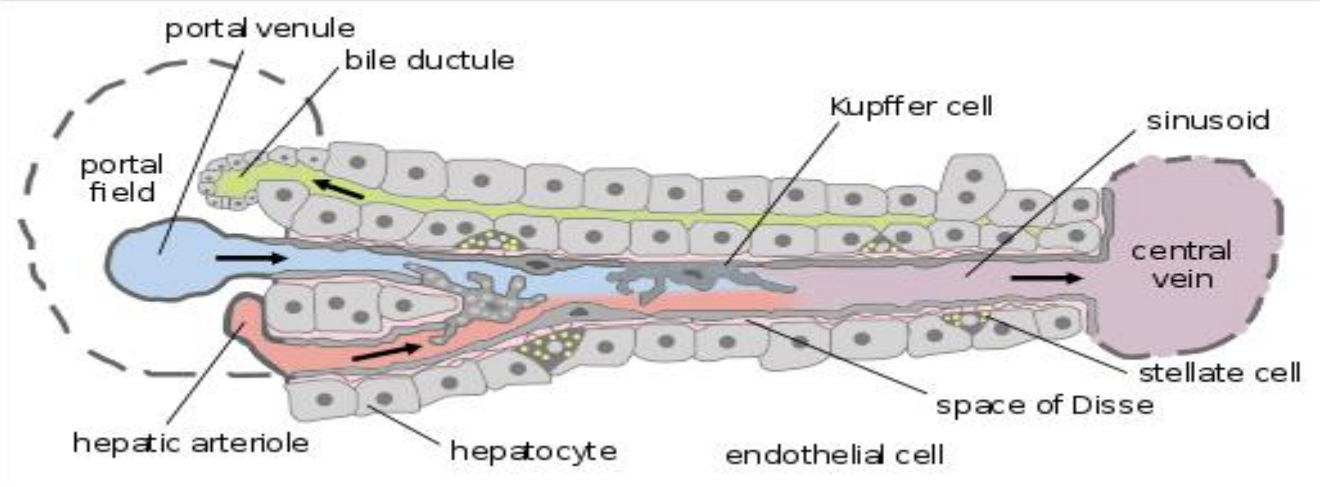
PATHOLOGY OF THE LIVER

Liver failure
Cholestatic liver diseases (PSC, PBC),
Jaundice, causes, pathophysiology and defects 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

Histology

Cell	Location	Function	Special characteristics
Hepatocyte (Q)	Hepatocellular Plate	1. Metabolic Function 2. Secretion of Bile	Damage causes ↑ ALT,AST
Kupffer Cell	Line inner sinusoidal wall	Phagocytosis of foreign matter and bacteria	
Endothelial cells	Form sinusoidal wall	Separated forming fenestrations	Allow lymph to bath space of Disse
Stellate Cells (Q)	Space of Disse	Vitamin A storing cell	Plays important role in cirrhosis



Mechanism of hepatocyte injury

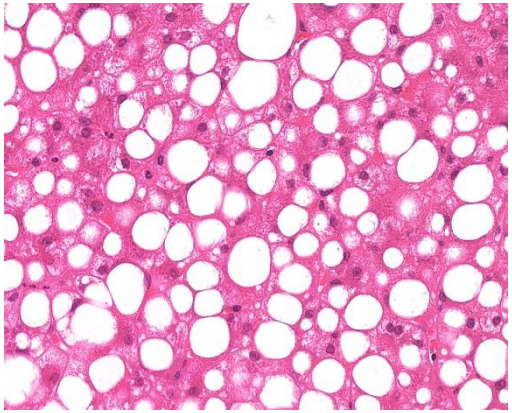
Mild and short-term stimulus

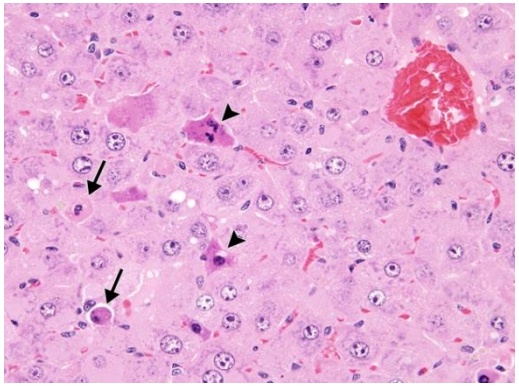
Severe and/or prolonged stimulus

Reversible forms

Irreversible forms

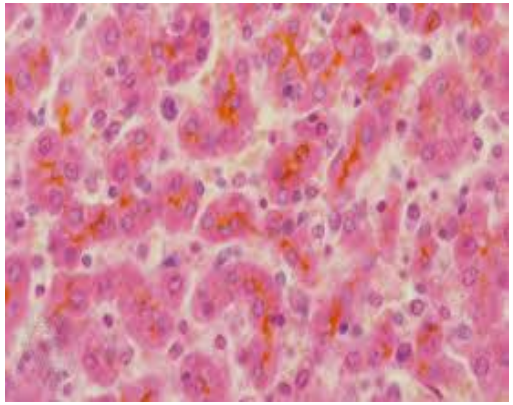
Steatosis

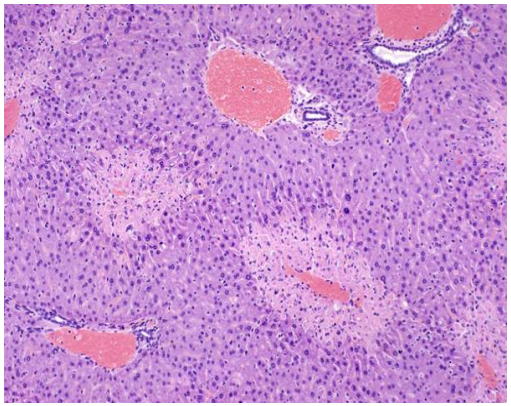




Apoptosis

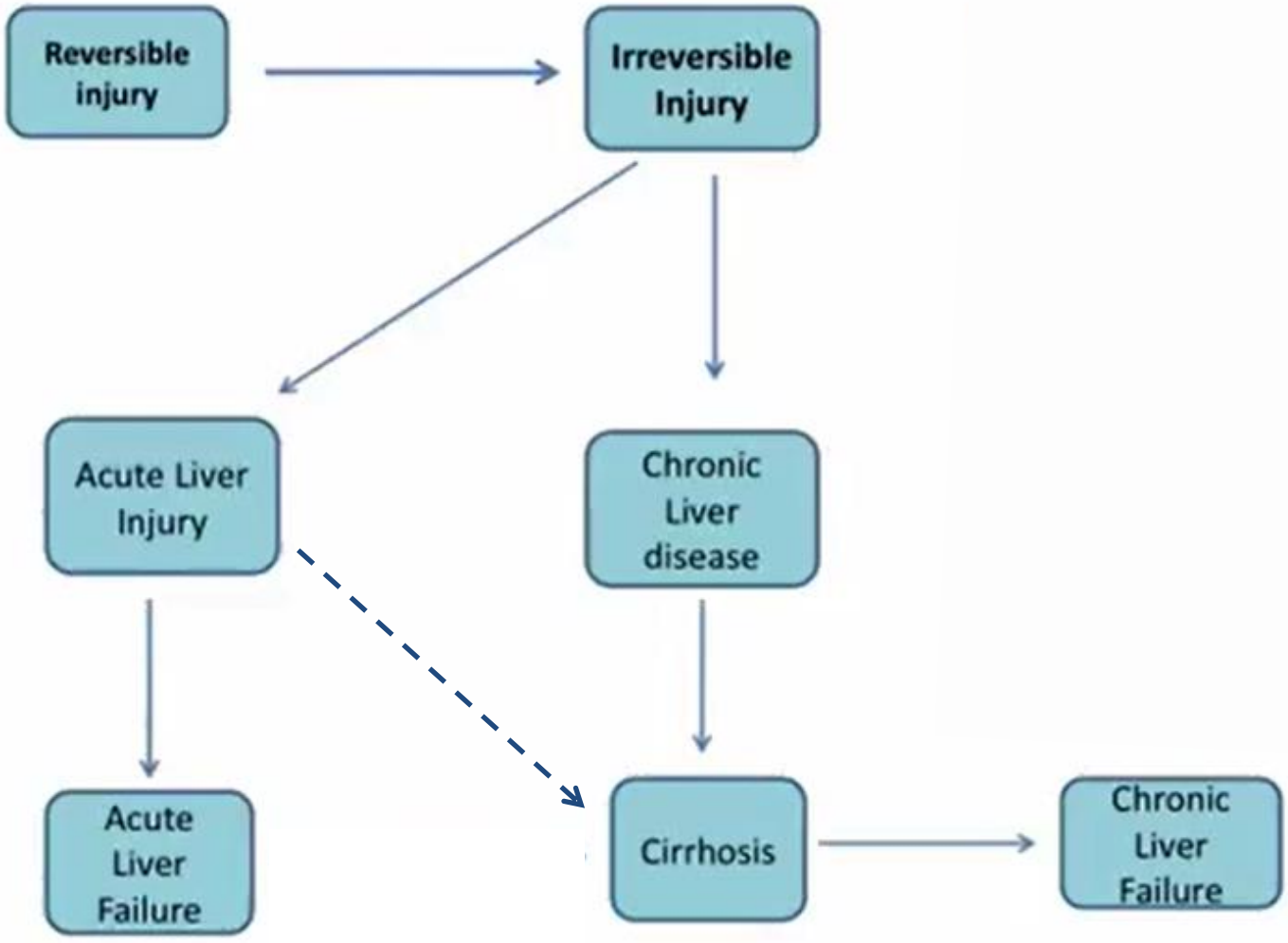
Cholestasis





Necrosis

Liver failure

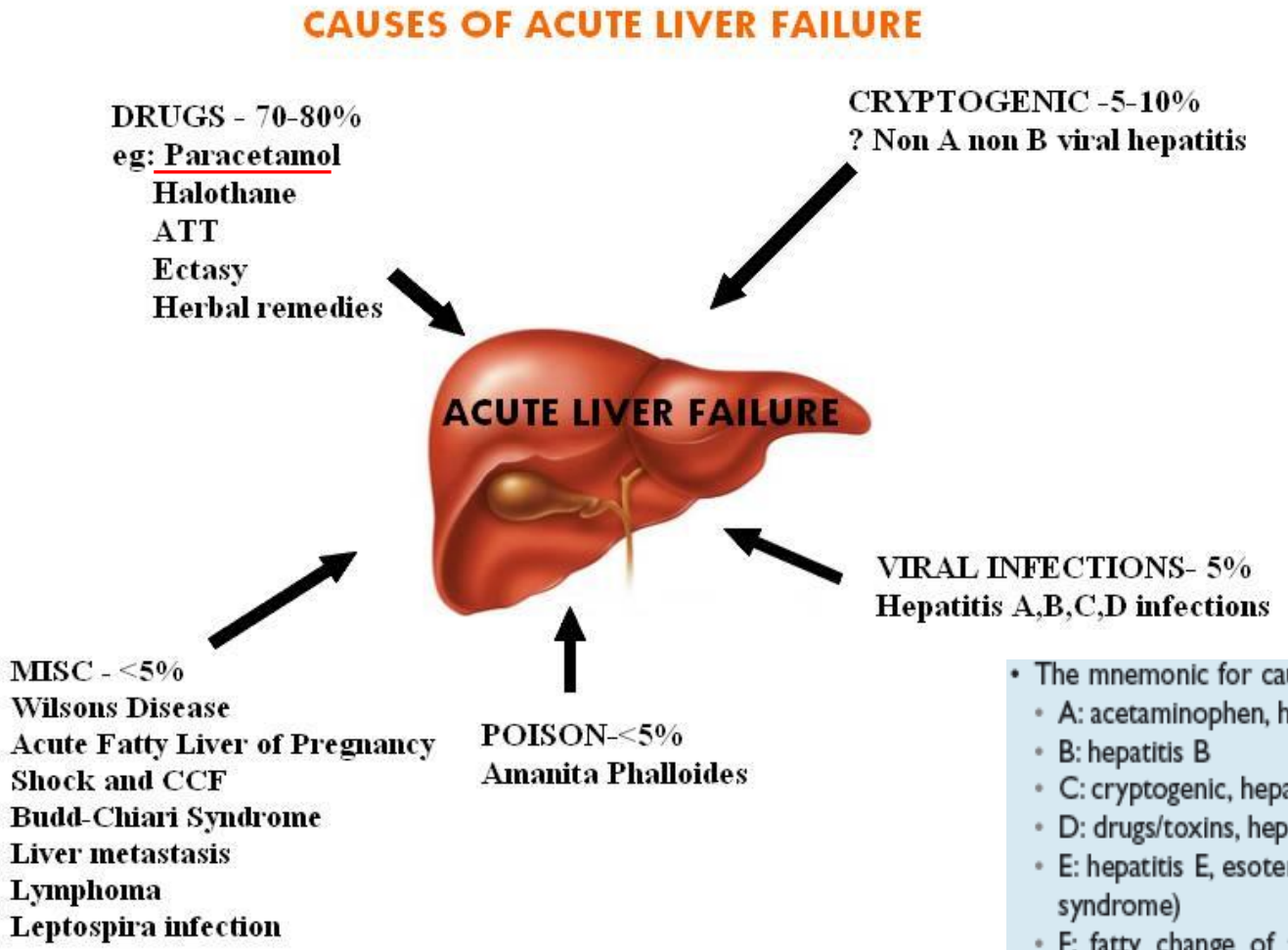


-Acute liver failure (massive liver necrosis or liver dysfunction without overt necrosis)
-Chronic liver failure (main cause -cirrhosis)
-Acut-on- chronic failure (ACLF)- unrelated acute injury supervenes on a well-compensated late-stage chronic disease

Acute liver failure

Fulminant/acute liver failure

-the severe impairment of hepatic functions or severe necrosis of hepatocytes in the absence of preexisting liver disease (Acute/Fulminant - encephalopathy within 8 weeks of the onset of symptoms in a previously healthy liver; Subacute/Subfulminant 26 weeks)

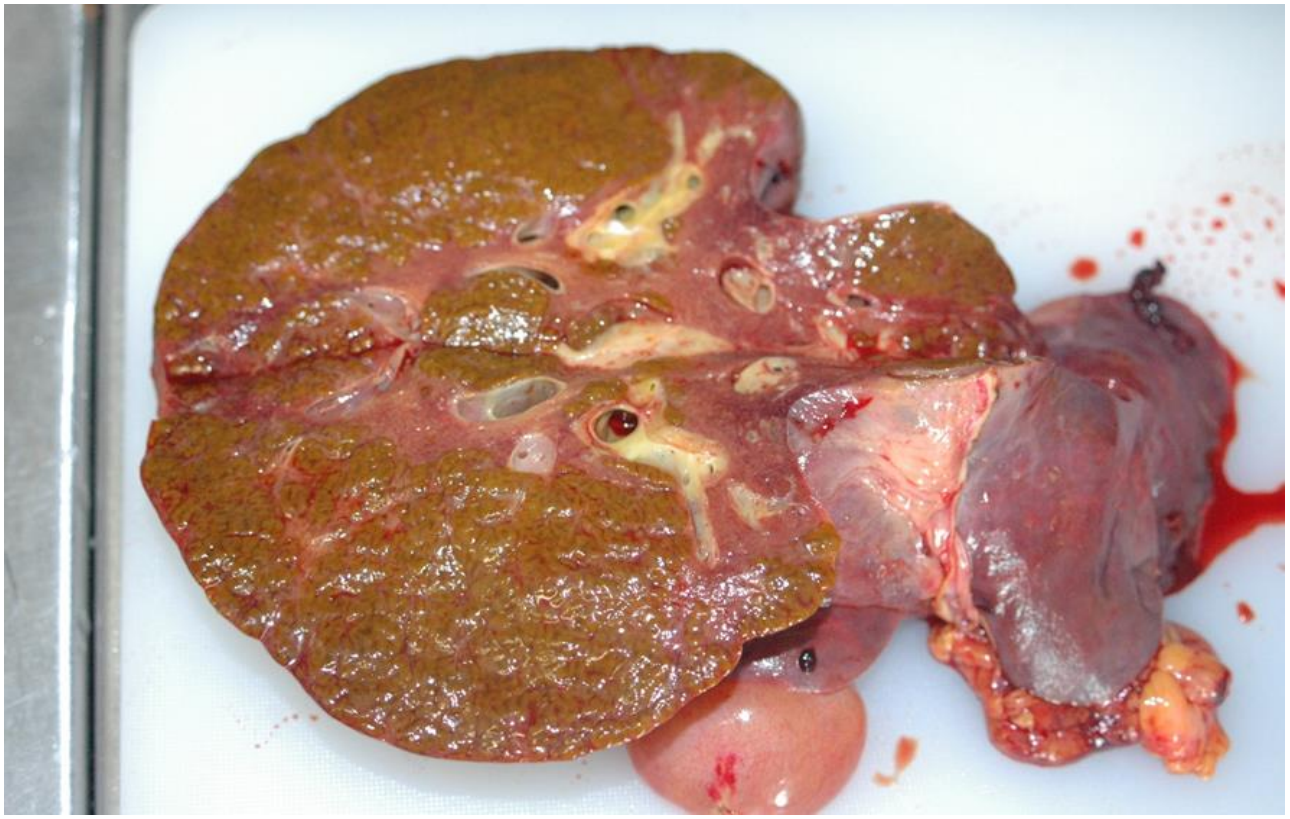


- The mnemonic for causes of acute liver failure are as follows:
  - A: acetaminophen, hepatitis A, autoimmune hepatitis
  - B: hepatitis B
  - C: cryptogenic, hepatitis C
  - D: drugs/toxins, hepatitis D
  - E: hepatitis E, esoteric causes (Wilson disease, Budd-Chiari syndrome)
  - F: fatty change of the microvesicular type (fatty liver of pregnancy, valproate, tetracycline, Reye syndrome)

Acute liver failure

+/-portal hypertension and ascites……..it is more common in chronic liver failure

Acute liver failure

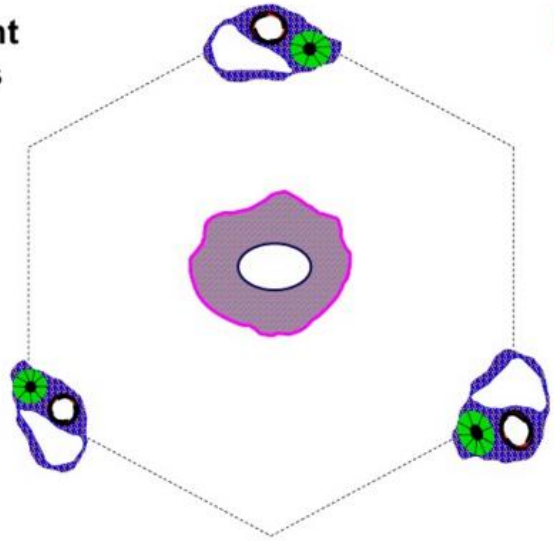


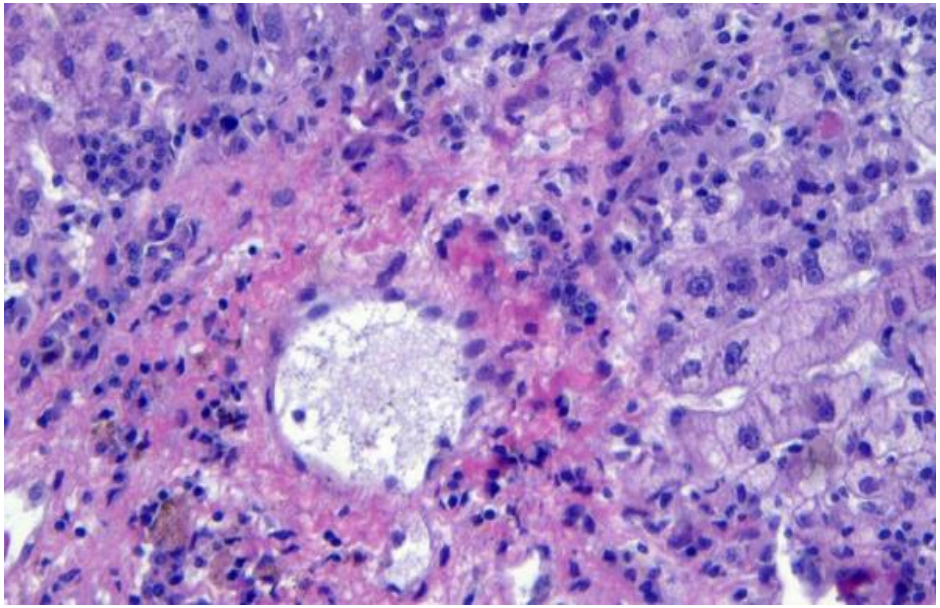
Acute liver failure -
Atrophia hepatis flava

The liver is small and shrunken

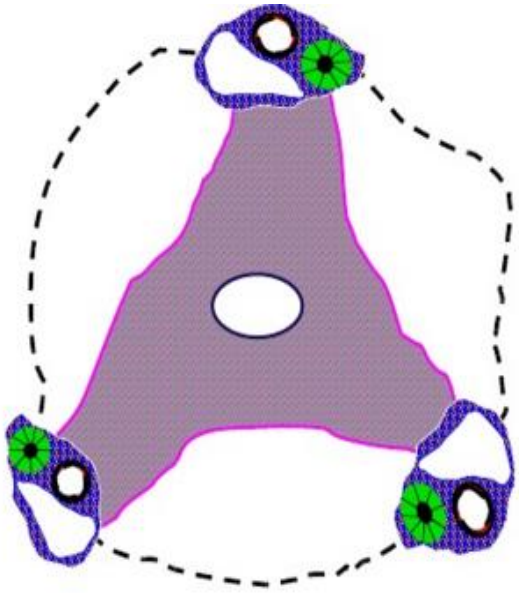
Acute liver failure

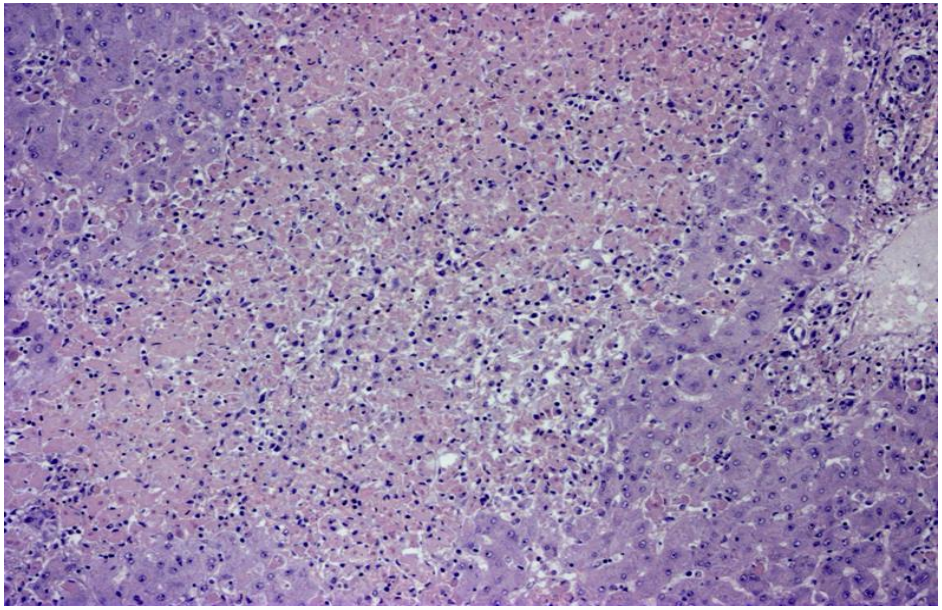
Confluent Necrosis



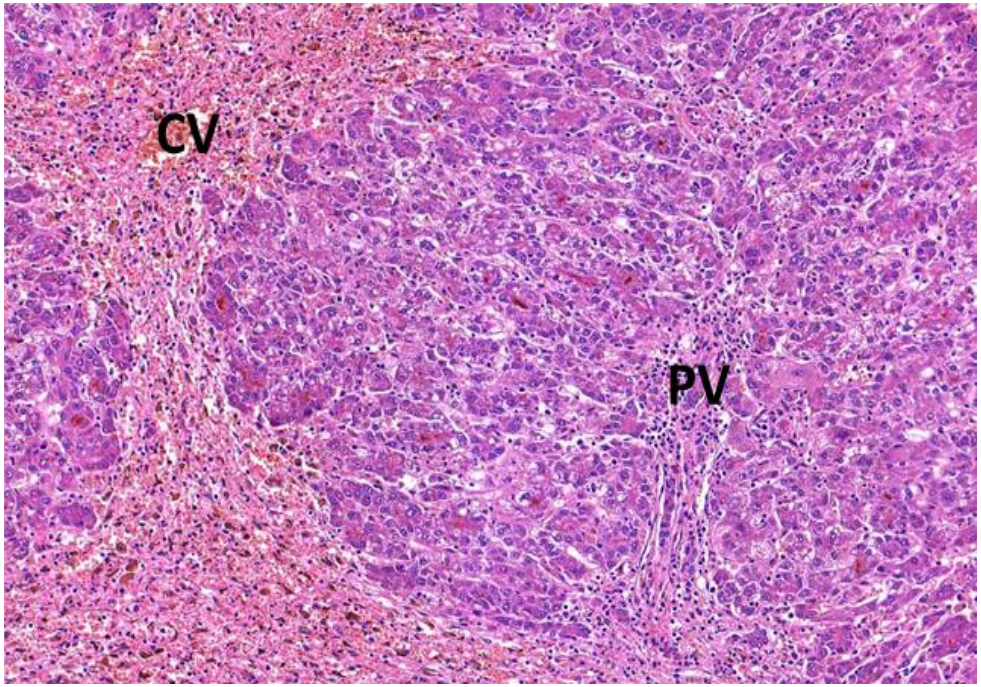


Bridging Necrosis





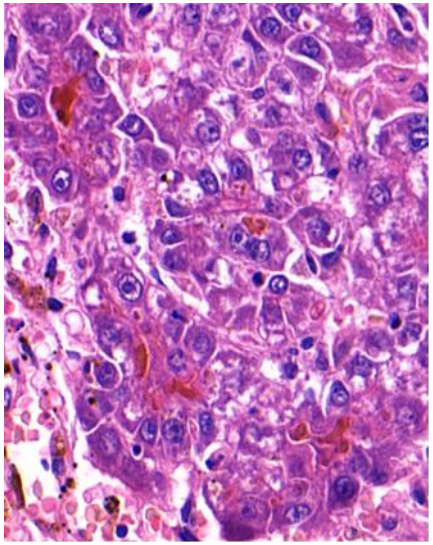
Acute liver failure

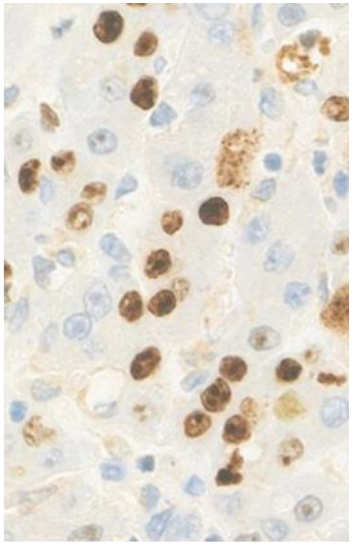


Regeneration from surviving hepatocytes

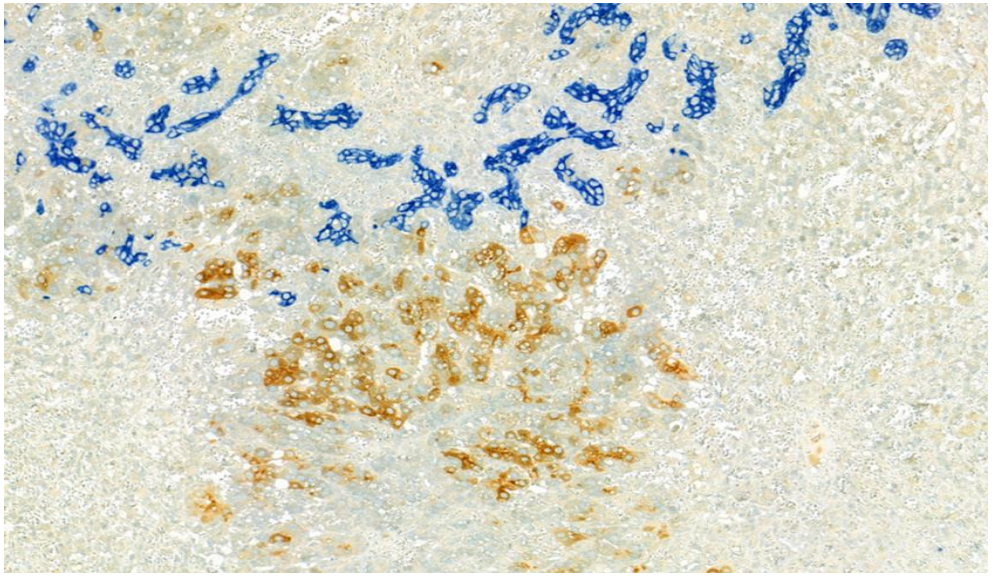
-acinary or pseudoglandularly arranged hepatocytes

- cholestasis
- AFP expression





Ki-67



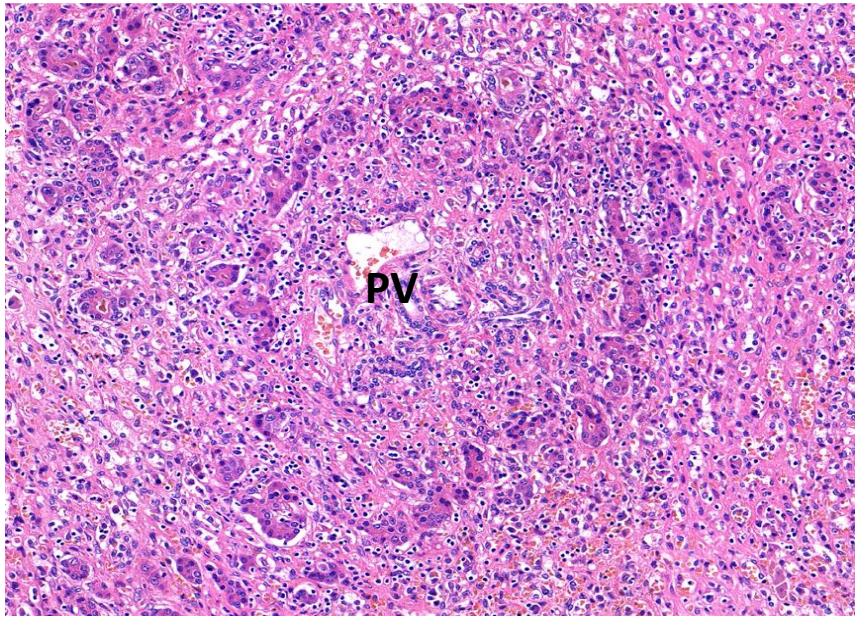
AFP- CK19

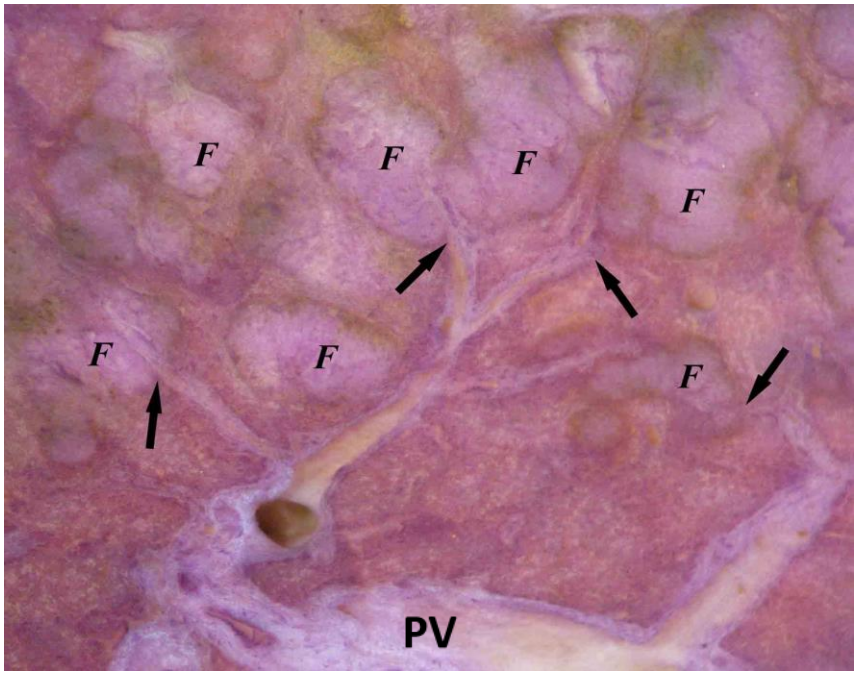
Dezso et al; J Gastroenterol Hepatol. 2020 Jan;35(1):124-134

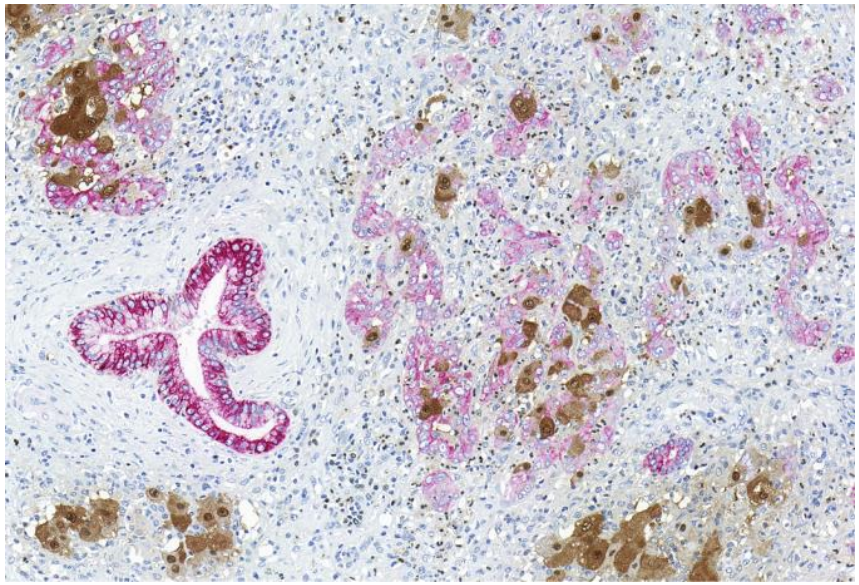
Regeneration from stem cells

Acute liver failure

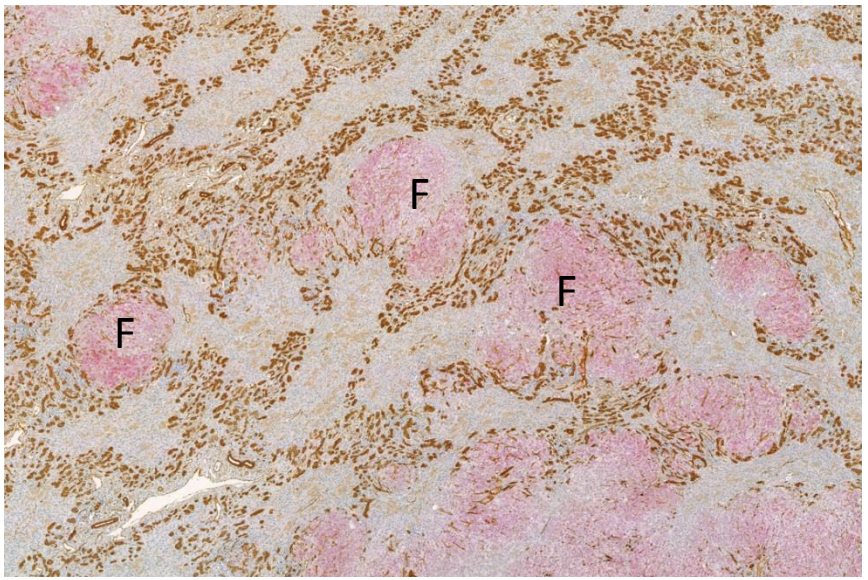
-in areas of parenchymal loss the stem cell located in bile ducts differentiate into small hepatocytes, and these small hepatocytes form foci







Arginase-1- CK19

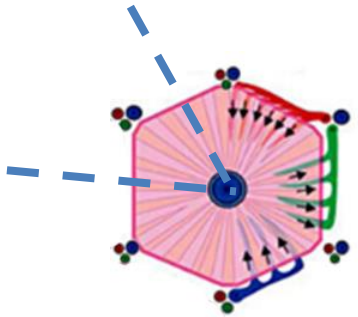


Arginase-1- CK19

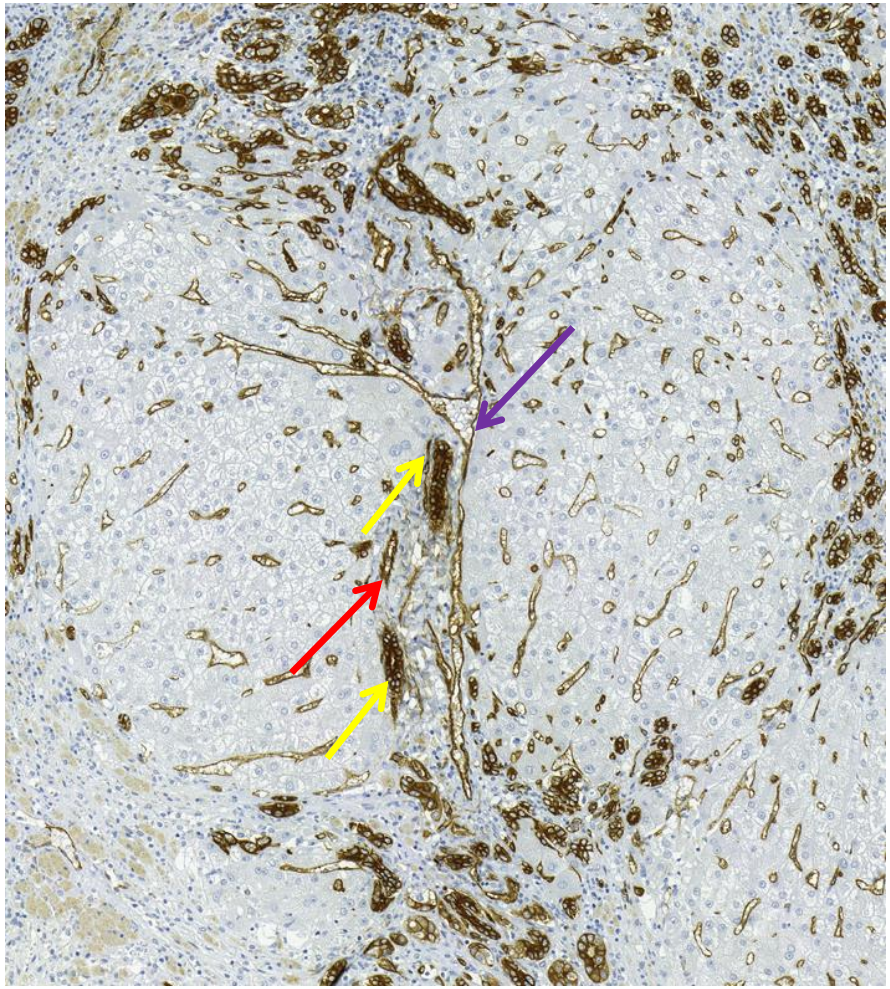
Dezso et al; J Gastroenterol Hepatol. 2020 Jan;35(1):124-134

Acute liver failure

Regeneration from stem cells

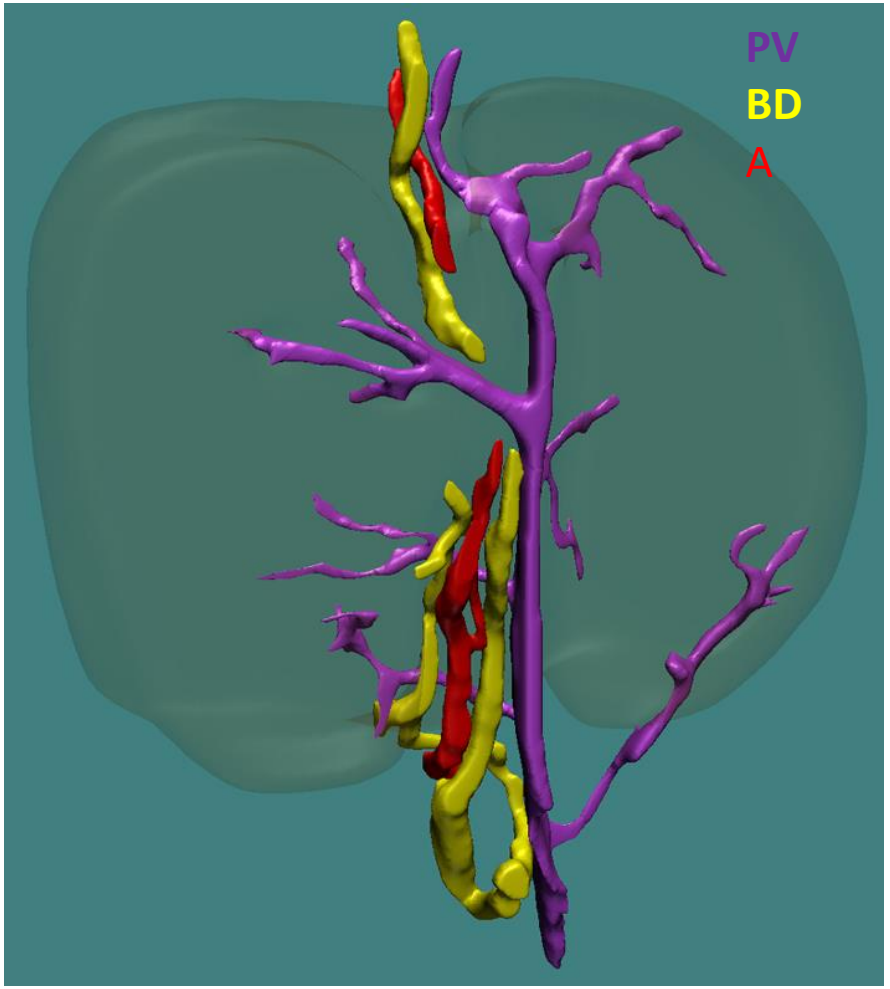


In the center of the foci complete portal triads are present



Dezso et al; J Gastroenterol Hepatol. 2020 Jan;35(1):124-134

CD34-CK19



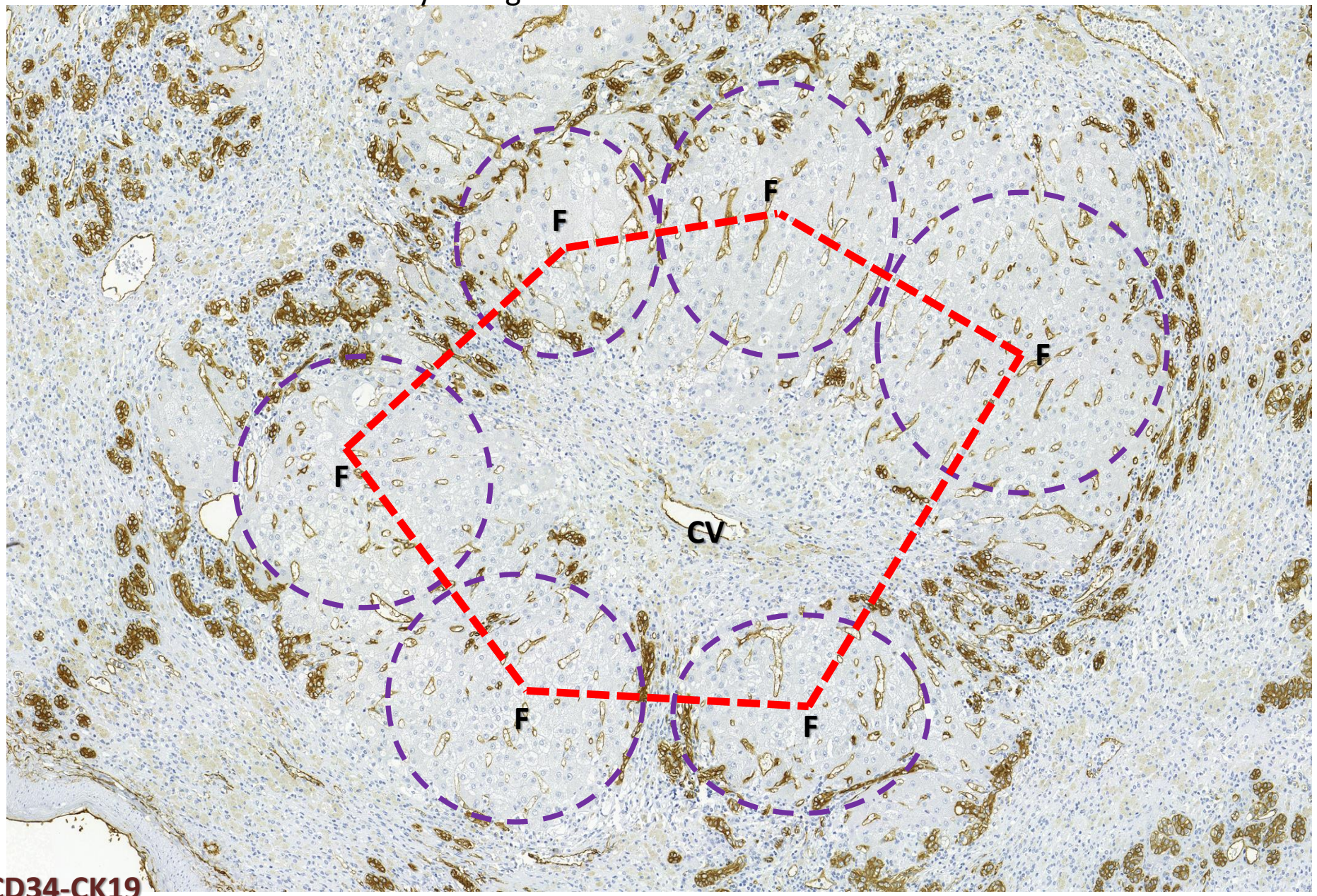
3D reconstruction

Regeneration from stem cells

.

- Fused foci try to regenerate the classic liver lobule

Acute liver failure



CD34-CK19

Dezso et al; J Gastroenterol Hepatol. 2020 Jan;35(1):124-134

Chronic Liver Failure

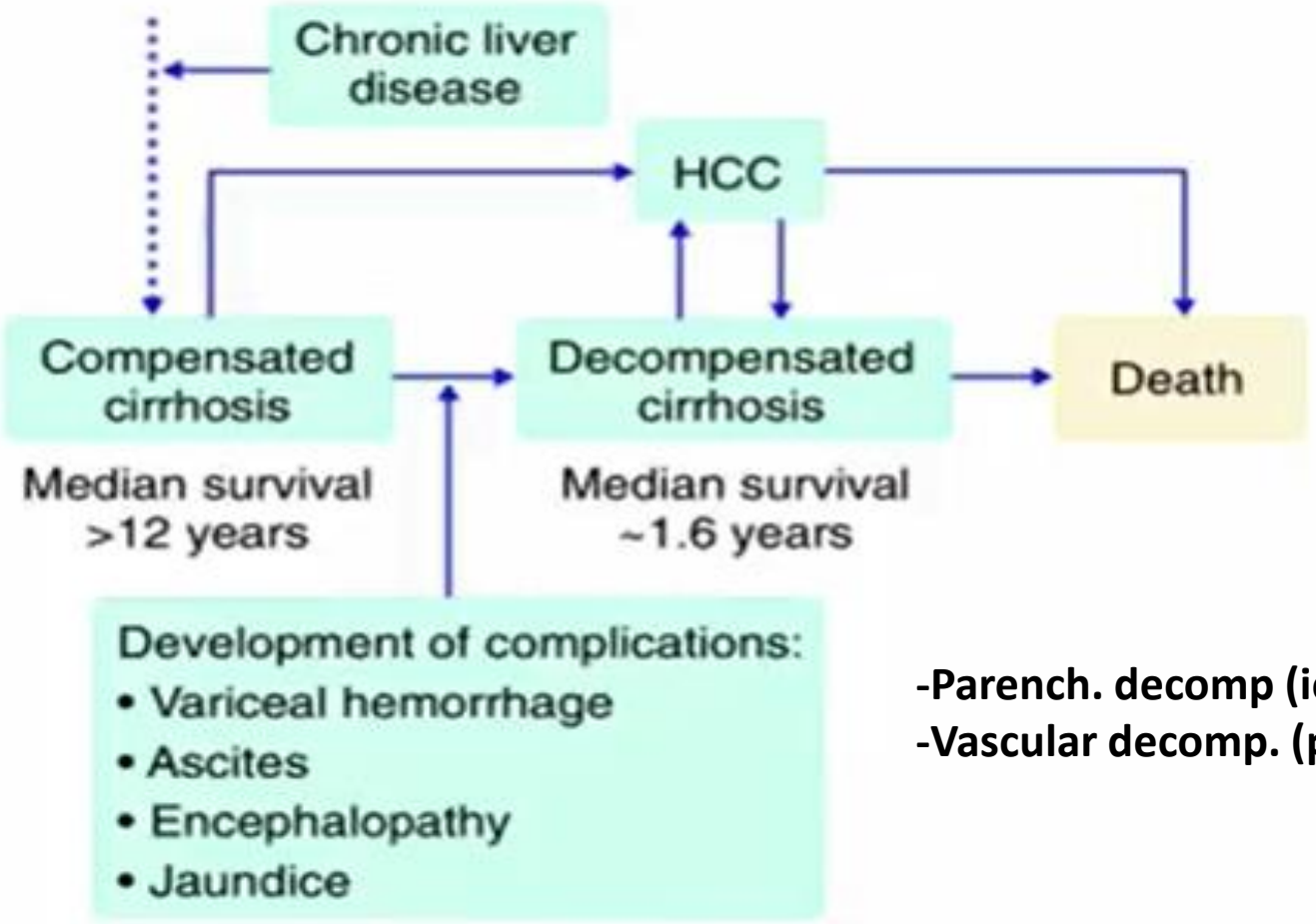
- Definition: Progressive loss of liver function occurring over a long period of time as a result of chronic liver disease.

The leading causes of chronic liver failure worldwide include chronic hepatitis B, chronic hepatitis C, non-alcoholic fatty liver disease, and alcoholic liver disease.

Liver failure in chronic liver disease is most often associated with cirrhosis, a condition marked by the diffuse transformation of the entire liver into regenerative parenchymal nodules surrounded by fibrous bands and variable degrees of vascular (often portosystemic) shunting

Not all cirrhosis leads inexorably to chronic liver failure and not all end-stage chronic liver disease is cirrhotic !!!!!!!

Chronic Liver Failure



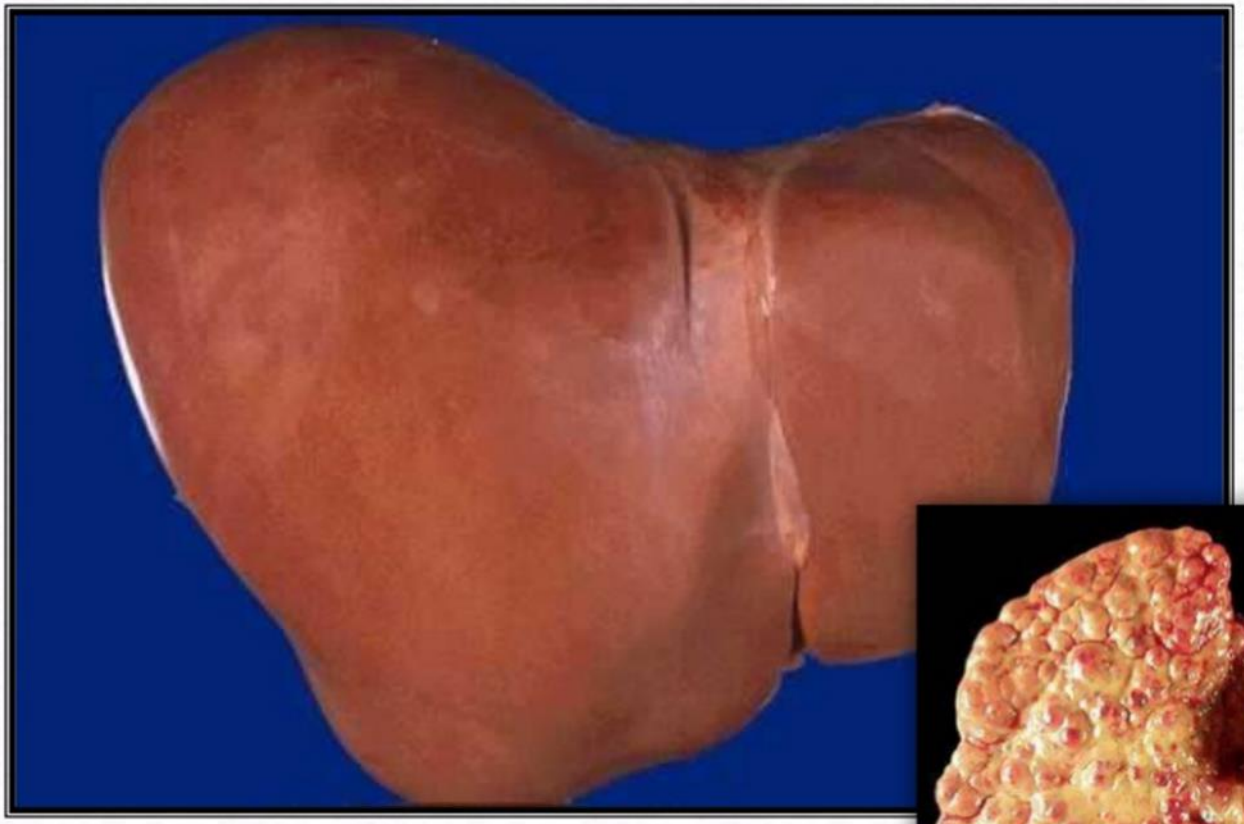
-Parench. decomp (icterus)
-Vascular decomp. (portal p↑)

MELD score uses the patient's values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time (INR) to predict survival.

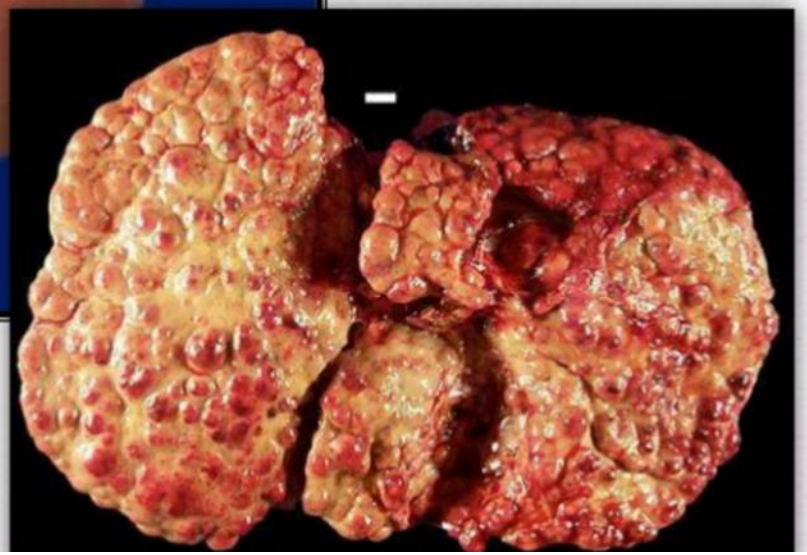
Child-Pugh Score:Bilirubin, Albumin, PT prolongation (INR), Ascites, Encephalopathy

Cirrhosis

Cirrhosis occurs diffusely throughout the liver, which is comprised of regenerating parenchymal nodules surrounded by dense bands of scar and variable degrees of vascular shunting

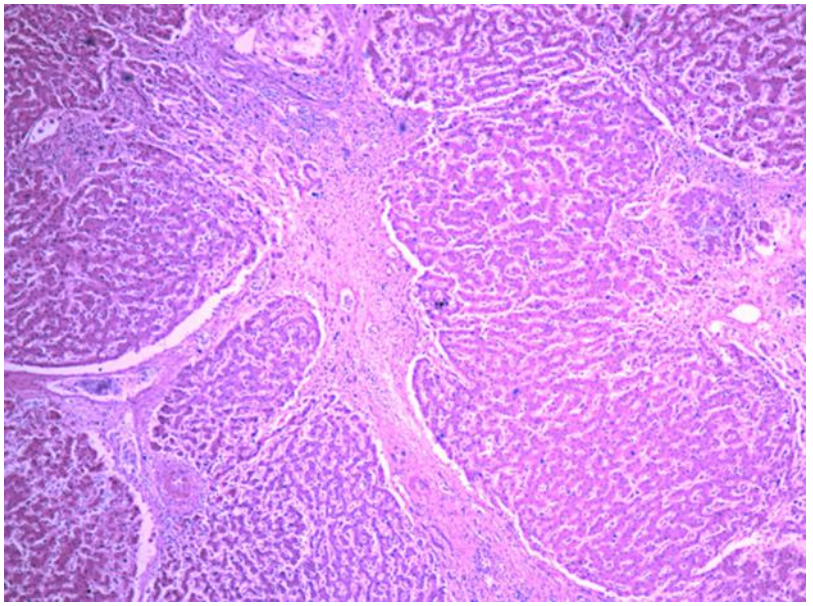


Healthy liver



Cirrhosis

Cirrhosis



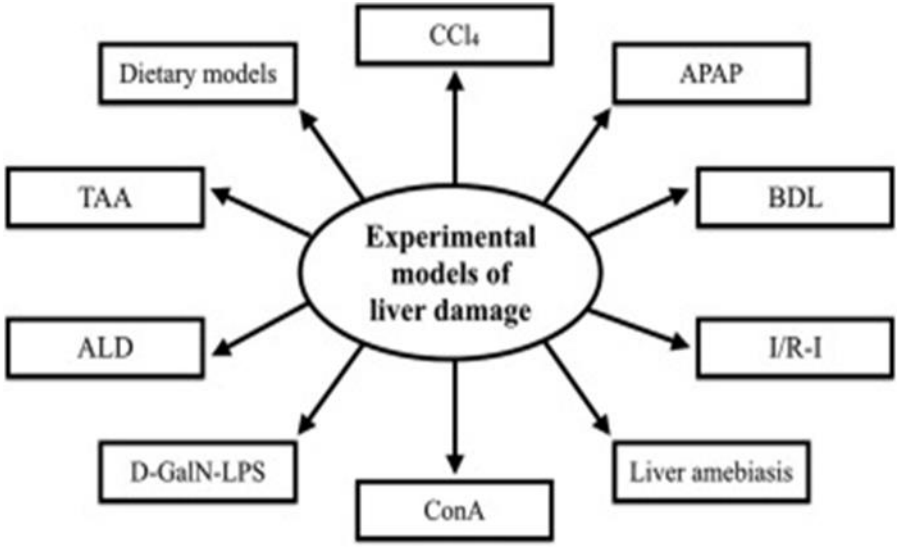
Major Causes of Cirrhosis

Alcoholic liver disease
Nonalcoholic fatty liver disease
Chronic hepatitis
- Chronic viral hepatitis
- Autoimmune hepatitis
- Drugs

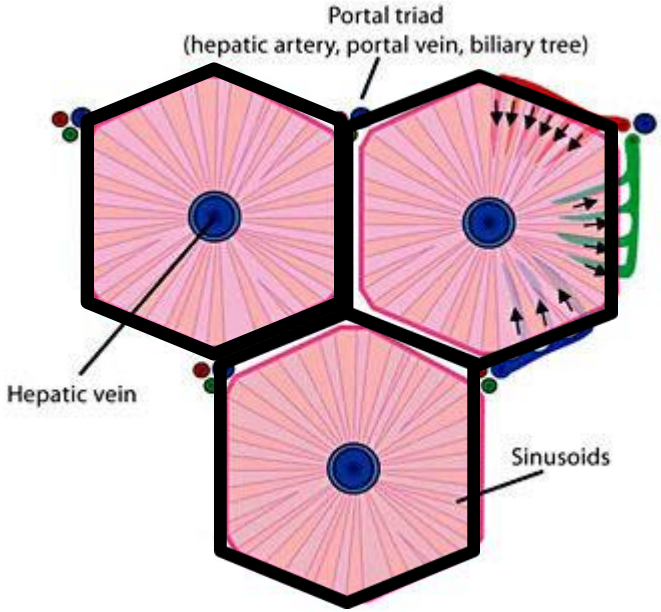
Biliary disease
- Extrahepatic biliary obstruction
- Primary biliary cholangitis
- Sclerosing cholangitis

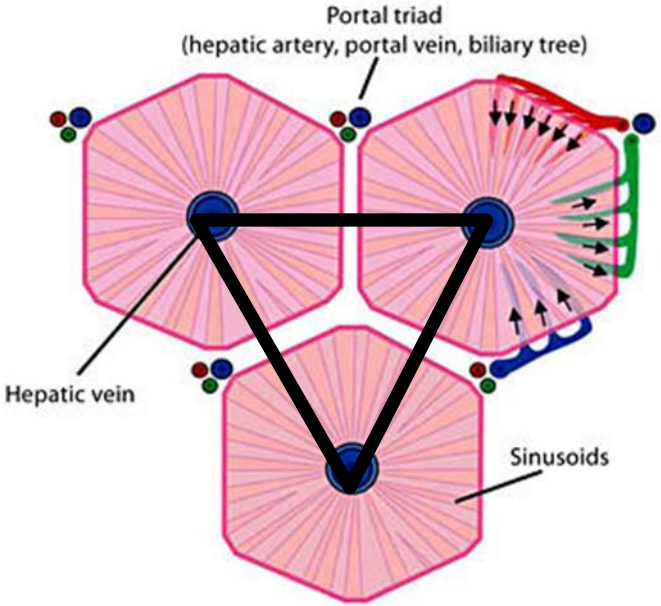
Metabolic disease
- Hemochromatosis
- Wilson disease
- Alpha-1-Antitrypsin deficiency
- Tyrosinemia
- Glycogen storage disease
- Hereditary fructose intolerance
- Hereditary storage diseases
- Galactosemia

Cryptogenic



Cirrhosis



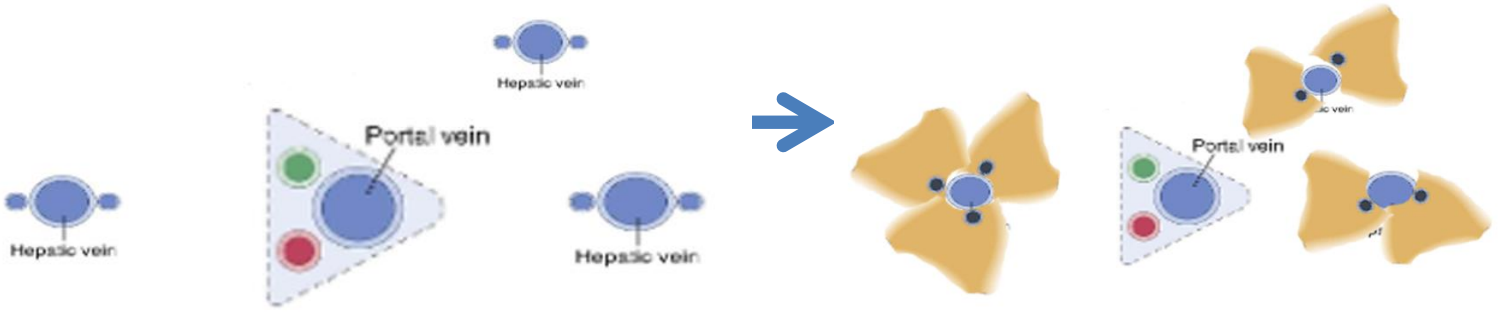


Hepatocyte Buds Derived From Progenitor Cells Repopulate Regions of Parenchymal Extinction in Human Cirrhosis

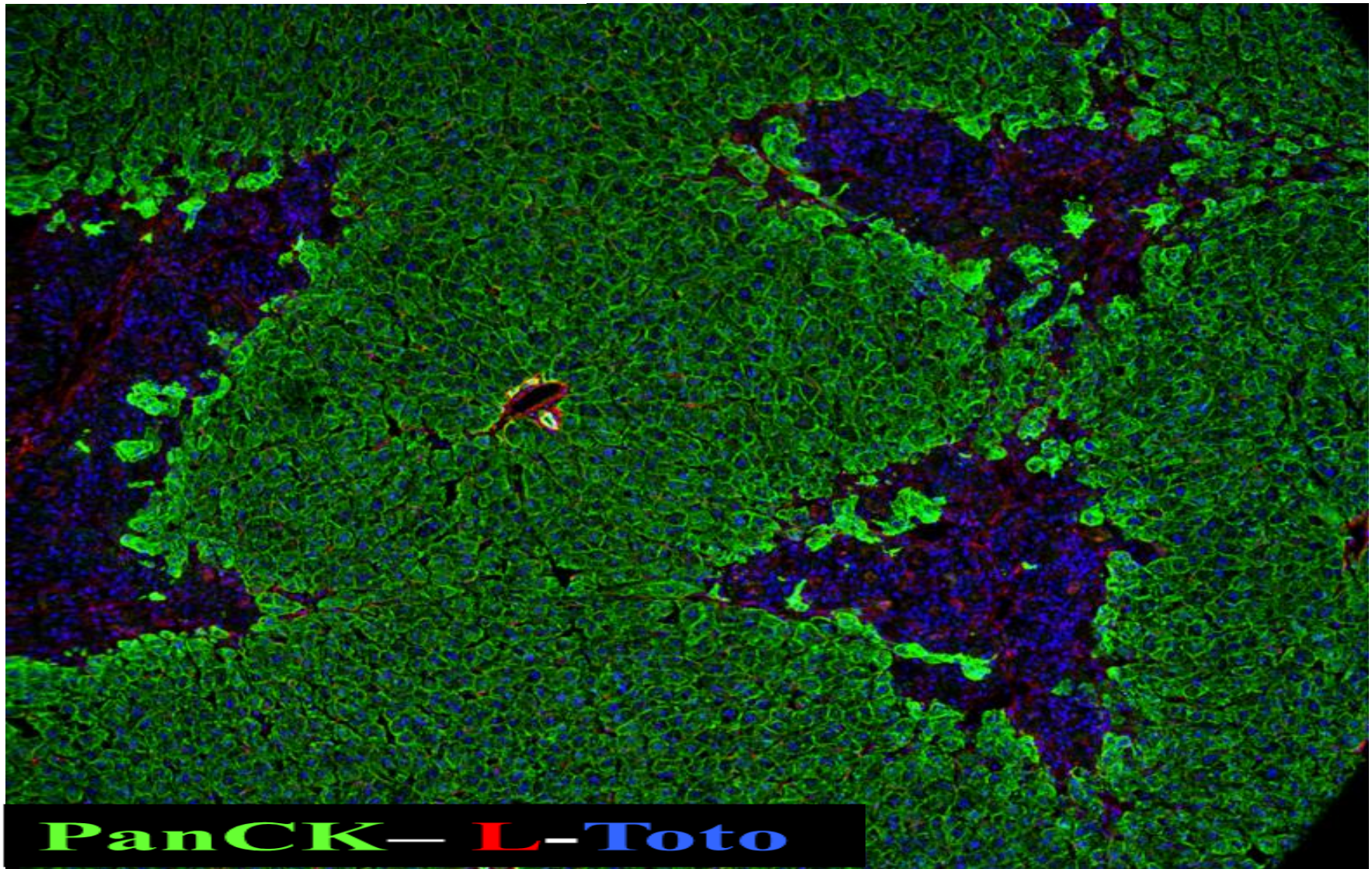
Ashley E. Stueck and Ian R. Wanless

The Histogenesis of Regenerative Nodules in Human Liver Cirrhosis

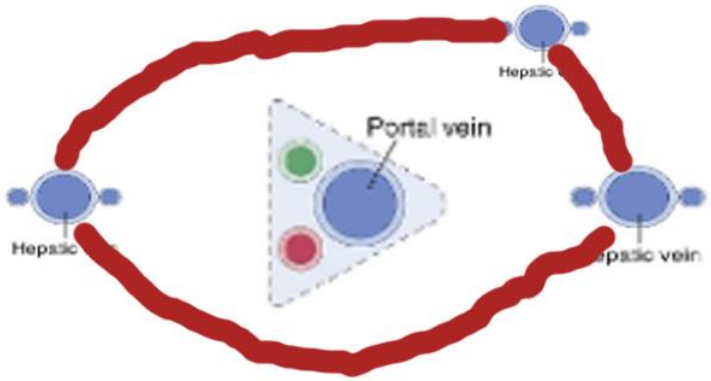
Wey-Ran Lin,[1,2] Siew-Na Lim,[3,4] Stuart A. C. McDonald,[5,6] Trevor Graham,[5] Victoria L. Wright,[1] Claire L. Peplow,[1] Adam Humphries,[5] Hemant M. Kocher,[7] Nicholas A. Wright,[1,5] Amar P. Dhillon,[8] and Malcolm R. Alison[1]

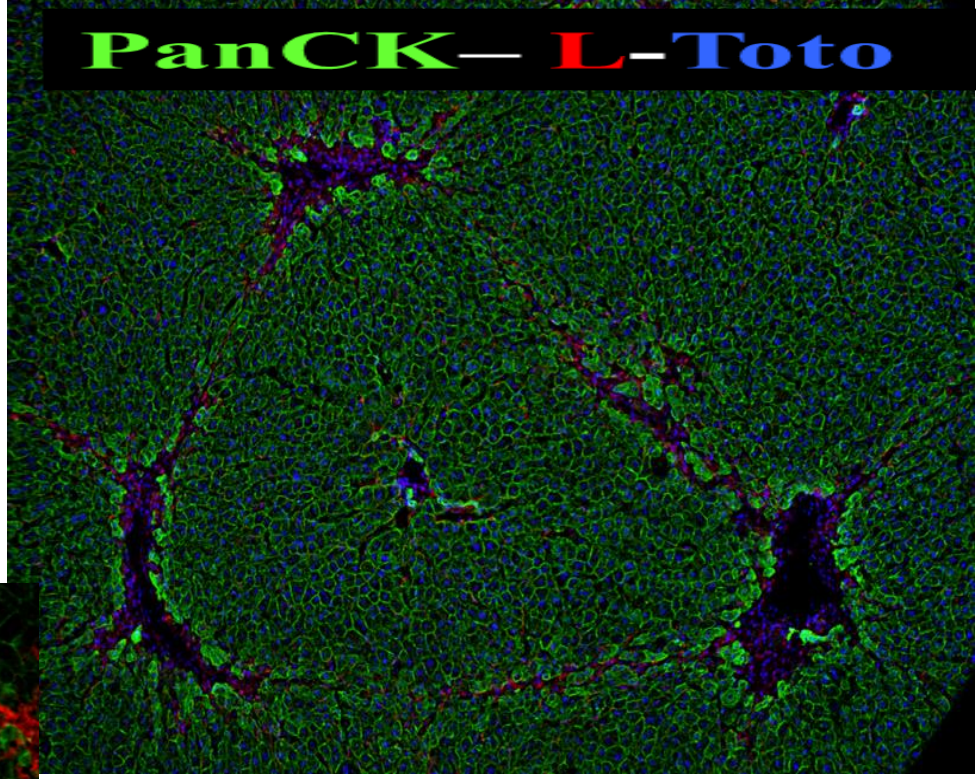


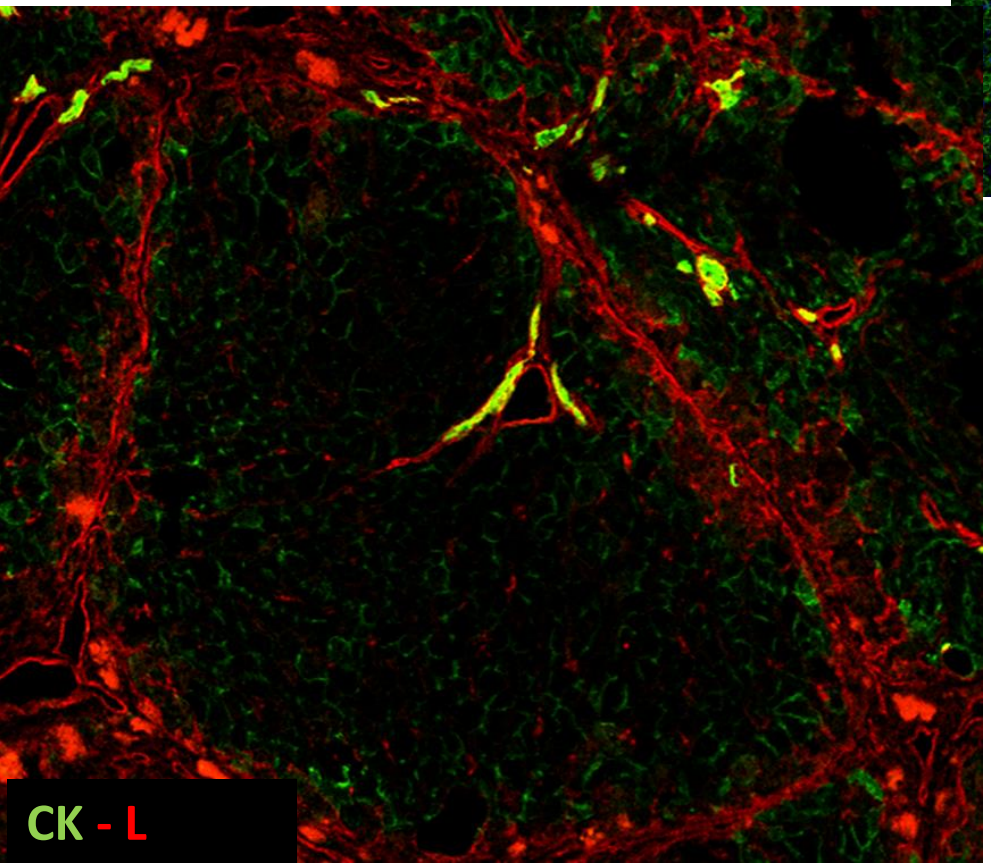
Cirrhosis-early



Cirrhosis-Early





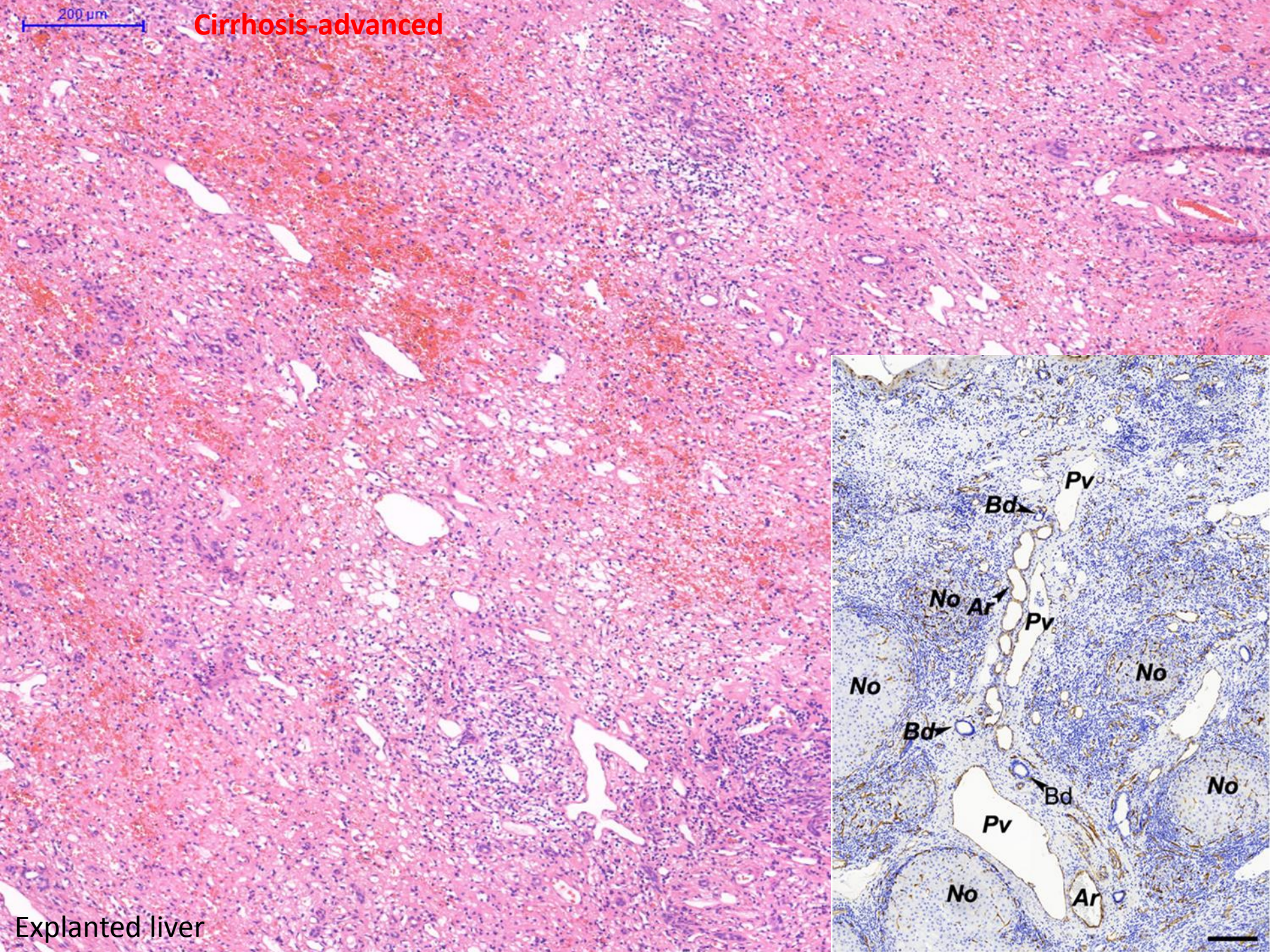


The definition of the cirrhosis is fulfilled

BUT

In early stages of experimental cirrhotic models complete portal triads can be seen in the middle of cirrhotic nodules

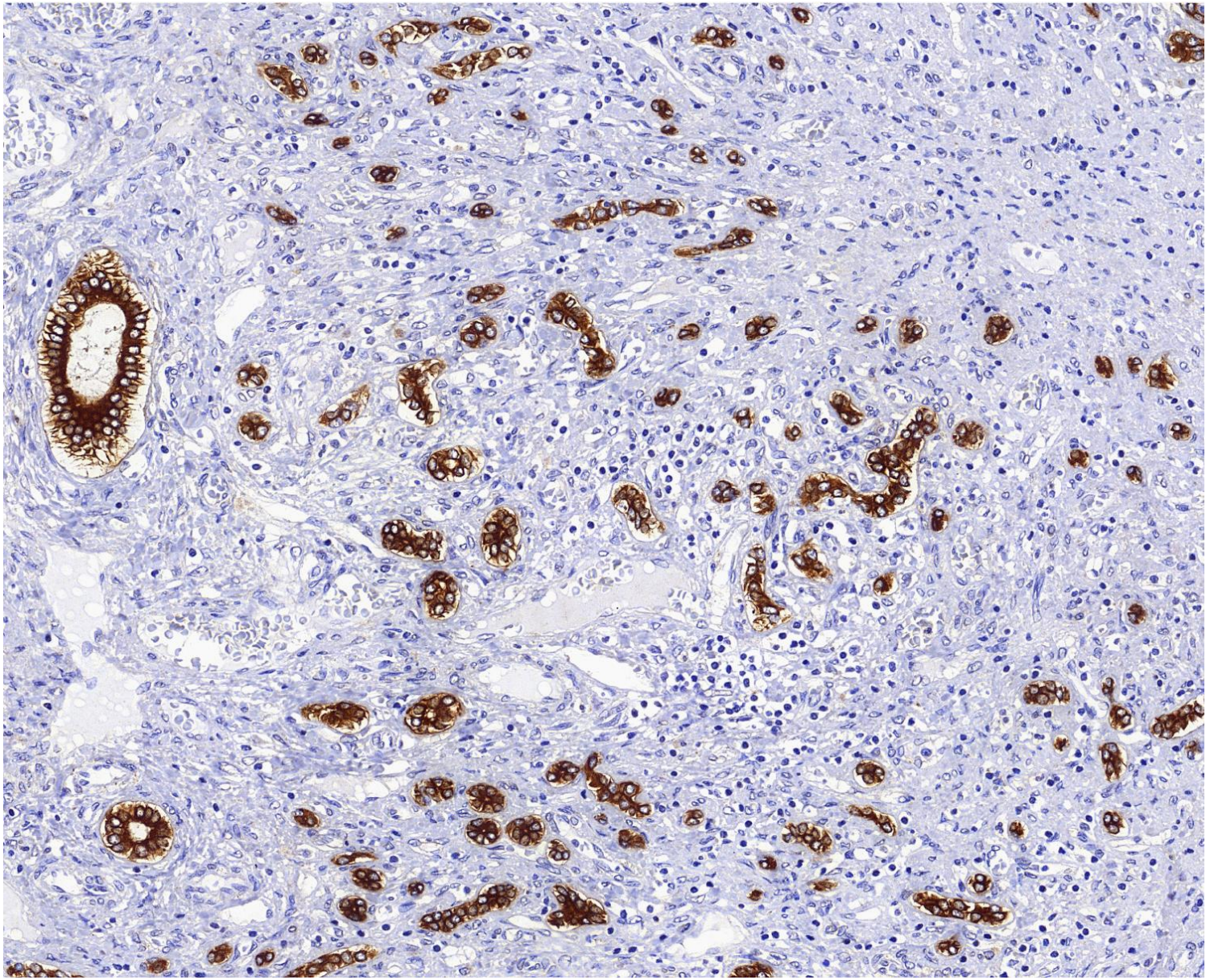
Reversible???????????


200 µm
Cirrhosis-advanced
Pv
Bd
No
Ar
Pv
No
No
Bd
Bd
No
Pv
No
Ar
Explanted liver

Cirrhosis-advanced

Explanted liver

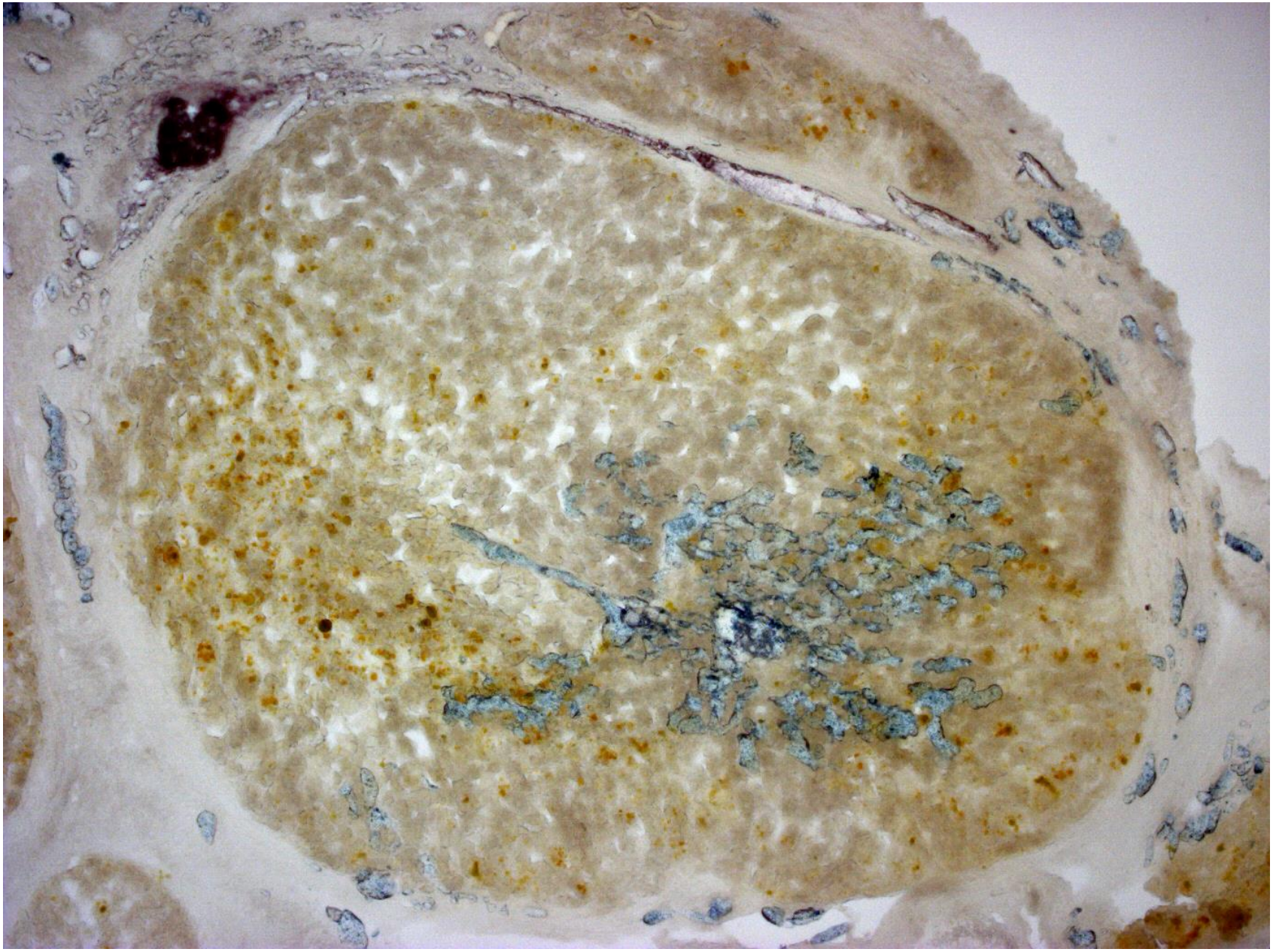
CK7 stains the bile ducts containing liver stem cells



Dezso et al. J Hepatol. 2017 Apr;66(4):778-786

Portal vein-central vein

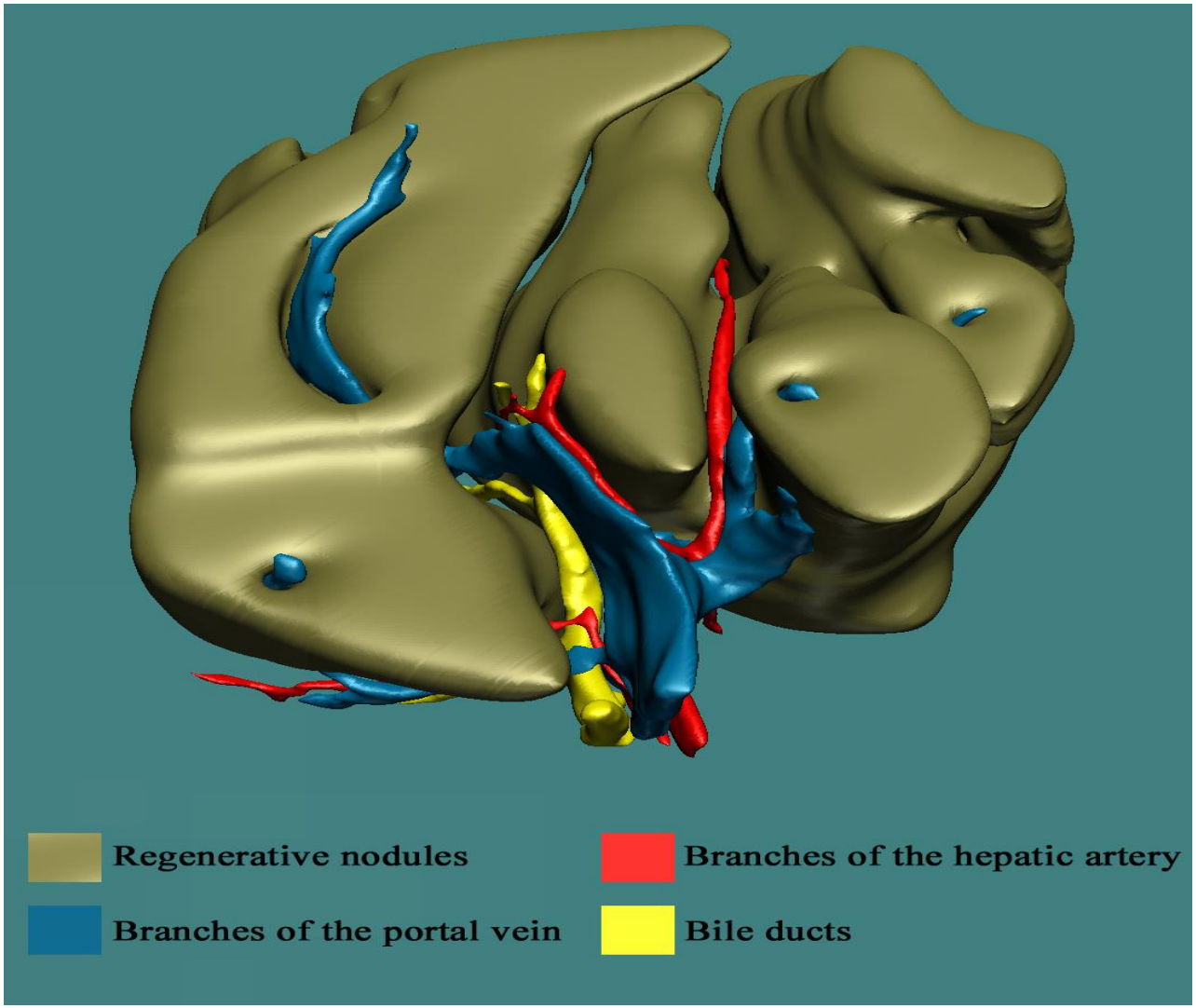
Cirrhosis-advanced

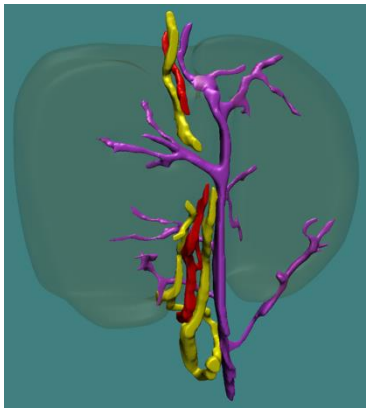


Explanted liver

Dezso et al. J Hepatol. 2017 Apr;66(4):778-786

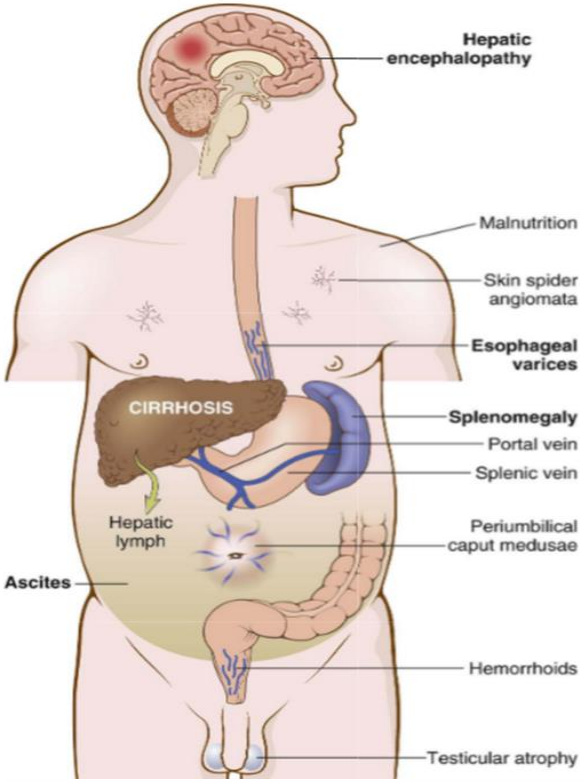
Cirrhosis-advanced

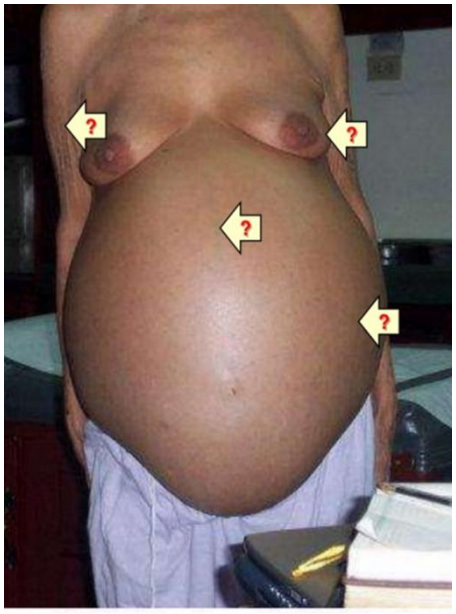


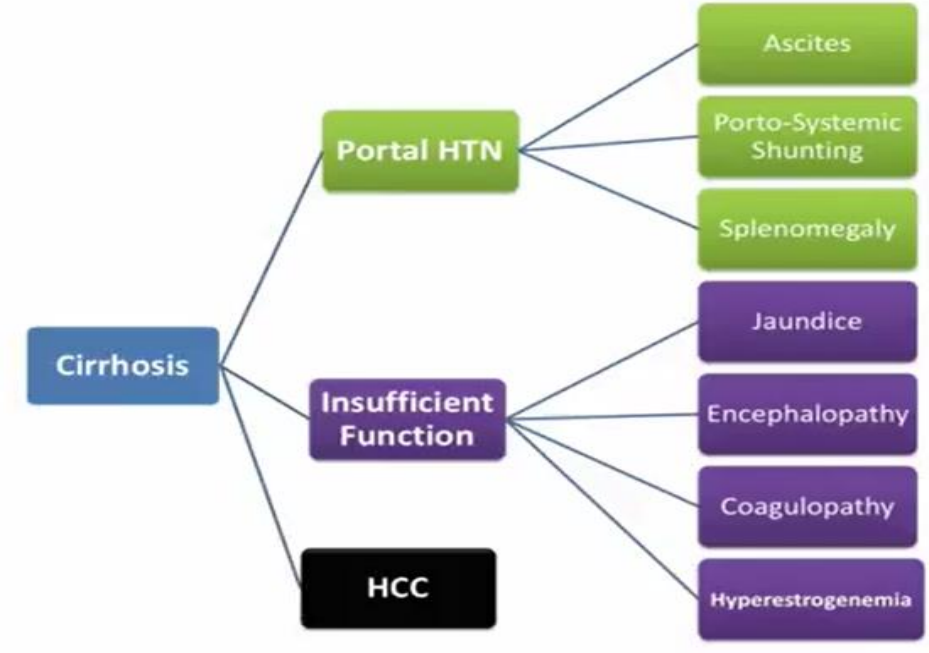


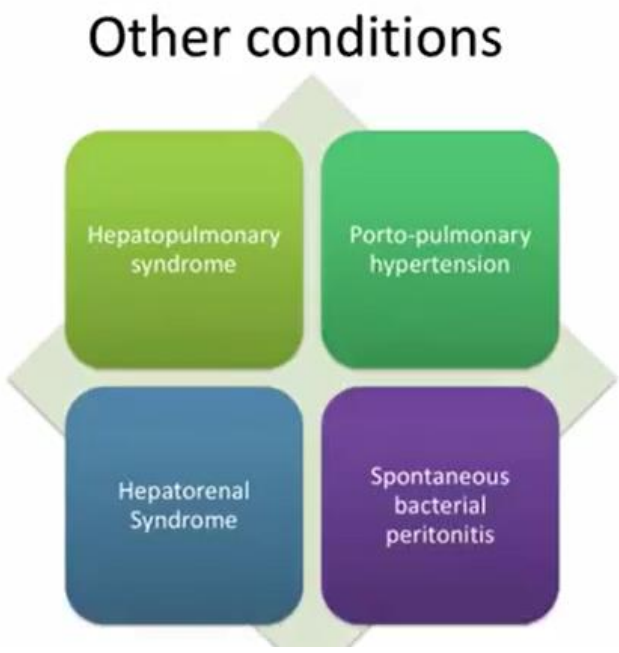
The structure of regenerative nodules (centrally located portal vein branches, bile ducts at the periphery, hepatic veins and arteries in the connective tissue) impedes the restoration of normal liver structure, the basic architecture of hepatic tissue suffers permanent damage.

Dezso et al. J Hepatol. 2017 Apr;66(4):778-786

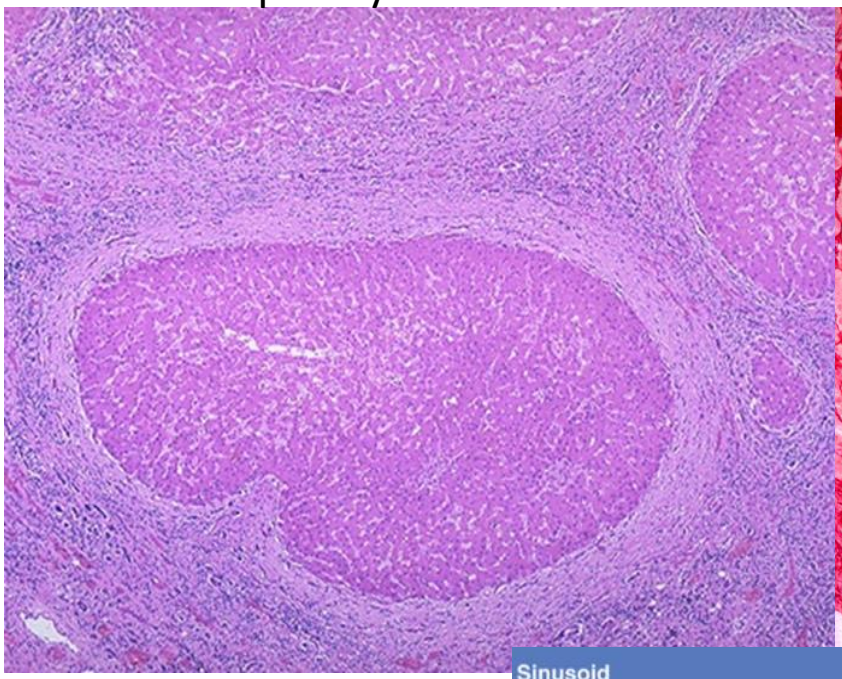

Hepatic encephalopathy
Malnutrition
Skin spider angiomata
Esophageal varices
CIRRHOSIS
Splenomegaly
Portal vein
Splenic vein
Hepatic lymph
Periumbilical caput medusae
Ascites
Hemorrhoids
Testicular atrophy

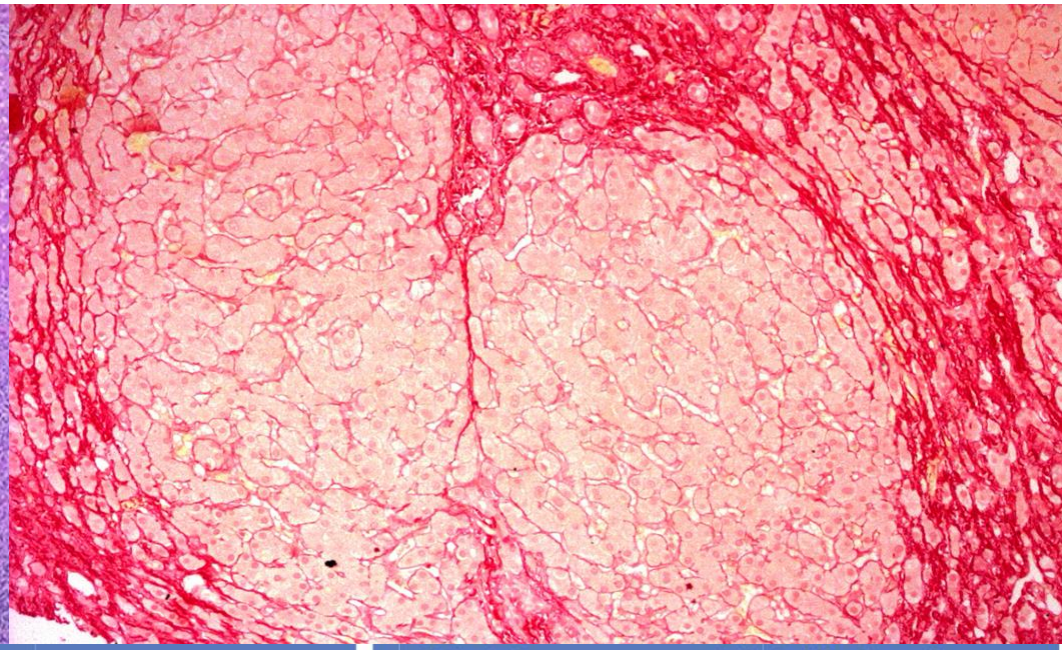


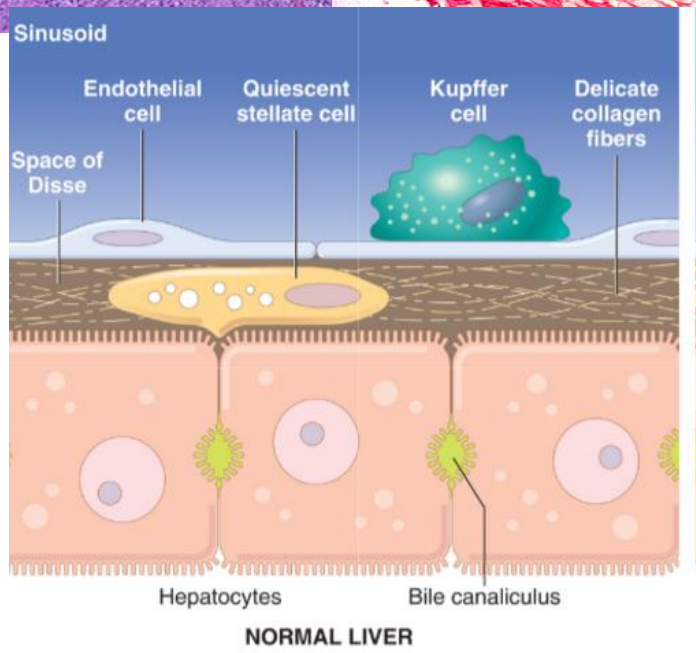

Cirrhosis
Portal HTN
Ascites
Porto-Systemic Shunting
Splenomegaly
Insufficient Function
Jaundice
Encephalopathy
Coagulopathy
Hyperestrogenemia
HCC

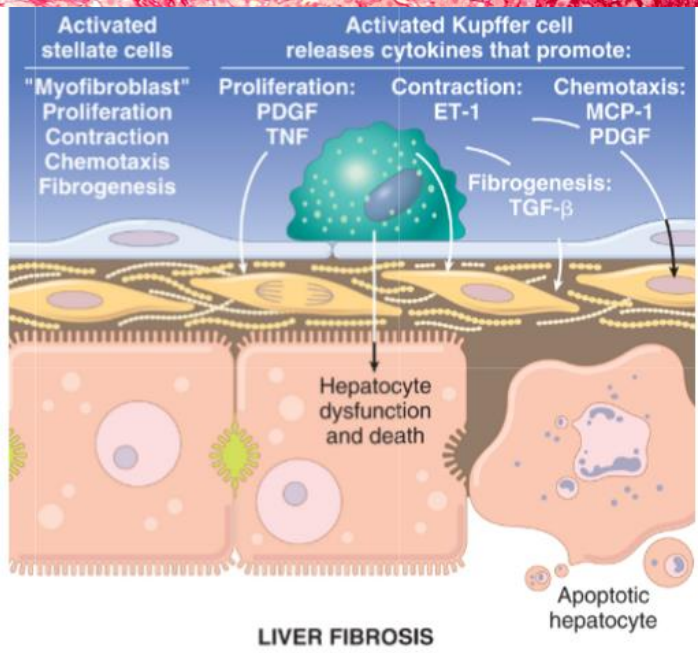

Other conditions
Hepatopulmonary syndrome
Porto-pulmonary hypertension
Hepatorenal Syndrome
Spontaneous bacterial peritonitis

Porto-central/porto-portal/porto-arterial shunts, capillarisation: failed communication between hepatocytes and blood





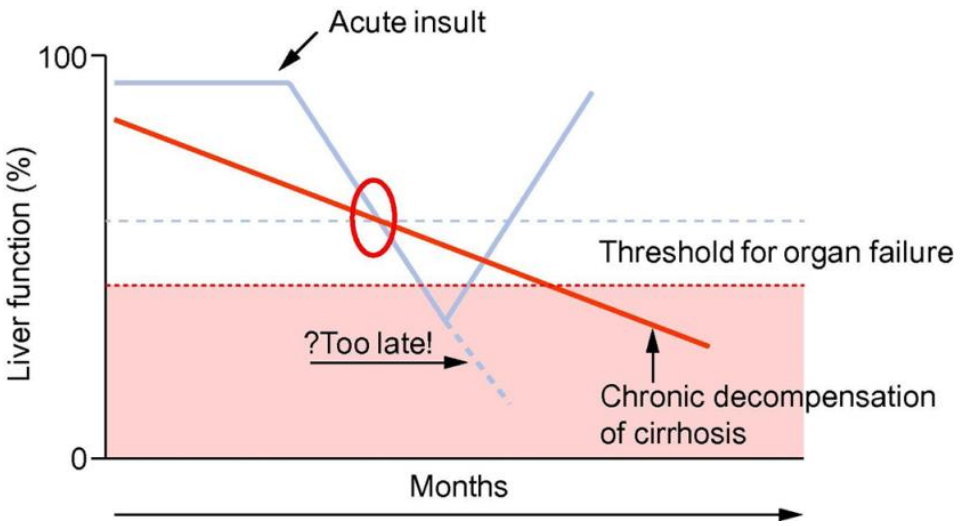




Cirrhosis

Acut-on- chronic liver failure (ACLF)

The short-term mortality of patients with this form of liver failure is around 50%.



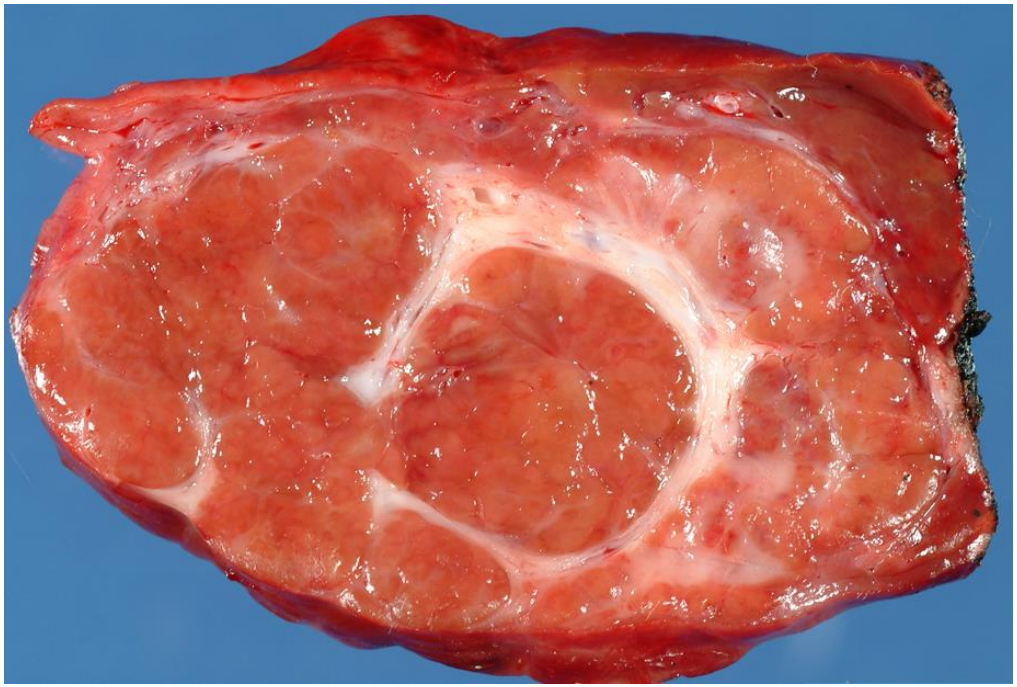
Key Points

- Acute-on chronic liver failure is a syndrome that defines a subgroup of cirrhotic patients who develop organ failure following hospital admission with or without an identifiable precipitating event and have increased mortality rates
- Altered host response to injury such as deranged systemic inflammatory response plays an important pathophysiological role
- Bacterial infection that occurs on the background of varying degrees of immune paralysis plays an important role in determining the outcome of this syndrome
- Systemic, cardiac and hepatic hemodynamics are important determinants of outcome
- The end-organs such as the kidney and the brain show evidence of inflammation
- Survival of patients is dependent upon the severity of organ failure

Journal of Hepatology 2012 57, 1336-1348DOI: (10.1016/j.jhep.2012.06.026)

LIVER TUMORS AND TUMOR LIKE LESIONS

Tumor like lesions: Focal nodular hyperplasia



-most commonly in women of reproductive age
-well-demarcated, but poorly encapsulated lesion, consisting of hyperplastic hepatocyte nodules with a central, stellate fibrous scar.

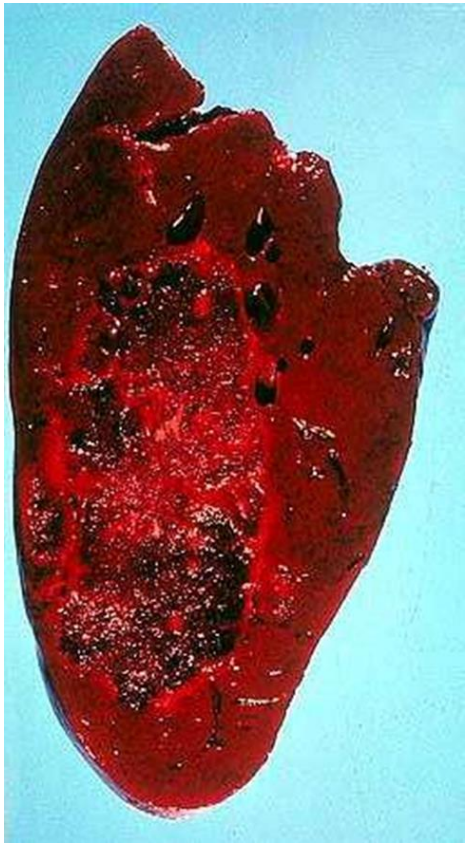
-from 1 cm to many centimeters

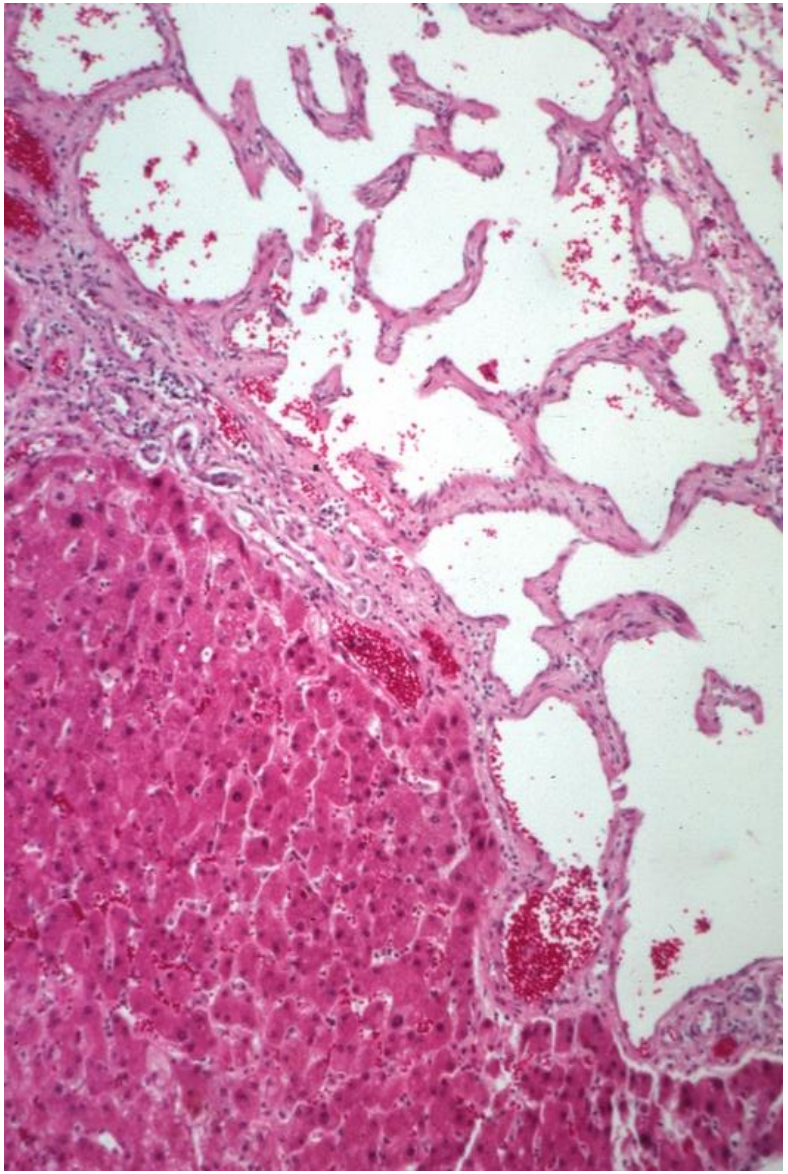
Risk factors: estrogens, including those found in contraceptive pills

No risk for malignancy

Benign tumors

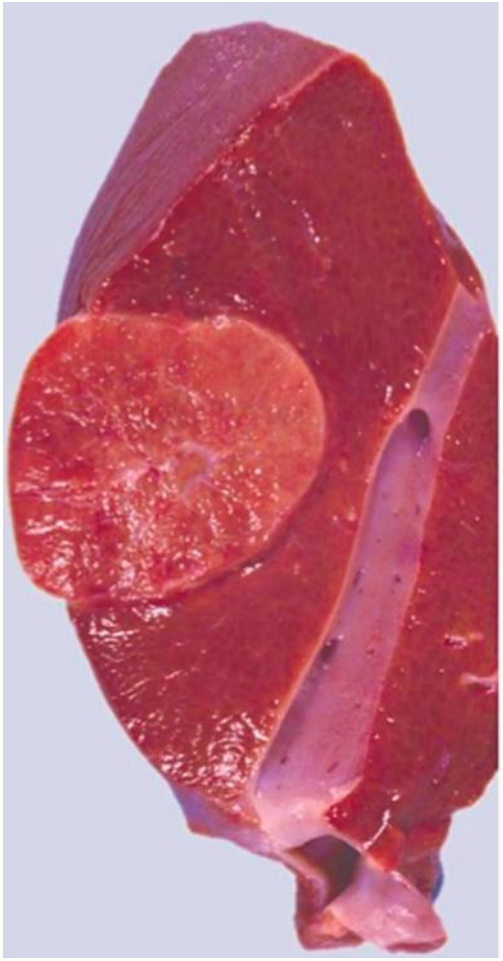
Hemangioma cavernosum





Benign tumors

Hepatocellular adenoma (pills)



Usually, solitary and asymptomatic
Large tumors –risk of rupture or bleed spontaneously,

Classification:

4 subtypes
(1) HAs with inactivating mutations of hepatocyte nuclear factor 1a (HNF1A; HA-H),

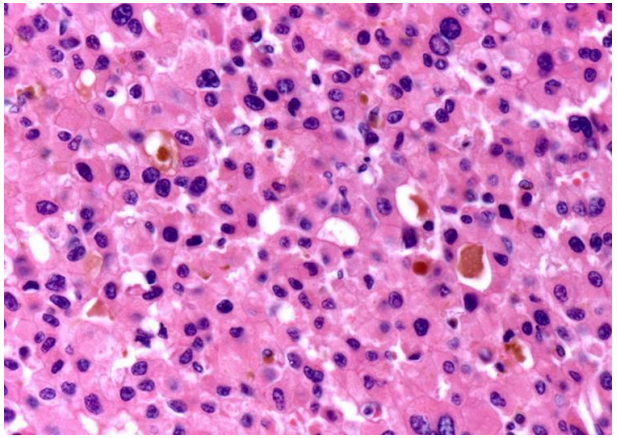
(2) HAs with activating mutations of b-catenin gene (HA-B), ***increased potential for malignant transformation!!!!!***

(3) HAs without mutations of the HNF1A or b-catenin genes and with inflammatory features (HA-I),

(4) unclassified HAs that have no specific gene mutations or unique morphologic
features (HA-U)

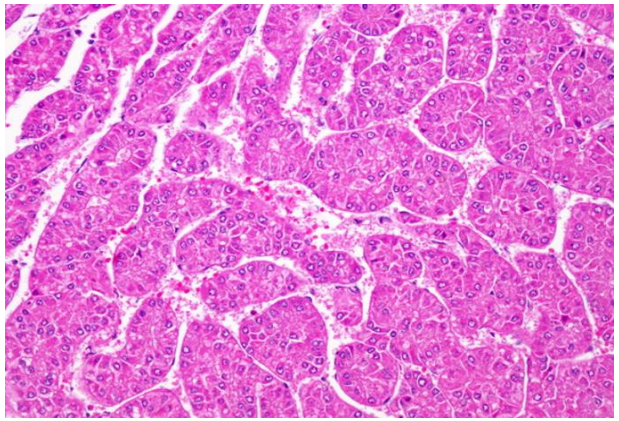
Malignant tumors

Hepatocellular carcinoma



Pathogenesis:

HBV or HCV,
alcoholic cirrhosis,
aflatoxin exposure
NAFLD
AT deficiency
hemochromatosis

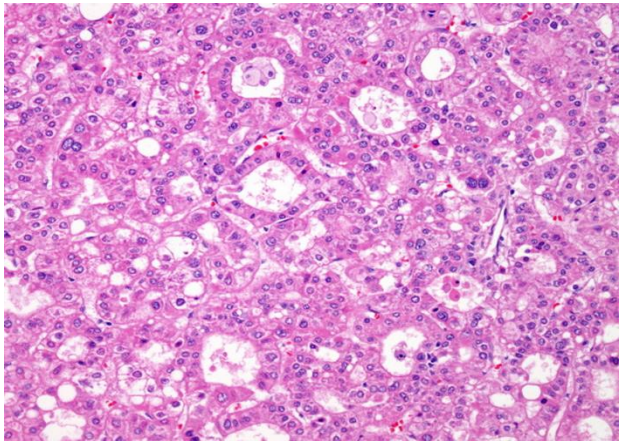


Morphology:

-unifocal, usually massive tumor;
-multifocal tumor made of nodules of variable size;
-diffusely infiltrative

Paraneoplastic manifestations

(e.g., polycythemia, hypoglycemia, hypercalcemia) as a result of hormone production by the tumor.
Alpha-Fetoprotein levels are often elevated in HCC

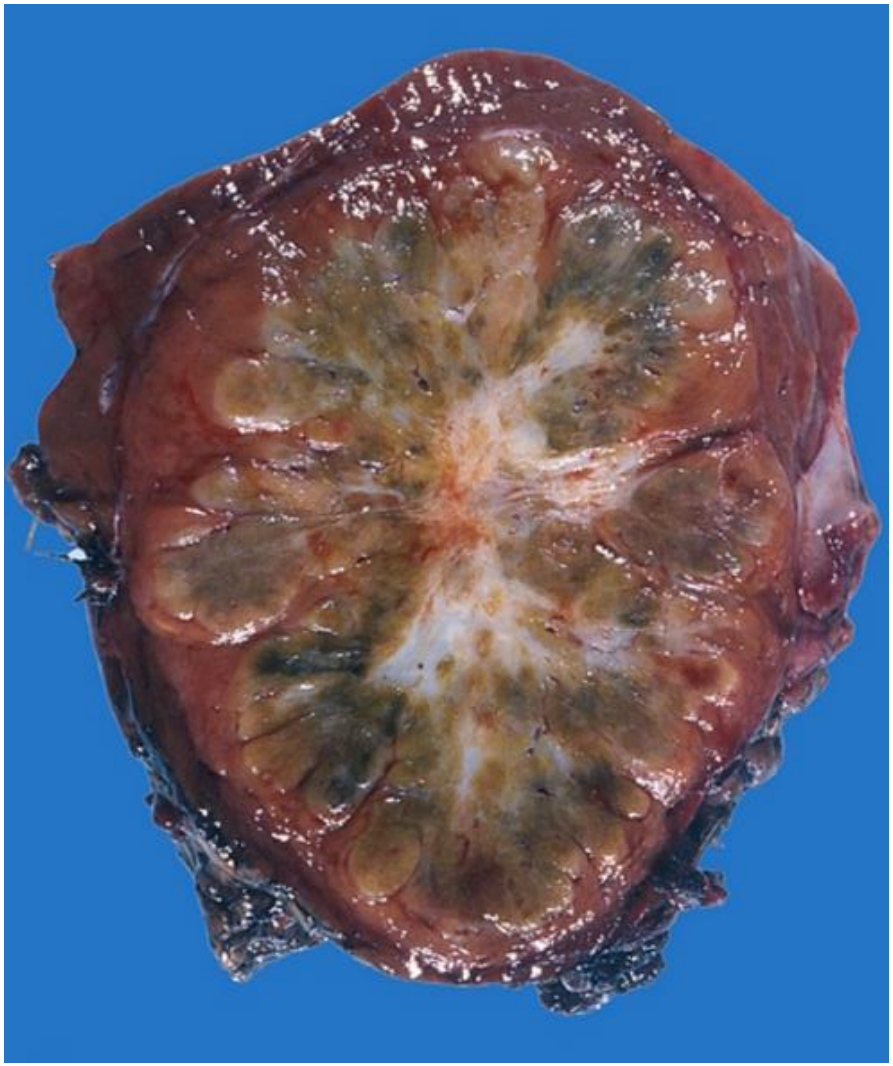


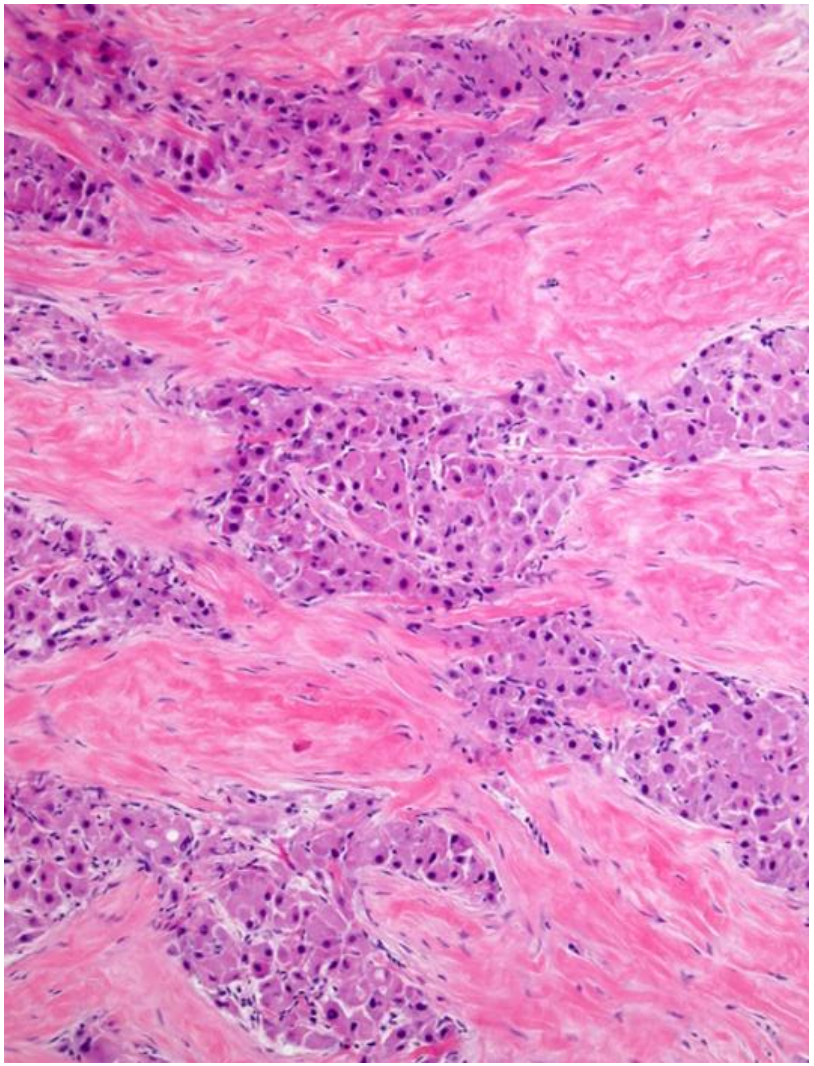
Treatment:

segmental resections
hepatic transplantation

Malignant tumors

A distinctive clinicopathologic variant of HCC is the ***fibrolamellar carcinoma***. It occurs in young male and female adults (20 to 40 years of age) with equal incidence and has no association with cirrhosis or other risk factors.



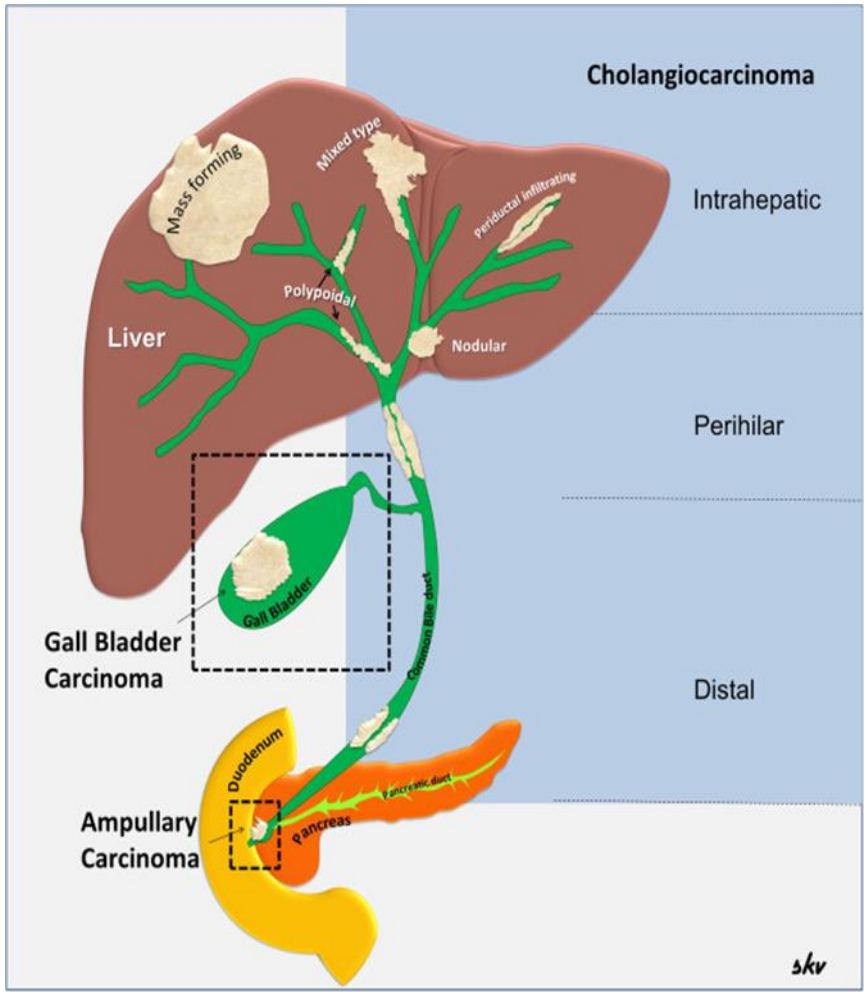


Malignant tumors

Cholangiocarcinoma

Intrahepatic cholangiocarcinoma is the second most common primary liver cancer after hepatocellular carcinoma.

Frequent in the parts of Asia in which the liver fluke (Clonorchis sinensis, *Opisthorchis*) is endemic



Hennedige *et al. Cancer Imaging* 2014 **14**:14

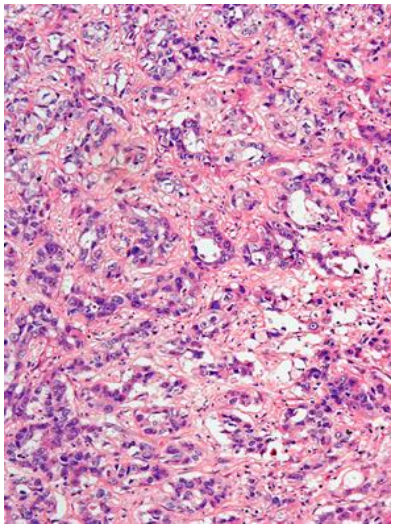
Histological Classification of Intrahepatic Cholangiocarcinoma

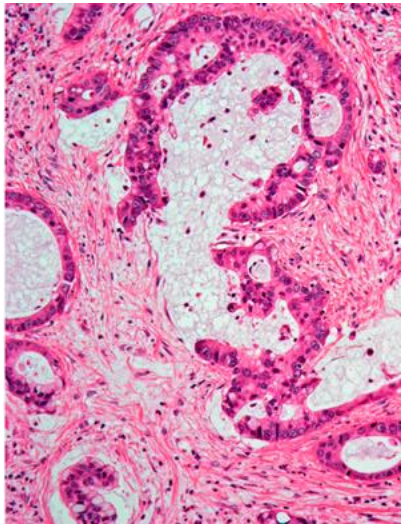
-cholangiolar type

-IDH1 mutation (p.R132C)

-IDH2 mutation(p.R172W)

-bile duct type

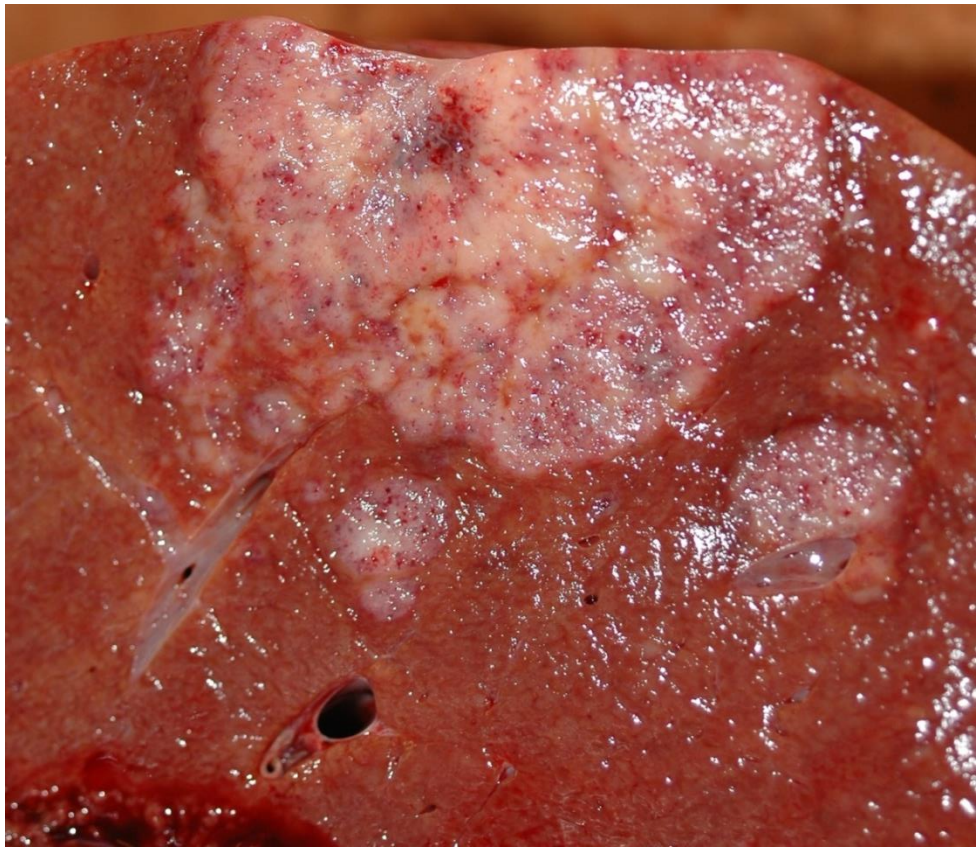


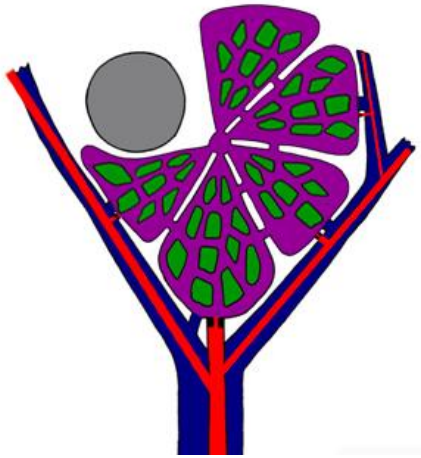


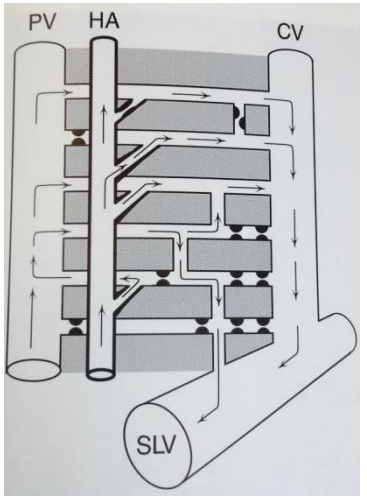
Liau et al, Modern Pathology (2014) **27,** 1163–1173

Malignant tumors

Metastases







Portal vein-hepatic artery

The liver is involved in a third of all metastatic cancers, including half of those of the ***gastrointestinal tract***, ***breast***, and ***lung***.
Other tumors that characteristically metastasize to the liver are pancreatic carcinoma and malignant melanoma

Alcohol- and Drug-induced liver disease

(DILI)TOXIC LIVER DAMAGE

CAN MIMIC ANY KIND OF LIVER DISEASES

-Predictable (Amanita phalloides poisoning, CCl4)

-Unpredictable /idiosyncratic (not directly toxic compounds e.g. Halothan)

Reye syndrome: liver failure in children, microfatty steatosis (viral infection+acetylsalicic acid)

Exposure to a toxin or therapeutic agent should always be included in the differential diagnosis of any form of liver disease.

Table 15–4 Different Forms of Drug- or Toxin-Induced Hepatic Injury

Pattern of Injury	Morphologic Findings	Examples of Associated Agents
Cholestatic	Bland hepatocellular cholestasis, without inflammation	Contraceptive and anabolic steroids; estrogen replacement therapy
Cholestatic hepatitis	Cholestasis with lobular inflammation and necrosis; may show bile duct destruction	Numerous antibiotics; phenothiazines
Hepatocellular necrosis	Spotty hepatocyte necrosis Submassive necrosis, zone 3 Massive necrosis	Methyldopa, phenytoin Acetaminophen, halothane Isoniazid, phenytoin
Steatosis	Macrovesicular	Ethanol, methotrexate, corticosteroids, total parenteral nutrition
Steatohepatitis	Microvesicular, Mallory bodies	Amiodarone, ethanol
Fibrosis and cirrhosis	Periportal and pericellular fibrosis	Methotrexate, isoniazid, enalapril
Granulomas	Noncaseating epithelioid granulomas	Sulfonamides, numerous other agents
Vascular lesions	Sinusoidal obstruction syndrome (venoocclusive disease): obliteration of central veins Budd-Chiari syndrome Sinusoidal dilatation Peliosis hepatis: blood-filled cavities, not lined by endothelial cells	High-dose chemotherapy, bush teas Oral contraceptives Oral contraceptives, numerous other agents Anabolic steroids, tamoxifen
Neoplasms	Hepatic adenoma Hepatocellular carcinoma Cholangiocarcinoma Angiosarcoma	Oral contraceptives, anabolic steroids Thorotrast Thorotrast Thorotrast, vinyl chloride

Alcoholic Liver Disease

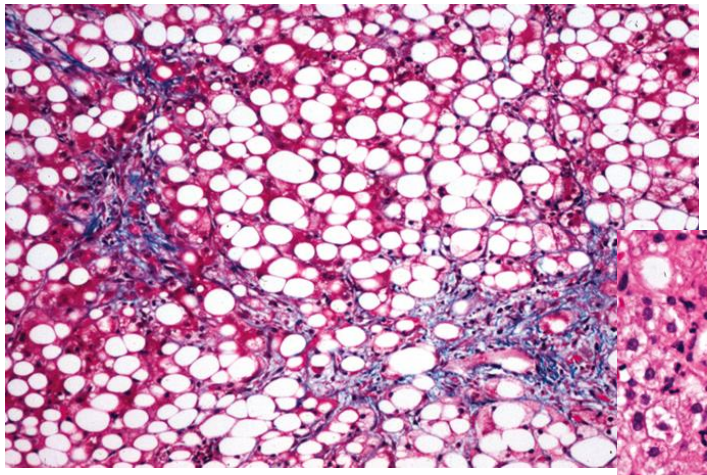
(females are more sensitive)

Forms: -Hepatic steatosis

-Alcoholic hepatitis (**Acetaldehyde, Reactive oxygen species, Mallory-Denk bodies, Cytokine-mediated inflammation**)

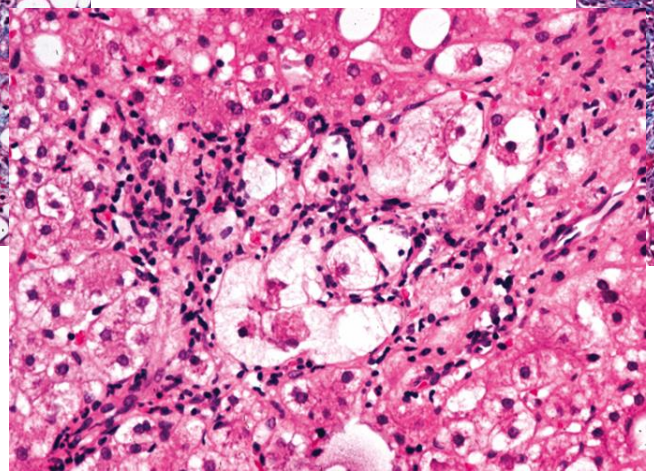
-Alcoholic cirrhosis (usually after 10 to 15 years of drinking or more, but only occurs in a small proportion of chronic alcoholics

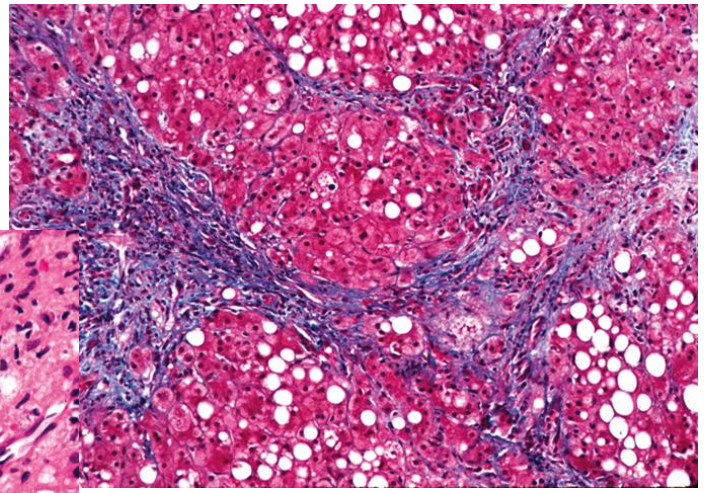
By far the most important agent that produces toxic liver injury is alcohol; its characteristic histologic (but not clinical) features are shared with nonalcoholic fatty liver disease (NAFLD) and therefore it is discussed in that section.



Steatosis

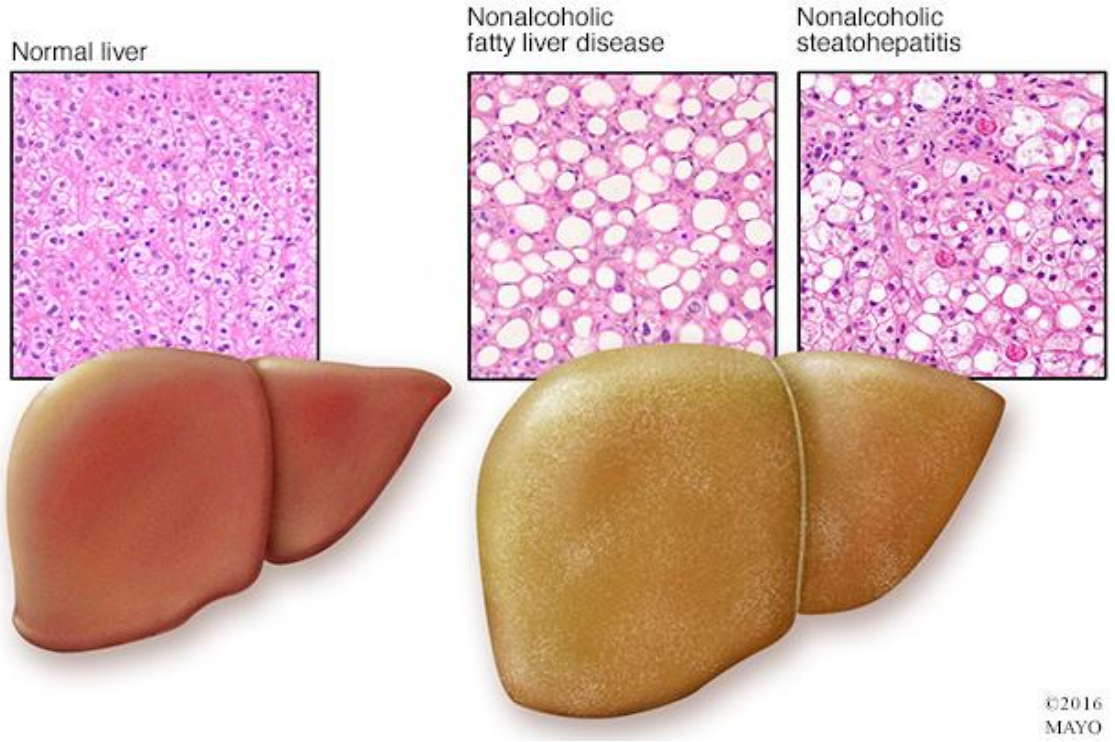
Hepatocyte ballooning
Mallory bodies
Neutrophils





Pericellular and perivenular fibrosis

NAFLD



Risk factors:

- High cholesterol
- High levels of TG in the blood
- Metabolic syndrome
- Obesity, particularly when fat is concentrated in the abdomen
- Polycystic ovary syndrome
- Hypothyroidism
- Hypopituitarism

Causes:

- Overweight or obesity
- Insulin resistance, in which your cells don't take up sugar in response to the hormone insulin
- High blood sugar (hyperglycemia), indicating prediabetes or actual type 2 diabetes
- High levels of fats, particularly triglycerides, in the blood

Complications:

- Cirrhosis-End-stage liver failure
- Liver cancer