GNT Module, Pathology
PATHOLOGY & PATHOGENESIS OF LIVER CIRRHOSIS

Dr. Wajd Althakfi, MD

Consultant Histopathology

King Saud University - Faculty of Medicine

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OBJECTIVES

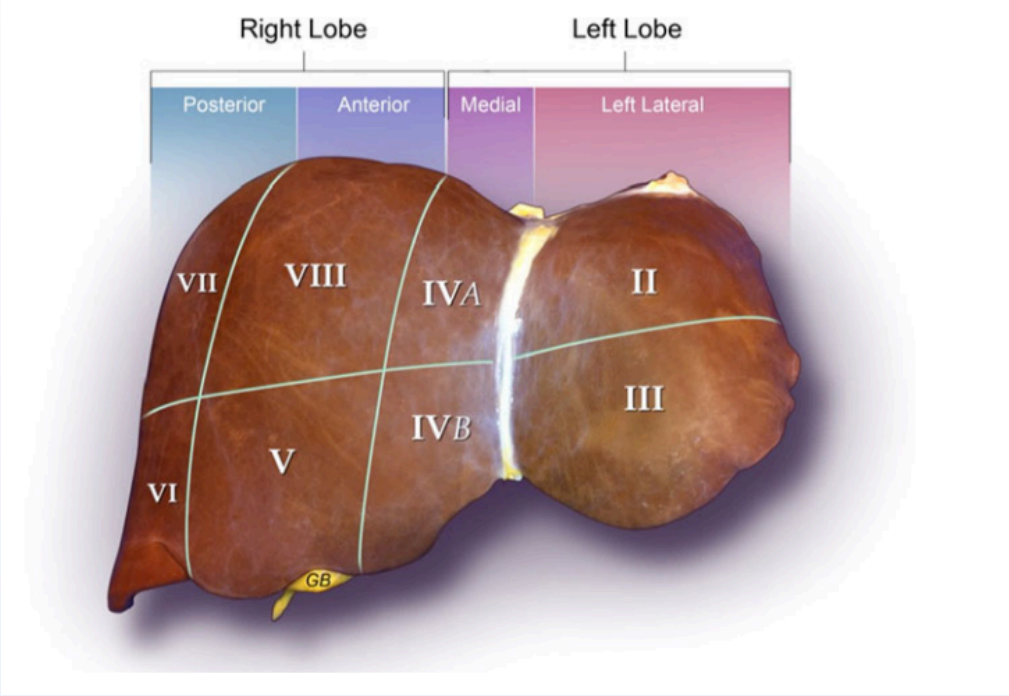
- Introduction
- Define Cirrhosis
- Recognize the types and classification of cirrhosis
- Recognize the causes and the pathogenic mechanisms leading to cirrhosis
- Describe the pathological findings in cirrhotic livers

Introduction

- Normal adult liver weighs approximately 1400 g in females and 1800 g in males
- Has dual blood supply:
  ✓ Portal vein providing 60 - 70% of hepatic blood flow
  ✓ Hepatic artery supplies remaining 30 - 40%
- Both portal vein & hepatic artery enter the inferior aspect of the liver through the hilum "*porta hepatis*"
- Within the liver, the branches of the portal veins, hepatic arteries & bile ducts travel in parallel within *portal tracts*

Introduction

- Based on Couinaud classification, the liver is divided into eight independent functional segments
- Each segment has its own portal pedicle consisting of the hepatic arterial branch, portal branch, and the bile duct with a separate hepatic venous branch

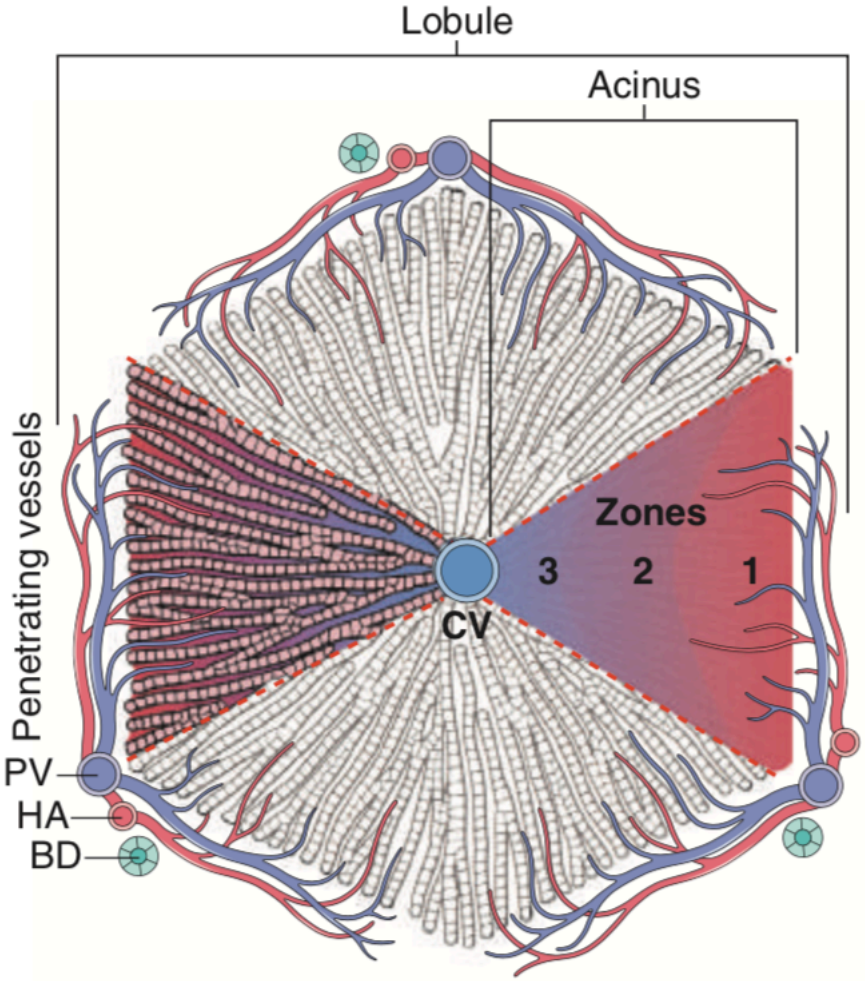


Introduction

Lobule:

- ✓Liver cells **"hepatocytes"** are arranged radially around the central vein "terminal hepatic vein"
- ✓**Porta tract** are present at the periphery
- ✓These lobule are often drawn as hexagonal structures

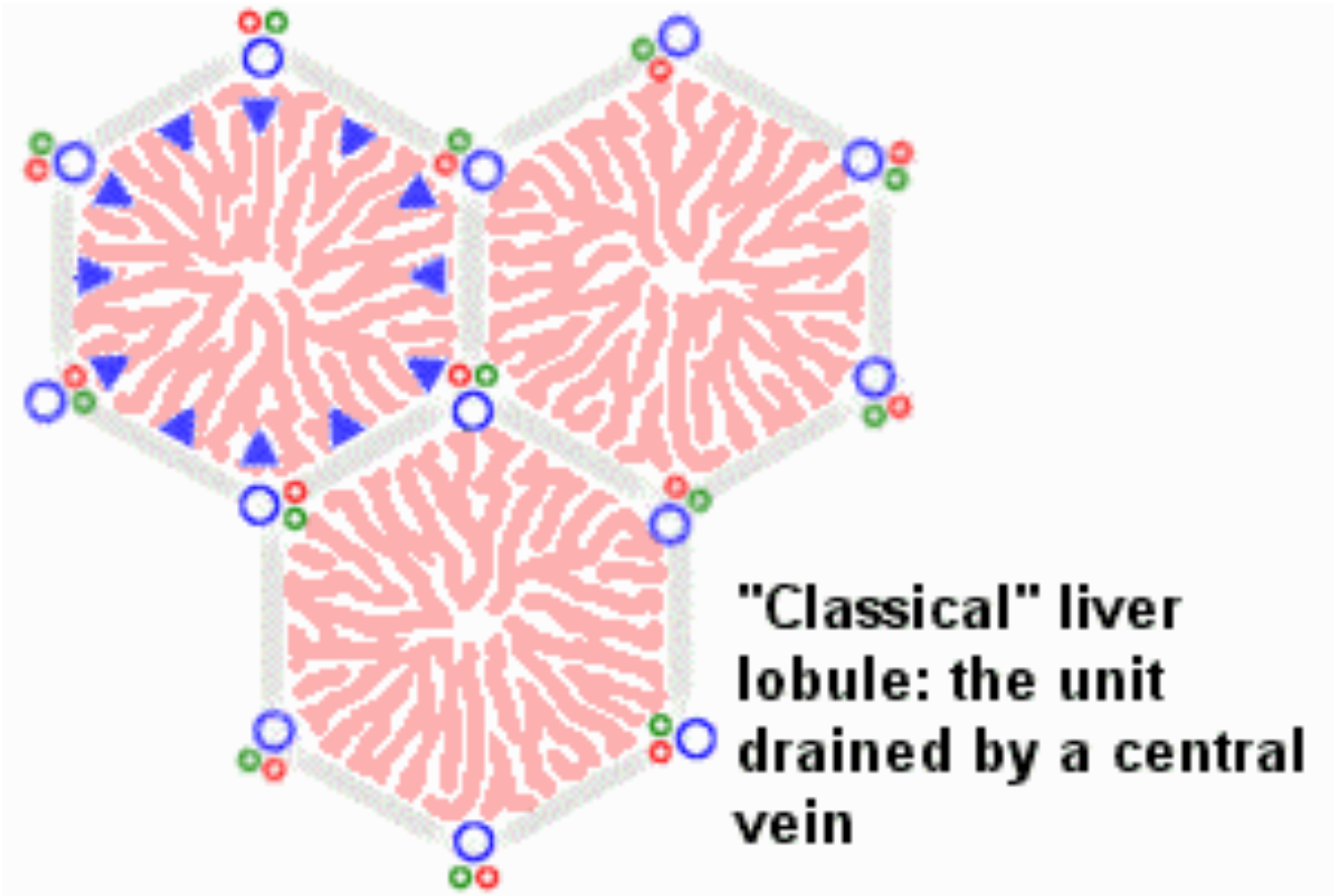
- Smallest structural unit of the liver is the lobule
- The smallest functional unit is the acinus



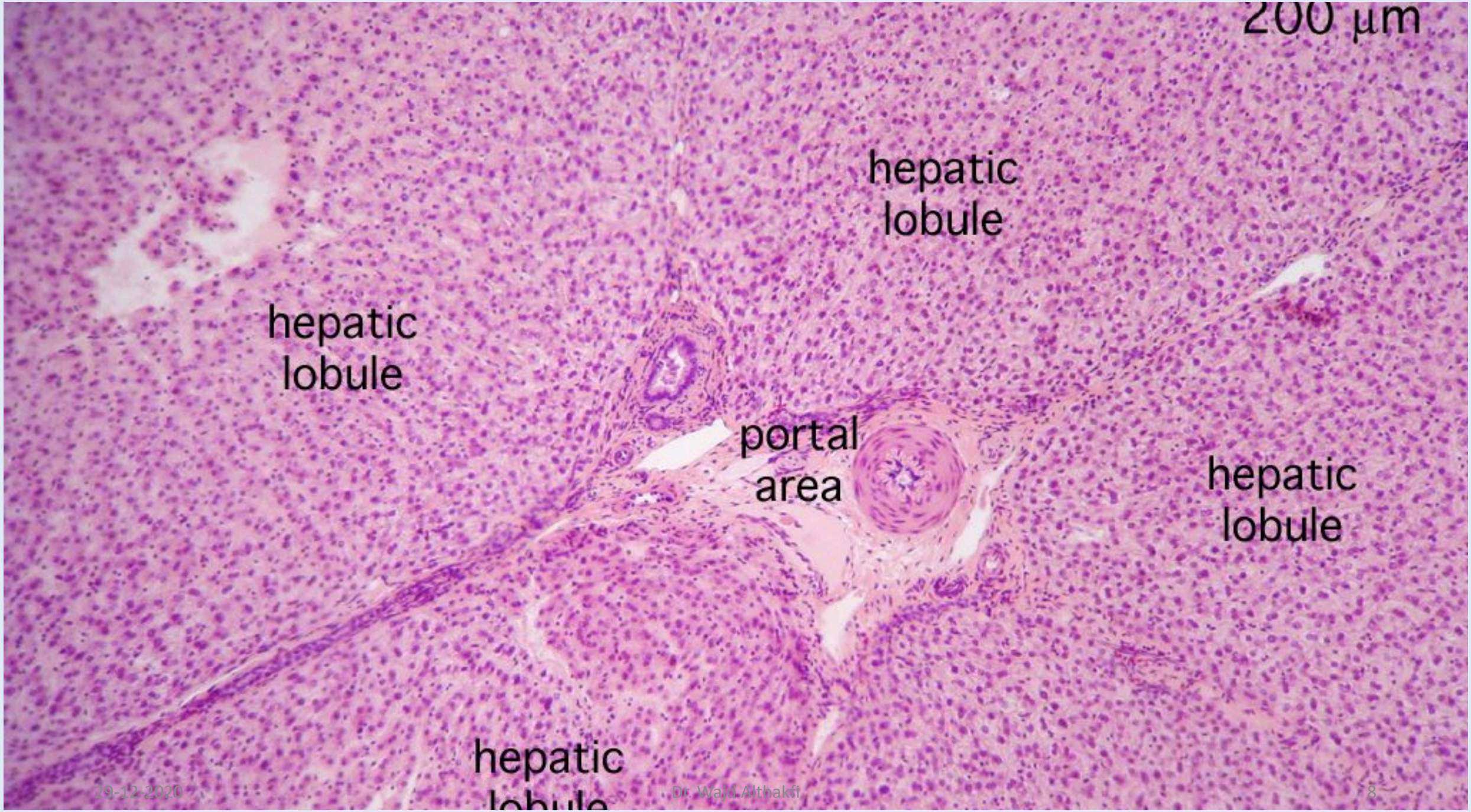
Introduction

- **Physiologically** it is more useful to think of liver architecture in terms of **functional unit "acinus"**
- Depends on position of hepatocytes relative to their blood supply
- Three zones are identified in term of oxygenation & nutrient supply

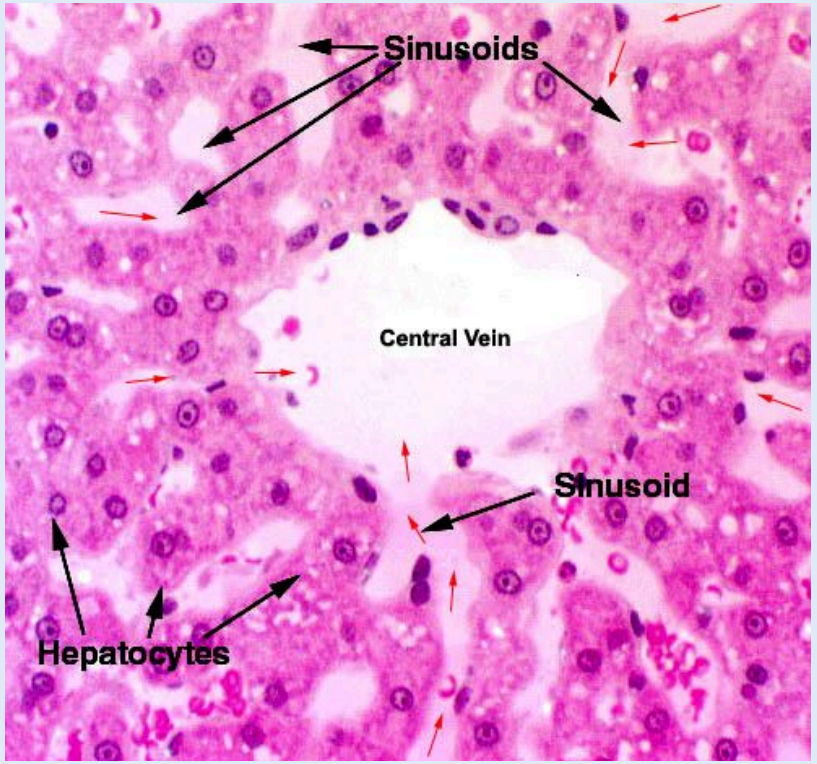
Division of the lobular parenchyma into zones is an important concept because each zone differs with respect to its metabolic activities and susceptibility to certain forms of hepatic injury

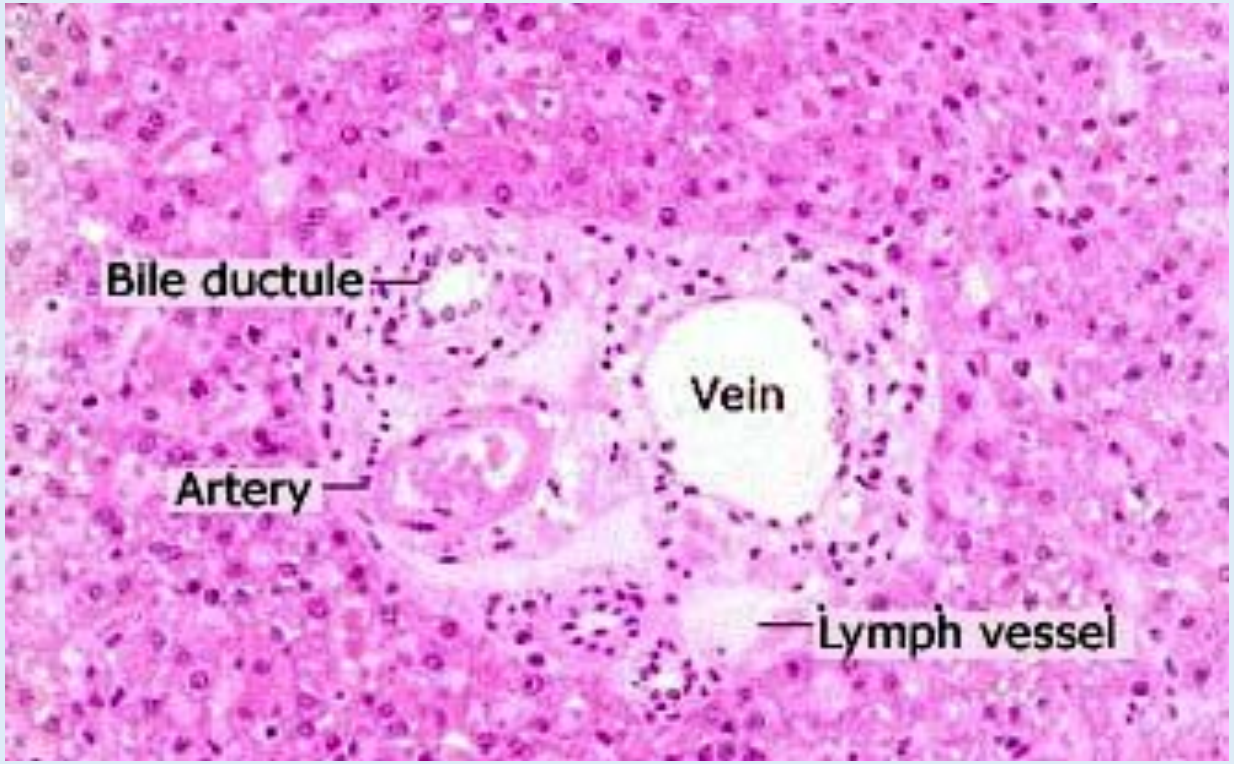


Portal triad


200 µm
hepatic lobule
hepatic lobule
portal area
hepatic lobule
hepatic lobule

Normal liver lobules





Introduction

- Generally, liver disease is an insidious process in which the signs & symptoms of hepatic decompensation appear weeks, months, or even years after the onset of injury

- The hepatic injury may be imperceptible to the patient and to be manifest only by laboratory test abnormalities

Mechanism of injury and repair

- Injured hepatocytes may show several potentially reversible changes, such as accumulation of fat and bilirubin (cholestasis)

- When injury is not reversible, hepatocytes die by necrosis or apoptosis:
  - ✓**Necrosis is commonly seen following hepatic injury caused by hypoxia & ischemia**
  - ✓**Apoptotic cell death predominates in viral, autoimmune & and drug- and toxin-induced hepatitis**

Chronic liver failure and cirrhosis

- Cirrhosis is the morphologic change most often associated with chronic liver disease
- It refers to the diffuse transformation of the liver into regenerative parenchymal nodules surrounded by fibrous bands
- It is among the top 10 causes of death in the Western world.
- It is the end-stage of chronic liver disease
- Not all chronic liver disease terminates in cirrhosis & not all cirrhosis leads to end stage liver disease

Cirrhosis

Cirrhosis, as the end stage of chronic liver disease, is defined by three main morphologic characteristics:

1. Fibrosis: in the form of delicate bands or broad scars/septa (Bridging fibrous septa)
2. Parenchymal nodules containing hepatocytes encircled by fibrosis, with diameters varying from very small (<0.3 cm, micronodules) to large (several centimeters, macronodules)
3. Disruption of the architecture of the entire liver

Causes

- Worldwide leading causes

1. Chronic hepatitis B, chronic hepatitis C
2. Non-alcoholic fatty liver disease (NAFLD)
3. Alcoholic liver disease

Classification of cirrhosis based on causes

• Alcoholic liver disease	60% to 70%
• Viral hepatitis	10%
• Biliary diseases	5% to 10%
• Primary hemochromatosis	5%
• Wilson disease	Rare
• α1-Antitrypsin deficiency	Rare
• Cryptogenic cirrhosis	10% to 15%

Classification of cirrhosis
(Infrequent types of cirrhosis)

- The cirrhosis developing in infants and children with galactosemia and tyrosinosis
- Drug-induced cirrhosis (methotrexate, enalapril, vitamin A)
- Severe fibrosis can occur in the setting of cardiac disease "cardiac cirrhosis"
- In some cases, there is no cause, and these are referred to cryptogenic cirrhosis
- Once cirrhosis is established, it is usually impossible to establish an etiologic diagnosis on morphologic grounds alone

Pathogenesis of liver cirrhosis

- Principal cell type involved in scar deposition is the perisinusoidal hepatic stellate cell
- These cells are located in the space of Disse and in normal liver has a role in the storage of vitamin A
- Following liver injury, stellate cells become activated by several mechanisms and convert into highly fibrogenic myofibroblasts, which produce the fibrous scar

Pathogenesis of liver cirrhosis

The stimuli for stellate cell activation may originate from several sources

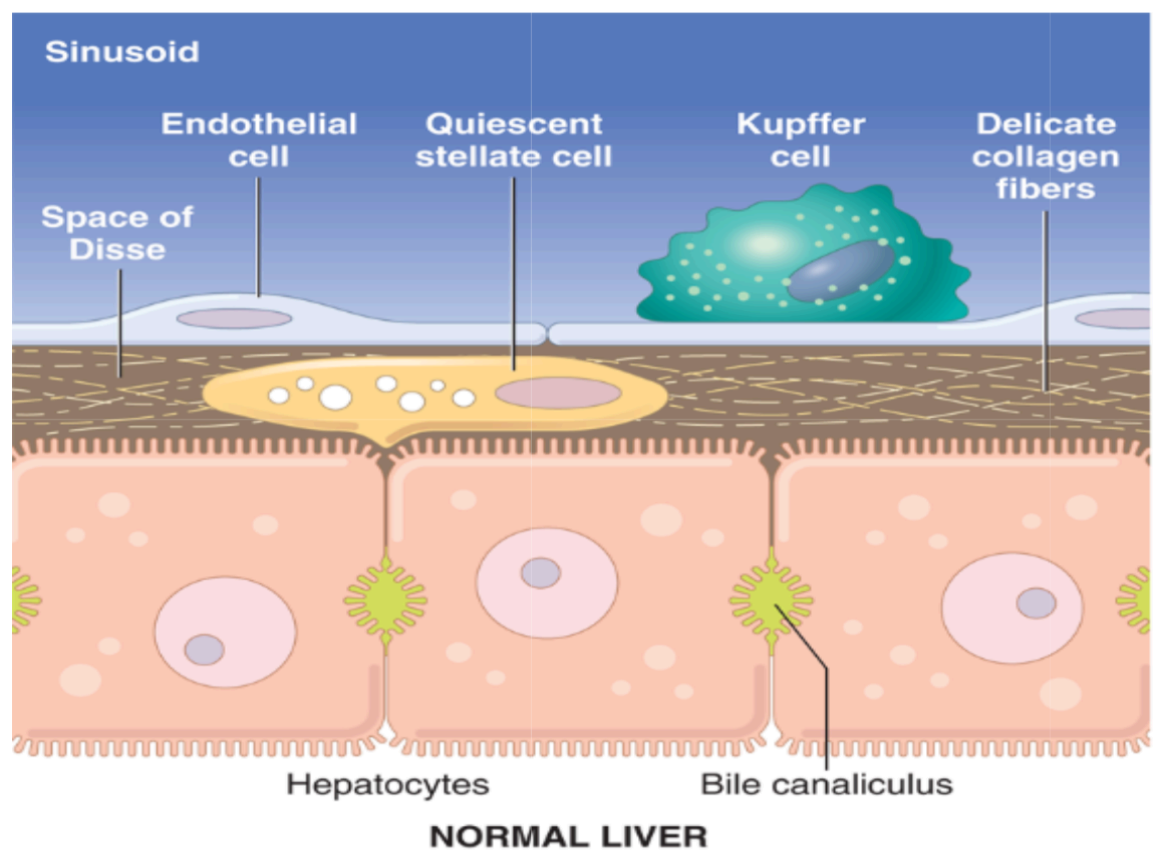
- Proliferation of hepatic stellate cells and their activation into myofibroblasts is initiated by a series of changes that include an increase in the expression of platelet-derived growth factor receptor β (PDGFR-β) in the stellate cells

- Chronic inflammation, with production of inflammatory cytokines such as tumor necrosis factor (TNF), lymphotoxin, and interleukin 1β (IL-1β), and lipid peroxidation products

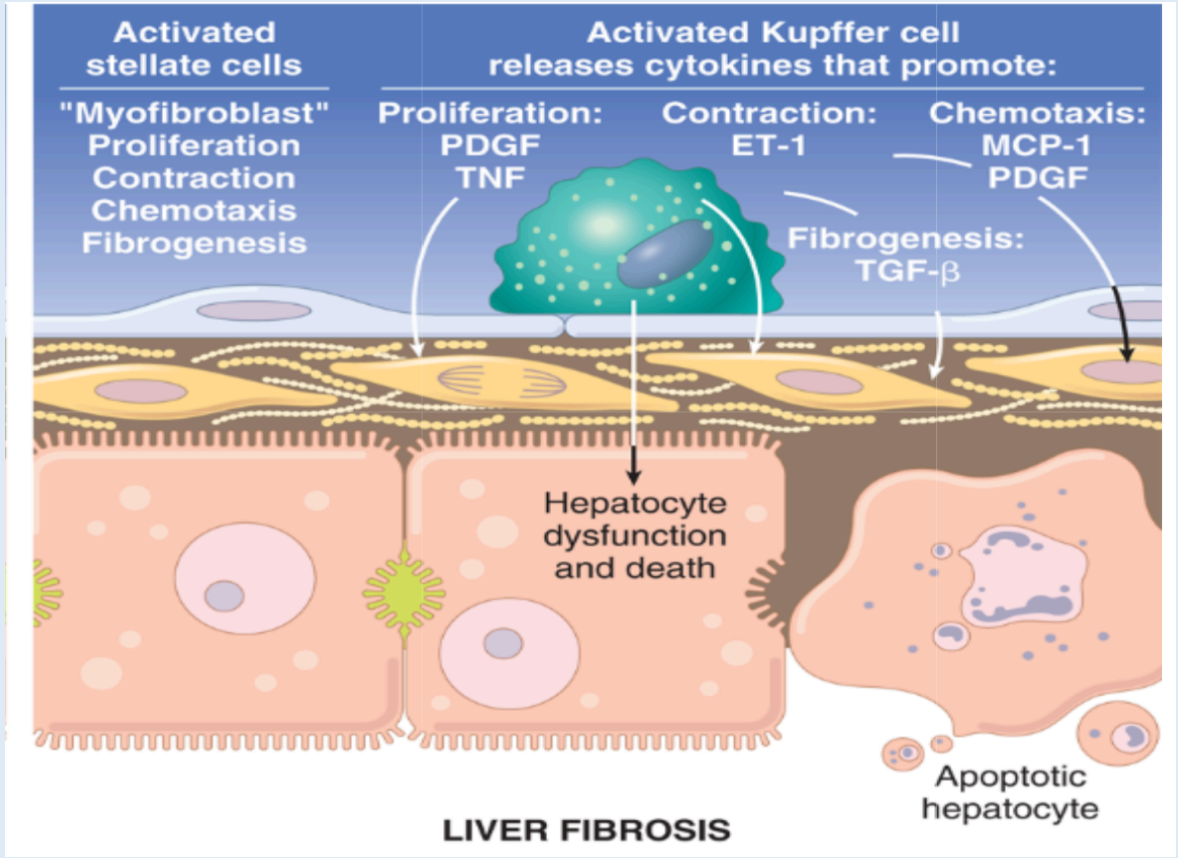
Pathogenesis of liver cirrhosis

- At the same time, Cytokine and chemokine production by Kupffer cells, endothelial cells leads to direct stimulation of stellate cells by these toxins

Pathogenesis of liver cirrhosis



In the normal liver, interstitial collagens (types I and III) are concentrated in portal tracts and around central veins. The type IV collagen (reticulin) is in the space of Disse



Types I and III collagen are deposited in the space of Disse, creating fibrotic septal tracts, accompanied by the loss of fenestrations of sinusoidal endothelial cells (capillarization)

Pathogenesis of liver cirrhosis

- **In summery:**

Severe injury→ death of large number of hepatocytes & drop out of liver cells→ collapse of the underlying reticulin→ prevent orderly regeneration of hepatocytes→ activation of stellate cells→ replacement of areas of liver cell loss by fibrous septae→ fibrous septa encircle surviving, regenerating hepatocytes in late-stage chronic liver disease ➔*cirrhosis*

Clinical manifestation

- About 40% of patients are asymptomatic until most advanced stages of disease

- Non-specific symptoms such as anorexia, weight loss, weakness & eventually signs & symptoms of liver failure (jaundice, encephalopathy & coagulopathy), much as the same as in acute liver hepatitis

Clinical coarse of the disease

- Widely variable from patient to patient

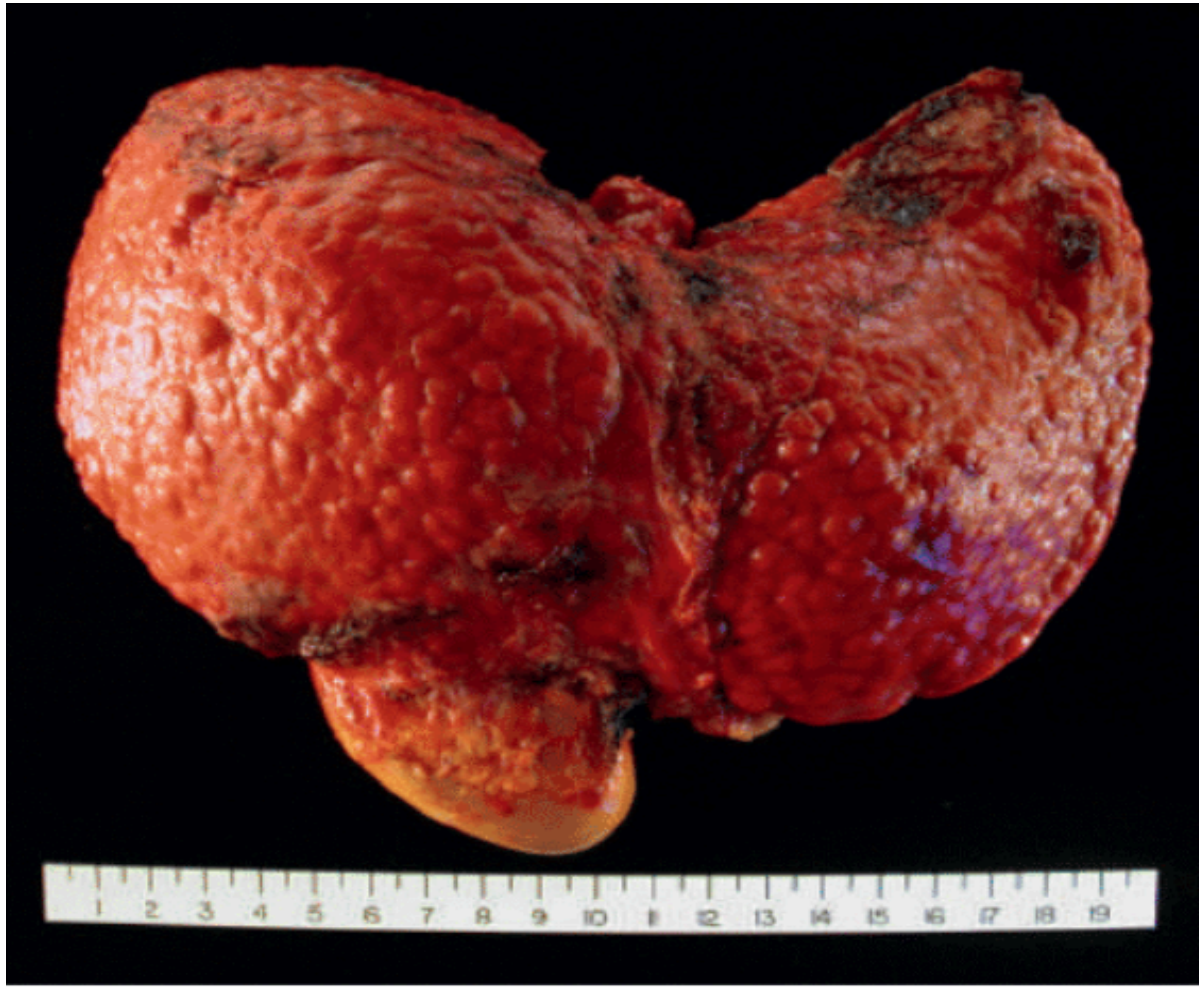
- In some patient's disease remission or cure, however, portal hypertension may persist due to presence of irreversible shunts

- In fibrosis regression scars become thinner, more densely compacted & eventually start to fragment. Adjacent parenchymal regenerating nodules coalesce into larger islands

Causes of deaths

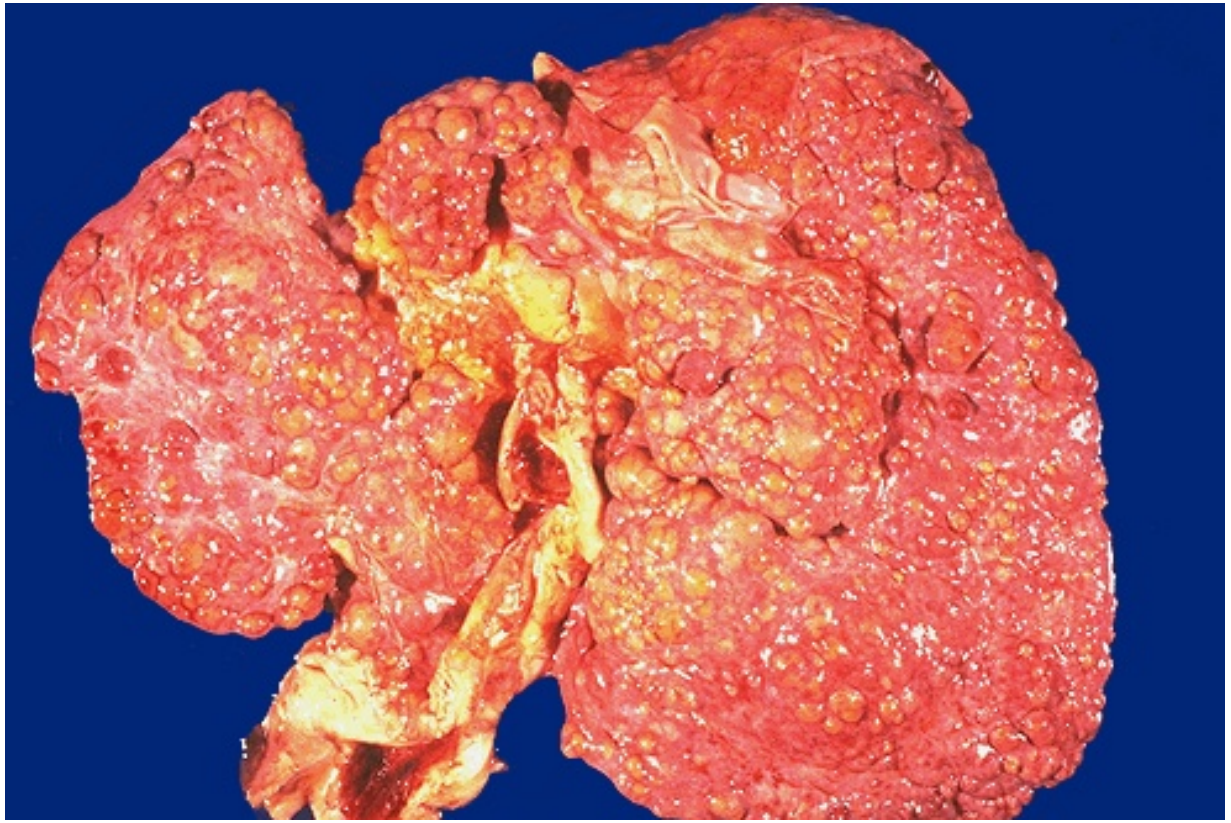
1. Progressive liver failure
2. A complication related to portal hypertension
3. Hepatocellular carcinoma

Gross Morphology

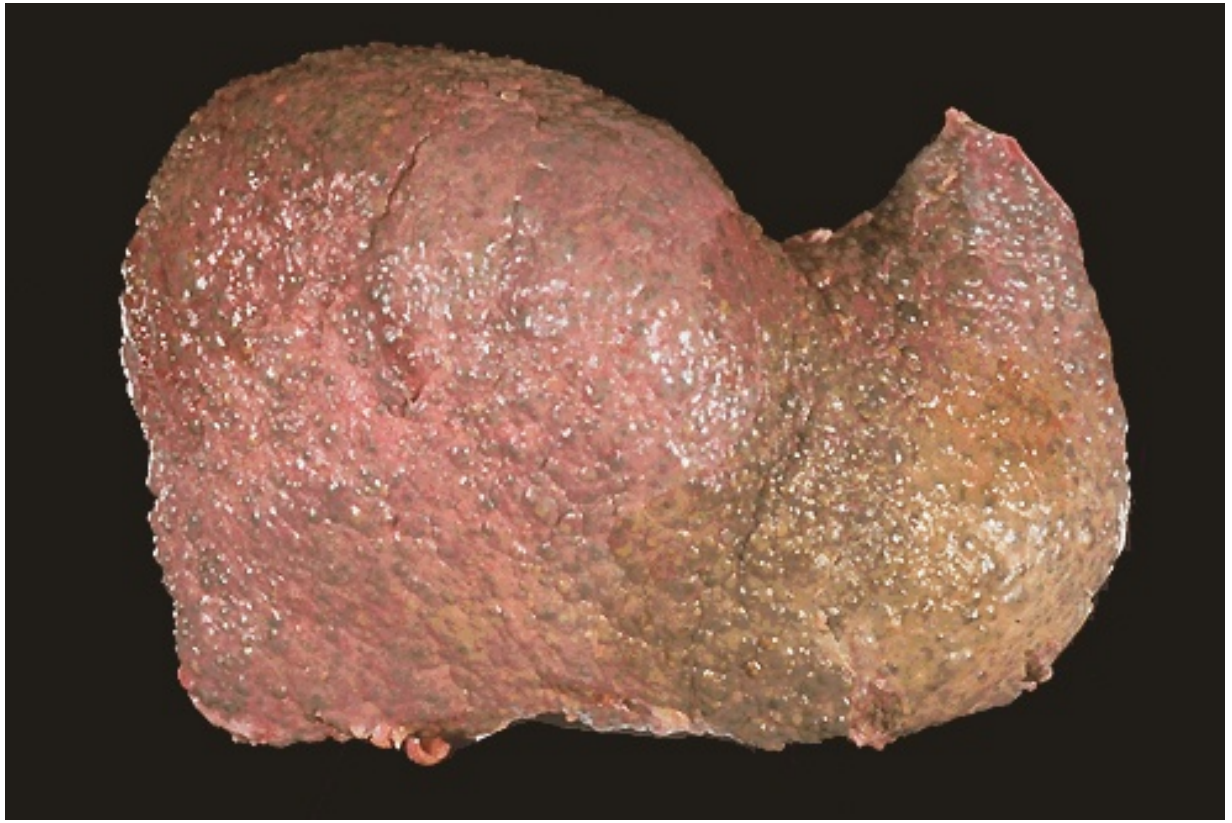


The broad scars separating bulging regenerative nodules over the liver surface

Gross Morphology

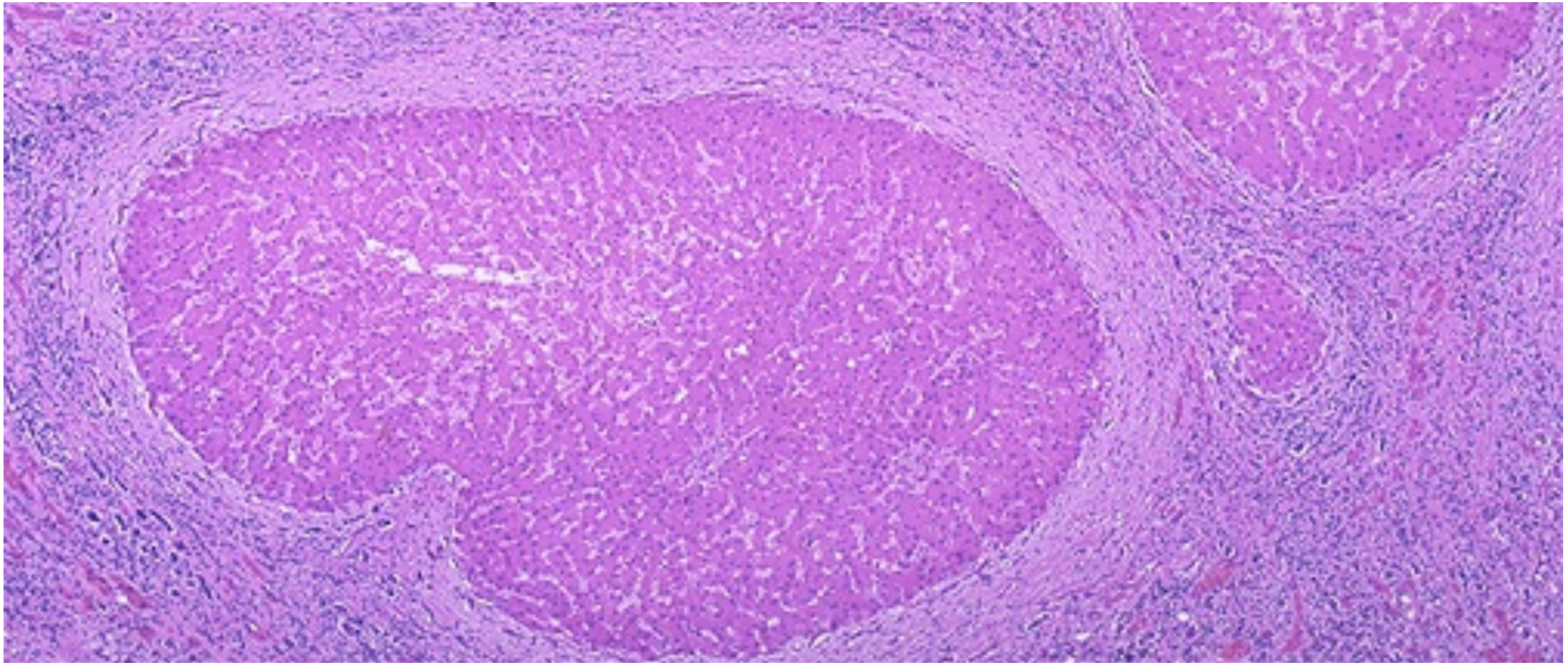


The nodules seen here are larger than 3 mm, this is an example of "macronodular" cirrhosis.

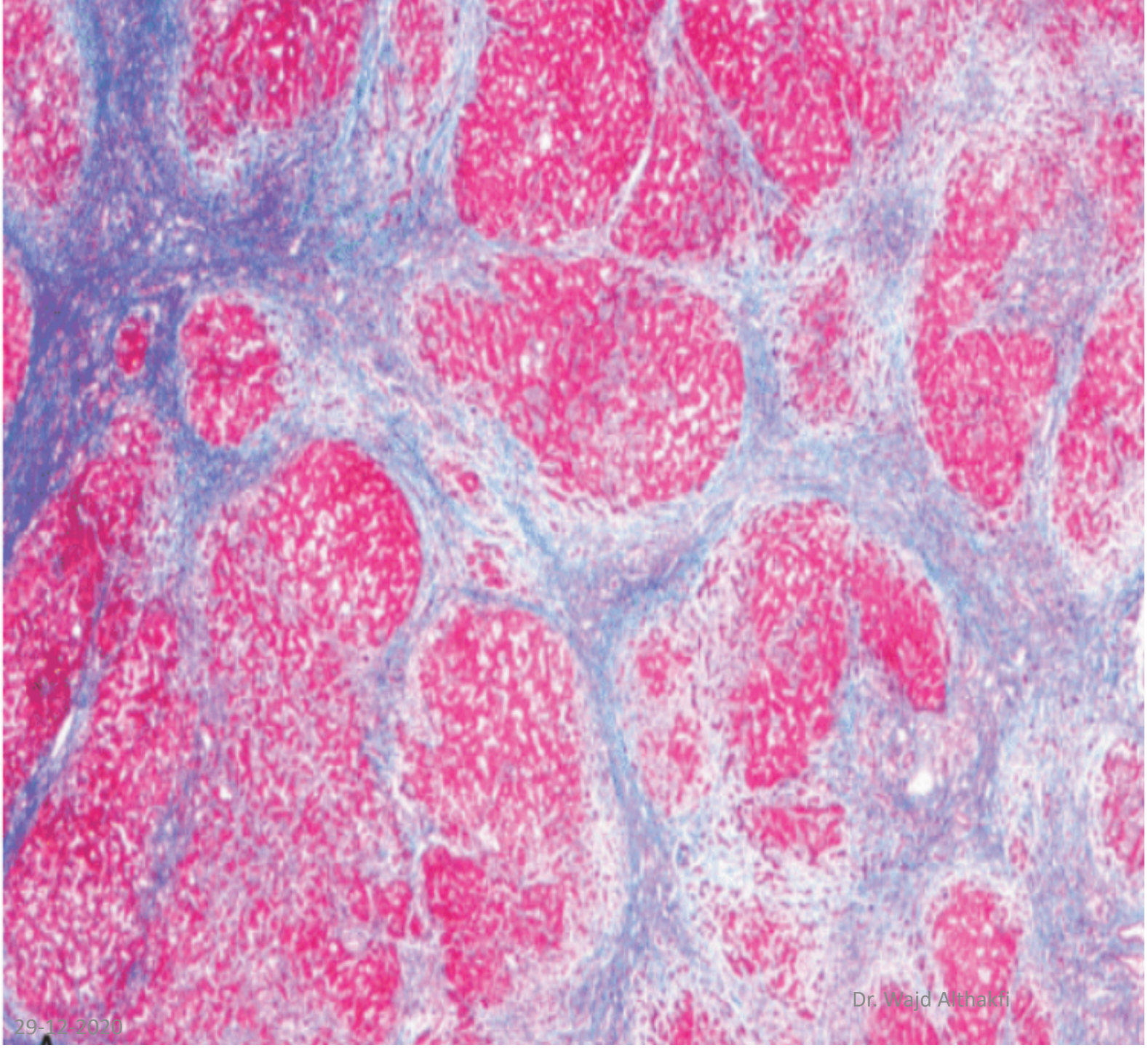


Micronodular cirrhosis : The regenerative nodules are quite small, averaging less than 3 mm in size. The most common cause for this is chronic alcoholism

Microscopically

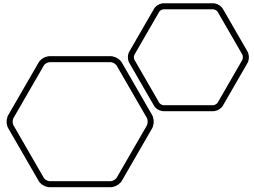


Regenerative nodules of hepatocytes are surrounded by fibrous connective tissue that bridges between portal tracts. Within this collagenous tissue are scattered lymphocytes as well as a proliferation of bile ducts

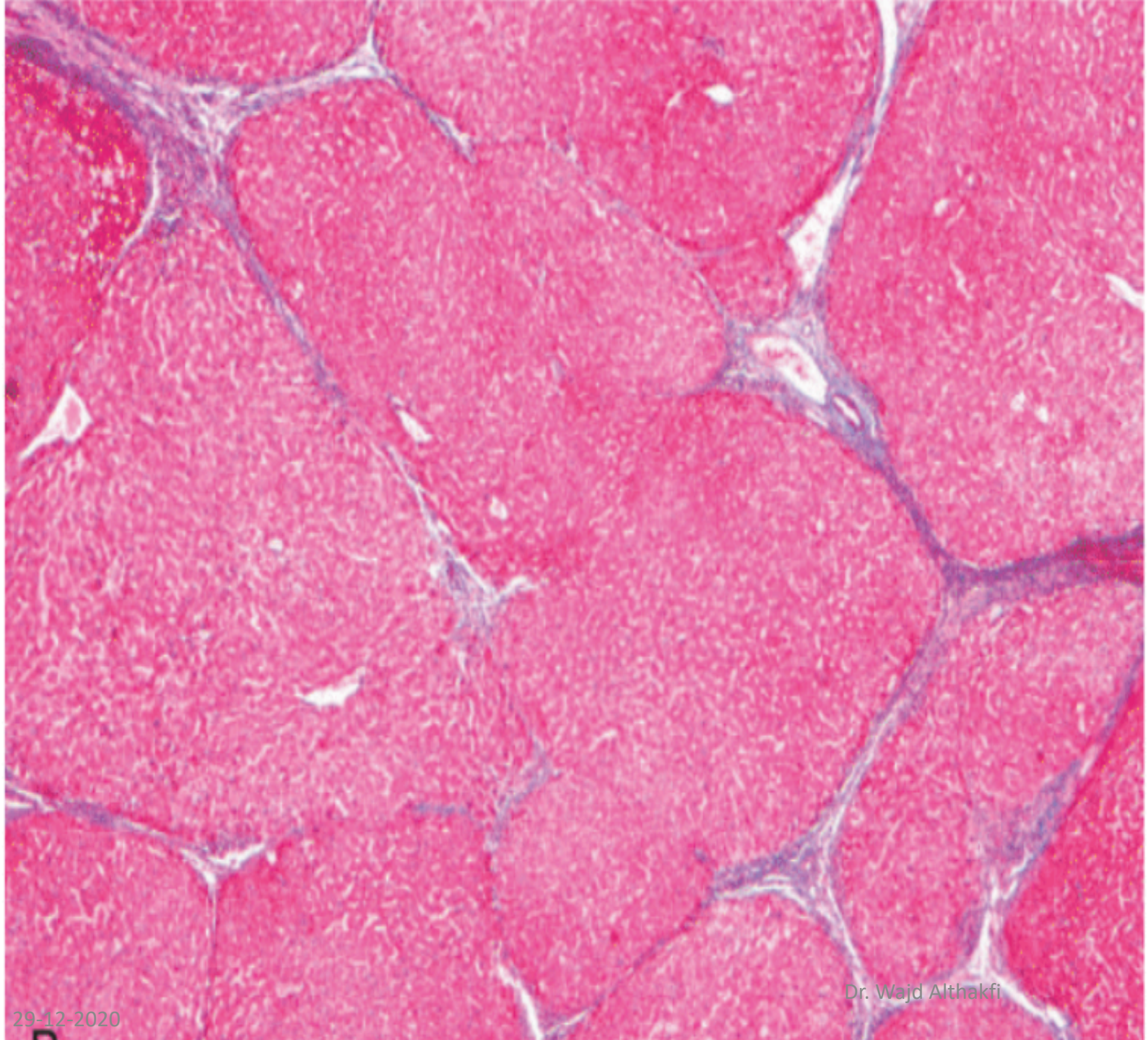


Microscopically

- Diffuse transformation of liver parenchyma in to
- Regenerative parenchymal nodules surrounded by thick fibrous or collagen bands
- Vascular architecture is reorganized with the formation of abnormal interconnections between vascular inflow and hepatic vein outflow
- Fibrosis is the key feature of progressive damage to the liver

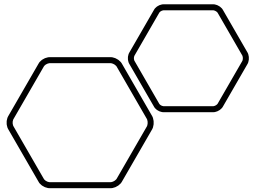


Masson trichrome stain



Microscopically

- Regression of fibrosis and most scars are gone
- Scars become thinner and more densely compact



SUMMARY

LIVER FAILURE

- Liver failure may follow acute injury or chronic injury, or it may occur as an acute insult superimposed on otherwise well-compensated chronic liver disease.
- 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)
- Potentially fatal sequelae of liver failure include coagulopathy, encephalopathy, portal hypertension and ascites, hepatorenal syndrome, and portopulmonary hypertension.

Morphology of common causes of liver cirrhosis

Infectious:

- Viruses (hepatitis B and C virus)

Others:

- Autoimmune hepatitis
- Alcoholic liver disease
- Biliary Cirrhosis

Viral Hepatitis

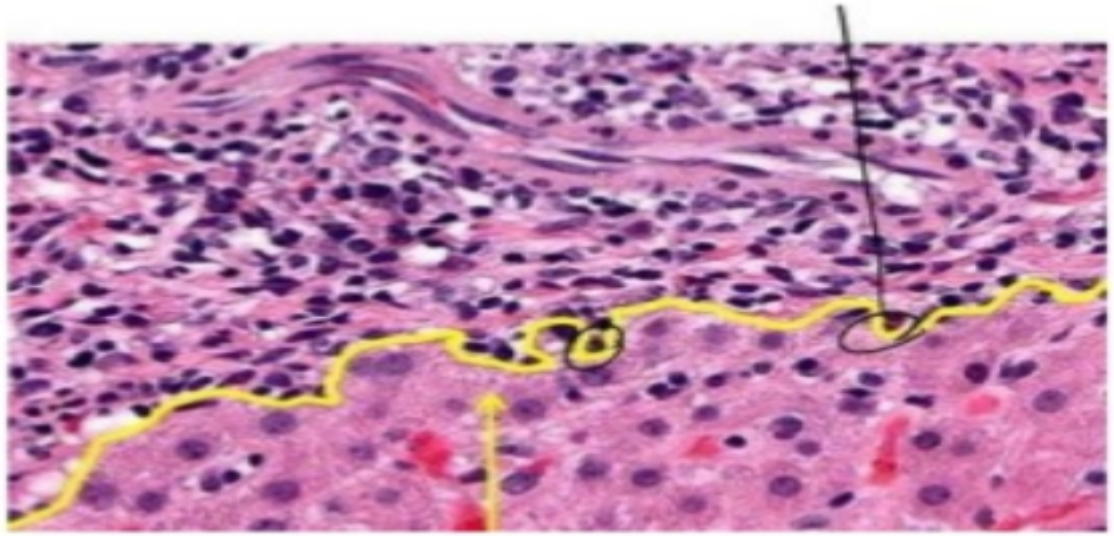
- Inflammatory disorders of the liver dominate the clinical practice of hepatology
- *Hepatitis* is the name applied to viruses (hepatitis A, B, C, D, and E virus) that are *hepatotropic,* that is, have a specific affinity for the liver
- The morphologic changes in acute and chronic viral hepatitis are shared among the hepatotropic viruses and can be mimicked by drug reactions or autoimmune hepatitis

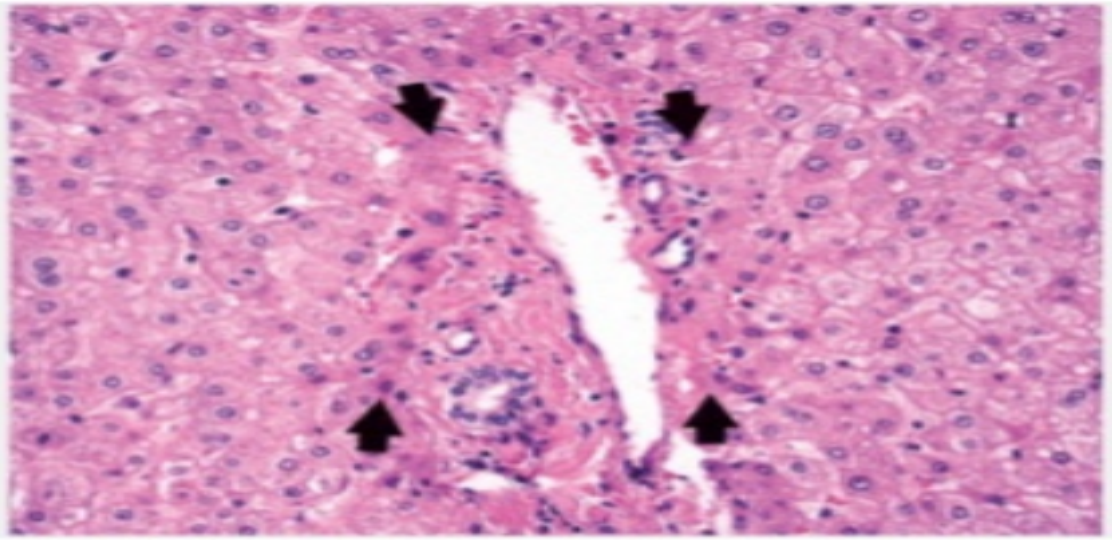
Hepatitis Morphology

Some changes are shared with acute hepatitis:

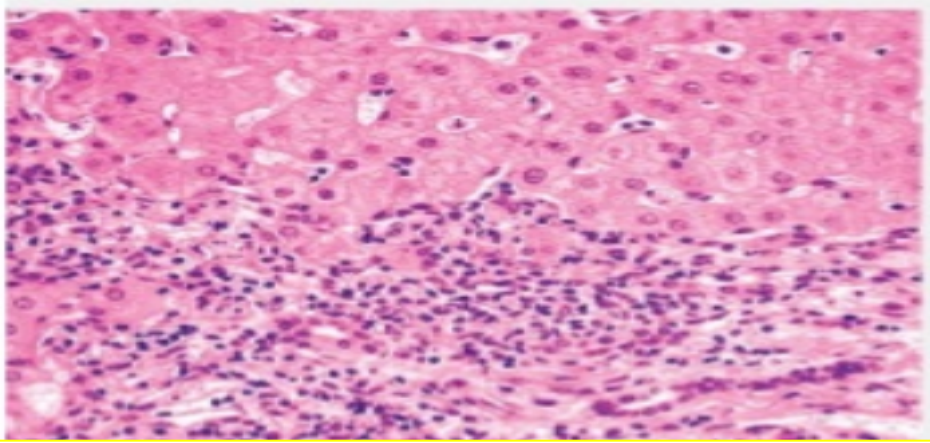
- Hepatocyte injury, necrosis, and regeneration
- Sinusoidal cell reactive changes
- Portal tract Inflammation:
  - ✓ Confined to portal tracts *or*
  - ✓ Spillover into adjacent parenchyma, with necrosis of hepatocytes ("interface hepatitis") *or*
  - ✓ Bridging inflammation and necrosis

Viral hepatitis- Microscopic morphology





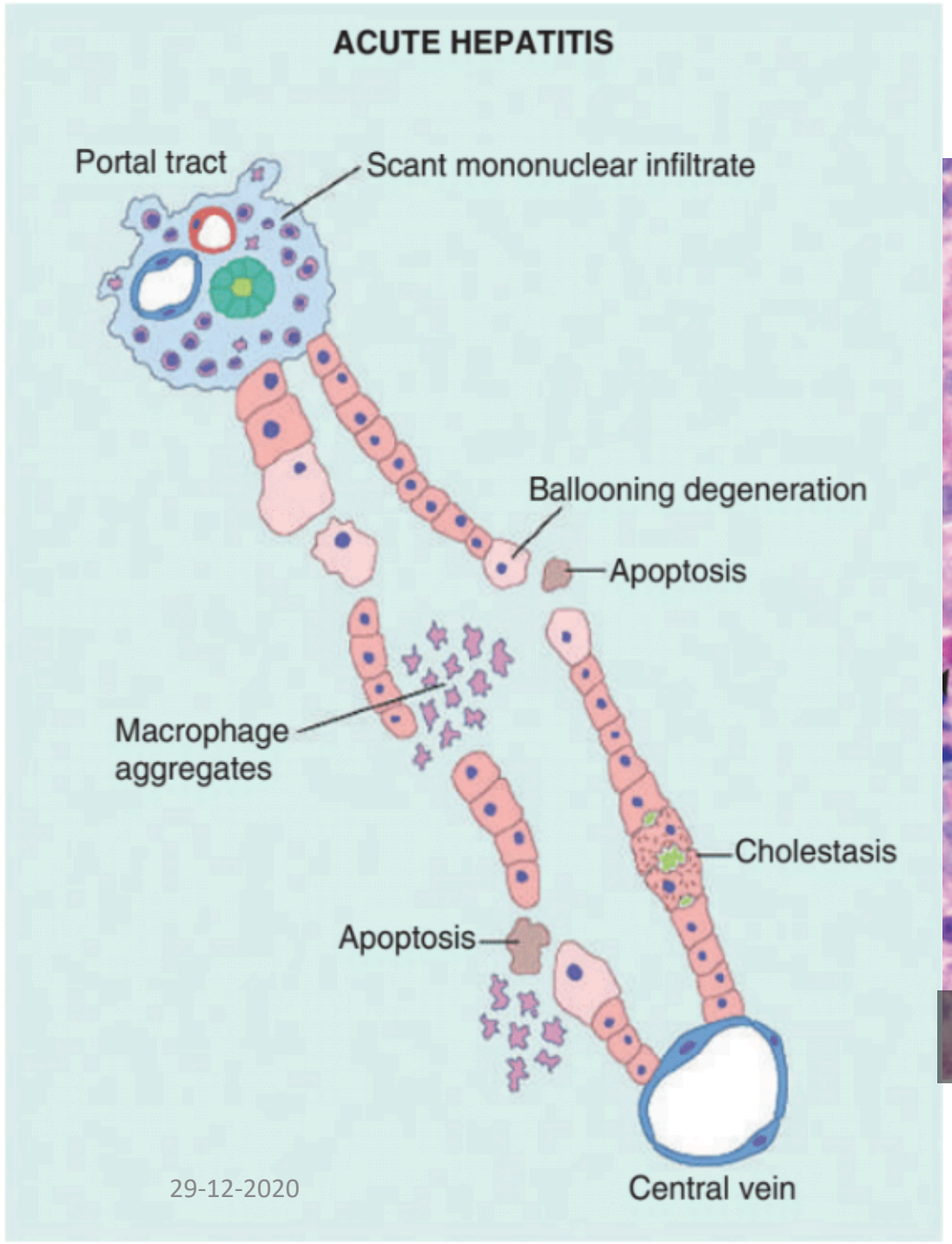
Spillover into adjacent parenchyma, with necrosis of hepatocytes "interface hepatitis

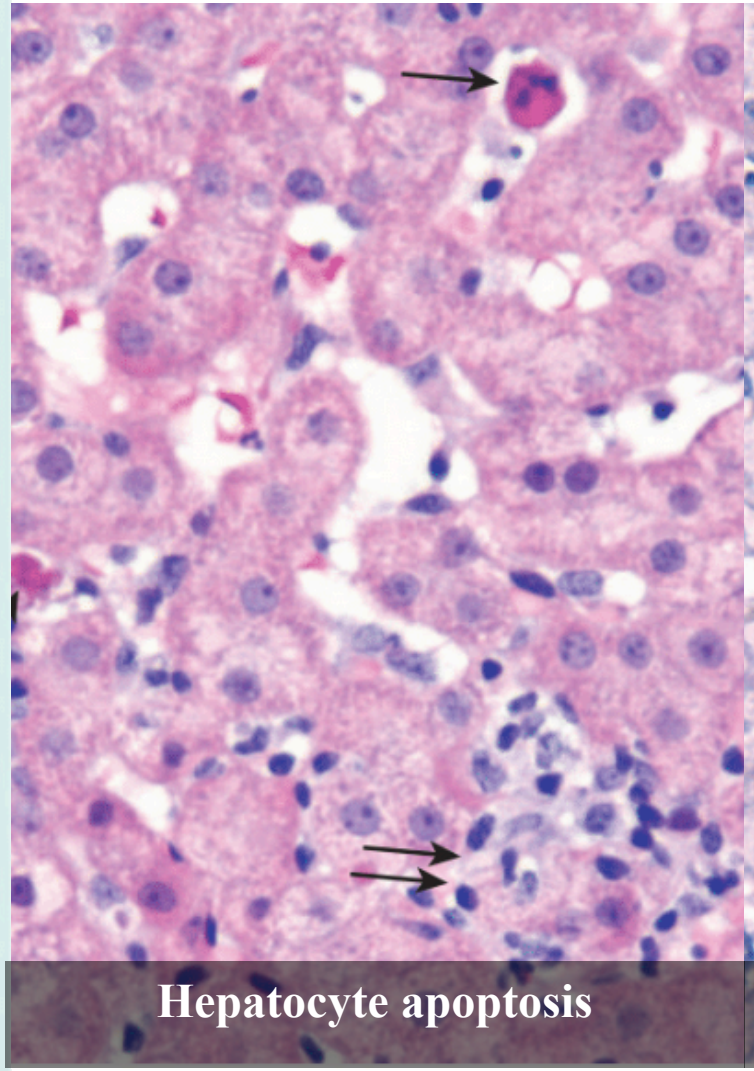


Piecemeal necrosis in Chronic hepatitis

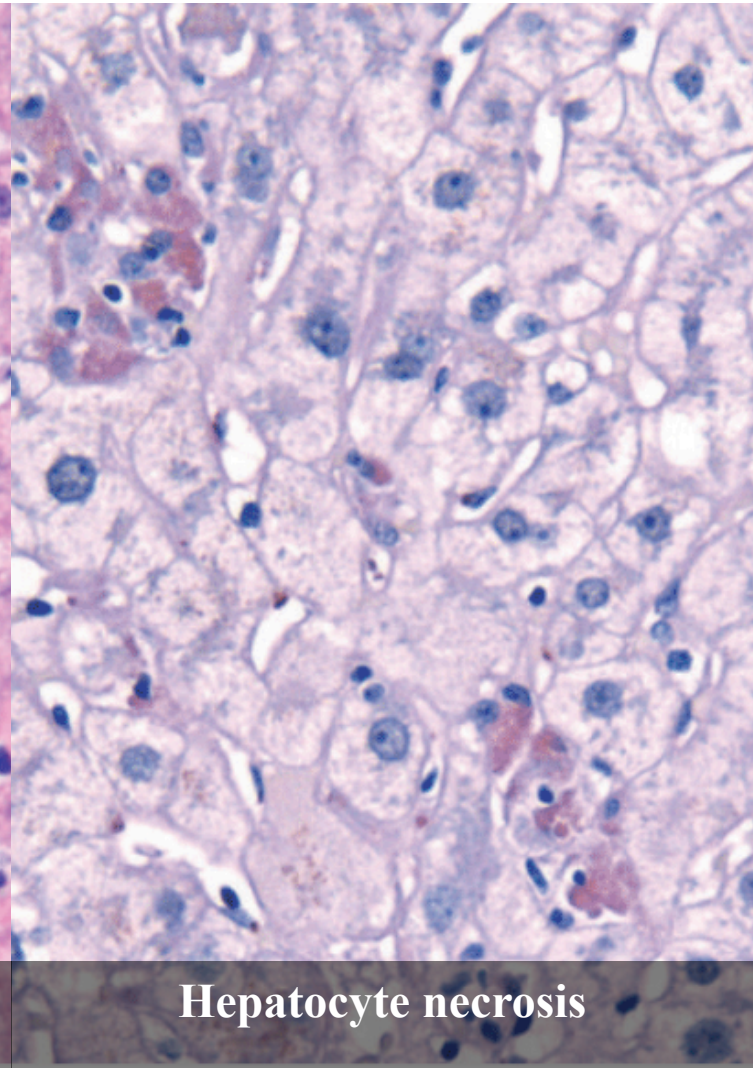
Acute viral hepatitis- Microscopic morphology

- Predominately mononuclear inflammatory cell infiltrate, rich in plasma cells in Hepatitis A infection
- Portal inflammation: Minimal or absent
- Scattered parenchymal injury throughout the hepatic lobules "spotty necrosis or lobular hepatitis"
- Hepatocyte injury my result in either:
  - ✓ Necrosis: Cytoplasm appears empty with eventual rupture of cell membrane → "drop out " of hepatocytes ➔ collapse in sinusoidal collagen reticulin framework
  - ✓ Apoptosis ➔ shrunken, intensely eosinophilic cells with pyknotic & fragmented nuclei
- In sever acute hepatitis ➔ central portal bridging necrosis ➔ parenchymal collapse





Hepatocyte apoptosis



Hepatocyte necrosis

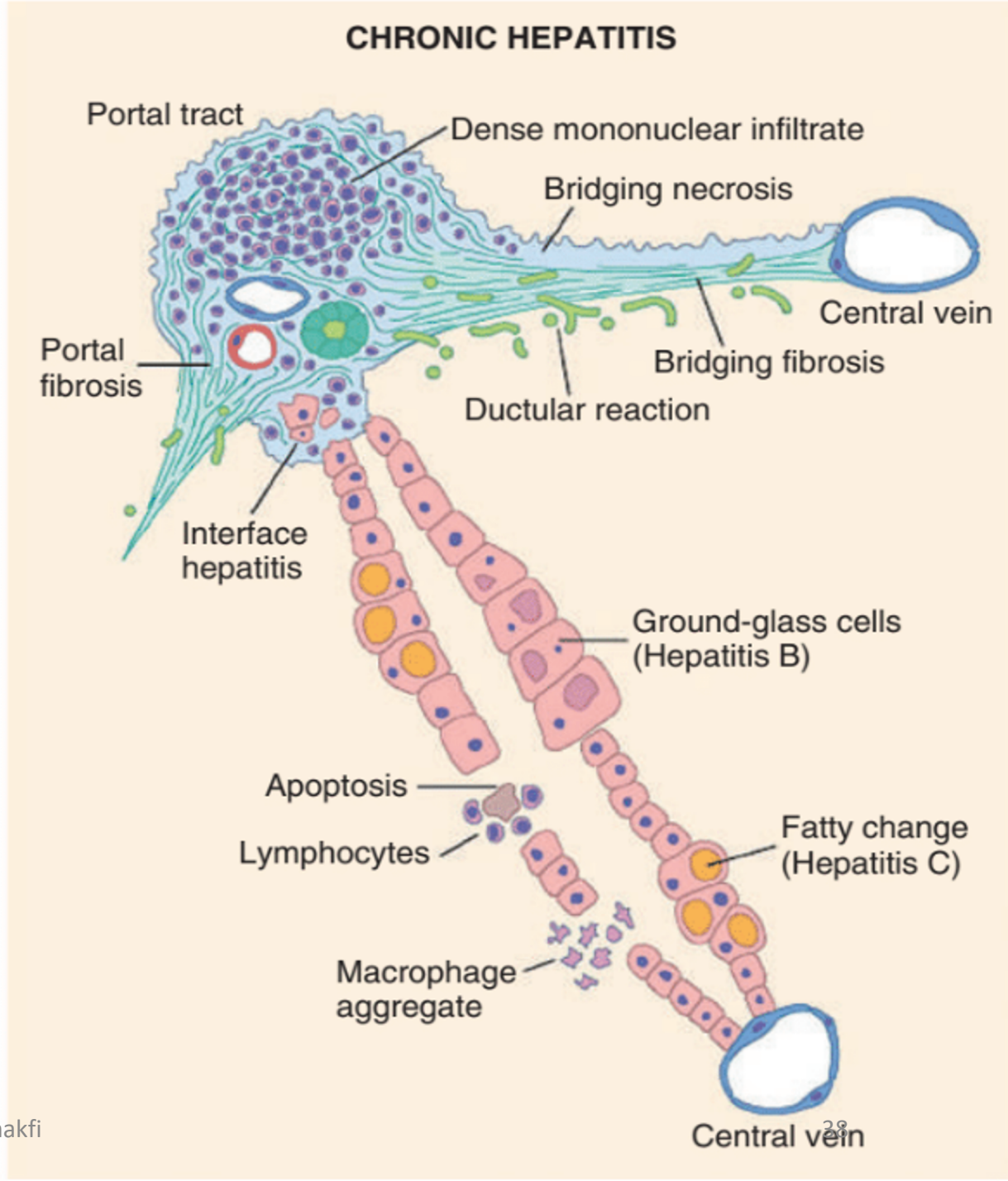
Chronic viral hepatitis- Microscopic morphology

The defining histologic feature:

- ✓ Mononuclear portal infiltration in portal tract
- ✓ Interface hepatitis is present as well: Located at the interface between hepatocellular parenchyma & portal tract stroma
- ✓ Lobular hepatitis

- The hallmark of progressive chronic liver damage is scarring
  ✓ At first, only portal tracts exhibit fibrosis→
  ✓ In some patients, with time, fibrous septa "bands of dense scar" will extend between portal tracts ✓ In most severe cases, continued scarring and nodule formation ➔ cirrhosis

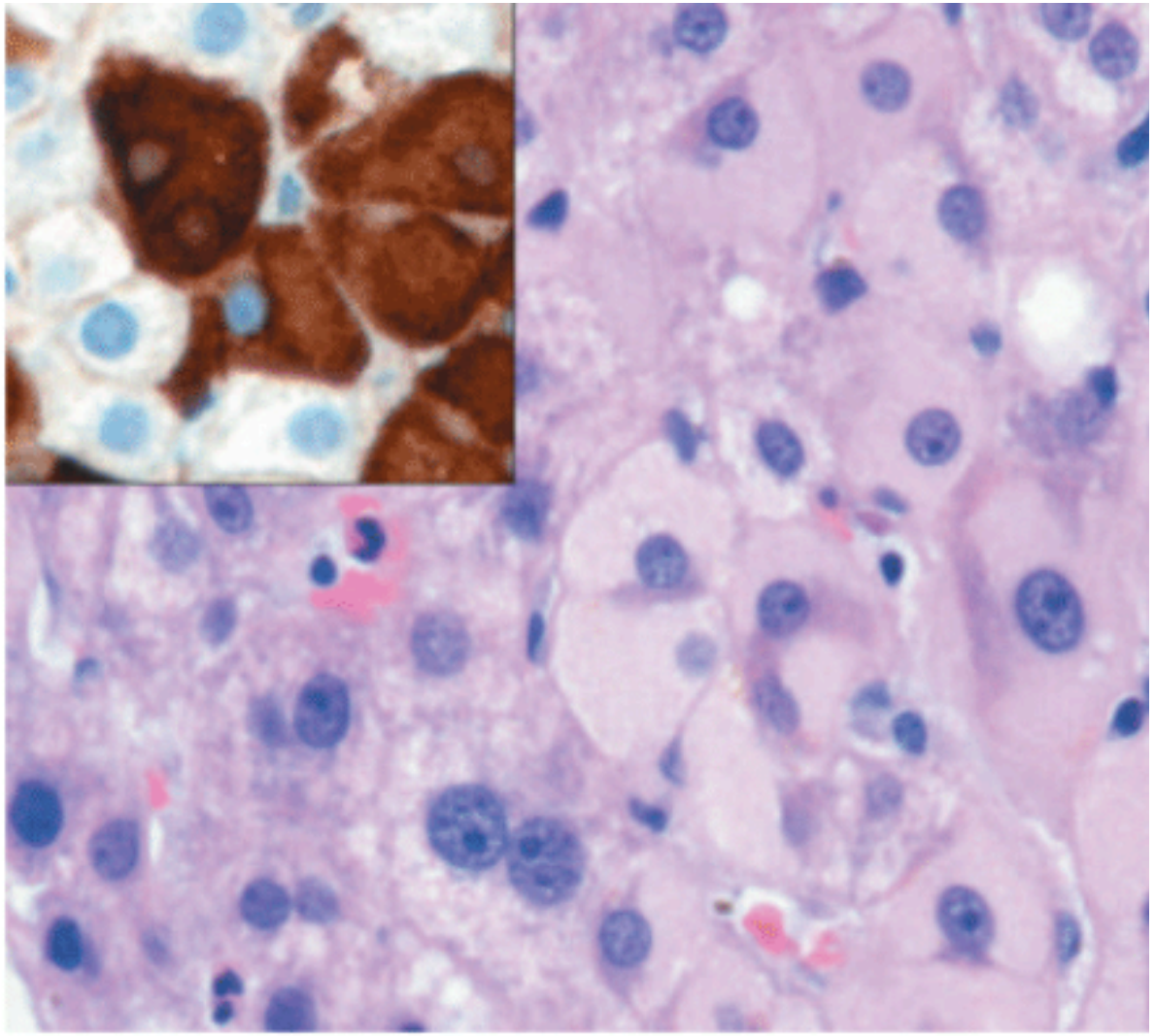
Chronic viral hepatitis- Microscopic morphology



Chronic viral hepatitis- Microscopic morphology

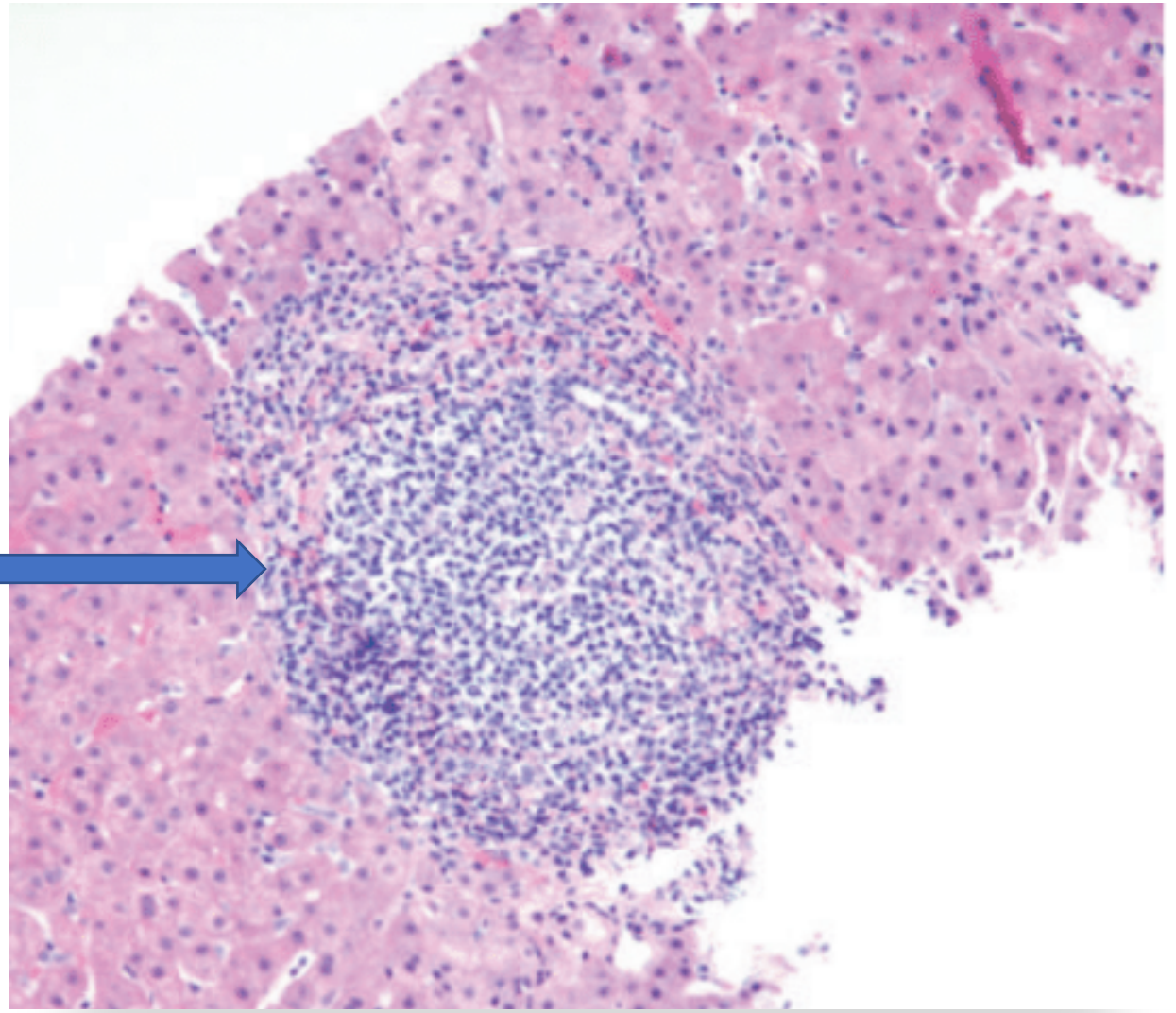
Certain histologic features point to specific viral etiologies

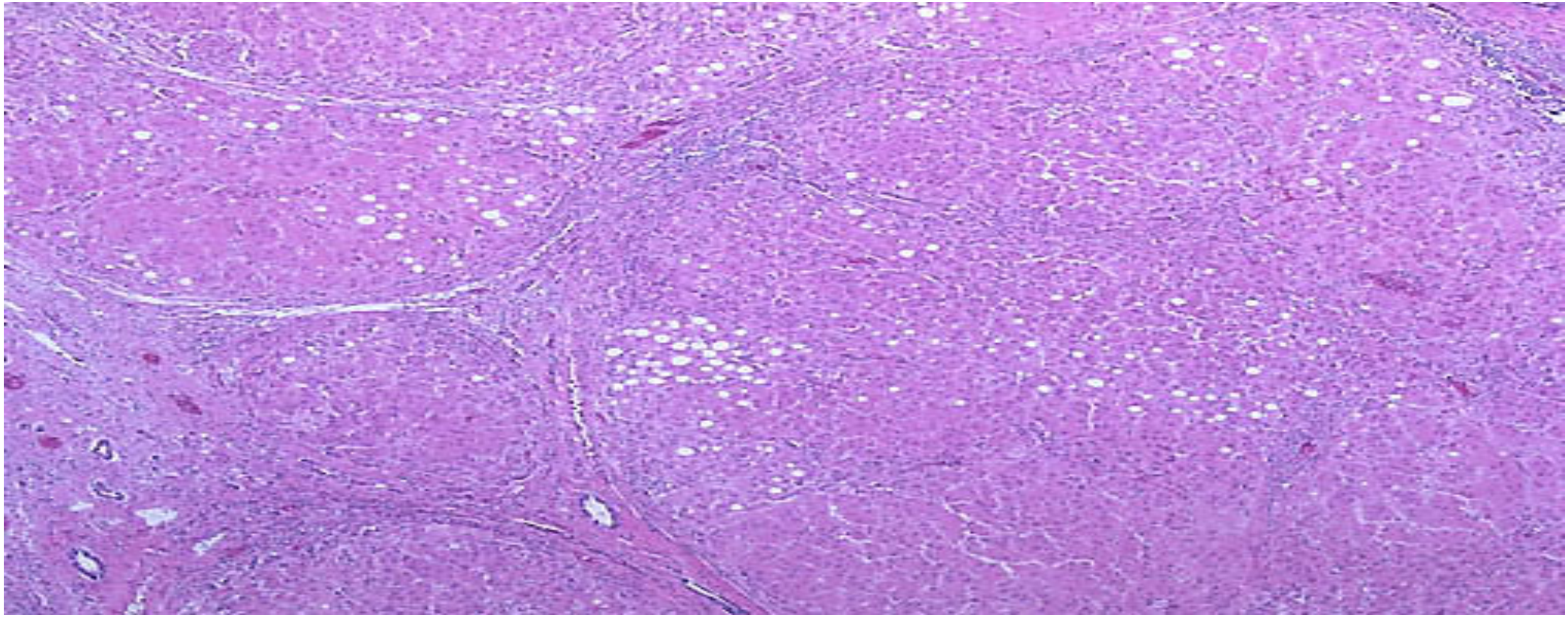
- ***HBV:***
  - ✓ Ground glass hepatocytes "finely granular eosinophilic cytoplasm = massive amount of HBsAg within endoplasmic reticulum"
  - ✓ Can be confirmed by immunostaining



Chronic viral hepatitis- Microscopic morphology

- **Certain histologic features point to specific viral etiologies**
  - **HVC**
    - ✓Large lymphoid aggregates in portal tract
    - ✓Mild steatosis (fatty changes)
    - ✓Bile duct injury





Viral hepatitis C which is at a high stage with extensive fibrosis and progression to macronodular cirrhosis, as evidenced by the large regenerative nodule at the center right

Autoimmune hepatitis

- Is a chronic, progressive hepatitis with all the features of autoimmune diseases in general:
  - Genetic predisposition
  - Association with other autoimmune diseases
  - Presence of autoantibodies
  - Therapeutic response to immunosuppression Like steroids
- Risk for AIH is associated with certain HLA alleles, such as the DRB1 allele in Caucasians
- But as in other autoimmune disorders the mechanistic basis for this relationship is unclear
- Triggers for the immune reaction may include viral infections or drug or toxin exposures

Clinical features

- Diagnosis & intervention are imperative
- Acute clinical illness is a common presentation (40%)
- Sometimes the disease is fulminant, progressing to hepatic encephalopathy within 8 weeks of onset
- Mortality for patients with severe untreated AIH is ~ 40% within 6 months of diagnosis & cirrhosis develops in at least 40% of survivors

Clinical features

- Associated with other autoimmune diseases eg. rheumatoid arthritis, Sjogren's syndrome etc
- Immunosuppressive therapy is usually effective ➔ remission in 80% of patients & enables long-term survival
- End-stage disease is an indication for liver transplantation:
  - ✓ The 10-year survival rate after liver transplant is 75%
  - ✓ Recurrence in the transplanted organ occurs in 20% of cases

Clinicopathologic features

- The annual incidence is highest among white northern europeans, but all ethnic groups are susceptible
- Female predominance (78%)
- Classified into two types, based on the patterns of circulating antibodies:

1. Type

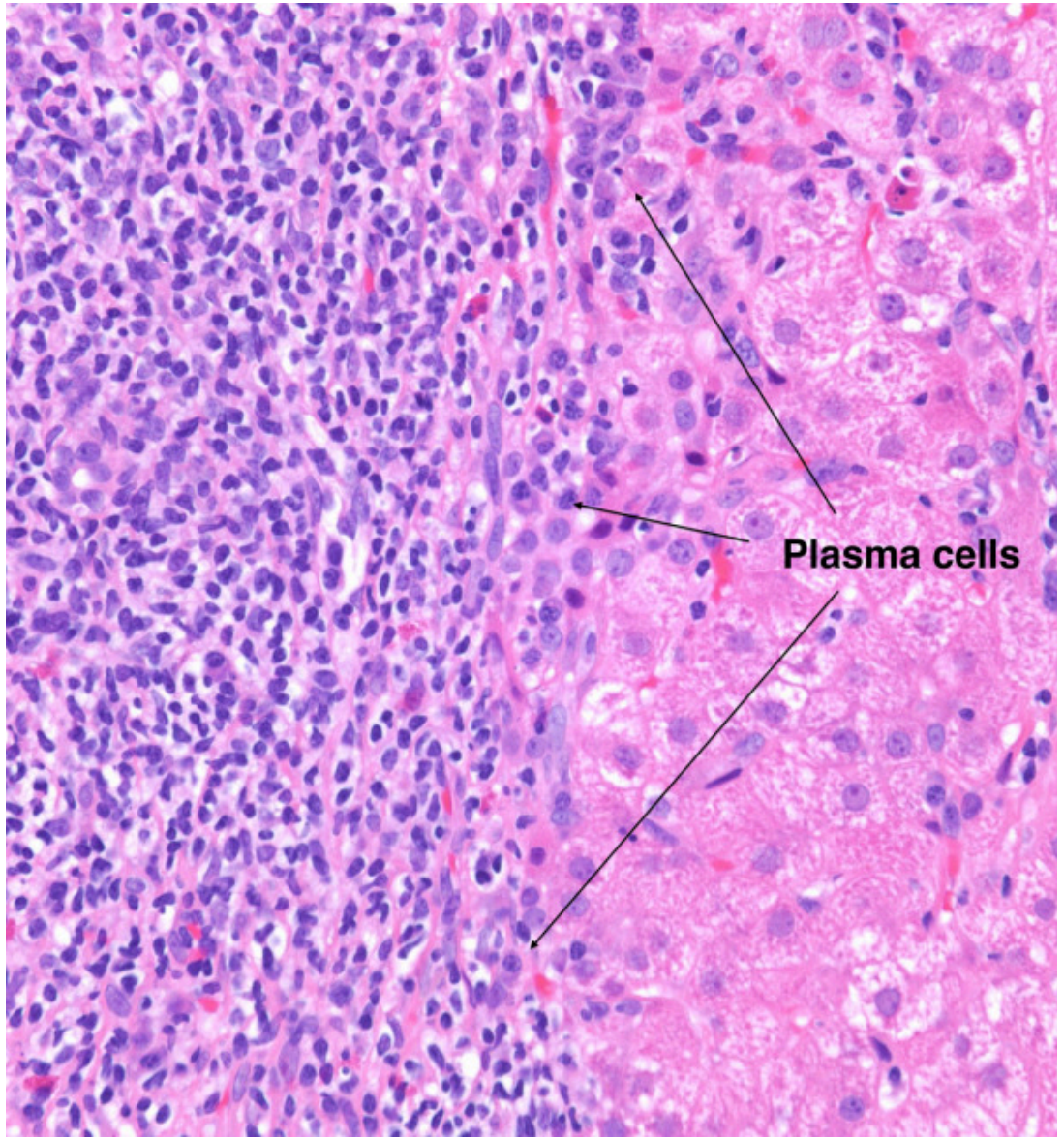
- ✓ More common in middle-age & older individuals
- ✓ Characterized by the presence of anti-nuclear (ANA), anti–smooth muscle actin (SMA), anti-mitochondrial (AMA) & anti–soluble liver antigen/liver-pancreas antigen (anti-SLA/LP) antibodies

2. Type

- ✓ Usually seen in children and teenagers
- ✓ Characterized by the presence of anti–liver kidney microsome-1 antibodies & anti–liver cytosol-1 antibodies

Microscopic morphology

- AIH shares patterns of injury with acute or chronic viral hepatitis, but with some difference
  - There is a nearly phase of **sever** parenchymal destruction followed **rapidly** by scarring
- **Typical features of AIH:**
  1. Necrosis and inflammation
  2. Plasma cell predominance
  3. Hepatocyte “rosettes” in areas of marked activity



SUMMARY

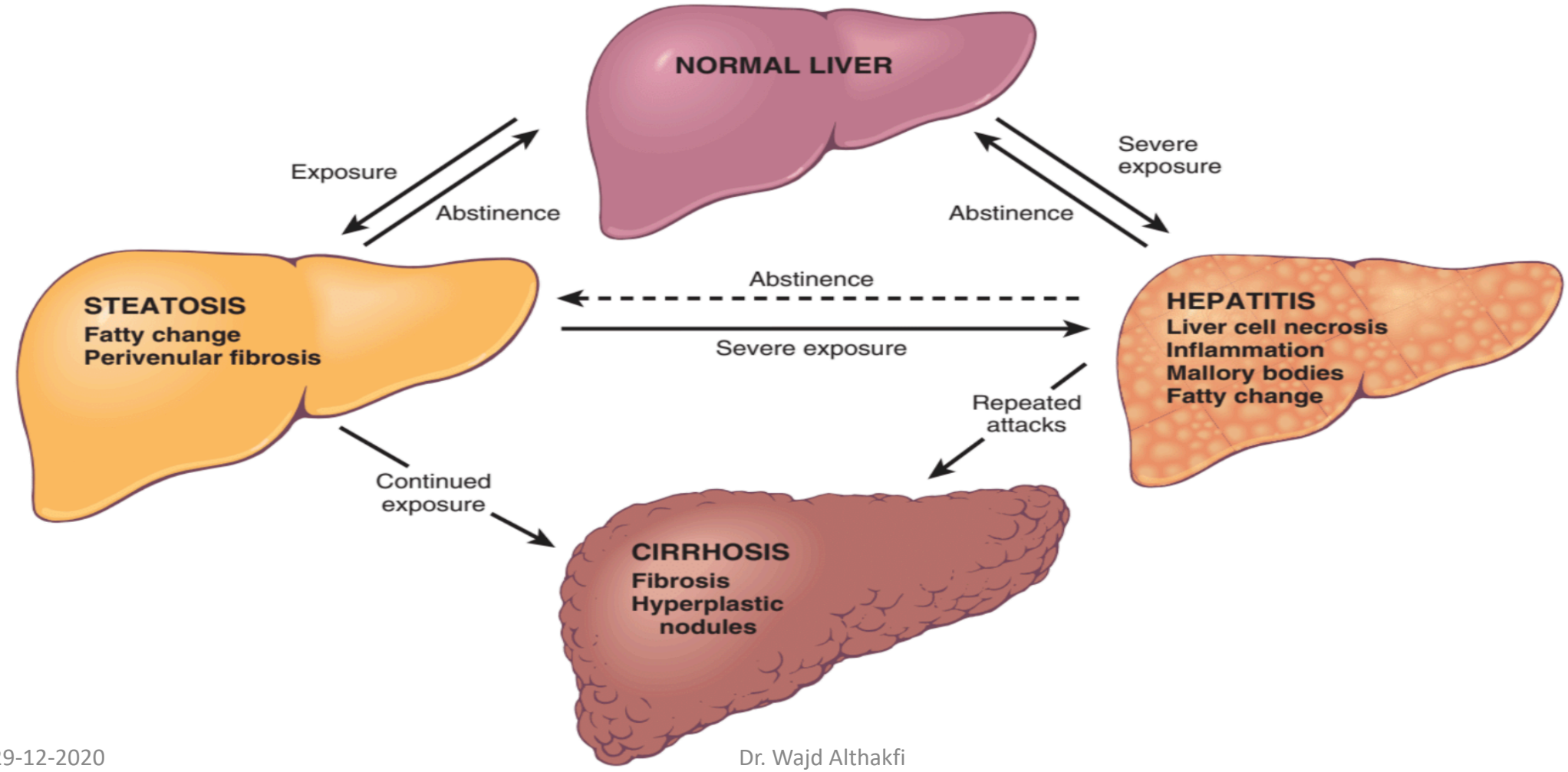
- There are two primary types of autoimmune hepatitis:
  - Type 1 autoimmune hepatitis is most often seen in middle-age women and is characteristically associated with anti-nuclear and anti–smooth muscle antibodies.
  - Type 2 autoimmune hepatitis is most often seen in children or teenagers and is associated with anti–liver kidney microsomal autoantibodies.
- Autoimmune hepatitis may either develop with a rapidly progressive acute disease or follow a more indolent path; if untreated, both are likely to lead to liver failure.
- Plasma cells are a prominent and characteristic component of the inflammatory infiltrate in biopsy specimens showing autoimmune hepatitis.

Alcoholic liver disease

- Excessive ethanol consumption causes more than 60% of chronic liver disease in Western countries and accounts for 40% to 50% of deaths due to cirrhosis
- **Features:**

1. Hepatic steatosis
2. Alcoholic hepatitis
3. Fibrosis and cirrhosis

Key morphologic features of alcoholic hepatitis



Alcoholic liver disease

- The cause of alcoholic hepatitis is uncertain, but it may stem from one or more of the following toxic by products of ethanol and its metabolites:
  - ✓Acetaldehyde (a major metabolite of ethanol)
  - ✓Alcohol directly affects mitochondrial function and membrane fluidity.
  - ✓Reactive oxygen species

Alcoholic liver disease

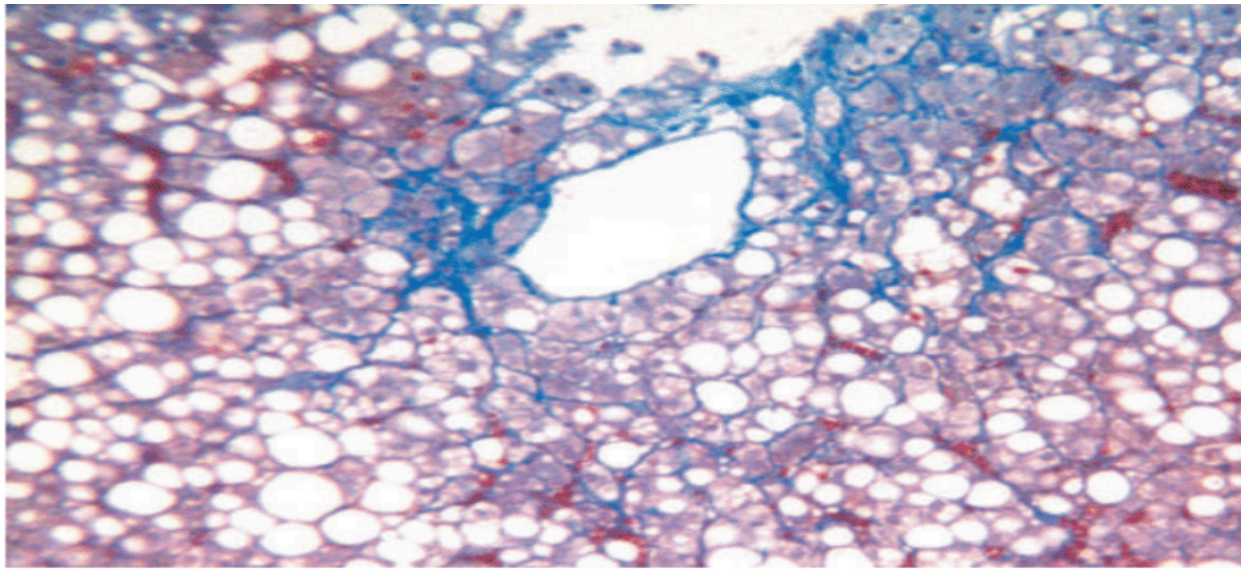
- It is estimated that 15 to 20 years of excessive drinking are necessary to develop alcoholic cirrhosis
- Cirrhosis typically develops after more than 10 years of heavy drinking
- Cirrhosis occurs in a small proportion of chronic alcoholics
- Alcoholic cirrhosis has similar clinical signs and symptoms as cirrhosis caused by viral hepatitis

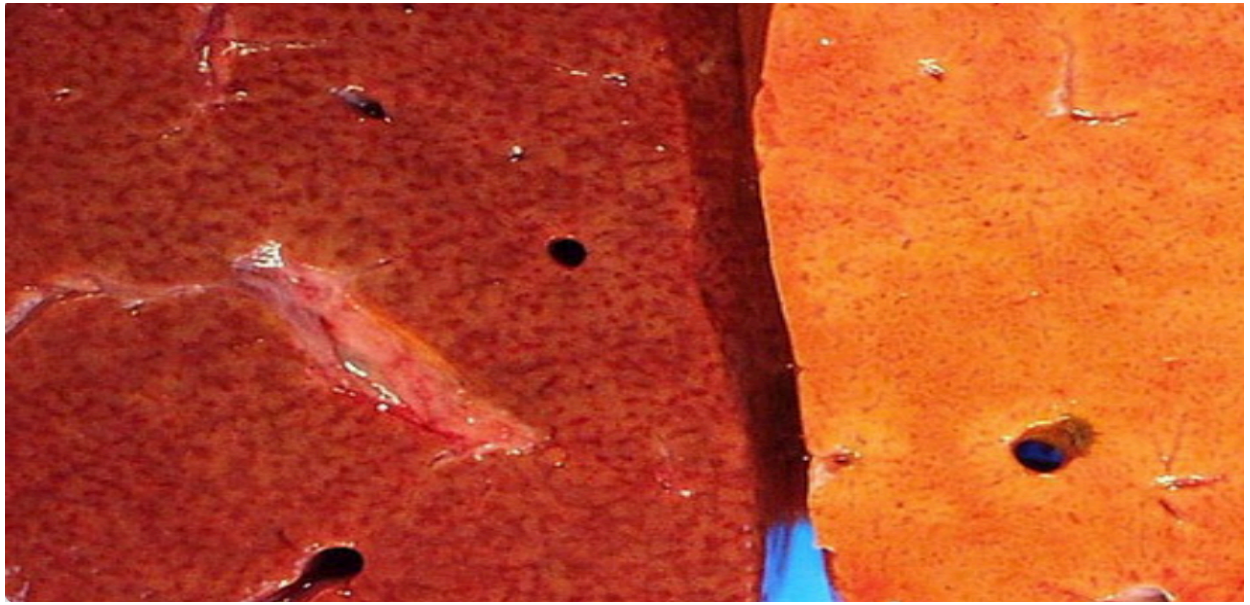
Alcoholic liver disease

- The immediate causes of death are as follows:
  - ✓Hepatic failure
  - ✓Massive gastrointestinal hemorrhage
  - ✓Intercurrent infection (to which affected individuals are predisposed)
  - ✓Hepatorenal syndrome
  - ✓Hepatocellular carcinoma(3%–6%) of cases

Morphology

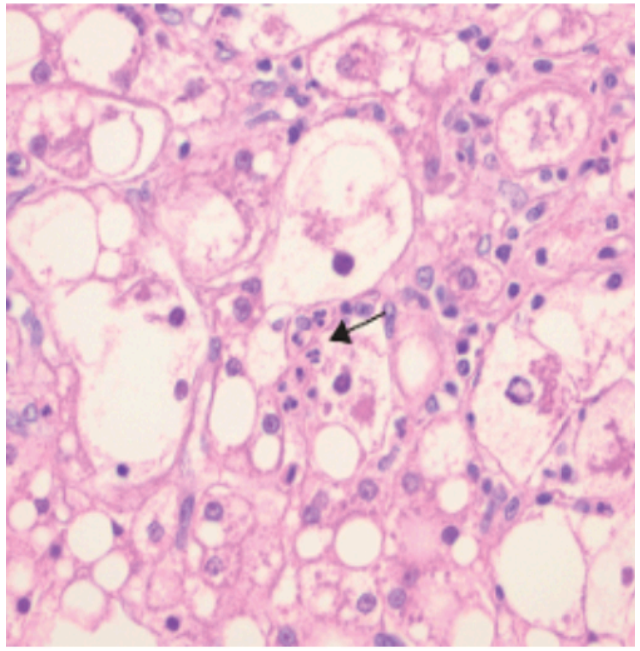
Hepatic Steatosis (Fatty Liver)

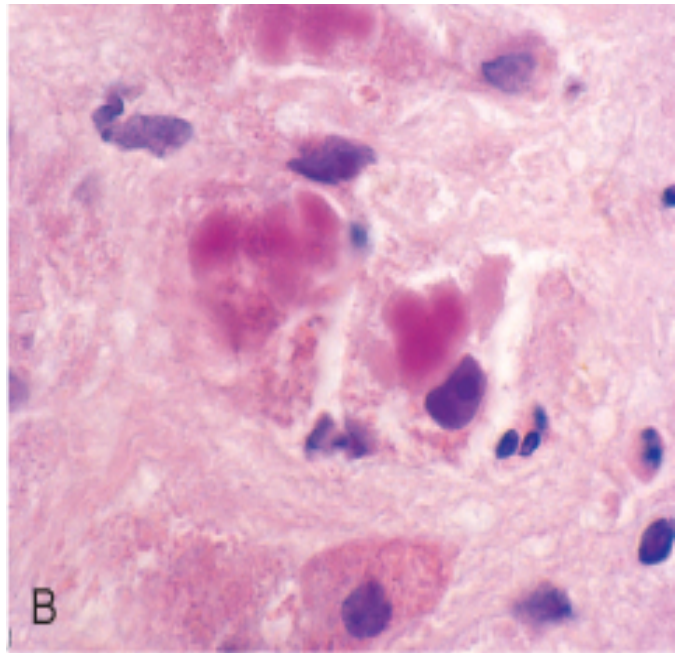


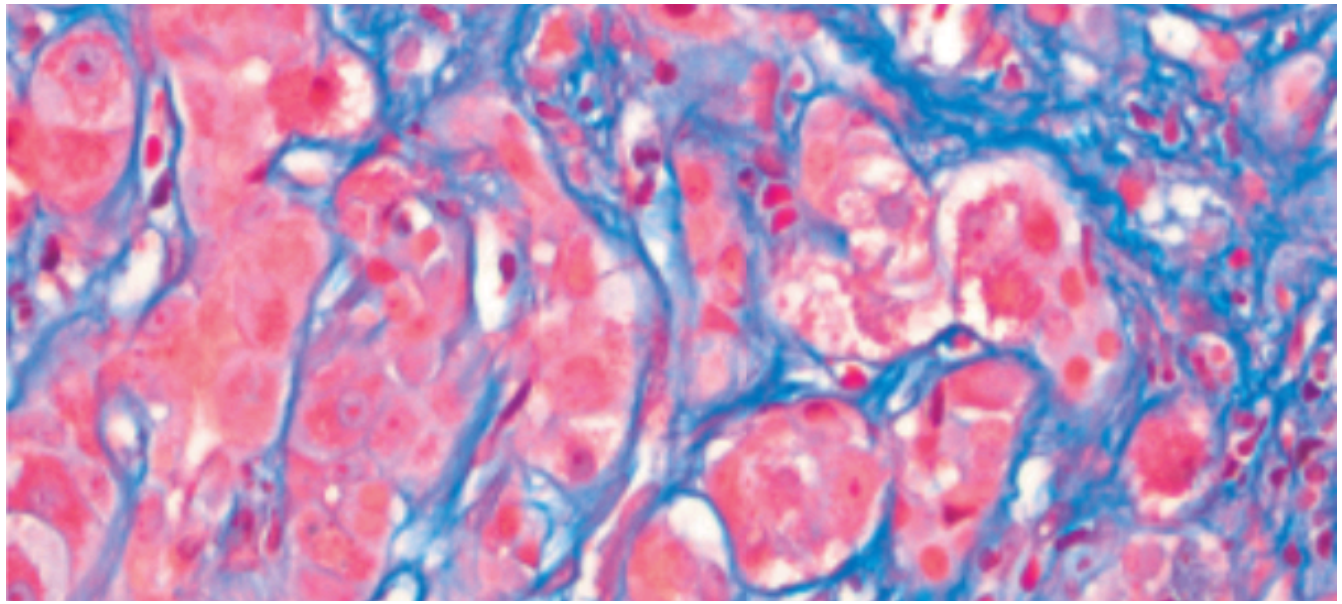


Morphology

- **Alcoholic Hepatitis (Alcoholic Steatohepatitis):**
  - Hepatocyte swelling necrosis
  - Mallory bodies
  - Neutrophilic reaction
  - fibrosis

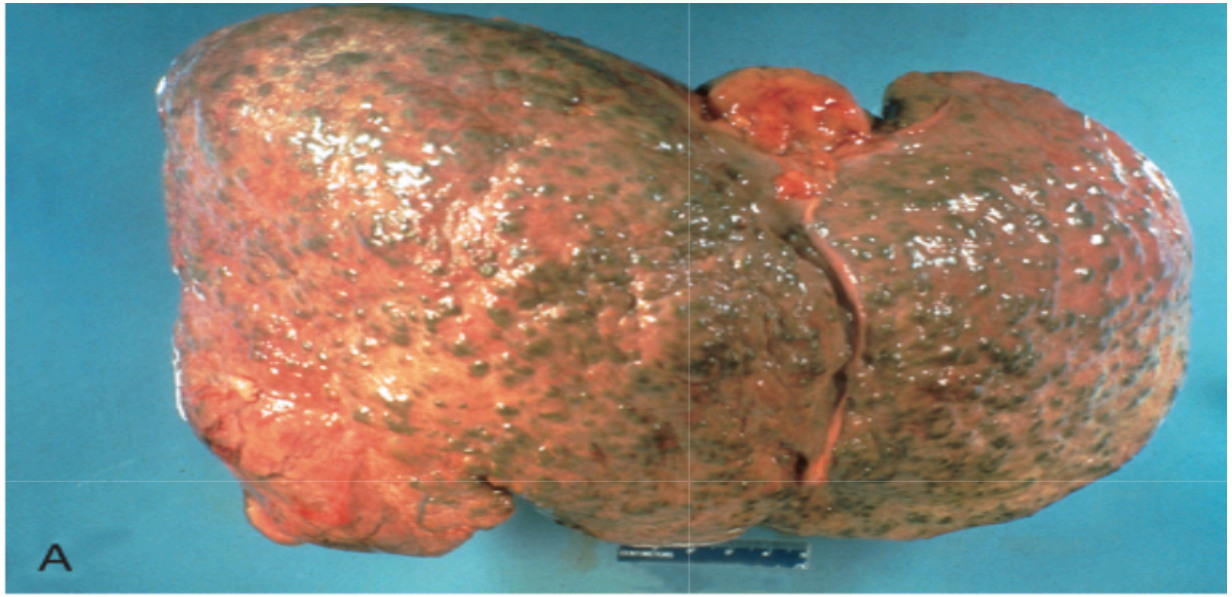


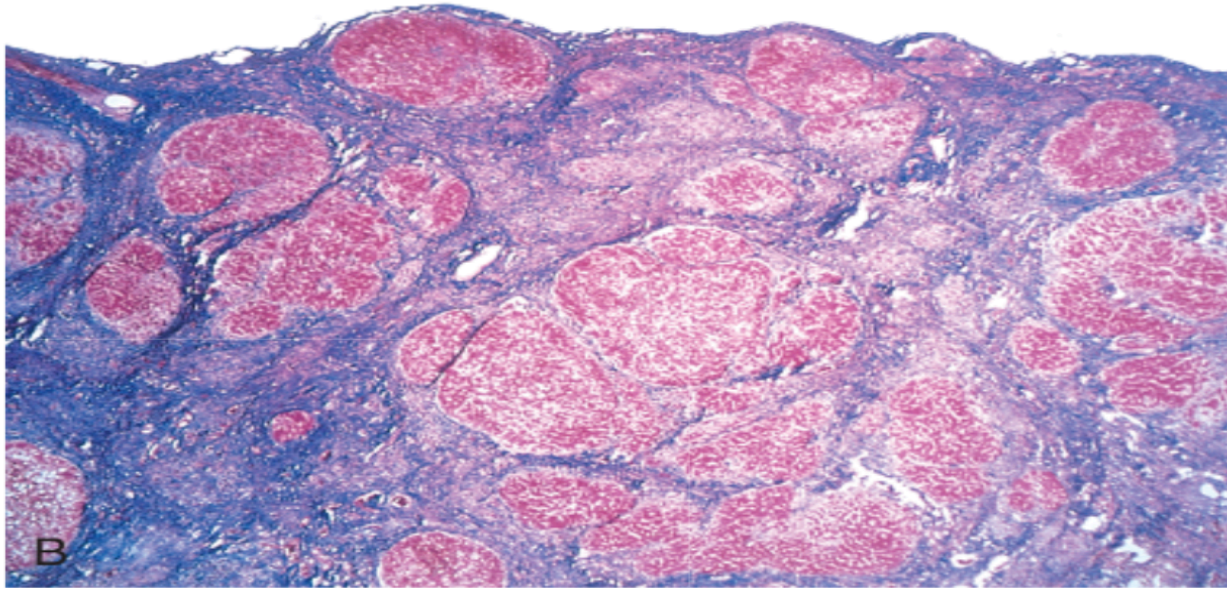




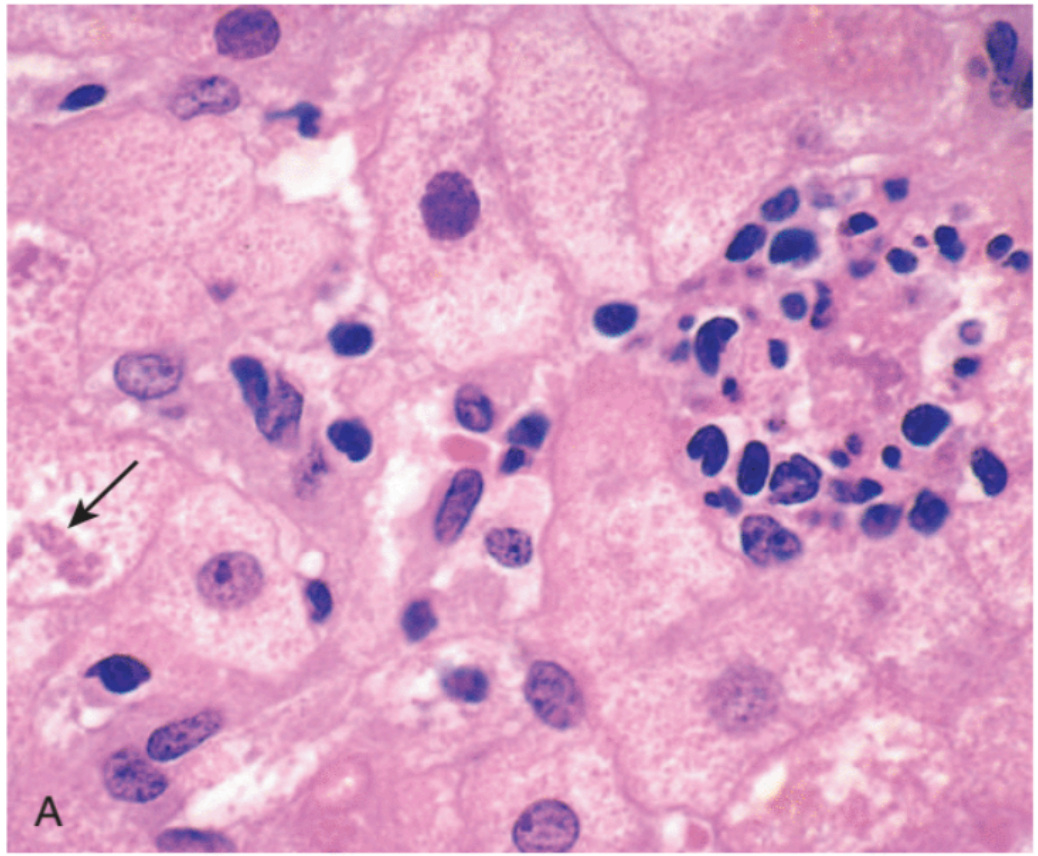
Morphology

Alcoholic Cirrhosis
(Micronodular cirrhosis)

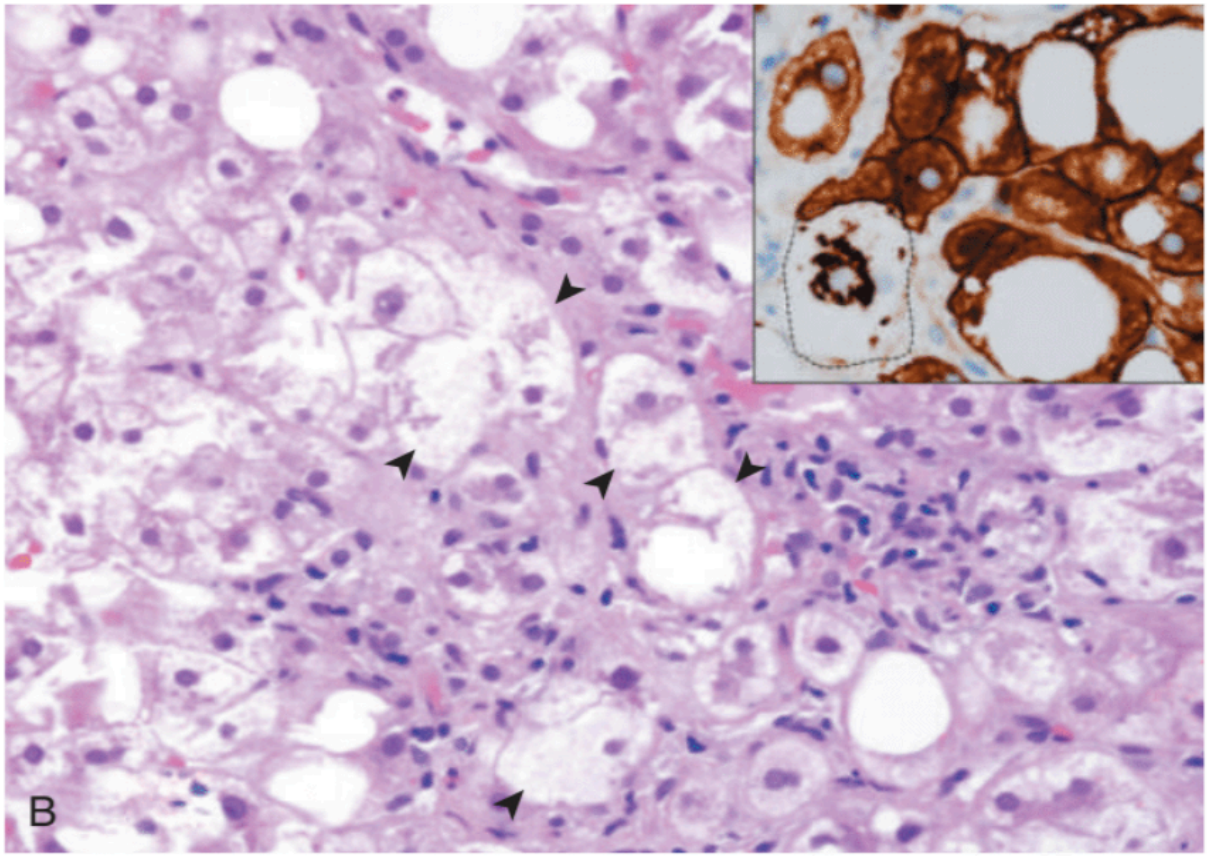




Morphology



- Cluster of inflammatory cells
- Mallory-Denk bodies



Ballooned hepatocytes (seen with CK IHC)

SUMMARY

ALCOHOLIC LIVER DISEASE

- Alcoholic liver disease has three main manifestations, hepatic steatosis, alcoholic hepatitis, and cirrhosis, which may occur alone or in combination.
- Cirrhosis typically develops after more than 10 years of heavy drinking, but only occurs in a small proportion of chronic alcoholics; alcoholic cirrhosis has similar clinical signs and symptoms as cirrhosis caused by viral hepatitis.
- The multiple pathologic effects of alcohol include changes in lipid metabolism, decreased export of lipoproteins, and cell injury caused by reactive oxygen species and metabolites of alcohol.

Intrahepatic Biliary Tract Disease

Three disorders of intrahepatic bile ducts:

1. Secondary biliary cirrhosis
2. Primary biliary cirrhosis
3. Primary sclerosing cholangitis

TABLE 18–8 Distinguishing Features of the Major Intrahepatic Bile Duct Disorders

	Secondary Biliary Cirrhosis	Primary Billiary Cirrhosis	Primary Sclerosing Cholangitis
Etiology	Extrahepatic bile duct obstruction: biliary atresia, gallstones, stricture, carcinoma of pancreatic head	Possibly autoimmune	Unknown, possibly autoimmune; 50% to 70% associated with inflammatory bowel disease
Sex predilection	None	Female to male, 6:1	Female to male, 1:2
Symptoms and signs	Pruritus, jaundice, malaise, dark urine, light stools, hepatosplenomegaly	Same as secondary biliary cirrhosis; insidious onset	Same as secondary biliary cirrhosis; insidious onset
Laboratory findings	Conjugated hyperbilirubinemia, increased serum alkaline phosphatase, bile acids, cholesterol	Same as secondary biliary cirrhosis, plus elevated serum IgM autoantibodies (especially M2 form of anti-mitochondrial antibody)	Same as secondary biliary cirrhosis, plus elevated serum IgM, hypergammaglobulinemia
Important pathologic findings before cirrhosis develops	Prominent bile stasis in bile ducts, bile ductular proliferation with surrounding neutrophils, portal tract edema	Dense lymphocytic infiltrate in portal tracts with granulomatous destruction of bile ducts	Periductal portal tracts fibrosis, segmental stenosis of extrahepatic and intrahepatic bile ducts

Secondary Biliary Cirrhosis

- Secondary inflammation resulting from biliary obstruction initiates periportal fibrosis, which eventually leads to hepatic scarring and nodule formation, generating secondary biliary cirrhosis

Secondary Biliary Cirrhosis

- The most common cause of obstruction in adults is extrahepatic cholelithiasis (gallstones), followed by malignancies of the biliary tree or head of the pancreas and strictures resulting from previous surgical procedures

- Obstructive conditions in children include biliary atresia, cystic fibrosis, choledochal cysts (a cystic anomaly of the extrahepatic biliary tree)

Secondary Biliary Cirrhosis
General morphological features

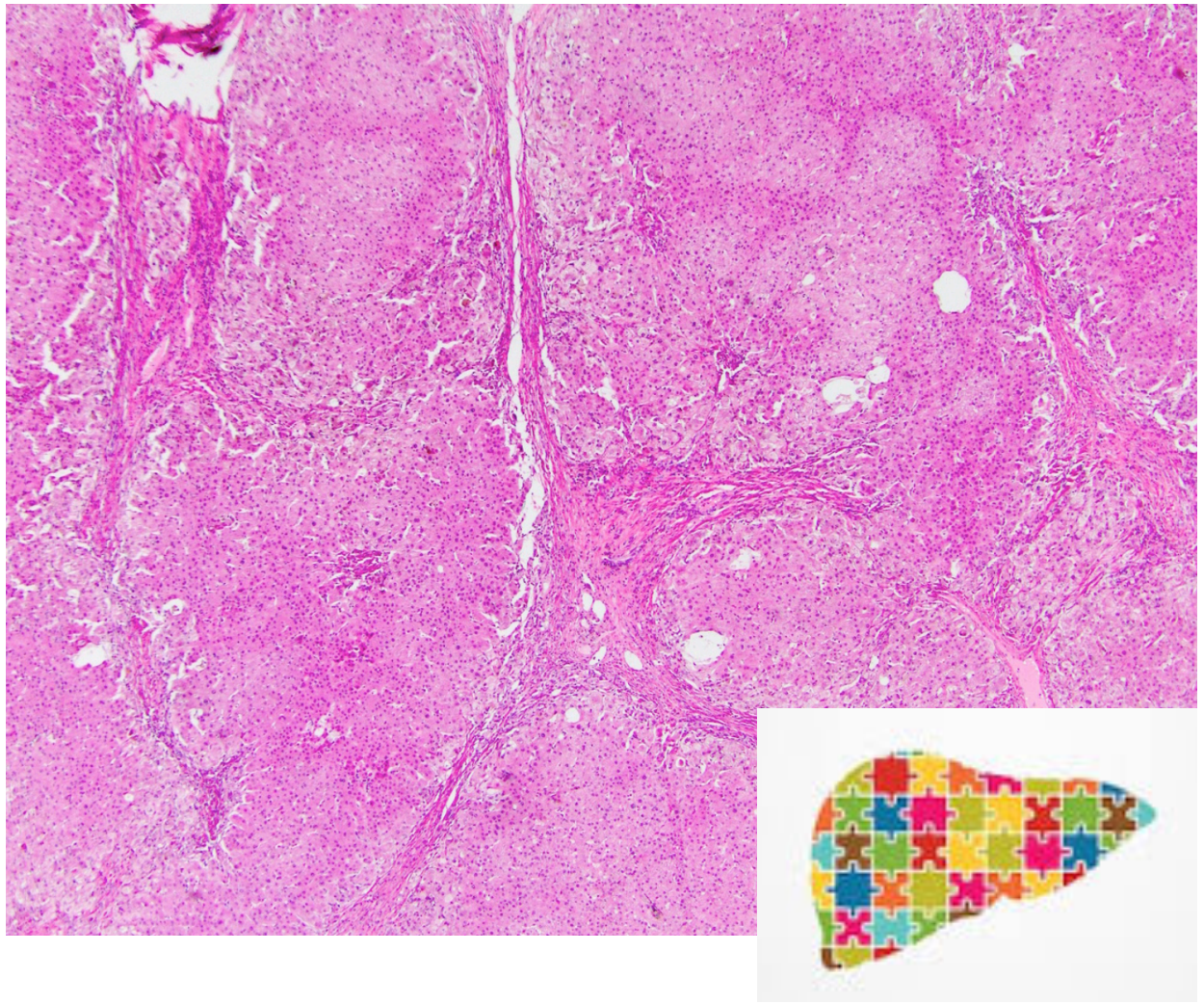
- Cholestasis are entirely reversible with correction of the obstruction
- Secondary inflammation resulting from biliary obstruction initiates periportal fibrosis, which eventually leads to hepatic scarring and nodule formation, generating secondary biliary cirrhosis
- Subtotal obstruction may promote secondary bacterial infection of the biliary tree (ascending cholangitis), which aggravates the inflammatory injury. Enteric organisms such as coliforms and enterococci are common culprits

Secondary Biliary Cirrhosis – Gross Morphology

- The end-stage obstructed liver shows:
  - Yellow-green pigmentation that is accompanied by marked icteric discoloration, body tissues and fluids
- On cut surface the liver is hard, with a finely granular appearance

Secondary Biliary Cirrhosis – Microscopic Morphology

- Characterized by coarse fibrous septa that subdivide the liver in a jigsaw-like pattern
- Extensive proliferation of smaller bile ductules
- Cholestatic may be severe, with extensive feathery degeneration and formation of bile lakes
- Ascending bacterial infection incites a robust neutrophilic infiltration of bile ducts



Etiology	Extrahepatic bile duct obstruction: biliary atresia, gallstones, stricture, carcinoma of pancreatic head
Sex predilection	None
Symptoms and signs	Pruritus, jaundice, malaise, dark urine, light stools, hepatosplenomegaly
Laboratory findings	Conjugated hyperbilirubinemia, increased serum alkaline phosphatase, bile acids, cholesterol No increase in serum AMA or IgM
Important pathologic findings before cirrhosis develops	Prominent bile stasis in bile ducts, bile ductular proliferation with surrounding neutrophils, portal tract edema

Primary Biliary Cirrhosis

- Is an autoimmune disease whose primary feature is nonsuppurative, inflammatory destruction of small- and medium-sized intrahepatic bile ducts
- It is accompanied by portal inflammation, scarring, and eventual development of cirrhosis and liver failure

Primary Biliary Cirrhosis

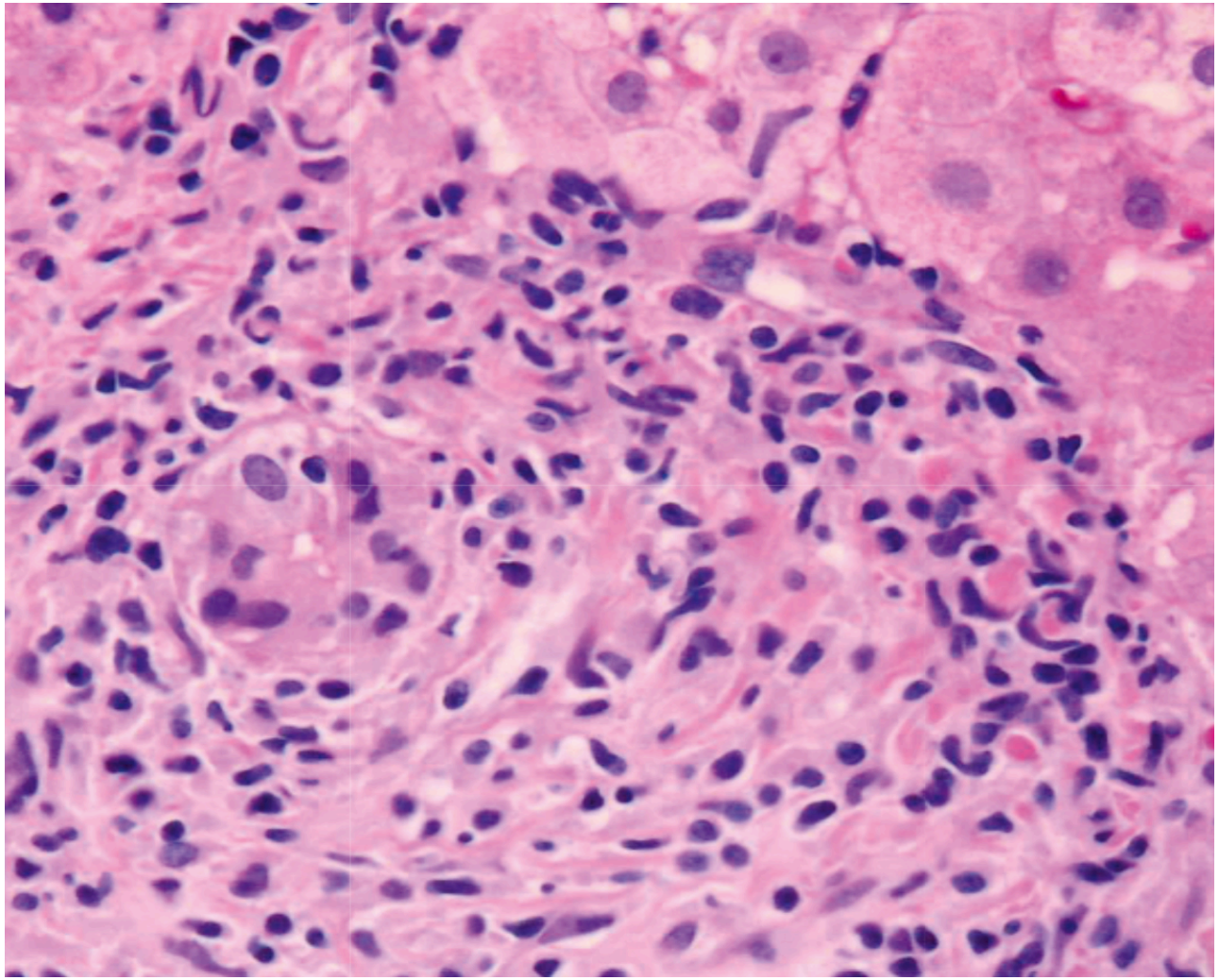
- Middle-aged
- Female predominance over males in excess of 6 : 1
- It may occur between the ages of 20 and 80 years, with peak incidence between 40 and 50 years of age
- Serum *alkaline phosphatase and cholesterol are almost always elevated*
- *Antimitochondrial* antibodies are present in 90% to 95% of patients (highly characteristic of PBC)
- Hyperbilirubinemia is a late development and usually signifies incipient hepatic decompensation

Primary Biliary Cirrhosis- Clinical features

- Insidious onset
- Patients may be symptom-free for many years
- Eventually, pruritus, fatigue, and abdominal discomfort develop
- General features of jaundice and hepatic decompensation, including portal hypertension and variceal bleeding, mark entry into the end stages of the disease
- Secondary features: skin pigmentation, xanthelasmas, steatorrhea, and vitamin D malabsorption–related osteomalacia and/or osteoporosis
- May also have extrahepatic manifestations of autoimmunity, including Sjögren syndrome; systemic sclerosis….

Primary Biliary Cirrhosis - Morphology

- Pre-cirrhotic stage:
  - ✓ Portal tracts and bile ducts are infiltrated by lymphocytes, macrophages, plasma cells, and occasional eosinophils
  - ✓ Noncaseating granulomatous inflammation
  - ✓ Bile duct destruction
- With time:
  - ✓ Progressive obstruction ➔ damage bile ducts and ductular proliferation, inflammation, and necrosis of the adjacent periportal hepatic parenchyma
- Over years to decades, relentless portal tract scarring and bridging fibrosis lead to cirrhosis



Primary Biliary Cirrhosis

In most cases, the end-stage picture is indistinguishable from secondary biliary cirrhosis or the cirrhosis that follows chronic hepatitis from other causes

Etiology	Possibly autoimmune
Sex predilection	Female to male: 6:1
Symptoms and signs	Same as secondary biliary cirrhosis (Pruritus, jaundice, malaise, dark urine, light stools, hepatosplenomegaly)
Laboratory findings	Same as secondary biliary cirrhosis (Conjugated hyperbilirubinemia, increased serum alkaline phosphatase, bile acids, cholesterol) plus elevated serum autoantibodies (especially antimitochondrial antibody-AMA)
Important pathologic findings before cirrhosis develops	Dense lymphocytic infiltrate in portal tracts with granulomatous destruction of bile ducts

Primary sclerosing cholangitis

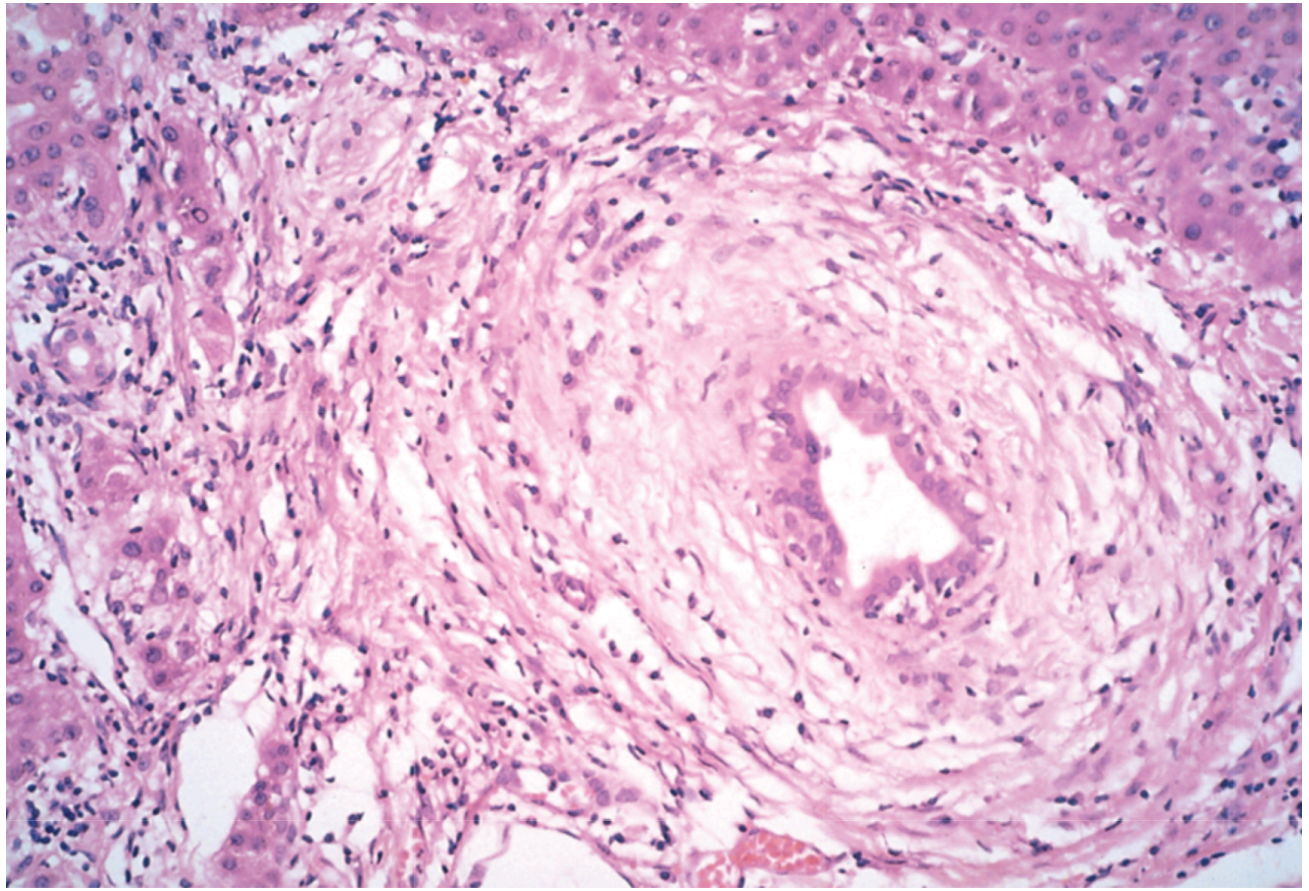
- Characterized by inflammation and obliterative fibrosis of intrahepatic and extrahepatic bile ducts, with dilation of preserved segments
- Characteristic by irregular biliary strictures and dilations cause the characteristic “beading” of the intrahepatic and extrahepatic biliary tree seen by MRI.
- It is commonly seen in association with inflammatory bowel disease , particularly chronic ulcerative colitis
- Males predominate 2:1
- Pathogenesis: unknown

Primary sclerosing cholangitis- Clinical features

- Asymptomatic patients may come to attention only because of persistent elevation of serum alkaline phosphatase
- Progressive fatigue, pruritus, and jaundice may develop
- Approximately 7% of individuals with PSC develop cholangiocarcinoma

Primary sclerosing cholangitis – Morphology

- Fibrosing cholangitis of bile ducts, with a lymphocytic infiltrate, progressive atrophy of the bile duct epithelium, and obliteration of the lumen
- The concentric periductal fibrosis around affected ducts "onion-skin fibrosis" is followed by their disappearance, leaving behind a solid, cordlike fibrous scar
- As the disease progresses, the liver becomes cirrhotic like that seen with primary and secondary biliary cirrhosis



Etiology	Unknown, possibly autoimmune; 50-70% associated with inflammatory bowel disease
Sex predilection	Female to male: 1:2
Symptoms and signs	Same as secondary biliary cirrhosis (Pruritus, jaundice, malaise, dark urine, light stools, hepatosplenomegaly) insidious onset
Laboratory findings	Same as secondary biliary cirrhosis (Conjugated hyperbilirubinemia, increased serum alkaline phosphatase, bile acids, cholesterol) plus elevated serum IgM, hypergammaglobulinemia
Important pathologic findings before cirrhosis develops	Periductal portal tract fibrosis, segmental stenosis of extrahepatic and intrahepatic bile ducts

Parameter	Primary Biliary Cholangitis	Primary Sclerosing Cholangitis
Age	Median age 50 years	Median age 30 years
Gender	90% female	70% male
Clinical course	Progressive	Unpredictable, but progressive
Associated conditions	Sjögren syndrome (70%)	Inflammatory bowel disease (70%)
	Scleroderma (5%)	Pancreatitis (≤25%)
	Thyroid disease (20%)	Idiopathic fibrosing diseases (retroperitoneal fibrosis)
Serology	95% AMA-positive	0%–5% AMA-positive (low titer)
	20% ANA-positive	6% ANA-positive
	40% ANCA-positive	65% ANCA-positive
Radiology	Normal	Strictures and beading of large bile ducts; pruning of smaller ducts
Duct lesion	Florid duct lesions and loss of small ducts only	Inflammatory destruction of extrahepatic and large intrahepatic ducts; fibrotic obliteration of medium and small intrahepatic ducts

Thank you for your attention

References:

- **ROBBINS BASIC PATHOLOGY, TENTH EDITION**