King Saud University
College of Medicine
Second year – GIT block

Liver Cirrhosis

Lecture 10

430 Pathology Team

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Cirrhosis:

Definition: a *diffuse process characterized by fibrosis and abnormal nodules.*
Incidence: it is among the top 10 causes of death in the Western world.

Causes:

- alcohol abuse
- Viral hepatitis.

} Majority of cases

- Biliary disease
- Iron overload.

Prognosis: it is the end-stage of chronic liver disease.

Characteristics:

1. **Fibrosis** in the form of delicate bands or broad scars/septa.
2. **Nodules** containing regenerating hepatocytes encircled by fibrosis, with diameters varying from very small (<3 mm, micronodules) seen in alcoholism to large (several centimeters, macronodules).
3. **Disruption of the architecture** of the entire liver that can be seen by silver stain.

Features:

- Vascular architecture is reorganized by the parenchymal damage and scarring, with the formation of abnormal interconnections between vascular inflow and hepatic vein outflow channels.
- Fibrosis is the key feature of progressive damage to the liver. Once cirrhosis has developed, reversal is thought to be rare.

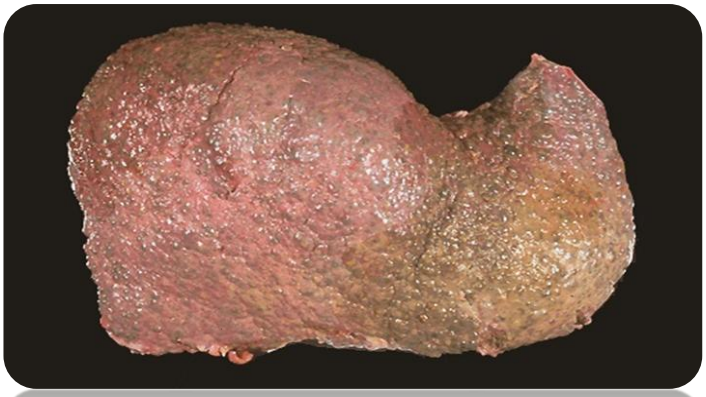
Classification:

The classification is based on the underlying etiology.

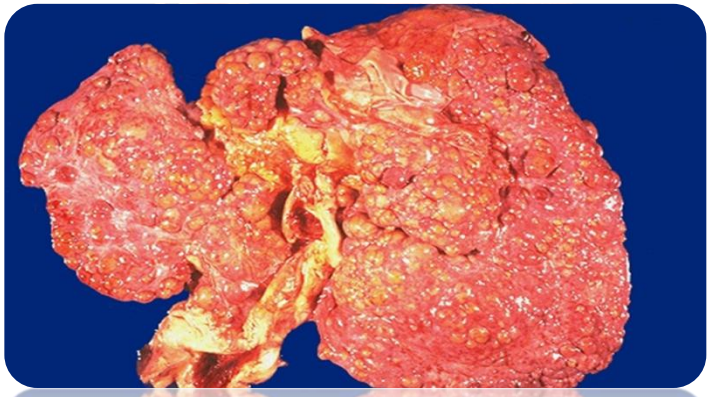
Alcoholic Liver Disease	60% to 70%
Viral Hepatitis	10%
Biliary Diseases	5% to 10%
Primary Hemochromatosis	5%
Wilson Disease	Rare
α1-Antitrypsin Deficiency	Rare
Cryptogenic Cirrhosis	10% to 15%

The way in which alcohol causes chronic liver disease and cirrhosis is not completely understood, but some suggested mechanisms include: impaired protein synthesis and secretion, mitochondrial injury, formation of acetaldehyde, induction of different liver functions, cellular hypoxia, and other ways.

Many forms of cirrhosis (particularly alcoholic cirrhosis) are initially micronodular, but there is a tendency for nodules to increase in size with time.



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



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

Infrequent types of cirrhosis also include

- the cirrhosis developing in infants and children with galactosemia (autosomal recessive) in which an enzyme needed to metabolize galactose is deficient or absent)and tyrosinosis (a condition of faulty metabolism of tyrosine marked by the excretion of unusual amounts of tyrosine in the urine)
- Drug-induced cirrhosis, e.g: prolong use of NSAIDs.
- Severe fibrosis can occur in the setting of cardiac disease such as heart failure (sometimes called "cardiac cirrhosis,").
- In some cases there is no cause and these are referred to as *cryptogenic cirrhosis.*

Once cirrhosis is established, it is usually impossible to establish an etiologic diagnosis on morphologic grounds alone.

Pathogenesis:

The pathogenetic processes in cirrhosis are progressive fibrosis and reorganization of the vascular microarchitecture of the liver

The major mechanisms that combine to create cirrhosis are:

1. Hepatocellular death that maybe a result of toxins or chronic infections
2. Regeneration
3. Progressive fibrosis: that are a result of wound healing, direct insult by a toxin, or may be due to a direct immune response
4. Vascular changes:
   Consisting of the loss of sinusoidal endothelial cell fenestrations (causing resistance to the intrahepatic blood flow by intrasinusoidal hypertension) and the development of portal vein-hepatic vein and hepatic artery-portal vein vascular shunts, which also contribute to defects in liver function.
   Transforming growth factor β (TGF) is the main fibrogenic agent for stellate cells and the main factor in fibroses.

Normally: 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 (sinusoidal space)

In cirrhosis:

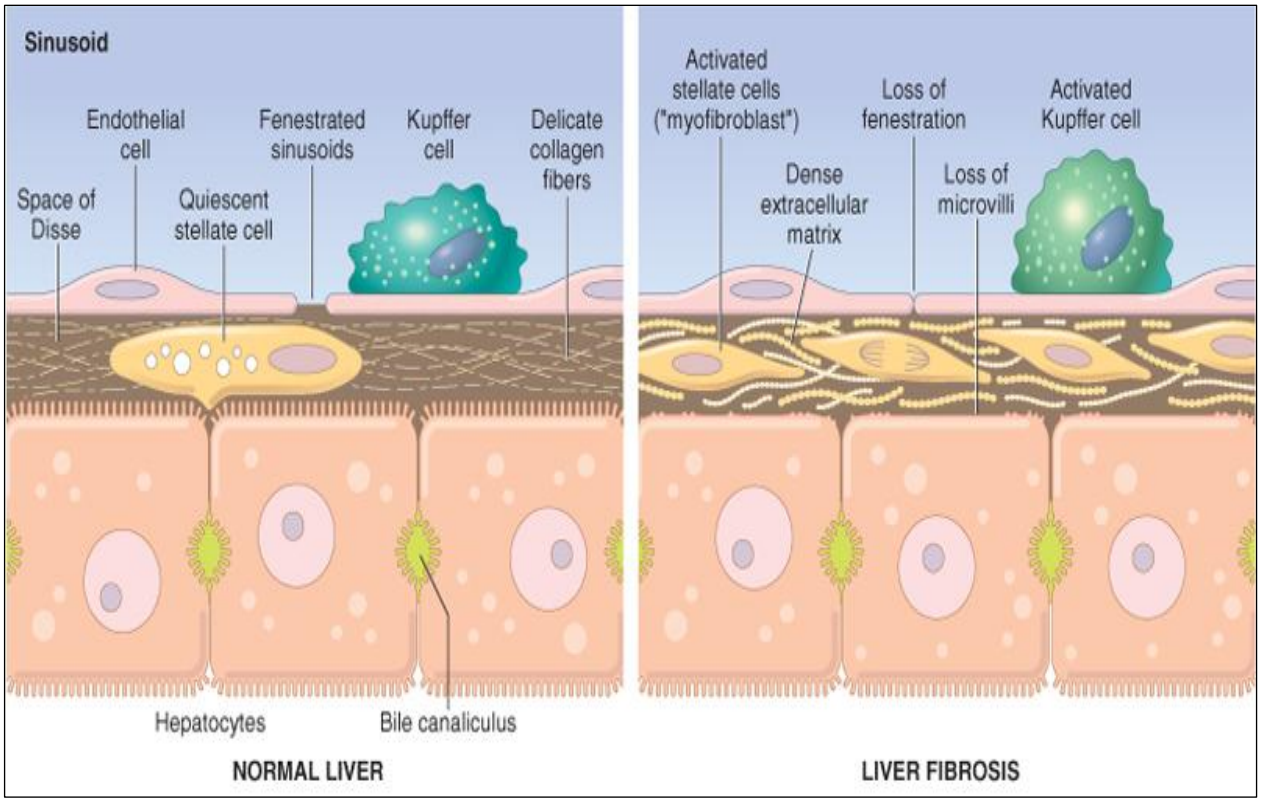
- Types I and III collagen and other ECM (extracellular matrix) components are deposited in the lobule, creating delicate or broad septal tracts.

- There is loss of fenestrations in the sinusoidal endothelial cells (capillarization of sinusoids that is the sinusoidal space comes to resemble a capillary rather than a channel for exchange of solutes between hepatocytes and plasma). This deposition markedly impairs movement of solutes and proteins (e.g., albumin, clotting factors, lipoproteins) between hepatocytes and the plasma.

The major source of excess collagen in cirrhosis is the perisinusoidal stellate cells (Ito cells), which lie in the space of Disse. Although normally functioning as vitamin A fat-storing cells, during the development of cirrhosis they become activated and transform into myofibroblast-like cells. Activated stellate cells produce growth factors, cytokines, and chemokines that cause their further proliferation and collagen synthesis.

Collagen synthesis is stimulated by

1. Chronic inflammation, with production of inflammatory cytokines.
2. Cytokine production (most importantly TNF) by activated endogenous cells (Kupffer cells, endothelial cells, hepatocytes, and bile duct epithelial cells).
3. Disruption of the normal extracellular matrix.
4. Direct stimulation of stellate cells by toxins.



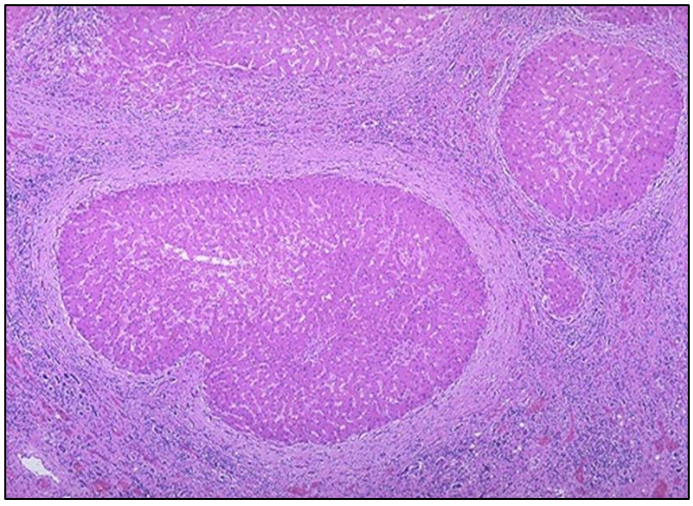
Clinical Features:

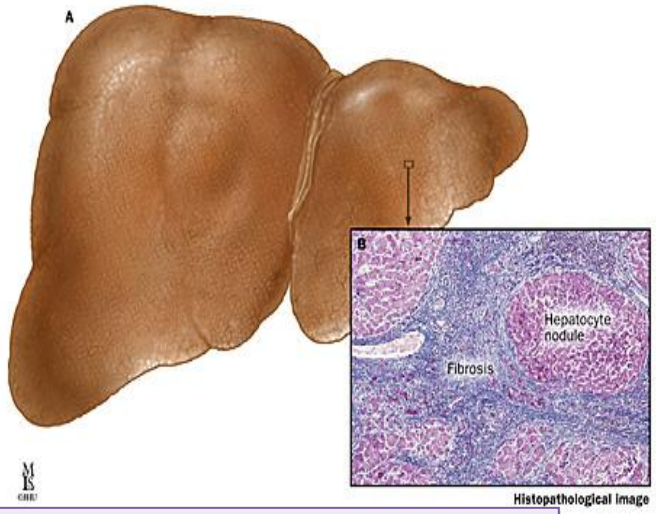
- All forms of cirrhosis may be clinically silent. This is because the liver is a huge organ and not all of the liver cells are affected, where some are still normal and try to compensate the function of the affected ones.
- When symptomatic they lead to nonspecific clinical manifestations: anorexia, weight loss, weakness, osteoporosis, and, in advanced disease, frank debilitation. Most importantly jaundice
- Incipient (beginning) or overt hepatic failure may develop.

Complications

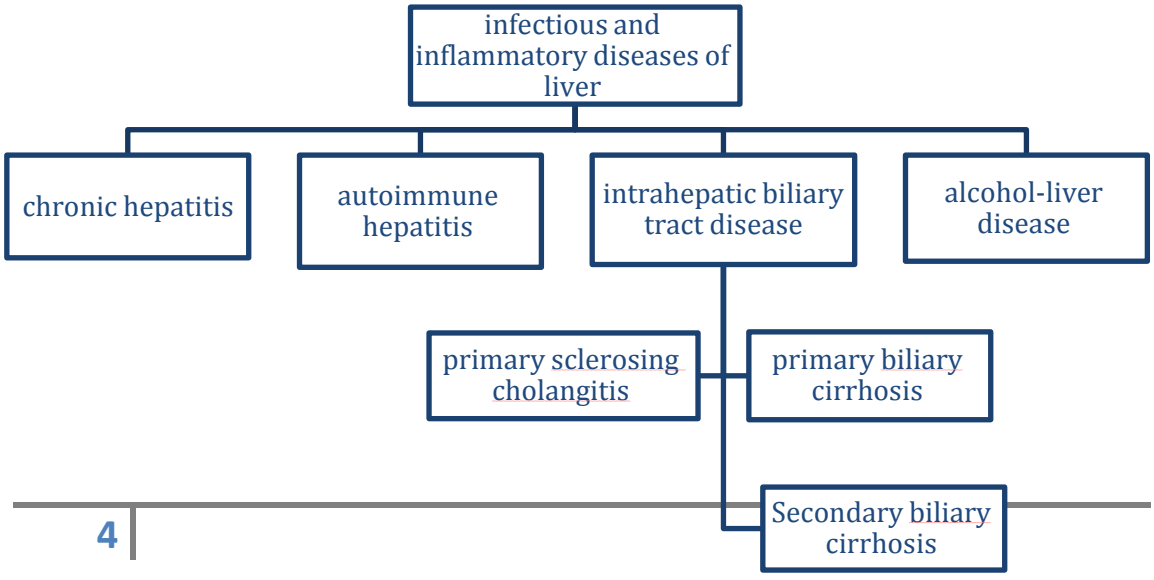
Death from:

- Progressive liver failure.
- Complication related to portal hypertension such as hematemesis.
- The development of hepatocellular carcinoma.





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 proliferating bile ducts.



Chronic Hepatitis:

Definition: symptomatic, biochemical, or serologic evidence of continuing or relapsing hepatic disease for more than 6 months.

Morphology:

Some changes are shared with acute hepatitis.

- Hepatocyte injury, necrosis, and regeneration
- Sinusoidal cell reactive changes
- Portal tract Inflammation (in mild cases):
    1. Confined to portal tracts.
    2. Spillover into adjacent parenchyma, with necrosis of hepatocytes ("interface hepatitis"- inflammatory cells between inflamed portal tracts and periportal parenchyma).
    3. Bridging inflammation and necrosis.
- Fibrosis:

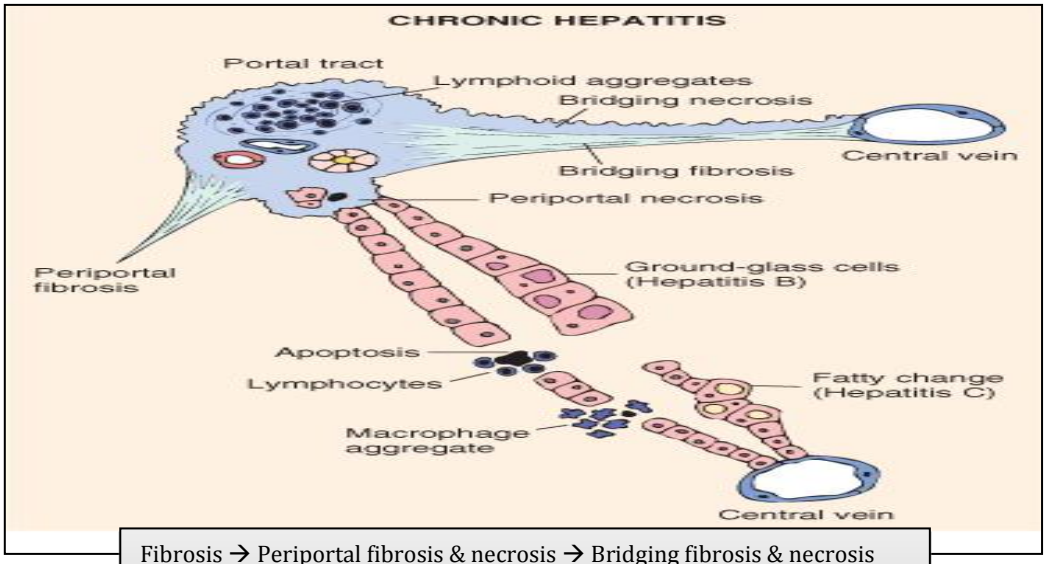
Continued loss of hepatocytes results in fibrous septa formation which ultimately leads to cirrhosis.

In HBV (Hepatitis B Virus): "ground-glass" hepatocytes, "sanded" nuclei.

These nuclei are filled with HBV antigens producing a granular appearance.

In HCV (Hepatitis C Virus): bile duct damage, lymphoid aggregate formation

Prognosis: cirrhosis is the end-stage outcome with fibrous septa around regenerating nodules.



Fibrosis → Periportal fibrosis & necrosis → Bridging fibrosis & necrosis

Staging: Extension of fibrosis

Stage (1): Portal tract fibrosis
Stage (2): Bridging fibrosis between portal tract and another portal tract
Stage (3): Bridging fibrosis between portal tract and central vein
Stage (4): Nodule formation (*Cirrhosis*)

Autoimmune hepatitis:

Definition: it is a chronic hepatitis with histologic features like that of chronic viral hepatitis.

Incidence: female predominance, particularly in young and perimenopausal women.

Causes: unknown

Laboratory findings: this disease may run an indolent (little or no pain) or severe course; salient (Most noticeable or important) features include the following:

- The absence of viral serologic markers
- Elevated serum IgG and γ-globulin levels (>1.5 times normal)
- High serum titers of autoantibodies in 80% of cases, including antinuclear (ANA), antismooth muscle (SMA) etc.
- Negative anti-mitochondrial antibodies.
- Presence of plasma cells.

Prognosis:

- In untreated severe disease, as many as 40% of patients die within 6 months of diagnosis, and cirrhosis develops in at least 40% of survivors.
- Associated with other autoimmune diseases eg. Rheumatoid arthritis, Sjogren's syndrome etc.

Treatment: include immunosuppressive therapy, and liver transplantation.

Intrahepatic Biliary Tract Disease:

1. Secondary biliary cirrhosis:

Prolonged obstruction of the extrahepatic biliary tree results in profound alteration of the liver itself.

Causes:

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.

In children include: biliary atresia, cystic fibrosis, choledochal cysts (a cystic anomaly of the extrahepatic biliary tree).

Morphology:

- 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.

Etiology	Extrahepatic bile duct obstruction: biliary atresia, gallstones, stricture, carcinoma of pancreatic head
Sex predilection Symptoms and signs	None. Pruritus, jaundice, malaise, dark urine, light stools, hepatosplenomegaly
Laboratory findings	Conjugated hyperbilirubinemia, increased serum alkaline phosphatase, bile acids, cholesterol
Important pathologic findings before cirrhosis develops	Prominent bile stasis in bile ducts, bile ductular proliferation with surrounding neutrophils, portal tract edema

2. Primary Biliary Cirrhosis:

Definition: it is a chronic, progressive, and often fatal cholestatic liver disease, characterized by the destruction of intrahepatic bile ducts, portal inflammation and scarring, and the eventual development of cirrhosis and liver failure.

Feature: the primary feature of this disease is a nonsuppurative, inflammatory destruction of medium-sized intrahepatic bile ducts.

Incidence: female:male predominance (6:1), middle-aged women,

Pathogenesis: autoimmune etiology.

Clinical features:

- pruritus, jaundice, and hepatomegaly.
- Xanthomas and xanthelasmas arise owing to cholesterol retention.
- Over a period of time patients develop portal hypertension and hepatic encephalopathy.

Laboratory findings:

- Serum alkaline phosphatase and cholesterol are elevated; hyperbilirubinemia is a late development .
- 90% of patients have circulating "antimitochrondrial antibodies."

Morphology:

- During the precirrhotic stage, portal tracts and bile ducts are infiltrated by lymphocytes and may exhibit noncaseating granulomatous inflammation. There is bile duct destruction.
- With time, there is bile ductular proliferation to compensate the bile duct destruction, inflammation, and necrosis of the adjacent periportal hepatic parenchyma.
- Over years to decades, relentless portal tract scarring and bridging fibrosis lead to cirrhosis.

Complication: cirrhosis develops only after many years.

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 Symptoms and signs	Female to male: 6:1 Same as secondary biliary cirrhosis
Laboratory findings	Same as secondary biliary cirrhosis, 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

3. Primary Sclerosing Cholangitis:

Definition: it is characterized by inflammation and obliterative fibrosis of intrahepatic and extrahepatic bile ducts, with dilation of preserved segments.

Incidence: males predominate 2:1

Features:

- Characteristic "beading" of a barium column in radiographs of the intrahepatic and extrahepatic biliary tree is attributable to the irregular strictures and dilations of affected bile ducts.
- It is commonly seen in association with inflammatory bowel disease , particularly chronic ulcerative colitis,

Pathogenesis: unknown.

Morphology:

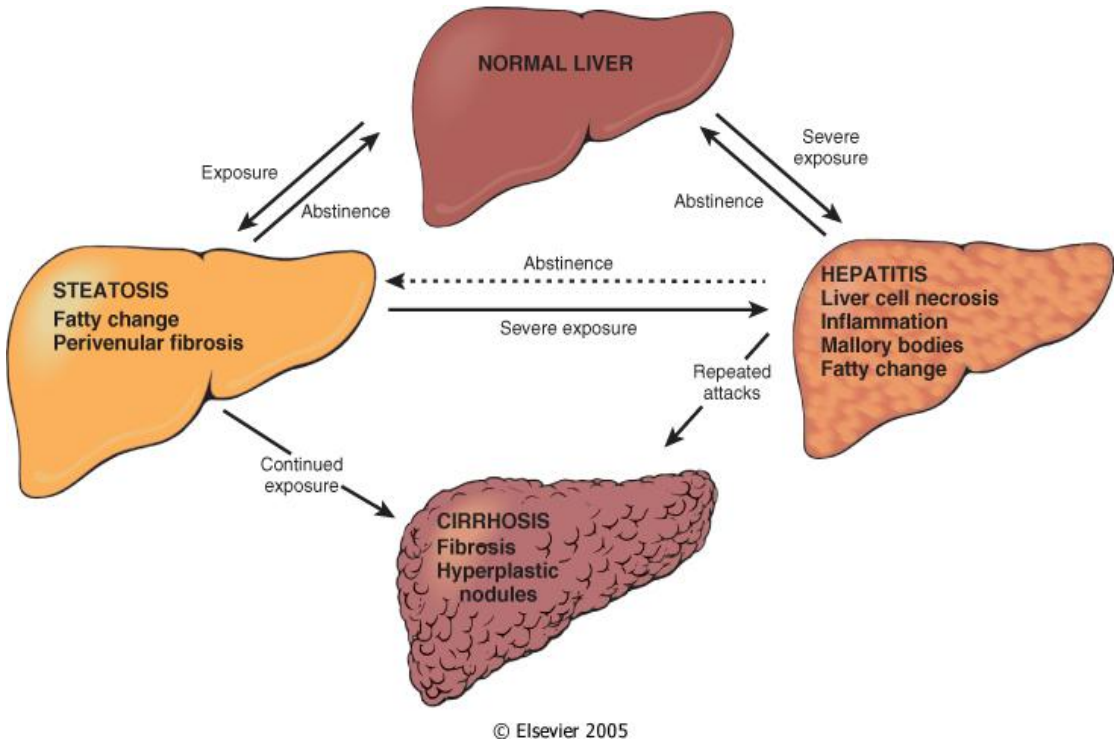
- Primary sclerosing cholangitis is a fibrosing cholangitis of bile ducts, with a lymphocytic infiltrate, progressive atrophy of the bile duct epithelium, and obliteration of the lumen.

- 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 Symptoms and signs	Female to male: 1:2 Same as secondary biliary cirrhosis; insidious onset
Laboratory findings	Same as secondary biliary cirrhosis, plus elevated serum IgM, hypergammaglobulinemia
Important pathologic findings before cirrhosis develops	Periductal portal tract fibrosis, segmental stenosis of extrahepatic and intrahepatic bile ducts

Alcoholic liver disease:



Alcoholic liver disease is a term that encompasses the hepatic manifestations of alcohol overconsumption, including fatty liver, alcoholic hepatitis, and chronic hepatitis with hepatic fibrosis or cirrhosis:

(1) Hepatic steatosis (*fatty liver*).
(2) Alcoholic hepatitis.
(3) Cirrhosis, collectively

Ingestion of alcohol even in low quantities can cause steatosis. Steatosis is not only caused by alcohol intake, but can be associated with diabetes, obesity, and other factors.

Steatosis is still a completely reversible change, but with persistent drinking this can cause alcoholic hepatitis, bordering on a irreversible state.

Some sever cases of alcoholic intake, especially if genetically predisposed, can cause direct alcoholic hepatitis skipping the fatty stage.

The degree of insult and fibrosis depends on the amount and duration of alcoholism.