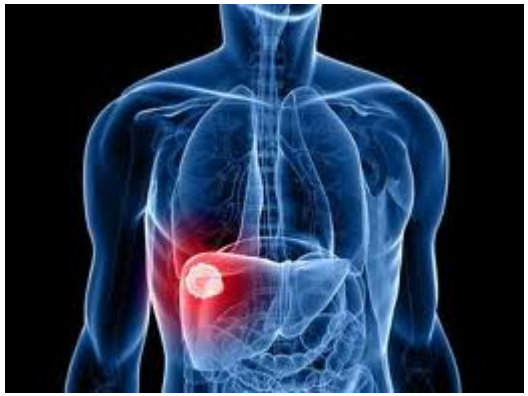

FRCPath Course
Algorithmic approach to diagnosis of liver pathology

Dr Tu Vinh Luong
Consultant Histopathologist

Wednesday 16th September 2020

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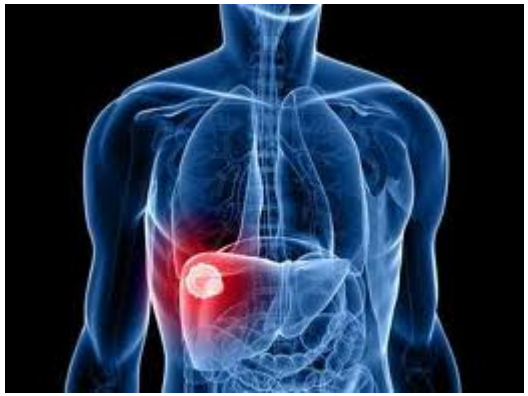


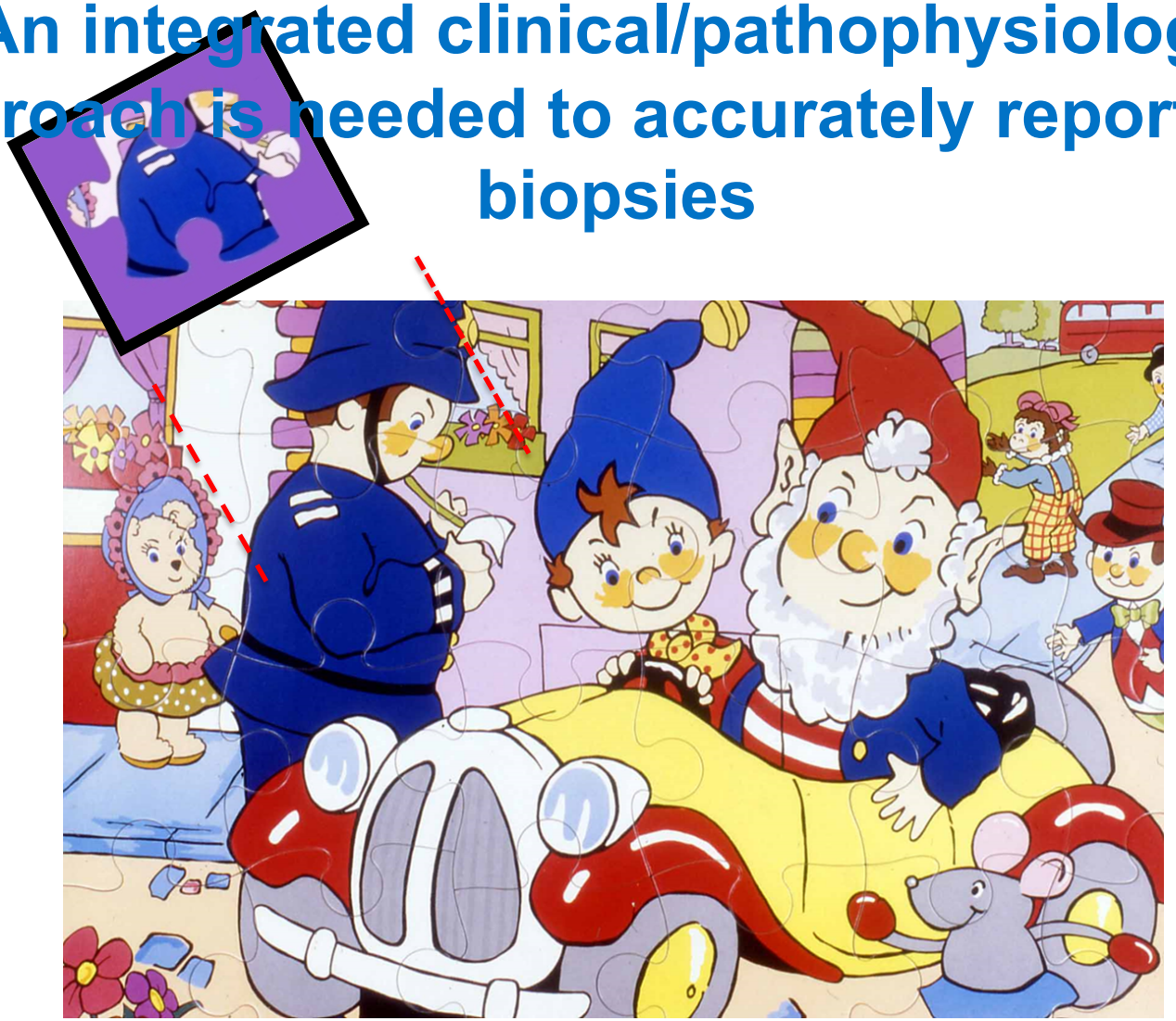
Acknowledgments

Some images and cartoons are from Dr Neil Theise's presentation downloaded from SlideShare.net and Neil Theise's and Romil Saxena's chapter in the Odze and Goldblum Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas book.

Liver biopsy is part of the general assessment of patients with liver disease

- Rockey DC, Caldwell SH, Goodman ZD et al; AASLD position paper: liver biopsy. Hepatology 49,1017;2009
  - 'The use of liver biopsy to obtain tissue for histological interpretation is a long-standing pillar of the practice and science of hepatology and remains a standard for diagnosis and treatment'.
- Histopathology is a part of the diagnostic jigsaw puzzle
  - Together with the other pieces of the puzzle, it can be an important part of the overall picture
  - By itself, it can be irrelevant or confusing

An integrated clinical/pathophysiologic approach is needed to accurately report liver biopsies



There is considerable overlap in morphologic patterns of injury among the various types of liver diseases.

An important starting point is the adequate biopsy!!

- Average liver biopsy consists of 1/ 50,000 of total hepatic mass
- No universally agreed upon standard of specimen adequacy
- Sample adequacy depends on:
  - Disease aetiology
  - Disease distribution
  - Stage of disease
  - Diameter of needle biopsy

Liver biopsy adequacy

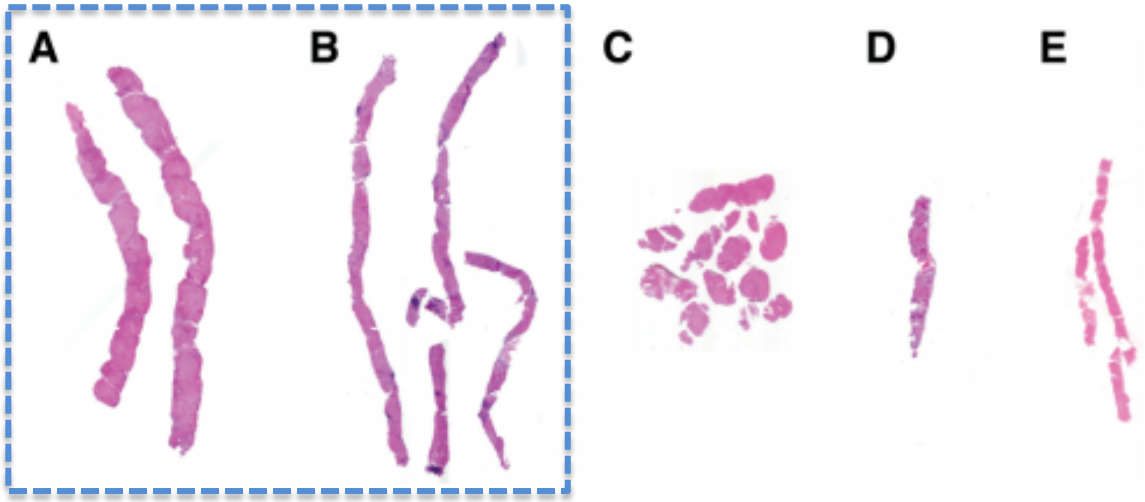


Fig. 1. Specimens of liver biopsies obtained with various sized needles and differing techniques. All five biopsies shown in this figure were submitted for grading and staging of chronic hepatitis C. However, only (A) and (B) are felt to provide enough tissue for adequate histologic analysis. (A) Shown is a biopsy specimen 2.7 cm in length obtained with two passes of a 16-gauge cutting needle. (B) Shown is a biopsy specimen 4.8 cm in length obtained with three passes of an 18-gauge cutting needle. (C) Shown is a fragmented biopsy, 1.1 cm in total specimen length, obtained with a 16-gauge suction needle. (D) Shown is a biopsy specimen 0.5 cm in length obtained with an 18-gauge needle. (E) Shown is a biopsy specimen 1.5 cm in length obtained with a 20-gauge needle.

An important starting point is the adequate biopsy!!

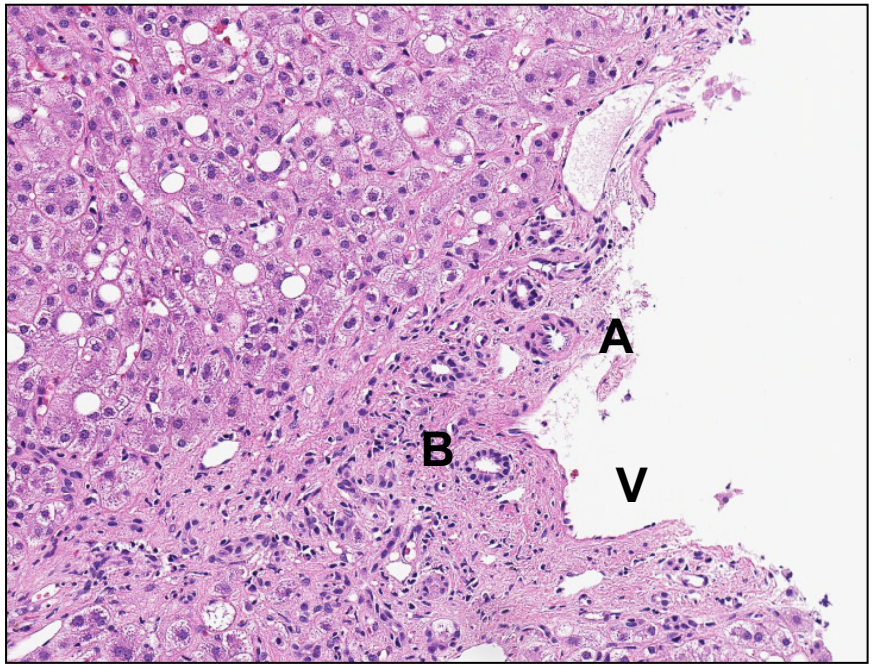
In most diffuse liver diseases examination of

- a total of 2.0 cm of liver tissue
- containing 11–15 portal tracts (optimal value, to avoid underscoring of stage of disease) is necessary

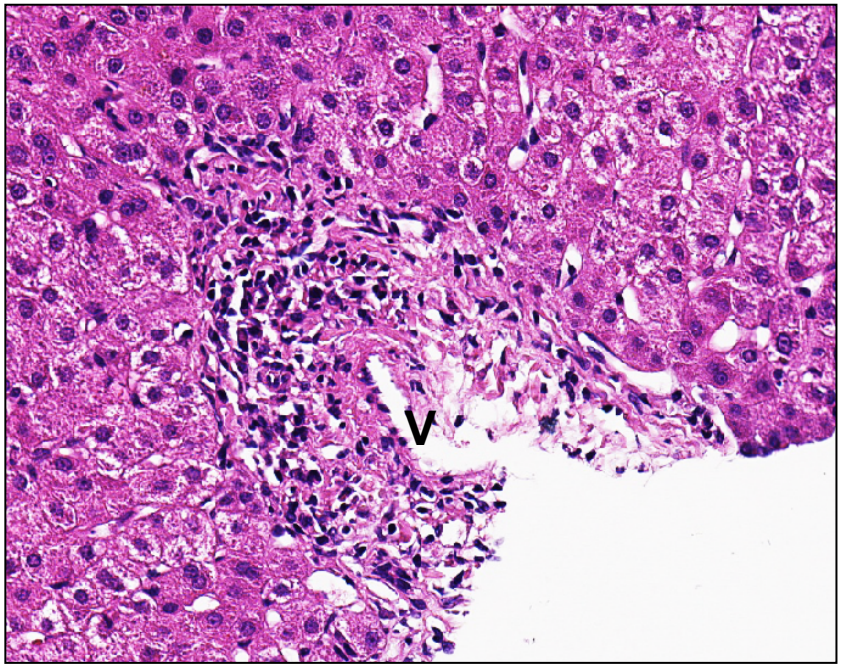
Current acceptable recommendations

- 5 complete portal areas minimum (complete circumference and contains at least 2 portal structures)

Complete portal tract

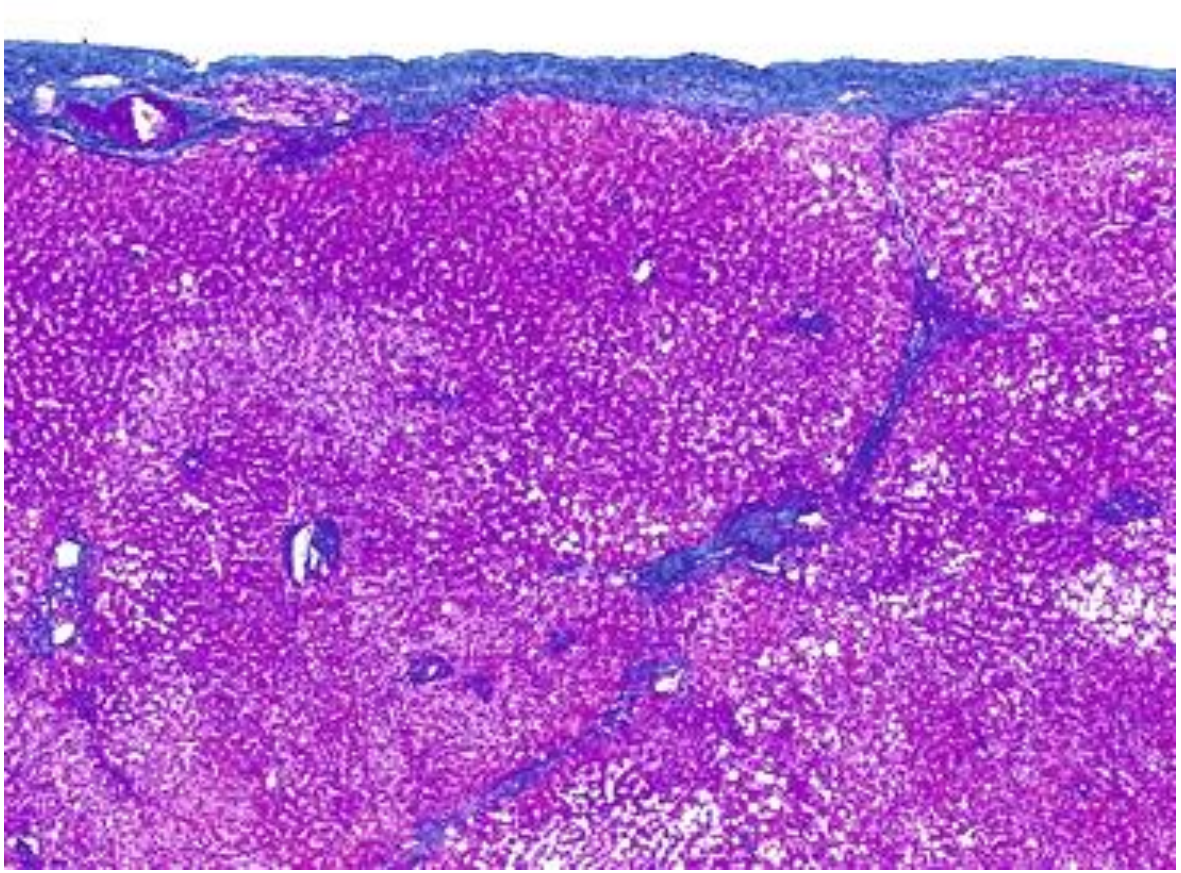


complete



incomplete

Avoid staging subcapsular samples

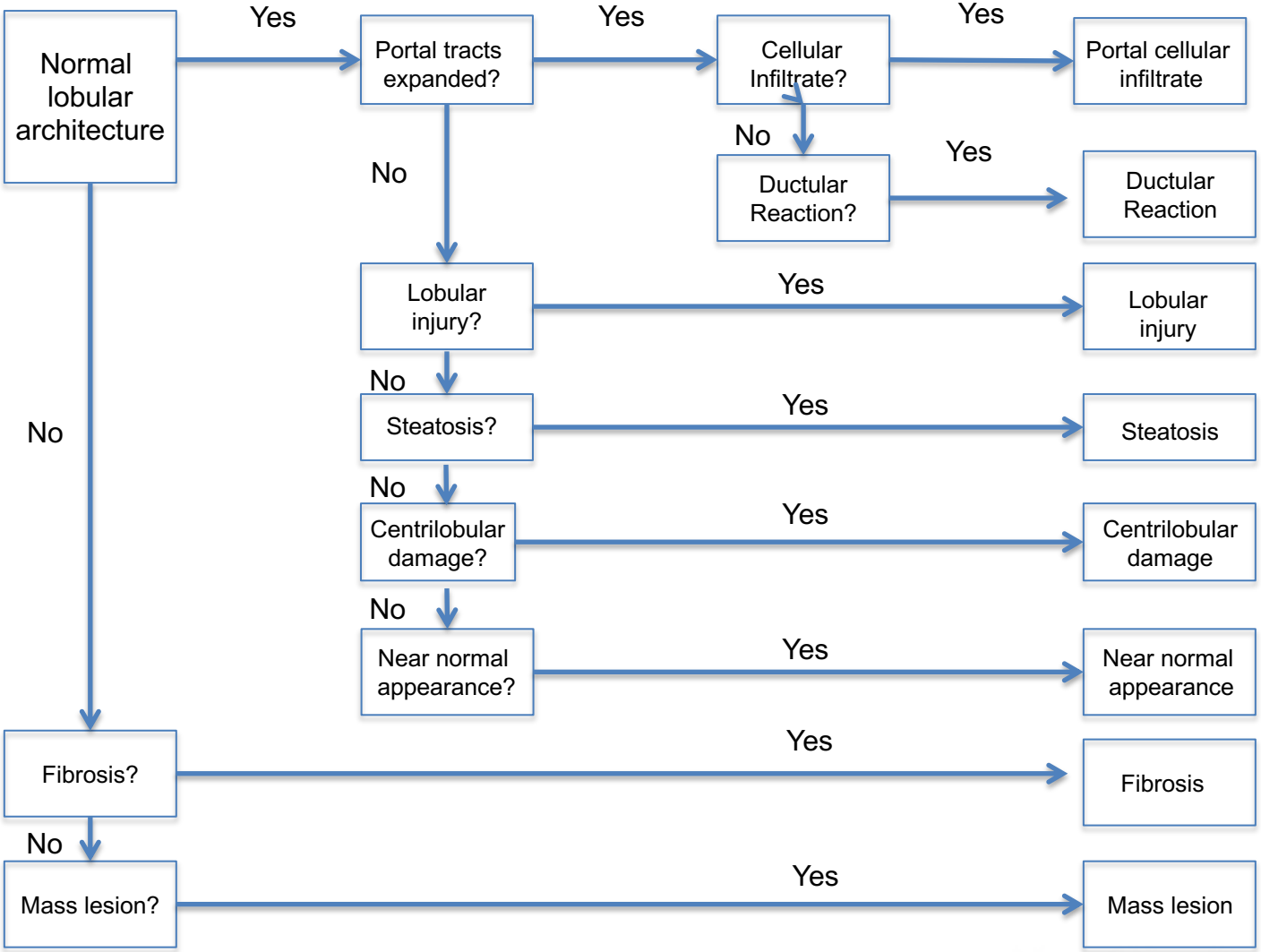


In the subcapsular liver parenchyma, the mature fibrous framework extends from the capsule.

Approach to reporting

- Architecture
- Portal tracts
- Inflammation: portal, interface, parenchyma
- Parenchyma
- Relevant negatives
- Conclusion

Algorithmic approach
Identification of major pattern of injury



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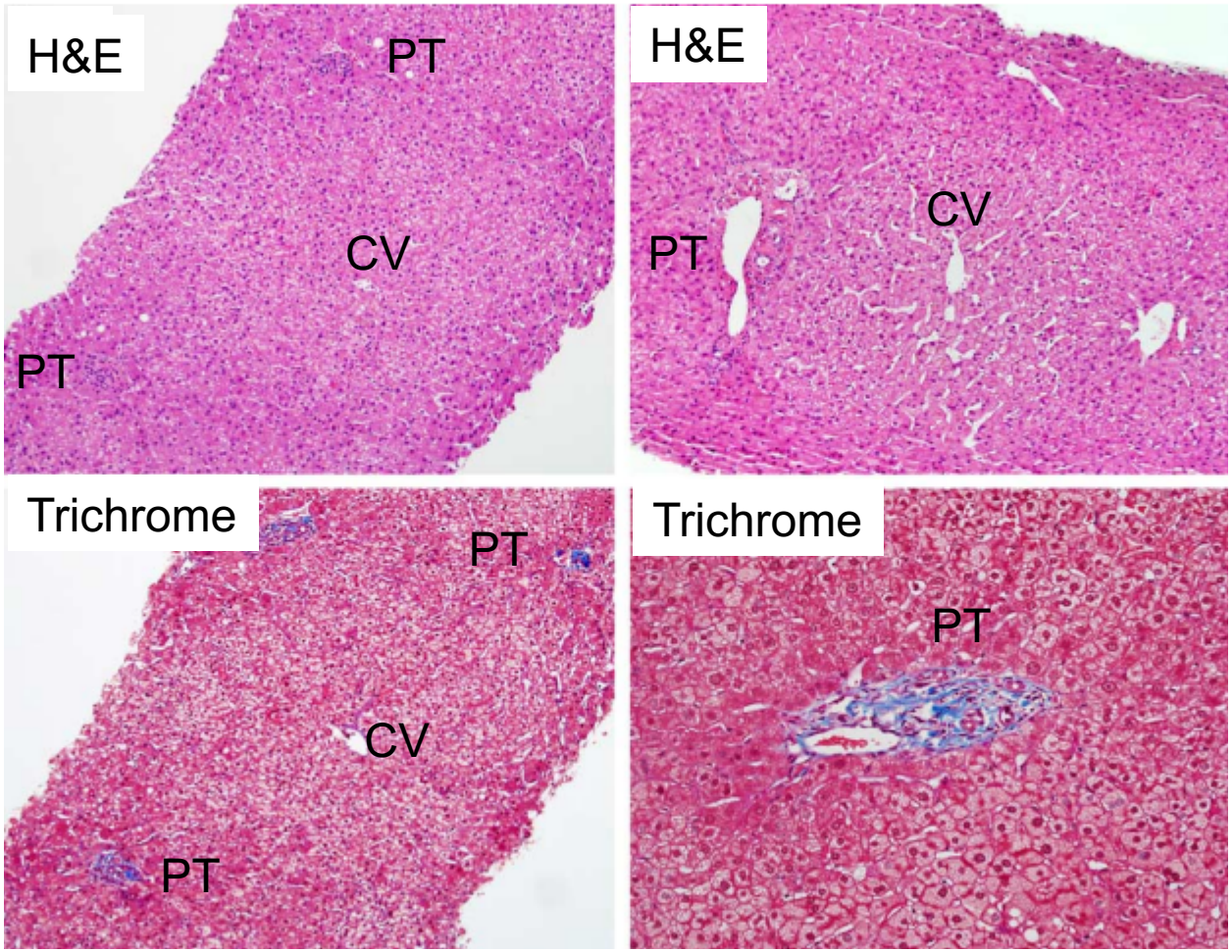
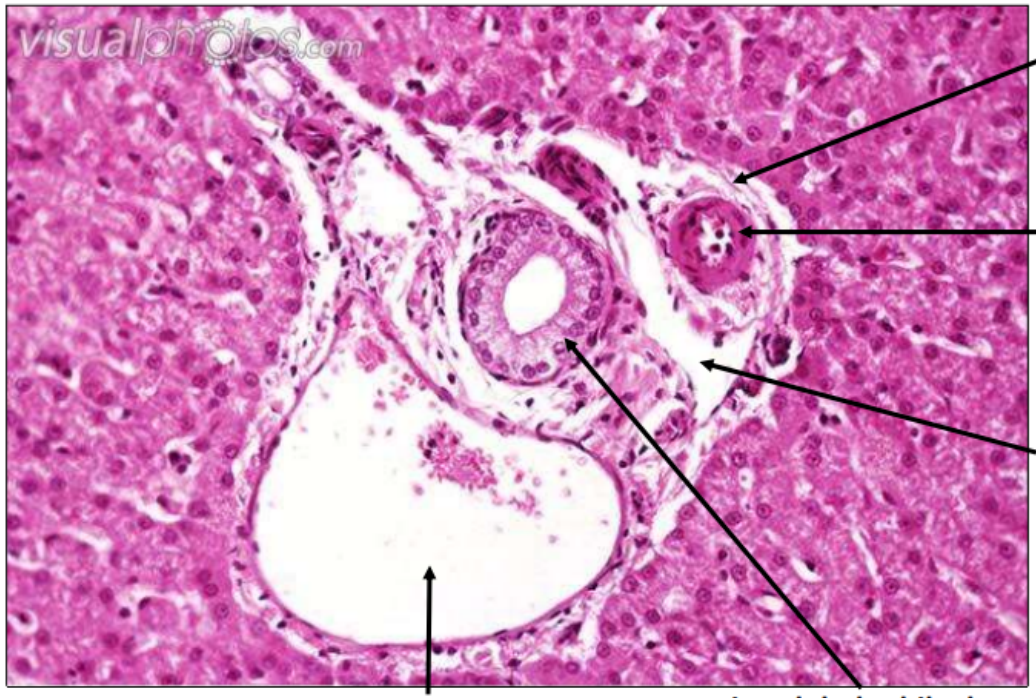
Normal liver



Portal triad



Limiting plate

interlobular artery
- round or oval shape
- muscular media
- may contain red blood cells

lymph vessel
- irregular shape
- very delicate wall
- no red blood cells

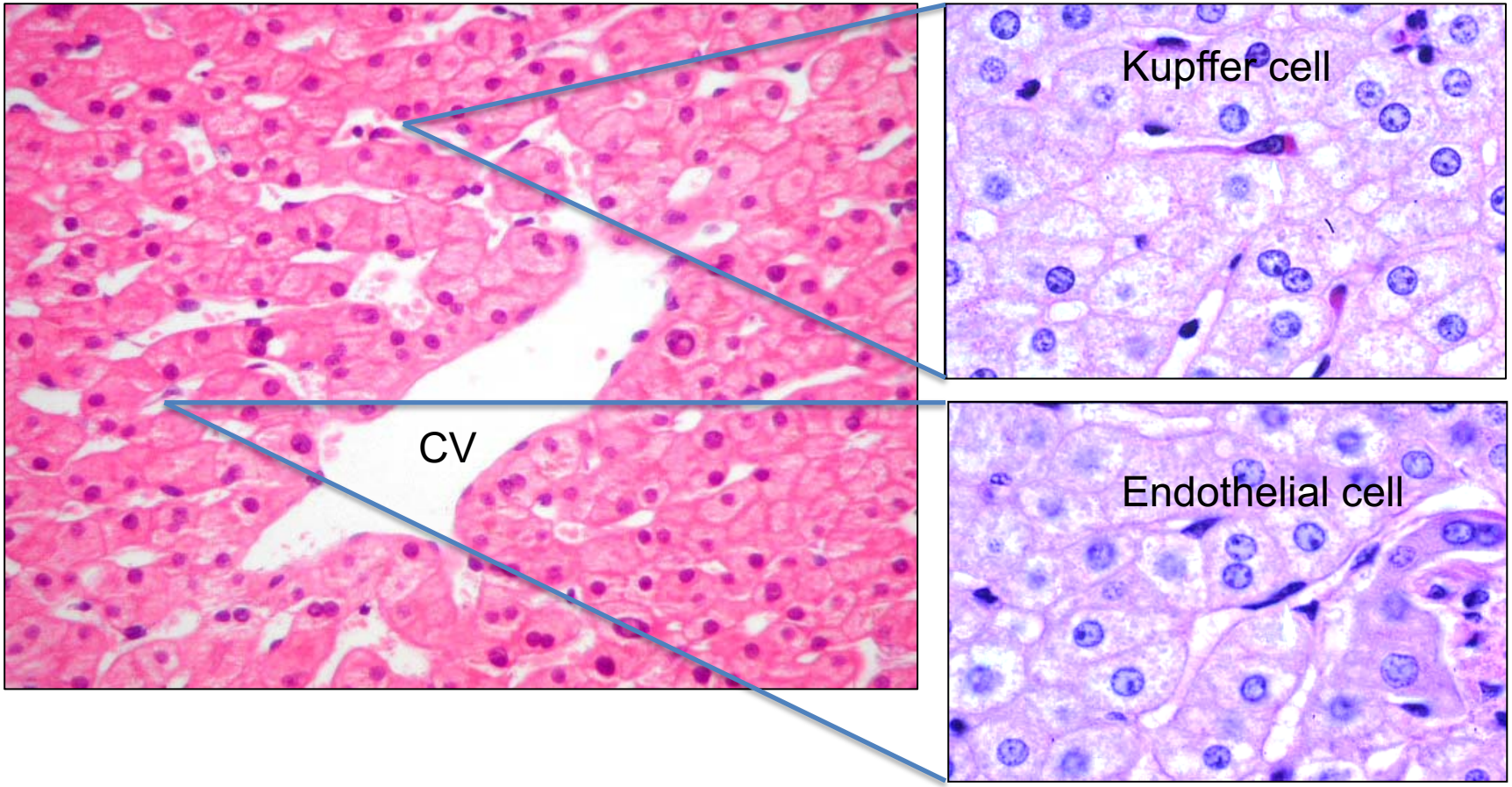
Nerves may be present.

interlobular vein
- irregular shape
- thin wall, only endothelial lining
- surrounding pericytes
- may contain red blood cells

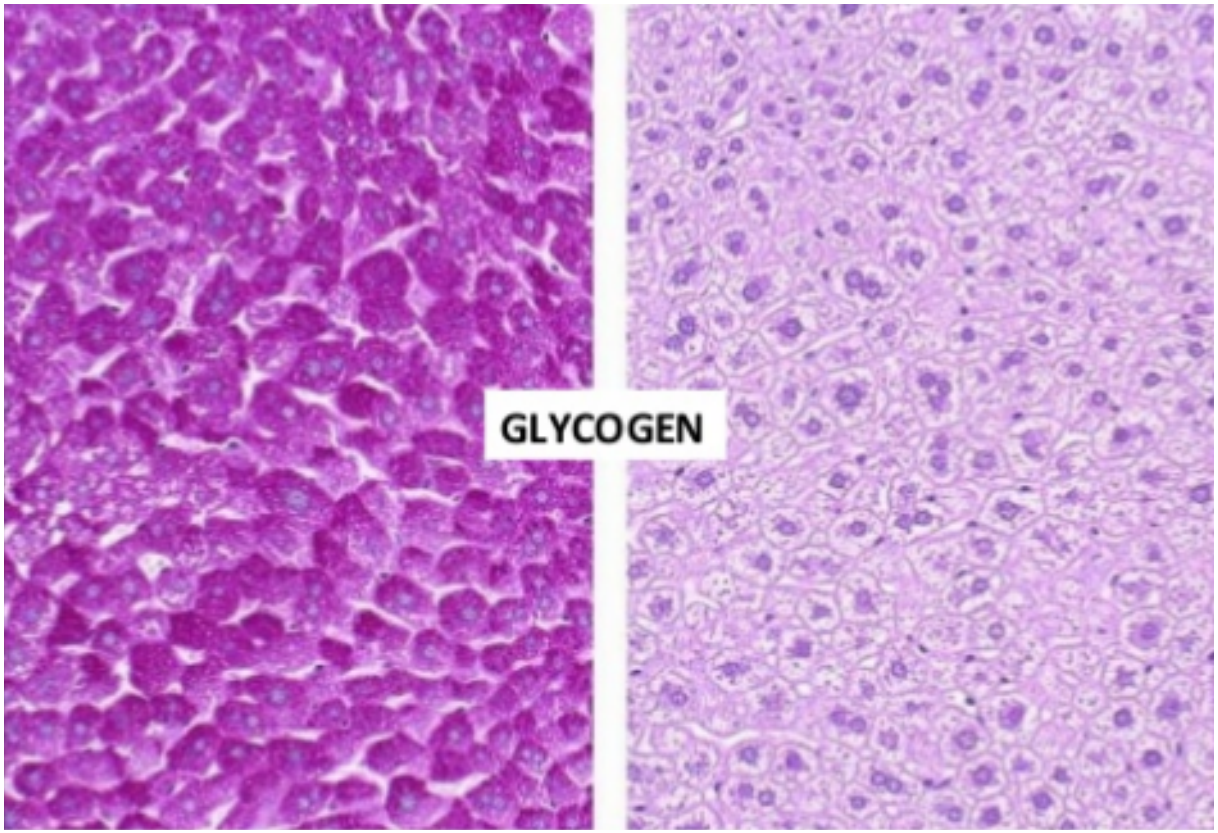
interlobular bile duct
- round or oval shape
- simple cuboidal (small ones)

or columnar (larger ones) epithelium

Normal liver



Normal liver



PAS PASD

https://www.slideshare.net/mannanrifat/histology-of-normal-liver

Normal liver

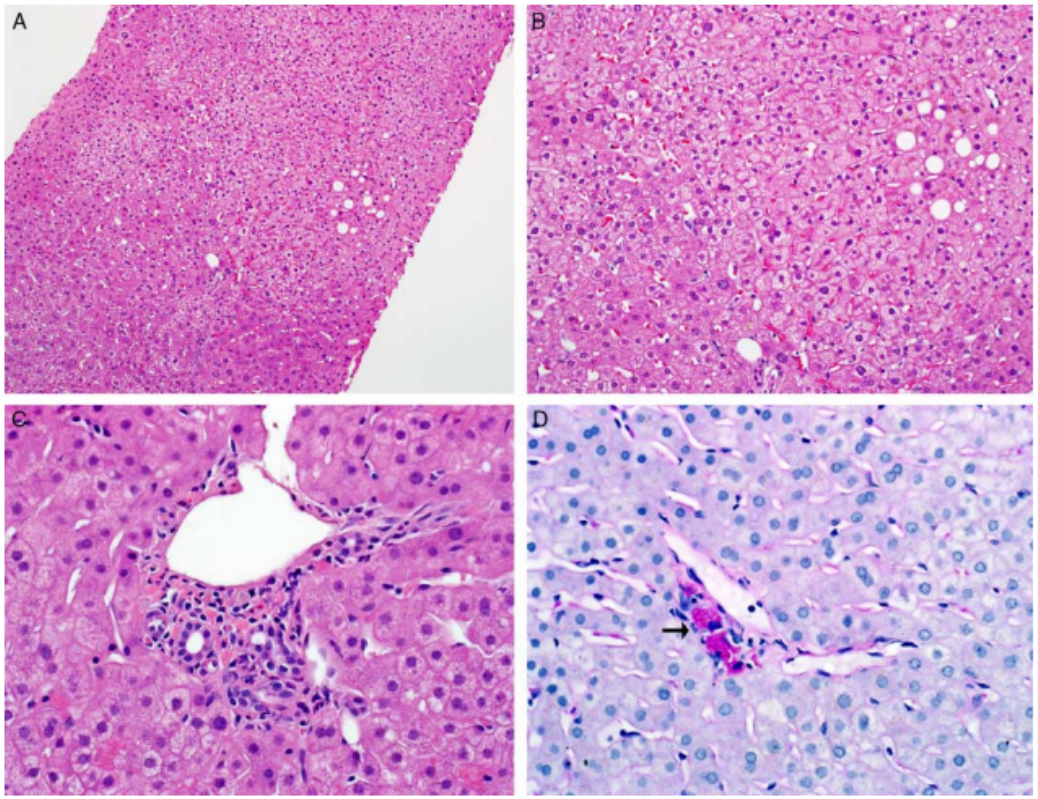
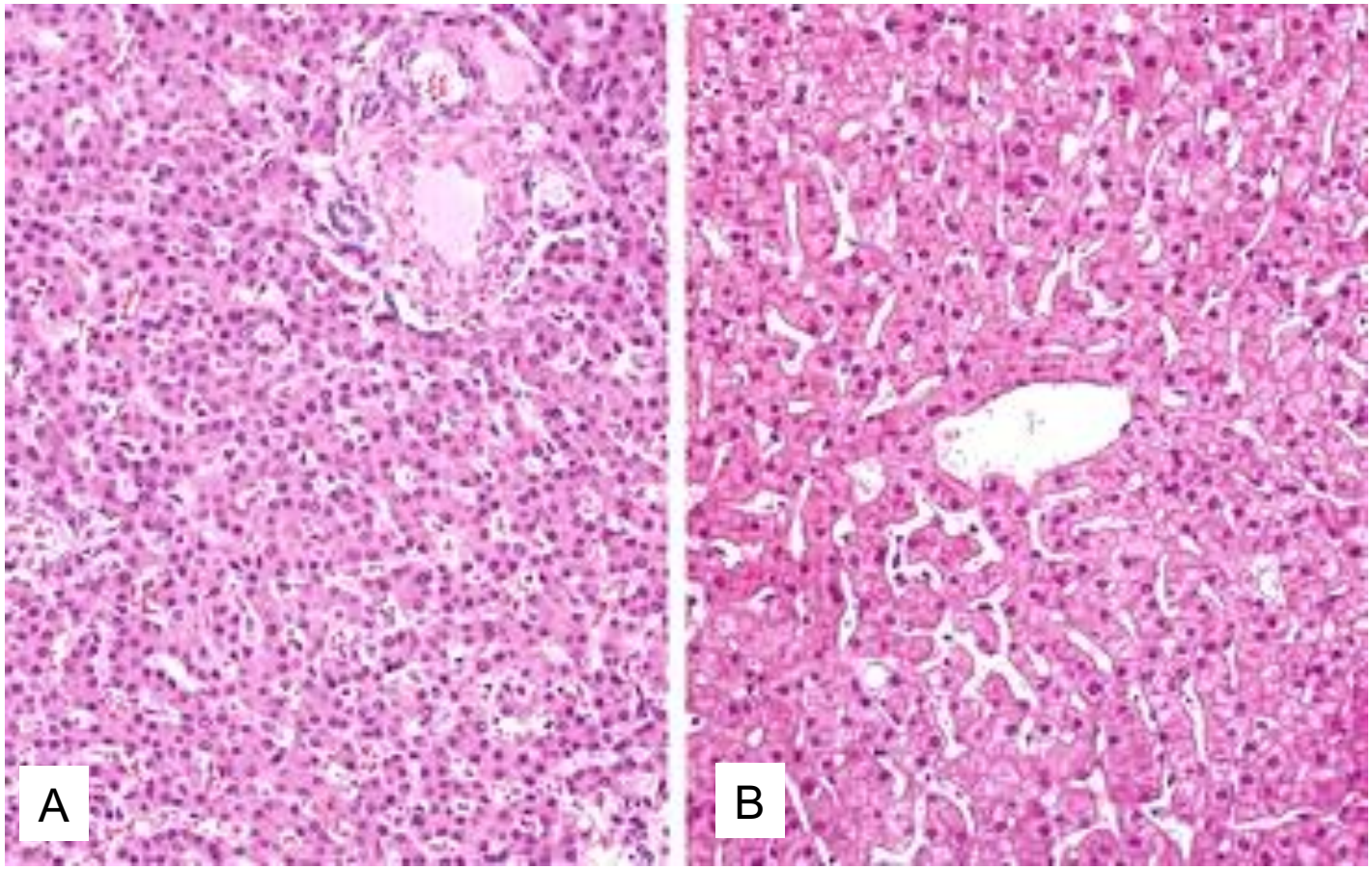
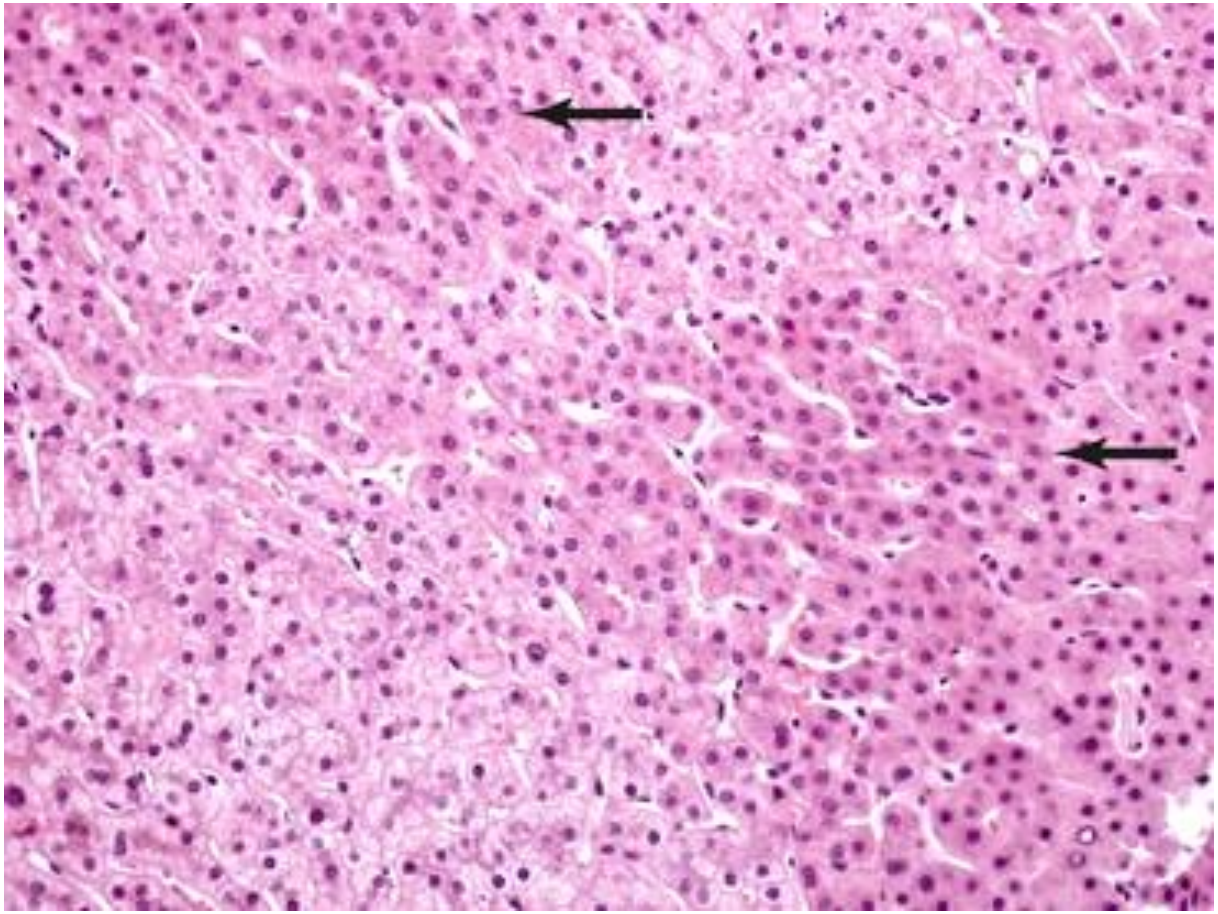


FIGURE 2. Only very minimal changes were allowed in nearly normal liver biopsies. A and B, Only minimal (<5%) steatosis was allowed for inclusion in the study (hematoxylin and eosin). C, Only focal minimal portal inflammation is seen (hematoxylin and eosin). D, Only very rare ceroid-laden macrophages (arrow) were considered acceptable in nearly normal liver biopsies (PAS-D).

A) Child vs B) Adult

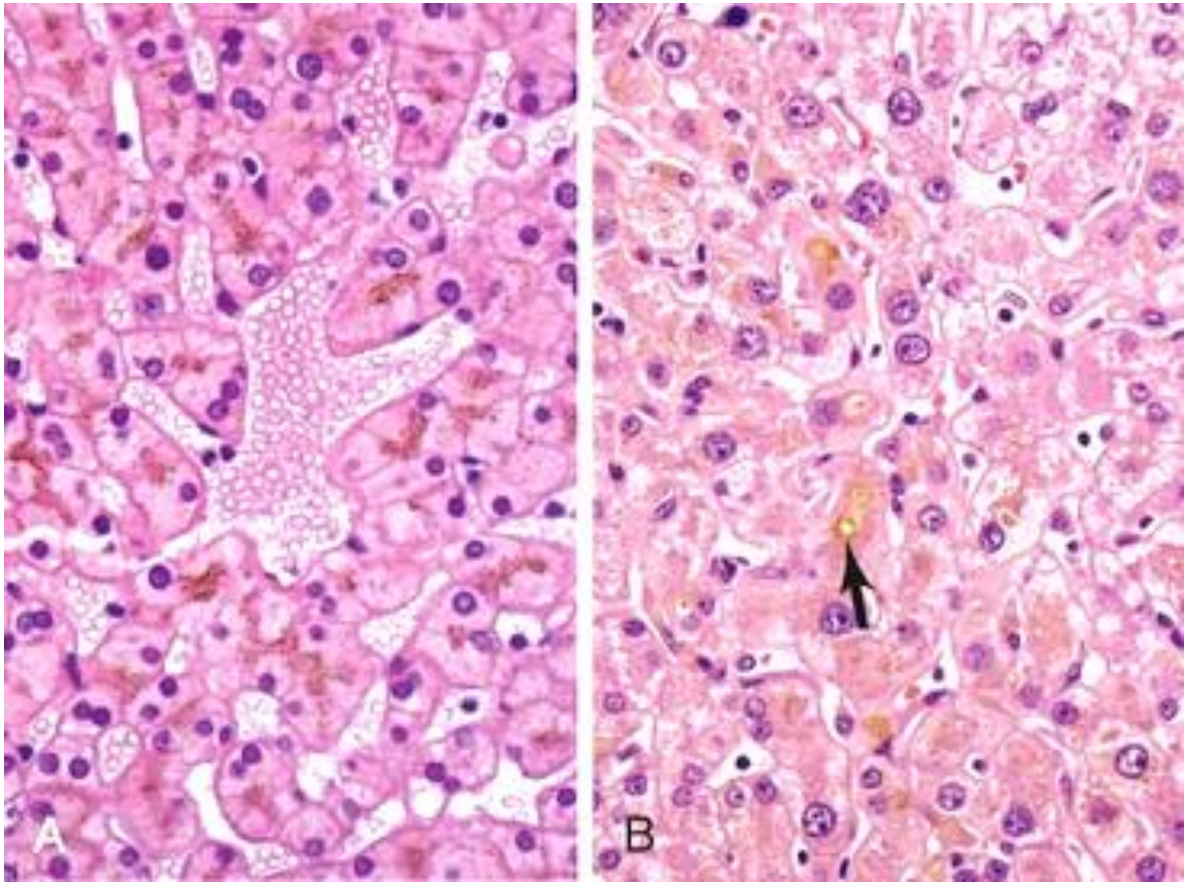


Hepatocyte regeneration



Dark staining and thickening of hepatocyte cords *(arrows)* indicate hepatocyte regeneration in adults

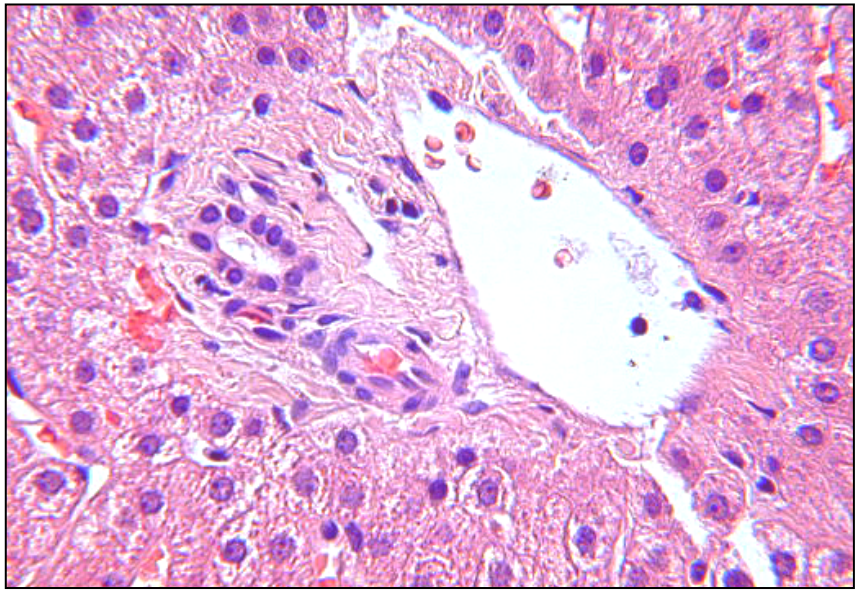
Normal liver



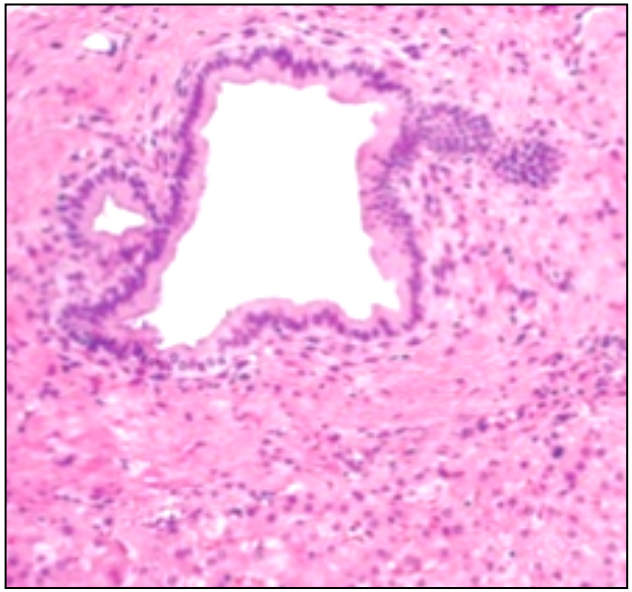
Lipofuscin

Bile

Bile ducts



Interlobular bile ducts
cuboidal/low columnar cells

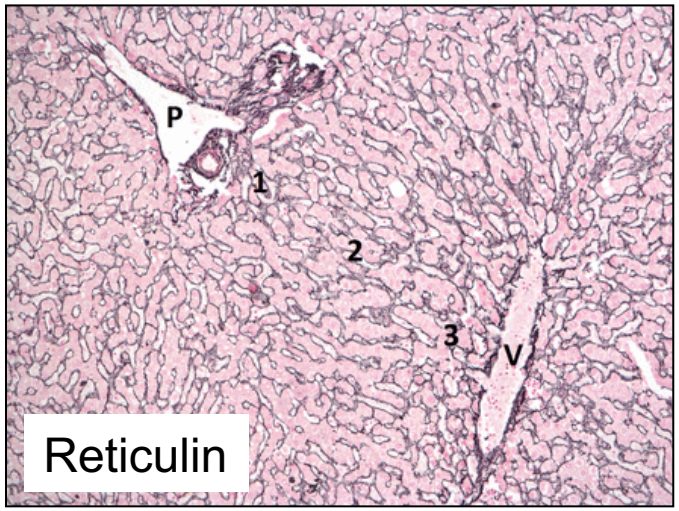


Septal bile ducts
tall columnar cells

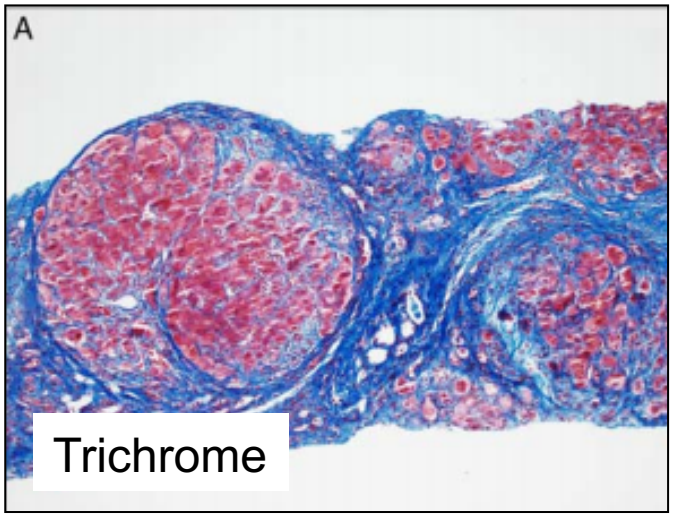
Up-front stains

- H&E
- Connective tissue (Reticulin, Sirius Red and Trichrome)
- PAS with diastase
- Iron (Perl's)
- Copper associated binding protein (orcein, VB)
- Elastic fibres (EVG, orcein, VB)

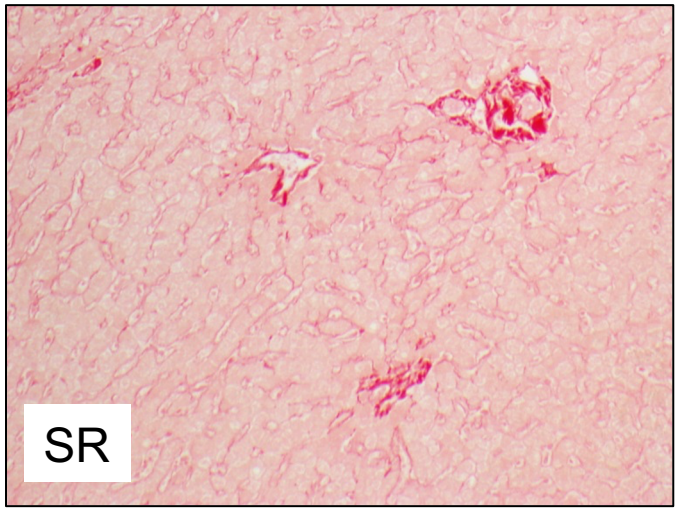
Connective tissue stains

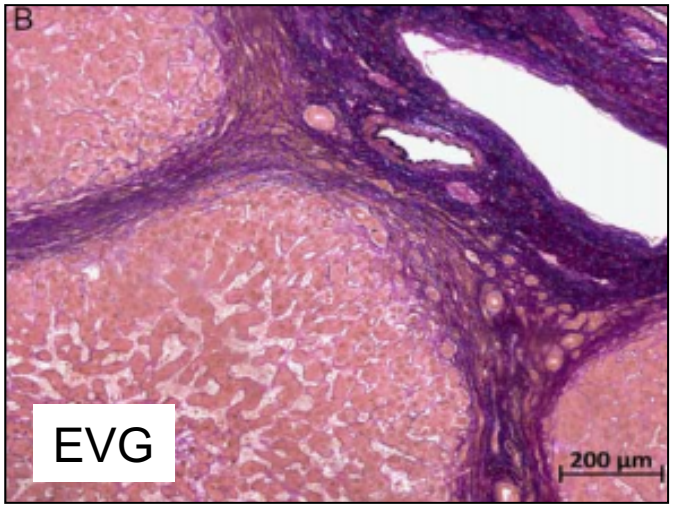


Reticulin



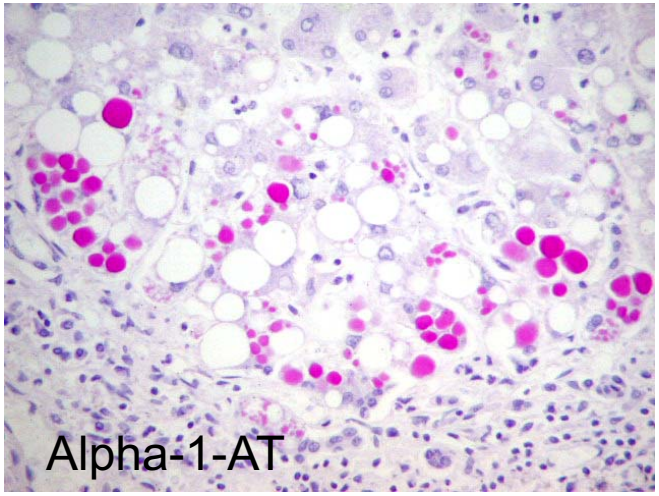
Trichrome

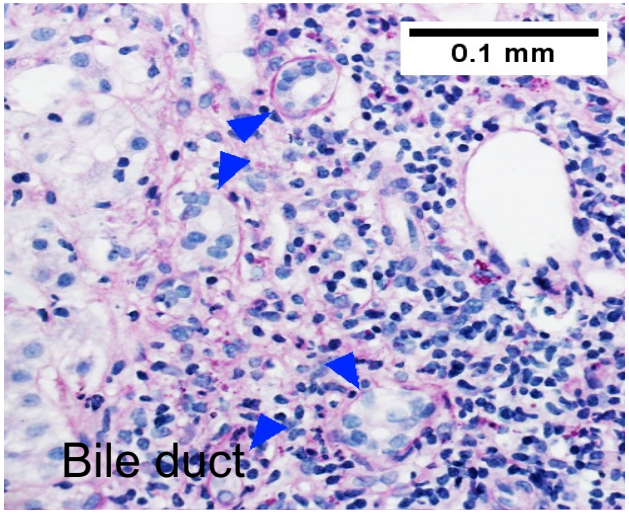

SR

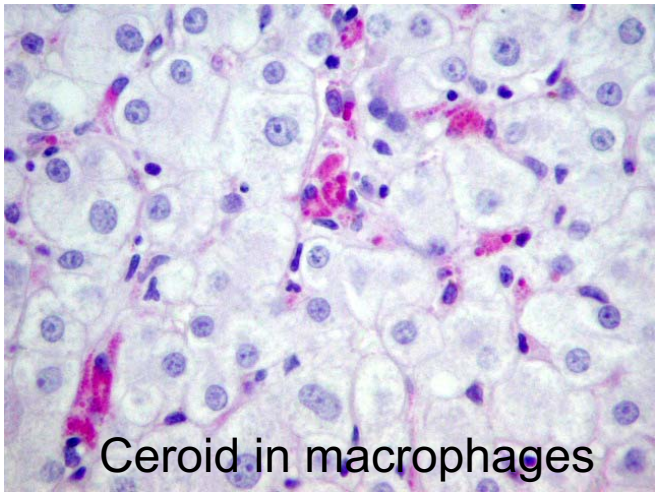


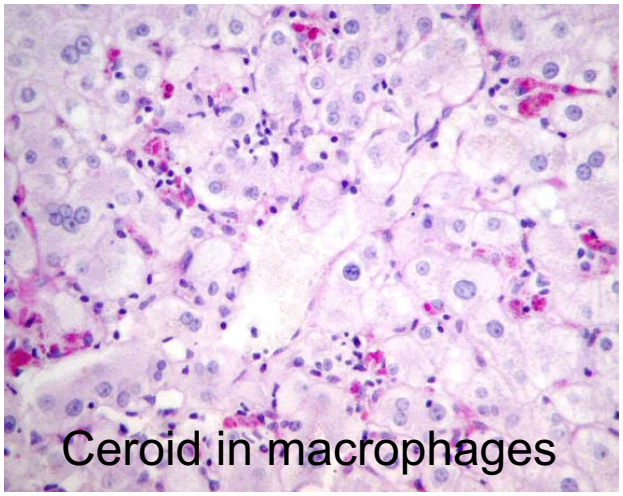
EVG

DPAS

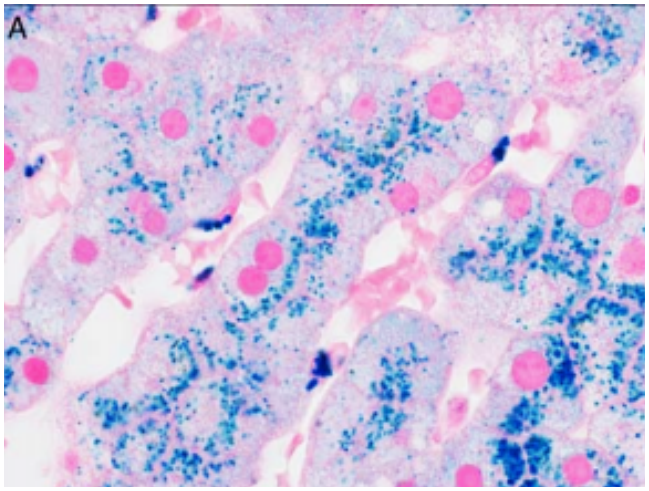

Alpha-1-AT


0.1 mm
Bile duct


Ceroid in macrophages


Ceroid in macrophages

Perl's stain



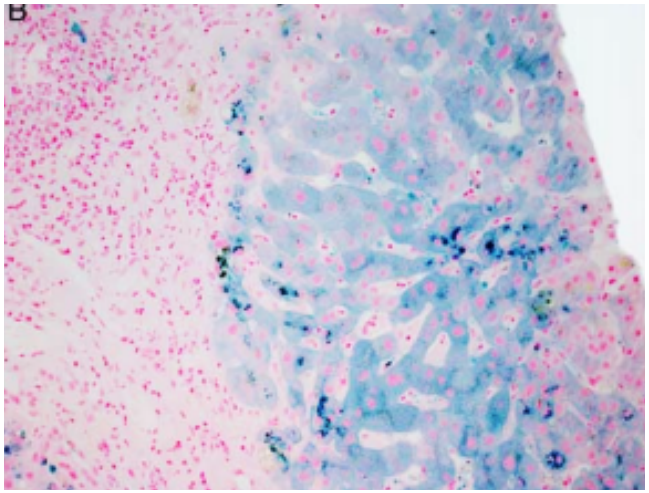
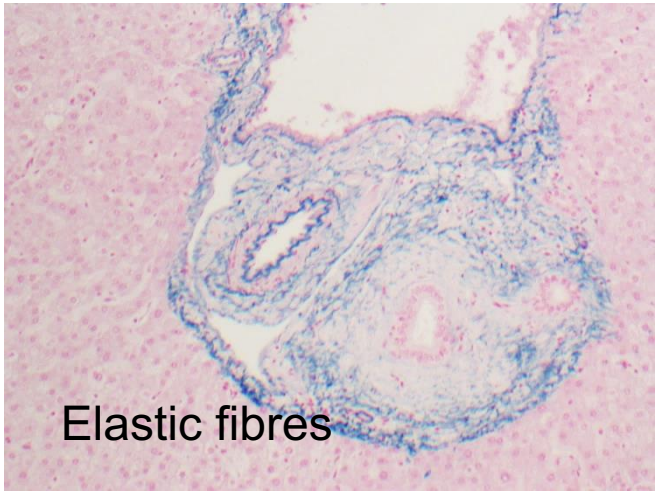


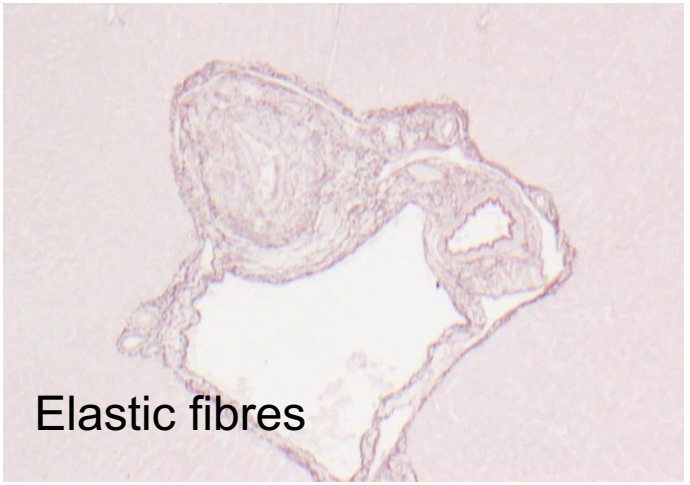
TABLE 2. Modified Scheuer's Grading System for Iron in the Liver[1]

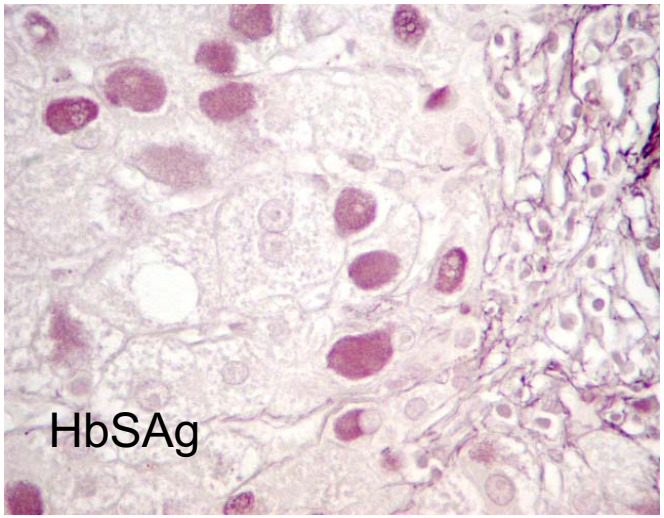
Grade	Description
0	Iron granules are absent or the iron granules are barely seen at ×400
1	Iron granules are resolved at ×250
2	Iron granules are resolved at ×100
3	Iron granules are resolved at ×25
4	Iron deposits are resolved at ×10 or iron deposits are visible without magnification

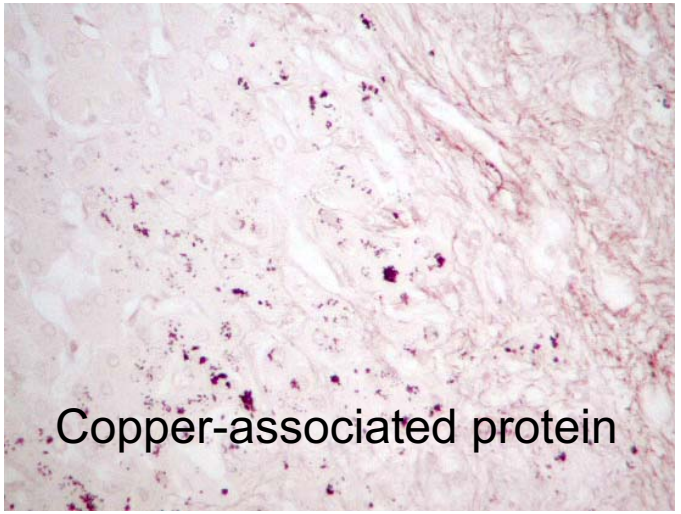
The term resolved means that the individual granules of iron deposits are evident at that magnification. Iron deposits in both the hepatocytes and the Kupffer cells should be scored separately.

Orcein and Victoria Blue

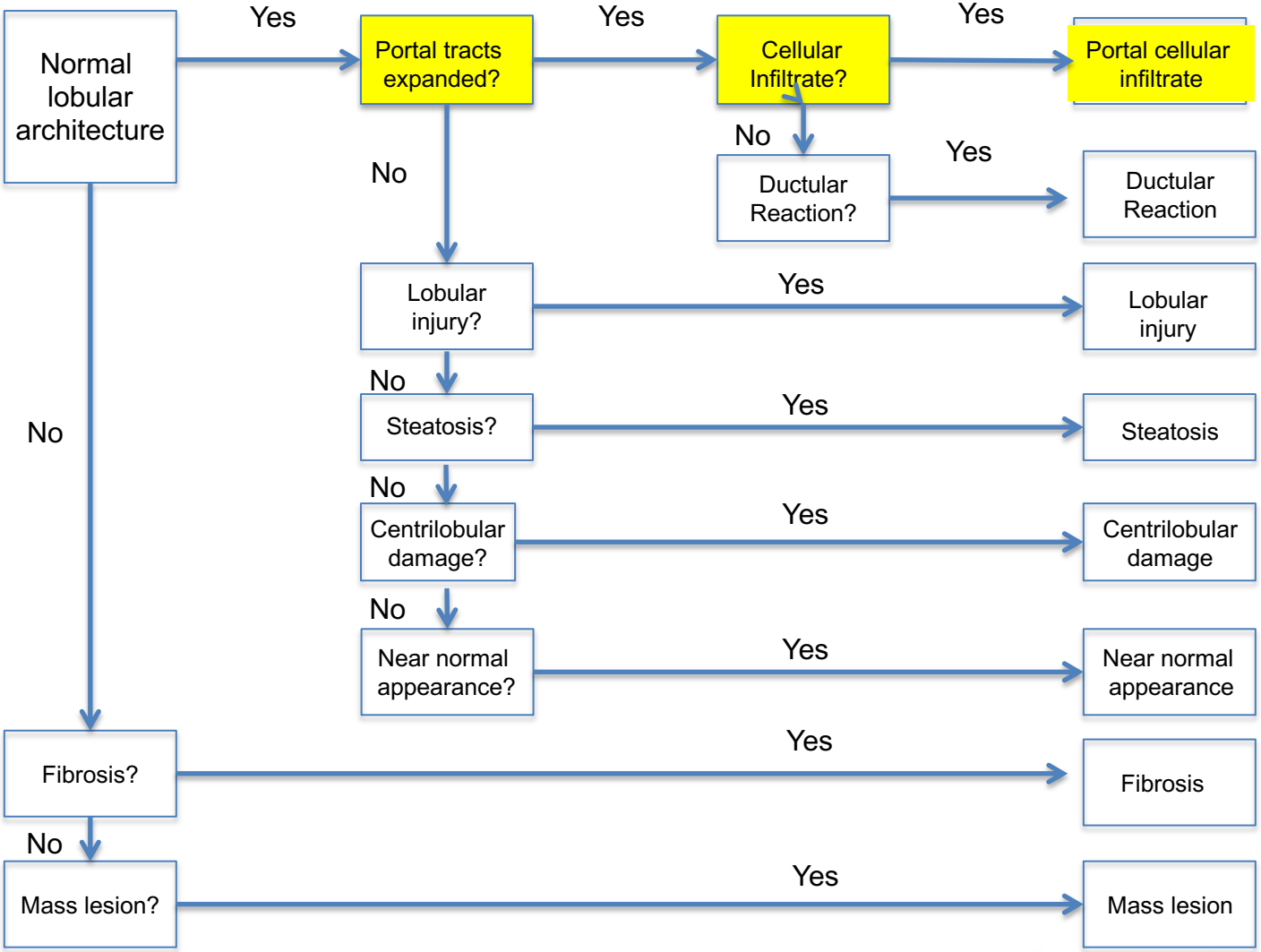








Algorithmic approach
Identification of major pattern of injury



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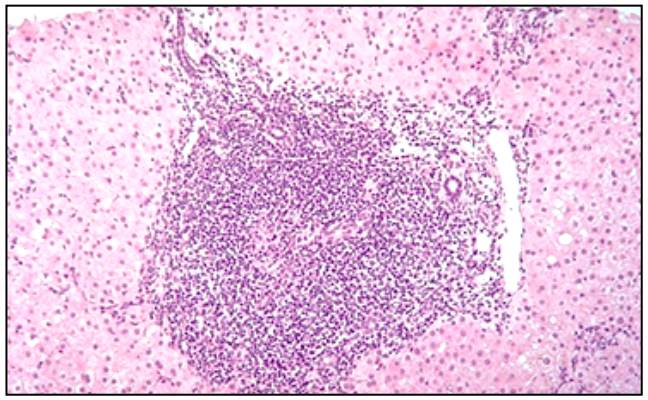
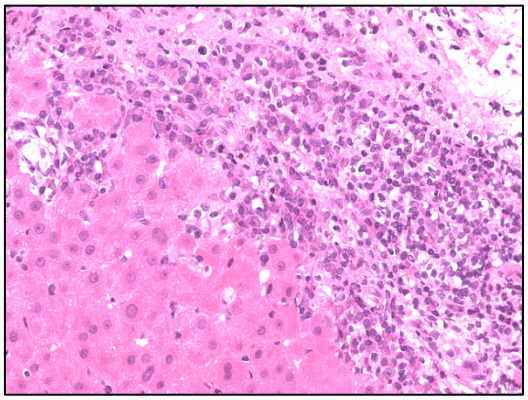
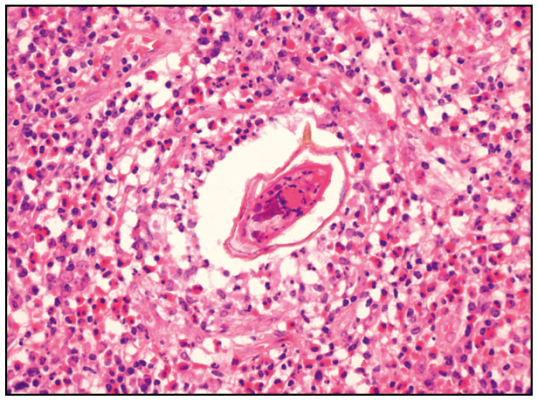
PREDOMINANTLY PORTAL INFLAMMATION



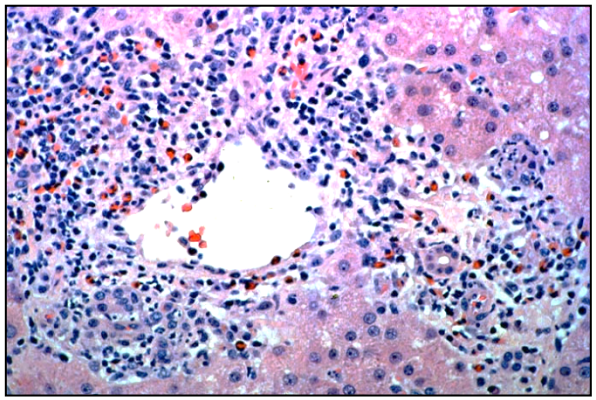
Predominantly lymphocytic
(HCV, HBV, AIH, PBC)



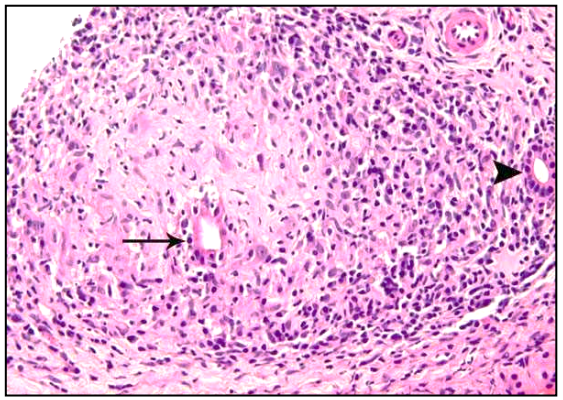
Predominantly plasma cells
(AIH, PBC)



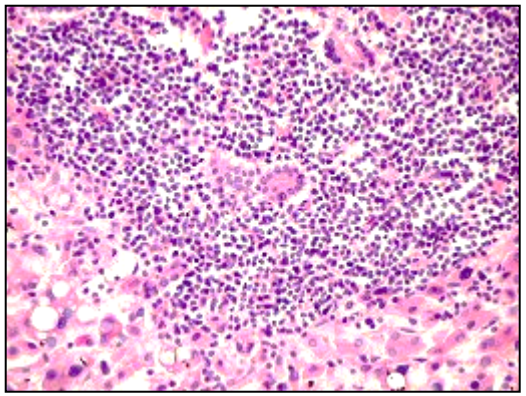
Predominantly eosinophils
(Parasites, drug, AIH, PBC/PSC)



Predominantly mixed
(Acute cellular rejection, Hodgkin)



Predominantly granulomatous
(PBC, TB, sarcoidosis, drug, Q fever)



Atypical infiltrate
(Leukemia, lymphoma, PTLD, EBV)

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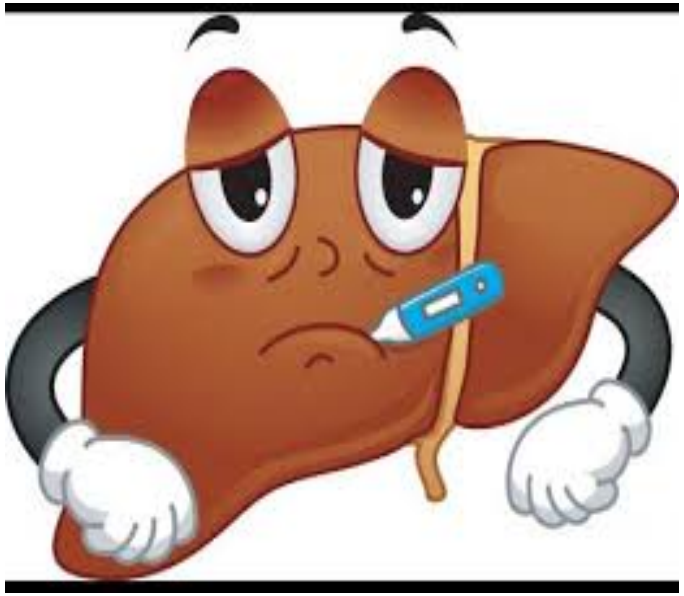
CHRONIC HEPATITIS



CHRONIC HEPATITIS

- **Definition**: “Diffuse inflammation of the liver lasting longer than 6 months”
- **Diagnosis**: combination of clinical, biochemical, histological and immunological findings
- **Histology**: - chronic inflammatory infiltrate

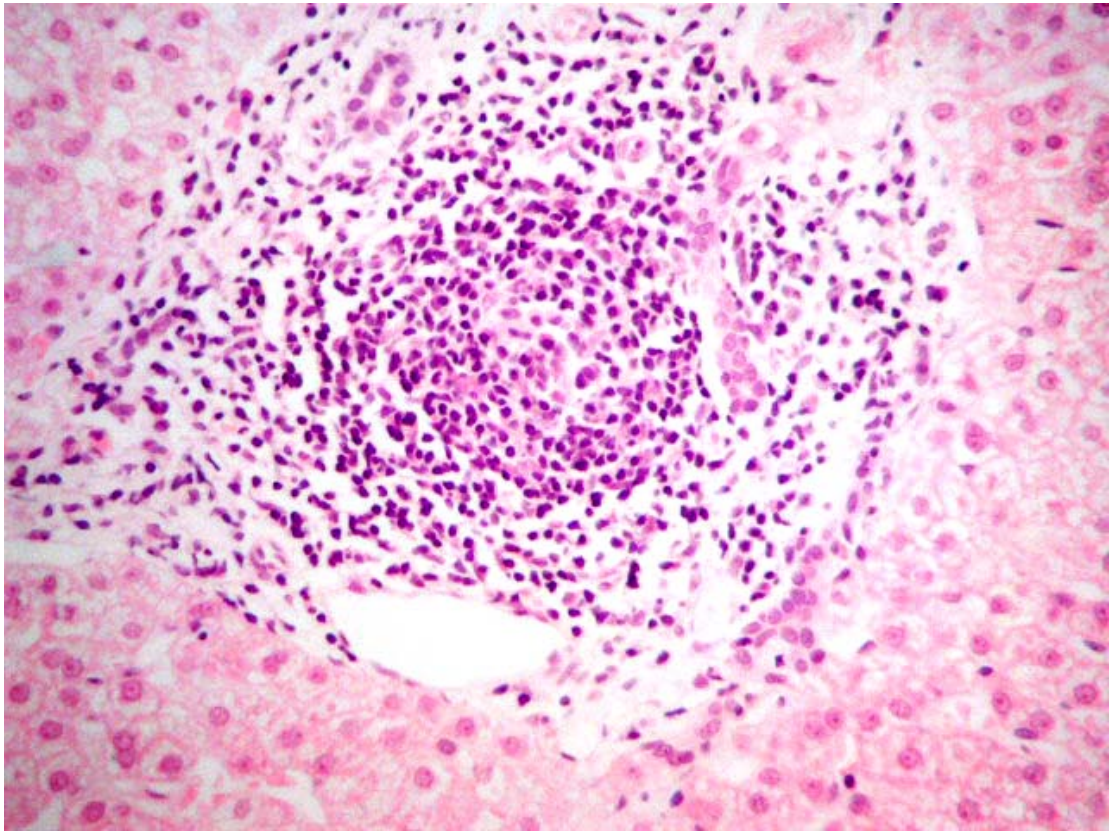
  (portal, periportal, lobular)

  - hepatocellular damage

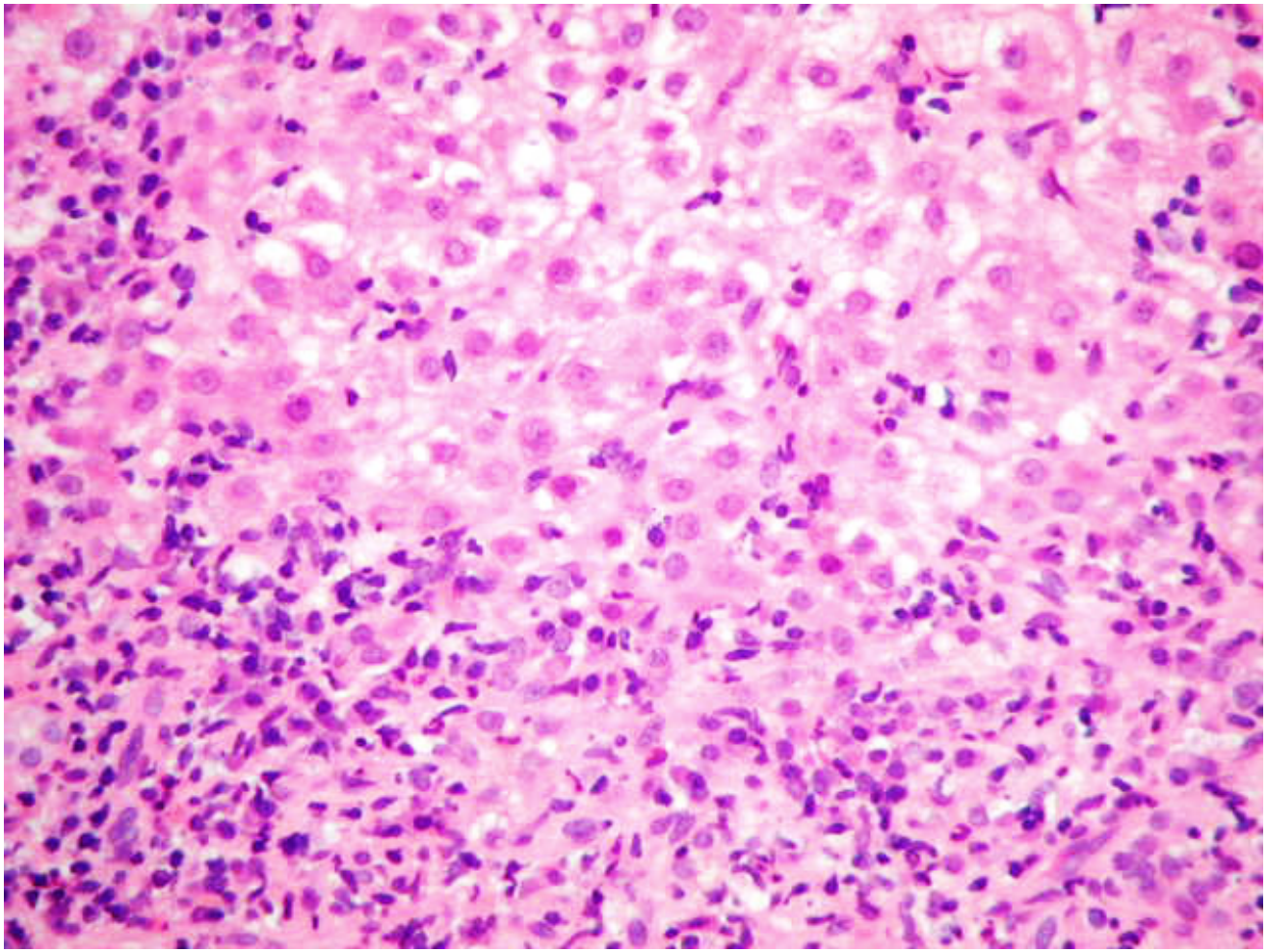
  - fibrosis

Histology: portal inflammation

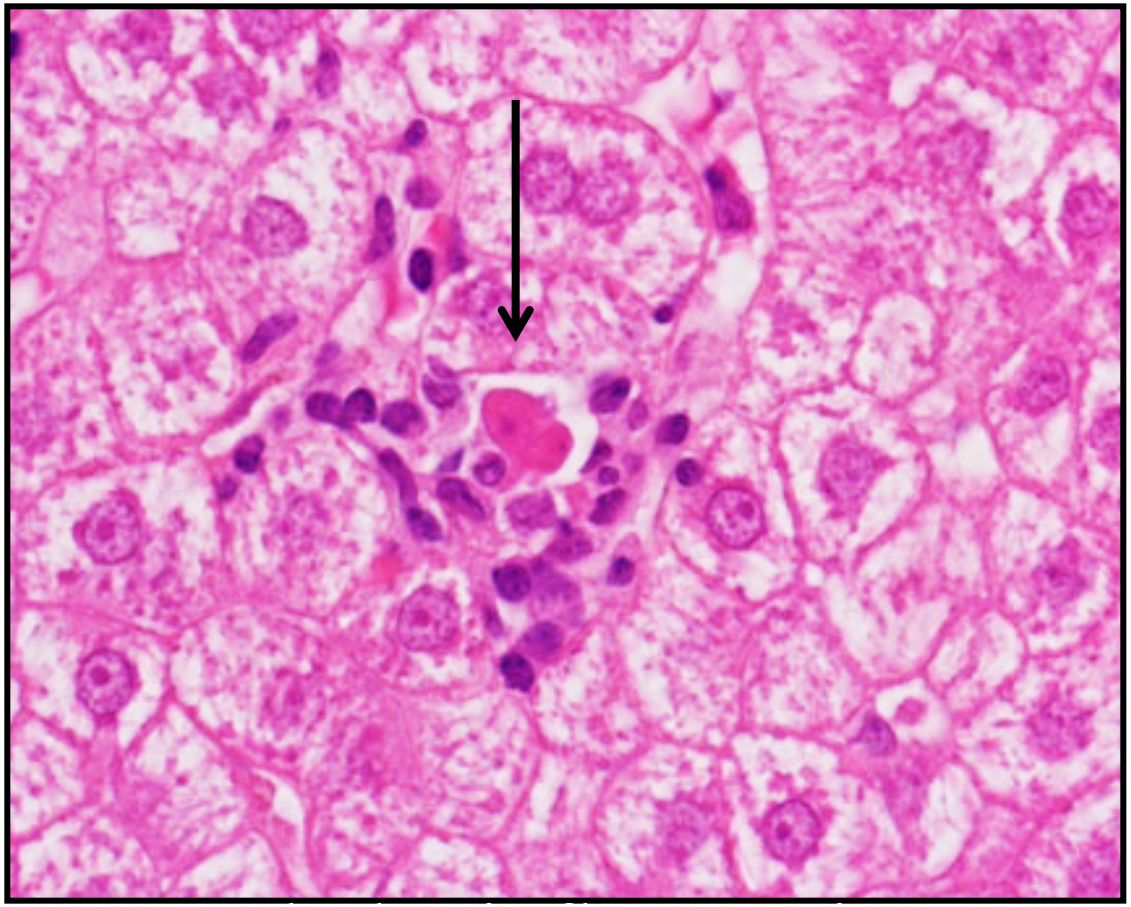
Mononuclear infiltration of portal tracts is the defining lesion of chronic hepatitis of any cause



Interface hepatitis



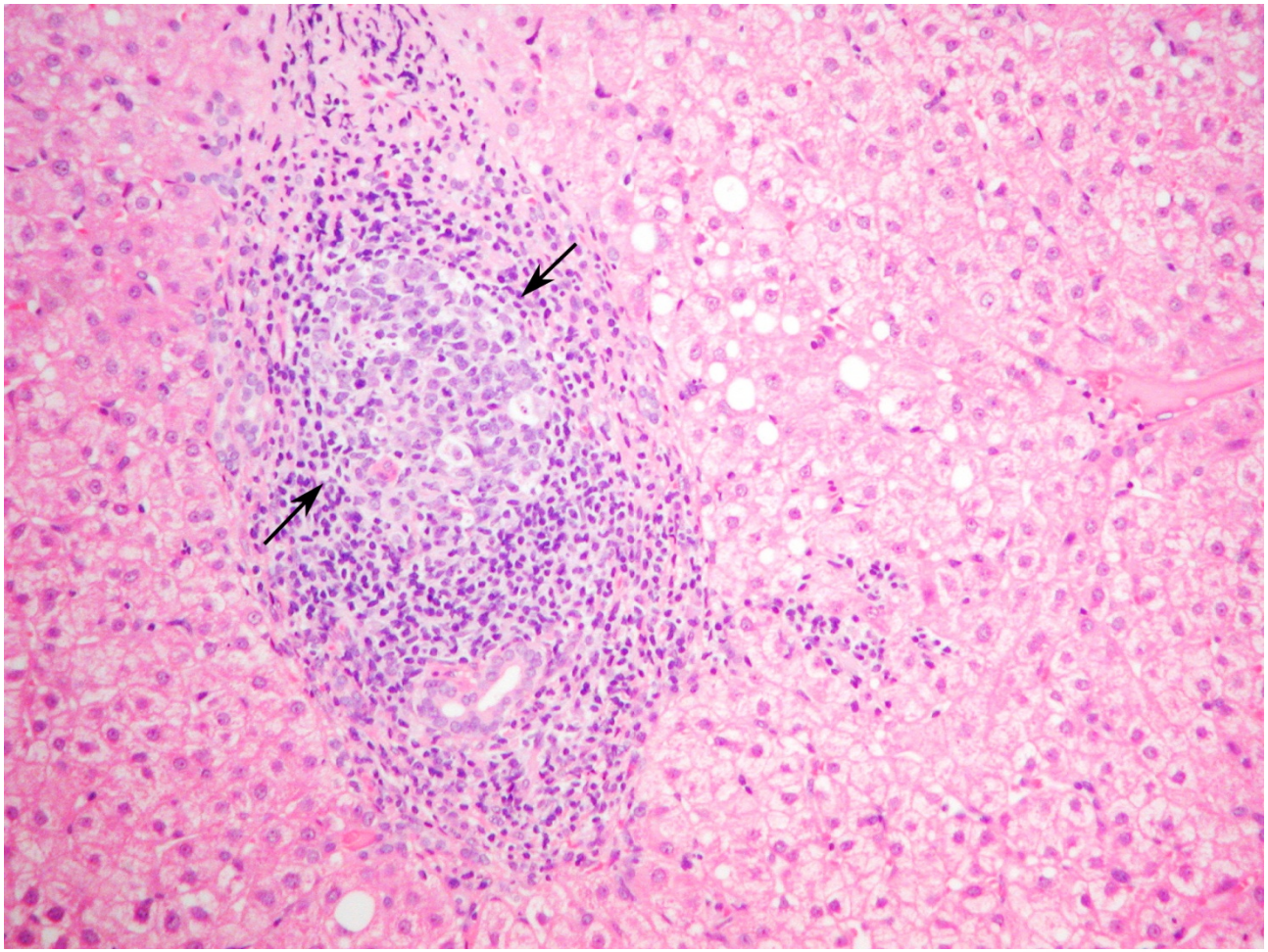
Intra-acinar changes



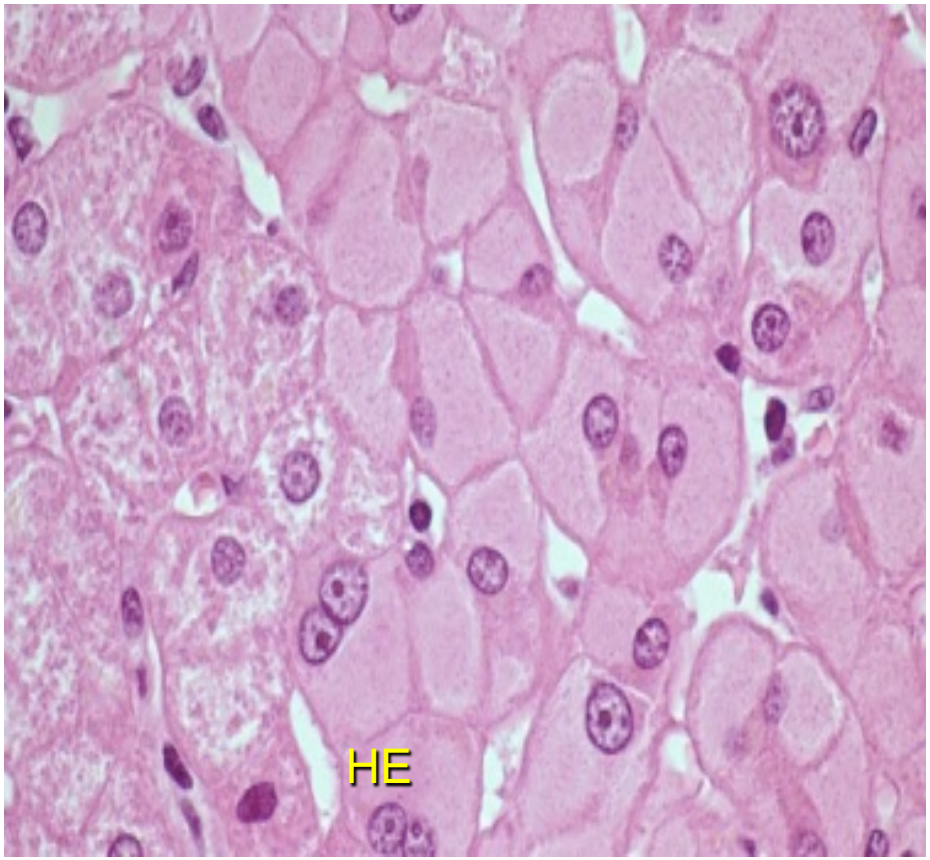
VIRAL HEPATITIS

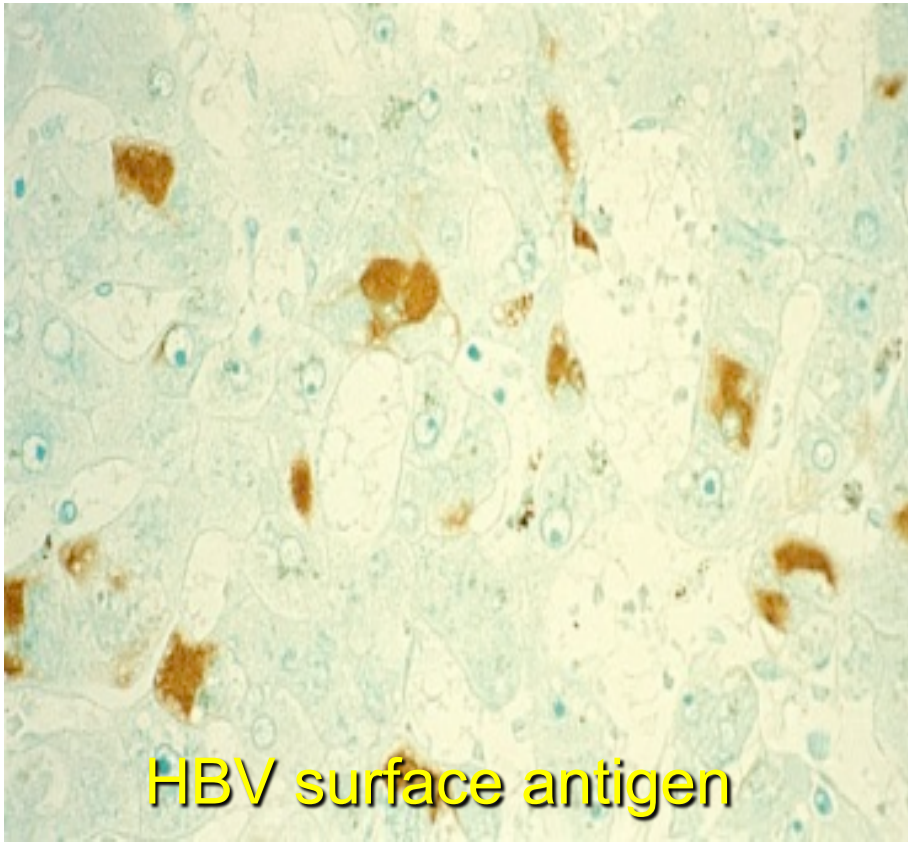
HBV	HCV
Ground glass hepatocytes	Lymphoid aggregates Steatosis

HCV: Lymphoid follicle



HBV: Ground glass hepatocytes



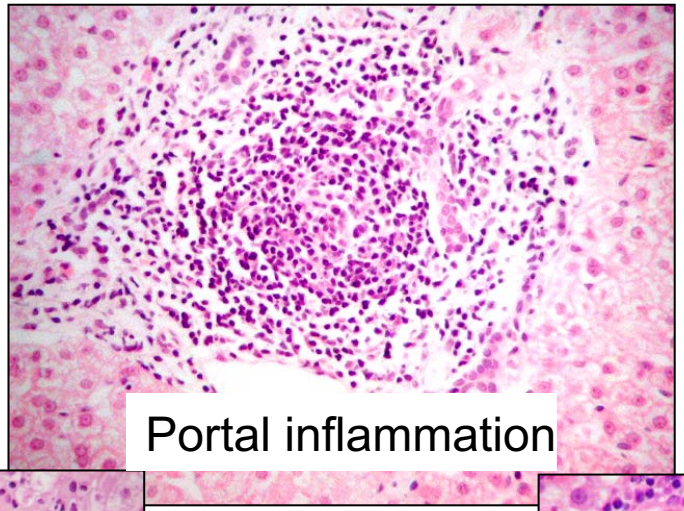


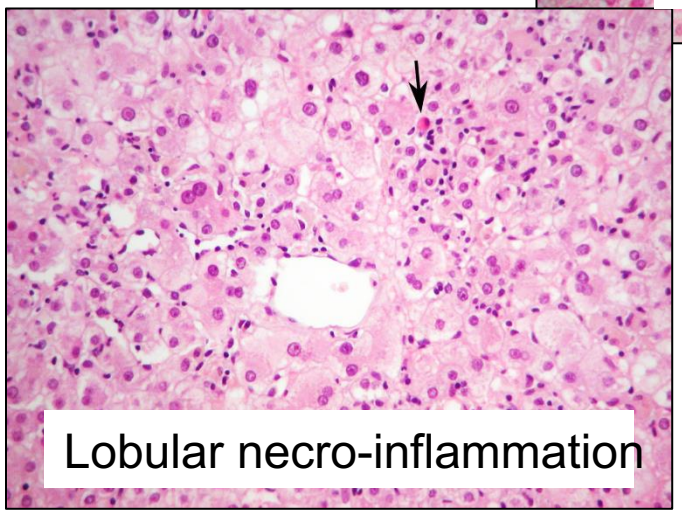
Autoimmune Hepatitis

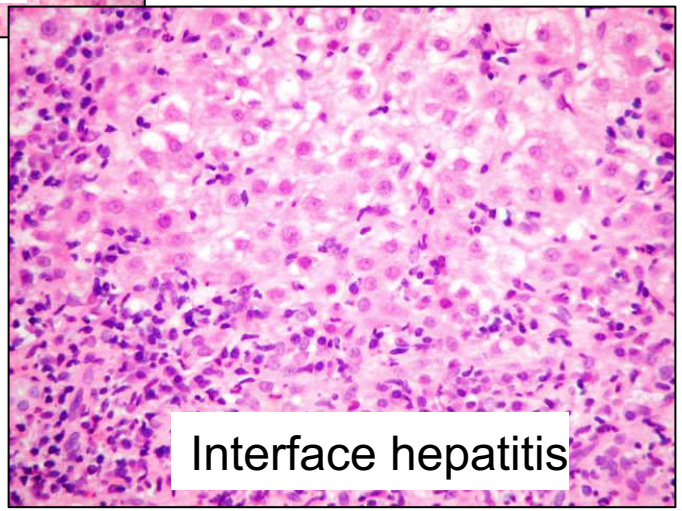
Autoimmune hepatitis

- Usually females
- High autoantibody titres
  - (anti-smooth muscle, anti-nuclear, and/or anti-liver-kidney microsomal antibodies)
- Hepatitic derangement of liver enzymes
- Chronic inflammation
- Inflammatory cell = plasma cell
- Marked interface hepatitis
- +/- fibrosis

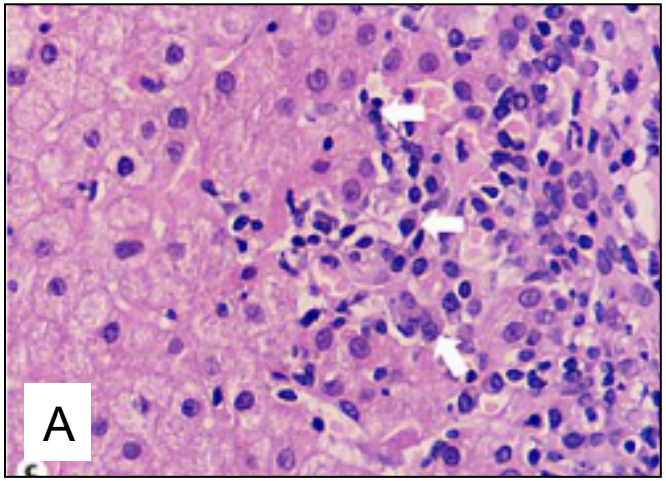
Histology: chronic hepatitis pattern of injury



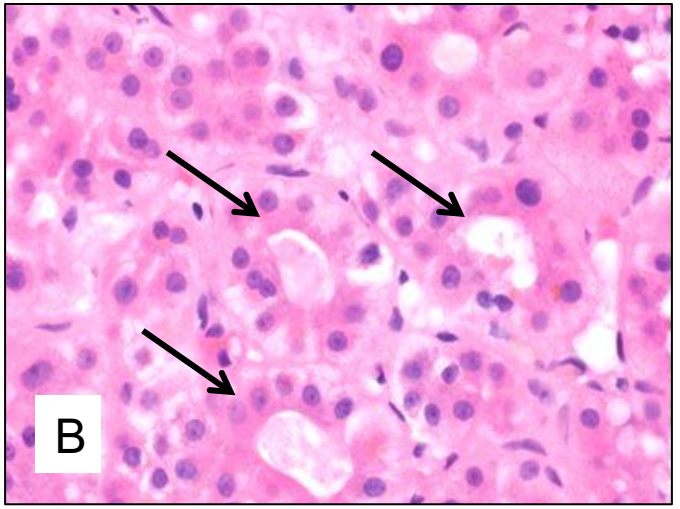




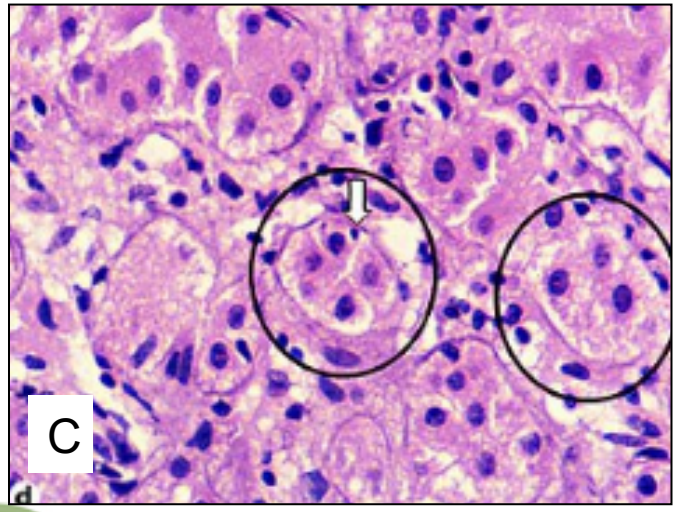
Typical histological features of AIH



A. Predominance of plasma cells in the portal infiltrate and interface

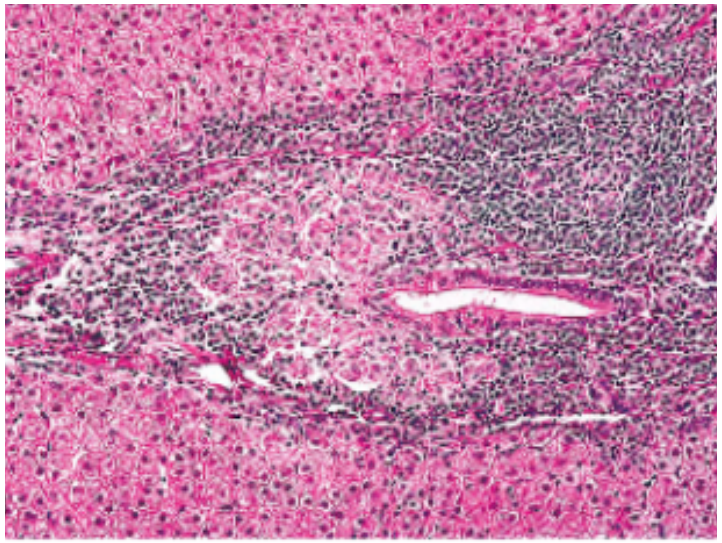


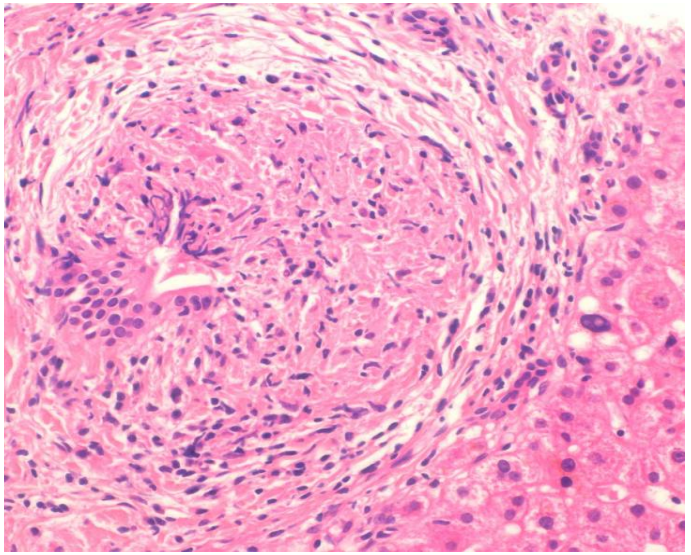
B. Hepatic rosette

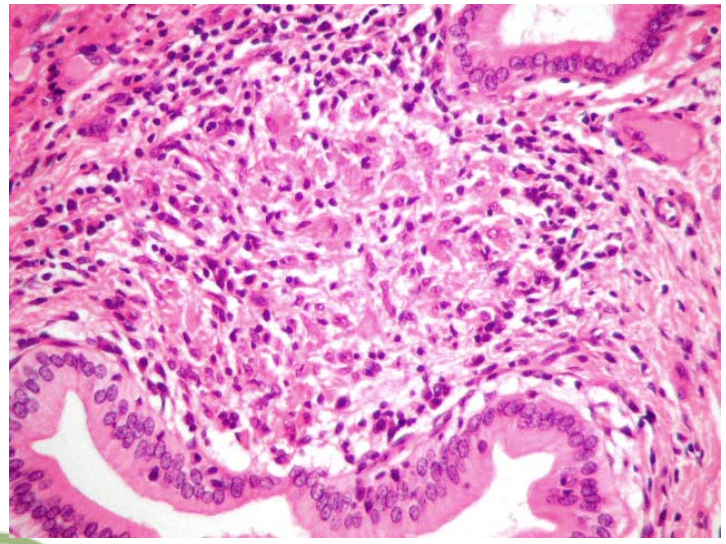


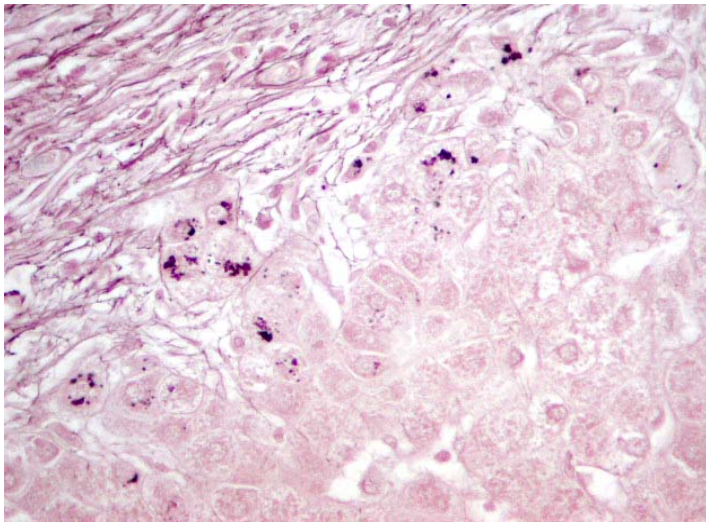
C. Emperipolesis (presence of a lymphocyte
within the cytoplasm of hepatocytes)

Diagnostic features of PBC



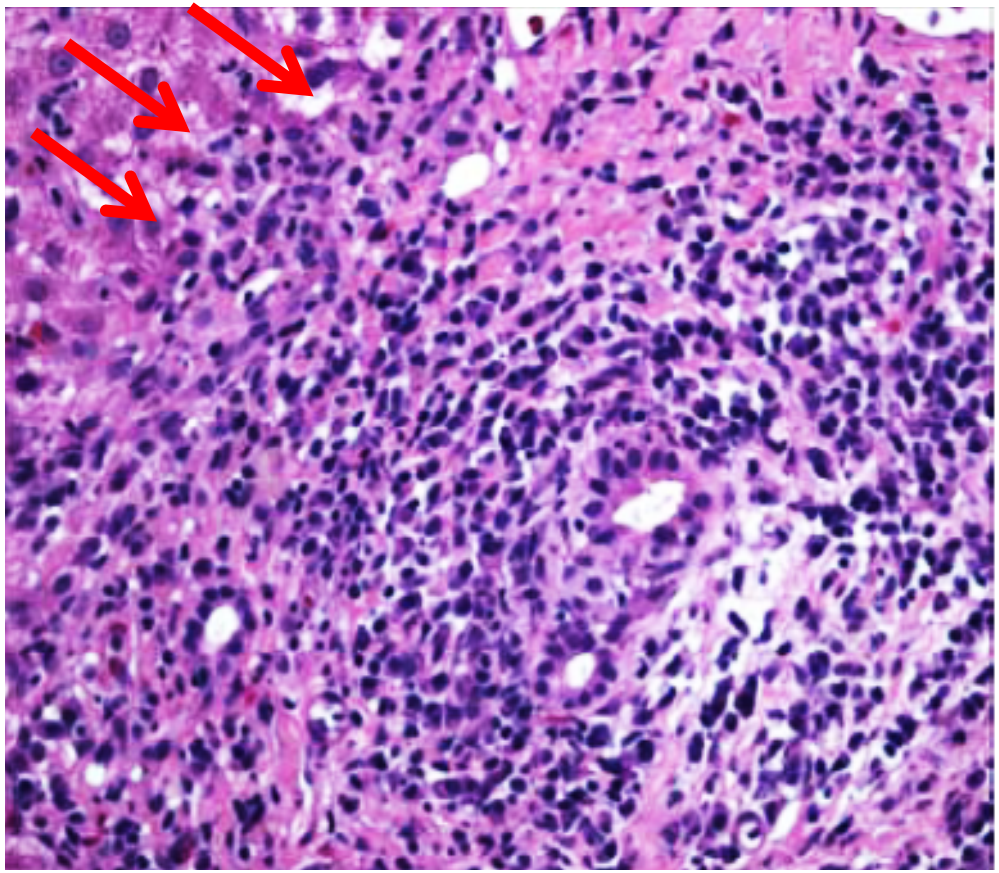






The hallmark lesion: Non suppurative destructive cholangitis with granulomas

Histology

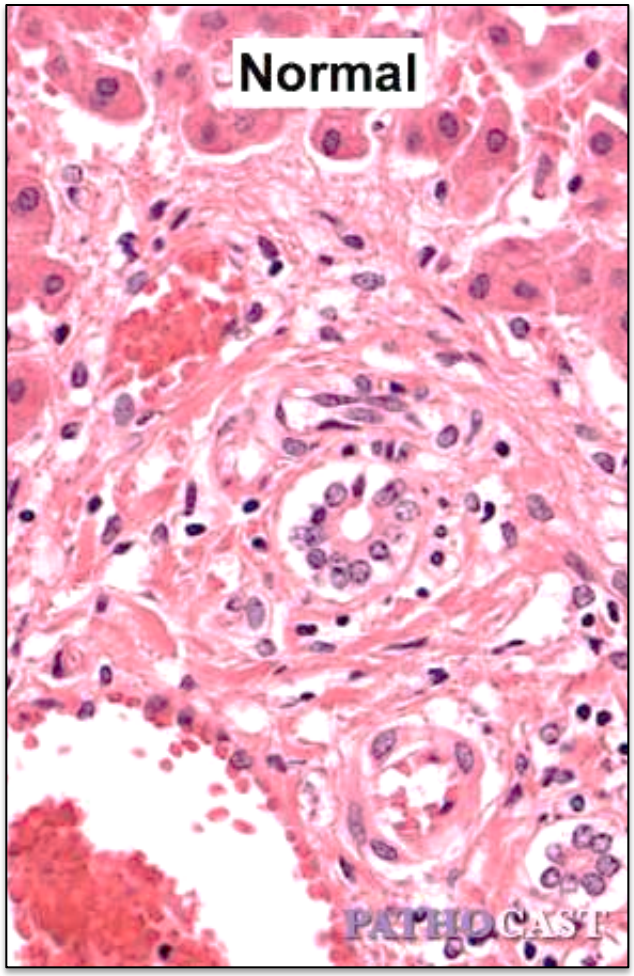


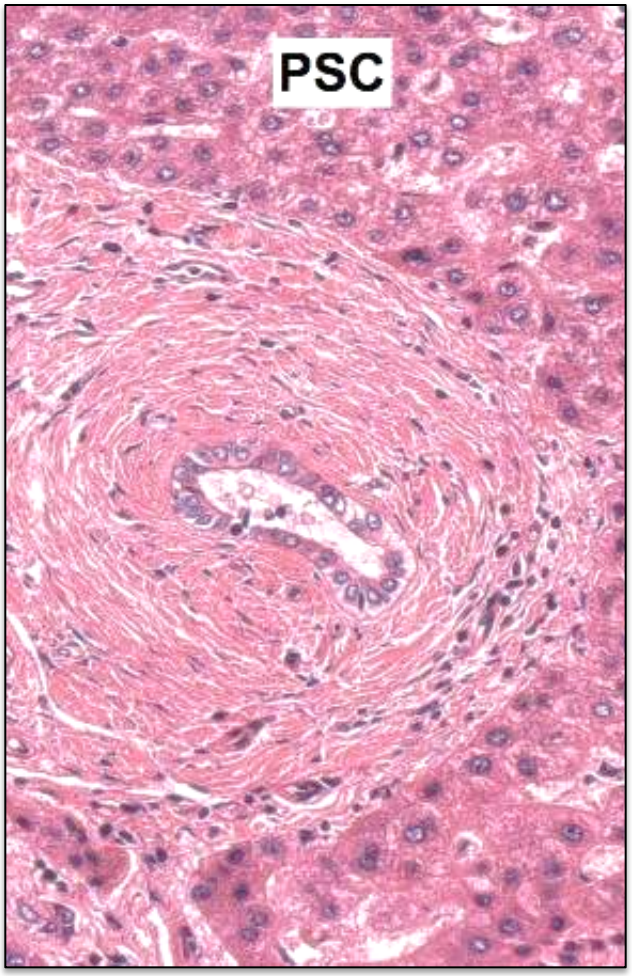
Moderate interface hepatitis

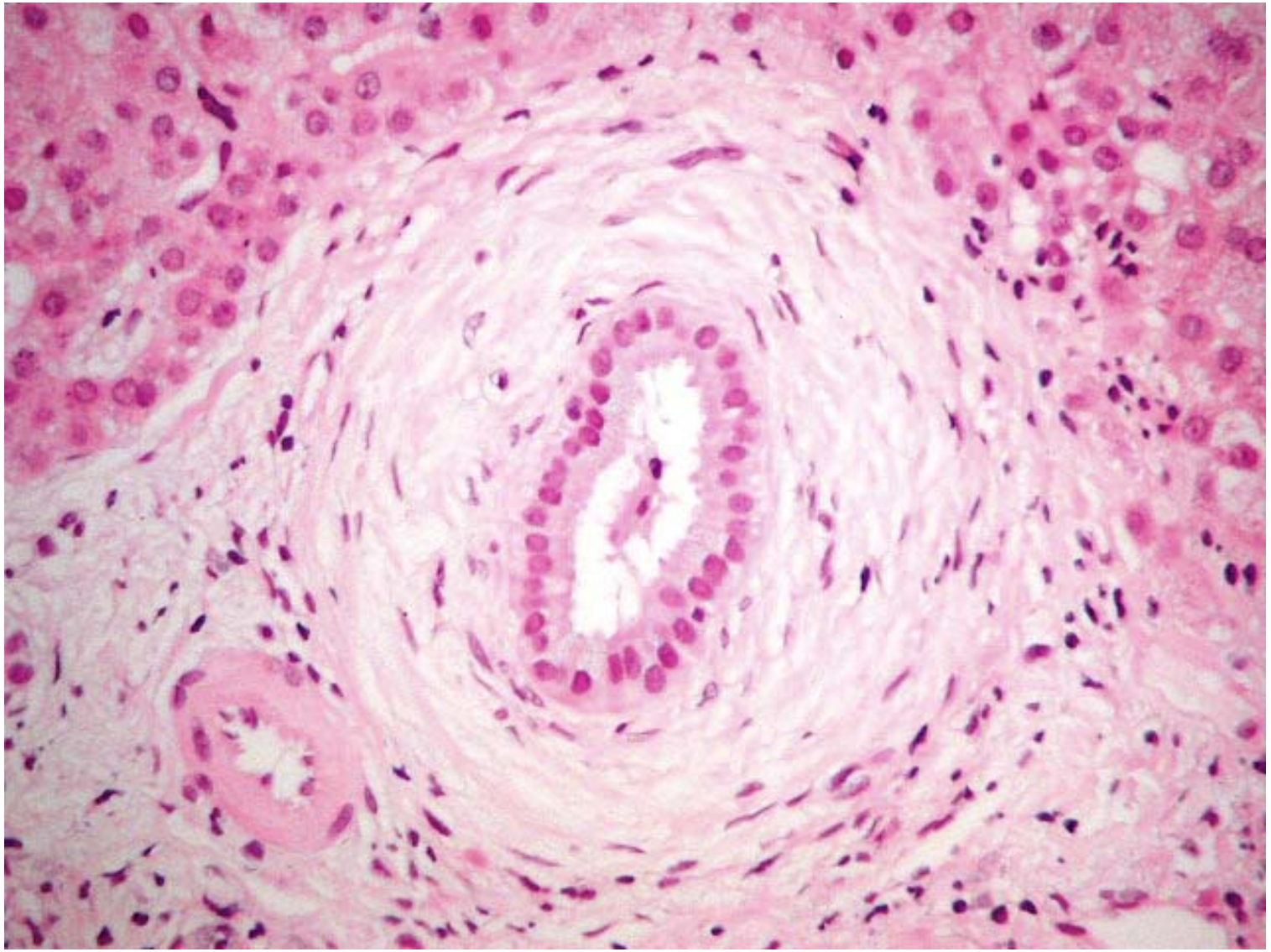
PSC

- PSC is a chronic biliary disease characterized by inflammation, strictures and saccular dilatation in the biliary tree.
- Although PSC primarily affects large bile ducts, any part of the biliary tree may be affected.
- Approximately 6% of cases show only intrahepatic biliary involvement (i.e., small duct PSC).
- By definition, the disease is idiopathic (i.e., primary) and does not result from other causes of cholangitis.

Histological hallmark of PSC
"onion-skinning fibrosis" around bile ducts

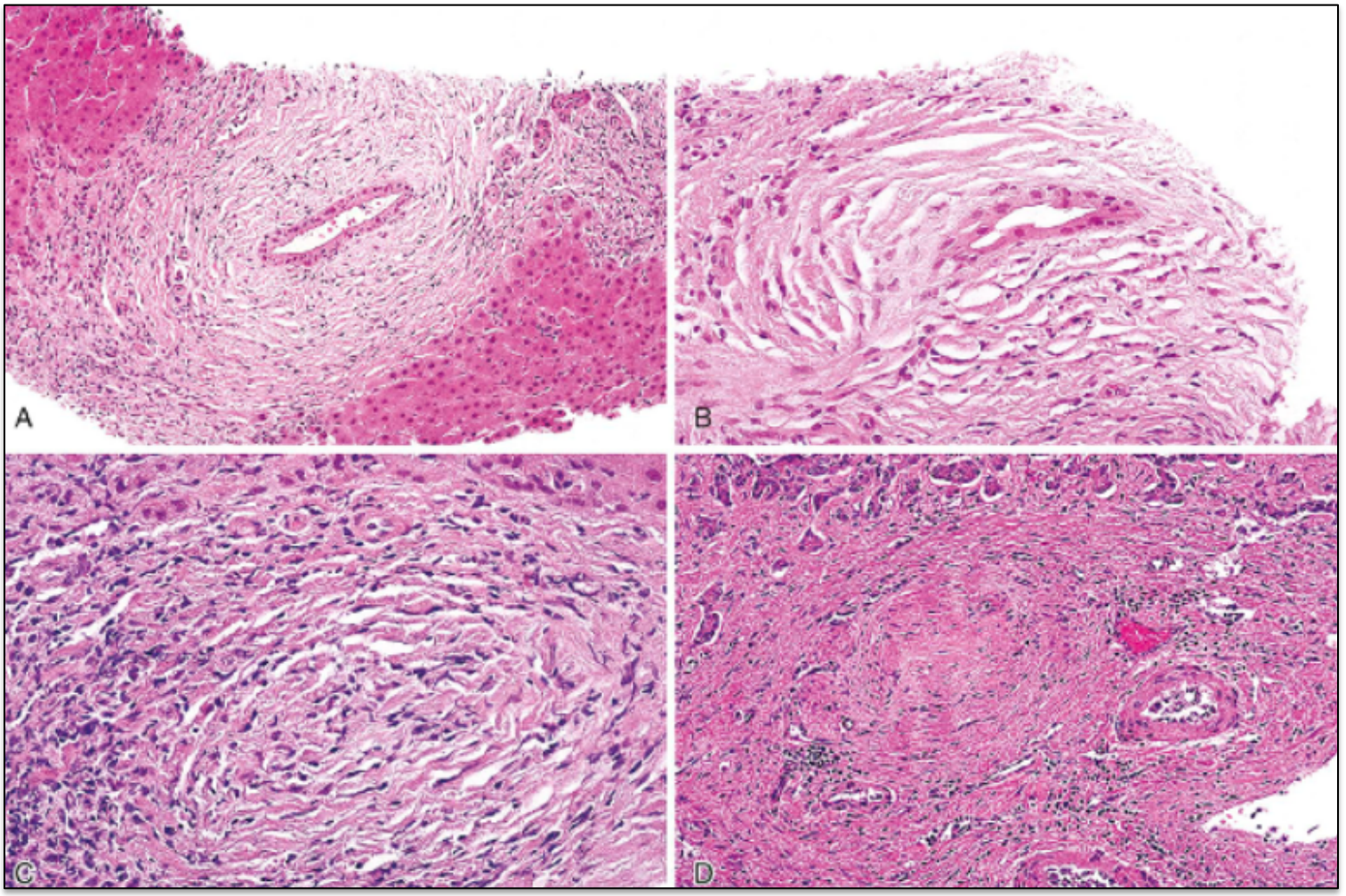




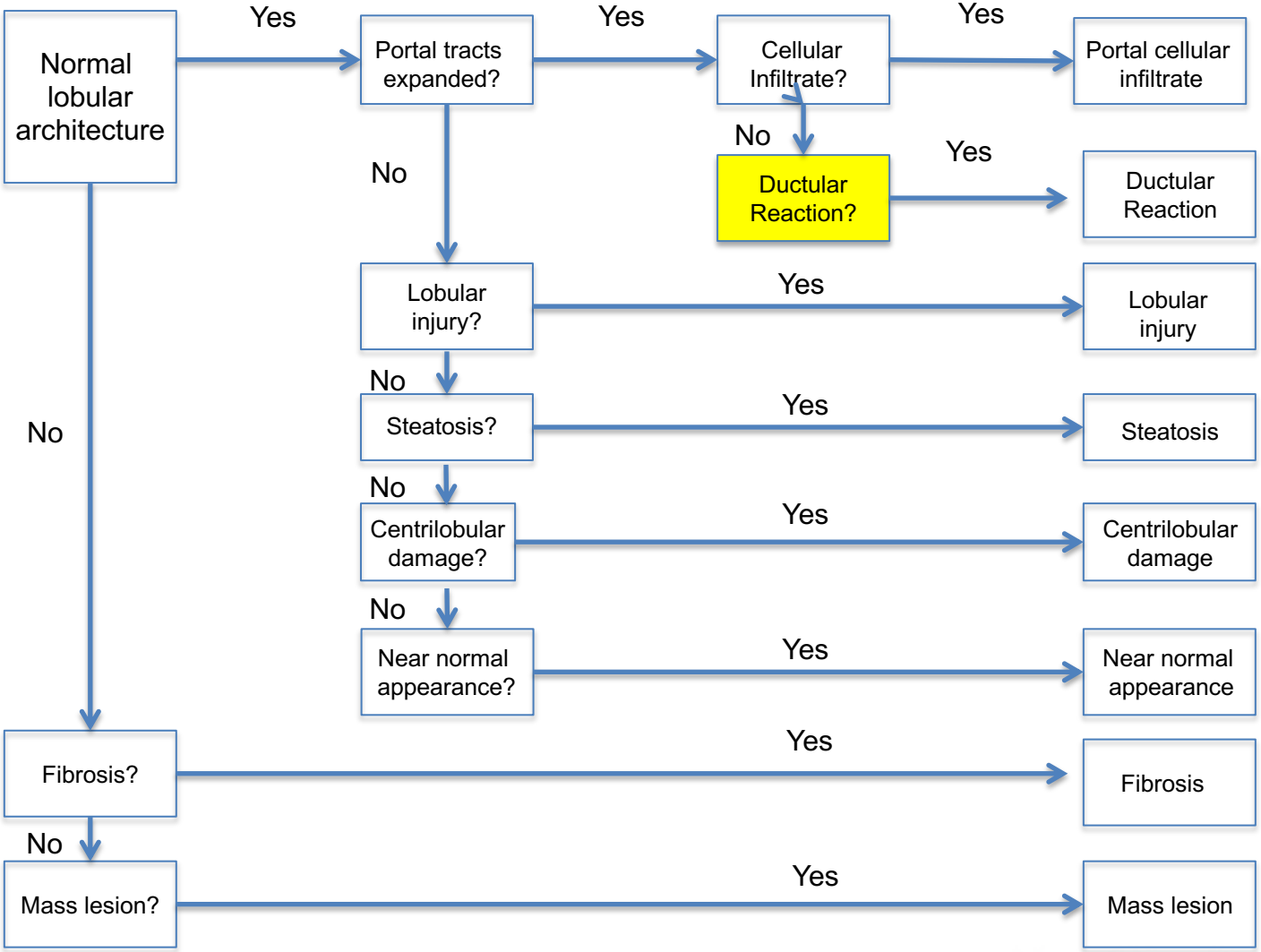


concentric periductal fibrosis

Histological hallmark of PSC



Algorithmic approach
Identification of major pattern of injury



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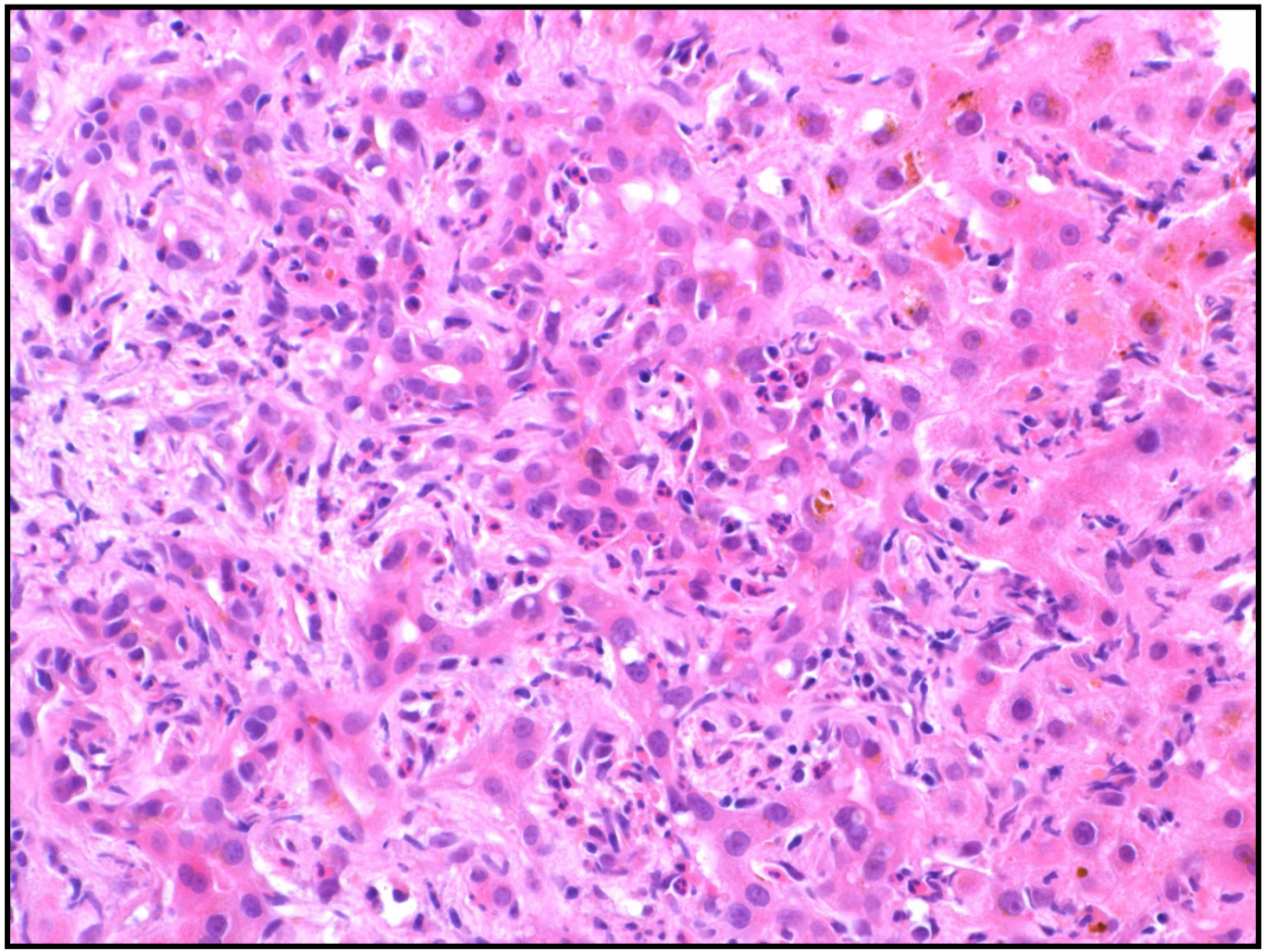
DUCTULAR REACTION

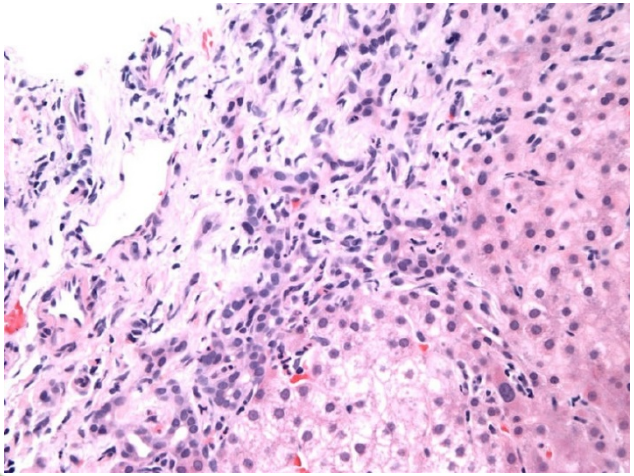
(proliferation of bile ductules at the interface of portal tracts and parenchyma associated with neutrophils)



DUCTULAR REACTION

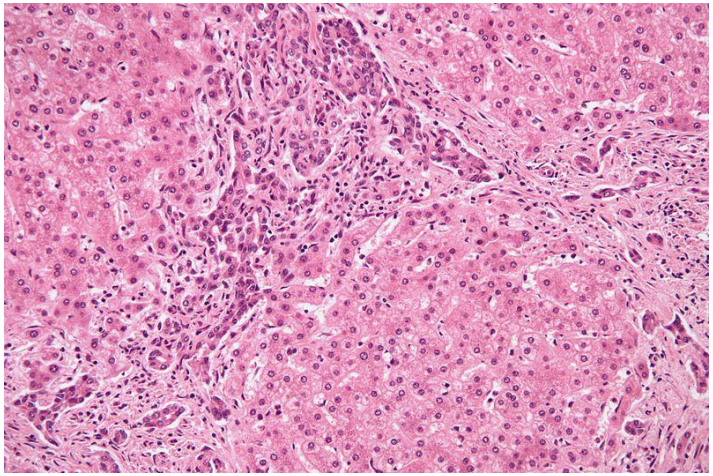
ACUTE FORMS

- Acute bile duct obstruction
- Acute hepatitis with submassive/massive hepatic necrosis

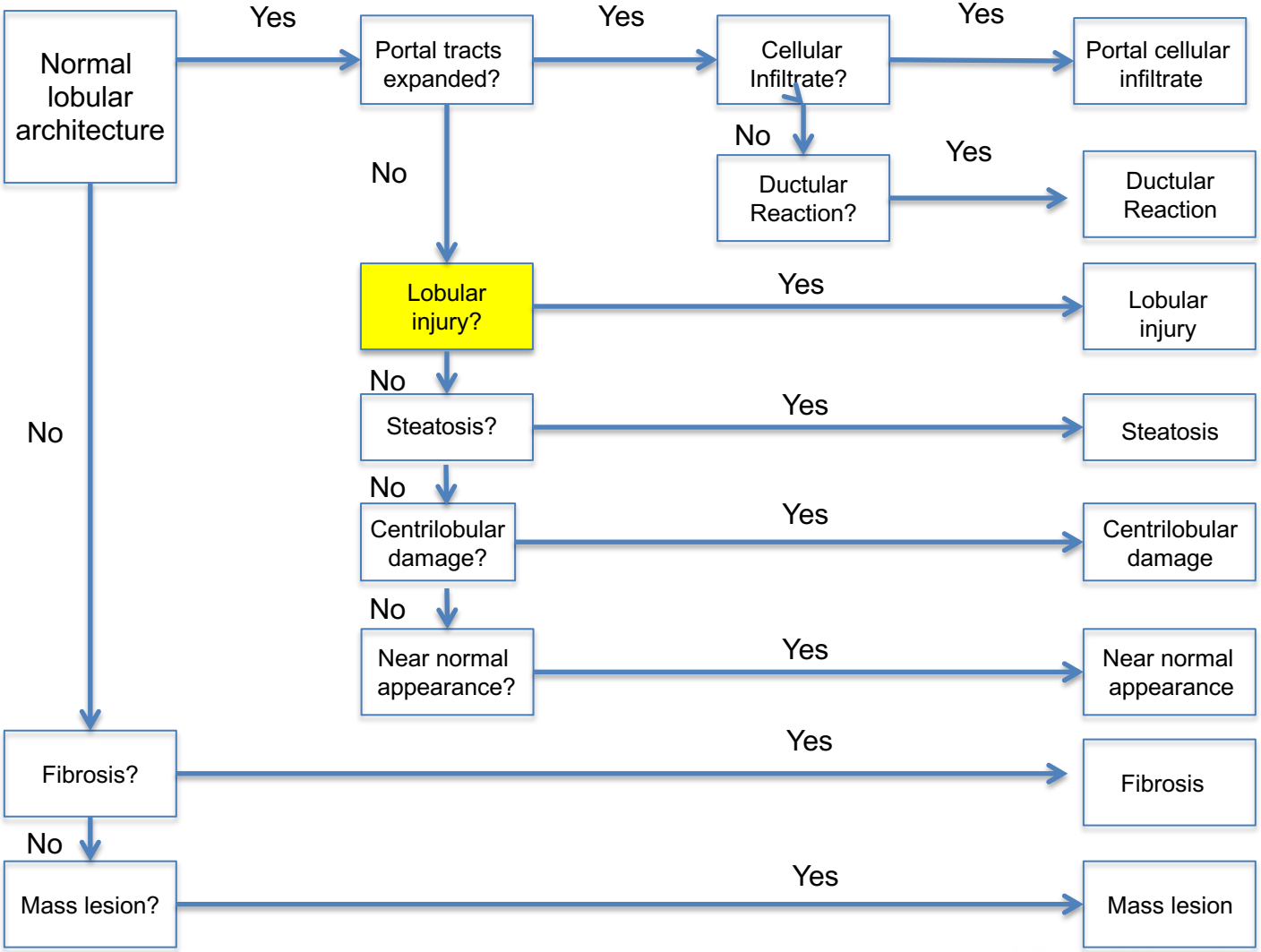


CHRONIC FORMS

- Chronic bile duct obstruction (PBC/PSC)
- Mass lesions (FNH, HCC, HCA, space occupying lesions)



Algorithmic approach
Identification of major pattern of injury



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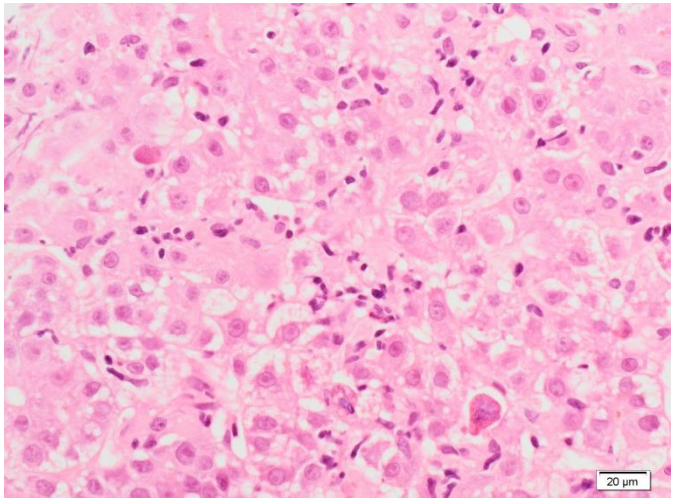
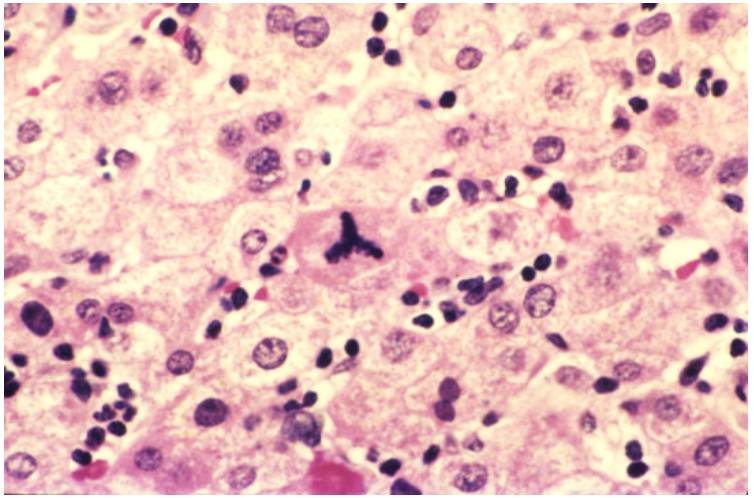
PROMINENT LOBULAR INFLAMMATION

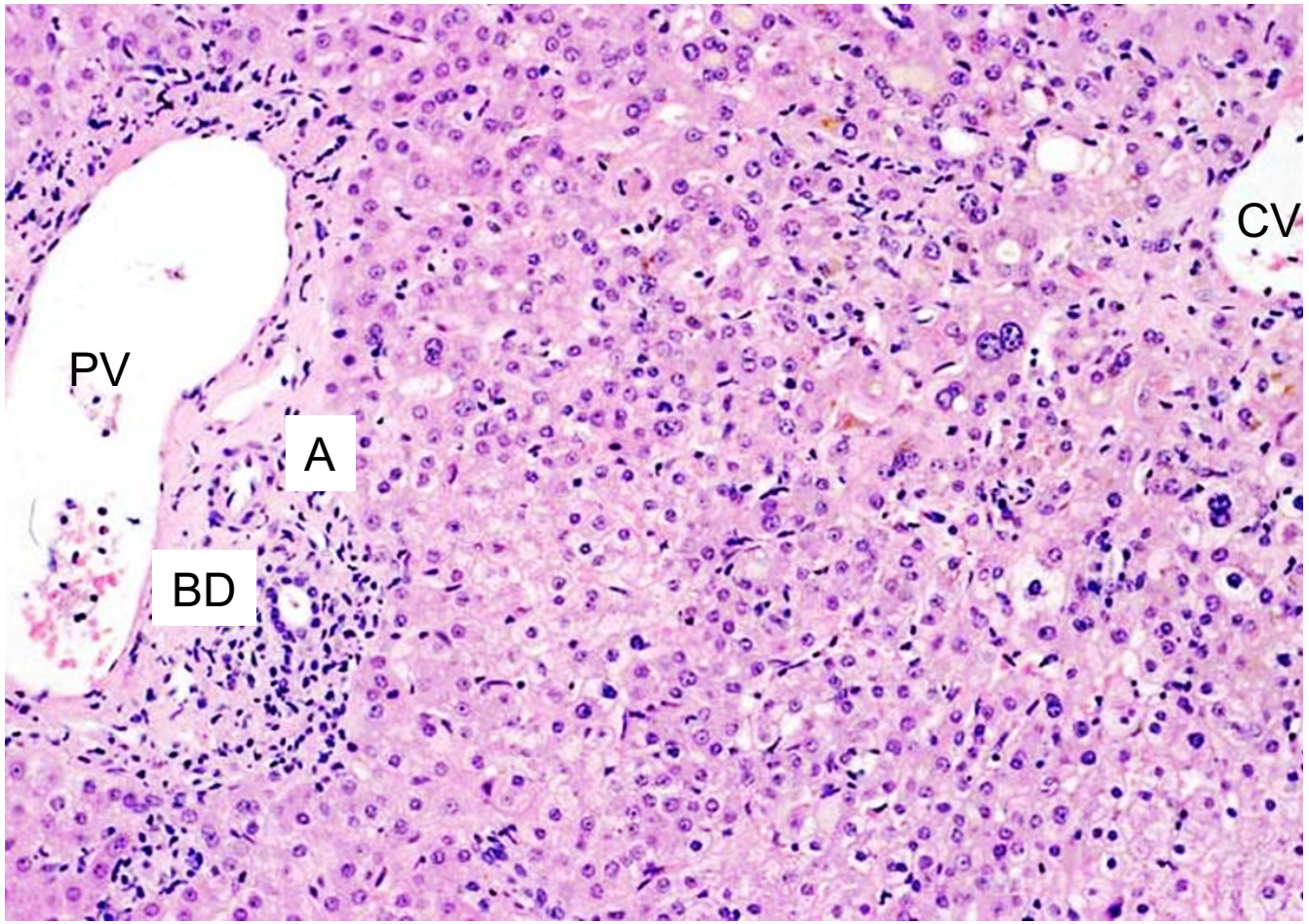
- Non-sinusoidal pattern
  - Acute hepatitis (viruses, drug, AIH)
  - Recent/subacute hepatitis



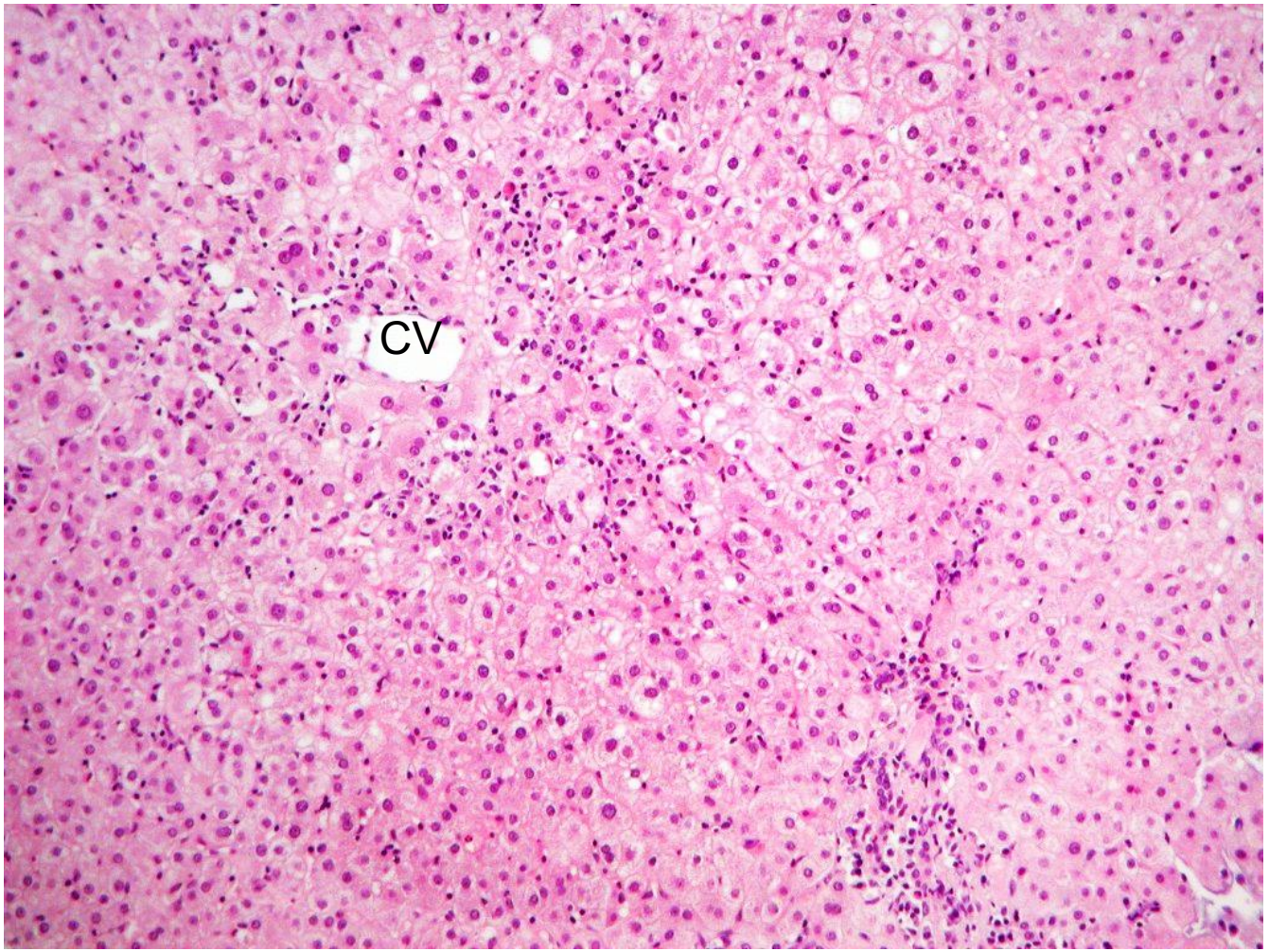
- Sinusoidal pattern
  - EBV
  - Extramedullary hematopoiesis
  - Lymphoma/Leukemia



PROMINENT LOBULAR INFLAMMATION NON SINUSOIDAL PATTERN



PROMINENT LOBULAR INFLAMMATION NON SINUSOIDAL PATTERN



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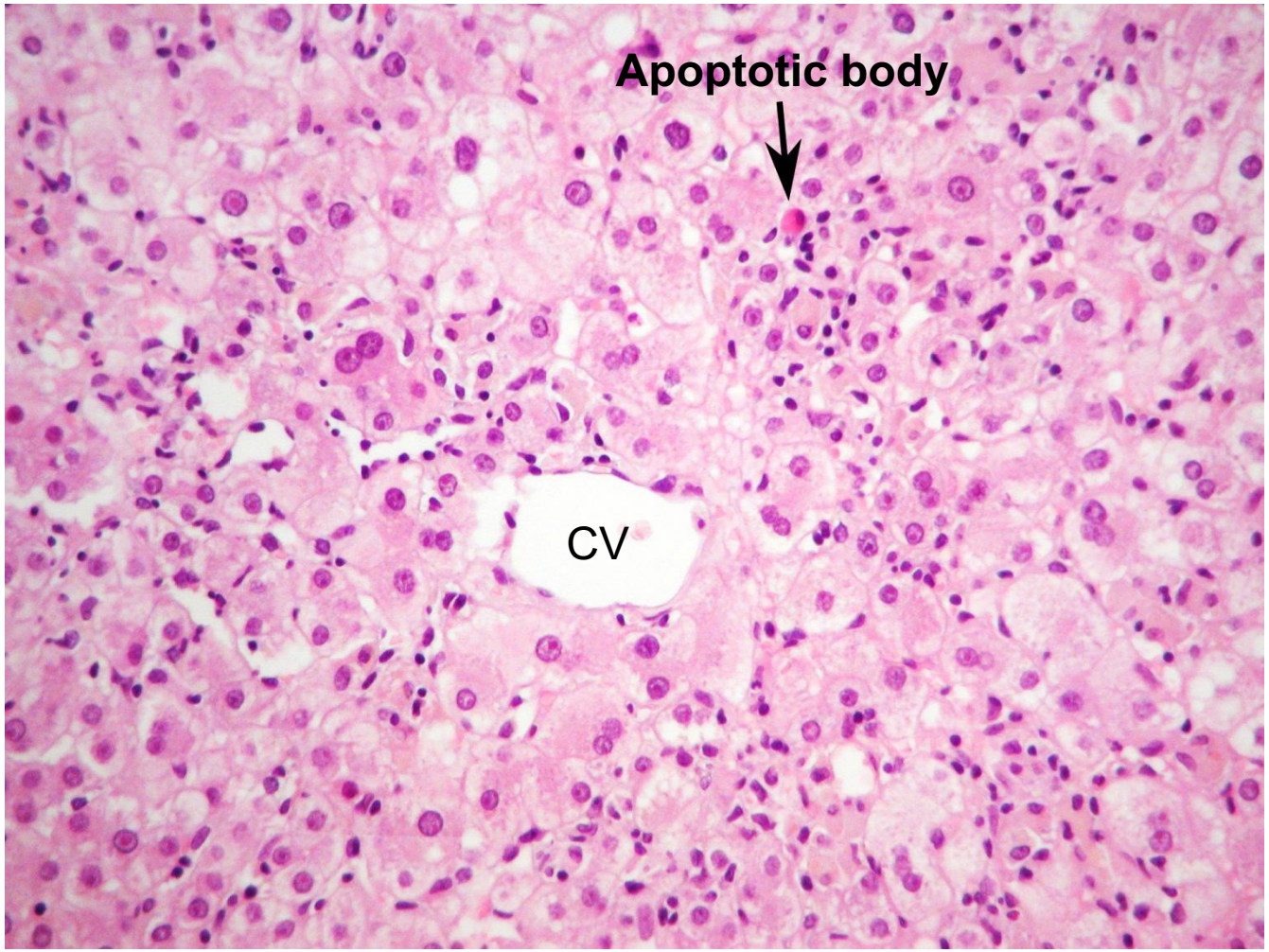
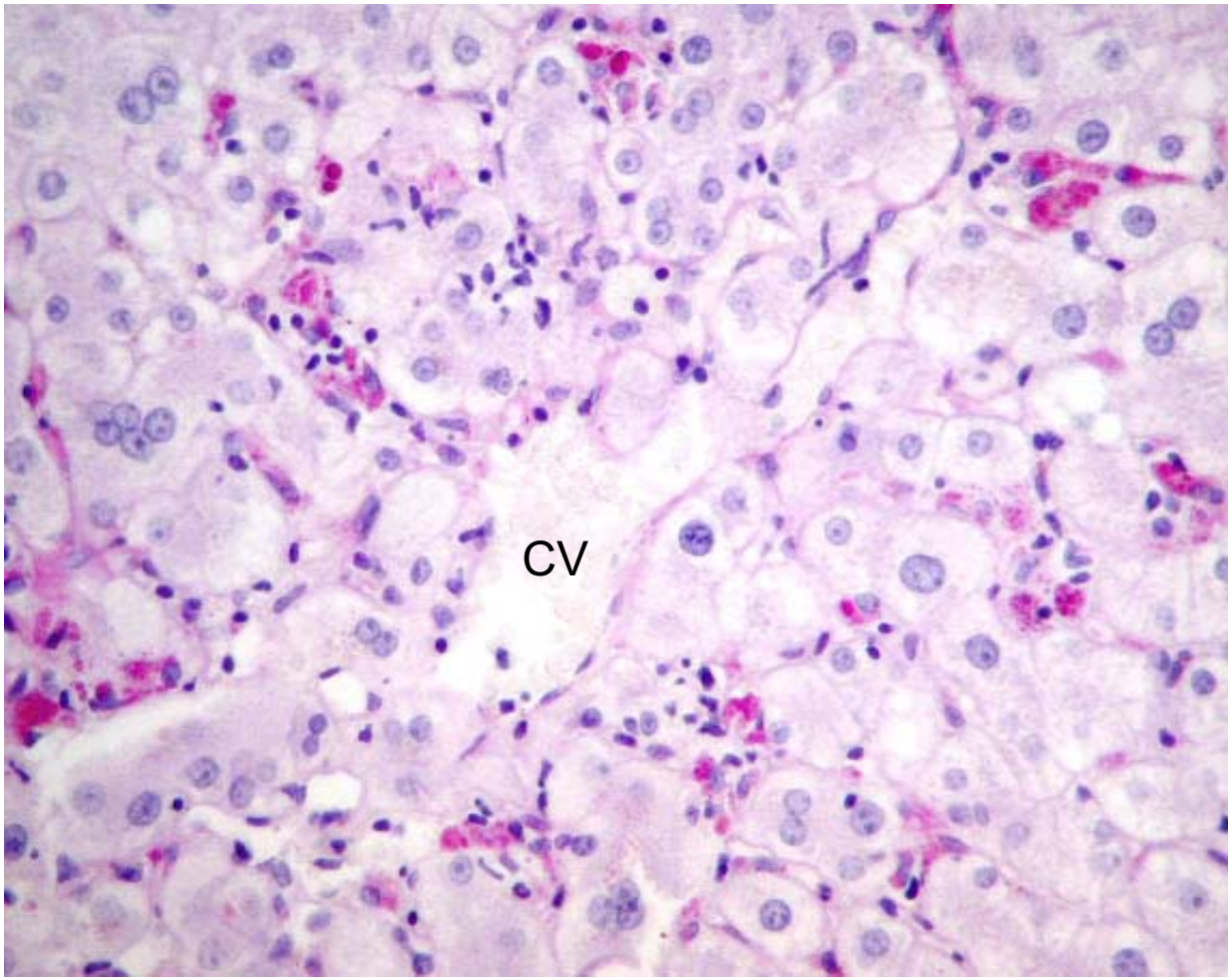
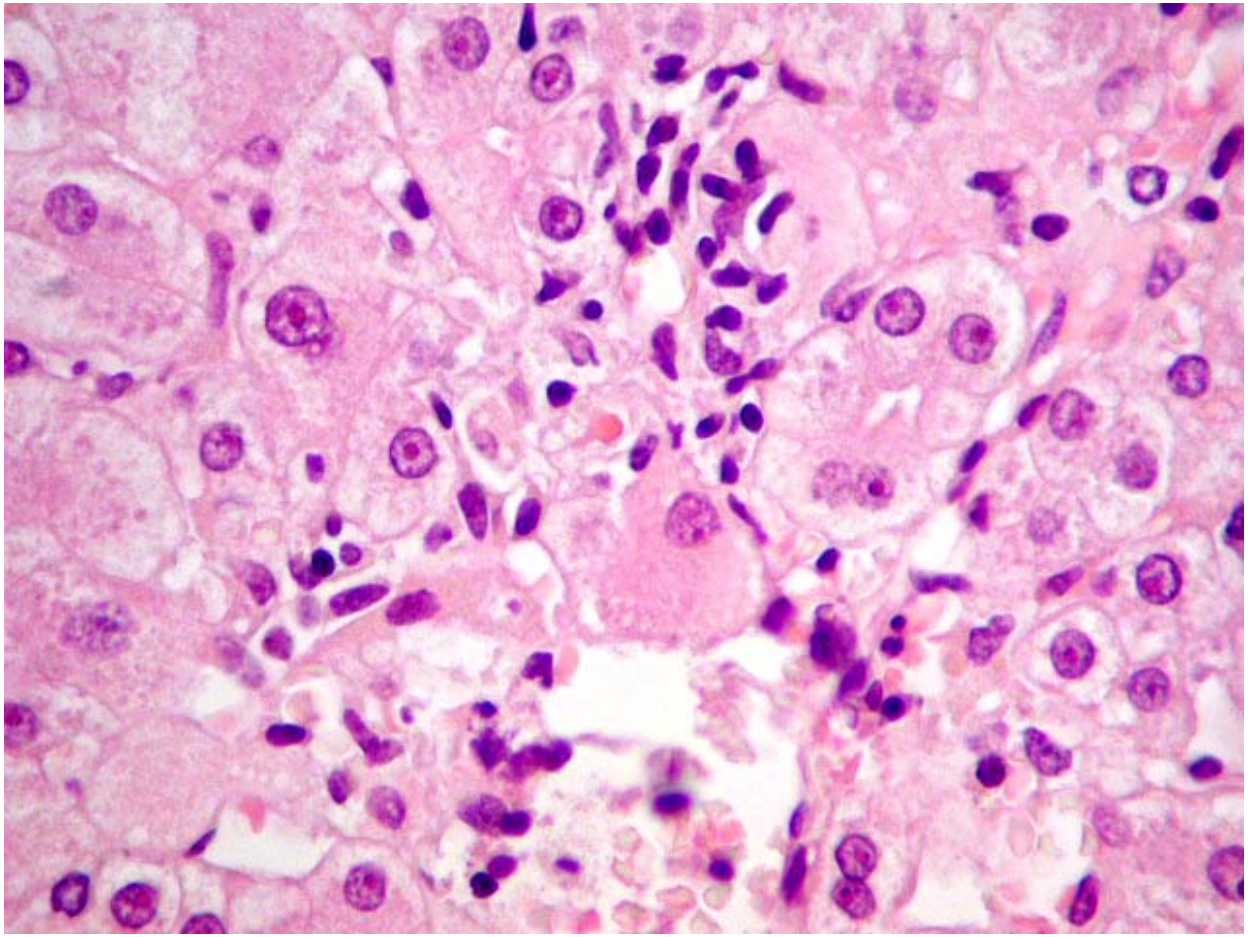


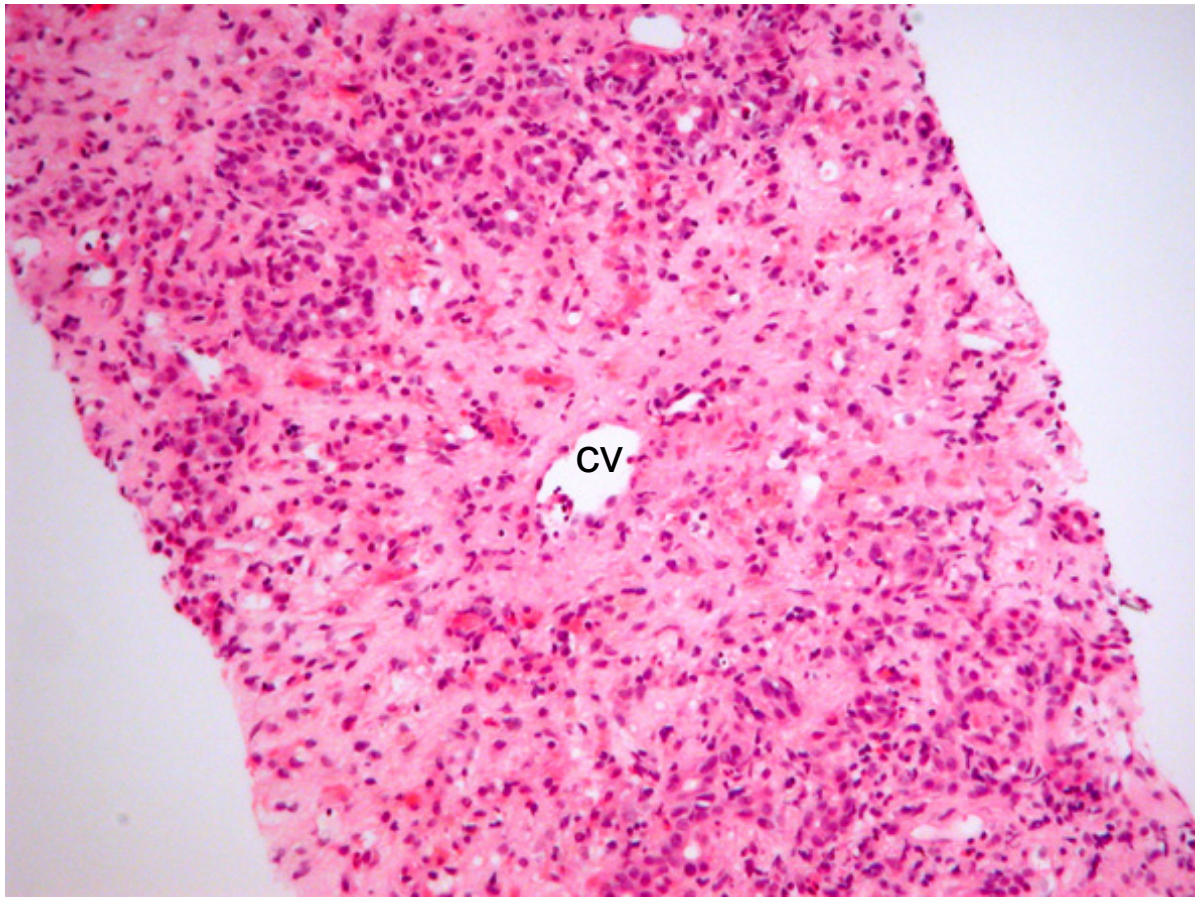
PROMINENT LOBULAR INFLAMMATION NON SINUSOIDAL PATTERN - DPAS



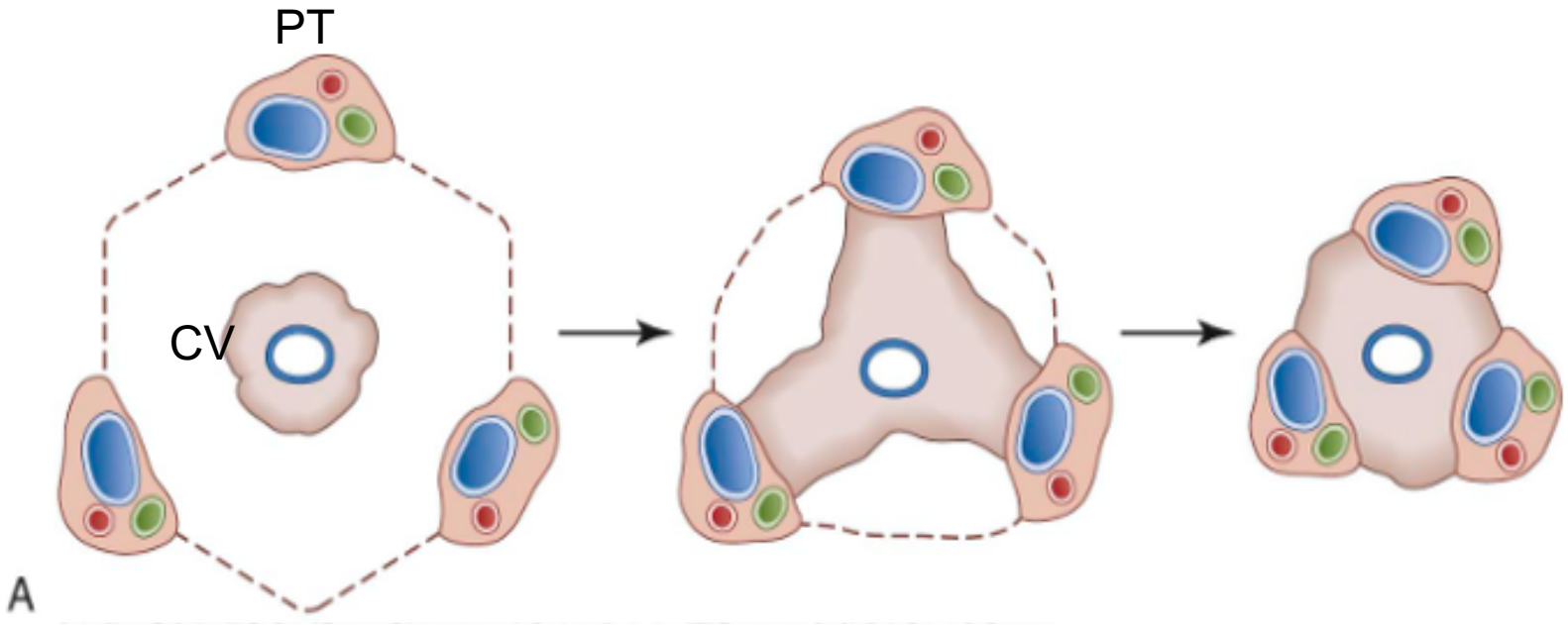
Spotty necrosis



Confluent necrosis



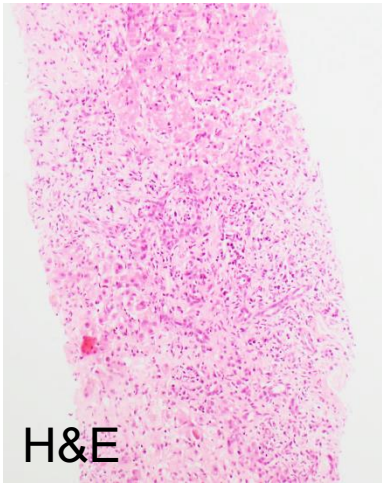
Confluent necrosis in liver biopsy specimens

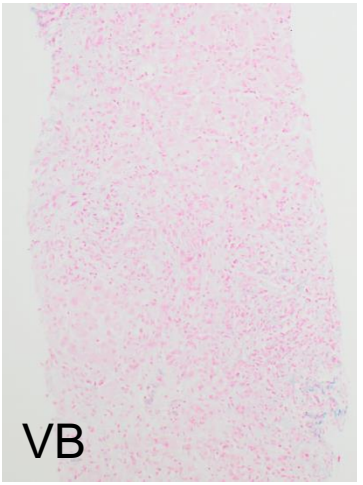


Confluent necrosis may result in varying degrees of injury: perivenular dropout of hepatocytes (left), bridging necrosis (middle), and parenchymal collapse (right).

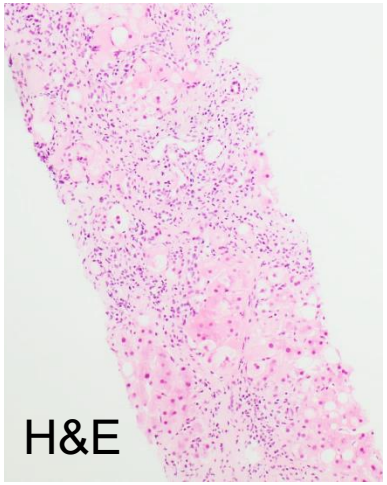
Odze and Goldblum Surgical Pathology of the GI Tract

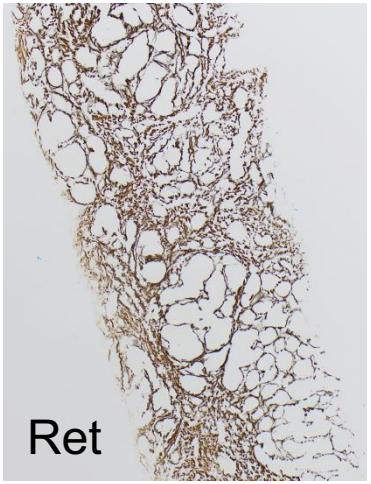
Acute collapse vs cirrhosis

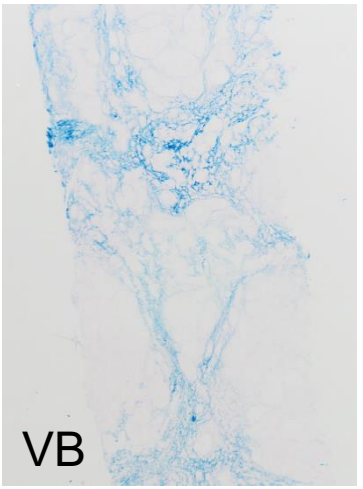




Severe acute hepatitis with submassive necrosis: nodular appearance on H-E and reticulin, but negative on VB

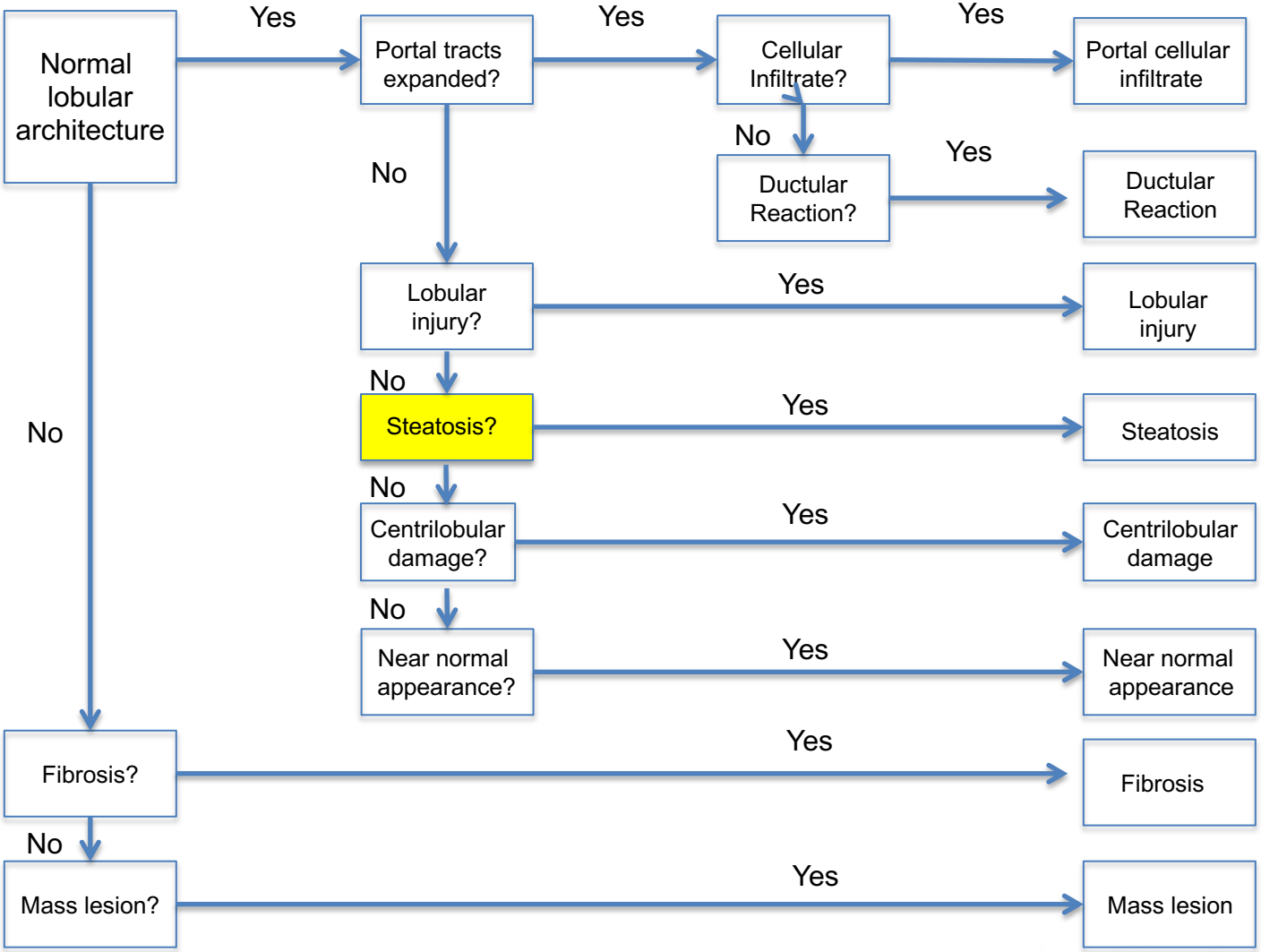






cryptogenic cirrhosis: nodular appearance with VB+ in fibrous septa

Algorithmic approach
Identification of major pattern of injury



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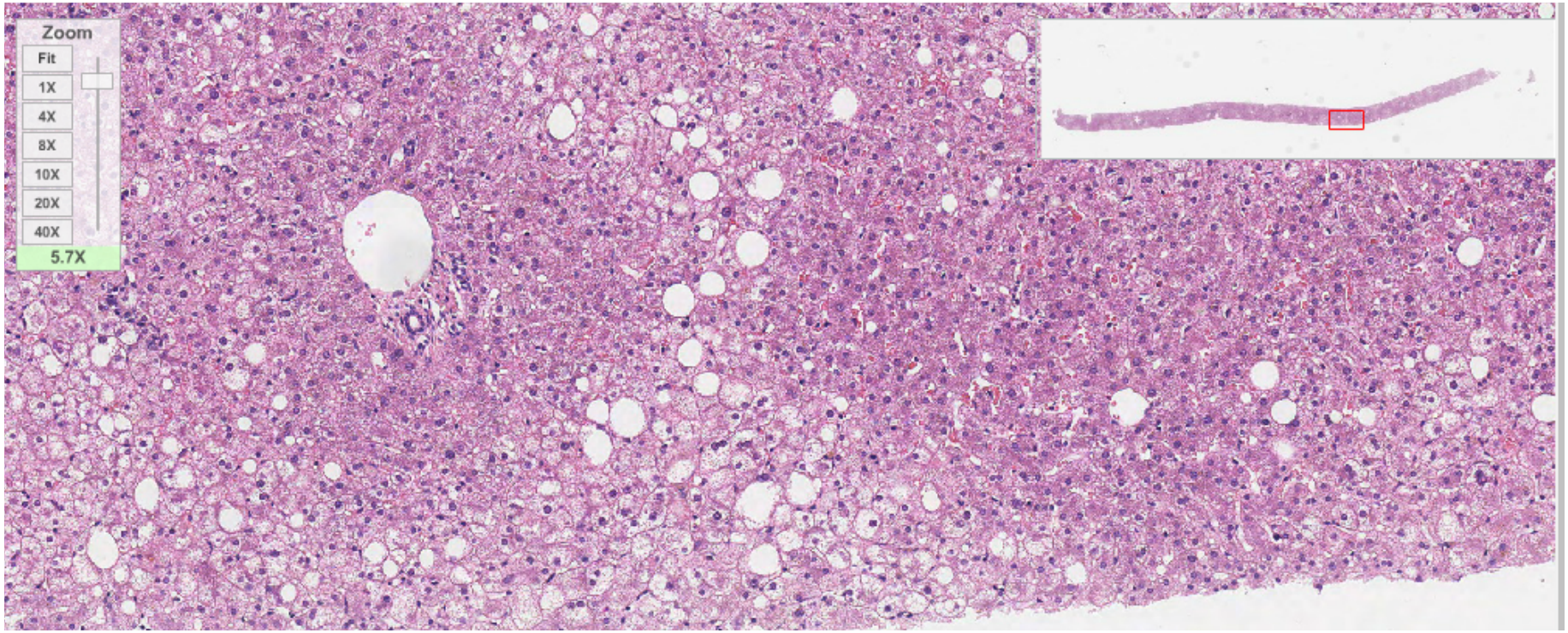
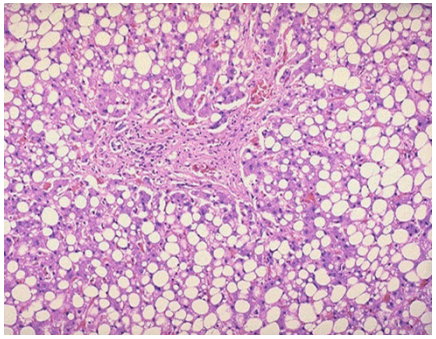
Fatty Liver Disease

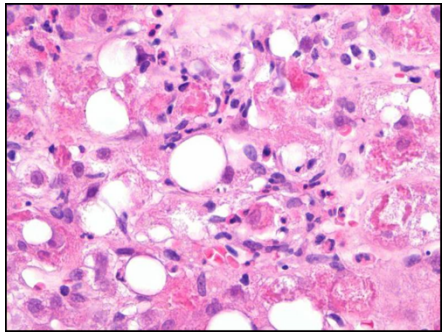


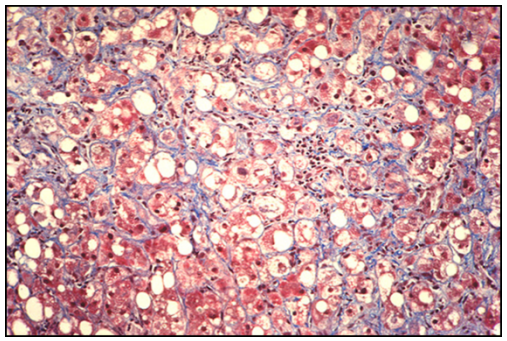
Histology in Fatty Liver Disease

FATY LIVER EVALUATION

- Assess steatosis
- Assess steatohepatitis
- Assess steatofibrosis
- Assess causes
  - ALD VS NAFLD







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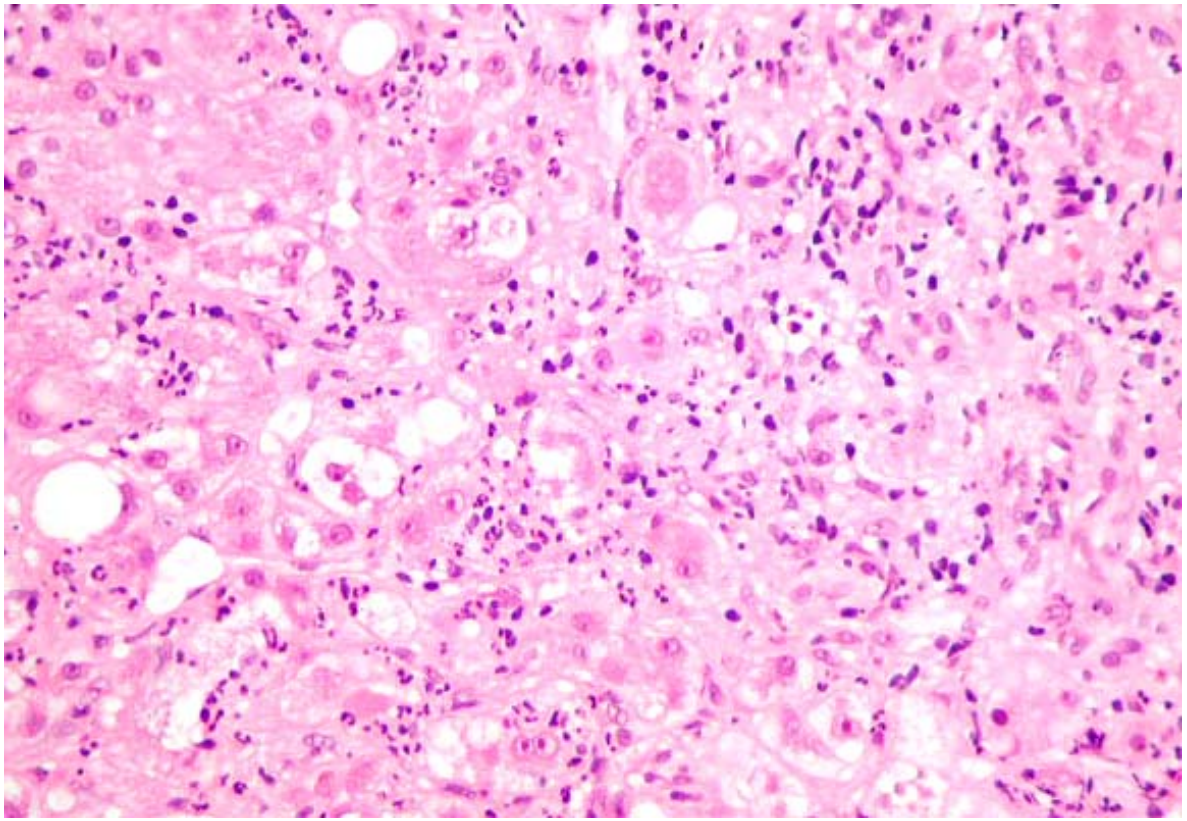
Steatohepatitis

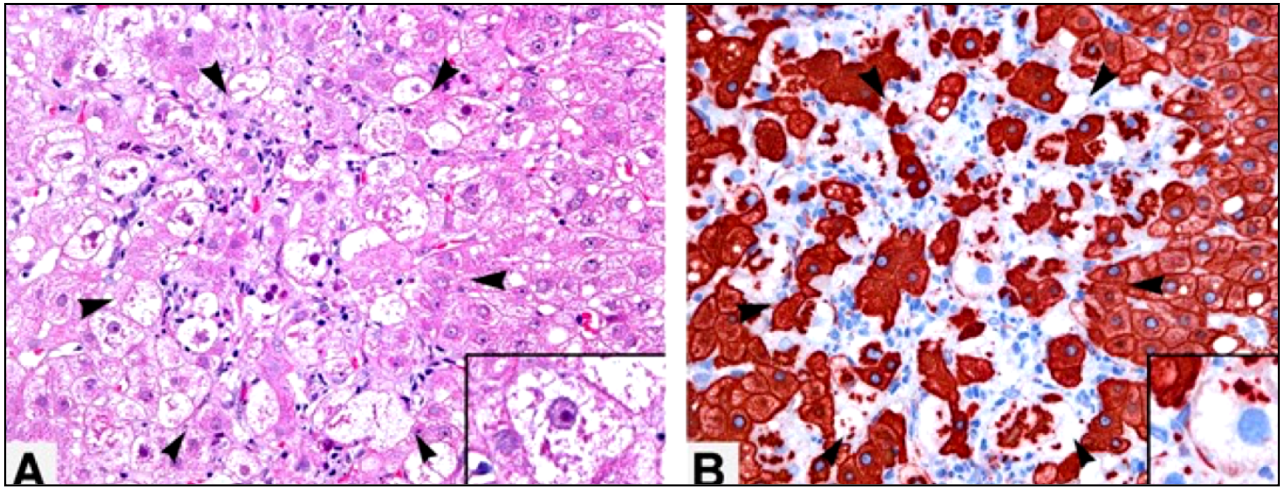


Active steatohepatitis:

- Steatosis
- Hepatocyte ballooning
- Mallory Bodies
- Neutrophil-rich parenchymal inflammation

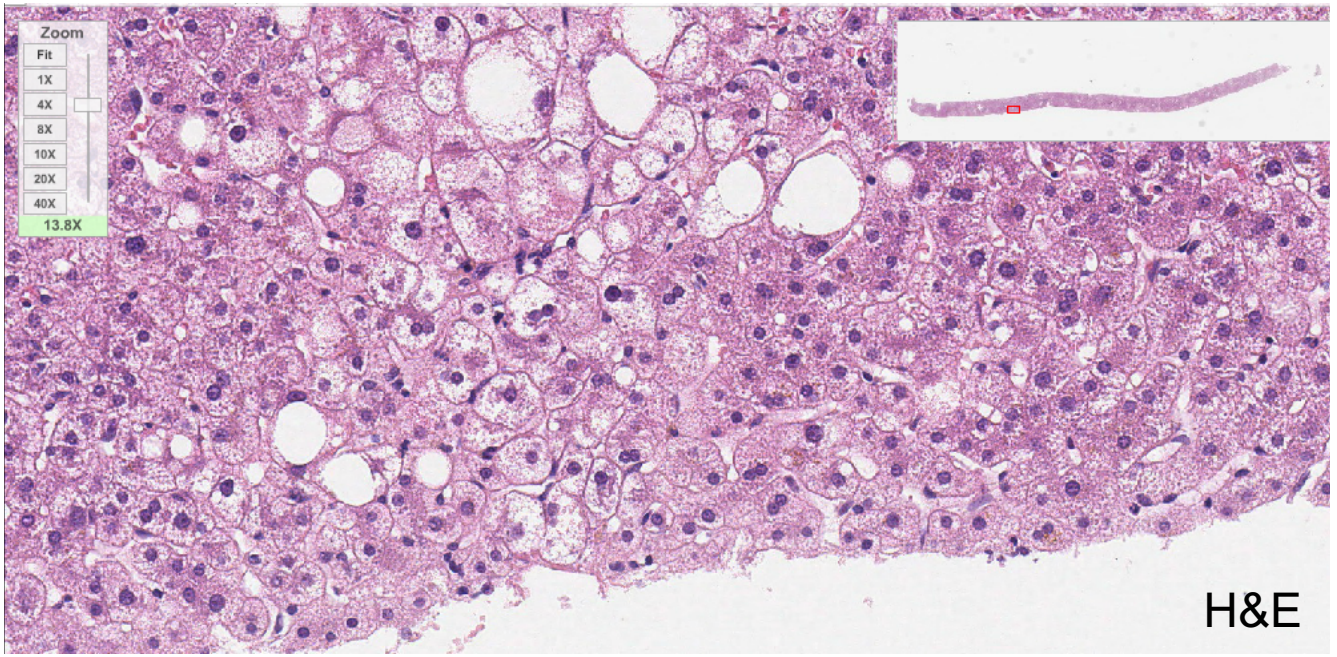
Hepatocyte ballooning

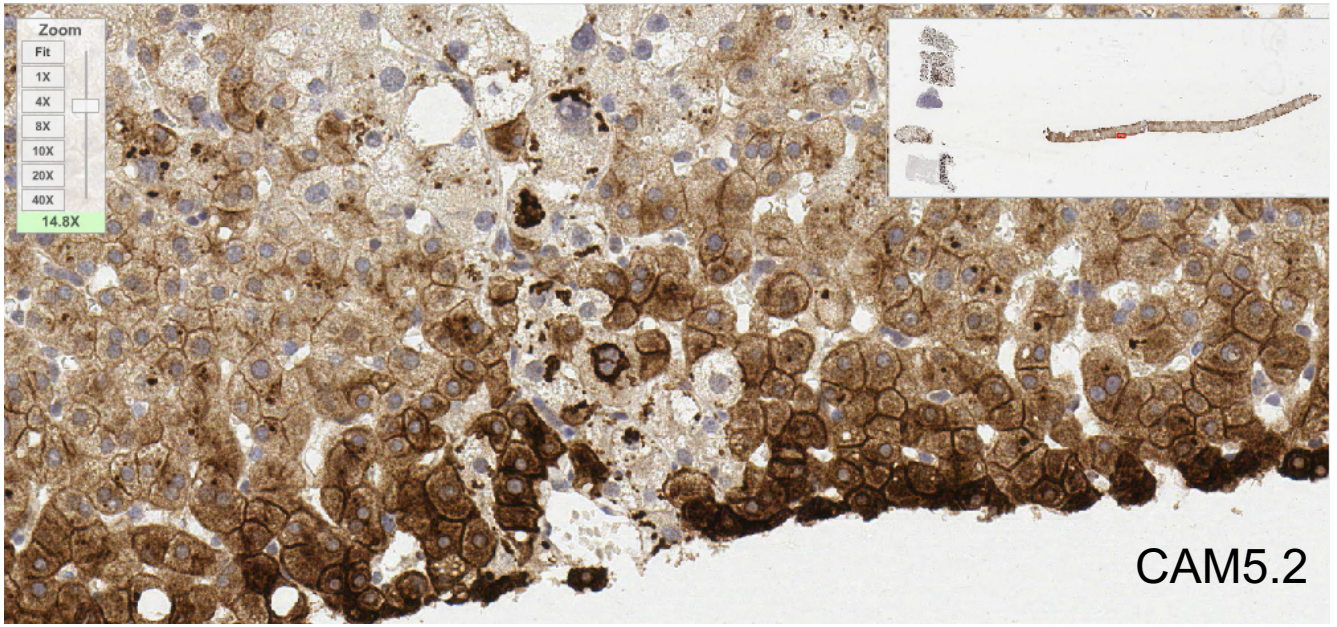
“Ballooning” is a frequently used yet ill-defined term in liver morphology indicating hepatocyte degeneration associated with enlargement, swelling, rounding and characteristic reticulated cytoplasm.



The ballooned hepatocytes lack CK8/18 immunostaining (inset with higher magnification), whereas Mallory bodies are keratin positive.

C. Lackner et al. / Journal of Hepatology 48 (2008) 821–828





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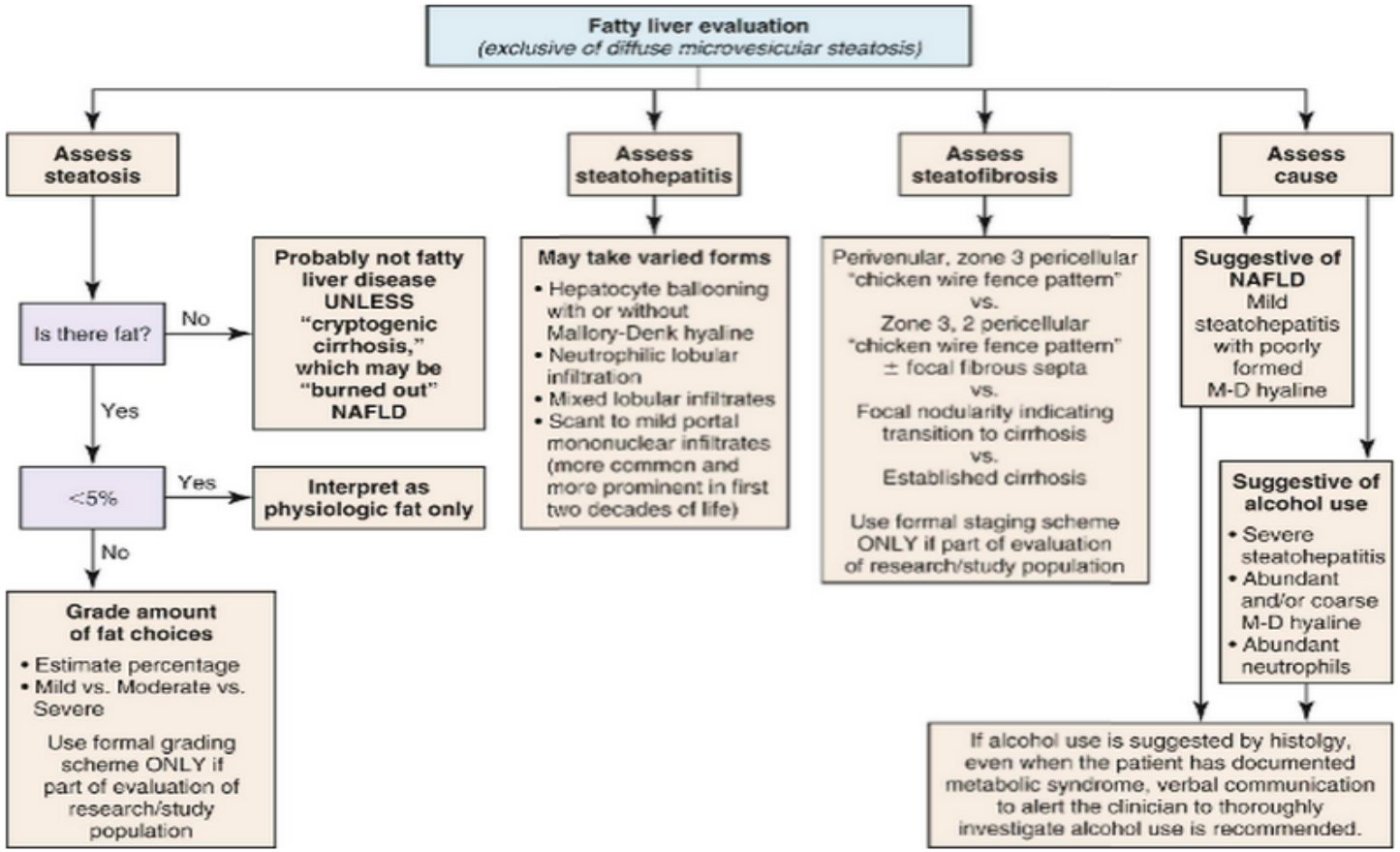
FATTY LIVER EVALUATION



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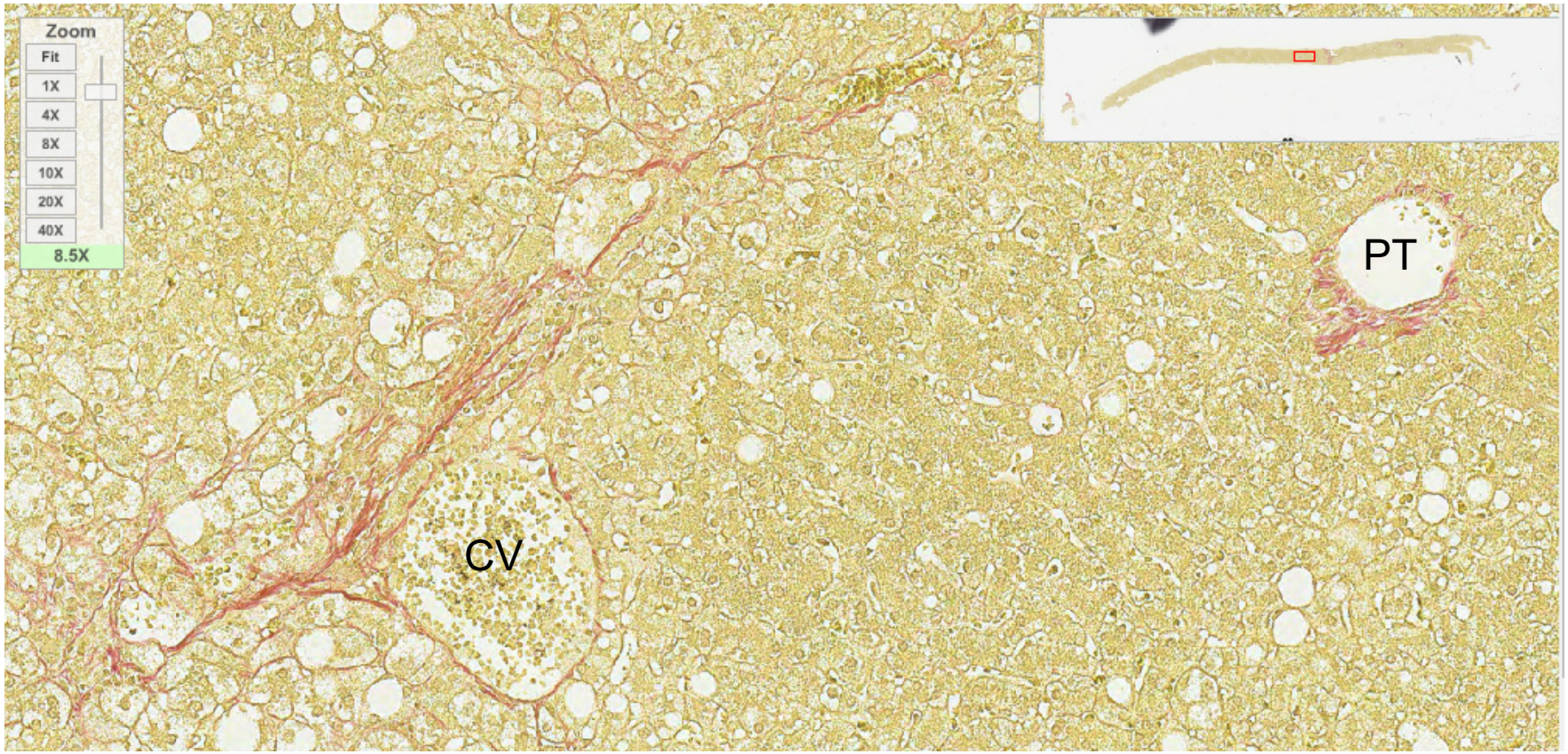
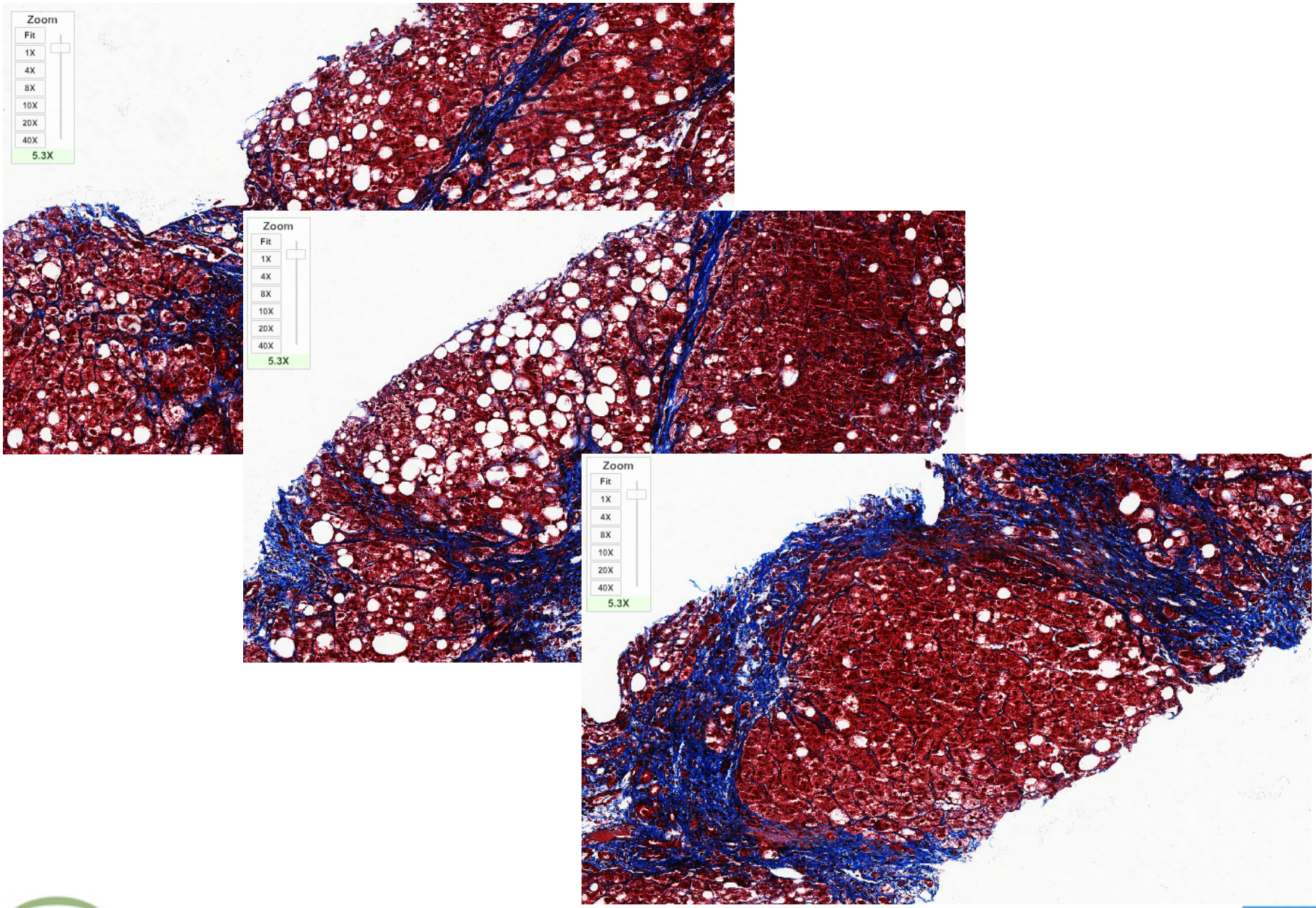
Steatofibrosis





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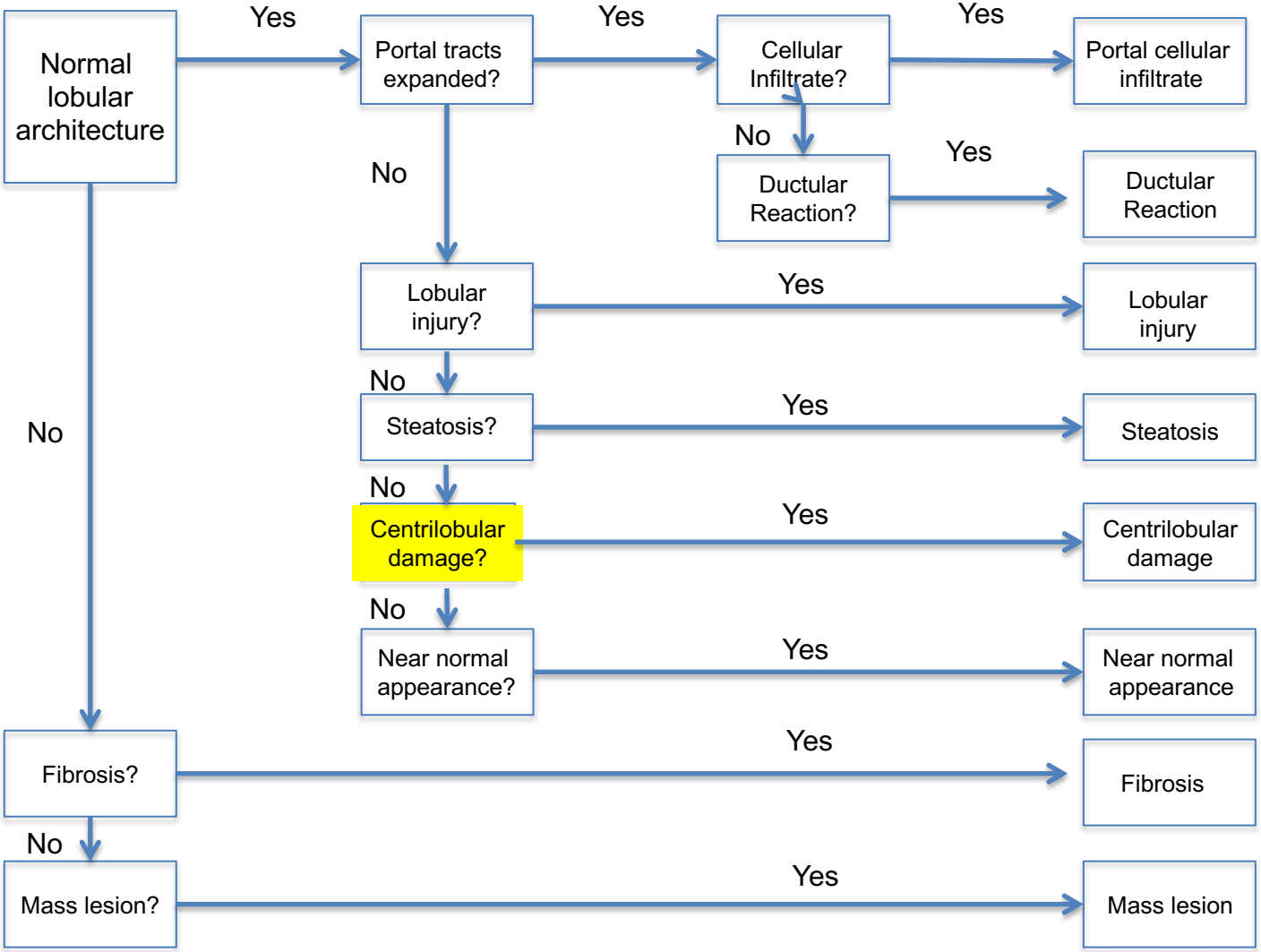
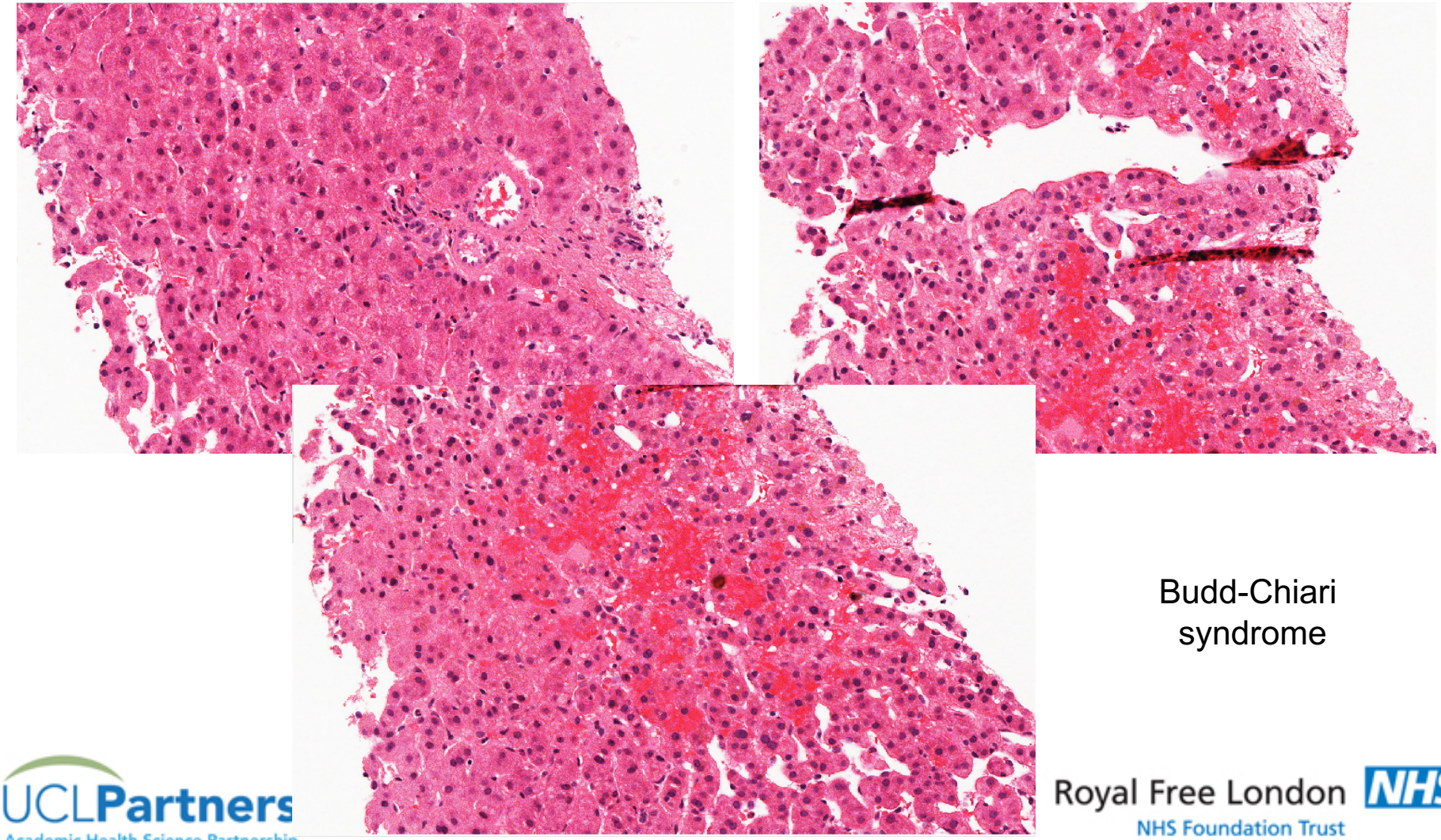
Algorithmic approach
Identification of major pattern of injury

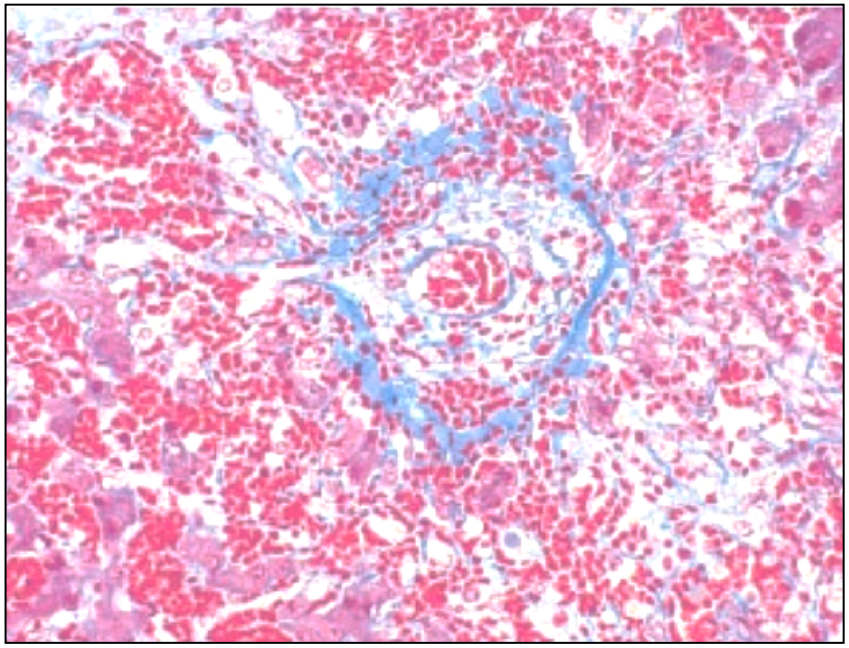


PREDOMINANTLY CENTRILOBULAR INJURY

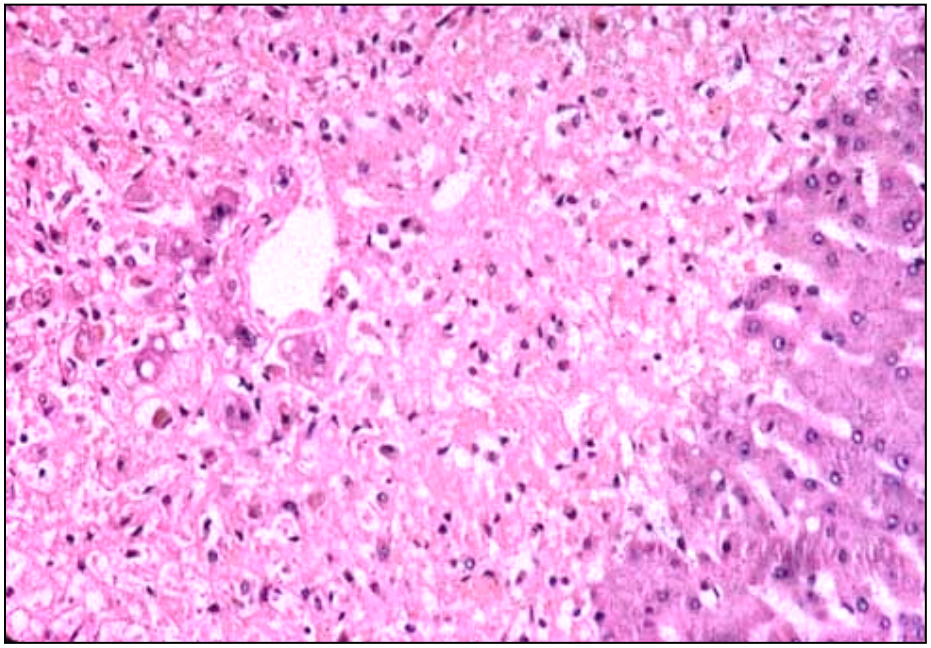


Budd-Chiari syndrome

PREDOMINANTLY CENTRILOBULAR INJURY

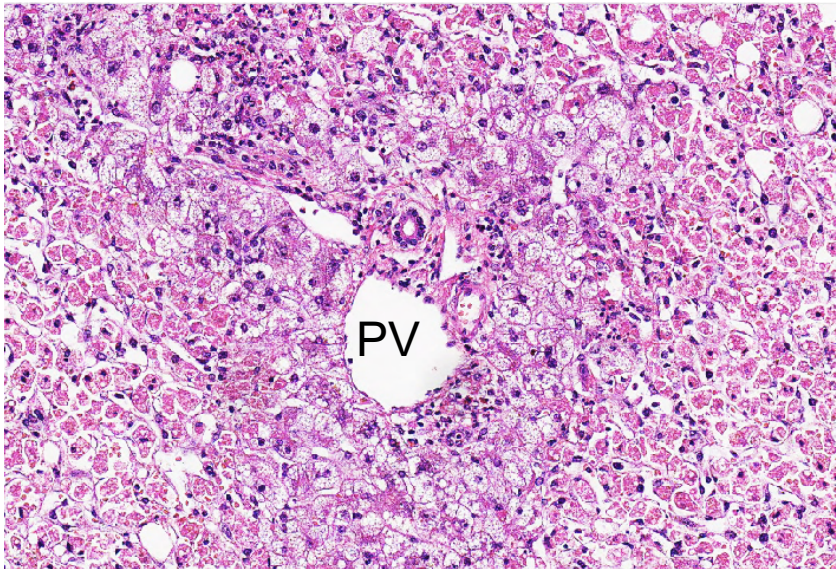


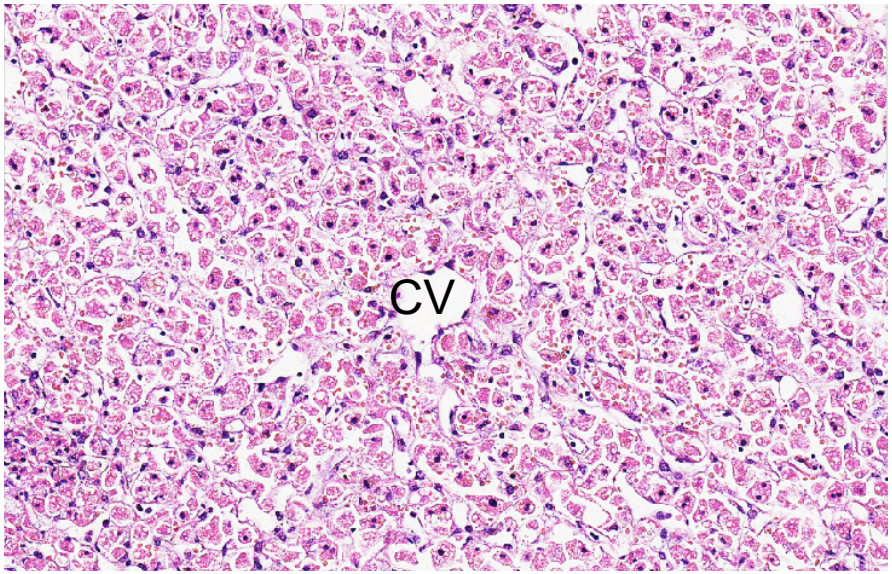
VOD
(myeloablative regimens, oxaliplatin-based chemo)



Ischemia and shock
(heart failure, circulatory shock
from hypovolemia, trauma, sepsis)

PREDOMINANTLY CENTRILOBULAR INJURY





Drug-induced injury
(acetaminophen, cocaine, Amanita phalloides…)

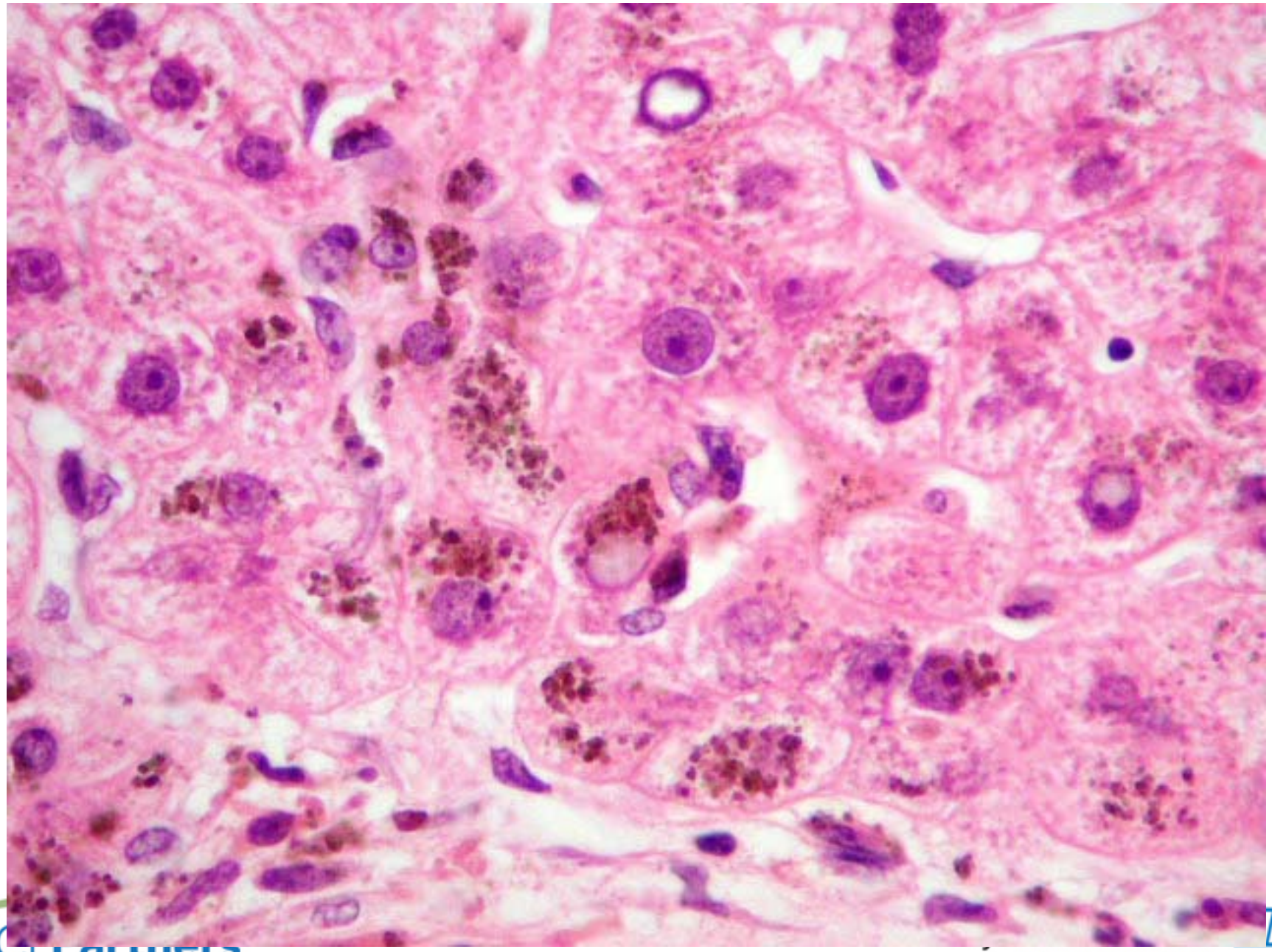
Metabolic disorders

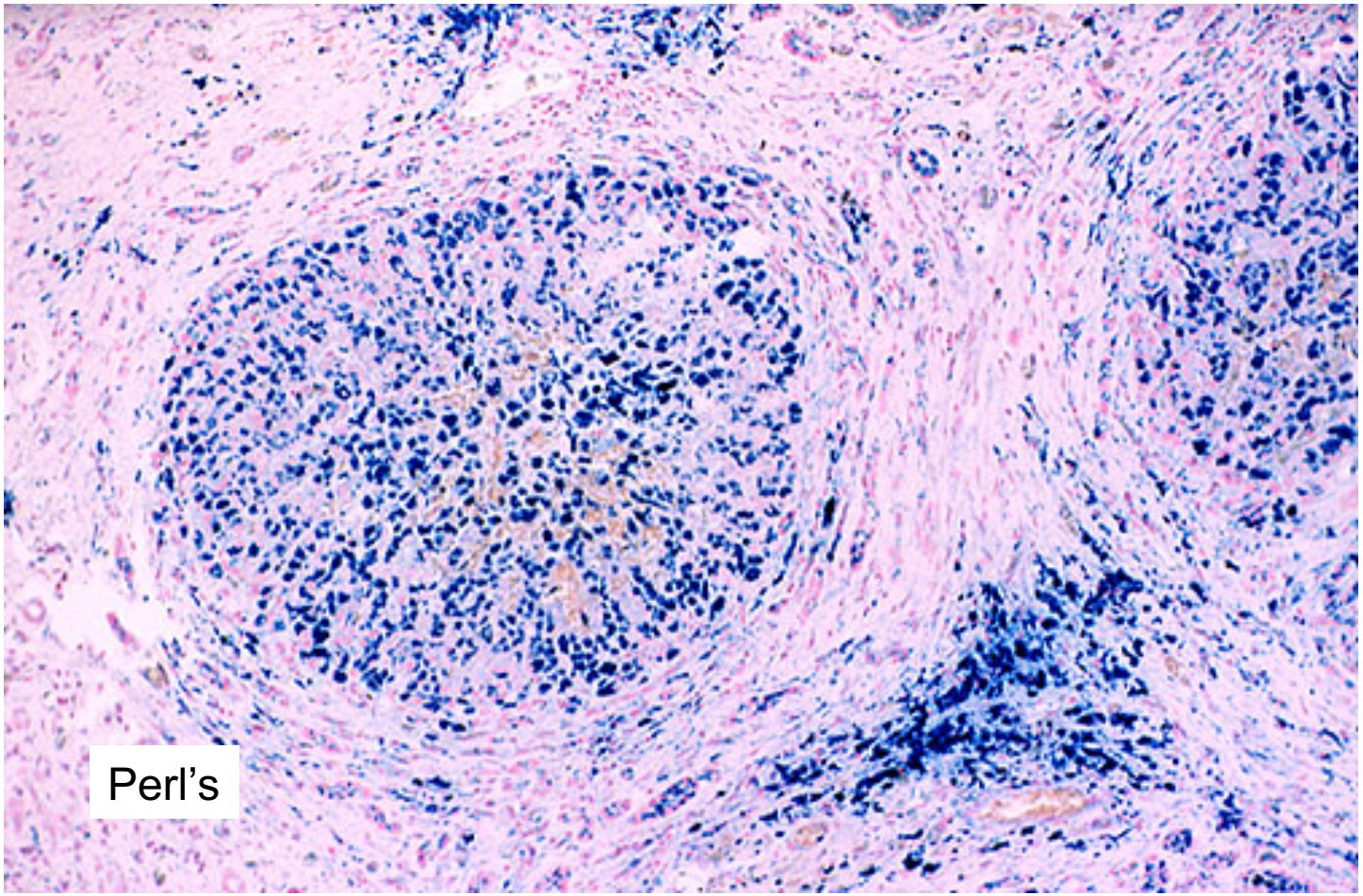
- Architecture
- Portal tracts
- Inflammation: portal, interface, parenchyma
- Parenchyma
- Relevant negatives
- Conclusion

Metabolic disorders

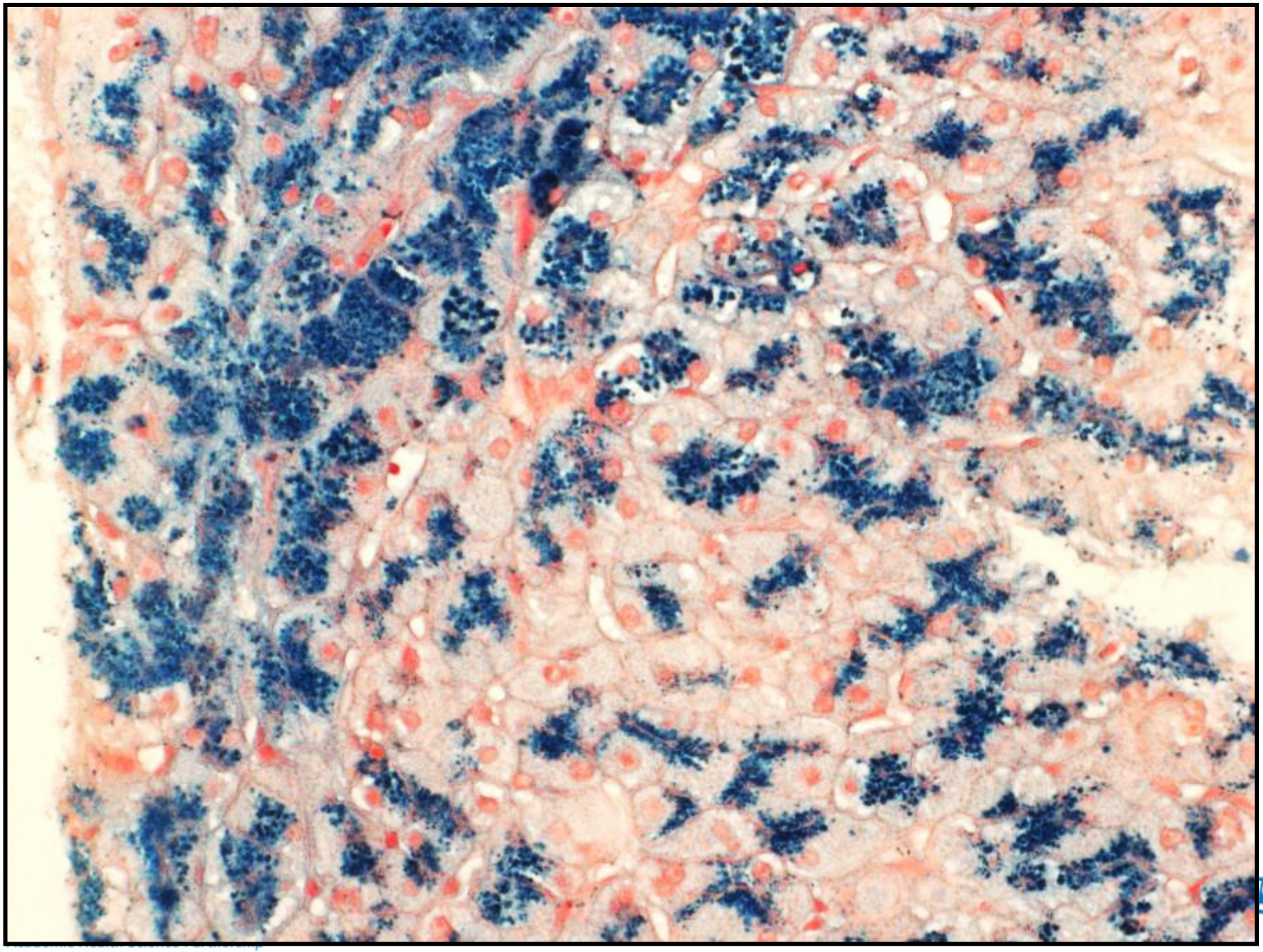
Three main disorders

- Haemochromatosis
- Wilson disease
- Alpha-1-antitrypsin deficiency





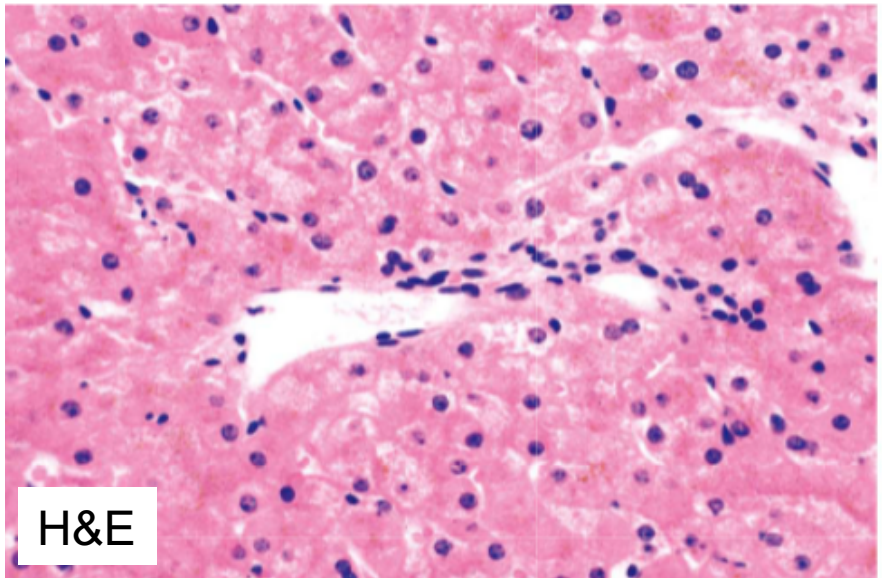
Cirrhotic liver with severe hepatic hemosiderin deposition (grade 4 of 4)

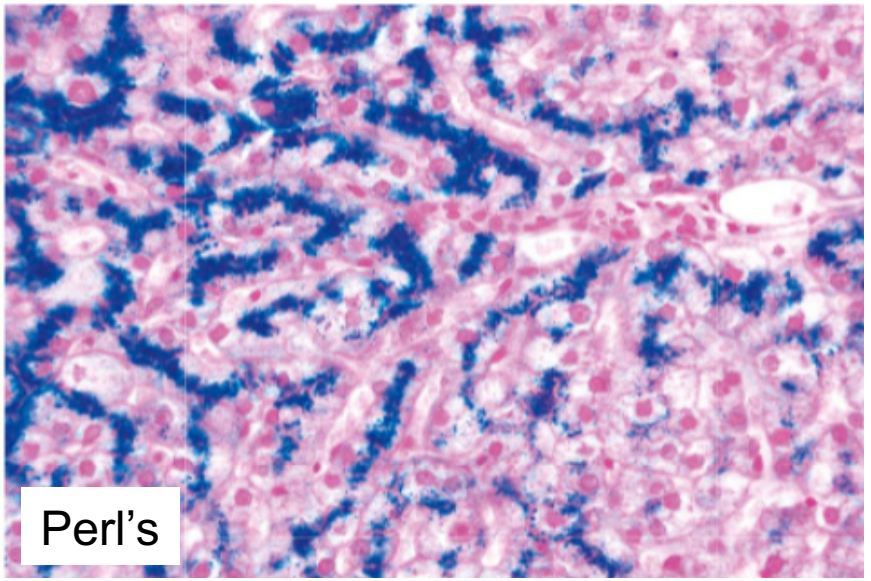


HFE associated Haemochromatosis

- Autosomal recessive, HFE gene (chr 6) – homozygosity for C282Y mutation, heterozygosity for C282Y/H63D mutations.
- 10% of northern Europeans
- Women present later than men
- Very little inflammation, iron deposition in hepatocytes Grade 0 -4
- Increased risk of HCC

Hereditary hemochromatosis

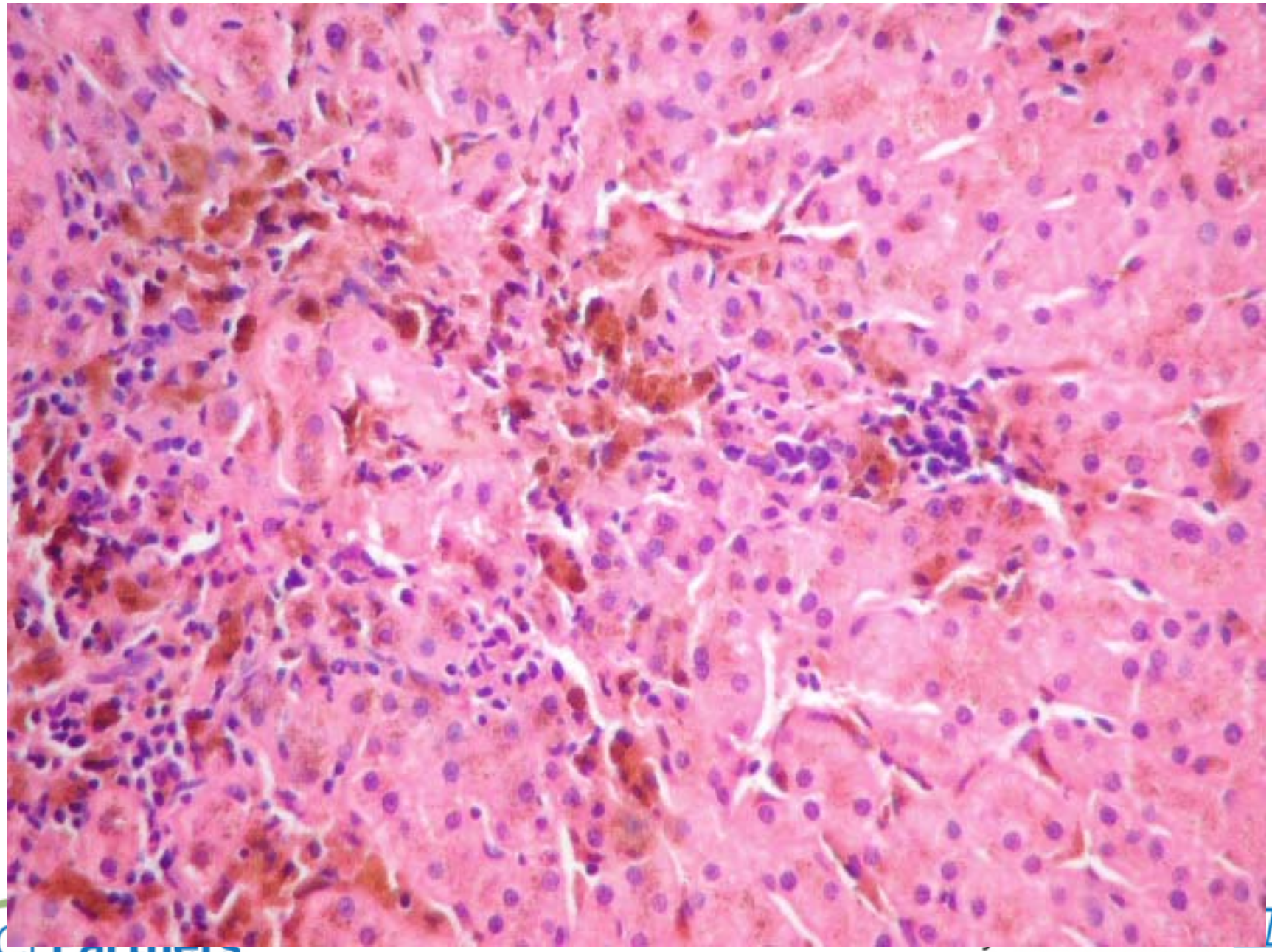




Pericanalicular brown granules are seen in periportal hepatocytes with sparing of Kupffer cells. No inflammation (iron is a direct hepatotoxin)

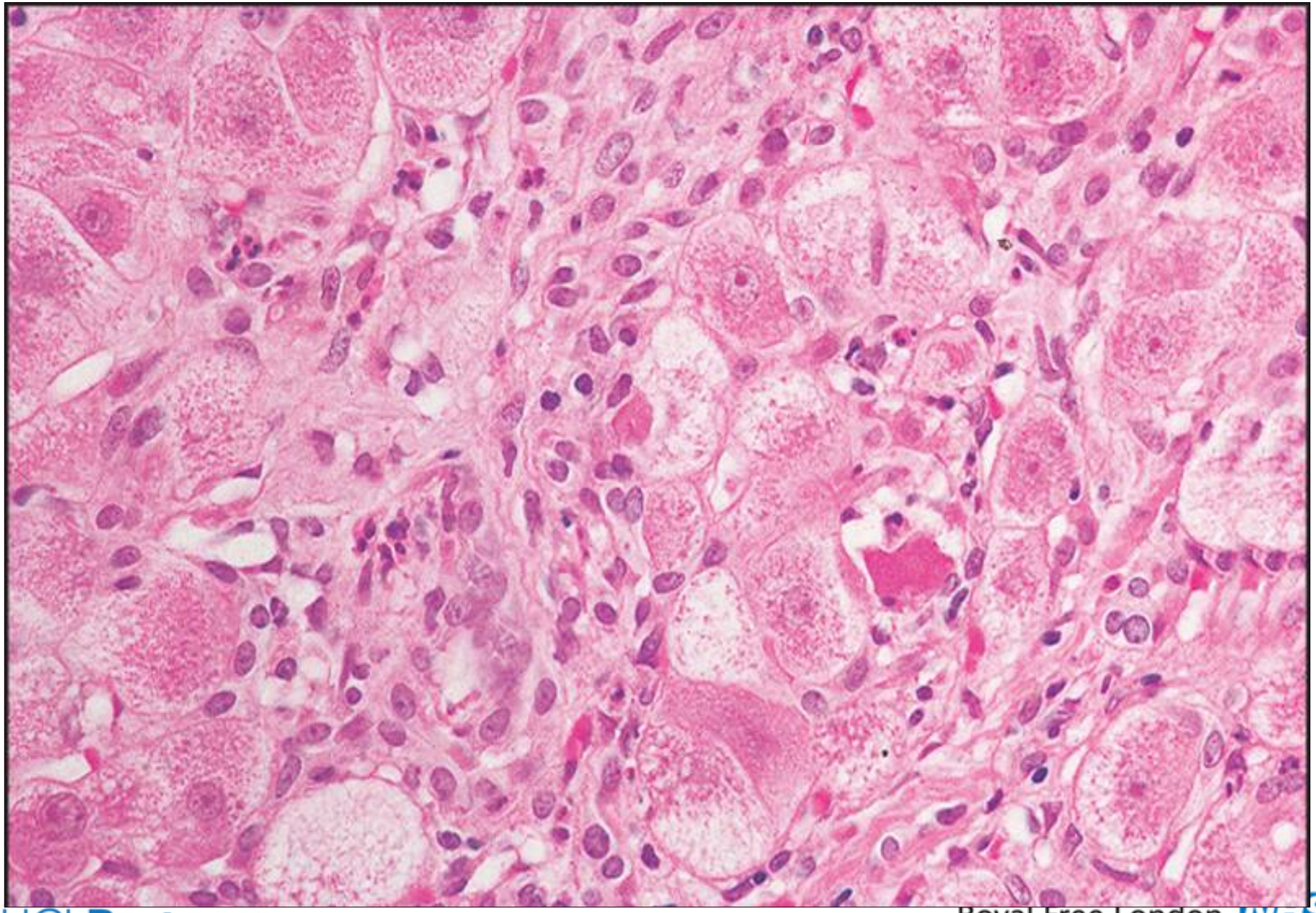
Ferroportin-associated iron overload (type 4)

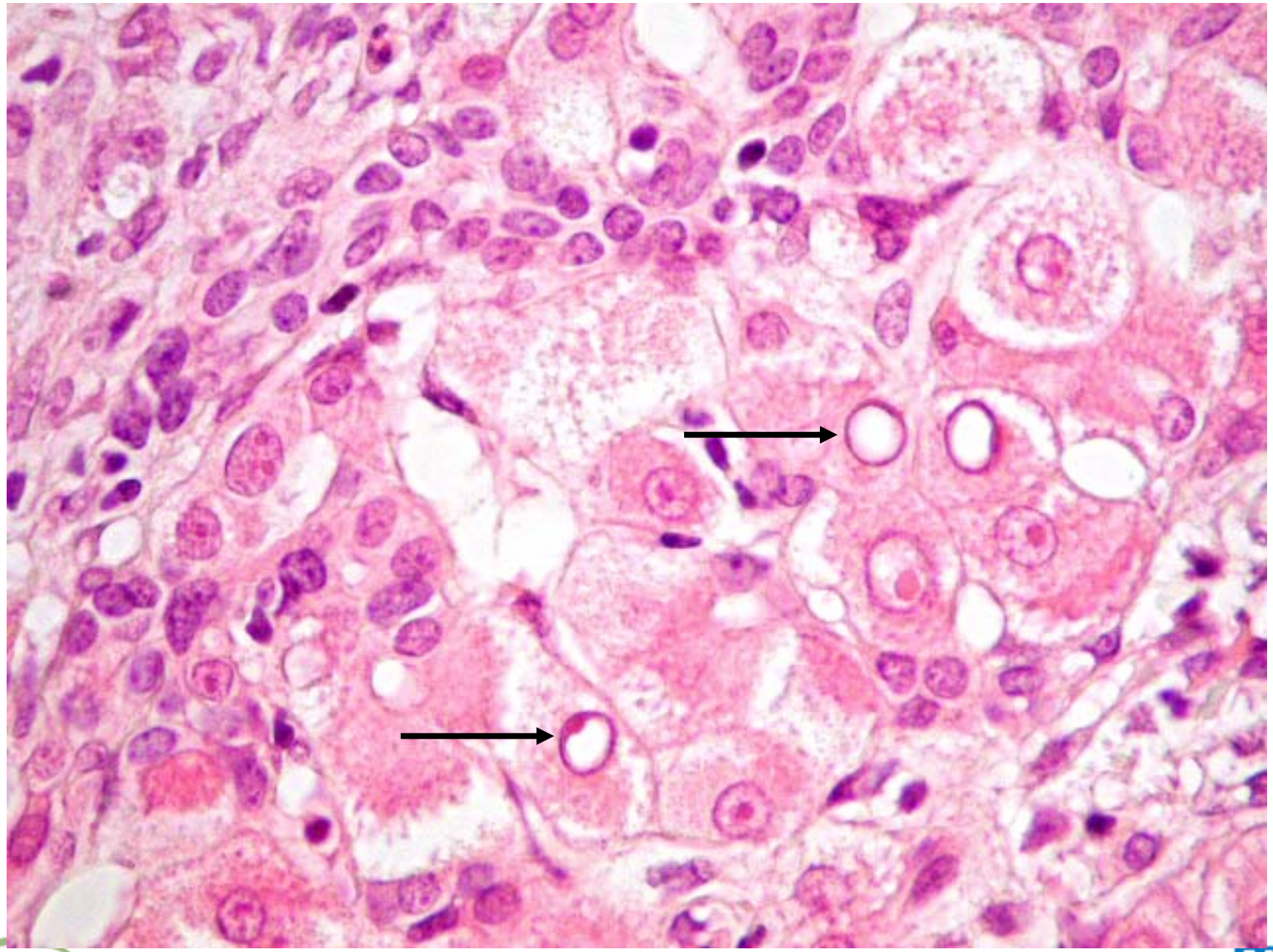
- Different mutation lead to different patterns
- Accumulation of iron in Kupffer cells
- Later in hepatocytes
- Giving mixed reticuloendothelial and hepatocyte iron

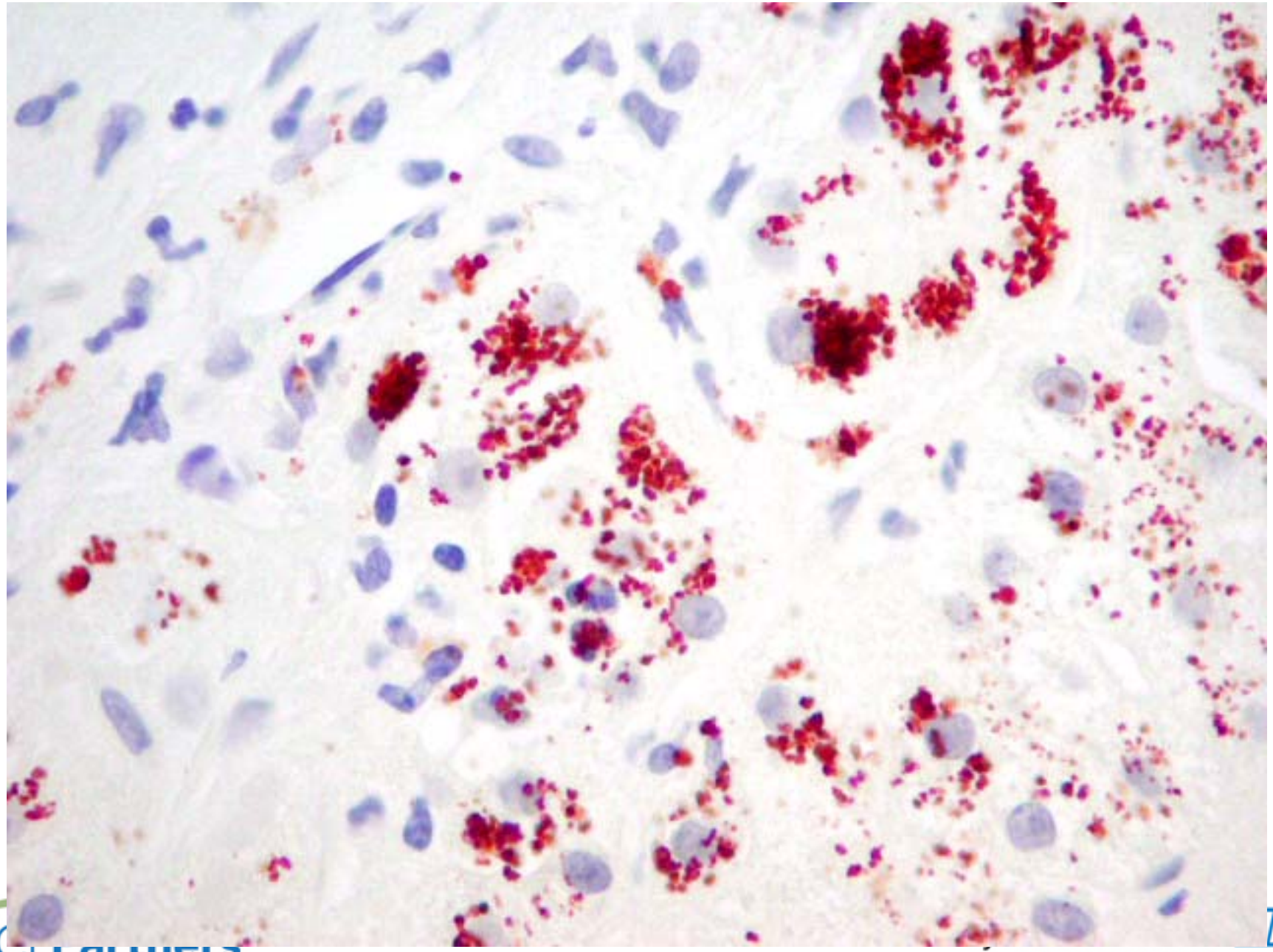


Wilson Disease

- Autosomal recessive disorder caused by mutations in copper-transporting ATPase (ATP7B) *ATP7B,* is marked by accumulation of toxic levels of copper in the liver, brain, kidney, and cornea.
- Histologically – ANY PATTERN OF CHRONIC LIVER DISEASE
    - Steatosis, nuclear glycogenation, lipofuscin, ballooned hepatocytes with Mallory bodies and neutrophils
    - Fulminant hepatic failure
    - Copper and copper associated protein deposition (can be patchy)

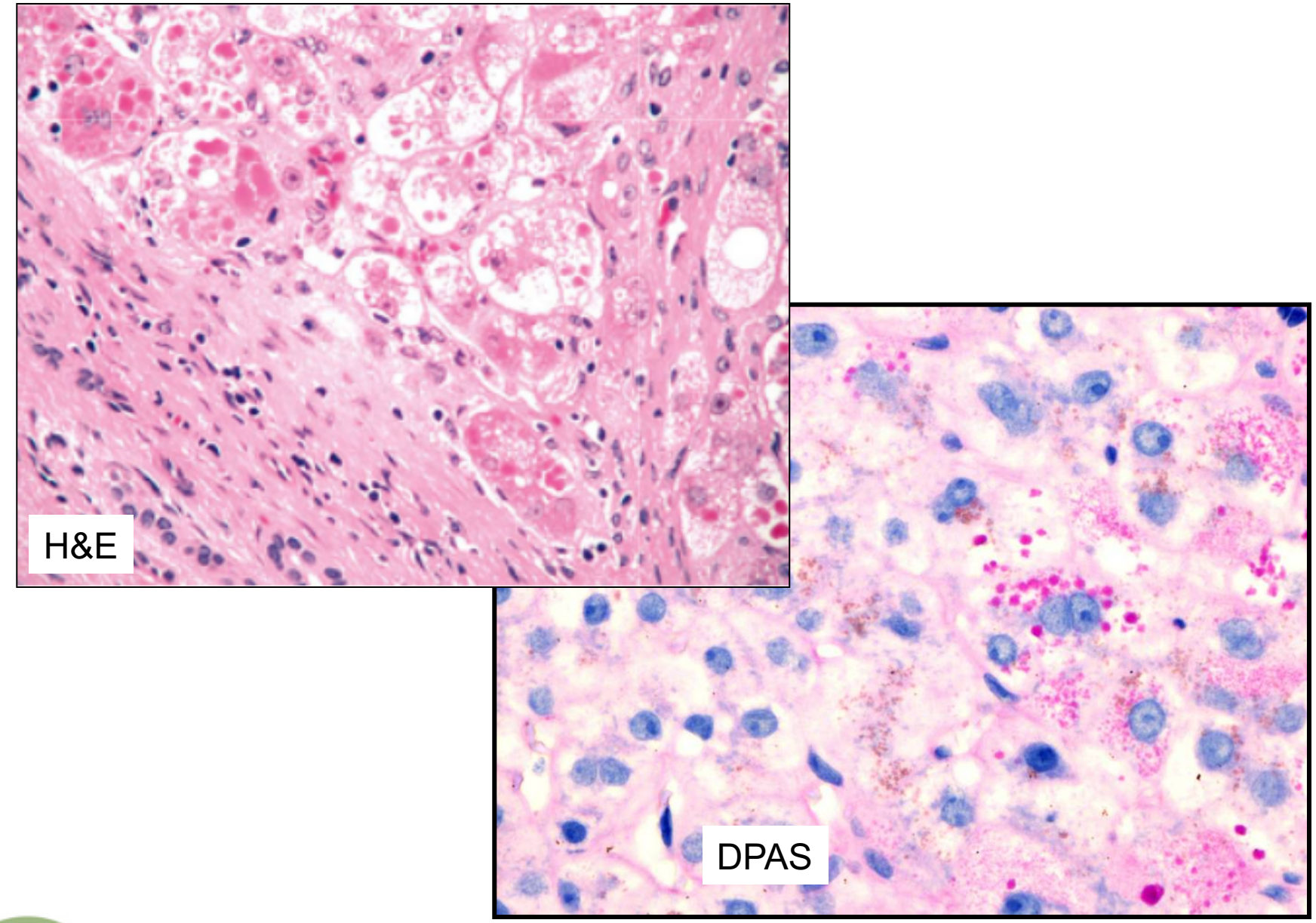




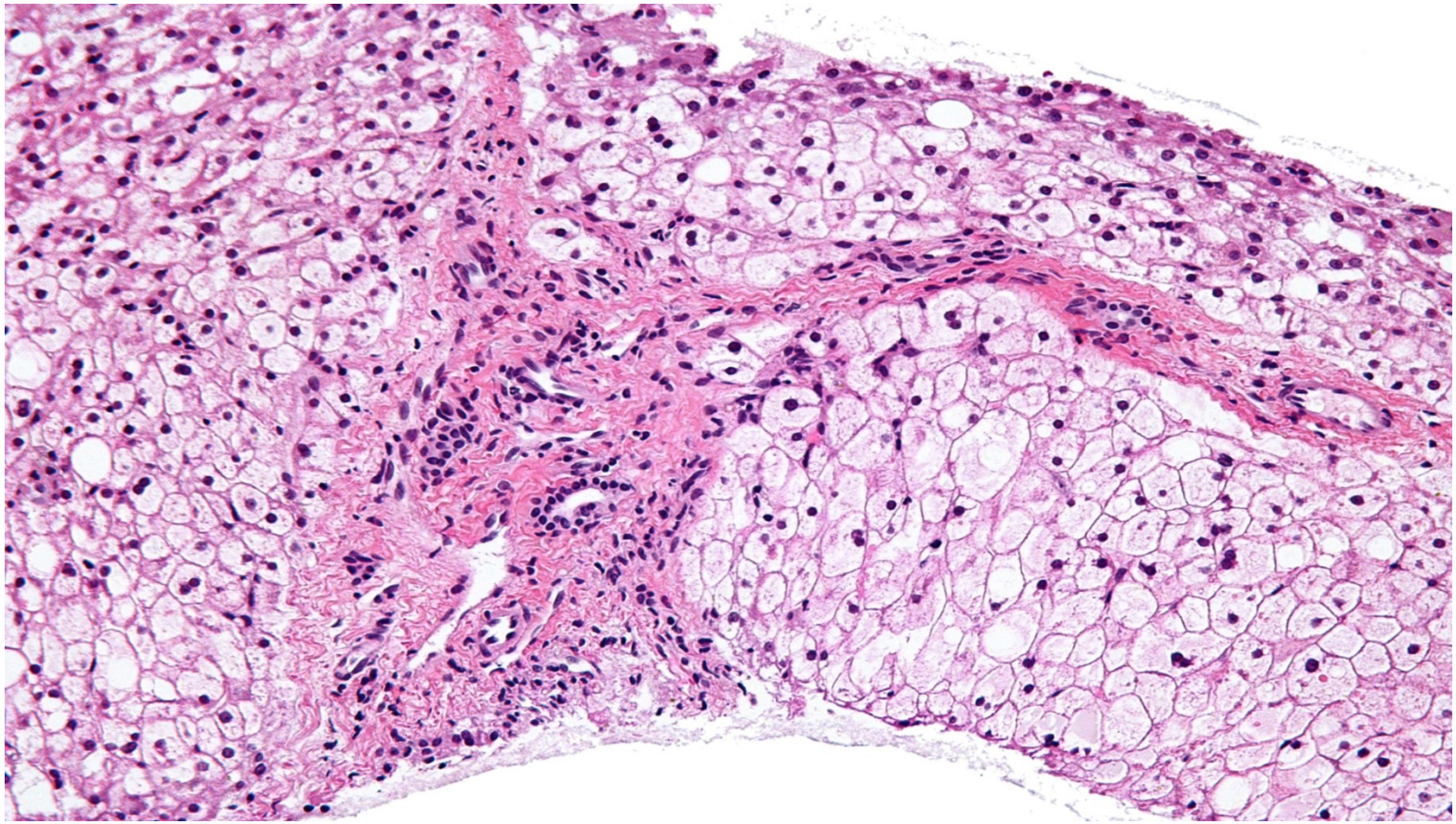


Alpha-1-antitrypsin Deficiency

- Variety of mutations lead to alpha-1-antitrypsin deficiency
- Commonest PiMM – relatively mild
- PiZZ – profound decrease in serum AAT
- DPAS +ve globules esp periportal
- Confirm on immunohistochemistry
- If present is not diagnostic needs genetic testing

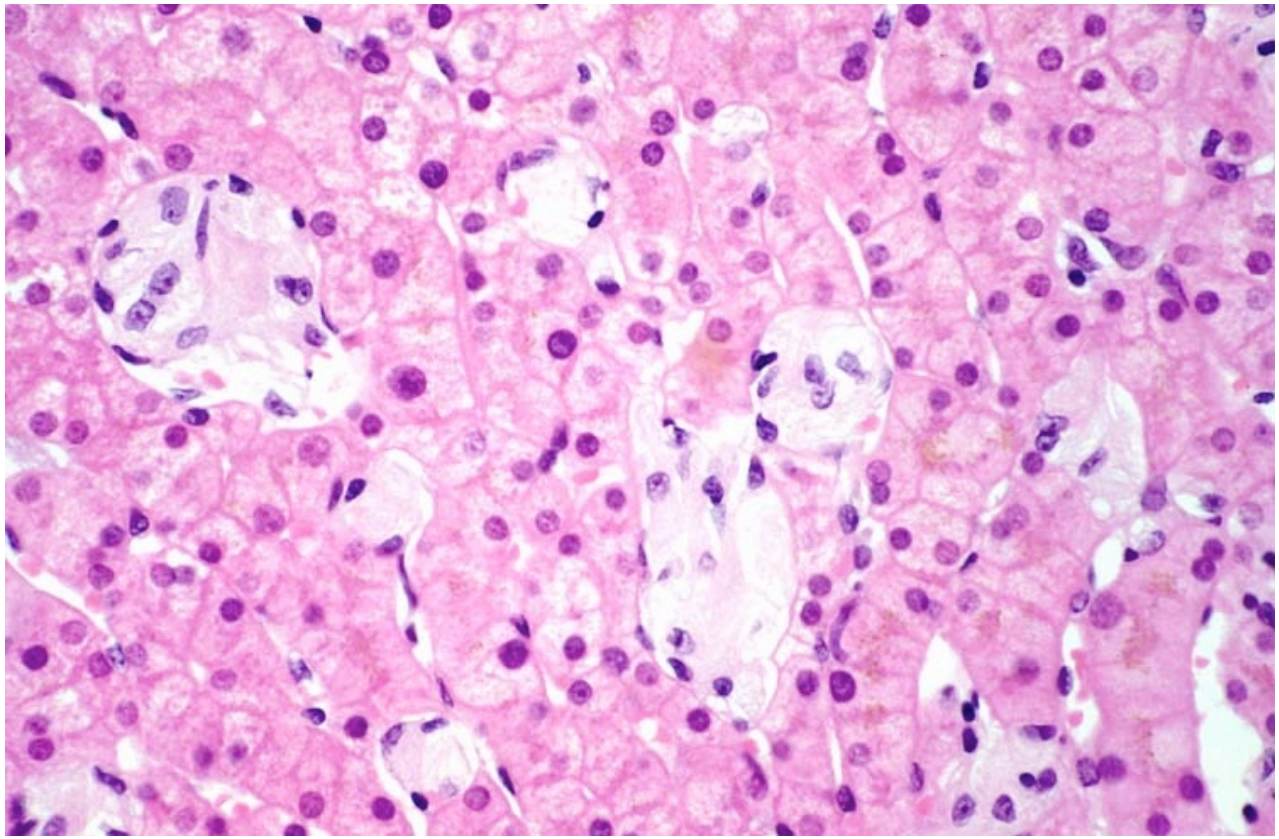

H&E
DPAS

Glycogen storage disease



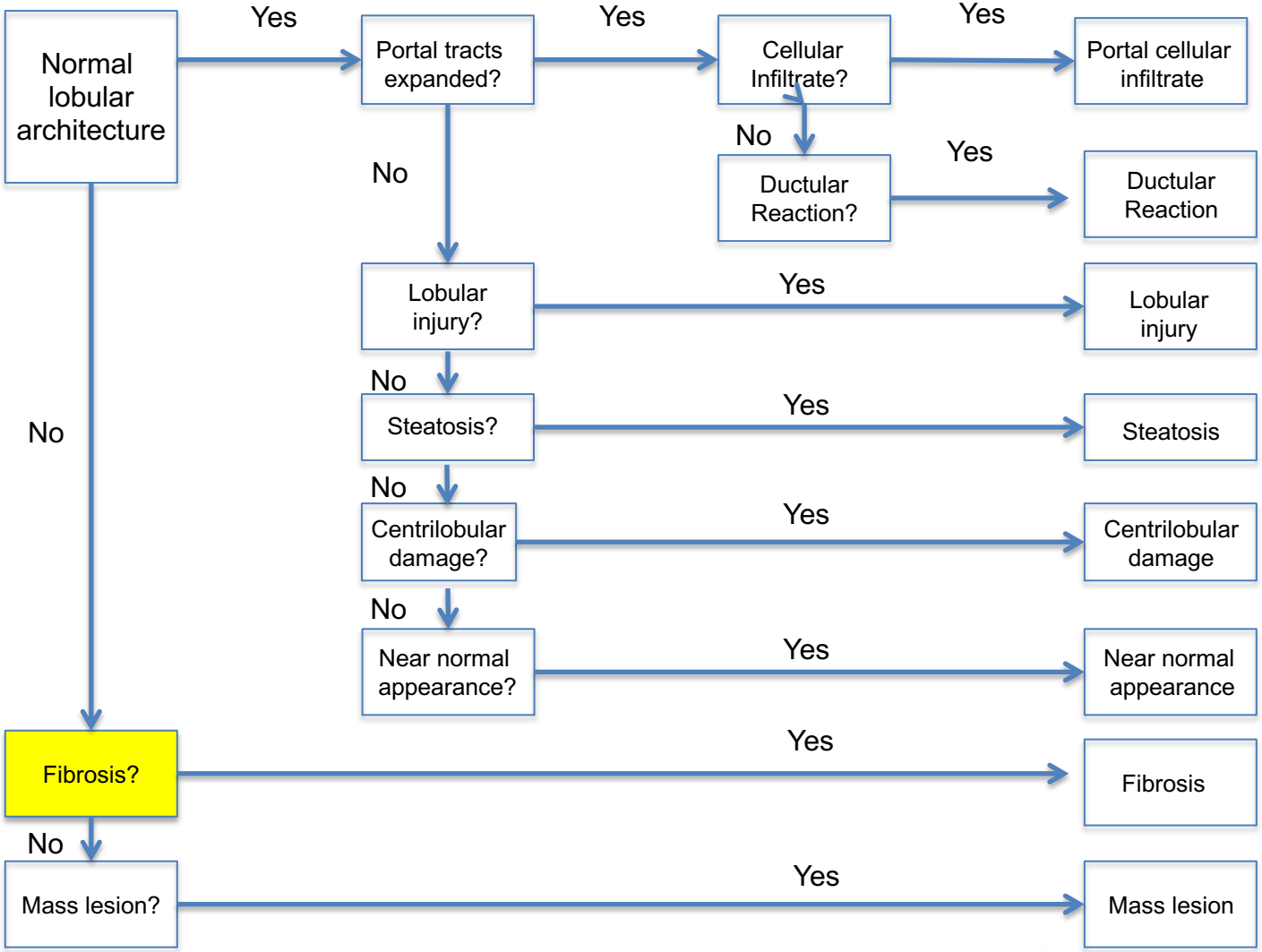
enlarged hepatocytes (≥2 × normal size) with wispy, pink, rarified cytoplasm and a centrally placed nucleus. The hepatocyte cell membranes are thickened.

Lipidosis – gauchers disease



Accumulation of glucocerebroside within macrophage lysosomes: the glycolipid is stored in elongated lysosomes that fill the cytoplasm of macrophages, imparting a characteristic fibrillar or striated appearance similar to crinkled paper.

Algorithmic approach
Identification of major pattern of injury



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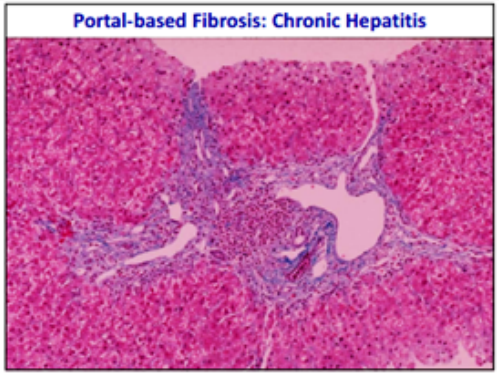
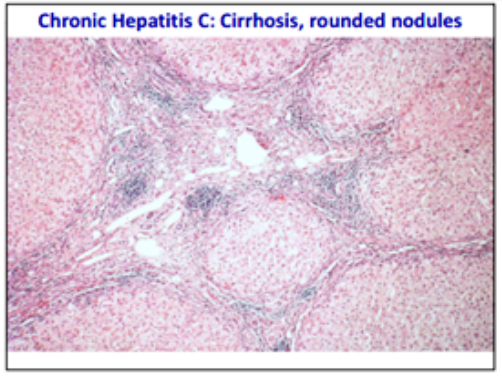
FIBROSIS

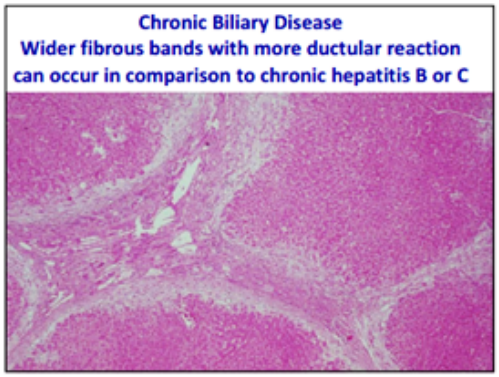
Two major patterns for early scarring of the liver

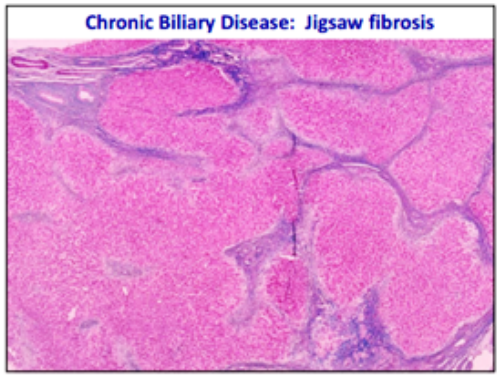
1. Portal-based Fibrosis

- Chronic hepatitis
  - Hepatitis B, C
  - Autoimmune hepatitis
  - Alpha-1-antitrypsin
  - Wilsons disease
- Biliary Disease
  - PBC, PSC,
  - Chronic obstruction
- Hemochromatosis









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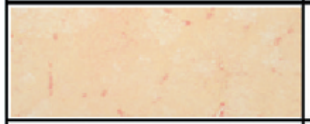
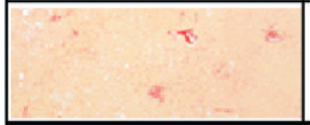
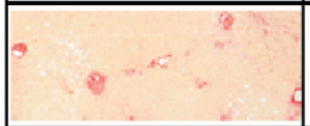
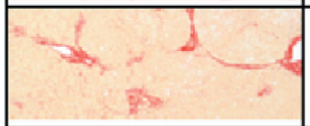
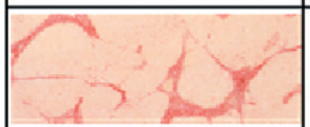
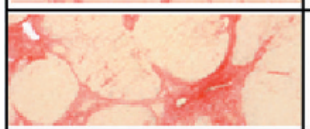
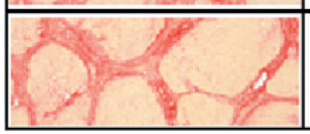
PORTAL-BASED FIBROSIS CHRONIC HEPATITIS

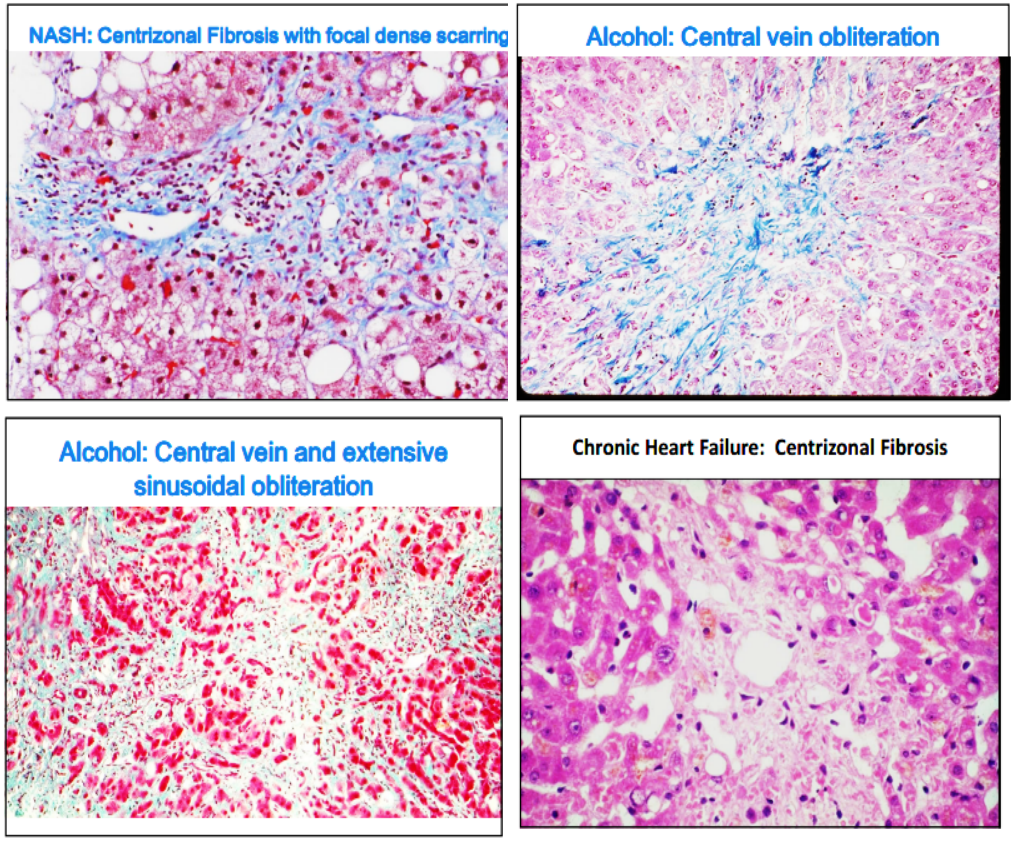
Appearance	Ishak stage: Categorical description	Ishak stage: Categorical assignment
	No fibrosis (normal)	0
	Fibrous expansion of some portal areas ± short fibrous septa	1
	Fibrous expansion of most portal areas ± short fibrous septa	2
	Fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging	3
	Fibrous expansion of portal areas with marked bridging (portal to portal (P-P) as well as portal to central (P-C))	4
	Marked bridging (P-P and/or P-C), with occasional nodules (incomplete cirrhosis)	5
	Cirrhosis, probable or definite	6

FIBROSIS

Two major patterns for early scarring of the liver

2. Central-based Fibrosis

- Chronic steatohepatitis
  - Nonalcoholic types (NASH)
  - Alcoholic types (ASH)
- Chronic venous outflow obstruction



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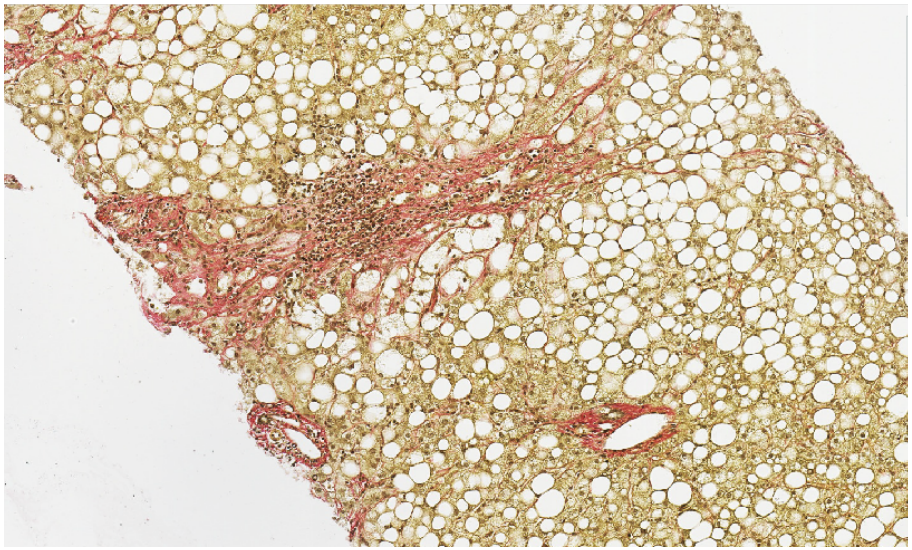
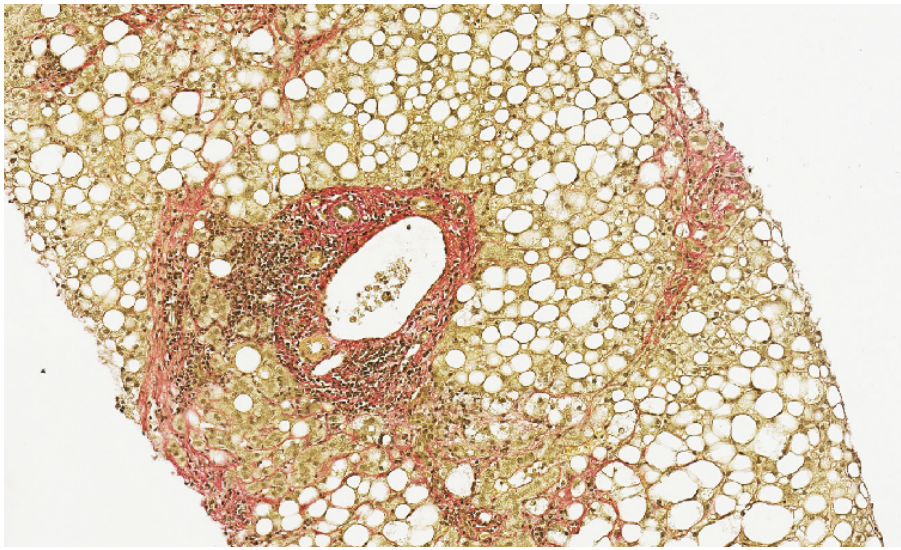
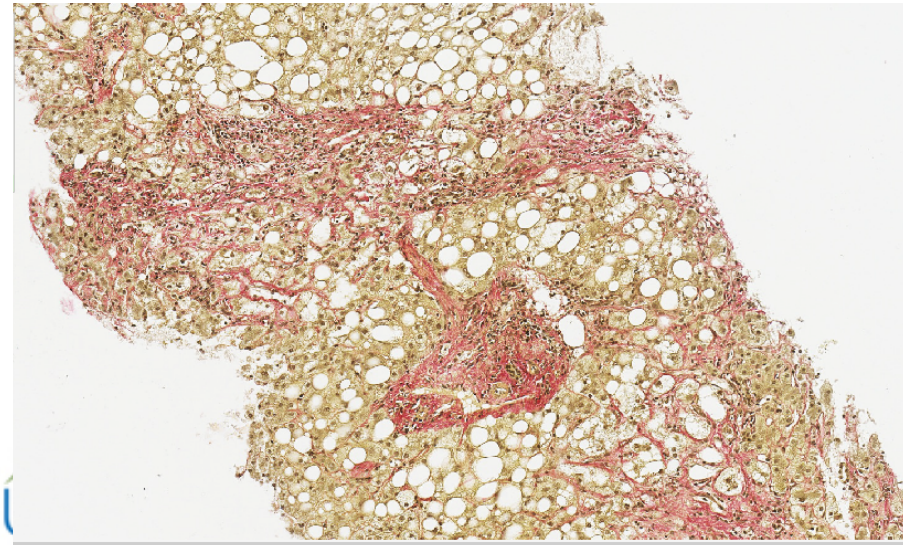
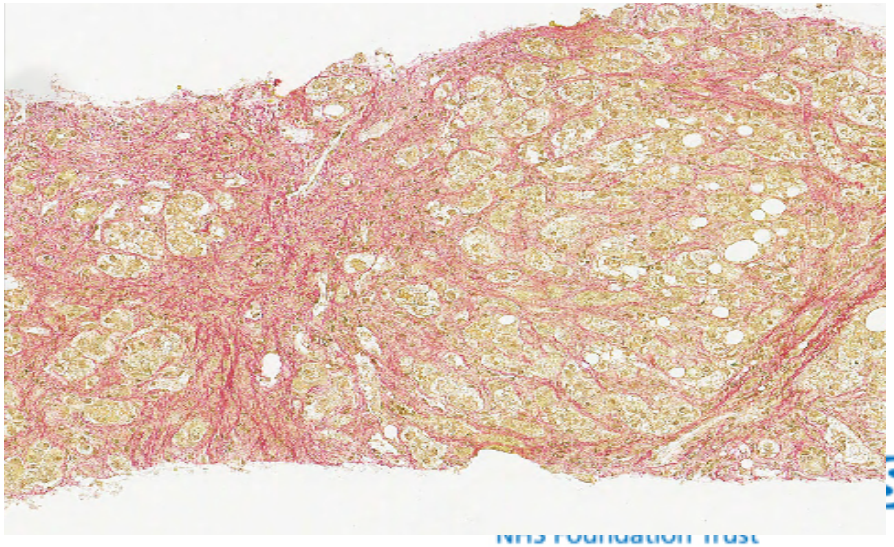
CENTRAL-BASED FIBROSIS

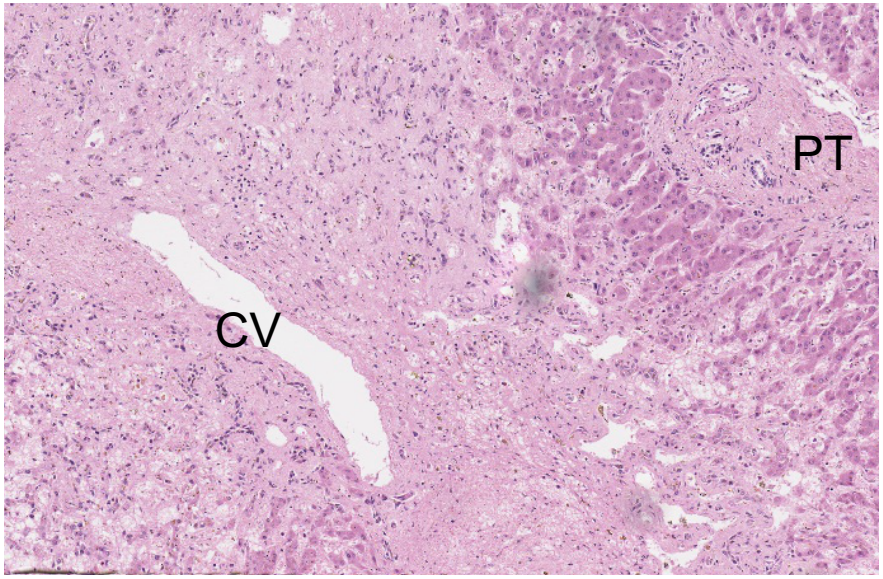


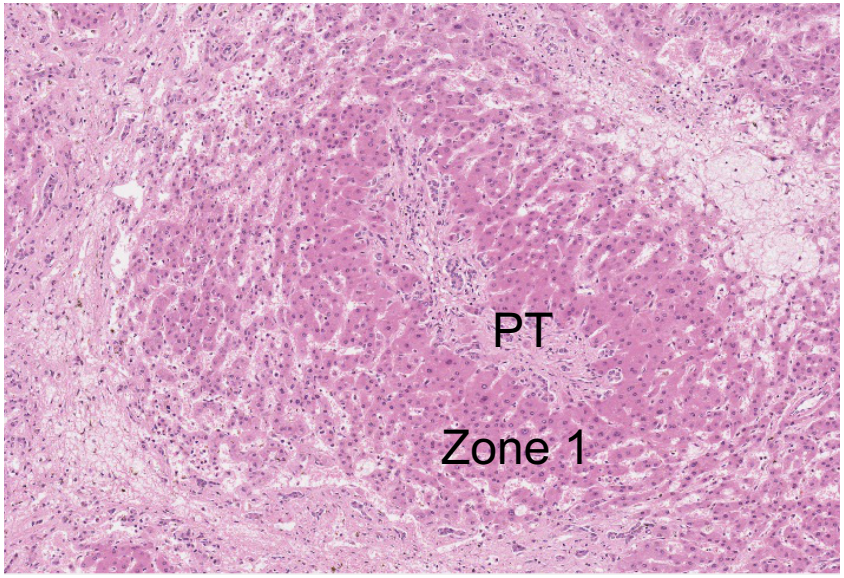






CENTRAL-BASED FIBROSIS

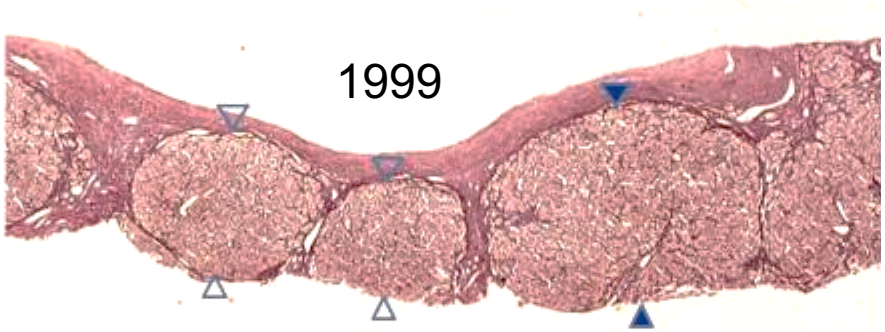




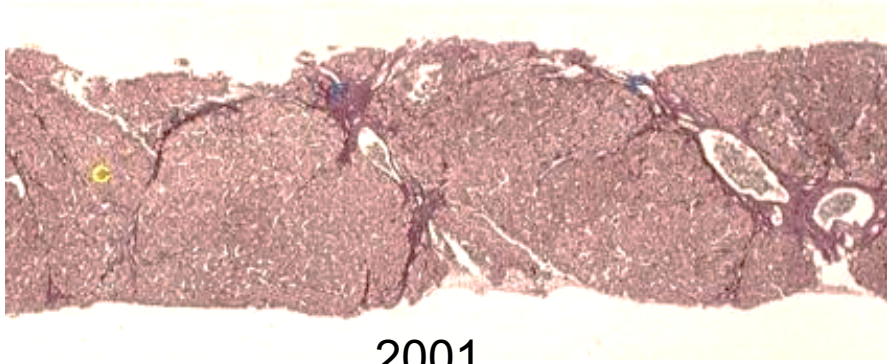
Chronic Budd-Chiari syndrome

Cirrhosis improvement to alcoholic liver fibrosis after passive abstinence. Hideaki Takahashi et al. BMJ Case Rep. 2014

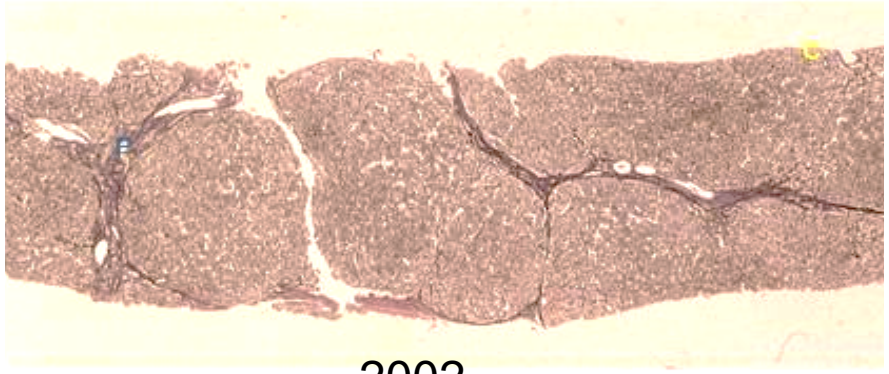
1991



1999



2001



2002

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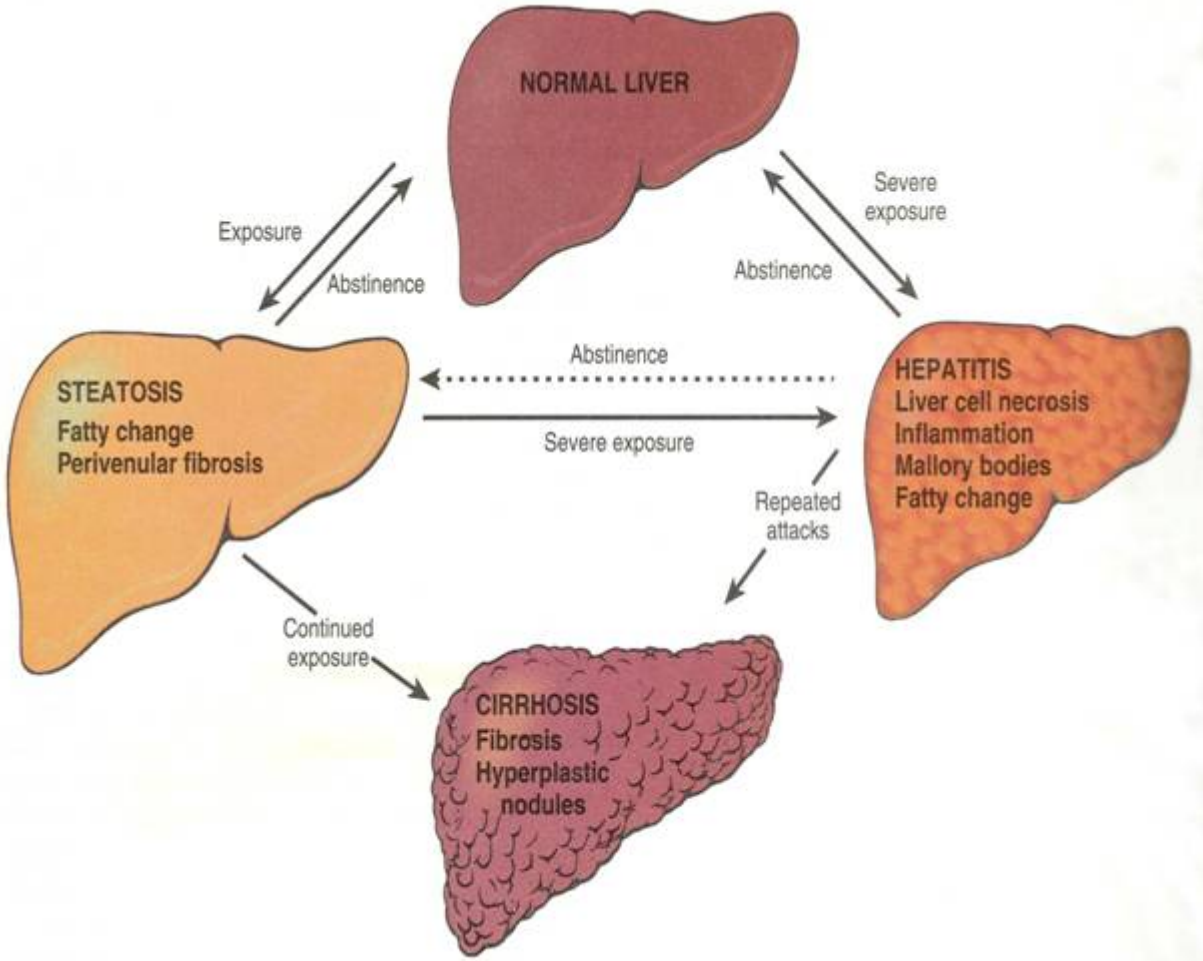
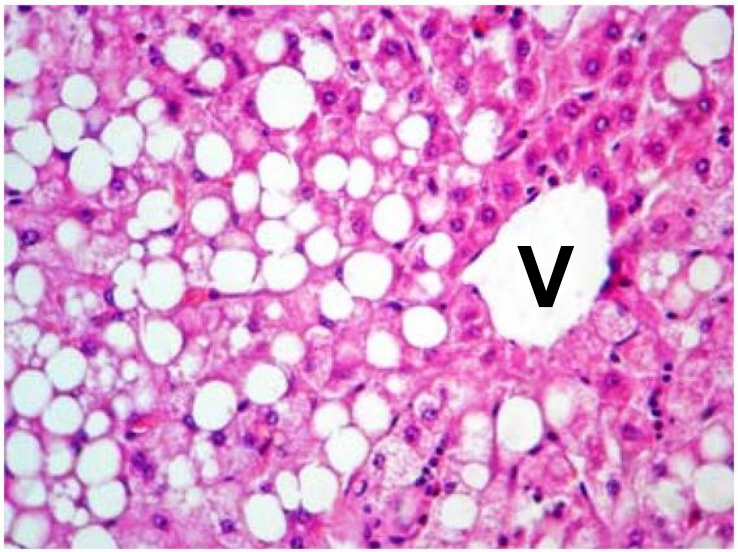
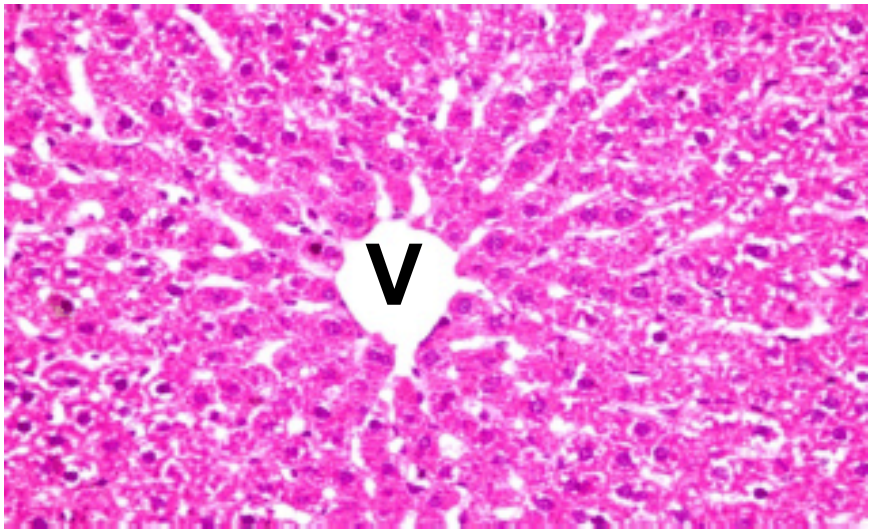
Changes With Abstinence



Changes With Abstinence

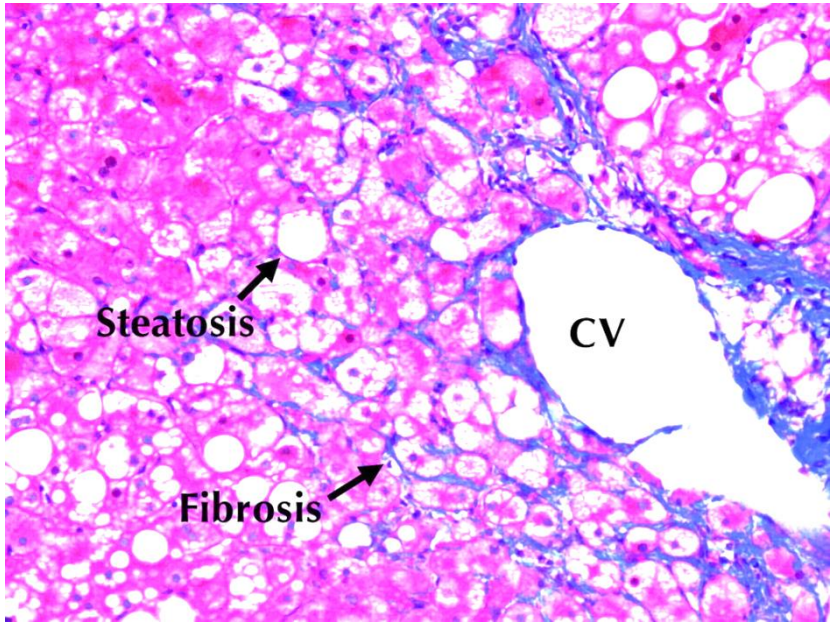


Simple steatosis

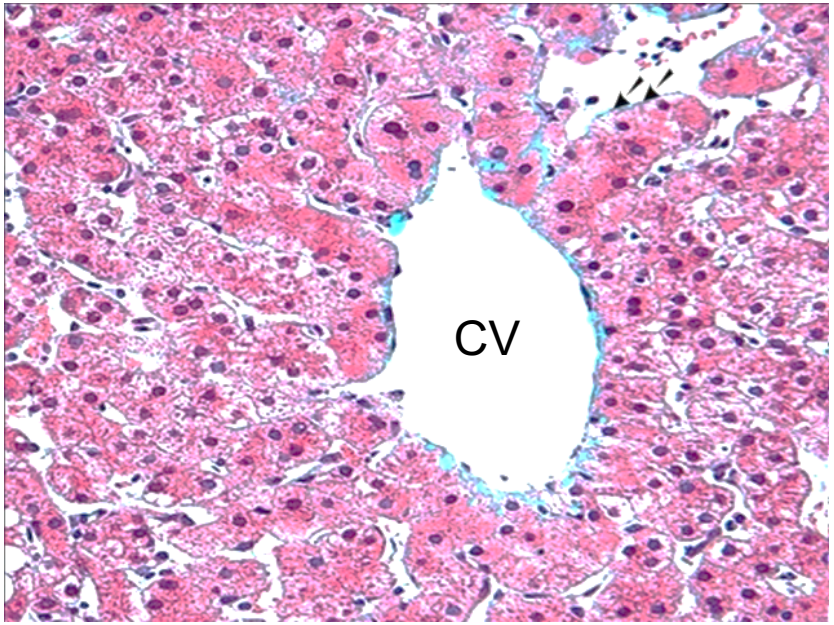


Normal

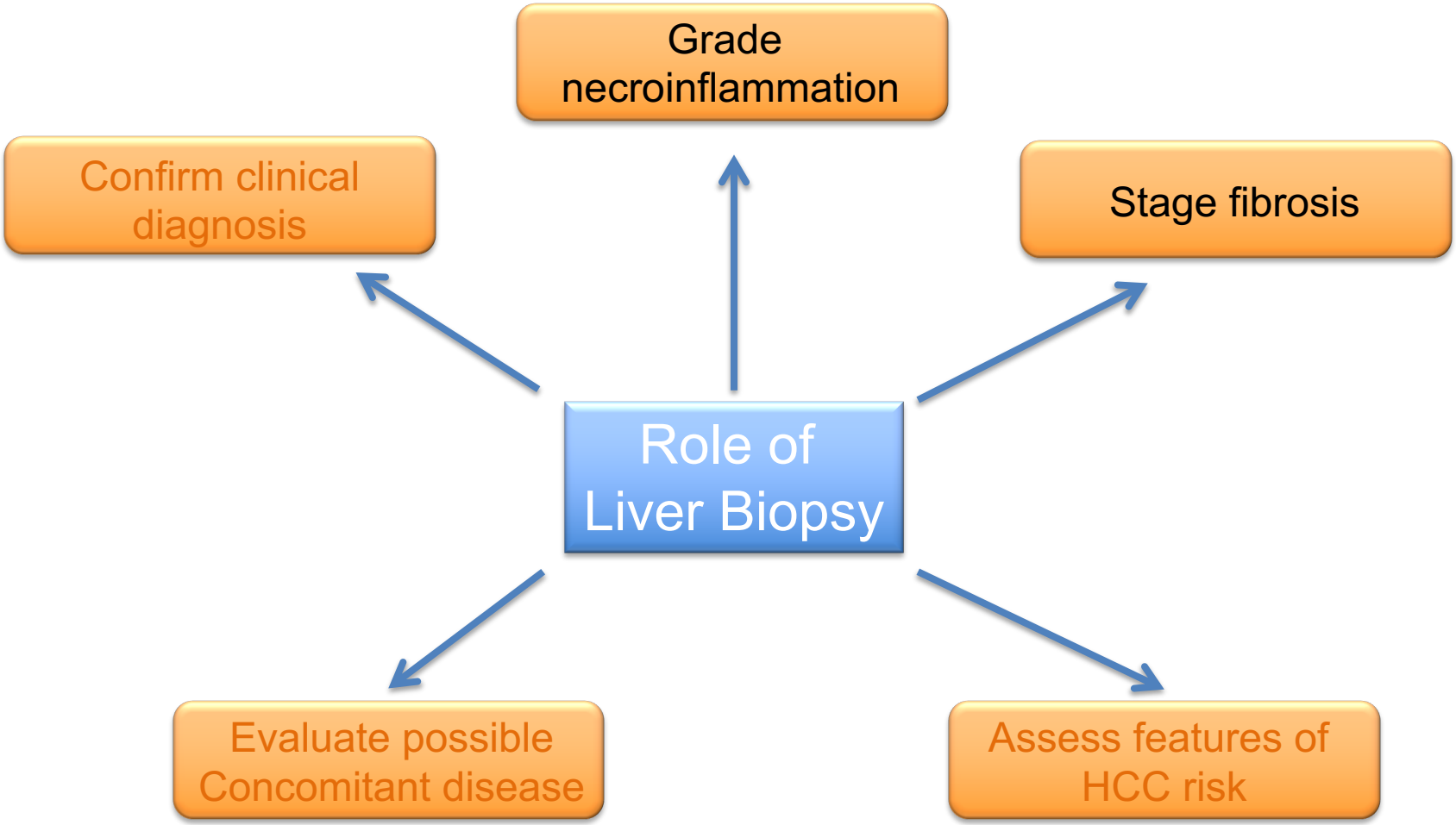
Features of fibrotic regression after sustained abstinence



Perivennular fibrosis/early stage



Normal/no fibrosis


Grade necroinflammation
Confirm clinical diagnosis
Stage fibrosis
Role of Liver Biopsy
Evaluate possible Concomitant disease
Assess features of HCC risk

Chronic Hepatitis

Commonly used Grading/ Staging systems

ND Thiese. Modern Pathology (2007) 20, S3-S14

- Scheuer/Batts-Ludwig/Tsui:
  - Grade and Stage on scale 0-4
  - Simple, reproducible, validated clinically
- METAVIR:
  - Grade 0-3, Fibrosis 0-4
  - Simple, reproducible, validated clinically
- Ishak, et al:
  - Grades four categories of activity/necrosis, 0-4 or 0-6

Generally considered too complex, not necessary

  - Staging 0-6
    - Preferred in many clinical trials
    - Still reproducible and validated clinically

Modified ISHAK and METAVIR grading systems

Table 1 Ishak modification for hepatic activity index (HAI) for scoring of necroinflammatory activity in chronic hepatitis

(*A*) *Periportal or periseptal interface hepatitis (piecemeal necrosis)*	
Absent	0
Mild (focal, few portal areas)	1
Mild/moderate (focal, most portal areas)	2
Moderate (continuous around <50% of tracts or septa)	3
Severe (continuous around >50% of tracts or septa)	4
(*B*) *Confluent necrosis*	
Absent	0
Focal confluent necrosis	1
Zone 3 necrosis in some areas	2
Zone 3 necrosis in most areas	3
Zone 3 necrosis+occasional portal-central (P-C) bridging	4
Zone 3 necrosis+multiple P-C bridging	5
Panacinar or multiacinar necrosis	6
(*C*) *Focal (spotty) lytic necrosis, apoptosis and focal inflammation*	
Absent	0
One focus or less per ×10 objective	1
Two to four foci per ×10 objective	2
Five to ten foci per ×10 objective	3
More than ten foci per ×10 objective	4
(*D*) *Portal inflammation*	
Absent	0
Mild, some or all portal areas	1
Moderate, some or all portal areas	2
Moderate/marked, all portal areas	3
Marked, all portal areas	4

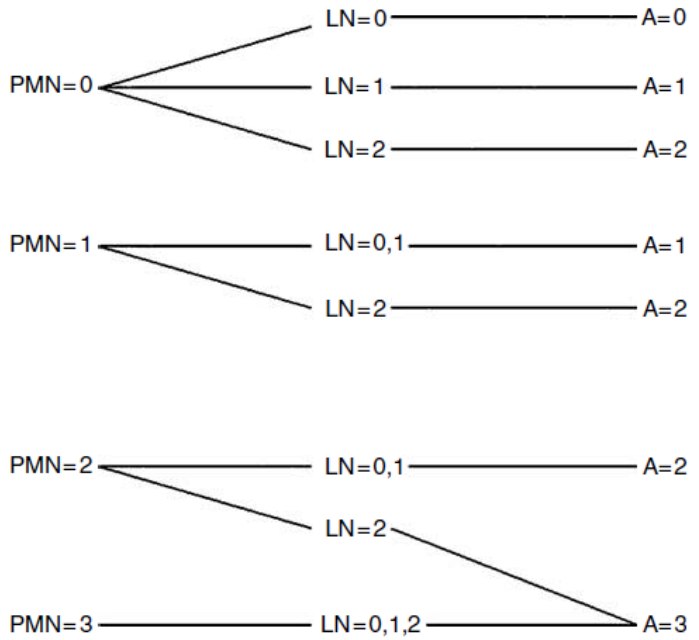


Figure 2 Metavir algorithm for the evaluation of histological activity. PMN, piecemeal necrosis; 0, none; 1, mild; 2, moderate; 3, severe; LN, lobular necrosis; 0, no or mild; 1, moderate; 2, severe; A, histological activity score; 0, none; 1, mild; 2, moderate; 3, severe.

Batts-Ludwig and Scheuer grading systems

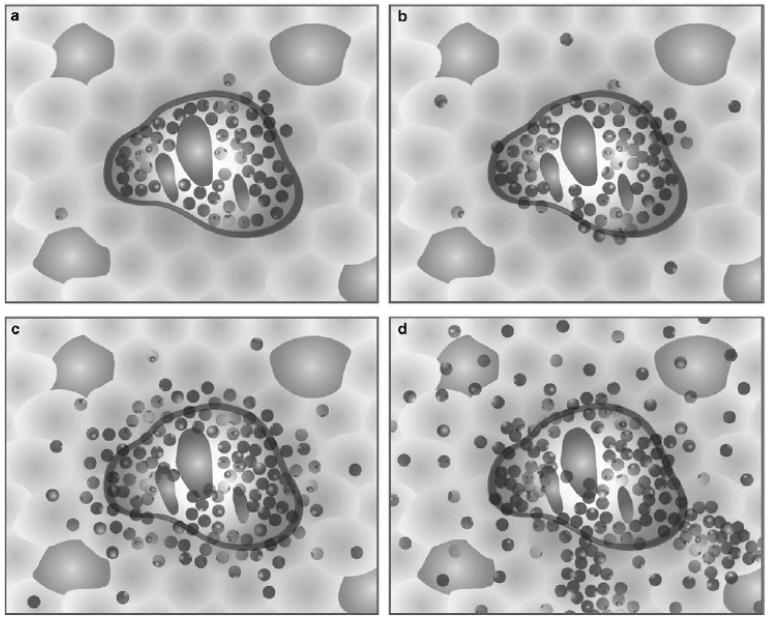


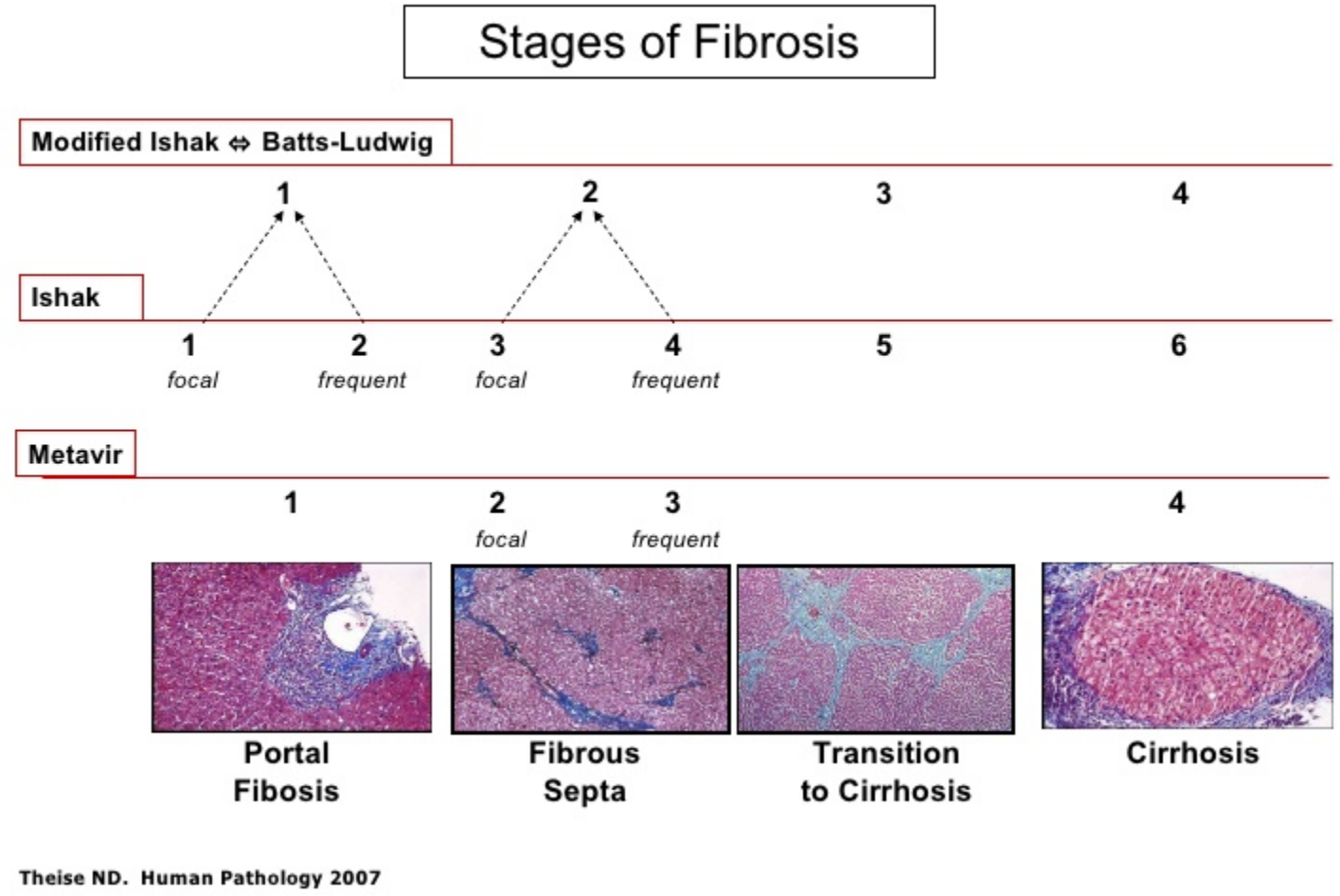
Figure 3 Batts–Ludwig diagrams of necroinflammatory activity. Note that all grades of activity contain portal inflammation; therefore, it is a defining feature of chronic hepatitis and not assessed separately from other necroinflammatory lesions. (**a–c**) Activity grades 1 through 3. Confluent necrosis, in the form of bridging necrosis, is present only in activity grade 4 (**d**). These versions adapted with permission from Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. *Am J Surg Pathol* 1995;19:1409–1417.[15]

Table 2 Scheuer classification for grading and staging of chronic hepatitis

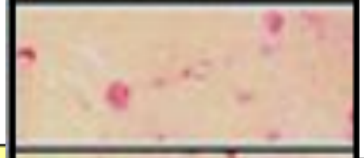
Grade	*Portal/periportal activity*	*Lobular activity*
0	None	None
1	Portal inflammation	Inflammation but no necrosis
2	Mild piecemeal necrosis	Focal necrosis or acidophil bodies
3	Moderate piecemeal necrosis	Severe focal cell damage
4	Severe piecemeal necrosis	Damage includes bridging necrosis

Stage	*Fibrosis*
0	None
1	Enlarged, fibrotic portal tracts
2	Periportal or portal-portal septa, but intact architecture
3	Fibrosis with architectural distortion, but no obvious cirrhosis
4	Probable or definite cirrhosis

Portal-Based Stages of Fibrosis



Theise ND. Human Pathology 2007

METAVIR		Modified Ishak	
			None
Stellate fibrous expansion of portal tracts (spurs, no septa)		Fibrous expansion of some portal tracts (+/- spurs)	Minimal
		Fibrous expansion of most portal tracts (+/- spurs)	Mild
Rare septa		Occasional porto-portal fibrosis	Mild-mod
Many septa		Marked bridging (porto-portal + porto-central)	Moderate
		Marked bridging + occasional nodules	Mod-sev
Cirrhosis		Cirrhosis, probable or definate	Severe

StandishRA2005

Portal-Based Fibrosis
Which scoring system to use?

- All three systems are reasonable
- Scheuer and Batts/Ludwig 0-4 scales works well for chronic hepatitis B and C and is simple
  - Validated by many studies

Limitations:

- Doesn't apply to centrizonal liver disease
- Mixed etiologies (Example: Alcohol + HBV)
- Doesn't evaluate for remodelling/regression

FATTY LIVER DISEASE

Necessary features to diagnose steatohepatitis

AASLD single topic conference NASH Atlanta, 2002

- Necessary components – *must see*
  - Steatosis, Macro>micro, mainly zone 3
  - Mixed mild lobular inflammation
  - Hepatocyte ballooning, most apparent near steatotic cells
- Usually present, not necessary for diagnosis – *often see*
  - Perisinusoidal fibrosis (zone 3)
  - Glycogenated nuclei (zone 1)
  - Lipogranulomas (usually small)
  - Occasional apoptotic hepatocytes/PASD+ve Kupffer cells
- May be present, not necessary for diagnosis – *may see*
  - Mallory's hyaline, usually zone 3,
  - Mild siderosis,
  - Megamitochondria
- Not present in NASH – *don't see*

consider other causes of liver disease *Next slide*

Hepatology. 2003 May;37(5):1202-19.

FATTY LIVER DISEASE

BRUNT grading and staging system

Medscape® www.medscape.com

GRADE 1, MILD

- Steatosis: predominantly macrovesicular, involves < 33 up to 66% of the lobules
- Ballooning: occasionally observed; zone 3 hepatocytes
- Lobular inflammation: scattered and mild acute (polymorphs) inflammation and occasional chronic inflammation (mononuclear cells)
- Portal inflammation: none or mild

GRADE 2, MODERATE

- Steatosis: any degree and usually mixed macrovesicular and microvesicular
- Ballooning: obvious and present in zone 3
- Lobular inflammation: polymorphs may be noted associated with ballooned hepatocytes, pericellular fibrosis; mild chronic inflammation may be seen
- Portal inflammation: mild to moderate

GRADE 3, SEVERE

- Steatosis: typically > 66% (panacinar); commonly mixed steatosis
- Ballooning: predominantly zone 3; marked
- Lobular inflammation: scattered acute and chronic inflammation; polymorphs may appear concentrated in zone 3 areas of ballooning and perisinusoidal fibrosis
- Portal inflammation: mild or moderate

Steatosis: grade 1 = 0–33%, 2 = 33%–66%, 3 = >66%

Ballooning: zonal location noted and severity (mild or marked) recorded according to estimate of numbers of hepatocytes involved

Lobular inflammation: 0–3 based on observations of foci per 20 × field; 1 = 1–2 foci, 2 = up to 4 foci, 3 = > 4 foci. In addition, cell types (acute or chronic) and location were noted

Portal inflammation: 0–3, 1 = mild, 2 = moderate, 3 = severe

STAGING FIBROSIS IN NASH

- Stage 1: Zone 3 perivenular perisinusoidal/pericellular fibrosis, focal or extensive
- Stage 2: As above with focal or extensive periportal fibrosis
- Stage 3: Bridging fibrosis, focal or extensive
- Stage 4: Cirrhosis

(Modified from Brunt[5])

FATTY LIVER DISEASE

Kleiner (NASH CRN) system

Histological Scoring System for Nonalcoholic Fatty Liver Disease (NAFLD)

Components of NAFLD Activity Score (NAS) and Fibrosis Staging

NAS Components (see scoring interpretation)			
Item	**Score**	**Extent**	**Definition and Comment**
Steatosis	0	<5%	Refers to amount of surface area involved by steatosis as evaluated on low to medium power examination; minimal steatosis (<5%) receives a score of 0 to avoid giving excess weight to biopsies with very little fatty change
	1	5-33%	
	2	>33-66%	
	3	>66%	
Lobular Inflammation	0	No foci	Acidophil bodies are not included in this assessment, nor is portal inflammation
	1	<2 foci/200x	
	2	2-4 foci/200x	
	3	>4 foci/200x	
Hepatocyte Ballooning	0	None	
	1	Few balloon cells	The term "few" means rare but definite ballooned hepatocytes as well as cases that are diagnostically borderline
	2	Many cells/prominent ballooning	Most cases with prominent ballooning also had Mallory's hyalin, but Mallory's hyaline is not scored separately for the NAS
Fibrosis Stage (Evaluated separately from NAS)			
Fibrosis	0	None	
	1	Perisinusoidal or periportal	
	1A	Mild, zone 3, perisinusoidal	"delicate" fibrosis
	1B	Moderate, zone 3, perisinusoidal	"dense" fibrosis
	1C	Portal/periportal	This category is included to accommodate cases with portal and/or peri portal fibrosis without accompanying pericellular/perisinusoidal fibrosis
	2	Perisinusoidal and portal/periportal	
	3	Bridging fibrosis	
	4	Cirrhosis	

Total NAS score represents the sum of scores for steatosis, lobular inflammation, and ballooning, and ranges from 0-8. Diagnosis of NASH (or, alternatively, fatty liver not diagnostic of NASH) should be made first, then NAS is used to grade activity. In the reference study, NAS scores of 0-2 occurred in cases largely considered not diagnostic of NASH, scores of 3-4 were evenly divided among those considered not diagnostic, borderline, or positive for NASH. Scores of 5-8 occurred in cases that were largely considered diagnostic of NASH.

FATTY LIVER DISEASE

SAF score

Bedossa et al.
HEPATOLOGY,
November 2012

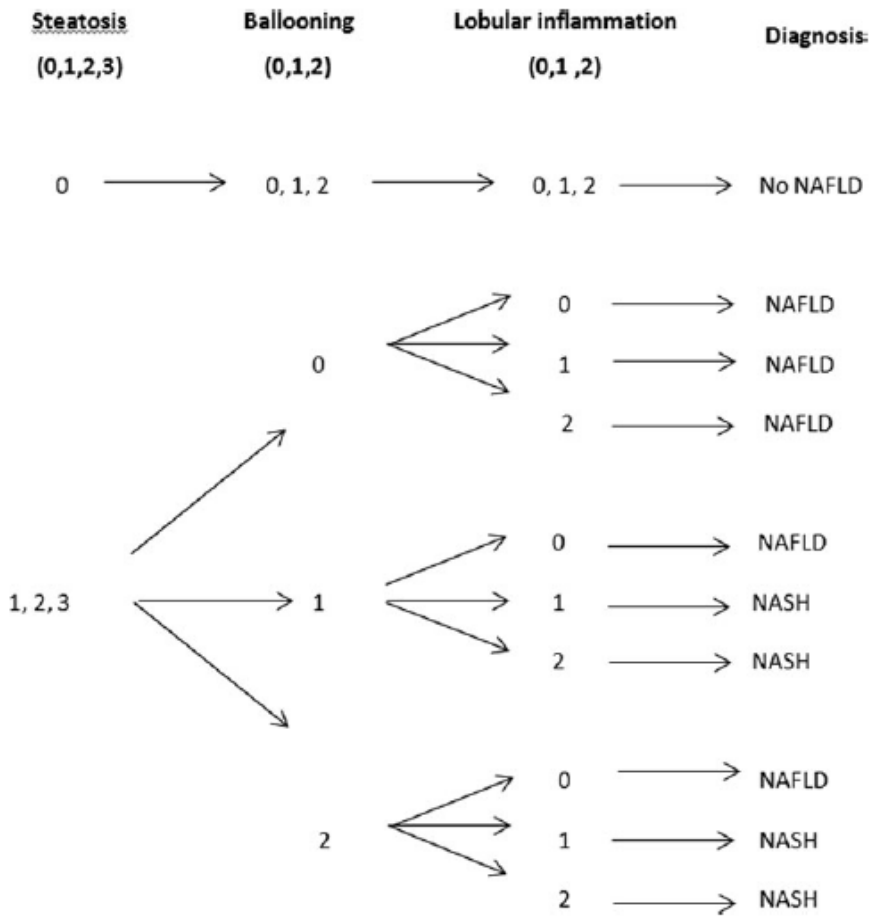


Fig. 2. Diagnostic algorithm for NASH.

Central- based Fibrosis

Which scoring system to use?

• Kleiner (NASH CRN) system covers broader spectrum for Stage 1 than older Brunt methodology but both cover most current demands

Limitations:

• Problems with stage 2 with only early centrizonal scarring combined with periportal scarring: many stage 1 lesions may be higher stage clinically
• Doesn't account for mixed portal/central lesions
• Doesn't evaluate for remodelling/regression

CHRONIC BILIARY DISEASE

Staging of PBC

	Rubin et al (1965)	Scheuer (1967)	Ludwig et al (1978)
Stage 1	Damage to intrahepatic ducts	Florid bile duct lesions	Portal hepatitis
Stage 2	Ductular proliferation	Ductular proliferation	Periportal hepatitis
Stage 3	Ductular proliferation	Scarring	Bridging necrosis or fibrosis (or both)
Stage 4	Cirrhosis	Cirrhosis	Cirrhosis

Histologic scoring system for primary sclerosing cholangitis

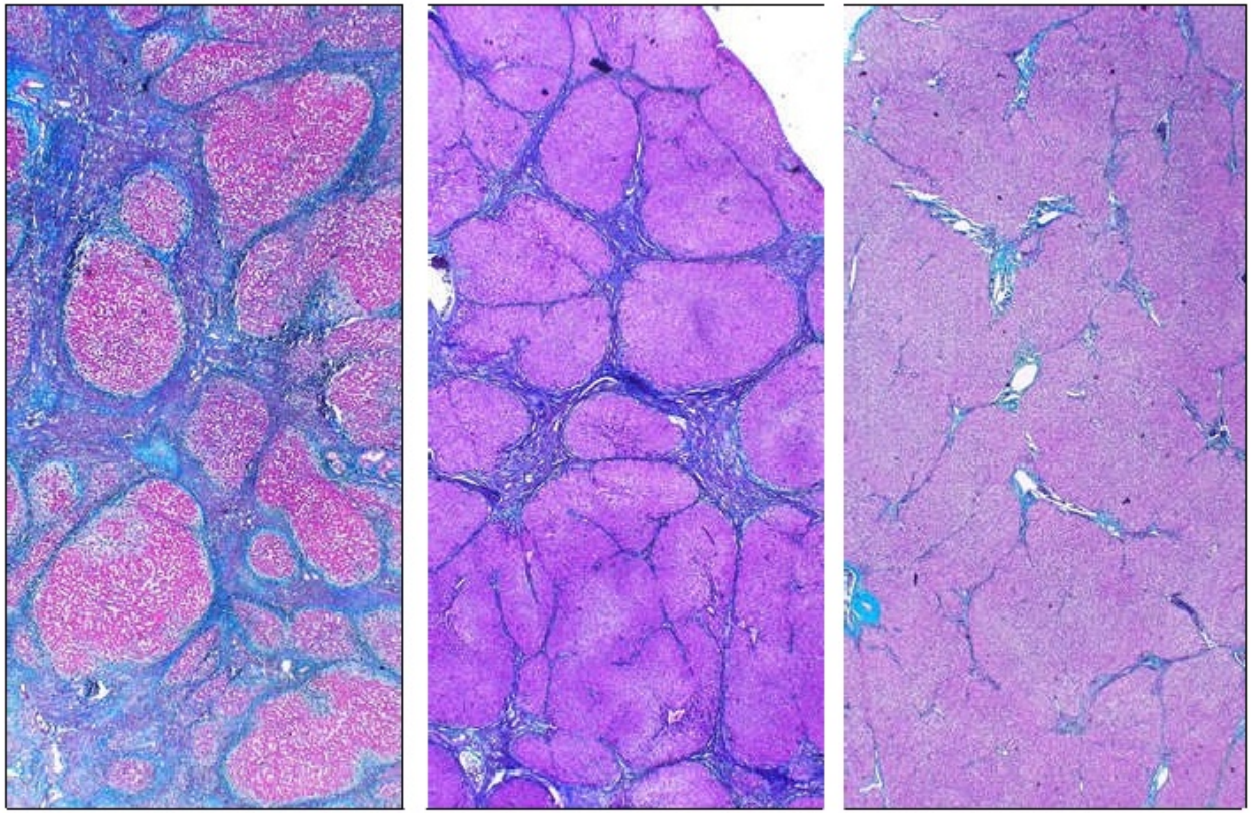
Stage	Definition
1	Cholangitis or portal hepatitis
2	Expansion of portal triads with fibrosis extending into the surrounding parenchyma
3	Septal fibrosis and/or bridging fibrosis
4	Cirrhosis

WHAT DO I DO FOR GRADING AND STAGING?

ND Thiese. Modern Pathology (2007) 20, S3–S14

- It does not matter which system you use!
- It is up to the pathologist working with the clinicians to figure out the needs of the clinician and to determine what is most comfortable and what makes sense
- Selection of a system depends more on comfort of the pathologist and the needs and expectations of the involved clinicians, that is personal preference
- Name the system clearly in your diagnosis and communicate with your clinicians the meaning of the different scorings in that system
- Provide words, not just the numbers

Regression fibrosis



Active EtOH Use

> 6 months abstinence

4 years abstinence

Linda Ferrell's lecture

Writing a diagnosis

Each written diagnosis should contain four pieces of information:

1. Pattern of injury (e.g. acute hepatitis, chronic hepatitis, steatosis, chronic biliary disease, coagulative necrosis…)
2. The grade of activity (including the name of the scoring system used);
3. The stage of activity (including the name of the scoring system used);
4. The known or suspected cause of the disease.

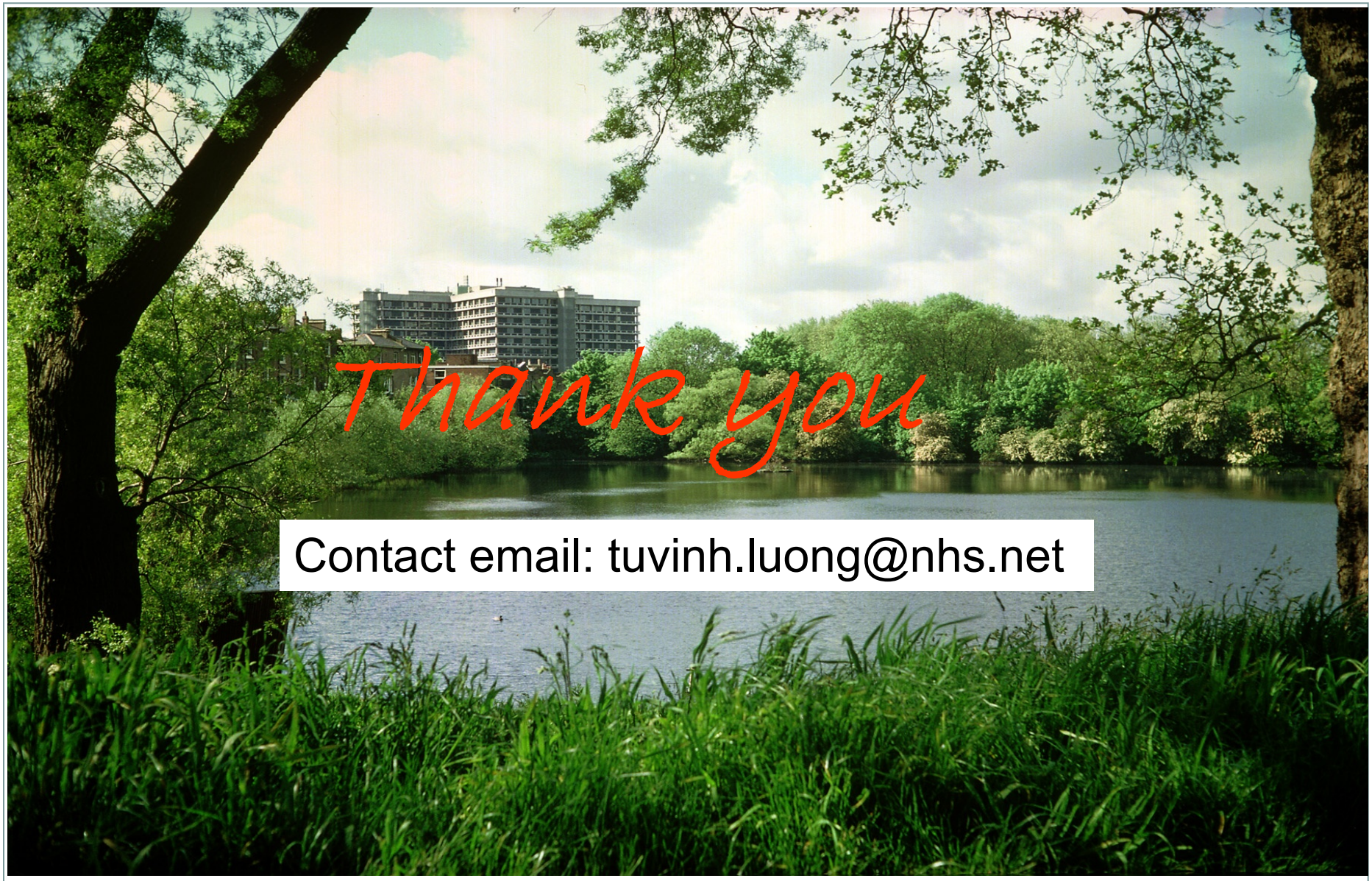
Examples of diagnoses

Using different scoring systems:

- Chronic hepatitis with Scheuer activity grades 2/4 (portal/periportal) and 1/4 (lobular), stage 3/4 (septa and focal architectural distortion), compatible with hepatitis C
- Steatosis with NAS activity of 5/8, stage 1b (moderate zone 3 perisinusoidal), in keeping with NASH

My own practice:

- Chronic hepatitis, mildly active with severe fibrosis amounting to developing cirrhosis (Ishak stage 5/6), compatible with hepatitis C.
- Steatosis with mild active steatohepatitis and extensive, dense zone 3 perisinusoidal/pericellular fibrosis (NASH CRN stage 1b), in keeping with NASH



Contact email: tuvinh.luong@nhs.net

Royal Free London NHS
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