LIVER CIRRHOSIS

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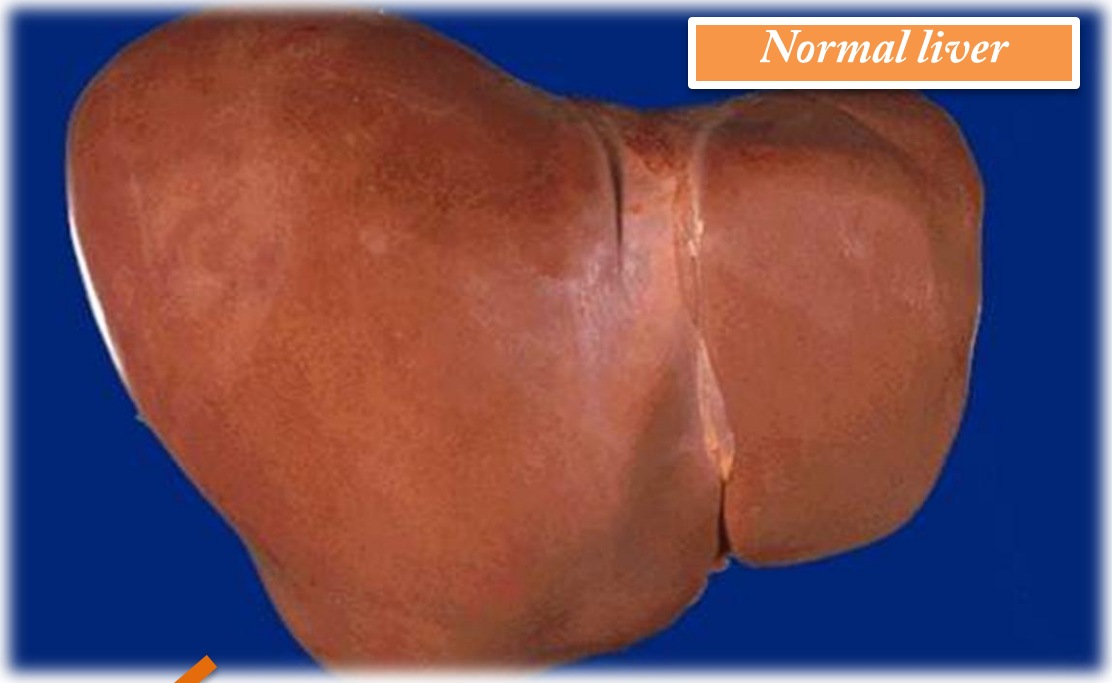
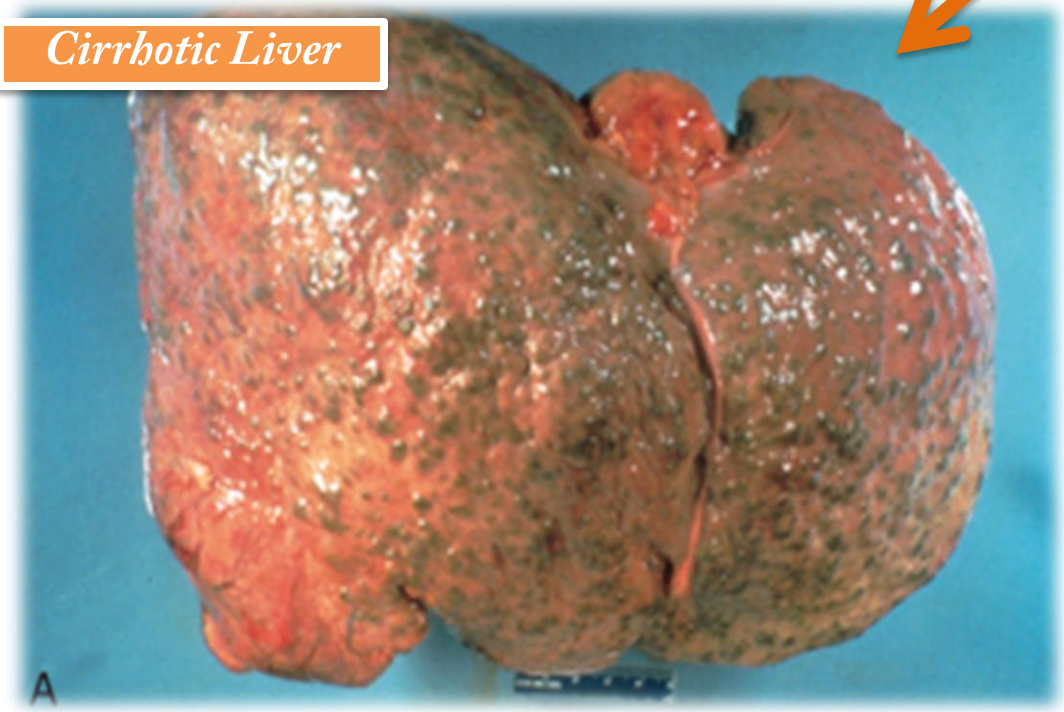
N.B: ***RED !!*** → ***Important Point***

STAR !! → ***Important Slide***

Normal liver



Cirrhotic Liver



Cirrhosis

- Among the **top 10** causes of **death**

- It is the end-stage of any *chronic liver disease.*
- Chief Causes: **alcohol abuse** and **viral hepatitis**.
- Other causes: **biliary disease** and **iron overload**.

Iron Overload: Accumulation of iron in the body due to any cause

Cirrhosis ★

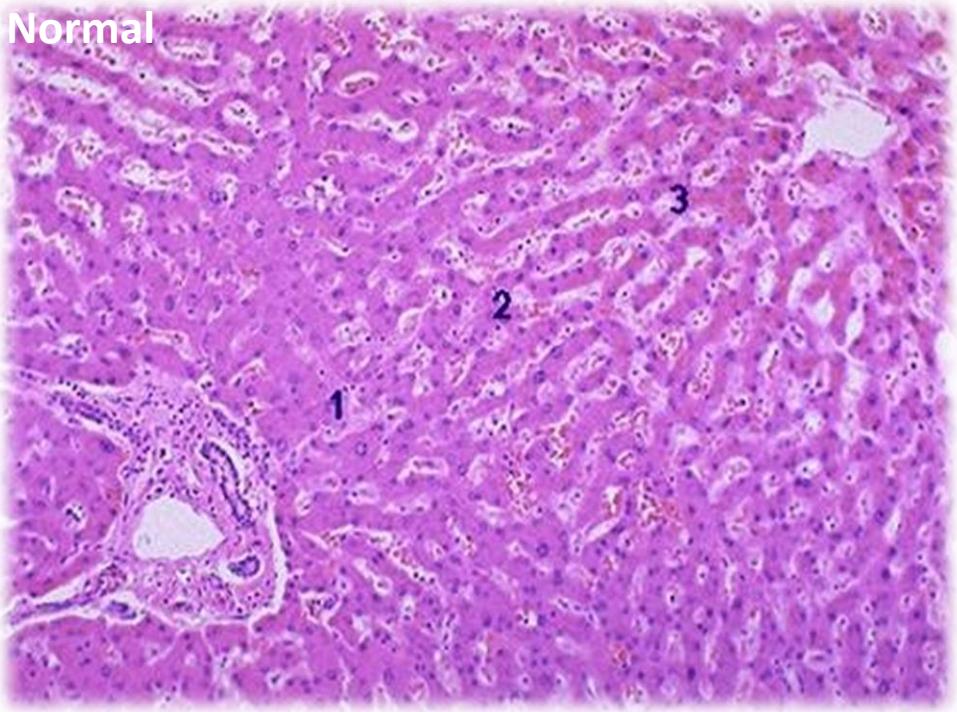
Characteristics: defined by 3:

1)*Fibrosis*
in the form of delicate bands or broad scars/septa

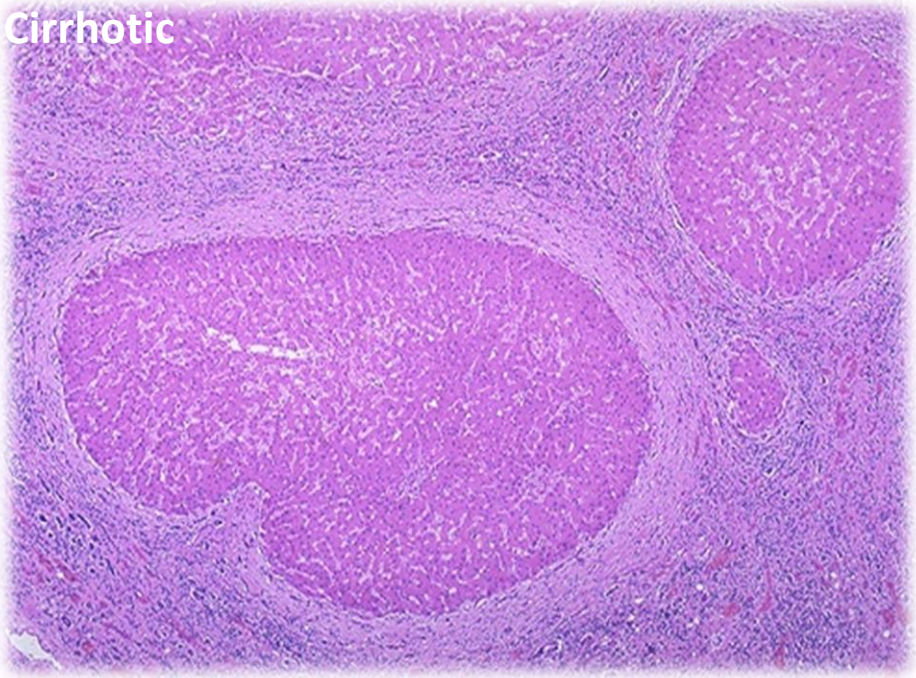
2)*Nodules* containing regenerating hepatocytes encircled by fibrosis, with diameters varying from very small (< 3 mm, micronodules) --> large (several centimeters, macronodules)

3)*Disruption of the architecture of the* ***entire*** *liver*

Normal



Cirrhotic



features of **cirrhosis**

- **Vascular architecture** → reorganized:
  by the parenchymal damage and scarring,
  → the formation of:
  Abnormal Interconnections
  between *vascular* ***inflow*** & *hepatic vein* ***outflow*** channels.

- **Fibrosis:** is the key feature of progressive damage to the liver.

- **Cirrhosis** is irreversible.

Classifiation of cirrhosis

- Based on the underlying etiology.

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

Classification based on Etiology:

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

Classification Cont'd

Infrequent (not common) types of cirrhosis also include:

- the cirrhosis developing in infants and children with **Galactosemia** and **Tyrosinosis**
- drug-induced cirrhosis.
- Severe fibrosis can occur in the setting of cardiac disease (sometimes called "cardiac cirrhosis")
  (↑ blood in liver → Portal hypertension)
- In some cases there is no cause and these are referred to as **Cryptogenic Cirrhosis**.

When we get an **already** cirrhotic liver, it's hard to predict etiology upon the morphologic feature.

Galactosemia: a rare genetic metabolic disorder that affects an individual's ability to metabolize the sugar galactose properly.
Tyrosinosis: A rare, possibly inherited disorder of tyrosine (an essential amino acid) metabolism.

Pathogenesis of cirrhosis

- The pathogenetic processes in cirrhosis are:
  -**Progressive fibrosis**
  -**Reorganization of the vascular microarchitecture**

A) In the normal liver:

-***Interstitial collagens (types I and III)*** →
Concentrated in portal tracts and around central veins.

-***The type IV collagen(reticulin)*** →
Is in the space of Disse.

B) In cirrhosis:

- Types I and III collagen →
deposited in the lobule, creating delicate (minor) or broad (major) septal tracts.

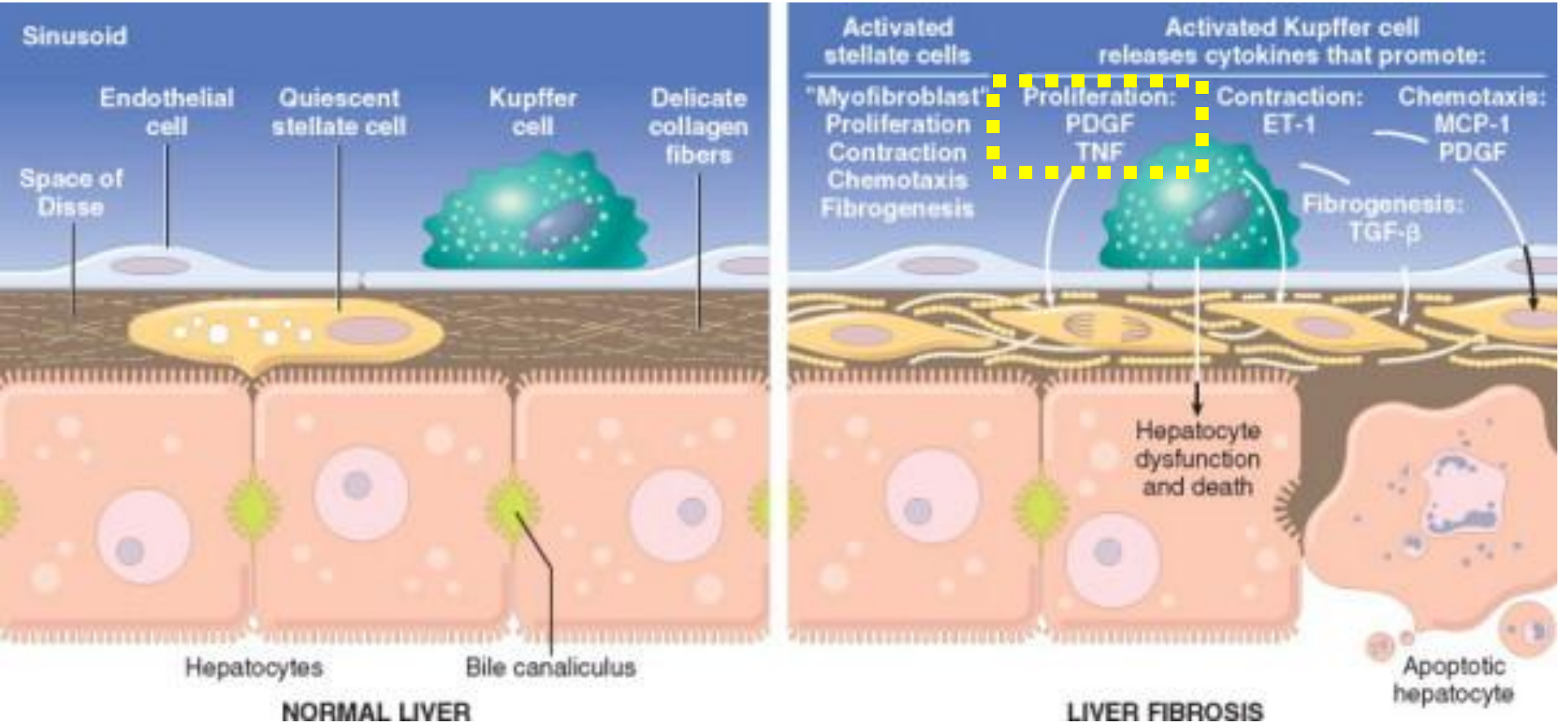
Pathogenesis cont'd

- 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)

>>> sinusoids in liver are for exchange → they have fenestrations.

Here, they lose this feature → become like normal capillaries ((check histology lecture))

Pathogenesis cont'd



Most important factor for <u>fibrosis</u>:

TNF

Pathogenesis cont'd

Ito cells >>> myofibroblasts >>>> fibrosis formation

- Cirrhosis has **excess collagen** mainly from:
  perisinusoidal stellate cells (Ito cells)
  which lie in the space of Disse

  They ***normally*** function as:
  vitamin A fat-storing cells

  During the ***development of cirrhosis*** :
  they become activated and transform into
  myofibroblast-like cells.

Pathogenesis cont'd

Collagen synthesis is stimulated by:

Chronic inflammation → production of inflammatory cytokines.

activated **endogenous cells** → Cytokine production

(endogenous cells: Kupffer cells, endothelial cells, hepatocytes, and bile duct epithelial cells).

Disruption of the normal extracellular matrix.

Direct stimulation of stellate cells by toxins

Clinical Features of cirrhosis

- **Asymptomatic:** almost all forms of cirrhosis may be clinically silent.
- **Symptomatic:** they lead to nonspecific clinical manifestations:
  - anorexia, weight loss, weakness
  - osteoporosis
  - in advanced disease, frank debilitation (weakeness).
  - Jaundice.
- Incipient (about to) or overt (shown) "hepatic failure" may develop.

Clinical Features cont'd

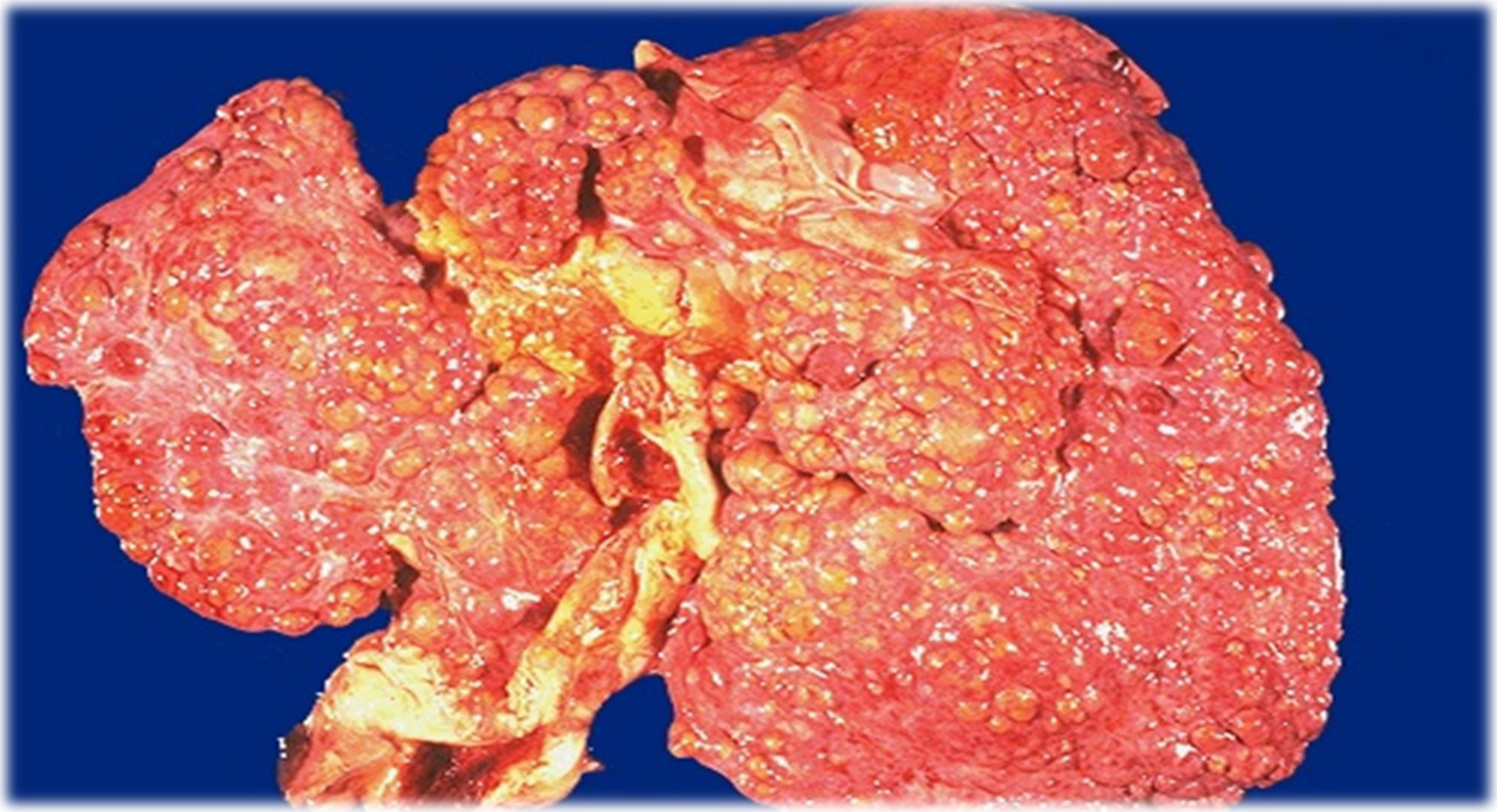
The ultimate mechanism of most cirrhotic deaths (ultimate complications):

(1) progressive liver failure.

(2) a complication related to **portal hypertension** ***(bleeding?!)***

(3) the development of hepatocellular carcinoma.

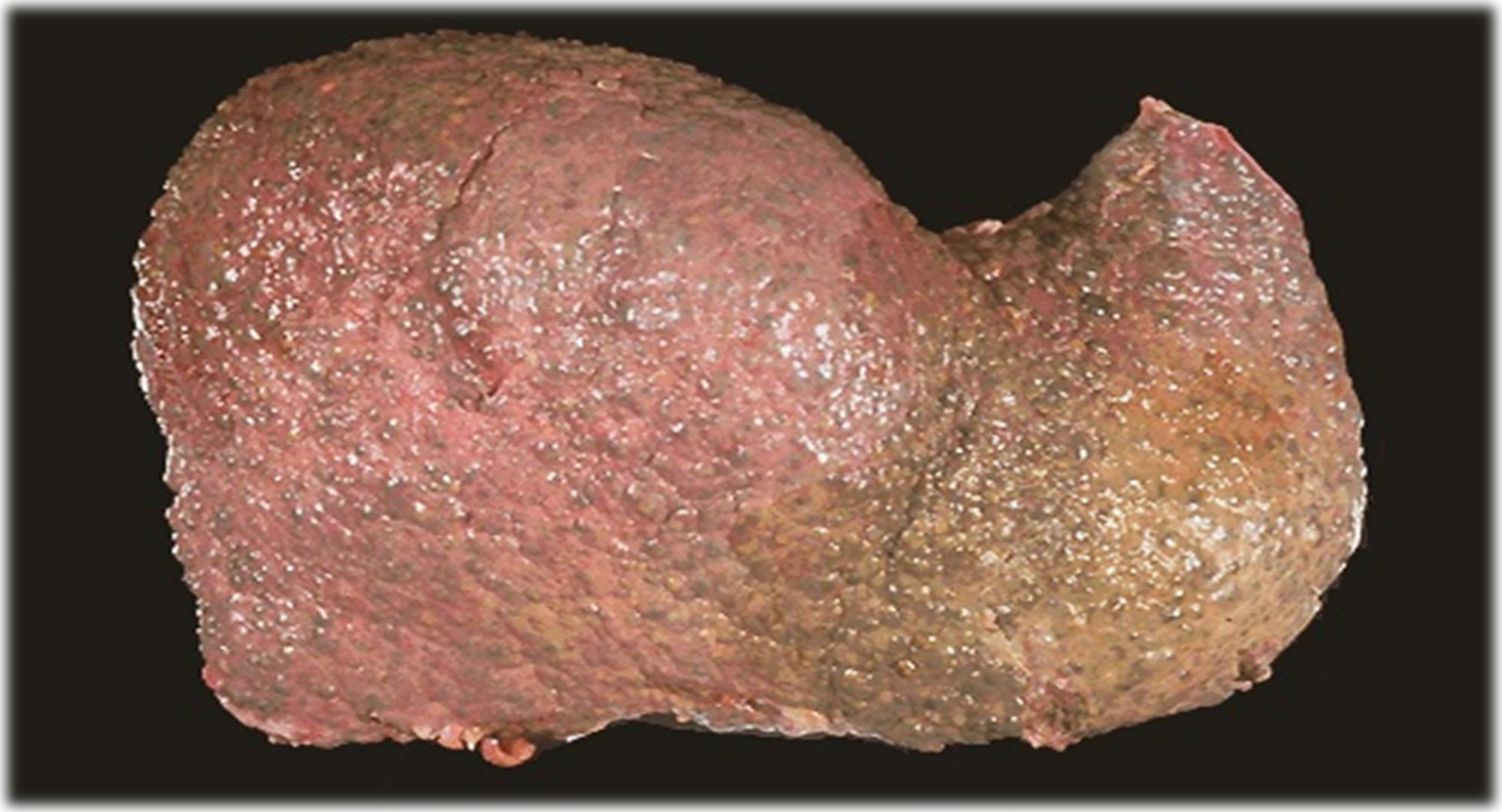
"macronodular" cirrhosis:
The nodules seen here are larger than 3 mm



“Micronodular” cirrhosis

The regenerative nodules are small, averaging < 3 mm in size.

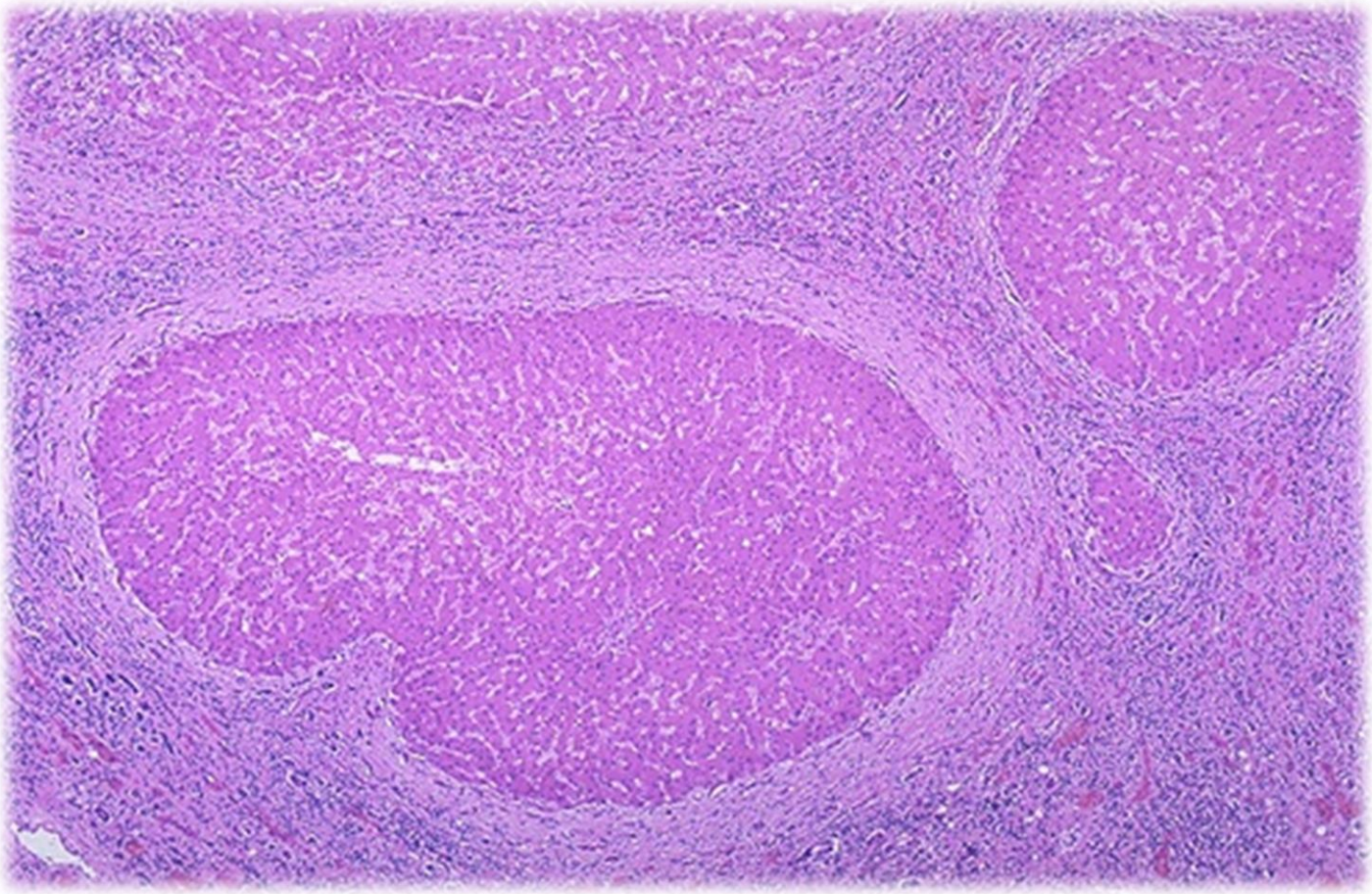
The most common cause for this is **chronic alcoholism**.



General Morphology:

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.



Classification according to Etiology:

1- Chronic Hepatitis

morphology:

Some changes are shared with acute hepatitis.

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

- **Fibrosis:**
  continuous loss of **hepatocytes** → fibrous septa formation → cirrhosis

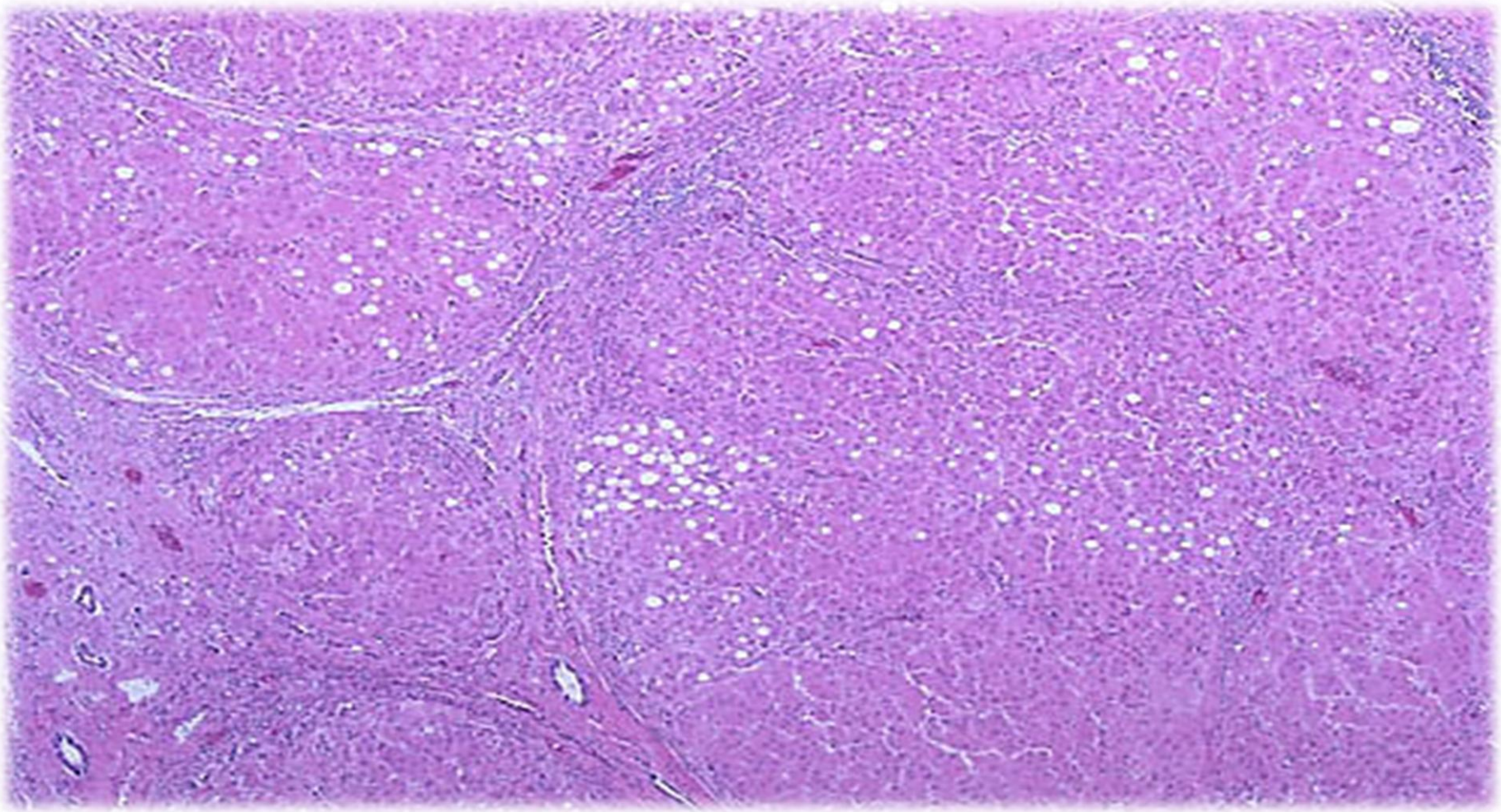
- **Hepatitis B Virus:** "ground-glass" hepatocytes, "sanded" nuclei
- **Hepatitis C Virus:** bile duct damage, lymphoid aggregate formation

- ***Cirrhosis: The end-stage outcome***

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.



2- *Autoimmune hepatitis*

Is a chronic hepatitis with histologic features, resembles chronic viral hepatitis

This disease may run an indolent **(slow and little)** or severe course

Clinical features:

- **Female predominance**, particularly in young and perimenopausal women.

Diagnosis:

The absence of viral serologic markers

- Elevated serum IgG **(increases in chronic diseases)** 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

Autoimmune hepatitis cont'd

- Associated with other autoimmune diseases (e.g. Rheumatoid arthritis, Sjogren's syndrome etc).

- 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.

- Treatment:
  include immunosuppressive therapy, and liver transplantation.

3- Intra-hepatic Biliary Tract Disease

Three disorders of intra-hepatic bile ducts:

A. secondary biliary cirrhosis
B. primary biliary cirrhosis
C. primary sclerosing cholangitis

A- Secondary biliary cirrhosis

- Prolonged obstruction of the extrahepatic biliary tree results in profound alteration of the liver itself.
- 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 (congenital disease), cystic fibrosis, choledochal cysts (a cystic anomaly of the extrahepatic biliary tree).
  All are congenital anomalies

B- Primary biliary cirrhosis

- Primary biliary cirrhosis 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.
- *The primary feature of this disease is a nonsuppurative (no pus), inflammatory destruction of medium-sized intrahepatic bile ducts.*
- Cirrhosis develops only after many years.

Primary biliary cirrhosis cont'd

- Most affected: middle-aged women,
- female:male predominance (6:1).
- **Pathogenesis:** autoimmune etiology. (not as 2ndary)

Clinical features:

- pruritus (itching)
- Jaundice
- Hepatomegaly
- Xanthomas (lipoma) and xanthelasmas arise owing to cholesterol retention
- Over a period of time patients develop portal hypertension and hepatic encephalopathy.
- Serum alkaline phosphatase and cholesterol are elevated
- hyperbilirubinemia is a late development
- 90% of patients have circulating "antimitochrondrial antibodies."

Primary biliary cirrhosis cont'd

Morphology:

- **During the pre-cirrhotic 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 duct proliferation
  -inflammation, and necrosis of the adjacent peri-portal hepatic parenchyma.
- **Over years to decades:**
  -relentless portal tract scarring
  -bridging fibrosis → cirrhosis.

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

Primary biliary cirrhosis cont'd

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 (esp anti-mitochondrial antibody - AMA)
Important pathologic findings before cirrhosis develops	Dense lymphocytic infiltrate in portal tracts with granulomatous destruction of bile ducts

C- Primary sclerosing cholangitis

- *Primary sclerosing cholangitis is characterized by inflammation and obliterative fibrosis* ***of intrahepatic and extrahepatic bile ducts****, with dilation of preserved segments.*
- 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,
- males predominate 2:1
- **Pathogenesis:** unknown.

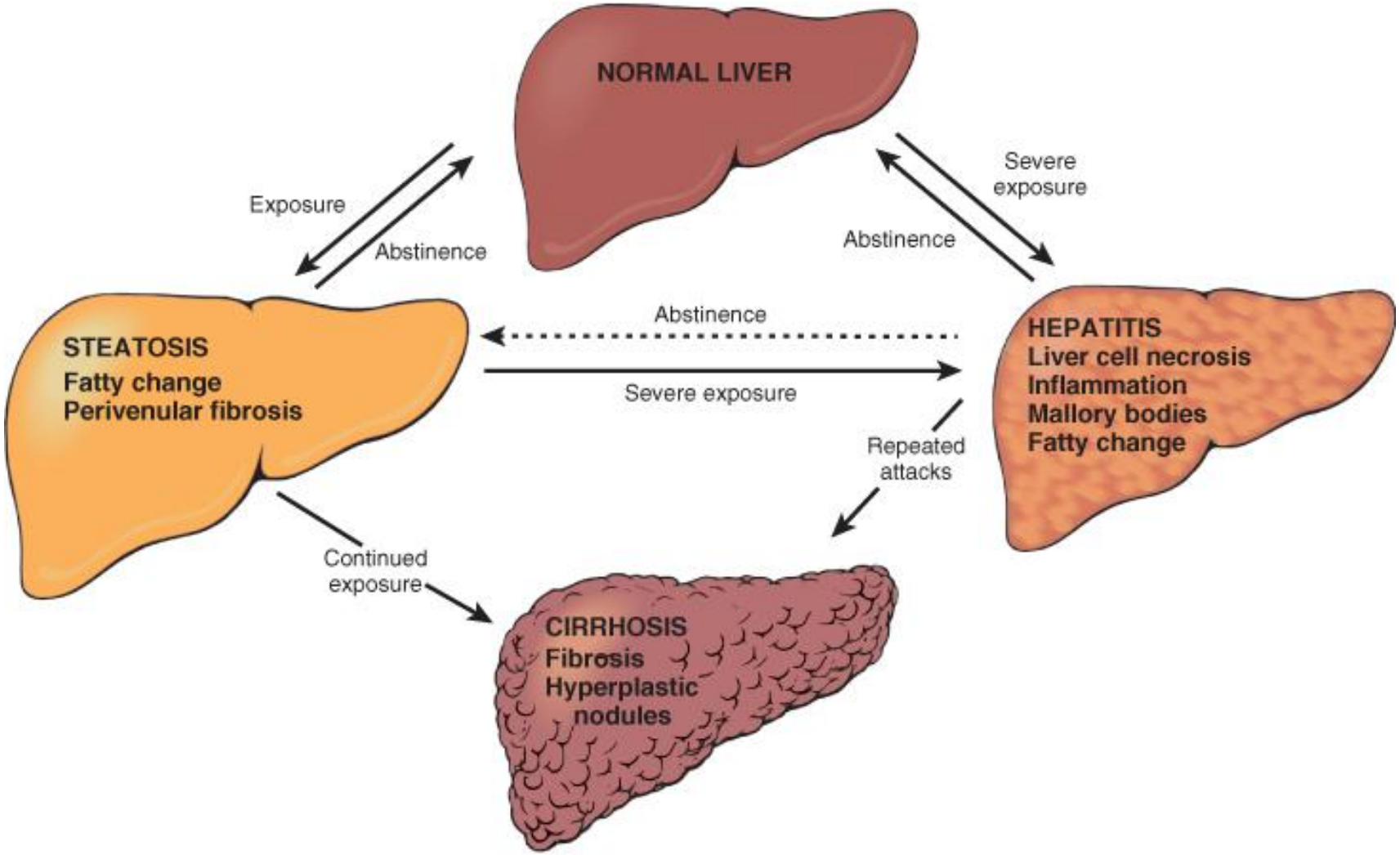
Primary sclerosing cholangitis Morphology

- **fibrosing cholangitis of bile ducts, with:**
  -lymphocytic infiltrate
  -progressive atrophy of the bile duct epithelium
  -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

Primary sclerosing cholangitis cont'd

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

4- Alcoholic liver disease



Alcoholic liver disease: marked by fat deposition