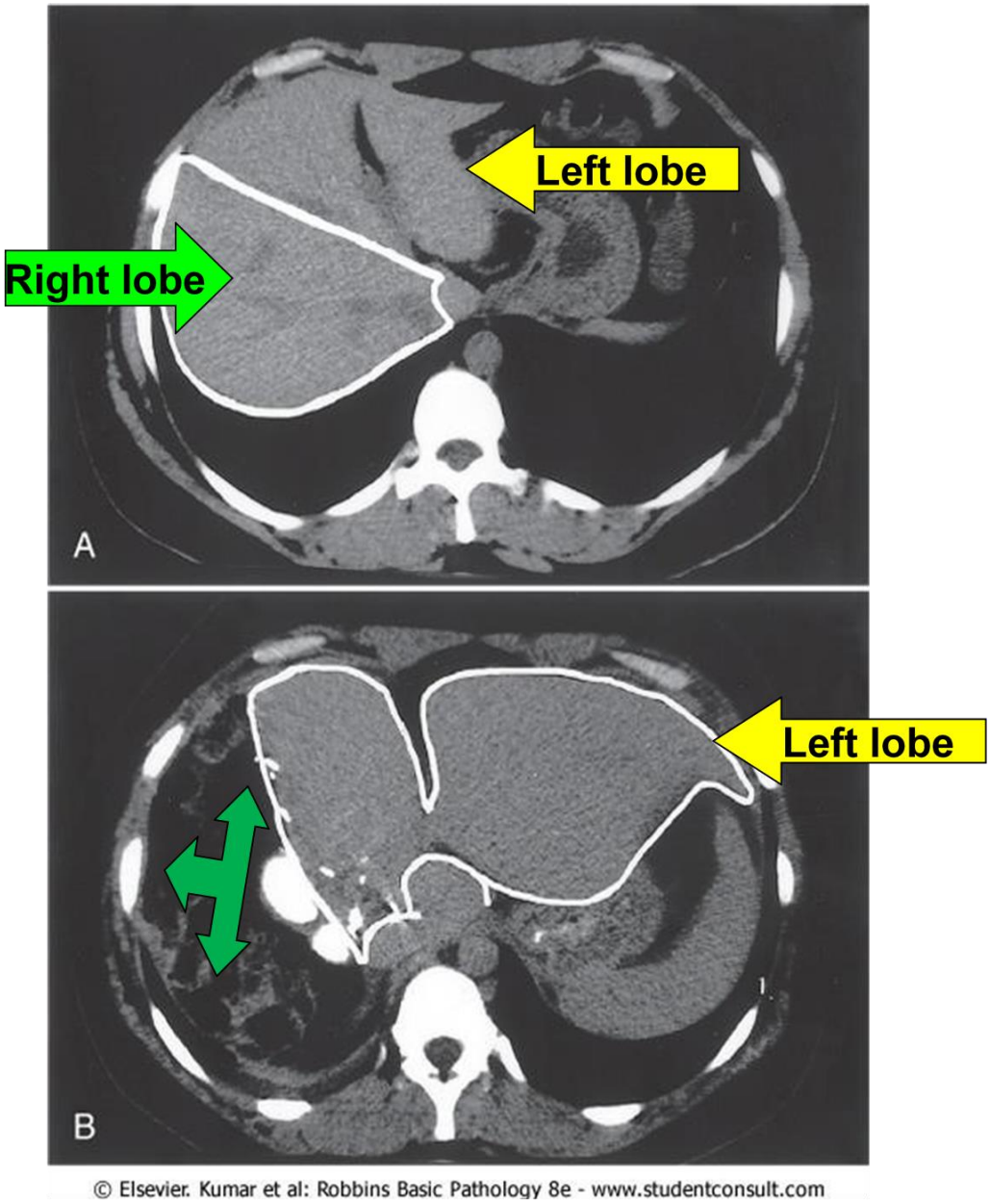
THE LIVER

- The liver maintains the body's metabolic homeostasis. This includes:
  - the processing of dietary carbohydrates, lipids, & vitamins;
  -synthesis of serum proteins;
  - detoxification & excretion into bile of endogenous waste products & xenobiotics.

  Thus, it is vulnerable to a wide variety of toxic (including Drugs), Viruses, circulatory & metabolic insults.

  The liver has enormous functional regeneration reserve:
- Surgical removal of 60% of the liver of a normal person produces minimal & transient hepatic impairment
  & regeneration restores most of the liver mass within 4 to 6 weeks.

- In persons with massive hepatocellular necrosis that has not destroyed the hepatic reticulin framework,
  perfect restoration may occur if the individual can survive the metabolic insult of liver failure.



Regeneration of human liver.
CTS of the donor liver in living-donor liver transplantation

A, The liver of the donor before the operation.
Note the right lobe (white outline), which will be resected & used as a transplant.

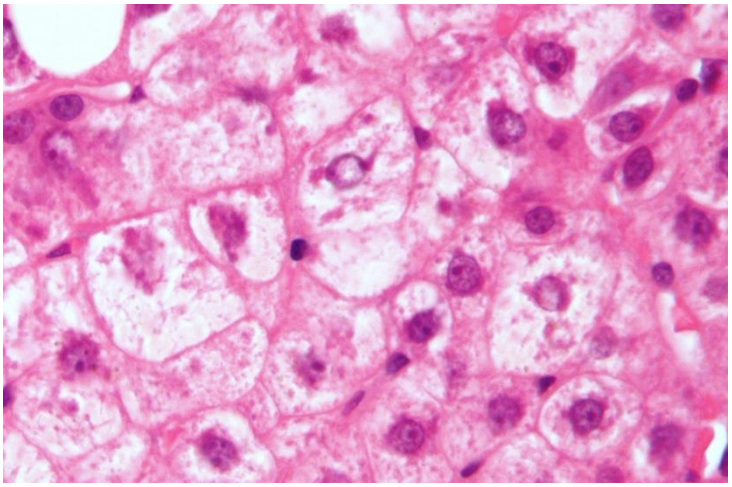
B, Scan of the same liver 1 week after resection of the right lobe;
note the enlargement of the left lobe (outline) without regrowth of the right lobe.

PATTERNS OF HEPATIC INJURY & RESPONSES

Degeneration

- Moderate cell swelling caused by toxic or immunologic insults is reversible.

- More serious damage cause enlargement of hepatocytes (H) {ballooning degeneration} with irregularly clumped cytoplasm showing large, clear spaces.

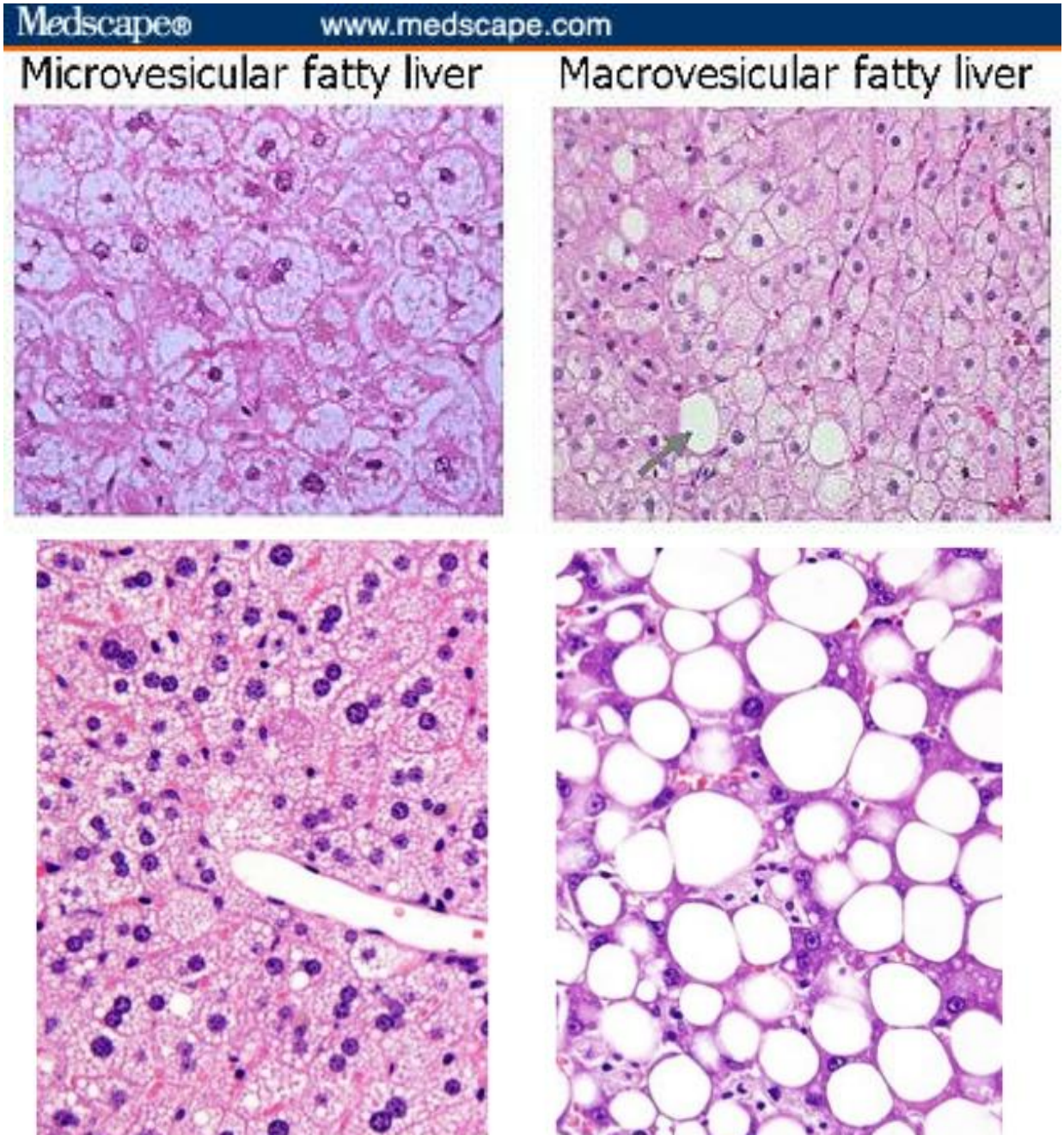


- Intracellular accumulation of fat, iron, copper, & retained biliary material may occur in H.

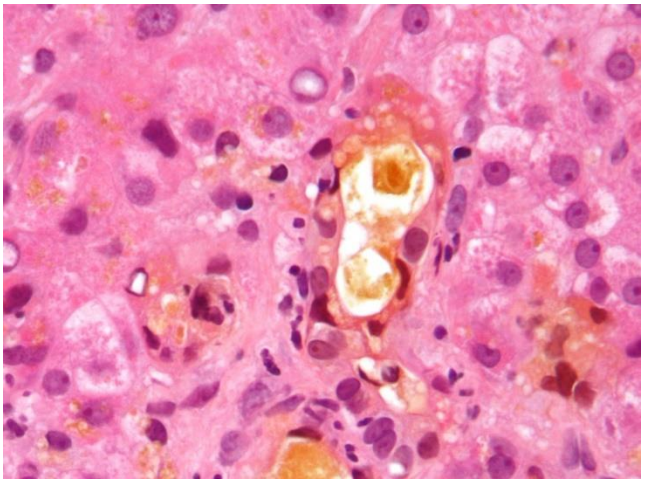
- Accumulation of fat droplets within H is known as steatosis or fatty change.

- multiple tiny droplets that do not displace the nucleus are known as microvesicular steatosis & appear in
  -alcoholic liver disease,
  -Reye syndrome, &
  - acute fatty liver of pregnancy.

- A single large fat droplet that displaces the nucleus, known as macrovesicular steatosis, may be seen in
  - alcoholic liver disease or
  - in the livers of obese or
  - diabetic individuals.



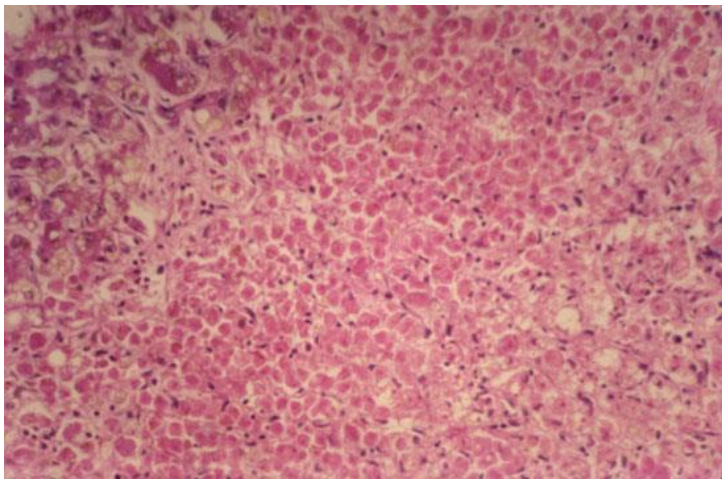
- Retained biliary material
  cause diffuse, foamy, swollen of H
  (feathery degeneration).



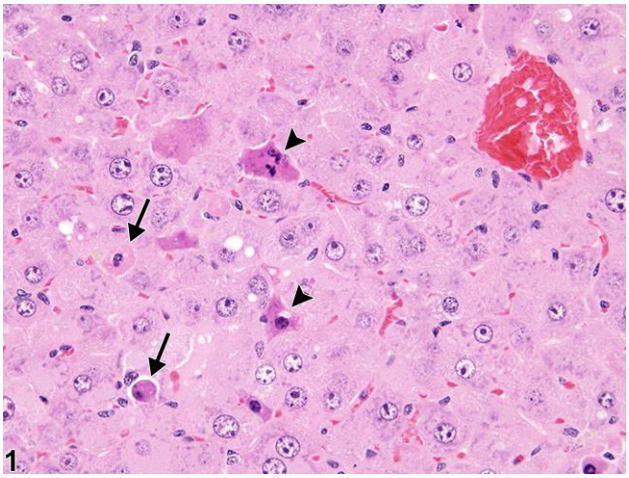
Necrosis & apoptosis.

- Any insult to the liver may cause H destruction.

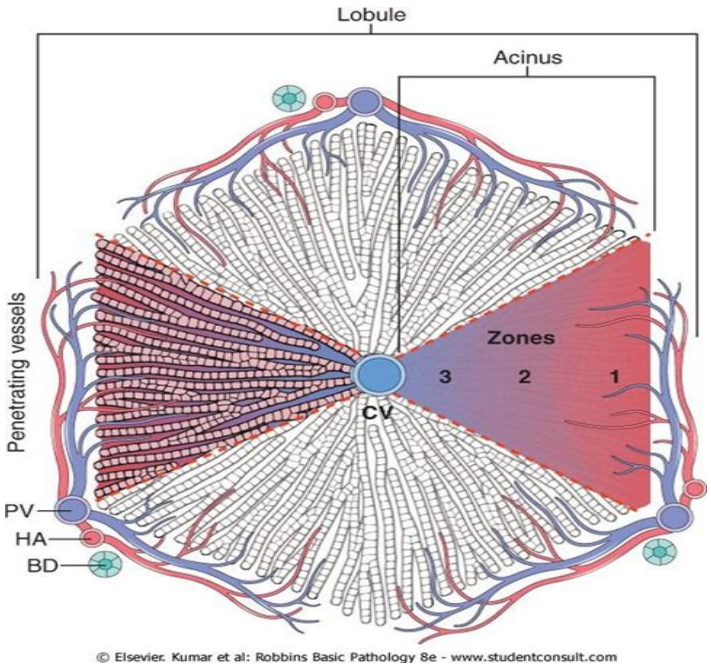
  Poorly stained mummified H seen in coagulative necrosis,

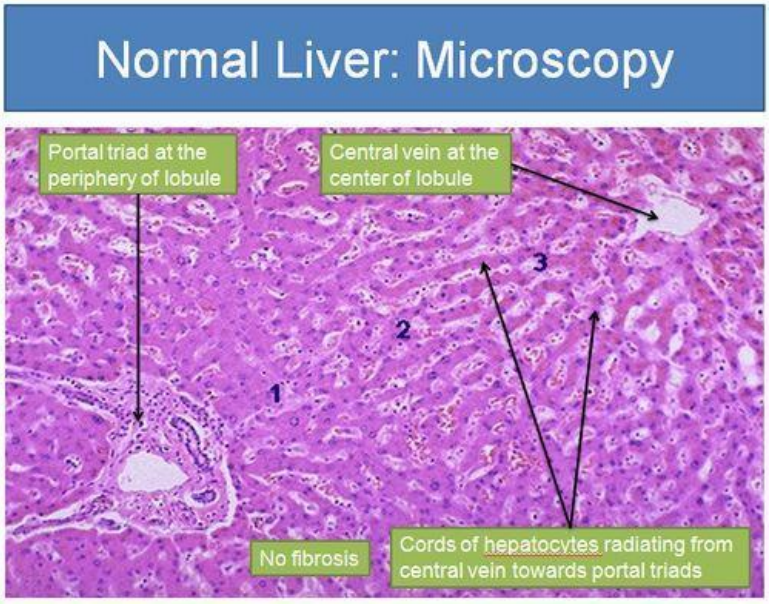


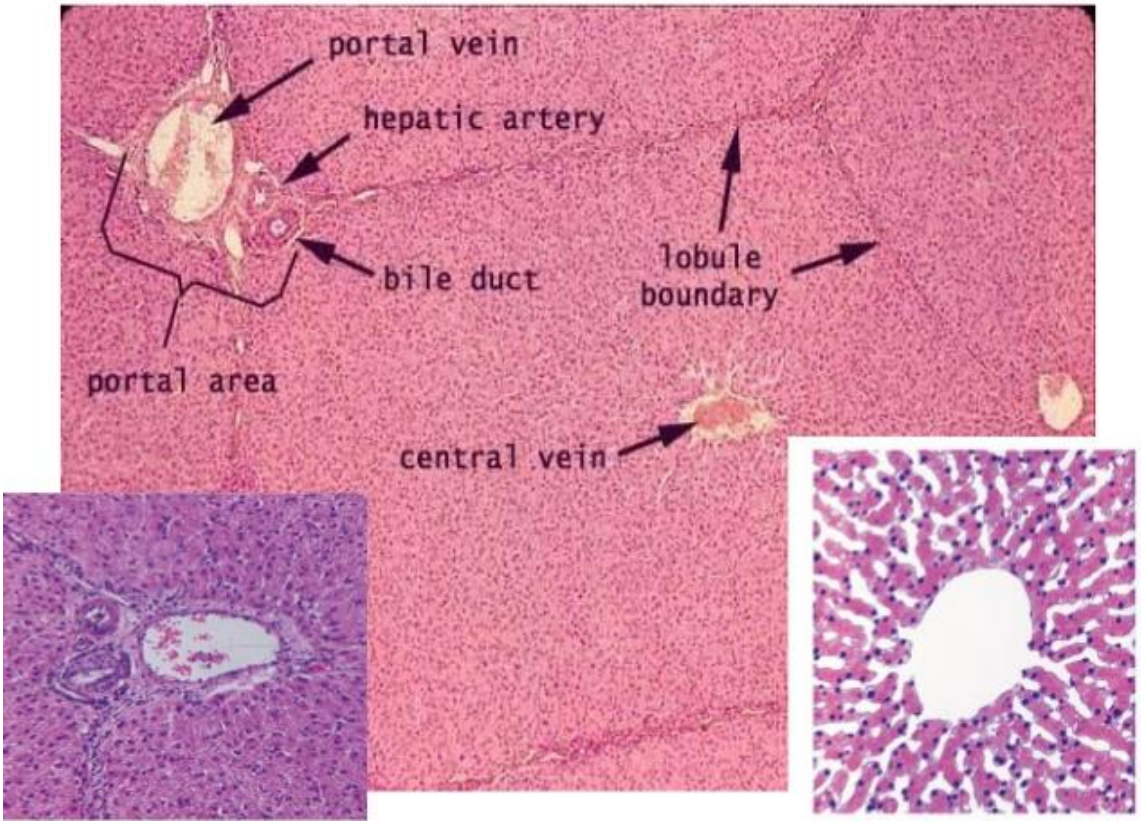
  while in apoptosis, isolated H are shrunken, pyknotic, & intensely eosinophilic.



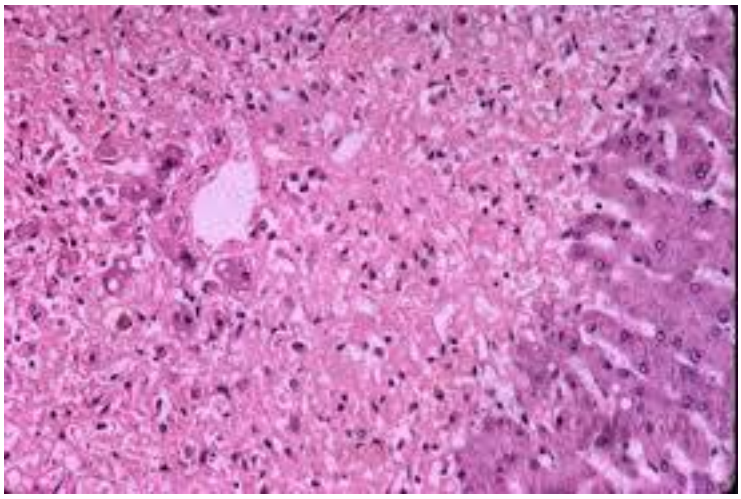
Microscopic architecture of the liver parenchyma.

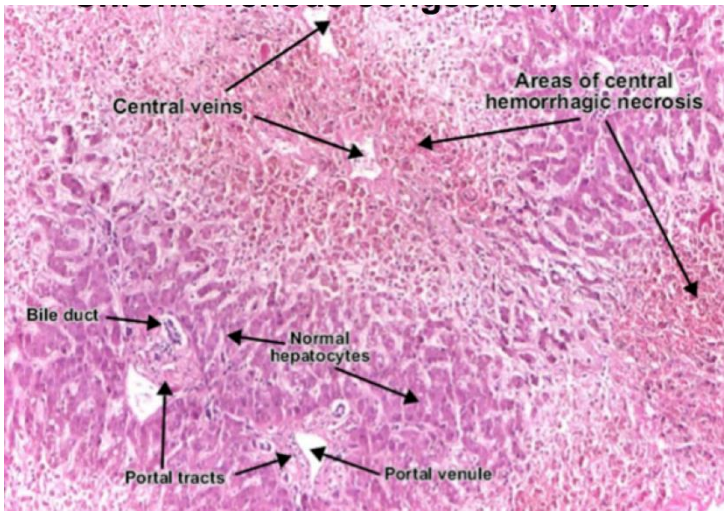






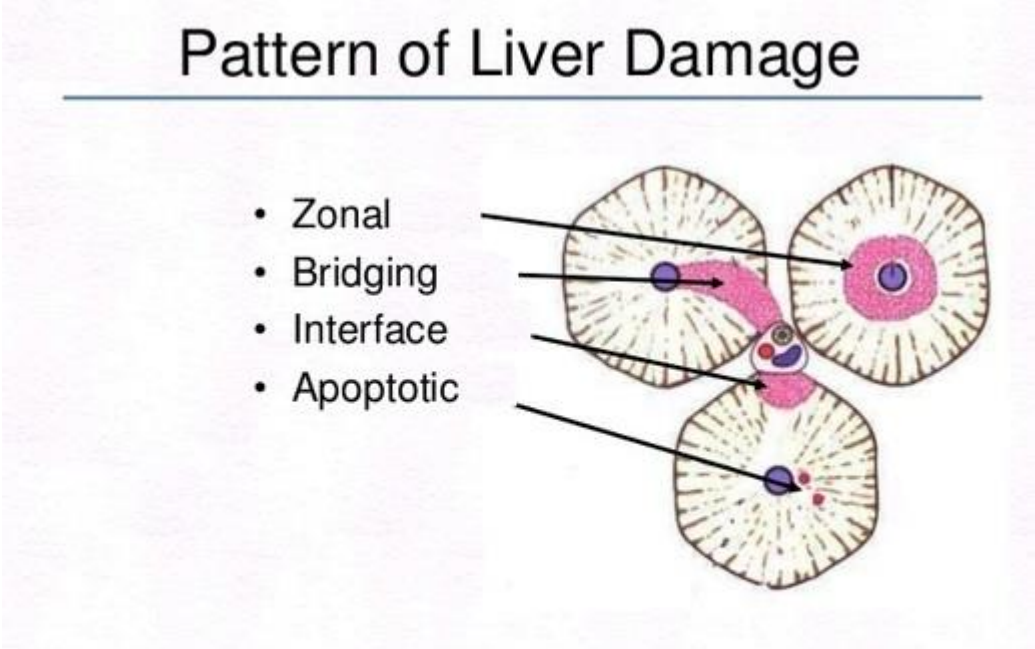
- In ischemia & several drug & toxic reactions, H necrosis is (centrilobular), distributed immediately around the central vein extending into the midzonal area. with variable mixture of inflammation & H death encountered. {Pure midzonal & periportal necrosis is rare},



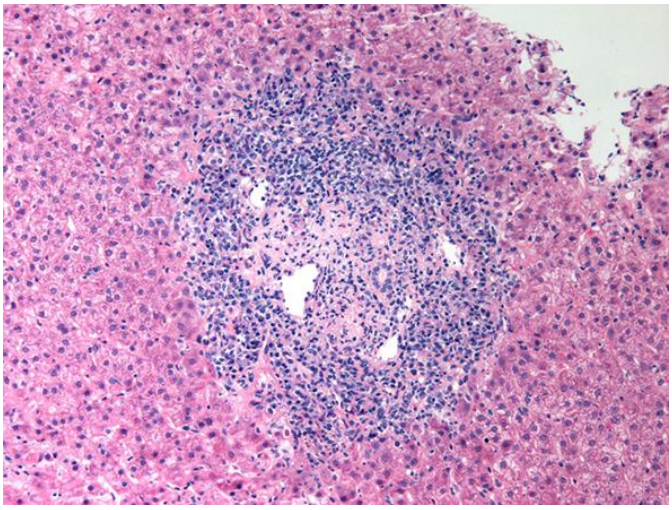


Necrosis & apoptosis may be limited to :

(1) scattered cells within the lobule, or to the interface between the periportal parenchyma & inflamed portal tracts

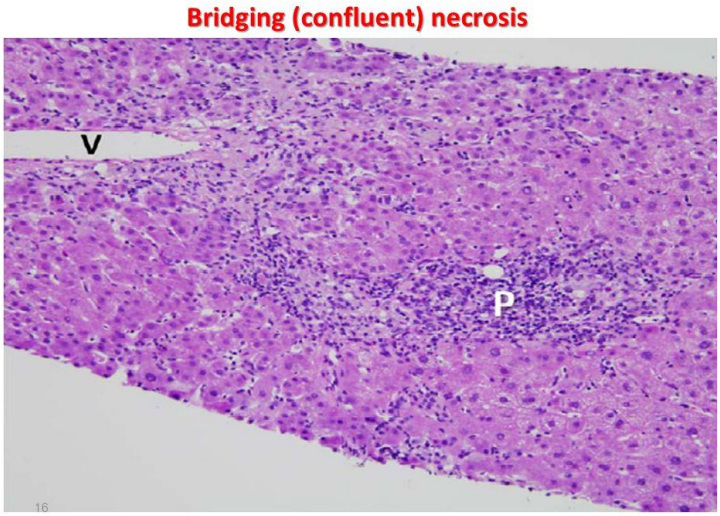


(2)”interface hepatitis”



(3)”bridging necrosis”

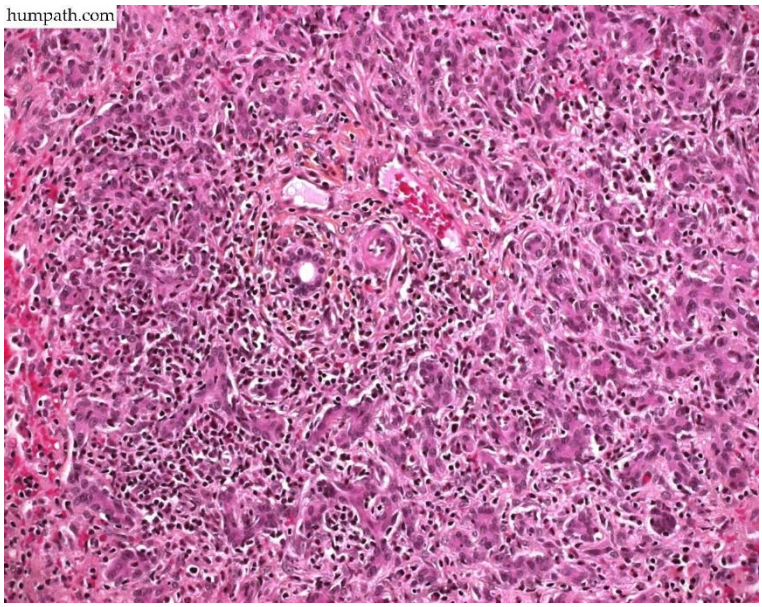
With more severe inflammatory or toxic injury, apoptosis or necrosis of contiguous H may span adjacent lobules in a portal-to-portal, portal-to-central, or central-to-central fashion



-Destruction of entire lobules
(4) “submassive necrosis”

or most of the liver parenchyma
(5) “massive necrosis” (pic)

is usually accompanied by hepatic failure.



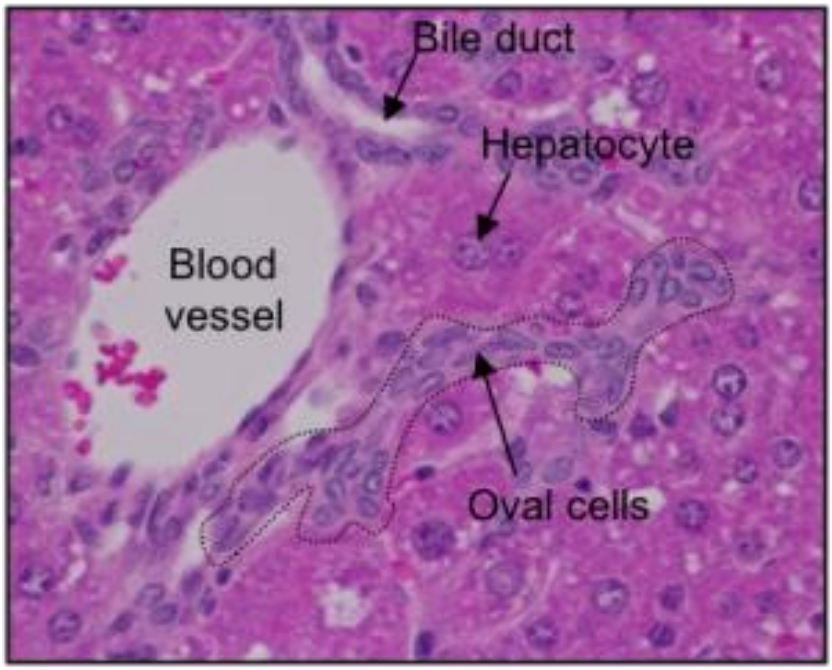
Regeneration.

- Cell death or tissue resection (such as in living-donor transplantation) triggers H replication, to compensate for the cell or tissue loss.

- (I)Hepatocyte proliferation is recognized by the presence of mitoses.

  (II) The cells of the bile canals of Hering (oval cells),
  constitute a reserve compartment of progenitor cells for H

  & bile duct cells proliferate when the H are unable to replicate or have exhausted their replicative capacity.



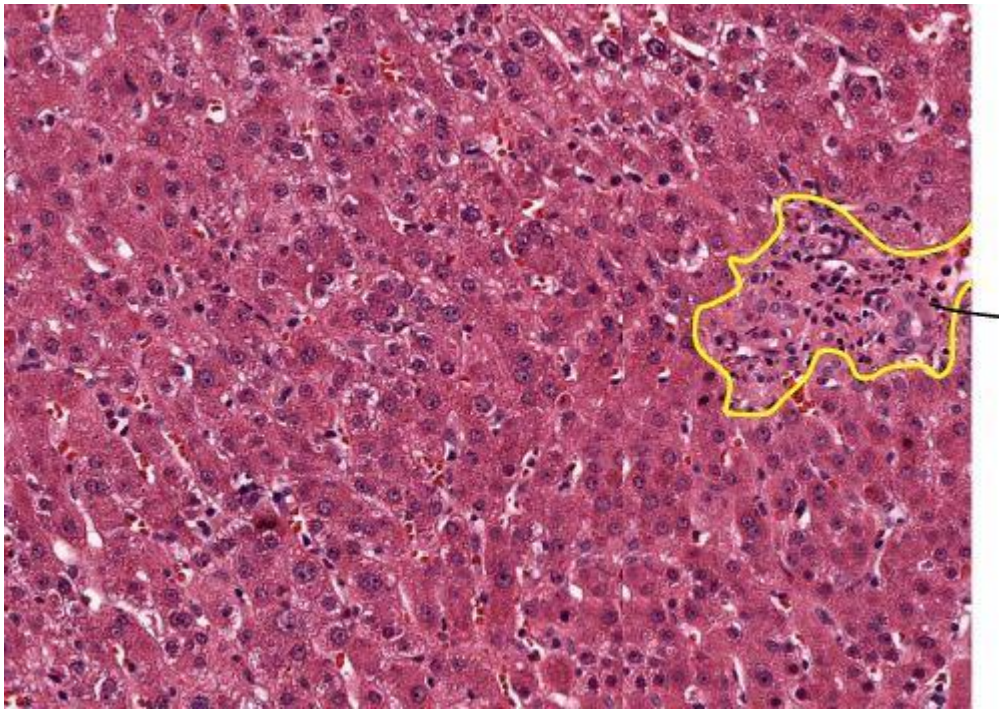
Inflammation

- hepatitis referred to injury to H associated with an influx of acute or chronic inflammatory cells.
- Although H necrosis may precede the onset of inflammation, the converse is also true.

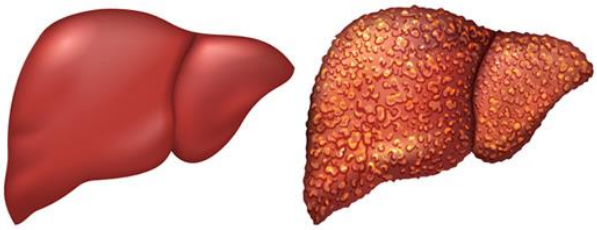
- Lysis of antigen expressing liver cells by sensitized T cells is the cause of liver damage in some forms of viral hepatitis.

- Inflammation may be limited to portal tracts or may spill over into the parenchyma.

- Foreign bodies, organisms, & a variety of drugs may incite a granulomatous reaction.



Chronic viral hepatitis



Fibrosis.

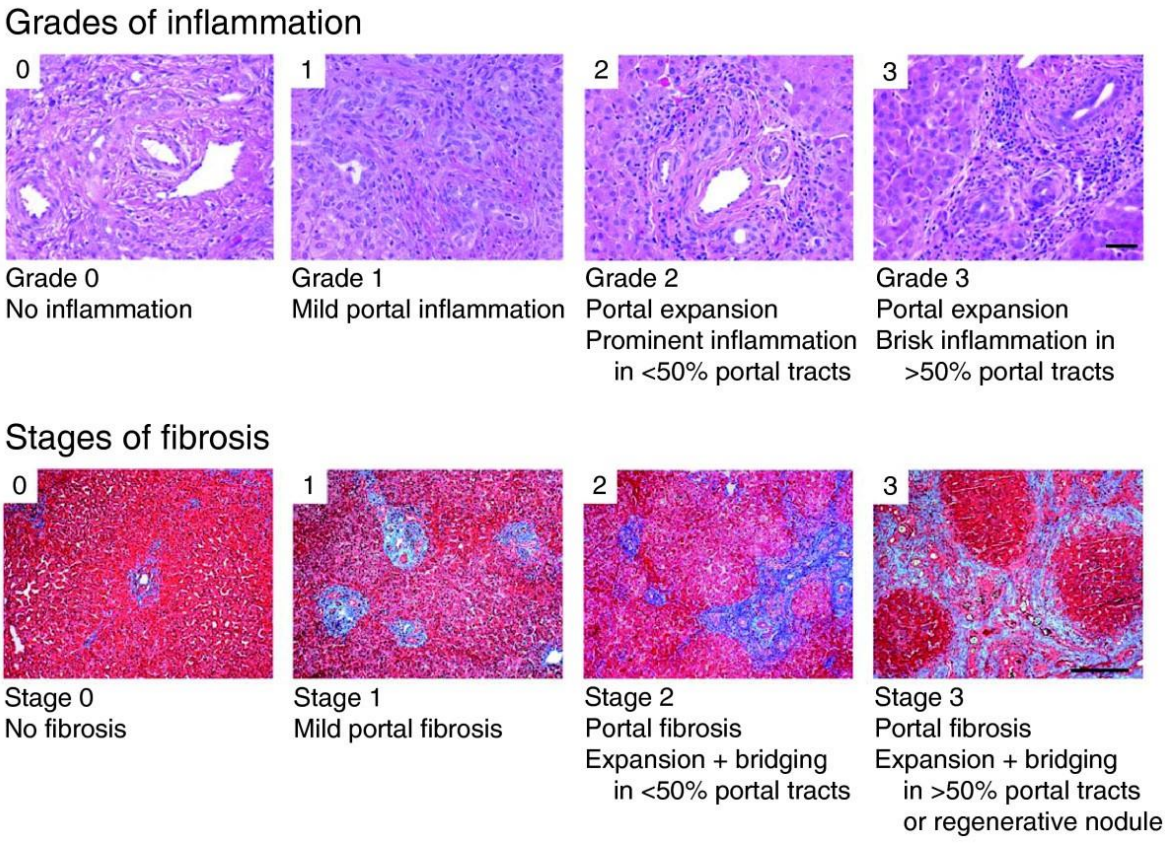
- Fibrous tissue is formed in response to inflammation or direct toxic insult to the liver, with long lasting effects on hepatic blood flow & perfusion of H.

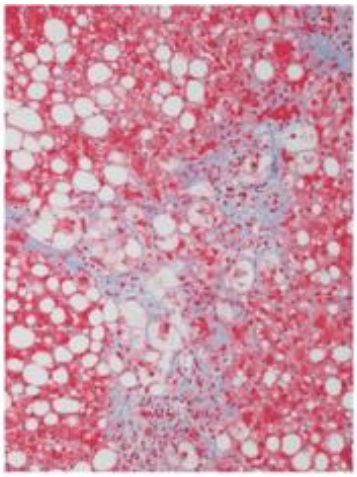
- In the initial stages, fibrosis may develop within or around portal tracts
  (1) “portal or periportal fibrosis”

  Or around the central vein
  (2) “perivenular

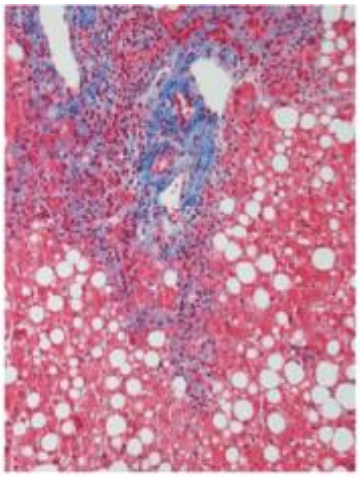
  or deposited directly within the sinusoids around single or multiple H
  (3) “pericellular fibrosis”

  With time, fibrous strands link regions of the liver (portal-to-portal, portal-to-central, central-to-central), a process called
  (4)“bridging fibrosis”



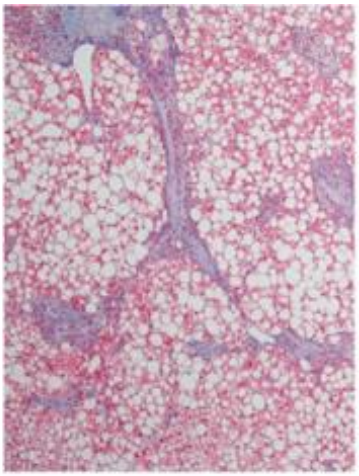


Perisinusoidal fibrosis

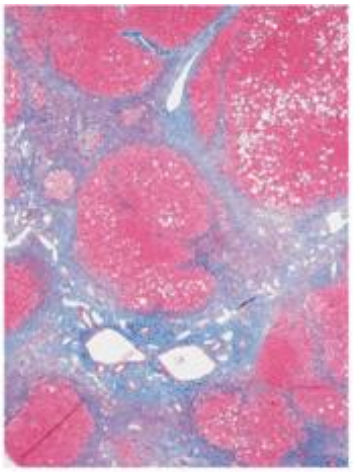


Periportal fibrosis

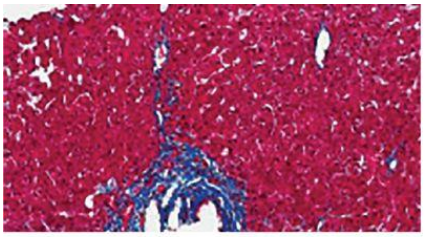
(Stage 1-2)



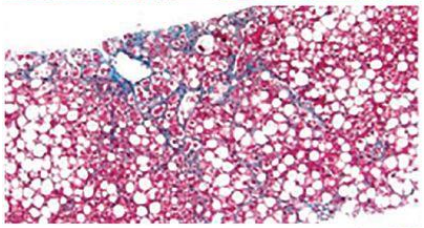
Bridging Fibrosis (Stage 3)



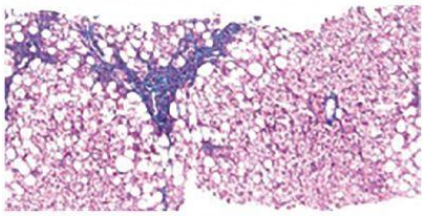
Cirrhosis (Stage 4)



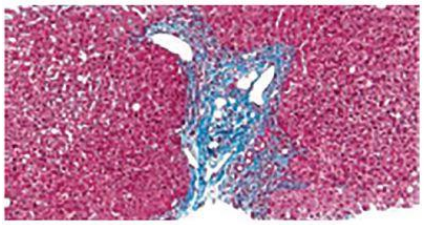
Expansion of portal tract by fibrosis (trichrome stain, × 100)



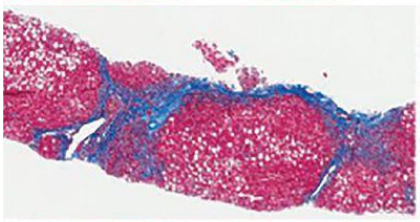
In the setting of steatohepatitis, fibrosis starts in the centrilobular perisinusoidal region (trichrome stain, × 100)



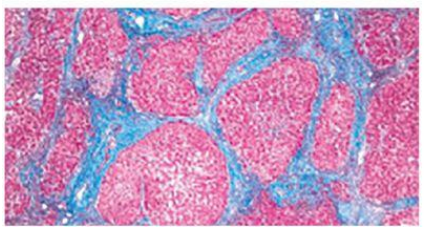
A subset of nonalcoholic steatohepatitis cases reveals only portal-based fibrosis, consistent with stage 1C (left); the centrilobular region seen on the right is intact (trichrome stain, × 100)



Periportal fibrosis is characterized by expansion of portal tracts with irregular border and focal entrapment of hepatocytes (trichrome stain, × 200)



Bridges of fibrous tissue connecting two portal tracts in a hepatitis C case, supporting stage 3 (bridging fibrosis) (trichrome stain, × 100)



End-stage liver disease with multiple cirrhotic nodules, surrounded by fibrous bands (trichrome stain, × 100)

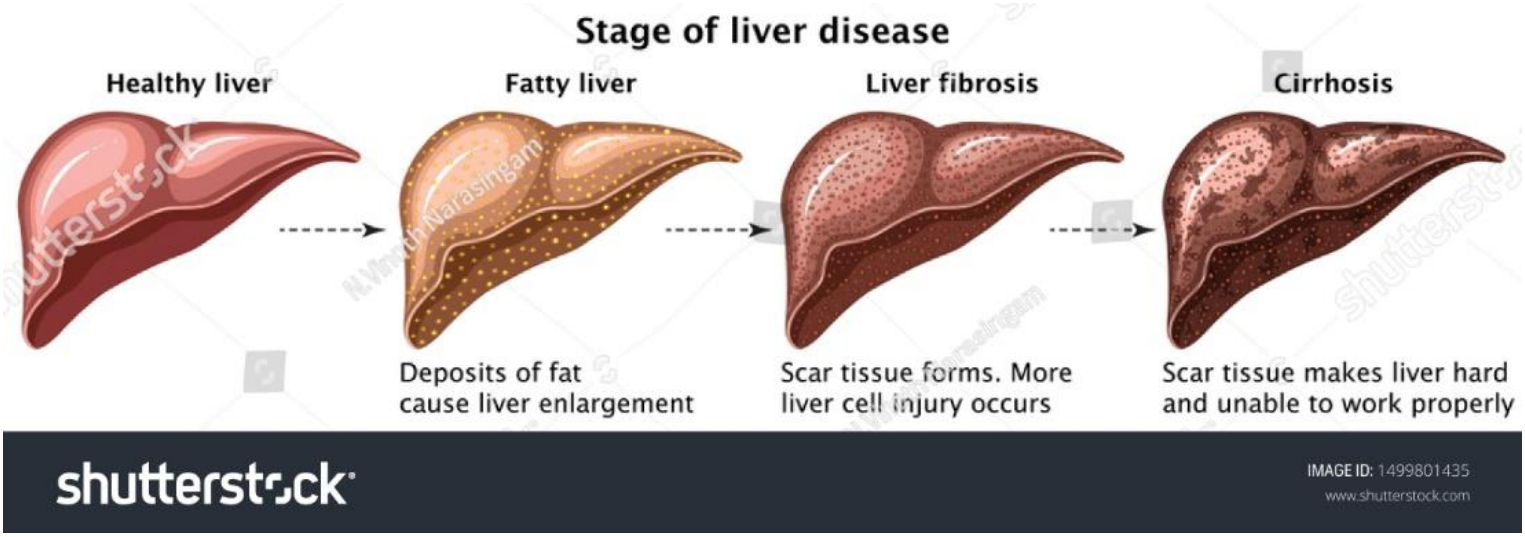
Cirrhosis (C)

- With progressive parenchymal injury & fibrosis,

  (1) the liver develops nodules of regenerating H,
  (2) Surrounded by bands of scar tissue. In this process, the
  (3) normal liver architecture is destroyed, & the condition called cirrhosis, which is the end-stage of liver disease,

- Depending on the size of the nodules (smaller or larger than 3 mm), C can be classified as being micronodular or macronodular. This classification has little significance.

- C increase the risk of liver malignancy.

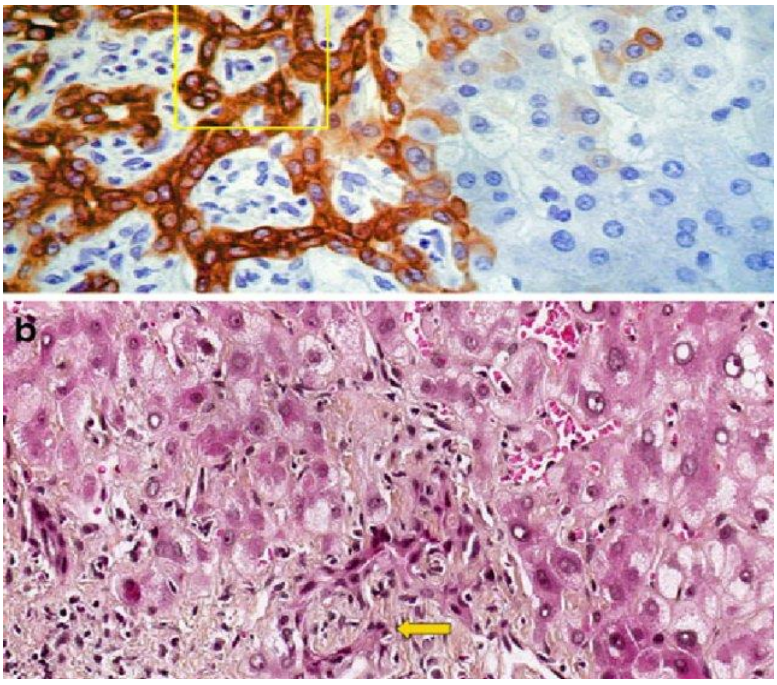


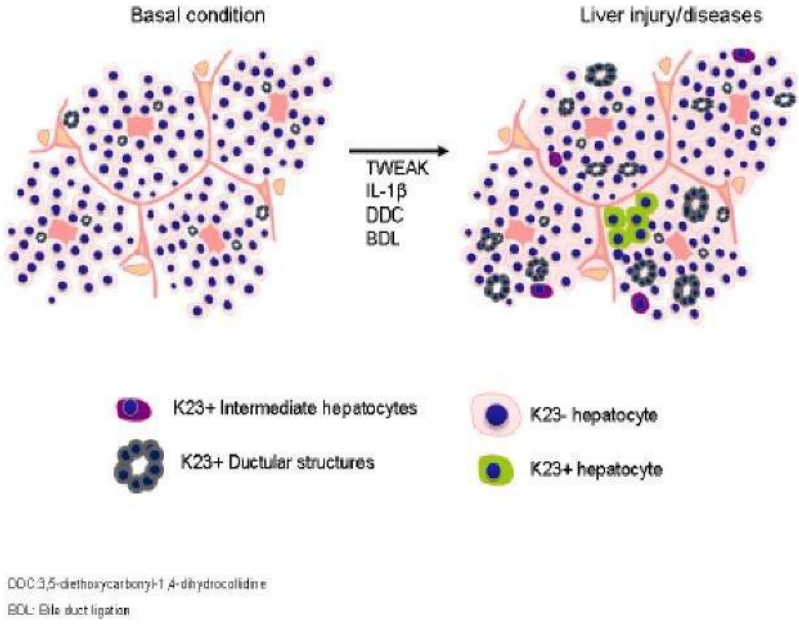
Ductular reaction.

In biliary & other forms of liver disease,
the number of intrahepatic bile ducts & canals of Hering may increase

This is known as a ductular reaction or proliferation, & it is usually associated with fibrosis & inflammation.

Ductular reaction has gained much interest recently, because some of the proliferating (Oval) cells originating from the canals of Hering can function as progenitor cells for hepatocytes & bile ducts.





CLINICAL SYNDROMES

The major clinical syndromes of liver disease are

hepatic failure, cirrhosis, portal hypertension, & cholestasis.

having characteristic clinical manifestations, & a battery of laboratory tests are used to diagnose these disorders These conditions are discussed next.

Clinical Consequences of Liver Disease :

- Severe Hepatic Dysfunction, Characteristic Signs:

  -Jaundice & cholestasis
  - Hypoalbuminemia
  - Hyperammonemia
  - Hypoglycemia
  -Palmar erythema
  -Spider angiomas
  - Hypogonadism
  -Gynecomastia
  -Weight loss
  -Muscle wasting.

- Portal Hypertension Associated with Cirrhosis:

  - Ascites
  - Splenomegaly
  -Esophageal varices,
  -Hemorrhoids,
  -Caput medusae of abdominal skin.

- Complications of Hepatic Failure:
  -Coagulopathy
  -Hepatic encephalopathy
  -Hepatorenal syndrome

Laboratory Evaluation of Liver Disease Test Category & Serum Measurement*

- Hepatocyte integrity:

  Cytosolic hepatocellular enzymes: *(an increase indicate liver ds)*
  - *Serum aspartate aminotransferase (AST),*
  - *Serum alanine aminotransferase (ALT),*
  -Serum lactate dehydrogenase (LDH)

- Biliary excretory function:

  Substances secreted in bile*: (an increase indicate liver ds)*
  -Serum bilirubin
  Total: unconjugated plus conjugated,
  Direct: conjugated only,
  Delta: covalently linked to albumin, Urine bilirubin, Serum bile acids.

  Plasma membrane enzymes (from damage to bile canaliculus):
  (increase indicate liver ds)
  - *Serum alkaline phosphatase*,
  - Serum γ-glutamyl transpeptidase,
  - Serum 5'-nucleotidase

- Hepatocyte function:

  Proteins secreted into the blood:
  -Serum albumin, (decrease indicate liver ds)
  -Prothrombin time (factors V, VII, X, prothrombin, fibrinogen),
  (increase indicate liver ds)

Hepatocyte metabolism:
- Serum ammonia*, (increase indicate liver ds)*
-Aminopyrine breath test (hepatic demethylation),
-Galactose elimination (intravenous injection).

*Most common tests are in italics.
†An elevation implicates liver disease.
‡A decrease implicates liver disease.

Hepatic or Liver Failure (LF)

- The severest clinical consequence of liver disease is LF.

It generally develops as the end point of progressive damage to the liver, either by:
(1) slow insidious destruction of H or
(2) by repetitive discrete waves of parenchymal damage
(3) Less commonly, LF is the result of sudden & massive destruction of hepatic tissue.

▼80% to 90% of hepatic function must be lost before hepatic failure develop.

In many cases, the balance is tipped toward decompensation by intercurrent diseases that place demands on the liver, including :
-systemic infections,
-electrolyte disturbances,
-stress (major surgery, heart failure),
-& GIT bleeding.

▼Alterations cause LF fall into 3 categories:

1. Acute LF with massive hepatic necrosis.

- The histologic correlate of which is massive hepatic necrosis.
- Mostly caused by drugs or fulminant viral hepatitis.
- Acute LF means clinical hepatic insufficiency that progresses from onset of symptoms to encephalopathy within 3 weeks,
  if the course extends for 3 months, it is called subacute LF.
- It is an uncommon life-threatening condition that often requires liver transplantation.

2. Chronic LF This is the most common route to hepatic failure & is the end point of cirrhosis.

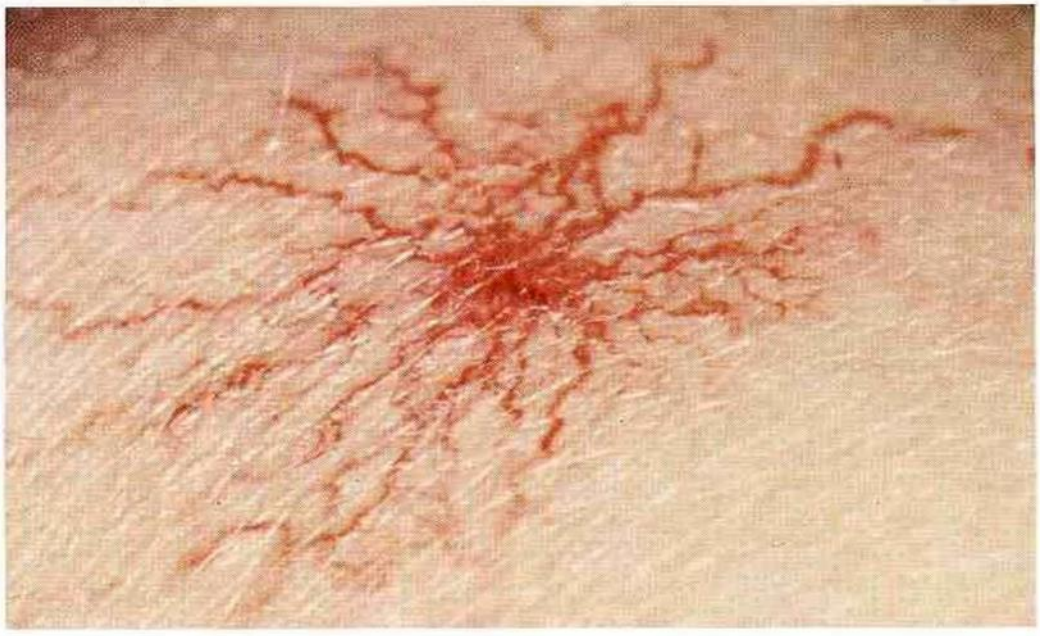
3. Hepatic dysfunction without overt necrosis.
   H may be viable but unable to perform normal metabolic function, as in:
   -acute fatty liver of pregnancy (which can lead to acute liver failure a few days after onset),
   -tetracycline toxicity,
   - & Reye syndrome (a rare syndrome of one per Million, of fatty liver & encephalopathy in children, associated with aspirin intake & virus infection).

Clinical Features of LF

- Jaundice {always present},
  acute LF may P/W jaundice or encephalopathy.

- Impaired hepatic synthesis & secretion of albumin leads to :
  -Hypoalbuminemia, predisposes to peripheral edema.
  -Hyperammonemia due to defective hepatic urea cycle function.
  -Impaired estrogen metabolism & consequent Hyperestrogenemia causes :
    -palmar erythema (local vasodilatation)
    -& spider naevus of skin,
    -& in male it leads to hypogonadism & gynecomastia.

Spider naevus:
radial, often pulsatile array of dilated subcutaneous arteries or arterioles (resembling legs)
about a central core (resembling a body) of spider,
that blanches when pressure is applied to its center,
usually seen in liver cirrhosis



14.18 Spider naevus

Prognosis:

- LF is life-threatening, due to the accumulation of toxic metabolites,
- & patients are highly susceptible to multi-organ failure.

- Thus, Respiratory failure with pneumonia **&** sepsis combines with Renal failure cause death of many patients with LF.

- Coagulopathy from impaired hepatic synthesis of blood clotting factors results in bleeding tendency which may lead to massive GIT bleeding.
- Intestinal absorption of blood ,places a metabolic load on the liver that increase the severity of LF.

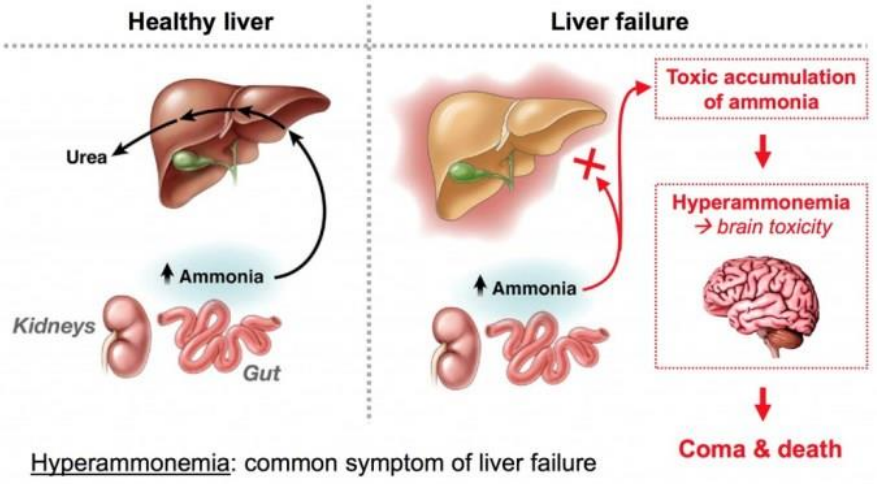
- The outlook of full-blown LF is particularly grave for persons with chronic liver disease.

- A rapid downhill course is usual, with death occurring within weeks to a few months in about 80% of cases.
- About 40% of individuals with acute liver failure may recover spontaneously.
- The others either die without transplantation (30%) or receive a liver transplant.

- Two serous complications of LF are
  - hepatic encephalopathy &
  - hepatorenal syndrome.

Hepatic Encephalopathy

- Hepatic encephalopathy is a feared complication of LF.

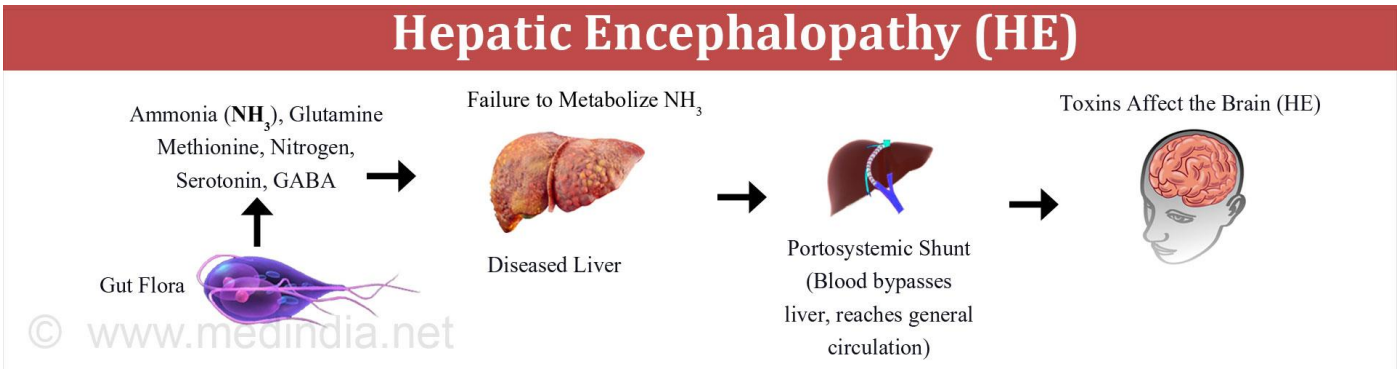


- Two factors are important in the genesis of this disorder:
  (1) Severe loss of hepatocellular function &
  (2) Shunting of blood from portal to systemic circulation,
  resulting in an elevation of blood ammonia,
  which impairs neuronal function & promotes generalized brain edema.

- Patients show a spectrum of disturbances in brain function, ranging from
  →subtle behavioral abnormalities
  →to marked confusion & stupor,
  →to deep coma & death.

- These changes may progress over hours or days as, eg,
  in fulminant hepatic failure or, more insidiously,
  in someone with marginal hepatic function from chronic liver disease.

- In the brain, there are only minor morphologic changes, including:
  edema & an astrocytic reaction.



Hepatorenal Syndrome

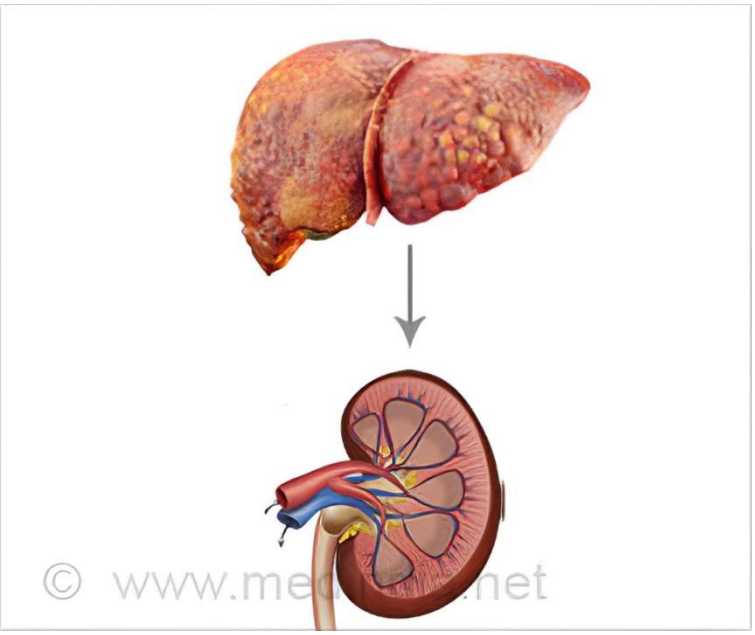
- Appears in individuals with LF, consists of development of renal failure without primary abnormalities of the kidneys themselves.

- {Excluded by this definition are concomitant damage to both liver & kidney, as may occur with exposure to
  -carbon tetrachloride &
  - certain mycotoxins,
  - the copper toxicity of Wilson disease, &
  -LF in which circulatory collapse leads to acute tubular necrosis & renal failure.

► Pathogenesis:

- unknown,
- but evidence points to splanchnic vasodilatation & systemic vasoconstriction, leading to severe reduction of renal blood flow, particularly to the cortex, with oligurea & uraemia.

- Kidney function promptly improves if hepatic failure is reversed.

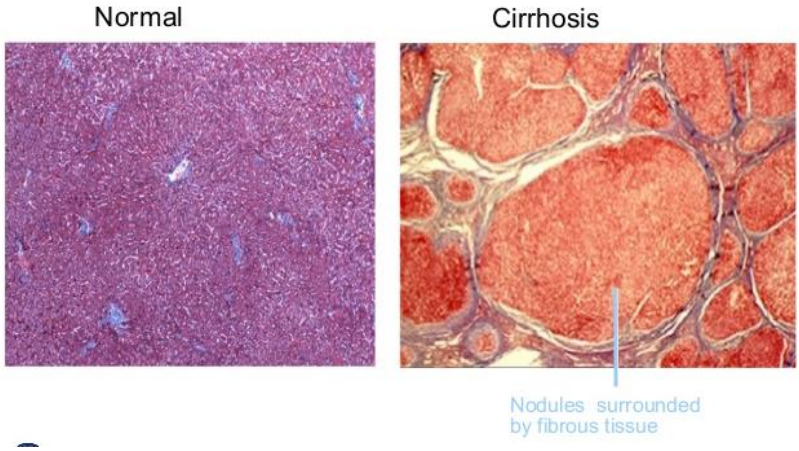


Cirrhosis (c)

- C is among the top 10 causes of death in the West.

- The most common causes of C are
  -chronic alcoholism &
  - chronic hepatitis B & C,
  - followed by biliary diseases & hemochromatosis.
- 10% of C remain unknown, referred to as cryptogenic cirrhosis.

- C is defined as a total diffuse conversion of normal liver architecture into abnormal hyperplastic nodules separated by bands of fibrosis.



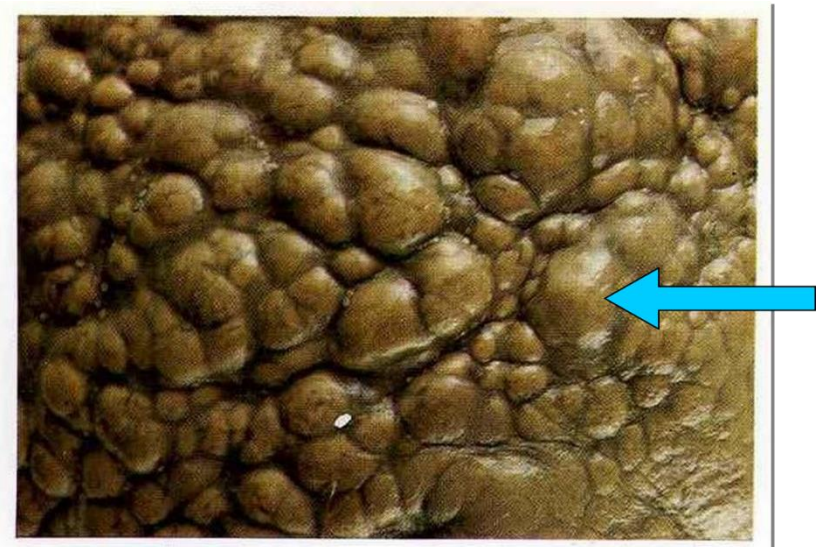
- Its three main characteristics are:

  (1) Bridging fibrous septa in the form of delicate bands or broad scars around multiple adjacent lobules. Long-standing fibrosis is irreversible

  (2) Parenchymal nodules, contain proliferating hepatocytes varying from very small (<3 mm, micronodules) to large (>3 mm in, macronodules), encircled by fibrotic bands.

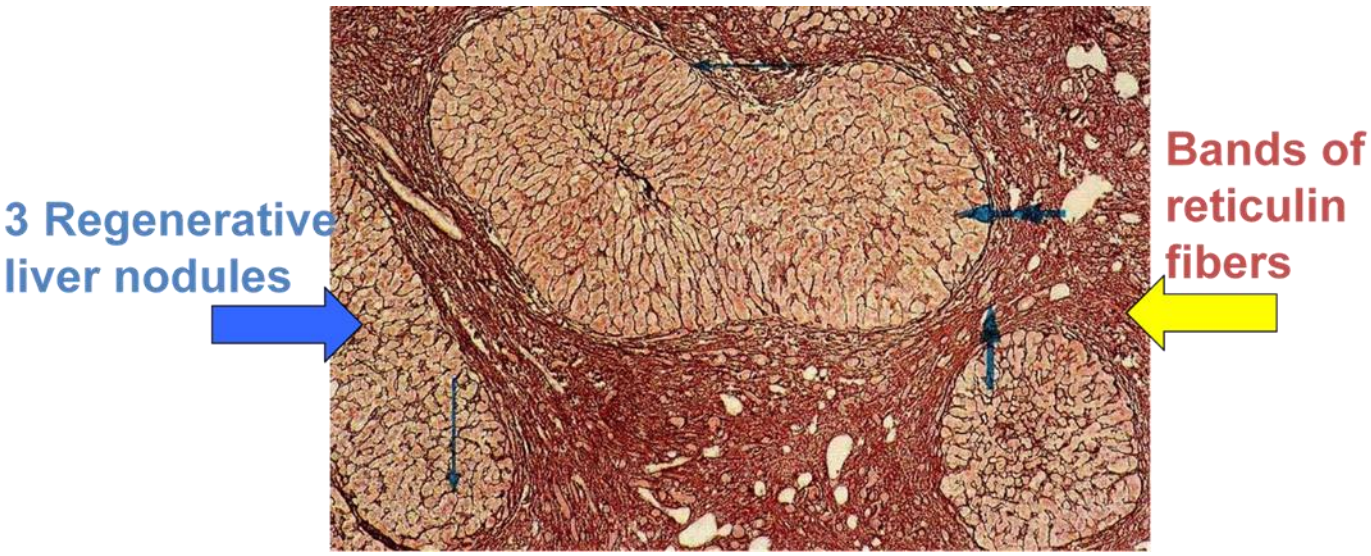
  (3) Disruption of the architecture of the entire liver.
  The parenchymal cell injury & fibrosis are diffuse, extending throughout the liver;
- focal injury with scarring (eg abscess) does not constitute cirrhosis

Macronodular cirrhosis: liver.
The entire normal smooth, red-brown liver is completely replaced by large number of pale, hyperplastic liver cell nodules, 0.5 to 2cm,
separated from each other by fibrous trabeculae,



5.19 Macronodular cirrhosis: liver

Cryptogenic cirrhosis:
X60 Liver section stained for reticulin, from a patient die from liver failure.
There are 3 regenerative liver nodules (double arrow),
separated by broad bands of reticulin fibers (thick arrow), which is, normally, completely absent.
An example of healing by combine regeneration & fibrosis which follows injury to the liver cells & stroma (commonly due to alcoholism or viral hepatitis),
but in this patient, the cause was unknown, i.e., cryptogenic



Pathogenesis of cirrhosis

- -H death,
  -regeneration,
  -fibrosis,
  - & vascular changes
  are the major mechanisms that combine to create C.

- Hepatocellular death causes are numerous, mostly due to toxins & viruses.

- The development of C requires that cell death &fibrosis occur over long periods of time.
- Regeneration is the compensatory response to cell death.
- Fibrosis, when the injury involves the parenchyma and the supporting connective tissue, then, fibrosis is the wound healing reaction that progresses to scar formation

- In the normal liver, ECM consisting of interstitial collagens (fibril-forming collagens types I, III, V, & XI) is present only in the:
  - liver capsule,
  - in portal tracts,
  -& around central veins.

- The normal liver has no true basement membrane; instead, a delicate framework containing type IV collagen lies in the space of Disse, between sinusoidal EC & hepatocytes

- By contrast, in cirrhosis, types I & III collagen & other ECM components are deposited in the space of Disse (F16-2).

- In advanced fibrosis & C, fibrous bands separate nodules of hepatocytes throughout the liver.

- Vascular changes consisting of the:
  (I) loss of sinusoidal EC fenestrations &
  (II) the development of portal vein-hepatic vein & hepatic artery-portal vein vascular shunts contribute to defects in liver function.

- Collagen deposition converts sinusoids with fenestrated endothelial channels that allow free exchange of solutes between plasma & H to higher pressure, fast-flowing vascular channels without such solute exchange

- In particular, the movement of proteins (e.g., albumin, clotting factors, & lipoproteins) between H & the plasma is markedly impaired.

- These functional changes are aggravated by the loss of microvilli from the H surface, which diminishes the transport capacity of the cell.

- The major source of excess collagen in C are the perisinusoidal stellate cells (Ito cells or fat-storing cells), which lie in the space of Disse, which are normally function as storage cells for vitamin A & fat,

  but during the development of fibrosis they become activated, & transform into myofibroblast-like cells, which express smooth muscle α-actin & glial fibrillary acidic protein.

  ►The stimuli for the activation of stellate cells & production of collagen are:
  -ROS,
  -GFs,
  -& cytokines {TNF, IL-1},
  -& lymphotoxins, which can be produced by damaged H or by stimulated Kupffer cells & sinusoidal EC.

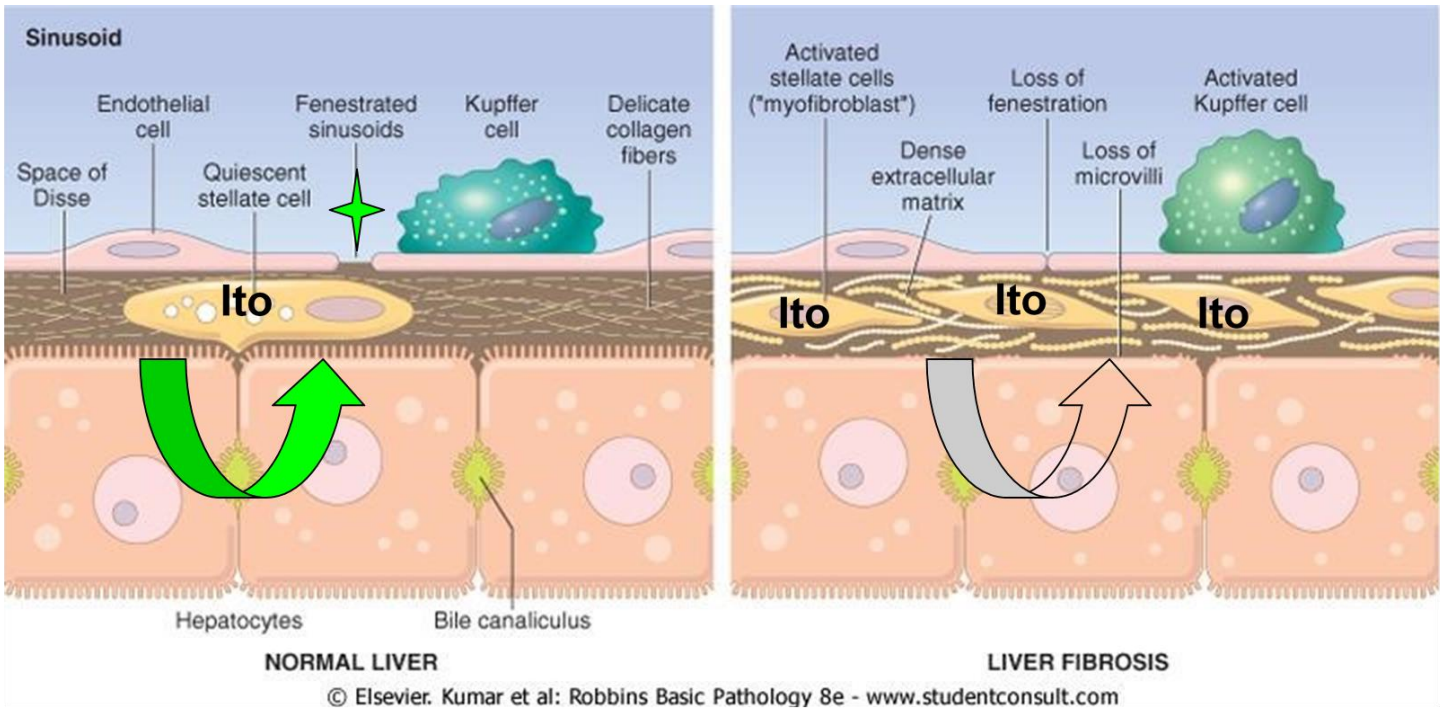
- Activated Ito stellate cells produce GFs, chemokines & cytokines that cause their further proliferation & collagen synthesis.
- TGF- β is the main fibrogenic agent for Ito cells.

In the normal liver, the perisinusoidal space of Disse contains a delicate framework of ECM components.

In liver fibrosis, Ito stellate cells are activated to produce a dense layer of ECM that is deposited in the space.

Collagen deposition blocks the EC fenestrations & prevents the free exchange of materials from the blood .

Kuppfer cells activation produce cytokines that involved in fibrosis.



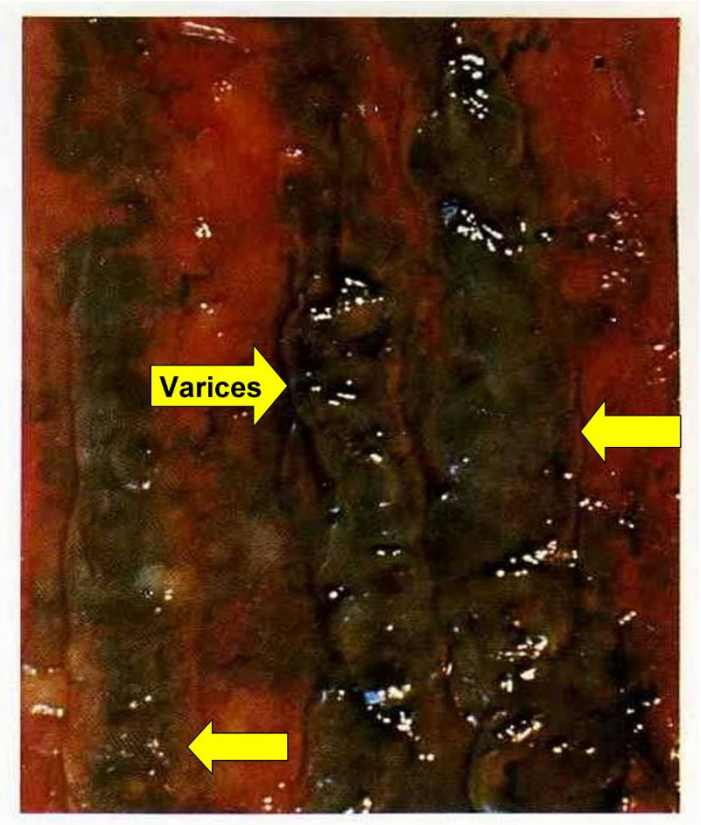
Clinical Features of cirrhosis

- All forms of C may be clinically silent.
- When symptomatic, they lead to nonspecific manifestations:
  -anorexia,
  -weight loss,
  - weakness,
  - &, in advanced disease, frank debilitation.

- Progression or improvement in cirrhosis depends to a large extent on the activity of the disease responsible for the C.

- Incipient or overt LF may develop, usually precipitated by imposition of a metabolic load on the liver, as from systemic infection or a GIT hemorrhage.

- The causes of death in patients with C is:
  (1) Progressive LF,
  (2) Rupture of esophageal varices due to portal hypertension, or
  (3) Development of liver carcinoma.



4.3 Varices: oesophagus

Esophageal varices in portal hypertension (seen by esophagoscopy) . Enormously-dilated, tortuous, bluishblack

Portal Hypertension

- increased resistance to portal blood flow may develop from prehepatic, intrahepatic, & posthepatic causes.

- The dominant intrahepatic cause is cirrhosis, accounting for most cases of portal hypertension.

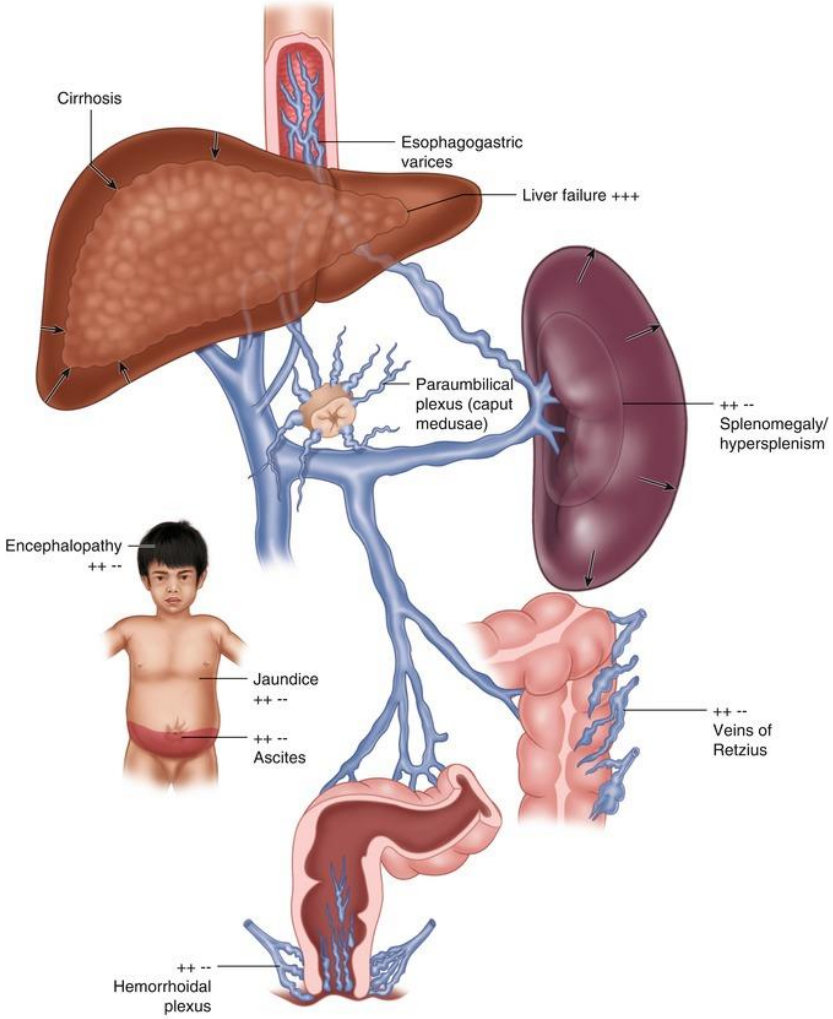
- Rare causes include
  - schistosomiasis,
  -massive fatty change,
  -diffuse granulomatous diseases,
  - & diseases affecting the portal microcirculation, eg nodular regenerative hyperplasia.

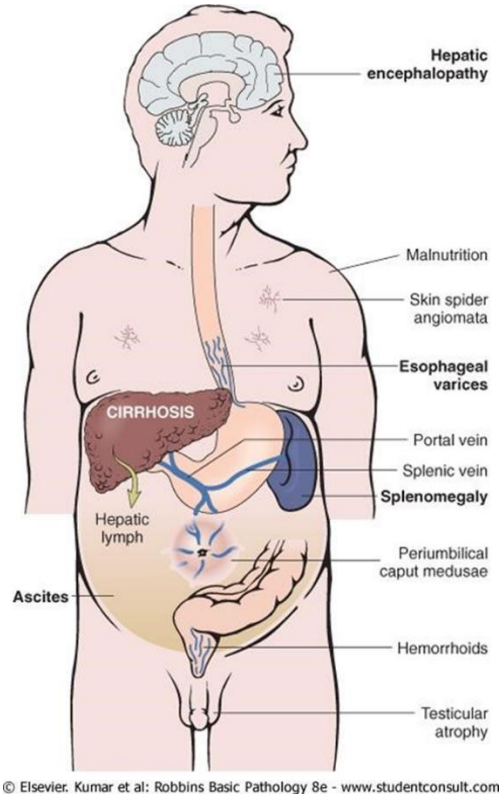
- Portal hypertension in C results from:

  (1) increased resistance to portal flow at the level of the sinusoids & compression of central veins by perivenular fibrosis & expanded parenchymal nodules, &

  (2) Anastomoses between the arterial & portal systems in the fibrous bands by imposing arterial pressure on the normally low-pressure portal venous system.

- 4 major clinical consequences of portal hypertension in the setting of C are described next , including:
  (1) Ascites,
  (2) Portosystemic venous Shunts (varices),
  (3) Splenomegaly, &
  (4) Hepatic encephalopathy (see above).





Some clinical consequences of portal hypertension in the setting of cirrhosis.

- The most important manifestations are shown in boldface type

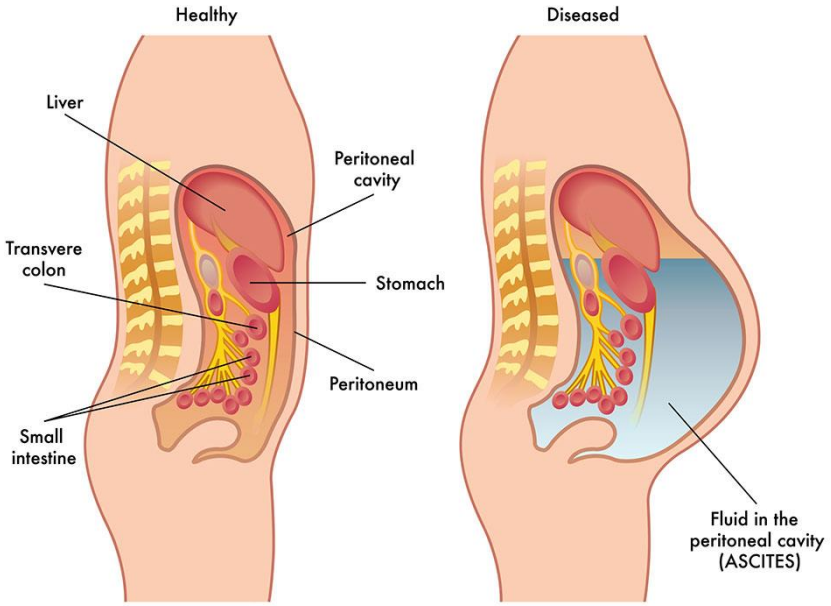
Ascites

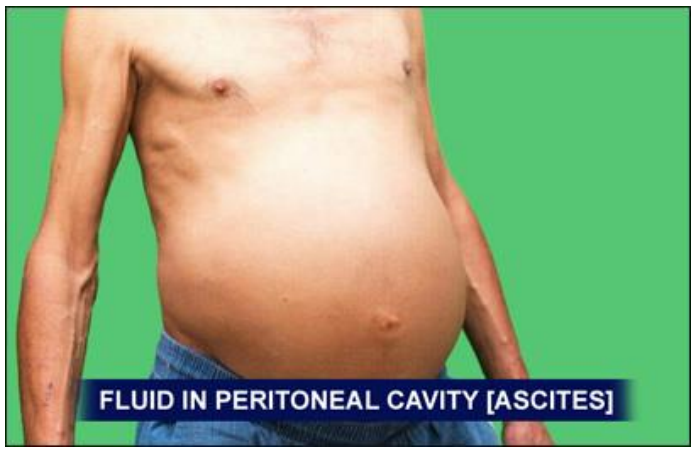
- Is collection of excess fluid in the peritoneal cavity,
- becomes clinically detectable when at least 500 mL have accumulated, but many liters may collect & cause massive abdominal distention

- It is generally a serous fluid having as much as 3 gm/dL of protein (largely albumin),
  may contain scant number of mesothelial cells & mononuclear leukocytes.

- Influx of neutrophils suggests secondary infection,
  whereas red cells point to possible disseminated intra-abdominal cancer.

- With long-standing ascites, seepage of peritoneal fluid through transdiaphragmatic lymphatics may produce hydrothorax,
  more often on the right side.





►**Pathogenesis** of ascites is complex, involving one or more of the following mechanisms:

(1) Sinusoidal hypertension (increased hydrostatic pressure)
alters Starling forces & drives fluid into the space of Disse, which is then removed by hepatic lymphatics;
this movement of fluid is also promoted by hypoalbuminemia.

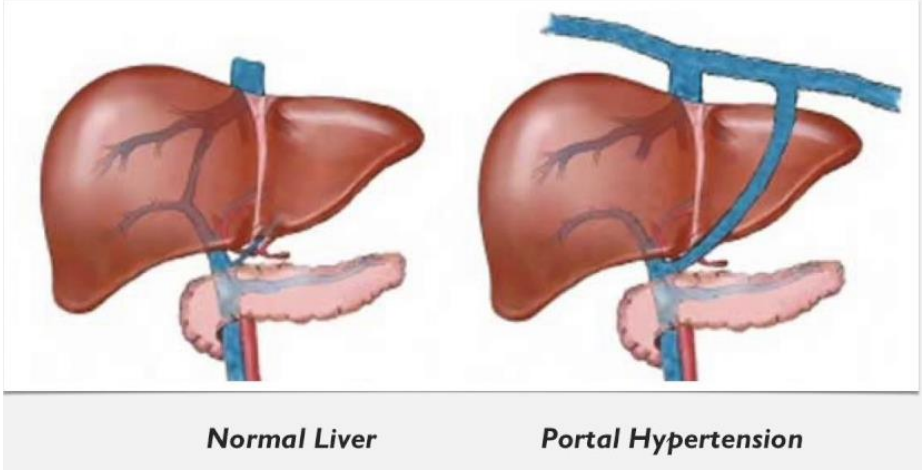
(2) Renal retention of sodium & water due to secondary hyperaldosteronism.

(3)Leakage of hepatic lymph into the peritoneal cavity:

-normal thoracic duct lymph flow approximates 1L/day.
-With C, hepatic lymphatic flow may approach 20 L/day, exceeding thoracic duct capacity.
-Hepatic lymph is rich in proteins & low in triglycerides, as reflected in the protein-rich ascitic fluid.

Portosystemic Shunt

►With increased portal venous pressure, bypasses develop wherever there is porto-systemic anastomoses circulations share capillary beds.



Principal sites are:

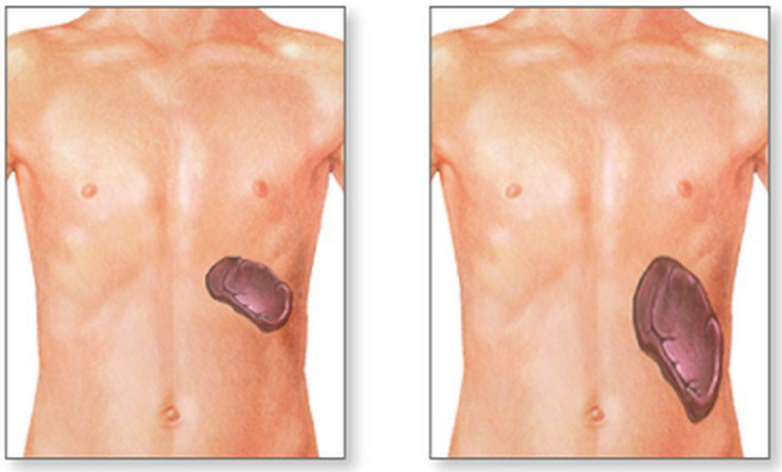
(1) Veins within & around the rectum (manifest as hemorrhoids), & although hemorrhoidal bleeding may occur, it is rarely massive or life threatening.

(2) The retroperitoneum & the falciform ligament of the liver (involving periumbilical & abdominal wall collaterals, which appear as dilated subcutaneous veins extending outward from the umbilicus (caput medusae)
& an important clinical hallmark of portal hypertension.

(3) The cardioesophageal junction (producing the much more important esophagogastric varices,), that appear in about 65% of those with advanced cirrhosis of the liver,
rupture of which cause massive hematemesis & death in about half of cirrhotic patients.

Splenomegaly

- Long-standing congestion may cause congestive splenomegaly.
- The degree of enlargement varies widely (usually ≤1Kg, ⍰ Normal spleen 150g).
- Massive splenomegaly may secondarily induce hypersplenism.



Normal spleen Splenomegaly

Jaundice & Cholestasis

- Jaundice is yellow discoloration of skin & sclerae (icterus),
- occurs when serum bilirubin levels are elevated above 2.0 mg/dL (the normal in the adult is <1.2 mg/dL).

- Cholestasis is defined as systemic retention of bilirubin & other solutes eliminated in bile (bile salts & cholesterol).

Pathogenesis & Clinical Features of jaundice

- In the normal adult the rate of bilirubin (B) production is equal to the rates of hepatic uptake, conjugation, & biliary excretion.

- Jaundice occurs (bilirubin levels may reach 30-40 mg/dL in severe disease) when the equilibrium between bilirubin production & clearance is disturbed by one or more of the following mechanisms (Table 16-3):

  (1) increased production of bilirubin,
  (2) decreased hepatic uptake,
  (3) Impaired conjugation,

  these 3 mechanisms Produce unconjugated hyperbilirubinemia,

  (4) decreased hepatocellular excretion, &
  (5) Impaired bile flow (both intrahepatic & extrahepatic)

  Produce predominantly conjugated hyperbilirubinemia.

- More than one mechanism may operate to produce jaundice, especially in hepatitis, which may produce conjugated & unconjugated hyperbilirubinemia.
- In general, however, one mechanism predominates.

Main Causes of Jaundice

Predominantly Unconjugated Hyperbilirubinemia:

-Excess production of bilirubin,
-Hemolytic anemias,
-Resorption of blood from internal hemorrhage
(e.g., GIT bleeding, hematomas),
- Ineffective erythropoiesis syndromes
(e.g., pernicious anemia, thalassemia),
-Reduced hepatic uptake,
-Drug interference with membrane carrier systems,
-Diffuse hepatocellular disease
(e.g., viral or drug-induced hepatitis, cirrhosis),
-Impaired bilirubin conjugation,
-Physiologic jaundice of the newborn.

Predominantly Conjugated Hyperbilirubinemia:

-Decreased hepatocellular excretion,
-Deficiency in canalicular membrane transporters,
- Drug-induced canalicular membrane dysfunction
(e.g., oral contraceptives, cycloporine),
-Hepatocellular damage or toxicity
(e.g., viral or drug-induced hepatitis, total parenteral nutrition, systemic infection),
-Impaired intra- or extra-hepatic bile flow,
-Inflammatory destruction of intrahepatic bile ducts
(e.g., primary biliary cirrhosis, primary sclerosing cholangitis, graft-versus-host disease, liver transplantation).

- Of the various causes of jaundice listed , the most common are :
(1) hepatitis,
(2) obstruction to the flow of bile, &
(3) hemolytic anemia.

- Because the hepatic machinery for conjugating & excreting bilirubin does not fully mature until about 2 weeks of age, almost every newborn develops transient & mild unconjugated hyperbilirubinemia,
  termed neonatal jaundice or physiologic jaundice of the newborn.

- Jaundice may result from inborn errors of metabolisms, including:

  --Gilbert syndrome

  - is a relatively common, benign, condition presenting as mild, fluctuating unconjugated hyperbilirubinemia.
  -The primary cause is decreased hepatic levels of glucuronosyltransferase.
  -Affecting up to 7% of the population,
  - the hyperbilirubinemia may go undiscovered for years
  -& does not have associated morbidity.

  --Dubin-Johnson syndrome

  -results from an autosomal recessive defect in the transport protein responsible for hepatocellular excretion of bilirubin glucuronides across the canalicular membrane.
  -These patients exhibit conjugated hyperbilirubinemia.
  - Other than having hepatomegaly,
  -patients are otherwise without functional problems.

Obstructive cholestasis

►Results from:-
(1) impaired bile flow due to hepatocellular dysfunction or
(2) biliary obstruction (intrahepatic or extrahepatic),

may present as:

- Jaundice, however, sometimes

- Pruritus is the presenting symptom,
  presumably related to the elevation in plasma bile acids & their deposition in peripheral tissues, particularly skin.

- Skin xanthomas (focal accumulations of cholesterol)
  sometimes appear the result of hyperlipidemia & impaired excretion of cholesterol.

- Obstructive cholestasis other manifestations relate to intestinal malabsorption,
  including inadequate absorptionof the fat-soluble vitamins A, D, & K.

- Obstructive cholestasis characteristic laboratory finding is
  elevated serum alkaline phosphatase, an enzyme present in bile duct epithelium & in the canalicular membrane of H.
  (An isozyme is normally present in many other tissues such as bone, therefore, the increased levels must be verified as being hepatic in origin).

- Extrahepatic biliary obstruction is frequently amenable to surgical alleviation,
- in contrast to Intrahepatic cholestasis caused by both
  (1) diseases of the intrahepatic biliary tree or
  (2) hepatocellular secretory failure,
  which cannot be benefited by surgery (short of transplantation),
  & the patient's condition may be worsened by an operative procedure.

- Thus, there is urgency in making a correct diagnosis of the cause of jaundice & cholestasis.

INFECTIOUS AND INFLAMMATORY DISORDERS

- The most common primary liver infection is viral hepatitis.
- Less common is a condition called autoimmune hepatitis.

- Systemic viral infections that can involve the liver include

(1) Infectious mononucleosis (Epstein-Barr virus);

(2) Cytomegalovirus or herpesvirus infections, particularly in the newborn or immunosuppressed; &

(3) Yellow fever, which has been a major & serious cause of hepatitis in tropical countries.

- The term viral hepatitis is reserved for infection of the liver caused by a small group of viruses having a particular affinity for the liver.
- The etiologic agents of viral hepatitis are hepatitis viruses
  A (HAV), B (HBV), C (HCV), D (HDV), & E (HEV).
  Table 16-4 summarizes some of the features of the hepatitis viruses.

- Because other infectious or noninfectious causes, specially drugs & toxins, can lead to essentially identical syndromes, serologic studies are critical for the diagnosis of viral hepatitis & identification of virus types.

Clinical Features & Outcomes of Viral Hepatitis

The clinical syndromes which may develop after exposure to hepatitis viruses include:

- Asymptomatic acute infection: serologic evidence only
- Acute hepatitis: with/without jaundice
- Chronic hepatitis: with/without progression to cirrhosis
- Chronic carrier state: asymptomatic
- Fulminant hepatitis: submassive to massive hepatic necrosis with acute liver failure
- HAV, HCV, & HEV do not generate a carrier state.
- HAV & HEV infections do not progress to chronic hepatitis.

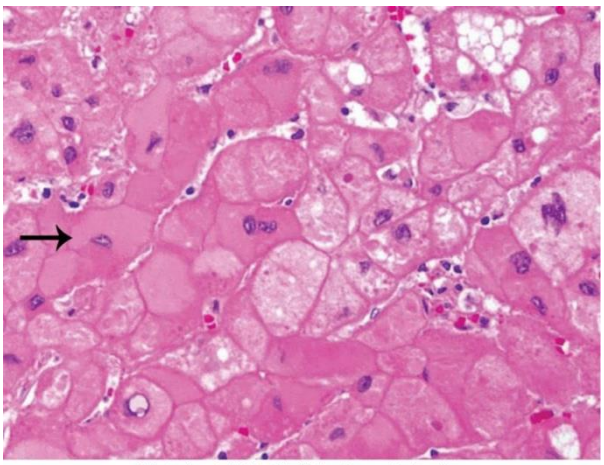
Morphologic features of acute & chronic viral hepatitis.

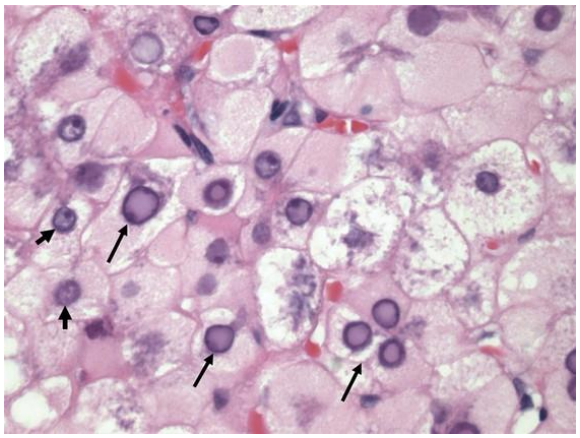
- The morphologic changes in acute & chronic viral hepatitis are shared among the hepatotropic viruses & can be mimicked by drug reactions.

- With acute hepatitis, there is ballooning degeneration of H. An inconstant finding is cholestasis.
- Fatty change is mild & is unusual except with HCV infection.

- Whether acute or chronic, HBV infection may generate "ground-glass" H
  : a finely granular, eosinophilic cytoplasm shown by EM to contain massive quantities of HBsAg in the form of spheres & tubules.

Ground-glass hepatocytes (arrow) in chronic hepatitis B,
caused by accumulation of HBsAg in cytoplasm.





- Other HBV-infected H may have "sanded" nuclei, resulting from abundant intranuclear HBcAg.

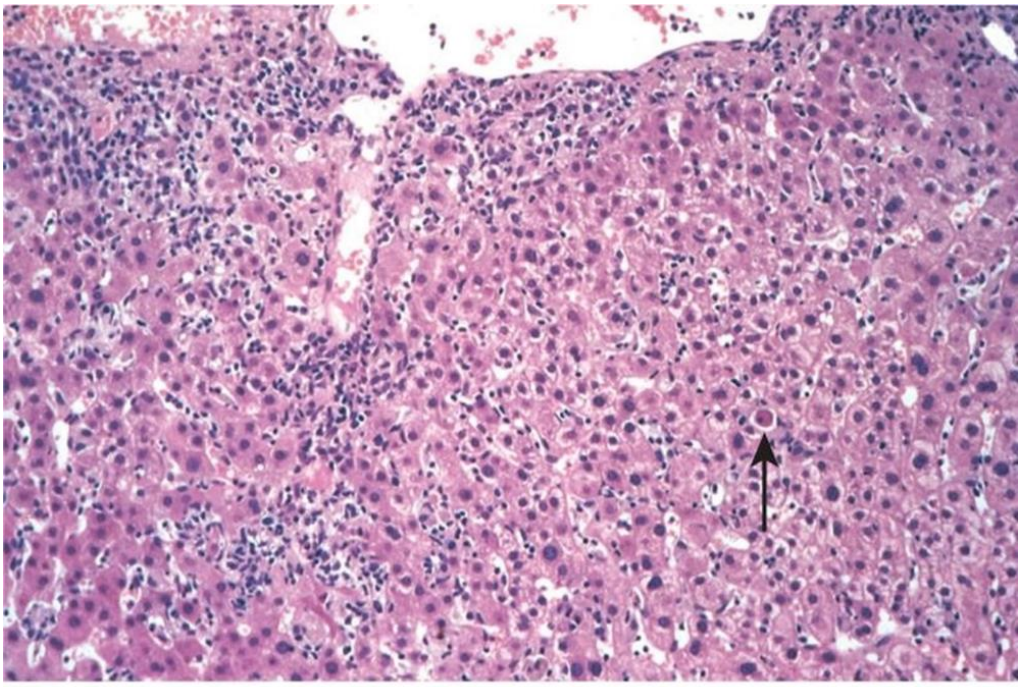
- Two patterns of hepatocyte death are seen.

(I) Cytolysis from cell membranes rupture leads to "dropped out“ necrotic cells with collapse of the sinusoidal collagen reticulin framework where the cells have disappeared; scavenger macrophage aggregates mark sites of dropout.

(II) Apoptosis, apoptotic H is shrink, intensely eosinophilic, & have fragmented nuclei; & effector T cells present in the immediate vicinity.

Apoptotic H are phagocytosed within hours by macrophages & hence may be difficult to find despite extensive ongoing apoptosis of H.

Acute viral hepatitis showing disruption of lobular architecture, inflammatory cells in sinusoids, & apoptotic cells



- Bridging necrosis connecting portal-to-portal, central-tocentral or portal-to-central regions of adjacent lobules, signifying a more severe form of acute hepatitis.

- H swelling, necrosis, & regeneration produce compression of the vascular sinusoids & loss of the normal radial array of the parenchyma (lobular disarray).

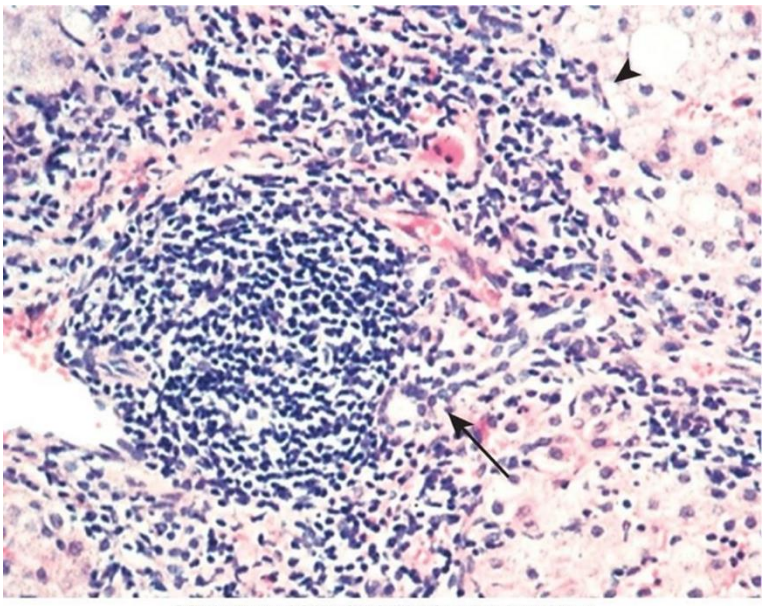
- Inflammation is prominent in acute hepatitis.
  The portal tracts are infiltrated with a mixed inflammatory cells, which may spill over into the parenchyma to cause necrosis of periportal hepatocytes (interface hepatitis), & Kupffer cells undergo hypertrophy & hyperplasia, & are laden with lipofuscin pigment caused by phagocytosis of H debris.

- Finally, bile duct epithelium may become reactive & even proliferate, particularly in cases of HCV hepatitis,
  forming poorly defined ductular structures in the midst of the portal tract inflammation. Bile duct destruction, does not occur.

-Chronic hepatitis C showing portal tract expansion with inflammatory cells & fibrous tissue (arrow),

- & interface hepatitis with spillover of inflammation into the parenchyma (arrowhead).

- A lymphoid aggregate is present in the center



- The **histologic** features of chronic hepatitis range from exceedingly mild to severe.

- Scattered H necrosis throughout the lobule may occur in all forms of chronic hepatitis.

- Continued periportal necrosis (piece-meal necrosis) & bridging necrosis are harbingers of progressive liver damage.

- In the mildest forms, significant inflammation is limited to portal tracts & consists of lymphocytes, macrophages, occasional plasma cells, & rare neutrophils or eosinophils.
- Lymphoid aggregates in the portal tract are often seen in HCV infection.
- Liver architecture is usually well preserved.

►The hallmark of serious liver damage is the deposition of fibrous tissue,

(1) At first, there is only portal tracts fibrosis, but with time

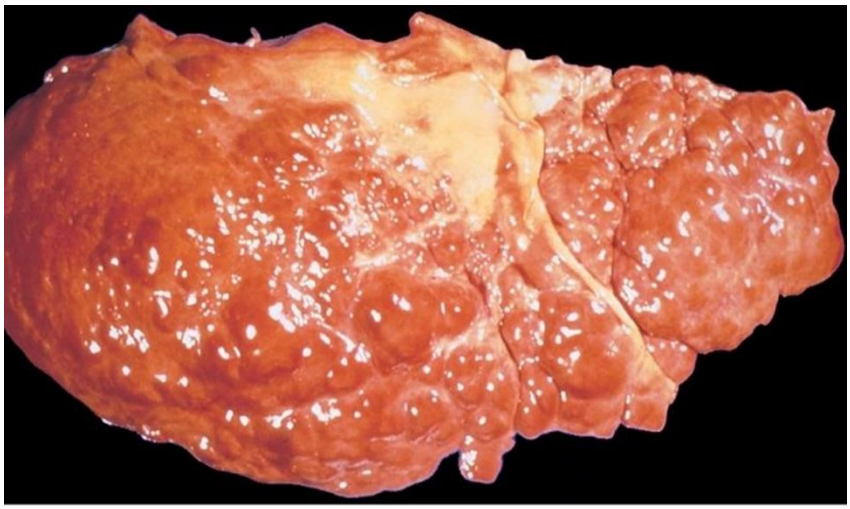
(2) periportal fibrosis occurs,&

(3) followed by bridging fibrosis.

▼Continued loss of hepatocytes & fibrosis results in C, with large, irregular nodules separated by broad scars {macronodular cirrhosis (F16-13)}.

Cirrhosis resulting from chronic viral hepatitis.

Note the irregular nodularity of the liver surface



Autoimmune Hepatitis

- Is a syndrome of mild or severe chronic hepatitis, which responds dramatically to immunosuppressive therapy.

- H it is indistinguishable from chronic viral hepatitis. Features:
- Absence of serologic markers of a viral infection,
- Female predominance (70%), &
- Elevated (>2.5 g/dL), serum IgG
- High titers of autoantibodies in 80% of cases

{most patients have circulating antinuclear Abs, anti-smooth muscle Abs , liver kidney microsomal Ab, & anti-soluble liver/pancreas Ag}.

These Abs can be detected by immunofluorescence or enzyme-linked immunosorbent assays.

- The main effectors of cell damage in autoimmune hepatitis are CD4+ helper cells.

- Presence of other autoimmune diseases is seen in up to 60% of patients, like RA, UC, thyroiditis, Sjögren syndrome

- The overall risk of C, the main cause of death, is 5%.

ALCOHOL- AND DRUG-INDUCED LIVER DISEASE

- The liver is the major drug metabolizing & detoxifying organ in the body, thus, it is subjected to injury from an enormous therapeutic & environmental chemicals. Injury may result :

(1) From direct toxicity,

(2) Hepatic conversion of a xenobiotic to an active toxin, or be

(3) Produced by immune mechanisms, usually by the drug, or a metabolite acting as a hapten to convert a cellular protein into an immunogen.

▼ A diagnosis of drug-induced liver disease may be made on

(1) the basis of an association of liver damage following drug administration &, it is hoped, recovery on removal of the drug, with

(2) exclusion of other potential causes.

- Exposure to a toxin or therapeutic agent should always be included in the differential diagnosis of any form of liver disease.

- By far, the most important agent that produces toxic liver injury is alcohol.

Alcoholic Liver Disease

- Excessive ethanol consumption causes more than 60% of chronic liver disease in the West & accounts for 50% of deaths due to C.

- More than 10 million Americans are alcoholics; & in USA,
- Alcohol abuse: is the 5th leading cause of death (after IHD, Cancer, CVA, & COPD);
- it causes 100,000 to 200,000 deaths annually.
  Of these deaths, 20,000 are attributable directly to end-stage cirrhosis;
  many more are the result of automobile accidents (Road Traffic Accidents, RTA).

- The 3 distinctive, albeit overlapping forms, collectively referred to as alcoholic liver disease are:

  1. Hepatic steatosis (fatty liver),

  2. Alcoholic hepatitis,

  3. Cirrhosis.

- 90% to 100% of heavy drinkers develop fatty liver, &

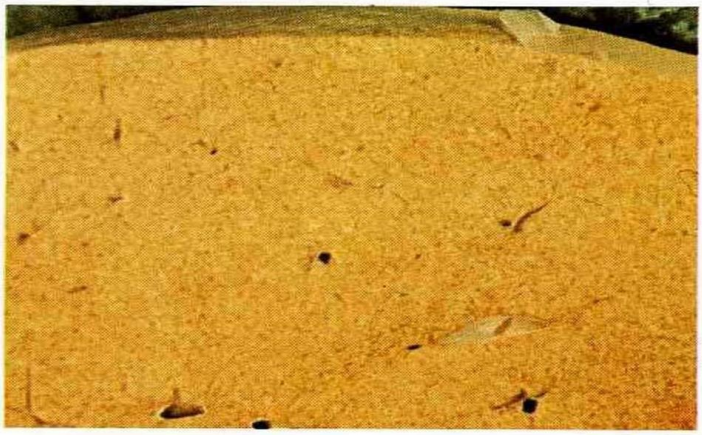
- 10% to 35% develop alcoholic hepatitis. However,

- 8% to 20% of chronic alcoholics develop cirrhosis.

(1) Hepatic Steatosis (Fatty Liver)

- After even moderate intake of alcohol, microvesicular lipid droplets accumulate in H.
- With chronic intake of alcohol, lipid accumulates becomes macrovesicular,
- initially centrilobular, but in severe cases it may involve the entire lobule
- Grossly, the liver is large (≤4-6 kg, Normal 1.5Kg), soft, yellow, & greasy.
- The fatty change is completely reversible if there is abstention from further alcohol intake.

Fatty change: liver.
The patient was chronic alcoholic. The presence of large quantities of neutral fat within the liver cells result in a uniform yellow appearance of the liver section

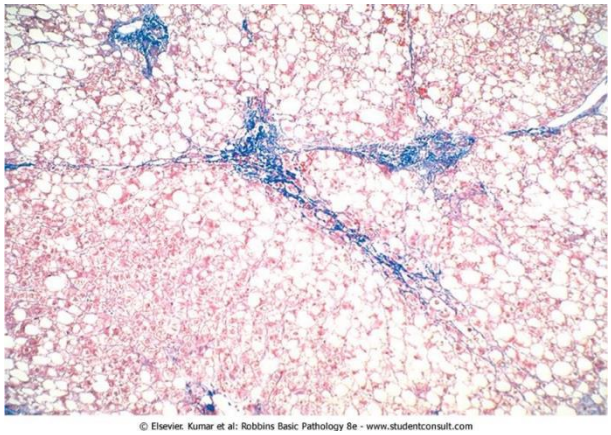


5.4 Fatty change: liver

Alcoholic liver disease:

Steatosis involving most regions of the hepatic lobule, with the intracytoplasmic fat seen as clear vacuoles.

Some early fibrosis (stained blue) is present (Masson trichrome stain).



(2)Alcoholic Hepatitis:

This is characterized by:

- Hepatocyte Swelling & Necrosis:
  Single or scattered foci of H undergo balloon swelling {resulting from accumulation of fat, water & proteins that normally are exported} & necrosis.

- Mallory Bodies.
  Scattered H accumulate tangled skeins of intermediate filaments, visible as eosinophilic cytoplasmic inclusions in degenerating H , which are a characteristic but not specific feature of alcoholic liver disease, because they are also seen in:
  - PBC,
  -hepatocellular tumors,
  - Wilson disease, &
  - chronic cholestatic syndromes.

- Neutrophil Infiltration.
  Neutrophils infiltrate the lobule & accumulate around degenerating H, particularly those containing Mallory bodies.
  Lymphocytes & macrophages also enter portal tracts & spill into the parenchyma.

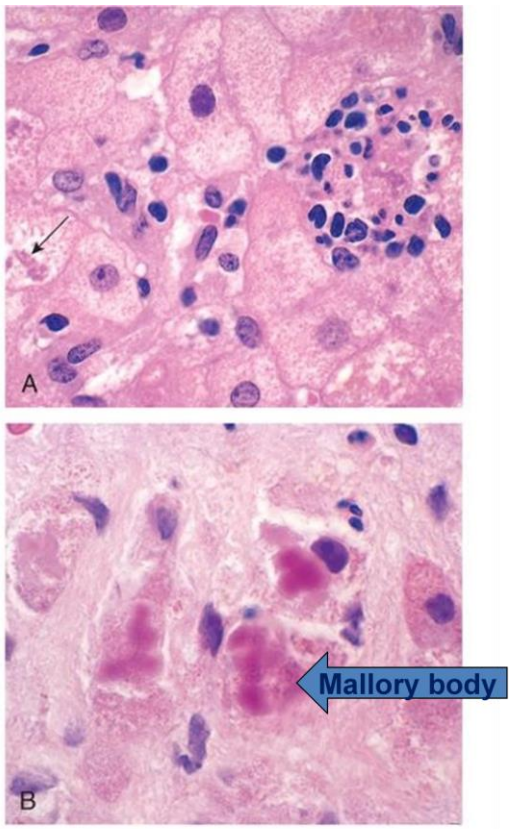
- Fibrosis.
  Alcoholic hepatitis is almost always accompanied by a brisk sinusoidal & perivenular fibrosis;
  occasionally periportal fibrosis may predominate, particularly with repeated bouts of heavy alcohol intake.
  In some cases there is cholestasis & mild deposition of hemosiderin (iron) in hepatocytes & Kupffer cells.
  Grossly, the liver is mottled red with bile-stained areas

Alcoholic hepatitis.

A, The cluster of inflammatory cells marks the site of a necrotic hepatocyte.

A Mallory body is present in another hepatocyte (arrow).

B, Eosinophilic Mallory bodies are seen in hepatocytes, which are surrounded by fibrous tissue (H&E)



(3) Alcoholic Cirrhosis.

- This is the final & irreversible form of alcoholic liver disease,
- usually develops slowly; {but may develop more rapidly, within 1 to 2 years, in the setting of alcoholic hepatitis}.

- At first the C liver is yellow-tan, fatty, & enlarged, usually weighing over 2 kg. Within years it is transformed into a brown, nonfatty, shrunken liver, weighing less than 1 kg.
- Initially the developing fibrous septa are delicate & extend through sinusoids from central vein to portal regions as well as from portal tract to portal tract.

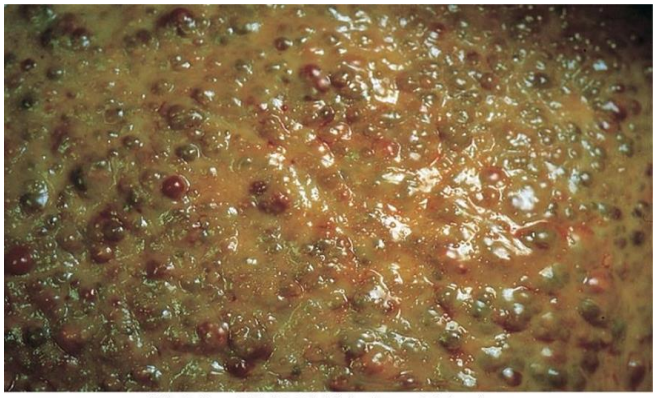
- Regenerative activity of entrapped parenchymal hepatocytes generates (micronodular C vs. the macronodular C described for viral hepatitis),
- but The nodularity eventually becomes more prominent; scattered larger nodules create a "hobnail" appearance on the surface of the liver (F16-17),

- & eventually, the C is converted into a mixed micronodular & macronodular pattern

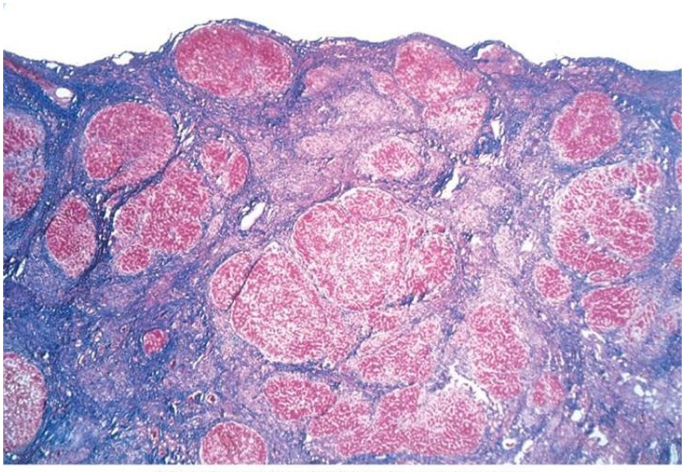
- Bile stasis often develops;
  Mallory bodies are only rarely evident at this stage.

- Thus, end-stage alcoholic cirrhosis eventually comes to resemble, both macroscopically & microscopically, the cirrhosis developing from viral, autoimmune hepatitis and other causes.

Alcoholic cirrhosis
-showing the characteristic diffuse nodularity of the surface induced by the underlying fibrous scarring.
-The average nodule size is 3 mm in this close-up view.
-The greenish tint is caused by bile stasis.



Nodules of varying sizes are entrapped blue-staning fibrous tissue (Masson trichrome stain



Pathogenesis

- Short-term ingestion of as much as 80 gm of ethanol per day (8 beers) produces mild, reversible hepatic fatty liver.
- Chronic intake of 60 gm/day is considered a borderline risk for severe injury.

- Women seem to be more susceptible to hepatic injury than are men.

- Binge (party) drinking causes more liver injury (note that beer binge drinking is, unfortunately, the preferred modality of drinking in college student parties).

- Steatosis & alcoholic hepatitis may develop independently,
  & thus, they do not necessarily represent a continuum of changes.
- There is an inconstant relationship between hepatic steatosis & alcoholic hepatitis as precursors to cirrhosis, which may develop without antecedent evidence of steatosis or alcoholic hepatitis!

- In the absence of a clear understanding of the pathogenetic factors influencing liver damage,
  no "safe" upper limit for alcohol consumption can be proposed.

- The causes of Hepatocellular steatosis results from:

  (1) the shunting of normal substrates away from catabolism & toward lipid biosynthesis,

  (2) Impaired assembly & secretion of lipoproteins; &

  (3) increased peripheral catabolism of fat.

- The causes of alcoholic hepatitis are uncertain, but the following alterations caused by alcohol are important:

  (1) Acetaldehyde
  -(the major intermediate metabolite of alcohol en route to acetate production)
  -induces lipid peroxidation & acetaldehyde-protein adduct formation,
  -which may disrupt cytoskeletal & membrane function,

  (2) Alcohol directly affects:
  - microtubule organization (as illustrated by the detection of Mallory's hyaline),
  -mitochondrial function, &
  - membrane fluidity,

  (3) ROS
  -are generated during oxidation of ethanol by the microsomal ethanol oxidizing system; in addition,
  -the ROS are also produced by neutrophils, which infiltrate areas of H necrosis.
  -These ROS reacts with membranes & proteins.

  - The ROS are the main stimuli for the production of cytokines in alcoholic liver disease (TNF, IL-6, IL-8, & IL-18),
  -This abnormal cytokine regulation is a major feature of alcoholic hepatitis & alcoholic liver disease in general,
  & the TNF is considered to be the main effector of injury.

  -Concurrent viral hepatitis, particularly hepatitis C, is a major accelerater of liver disease in alcoholics,
  - prevalence of hepatitis C in individuals with alcoholic disease is about 30%.

► **Clinically**,

- Hepatic steatosis give rise to hepatomegaly

- It is estimated that 15 to 20 years of excessive drinking are necessary to develop alcoholic hepatitis, which appear relatively acutely, usually after a bout of heavy drinking.
- The outlook is unpredictable; each bout of hepatitis carries about a 10% to 20% risk of death.

- With repeated bouts, C appears in about 1/3 of patients within a few years;
- alcoholic hepatitis may be superimposed on C.

- With proper nutrition & total cessation of alcohol consumption, alcoholic hepatitis may clear slowly,
  however, in some the hepatitis may persists despite abstinence & progresses to C.

- Alcoholic C manifestations are similar to other forms of C, presented earlier, including complications of portal hypertension (varices) or hepatic encephalopathy.

- Finally, C may be clinically silent, discovered only at autopsy or when stress such as infection or trauma tips the balance toward hepatic insufficiency.

- The most important aspect of treatment is abstinence from alcohol.

- In the end-stage alcoholic, the immediate causes of death are
  (1) LF,
  (2) Massive GIT hemorrhage,
  (3) an intercurrent Infection,
  (4) Hepatorenal syndrome after a bout of alcoholic hepatitis, &
  (5) Liver cell ca (3%-6% of cases).

Drug-induced liver disease

- Common condition that may present as a mild reaction or, much more seriously, as acute LF.

- A large number of drugs & chemicals can produce liver injury
- Drug reactions may be classified as predictable (intrinsic) reactions or unpredictable (idiosyncratic) ones.

- Predictable drug reactions may occur in anyone who accumulates a sufficient dose.

- Unpredictable reactions depend on idiosyncrasies of the host, particularly the host's propensity to mount an immune response to the antigenic stimulus, & the rate at which the host metabolizes the agent. The injury may be immediate or take weeks to months to develop.

- Rule: Drug-induced chronic hepatitis is histologically & clinically indistinguishable from chronic viral hepatitis or autoimmune hepatitis,
- & hence serologic markers of viral infection are critical for making the distinction.

- Among the hepatotoxic agents, predictable drug reactions are ascribed to:

  -acetaminophen (Paracetamol) ,
  -tetracycline,
  -antineoplastic agents,
  -Amanita phalloides toxin,
  -carbon tetrachloride (CCl_4).

- Examples of drugs that can cause idiosyncratic reactions include:

  -chlorpromazine,
  -halothane anesthetic (which can cause a fatal immune-mediated hepatitis),
  -sulfonamides,
  - α-methyldopa, &
  -allopurinol .

- The mechanism of liver injury may be direct toxic damage to hepatocytes (e.g., acetaminophen , CCl4, & mushroom toxins)
- but also involves a variable combination of toxicity & inflammation with immune-mediated hepatocyte destruction.

- Depending on the drug, the patterns of drug-induced liver injury may include one or more of the following:

  -Steatosis
  - steatohepatitis
  - hepatocellular necrosis
  -cholestasis
  - fibrosis
  -& vascular lesions.

- Among drugs that may cause acute liver failure are :

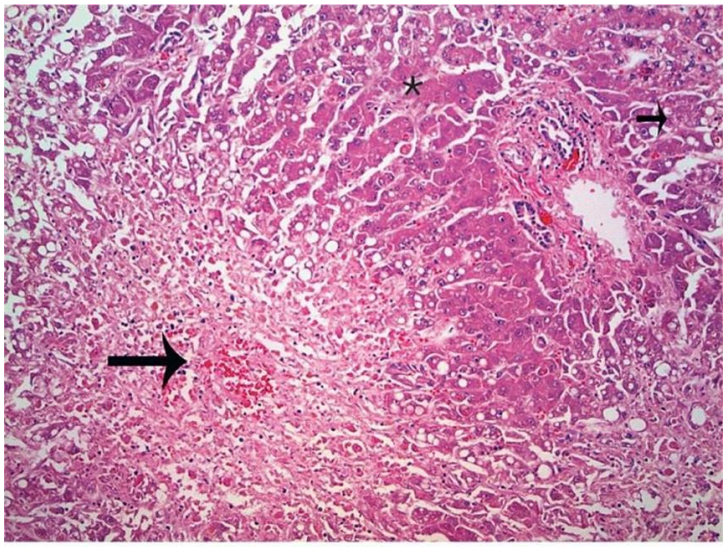
  -acetaminophen ,
  -halothane ,
  - anti TB drugs (rifampin , isoniazid),
  -antidepressant monoamine oxidase inhibitors,
  -CCl4
  -& Amanita phalloides toxin poisoning.

- 46% of cases of acute LF caused by acetaminophen intoxication,
- & 60% of these are accidental overdosage.

Hepatocellular necrosis caused by acetaminophen (Paracetamol overdose).

Confluent perivenular necrosis is seen (large arrow), with little inflammation.

The normal residual tissue is indicated by the (asterisk).



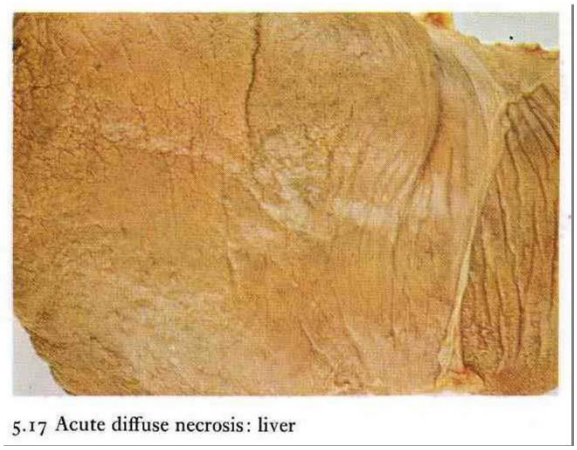
Acute diffuse necrosis; liver.

The patient died after an operation in which halothane was the anesthetic.

This shows the diaphragmatic surface of the liver.

(1) The normal liver deep brown color has been replaced by a very light brown color,

(2) The capsule is wrinkled as a result of shrinkage of the liver tissue


5.17 Acute diffuse necrosis: liver

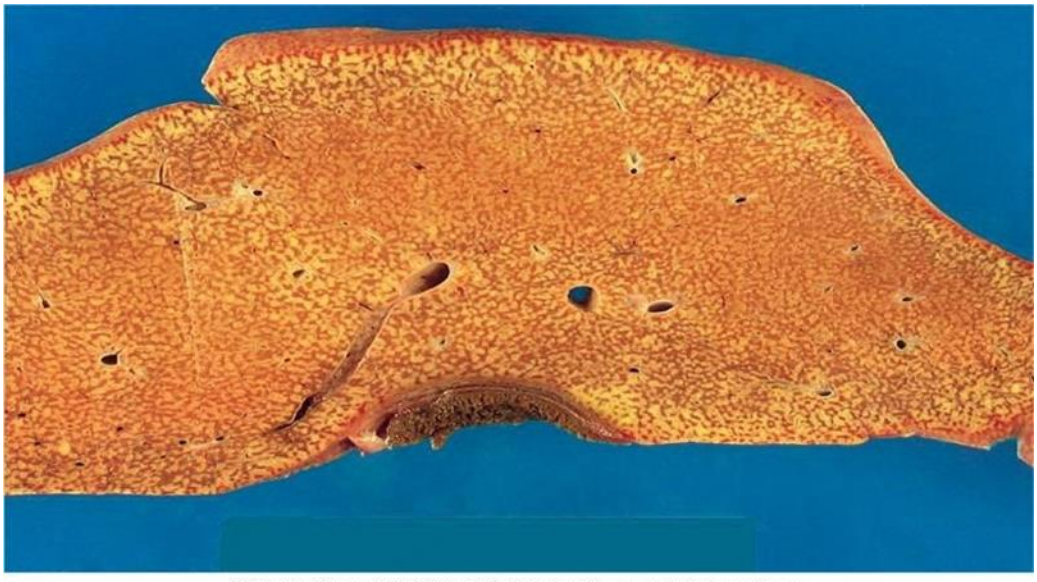
(in this case, the liver weighed only 444gm) & microscopically show diffuse massive liver necrosis

- With massive H necrosis the entire liver is involved, &
  M, complete destruction of H leaves only a collapsed reticulin framework & preserved portal tracts,
  with surprisingly little inflammatory reaction .

- However, with survival for several days there is a
  massive influx of inflammatory cells to begin the clean-up process.

- Patient survival for more than a week permits regeneration of surviving H,
- & if the parenchymal framework is preserved, regeneration is complete & normal liver architecture is restored.
- More massive destruction regeneration yield C.

Massive liver necrosis:
Soft, congested, bile stained small liver weighing 700 grams only (Normal 1500grams)



METABOLIC & INHERITED LIVER DISEASE

- The most common metabolic liver disease is:
  (1)nonalcoholic fatty liver disease (NAFLD),

  other metabolic diseases attributable to inborn errors of metabolism include:
  (2) hemochromatosis
  (3) Wilson disease
  (4) α1-antitrypsin deficiency.

Nonalcoholic Fatty Liver Disease

- NAFLD is a common condition, which was first recognized in 1980.
- It is a condition in which fatty liver & liver disease develop in individuals who do not drink alcohol.
- It may present as:
  (I) steatosis or as
  (II) nonalcoholic steatohepatitis (NASH)
  similar to alcoholic hepatitis & involves H destruction, inflammation with neutrophils & mononuclear cells, & progressive pericellular fibrosis.

- NAFLD & NASH are most consistently associated with:
  - Insulin resistance.

- Other key associated variables are:
  -Type 2 diabetes (or family history)
  -Obesity (BMI >25 kg/m2 in Asians)
  - Dyslipidemia (hypertriglyceridemia, low high-density lipoprotein Ch, high low-density lipoprotein Ch)

Inherited Diseases: Hereditary Hemochromatosis (HH)

- Normal adults total body iron pool is 2 to 6 gm,
  about 0.5 gm is stored in the liver.

- In HH, the total body iron may exceed 50 gm,
  over 1/3 of which is in the liver!

- HH is an autosomal recessive disease of adult onset
- {first appear in the 5th to 6th decades}
- caused by:
  →mutations in the HFE gene, leading to
  →increased intestinal absorption of dietary iron, net 0.5 to 1.0 gm/year iron accumulation &
  →deposition in different organs such as liver, pancreas, & skin.

- Fully developed HH show cirrhosis {100% of cases}, DM & skin pigmentation (80% in each = Bronze Diabetes).

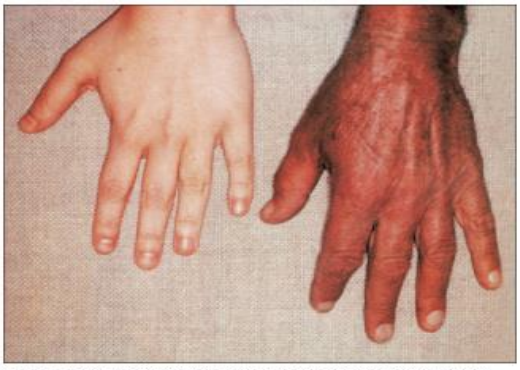


Figure 1 – The hand on the right is that of a 60-year-old white man with hereditary hemochromatosis. It is shown next to the hand of an unaffected person for comparison. The hyperpigmentation—characteristically golden brown or bronze—is generalized, but appears most prominently on sun-exposed or traumatized areas.

(Courtesy of Eugene Wong, MD, and Peter Petropoulos, MD.)

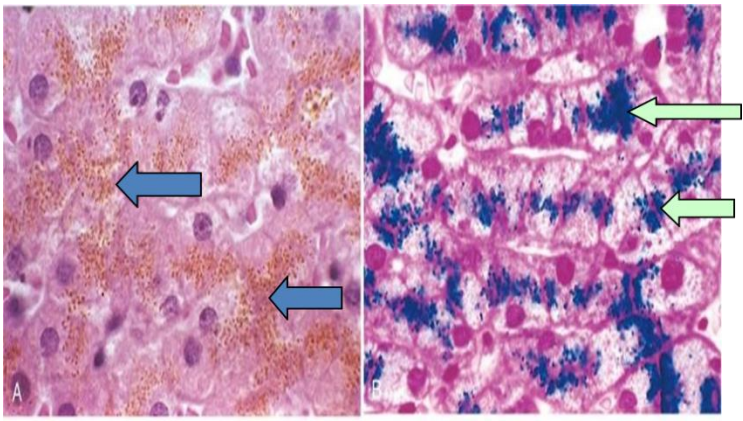
- Acquired forms of iron accumulation from known sources called Hemosiderosis or secondary iron overload, e.g.,
  - multiple transfusions,
  -ineffective erythropoiesis {Sideroblastic anemia & β-thalassemia}
  -& increased iron intake {Bantu siderosis}.

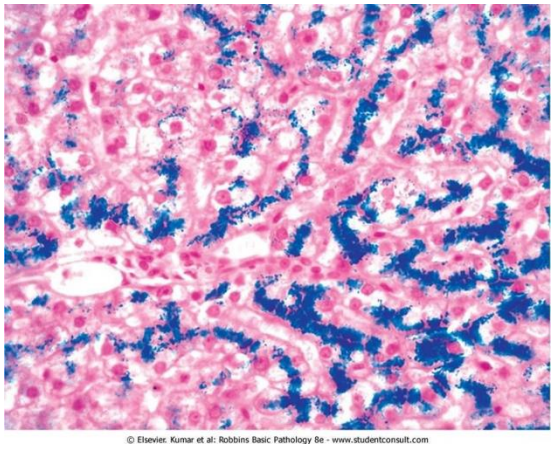
- In HH, there is deposition of hemosiderin in the following organs (in decreasing order of severity):
  -liver with C {see below},
  -pancreas
  {with diffused interstitial fibrosis & parenchymal atrophy & consequent DM},
  - myocardium {Cardiomyopathy}
  - pituitary,
  -adrenal,
  -thyroid
  -& parathyroid glands,
  -joints
  -, & skin
  {pigmentation, partially due to hemosiderin deposition in dermal macrophages & from increased epidermal melanin production, both renders the skin slategray, hence the term Bronze Diabetes}.

- In the liver, first, there is golden-yellow hemosiderin granules in the cytoplasm of periportal H which stain blue with the Prussian blue, stain .
- Eventually, with increased iron load, there is progressive involvement of the rest of the lobule, bile duct epithelium & Kupffer cell.

Hemosiderin granules in liver cells.

A, H&E section showing golden-brown, finely granular pigment,
which gives… Positive Prussian blue reaction, specific for iron, in B.





Hereditary hemochromatosis.
In this Prussian blue stained section hepatocellular iron appears blue.
The parenchymal architecture is normal.

- Iron is a direct hepatotoxin, & inflammation is characteristically absent.
- Fibrosis develop slowly, leading ultimately to cirrhosis

►**Pathogenesis**:

Excessive iron is directly toxic to tissues by the following mechanisms:

(1) Lipid peroxidation by iron-catalyzed free-radical reactions,

(2) Stimulation of collagen formation, &

(3) Direct interactions of iron with DNA.

- Iron actions may be reversible, with the exception of nonlethal DNA damage.

► **Clinically**,

- males predominate (M/F ratio of 5 to 7: 1),
- patients usually present with classic clinical triad of cirrhosis with:
  -hepatomegaly,
  -DM,
  -skin pigmentation.

- Death may result from:
  - cirrhosis,
  - hepatocellular carcinoma,
  -or cardiac disease.

- Treatment of iron overload {phlebotomy & the use of iron chelators)
  does not remove the risk for development of hepatocellular ca (a 200-fold higher than normal)
  because of the iron induced oxidative damage of DNA.

- HH can be diagnosed early, before irreversible tissue damage has occurred.

Wilson Disease

- An autosomal recessive disorder of copper metabolism,
- characterized by the accumulation of toxic levels of copper in many tissues & organs, principally the liver, brain, & eye.

- The responsible genetic defect is a mutation in ATP7B.
- Incidence 1: 30,000; much less common than HH.

- Normal copper physiology involves

(1) absorption of ingested copper (2-5 mg/day);
(2) plasma transport in complex with albumin;
(3) hepatocellular uptake, followed by incorporation into an α2-globulin to form ceruloplasmin;
(4) secretion of ceruloplasmin into plasma,
where it accounts for 90% to 95% of plasma copper; &
(5) hepatic uptake of desialylated, senescent ceruloplasmin from the plasma,
followed by lysosomal degradation & secretion of free copper into bile.

- In Wilson disease, defective function of ATP7B inhibit the:
  (I) secretion of ceruloplasmin into the plasma (Step 4 above) &
  (II) excretion of copper into bile (Step 5),
  which is the primary route for copper elimination from the body,

  resulting in copper accumulation in the liver, causing toxic liver injury by:

  (1) Promoting the formation of FR,

  (2)Binding to sulfhydryl groups of cellular proteins, &

  (3)Displacing other metals in hepatic metalloenzymes.

- In addition to the liver damage, usually, by the age of 5 years,
  copper that is not ceruloplasmin bound spills over into the circulation, causing pathologic changes to other sites.

- The hepatic changes range from minor to massive damage, include :
  -fatty change,
  - acute hepatitis, or
  -chronic hepatitis {resembles chronic hepatitis of viral, drug, or alcoholic origin},
  - progressing to cirrhosis.

- Excess copper deposition can be demonstrated by special stains
  (eg rhodanine stain for copper,
  orcein stain for copper-associated protein).

- Because copper also accumulates in chronic obstructive cholestasis,
  & because histology cannot reliably distinguish Wilson disease from viral- & drug-induced hepatitis,
- demonstration of hepatic copper content in excess of 250 µg/gm dry weights is most helpful for making a diagnosis.

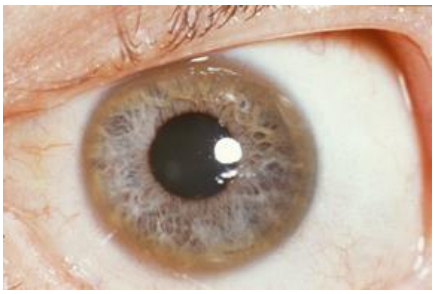
- The biochemical diagnosis of Wilson disease is based on a:

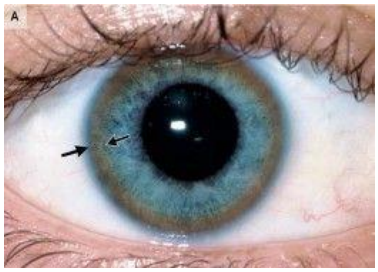
- Decreased serum ceruloplasmin,

-increased hepatic copper content,

-increased urinary excretion of copper.

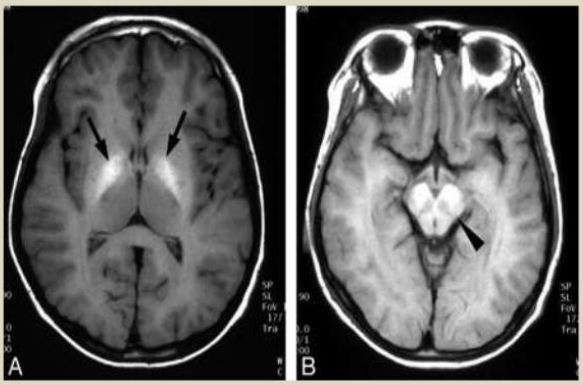
- All patients show eye lesions called Kayser-Fleischer rings
  (green to brown deposits of copper in Descemet membrane in the limbus of the cornea).





- Hence the alternative designation of this disease as hepatolenticular degeneration.

- In the brain, toxic injury primarily affects the putamen of the basal ganglia, which demonstrates atrophy & cavitation.



Wilson disease in a 13-year-old boy with abdominal distention. A and B, T1-weighted axial MR images show bilateral increased signal intensity in the globus pallidus (arrows) and midbrain (arrowhead).

- Early recognition & long-term copper chelation therapy (as with D-penicillamine)
  have dramatically altered the usual progressive downhill course of the disease.

α1-Antitrypsin (AAT) Deficiency

- AAT deficiency is an autosomal recessive disorder
  marked by abnormally low serum levels of AAT protease inhibitor.

- The major function of AAT is the inhibition of proteases,
  particularly neutrophil elastase released at sites of inflammation.

- AAT deficiency leads to pulmonary emphysema, because a relative lack of this protein permits the unrestrained activity of tissue-destructive proteases.

- Homozygotes for the Z allele (PiZZ genotype) have circulating AAT levels that are only 10% of normal levels.

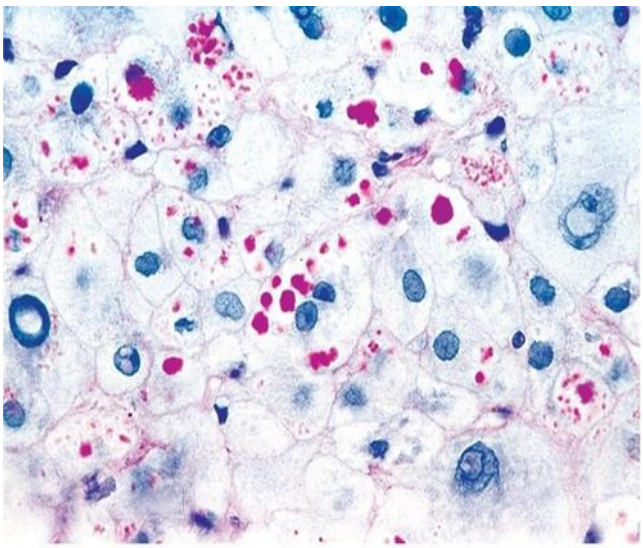
- The defect results in misfolding of the nascent polypeptide in the hepatocyte ER,
  & because it cannot be secreted by the liver cells, it remain accumulated in ER
  & undergoes excessive lysosomal degradation,
  & appears as round to oval cytoplasmic globular inclusions of retained AAT

- Curiously, 100% of individuals with the PiZZ genotype accumulate AAT in the liver H,
- but only 8% to 20% develop significant liver damage.
- This may be related to a genetic tendency that causes susceptible individuals to be less able to degrade accumulated AAT protein within H.

H,

- the H in AAT deficiency contain round to oval cytoplasmic globular inclusions of retained AAT, which are strongly positive in PAS stain
- By EM they lie within SER & sometimes RER.
- The hepatic injury associated with PiZZ homozygosity may range from:
  → marked cholestasis with H necrosis in newborns,
  → to childhood C.

α1-Antitrypsin (AAT) Deficiency . PAS stain of liver, high-lighting the characteristic red cytoplasmic granules



►**Clinically,**

- among newborns with AAT deficiency, 10% to 20% show cholestasis.
- In older children, adolescents, & adults, the presenting symptoms may be related to chronic hepatitis, cirrhosis, or pulmonary disease.

- The treatment & cure for the severe hepatic disease is orthotopic liver transplantation.

Neonatal Cholestasis

- Mild transient elevations in serum unconjugated bilirubin are common in normal newborns.
- Prolonged conjugated hyperbilirubinemia in the newborn, termed neonatal cholestasis, affects 1 in 2500 live births.

- The major **causes** are :
  (I) extrahepatic biliary atresia, discussed later

  & a variety of other disorders collectively referred to as
  (II) neonatal hepatitis.

- Neonatal hepatitis is not a specific entity, nor is the disorders necessarily inflammatory.
  Instead, the finding of "neonatal cholestasis" should evoke a diligent search for recognizable toxic, metabolic, & infectious liver diseases
  .
- Idiopathic neonatal hepatitis constitutes as many as 50% of cases of neonatal hepatitis!

► **Clinical presentation** of infants with any form of neonatal cholestasis is fairly typical, with

-jaundice,

- dark urine,

- light or acholic stools,

- & hepatomegaly.

- Differentiation between the two most common causes of neonatal cholestasis (extrahepatic atresia & idiopathic hepatitis) assumes great importance,
- because definitive treatment of biliary atresia requires surgical intervention,
- whereas surgery may adversely affect the clinical course of a child with idiopathic neonatal hepatitis.

- Fortunately, discrimination between these diseases can be made in 90% of cases using clinical data and liver biopsy.

Reye Syndrome

- A rare (1 per Million) disease characterized by :
  fatty change in the liver & encephalopathy,
  and can be fatal.

- It primarily affects children < 4 years of age,
  typically developing 3 to 5 days after a viral illness.

- The **onset** is:
  - heralded by pernicious (severe) vomiting,
  - & is accompanied by irritability or lethargy
  -& hepatomegaly.

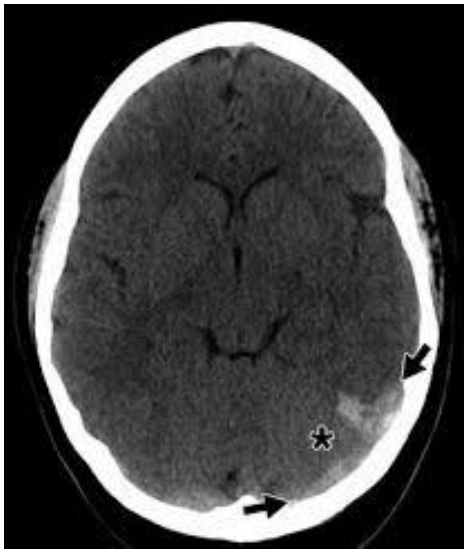
- Although most patients recover,
- about 25% progress to coma, accompanied by LF, with elevations in the serum levels of:
  - aminotransferases,
  - bilirubin,
  -& particularly ammonia.
- Death occurs from coma or liver failure.

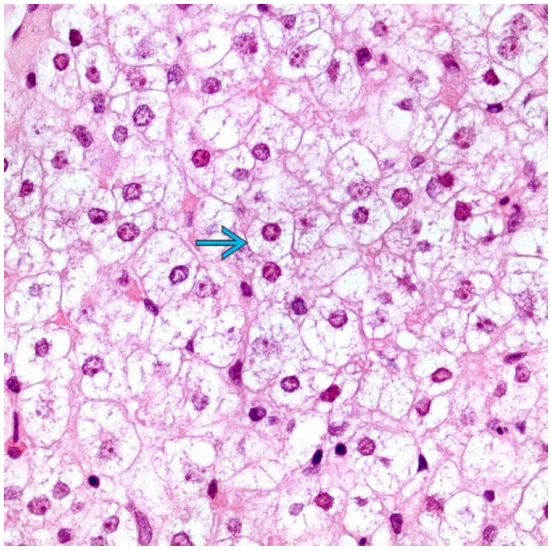
- The **pathogenesis** of Reye syndrome involves :
  a generalized loss of mitochondrial function.

- Reye syndrome has been associated with aspirin administration during viral illnesses,
- but there is no evidence that salicylates play a causal role in this disorder.

- Although the case rate for classic Reye syndrome in the United States is less than 1 per million per year,
  this disorder & "Reye-like syndromes" must be considered in the differential diagnosis of postviral disorders in children.

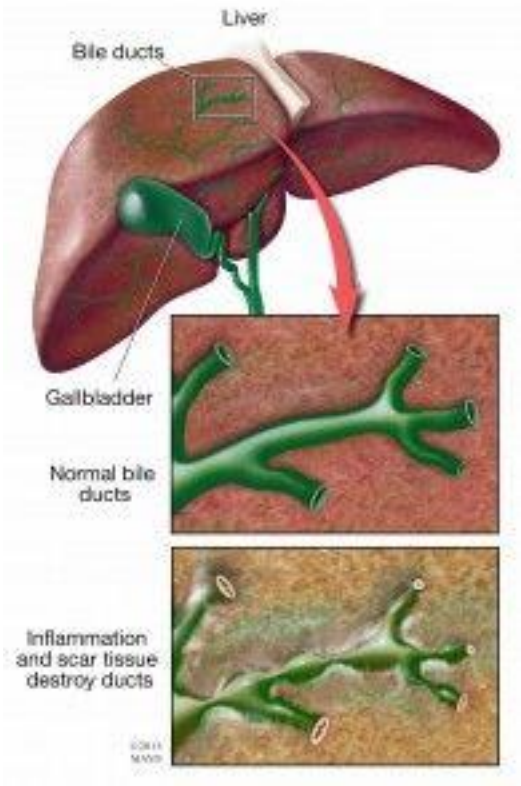
- The **key pathologic finding**
  - in the liver is:
  microvesicular steatosis,
  -& in the brain:
  cerebral edema is usually present.





DISEASES OF THE INTRAHEPATIC BILIARY TRACT

Primary Biliary Cirrhosis (PBC)



- PBC is chronic, progressive, & often fatal cholestatic (obstructive) liver disease.

- PBC characterized by:

  - nonsuppurative destruction of small & medium-sized intrahepatic bile ducts (BD),
  - portal inflammation,
  -scarring with eventual late cirrhosis
  - & LF over years or decades.

- PBC is primarily a disease of middle-aged women, & peak incidence between 40 & 50 years of age.

PBC **pathogenesis**:

- <90% of patients have high titers of antimitochondrial antibodies (AMA).

- PBC is almost always associated with elevated :
  -serum alkaline phosphatase
  - & cholesterol levels,
  - hyperbilirubinemia is a late & usually signifies incipient hepatic failure.

- PBC associated extrahepatic conditions include :
  -Sjögren syndrome,
  - scleroderma,
  -thyroiditis,
  - RA,
  - membranous GN,
  - Raynaud phenomenon,
  - & celiac disease.

Clinically,

- PBC onset is insidious, usually presenting as pruritus;
  jaundice develops late.
- Over a period of 20 years or more, the individuals develop LF.

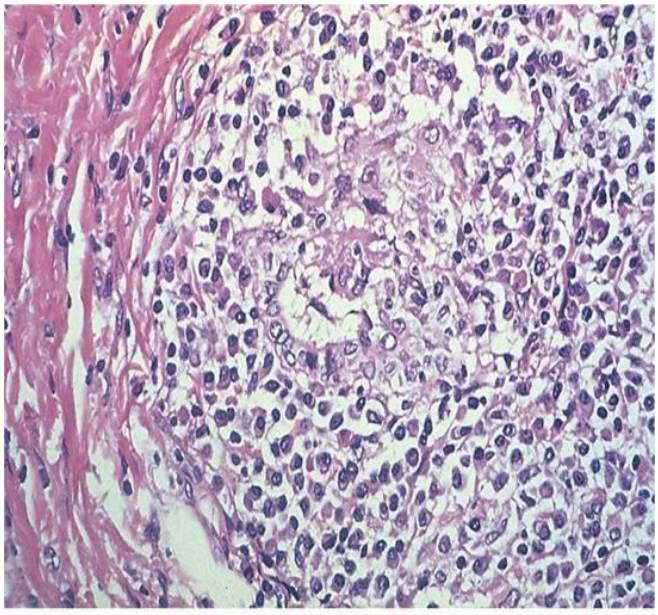
- In PBC precirrhotic stage,
  -there is a dense lymphocyte/plasma cell infiltrate around small BD in portal tracts,
  - granulomatous lesions may also appear (F 16-24).

  Interlobular BD are destroyed by inflammation (the florid duct lesion),

Primary biliary cirrhosis (PBC).

(1) A portal tract is markedly expanded by lymphocytes & plasma cells infiltration.

(2) Note the granulomatous reaction to a bile duct undergoing destruction (florid duct lesion).

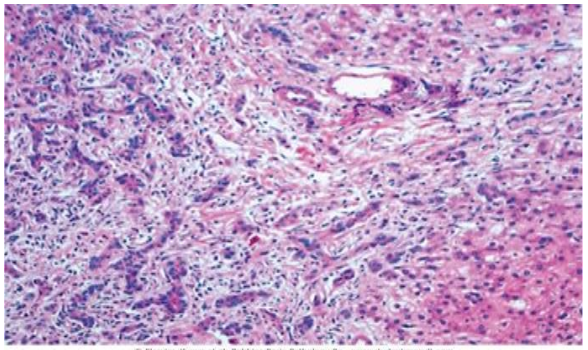


- The obstruction to intrahepatic bile flow leads to:

  - upstream BD proliferation,
  - inflammation
  -& necrosis
  of the adjacent periportal hepatic parenchyma,

  -& generalized cholestasis.

An example of ductular proliferation in a fibrotic septum.



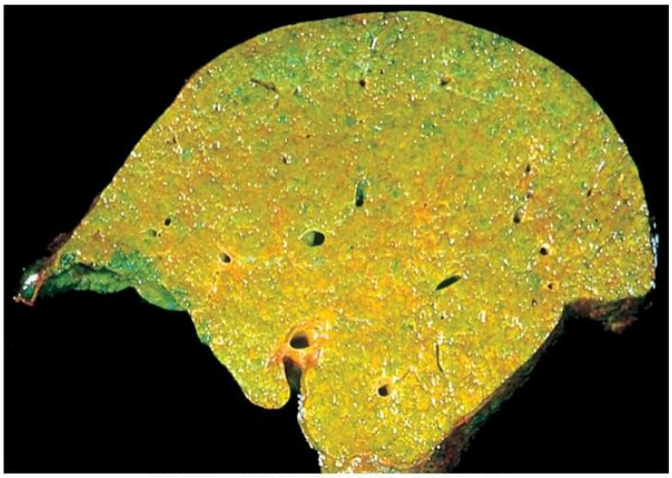
- In the end stage of PBC, interlobular BD are absent
- Over years to decades,
  relentless (progressive) portal tract scarring & bridging fibrosis leads to cirrhosis.

- The end-stage liver of PBC (and of PSC) showing marked yellow-green pigmentation & the liver cut surface is hard, with a finely granular appearance

Primary biliary cirrhosis (PBC).

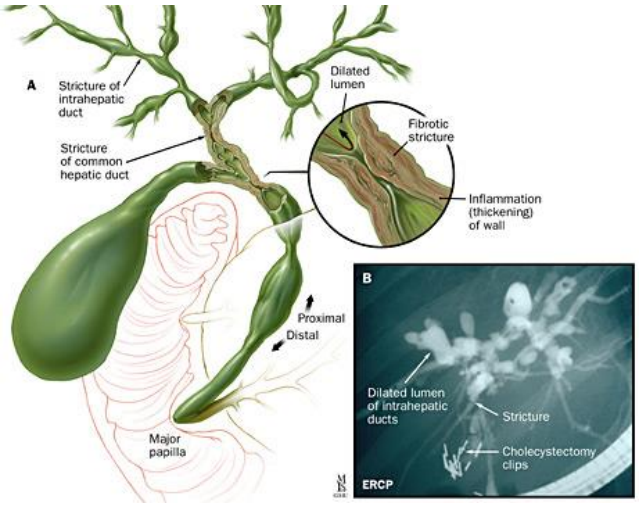
This sagittal section through the liver demonstrates the fine nodularity

& bile staining of end-stage PBC

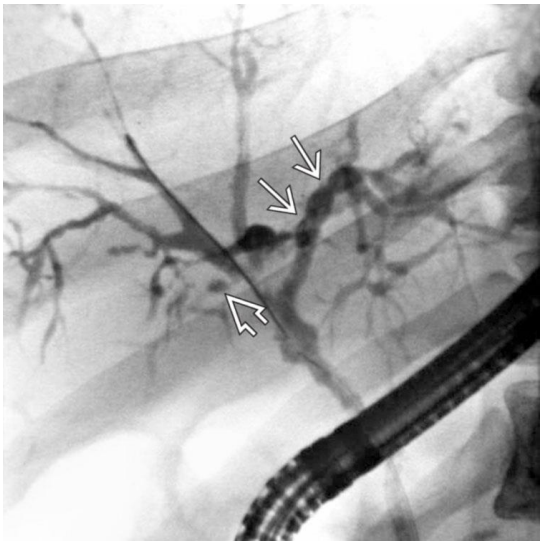


Primary Sclerosing Cholangitis {PSC}

- PSC is a chronic, obstructive, fibrosing cholangitis disorder,
- characterized by:
  - progressive destruction
  -& fibrosis of extrahepatic
  -& large intrahepatic bile ducts.



- Because the changes in the ducts are patchy, retrograde cholangiography shows a characteristic "beading" of the contrast medium in the affected biliary tree segments.



(primary sclerosing cholangitis (PSC) shows multiple segmental strictures of the biliary tree, resulting in a beaded appearance image (→).

There are also diverticular outpouchings of dilated bile ducts image .)

- The large BD show periductal fibrosis that obliterates the lumen, leaving a solid cord scar with few inflammatory cells.

- PSC is commonly seen in association with IBD, particularly chronic UC,
- UC coexists in 70% of individuals with PSC.
- Conversely, the prevalence of PSC in persons with UC is about 4%.

- PSC cause is unknown, but the association with UC,
  linkage with certain HLA-DR alleles, & presence of antinuclear cytoplasmic antibodies with a perinuclear localization in 80% of cases
- all suggest that this is an immunologically mediated disease.

- PSC tends to occur in the 3rd to 5th decades,
  most often after development of IBD.
- M/F ratio is 2 : 1.
- Symptoms include :
  -pruritus,
  -jaundice,
  - weight loss,
  - ascites,
  -variceal bleeding,
  - & encephalopathy.

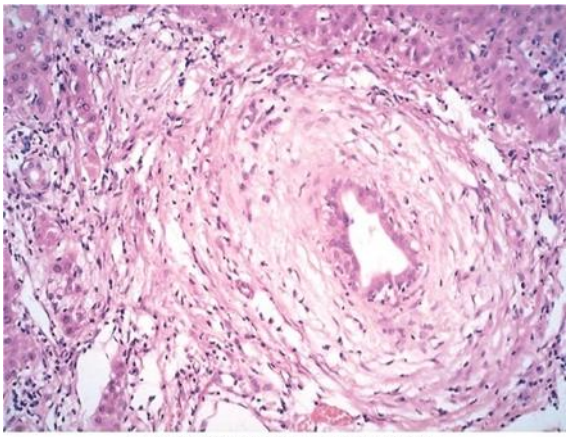
- Cholangiocarcinoma develop in 10% to 15% of PSC,
  with a median time of 5 years from diagnosis.

- There is no effective therapy for PSC & the disease has become an important indication for liver transplantation.

- ◙ PSC Characteristic feature is
  a fibrosing cholangitis of BD.

- Specifically, affected portal tracts show concentric periductal onion-skin fibrosis & mild lymphocytic infiltrate (F16-26).

A bile duct undergoing degeneration is entrapped in a dense, “onion-skin” concentric scar.



- Progressive atrophy of the bile duct epithelium leads to obliteration of the lumen, leaving behind a solid, cordlike fibrous scar.
- In between areas of progressive stricture, bile ducts become ectatic (dilated) & inflamed, presumably the result of down-stream obstruction.

- Ultimately, biliary cirrhosis develops, much like that seen with primary & secondary biliary cirrhosis.

❖ (**Remember:**
Secondary biliary cirrhosis to:
- stone,
-stricture
-or tumor
is much more common than both PBC & PSC).

TUMORS & HEPATIC NODULES

- The liver & lungs are the most commonly involved organs by metastatic cancer secondaries.

- Indeed, the most common hepatic tumors are metastatic carcinomas, mainly from:
  - colon
  - lung
  - breast

  primaries.

- The main two primary liver cancers are:
  (1) hepatocellular carcinomas (HCC),
  which is the most common primary hepatic malignancy,
  (2) cholangiocarcinomas

• Two rare primary liver tumors (not discussed further):

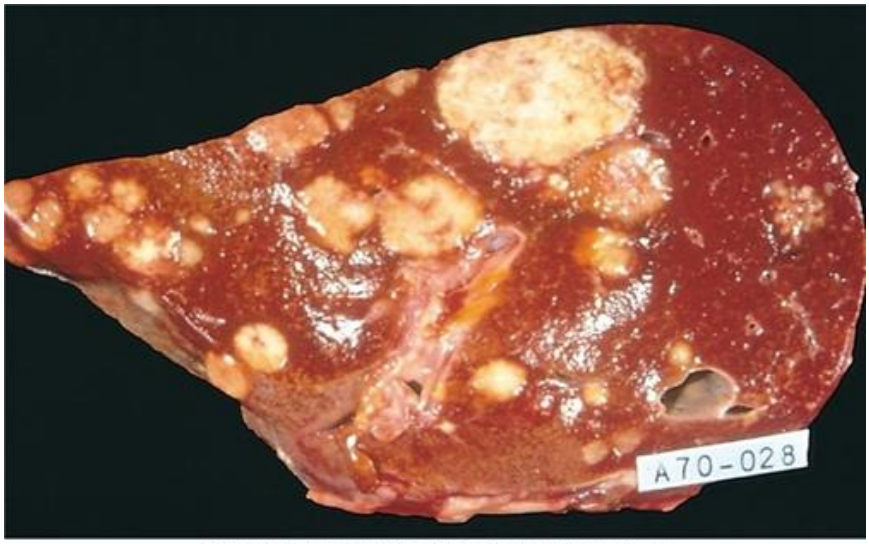
-Hepatoblastoma,
a childhood hepatocellular tumor, &

-Angiosarcoma of blood vessels
that is associated with exposure to:
vinylchloride & arsenic, & Thorotrast.

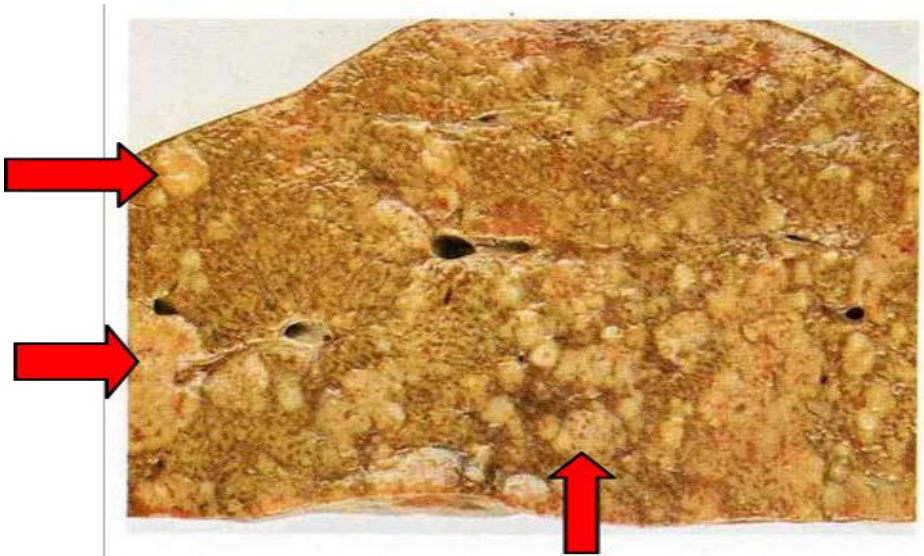
Clinically,

- hepatic masses may
  (1) cause epigastric fullness,
  (2) be detected by routine physical ex, or
  (3) be incidental finding during X-ray ex. for other indications.

Liver,
studded with multiple whitish metastatic cancer secondaries.
Q: What are the possible sites of primary?

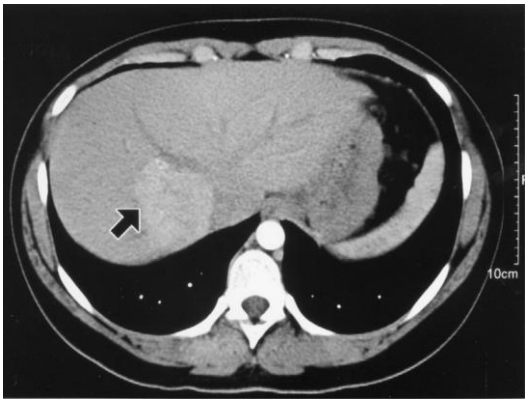


Secondary carcinoma: liver.
The liver is pale, from fatty change & large number of pinkish-white deposits of ca breast secondaries scattered through out it.


5.27 Secondary carcinoma: liver

Hepatocellular Nodules

- Solitary or multiple benign hepatocellular (H) nodules which may develop in the liver are of 3 types,
  (I) focal nodular hyperplasia,
  (II) macroregenerative, &
  (III) dysplastic nodules



Focal nodular hyperplasia

- Is not a tumor, but a nodular regeneration.

- Is a localized, well-demarcated, but poorly encapsulated lesion,
- consisting of hyperplastic H nodules with a central fibrous scar, may reach up to many cm in □.

- Nodules appear in noncirrhotic livers.

- Occurs in response to local vascular injury,
- & in about 20% of cases, it coexists with hepatic cavernous hemangiomas.

- Occurs usually as an incidental finding, commonly in women of reproductive age,

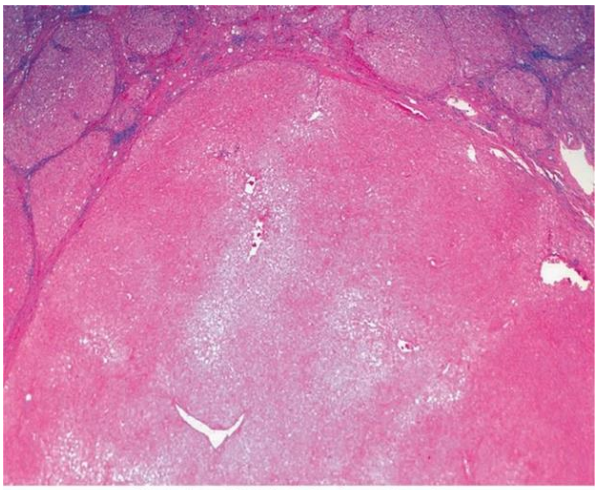
- & does not carry a risk for cancer.

Macroregenerative nodules

- Appear in cirrhotic livers,
  -larger than surrounding cirrhotic nodules;
  -but do not display atypical features.

- Nodules contain more than one portal tract,
  have an intact reticulin framework,
- & are not precursors of cancer

Large macroregenerative nodule in a cirrhotic liver.



Dysplastic nodules

- Nodules less than1 mm that appear in cirrhotic liver.

- The H in dysplastic nodules & in smaller lesions called dysplastic foci,
  -are highly proliferative
  - & show low or high grade atypical features,
  - i.e., crowding & pleomorphism.

- High-grade dysplastic lesions are considered to be precursors of HCC,
  - are often monoclonal,
  -& may contain chromosome aberrations similar to those present in HCC.

- Dysplastic nodules are subdivided into small-cell & largecell dysplastic nodules or foci.
- Only small-cell dysplasias are precursors to HCC;
- H in large-cell dysplastic lesions are apparently have reached replicative senescence.

Benign Tumors

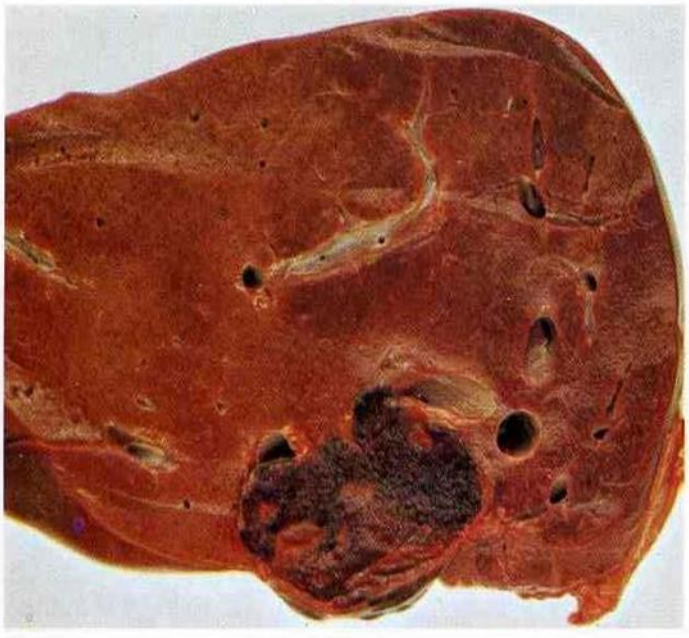
- Cavernous hemangioma is the commonest BT of the liver.
- Well-circumscribed lesions,
- consist of EC-lined vascular channels & intervening stroma
- Appear as discrete red-blue, subcapsular, soft nodules, less than 2 cm

Clinical significance:

(A) blind percutaneous needle biopsy may cause severe intra-abdominal bleeding, &
(B) importance of not mistaking them for metastatic cancer.

Hemangioma: liver.

Red, hemorrhagic 4cm unencapsulated mass on the undersurface of the liver.



5.11 Haemangioma: liver

Hepatic Adenoma

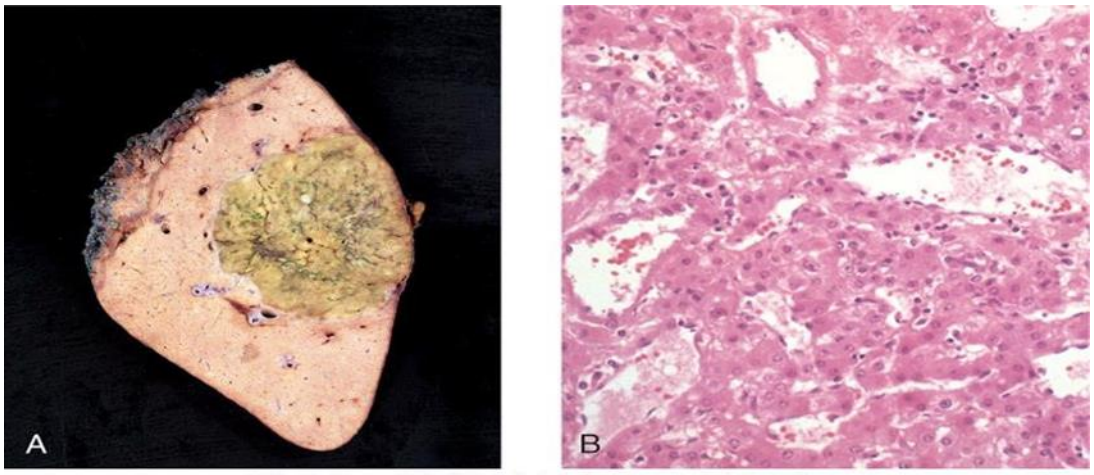
- BT of H,
- usually occurs in women of childbearing age
  who have used oral contraceptive steroids,
  & it may regress on discontinuance of hormone use.

- These T may be yellow-tan pale, or bile-stained, well-demarcated nodules
  found anywhere in the hepatic substance
  but, often subcapsular
- They may reach 30 cm in □.

H,

- composed of sheets & cords of cells that resemble normal H.
- Portal tracts are absent;
- instead, prominent arteries & veins are distributed through the tumor.

A, Surgically resected specimen showing subcapsular discrete mass.
B, H, showing adenoma, with cords of hepatocytes.



Clinically,

hepatic adenomas are significant for 3 reasons:

(1)They may be mistaken for HCC;

(2)Subcapsular adenomas are at risk for rupture,
particularly during pregnancy (under estrogenic stimulation),
causing life-threatening intra-abdominal hemorrhage; &

(3)Although adenomas are not considered precursors of HCC,
adenomas carrying β-catenin mutations carry a risk of developing into cancers.

Hepatocellular Carcinomas (HCC)

- Epidemiology, worldwide, HCC (also known as liver cell carcinoma or, erroneously, hepatoma,)
  constitutes 5.4% of all cancers,
  but the incidence varies widely in different areas of the world.

- More than 85% of cases occur in countries with high rates of chronic HBV infection.

- Highest incidences are found in

  Asian countries (Southeast China, Korea,& Taiwan)

  & African countries such as Mozambique,
  -in which HBV is transmitted vertically,
  -& in which carrier state starts in infancy.

- Moreover, many of these populations are exposed to aflatoxin,
  which, combined with HBV infection,
  increase the risk of HCC development by more than 200-fold
  over noninfected, nonexposed populations.

- The peak incidence of HCC in these areas is between 20 & 40 years of age,
- & in almost 50% of cases, the HCC appear in the absence of cirrhosis!

- HCC incidence is rapidly increasing in the West.
  It tripled in the US during the last 25 years,
  but it is still much lower (8- to 30fold) than the incidence in some Asian countries.

- In the West, HCC is rarely present before age 60,
  & in 90% of cases, HCC develop in persons with cirrhosis!

- There is a marked male preponderance of HCC throughout the world;
  3:1 in low-incidence areas &
  as high as 8:1 in high-incidence areas.
- These differences may be related to the greater prevalence of HBV infection, alcoholism, & chronic liver disease among males.

Pathogenesis of HCC

- 3 major etiologic associations have been established:
  -HBV or HCV infection
  -chronic alcoholism
  - aflatoxin exposure.

- Other conditions include hemochromatosis & tyrosinemia.

- Many variables, including age, gender, chemicals, viruses, hormones, alcohol, & nutrition, interact in the development of HCC,
- e.g., the disease most likely to give rise to HCC is, in fact, the extremely rare hereditary tyrosinemia,
  in which 40% of patients develop HCC despite dietary control.

- The development of cirrhosis seems to be an important, but not requisite, contributor to the emergence of HCC.

- Carcinogenesis is greatly enhanced in the presence of cell injury & replication, as occurs in chronic viral hepatitis.

- In many parts of the world, including Japan & Central Europe,
  chronic HCV infection is the greatest risk factor in the development of liver cancer.

- HCC in patients with hepatitis C occurs almost exclusively in the setting of C.

- In China & South Africa, where HBV is endemic,
  there is also high exposure to dietary aflatoxins derived from the fungus Aspergillus flavus.
  These carcinogenic toxins are found in "moldy" grains & peanuts.
  Aflatoxin can bind covalently with cellular DNA & cause a mutation in p53.

- Despite the detailed knowledge about the etiologic agents of HCC, the pathogenesis of HCC is still uncertain.

►**Origin:**

- HCC seems to arise from both mature hepatocytes & progenitor cells (known as ductular cells or oval cells).
- In most cases, it develops from small-cell, high-grade dysplastic nodules in cirrhotic livers,
  these nodules may be monoclonal & may contain chromosomal aberrations similar to those seen in HCC.

- Distinguishing high-grade dysplastic nodules from early HCC is difficult even in biopsies,
  because there are no molecular markers specific for these stages.

- An important criterion of HCC is tumor nodule vascularization, visualized by imaging (U/S),
  which is almost always a clear indication of malignancy.

- An almost universal feature of HCC is the presence of structural & numeric chromosomal abnormalities.
  The precise origin of HCC genetic instability is not known.

- -Cell death,
  -H replication,
  -& inflammation
  seen in all forms of chronic hepatitis, are believed to be main contributors to DNA damage.

- Poor regulation of H replication can occur by:
  (1) point mutations or
  (2) overexpression of specific cellular genes (such as β-catenin),
  (3) mutations or loss of heterozygosity of tumor suppressor genes (such as p53),
  (4) methylation changes, &
  (5) constitutive expression of GFs,
  (6) Defects in DNA repair, particularly those in repair systems for double stranded DNA breaks, perpetuate DNA damage & may cause chromosome defects.

- Neither HBV nor HCV contains oncogenes,
  & the tumorigenic capacity of these viruses probably relates primarily to their capacity to cause continuing cell death, regeneration & chronic inflammation.

Morphology:

- HCC may appear grossly as a
  (1) Unifocal, single massive tumor
  (2) Multifocal, made of multiple nodules of variable size; or
  (3) Diffusely infiltrative cancer which may involves the entire liver.

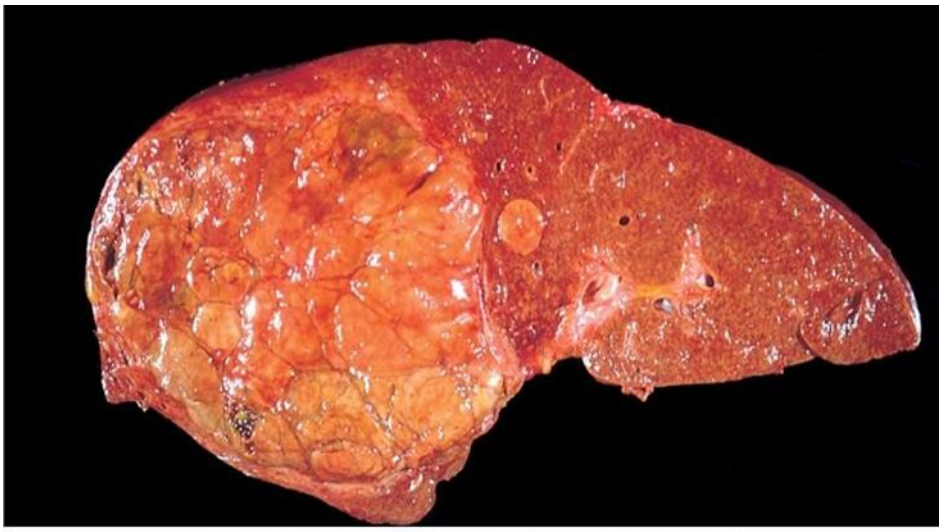
  In the latter two patterns,
  it may be difficult to distinguish regenerative nodules of cirrhotic liver from cancer nodules of similar size!.

- Tumor masses are grossly yellow white, punctuated sometimes by bile staining & areas of hemorrhage or necrosis.

Hepatocellular carcinoma, unifocal, massive type.

A large tumor with areas of necrosis has replaced most of the right hepatic lobe in this noncirrhotic liver.

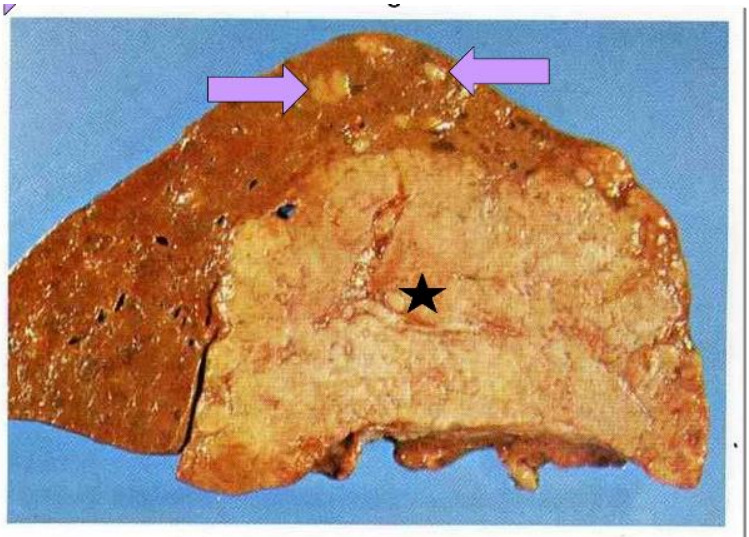
A satellite tumor nodule is directly adjacent



Hepatocellular carcinoma: liver.

Single large tumor replacing most of the right liver lobe with several small satellite → nodules in the surrounding liver.

There is no cirrhosis



5.23 Hepatocellular carcinoma: liver

Vascular invasion:

- all HCC have a strong propensity for invasion of vascular channels, resulting in extensive intrahepatic metastases,
  & occasionally snakelike cancer masses invade the portal vein (causing occlusion) or the inferior vena cava, extending into the right side of the heart!

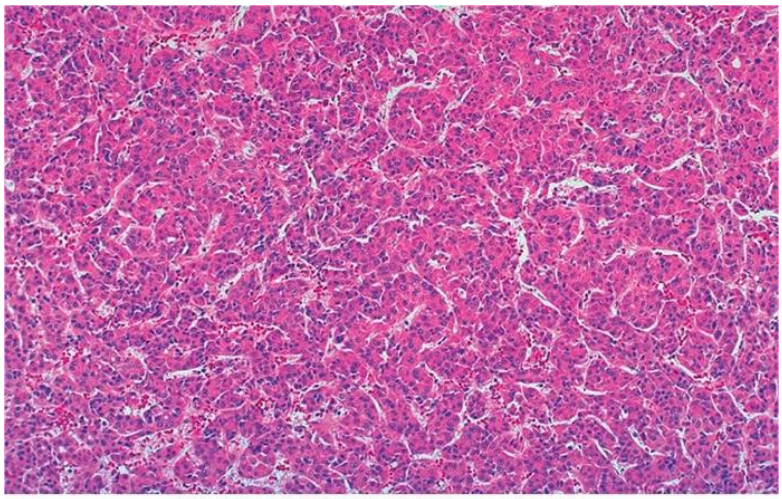
H,

- HCC range from well-differentiated T that reproduce H arranged in cords, trabeculae or glandular patterns (F16-34),
- to poorly differentiated T, often composed of large multinucleate anaplastic T giant cells.

- In the better differentiated variants,
  -Globules of bile may be found within the cytoplasm of cells & in pseudocanaliculi between cells, &
  -acidophilic hyaline intracytoplasmic inclusions (Mallory bodies) may be seen.

- There is surprisingly scant stroma in most HCC, explaining the soft consistency of these T.

Hepatocellular carcinoma.
Carcinoma cells forming trabecular, & pseudoacinar, & pseudoglandular architecture



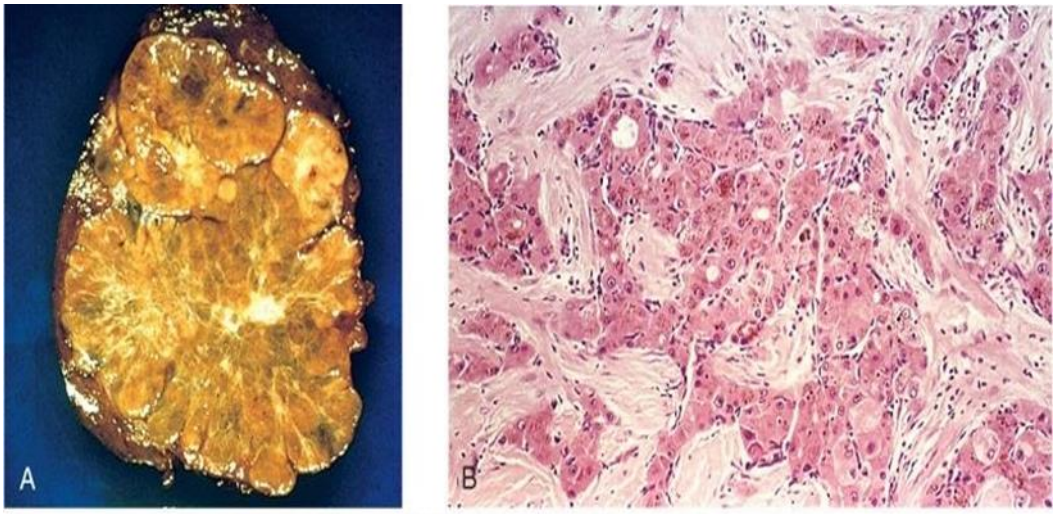
Fibrolamellar carcinoma

- is a distinctive clinicopathologic variant of HCC
- which occurs in young (20-40 years of age) with equal sex incidence,
- has no association with cirrhosis or other risk factors (F16-35),
- usually consists of a single large, hard "scirrhous" tumor with fibrous bands coursing through it, resembling focal nodular hyperplasia.

H,

- composed of well-differentiated polygonal cells growing in nests or cords & separated by parallel lamellae of dense collagen bundles.

A, Resected specimen with an outer rim of normal liver.
B, Nests & cords of tumor cells separated by dense bundles of collagen.



Clinical Features

- Although HCC may present with silent hepatomegaly,
  HCC are often encountered in individuals with cirrhosis who already have symptoms of it.

- In cirrhotic persons,
  -a rapid increase in liver size,
  -sudden worsening of ascites,
  - or the appearance of bloody ascites,
  -fever,
  -& pain
  call attention to the development of HCC.

- Laboratory studies are helpful but not diagnostic.
- 50% of patients have elevated serum α-fetoprotein.
  However, this T "marker" lacks specificity,
  because modest elevations are also encountered in other conditions, such as:
  -cirrhosis
  - chronic hepatitis,
  - normal pregnancy,
  -fetal distress
  - death,
  -& gonadal germ cell T.

- Very high levels (>1000 ng/mL), however, are rarely encountered except in HCC.
- Final diagnosis is by histopathological examination of liver biopsy.

Prognosis of HCC

- Is grim;
- But it is significantly better for individuals who have a single tumor less than 2 cm in diameter & good liver function.

- The median survival is 7 months, with death from:
  (1) Profound cachexia
  (2) Bleeding esophageal varices
  (3) LF with hepatic coma, or rarely
  (4) Rupture of the tumor with fatal hemorrhage.

- Early detection of HCC is critical for successful treatment.
- The most effective therapies are surgical resection of smaller T detected by U/S screening of persons with chronic liver disease, & liver transplantation for patients with small tumors & good liver function.

- T recurrence rate is greater than 60% at 5 years.
- Best hope for preventing HCC in regions endemic for HBV infection is a comprehensive anti-HBV immunization program