LIVER CIRRHOSIS

GASTROINTESTINAL BLOCK

PATHOLOGY

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Liver cirrhosis

- Define Cirrhosis.
- Recognize the types of cirrhosis.
- Recognize the major causes and the pathogenetic mechanisms leading to cirrhosis.
- Describe the pathological findings in cirrhotic livers.

Cirrhosis

- Cirrhosis is among the top 10 causes of death in the Western world. The chief worldwide contributors are alcohol abuse and viral hepatitis. Other causes include biliary disease, and iron overload. Cirrhosis is the end-stage of chronic liver disease

Define Cirrhosis.

Cirrhosis

Irreversible diffuse fibrosis of the liver with formation of regenerative nodules

Cirrhosis is defined by three characteristics

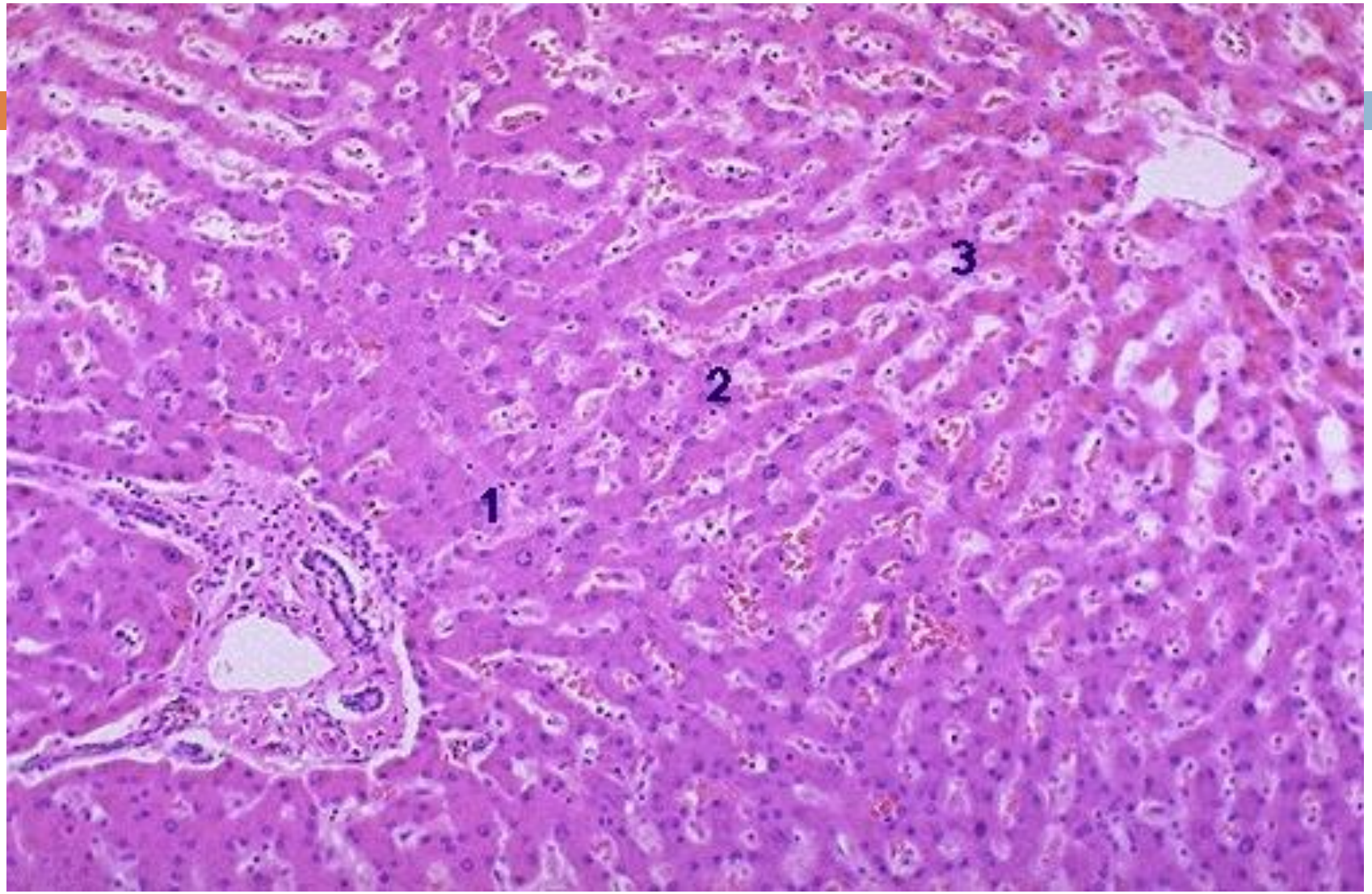
1) *Fibrosis* in the form of delicate bands or broad scars/septa

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

Hepatocyte reaction to injury

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

Lack of portal triads and sinusoids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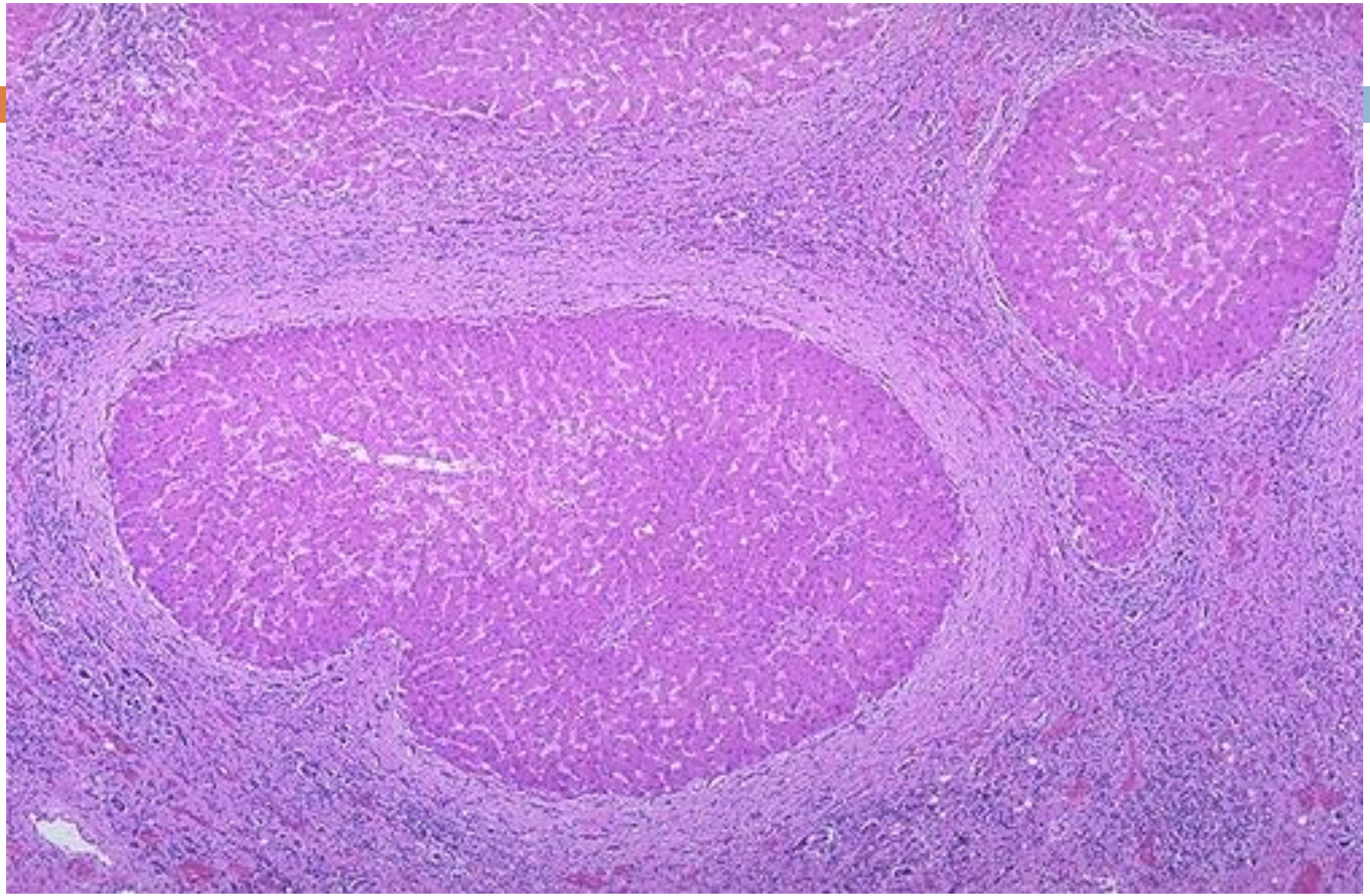


Define Cirrhosis.

Fibrosis

- *Fibrosis* in the form of delicate bands or broad scars/septa
- *Fibrosis is the key feature of progressive damage to the liver.* Once cirrhosis has developed, reversal is thought to be rare.

Define Cirrhosis.

Liver cirrhosis

- *As a result of fibrosis, vascular architecture is reorganized* due to parenchymal damage and scarring, with the formation of abnormal interconnections between vascular inflow and hepatic vein outflow channels.

Compress sinusoids and central venules
a. Intrasinusoidal hypertension
b. Reduction in the number of functional sinusoids
c. Increase in hydrostatic pressure in portal vein

Recognize the types of cirrhosis.

Classifiation of cirrhosis

- The classification is based on:

1) the size of regenerative nodules

Type	Nodule size
Micronodular	≤3 mm
Macronodular	3 mm–2 cm
Mixed micro- and macronodular	Mixture of small and large

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

2) the underlying etiology

Classifiation 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%

Classifiation of cirrhosis

Infrequent 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,").
- In some cases there is no cause and these are referred to as *cryptogenic cirrhosis*.

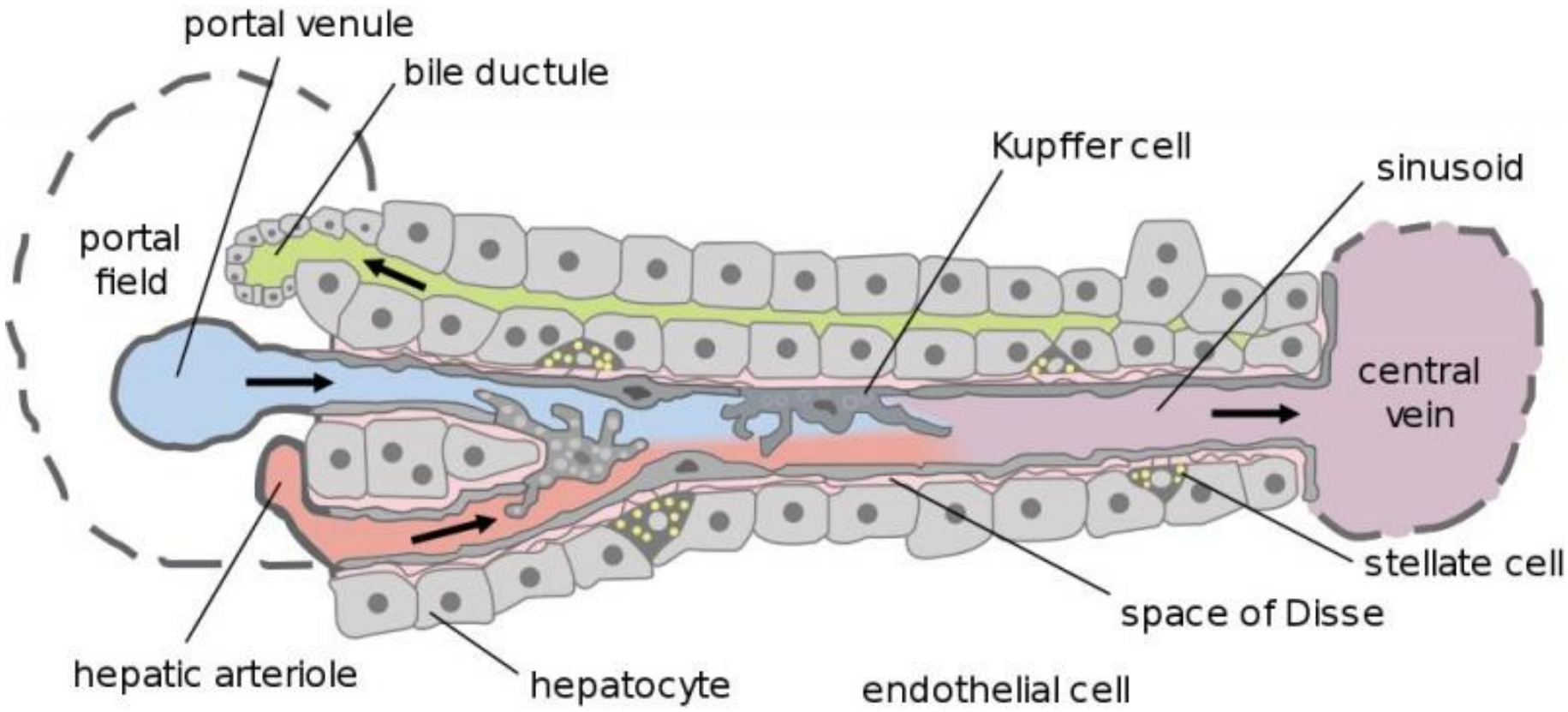
Recognize the types of cirrhosis.

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

Pathogenesis of cirrhosis

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

Pathogenesis of cirrhosis

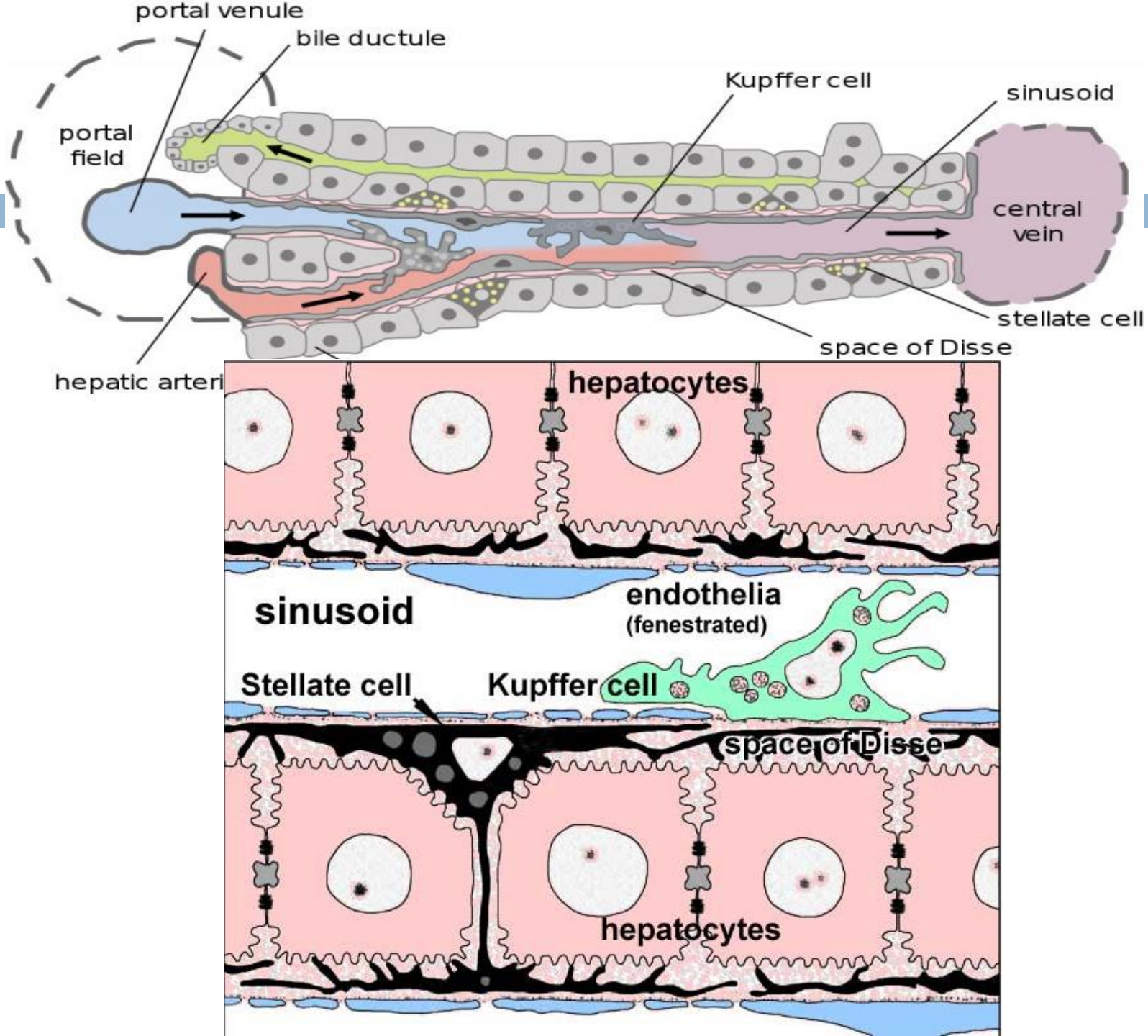


Pathogenesis of cirrhosis

- In cirrhosis, types I and III collagen 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).

Pathogenesis of cirrhosis

- 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.


portal venule
bile ductule
Kupffer cell
sinusoid
portal field
central vein
stellate cell
space of Disse
hepatic arteri
hepatocytes
sinusoid
endothelia
(fenestrated)
Stellate cell
Kupffer cell
space of Disse
hepatocytes

Pathogenesis of cirrhosis

Collagen synthesis is stimulated by

- Chronic inflammation, with production of inflammatory cytokines.
- Cytokine production by activated 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

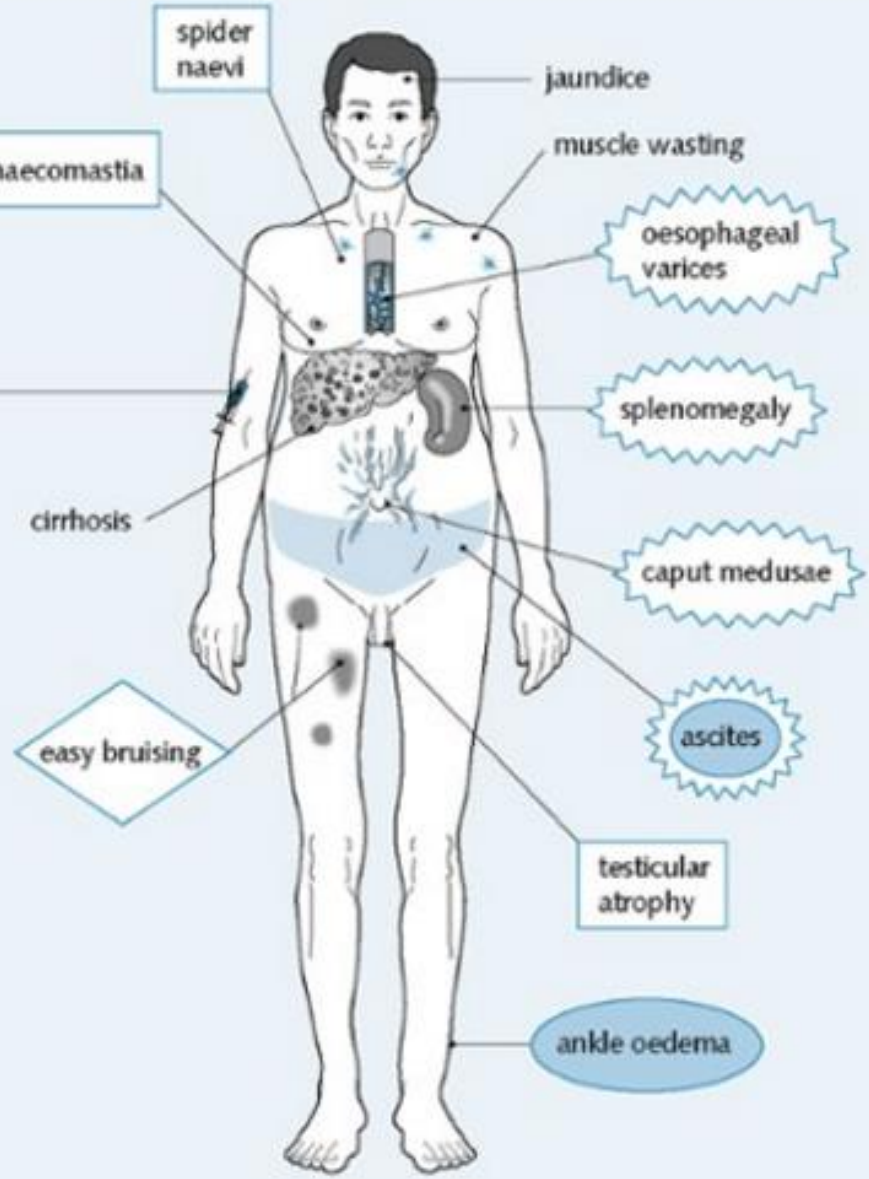
Clinical Features

- All forms of cirrhosis may be clinically silent.
- When symptomatic they lead to nonspecific clinical manifestations: anorexia, weight loss, weakness, osteoporosis, and, in advanced disease, frank debilitation.
- Incipient or overt hepatic failure may develop.

Clinical Features

Biochemical abnormalities:

- Alkaline phosphatase: may be greatly elevated if the cause is biliary obstruction.
- AST and ALT: transaminase levels are elevated, proportional to the activity of liver cell destruction.
- Bilirubin: elevated levels, which may be very high in cases caused by biliary obstruction.
- Serum albumin: low, as a result of failure of synthesis.
- Prothrombin time: prolonged because of failure of synthesis of coagulation factors.



= impaired metabolism of endogenous oestrogens

= low serum albumin

= portal hypertension

= failure to synthesize clotting factors

Clinical Features

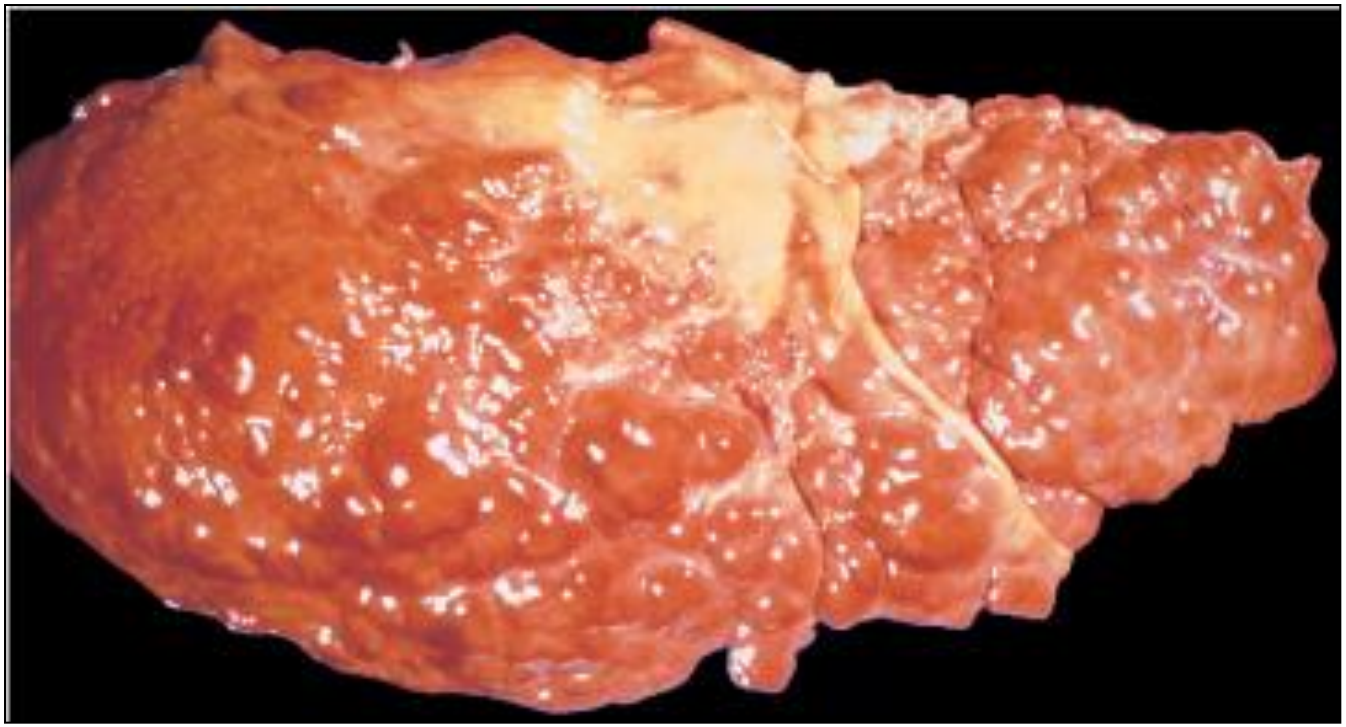
The ultimate mechanism of most cirrhotic deaths are:

(1) Progressive liver failure

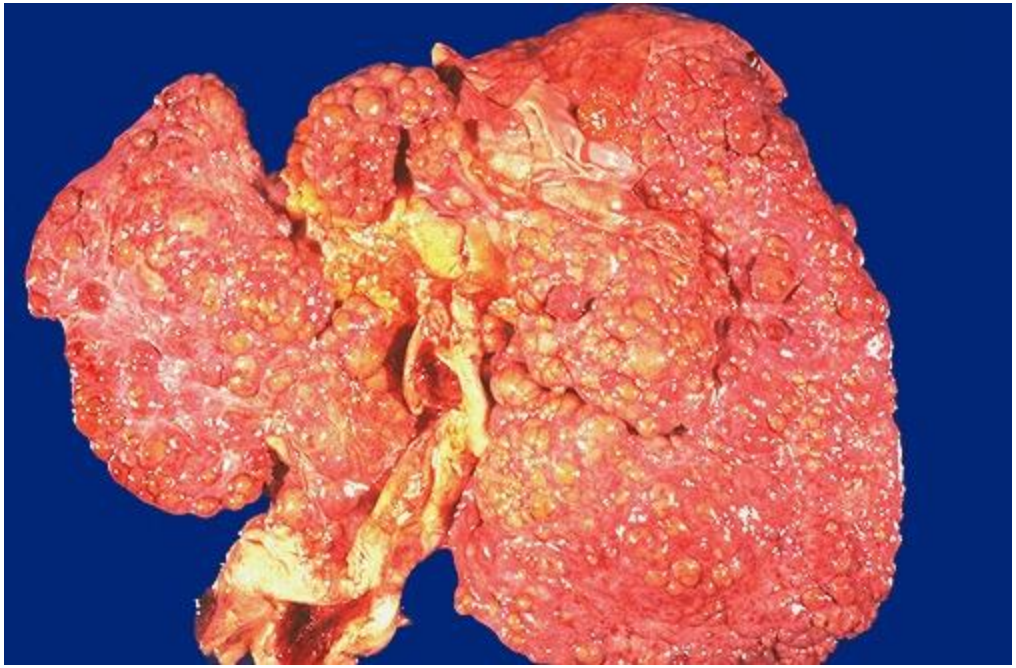
(2) A complication related to portal hypertension

(3) The development of hepatocellular carcinoma

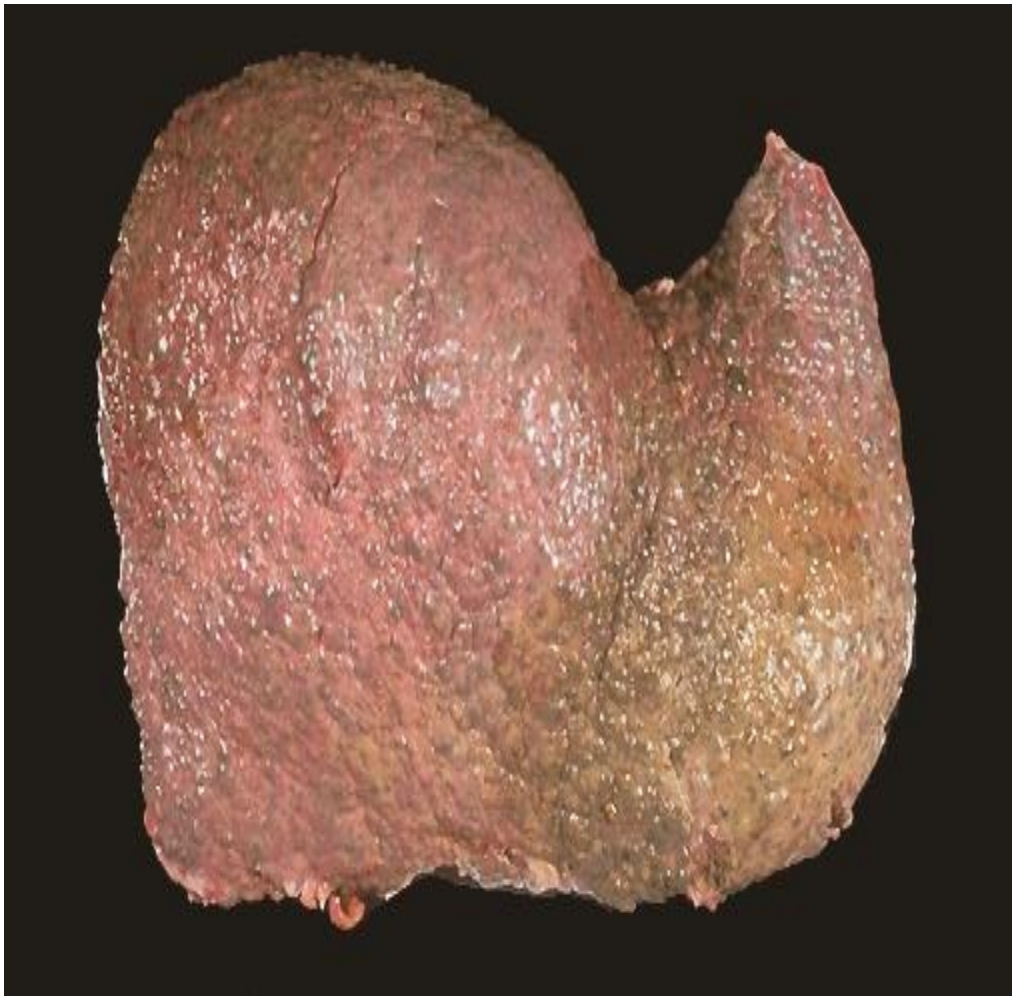
Liver Cirrhosis



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

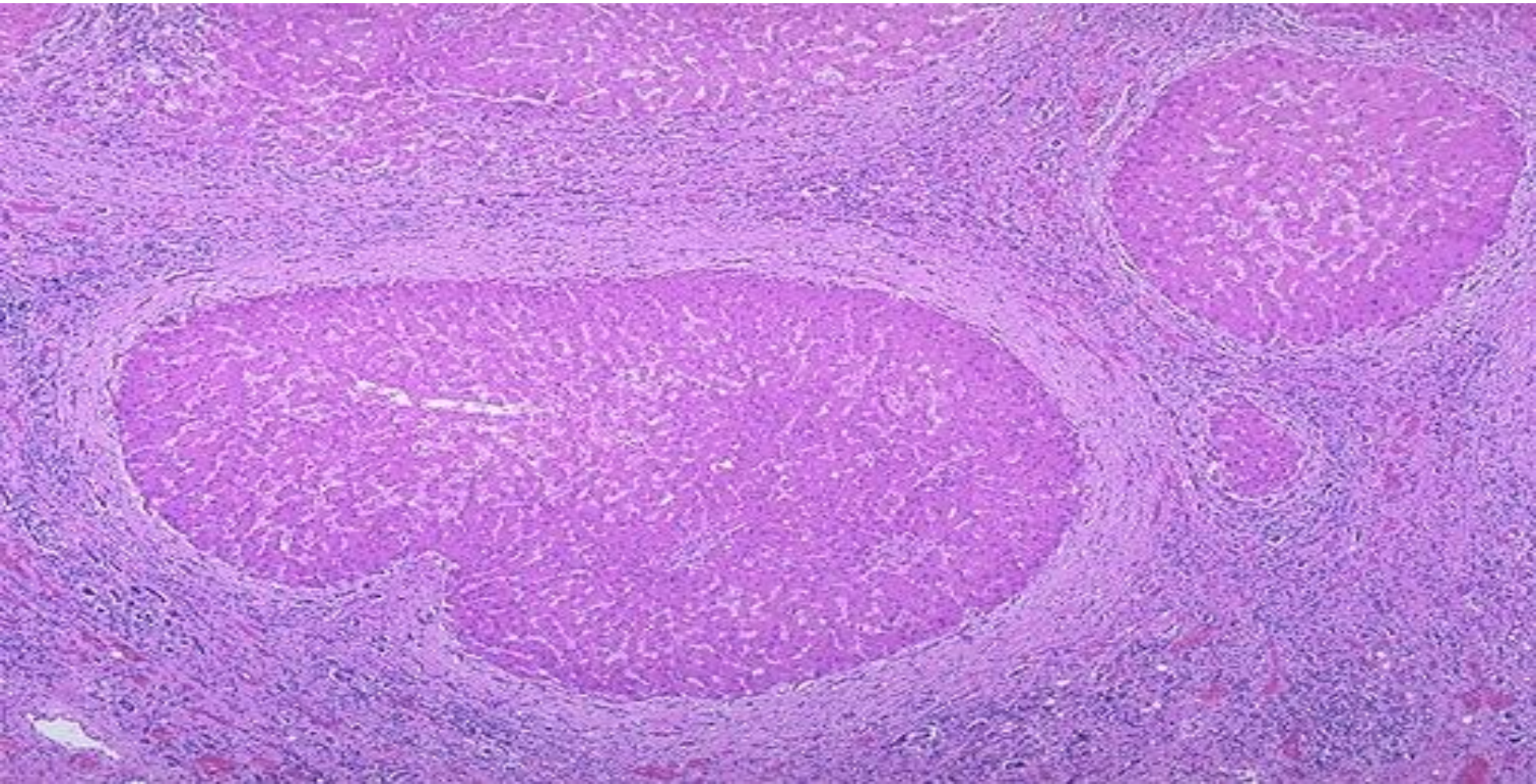


Micronodular cirrhosis: The regenerative nodules are quite small, averaging less than 3 mm in size. Chronic alcoholism.



Regenerative nodules of hepatocytes are surrounded by fibrous connective tissue that bridges between portal tracts. Collagenous

tissue , lymphocytes as well as a proliferation of bile ducts.



Chronic 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*

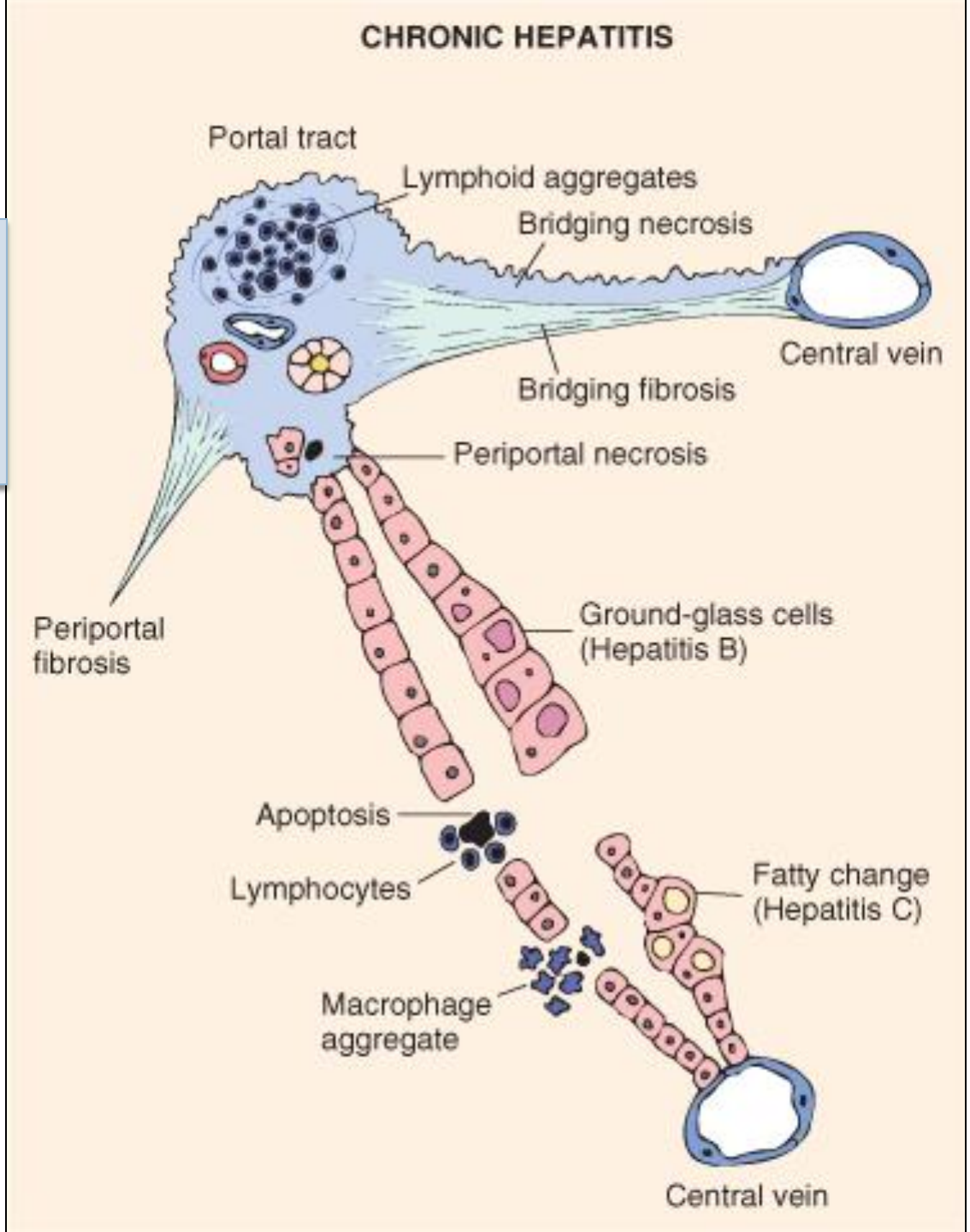
  -Spillover into adjacent parenchyma, with necrosis of hepatocytes ("interface hepatitis"), *or*

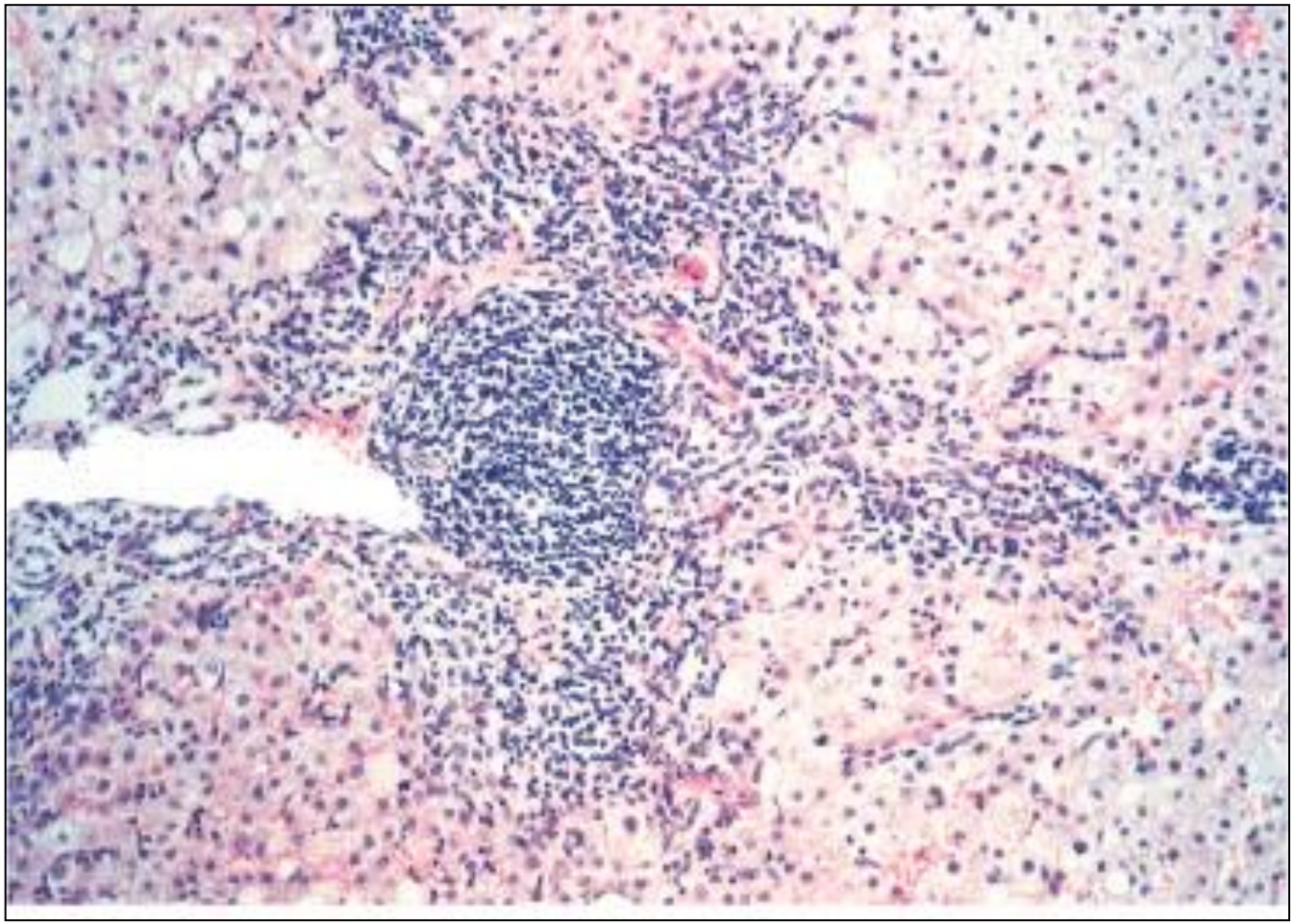
  -Bridging inflammation and necrosis
- Fibrosis:

  -continued loss of hepatocytes results in fibrous septa formation which ultimately leads to cirrhosis
- HBV: "ground-glass" hepatocytes, "sanded" nuclei
- HCV: bile duct damage, lymphoid aggregate formation
- ***Cirrhosis: The end-stage outcome***

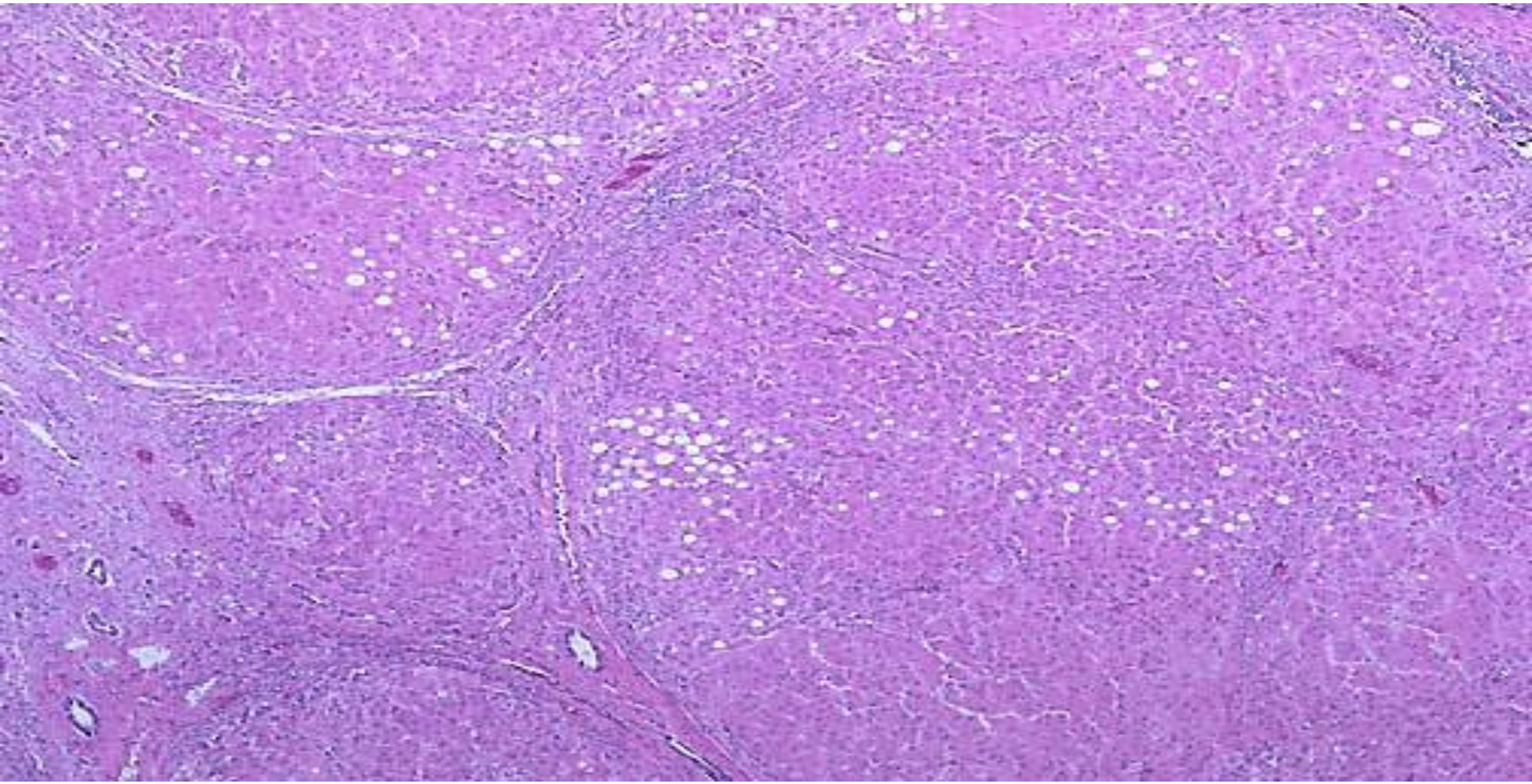
Chronic Hepatitis :

1. Portal tract Inflammation
2. Bridging inflammation and necrosis
3. Hepatocyte injury

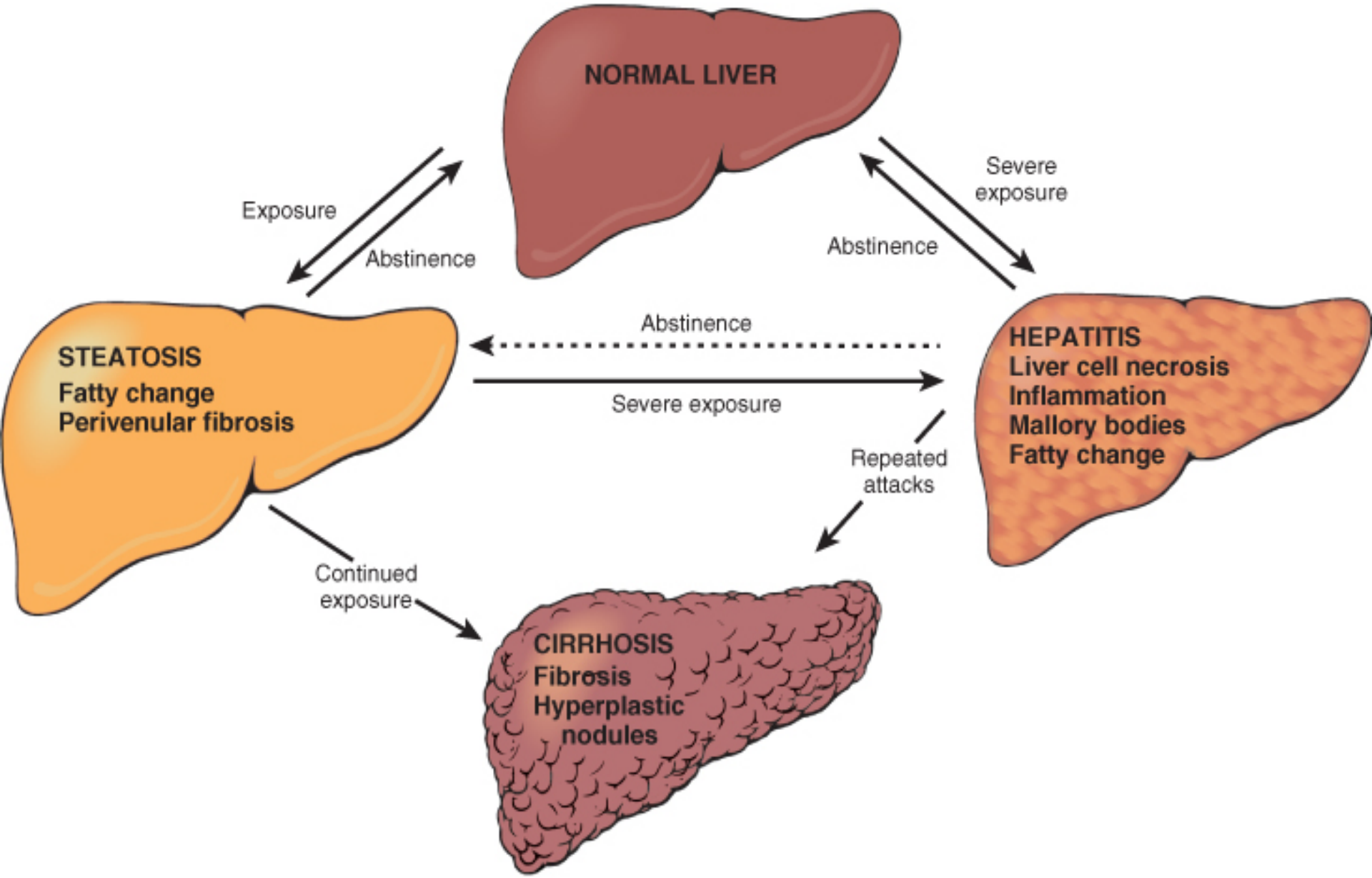




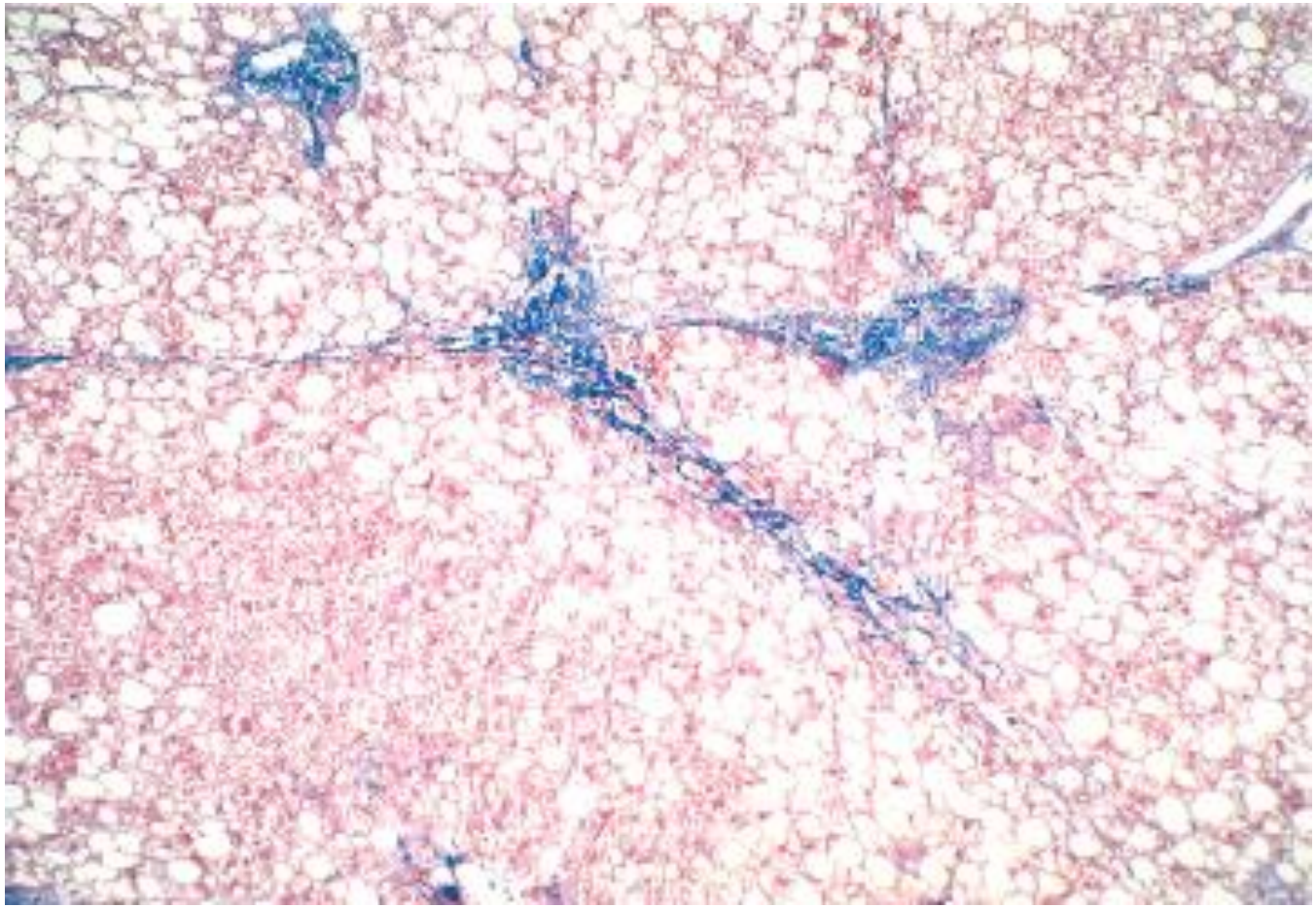
Viral hepatitis C which is at a high stage with extensive fibrosis and progression to macronodular cirrhosis, as evidenced by the large regenerative nodule at the center right.



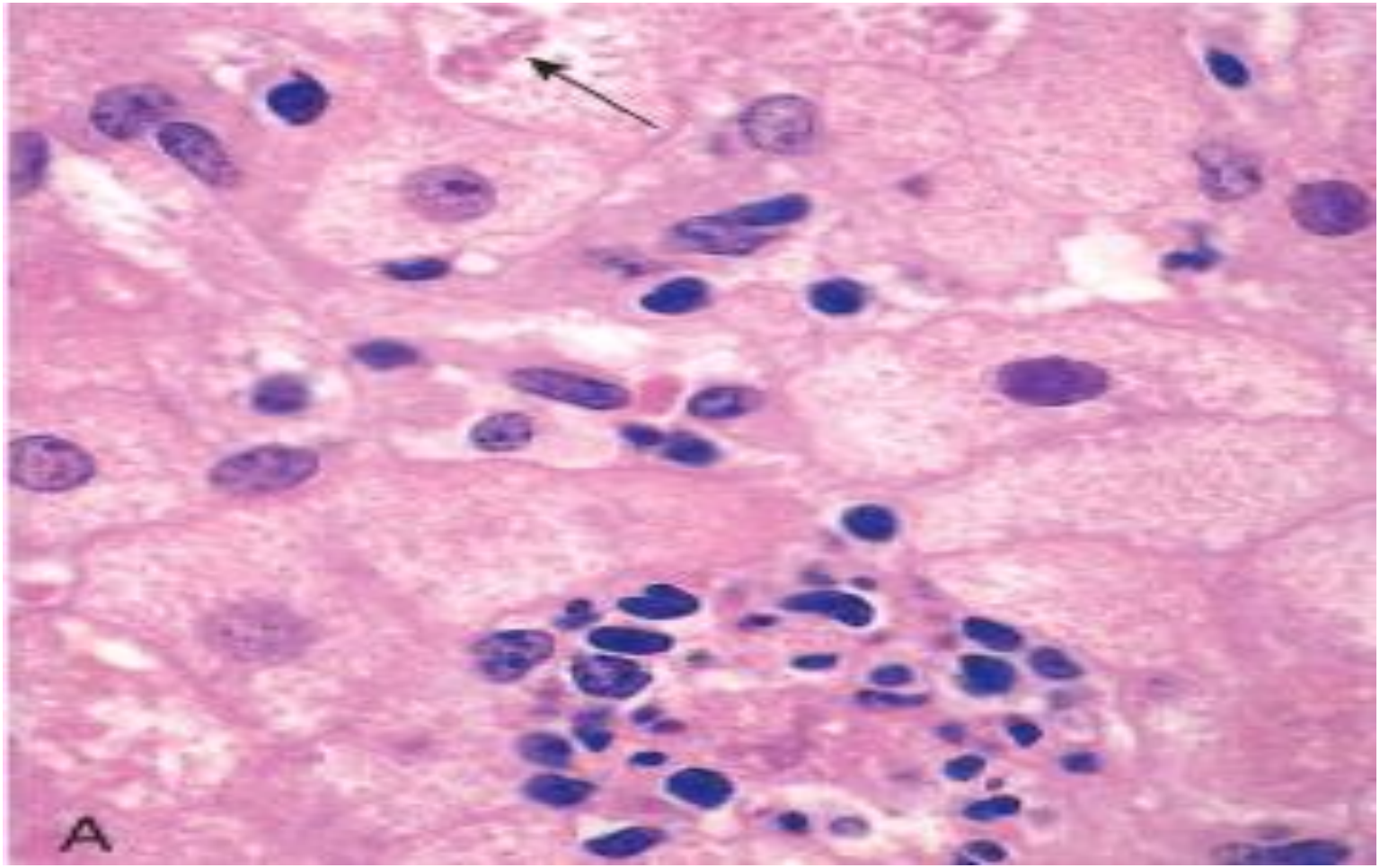
Alcoholic liver disease



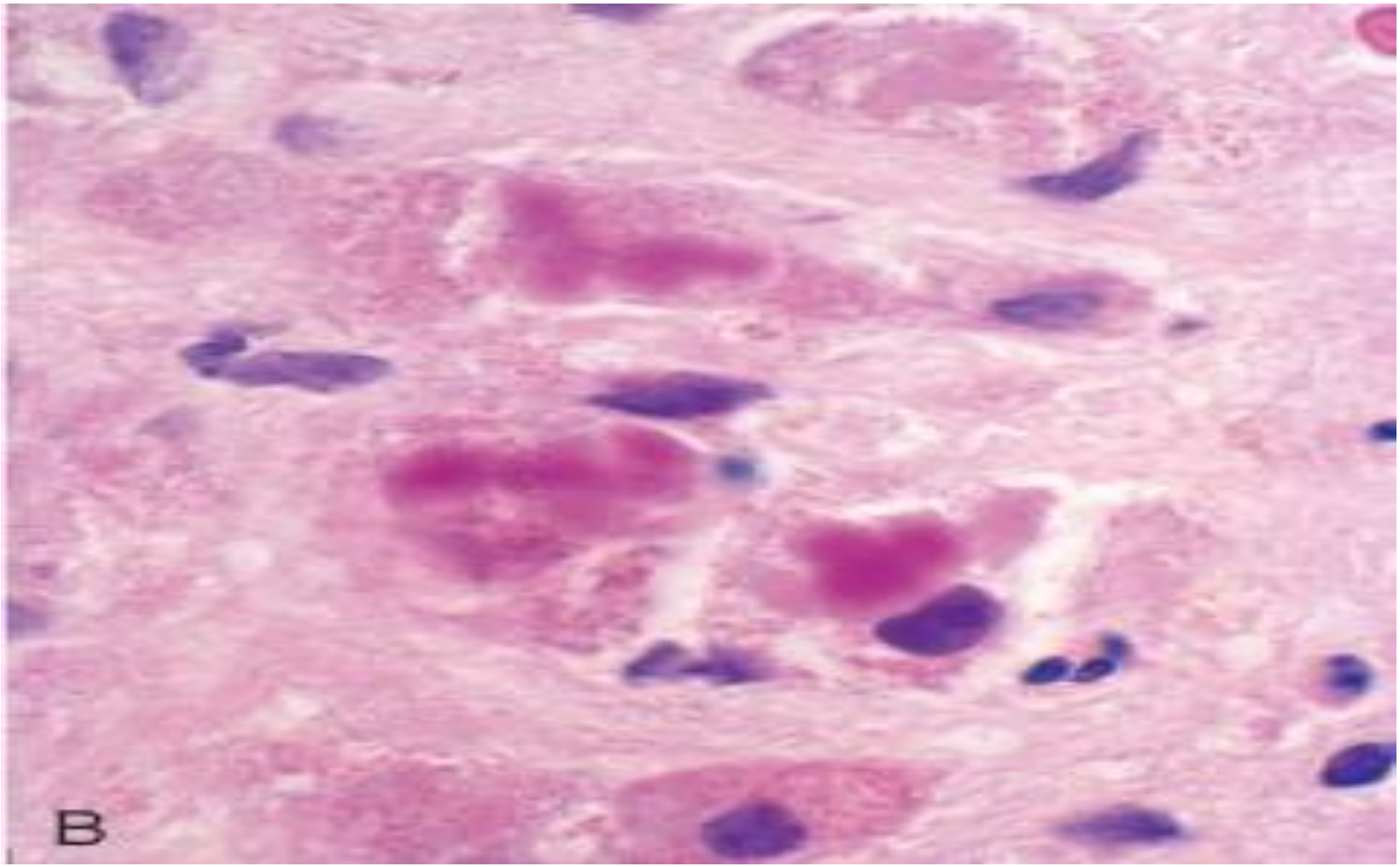
Alcoholic liver disease



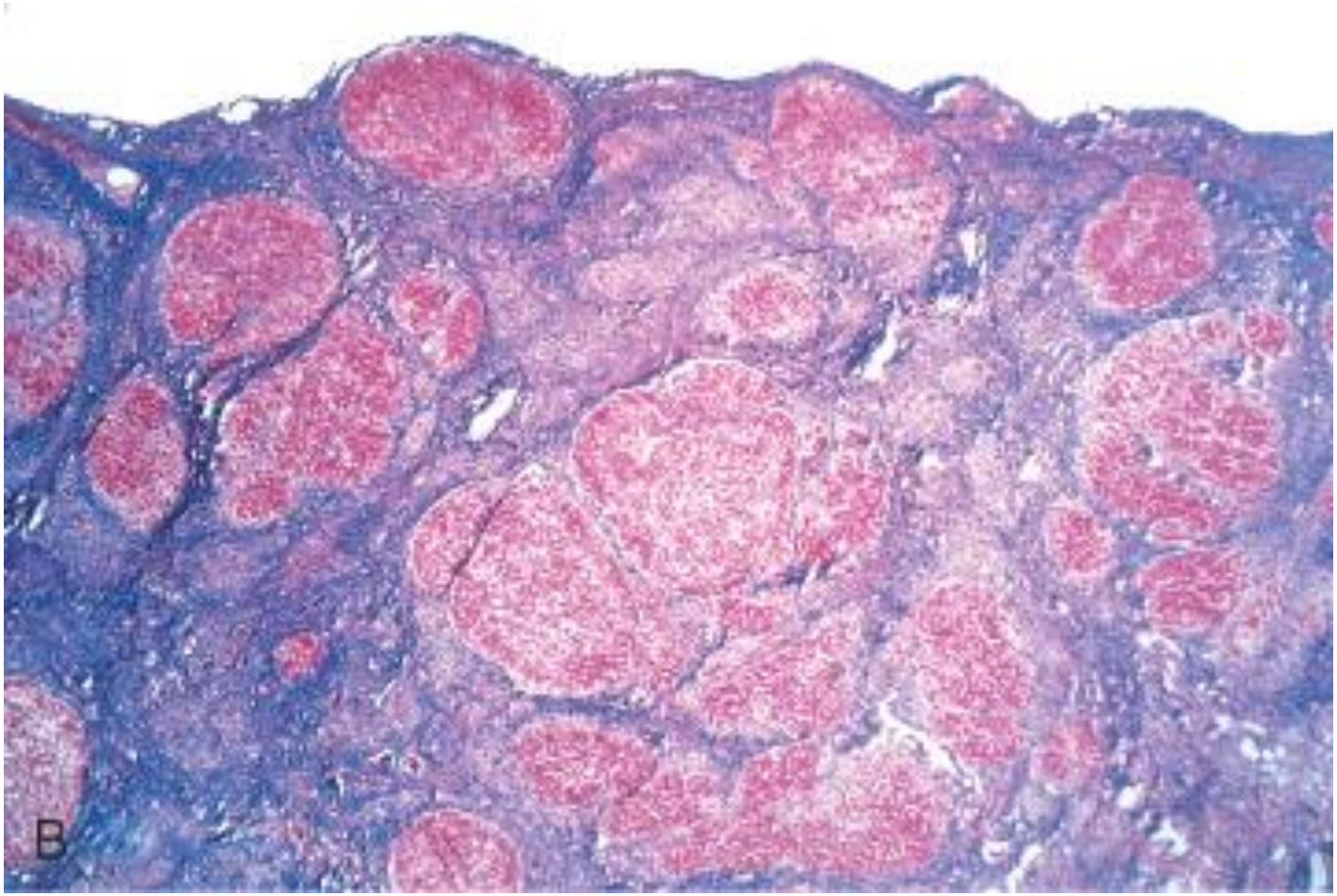
Alcoholic liver disease



Alcoholic liver disease



Alcoholic liver disease



Complications associated with cirrhosis: 1. Hepatic failure (end-point of progressive damage)

- Hypoalbuminemia from decreased synthesis of albumin
  - ✓ Produces dependent pitting edema and ascites due to a decrease in plasma oncotic pressure
- Hepatic encephalopathy
  - ✓ Reversible metabolic disorder results from:

(1) Increase in aromatic amino acids (e.g., phenylalanine, tyrosine, tryptophan) converted into false neurotransmitters (e.g., γ-aminobutyric acid)

(2) Increase in serum ammonia: Due to a defective urea cycle that cannot metabolize ammonia

Complications associated with cirrhosis: 1. Hepatic failure (end-point of progressive damage)

Variable coagulation defects

(1) Due to inability to synthesize coagulation factors, a patient can have a bleeding diathesis

(2) Due to decreased synthesis of proteins, a patient can be hypercoagulable.

Complications associated with cirrhosis: 2. Portal hypertension

- Pathogenesis

  1)Resistance to intrahepatic blood flow due to intrasinusoidal hypertension

  2)Anastomoses between portal vein tributaries and the arterial system

- Complications

1) Ascites

2) Congestive splenomegaly

3) Esophageal varices

4) Hemorrhoids

5) Periumbilical venous collaterals

Complications associated with cirrhosis: 3. Hepatocellular carcinoma