CIRRHOSIS OF LIVER

Cirrhosis is one of the leading cause of chronic liver failure..

Other causes of chronic liver failure are chronic hepatitis B & C ,alcoholic liver disease & NAFLD

Having following characteristics:

(1) Architecture of total liver is disorganised.

(2) Fibrosis in form of delicate band or broad scar replacing multiple adjacent nodule.

(3) Regenerating parenchymal nodules.

(4) Vascular architecture is re-organised & formation of abnormal arteriovenous interconnection.

CLASSIFICATIONS :

A. Based on morphology:

(1) Micronodular cirrhosis :

Majority of parenchymal nodules are < 3 mm. in diameter.

(2) Macronodular cirrhosis :

Majority of nodules > 3mm. in diameter.

(3) Mixed cirrhosis :

Some part show micronodular pattern other parts show macronodular pattern.

B. Based on etiology & pathogenesis :

1. Alcoholic cirrhosis. 60 to 70 %
2. Post necrotic cirrhosis. 10 %
3. Biliary cirrhosis. 5 to 10 %
4. Pigment cirrhosis (in haemochromatosis)
5. Wilson's disease.
6. Alpha-1 antitrypsin deficiency.
7. Cardiac cirrhosis.
8. Indian childhood cirrhosis.
9. Miscellaneous.
10. Cryptogenic cirrhosis.(NASH)

PORTAL HYPERTENSION

CAUSES :

(A) Intrahepatic :

1. Cirrhosis.
2. Metastatic tumor.
3. Diffuse granulomatous disease.
4. Extensive fatty change.

(B) Post hepatic :

1. Congestive heart failure.
2. Constrictive pericarditis.
3. Budd –chiari syndrome.

(C) Pre hepatic :

1. Portal vein thrombosis.
2. Structural abnormalities of portal vein.

- DESPITE ALL THESE POSSIBLE CAUSES PORTAL HYPERTENSION MEANS CIRRHOSIS UNTIL PROVED OTHERWISE.

PATHOPHYSIOLOGY OF PORTAL HYPERTENSION IN CIRRHOSIS

(1) ↑ed resistance to portal blood flow at sinusoids level owing to perisinusoidal deposition of collagen in space of Disse & narrowing of sinusoids.

(2) Compression of central vein by regenerative nodules contribute to out flow resistance.

(3) Arteriovenous anastomosis develope into fibrous septa , bringing to bear hepatic arterial pressure on portal circulation.

Clinical consequences of portal hypertension :

(1) Ascites.

(2) Formation of portosystemic venous shunts.

(3) Congestive splenomegaly.

(4) Hepatic encephalopathy.

ASCITES

- Refers to collection of excess fluid in peritoneal cavity.
- Many liters may collect to cause abdominal distention.
- Fluid is serous & protein rich.(albumin)
- Clinically detectable when > 500ml.
- Long standing cases also develop right sided hydro thorax.

PORTOSYSTEMIC SHUNTS

Principal sites :

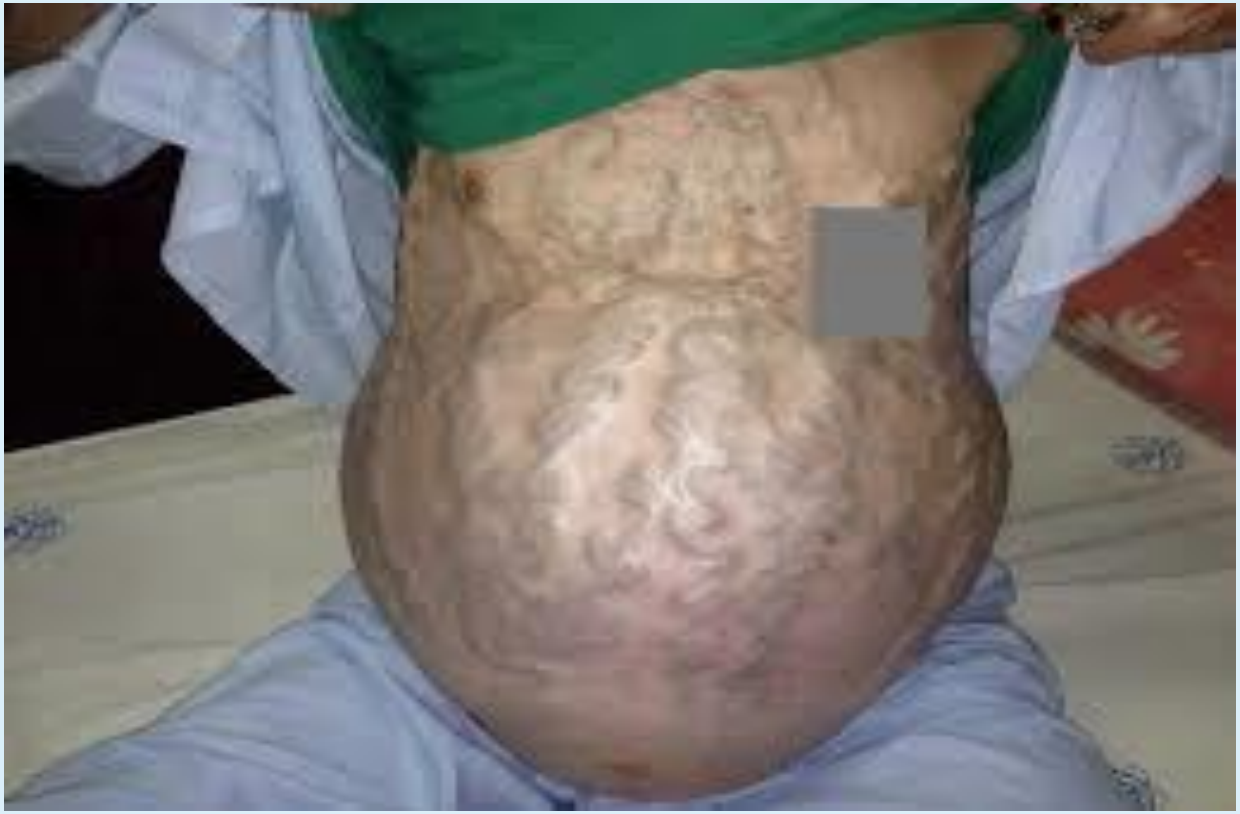
(1) Cardio esophageal junction.
(esophageal varices) manifested by massive haematemesis.

(2) Veins around & within the rectum.
(Hemorrhoids)

(3) Falciform ligament of liver – periumblical or abdominal wall collaterals.(caput medusae)

(4) Retroperitoneum.

CAPUT MEDUSAE



SPLENOMEGALY

Occurs due to long - standing congestion

- Leads to ,

(1) Anemia.

(2) Leucopenia.

(3) Thrombocytopenia.

- (HYPERSPLENISM) characterised by anemia, infection & bleeding.

HEPATIC ENCEPHALOPATHY

- Characterised by, disturbed consciousness ranging from behavioural abnormalities,to confusion & stupor , to deep coma & death.
- Associated neurological signs include rigidity & hyperreflexia.

- Asterixis – characteristic sign –non rhythmic, extension-flexion movement of head & extremities.
- It occurs due to abnormal arteriovenous interconnections leads entrance of portal blood to systemic circulation prior to detoxification in liver.

  Associated with increased ammonia level.

ALCOHOLIC LIVER DISEASE AND CIRRHOSIS :

- Chronic consumption of alcohol lead to three distinctive forms.

  (1) Hepatic steatosis.

  (2) Alcoholic hepatitis.

  (3) Cirrhosis.

- Alcoholic person progressive from fatty change to bouts of hepatitis to alcoholic cirrhosis in 10 to 15 years.

- All changes in alcoholic liver disease begin in acinus zone 3 & extend outward toward portal tracts.

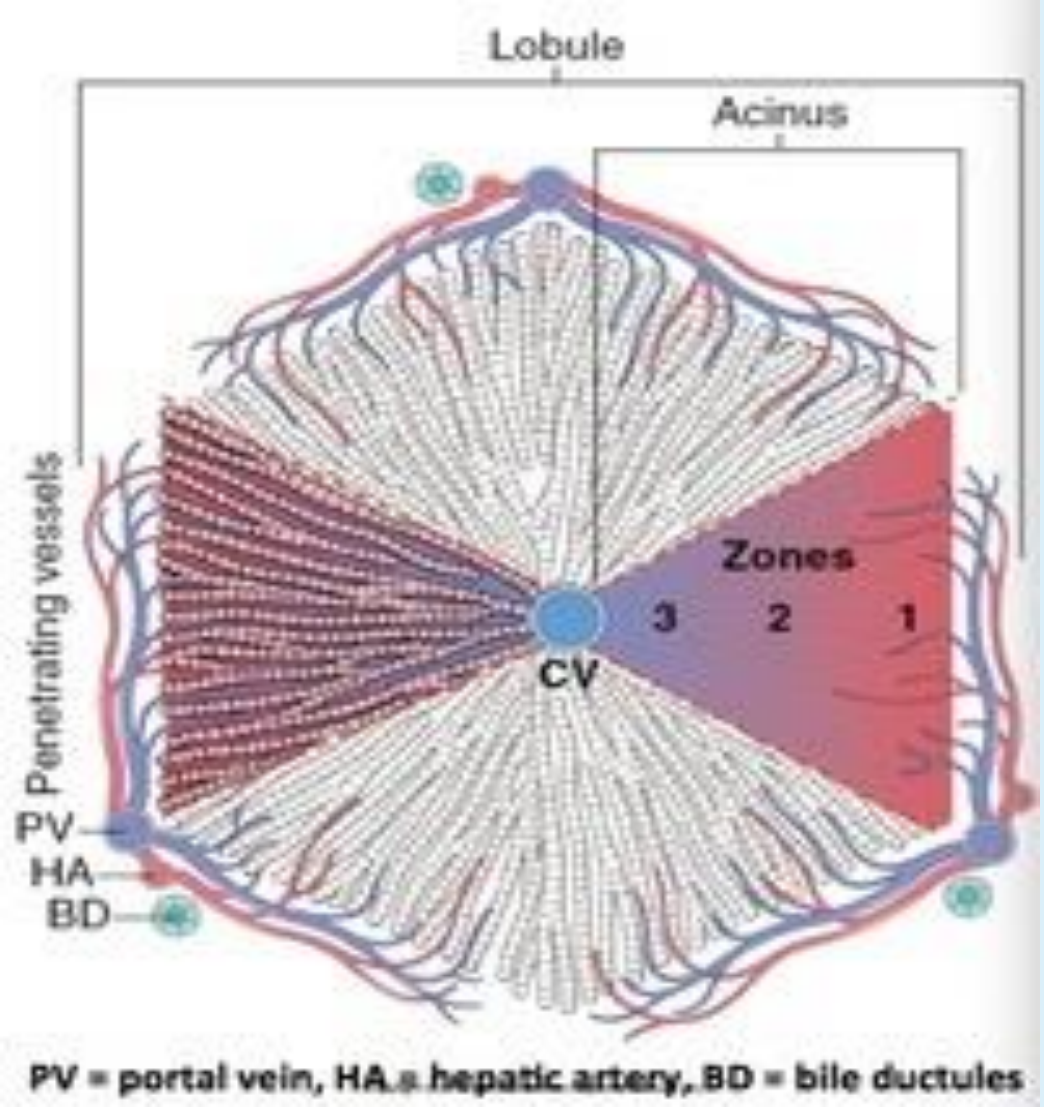
Hepatic steatosis (Fatty liver) :

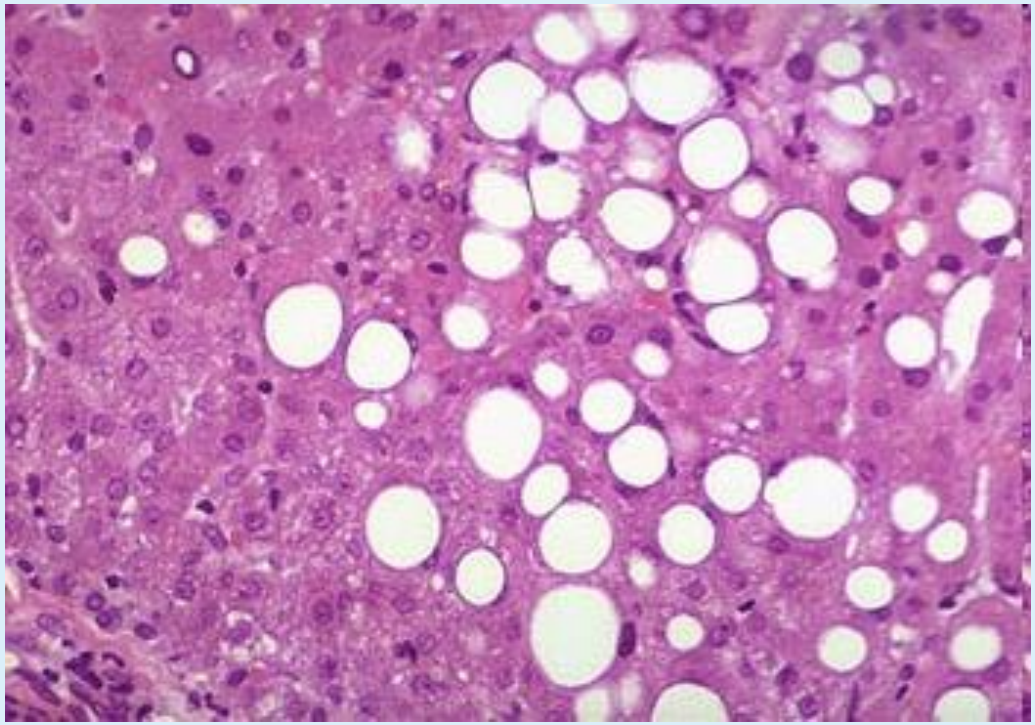
- Alcohol – hepatotoxic - alter mitochondrial & microsomal function.
- ↑ed synthesis of triglycerides due to ↑ed delivary of fatty acids to liver & ↑ed fatty acid synthesis.
- ↓ed fatty acid oxidation.
- ↓ed formation & release of lipoprotein.
- MaInutrition is cofactor in ethanol induced injury.

- LIVER is enlarged, soft, and yellow. It has a greasy texture.

- Hepatocellular fat accumulation begins in centrilobular hepatocytes.
- Lipid droplets may be small or large displacing the nucleus.
- With extensive disease lipid accumulation spreads into midlobule & periportal regions.
- Fatty change is completely reversible if there is abstention from further alcohol consumption

Hepatic Lobule





Hepatic steatosis may be associated with slight hepatomegaly and

elevations of serum bilirubin

and alkaline phosphatase.

Alcoholic hepatitis

- Associated with liver cell necrosis & inflammation.
- Reversible if initial injury mild & further exposure to alcohol prevented.

MORPHOLOGY :

(1) Hepatocytes ballooning & necrosis isolated or in small groups most prominent in the centrilobular regions.

(2) Mallory-Denk bodies in scattered hepatocytes as eosinophilic cytoplasmic inclusion in degenerating hepatocytes.

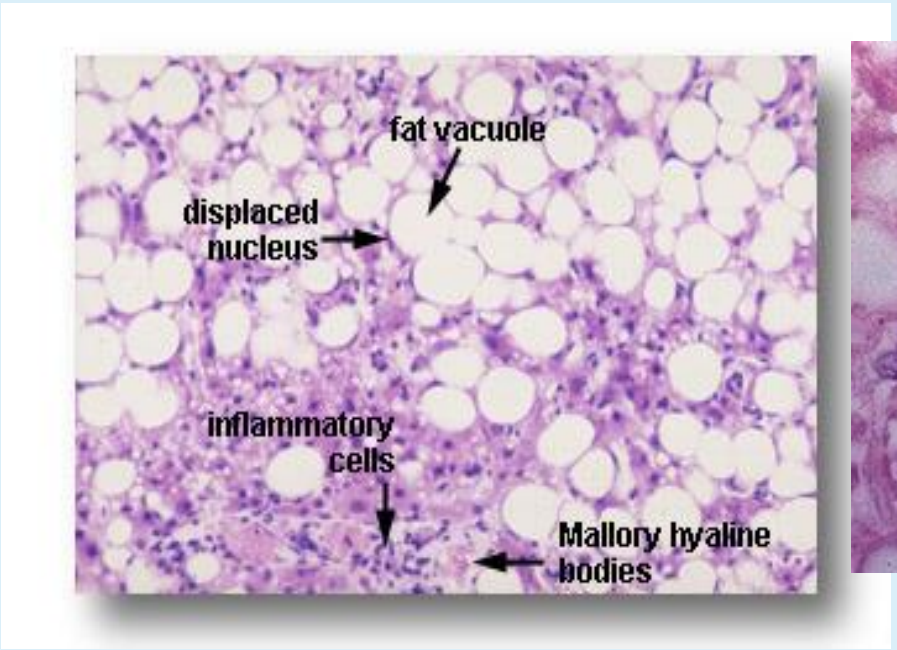
They consist of intermediate filaments like keratins 8 & 18 complex with proteins like Ubiquitin. (also present in NAFLD , Wilson's disease & chronic biliary disease.)

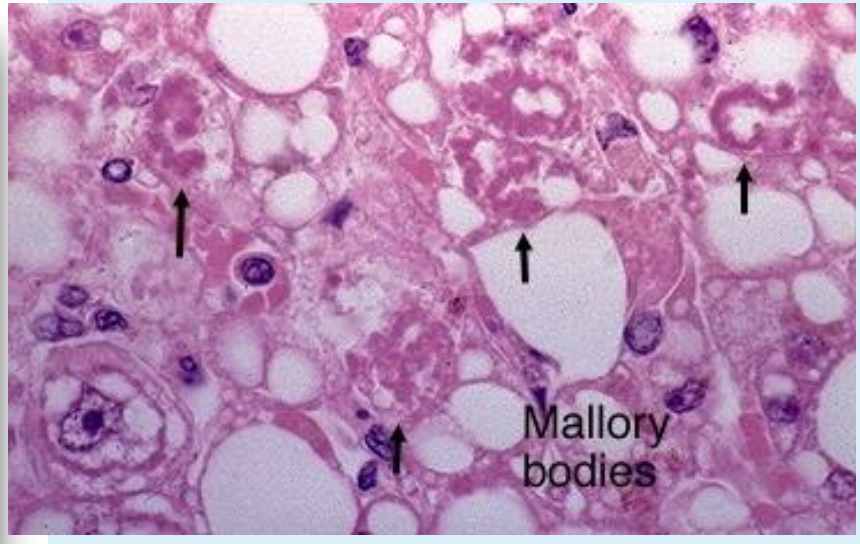
(3) Neutrophillic infiltration: at necrotic cells, portal triad & spill in to adjacent parenchyma.

(4) Fibrosis : First appears in centrilobular region as central vein sclerosis.

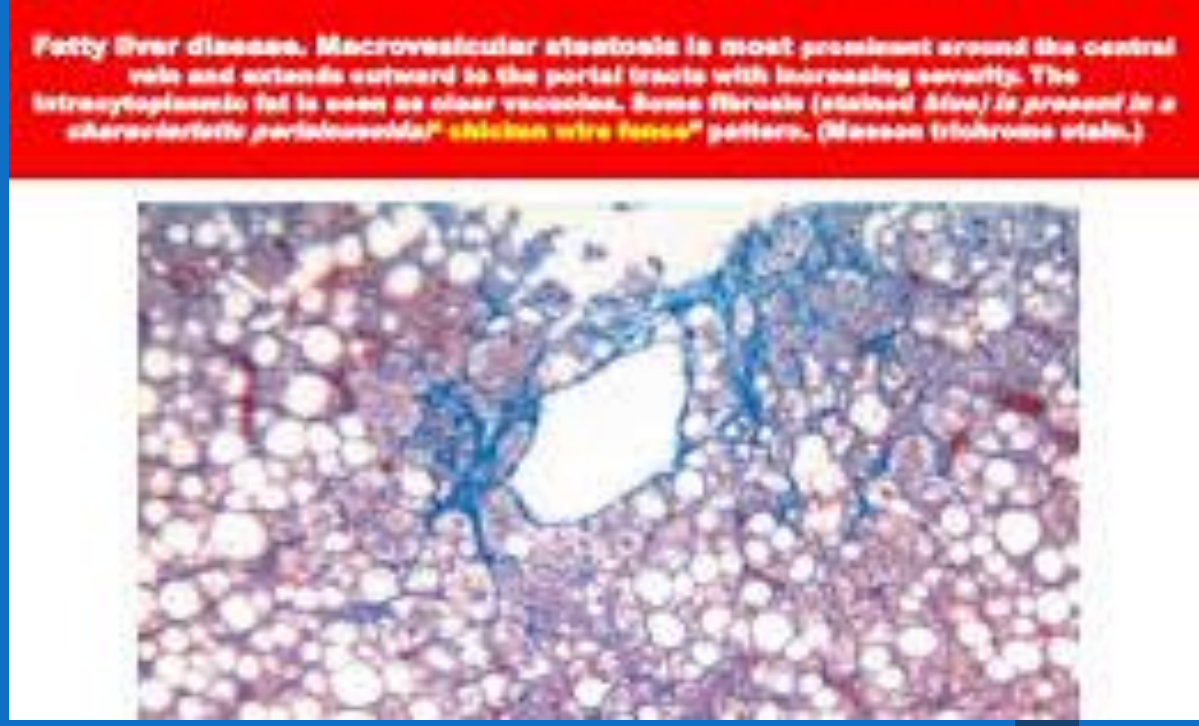
- Perisinusoidal scar then spreads outward encircling individual or small clusters of hepatocytes in a **chicken wire fence pattern.**

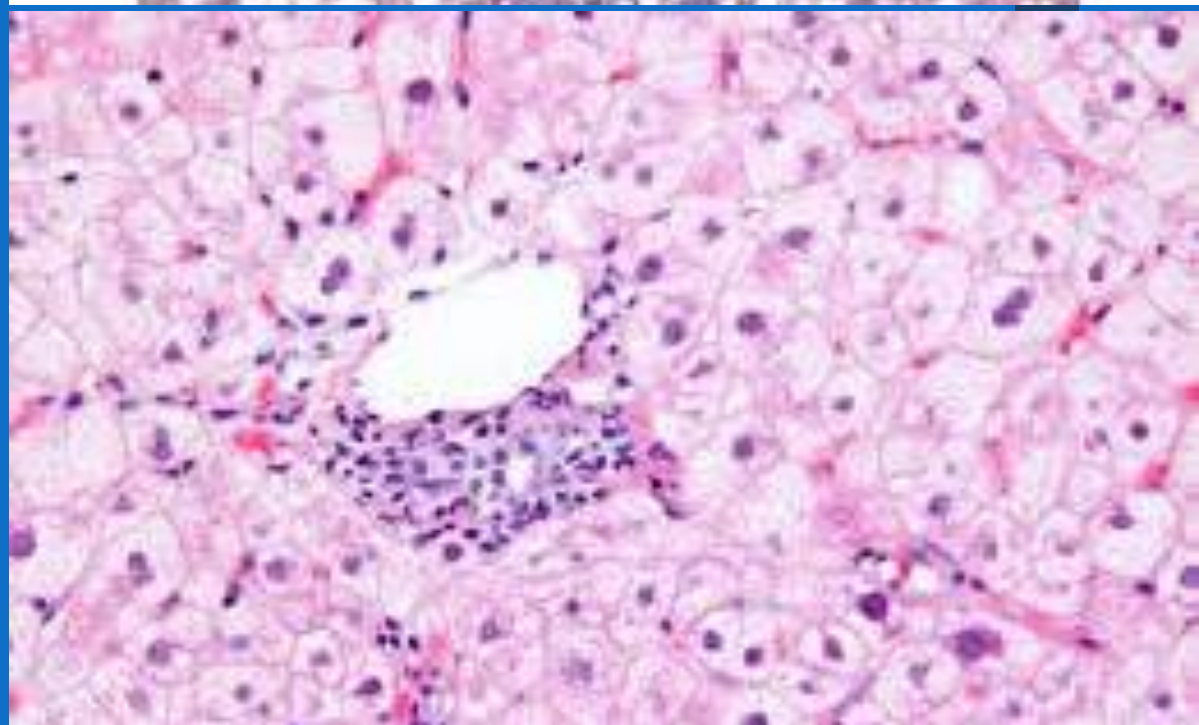
ALCOHOLIC HEPATITIS





CHICKEN WIRE FENCE PATTERN





- Eventually central- portal fibrous septa are created.
- As they become prominent liver is converted into the nodular cirrhotic liver.
- Early in the course, liver is yellow-tan, fatty and enlarge.
- Over the course of the years, liver turns into brown, shrunken & nonfatty organ with nodules
- Cirrhosis is micronodular or **Laennec cirrhosis.**(end stage alcoholic cirrhosis)

PATHOGENESIS

- Three processes are central to the pathogenesis of cirrhosis :
  1. death of hepatocytes
  2. extracellular matrix deposition
  3. vascular reorganization.

- In the normal liver collagen is present only in the liver capsule, in portal tracts and around central veins.

- In cirrhosis collagen and other ECM components are deposited in the space of Disse.
- The major source of excess collagen in cirrhosis are the perisinusoidal stellate cells, which lie in the space of Disse.
  (formarly known as ito cells)

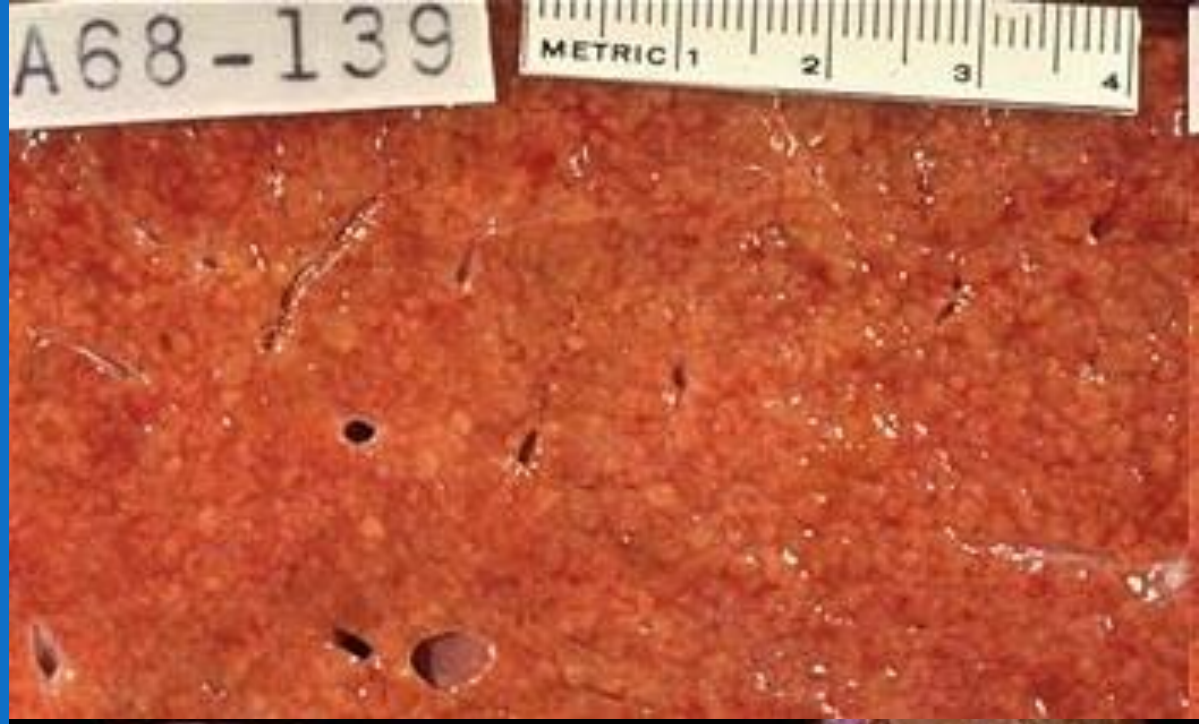
- During fibrosis they activate into myofibroblast. Stimuli for their activation are reactive oxygen species, growth factors and cytokines like IL-1 , TNF .
- Portal fibroblasts also contributes in fibrosis.
- If the disease process is eliminated, remodelling and restoration of liver function is possible (**cirrhotic regression**)

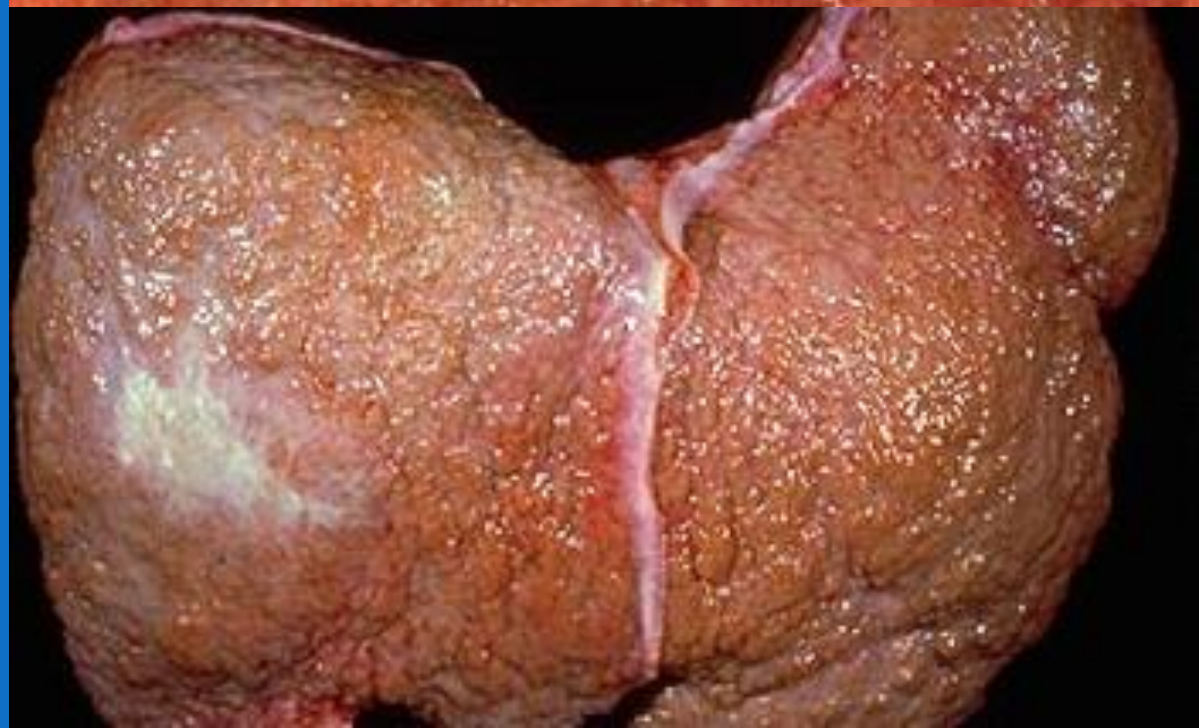
- Inflammation and thrombosis of portal veins,hepatic arteries and central veins may cause alternating zones of hypoperfusion and hyperperfusion.
- Development of portal vein-hepatic vein and hepatic artery-portal vein vascular shunts lead to abnormal vascular pressures and portal hypertension.

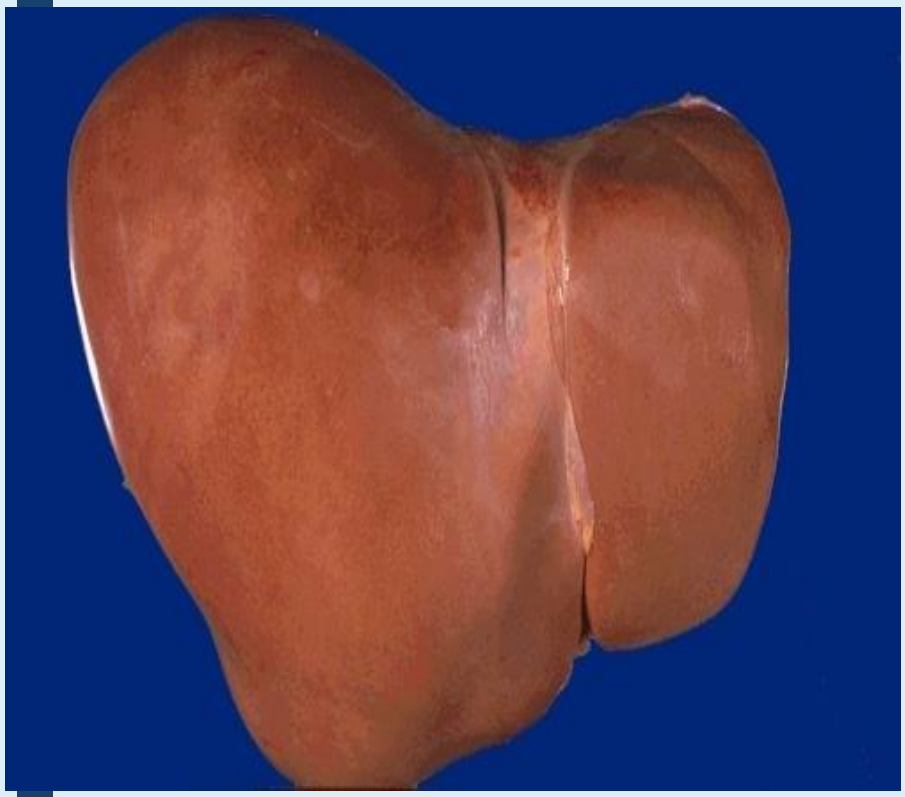
Morphology

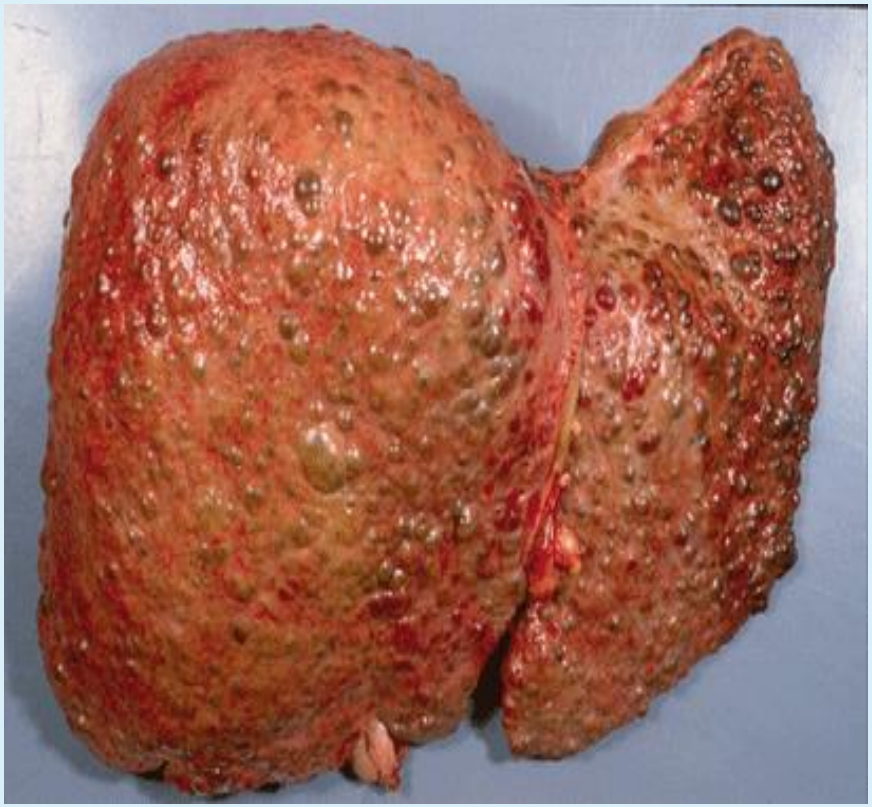
- Term cirrhosis derived from twany-yellow liver due to deposition of fat.
- Early stage slender fibrous septa between portal-portal, portal-central areas.
- Fibrosis more marked at expense of hepatic parenchyma.
- Residual hepatocytes show fatty change.
- Changes of hepatitis. (liver cell necrosis, Mallory bodies, inflammation.)
- Micronodular type of cirrhosis.

GROSS APPEARANCE

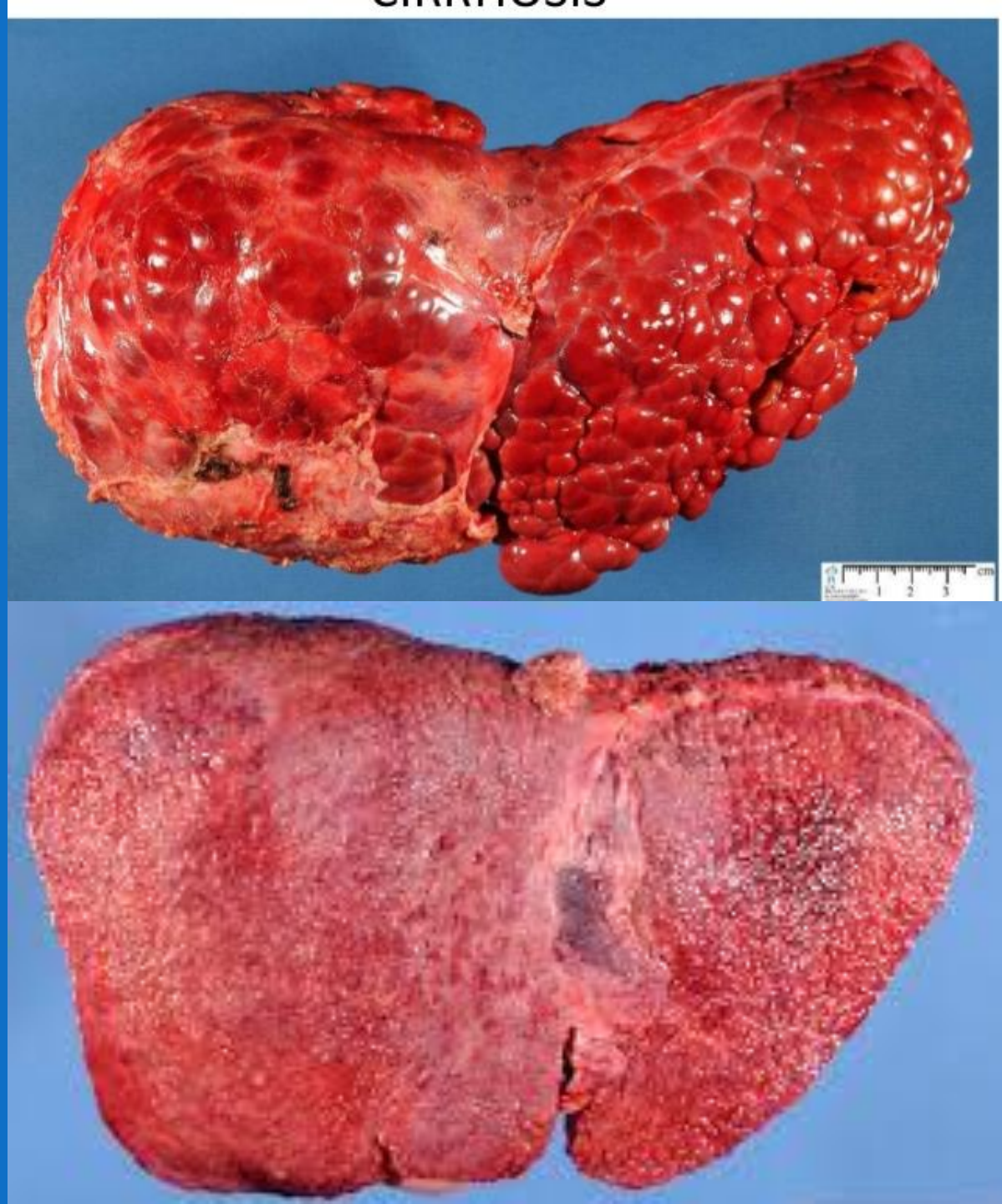




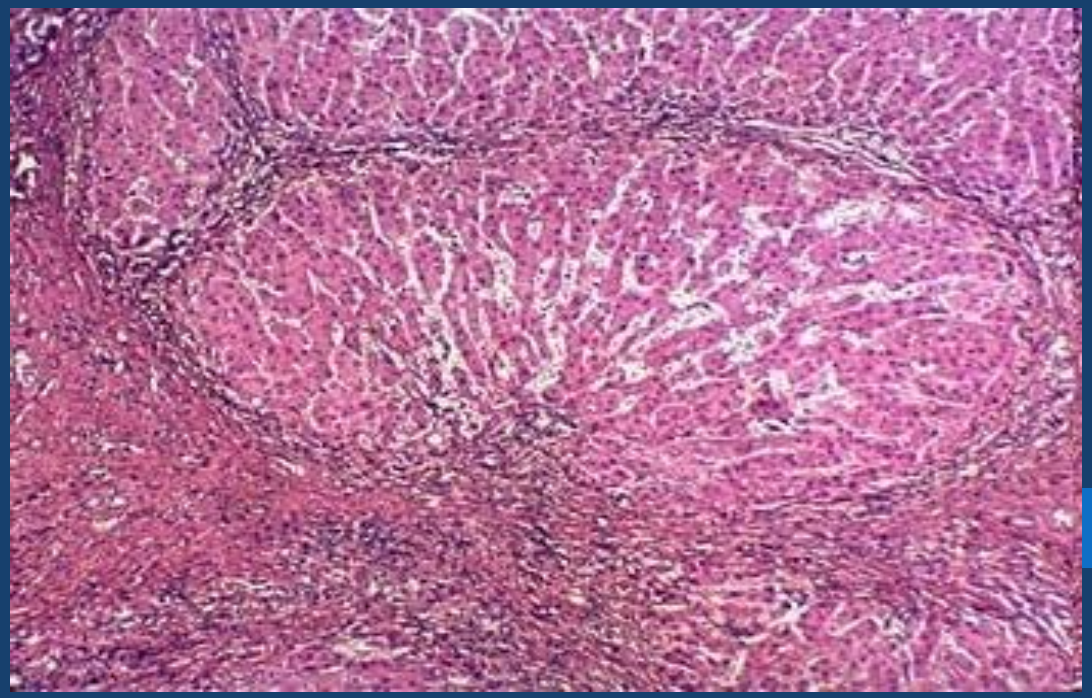


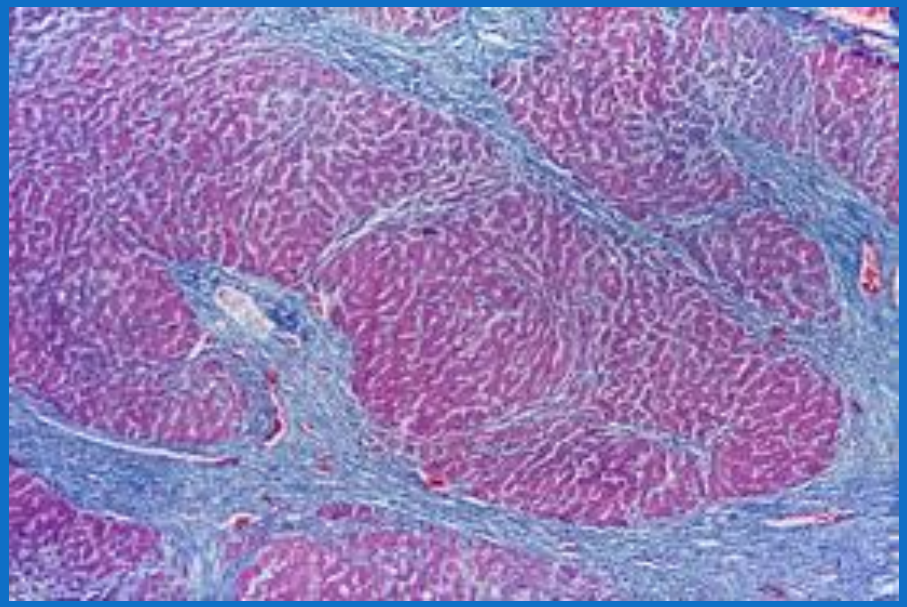


MICRONODULAR AND MACRONODULAR CIRRHOSIS



nodules of regenerating hepatocytes consist of disordered cords of cells of irregular thickness, many of which are two or more cell layers thick. Note the lack of central veins in these regenerative nodules. The nodules are surrounded by fibrous tissue containing variable amounts of chronic inflammatory cells and areas of bile ductular proliferation.





MASON TRICHROME STAIN

- Advanced disease liver shrinks progressively in size ,becomes more fibrotic, looses fat and converted in to macronodular pattern.

  (MACRONODULAR CIRRHOSIS)

- End stage alcoholic cirrhosis resemble post necrotic cirrhosis.

CLINICAL COURSE :

- Without symptoms - discovered at autopsy.
- Malaise, weakness, weightloss, loss of appetite & jaundice.
- Peripheral edema due to impaired synthesis of albumin.
- Palmar erythema, gynecomastia, gonadal atrophy, amenorrhoea due to hyperestrinism secondary to impaired hepatic metabolism of estrogen.
- Symptoms due to portal hypertension.
- Progressive liver failure.

LAB. INVESTIGATION

- Increased serum bilirubin.
- Increased serum amino transferase.
- Increased serum alkaline phosphatase.
- Anemia.
- Hypo proteinemia with reversal of albumin/ globulin ratio.

CAUSES OF DEATH

- Hepatic coma. Progressive liver failure.
- Massive hemorrhage from esophageal varices
- An intercurrent infection.
- **Hepatorenal syndrome**:
  sodium retention , impaired fluid excretion , diminished renal perfusion & ↓ GFR.
- **Hepatopulmonary syndrome**:
  hypoxia & resultant dyspnea (in upright position) leads to poor prognosis.
- **Hepatocellular carcinoma**


Thank You