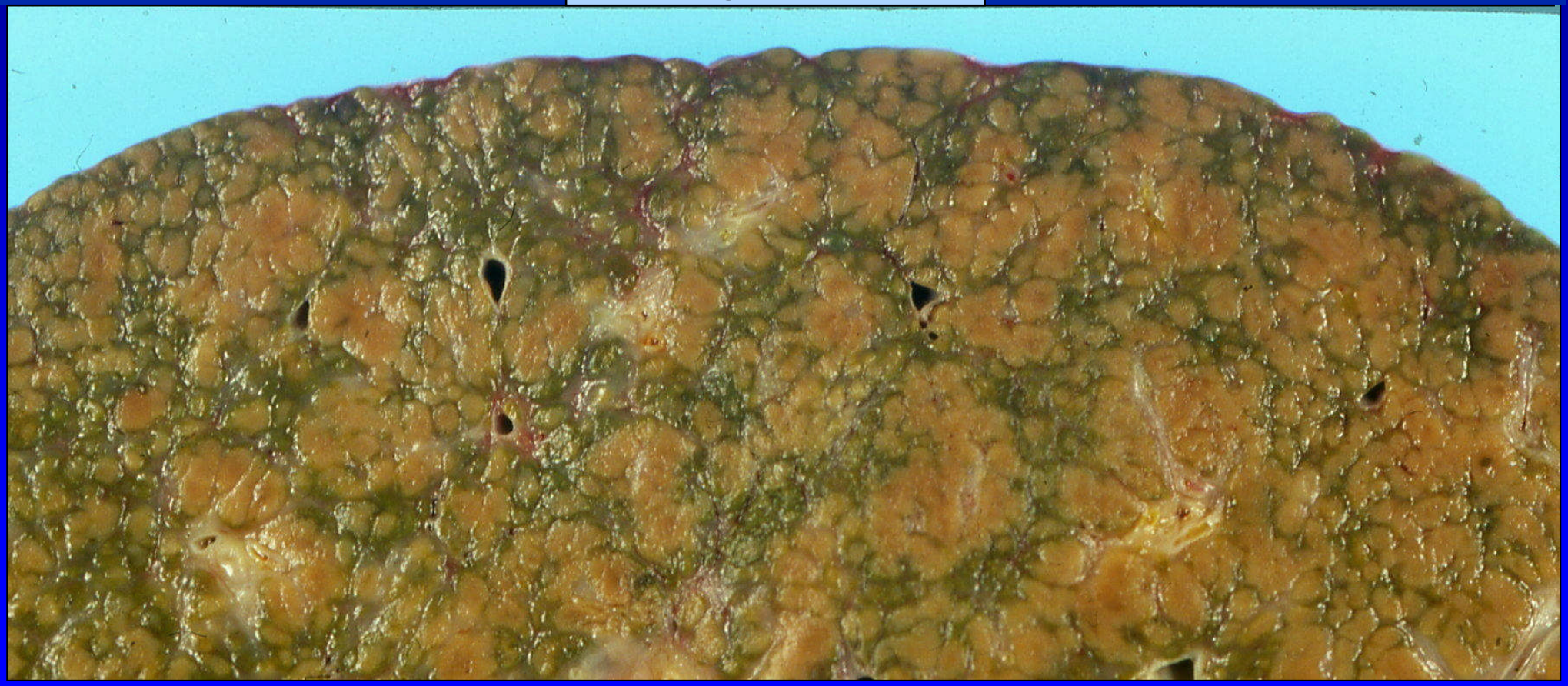
Biliary cirrhosis : Stage 4



- Portal-portal fibrosis with + / - preserved hepatic venules
- Biliary interface with halo, Mallory bodies, copper ± cholestasis
- Ductopenia

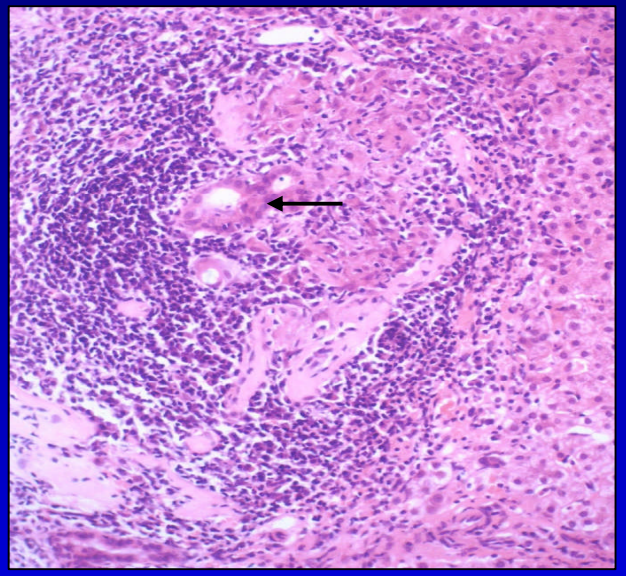


Biliary cirrhosis

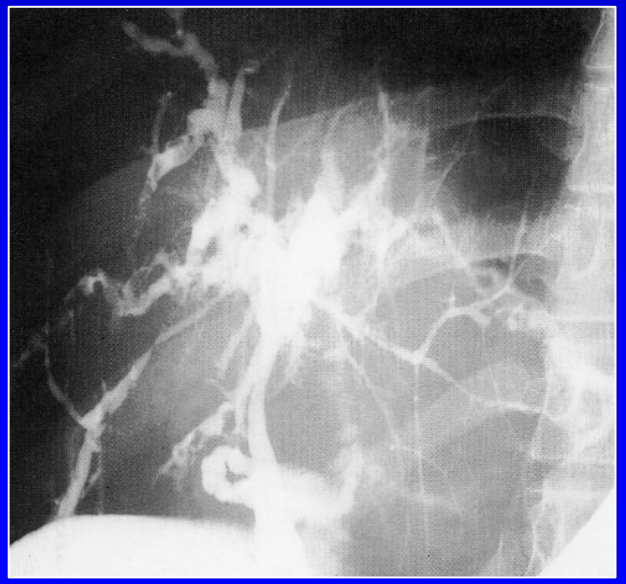


Primarily biliary disorders

- Disorders of small intrahepatic (interlobular) bile ducts
  - Primary biliary cirrhosis -



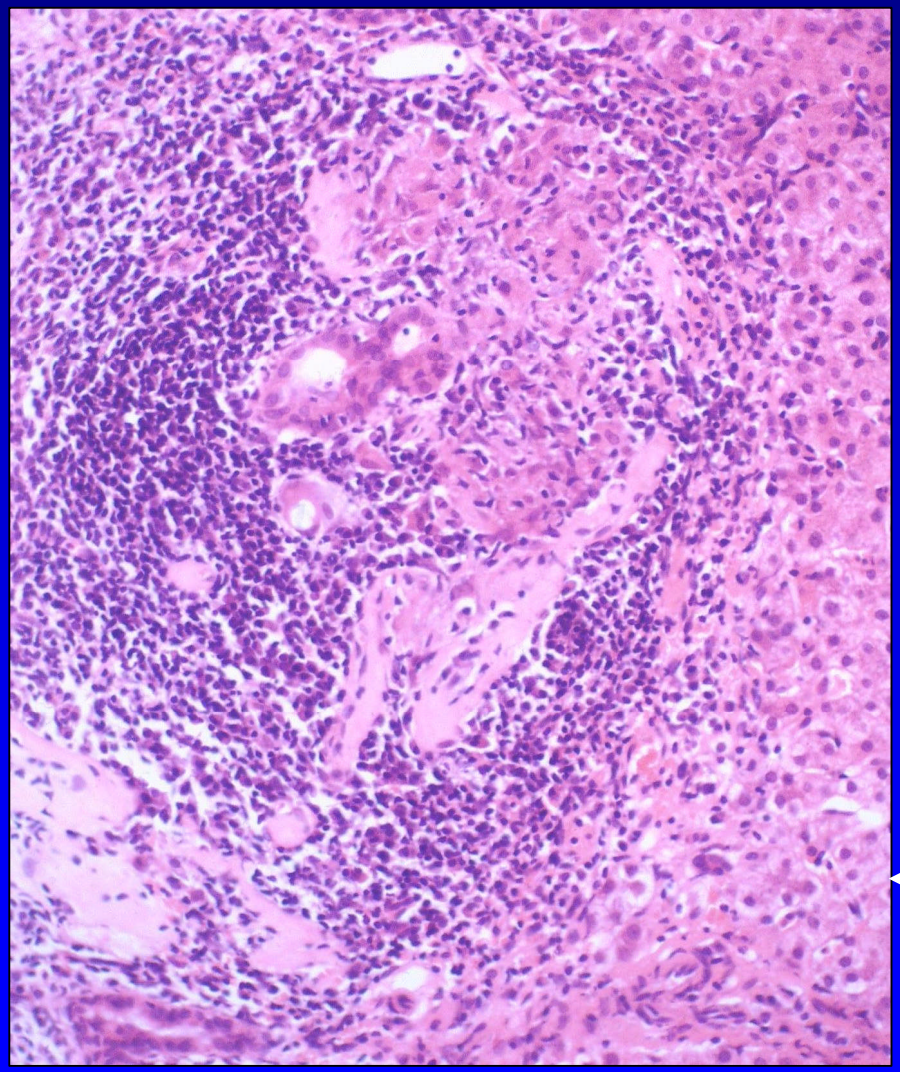
- Disorders affecting larger intra- and / or extrahepatic bile ducts
  - Sclerosing cholangitis -
    $\Rightarrow$ heterogenous disorder)



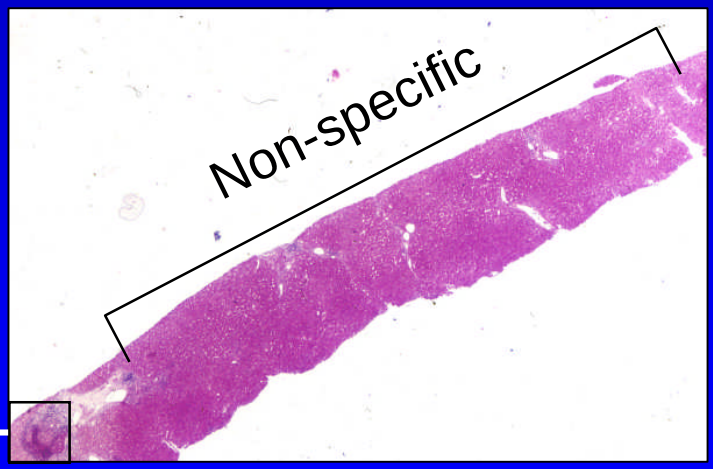
Primary biliary cirrhosis (PBC)

- **Middle-aged F : M = 9 :1 (not in children)**
- **Pruritus**, skin pigmentation
- Familial cases - Associated immune disorders
- **Raised IgM – Alk phos - γGT**
- **Anti-mitochondrial Abs** (E2 component) > 95%
- ANA (centromere type)
- **Morphology : Progressive destruction of small interlobular bile ducts ⇒ biliary fibrosis ⇒ cirrhosis**

Primary biliary cirrhosis : stage 1-2

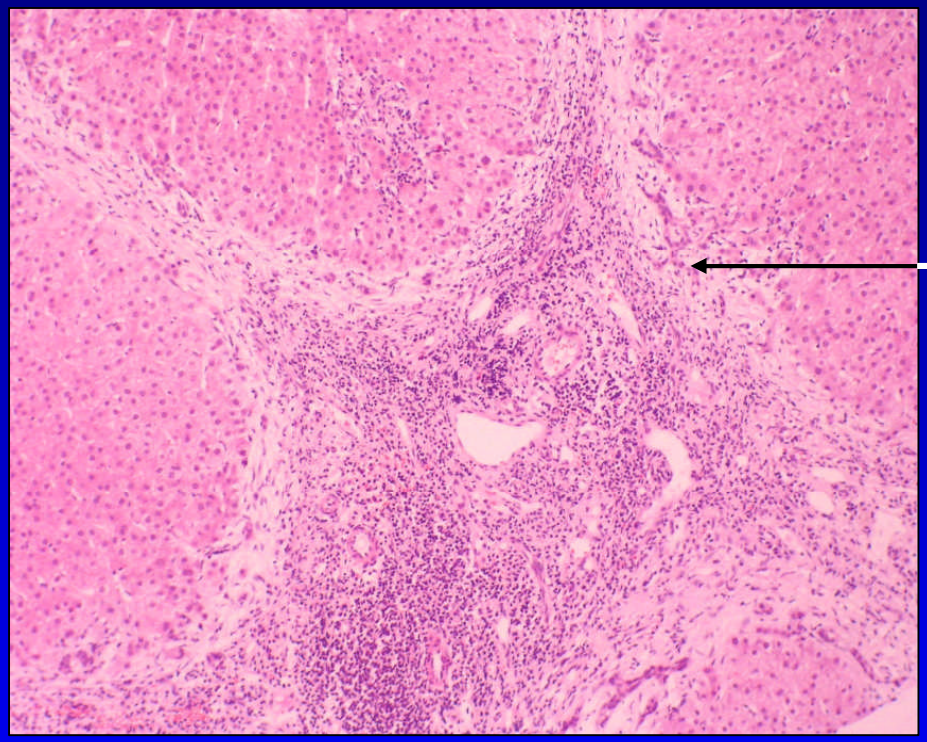


- Non-suppurative destructive
  ± granulomatous cholangitis
- Heterogenous distribution



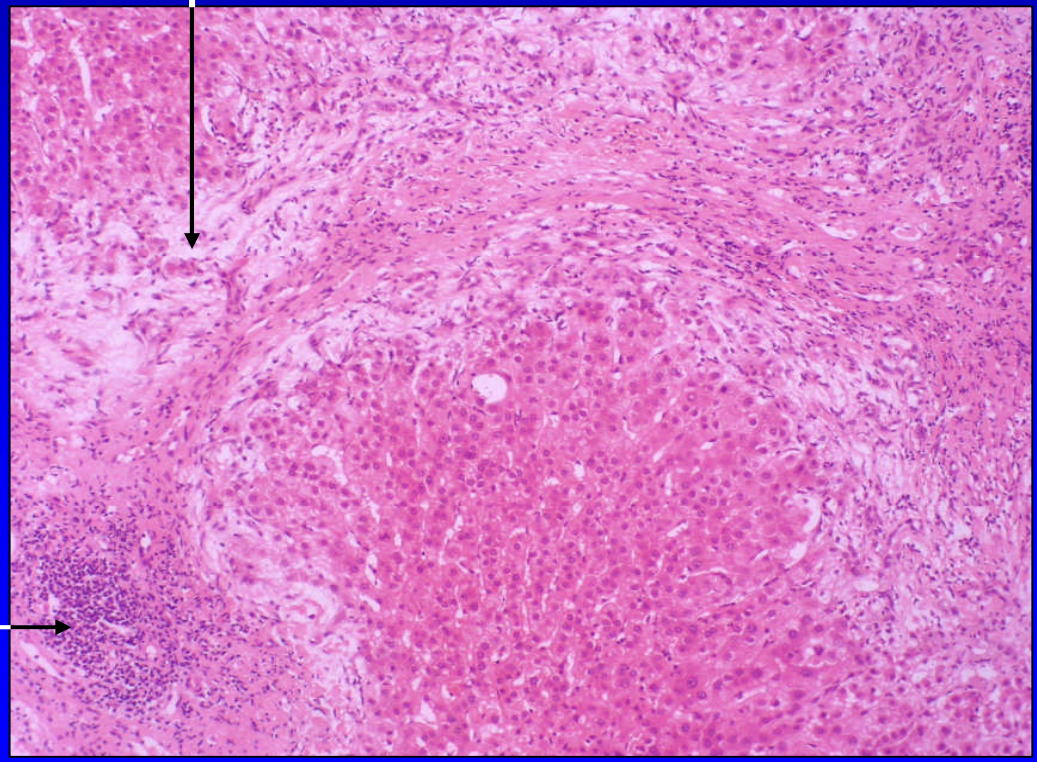
- No cholestasis

Primary biliary cirrhosis : progression



Portal tract expansion + radiating septa
+ absence of bile duct (ductopenia)

Biliary interface activity with ‘halo’



Development of porto-portal
bridging fibrous septa

Site previously
occupied by bile duct

Primary biliary cirrhosis

Variants

AMA negative PBC (autoimmune cholangitis)

- Overlap AIH / PBC

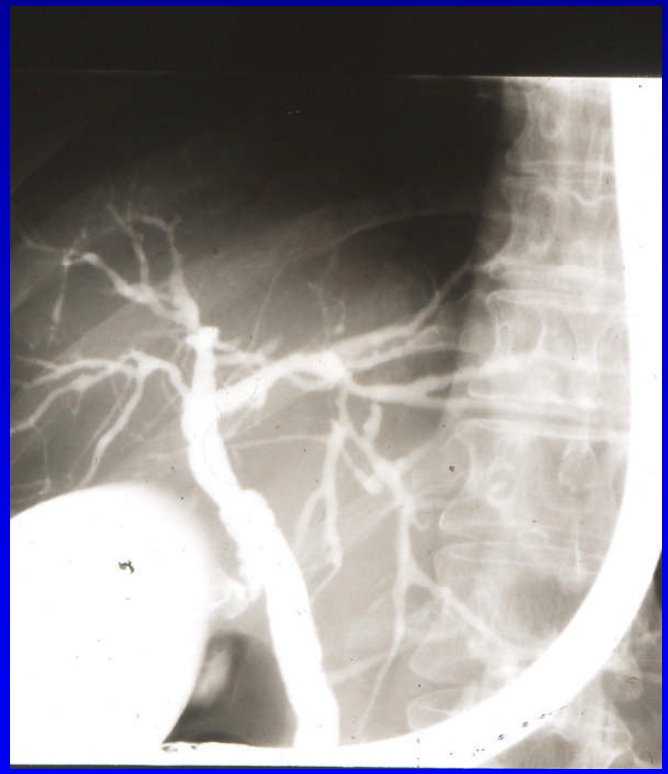
Differential diagnosis

Drug-induced injury

- Sarcoidosis

Primary sclerosing cholangitis (PSC)

- Sclerosing and focally destructive inflammatory process affecting the extra- and / or intrahepatic bile ducts
  ⇒ Unevenly distributed stenosis and ectasia (ERCP, MRCP)



- Confined to small intrahepatic bile ducts (5%) = small duct primary sclerosing cholangitis (biopsy)

‘Primary’ sclerosing cholangitis

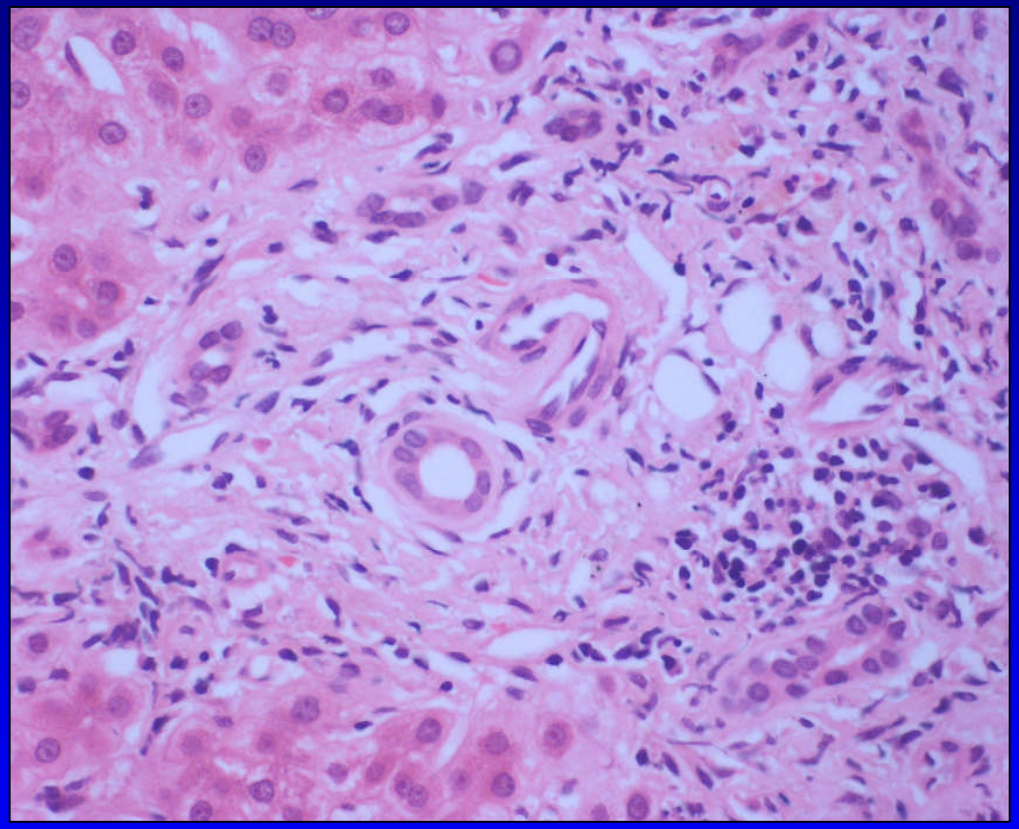
Clinically

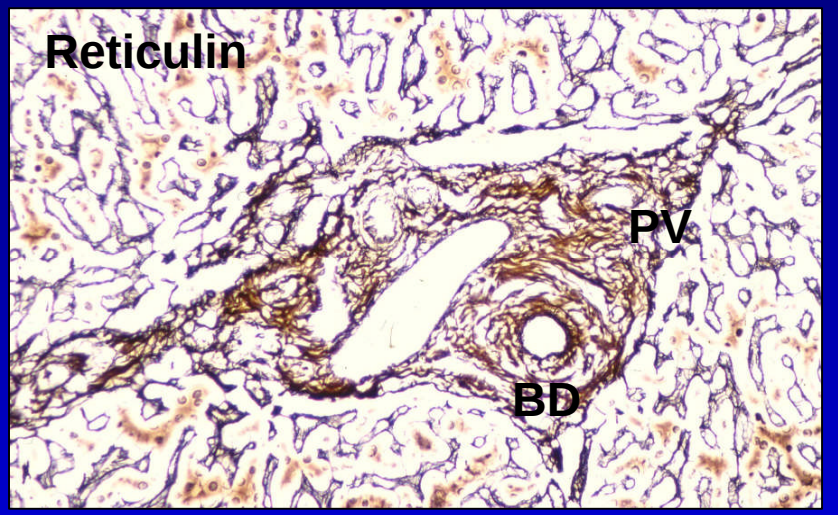
- M / F: 2-3 / 1 - Mean age : 38 (children too)
  - Inflammatory bowel disease (up to 75%)

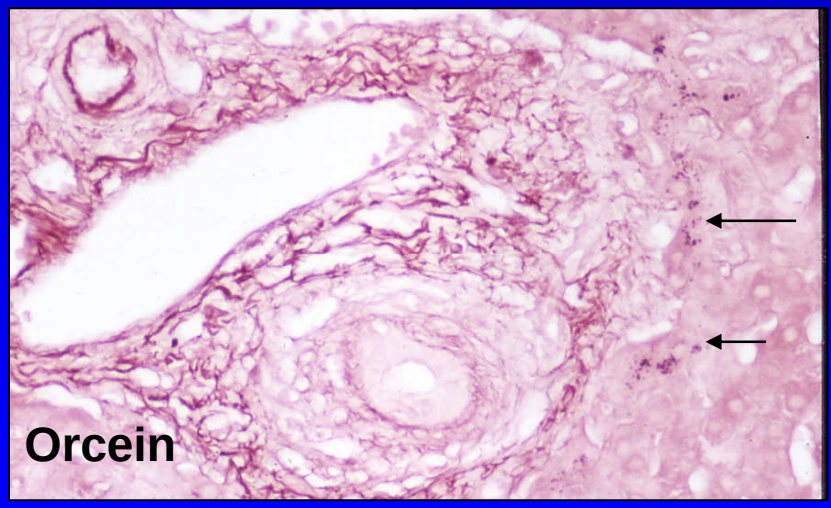
Laboratory

- Alkaline phosphatase +++ / γGT ++ / bilirubin +
- Autoantibodies pANCA (non-specific)
  SMA / ANA (>children)
- ↑ HLA B8 , DR3, DR2, DRw52a

PSC : early histological changes



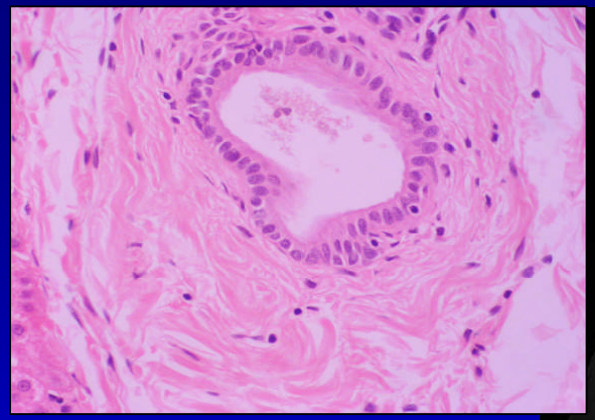


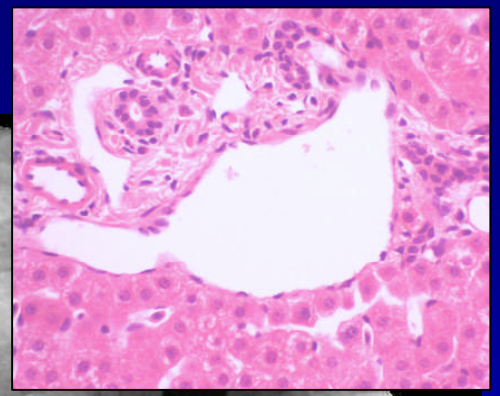


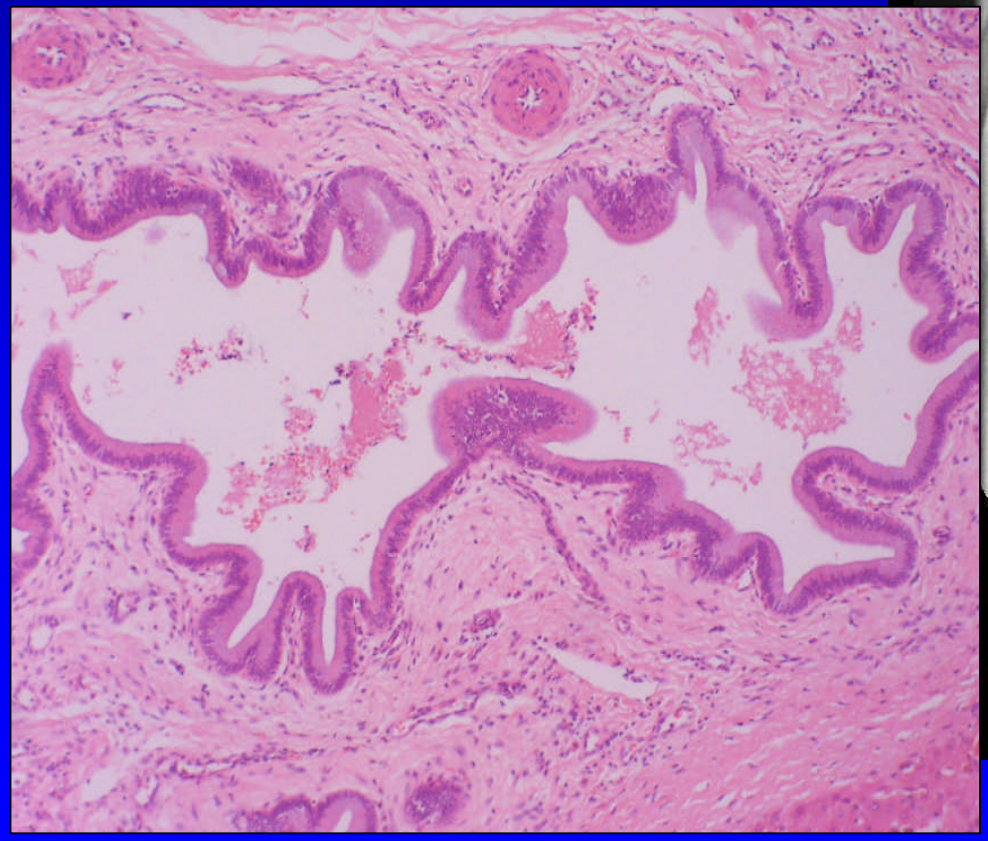
- Portal tract oedema - mild fibrosis
- Subtle ductular reaction
- Light inflammation - minimal interface activity

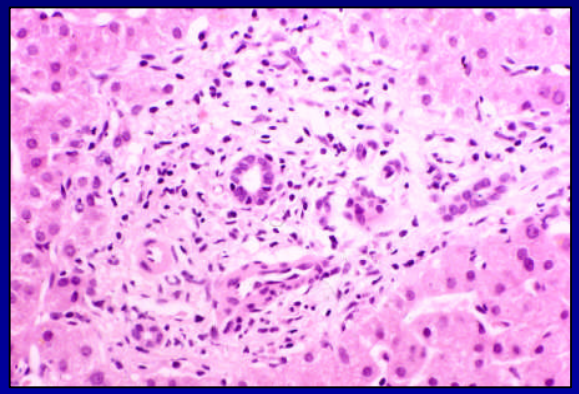
Copper-associated granules

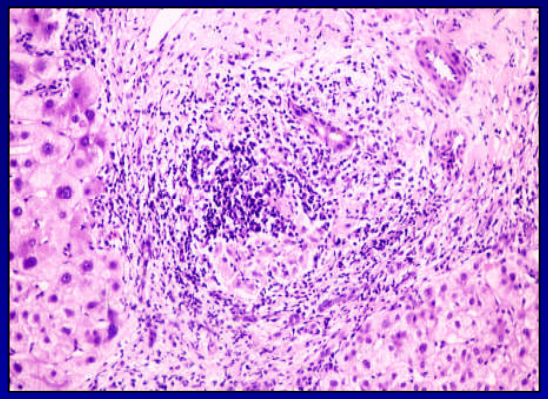
The normal bile ducts







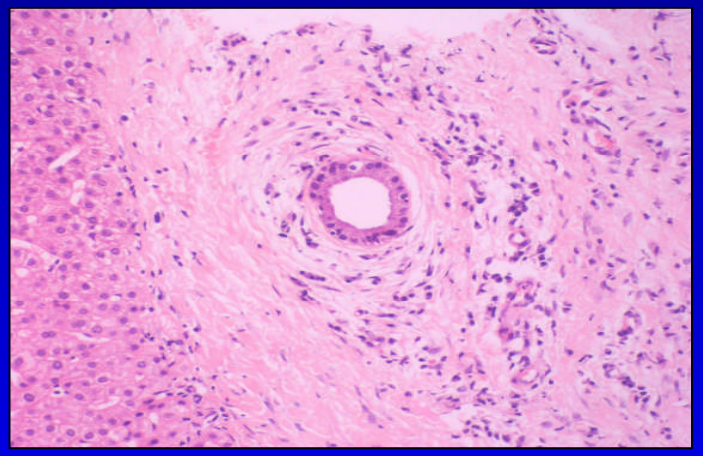


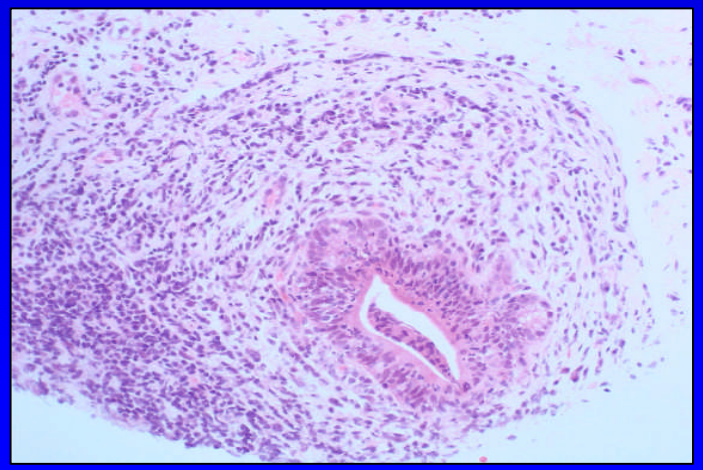


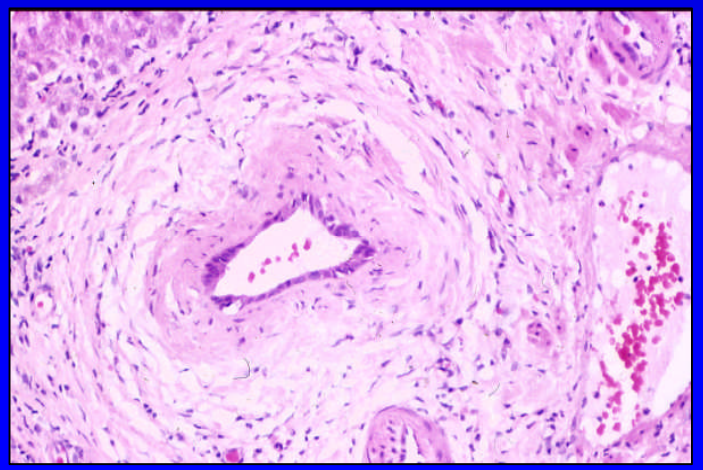
← Interlobular bile ducts

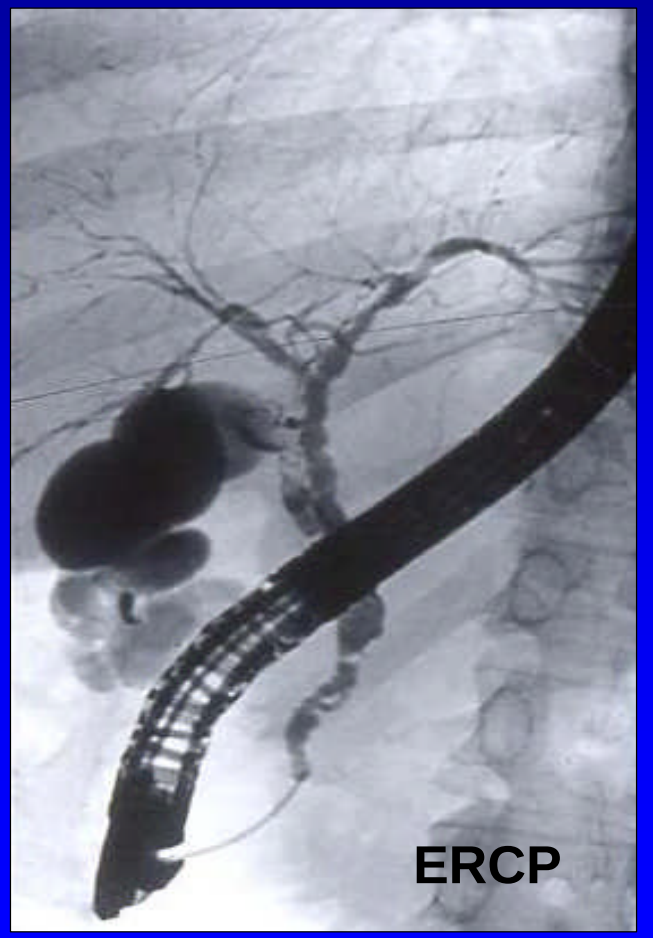
PSC: histology

Septal bile ducts
< 40% of biopsy specimens









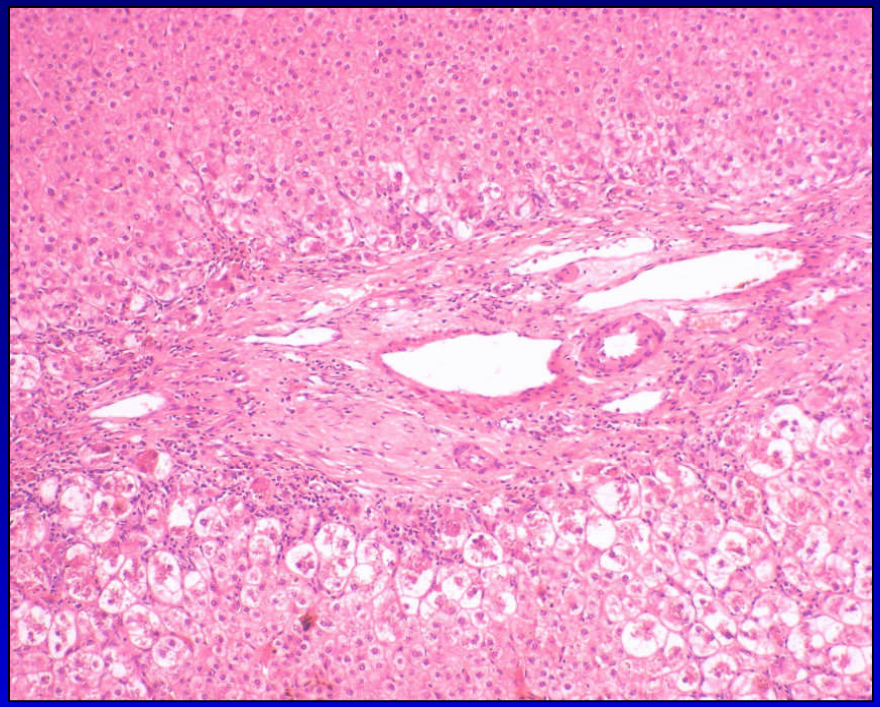
PSC : variable morphological changes

1. Size of bile ducts sampled by biopsy needle
2. Likely multifactorial process

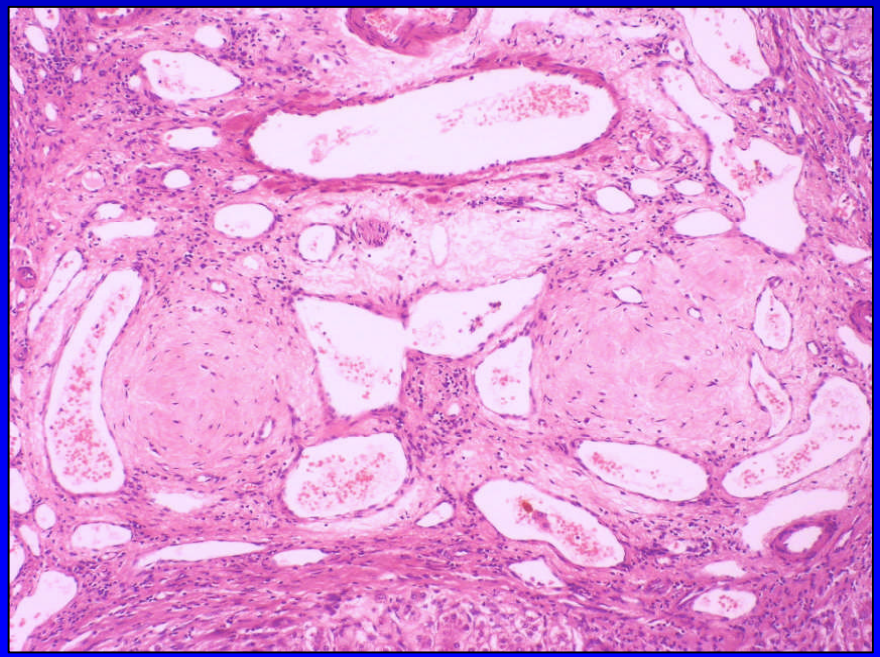
- Immunologically mediated injury targeted at variable segments of biliary tree ± extension to periportal parenchyma
- Retention of hydrophobic bile salts
- Ischaemia (portal phlebitis, obliteration of periductal capillary plexus
- Superimposed bacterial cholangitis

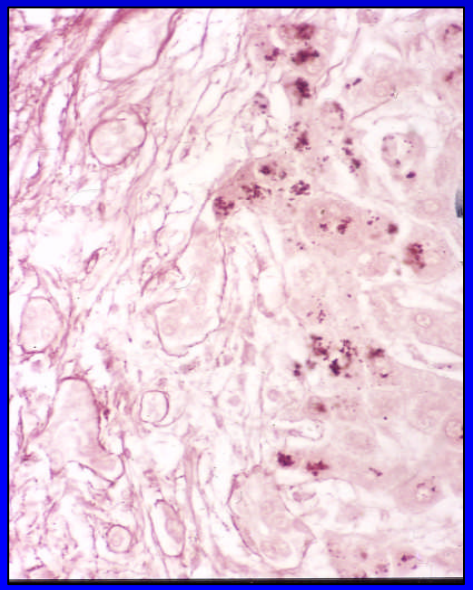
PSC: Histology (late)

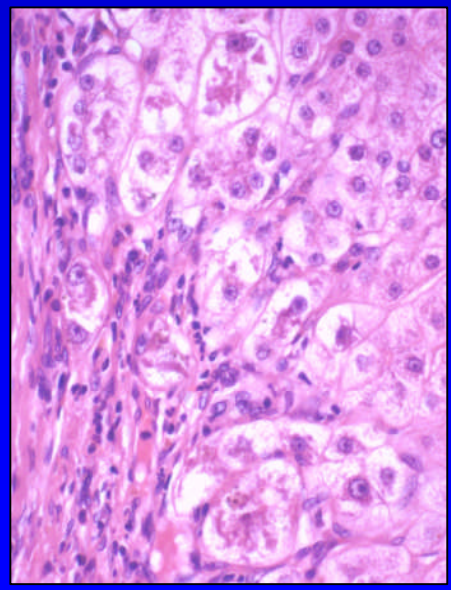
Ductopenia, biliary interface activity (cholate-stasis) →



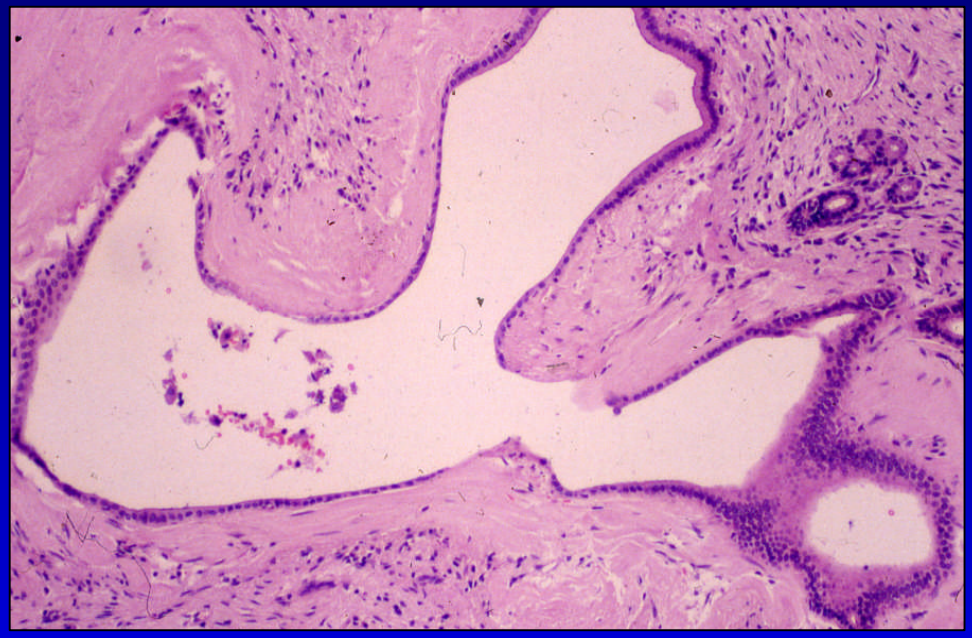
Fibro-obliterative bile duct lesion rare in biopsy specimens ↓

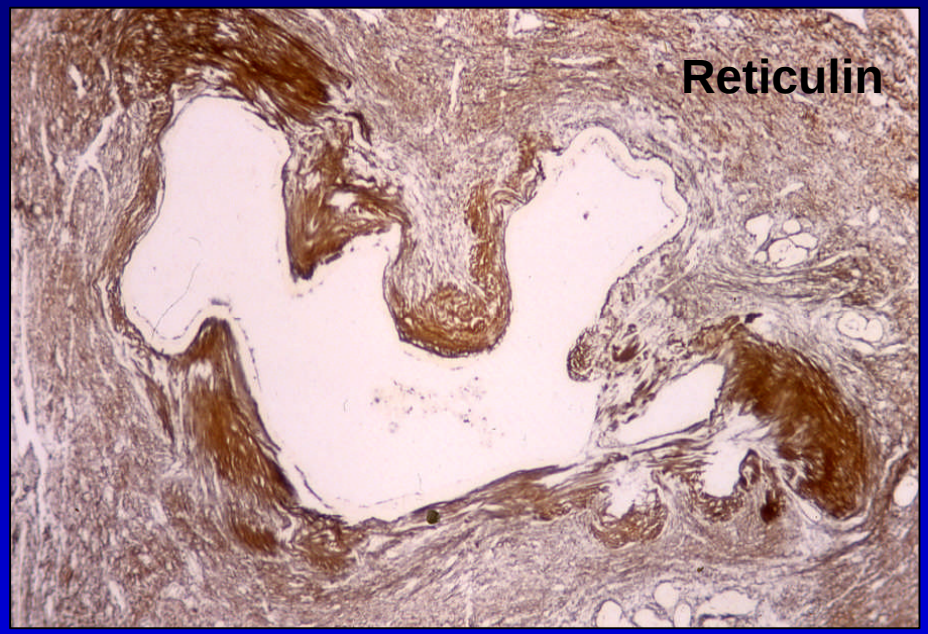


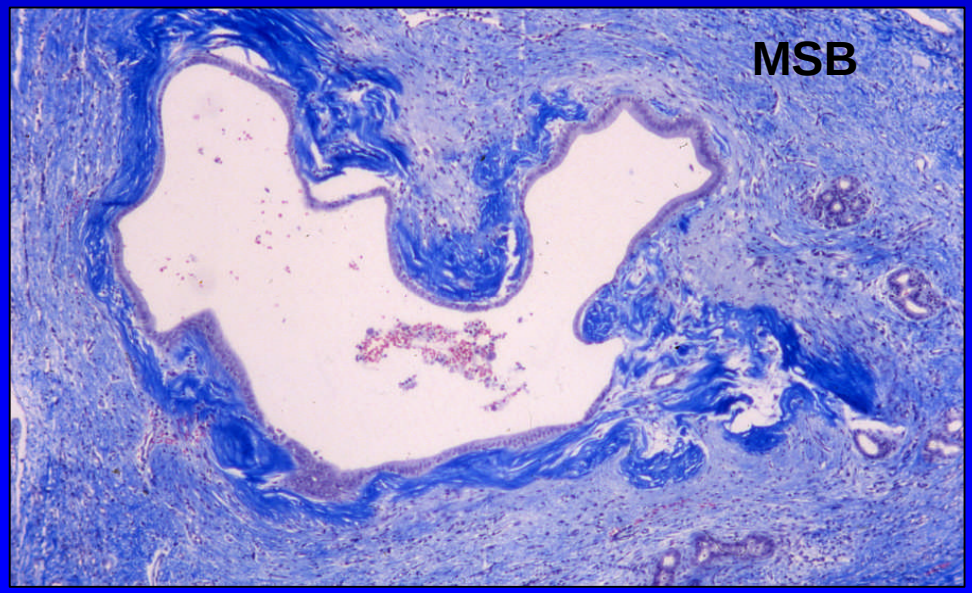


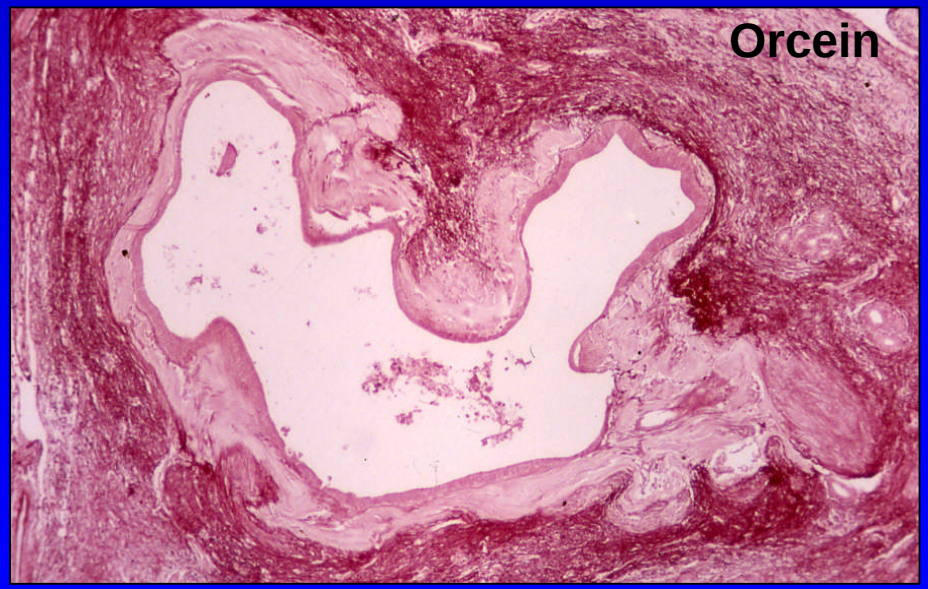


Primary sclerosing cholangitis / Periductal fibrosis

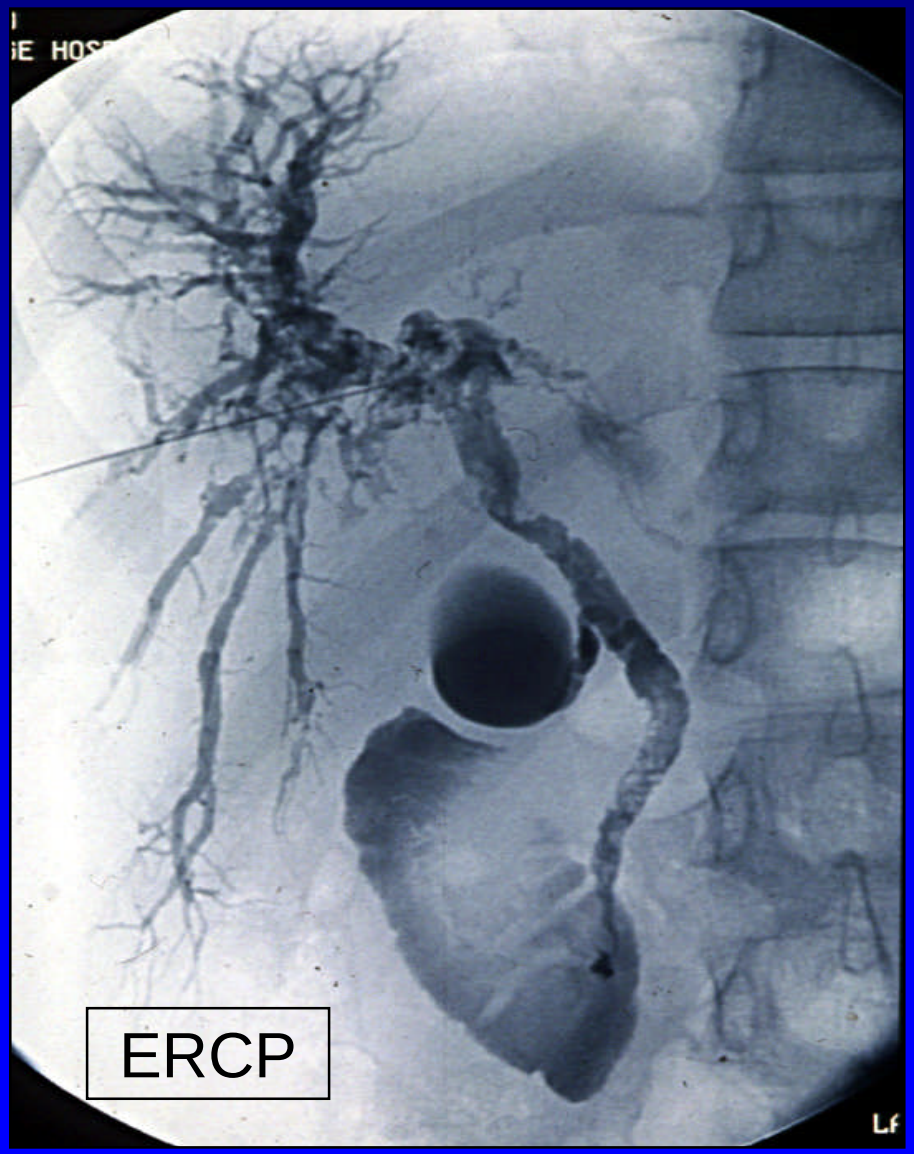


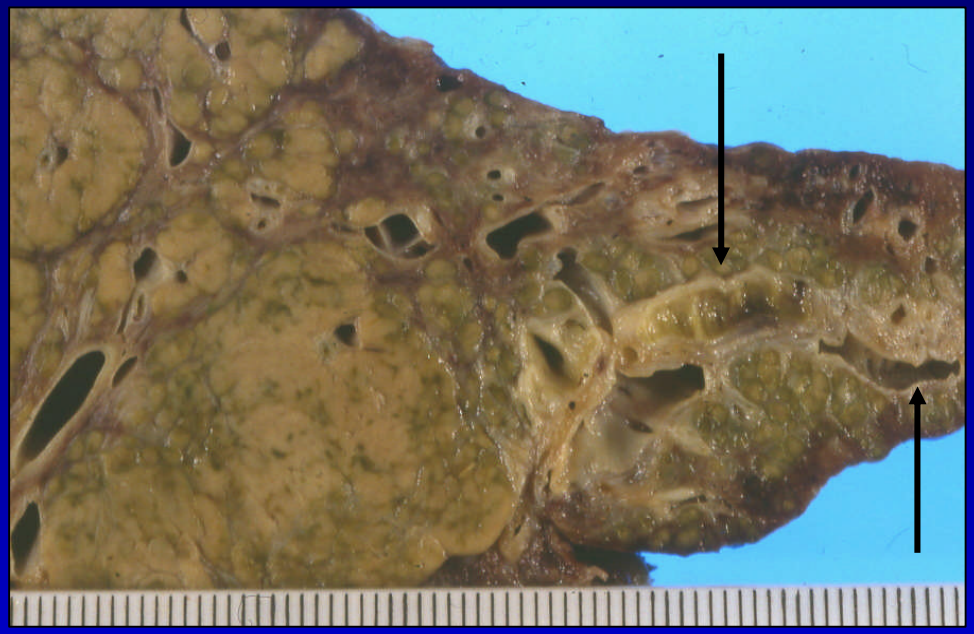


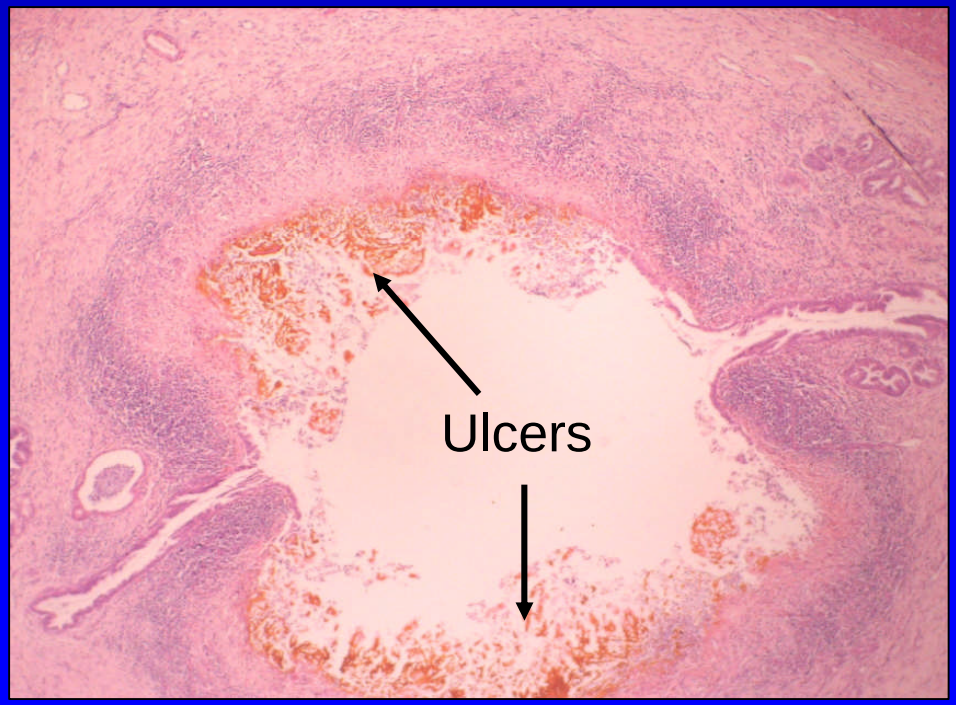




PSC : large bile ducts







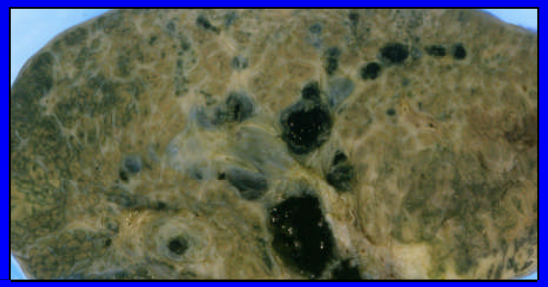
PSC and Autoimmune Hepatitis

- **50% of children with serology of AIH have ERCP changes of cholangiopathy** (***El Shabrawi et al, Gastroenterology 1987;92:1226)***
- **1/3 of adult patients with PSC score 10 to 15 (= probable AIH) when evaluated by the International AIH Group system**

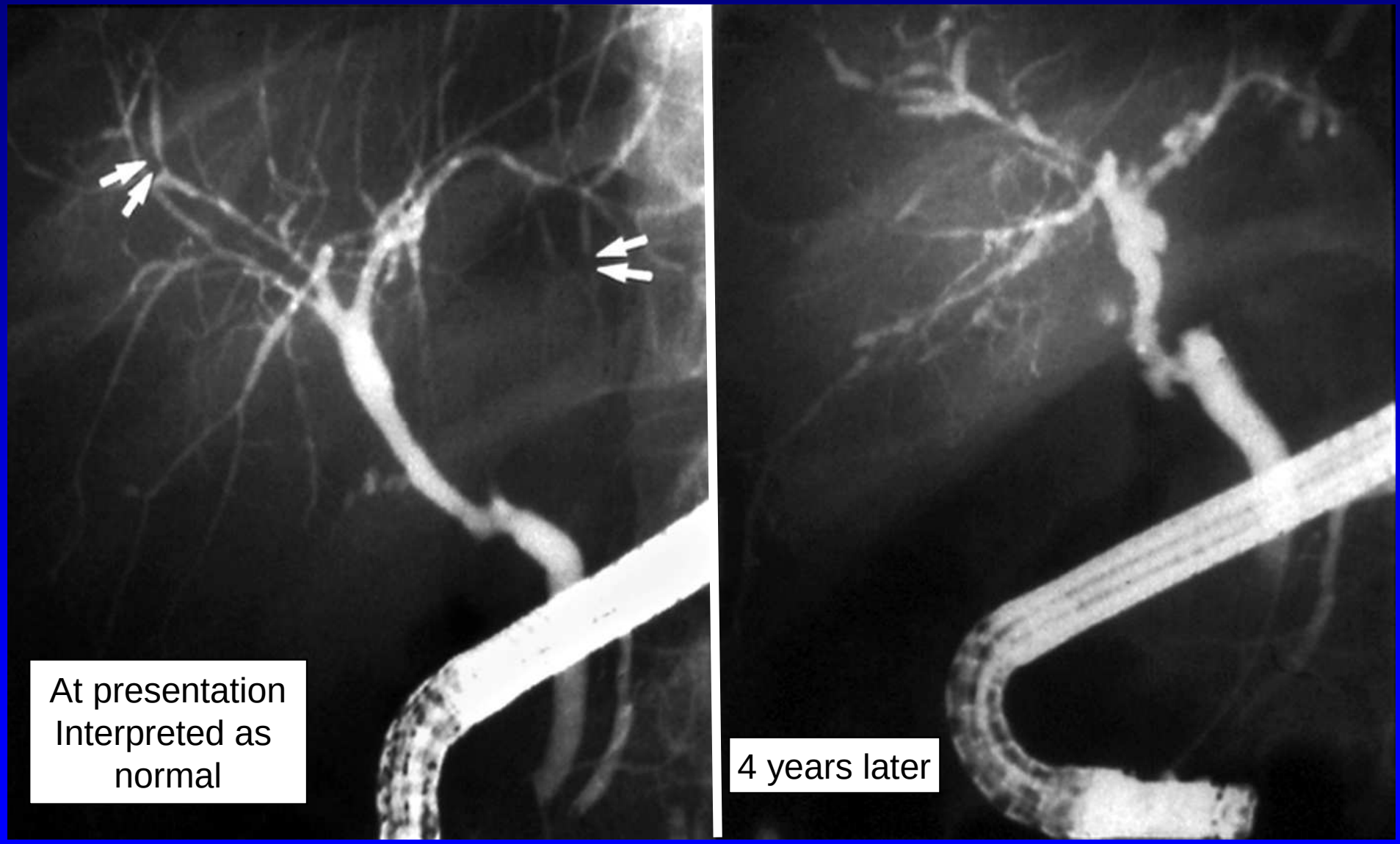
  Boberg KM et al Hepatology 1996; 23:1369

  - **Crossover AIH ⇒ PSC : some = misdiagnosis / but well documented cases**

- **Patients transplanted for end-stage AIH-cirrhosis ⇒ PSC in explanted liver**



? AIH → PSC (ERCP review)



Autoimmune Sclerosing Cholangitis *versus* Autoimmune Hepatitis in children

King's prospective study (1984-1997) N = 52 *

- Patients with clinical ± biochemical liver disease
  + serum autoantibodies + high IgG
- Exclusion of other causes of liver disease
- At presentation:
  - Cholangiography / sigmoidoscopy
  - Liver and rectal biopsies
- *Follow up* liver biopsy and cholangiography

**** Gregorio GV et al Hepatology, 2001; 33: 544***

Concept of Autoimmune Sclerosing Cholangitis (AISC)

Diagnostic criteria

- **High IgG**
- **Autoantibodies (ANA, SMA, LKM1)**
- **Abnormal cholangiogram**
  = distinguishing factor from AIH

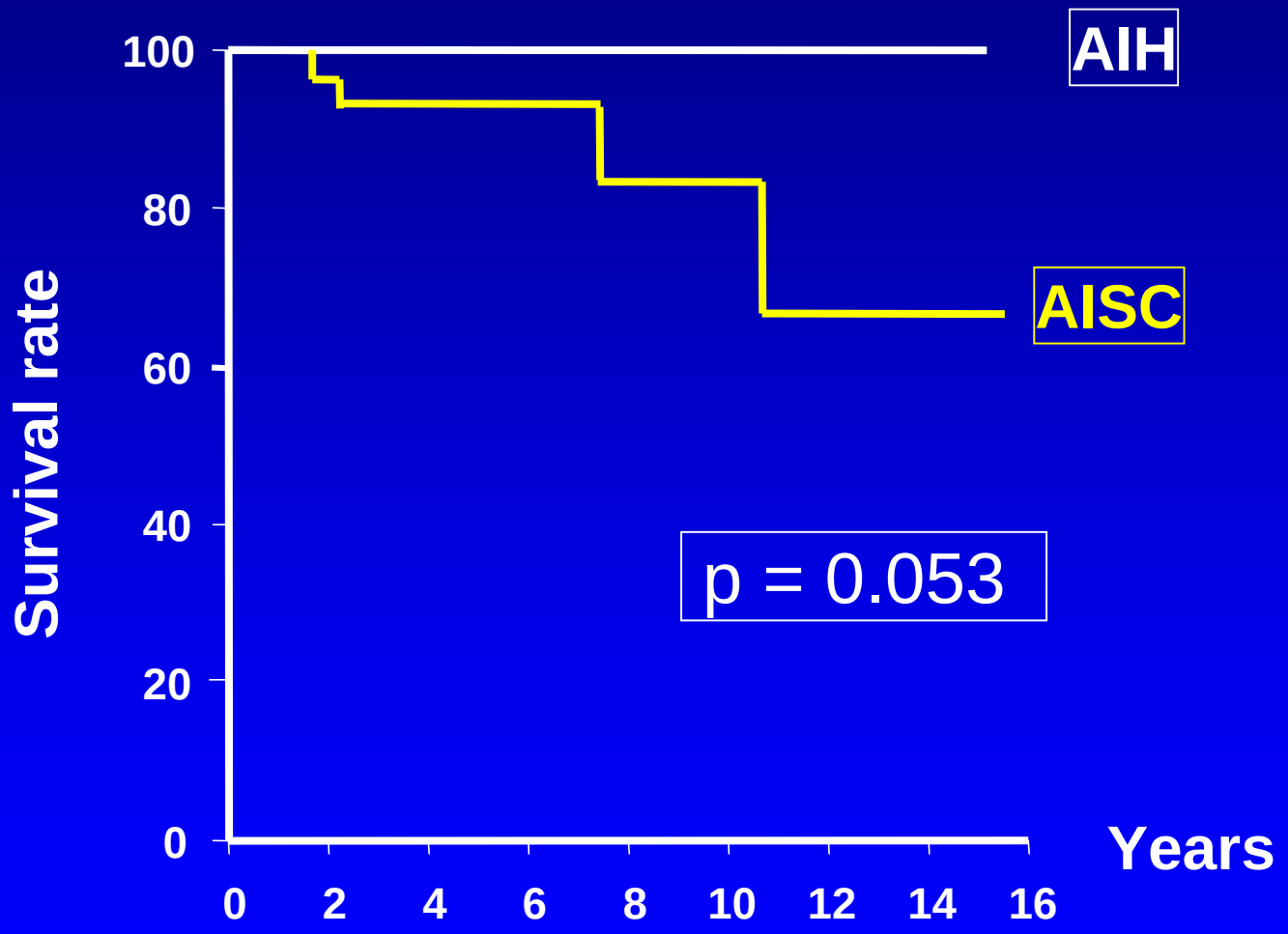
Autoimmune sclerosing cholangitis and hepatitis in children (N = 52)

Histological diagnosis	**AISC**	**AIH**
	(N=26)	**(N=26)**
Chronic hepatitis	6 (23)	17 (65)
Distal cholangiopathy (S-C)	11 (42)	1 (4)
Chronic hepatitis + biliary features	5 (19)	7 (27)
Minimal portal inflammation and fibrosis	3 (12)	1 (4)
Biliary cirrhosis	1 (4)	0

Gregorio GV et al Hepatology, 2001; 33: 544

Autoimmune Hepatitis / Sclerosing Cholangitis

Transplant-free survival - 7 years (2-16) from Δ



- **Response to immunosuppression is the same**
- **Medium-term OLT-free survival better in AIH**
- **Long term prognosis ?**

Gregorio GV et al Hepatology, 2001; 33: 544

Autoimmune Hepatitis / Sclerosing Cholangitis

- Overlap important particularly in children and young adults
  - ? Different diseases
  - ? Manifestations of the same disease
  - ? Adult PSC = burnt out AISC

- Diagnosis requires imaging
- Histology adds useful information

Sclerosing cholangitis

Primary or idiopathic ± ulcerative colitis

- Autoimmune (autoimmune sclerosing cholangitis)
  > in children and young adults
- Overlap AIH / PSC
- IgG4 associated (± chronic pancreatitis)

Acquired (secondary)

- Opportunistic infection (immunodeficiency, AIDS)
- Ischaemic (liver allograft, intraarterial chemotherapy)
- Toxic (hydatid cyst ± formalin)

Chronic biliary disorders
Clue to pathological diagnosis

- **Awareness of the condition(s)**
- **Evaluation of histological findings in conjunction with clinical and laboratory data** (↑ alk phos, γGT, autoAbs)
- **Awareness of histology drawbacks**
  - Lack of sampling of characteristic bile duct lesion
  - Overlapping features (chronic hepatitis)
  - Absence of cholestasis
- **Recognition of subtle biliary features** (orcein / copper)

King's 2000

Questions / Comments ?