Biliary cirrhosis :

Definition: Chronic disorder characterised by clinical, biochemical & morphologic features of long-continued cholestasis of intrahepatic or extrahepatic origin.

(1) Primary biliary cirrhosis.

(2) Secondary biliary cirrhosis.

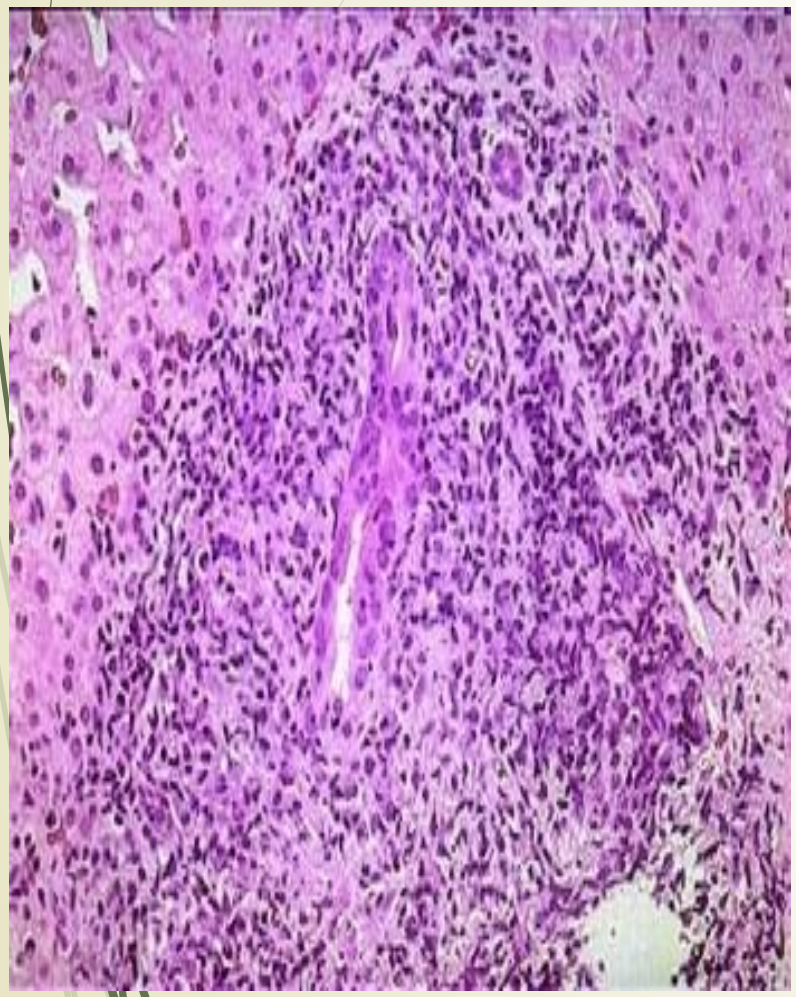
Primary Biliary Cirrhosis (PBC)

- More common in middle aged female.
- M : F = 1 : 9
- Peak incidence between 40 to 50 years of age.
- It is a chronic, progressive and at times fatal cholestatic liver disease characterized by destruction of intrahepatic bile ducts , portal inflammation and scarring , cirrhosis and liver failure.
- Cardinal feature of PBC is a nonsuppurative destruction of small and medium size intrahepatic bile ducts.

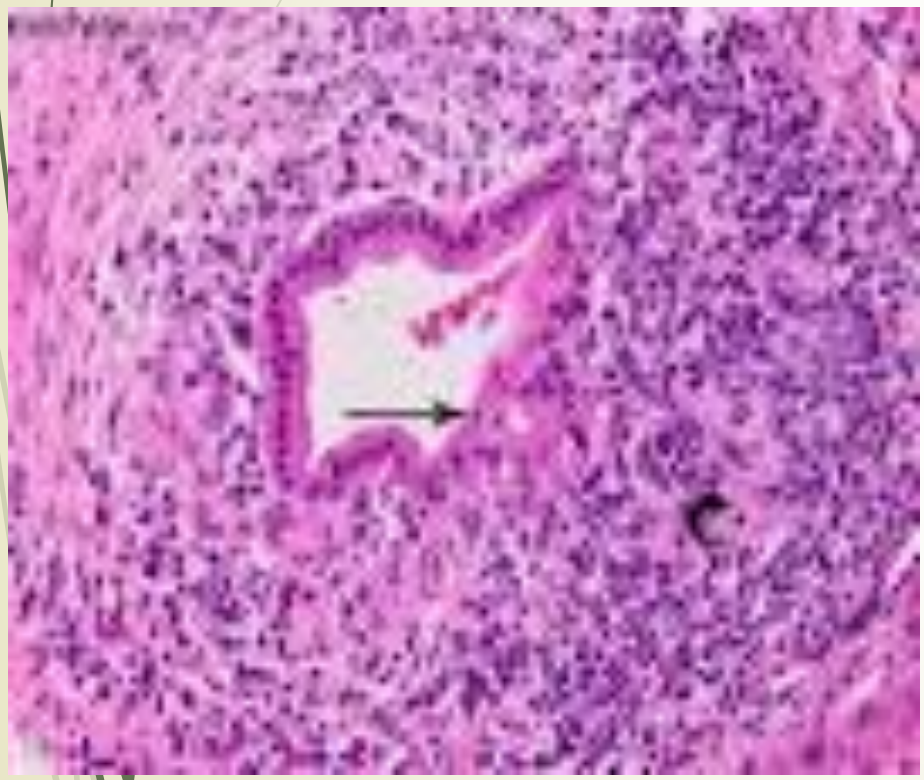
Pathogenesis :

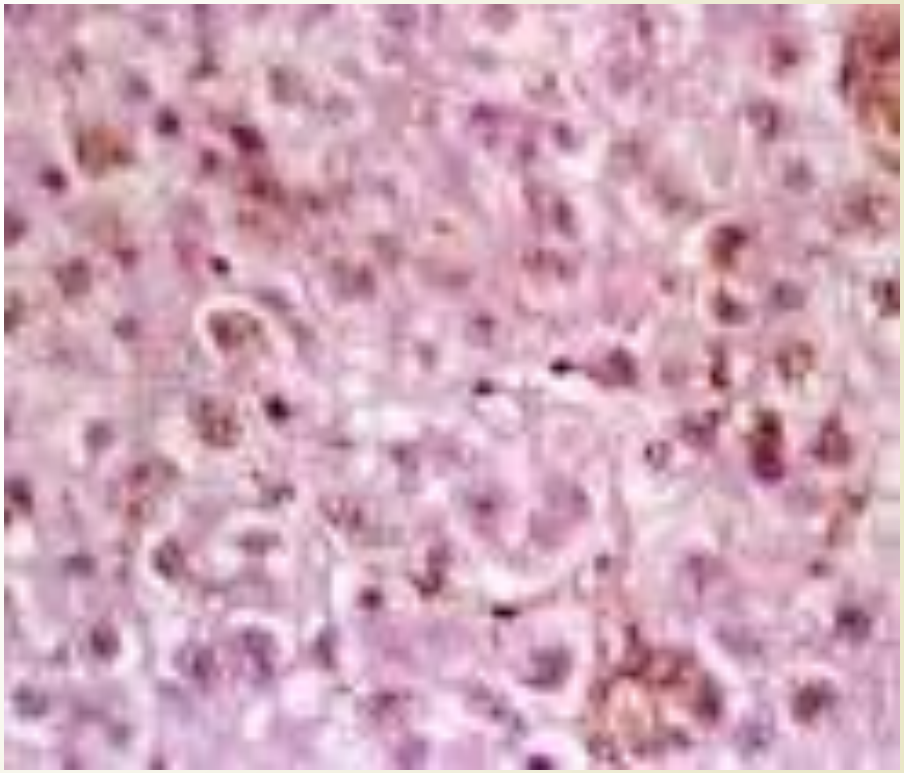
- Autoimmune etiology.
- Antimitochondrial antibodies (AMA) & antibodies against other cellular components (eg. Nucleus) of bile ducts.
- Associated autoimmune disease like Sjogren syndrome, scleroderma, thyroiditis.
- Elevated level of IgM type antibodies.

Biliary cirrhosis



chronic inflammation in the portal areas is associated with bile duct destruction by the inflammatory infiltrate comprising of lymphocytes & plasma cells with or without granulomas. These are the hallmarks of the **florid duct lesions** in primary biliary cirrhosis.





- Inflammation and necrosis of periportal parenchyma leads to portal septal fibrosis.
- Two end stage liver disease can occur

  (1) **Nodular regenerative hyperplasia**

  * Nodularity without fibrosis.
  * Vague nodularity.

(2) **Cirrhosis**

* **chronic cholestasis** (periportal)

* **feathery degeneration –** marked by balloon bile stain hepatocytes often with mallory- Denk bodies. (periportal)

End stage liver shows cirrhotic nodules & vivid green discolouration.

Micronodular biliary cirrhosis (Greenish)

Secondary biliary cirrhosis :

- **Causes :**

(1) Extrahepatic cholelithiasis (gallstone).

(2) Malignancy of biliary tree or head of pancrease.

(3) Stricture of biliary tree from previous surgical procedure.

(4) Obstructive condition in children. e.g Biliary atresia, cystic fibrosis, choledochal cyst.

Hemochromatosis

- Characterised by excessive accumulation of body iron, most of deposited in liver, pancreas and heart.
- Normal total body iron pool - 2 to 6 gm.
- About 0.5 gm is stored in liver mainly in hepatocytes

(1) Hereditary hemochromatosis.

(Primary hemochromatosis)

Homozygous recessive inherited disorder.

- Four genetic variants of hereditary hemochromatosis are recognized.
- Autosomal recessive disease of adult onset is most common caused by mutations in the HFE gene.
- Iron accumulates over the lifetime due to excessive intestinal absorption.

Total iron accumulation may exceed 50 gm.

Fully developed cases show ,

1. Cirrhosis in all patients
2. Diabetes mellitus in 75-80% of patients
3. Skin pigmentation in 75-80% of patients

Hemosiderosis (Secondary hemochromatosis)

(A) Parenteral iron overload.

(1) Multiple transfusion in Aplastic anemia ,Sickle cell anemia, Leukemia, Myelodysplastic syndrome, Beta thalassemia.

(2) Hemolytic anemia.

(3) Long term hemodialysis.

(4) Iron-dextran injection.

(B) Increased oral intake of iron eg. African iron overload (Bantu siderosis)

(C) Chronic liver disease.

it shows fibrous connective tissue bands separating regenerating nodules of chocolate-
brown hepatic parenchyma.

Pathogenesis :

- In hereditary hemochromatosis, there is a defect in the regulation of intestinal absorption of dietary iron, leading to net iron accumulation of 0.5-1 gm/yr.
- HFE gene responsible for this is called as hereditary hemochromatosis gene located on the short arm of chromosome 6.
- It leads to upregulated iron absorption and binding to **transferrin.**

- Other proteins particularly **Hepcidin** is also involved. HFE and other genes regulate levels of hepicidin (iron hormone).
- Hepcidin normally down regulates iron efflux from intestine and macrophages into plasma and inhibits the iron absorption.
- When hepcidin levels are reduced, increased iron absorption. So in all genetic forms of hemochromatosis, hepcidin levels are reduced.

- Hereditary hemochromatosis manifests after 20gm of storage iron has accumulated
- Excessive iron is directly toxic to host tissue by,

(1) Lipid peroxidation of cell organelles via iron catalysed free radical reaction.

(2) Stimulation of collagen formation.

(3) Interaction of reactive oxygen species & iron with DNA leading to lethal injury or predisposes to hepatocellular carcinoma.

Morphology :

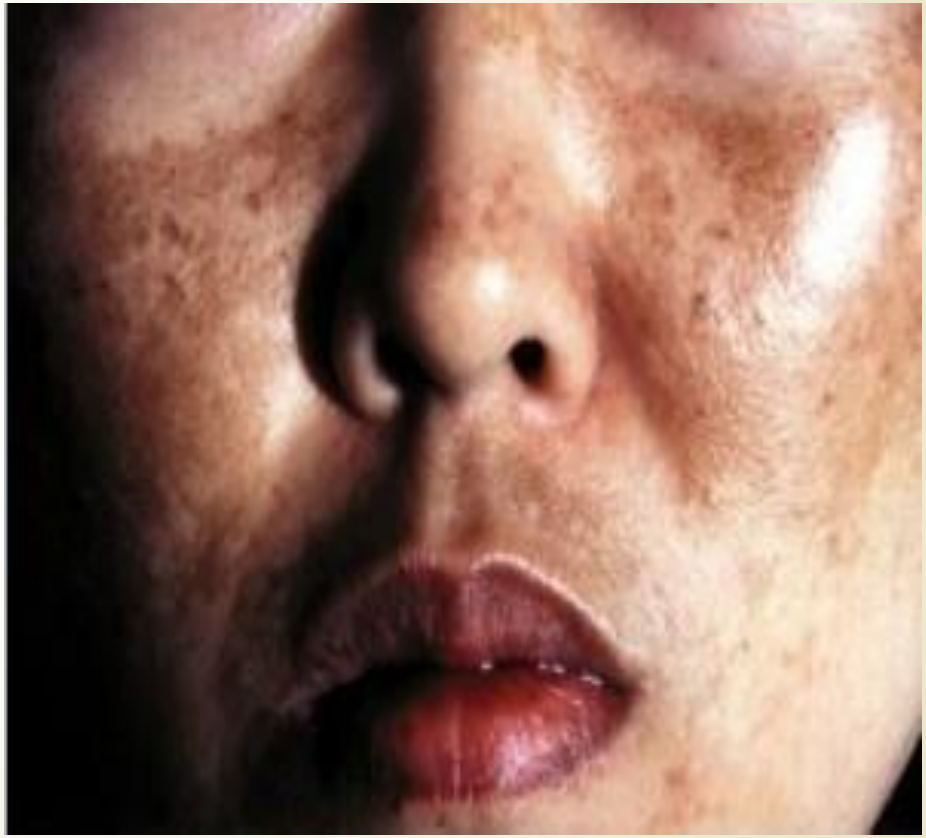
- Deposition of hemosiderin in liver, pancreas, myocardium, pituitary, adrenal gland, thyroid & parathyroid, joints & skin.(in ↓ing severity)
- Iron is seen as golden yellow hemosiderin granules in cytoplasm of periportal hepatocytes.
- With increasing iron load, rest of the lobule,

  bile duct epithelium & kupffer cells are involved.
- Liver becomes larger, dense and **chocolate brown**. Portal-portal fibrous septa leads to **cirrhosis.**

- Iron is directly hepatotoxic. Inflammation is absent.
- Pancreatic fibrosis leads to Diabetes.
- Skin pigmentation.
- Bronze Diabetes
- HEMOSIDERIN DETECTED BY PRUSSIAN BLUE REACTION.

- Copper – Bronze pigmentation due

  to hemosiderin & increased melanin.



- In normal person iron content of liver tissue is < 1000 microgm/gm dry weight.
- In hereditary hemochromatosis > 10000 microgm/gm dry weight.
- When in excess of 22000 microgm/gm dry weight it causes fibrosis and cirrhosis.

PANCREAS:

Intensely pigmented.

Diffused interstitial fibrosis.

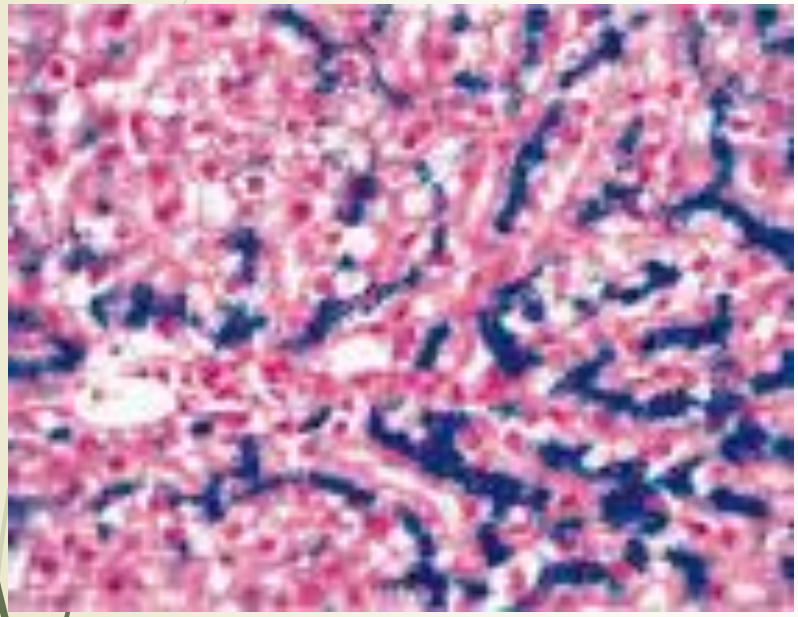
Some parenchymal atrophy.

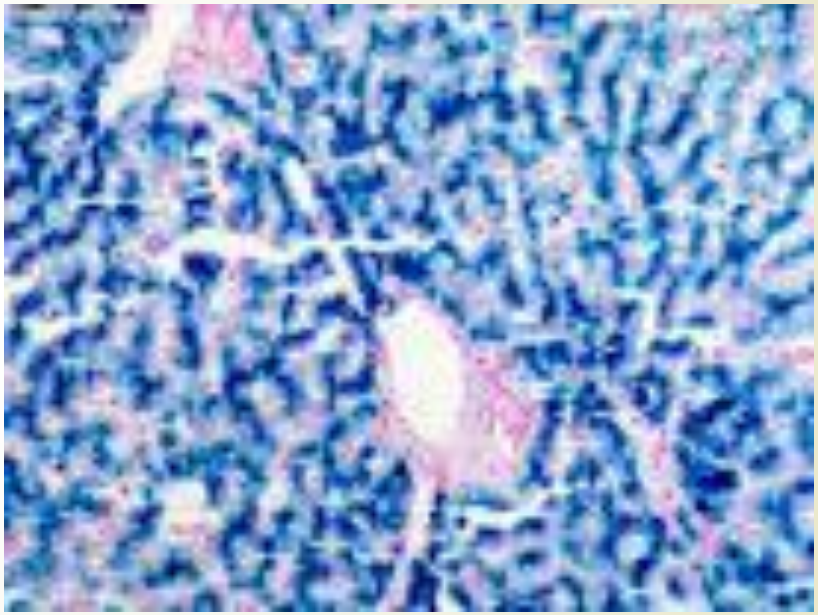
HEART: Enlarged, Hemosiderin granules in myocardial fibres, Brown pigmentation of myocardium, Delicate interstitial fibrosis

SKIN: Hemosiderin deposition in dermal macrophages & fibroblast , ↑ed epidermal melanin production , Combination of these pigments imparts slate grey colour.

In JOINTS: causes acute synovitis

Prussion Blue reaction





CLINICAL FEATURES :

- M : F = 5 to 7 : 1
- Earlier symptoms in male(no physiological loss of iron)
- 5^{th}-6^{th} decade in male , later in female.
- Hepatomegaly, skin pigmentation, abnormal glucose metabolism, cardiac dysfunction, atypical arthritis

- The classic clinical triad of cirrhosis with hepatomegaly, skin pigmentation & diabetes mellitus may not develop until late course of disease.

Causes of Death :

- Cirrhosis of liver.
- Cardiac disease.
- Hepatocellular carcinoma-200 fold greater risk.

Wilson disease

- Defi. Autosomal recessive disorder marked by accumulation of toxic level of copper in many tissues & organ principally liver, brain & eye.
- Mutation in ATP7B gene on chromosome 13.

- Pathogenesis :
- Normal physiology :

1) Absorption of ingested copper(2-5 mg/day)
2) plasma transport via albumin
3) Hepatocellular uptake and binding to alpha2 globulin to form **ceruloplasmin**
4) Secretion of ceruloplasmin in plasma (90% plasma copper)
5) Hepatic uptake of senescent ceruloplasmin , lysosomal degradation and secretion of free copper in bile.

- In wilson disease, absorption and transport are normal.
- Without ATP7B activity, copper can not bind to alpha2 globulin and therefore cannot be excreted into bile,**Primary route for copper elimination from body.**
- Copper accumulates in hepatocytes.

1) Formation of free radicals
2) Binding to sulfhydryl group of cell proteins
3) Displacing other metals in hepatic metalloenzyme

- Deposition in liver leads to ,

  (1) Fatty change.

  (2) Acute hepatitis-Mallory bodies are seen.

  (3) Chronic hepatitis.

  (4) Submassive hepatic necrosis.

  (5) Macronodular cirrhosis.

- Deposition in brain.
- Toxic injury to basal ganglia leads to atrophy & cavitation.
- Neuropsychiatric manifestations.

  i.e. behavioural changes, frank psychosis , parkinson disease like syndrome.

Deposition in eye **Kayser-fleischer rings -i.e**. green to brown deposits of copper in Descemet's memb. in limbus of cornea.

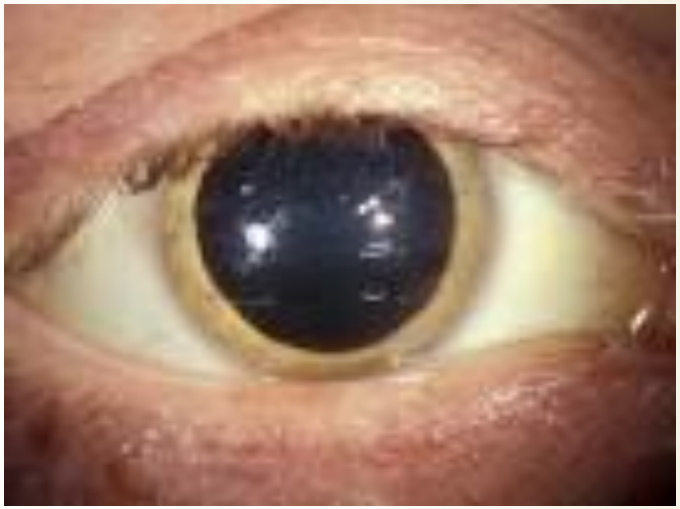
- Treatment- long term copper chelation therapy. D- penicillamine.
- Investigation.

  (1) Decreased in ceruloplasmin.

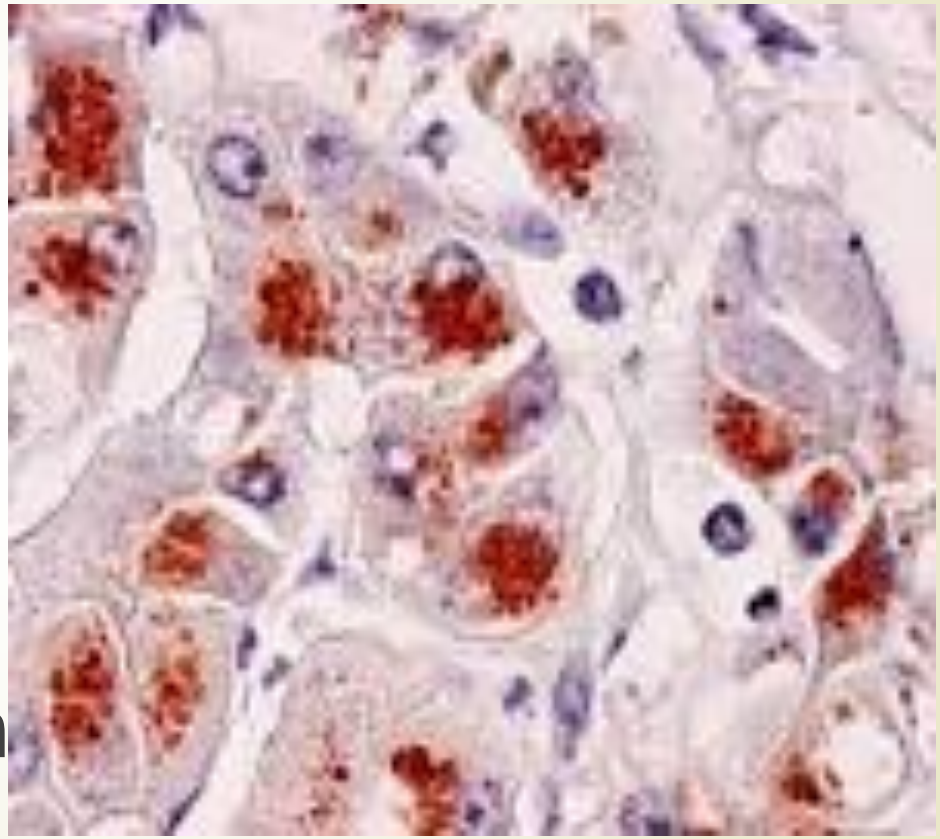
  (2) increased in hepatic copper content.

  (3) Increased urinary excretion of copper.
- Serum copper level no diagnostic value.

K-F Ring in Cornea



- (rhodanine stain) highlights the accumulation of copper in the hepatocytes of patients with Wilson disease.
- Copper stain orange to red with blue nuclei.



Alpha1-Antitrypsin deficiency

- Autosomal recessive disorder
- Low serum levels of this important protease inhibitor
- Also leads to pulmonary emphysema
- Hepatic disease results from accumulation of mutant AAT
- AAT gene is located on chromosome 14

- AAT gene is located on chromosome 14
- 75 forms of it have been identified
- Homozygous for Z allele PiZZ genotype have 10% of levels of AAT
- There is single aminoacid substitution results in misfolding of polypeptide in hepatocyte

- As mutant forms can not be secreted, they accumulate in hepatocytes and lead to apoptosis

Morphology:

- Hepatocytes show round to oval cytoplasmic globular inclusions containing AAT.
- PAS Positive & Diastase resistant.
- Hepatic injury with PiZZ range from cholestasis with hepatic necrosis to childhood cirrhosis in newborn.

CLINICAL FEATURES :

- Neonatal hepatitis with cholastatic jaundice
- In adolescence – Hepatitis or cirrhosis
- Hepatocellular carcinoma in 2-3 % of cases


Thank You