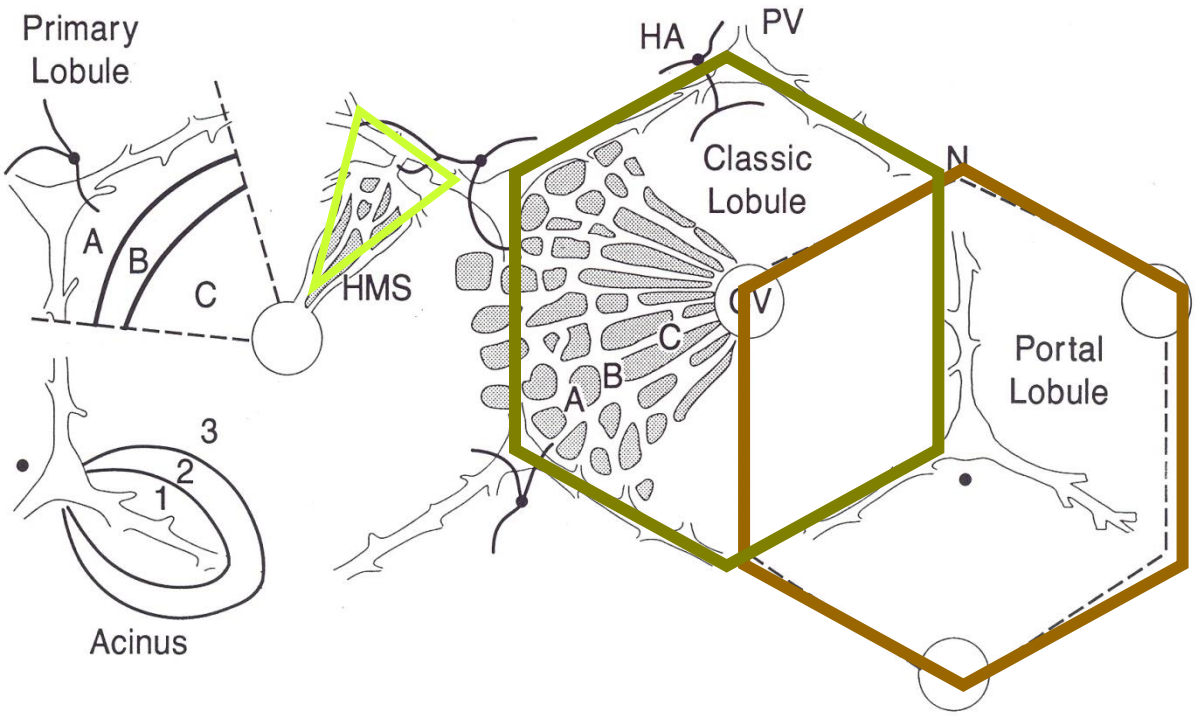
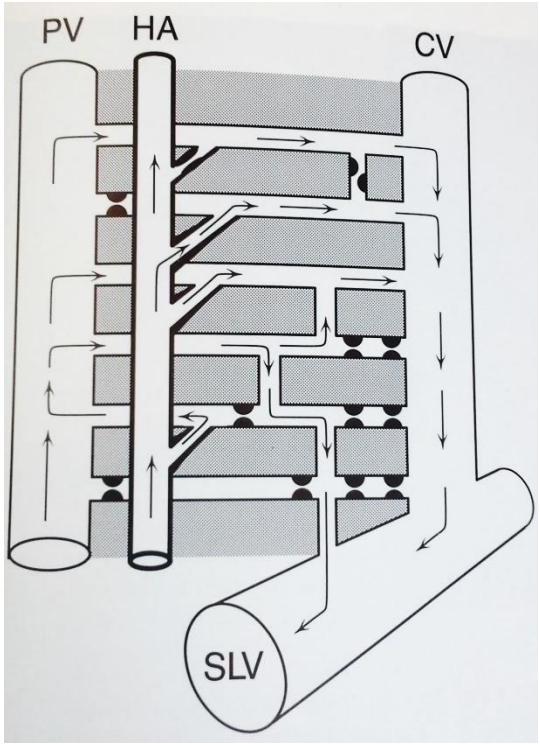
PATHOLOGY OF THE LIVER

Liver failure
Cholestatic liver diseases (PSC, PBC),
Jaundice, causes, pathophysiology and defectis in bilirubin metabolism(cholelithiasis)
Circulatory disorders of liver
Acute and chronic hepatitis
Alcohol- and Drug-induced liver disease
Metabolic and Inherited liver disease
Liver cirrhosis
Tumors and tumor-like lesions of liver

Microanatomy of the liver





Circulatory disorders of liver

1.-Hepatic artery compromise

Liver infarcts-rare, double blood supply!!!!!!
Thrombosis- A.hepatica-in transplanted liver 2-9%, bile duct destruction and graft dysfunction

2-Portal vein

-Forms -

Prehepatic (pylethrombosis): **portal vein obstruction**

Hepatic: **cirrhosism sickle cell disease, DIC, intrasinusoidal metastases**

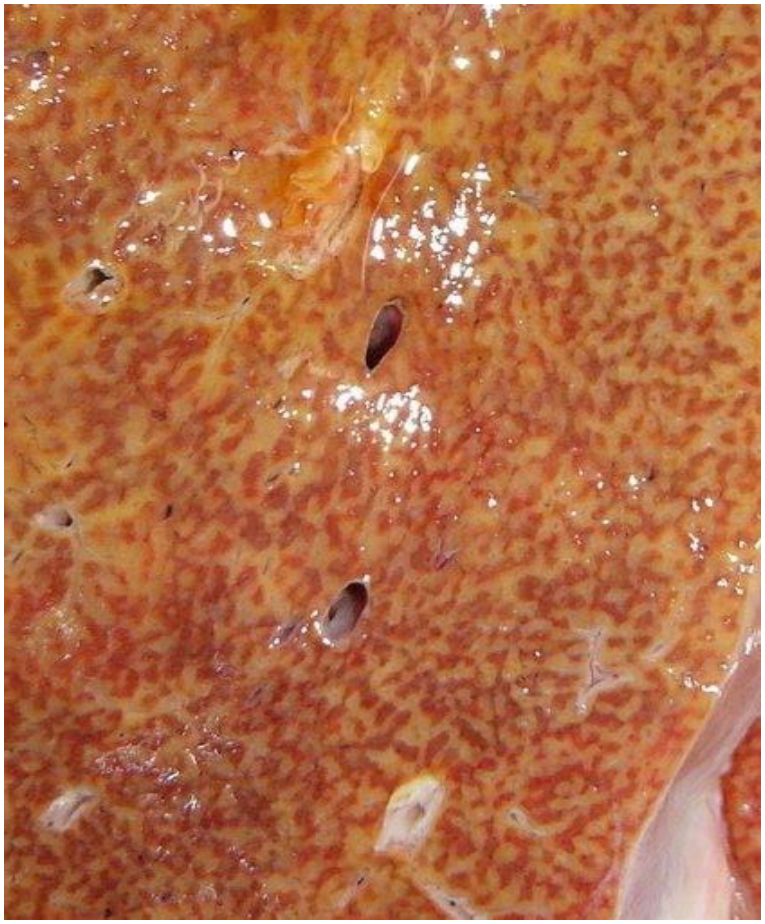
Posthepatic: **Right-sided heart failure, Budd-Chiari syndrome, (Hypercoagulable states)**
Liver cyst, liver abscess
Idiopathic
Sinusoidal obstruction

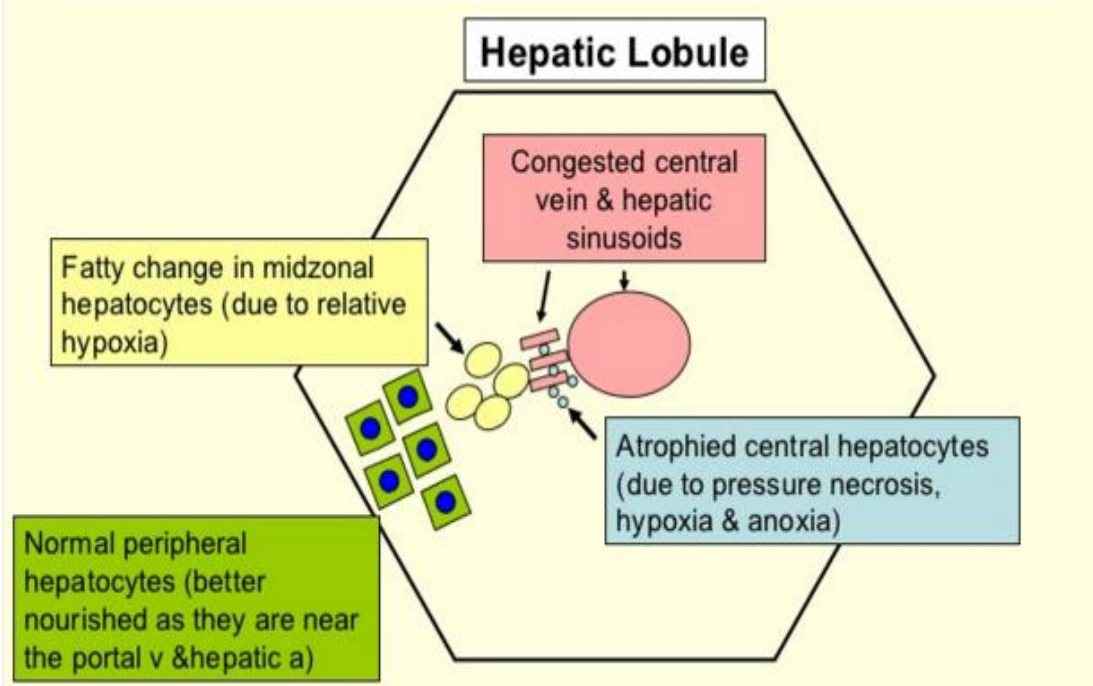
- Consequences-

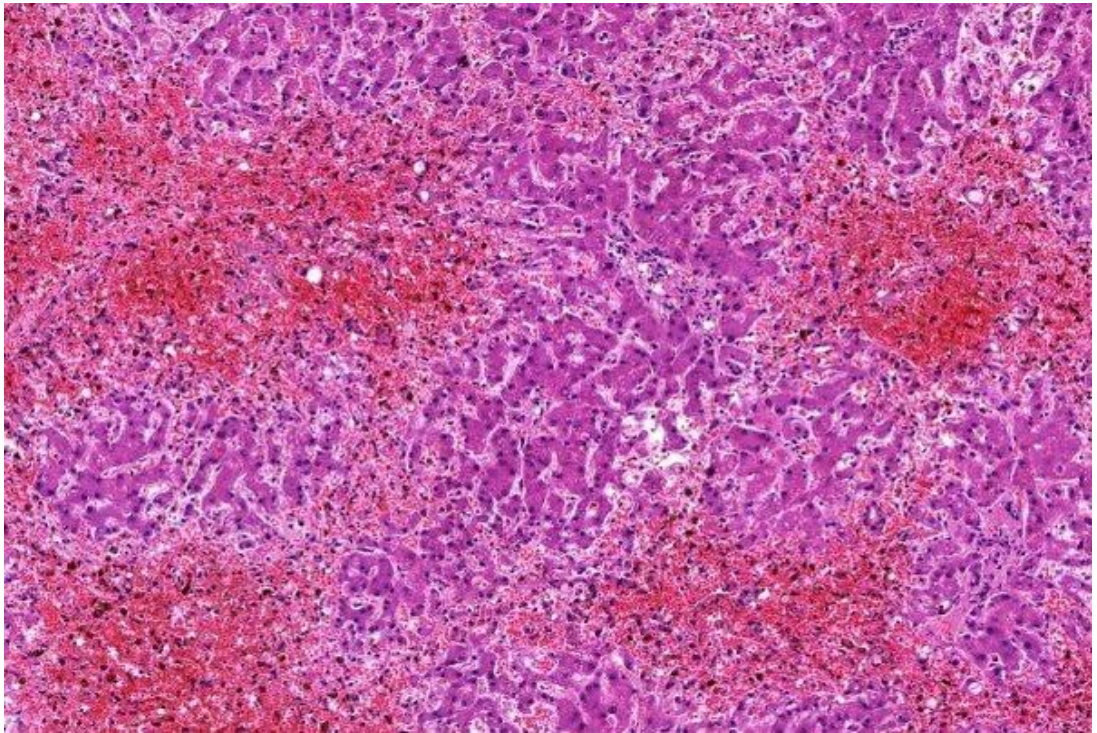
- Ascites (hypoalbuminaemia, sec hyperaldosteronismus)
- Splenomegaly
- Shunts, bleading

Circulatory disorders of liver

Liver congestion







Circulatory disorders of liver

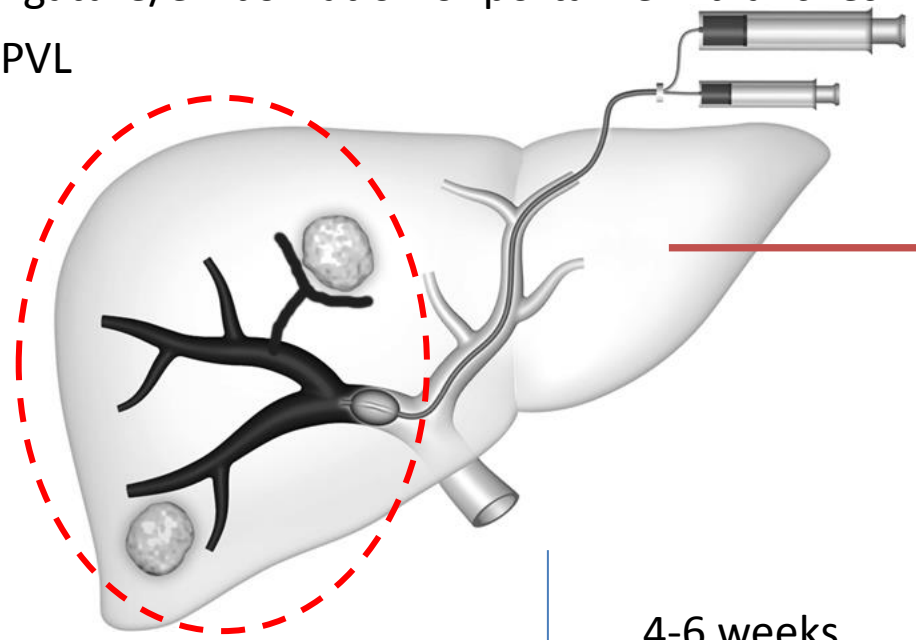
Obstruction of intrahepatic portal vein radicles does not cause ischemic infarction but instead results in a sharply demarcated area of red-blue discoloration called ***infarct of Zahn*** . There is **no necrosis**, only severe hepatocellular atrophy and marked congestion of distended sinusoids.

- Obstruction of intrahepatic portal vein radicles may be caused by **thrombosis or tumor**

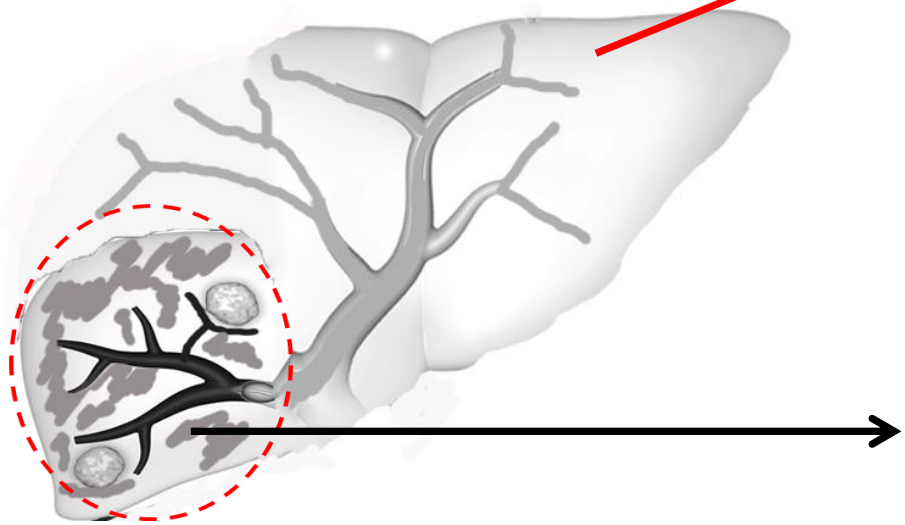
-The most common cause of small portal vein branch obstruction is s**chistosomiasis**

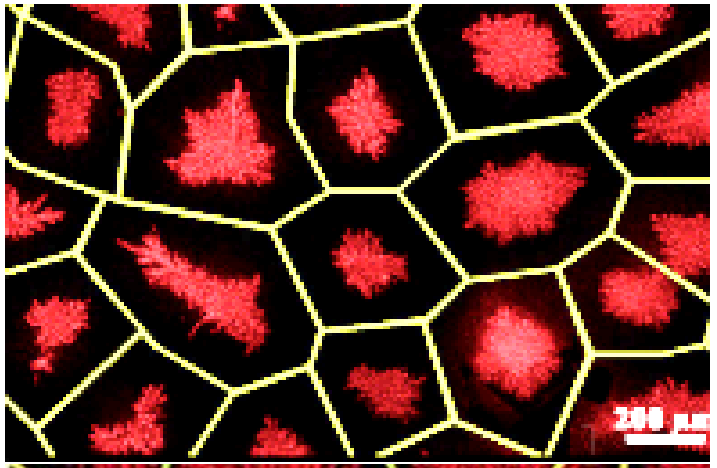
Ligature/embolization of portal vein branches

PVL



4-6 weeks





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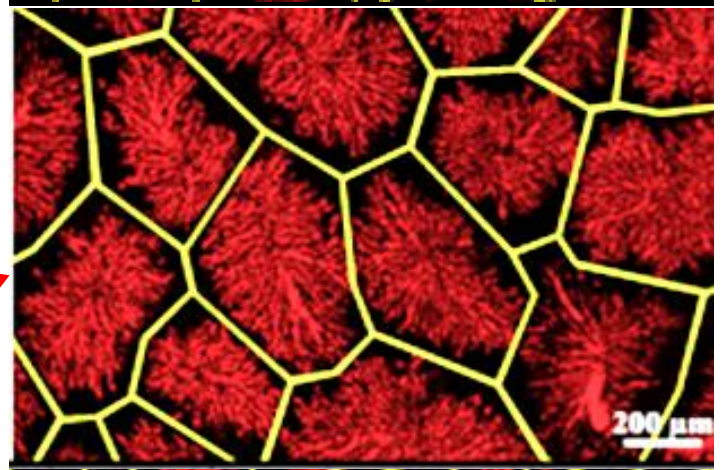
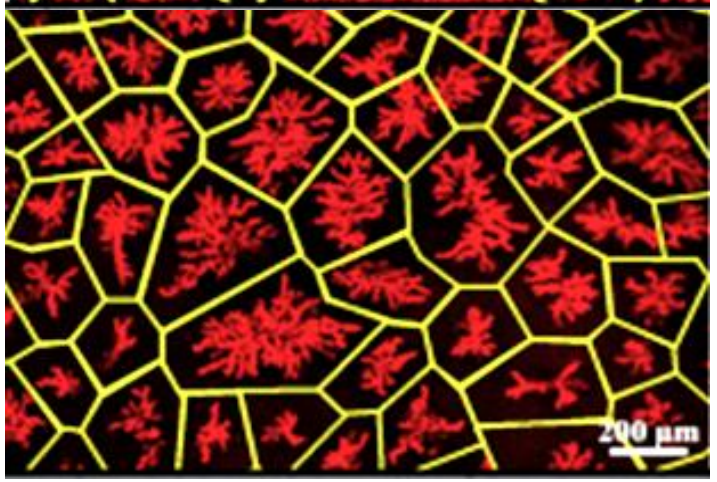


NPVL



PVL

Journal of surgical research 197 (2015) 307-317

Acute and chronic hepatitis (clinical syndromes)

Hepatitis is an *inflammation of the liver*. Hepatitis ***viruses*** are the most common cause of hepatitis in the world but other ***infections***, ***toxic*** substances (e.g. alcohol, certain drugs), and ***autoimmune*** diseases can also cause hepatitis.

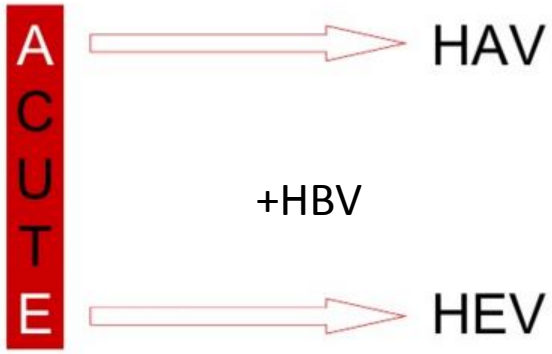
Clinicopathologic Syndromes of Viral Hepatitis

- **Acut asymptomatic** only serology or laboratory
- **Acut hepatitis (**with recovery) jaundice, fever, fatigue etc.
- **Chronic hepatitis** mild or no clinical symptoms!!!
  progressive disease>cirrhosis
  (interface hepatitis, Councilman bodies)
- **Fulminant** fulminant hepatic failure
- **Carrier** healthy ,but infected and infectious individuals
- **HIV+Chronic hepatitis**

Acute and chronic hepatitis

Features of virus hepatites

	Acut	Chronic	Fulminans	Carrier
A (feco-oral)	+		+/-	
B (horiz., blood, sex)	+	+	+	+
(vertical)				
C (blood,?)		+		+/-



The inflammatory cells in both acute and chronic viral hepatitis are mainly T cells; it is the pattern of injury that is different, not the nature of the infiltrate.

Other causes of hepatitis: non-hepatotropic viruses (dengue,hanta, ***HSV, EBV, CMV***)
autoimmune, toxic

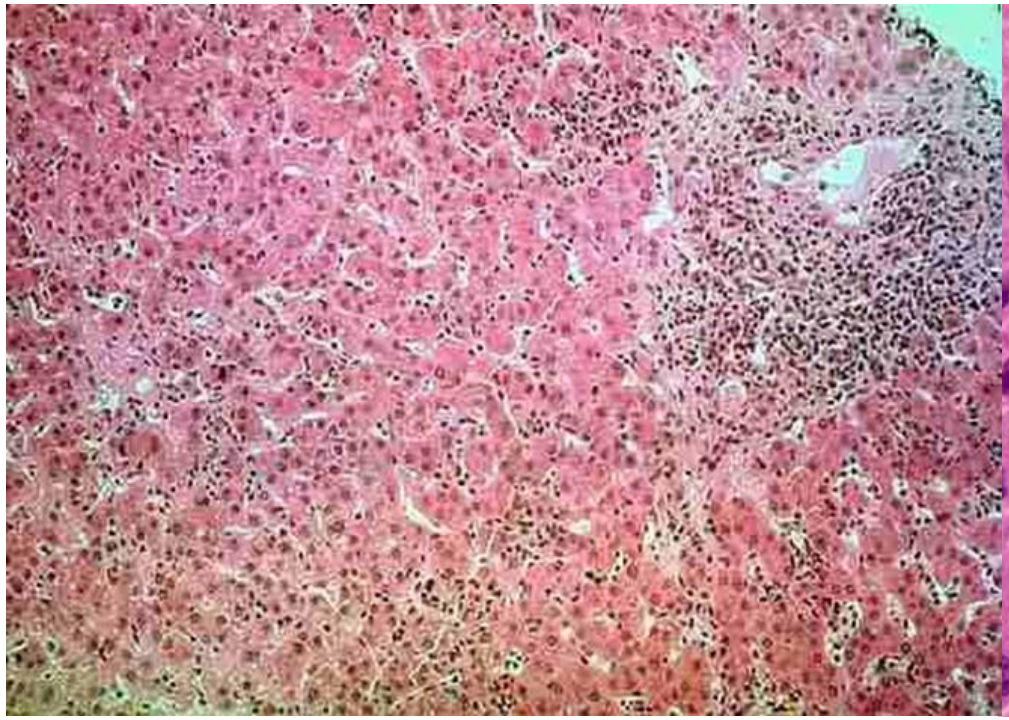
Acute and chronic hepatitis

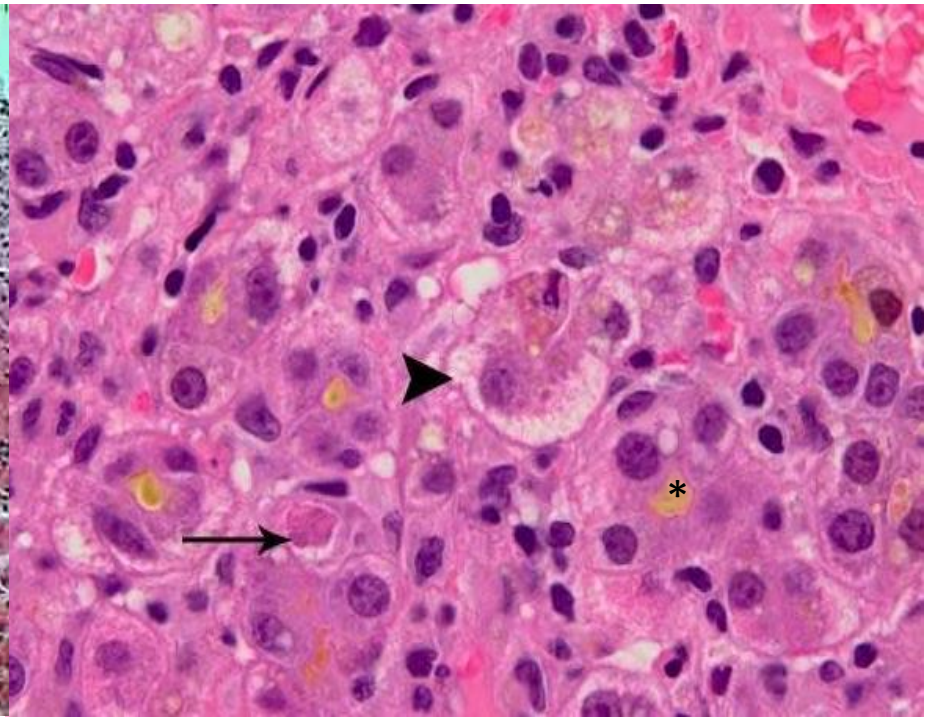
Acute hepatitis

Acute „lobular” hepatitis

Macro: normal or slightly mottled, greatly shrunken, green…….

Micro:

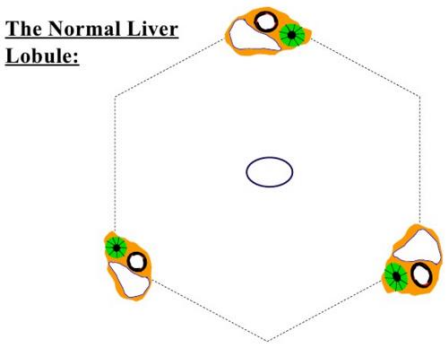


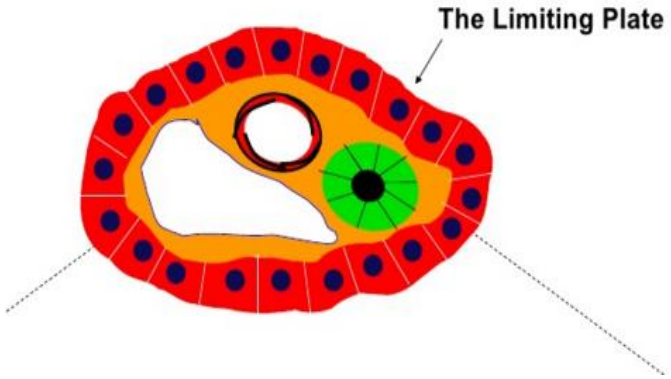


Lobular disarray, inflammatory cell in sinusoids, apoptotic bodies (arrow) balloning of hepatocytes(arrowhead) and cholestasis (star).

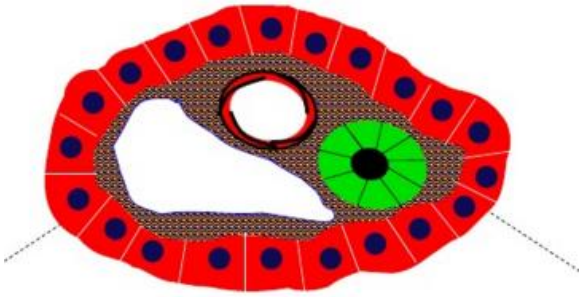
Conseq: „Self-limiting”, Acute liver failure (hepA and B less than 1%), chronic hepatitis (hepB)

Acute and chronic hepatitis





Chronic Hepatitis



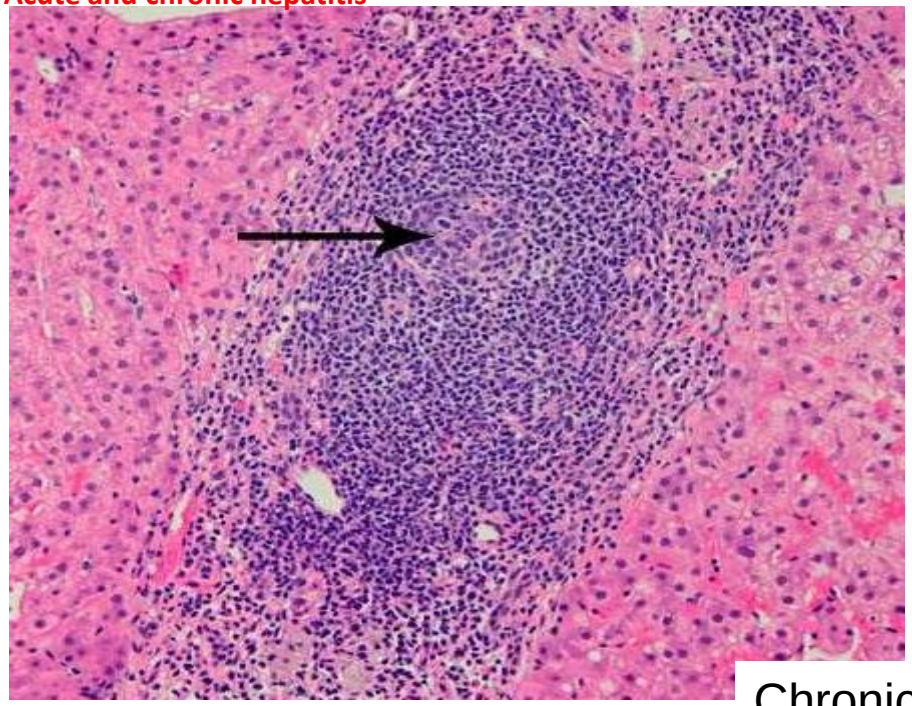
Portal inflammation
DEFINES
Chronic Hepatitis

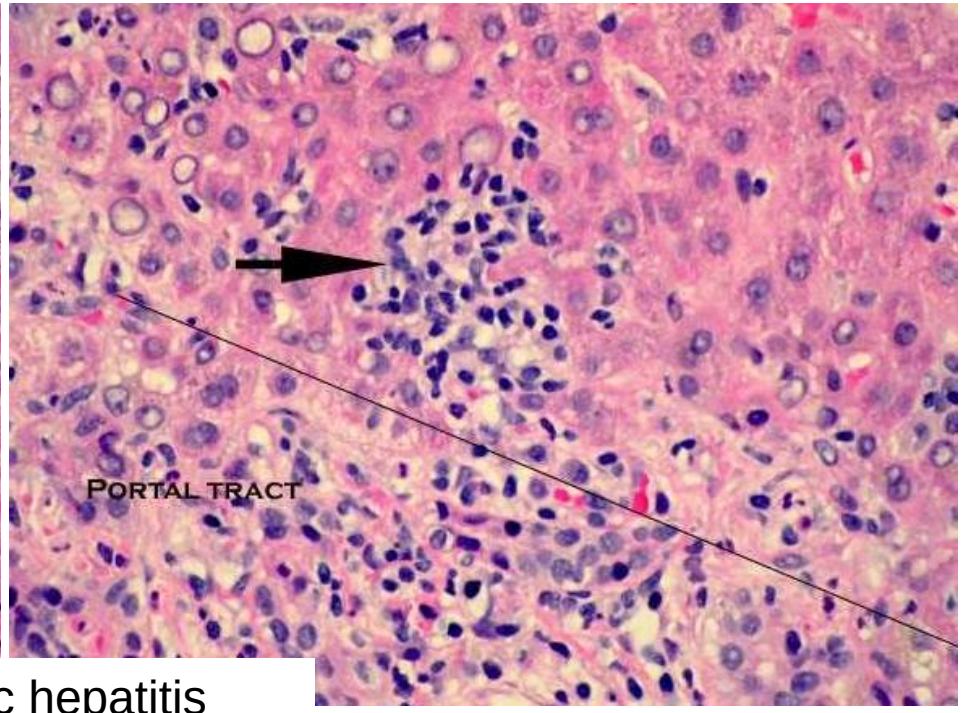
Interface hepatitis
Piecemeal necrosis*

↓

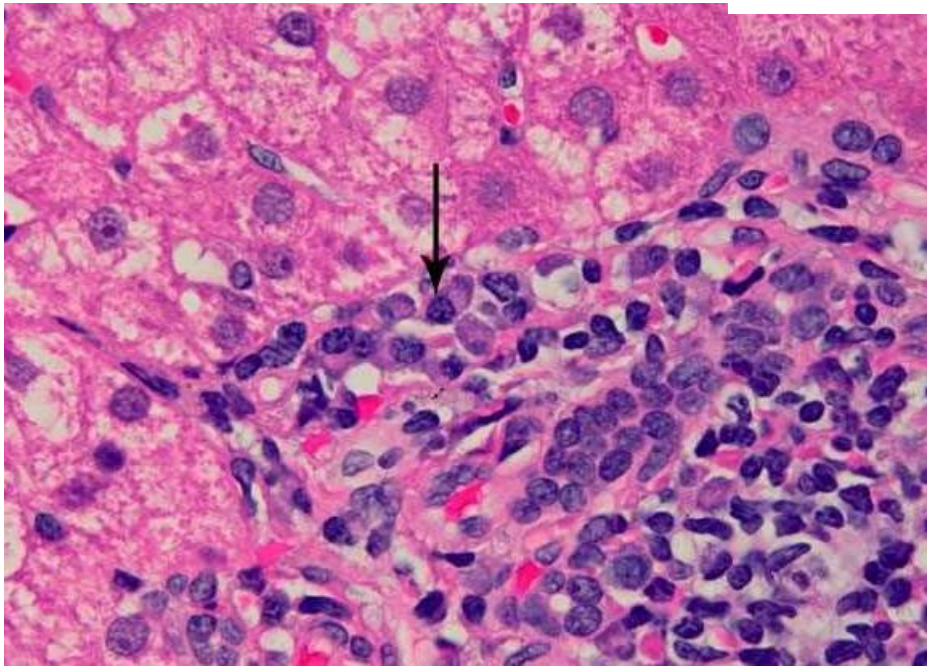
Misnomer because it is apoptosis

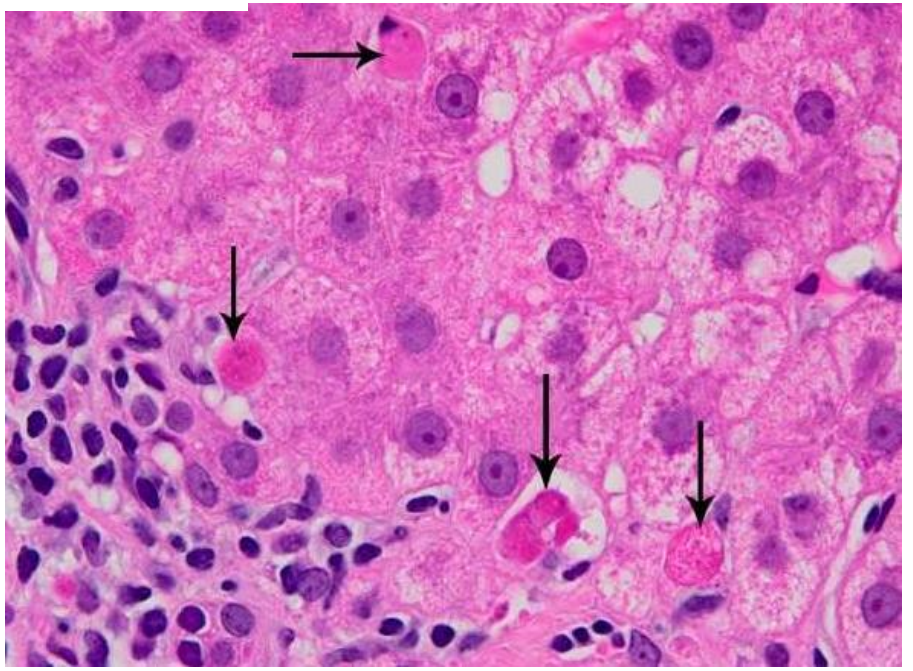
Acute and chronic hepatitis



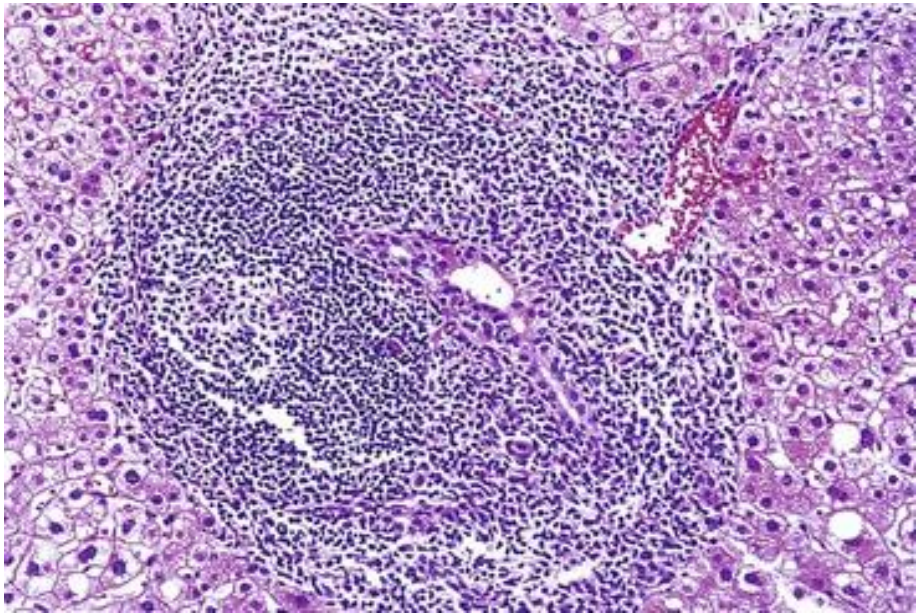


Chronic hepatitis

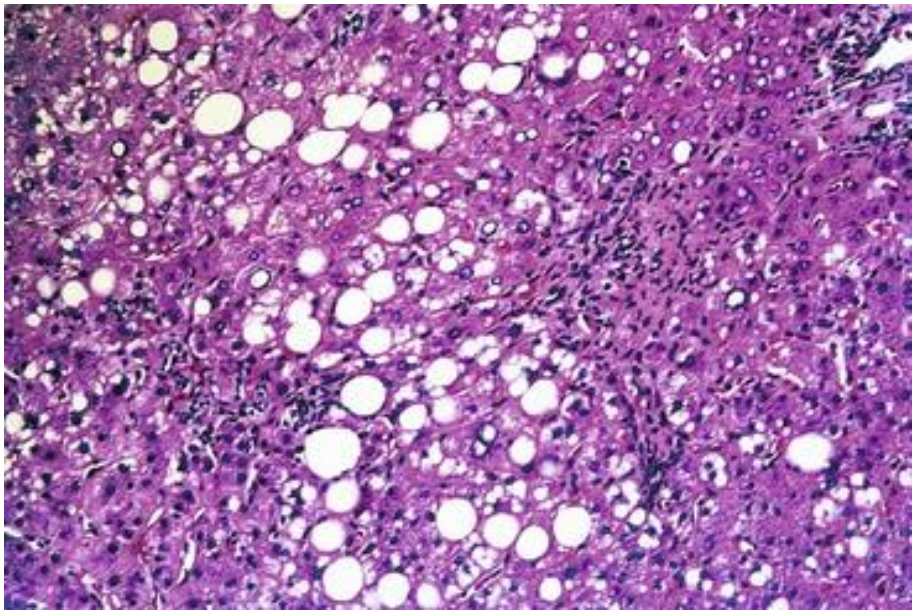




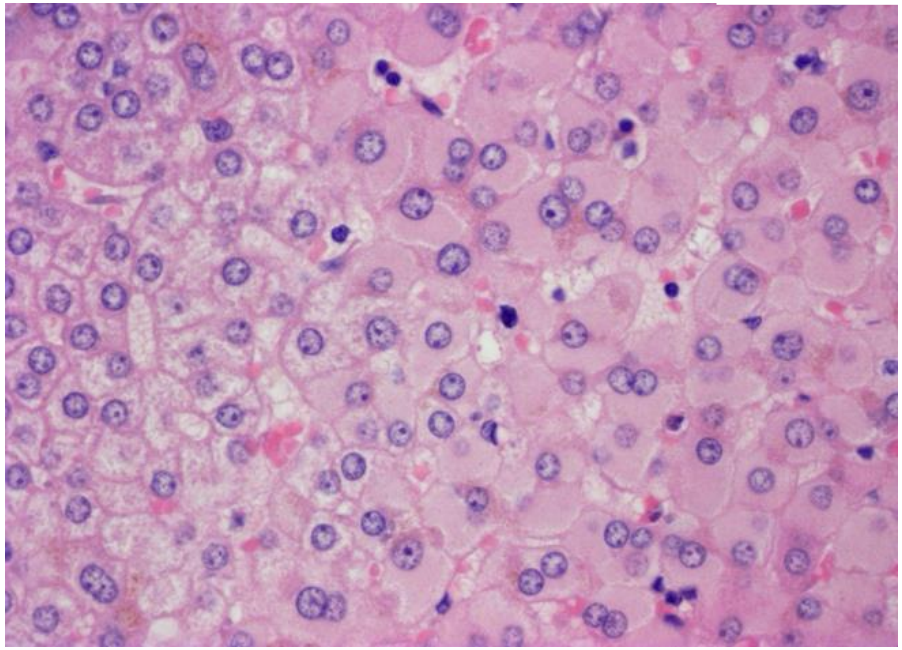
Ly aggregates +/- Germinal center (HCV)



Fatty degeneration+chr.inflammation (HCV)

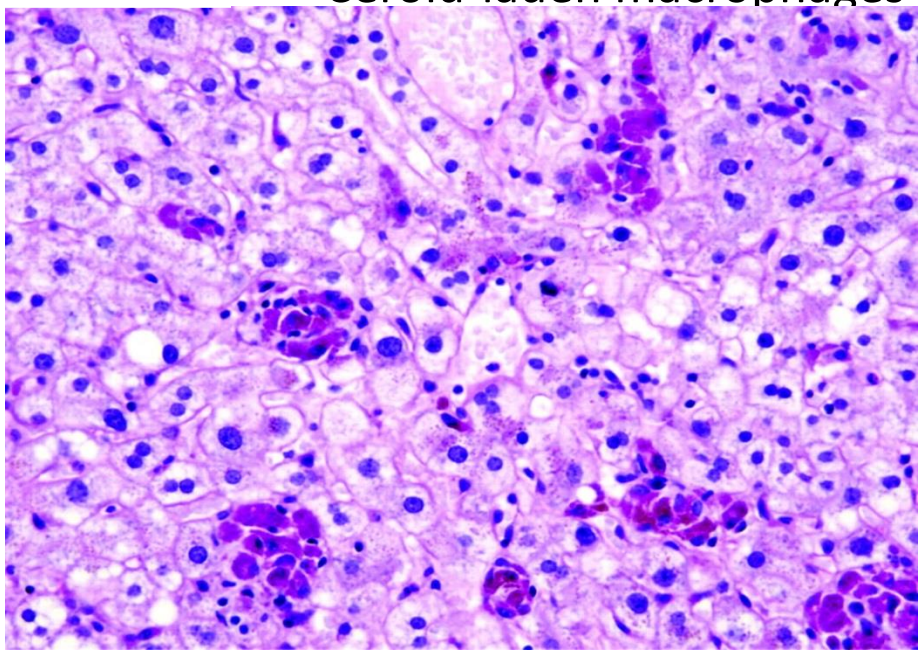


Ground-glass hepatocytes (HBV)



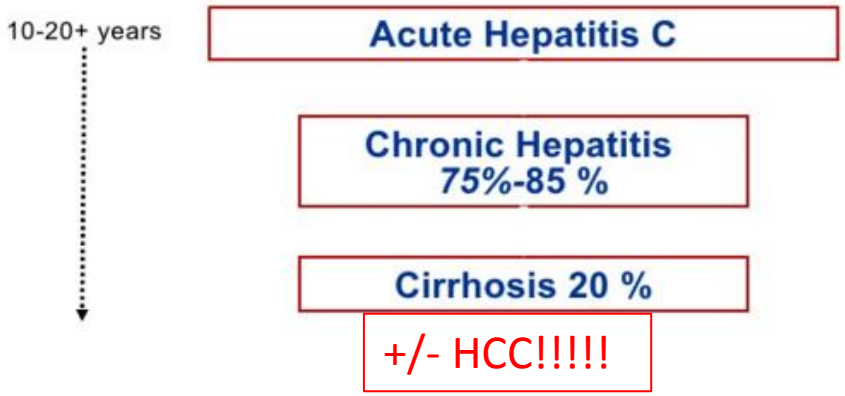
Chronic hepatitis

Ceroid-laden macrophages

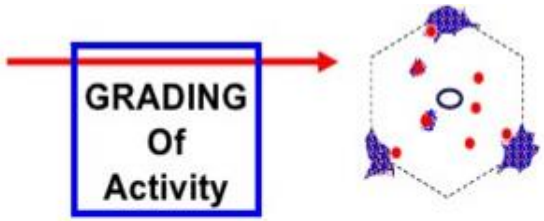


Acute and chronic hepatitis

Natural history of hepatitis C:



- Hoofnagle JH, Hepatology. 1997
- Di Bisceglie A, Hepatology, 2000

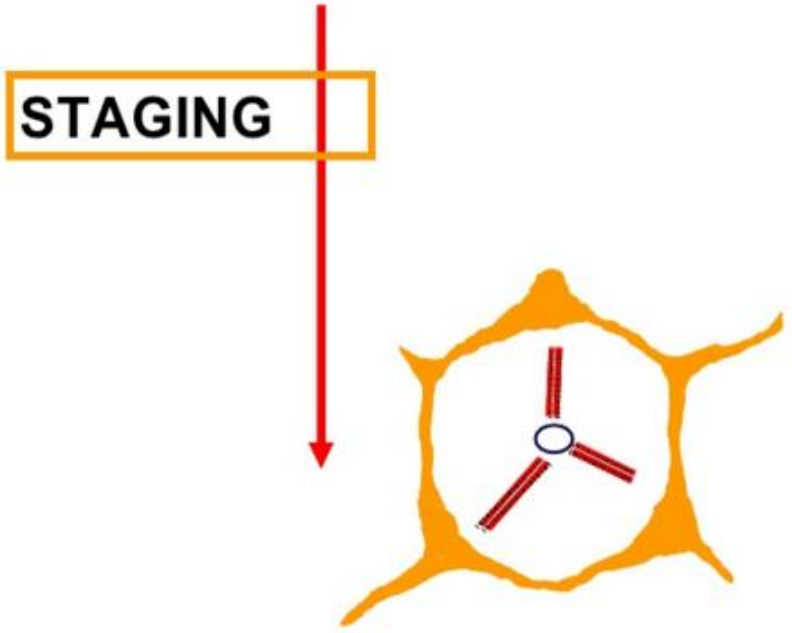


- Portal inflammation
- Interface hepatitis
- Lobular hepatitis
- Confluent necrosis

The progression depends on:

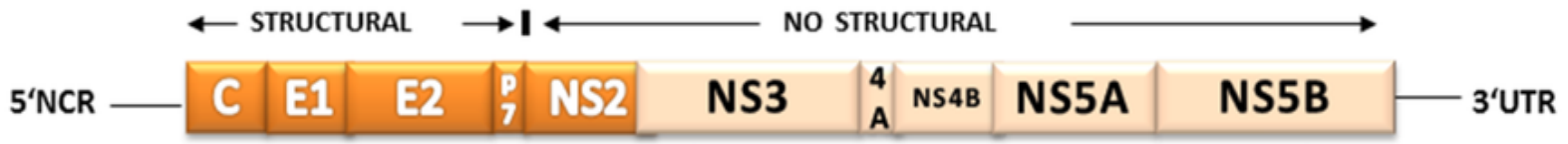
- **Alcohol consumption**
  - *30 g/day in men*
  - *20 g/day in women*

  } ~ 2 drinks per day
- **Disease acquisition at >40 years**
- **Male gender**
- **HIV co-infection** *(treated vs. untreated)*
- **Fatty liver**
- **Hepatitis B virus co-infection**
- **Immunosuppression**



NIH Consensus Development Conference Statement. 2002.
Poynard et al. *Lancet*. 1997;349:825-832.

Hepatitis C treatment



PROTEASE Inhibitors (PI)
Block active site viral enzyme
-PREVIR

LOW BR
1st Gen.1st wave (GT1):
TELAPREVIR *
BOCEPREVIR *
1st Gen.2nd wave (all GTs except 3)
SIMEPREVIR *
ASUNAPREVIR
PARITAPREVIR/ritonavir *
VANIPREVIR (MK-7009)
DANOPREVIR

HIGHER BR
2nd Generation. Pangenotyping less effective for GT3:
MK-5172 (Grazoprevir-GRZ)
ACH-2684

NS5A Inhibitors (NS5AI)
Block Replication complex, particle assembly & release
-ASVIR

LOW BR
1st Gen. (GT1 and GT4. Other genotypes variable)
DACLATASVIR *
LEDIPASVIR *
OMBITASVIR (ABT-267) *

Slighlty **HIGHER** BR
2nd Gen
Elbasvir
MK-87 **R)**
GS-5816
ACH3102
SAMATASVIR (IDX719)

NS5B Nucleos(t)ide Inhibitors (Nucs or NI)
Block active site.
Inhibits RNA elongation
-BUVIR

HIGH BR
Pangenotyping (less SVR GT3)
SOFOSBUVIR *
MERACITABINE
ACH-3422
IDX21437
IDX21459

NS5B Non-Nucleos(t)ide Inhibitors (Non-Nucs or NNI)
Allosteric site.
Change tridimensional structure
-BUVIR

LOW BR
Narrow genotyping coverage
DASABUVIR (ABT-333) *
DELEOBUVIR
BMS-791325 (Beclabuvir)
PPI-383
GS-9669
TMC647055

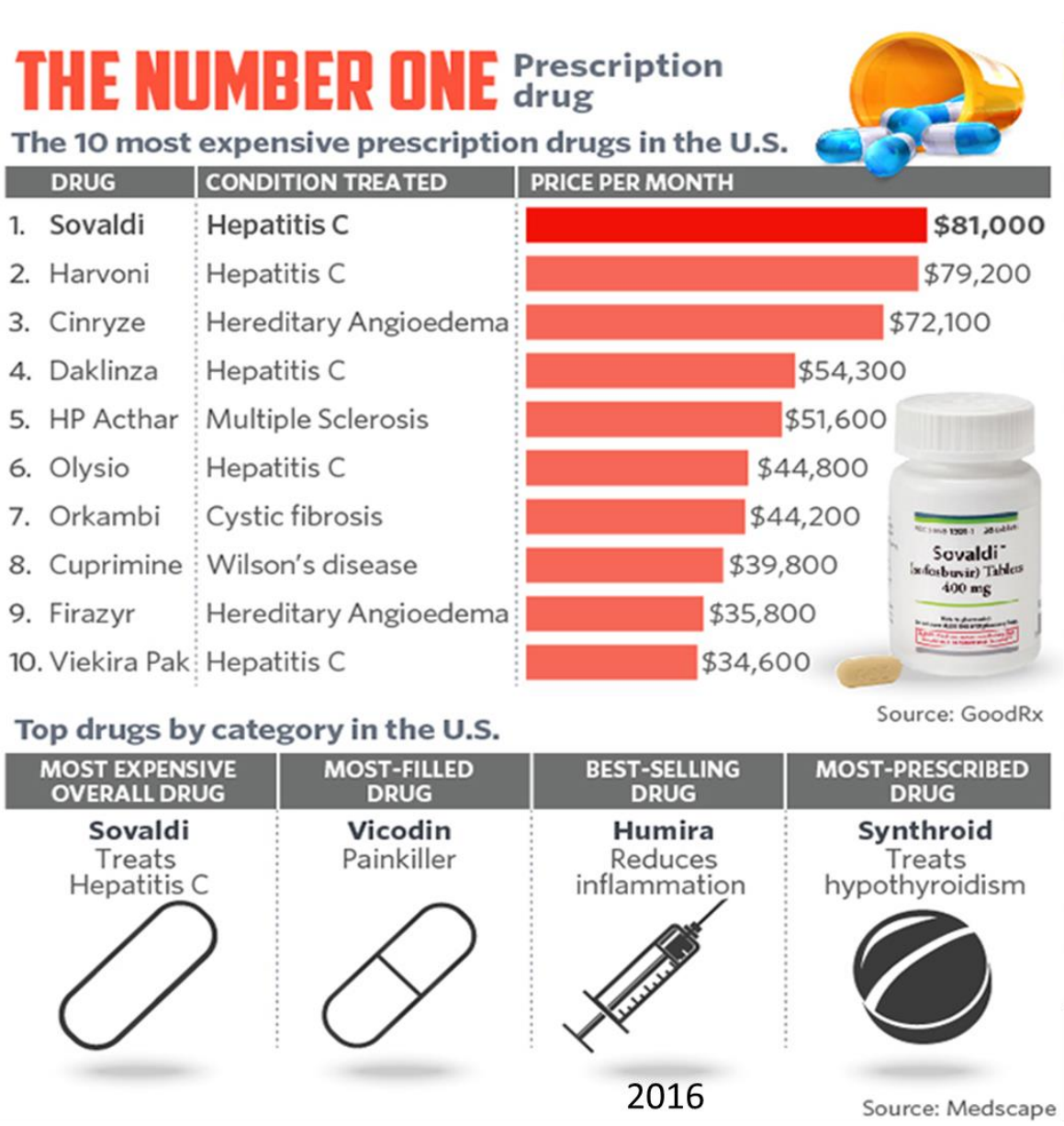
ORAL IFN-free treatment (+/- Ribavirin)
HARVONI: LEDIPASVIR+SOFOSBUVIR

ORAL IFN-free treatment (+/- Ribavirin)
VIEKIRAX: OMBITASVIR-PARITAPREVIR-ritonavir +
EXVIERA: DASABUVIR

BR= barrier to resistance. * Approved

Hepatitis C treatment

GoodRx creates a list of the most expensive prescriptions in the United States



The 20 Most Expensive Drugs

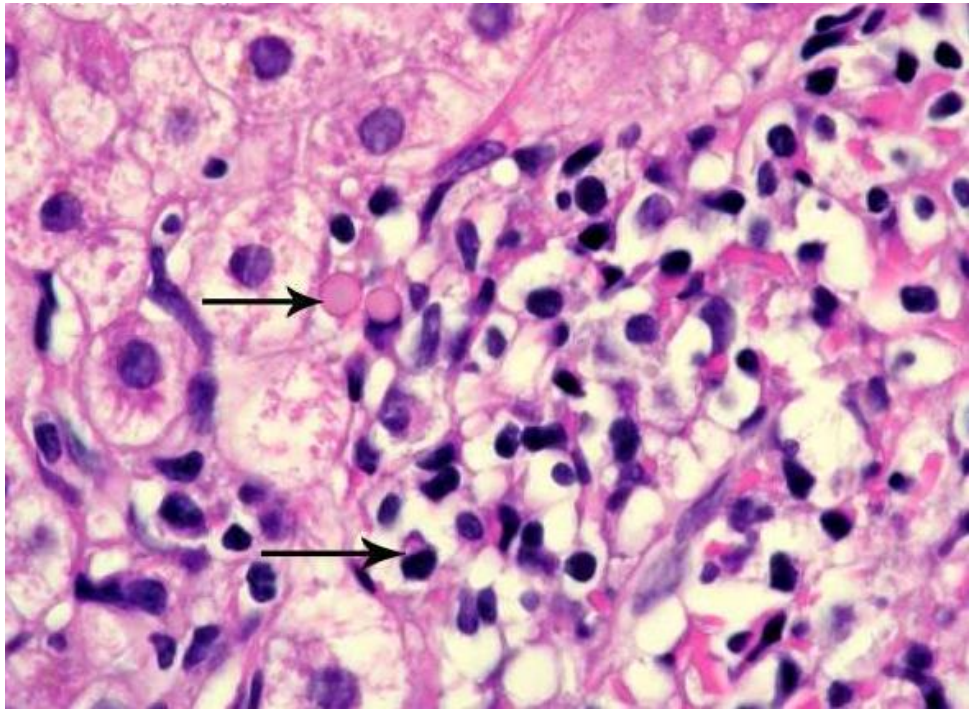
Drug	Manufacturer	List price
Actimmune	Horizon Pharma	$52,322
Daraprim	Vyera Pharmaceuticals	$45,000
Cinryze	Shire	$44,141
Takhzyro	Shire	$44,140
Chenodal	Retrophin, Inc	$42,570
Myalept	Aegerion Pharmaceuticals	$42,138
H.P. Acthar	Mallinckrodt Pharmaceuticals	$38,892
Juxtapid	Aegerion Pharmaceuticals	$36,992
Tegsedi	Akcea Therapeutics	$34,600
Firazyr	Shire	$32,468
Ravicti	Horizon Pharma	$32,004
Harvoni	Gilead	$31,500
Cuprimine	Valeant Pharmaceuticals	$31,426
Sovaldi	Gilead	$28,000
Viekira Pak	Abbvie	$27,773
Viekira XR	Abbvie	$27,773
Orfadin	Apotek Produktion & Laboratorier AB	$27,247
Zavesca	Actelion Pharmaceuticals	$26,820
Tibsovo	Agios Pharmaceuticals	$26,115
Remodulin	United Therapeutics	$25,466

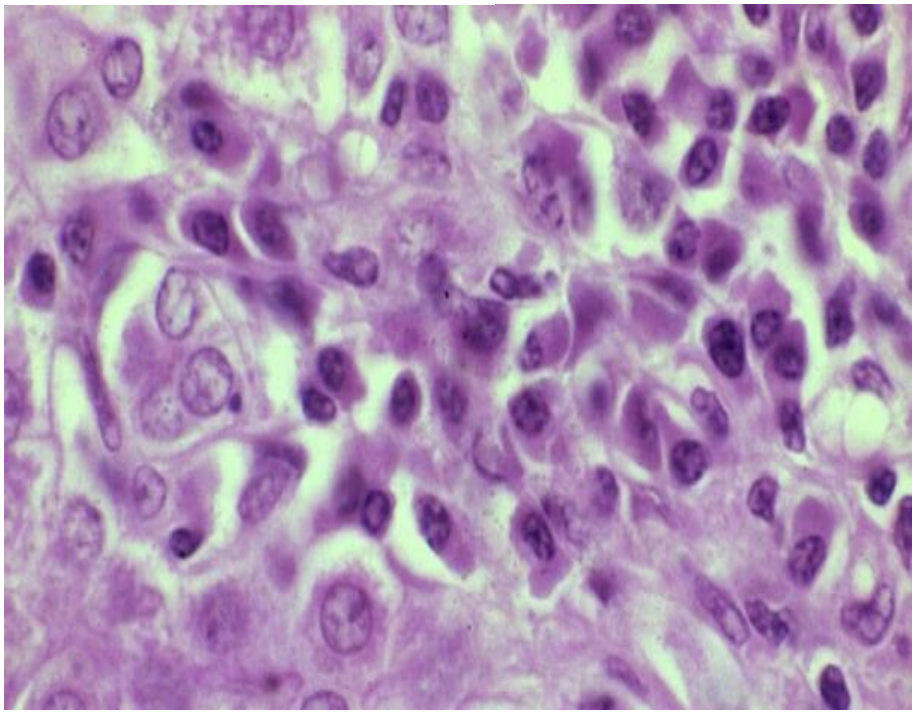
2018

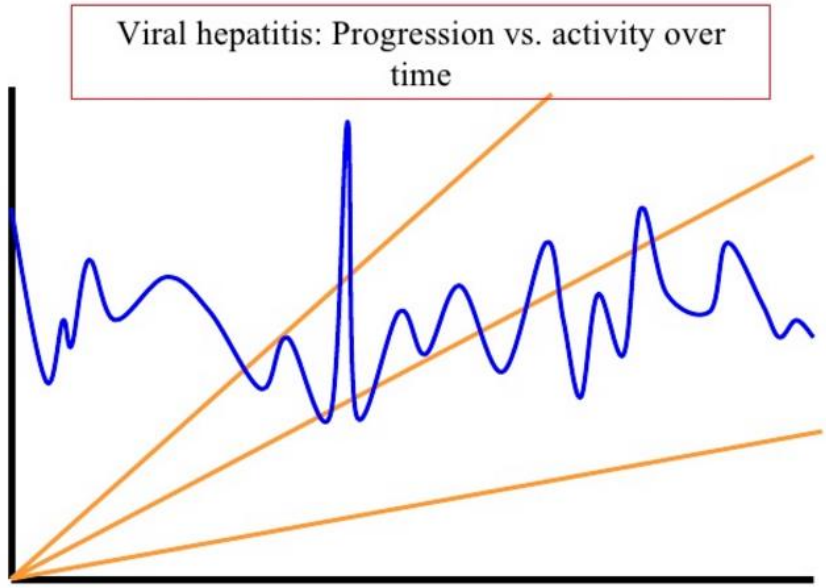
Acute and chronic hepatitis

Autoimmune hepatitis

Gender: Mostly female
Age: 40's - 60's
Autoantibodies: anti-nuclear (ANA)
anti-smooth muscle (ASMA)
anti-mitochondrial (AMA)
anti-liver kidney microsomal 1 (LKM1)
Presentation: Very severe activity &/or very late stage
Treatment: Immune suppression, transplant for endstage.

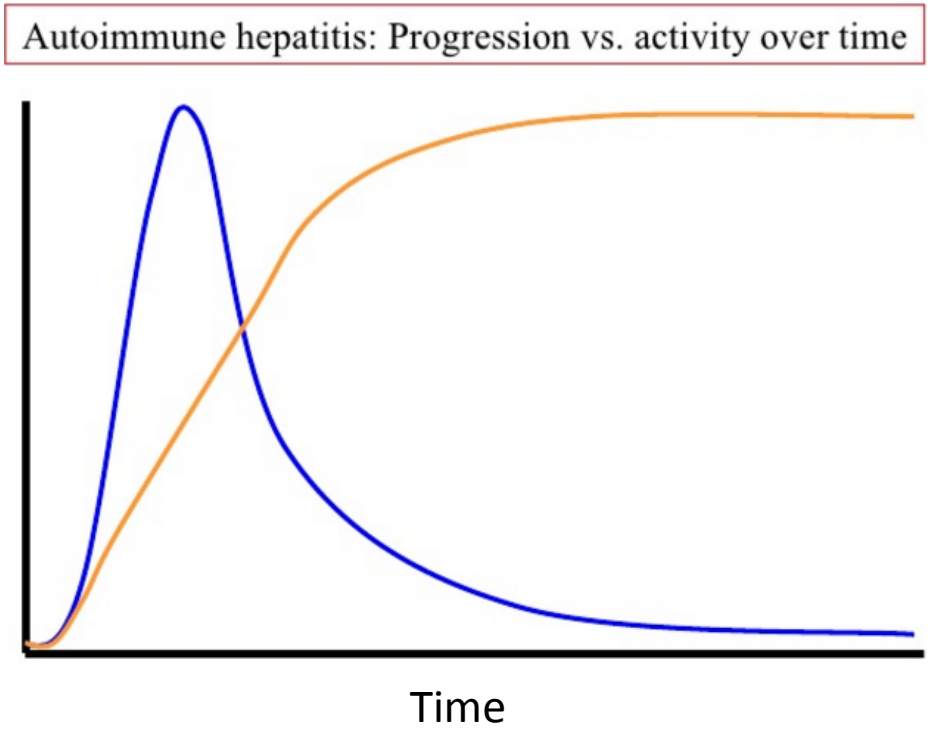






Inflammation

Fibrosis



Jaundice

Jaundice (icterus): elevated serum bilirubin

Non-Conjugated: non-water soluble, toxic
Conjugated: water-soluble, nontoxic bilirubin

Etiology:

Prehepatic **(**hemolysis, Physiologic jaundice of the newborn)

Hepatic**: liver diseases: hepatitis, cirrhosis**
Hereditary Hyperbilirubinemias: **Crigler-Najar**, **Dubin Johnson, Gilbert, Rotor**

Posthepatic**: biliary obstruction (gallstones, tumors)**

Cholestasis: bile retention

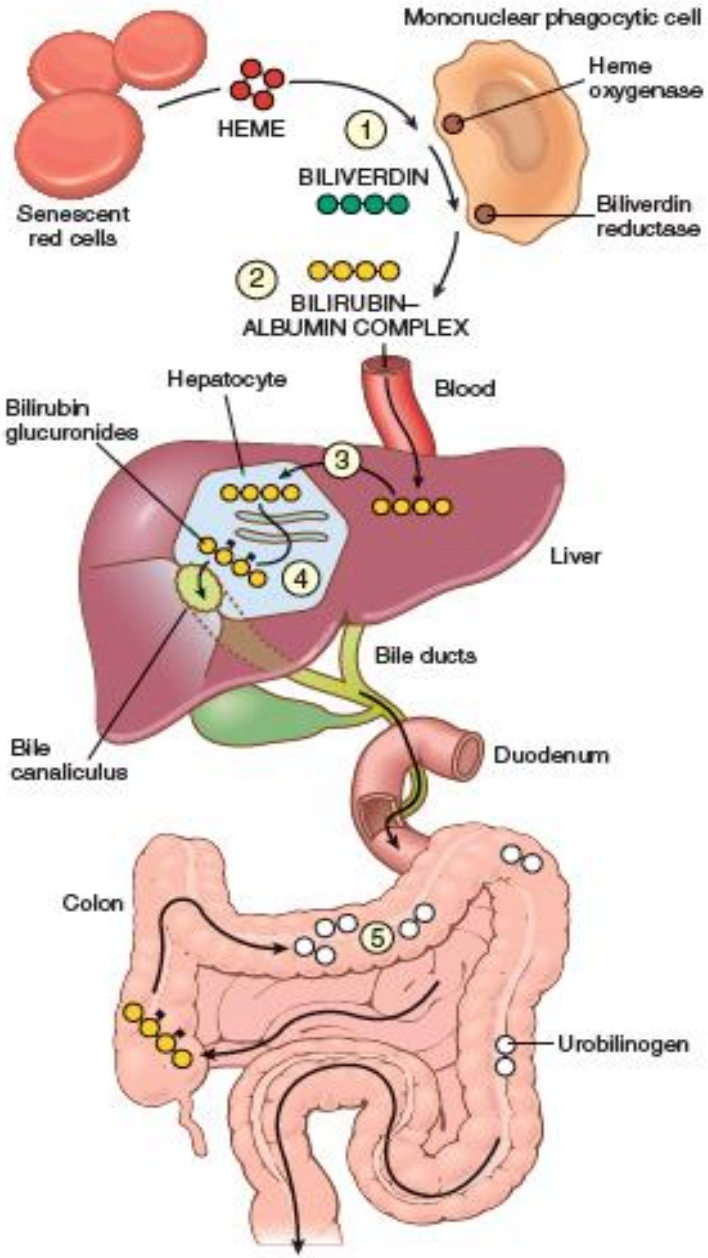


Fig. 16.22 Bilirubin metabolism and elimination.

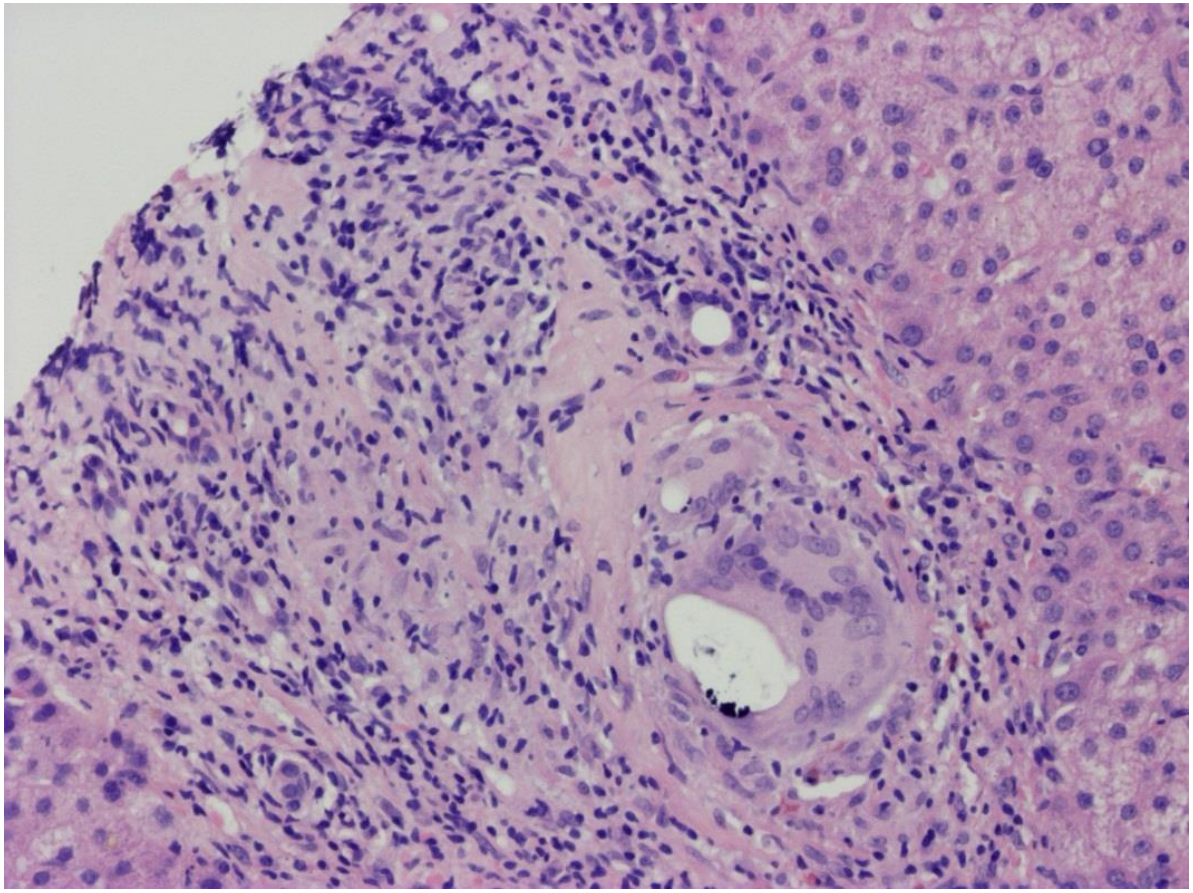
Cholestatic liver diseases (PSC, PBC)

PBC

PRIMARY BILIARIS CIRRHOSIS –

Primary biliary cholangitis

Gender: Women
Age: Middle aged to older
Associated diseases: Scleroderma
Hashimoto's thyroiditis
CREST syndrome
Sjogren's syndrome, etc....
Serologic markers: AMA (ASMA, ANA)
Bile ducts involved: Medium to small ducts ONLY



1st.Bile duct injury/loss
2st. Bile duct proliferation
3-4st.Fibrosis to Septal cirrhosis

„End-stage" PBC:
-Severe cholestasis , portal hypertension , without „full" cirrhosis"

Dg: Liver biopsy
(ERCP is not good, because only medium to small ducts are affected)

therapy: ursodezoxycholic acid, transplantation

Cholestatic liver diseases (PSC, PBC)

PRIMARY SCLEROSING CHOLANGITIS

Strongly association with UC (less with CD)

Inflammation, fibrosis and stricture of the intra/ extra hepatic ducts.

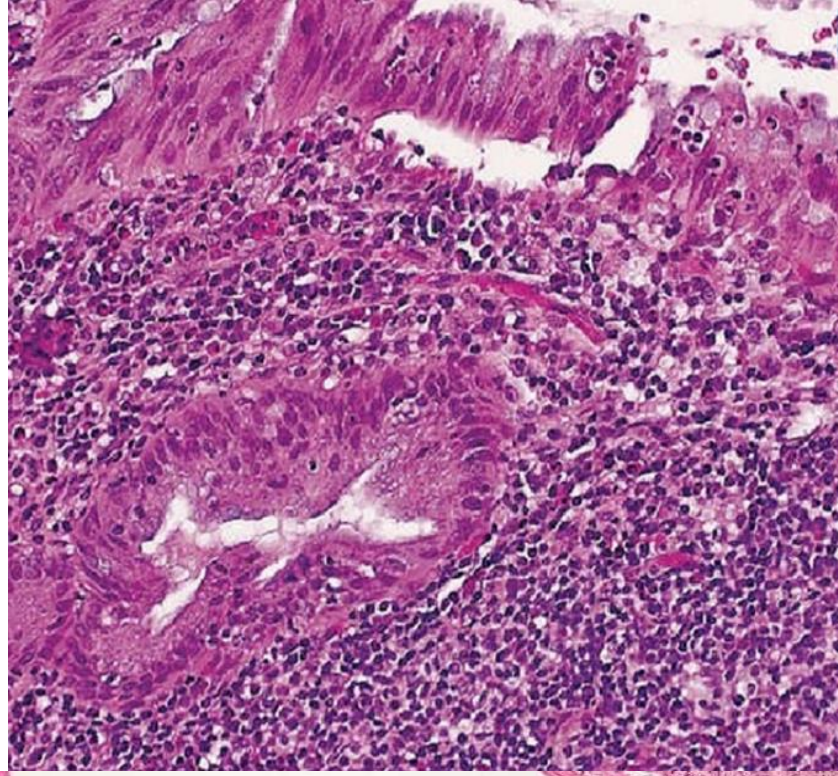
Signs of Live failure

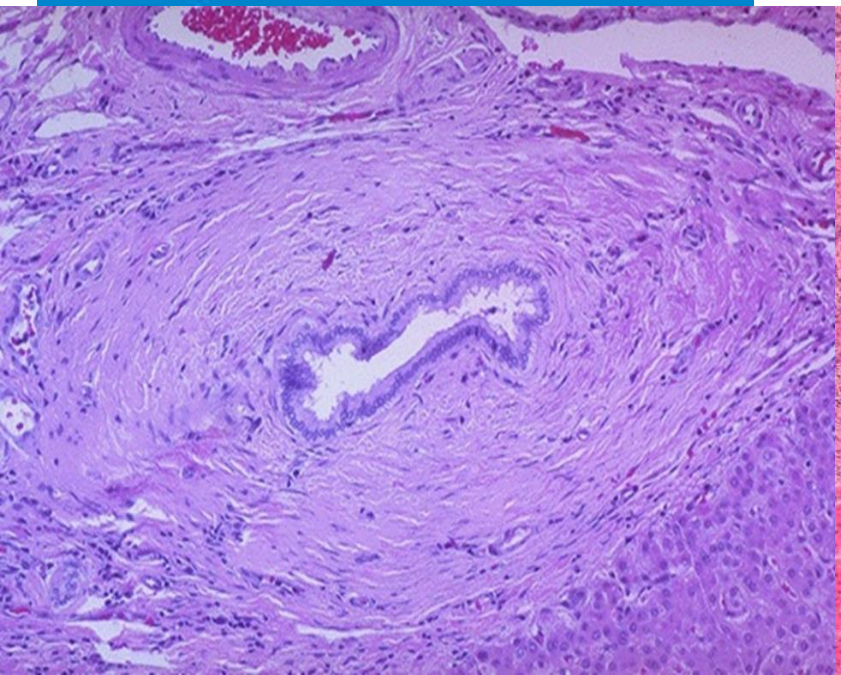
LFTS- Raised Alkaline Phosphatase, Bilirubin, hypergamaglobinumina

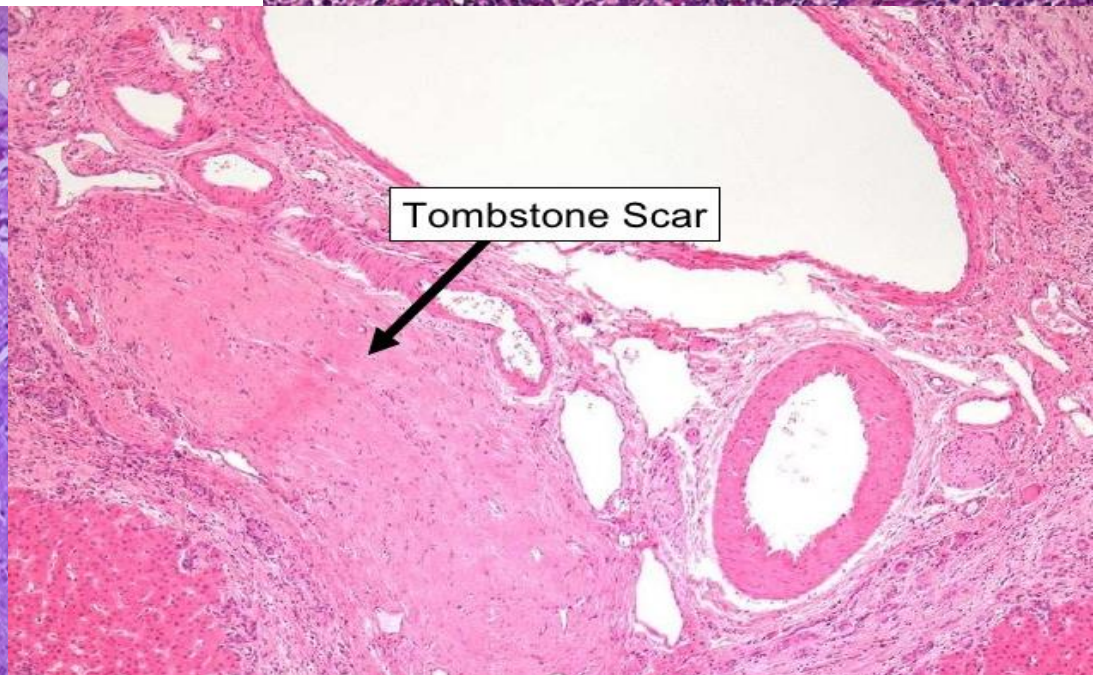
ANA, ANCA, SMA +VE

Poor prognosis – often need transplant and increases risk of cholangiocarcinoma

Males!!!!!



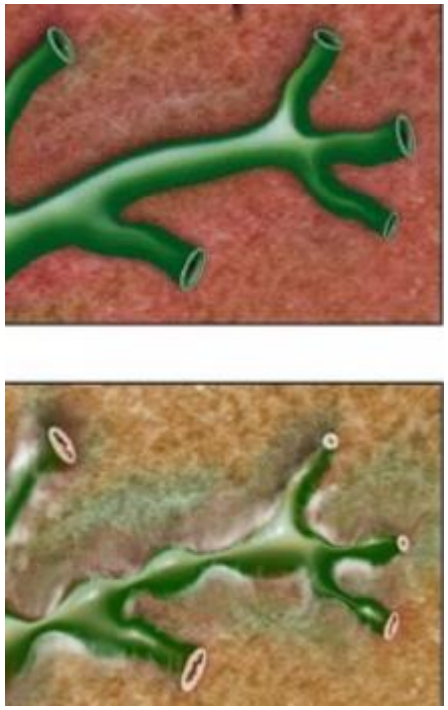


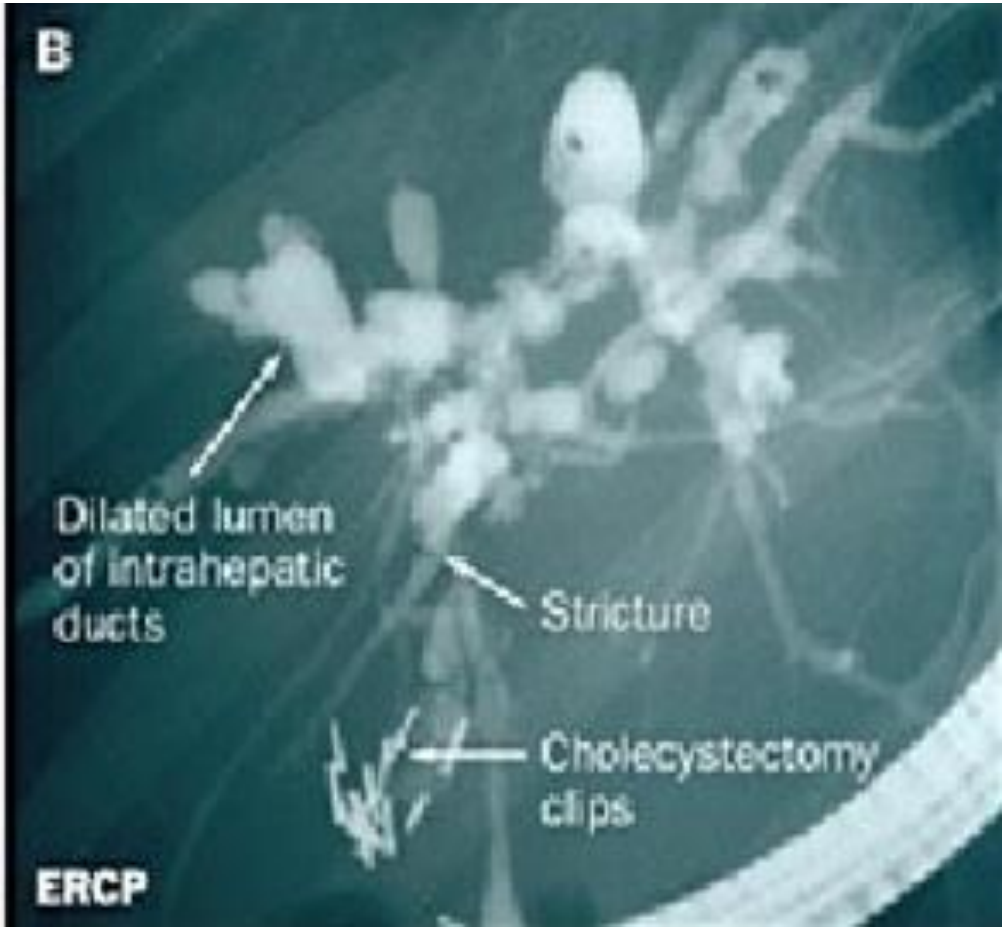


Cholestatic liver diseases (PSC, PBC)

PRIMARY SCLEROSING CHOLANGITIS

Dg: ERCP, liver biopsy is not good





Endoscopic retrograde cholangiopancreatography

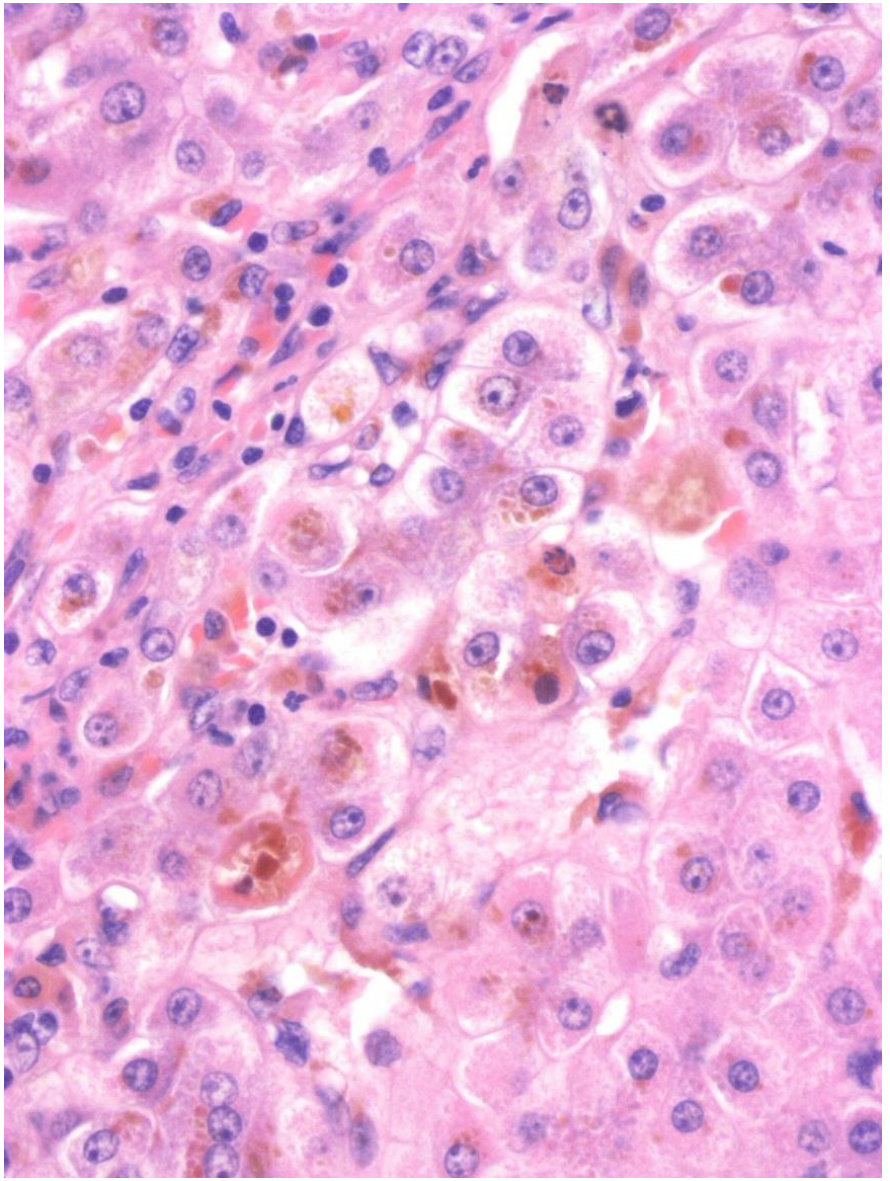
Therapy: Cholestyramine Resin, liver transplant

Cholestatic liver diseases (PSC, PBC)

"Overlap" Syndrome

Cholestatic liver diseases

SECONDARY BILIARIS CIRRHOSIS – chronic biliary obstruction



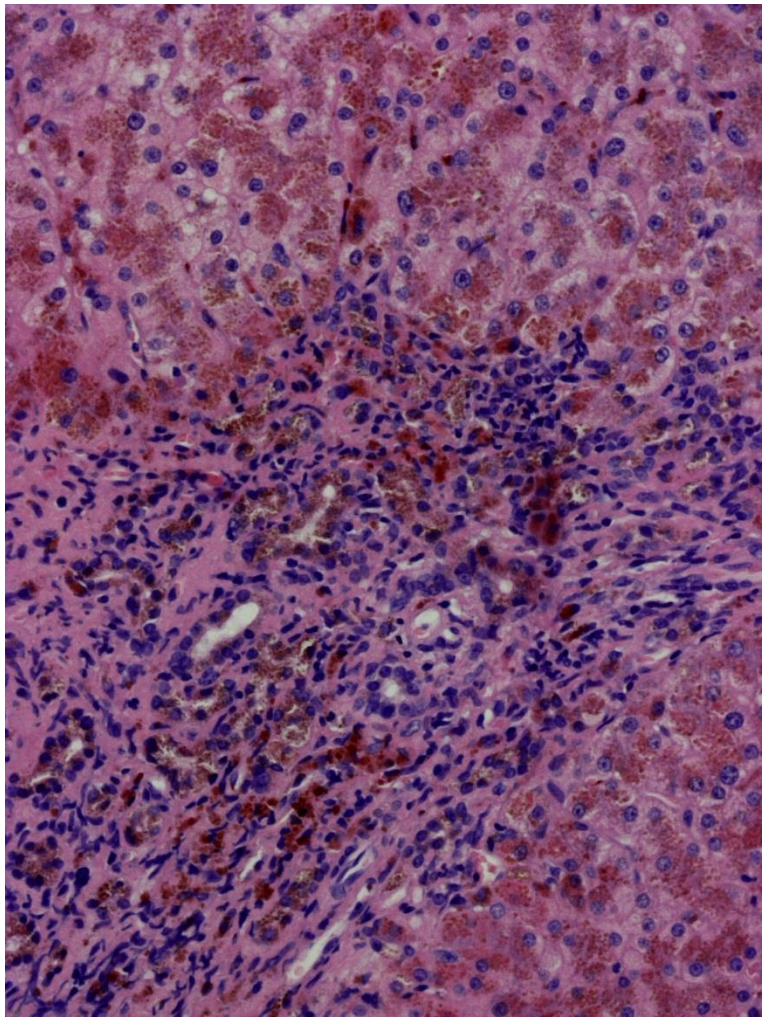
Metabolic and Inherited liver disease

HAEMOCHROMATOSIS

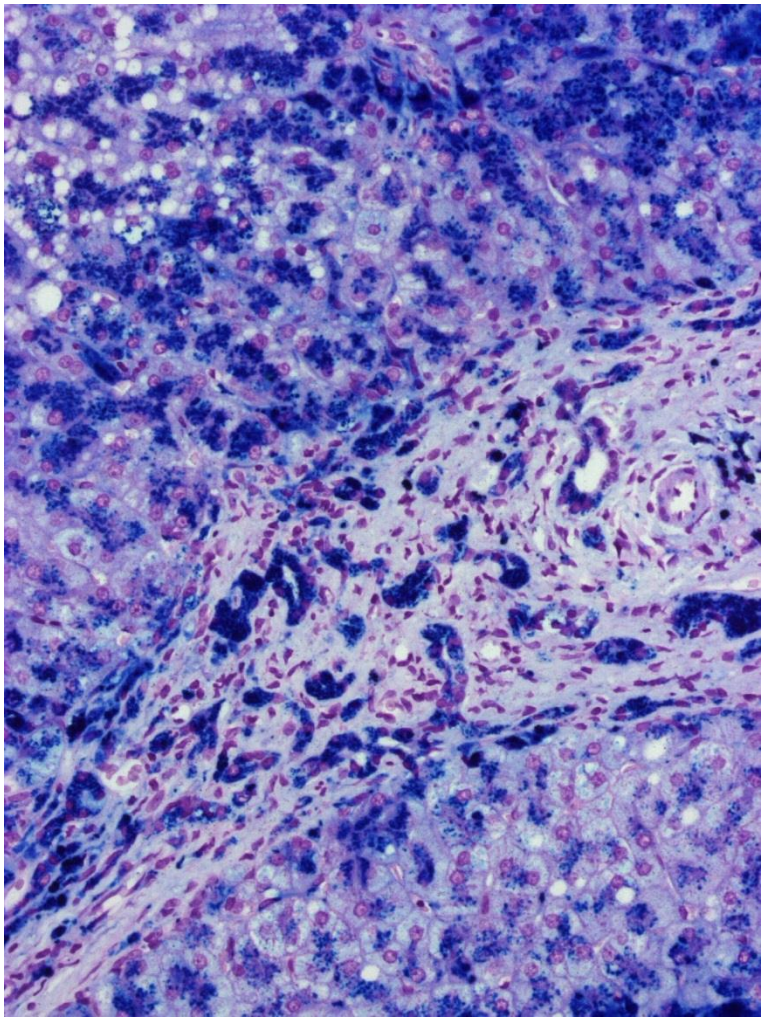
-excessive absorption of iron,

-liver and pancreas, as well as in the heart, joints, and endocrine o

- **hereditary hemochromatosis, AR, HFE mutation**
- *acquired hemochromatosis*



HE

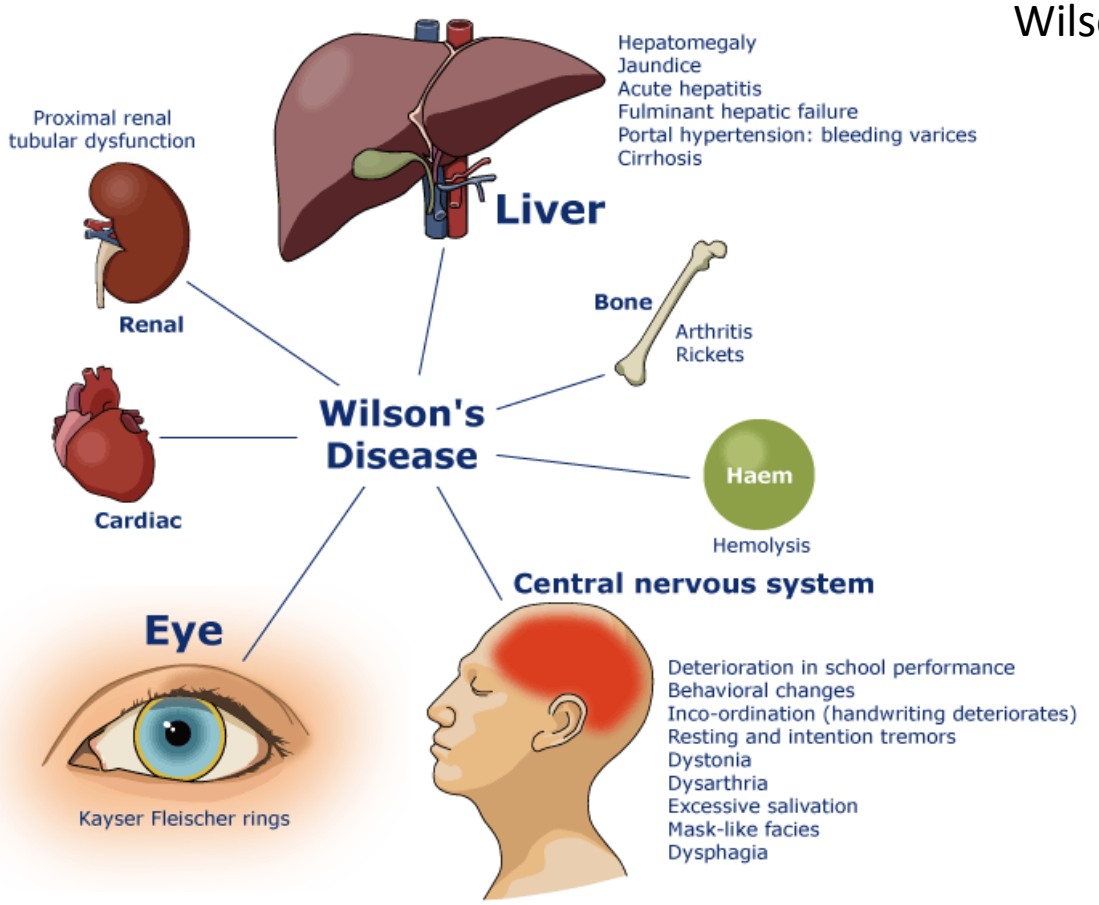


Prussian blue

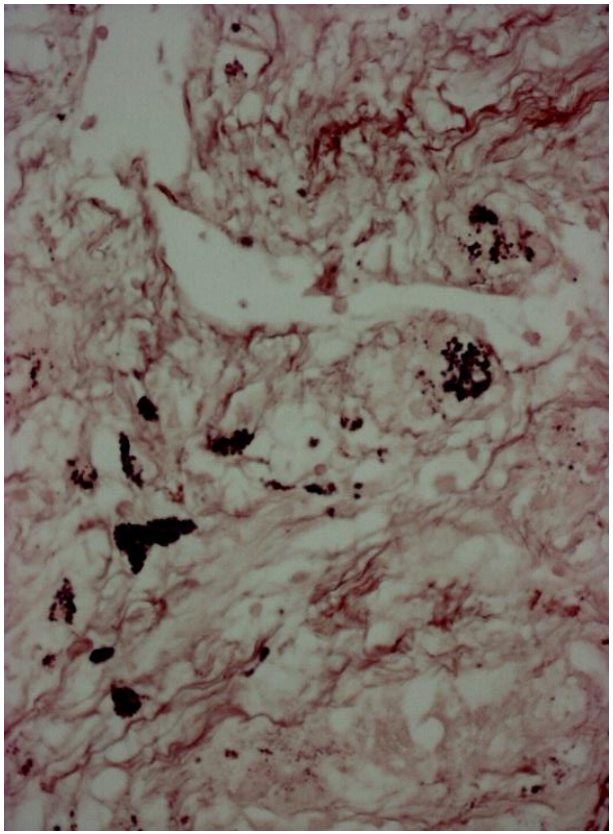
Metabolic and Inherited liver disease

Wilson's disease

autosomal recessive (AR) genetic disorder



The condition is due to mutations in the Wilson disease protein (ATP7B) gene.



Orcein-stain, copper-associated protein liver

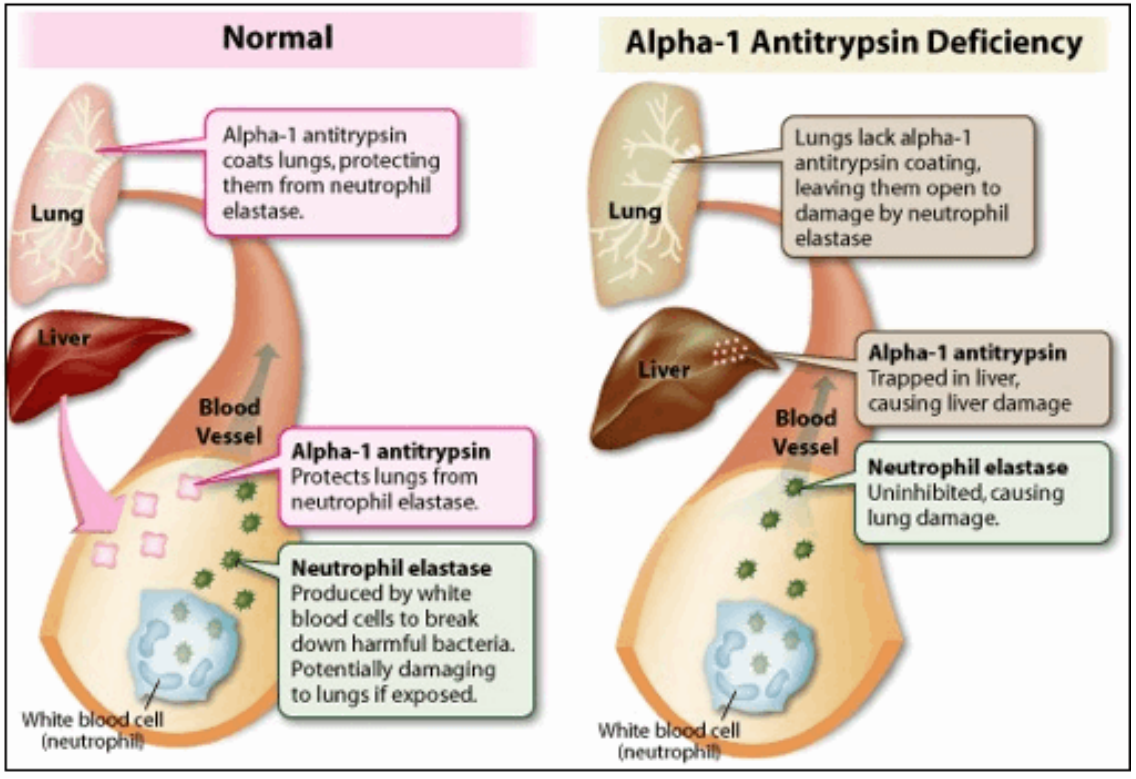
Metabolic and Inherited liver disease

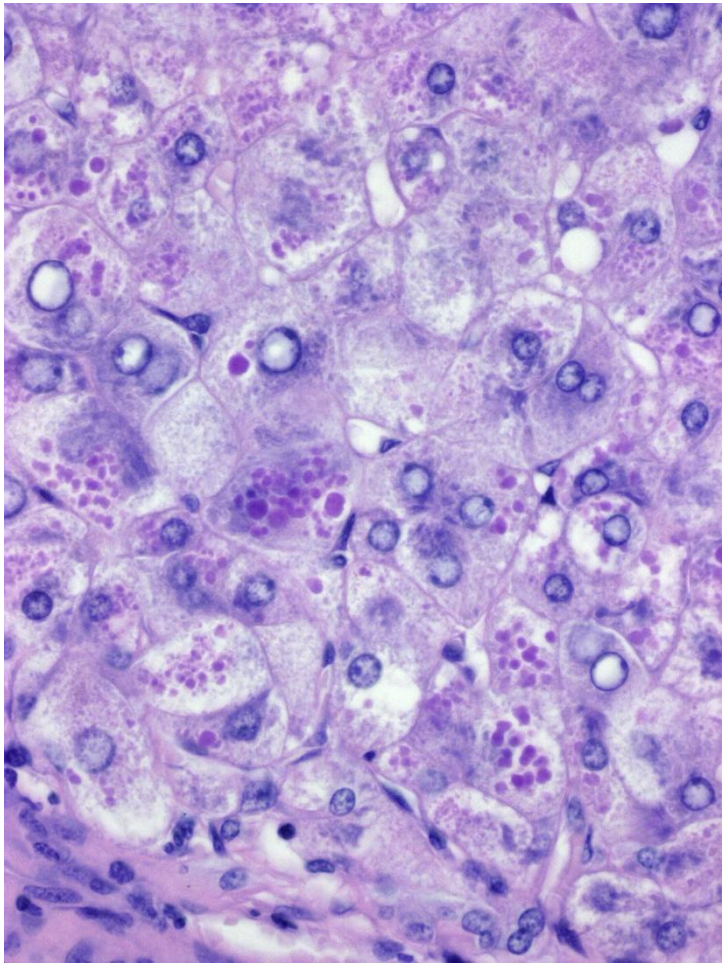
α-1 ANTiTRYPSIN deficiency (Pi gene mutation, PiZZ)

Table 2. Alpha-1-antitrypsin phenotypes and corresponding typical alpha-1-antitrypsin serum levels

Phenotype	Level, μM*
PIMM	20–48
PIMZ	12–35
PISS	15–33
PISZ	8–19
PIZZ	2.5–7.0
Null-Null	0

*Convert micromolar to mg/dL by multiplying by conversion factor of 5.2.





PAS-D