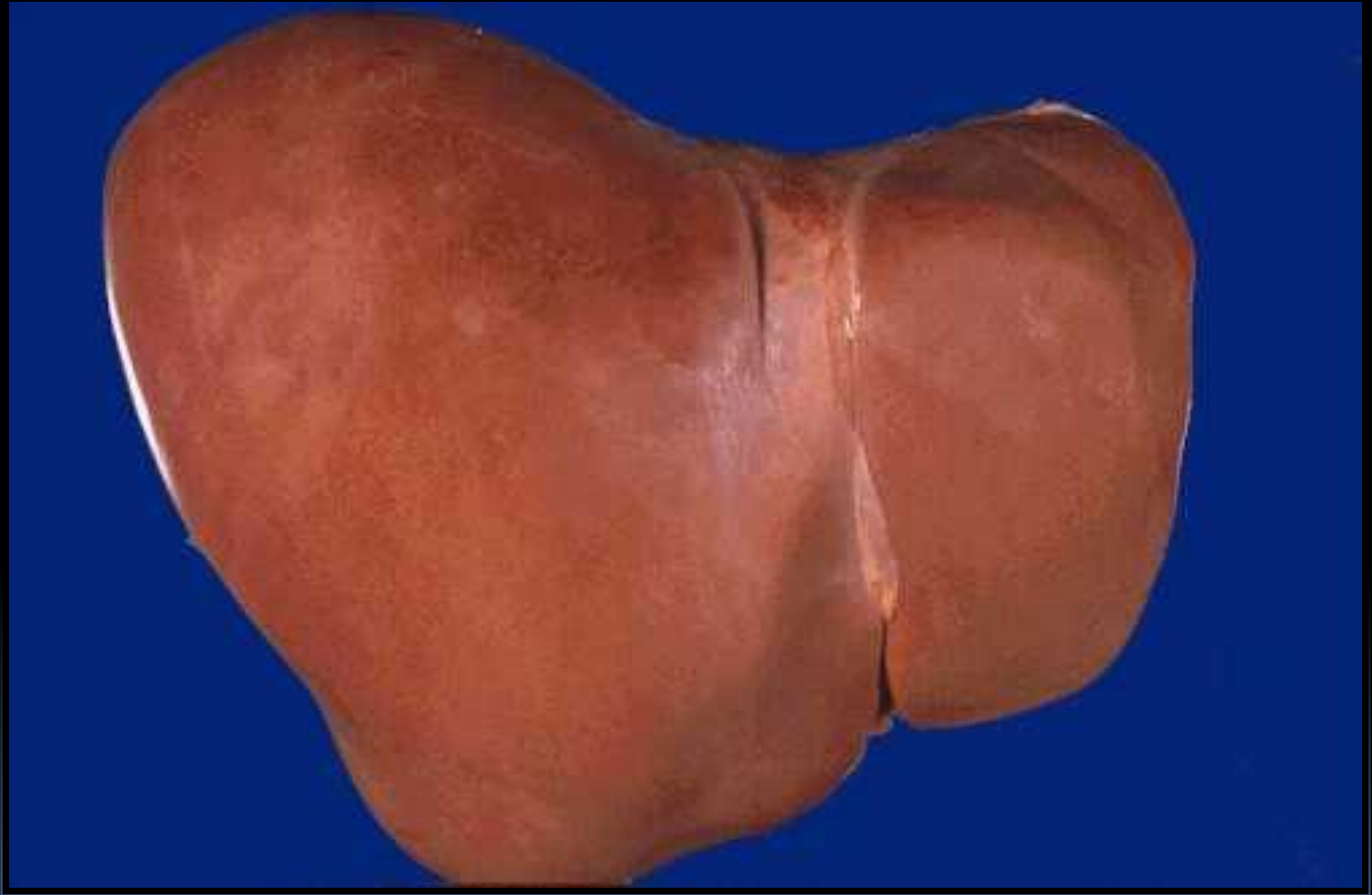




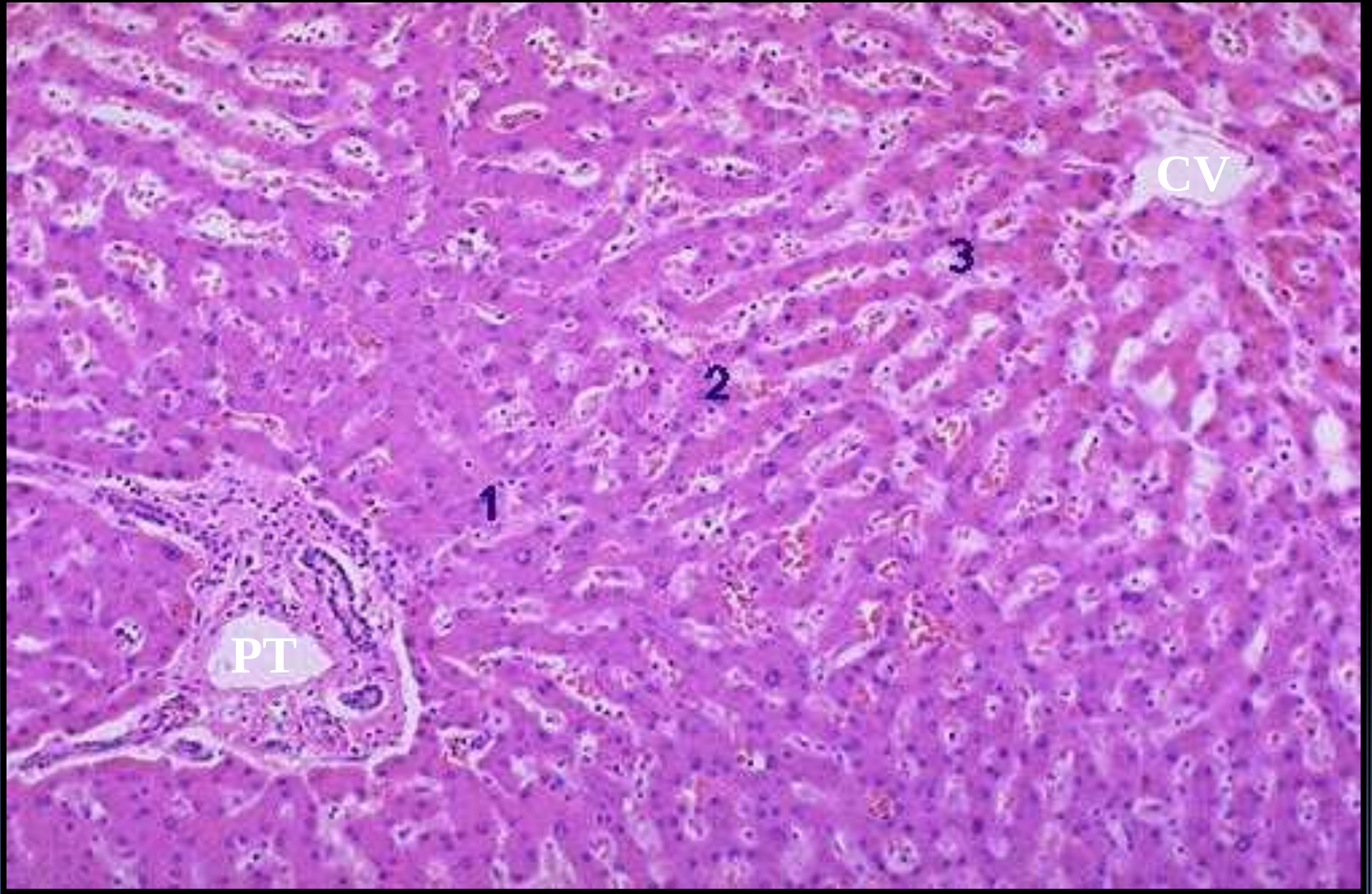
# LECTURE

## Diseases of Liver

# Normal Liver



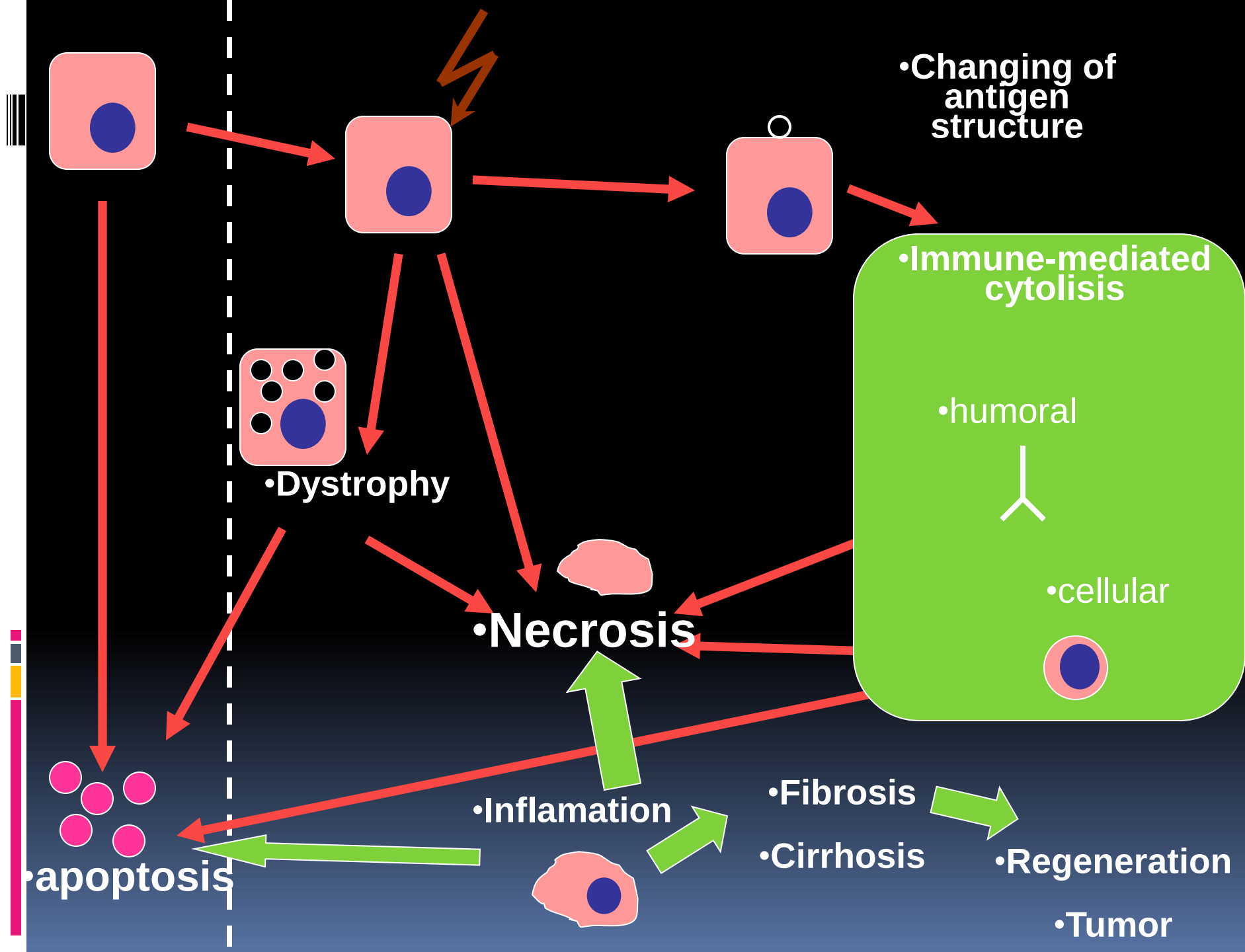
# Normal Liver Histology





## •Cell Injury

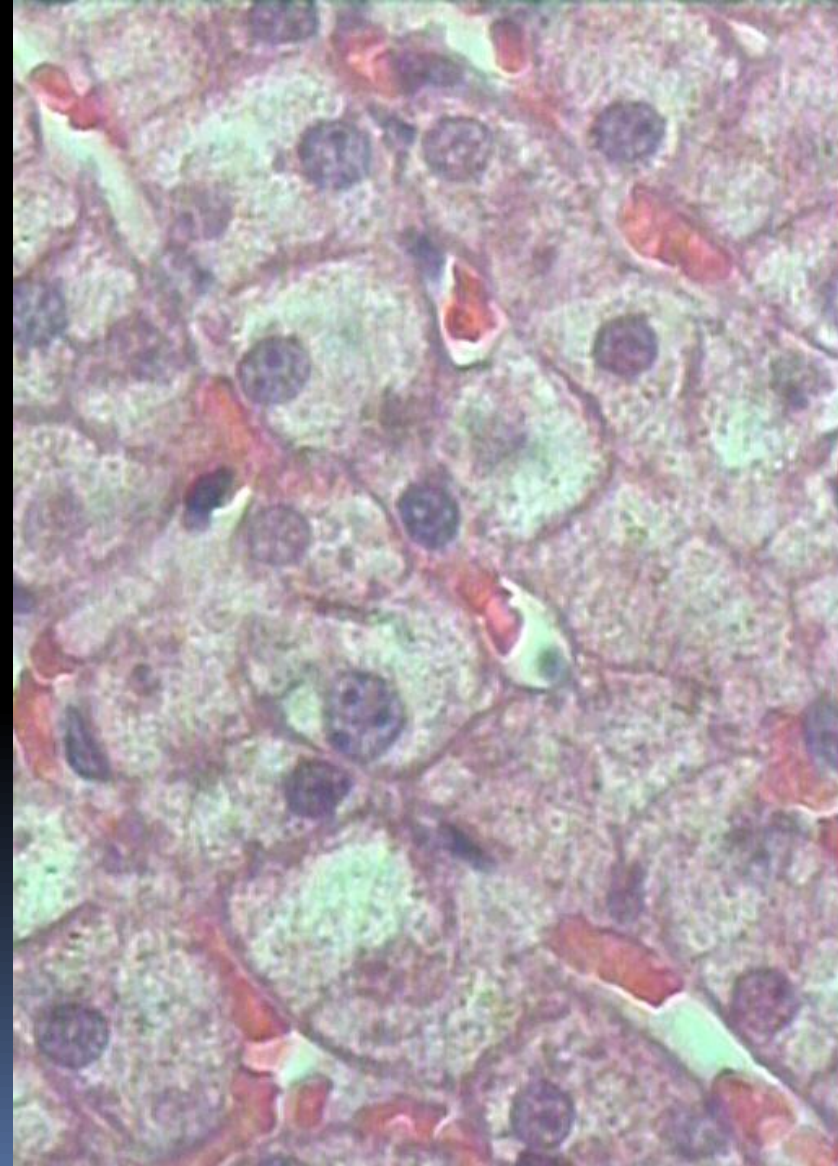
1. Dystrophy
  2. Apoptosis
  3. Necrosis
- 





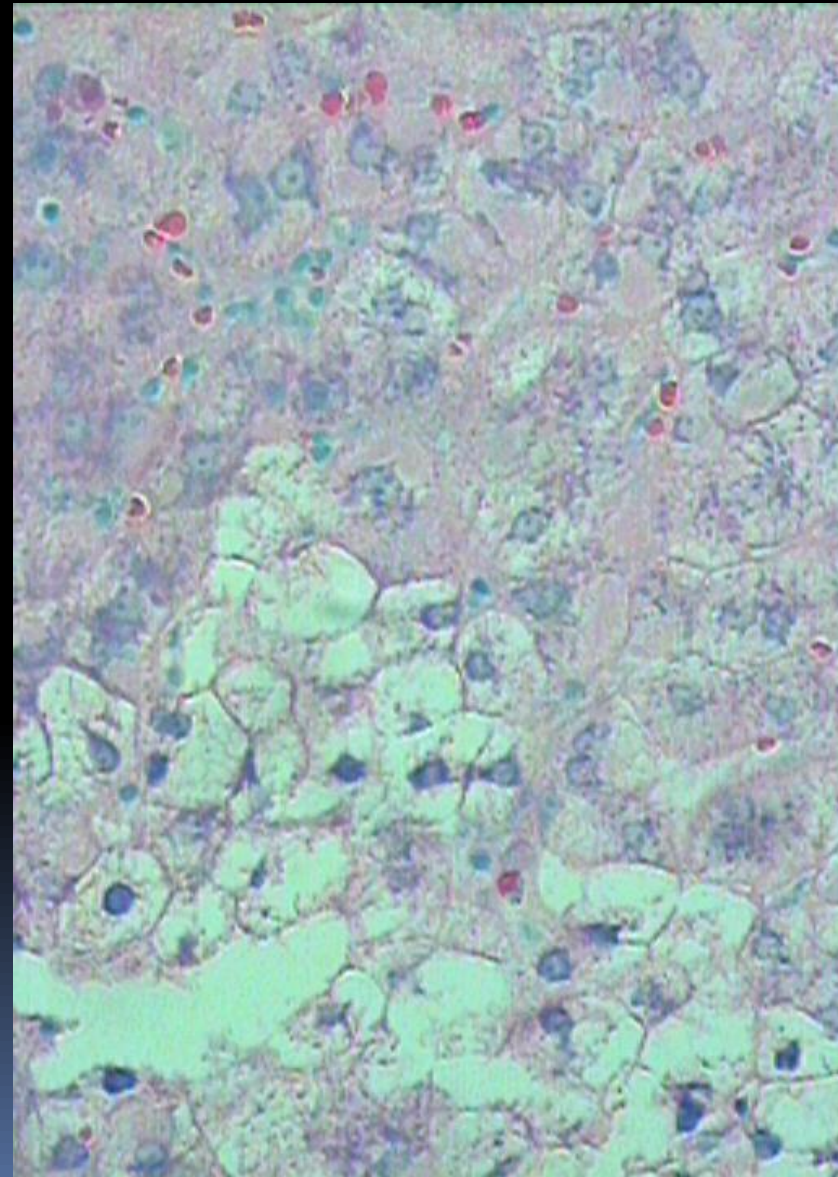
## •Cell Injury: Histological expressions

- Swelling or hydropic change.



## •Cell Injury: Histological expressions

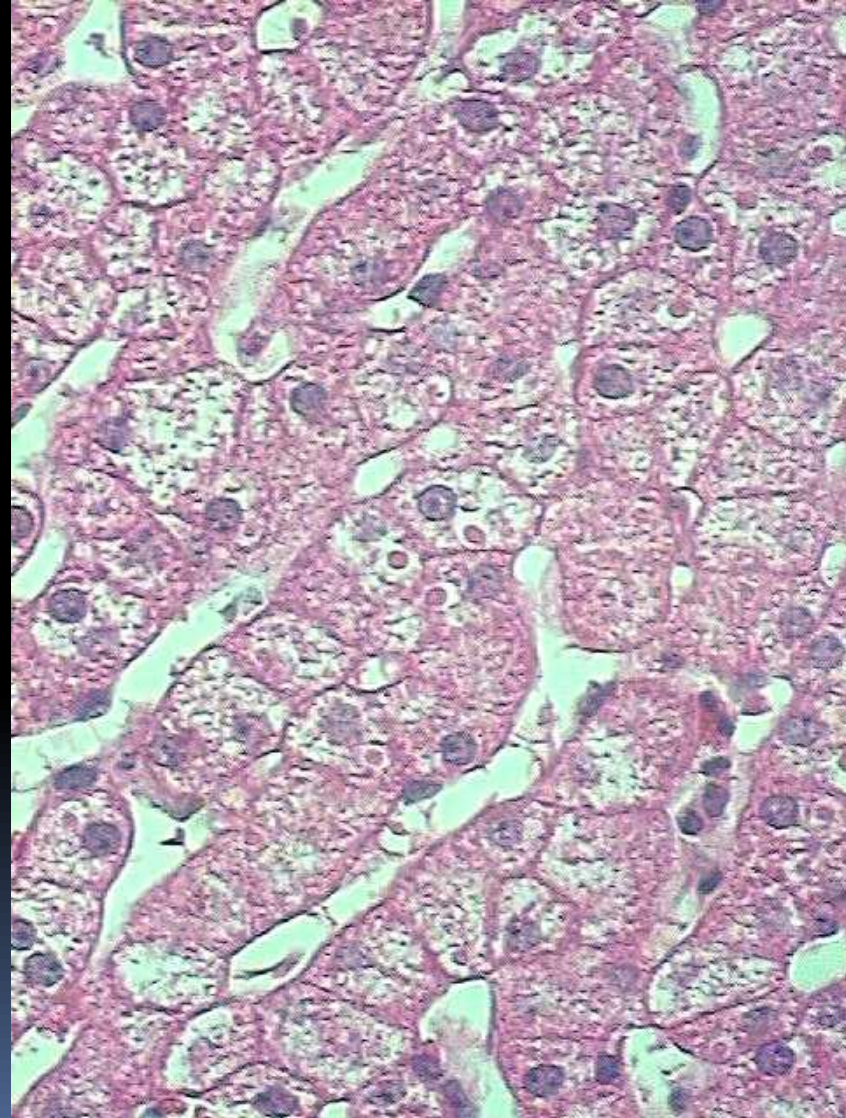
- Swelling or hydropic change. Probably the result of defects in membrane and/or mitochondrial function. This is common to many hepatic injuries.





## •Cell Injury: Histological expressions

- Hyaline droplet change. Mallory bodies (structural filaments).

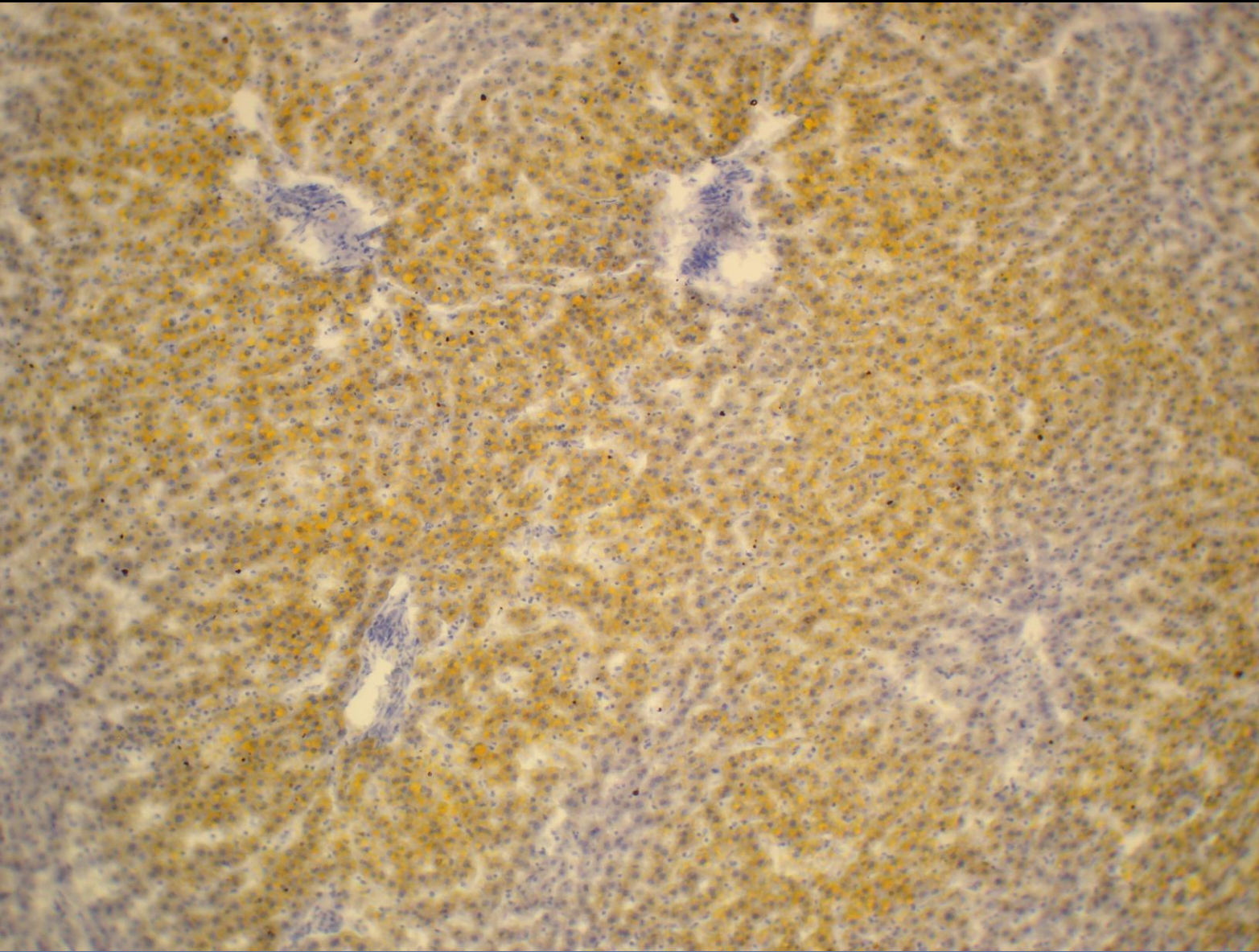




# Fatty Liver

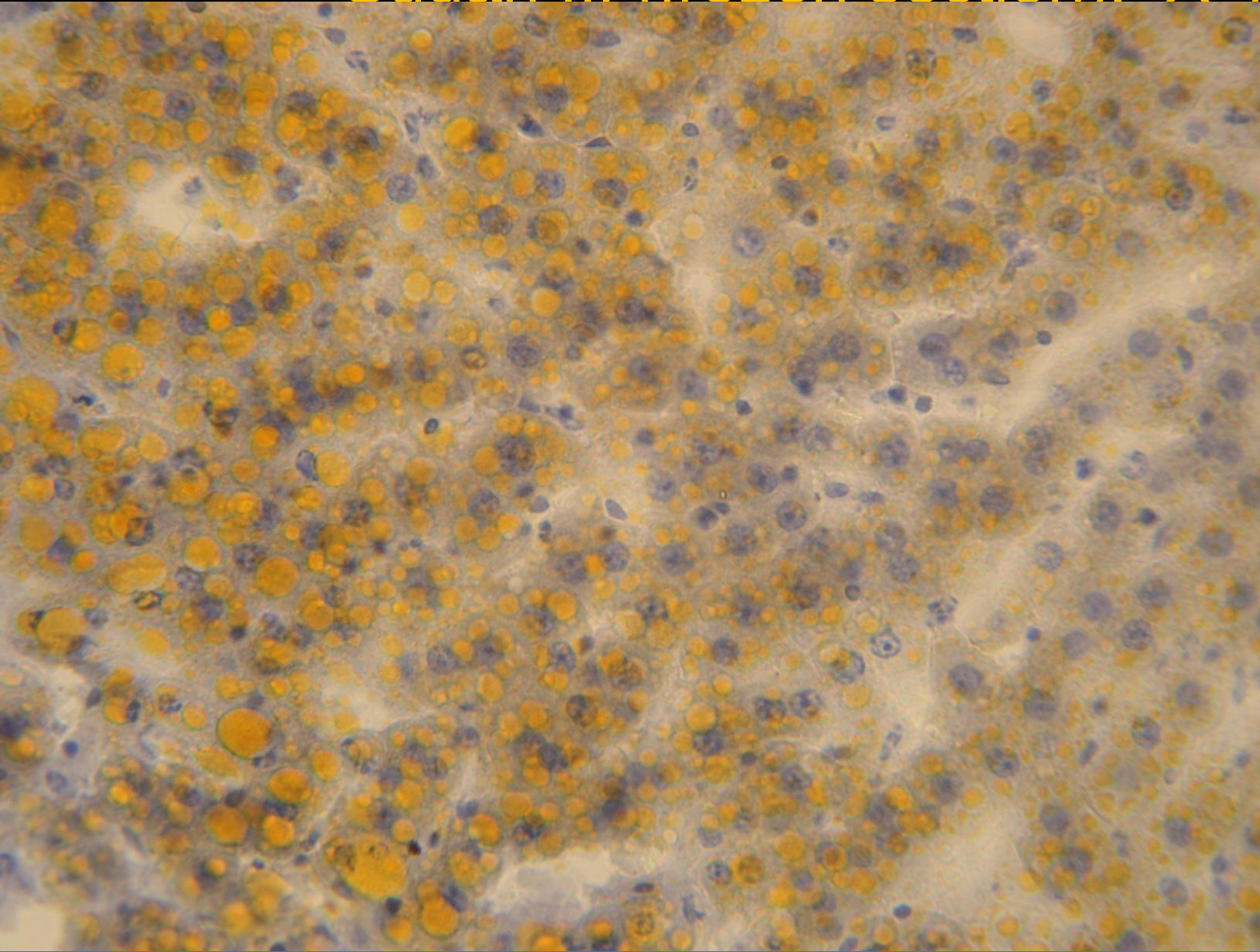


- Fatty Liver.
- Sudan III (frozen section). X 100.



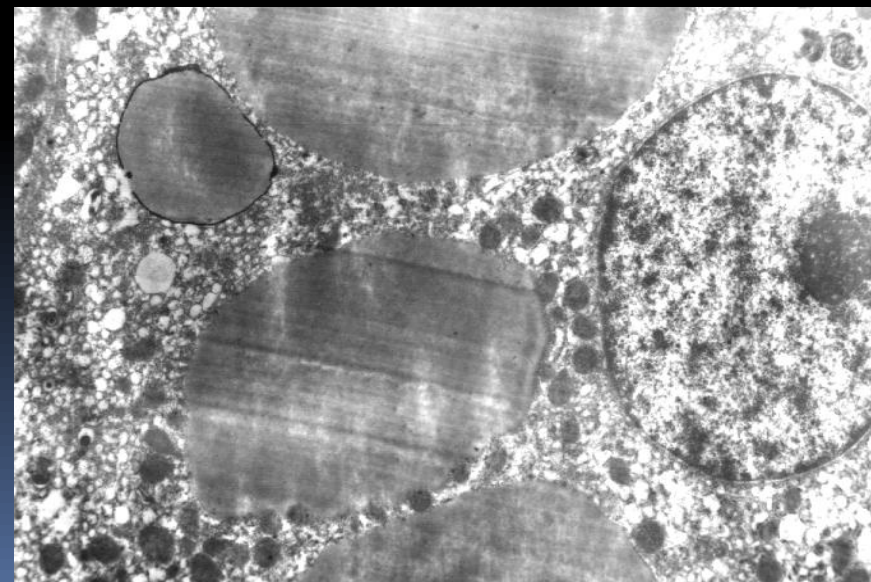
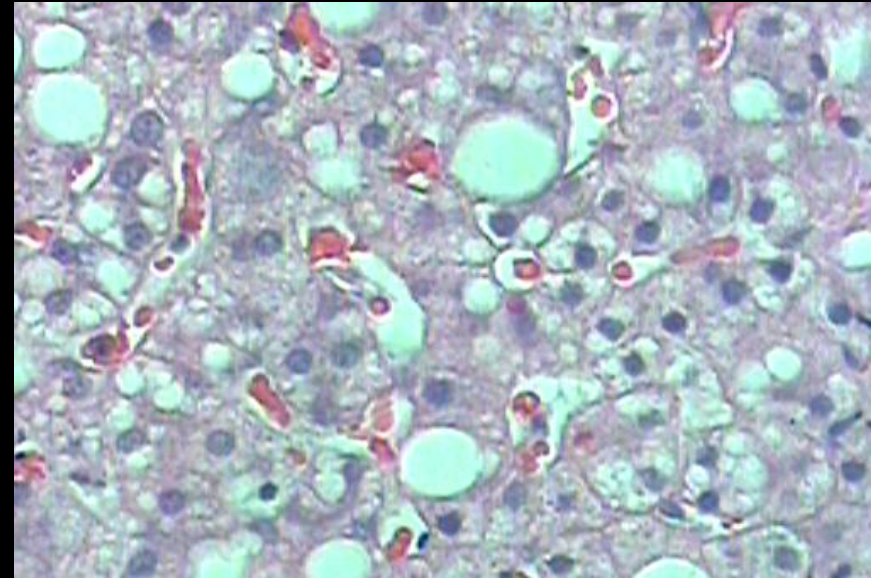


- Fatty Liver.
- Sudan III (frozen section). X 400.

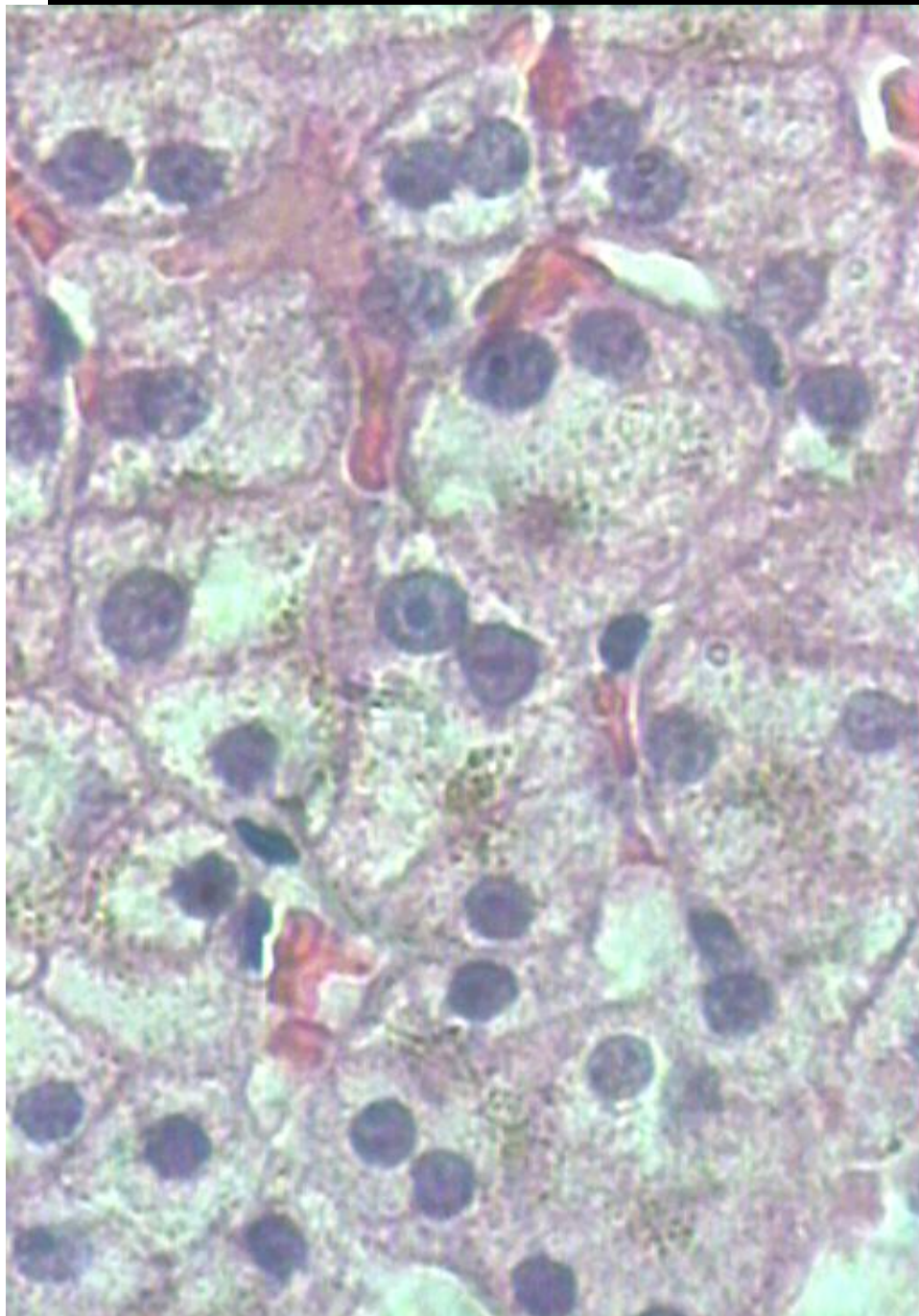


# •Cell Injury: Histological expressions

- Fat (neutral fat, triglyceride) in liver cells: indicates some defect in lipid metabolism or lipoprotein synthesis or unusual quantities of adipose or dietary lipid brought to liver. Also referred to as "steatosis".







•**Lipofuscin**

•H&E, x500.

# •Apoptosis & Necrosis

- centrilobular;

- apoptosis;

- midzonal;

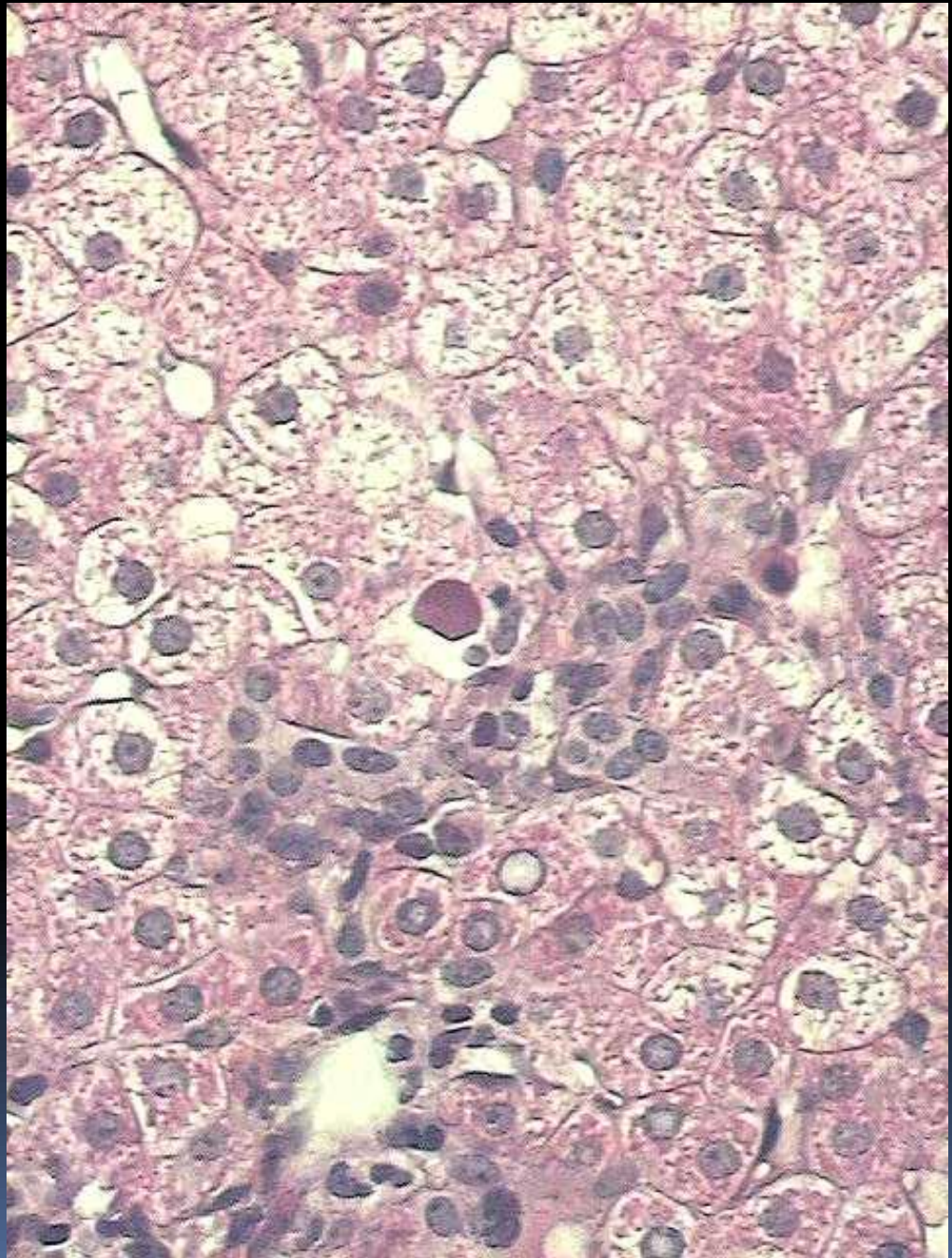
- periportal

- bridge necrosis

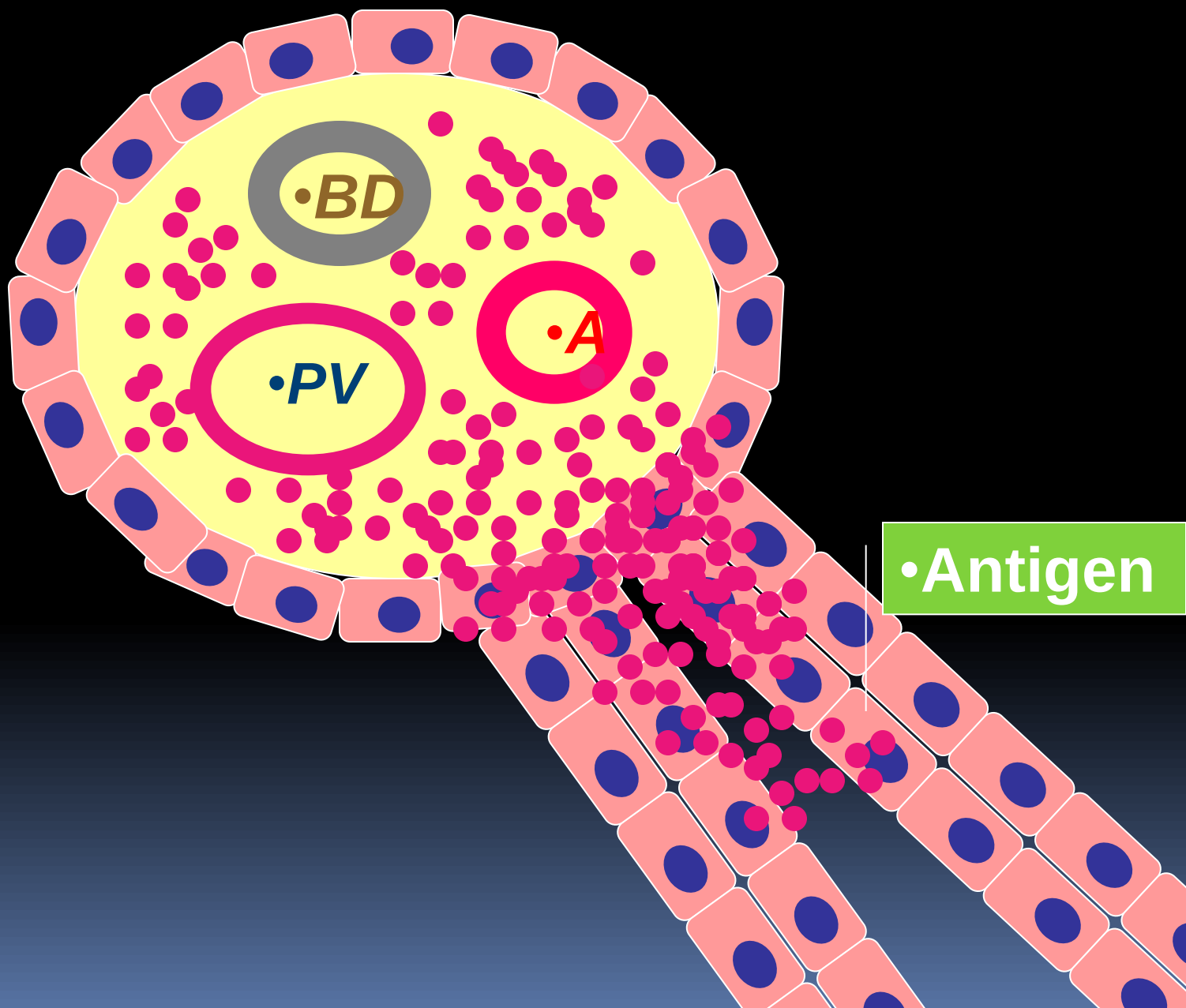


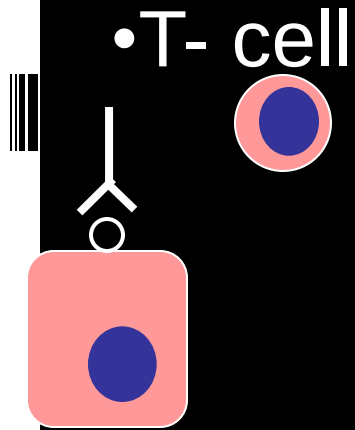
- apoptosis

- H&E, x125.



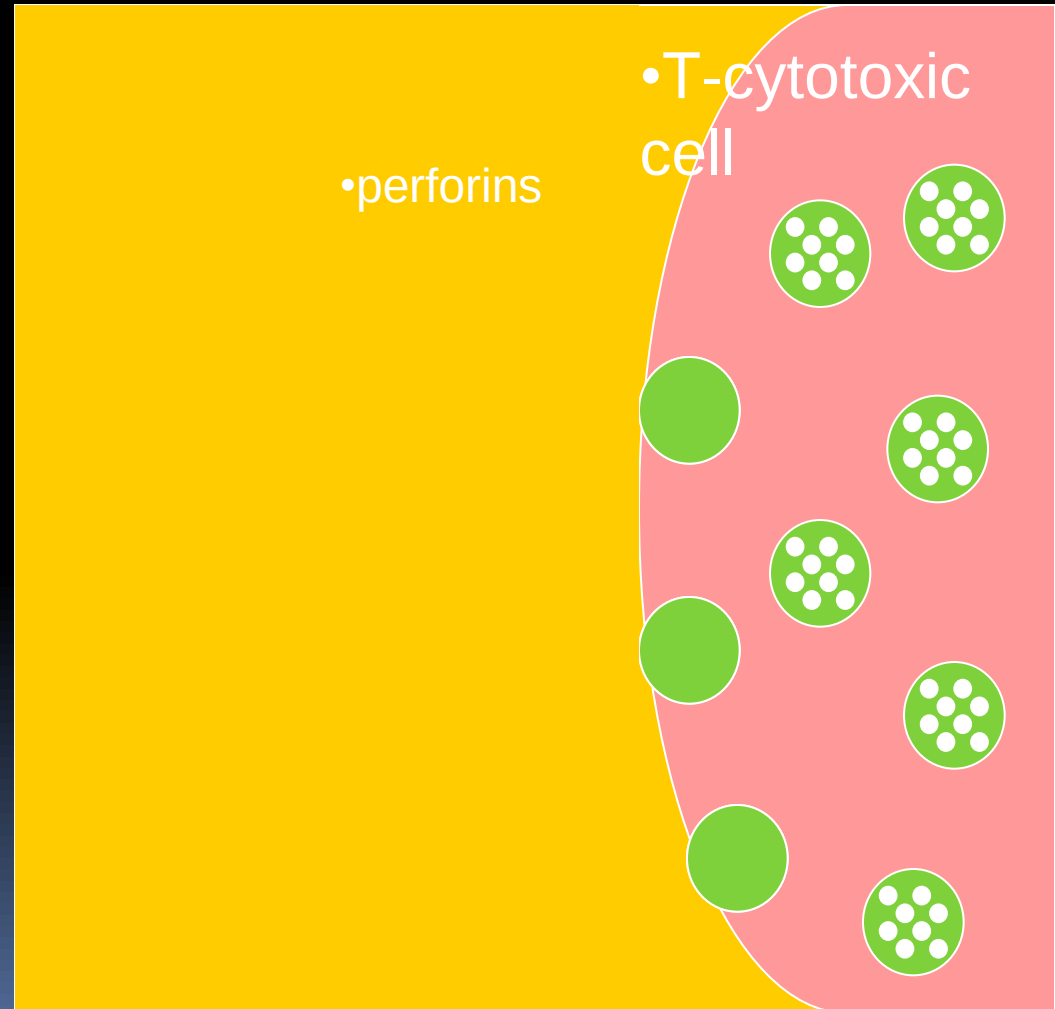






## Mechanism of cell-mediated reactions

- Injury of plasma membrane
- Apoptosis induction by enzymes
- via surface receptors

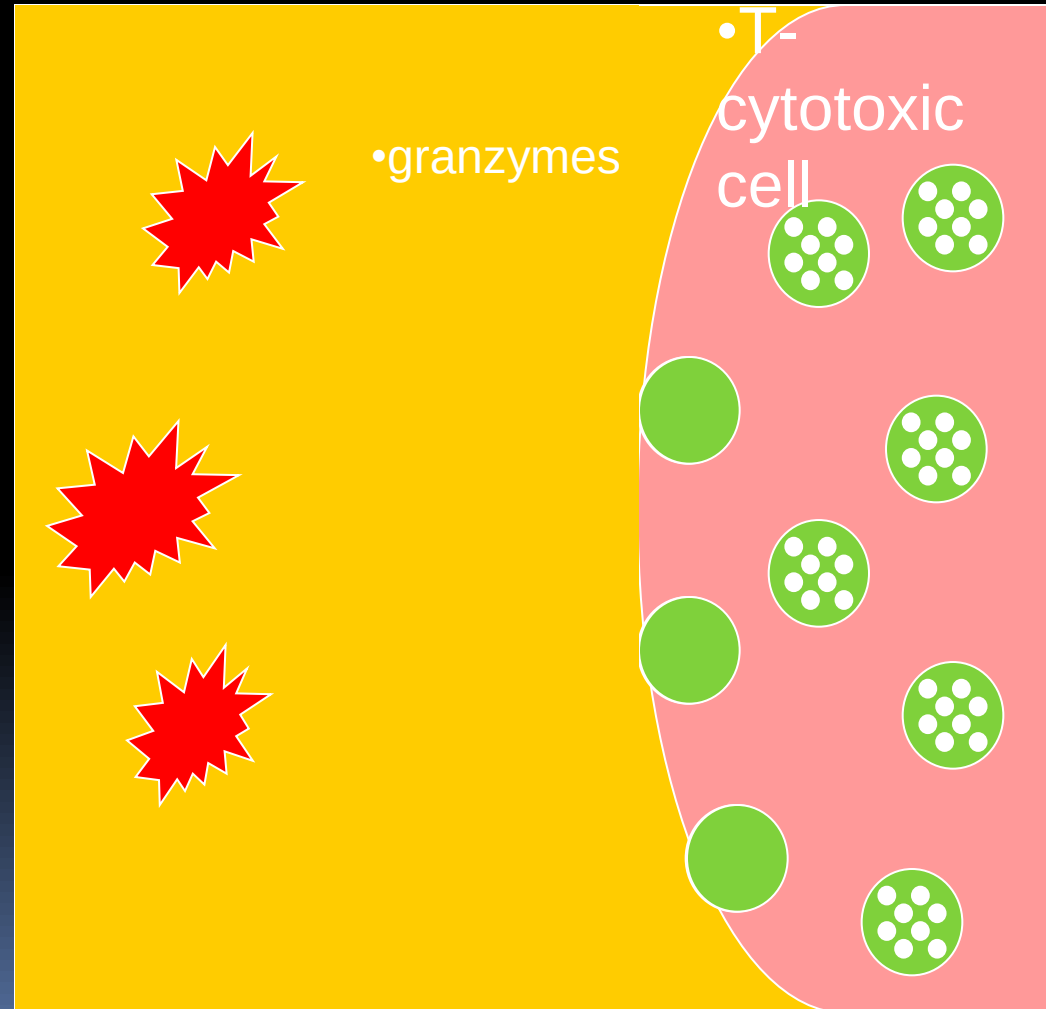


• T-cell



## Mechanism of cell-mediated reactions

- Injury of plasma membrane
- Apoptosis induction by enzymes
- via surface receptors



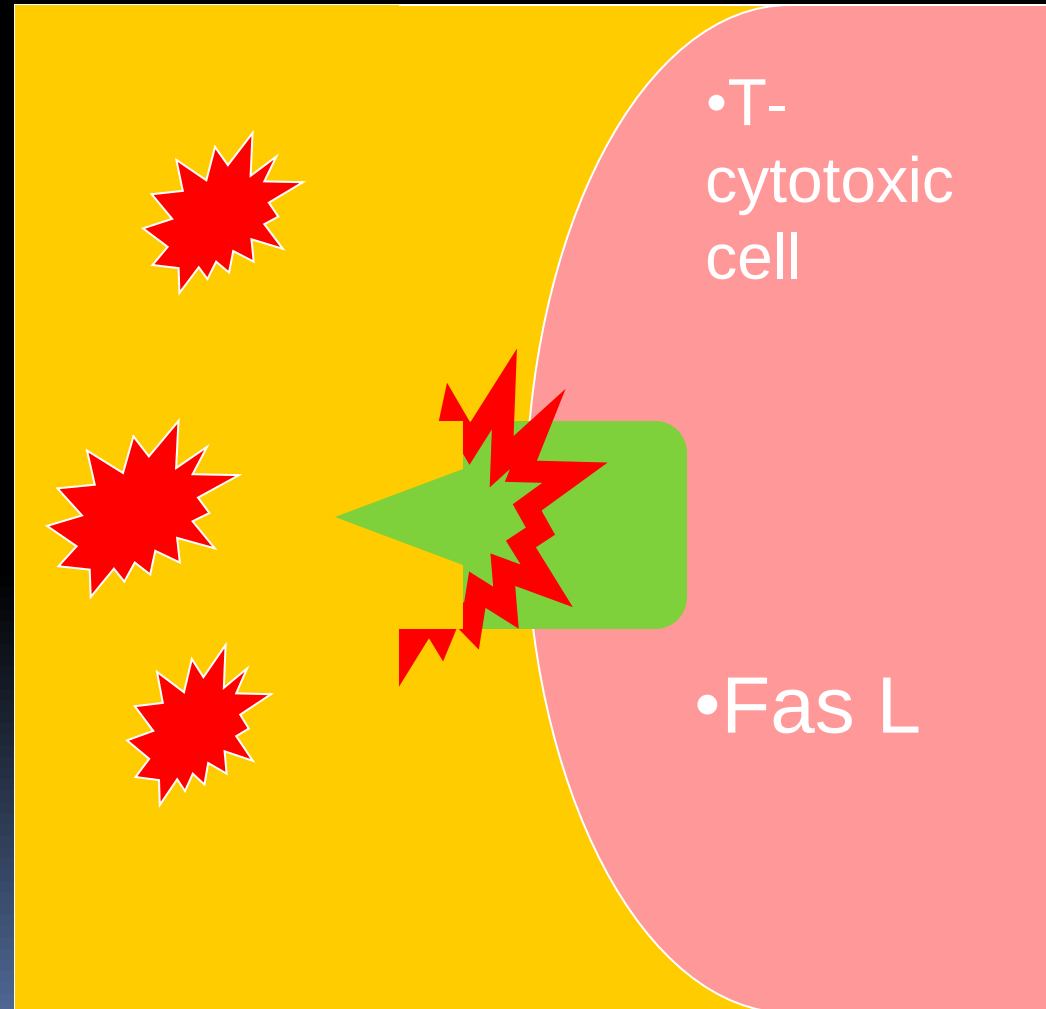


• T-cell



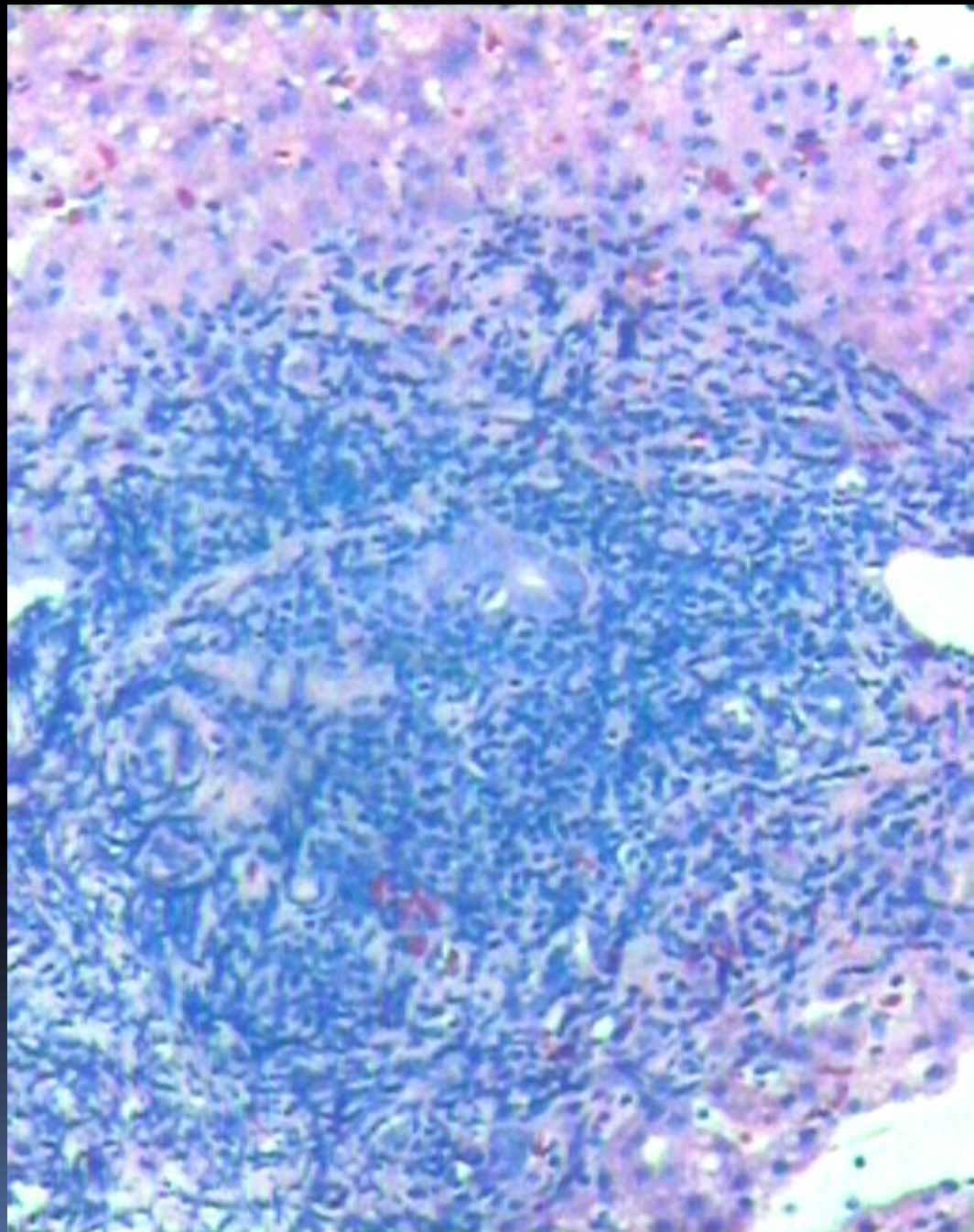
## Mechanism of cell-mediated reactions

- Injury of plasma membrane
- Apoptosis induction by enzymes
- via surface receptors



# Lymphoid follicles

- Azure & E, x125.





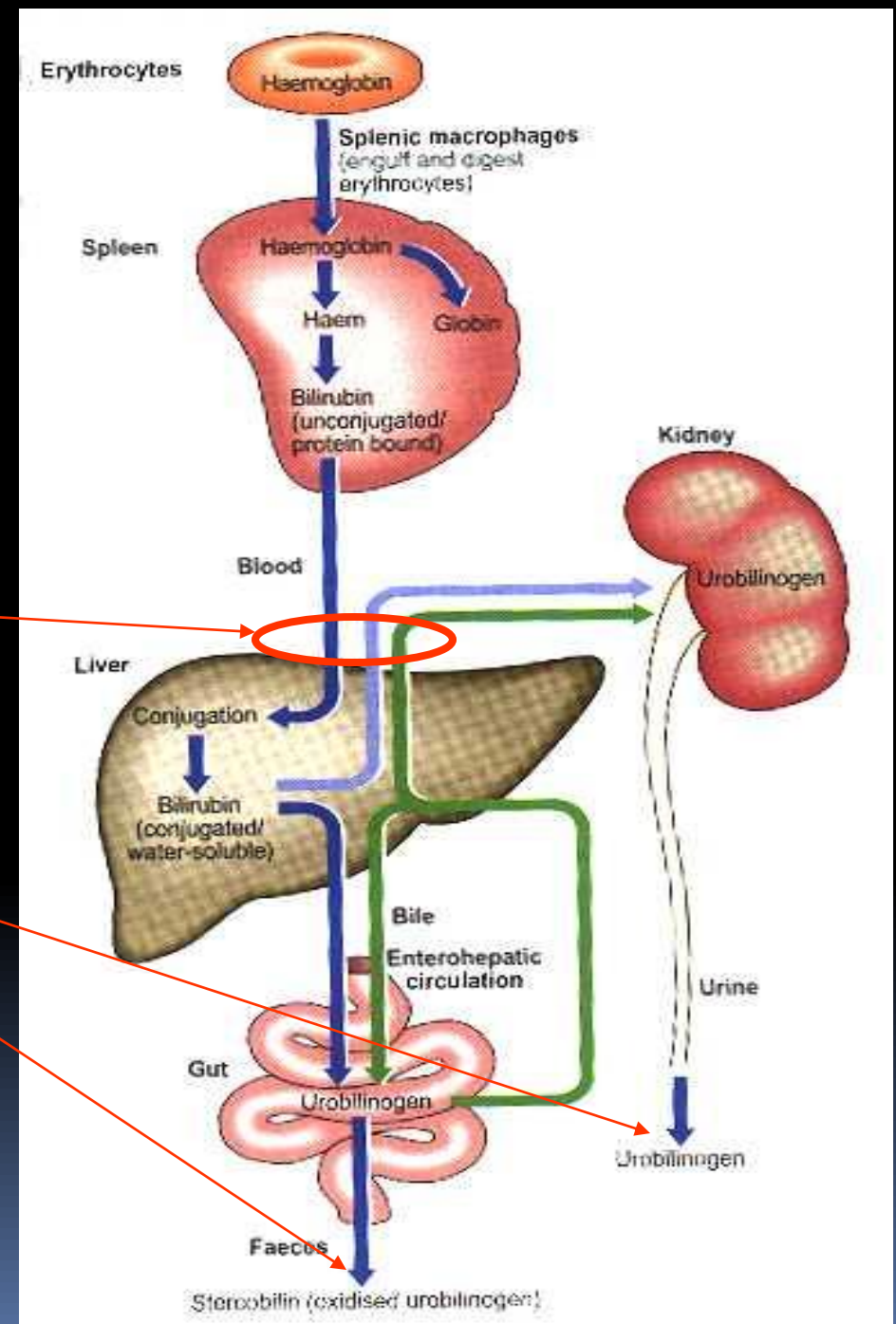
# Jaundice

- Yellow discoloration of skin & sclera due to excess serum bilirubin.  $> 40 \mu\text{mol/l}$ , (3mg/dl)
  - Not necessarily liver disease.
  - Conjugated & Unconjugated types
  - Obstructive & Non Obstructive
  - Pre-Hepatic, Hepatic & Post Hepatic types.
- 



# Bilirubin Metabolism

- Blood
- Conjugated & Conjugated
- Urine – Urobilinogen
- Stool – Stercobilin



# Jaundice



# Jaundice





# Jaundice

- Post Hepatic (Obstructive) – **Stone, tumor**
  - Conjugated/Direct Bil, High colored urine,
- Pre Hepatic (Acholuric) - **Hemolytic**
  - Unconjugated/Indirect Bil, pale urine
- Hepatocellular Jaundice - **Viral**
  - Liver damage - unconjugated
  - Swelling, canalicular obstruction - Conjugated
- Conjugated & Unconjugated types.

# ACUTE LIVER DISEASES

Acute presentation of liver disease is most commonly due to toxin or drug injury. Approximately 50% of cases are due to some drug and the most common drug is acetaminophen (an intrinsic hepatotoxin – toxic to everyone); many other drugs show hepatotoxicity only in a subset of the population (typically 1 in 10000 to 1 in 50000 individuals) (idiosyncratic hepatotoxins); generally drug was introduced within the most recent three months. Acute viral infection is histologically indistinguishable to mild drug injury. The most viruses most commonly responsible are hepatitis A virus > hepatitis B virus > hepatitis C virus.

Autoimmune hepatitis can have an acute presentation; suspect when abundant plasma cells are observed.

Many cases of acute liver injury can never be definitively assigned an etiology and are classified as idiopathic.

The most important hepatotropic viruses are A, B, and C. These viruses are most likely to have an acute presentation. Hepatitis B and C virus also have a significant incidence of chronic hepatitis.



# Hepatitis A virus



Single-stranded RNA virus; usually associated with epidemic outbreaks in populations where sanitary conditions are suboptimal; associated with consumption of food or water contaminated by sewage (fecal-oral); no chronic illness or carrier state; usually a self-limited disease; fulminant failure is uncommon but possible

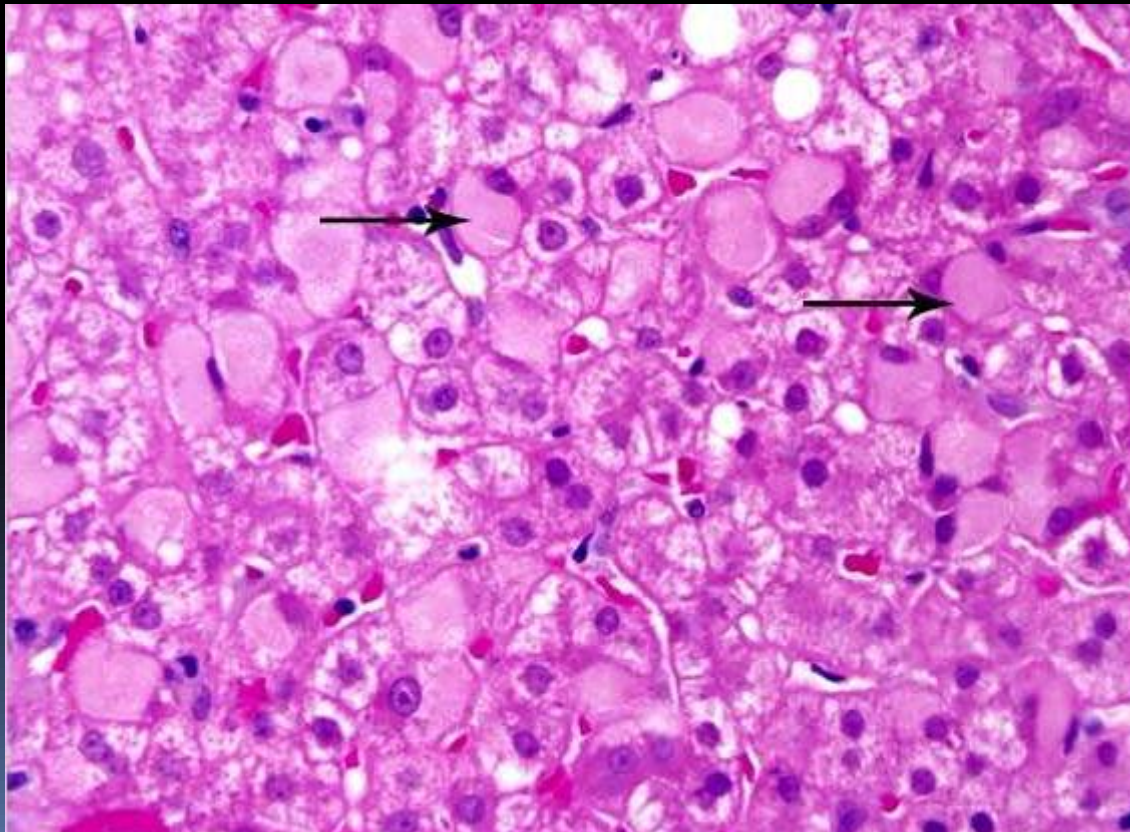
# Hepatitis B virus

Partially double-stranded DNA virus; transmitted by contact with contaminated blood or body fluids; vertical transmission from mother to baby at the time of delivery is common; acute phase lasts one to three months

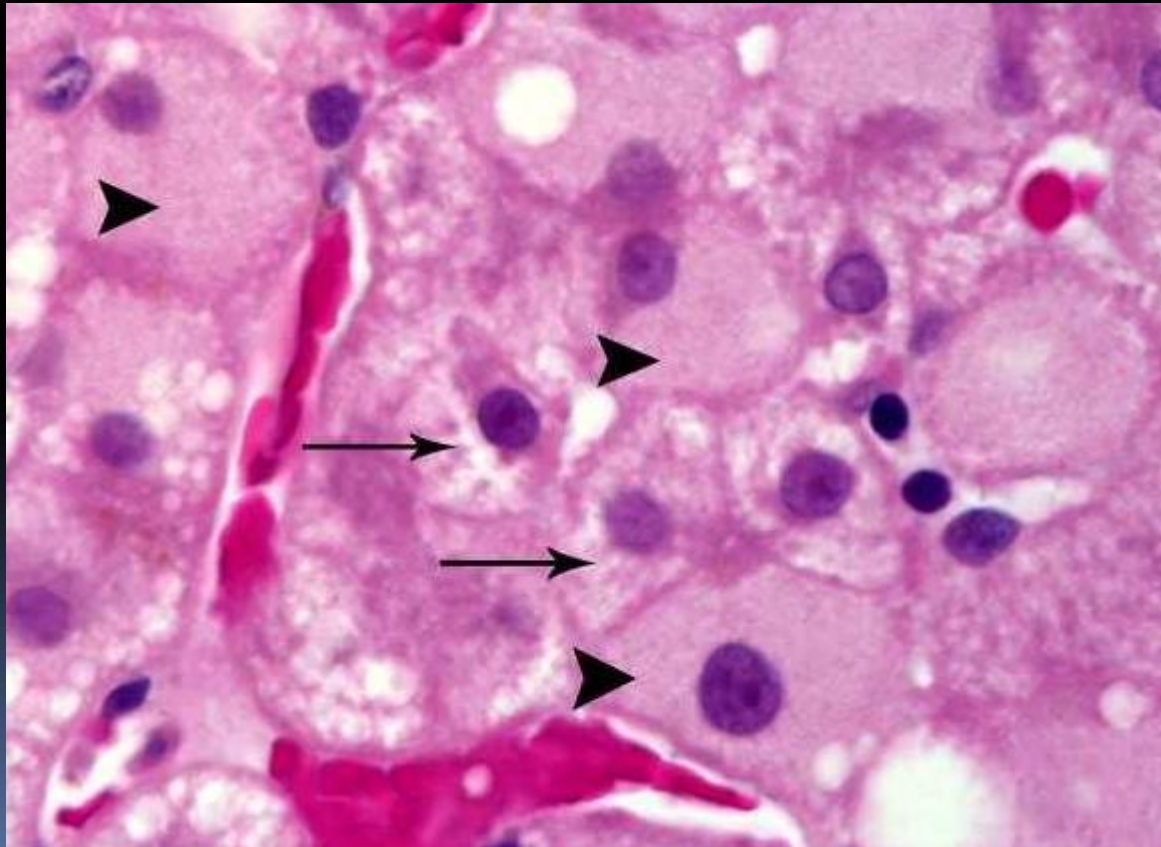
Although the vast majority of patients recover from their infection, there is a rare fulminant hepatitis ( $<1\%$ ) with high mortality and approximately 5% will have chronic infection with 20-50% of these patients progressing to cirrhosis (1-2.5% of all infected individuals); The incidence of chronic infection is much higher in patients infected perinatally (roughly 95%) than in young children (50% of children under 5 will suffer persistent infection) than in adults (5% overall) The serologic changes during HBV infection are well-characterized and can be used to determine the phase of illness of each patient Persistence of infection is indicated by HBsAg, HBeAg, HBV DNA, anti-HBc, and possibly anti-HBs; these tests indicate patients at risk of progressive liver injury



Liver biopsies from patients with chronic hepatitis B show pathomononic ground glass hepatocyte inclusions (arrows) distributed singly in a haphazard fashion with no zoning preference. When numerous, these cells appear in clusters and may resemble oncocyctic hepatocytes. However, in contrast to oncocyctic hepatocytes hepatitis B inclusions have an amorphous or finely granular and paler look.

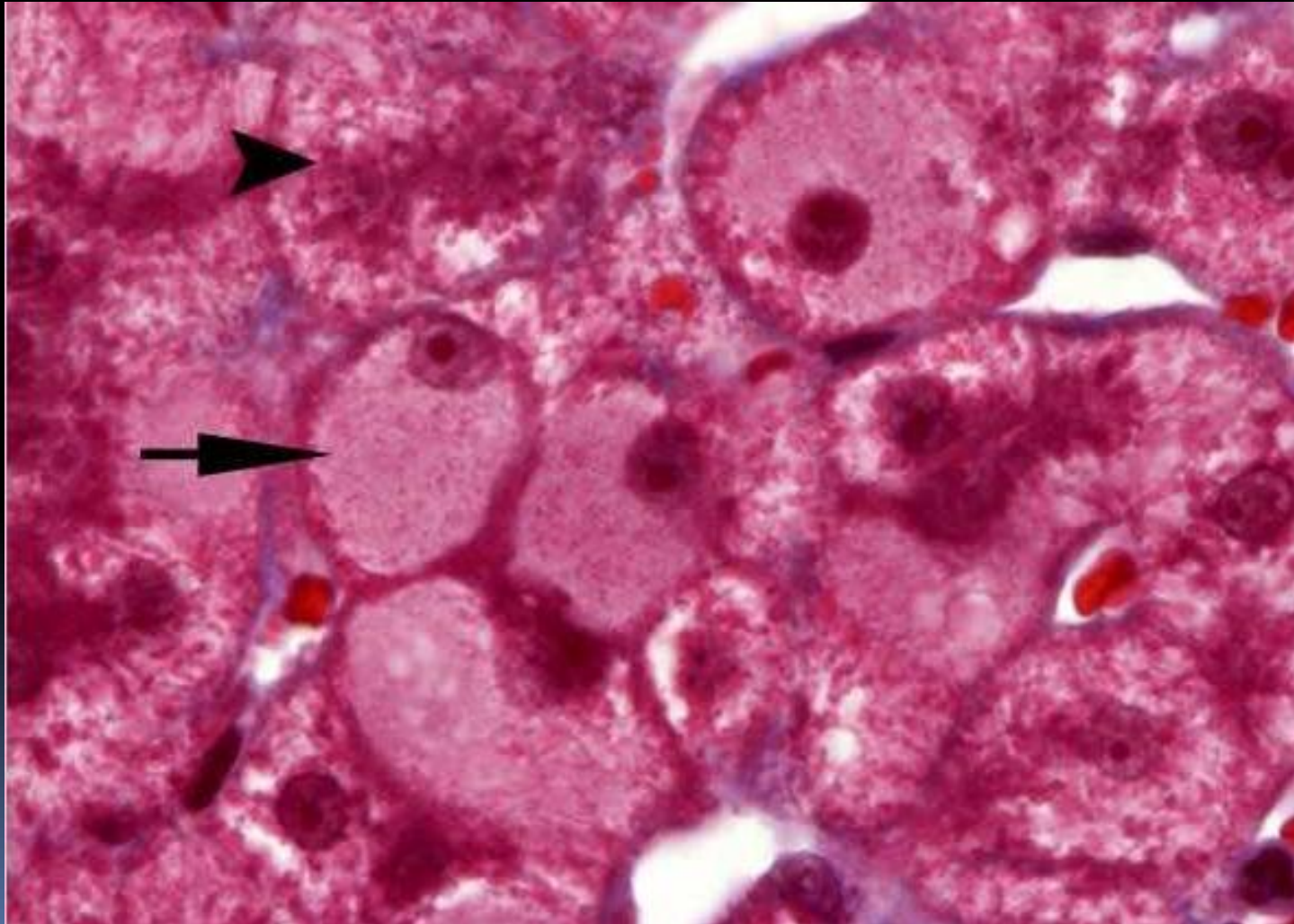


Three ground-glass hepatocytes are depicted (arrowheads) and shown in contrast to two hepatocytes without ground glass inclusions (two long arrows). The liver biopsy is, rarely if ever, performed to diagnose chronic hepatitis B since serologic tests are sufficiently sensitive to make that diagnosis. However, a liver biopsy may be indicated to grade and stage chronic hepatitis B.





A trichrome stain shows typical ground-glass appearance of cells containing hepatitis B inclusions (arrow). A hepatocyte without such inclusions is shown with an arrowhead.



Note the contrasting morphologic features of a hepatocyte with ground-glass hepatitis B inclusion (#1) and a normal hepatocyte (#2) without such inclusions. The ground-glass appearance is due to the presence of hepatitis B surface antigen within proliferated endoplasmic reticulum throughout the cell. The inclusion may become so big that it pushes the nucleus to the side.





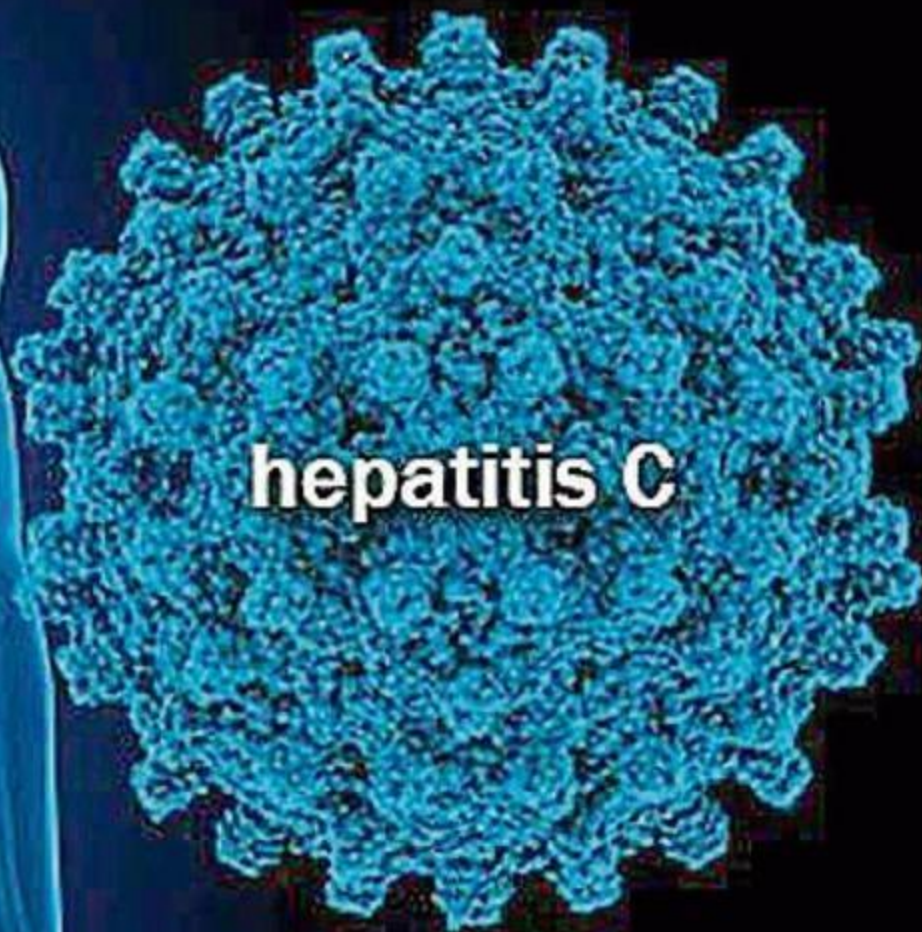


# Hepatitis C virus

- Single-stranded RNA virus; transmitted primarily by contact with contaminated blood; sexual transmission is theoretically possible but not well-documented; vertical transmission appears rare
  - The vast majority of patients (85%) become chronically infected, of these one fifth to one quarter progress to cirrhosis, and half of these will die of hepatic failure or carcinoma (approximately 10% of all infected individuals)
  - An anti-HCV antibody indicates exposure to the virus; PCR and quantitative methods are used to determine the presence and amount of viral RNA in serum
  - Progression of disease is best followed by liver biopsy
- 



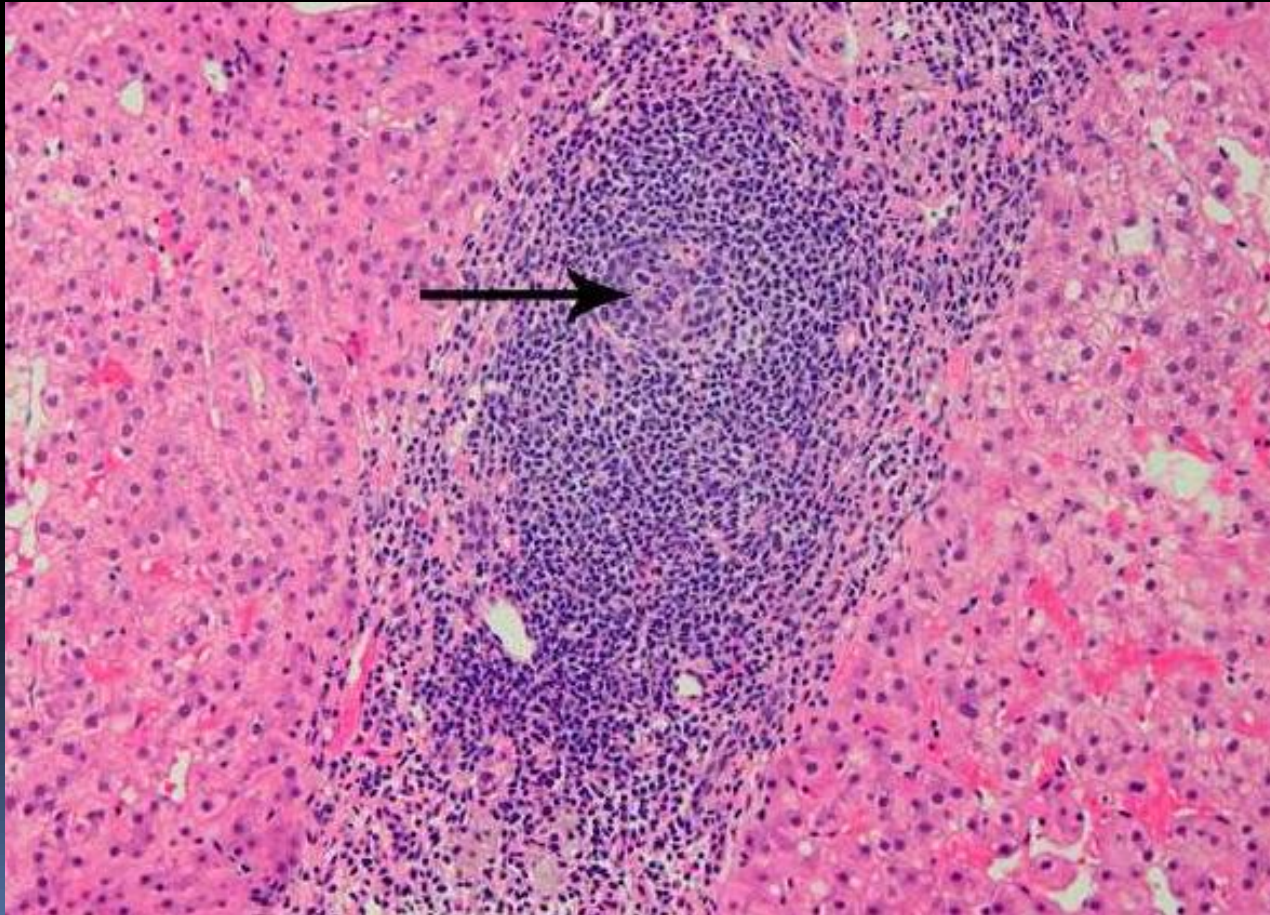
**liver**



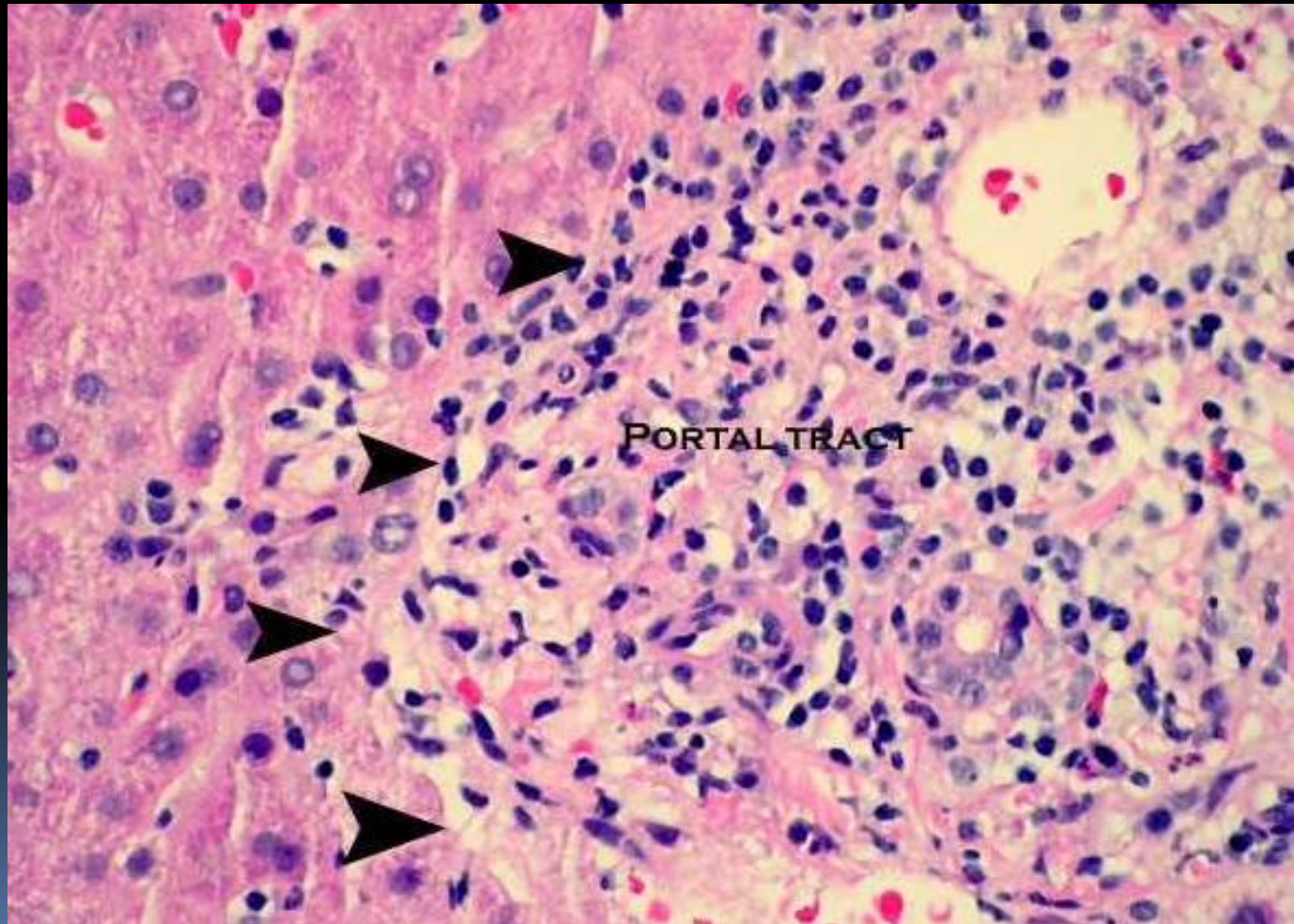
**hepatitis C**



Although portal tracts may contain lymphoid nodules in chronic hepatitis of any cause it is more commonly seen in chronic hepatitis C. Lymphoid follicles with germinal centers (arrow) may also occur. The portal tracts may be expanded because of lymphoid infiltrate.

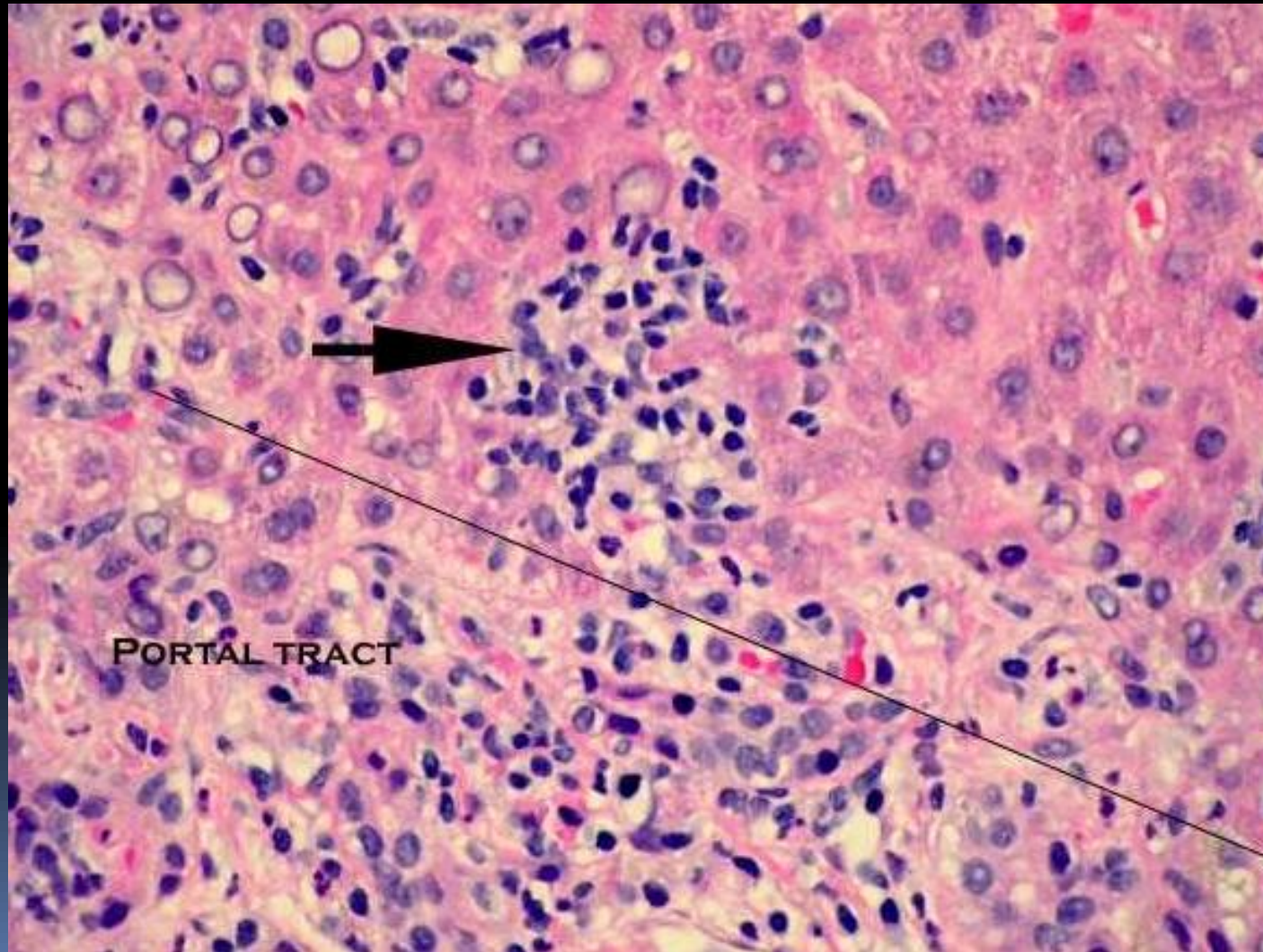


The region of hepatocytes that is in direct contact with the portal tract is known as limiting plate (multiple arrowheads). Inflammation of this region is called interface hepatitis and is a defining histopathologic feature of “activity” in chronic hepatitis. Note chronic inflammation extending focally outside the portal tract. This would be graded as grade 1 interface activity.



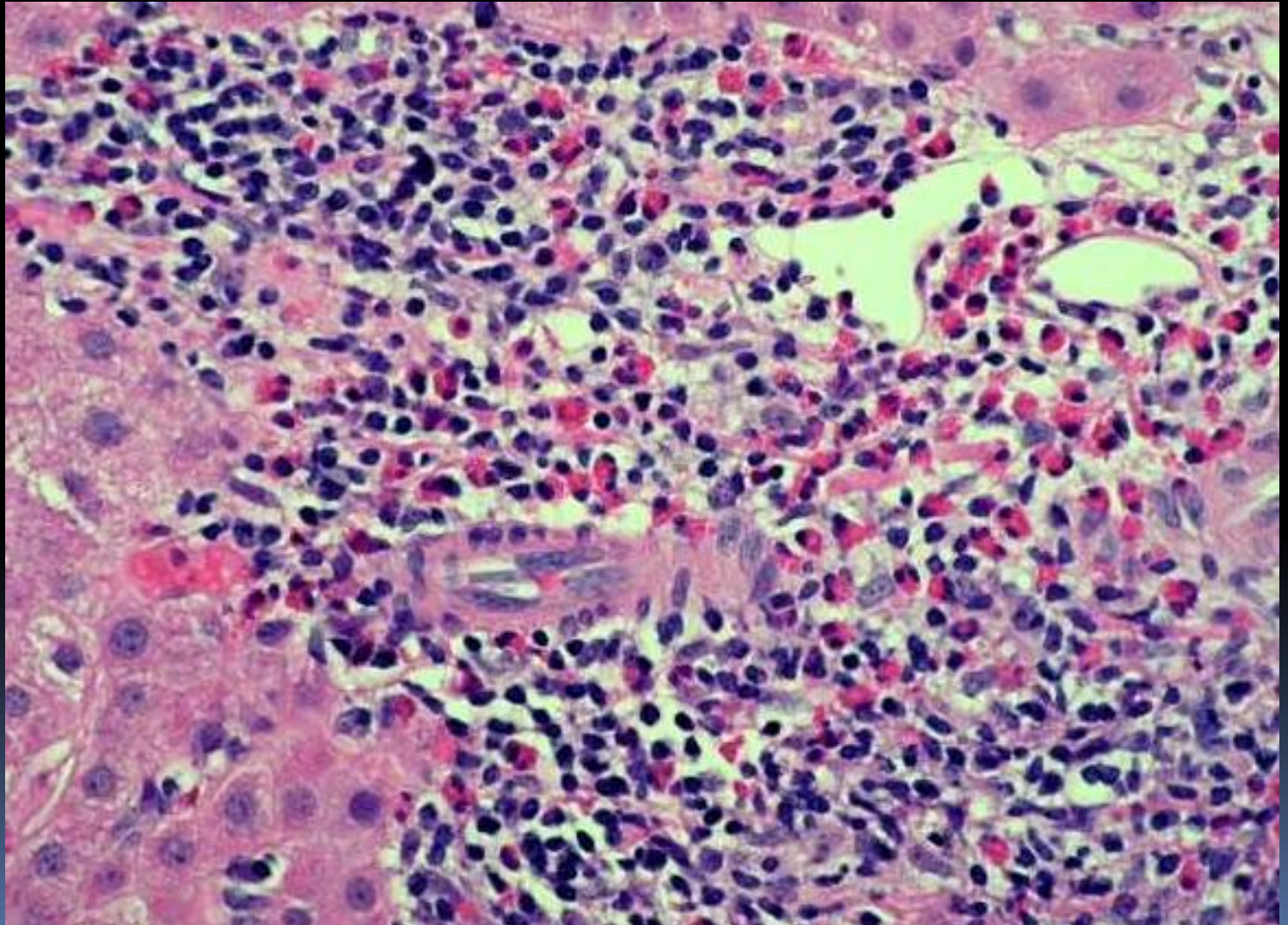


Interface hepatitis, previously known as “piecemeal necrosis” is the extension of inflammation into the periportal hepatocyte region. This would be grades as grade 2 interface activity (arrow).



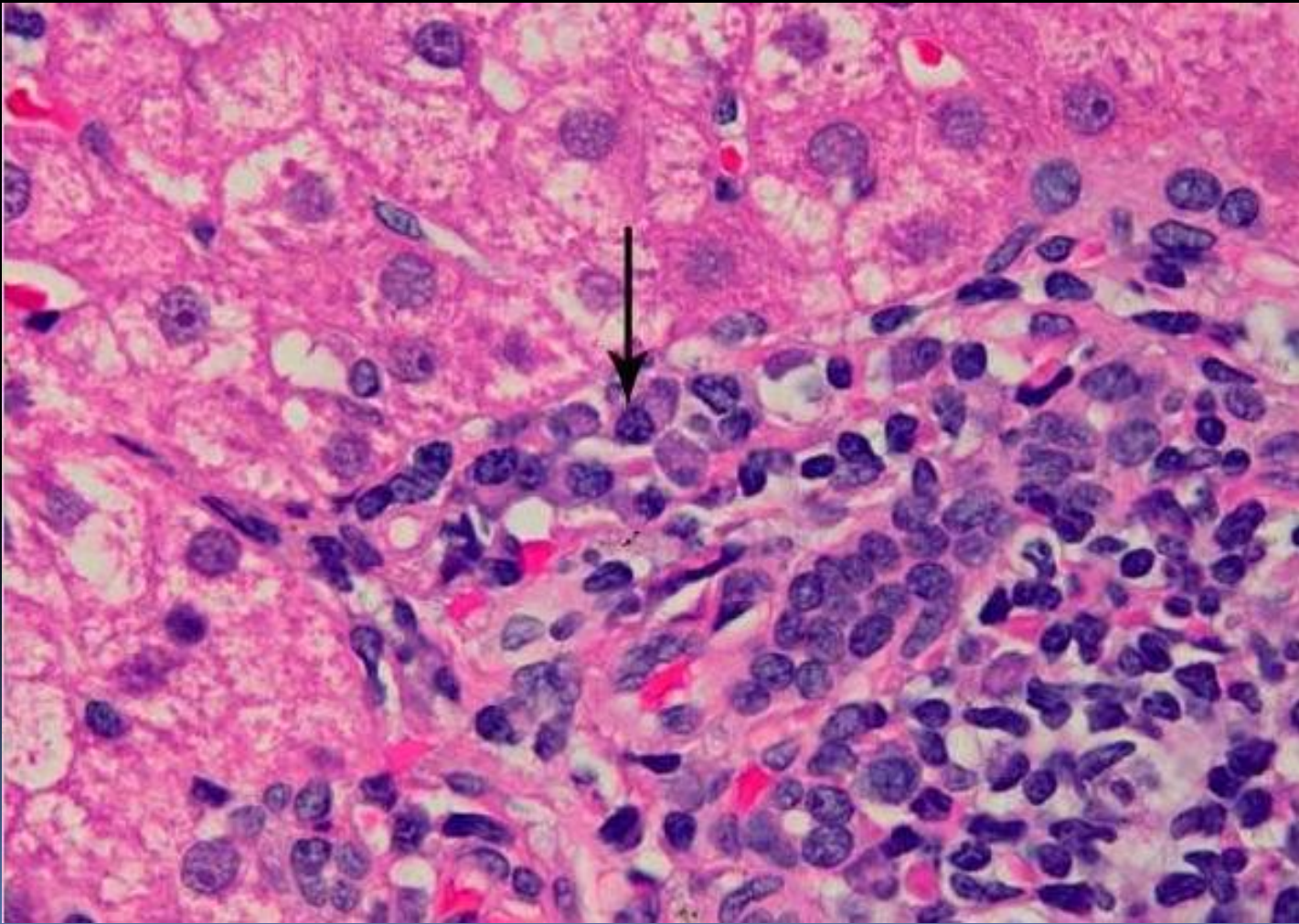


A variable number of eosinophils is generally seen in chronic hepatitis. This case shows an unusually high number of eosinophils in a case of chronic hepatitis C. Note the extension of inflammation into the periportal areas. The presence of increased eosinophils is also a characteristic feature of drug-associated hepatitis.



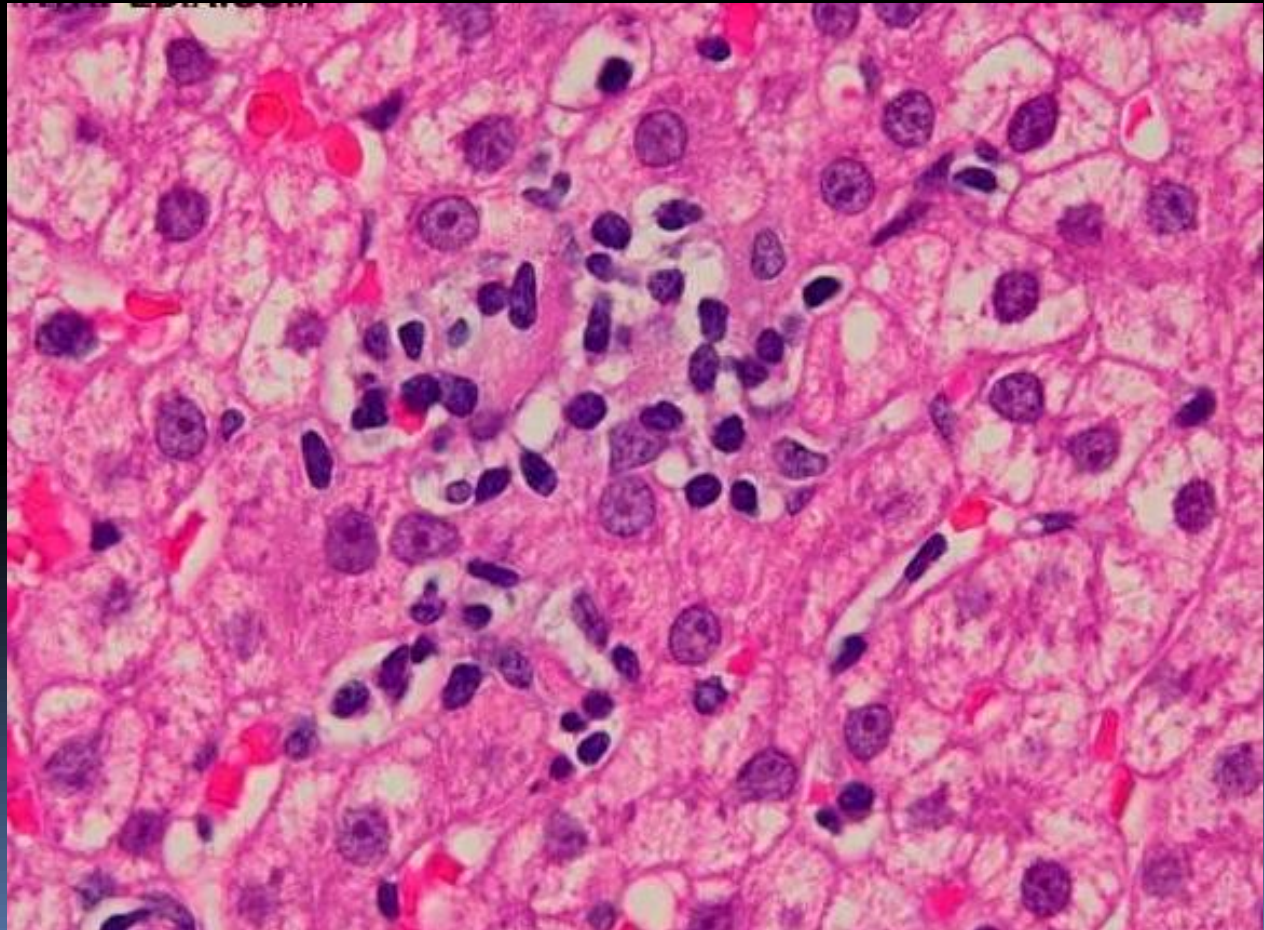


Plasma cells are almost always seen in portal tracts in patients of chronic hepatitis of any cause but the number may be high in patients with autoimmune hepatitis. This case of chronic hepatitis C shows a smaller population of plasma cells at the interface.

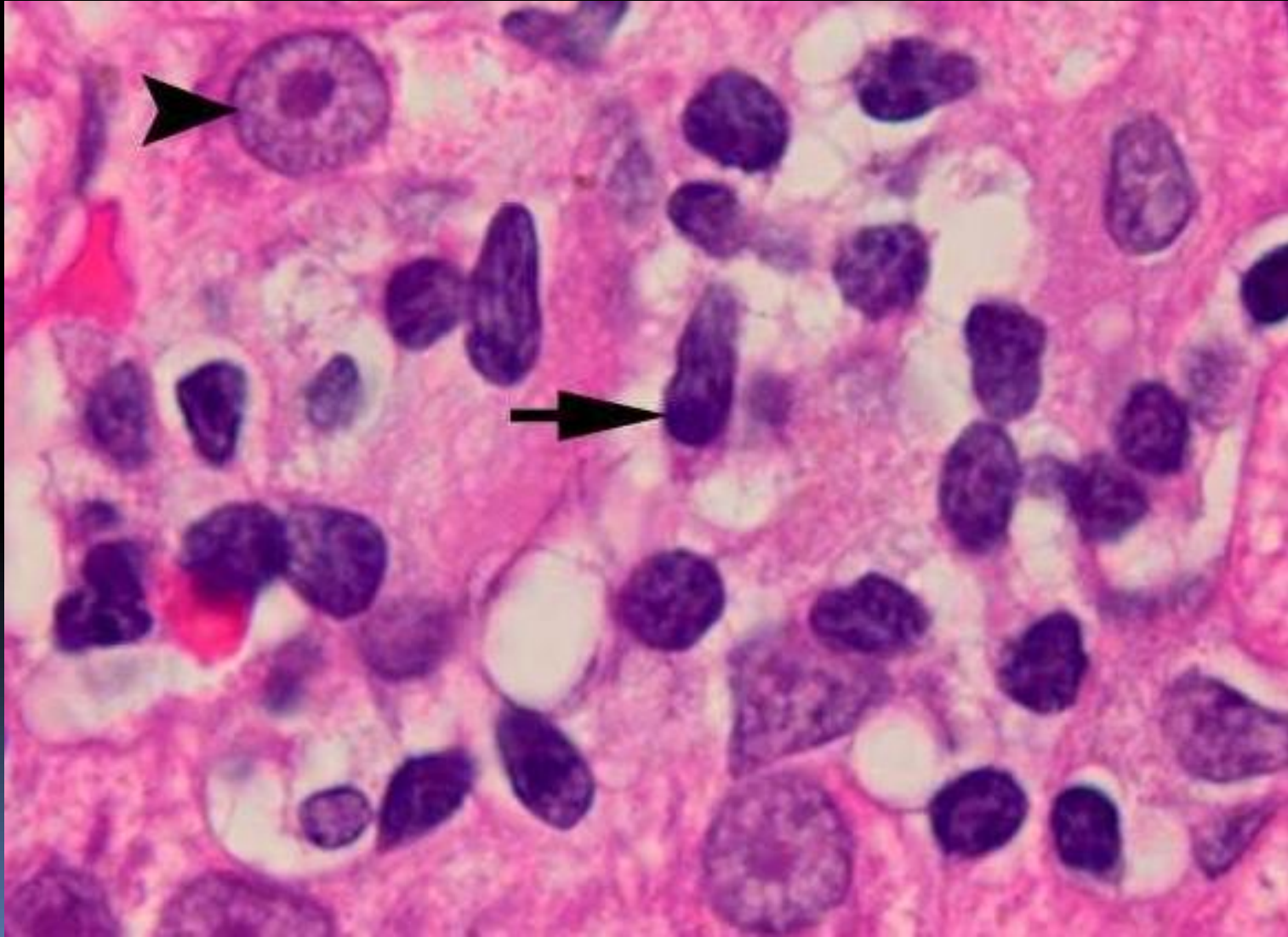




The presence of inflammation within hepatic lobules defines lobular hepatitis and disease activity. Inflammation without any significant hepatocellular necrosis is graded as grade 1/4 whereas focal hepatocellular necrosis as shown in this image is graded as grade 2/4.

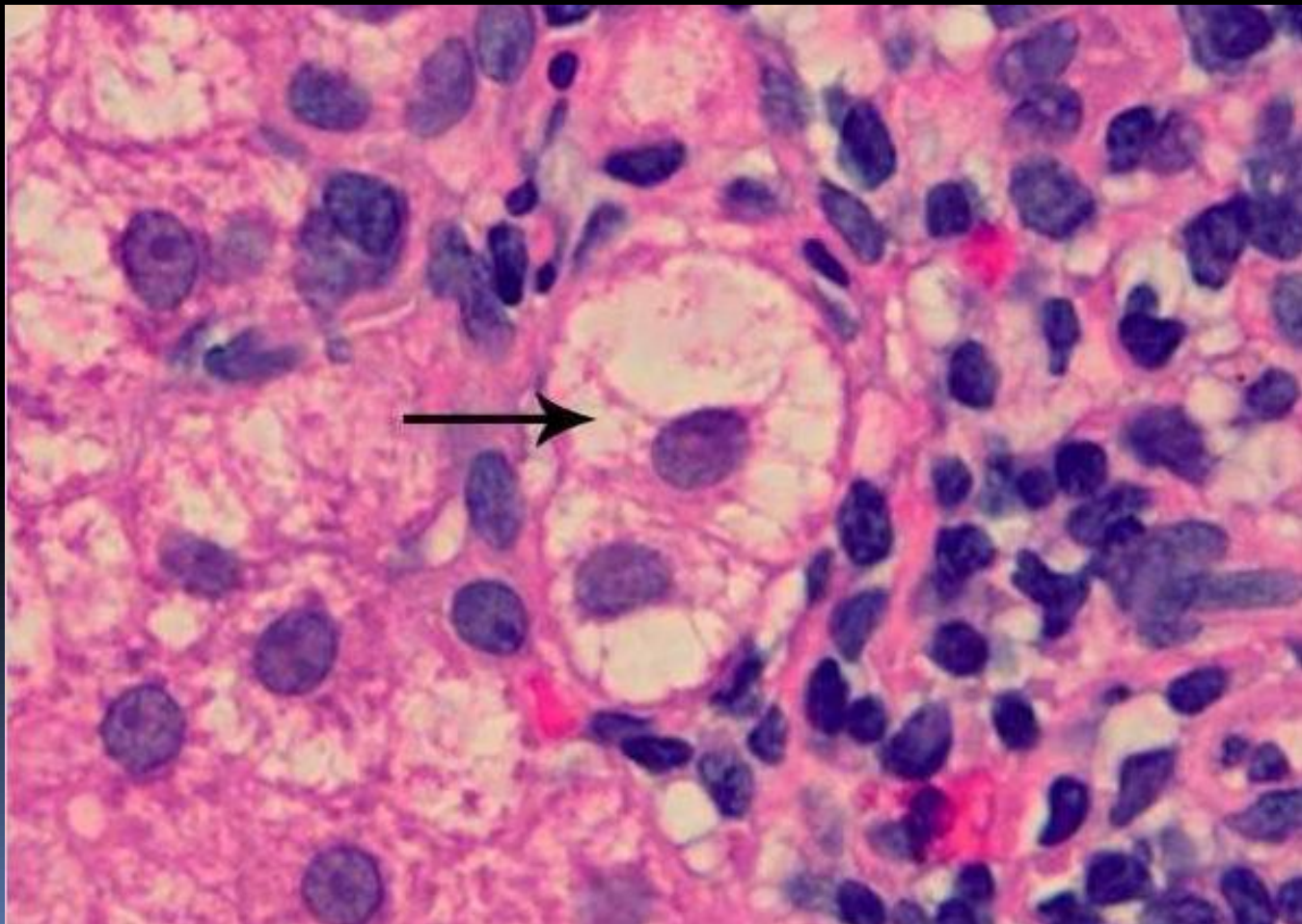


Note the presence of activated lymphocytes (arrow) within hepatic parenchyma with associated cellular necrosis. A hepatocyte with distinct nucleolus is also shown (arrowhead).



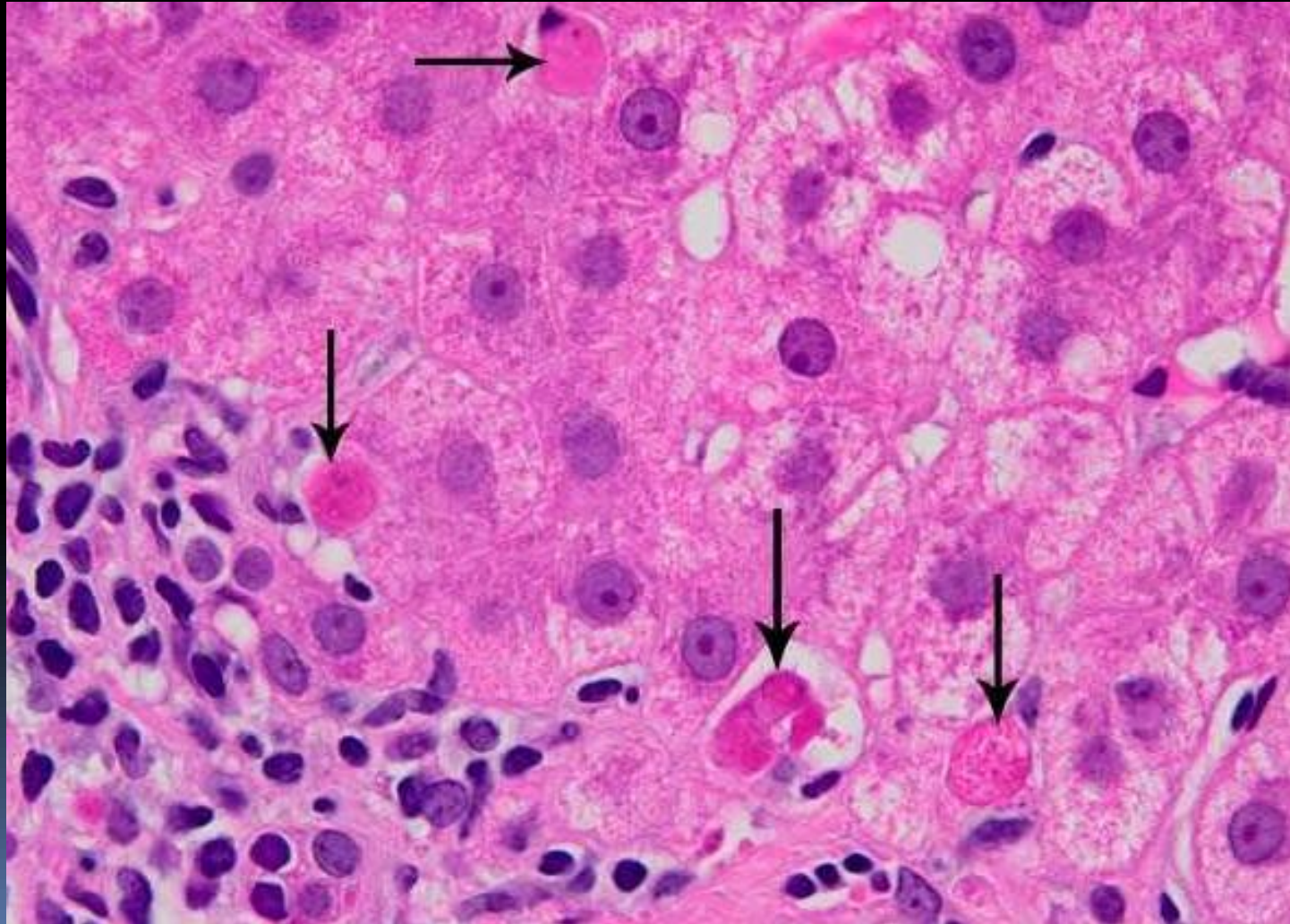


Inflammatory cellular injury may be manifested by ballooning enlargement of hepatocytes with disruption of normal cytoplasmic granular appearance called “ballooning degeneration.” This kind of cellular injury is not specific to any single entity but is commonly seen in chronic hepatitis C.



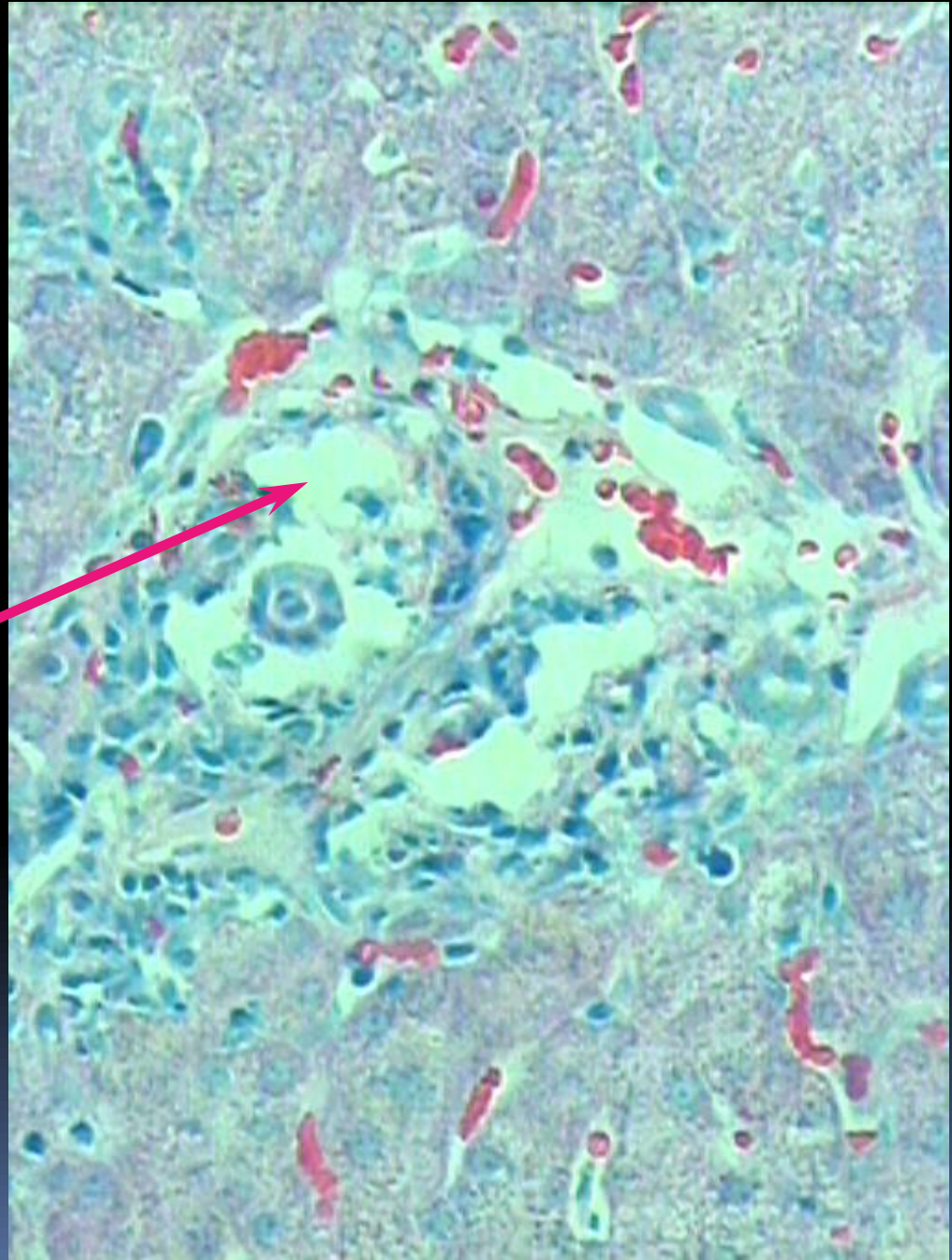


Hepatocellular death by apoptosis at the site of inflammation is a common feature of chronic viral hepatitis. Apoptotic cells show condensed eosinophilic cytoplasm and dark condensed nuclei. Nuclei may disappear leaving what is called “acidophil” bodies. The presence of hepatocellular necrosis at the interface is a pathognomonic feature of disease activity and damage of hepatocytes.



•Blood vessels in  
portal tract

•Azur&E, x80.



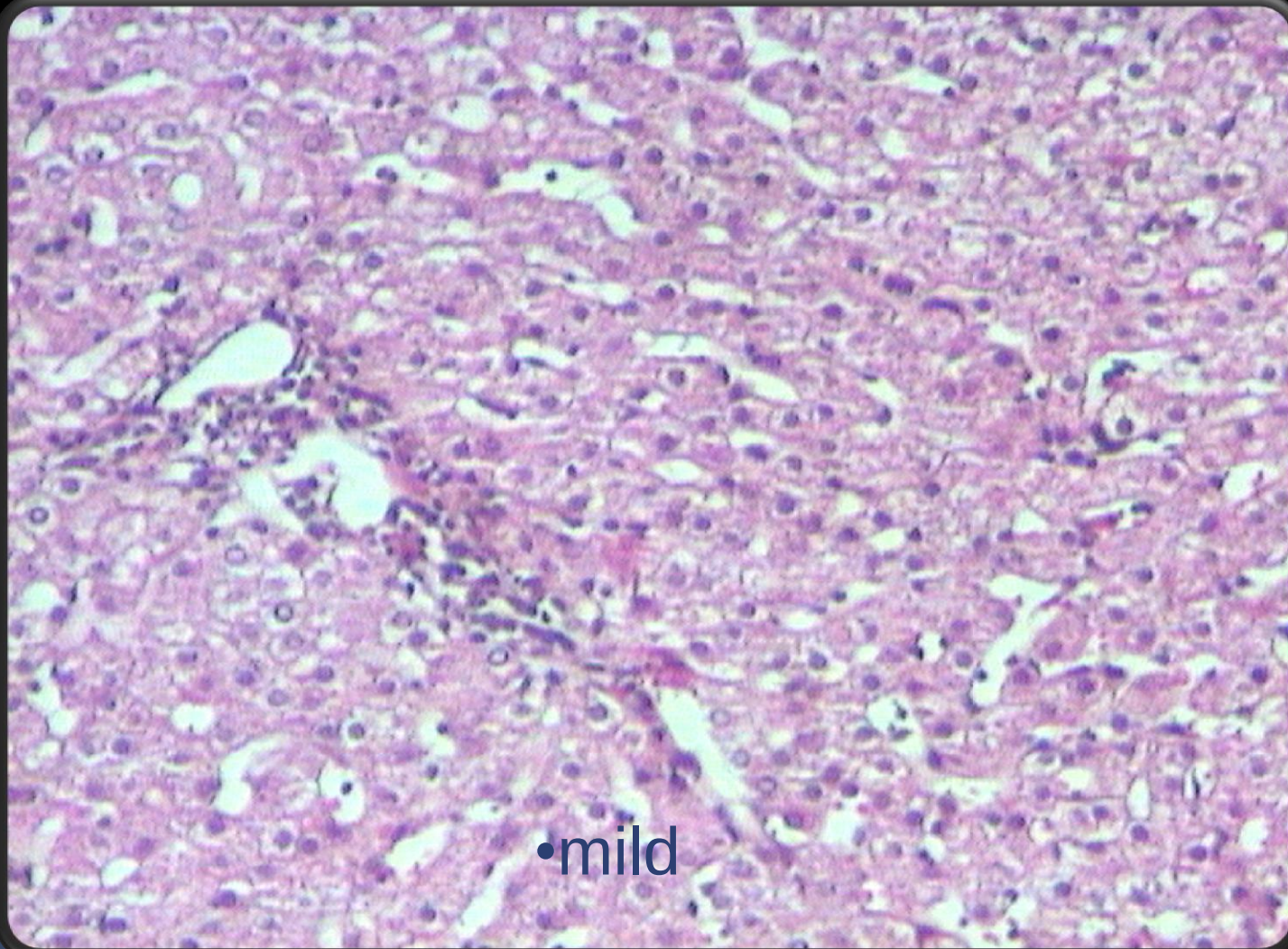


# Hepatitis D virus

- Replication incompetent RNA virus that depends on the presence of hepatitis B virus to cause pathology
  - HDV coinfection increases the damage caused by HBV and increases the likelihood of fulminant hepatitis, active hepatitis, and progressive liver injury due to HBV
  - HDV is found rarely in IV drug users and hemophiliacs; More common in the Mediterranean, Middle East, and Africa
- 



# •Chronic Viral Hepatitis





## •Hepatitis E virus

- Unenveloped single-stranded RNA virus
- Enterically transmitted water-borne infection; epidemics have been reported in Africa, Asia, and South America
- In the United States this is mainly a disease of travelers and immigrants
- The disease is generally self-limited but causes a high rate of mortality in pregnant women



## •Hepatitis G virus

- At present, no disease associated with infection; may actually protect HIV+ patients by inhibiting HIV replication
- 

# Alcoholic Fatty Liver





# Steatohepatitis

## Alcoholic

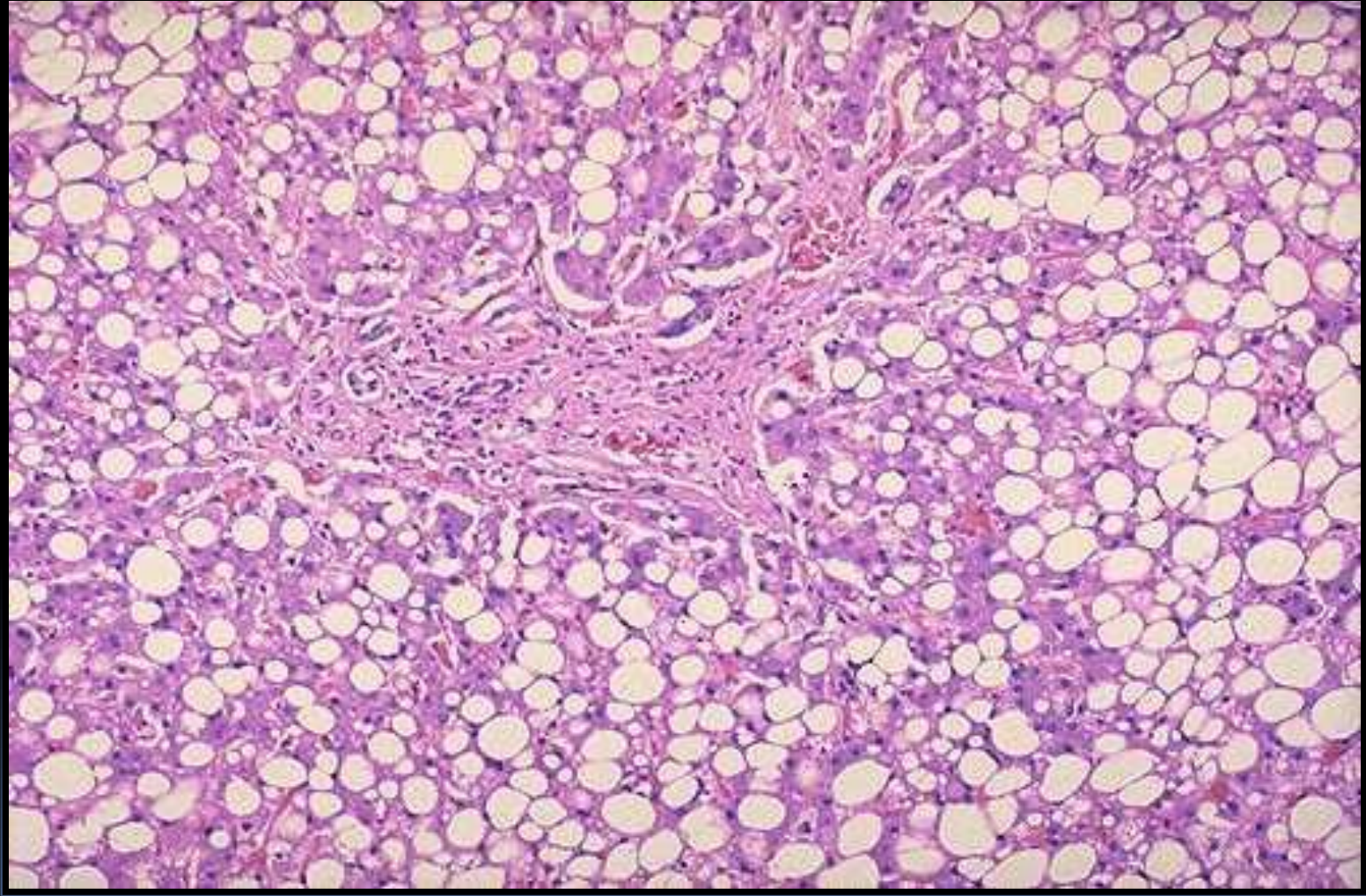
The most common cause of liver injury in the Western world. Early changes associated with alcohol use involve accumulation of lipid by centrilobular hepatocytes (zone 3 steatosis) with gradual extension of steatosis to involve the entire hepatic lobule.

Grossly, the liver is enlarged (4-6 kg vs 1.5 kg normal weight), yellow (because of lipid content) and easily injured.

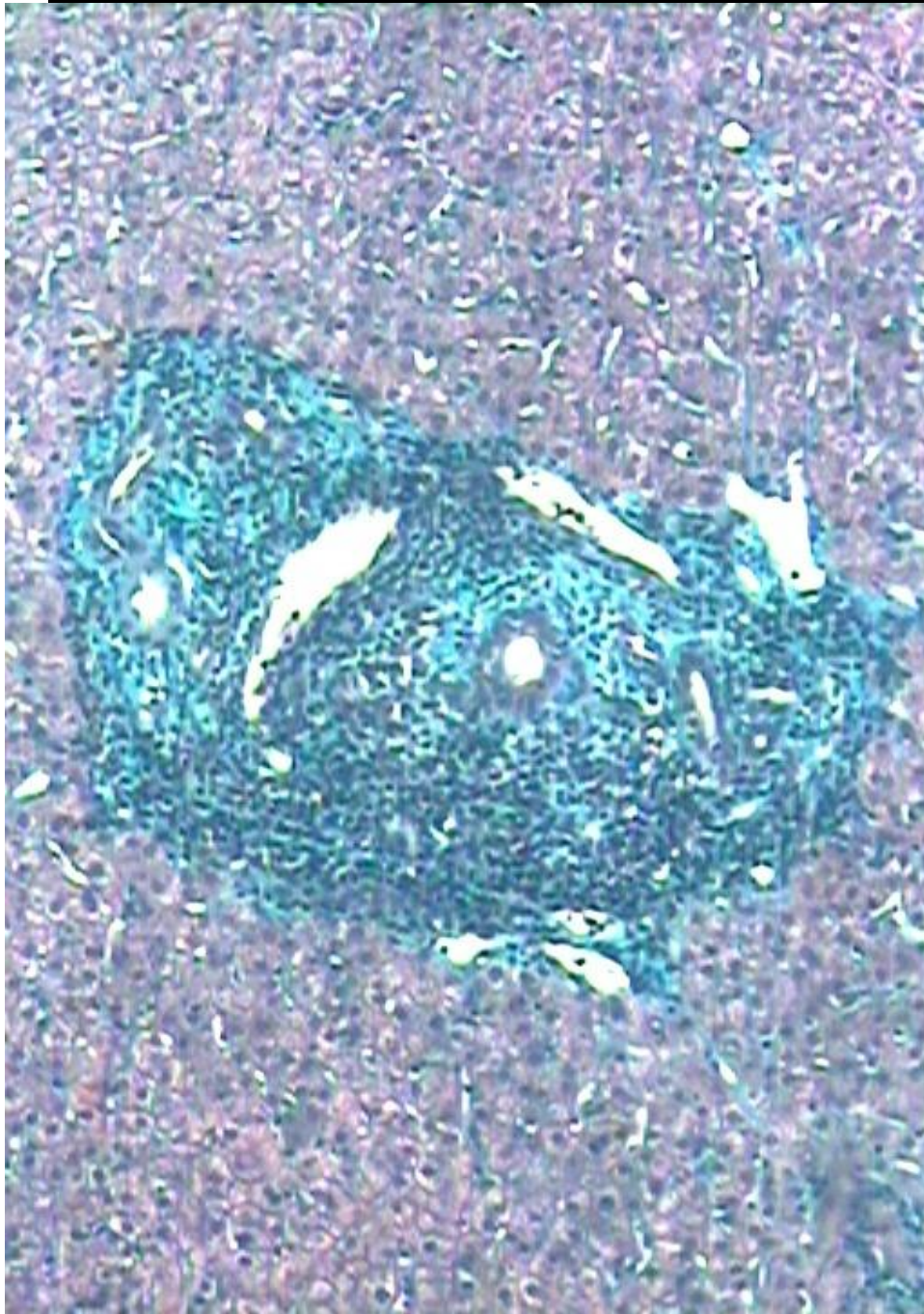
A fraction of patients develop superimposed hepatocytic injury (alcoholic hepatitis) as indicated by hepatocyte ballooning, neutrophilic inflammatory infiltrates, and intrahepatocytic inclusions (Mallory's hyaline)

Fibrosis begins around central veins with pericellular extension progressing to septal fibrosis and cirrhosis.

# Alcoholic Fatty Liver







- Fibrosis

- x80.



•Branch of PV

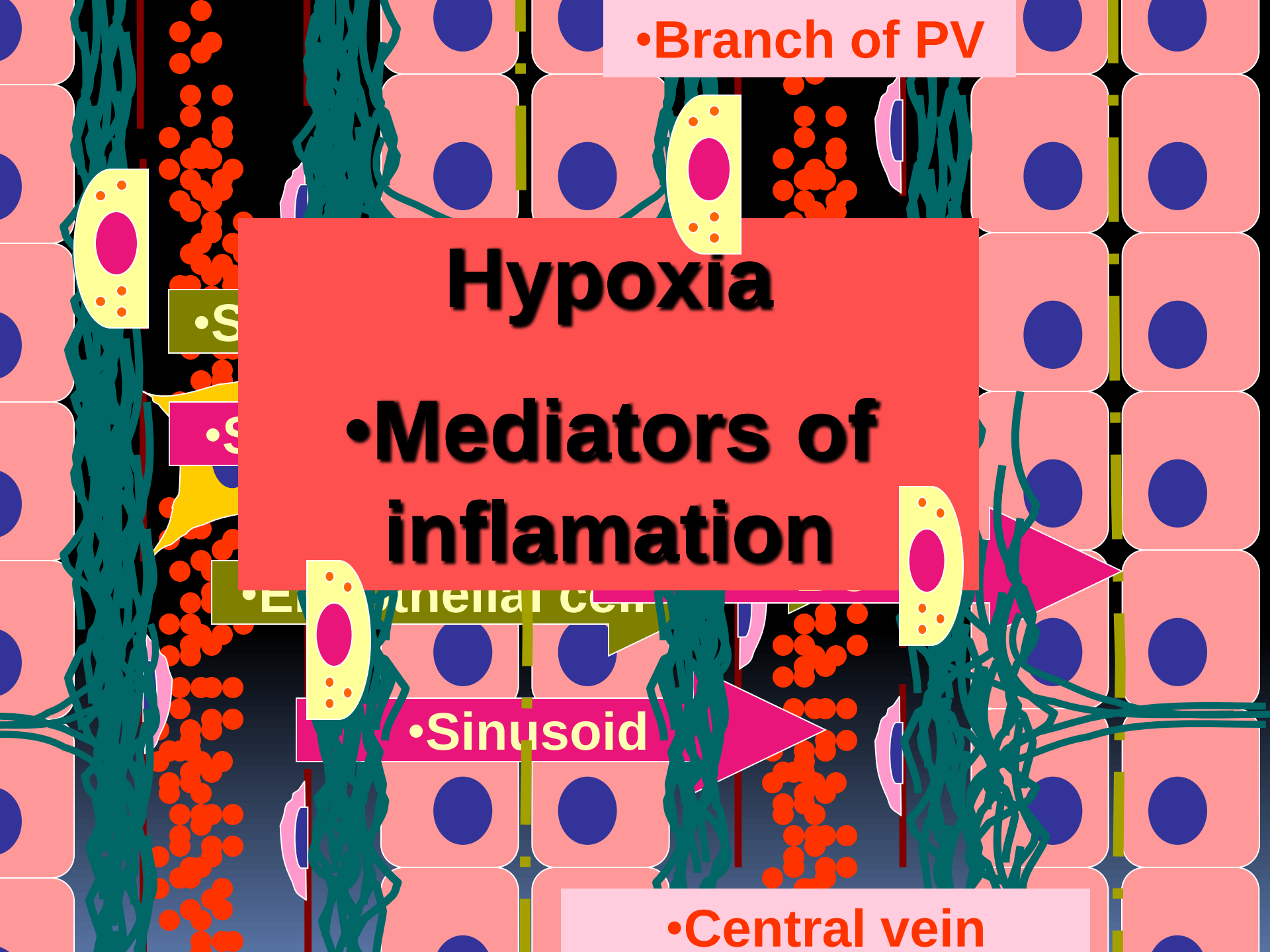
# Hypoxia

## •Mediators of inflammation

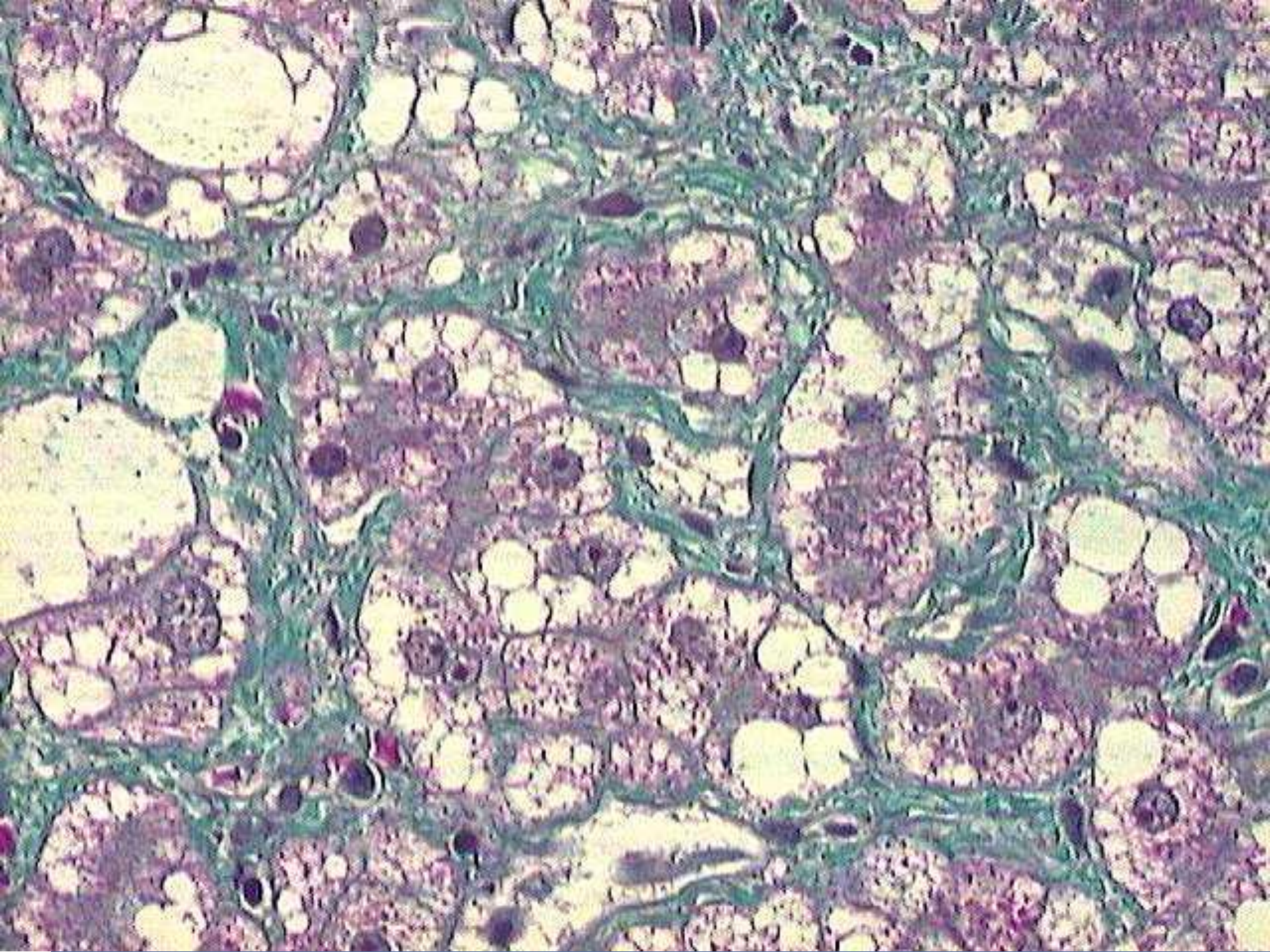
•Endothelial cell

•Sinusoid

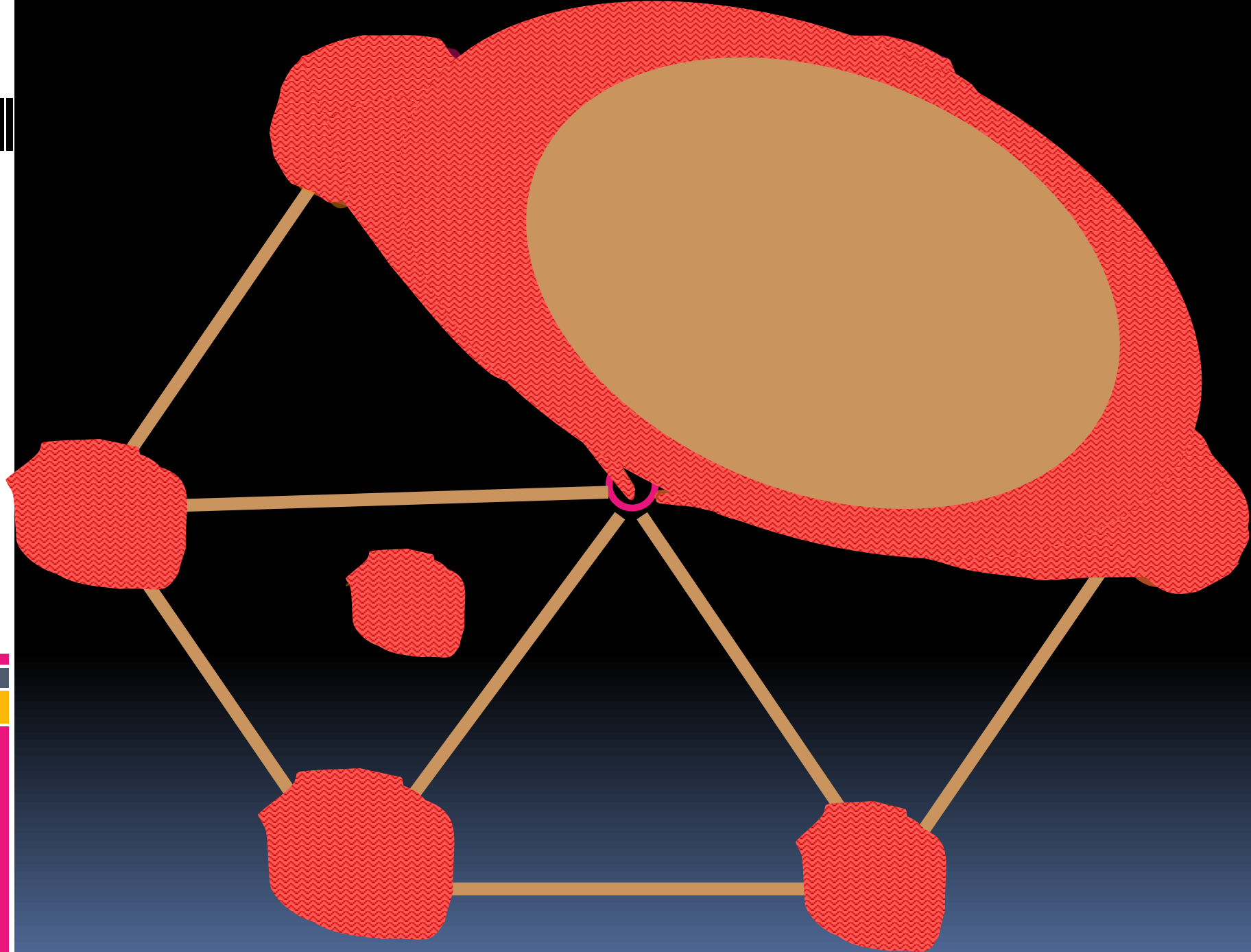
•Central vein





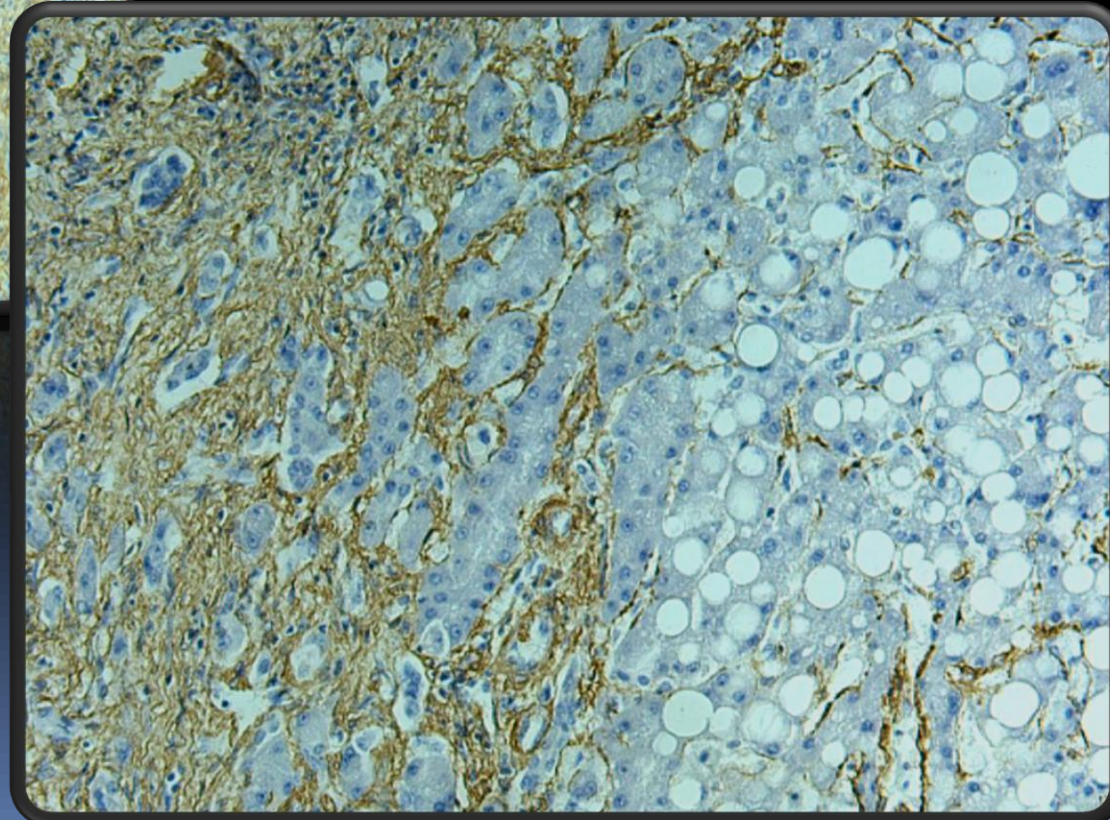
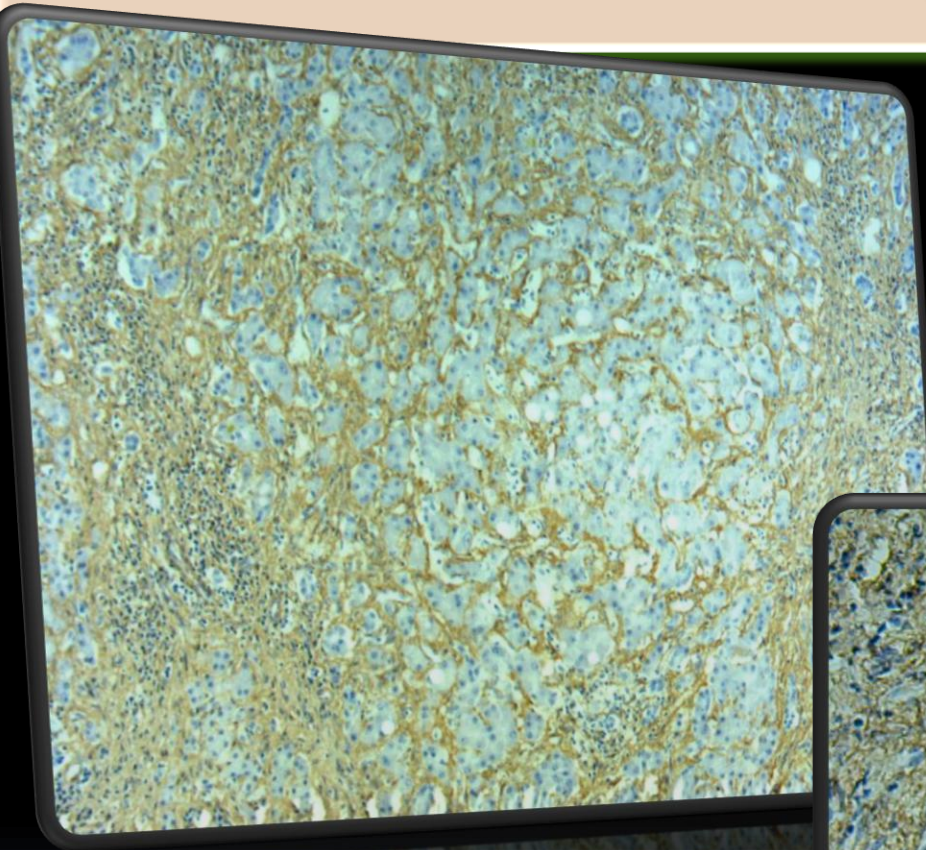




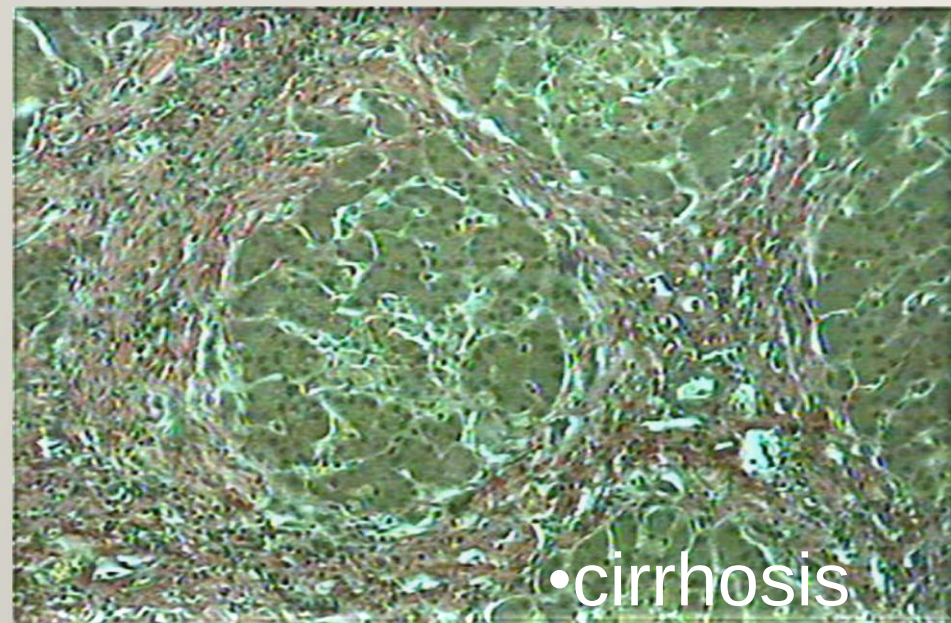
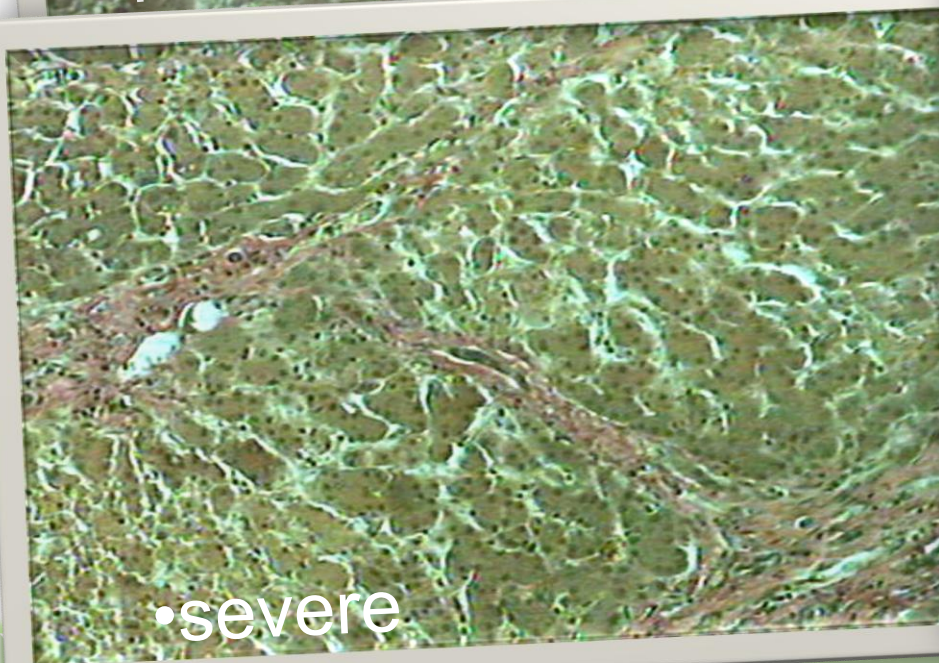
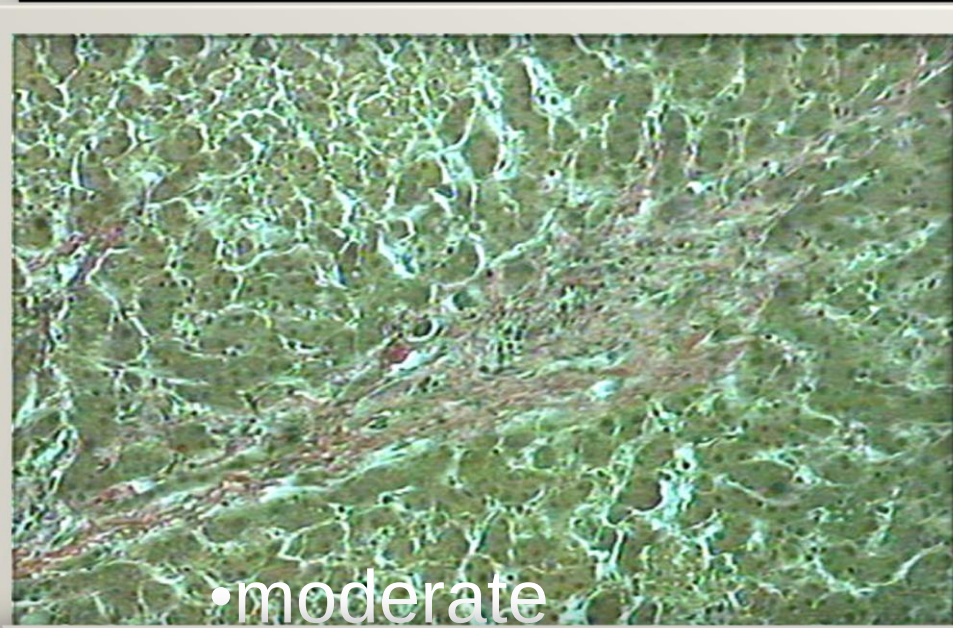
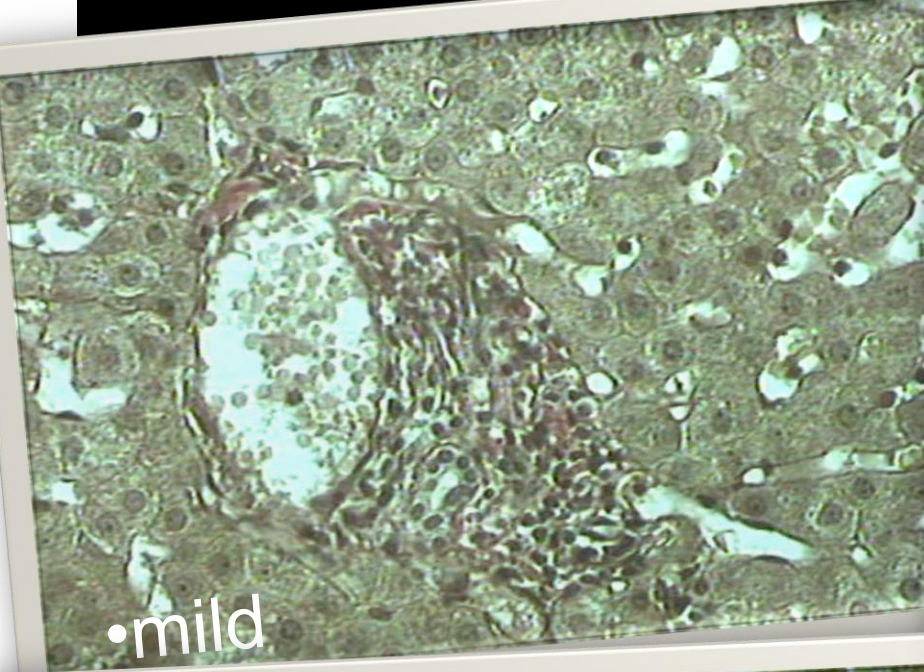




# •Fibrogenesis

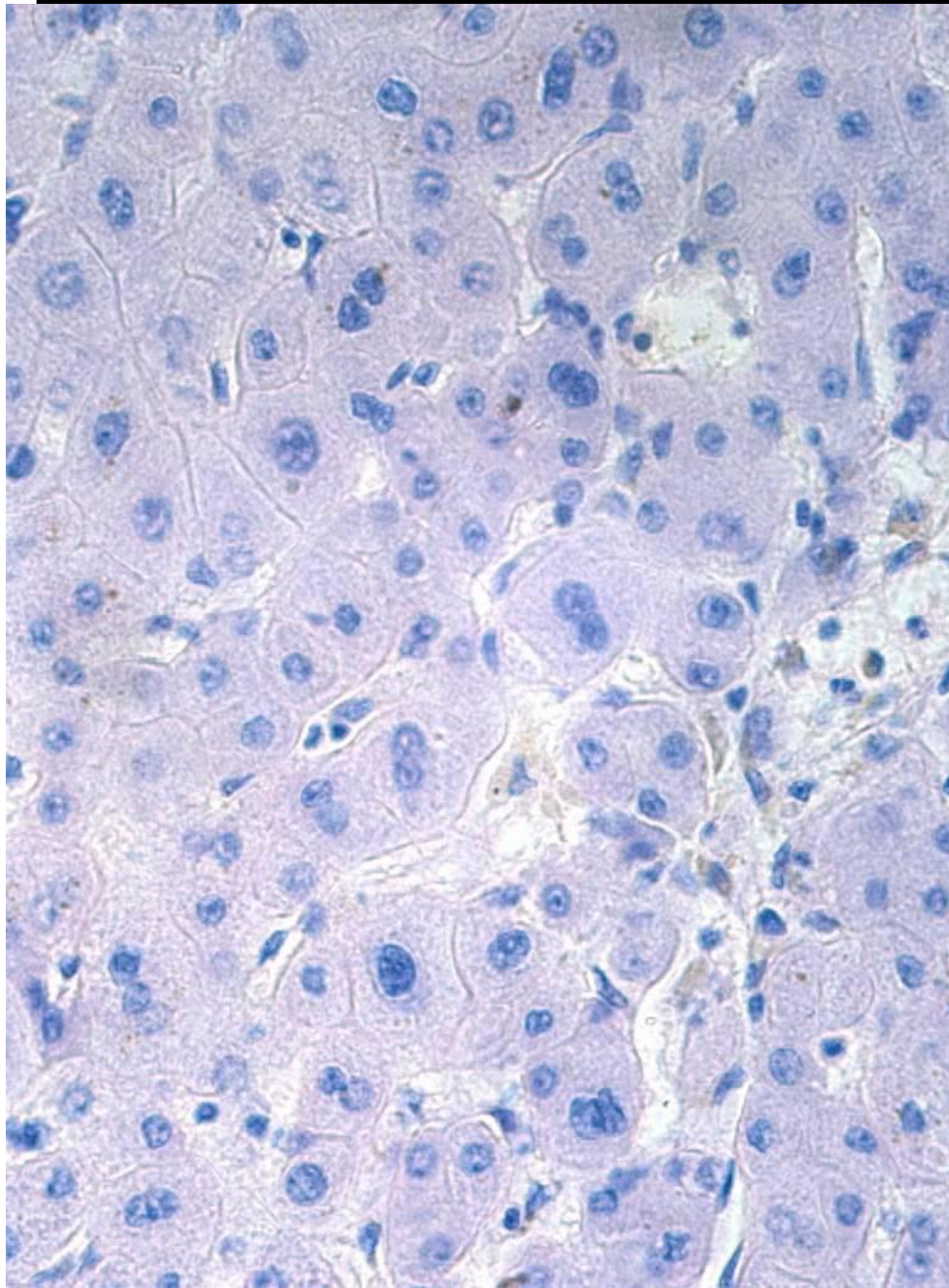






•Fibrosis (V.J.Desmet et al.)





## Regeneration

- H & E, x200.





# CIRRHOSIS

# Definition:

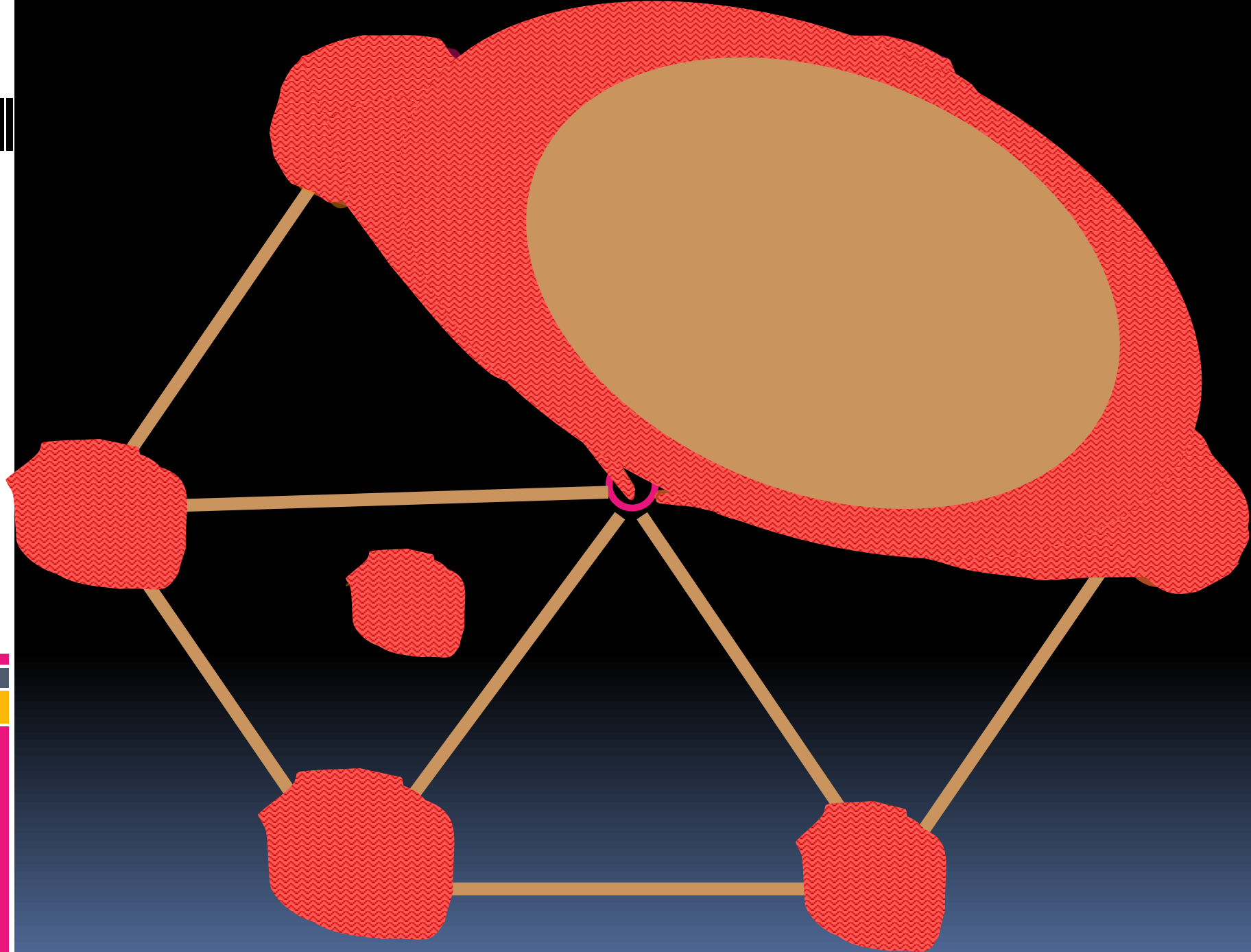
- Diffuse fibrous scarring of liver.
- Nodules of regenerating hepatocytes.
- The major complication of these architectural distortions is alteration in blood flow and blood supply to residual parenchyma.

1. End result of many diseases of liver.
2. Liver failure
3. Portal Hypertension –
  1. Splenomegaly
  2. Porta-systemic shunts.
  3. Ascitis

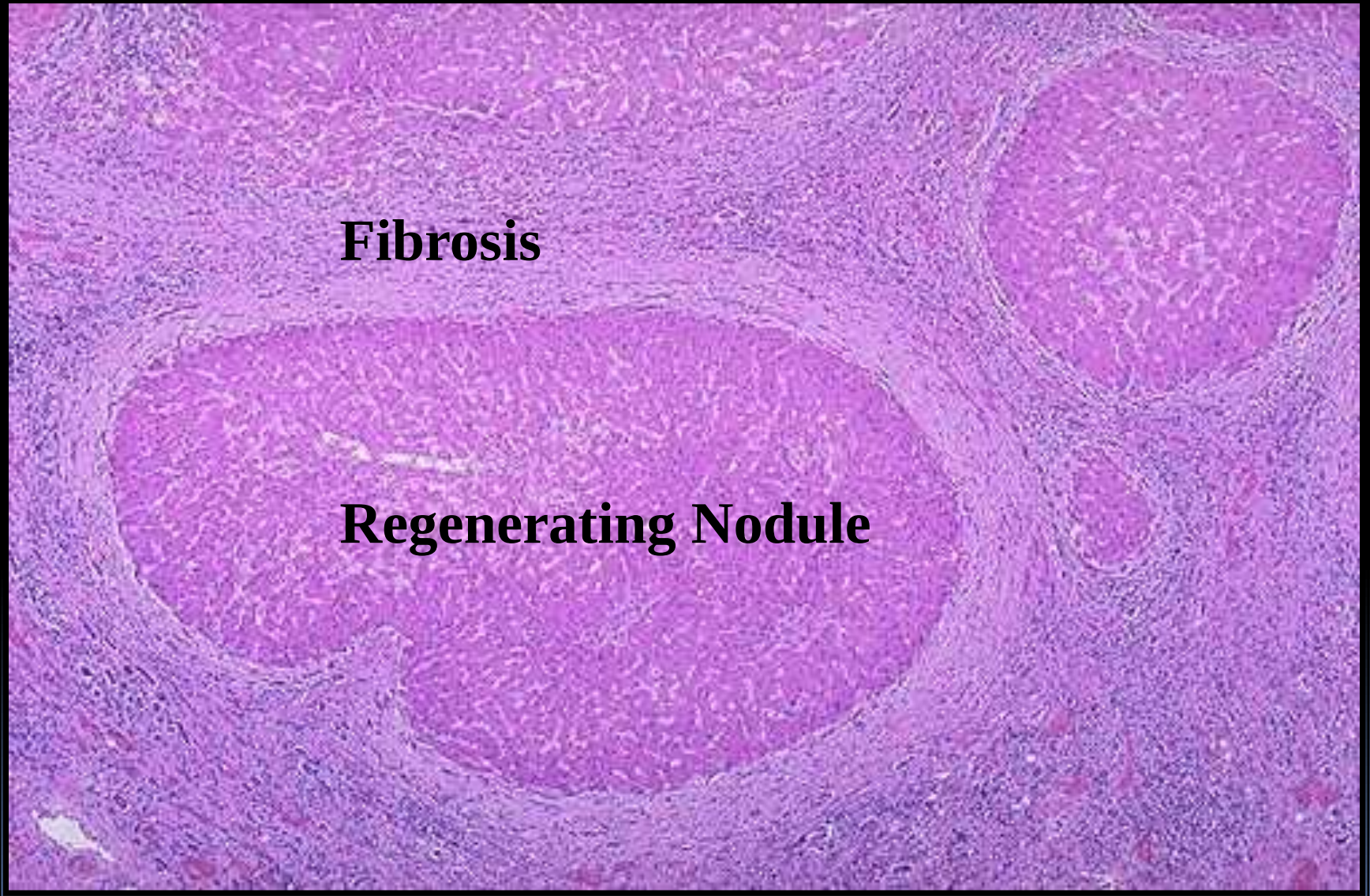
# Cirrhosis







# Cirrhosis



# Etiology of Cirrhosis

- Alcoholic liver disease 60-70%
- Viral hepatitis 10%
- Biliary disease 5-10%
- Primary hemochromatosis 5%
- Cryptogenic cirrhosis 10-15%
- Wilson's,  $\alpha_1$ AT def rare

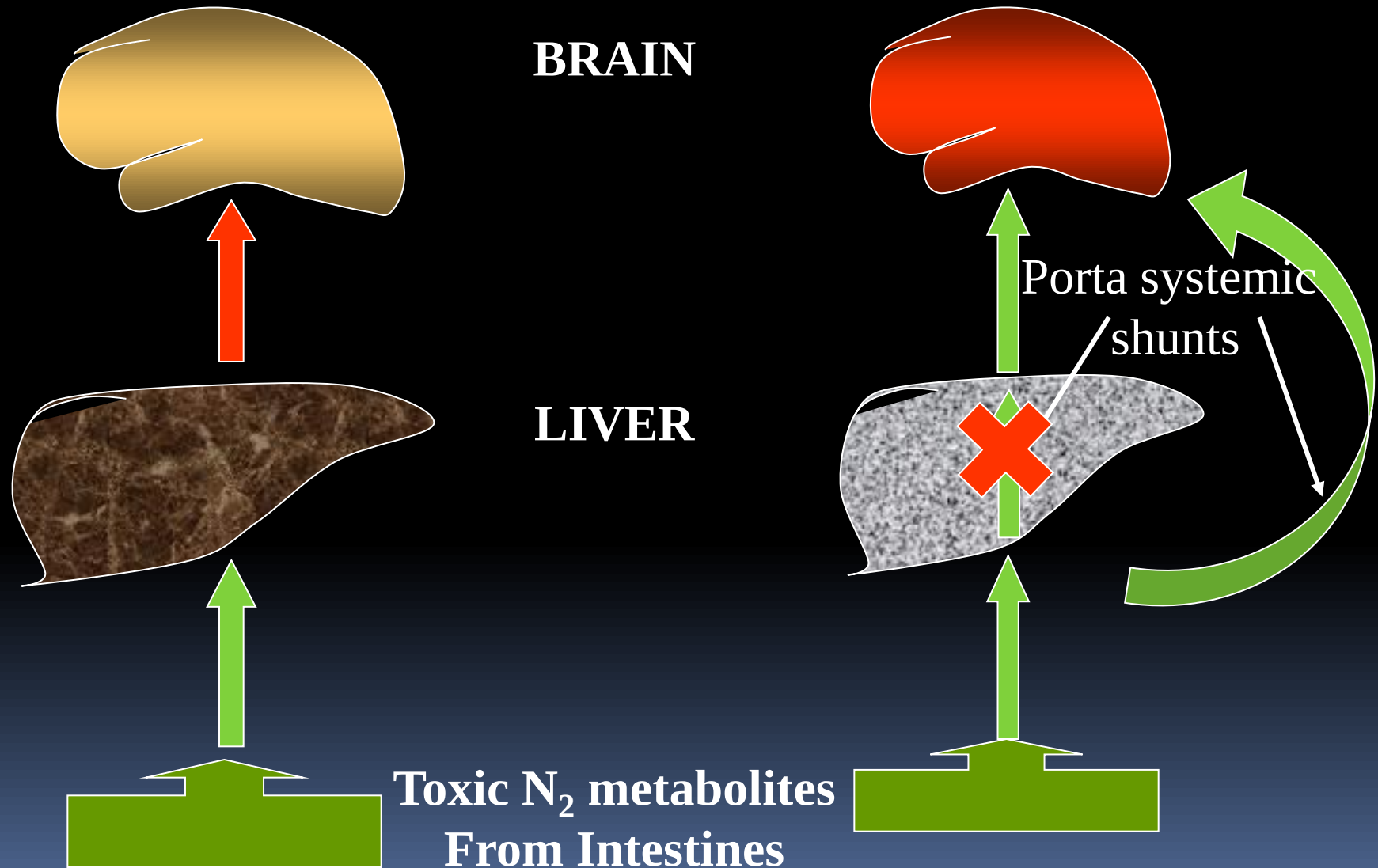




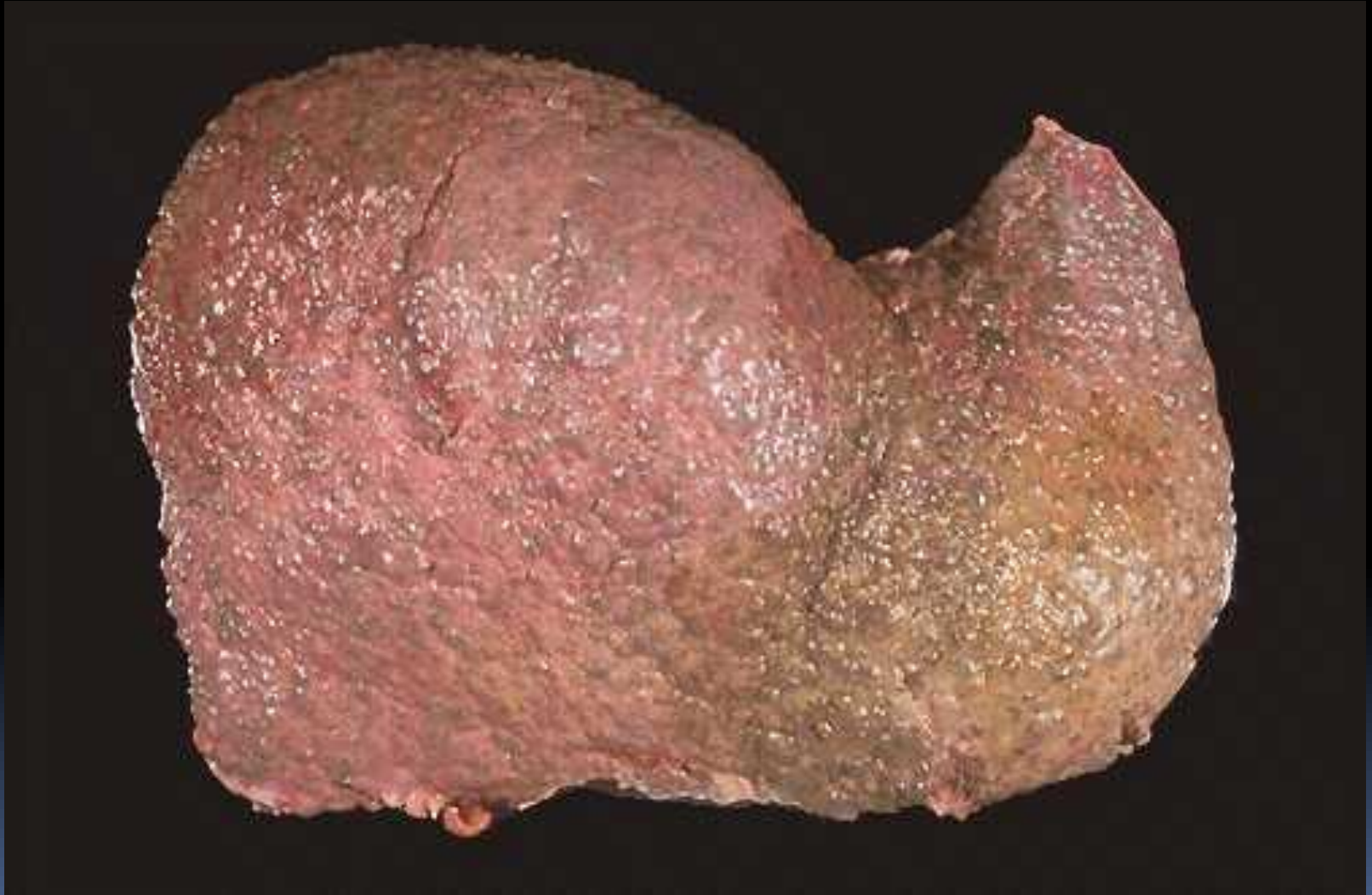
# Pathogenesis

- Hepatocyte injury & necrosis
  - Fibrous scarring
  - Parenchymal regeneration (non functional)
  - Loss of architecture & Vascular disruption
  - Portal hypertension
  - Liver failure – Hepatic coma.
- 

# Pathogenesis of Hepatic Encephalopathy



# Micronodular cirrhosis



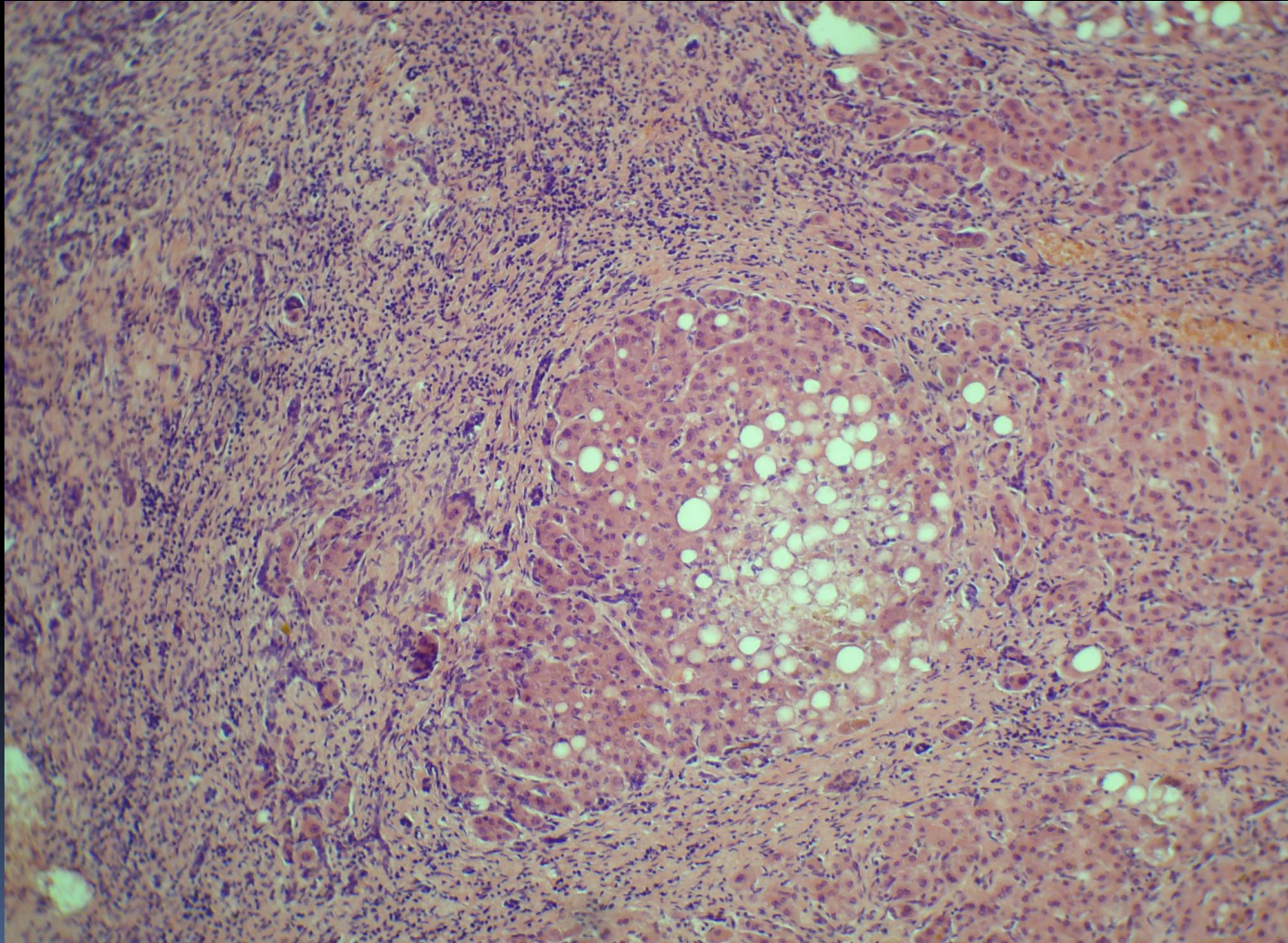


# Micronodular cirrhosis:



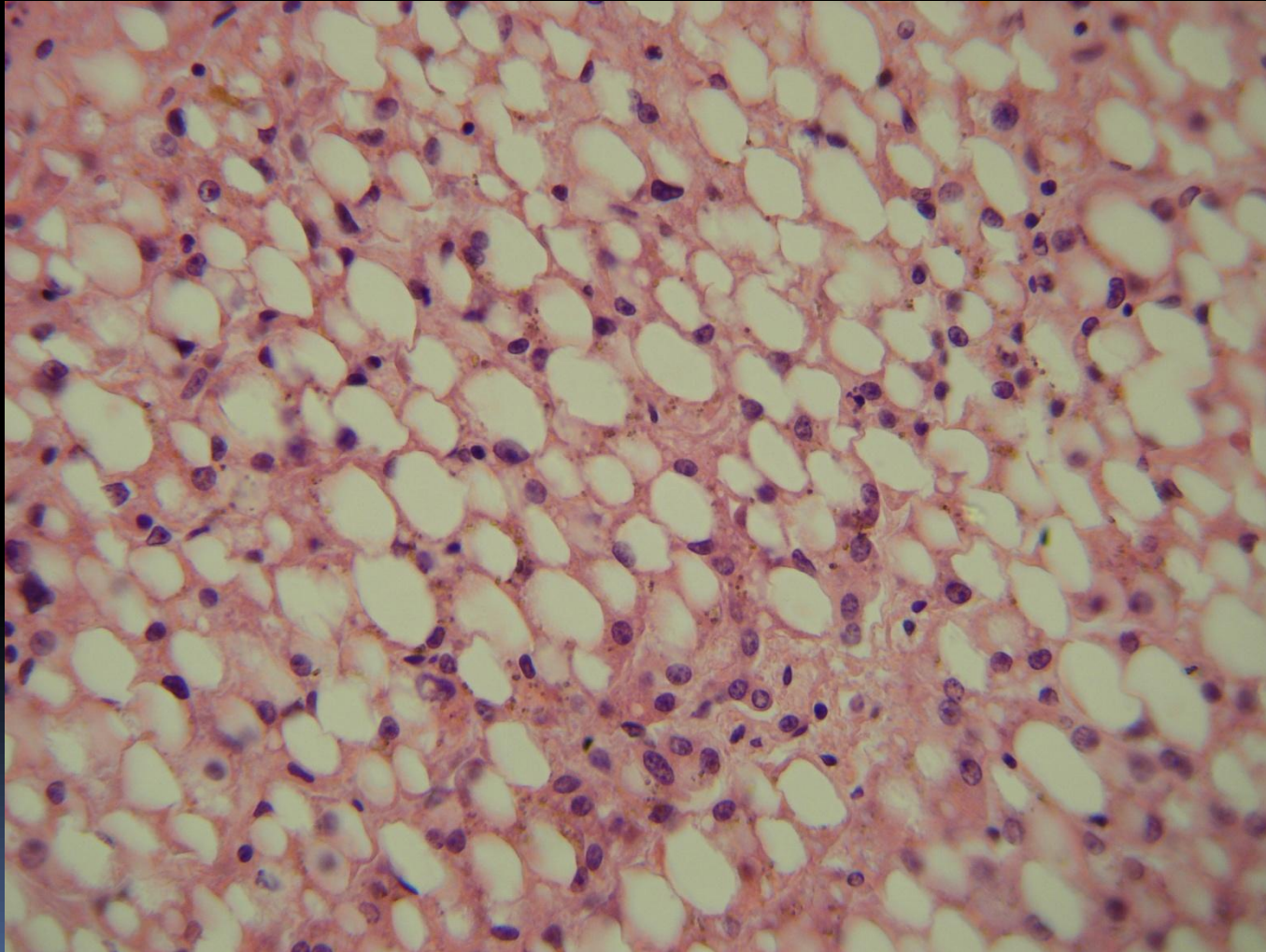


# Micronodular cirrhosis:



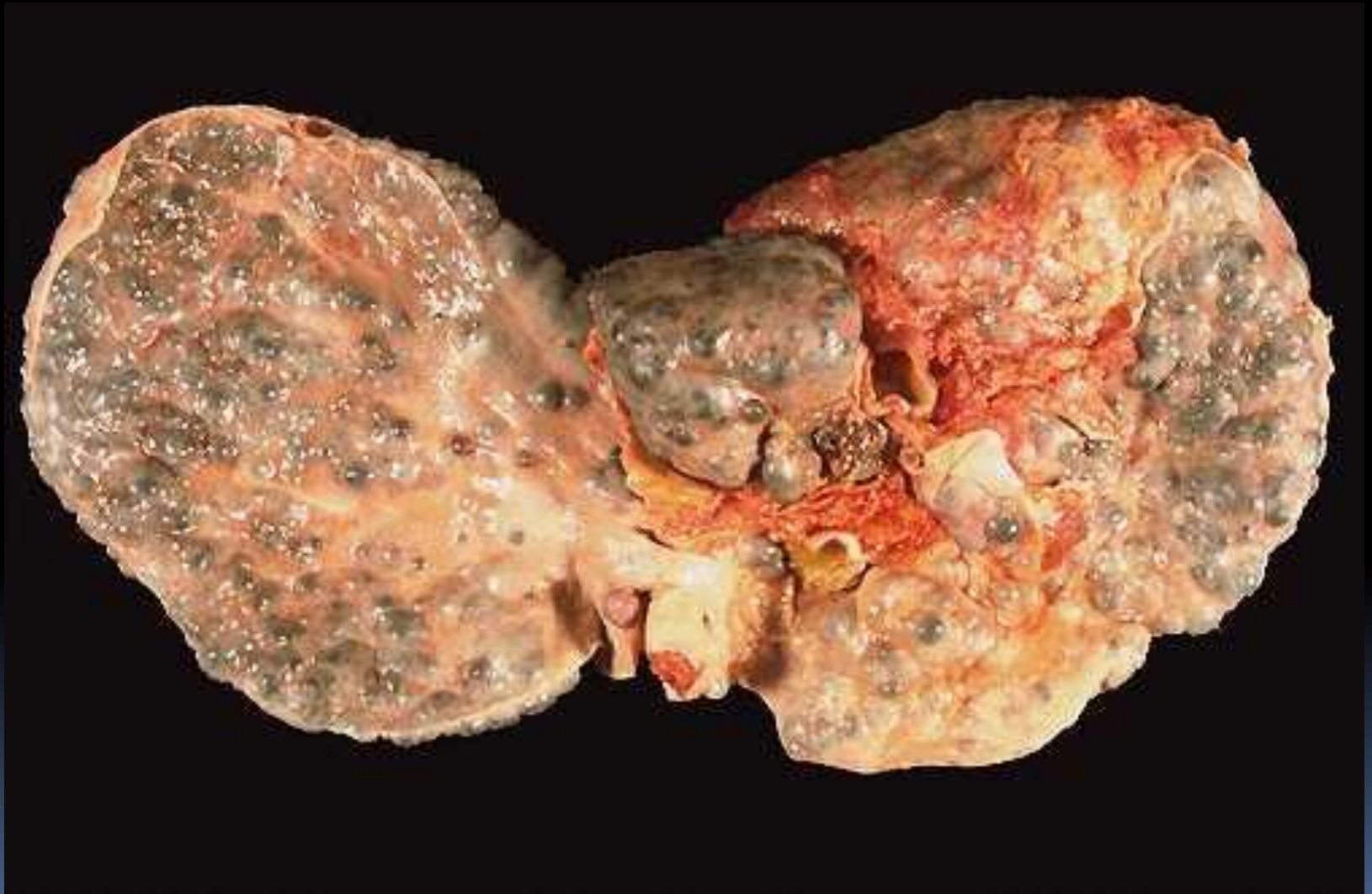


# Micronodular cirrhosis:

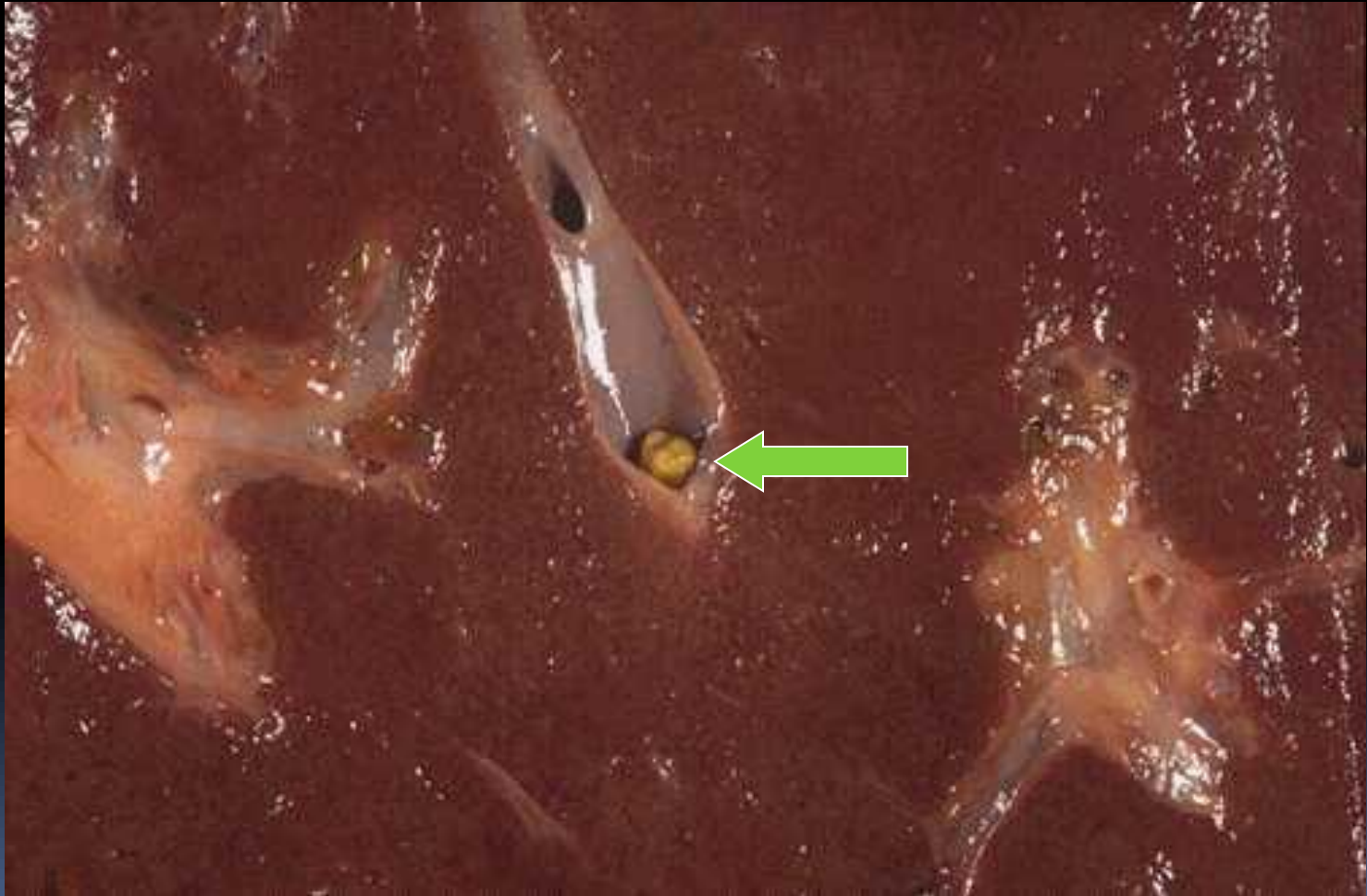




# Macronodular Cirrhosis

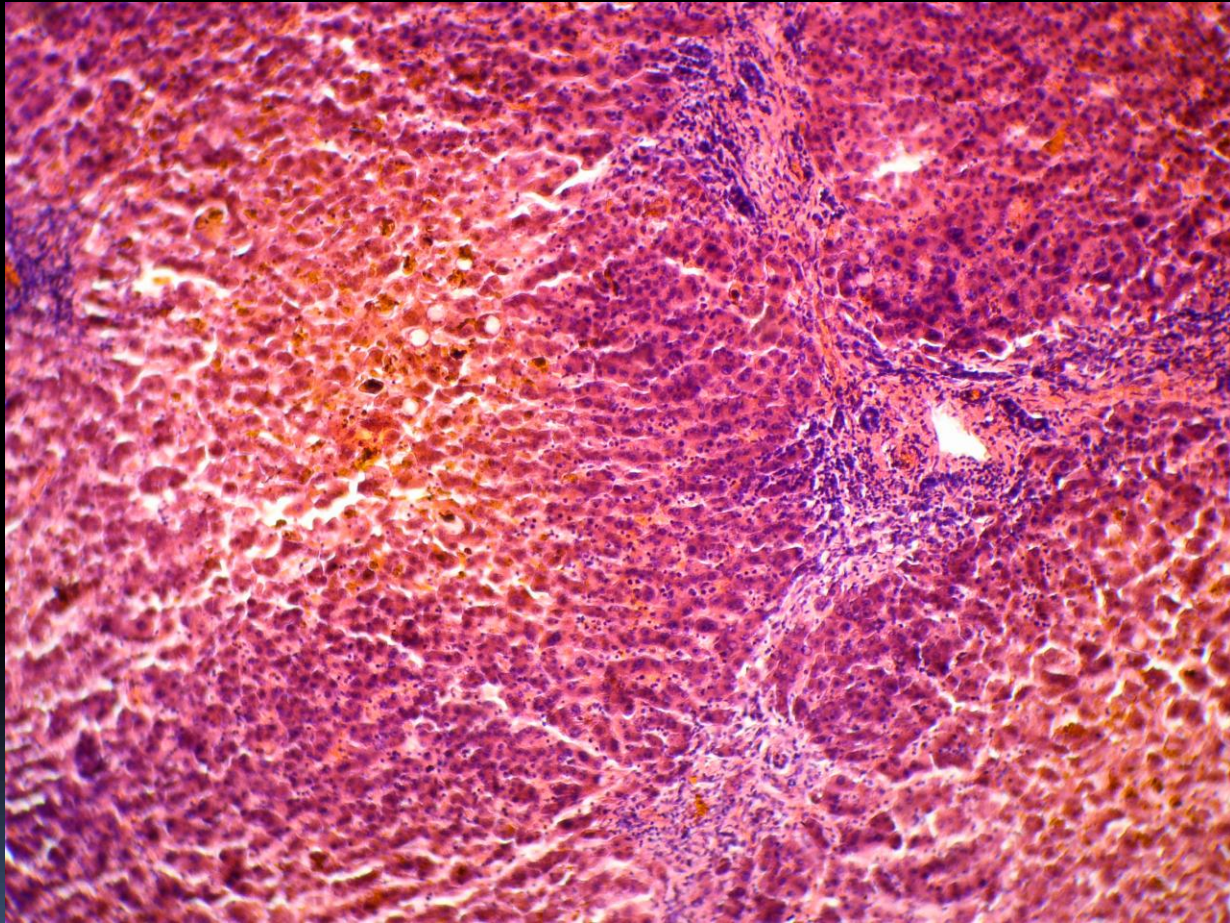


# Stone in Bile Duct



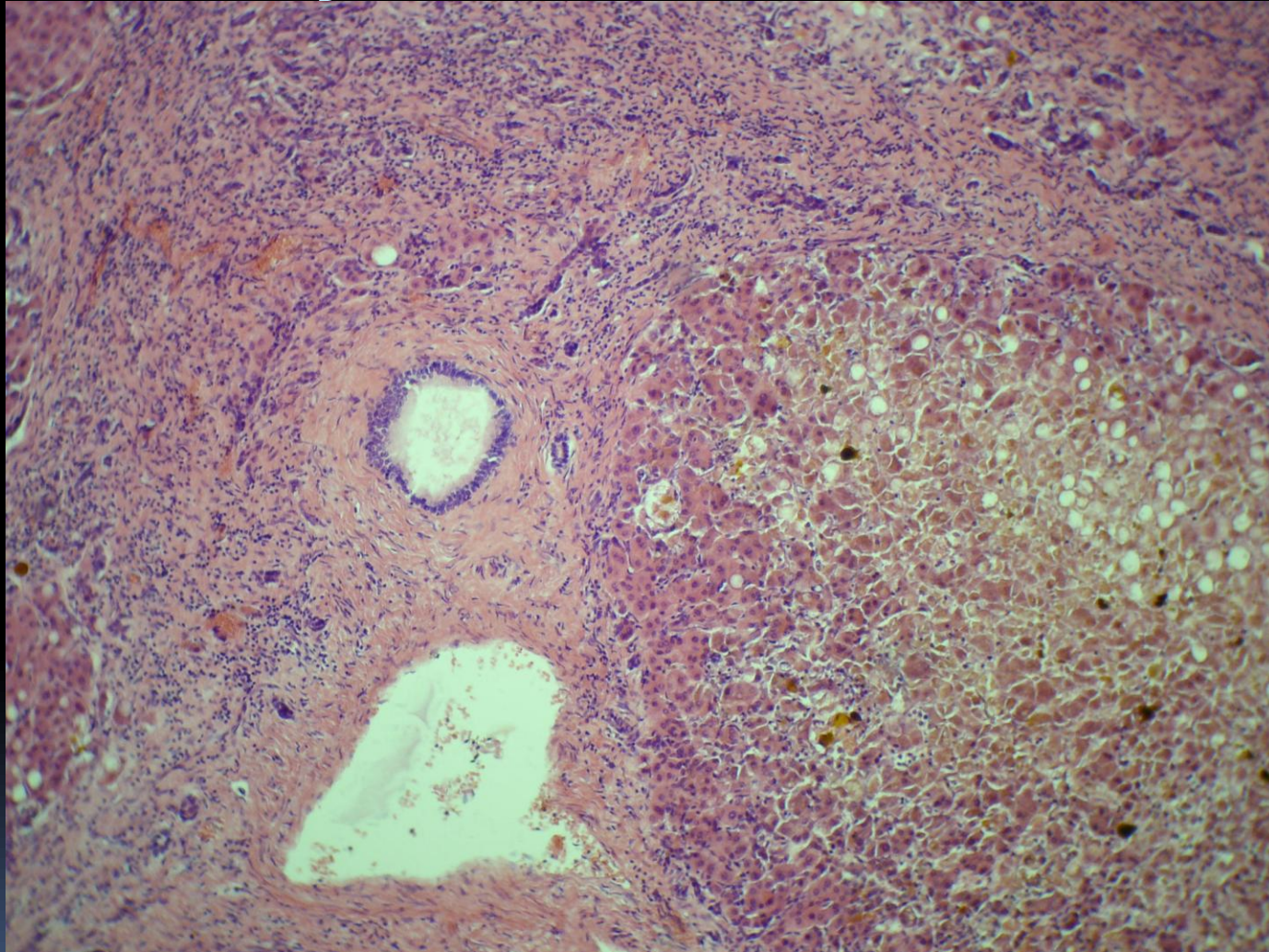


# Biliary Cirrhosis

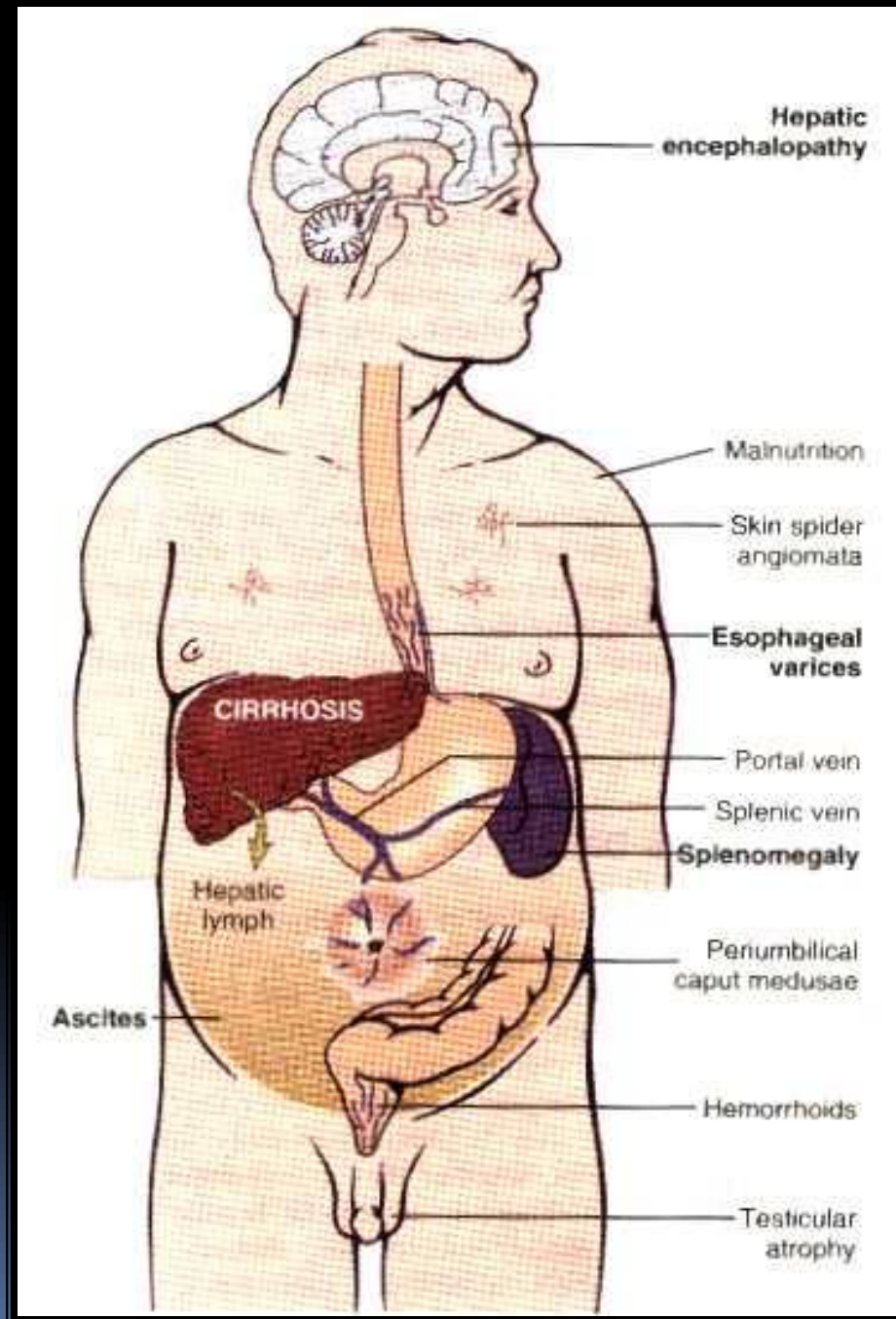




# Biliary Cirrhosis



# Cirrhosis Clinical Features





# Jaundice, Abdominal Striae

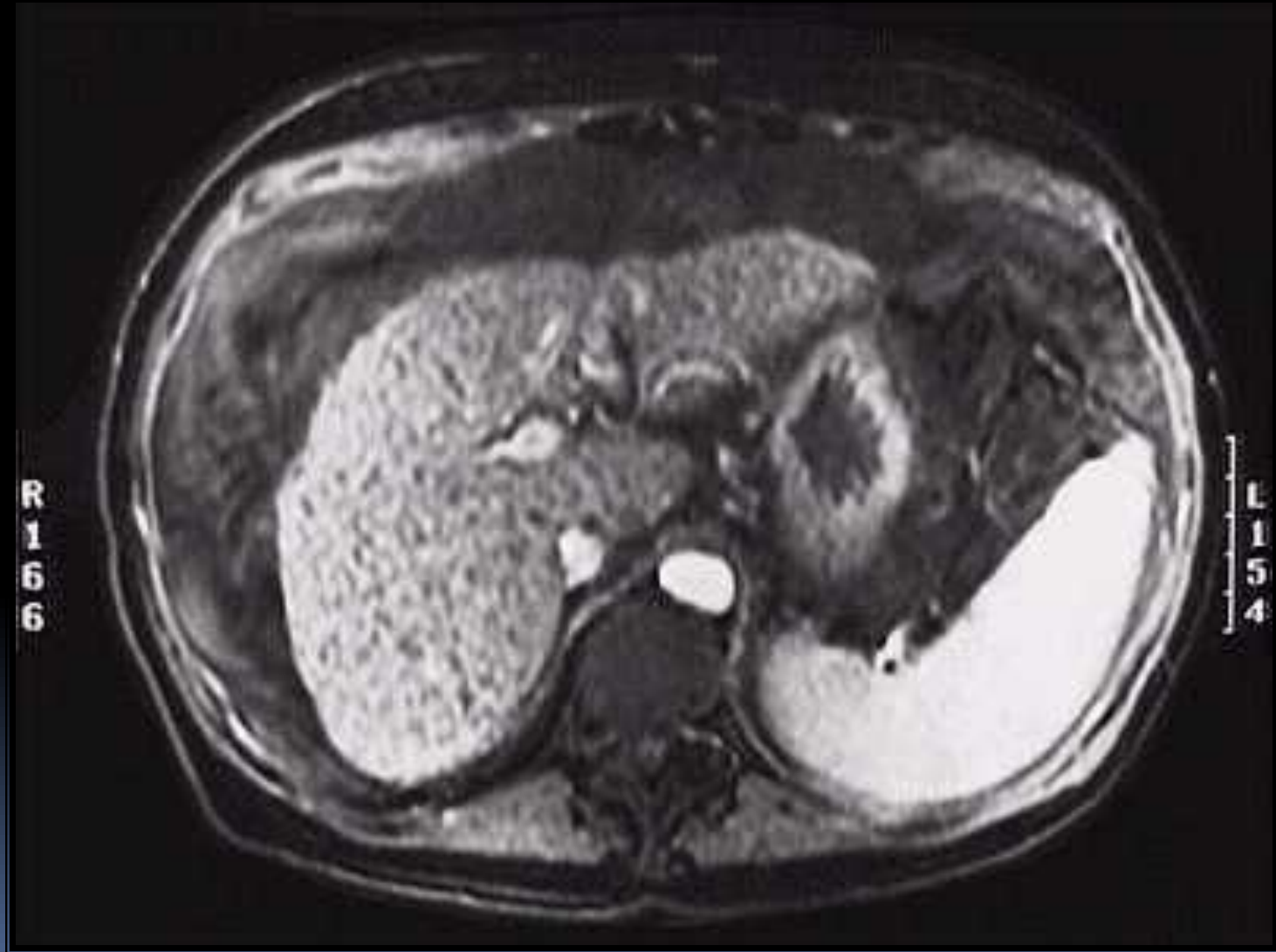




Porta-systemic anastomosis:  
Prominent abdominal veins.



# MRI Cirrhosis





# Complications:

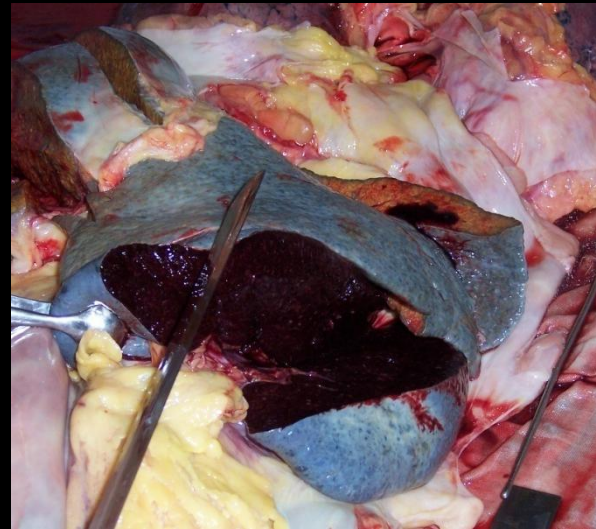
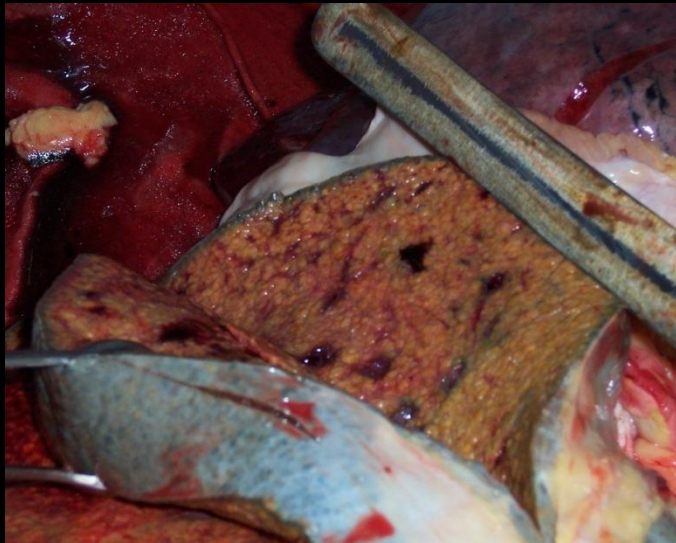
- Congestive splenomegaly.
  - Bleeding varices.
  - Hepatocellular failure.
    - Hepatic encephalitis / hepatic coma.
  - Hepatocellular carcinoma.
- 





# Conclusions:

- Common end result of diffuse liver damage.  
(common causes: Viral hepatitis & Alcohol)
  - Characterised by complete loss of architecture.
  - Replaced by fibrosis & regenerating parenchymal nodules.
  - Hepatocellular insufficiency & portal hypertension.
- 





# HEPATOCELLULAR CARCINOMA





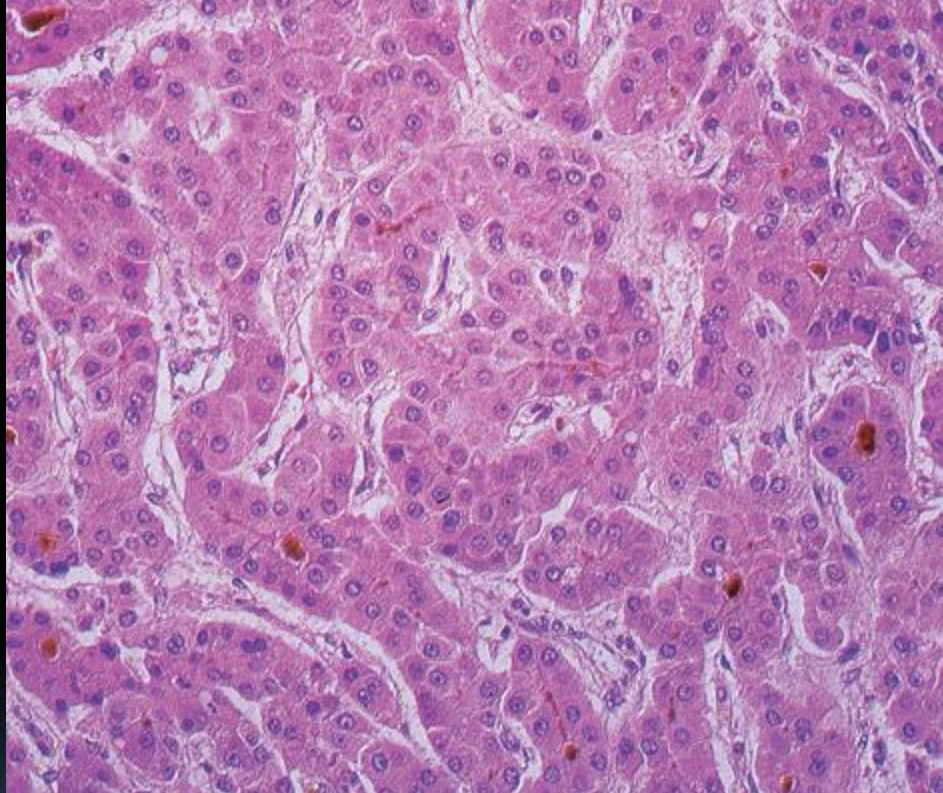
# Hepatocellular carcinoma

- Hepatocellular carcinoma (HCC), a common neoplasm worldwide with as many as one million new cases per year, is most common in Southeast Asia and Central Africa. In North America and Europe the incidence is rising. The most important risk factors are hepatitis B (HBV) and C (HCV) viral infection, hemochromatosis, cirrhosis of any cause including alcoholic liver disease, and many drugs and toxins
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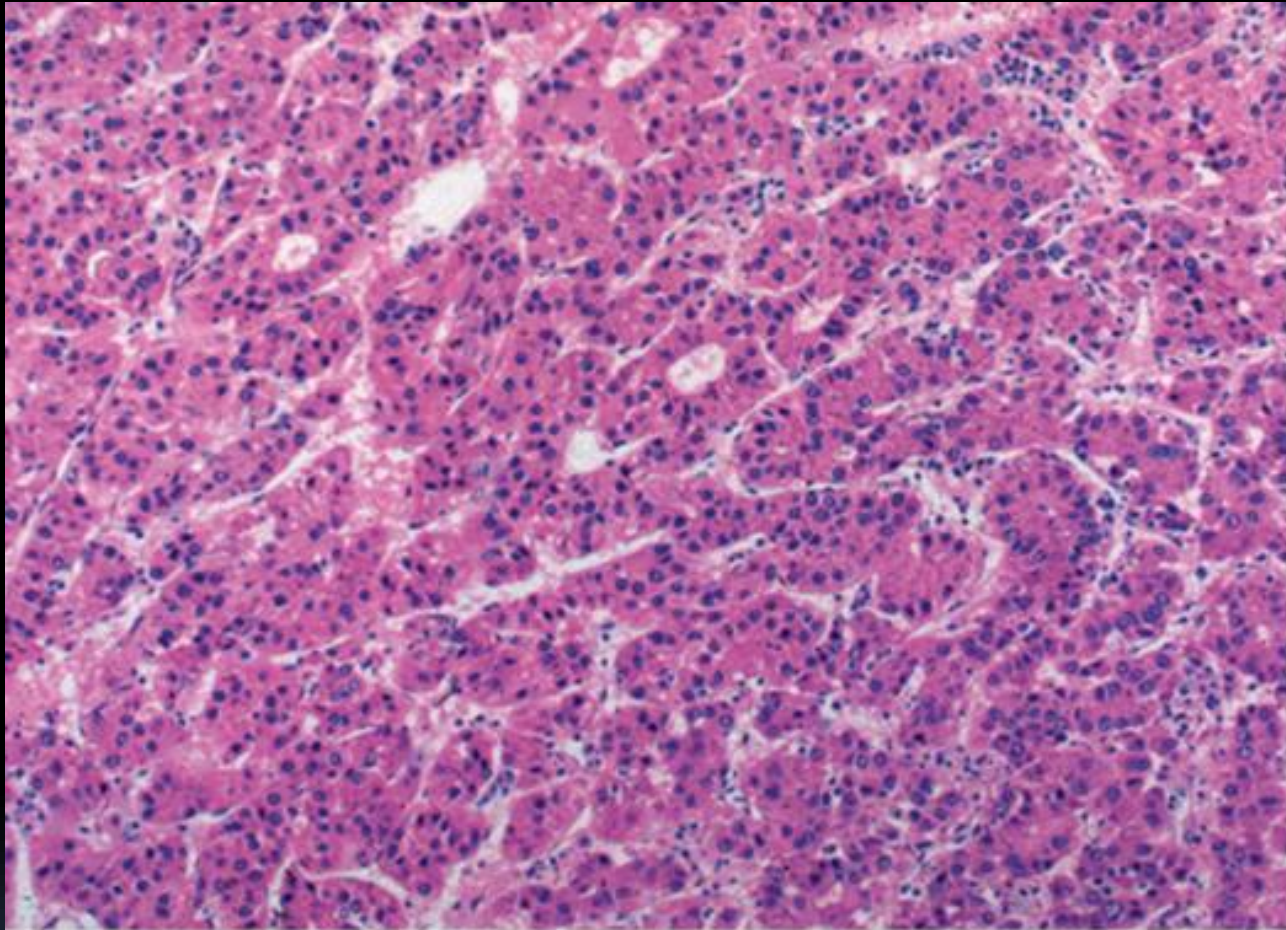
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Hepatocellular carcinoma, trabecular pattern (hematoxylin-eosin, original magnification  $\times 100$ ).



Thank you!

