Pathology Lectures

Gastro-esophageal reflux disease

Peptic Ulcer Disease

Pancreatitis

Diarrhea

Malabsorption

Inflammatory bowel disease-1

Inflammatory bowel disease-2

Colonic polyps and carcinoma-1

Colonic polyps and carcinoma-2

Cirrhosis

Cirrhosis

Cholecystitis

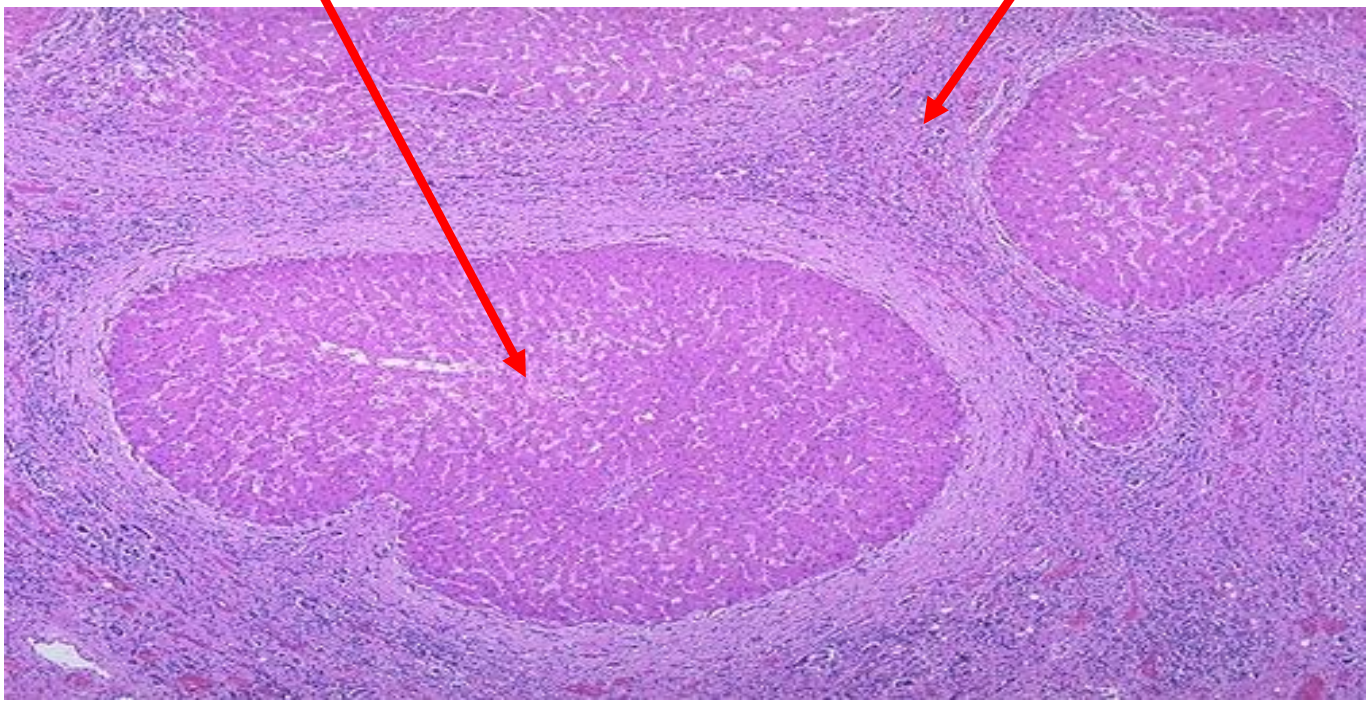
Tumors of liver and pancreas

Liver cirrhosis

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.

- Defined as a *diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules*



Classifiation of cirrhosis

- The classification is based on the underlying etiology.

- Many forms of cirrhosis (particularly alcoholic cirrhosis) are initially micronodular (less than 3 mm), but there is a tendency for nodules to increase in size with time.

Classifiation of cirrhosis based on causes

1. Alcoholic liver disease 60% to 70%
2. Viral hepatitis 10%
3. Biliary diseases 5% to 10%
4. Primary hemochromatosis 5%
5. Wilson disease Rare
6. α1-Antitrypsin deficiency Rare
7. Cryptogenic cirrhosis 10% to 15%

Classifiation of cirrhosis

Infrequent types of cirrhosis also include

1. The cirrhosis developing in infants and children with galactosemia and tyrosinosis

2. Drug-induced cirrhosis.

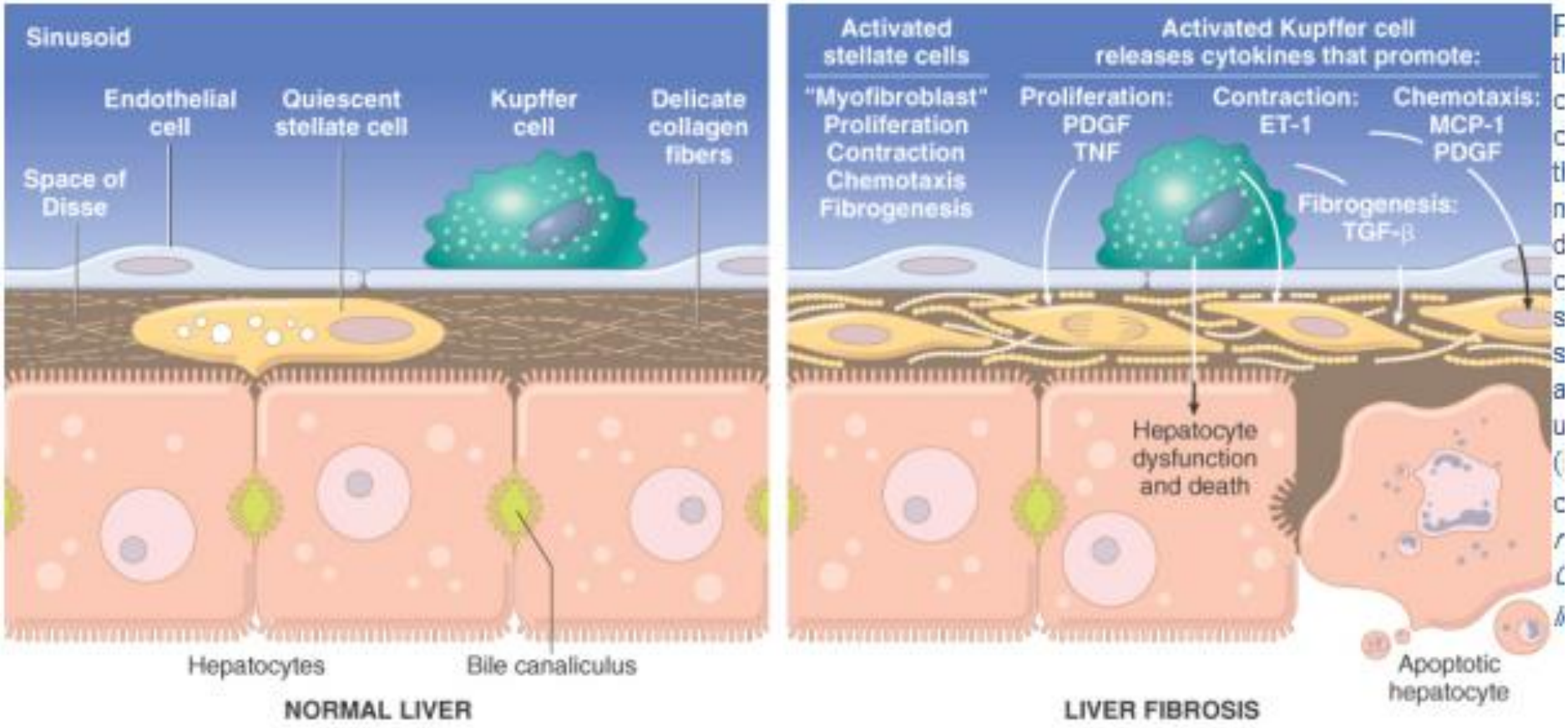
3. Severe fibrosis can occur in the setting of cardiac disease (sometimes called "cardiac cirrhosis,").

4. In some cases there is no cause and these are referred to as *cryptogenic cirrhosis.*

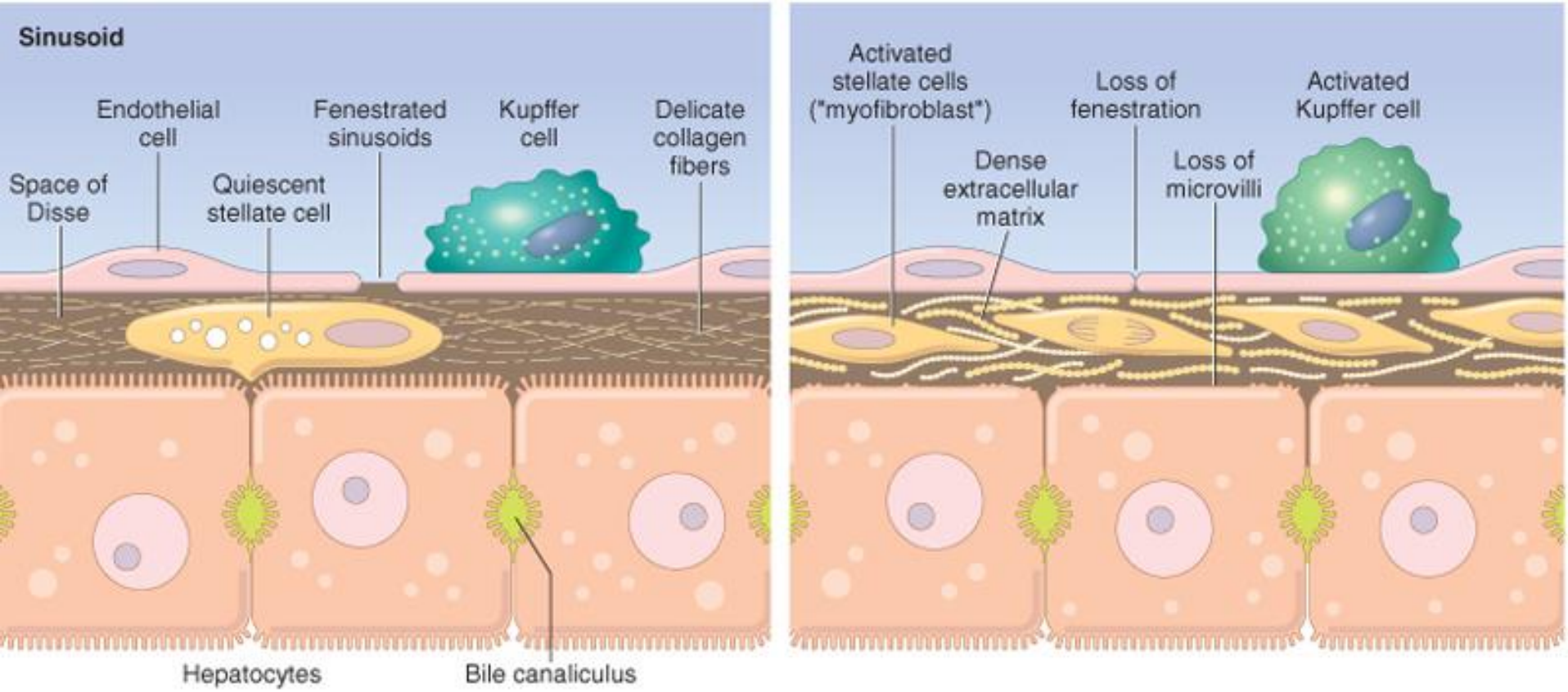
Once cirrhosis is established, it is usually impossible to establish an etiologic diagnosis on morphologic grounds alone

Pathogenesis of cirrhosis

types I and III collagen



Kupffer cell activation leads to secretion of multiple cytokines;
These cytokines "activate" stellate cells, and acquire a myofibroblastic state a major source of collagen in cirrhosis.
Kupffer cells also are a major source of TNF released into the system circulation.



NORMAL LIVER **LIVER FIBROSIS**

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.

Pathogenesis of cirrhosis

Collagen synthesis is stimulated by

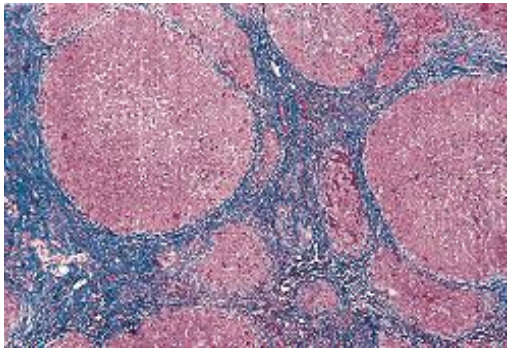
- Chronic inflammation, with production of inflammatory cytokines.
- Cytokine production by activated endogenous cells (Kupffer cells, endothelial cells, hepatocytes, and bile duct epithelial cells).

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.

> 3 mm

< 3 mm



Chronic Hepatitis, morphology

Some changes are shared with acute hepatitis.

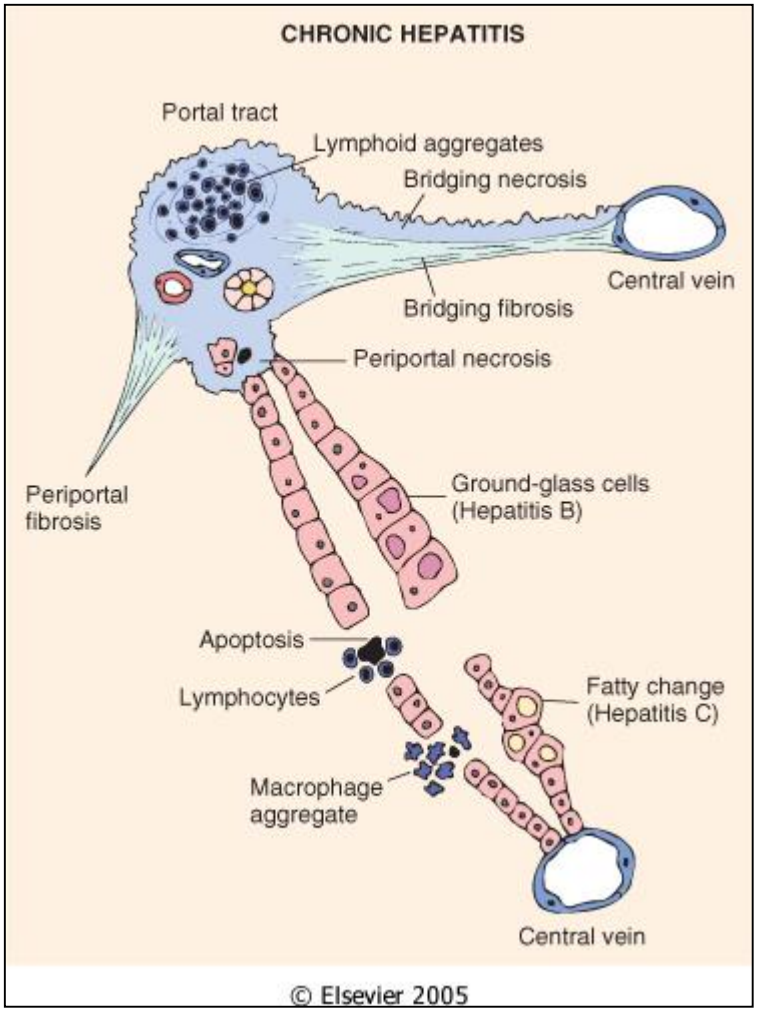
- Hepatocyte injury, necrosis, and regeneration
- **Portal tract Inflammation**:

  -Confined to portal tracts, *or*

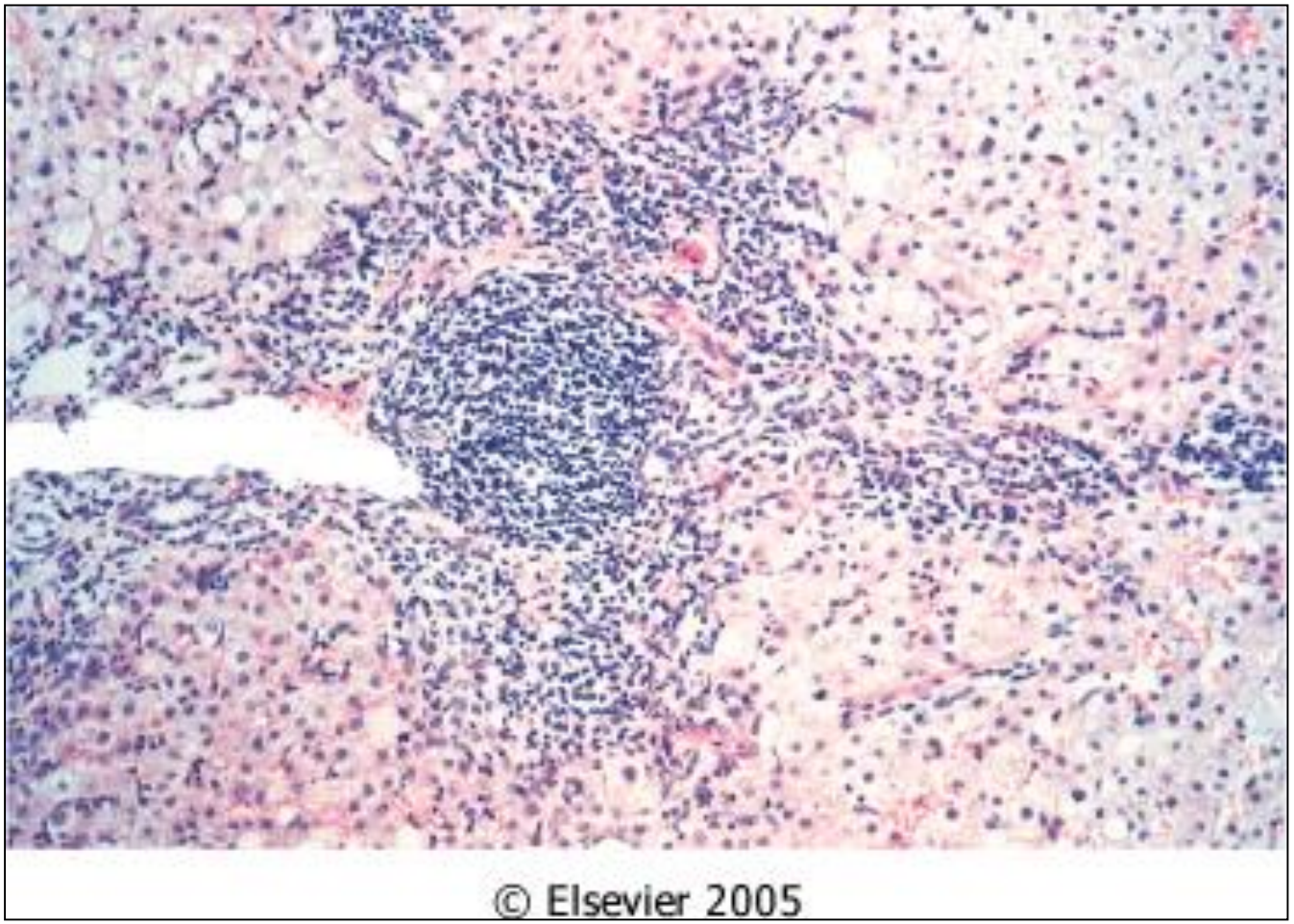
  -Spillover into adjacent parenchyma, with necrosis of hepatocytes ("interface hepatitis"), *or*

  -Bridging inflammation and necrosis
- **Fibrosis:**

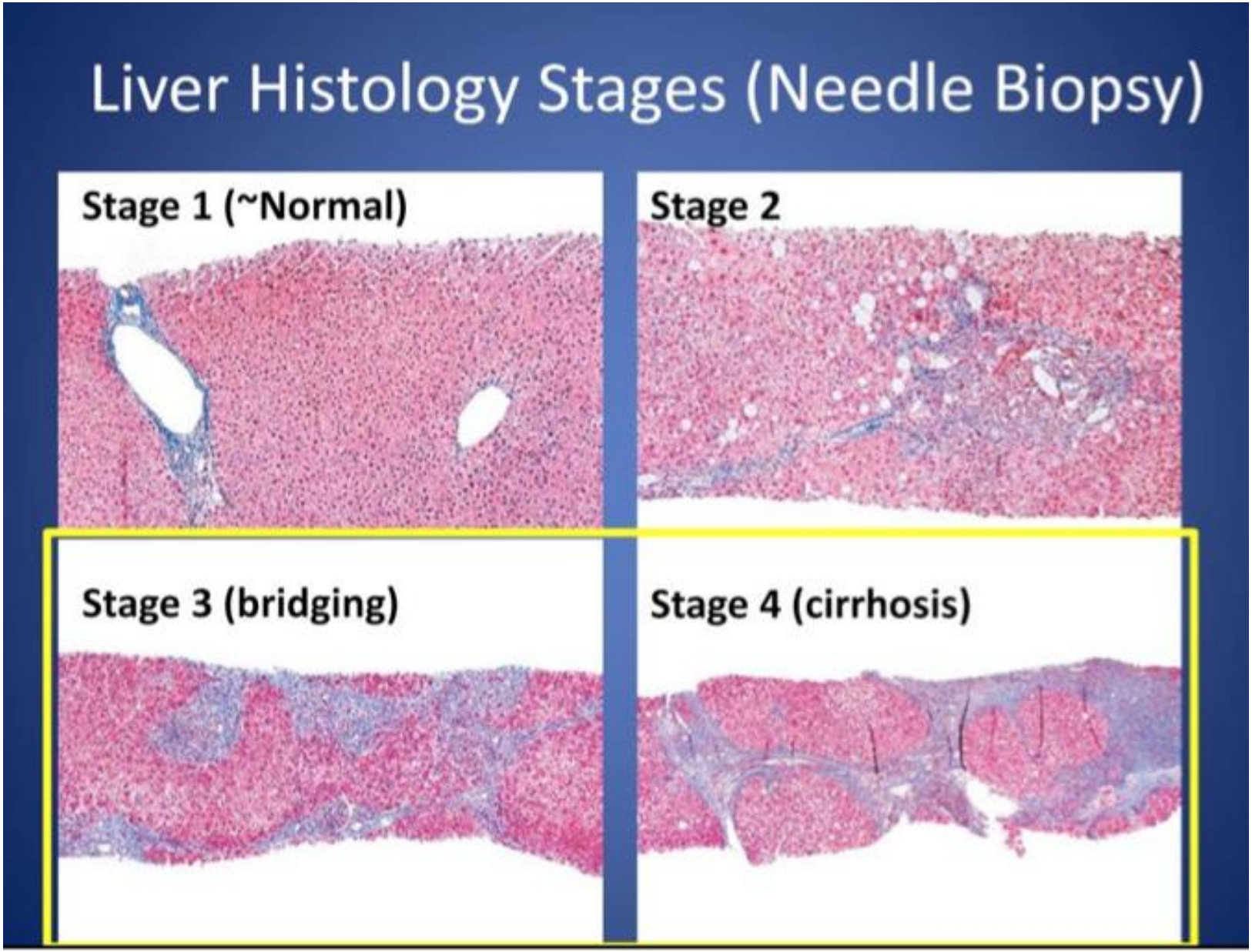
  -continued loss of hepatocytes results in fibrous septa formation which ultimately leads to cirrhosis
- HBV: "ground-glass" hepatocytes, "sanded" nuclei
- HCV: bile duct damage, lymphoid aggregate formation
- ***Cirrhosis: The end-stage outcome***



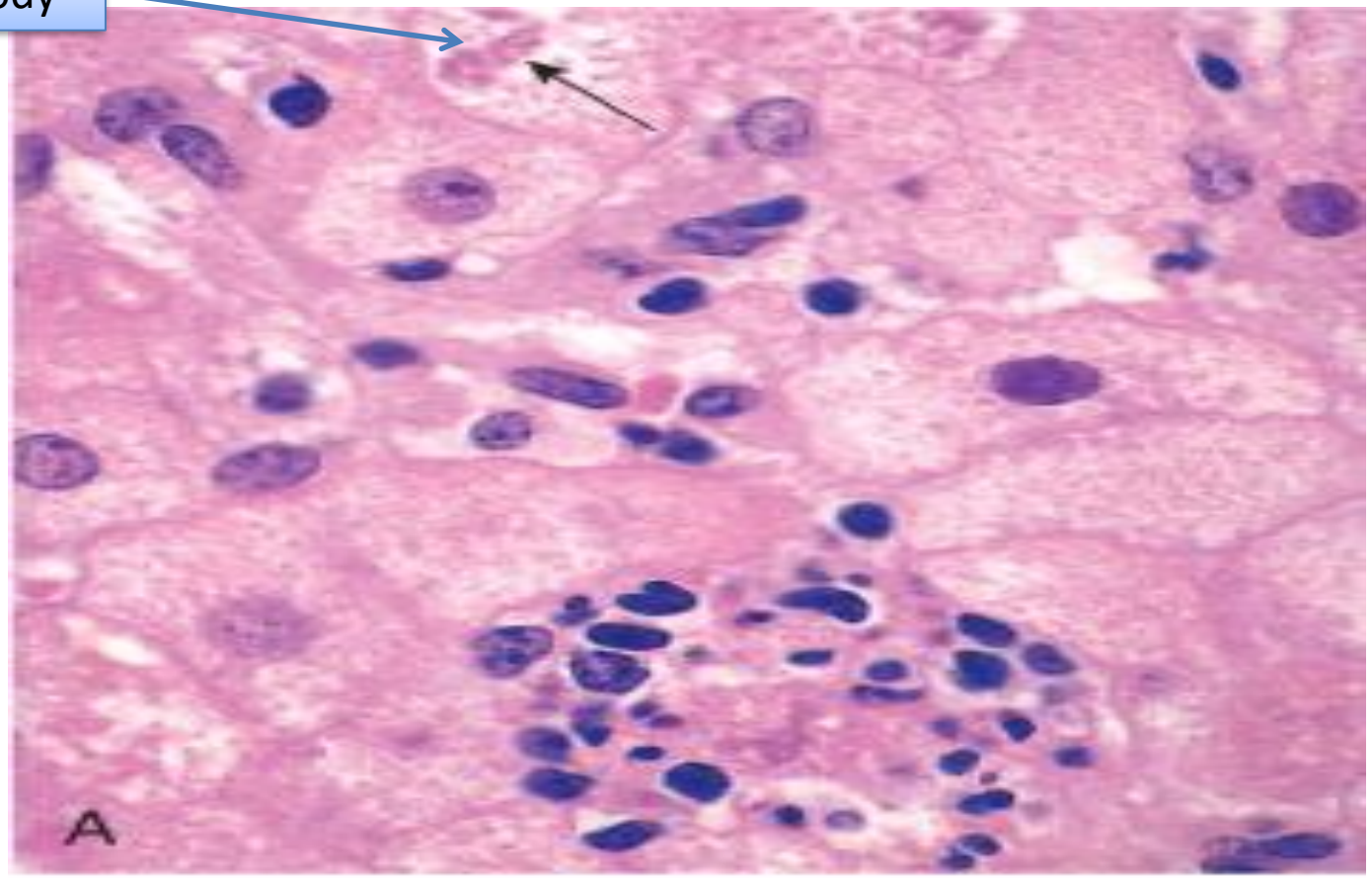
Lymphocytic infiltration of portal tract, a feature of chronic hepatitis



Stages of liver fibrosis



Alcoholic liver disease



OBJCTIVES

- **Define Cirrhosis.**
  - *End result of chronic liver diseases ……abnormal nodules + fibrosis*

- **Recognize the types of cirrhosis.**
  - Micronodular and macronodular …… not important
  - According to eotiology……..alcoholic, viral, biliary, inhireted ……..cryptogenic

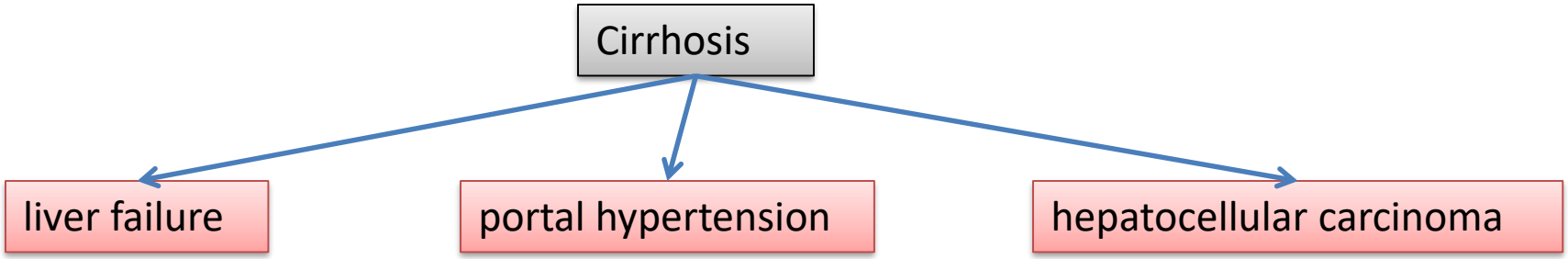
- **Recognize the major causes and the pathogenetic mechanisms.**
- Chronic inflammation…… → cytokines…… → stellate cells is The major source of collagen….fibrosis

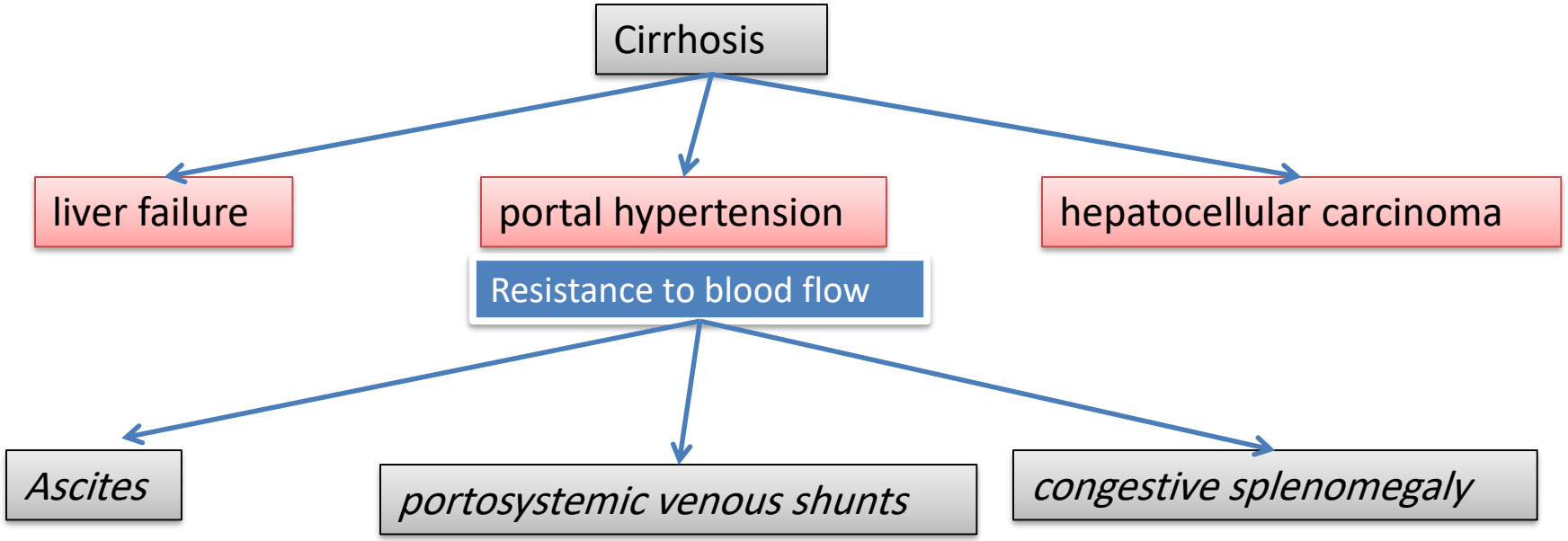
- **Describe the pathological findings in cirrhotic livers.**
- All types…….fibrosis and nodules
- Depend on the cause…
- Viral ……. ground-glass in hepatitis B
- Alcoholic ……. Mallory body

Complications of liver cirrhosis

Complications of liver cirrhosis

- Recognize the major complications of cirrhosis.
- Understand the pathogenetic mechanisms underlying the occurrence of the complications.
- Recognize the clinical features inherent to the above mentioned complications.
- Describe the pathological findings of the different complications.


Cirrhosis
liver failure
portal hypertension
hepatocellular carcinoma


Cirrhosis
liver failure
portal hypertension
hepatocellular carcinoma
Resistance to blood flow
Ascites
portosystemic venous shunts
congestive splenomegaly

Cirrhosis

liver failure

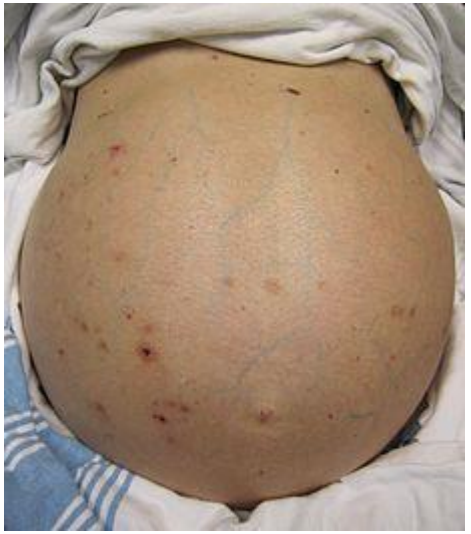
portal hypertension

hepatocellular carcinoma

Resistance to blood flow

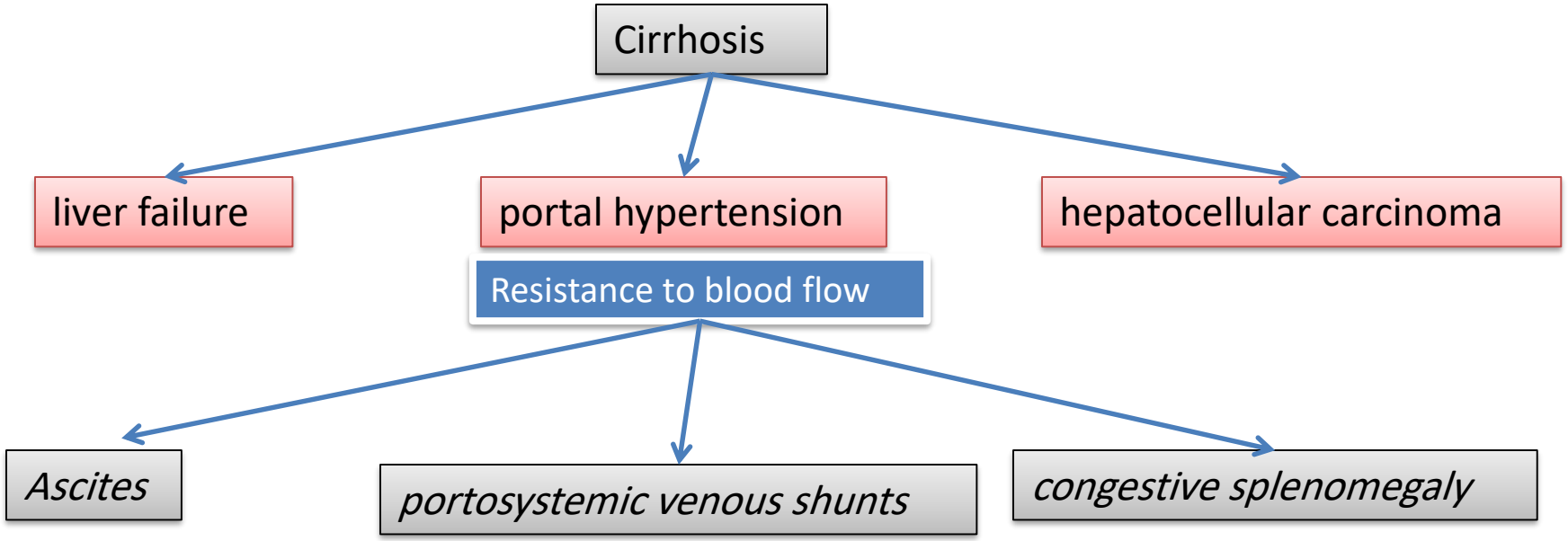
Ascites

Ascites is the accumulation of excess fluid in the peritoneal cavity: 85%



Pathogenesis

1. *Sinusoidal hypertension,* drives fluid into the space of Disse, which is then removed by hepatic lymphatics;
2. Hypoalbuminemia
3. *Leakage of hepatic lymph* into the peritoneal cavity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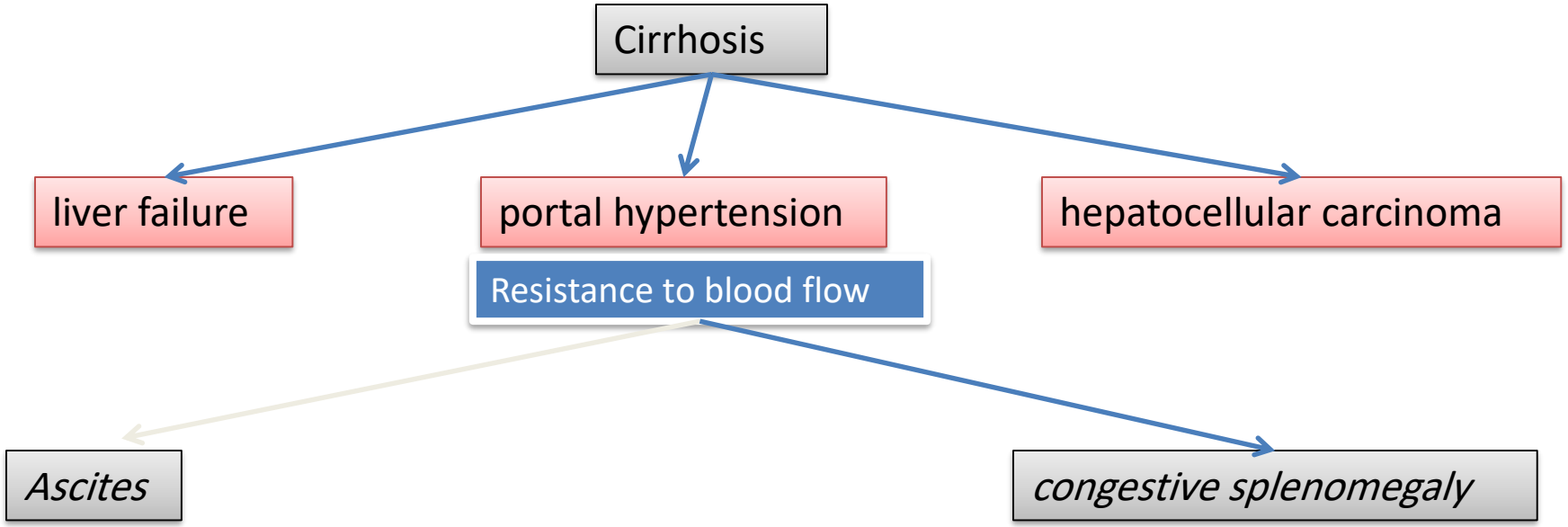


Long-standing congestion

Cirrhosis

liver failure

portal hypertension

hepatocellular carcinoma

Resistance to blood flow

portosystemic venous shunts

wherever the systemic and portal circulations share capillary beds

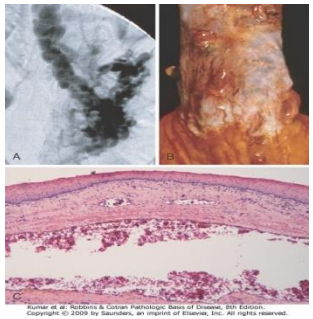
Rectum

cardioesophageal junction

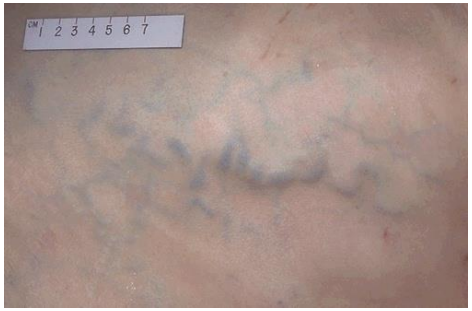
Abdominal wall

hemorrhoids

esophagogastric varices

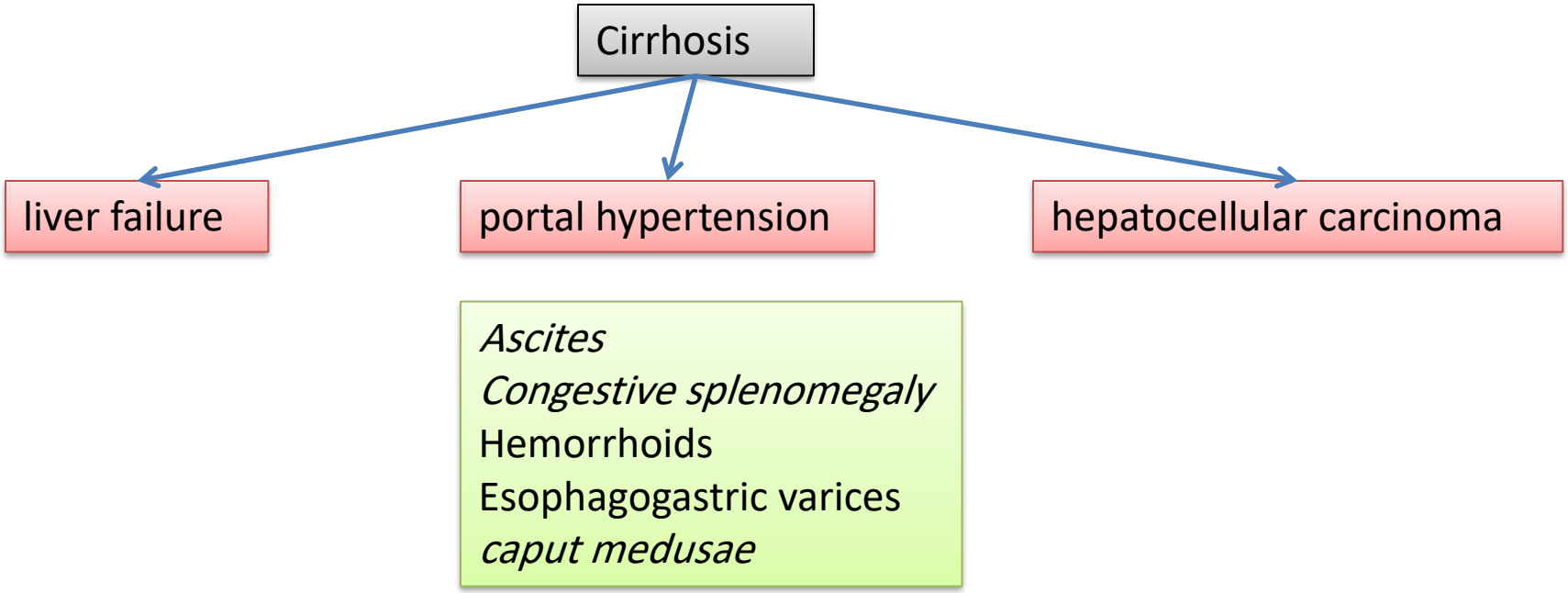


caput medusae



Esophageal varices

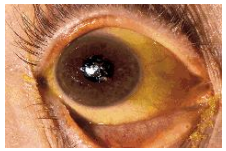
- Congested subepithelial and submucosal venous plexus within the distal esophagus. (*varices):*
- 90% of cirrhotic patients
- Variceal rupture results in hemorrhage into the lumen or esophageal wall…..Medical emergency
- Treated by sclerotherapy, balloon tamponade, rubber band ligation
- Half of patients die from the first bleeding episode either as a direct consequence of hemorrhage or following hepatic coma triggered by hypovolemic shock, Additional 50% within 1 year.


Cirrhosis
liver failure
portal hypertension
hepatocellular carcinoma
Ascites
Congestive splenomegaly
Hemorrhoids
Esophagogastric varices
caput medusae

liver failure

Metabolism catabolosim excretory

- Bilirubin
  - *Jaundice*



- Ammonia
  - *hyperammonemia*
    - *Hepatic encephalopathy*
- estrogens
  - hyperestrogenemia
    - *spider angiomas*
    - *hypogonadism*
    - *gynecomastia*

Synthesis

- Albumin
  - *Hypoalbuminemia*
    - Peripheral edema
    - Ascites
- clotting factors
  - *Coagulopathy and bleeding*
    - *Prothrombin time*

Hepatic encephalopathy

- A spectrum of disturbances in consciousness, ranging from subtle behavioral abnormalities to deep coma and death.
- Associated fluctuating neurologic signs include rigidity, hyperreflexia
- appears to be associated with elevated blood ammonia levels, which impair neuronal function and promote generalized brain edema.
- *only minor morphologic changes in the brain, such as edema and an astrocytic reaction.*
- Reversible if the underlying hepatic condition can be corrected.

Hepatorenal syndrome

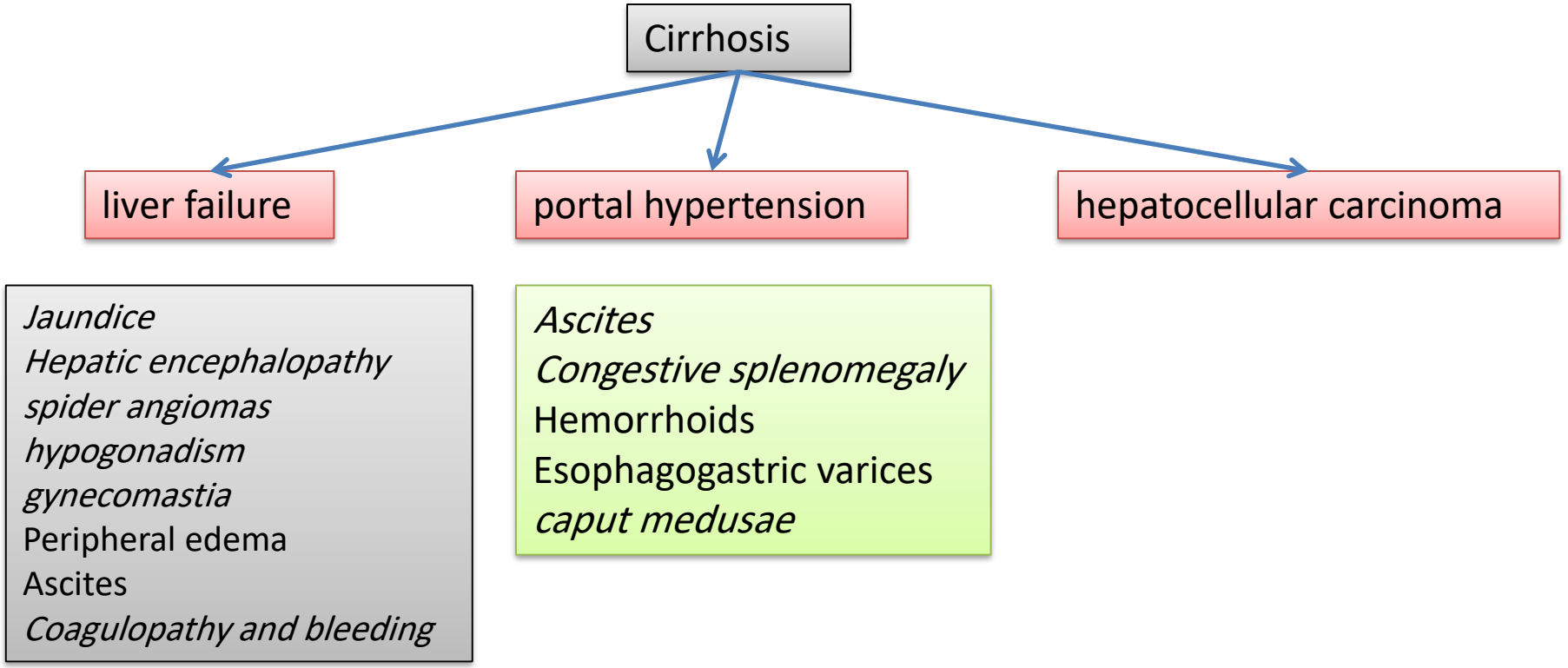
- *Renal failure in patients with severe chronic liver disease*,
- No intrinsic morphologic or functional causes for the renal failure.

- Sodium retention, impaired free-water excretion, and decreased renal perfusion and glomerular filtration rate are the main renal functional abnormalities.

- Several factors are involved in its development, including

1. Decreased renal perfusion pressure due to systemic vasodilation,
2. Activation of the renal sympathetic nervous system with vasoconstriction of the afferent renal arteriolae,
3. Increased synthesis of renal vasoactive mediators, which further decrease glomerular filtration.

- The prognosis is poor, with a median survival of only 2 weeks in the rapid-onset form and 6 months with the insidious-onset form.


Cirrhosis
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spider angiomas
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Coagulopathy and bleeding
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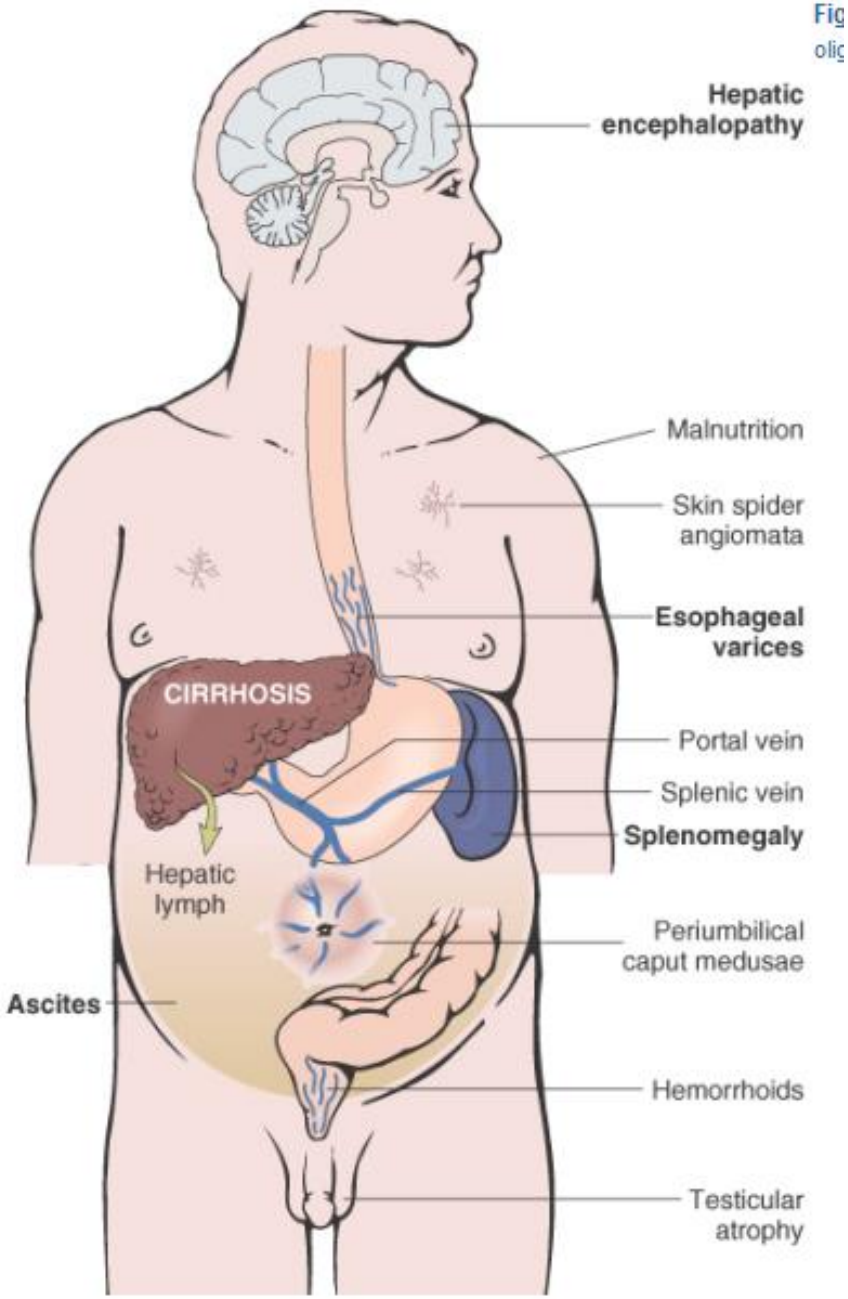
caput medusae


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

Objectives

- **Recognize the major complications of cirrhosis.**
  - *liver failure …..*
  - *portal hypertension…..*
  - *hepatocellular carcinoma*

- **Understand the pathogenetic mechanisms underlying the occurrence of the complications.**

1. *Hepatic encephalopathy*
2. Weight loss
3. *Bleeding*
4. *Jaundice*
5. *gynecomastia*
6. *Hepatorenal syndrome*
7. *Ascites*
8. *esophagogastric varices*
9. *hepatocellular carcinoma ..* cell injury and replication , viral oncogen

A. *liver failure*
B. *portal hypertension*

- **Recognize the clinical features inherent to the above mentioned complications.**

1. *Ascites*
2. Hematemesis
3. disturbances in consciousness Coma
4. Bleeding disorders
5. decreased urine output
6. Joundice

A. *liver failure*
B. *portal hypertension*

- **Describe the pathological findings of the different complications.**

1. *Hepatorenal syndrome …….no pathology*
2. *Hepatic encephalopathy……. only minor morphologic changes in the brain*
3. Esophageal varices…….. Congested subepithelial and submucosal venous plexus

Objectives

- **Recognize the major complications of cirrhosis.**
  - *liver failure ….. Jaundice, Hepatic encephalopathy , hypogonadism gynecomastia, Ascites, bleeding , Hepatorenal syndrome*
  - *portal hypertension….. Ascites, .esophagogastric varices, splenomegaly*
  - *hepatocellular carcinoma*

- **Understand the pathogenetic mechanisms underlying the occurrence of the complications.**
  - *Hepatic encephalopathy……. liver failure*
  - Weight loss…….liver *failure*
  - *Bleeding ……. liver failure*
  - *Jaundice ……. liver failure*
  - *gynecomastia ……. liver failure*
  - *Hepatorenal syndrome …….. liver failure*
  - *Ascites ……..portal hypertension, liver failure*
  - *esophagogastric varices ……..portal hypertension*
  - *hepatocellular carcinoma ..* cell injury and replication , viral oncogen

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  - *Hepatorenal syndrome …….no pathology*
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Example of liver cirrhosis

- A 62-year-old man is brought to the emergency room in a disoriented state. Physical examination reveals jaundice, splenomegaly, and ascites. The patient has a coarse flapping tremor of the hands, palmar erythema, and diffuse spider angiomata. The abdomen displays dilated paraumbilical veins. Serum levels of ALT, AST, alkaline phosphatase, and bilirubin are all mildly elevated. Soon after admission, the patient vomits a large amount of blood.

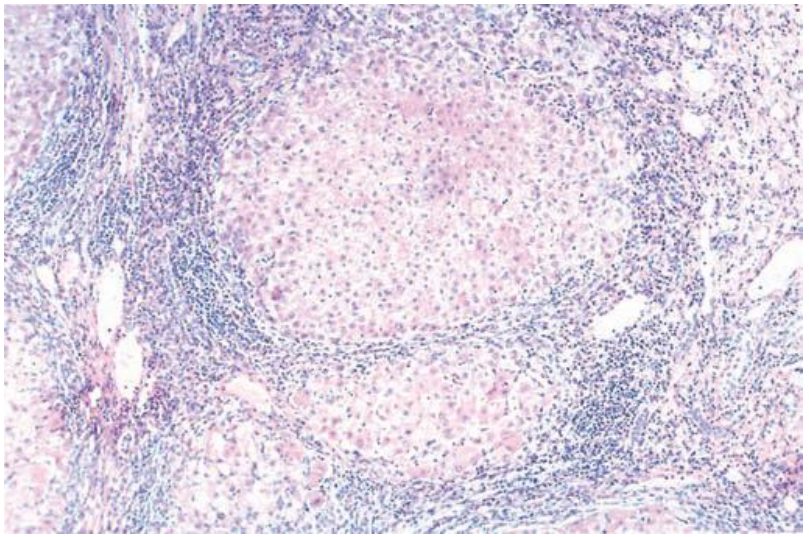
- A 62-year-old man is brought to the emergency room in a disoriented state. Physical examination reveals signs of poor hygiene and an odor of alcohol, as well as jaundice, splenomegaly, and ascites. The patient has a coarse flapping tremor of the hands, palmar erythema, and diffuse spider angiomata. The abdomen displays dilated paraumbilical veins. Serum levels of ALT, AST, alkaline phosphatase, and bilirubin are all mildly elevated. Soon after admission, the patient vomits a large amount of blood. Which of the following is the most likely underlying cause of hematemesis in this patient?
- (A) Acute alcoholic hepatitis
- (B) Acute gastritis
- (C) Cirrhosis
- (D) duodenal ulcer
- (E) Mallory-Weiss tear

- **The answer is C: Cirrhosis.**
- **Cirrhosis represents the end stage** of chronic liver disease and is characterized by extensive fibrosis and the formation of regenerative nodules. Patients with cirrhosis often present with complications of portal hypertension, including ascites, splenomegaly, and bleeding esophageal varices. Esophageal varices arise from the opening of portal-systemic venous collaterals. Engorged collaterals in the submucosa of the lower esophagus and upper stomach, which dilate and protrude into the lumen, are susceptible to bleeding. The prognosis of patients with bleeding esophageal varices is poor, with a 40% mortality rate.

- For the patient described in previous Question , which of the following pathophysiologic mechanisms is most directly associated with the development of ascites?
- (A) Decreased aldosterone secretion
- (B) Decreased intravascular volume
- (C) Hyperalbuminemia
- (D) Increased intravascular oncotic pressure
- (E) Increased portal hydrostatic pressure

- **The answer is E: Increased portal hydrostatic pressure.**
- **Ascites** refers to the accumulation of fl uid in the peritoneal cavity, often caused by portal hypertension. In the setting of cirrhosis,decreased intravascular oncotic pressure due to hypoalbuminemia is also an important factor in the pathogenesis of ascites (see choice D). Aldosterone secretion (choice A) is increased in cirrhotic patients. Overall, imbalances in Starling forces lead to transudation of fluid into the abdominal cavity

- A 30-year-old man presents with a 9-month history of fatigue and recurrent fever. He also complains of yellow skin and sclerae, abdominal tenderness, and dark urine.
- Physical examination reveals jaundice and mild hepatomegaly.
- Laboratory studies demonstrate elevated serum bilirubin (3.1 mg/ dL), decreased serum albumin (2.5 g/dL), and prolonged prothrombin time (17 seconds).
- Serologic tests reveal antibodies to hepatitis B core antigen (IgG anti-HBcAg). The serum is positive for HBsAg and HbeAg.
- A liver biopsy is shown in the image
- What is the most likely diagnosis?



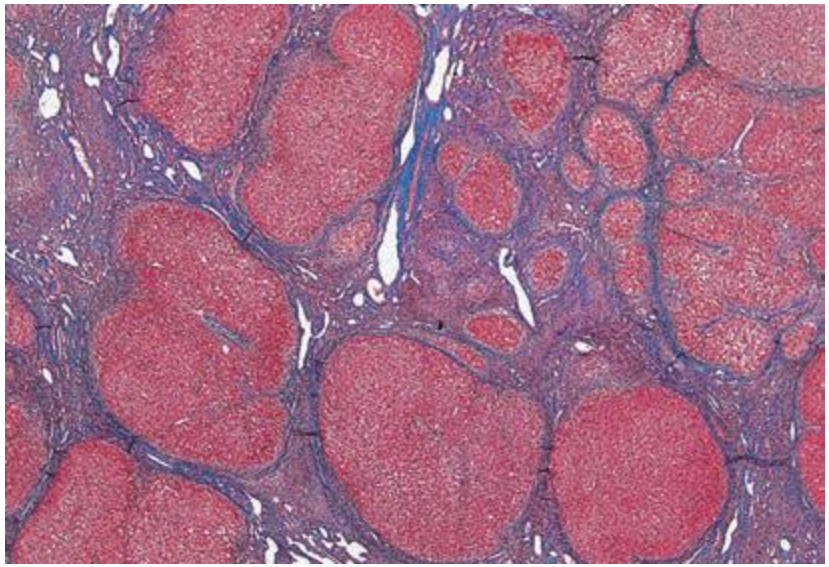
(A) Acute hepatitis B
(B) Alcoholic hepatitis
(C) Chronic hepatitis B
(D) Delta virus infection
(E) Subacute hepatic necrosis secondary to hepatitis B infection

The answer is C: Chronic hepatitis B.

Chronic hepatitis B refers to infection with hepatitis B virus (HBV) that is associated withnecrosis and inflammation in the liver for more than 6 months. HBV is a DNA virus that is transmitted through blood transfusion, sexual contact, or shared needles. Most patients recover completely from acute infection, but some 10% develop chronic infection. Of the latter, 10% to 30% develop chronic hepatitis and cirrhosis. The biopsy in this case shows hepatocellular nodules and chronically-inflamed fibrous septa (see photomicrograph). Surface antigen (HBsAg) is present in the serum of patients with chronic hepatitis B, and the presence of HbeAg is often associated with progression of the disease. Choices A, B, and E do not demonstrate cirrhosis as depicted and do not show the serologic characteristics of HBV infection.

- The patient described in previous Question is most likely to develop which of the following vascular inflammatory diseases?
- (A) Allergic angiitis
- (B) Buerger disease
- (C) Giant cell arteritis
- (D) Polyarteritis nodosa
- (E) Wegener granulomatosis

- A 60-year-old man is found in a state of disorientation and is
- brought to the emergency room in a comatose state. He had history of hepatitis c infection.
- Physical examination reveals an emaciated man with a distended
- abdomen, jaundice, ascites, and a slightly enlarged liver and spleen.
- A liver biopsy is shown in the image.
- What blood test would confirm a diagnosis of hepatic coma?
- (A) Alanine aminotransferase
- (B) Alkaline phosphatase
- (C) Ammonia
- (D) Bilirubin
- (E) Urea nitrogen



- **The answer is C: Ammonia. The photomicrograph shows cirrhosis,**
- with regenerative nodules of liver cells surrounded by
- fi brous septa. Hepatic encephalopathy, a syndrome frequently
- observed in patients with cirrhosis of the liver, is characterized
- by personality changes, intellectual impairment, and a
- depressed level of consciousness. The development of hepatic
- encephalopathy is caused by increased serum concentrations
- of neurotoxic substances, among which is ammonia. Choices
- A, B, and D are elevated in a variety of liver diseases but are
- unrelated to hepatic encephalopathy. Blood urea nitrogen
- (choice E) is used to assess kidney function.

- A 58-year-old man with longstanding alcoholic cirrhosis presents hematemesis.
- Physical examination reveals jaundice and a markedly distended abdomen.
- Prothrombin time is prolonged (20 seconds).
- Shortly after admission, the patient develops renal failure (oliguria and elevated serum levels of BUN and creatinine), leading to death within 3 days.
- Histologic examination of the patient's kidney at autopsy would most likely show which of the following?
- (A) Interstitial nephritis
- (B) Membranous nephropathy
- (C) No histologic changes
- (D) Proliferative glomerulonephritis
- (E) Pyelonephritis

- **The answer is C: No histologic changes.** Hepatorenal
- syndrome usually occurs in the setting of cirrhosis and heralds
- a poor prognosis. The disorder is characterized by features
- of renal hypoperfusion, including oliguria, azotemia,
- and increased levels of serum creatinine. Microscopically, the
- kidney appears normal. Renal failure is caused by vasoconstriction
- and hypoperfusion of the kidneys, a combination
- mediated by various hormones and vasoactive substances,
- some of which may not be cleared by the cirrhotic liver. Similarly,
- a kidney from a patient in hepatorenal failure may be
- successfully transplanted into another person and assume
- normal functioning. The other choices are associated with
- direct injury to the renal parenchyma and exhibit characteristic
- histologic findings.

Acquisition of myofibers by perisinusoidal stellate cells also increases vascular resistance within the liver parenchyma, since tonic contraction of these "myofibroblasts " constricts the sinusoidal vascular channel

•Throughout the process of liver damage and fibrosis, remaining hepatocytes are stimulated to regenerate and proliferate as spherical nodules within the confines of the fibrous septae.

•The net outcome is a fibrotic, nodular liver in which delivery of blood to hepatocytes is severely compromised, as is the ability of hepatocytes to secrete substances into plasma.

•Disruption of the interface between the parenchyma and portal tracts obliterates biliary channels as well. Thus, *the cirrhotic patient may develop jaundice and even hepatic failure, despite having a liver of normal mass*.

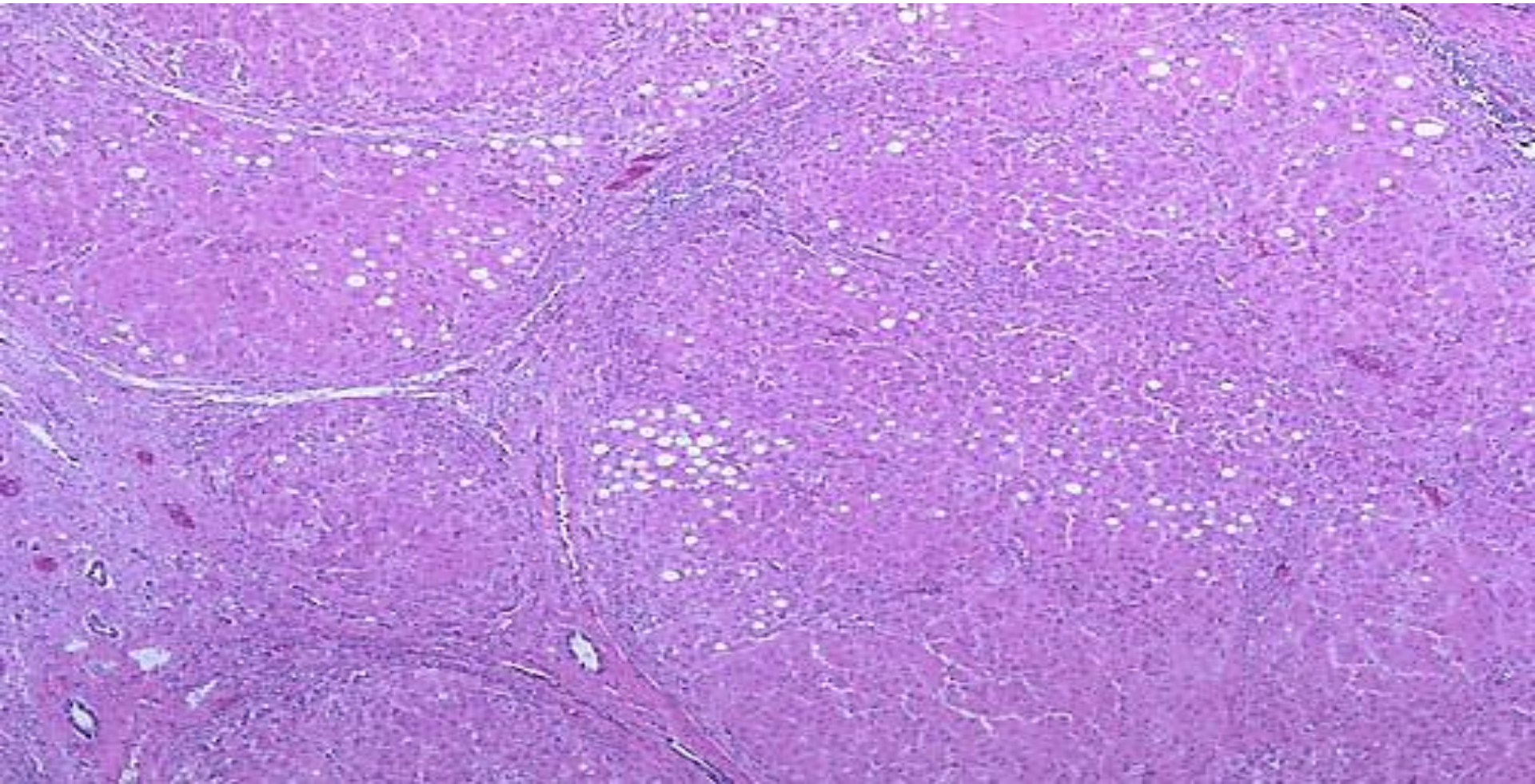
Pathogenesis of cirrhosis

- 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.

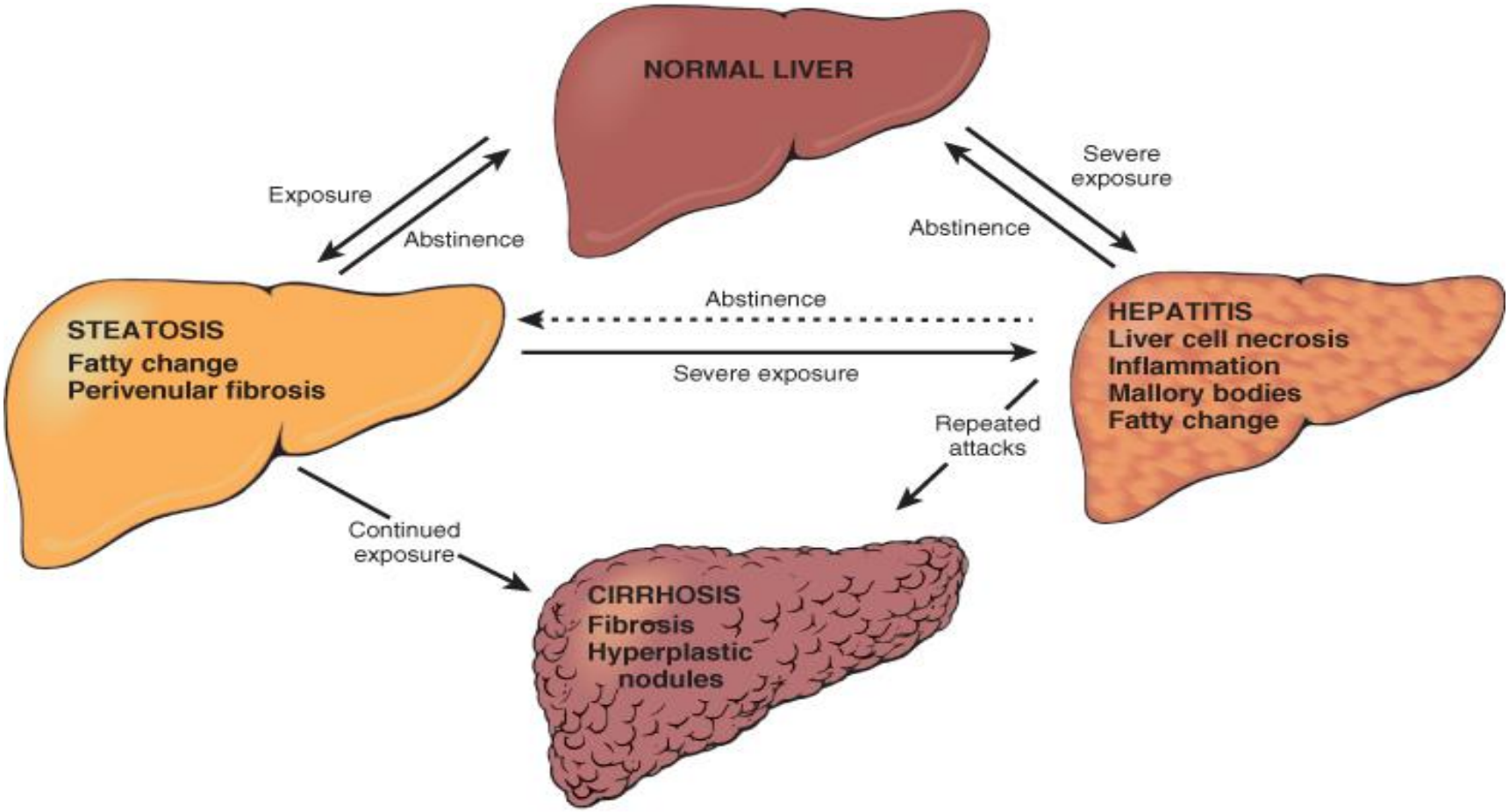
Pathogenesis of cirrhosis

- 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).

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