When is immunohistochemistry useful in adult medical liver disease?

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Edinburgh

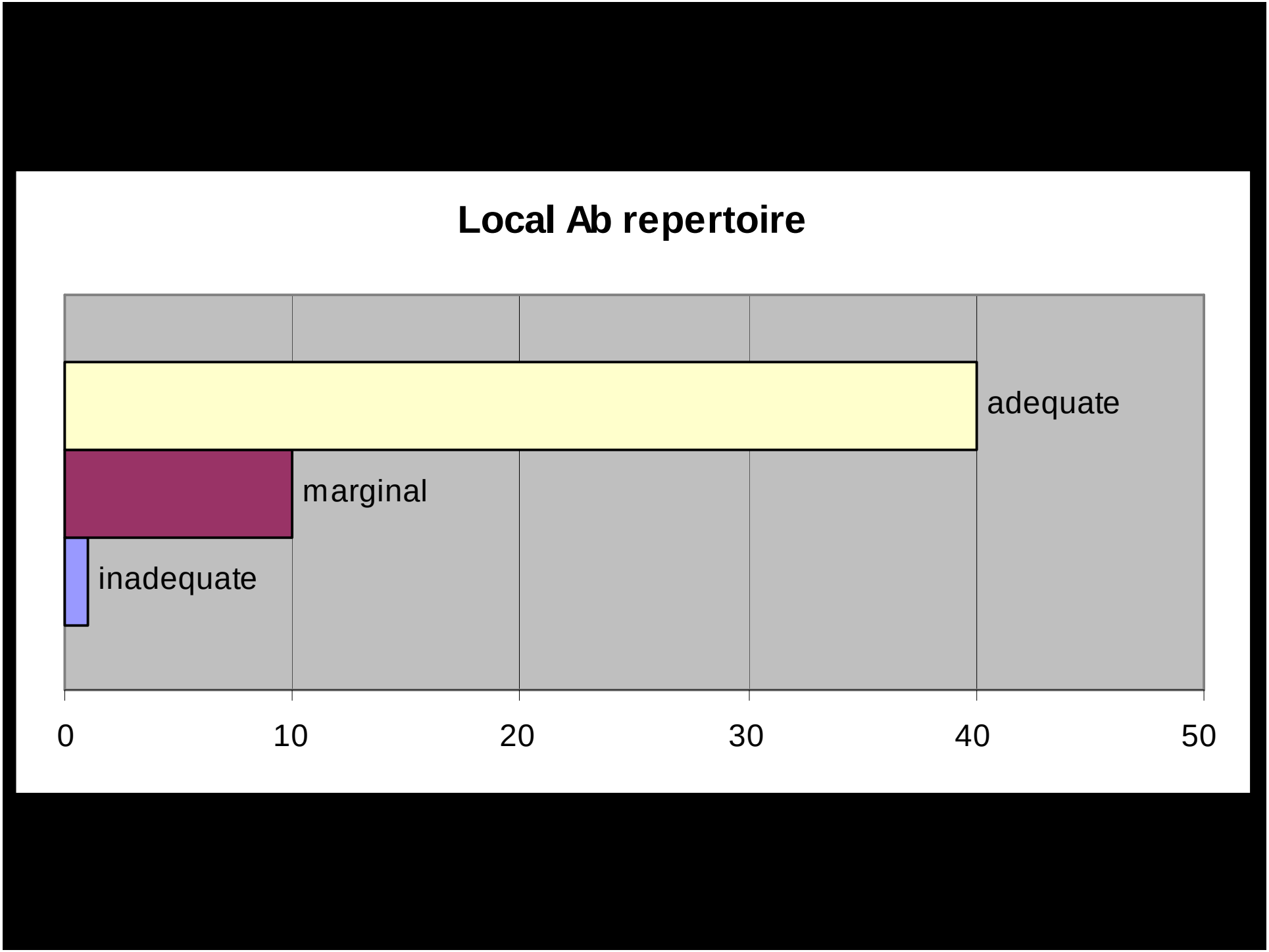
Plan

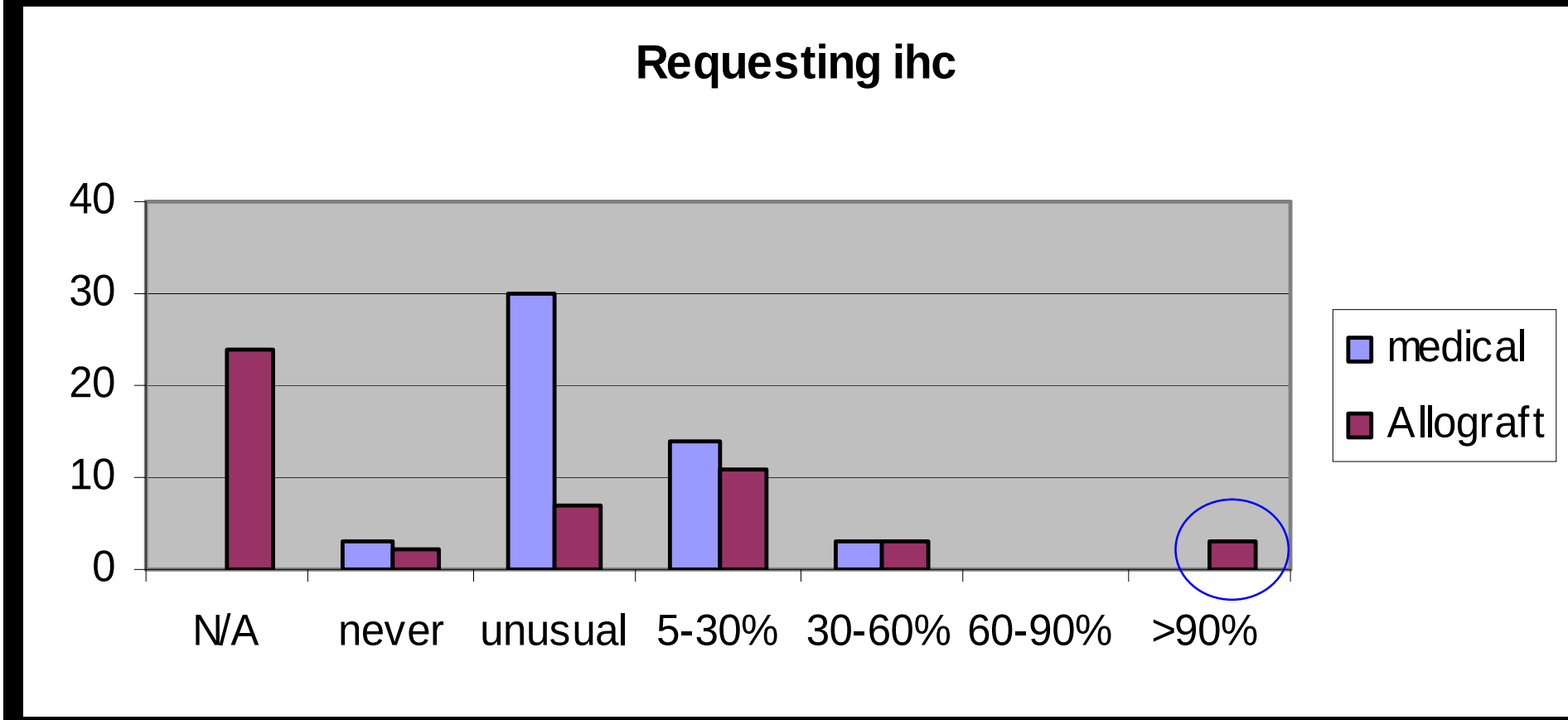
- examples
- 51 UK pathologists
  - -50 bx 20%
  - -100 bx 27%
  - -200 bx 27%
  - >200 bx 26%

paraffin sections: added value

- immunohistochemistry
  - antigen retrieval
  - enhanced detection
    - polymer (e.g. Envision dextrane chain)
- *in situ* hybridisation
  - oligonucleotide probes
  - peptide nucleic acid probes

- patch size - “clonality”
    - X-chromosome methylation (HUMARA)
- proteomics
  - comparative mass spectrometry
- expression microarrays
    - Exon chips

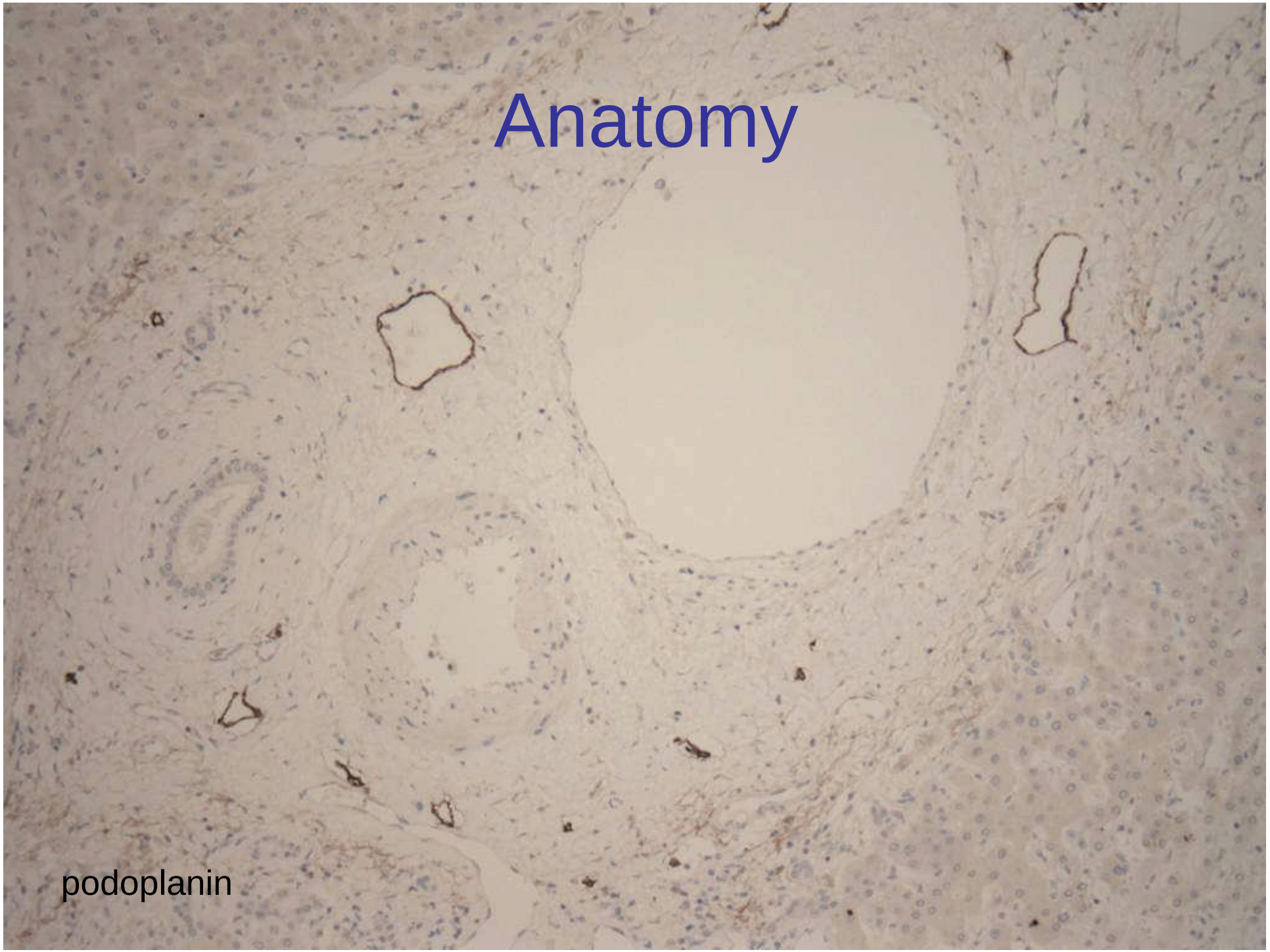

Local Ab repertoire
adequate
marginal
inadequate
0
10
20
30
40
50


Requesting ihc
40
30
20
10
0
N/A
never
unusual
5-30%
30-60%
60-90%
>90%
medical
Allograft

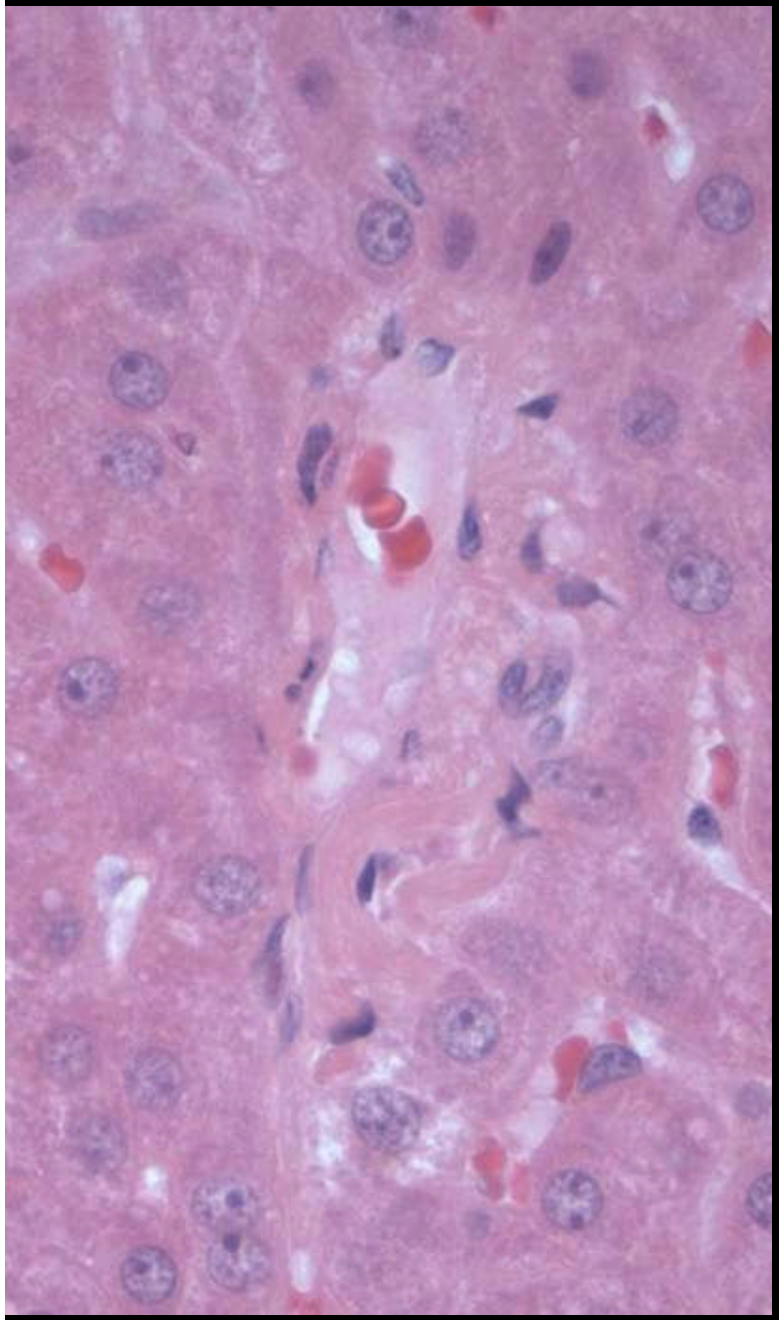
immunohistochemistry

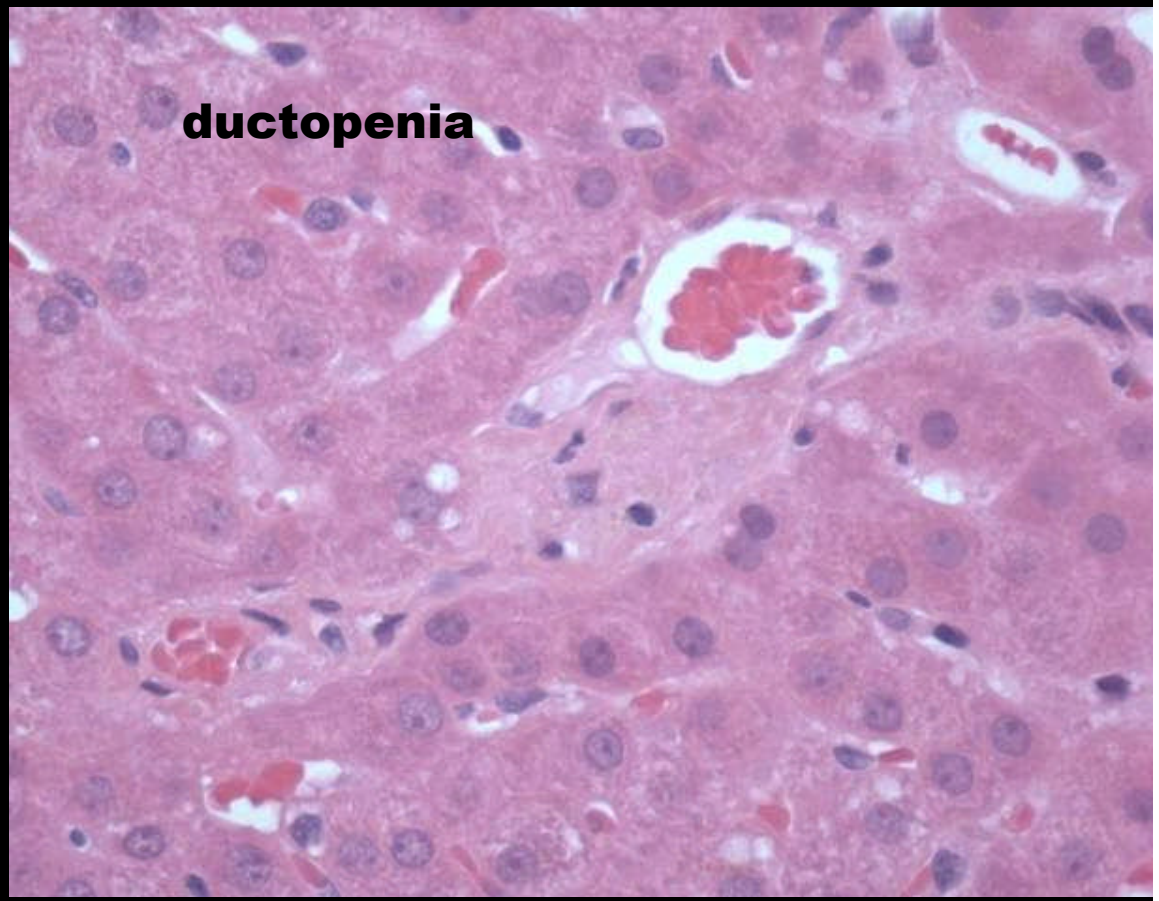
- **Anatomy**
  - decorate: arterioles, bile ducts, ductules, “capillarisation”, stellate cells, lymphatics, matrix
- **Foreign proteins**
  - extrinsic: infections
  - intrinsic: metastasis, inflammation, amyloid, Ab
- **Altered expression**
  - homeostasis: cell cycle, stress response, apoptosis
  - disorganised: storage disorder, Mallory
  - illicit: neoplasia

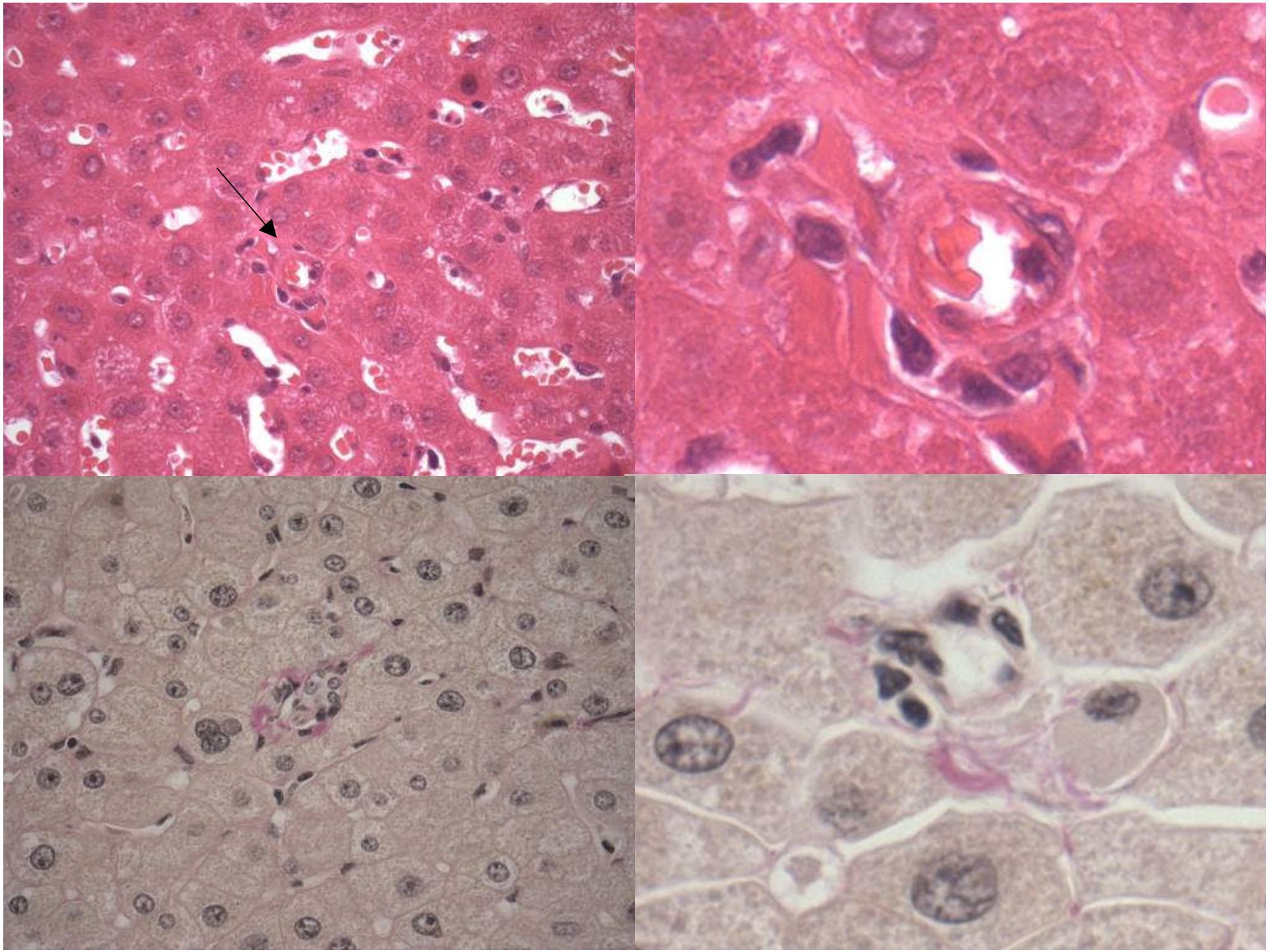
Anatomy

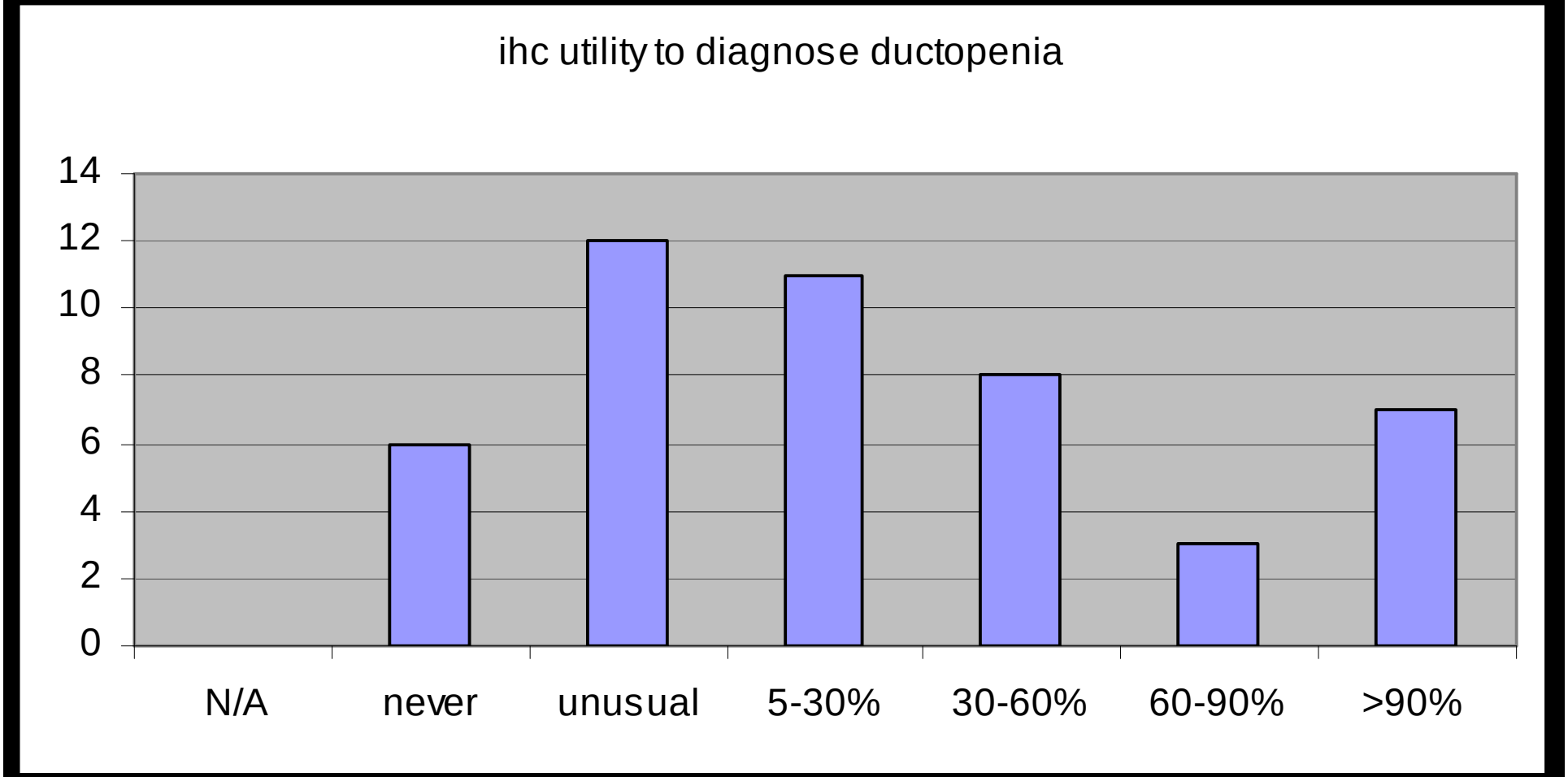


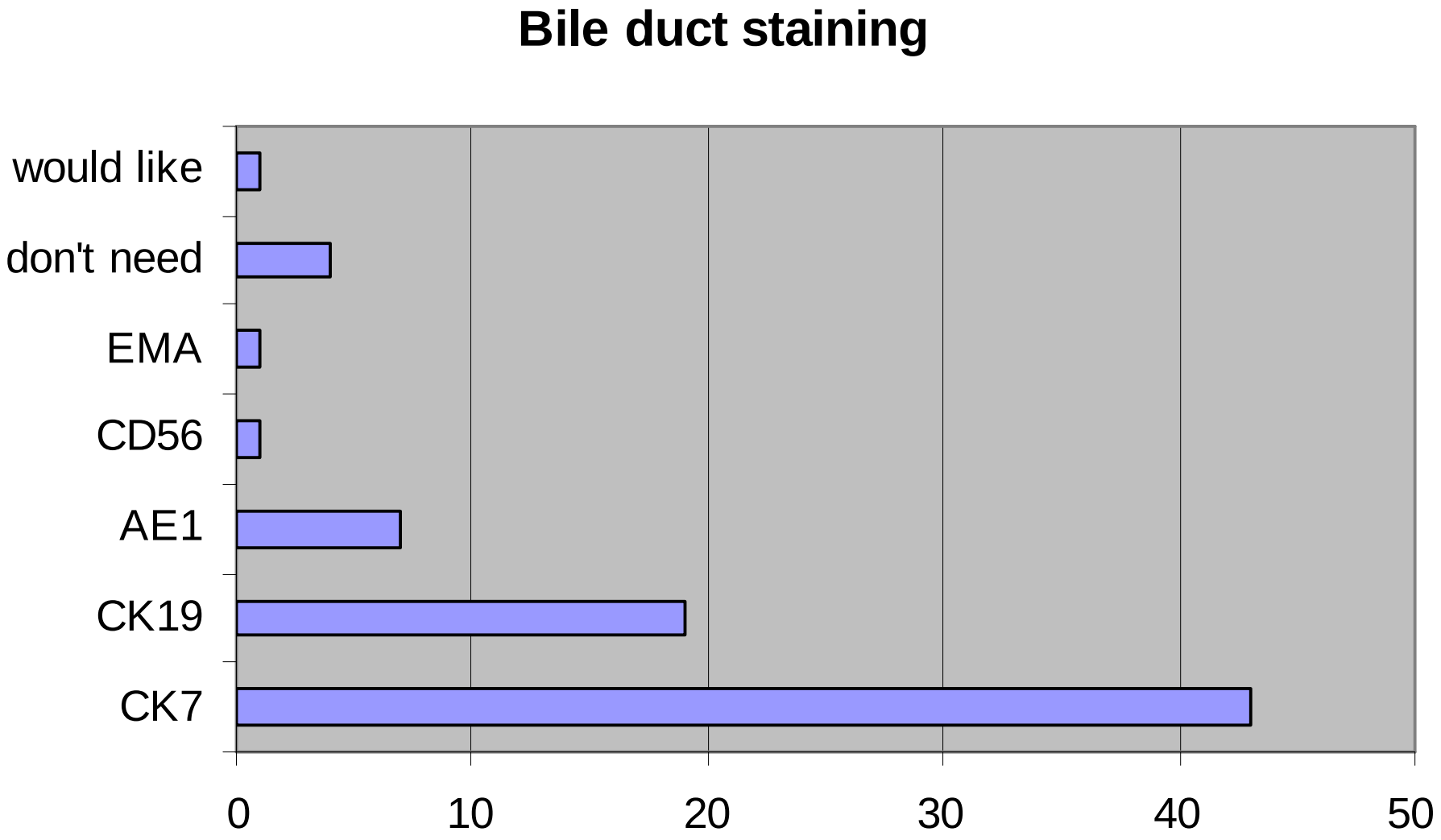
podoplanin




ductopenia



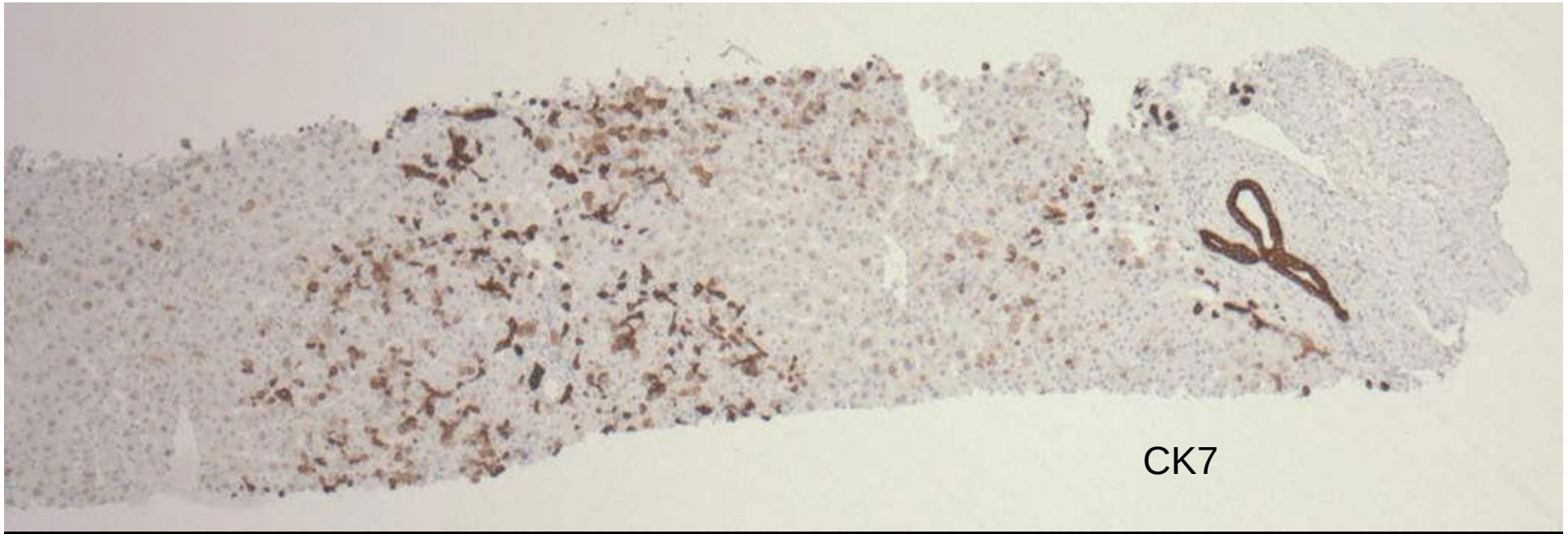

ihc utility to diagnose ductopenia
14
12
10
8
6
4
2
0
N/A
never
unusual
5-30%
30-60%
60-90%
>90%

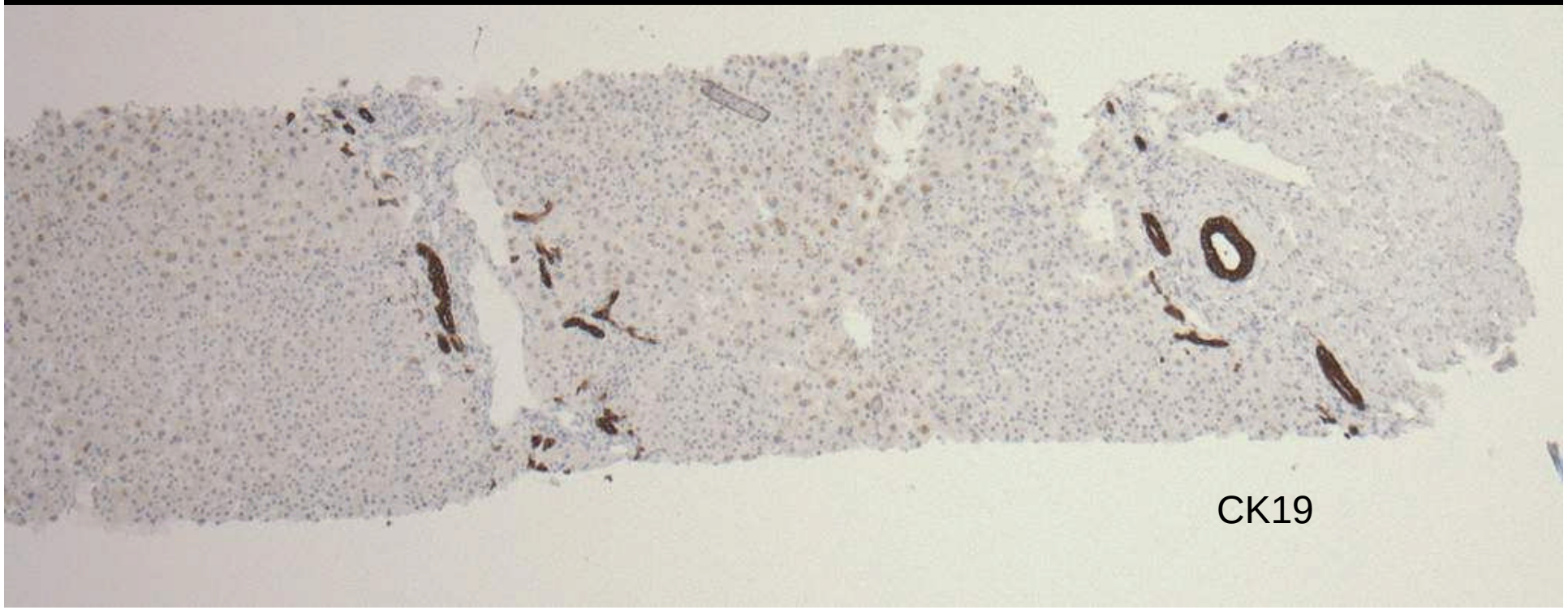

Bile duct staining
would like
don't need
EMA
CD56
AE1
CK19
CK7
0
10
20
30
40
50

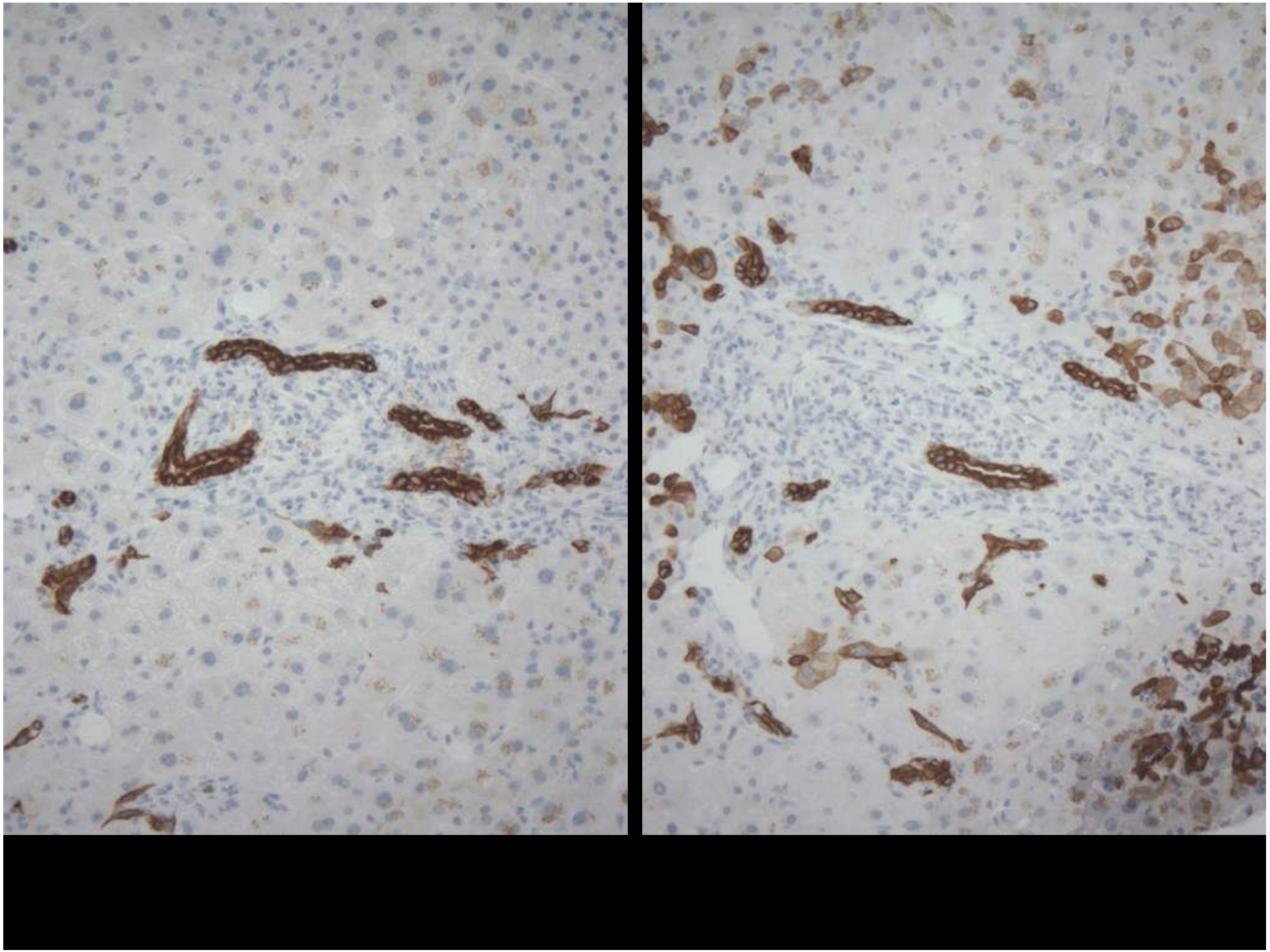
Bile ducts: CK7, CK19

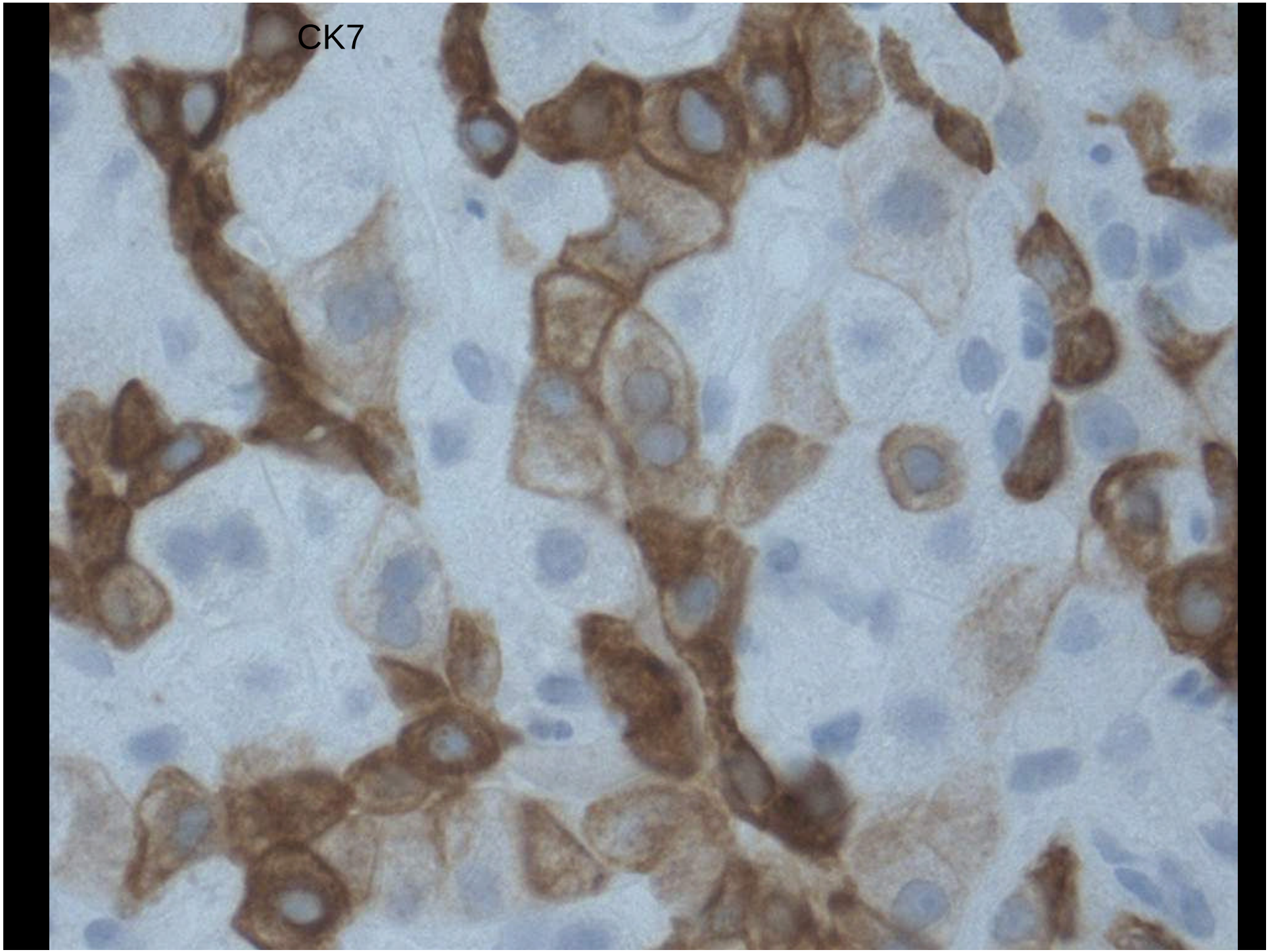
- also
  - canal of Hering cholangiocytes, “progenitors”
  - bile ductules

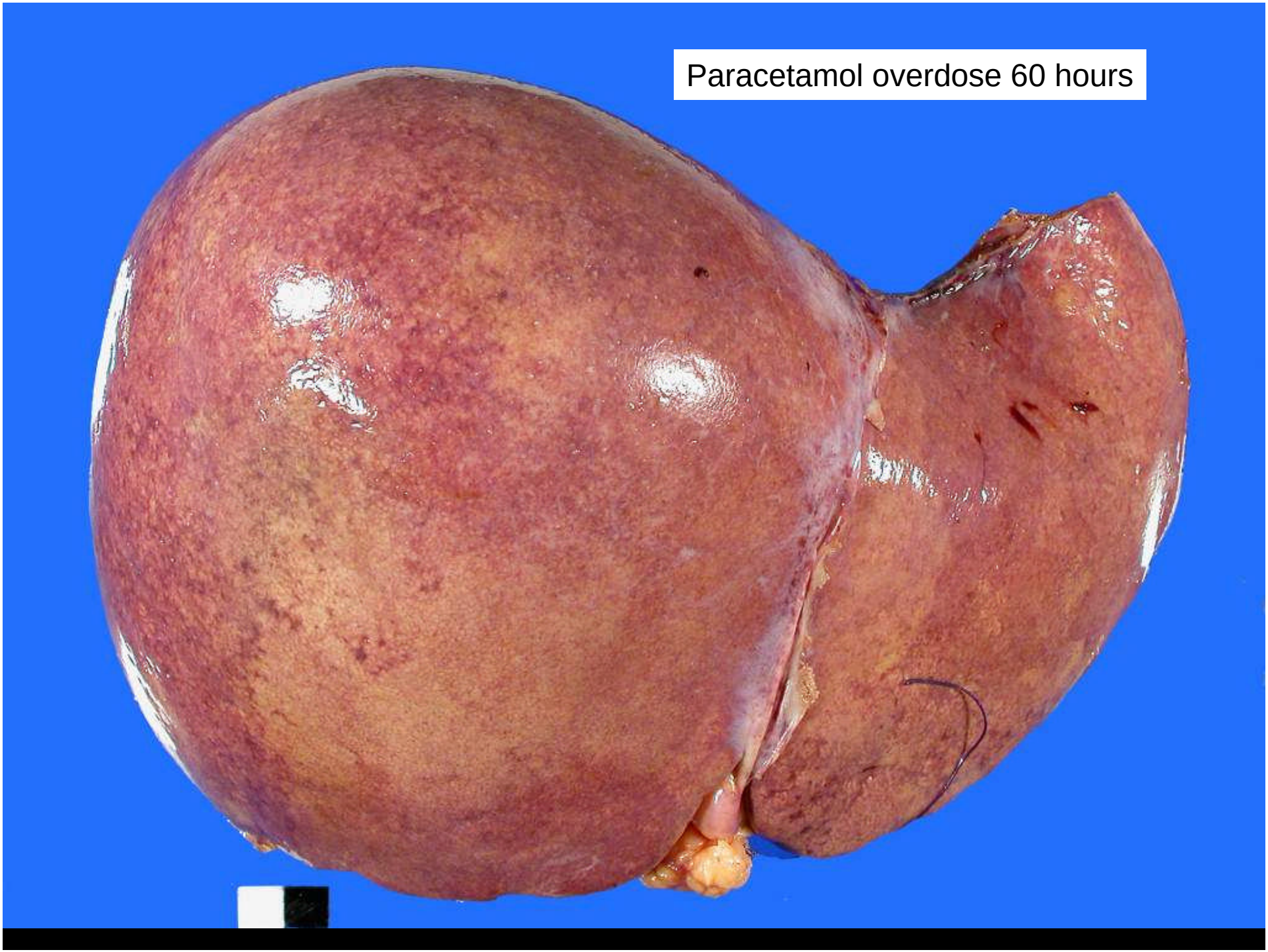
- in disease
  - ductular reaction radiating from coH
  - intermediate cells (6-40μ) (CK7) (adj to ductules)
  - cholate stasis in periportal hepatocytes (CK7)
  - cholestasis in chronic PBC (CK7) [Yabushita K, 2001]

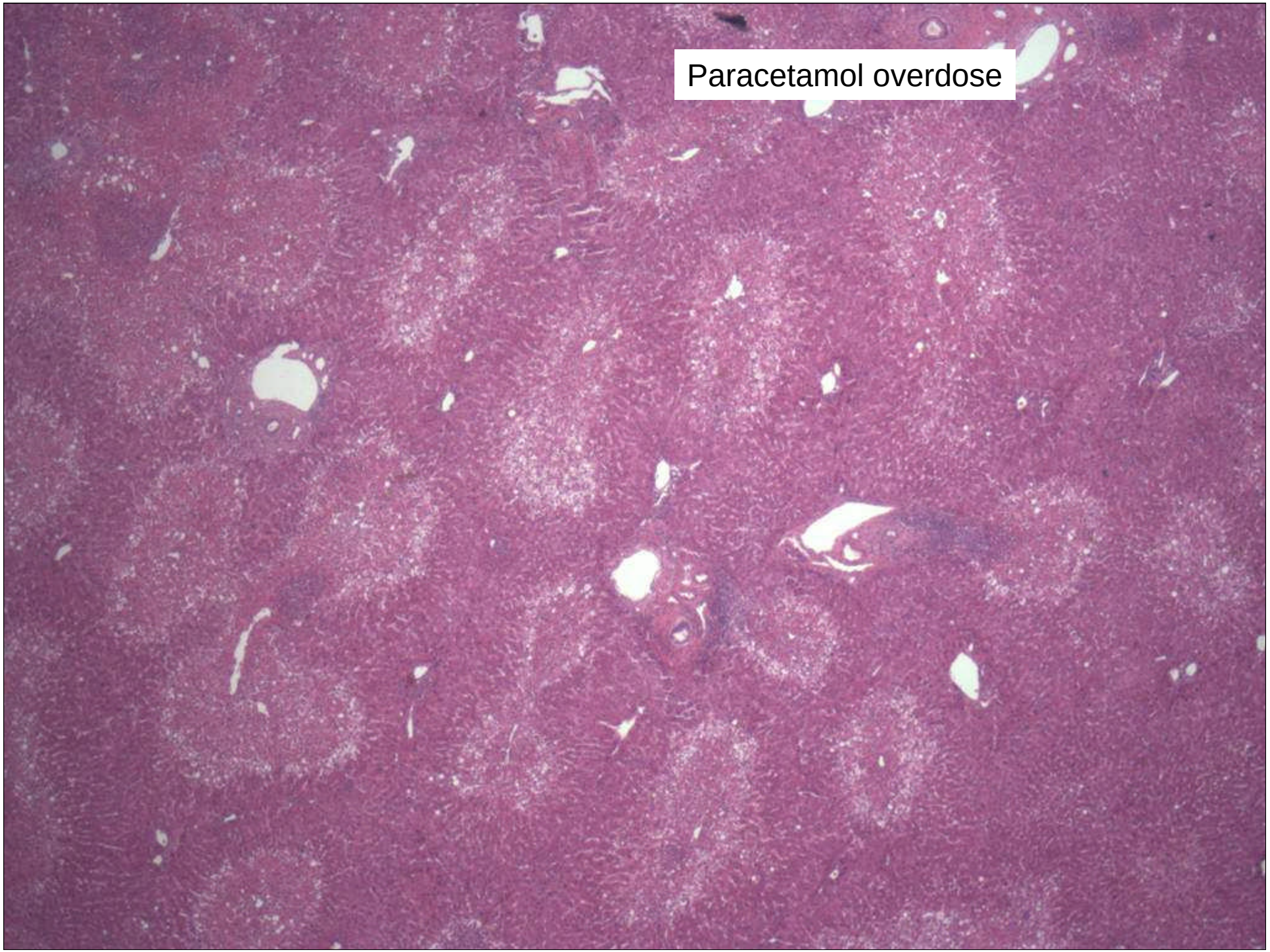

CK7

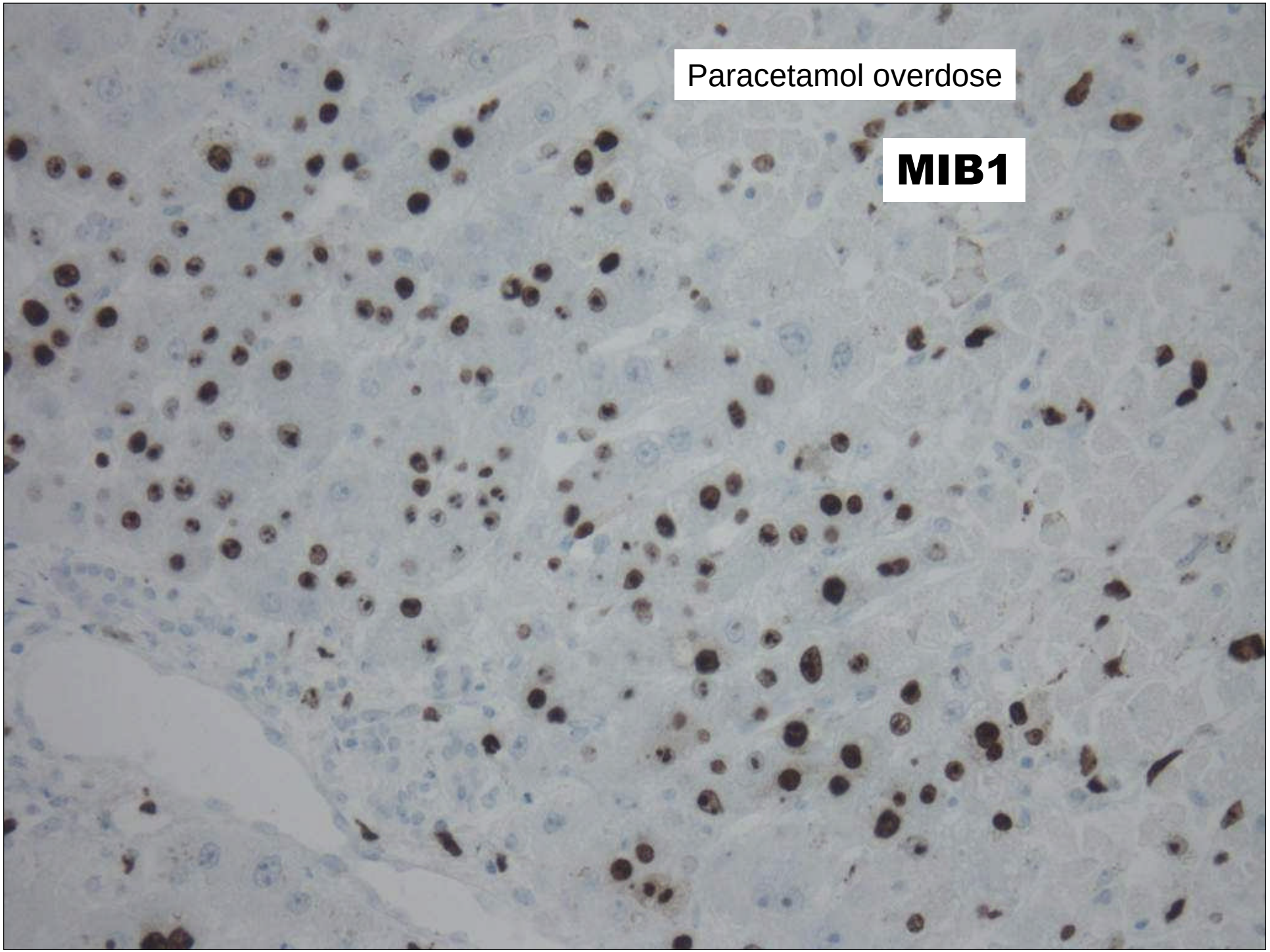

CK19

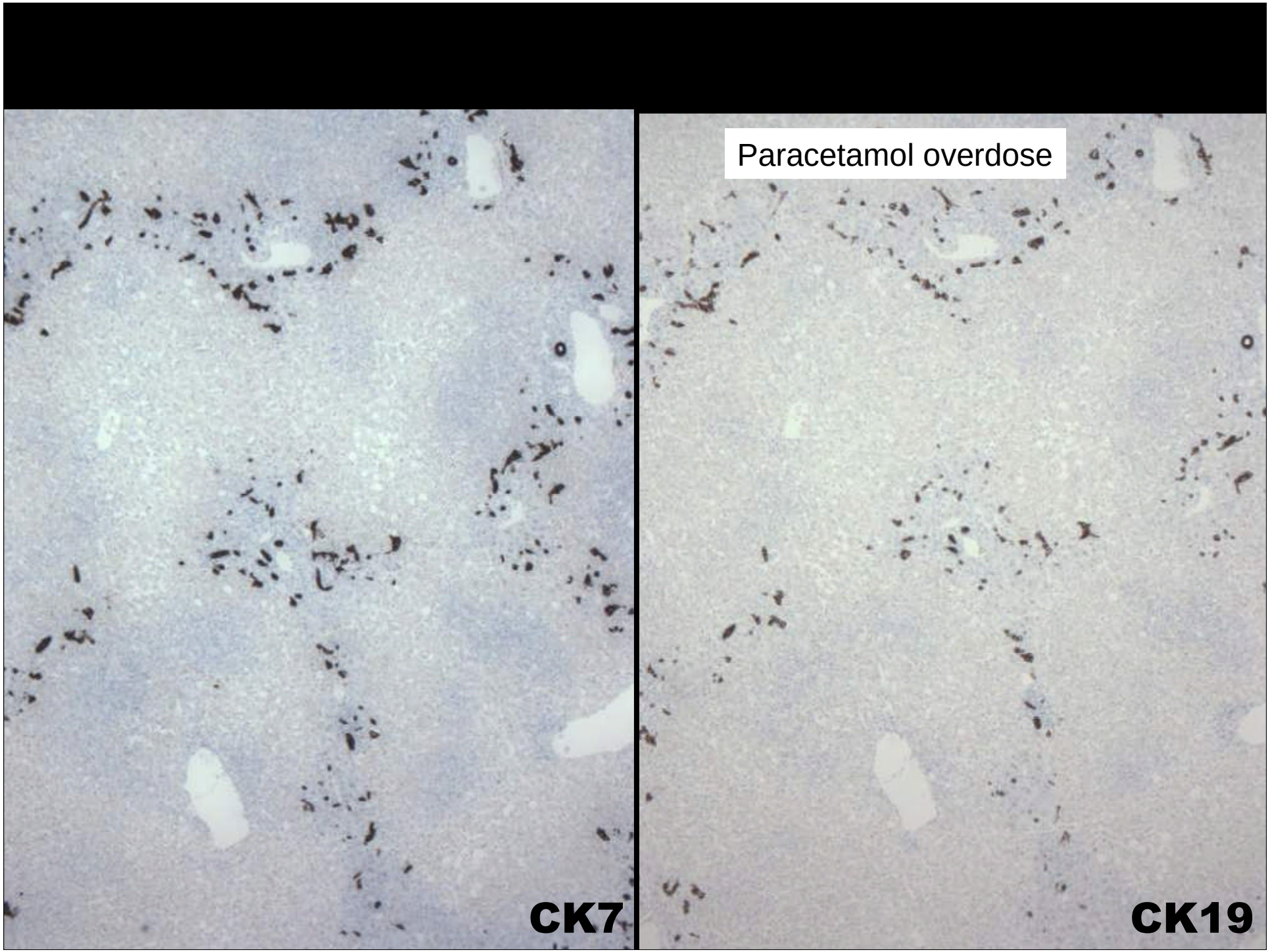



CK7

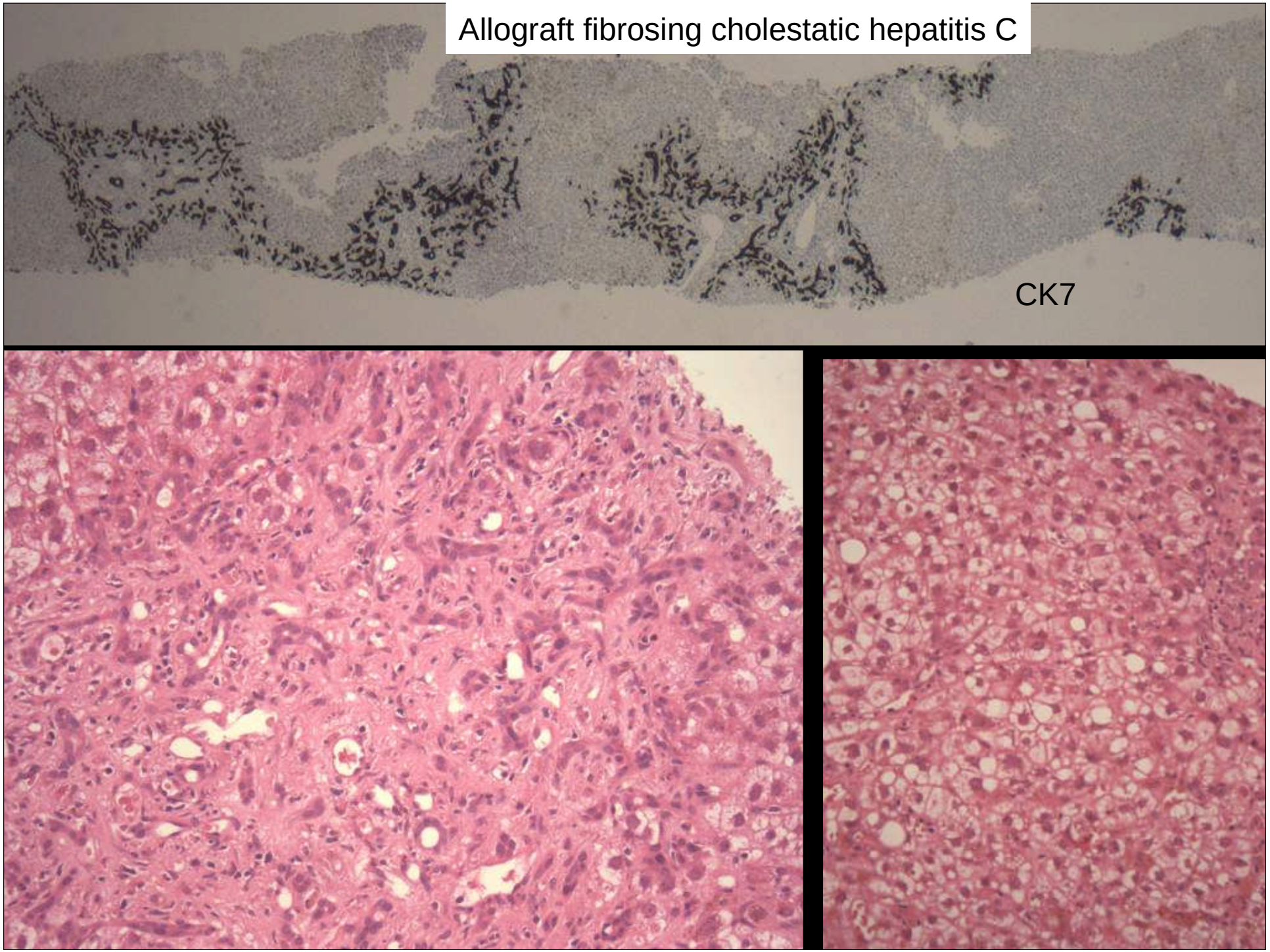

Paracetamol overdose 60 hours


Paracetamol overdose

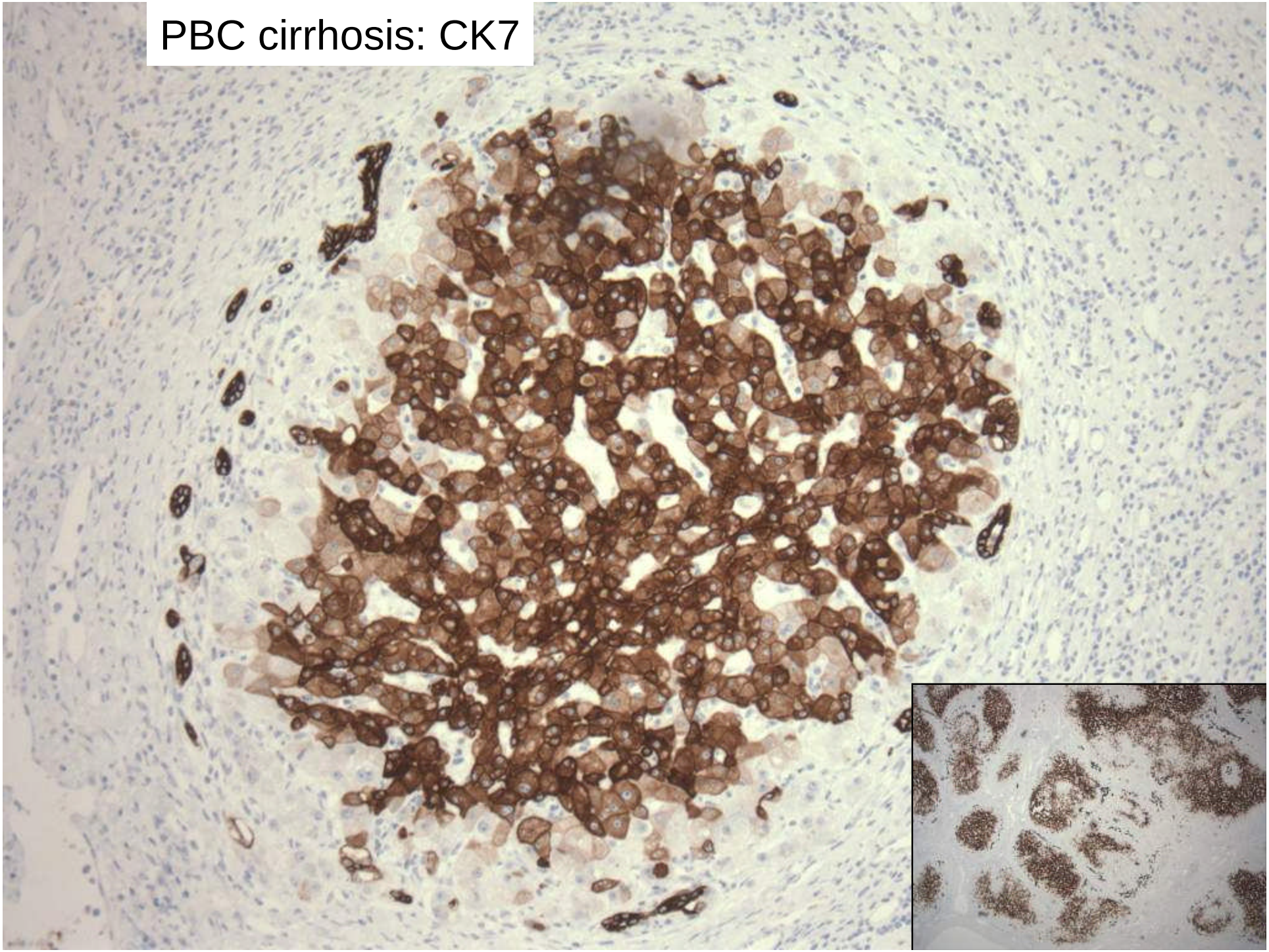

Paracetamol overdose
MIB1


Paracetamol overdose
CK7
CK19

Allograft fibrosing cholestatic hepatitis C



PBC cirrhosis: CK7



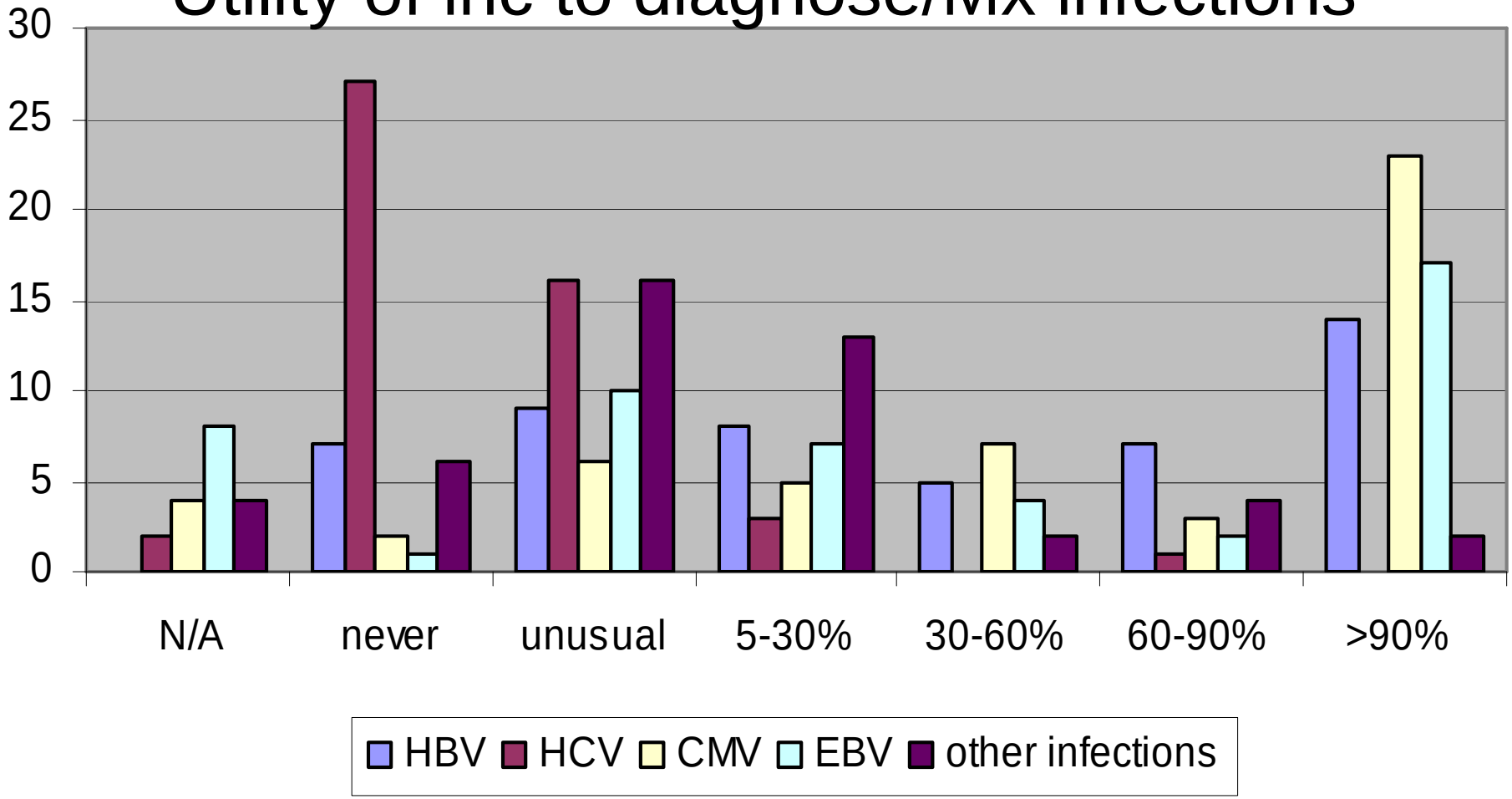
Infections

- Hepatitis B
- CMV
- EBV

    - Hepatitis D
    - Hepatitis C
    - Hepatitis A
    - Others

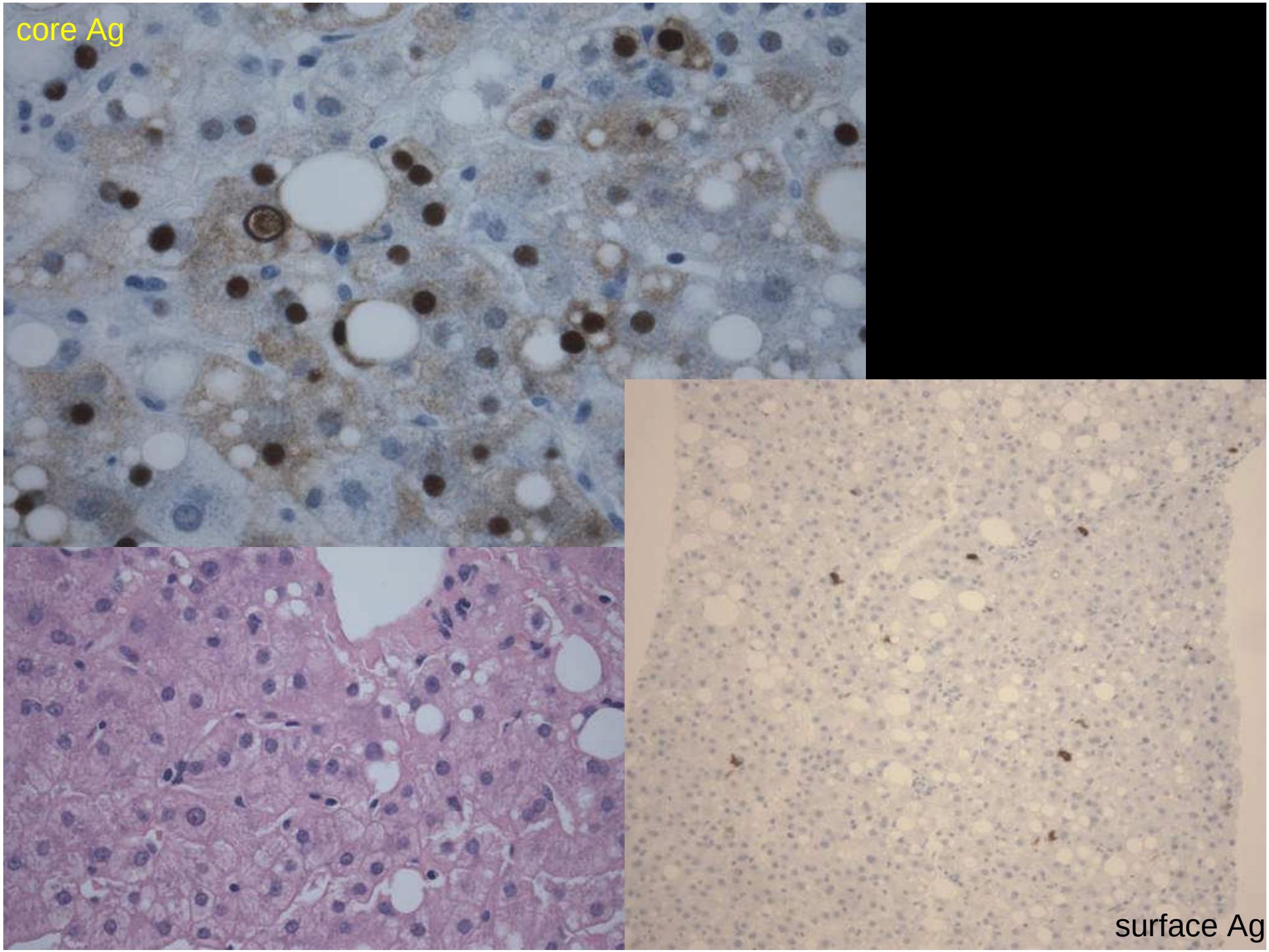
        – Hepatitis E [ZhaiQ,1991&1994]

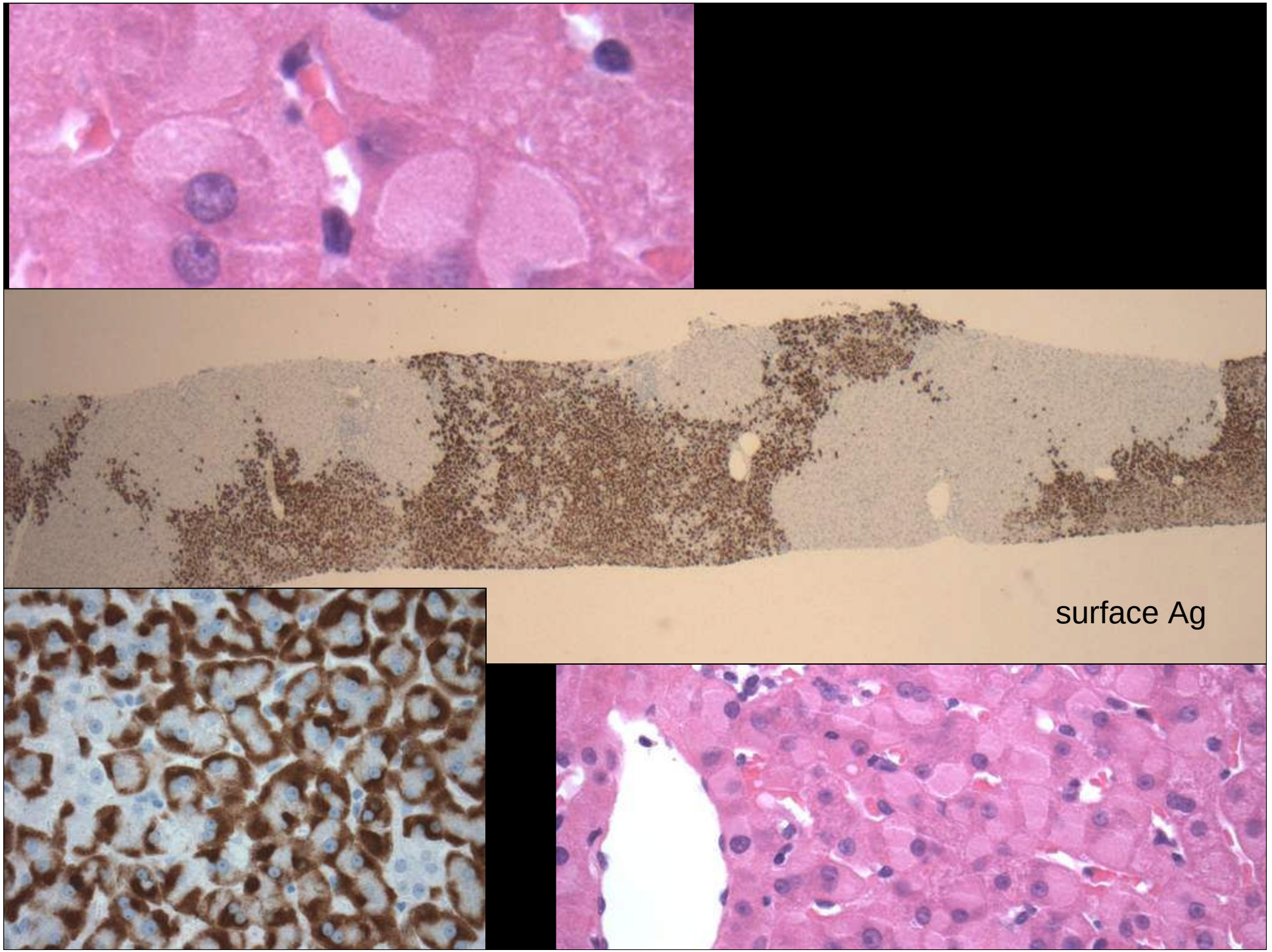
Utility of ihc to diagnose/Mx infections

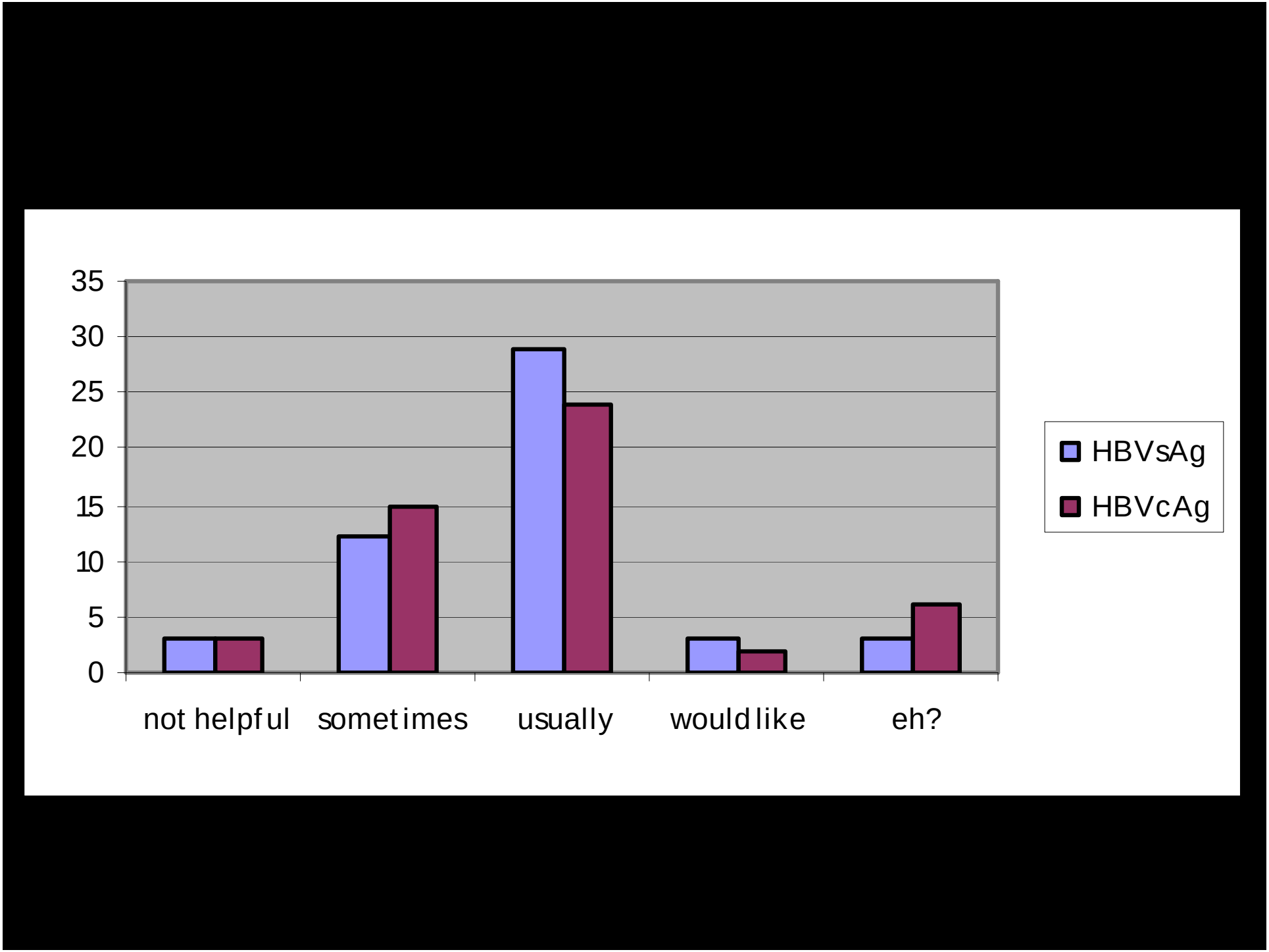


Hepatitis B

- nucleocapsid core protein (cAg)
  - viral replication
  - nuclear (+/- cytoplasmic)
- envelope surface protein (sAg)
  - cytoplasmic (+/- [sub]membranous)
  - “ground glass” cells
    - ΔΔ glycogen, cyanamide, “induction”


core Ag
surface Ag


surface Ag

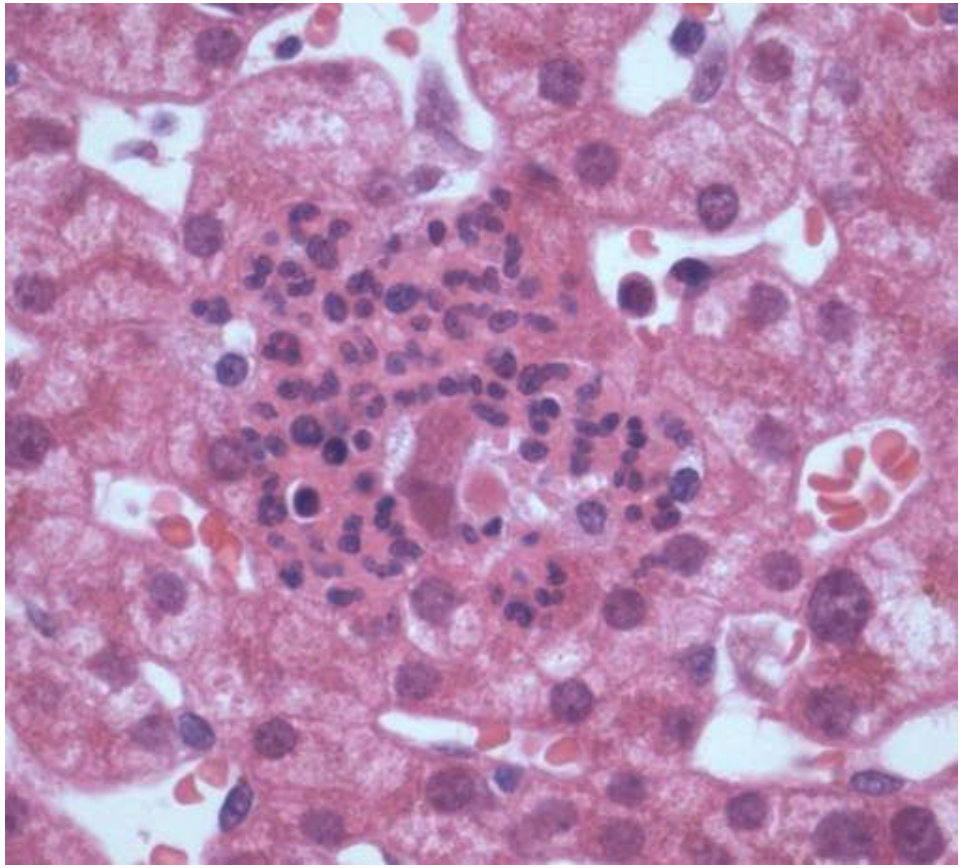

35
30
25
20
15
10
5
0
not helpful
sometimes
usually
would like
eh?
HBVsAg
HBVcAg

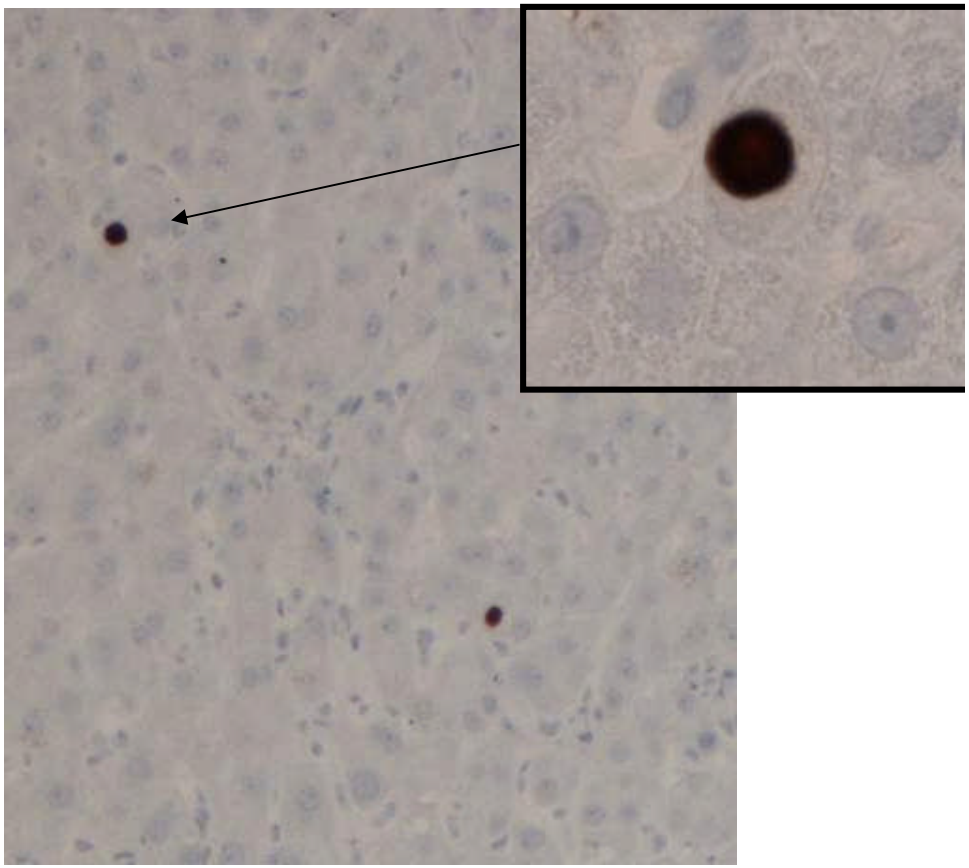
Hepatitis D ihc

- European genotype I
  - acute (replicating, HBV cAg suppression)
  - chronic (less replication & HBV suppression)
  - late
- ihc: nuclear positivity
  - sanded nuclei (HDAg)
  - weak/no cytoplasmic staining
  - useful to rapidly diagnose acute coinfection

CMV

- usually viral inclusions evident
- ihc to early Ag





Acute adult EBV hepatitis

- EBV early RNA (EBER)
- [SuhN, AJSPath, Sept 2007]
  - 8 patients: acute fever, J, lymphocytosis,
  - sinusoidal “beading”, portal mixed & variable interface/lobular hepatitis, venulitis, bile duct injury
  - very sparse EBER +ve lymphocytes (7/8)
  - LMP ihc negative (8/8)

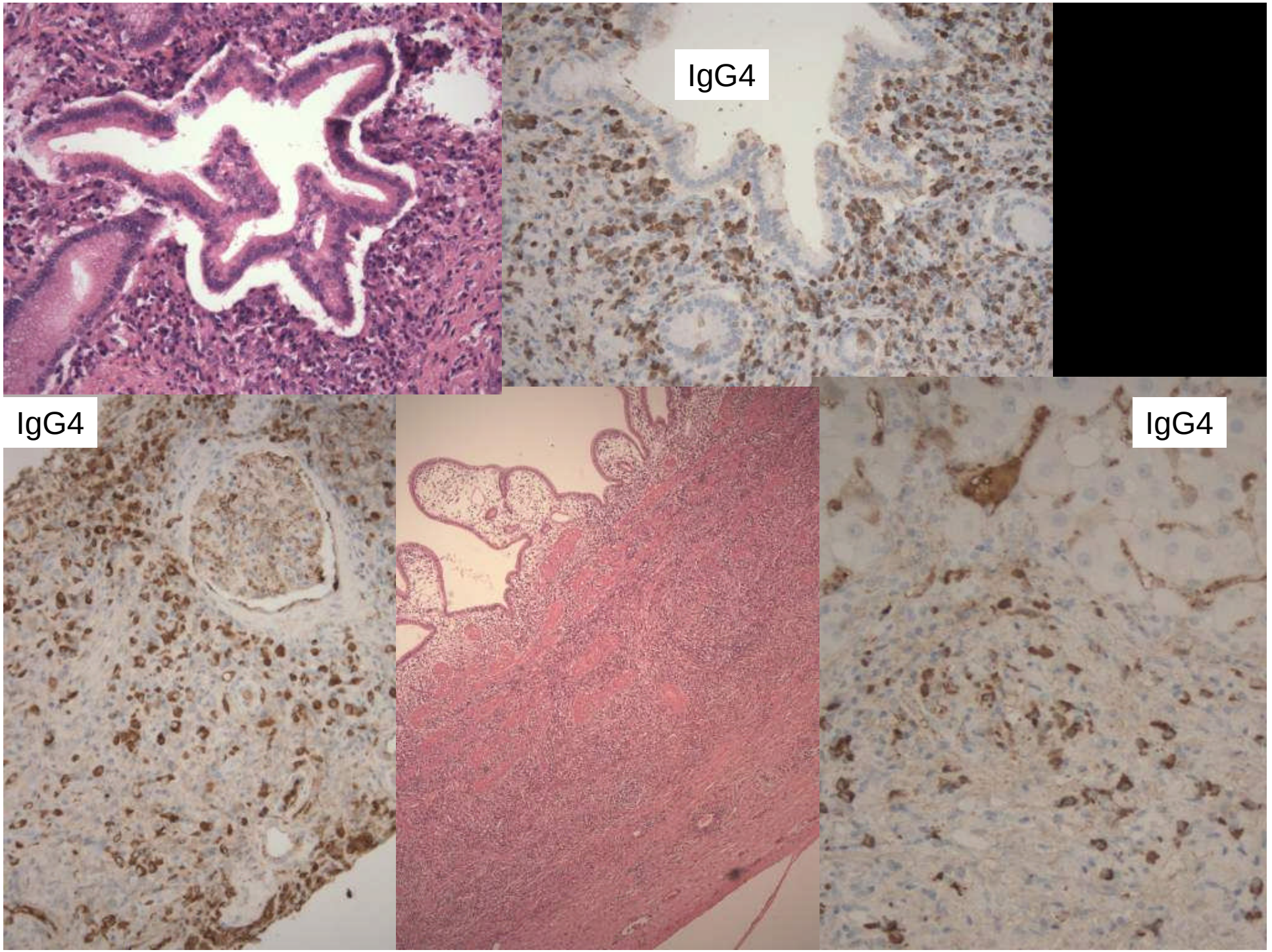
Systemic IgG_4 disease

- corticosteroid-sensitive multisystem nodular fibroinflammatory disease

- tissue infiltration with IgG_4 plasma cells
  - typically raised serum IgG_4
  - pancreatitis, cholecystitis, cholangitis, Mikulicz's disease, interstitial nephritis, pneumonitis, retroperitoneal fibrosis, gastric ulcer, "PBC-like" inflammation, inflammatory pseudotumour, fevers
  - bispecific, IL-4/T_{H2}

Systemic IgG_4 disease

- wide spectrum
- discrete, intense, mass-forming/segmental
- obliterative phlebitis
- eosinophilia/plasma cells
- sclerosis
- bottom heavy-mural infiltrate (gb, cbd)


IgG4
IgG4
IgG4

Systemic IgG_4 disease

- **liver biopsy involvement: sensitive**
  - large duct obstruction
  - plasma cell-rich portal inflammation +/-interface
  - lobular hepatitis
  - perivenular cholestasis
  - periportal fibrosis

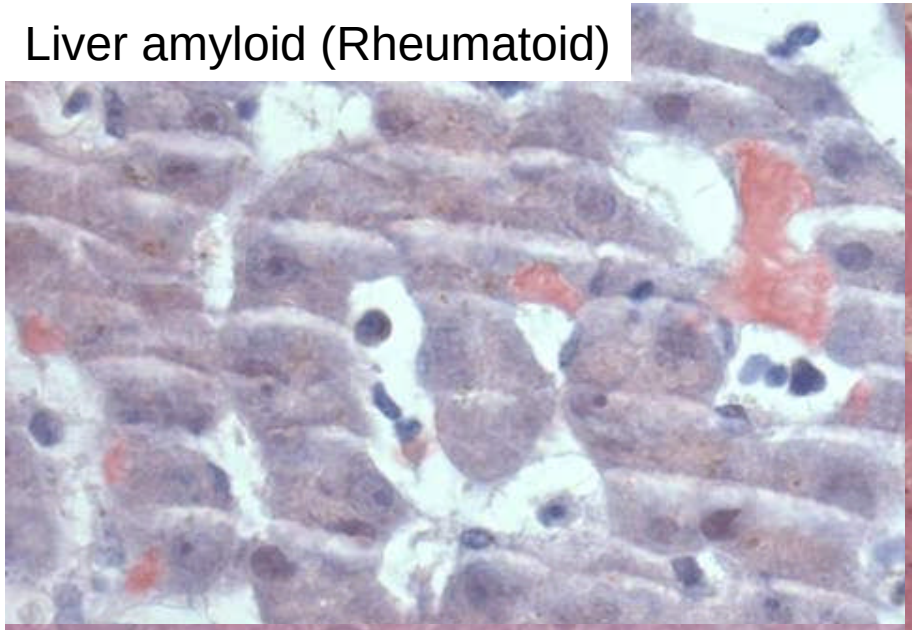
  ihc: >1/hpf or >20% [UmemuraT2007]

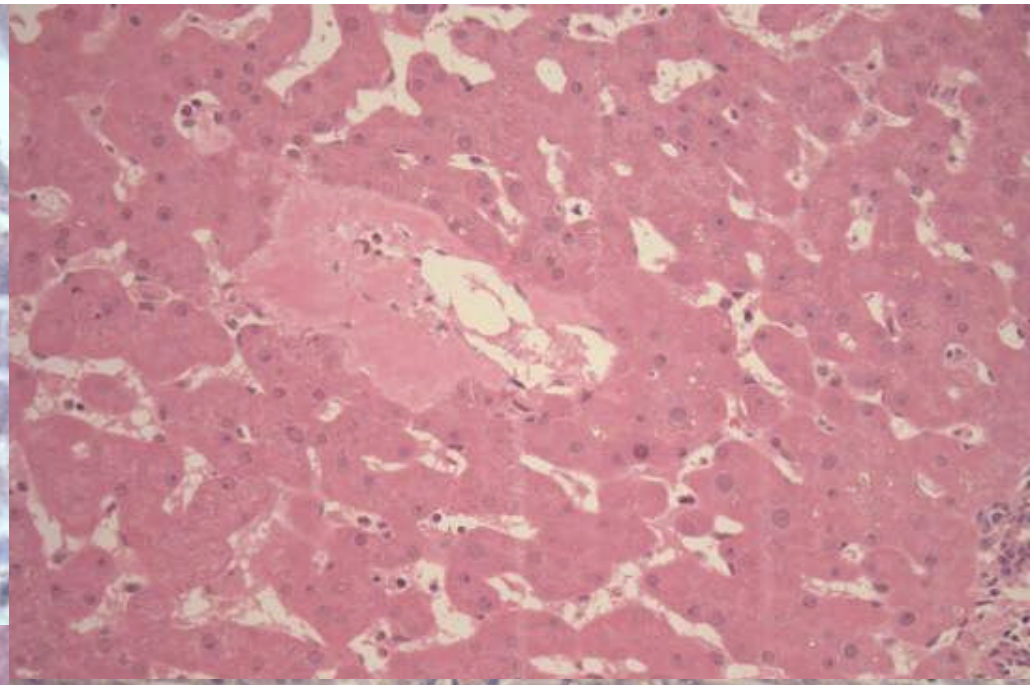
- **consider if**…“Sjogrens”, sialadenitis, cancer-negative Whipples, wheeze, dry eyes/mouth, interstitial nephritis…

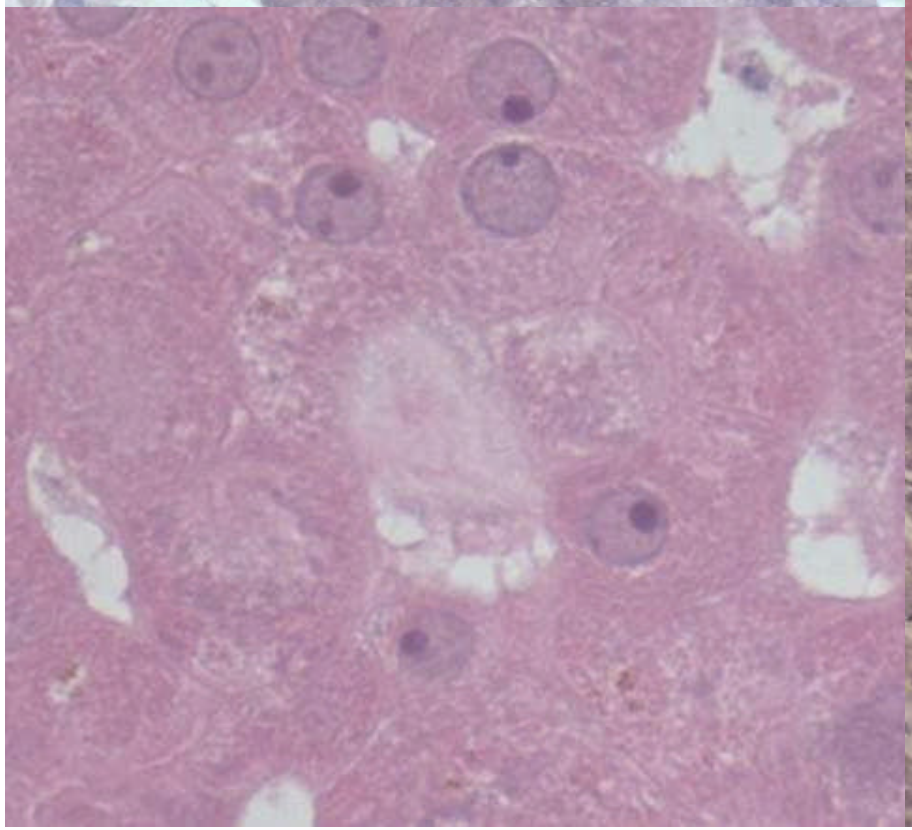
Amyloid, MIDD

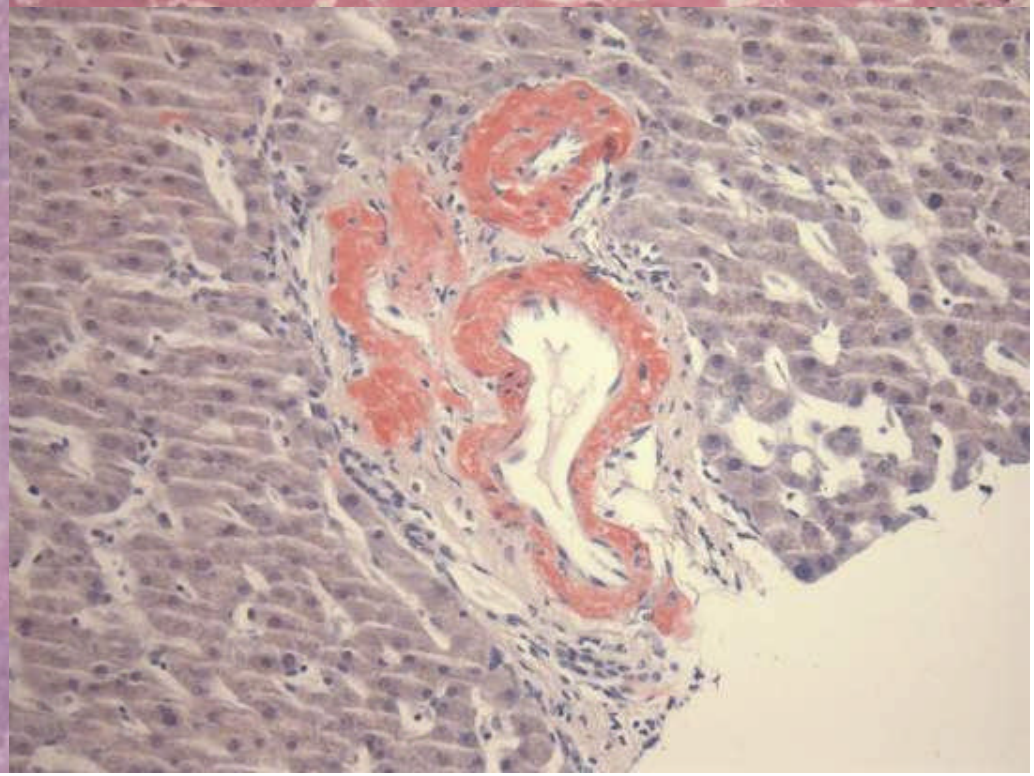
- acquired
  - AA
  - AL (lambda 3x kappa)
- hereditary
  - neuropathic
  - non-neuropathic
    - fibrinogen α chain, lysozyme, apolipoprotein A1
- MIDD (light+/heavy chain)

Liver amyloid (Rheumatoid)



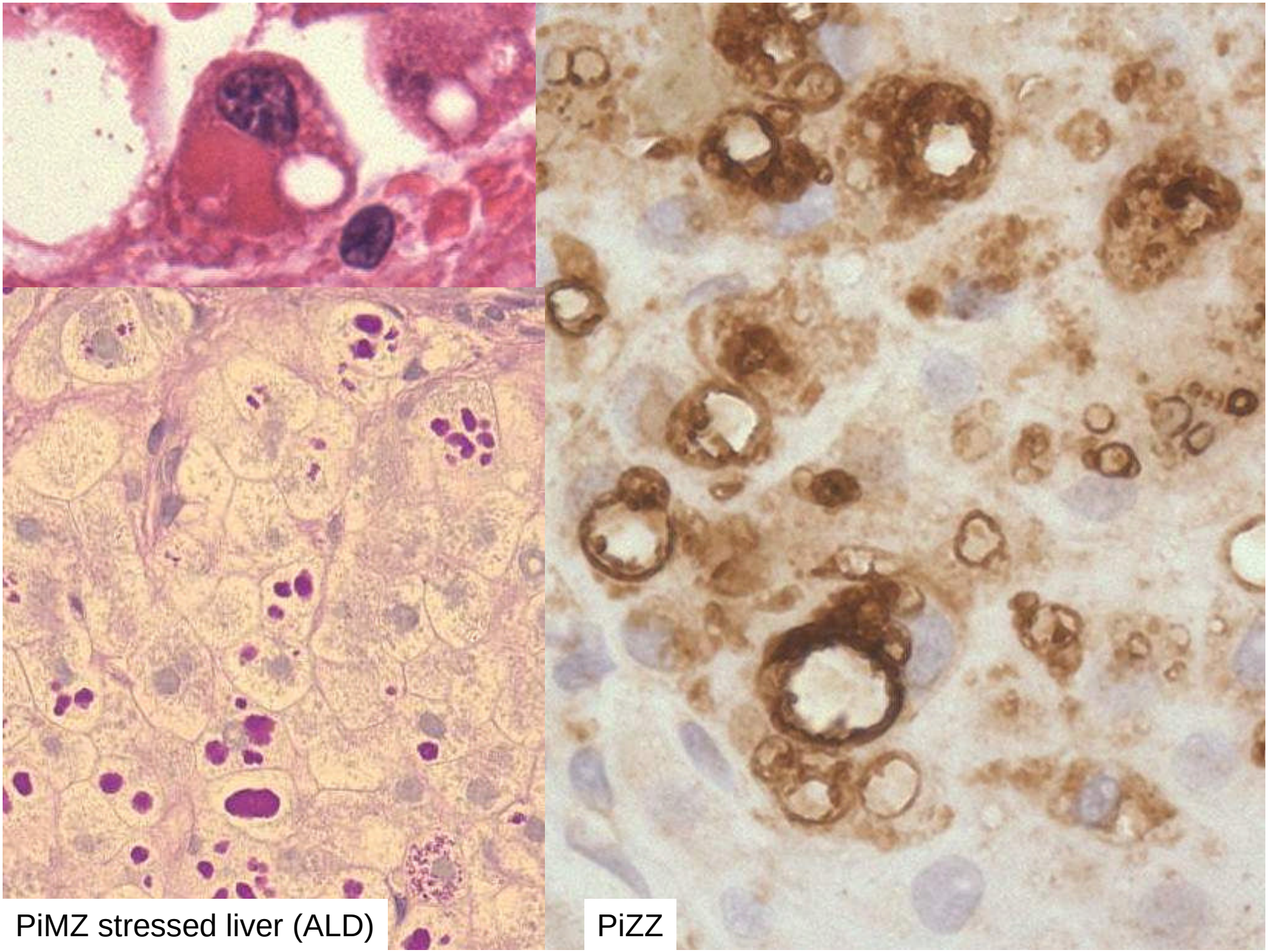






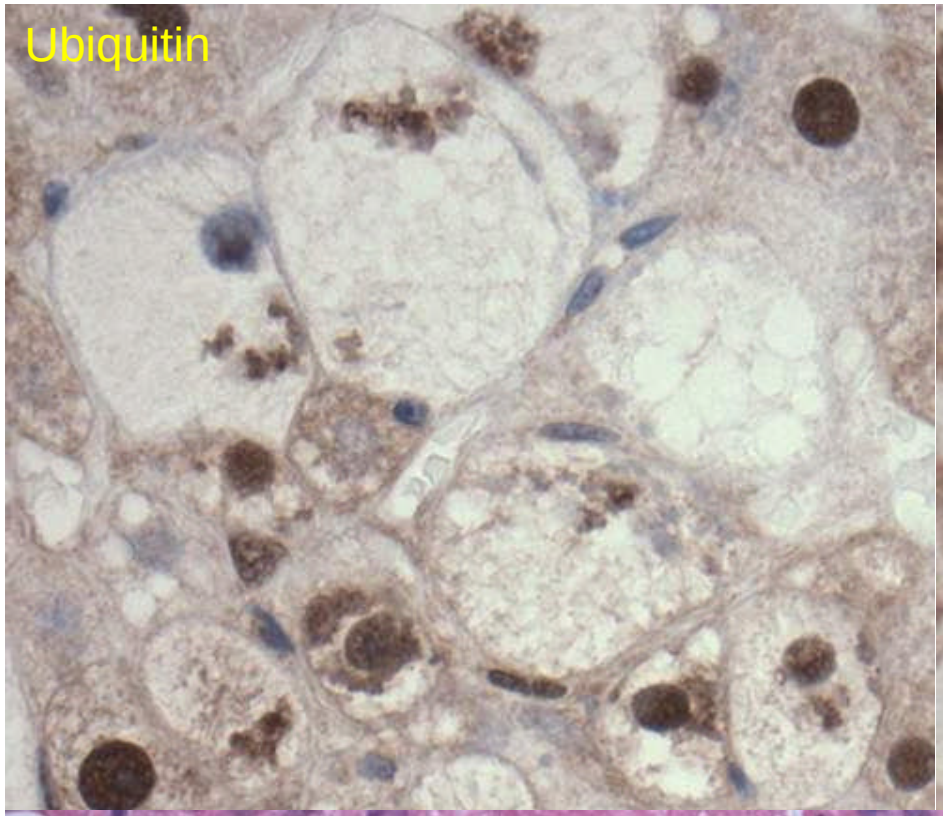
α1-antitrypsin deficiency

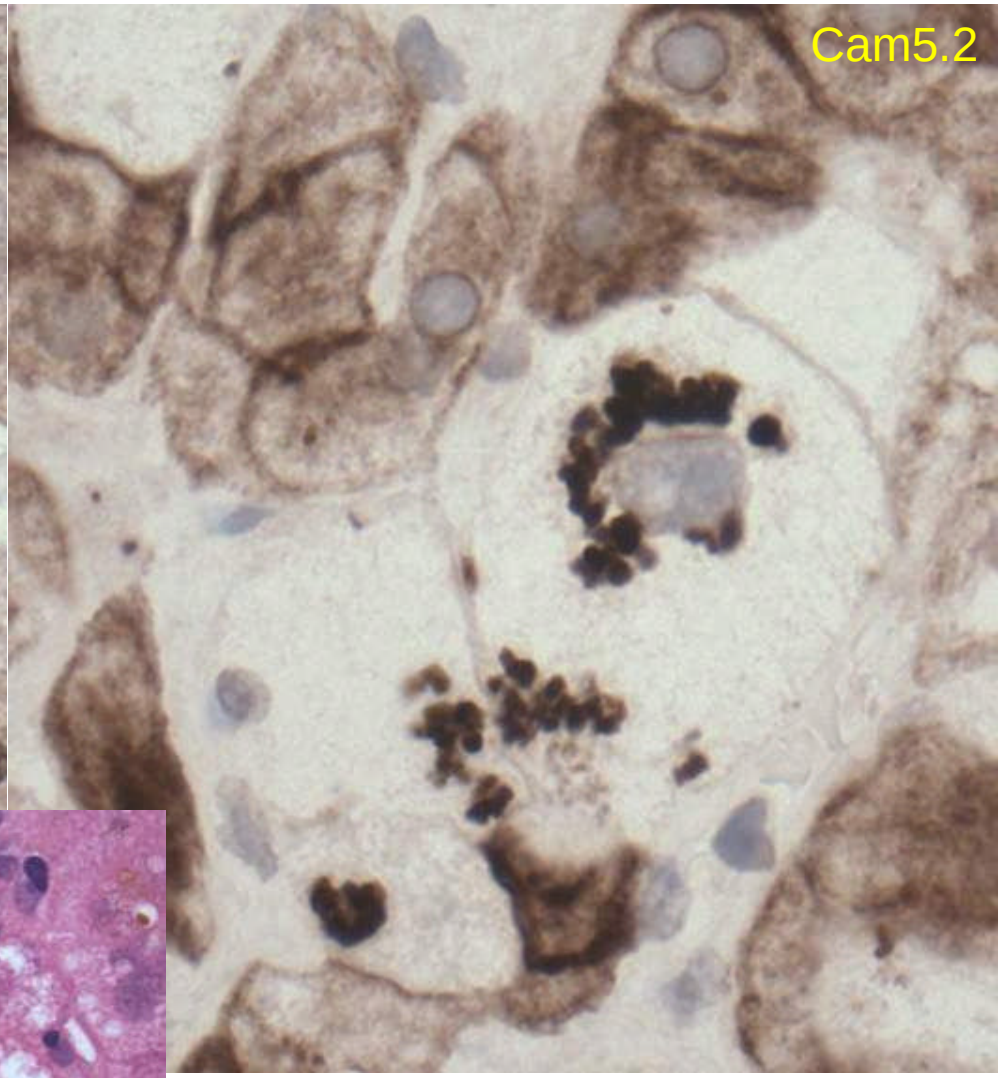
- Z mutant vs normal protein
- ihc more sensitive than PAS/D
  - missed 0 vs 5/33 adults [CalleaF,1986]
- globules >3u
  - specific but 47% of Z allele [ClausenPP1984]
- in cirrhosis with globules
  - 10% - but variety of phenotypes, some normal [IezzoniJC,1997]
- **a1antichymotrypsin deficiency**
  - smaller, weaker PAS/D+, ihc available [ThomasRM2000]
- **ΔΔ** stressed liver, congestion-associated, fibrinogen storage disease

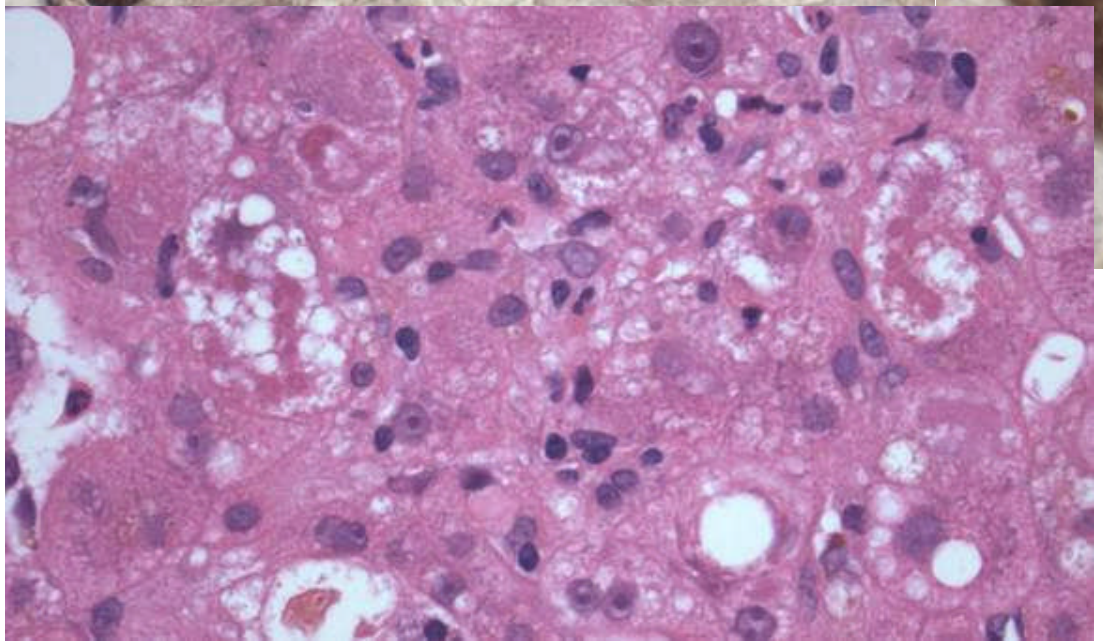


PiMZ stressed liver (ALD)

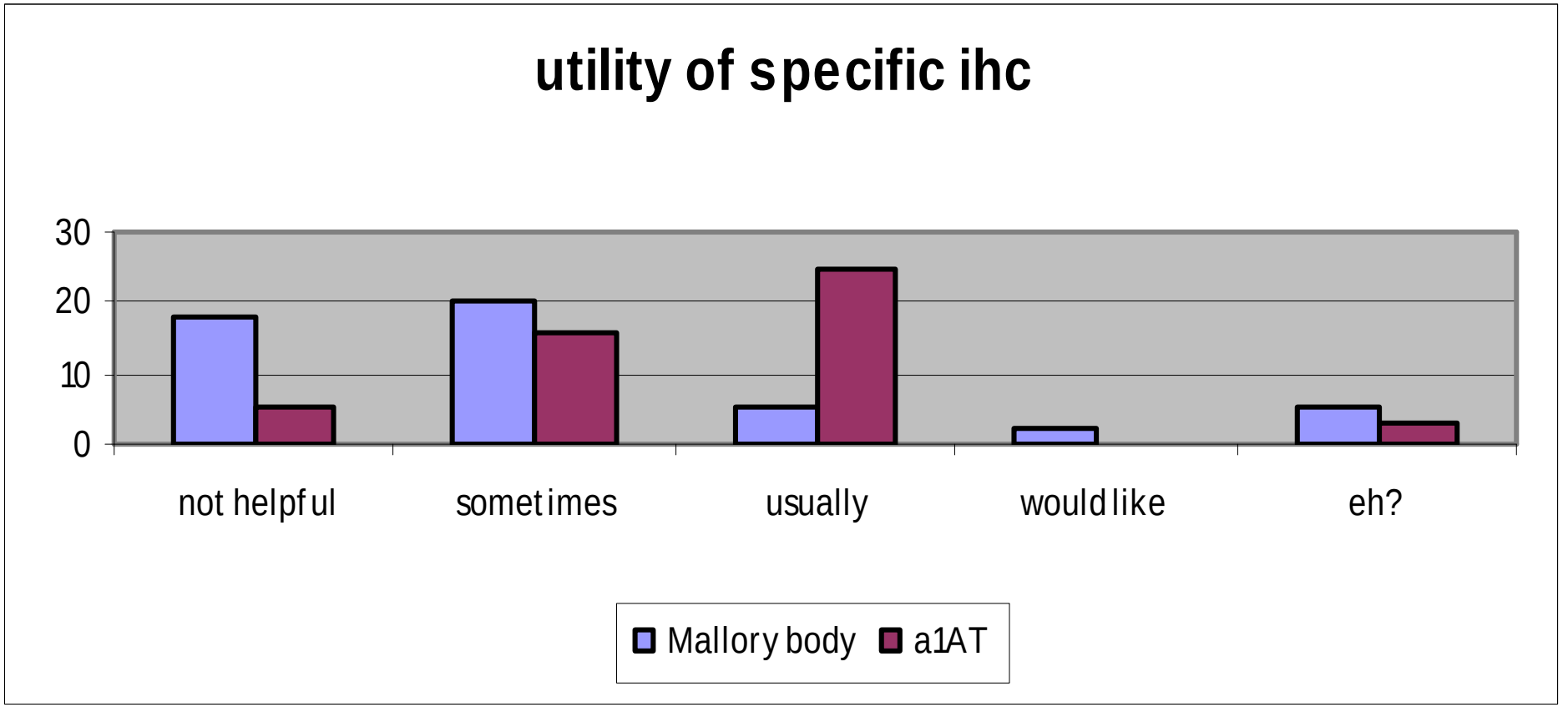
PiZZ

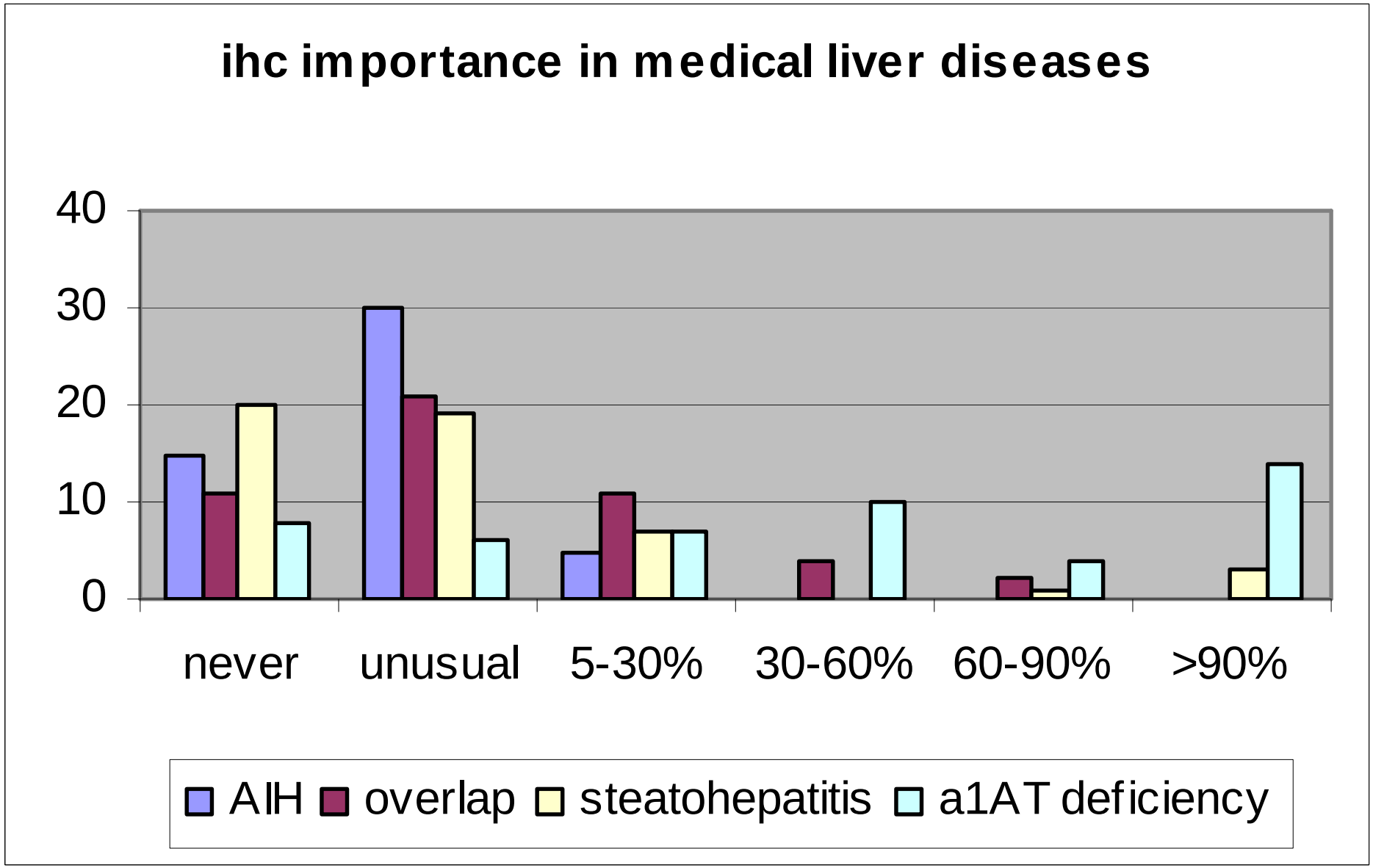




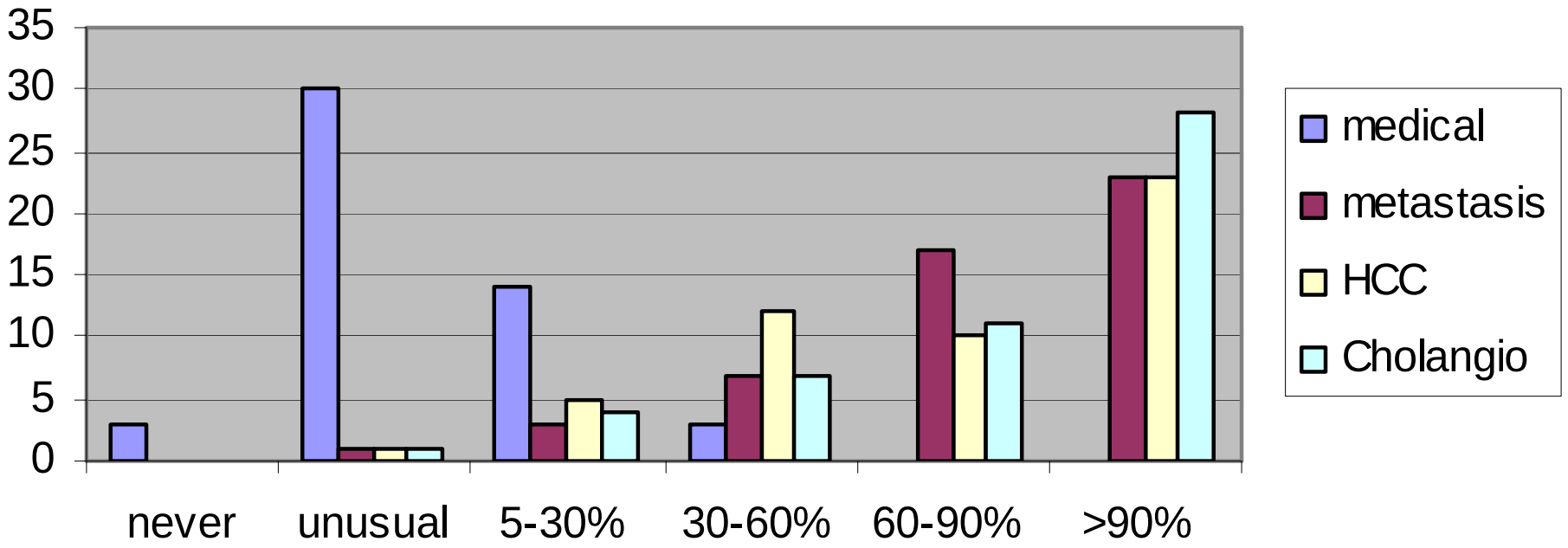


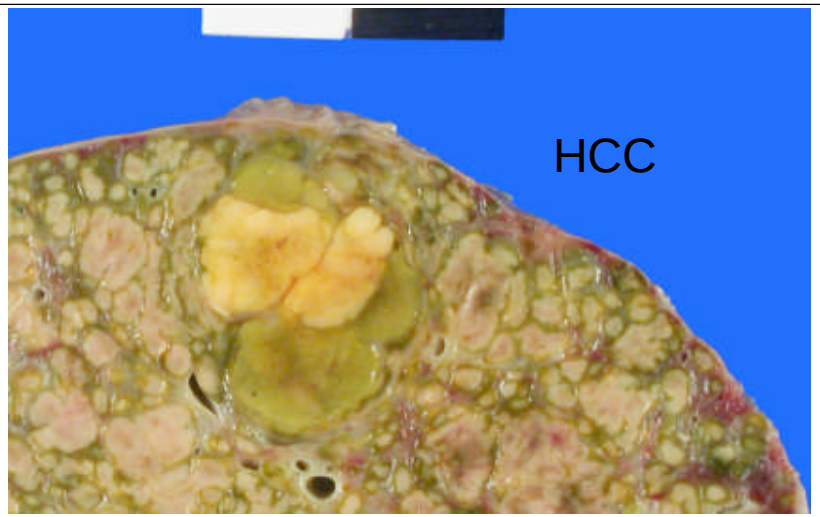
Mallory bodies

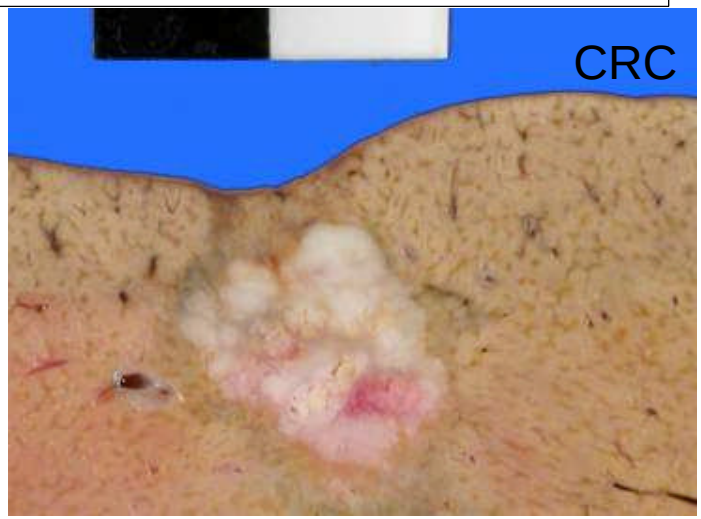

utility of specific ihc
30
20
10
0
not helpful
sometimes
usually
would like
eh?
Mallory body
a1AT


ihc importance in medical liver diseases
40
30
20
10
0
never
unusual
5-30%
30-60%
60-90%
>90%
AIH
overlap
steatohepatitis
a1AT deficiency

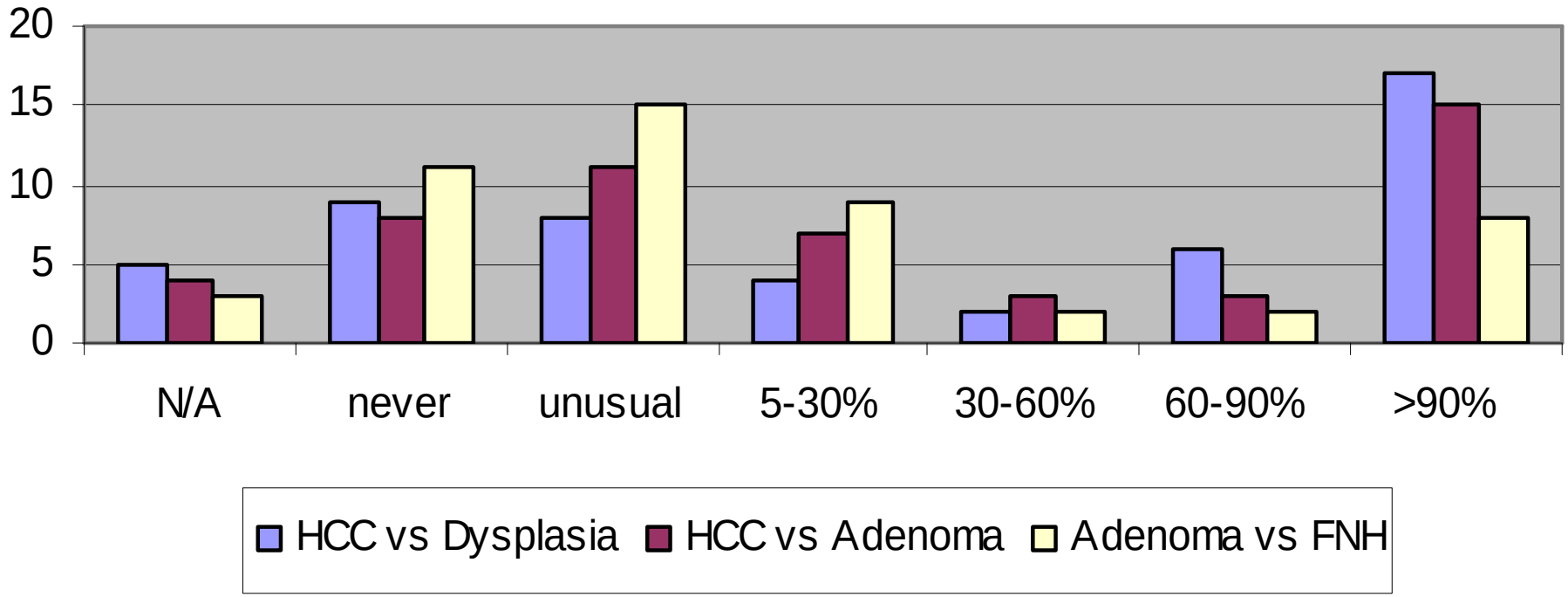
Requesting ihc in malignancy

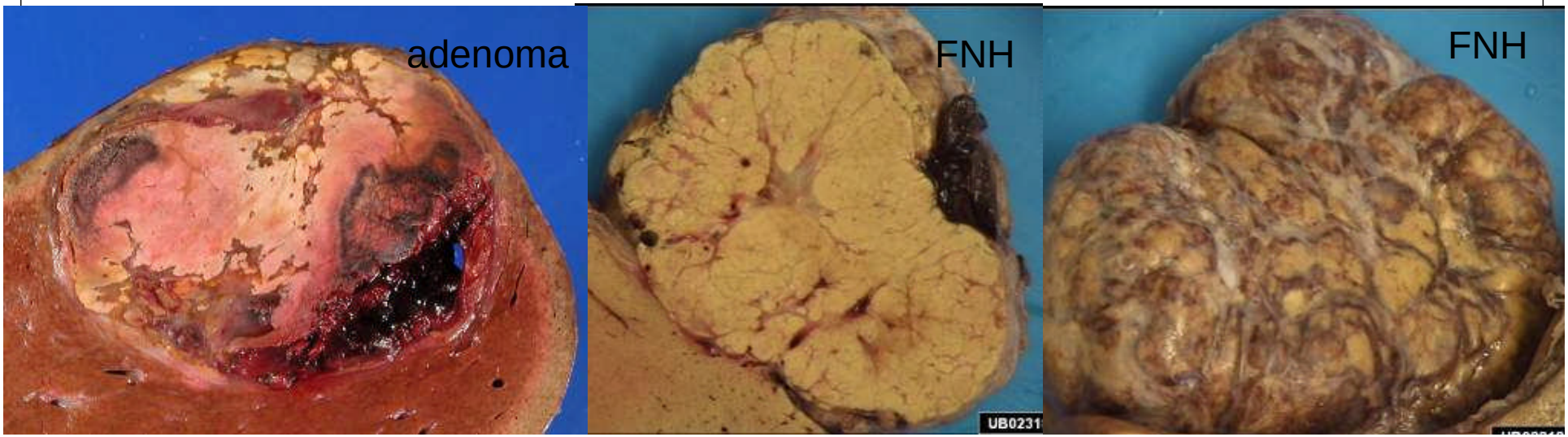


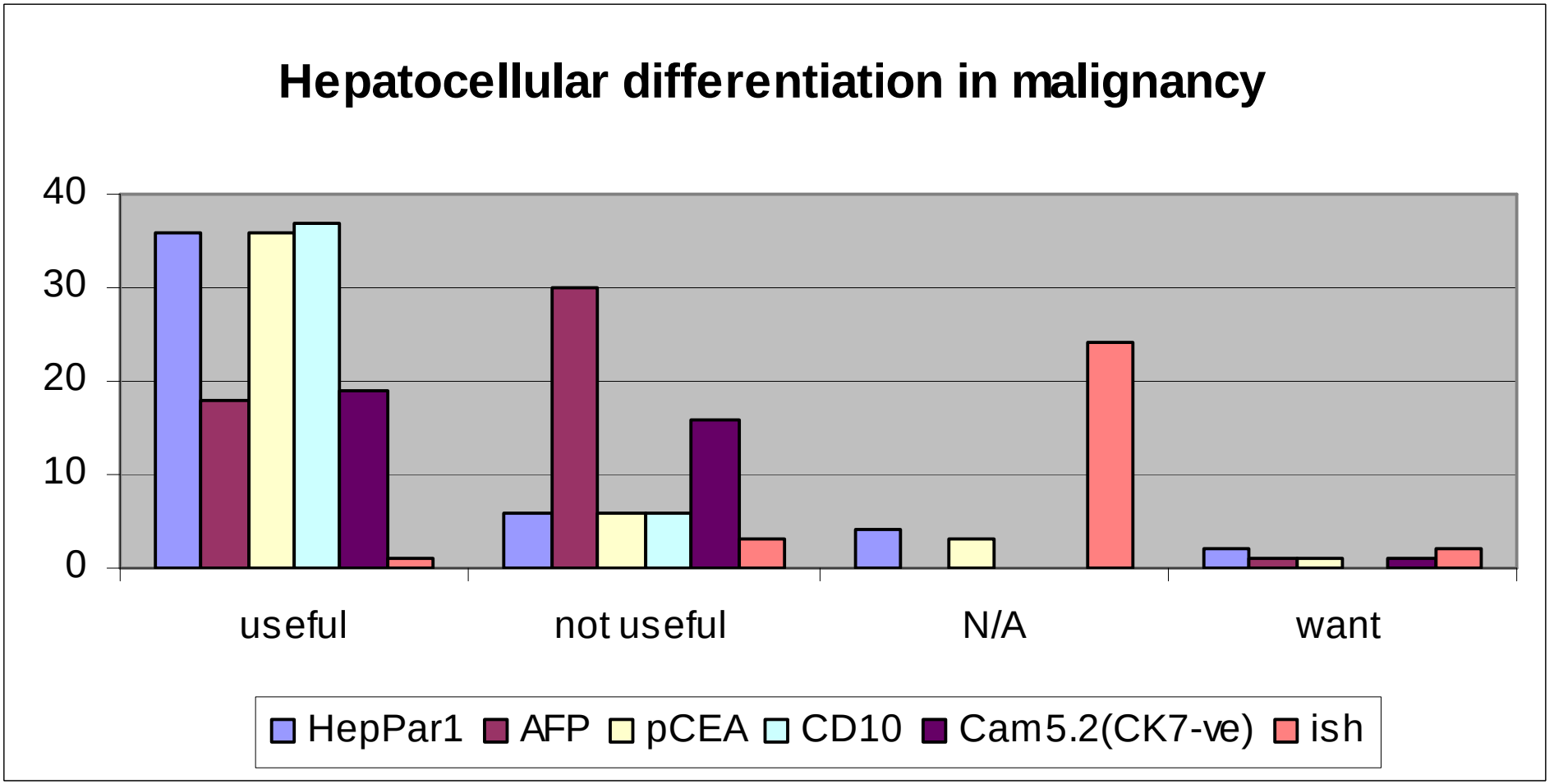




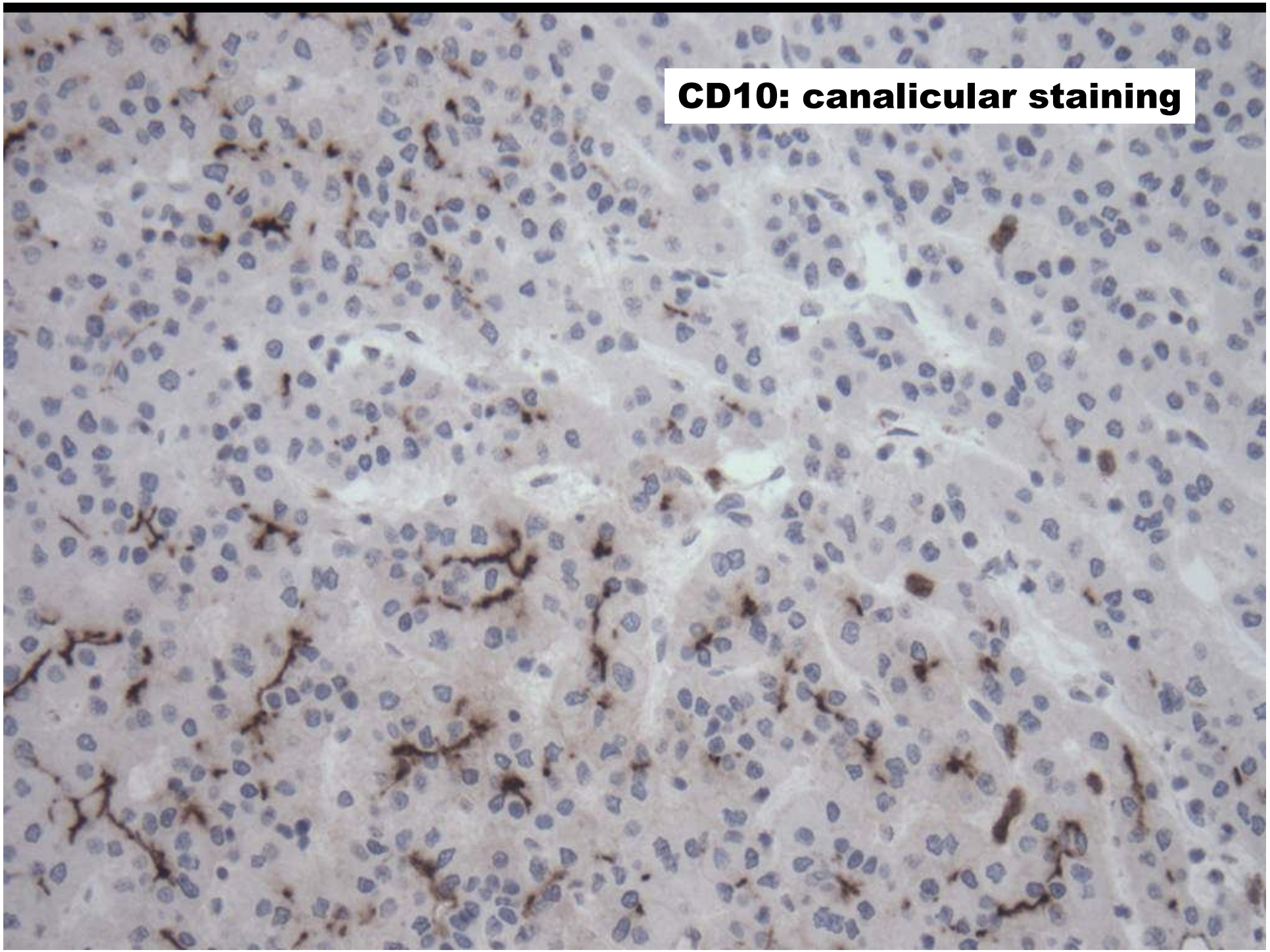
Requesting ihc in hepatocellular lesions



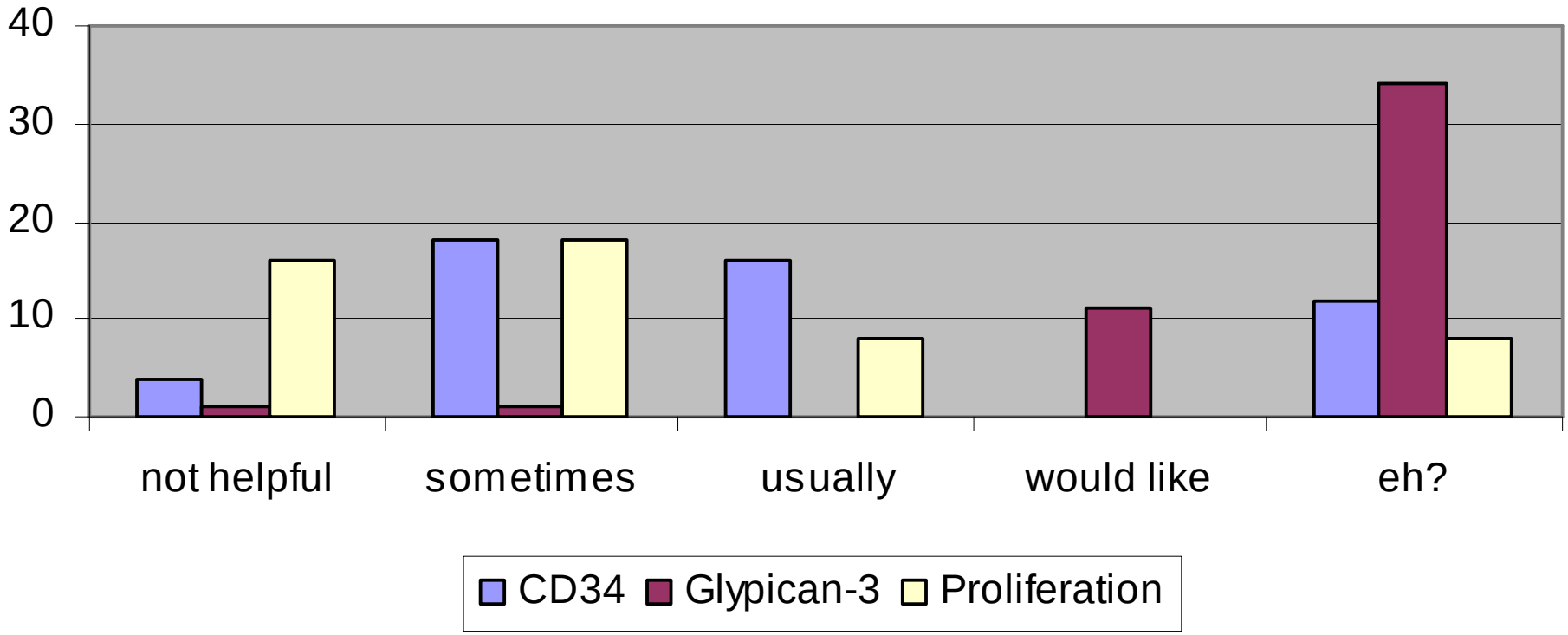


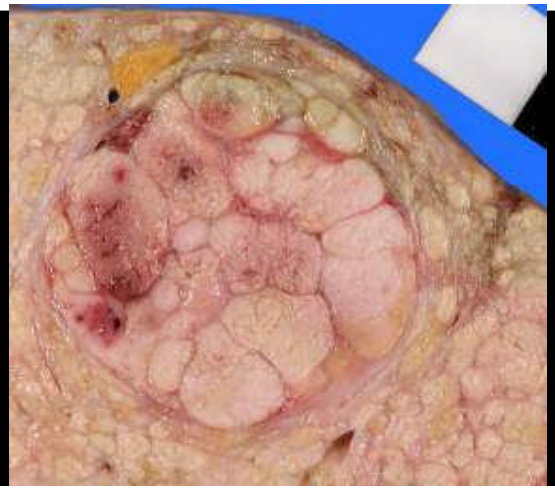


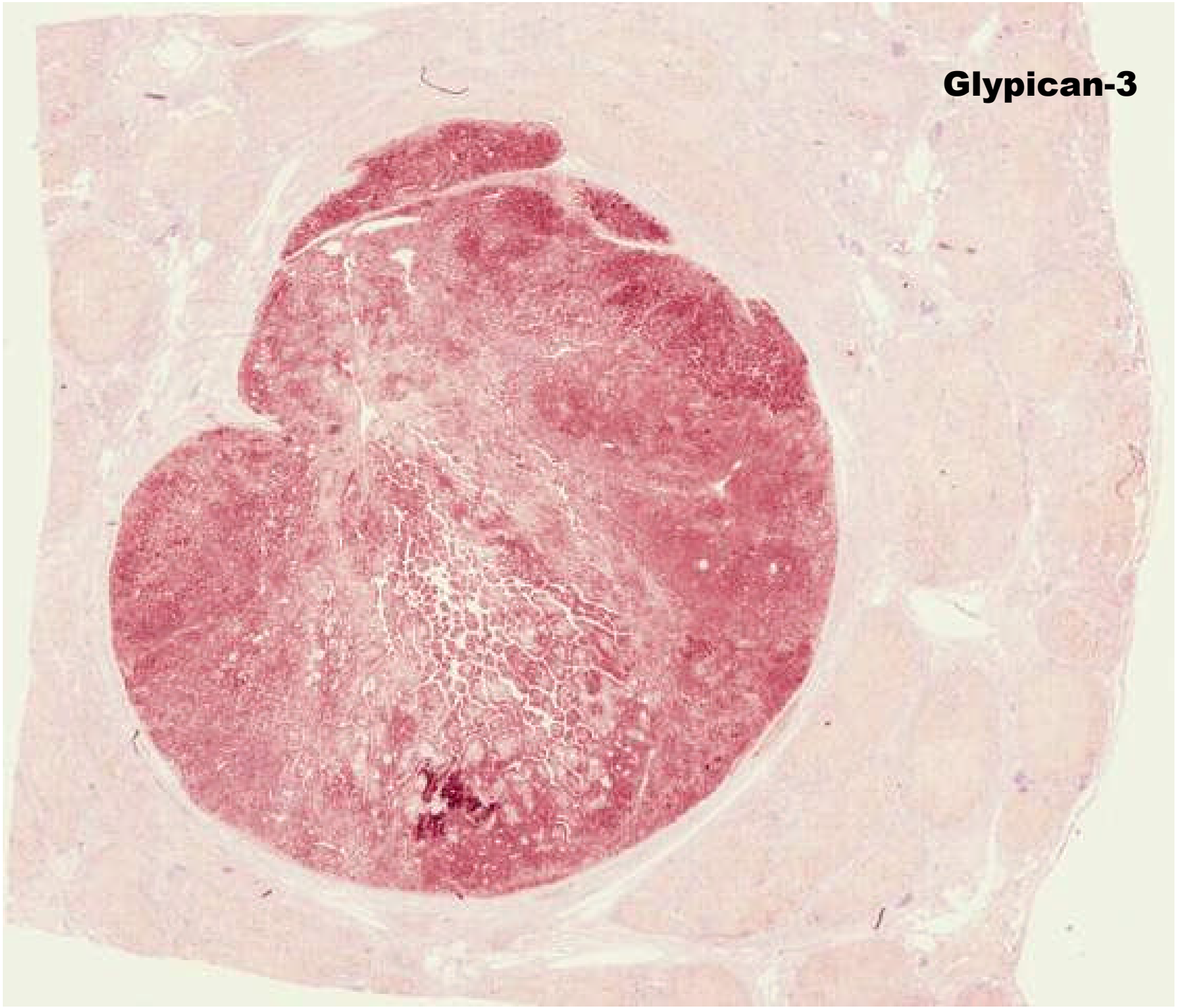
also CD13 (RockenC2005)

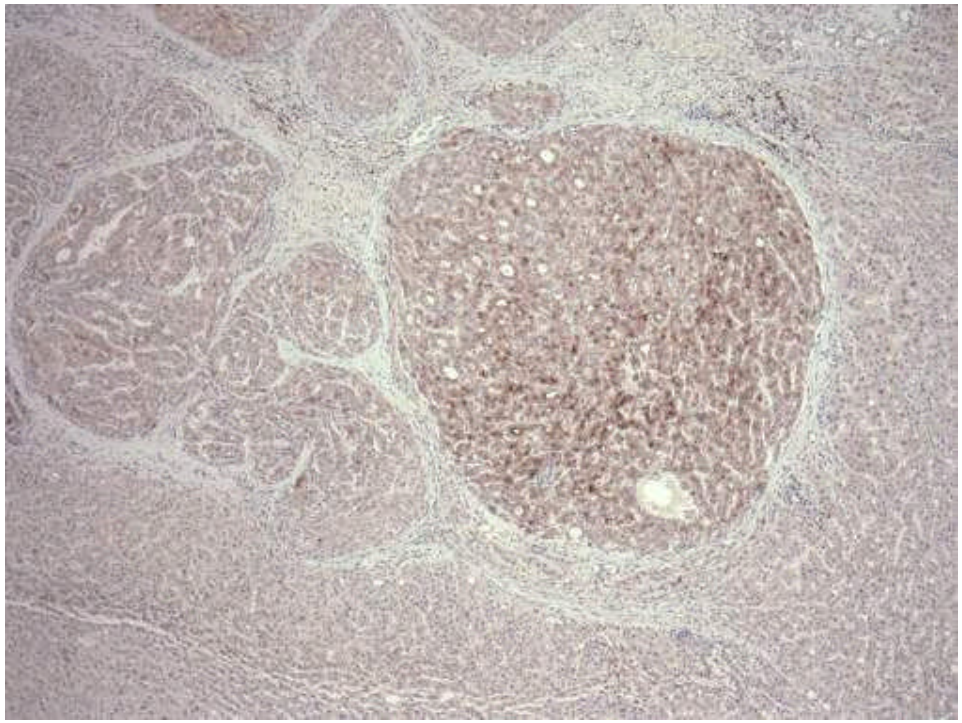

CD10: canalicular staining

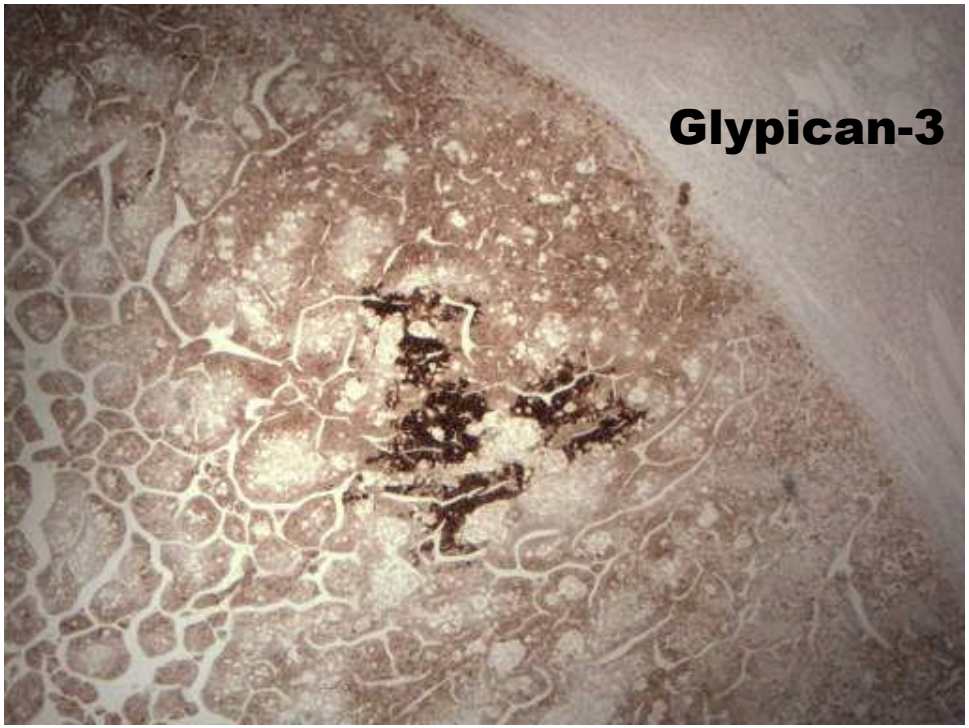
ihc in liver dysplasia/HCC





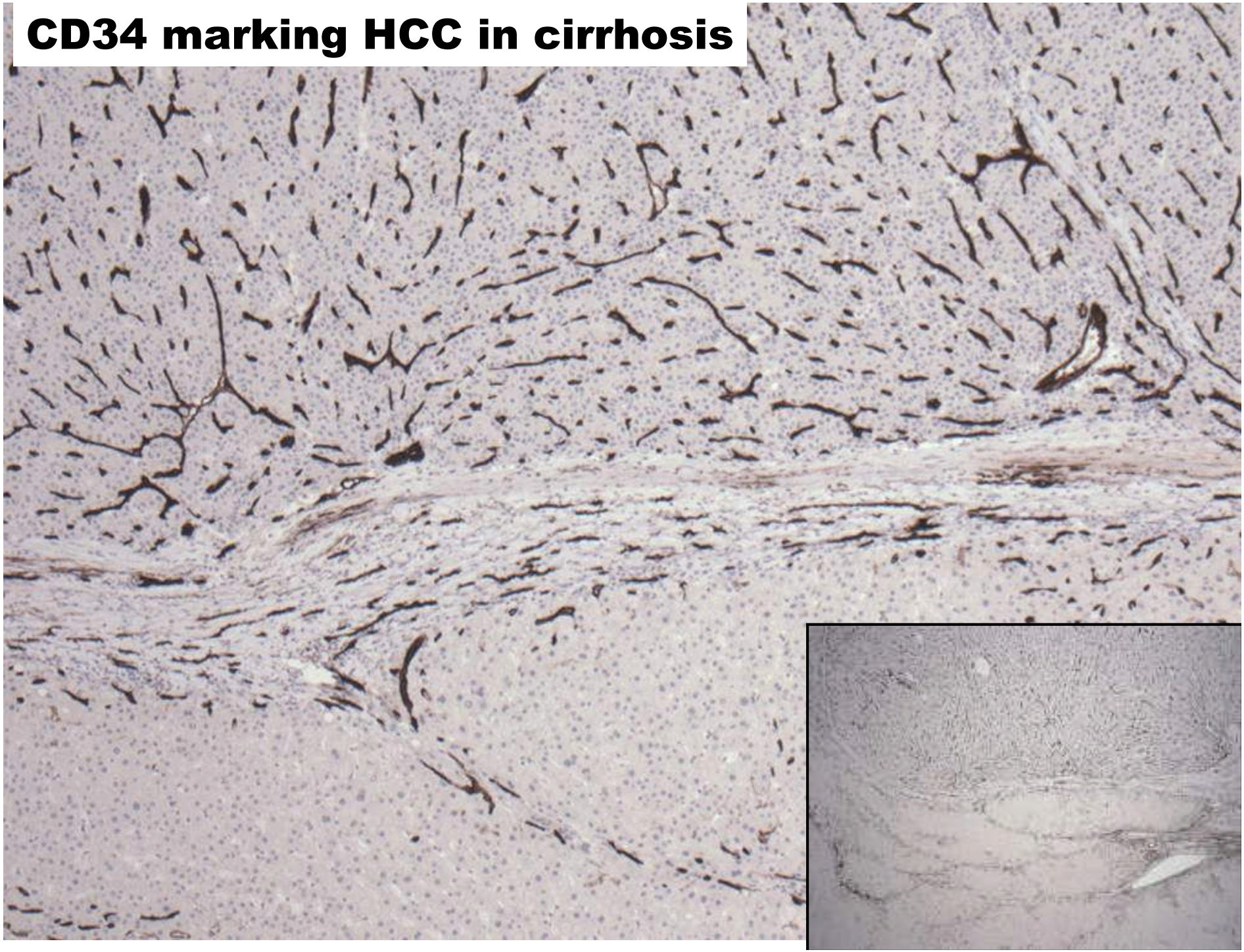

Glypican-3





- oncofoetal protein marking early HCC
- 70-90% HCC, esp in cirrhosis
- 10-50% HG dysplasia
- 0-3% LG dysplasia
- membranous, canalicular, cytoplasmic
- [ZhuHW2001, CapurroM2003, YamauchiN2005, WangXY2006, LibbrechtL2006]

CD34 marking HCC in cirrhosis



“capillarised” vessels in HCC, dysplasia

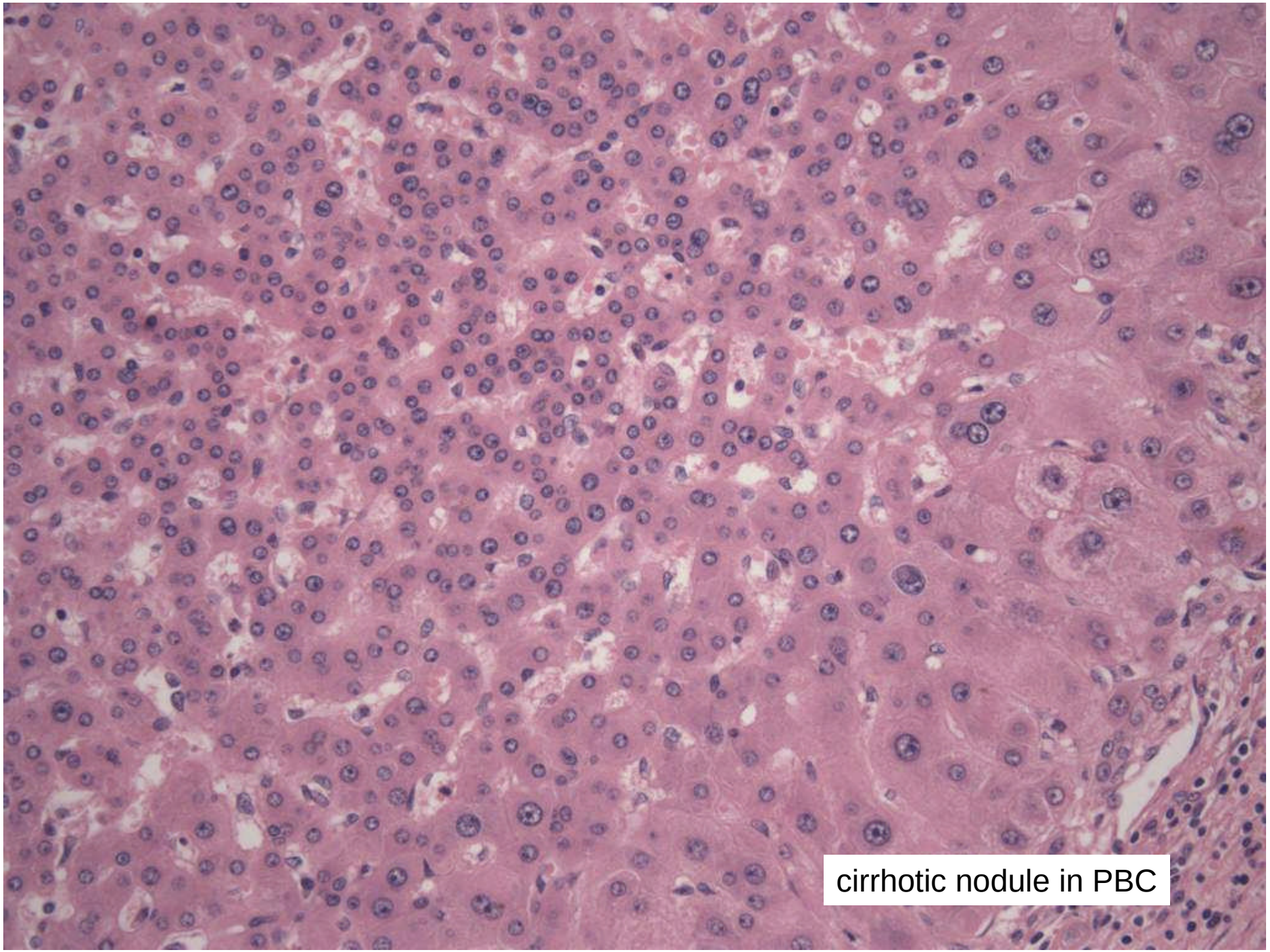
- CD34, CD31, BNH9
- 40% DN
- 85% HCC
- MotooY1993, RoncalliM1999, FrachonS2001

Adenoma typing & ihc

- Bioulac-Sage P: Hepatology, 2007

- HNF1α inactivation: absent L-FABP
- β-catenin activation: glutamine synthetase/β-catenin
- Inflammatory/telangiectatic: SAA↑↑, β-catenin N

- β-catenin mutated adenomas ? higher risk to be borderline or have HCC


cirrhotic nodule in PBC