College of medicine
Department of pathology
3rd year

# Hepatobiliary system

## LEC. 3

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# Portal hypertension

Def: It is mean increase resistance to portal blood flow which may be due to many causes. Include.

**Prehepatic portal hypertension** .this is mostly due to:

occlusive thrombosis &

narrowing of portal vein

2. **Post hepatic portal hypertension**. Mostly due to constrictive pericarditis,

severe right sided heart failure &

hepatic vein obstruction.

3. **Hepatic portal hypertension.** Mostly due to cirrhosis.

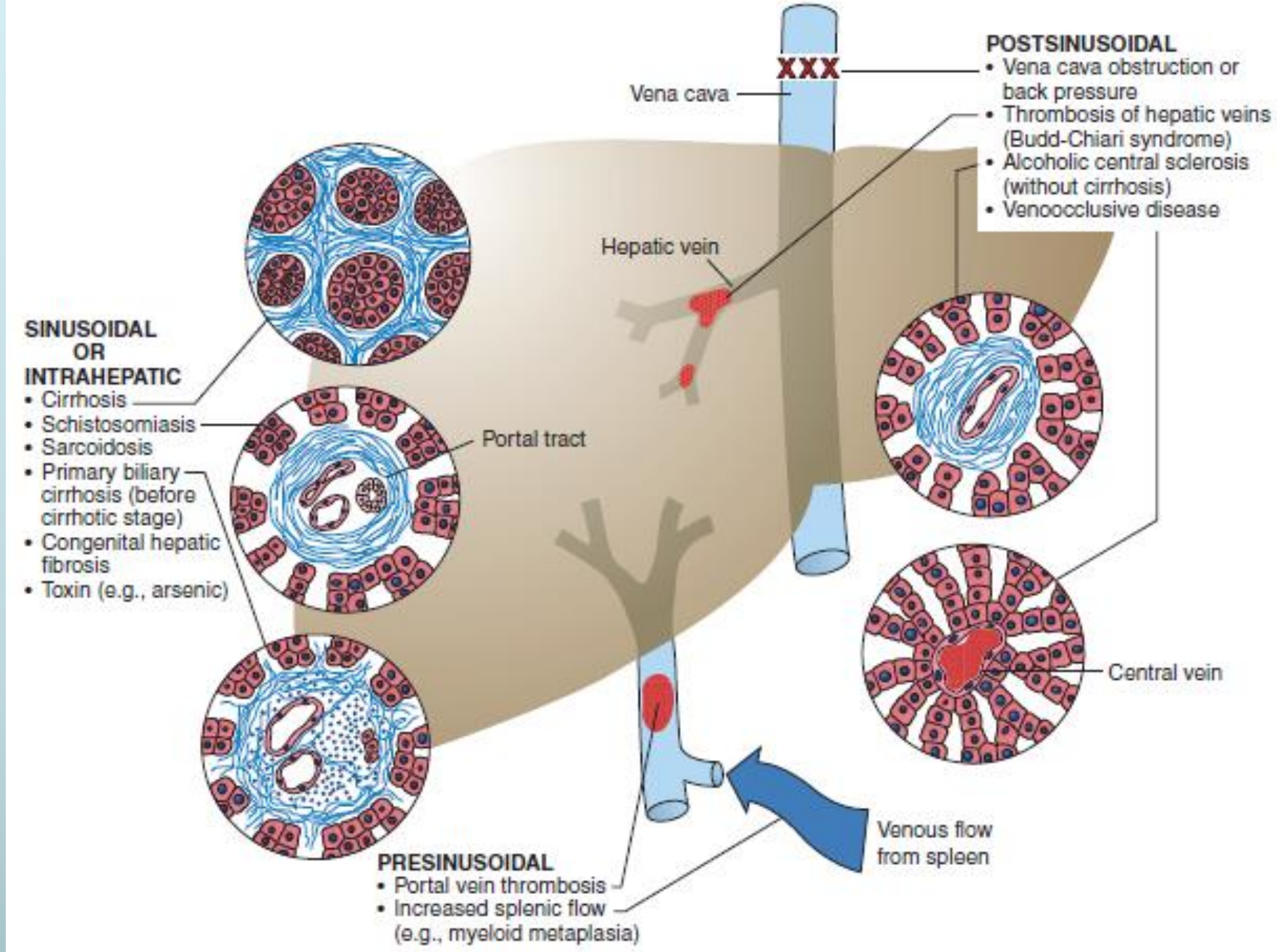



**FIGURE 14-9. Causes of portal hypertension.**

## Complications of portal hypertensions:

1. Ascites
2. Formation of Porto systemic shunt.
3. Congestive splenomegaly
4. Hepatic encephalopathy

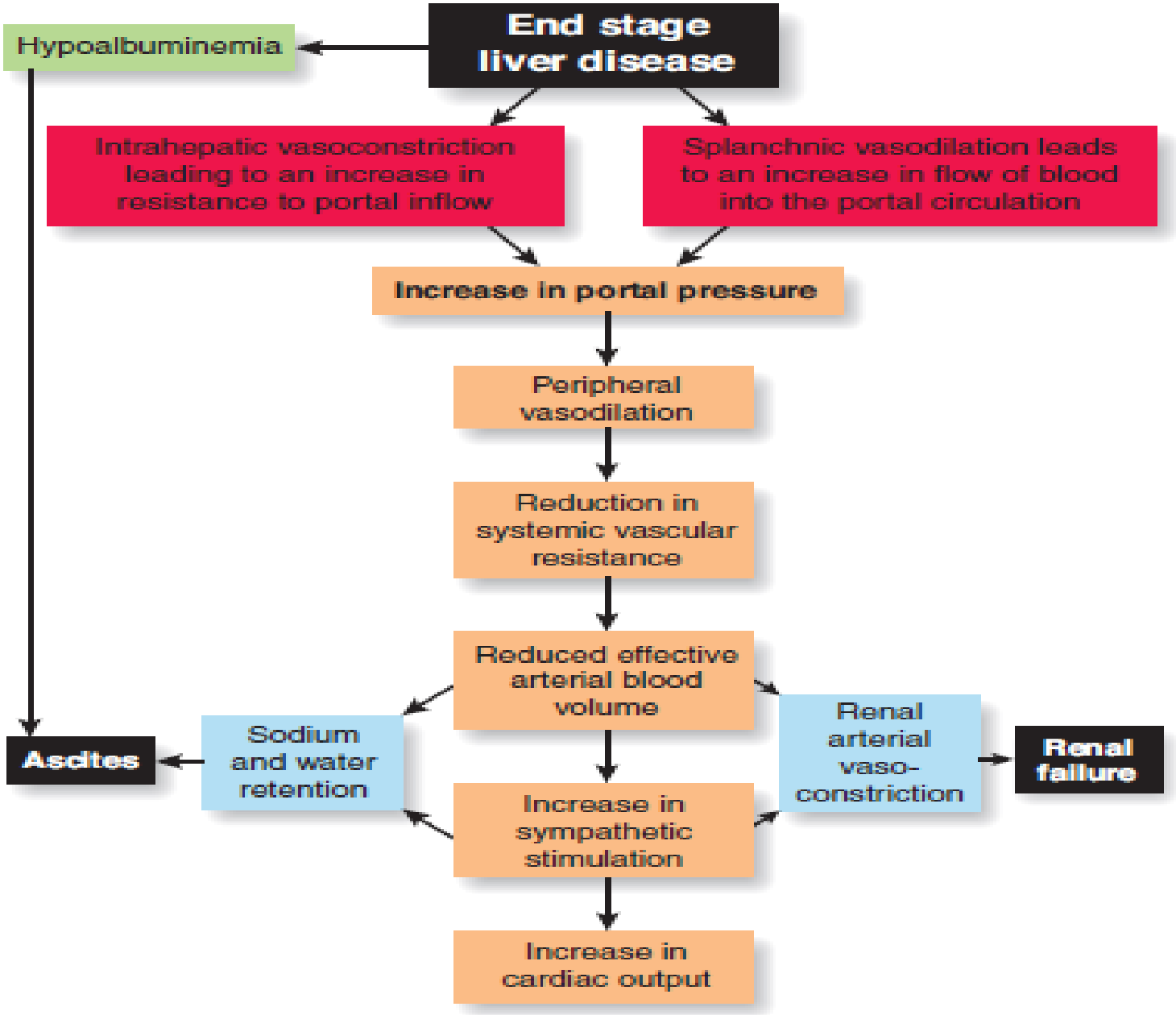



**FIGURE 14-10. Pathogenesis of ascites.**

# Pathophysiological basis of clinical features of chronic liver disease

| | |
|---|---|
| Oedema | Reduced albumin synthesis resulting in hypoalbuminaemia |
| Ascites | Hypoalbuminaemia, secondary hyperaldosteronism, portal hypertension |
| Haematemesis | Ruptured oesophageal varices due to portal hypertension |
| Spider naevi Gynaecomastia | Hyperoestrogenism |
| Purpura and bleeding | Reduced clotting factor synthesis |
| Coma | Failure to eliminate toxic gut bacterial metabolites ('false neurotransmitters') |
| Infection | Reduced Kupffer cell number and function |

# Tumors of the liver

- Either **benign** or **malignancy**

- **Malignant** tumors are either **primary** (carcinoma of liver) or **secondary** (metastatic cancers to the liver).

- Most common hepatic neoplasms are **metastatic** carcinomas & the sites of primary tumors are usually (colon, lung & breast).

# Benign tumors

a. cavernous hemangioma (commonest benign tumor of liver).

b. **liver cell adenoma.**

# Liver cell adenoma.

.In young childbearing age female who used oral contraceptive pills

it regresses on discontinuation of hormonal use.

**Gross.** Pale tan – yellow or bile stained, well demarcated nodules, often beneath the capsule of liver.

Mic.

composed of sheets or cords of cells that may resemble normal hepatocytes or have some variation in cells & nuclear size, portal tracts are absent instead prominent arterial vessels & veins are distributed throughout the tumor.

# these adenomas are significant because of 2 reasons:

1. **Misdiagnosed** as hepatocellular carcinoma.
2. Subcapsular adenoma is at risk of **rupture** particularly during pregnancy (life threatening intra abdominal hemorrhage).

# LIVER CELL ADENOMA

# MALIGNANT LIVER TUMORS

99% are metastatic, i.e., SECONDARY, esp. from portal drained organs(GIT) other: pancreas lung breast

**PRIMARY liver malignancies,**

**Hepatocellular carcinoma:**

HCC cell of origin hepatocyte

HCC arise in the background of already very serious liver disease chronic hepatitis/cirrhosis, are slow growing, and do NOT metastasize readily

**CHOLANGIOCARCINOMAS:**

are malignancies in the INTRA-hepatic bile ducts and look MUCH more like adenocarcinomas than do HCC

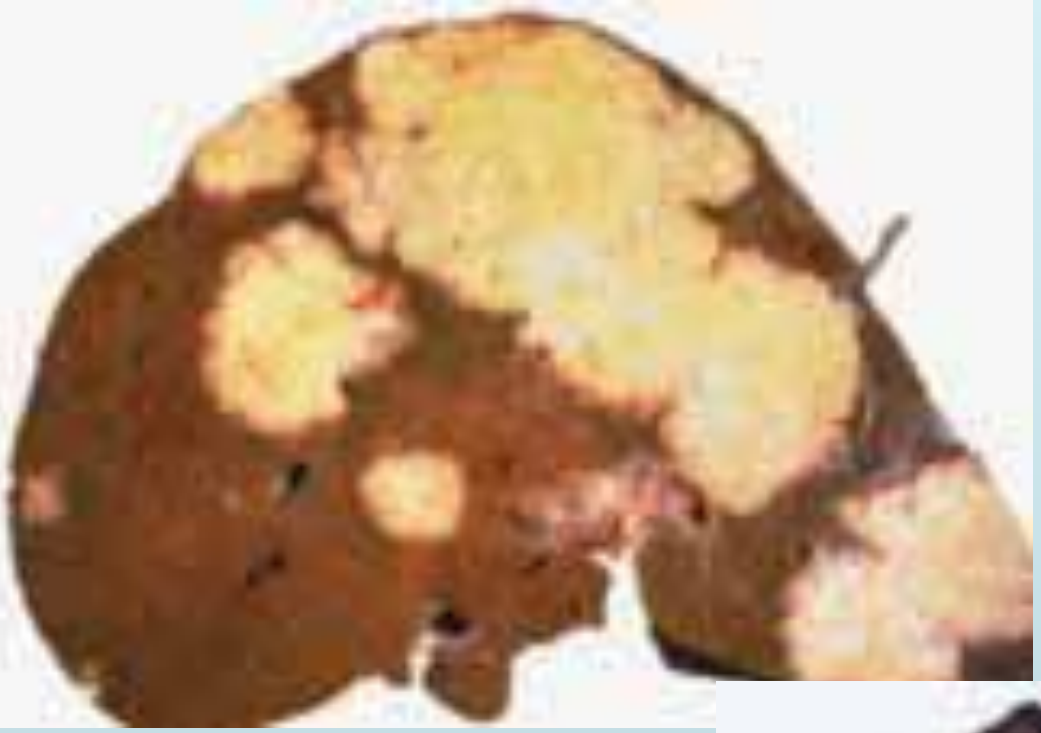
# Metastatic tumors to the liver:

More common than the primary, the most common carcinomas producing liver metastasis are:

- The breast, lung, colonic carcinomas, leukemia's & lymphomas.

***Grossly:*** appear as multiple nodular liver implants with hepatomegaly, jaundice & increased liver enzymes.

***Microscopically***: similar to the tissue of origin.



hepatic metastasis of colonic carcinomas

# Hepatocellular Carcinoma (HCC):

- Sex: **Male**> female (this is in high incidence areas related to greater prevalence of HBV infection, alcoholism & chronic liver diseases among the male).
- Race: Black > white.
- Age: In high incidence areas(Taiwan, shoutheast China, Africa)…….. arise in third to fifth decades of life

  Low incidence areas(Western countries and Australia)…. it is often arise in the 6th to 7th decades of life.

# Etiology:

1- **Cirrhosis**

is the major risk factor of hepatic carcinoma

**Cause:** Repeated cycles of cell death & regeneration with accumulation of mutations during continuous cycles of cell division.

**2-The HBV** :HBV DNA is integrated into host cell genome, inducing genomic instability .HBV genome encode the X-protein, a transcriptional activator of many genes which may disrupt normal growth control by activating host cell protooncogenes

HBV proteins bind & inactivate p53

3. Liver cell dysplasia . Small cell dysplasia more associated with HCC than large cell dysplasia.

4. Thorium dioxide exposure. (thorotrast a radiographic contrast). Develop HCC within 20 years of exposure.

5. Androgen- anabolic steroid. In male patient with long term used of androgen treatment .

6. **Progestational agent**. Several cases of HCC & also liver cell adenoma are associated with using of contraceptive pills.

7. **Aflatoxin.** This is a product of Aspergillus flavus (fungus found sometimes on grains or peanut) which is highly carcinogenic toxin proved to be an etiological factor in development of HCC.

This toxin cause DNA mutation in protooncogen or tumor suppressor gene P53. in some areas endemic for HCC like Africa and China, patients have mutation in hepatic enzymes that normally detoxify aflatoxin

8.Alcohol abuse.

# Symptoms:

abdominal pain, ascites, hepatomegaly, obstructive jaundice; also systemic manifestations.

**Laboratory:** elevated serum AFP (70% sensitive).

**Screening:** recommended to use ultrasound and serum AFP in patients with chronic liver disease; leads to diagnosis of tumors 2 cm or less

# Morphology

**Gross.** unifocal (massive single tumor).

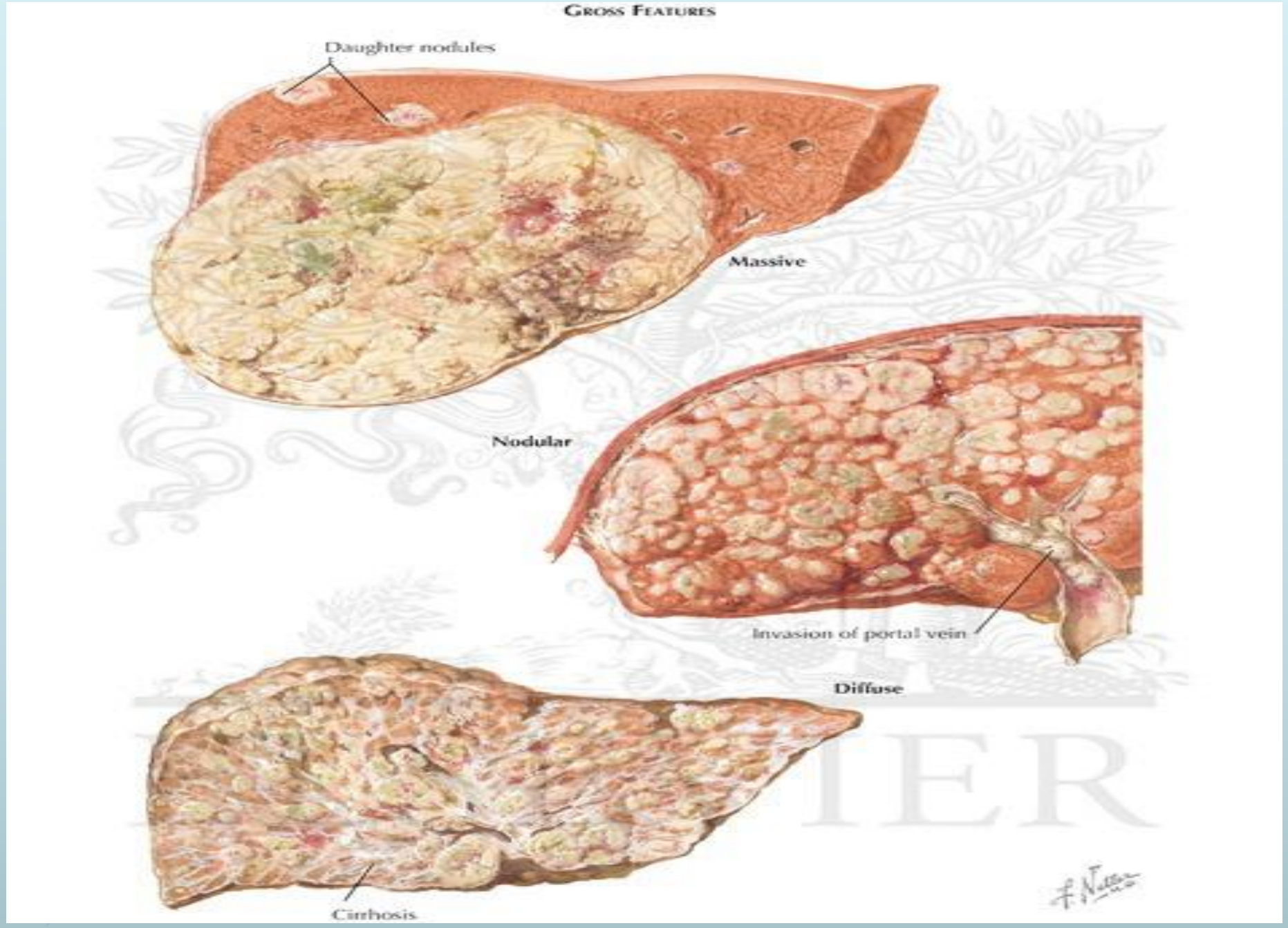
multifocal (wide distributed nodules).

diffuse infiltrative cancer (sometime involve the entire liver).

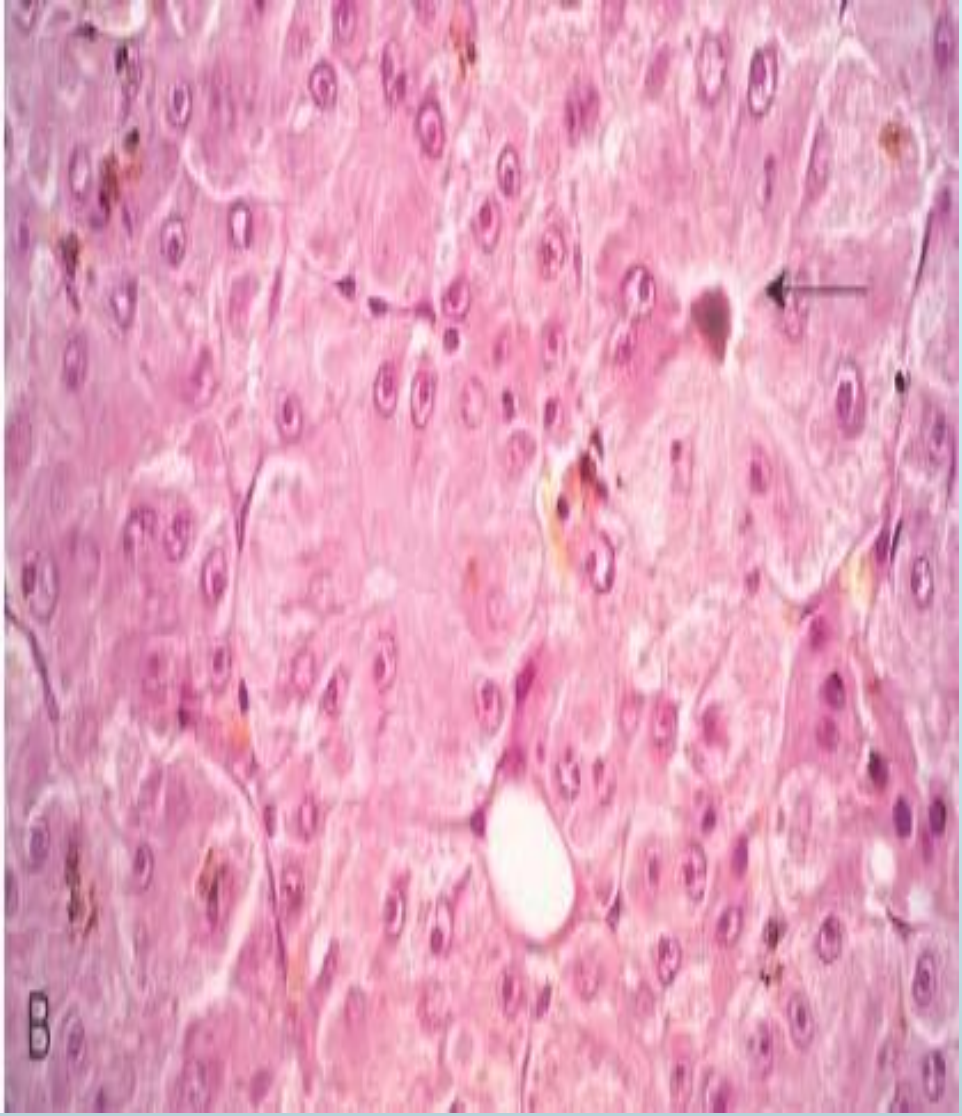
Mic.

- HCC ranges from well differentiated carcinoma that reproduces hepatocytes arranged in cords or small nests. To poorly differentiated lesion which often made up of large multinucleated anaplastic tumor cells.

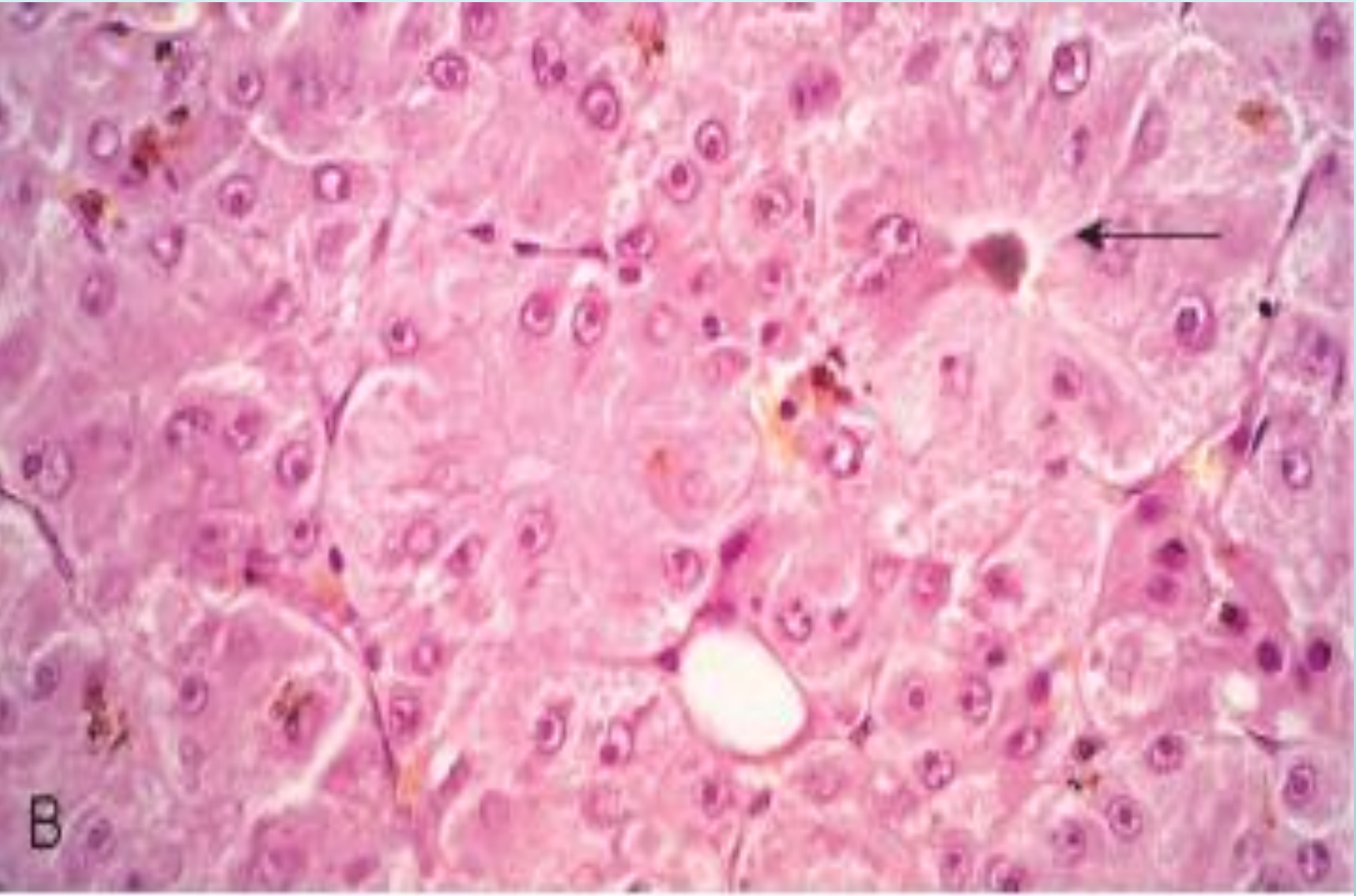
Scant stroma in most cases of HCC (so the tumor is usually soft).


GROSS FEATURES
Daughter nodules
Massive
Nodular
Invasion of portal vein
Diffuse
Cirrhosis

**Classical hepatocellular Carcinoma, HCC**

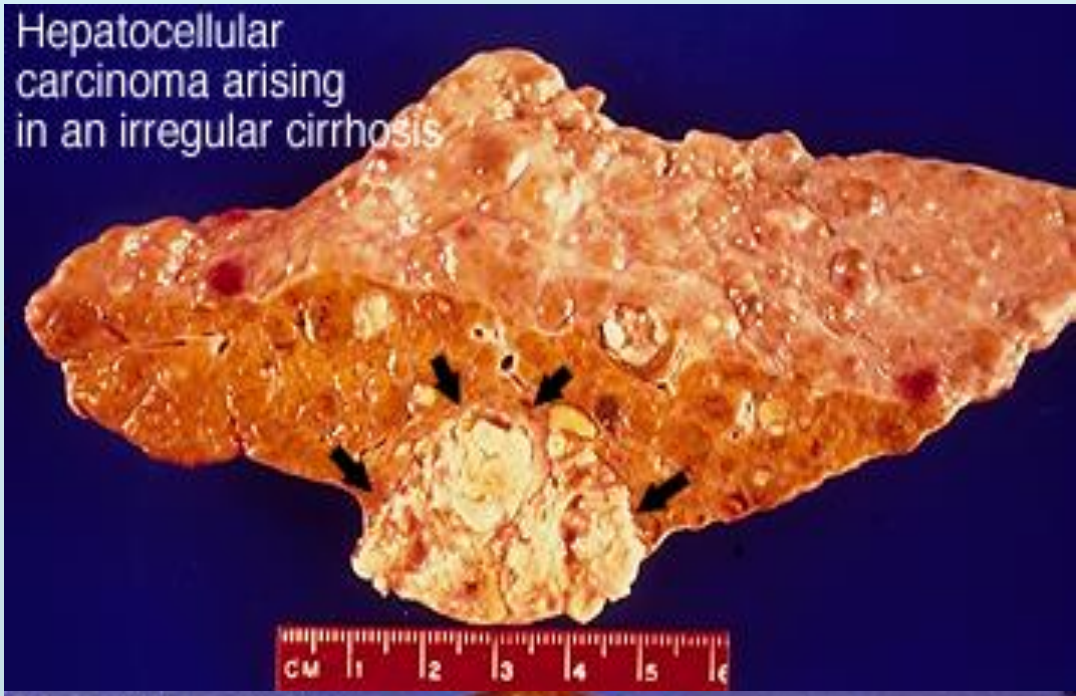




# HEPATOCELLULAR CARCINOMA



## PATHOLOGY OF HEPATOCELLULAR CARCINOMA

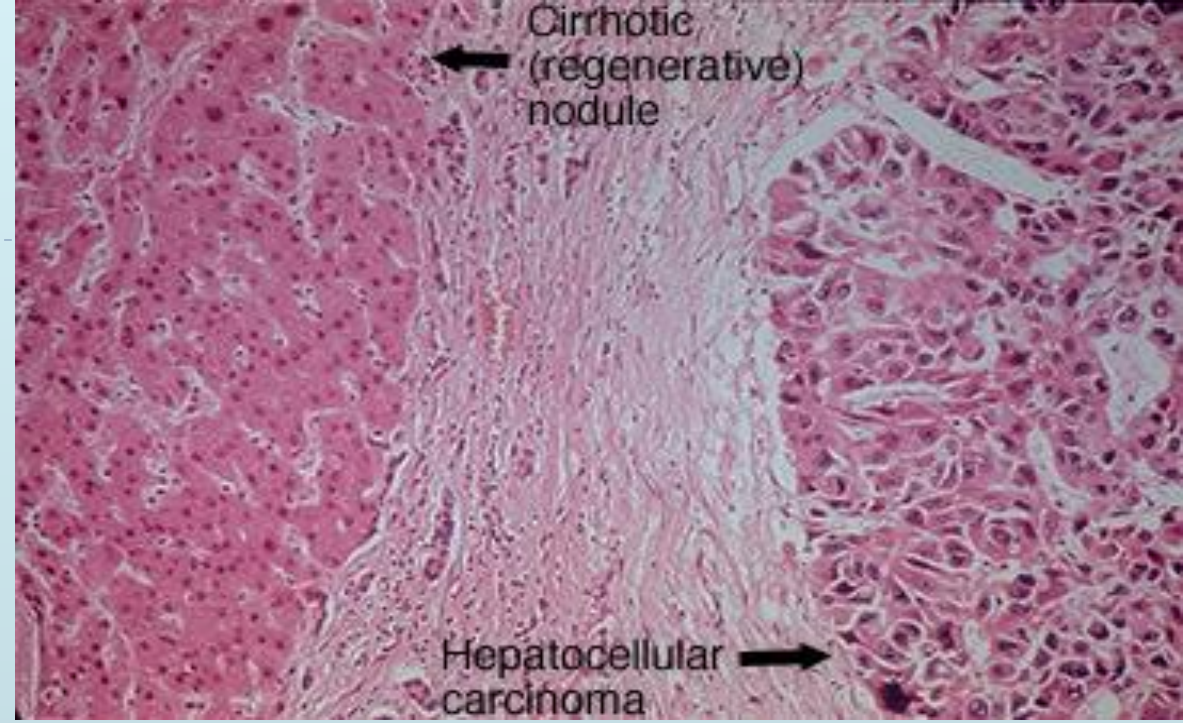
- **Unifocal, multifocal or diffusely infiltrative tumor involving entire liver**
- **Cirrhosis of surrounding liver parenchyma is frequently present**
- **Strong propensity for invasion of vascular channels**

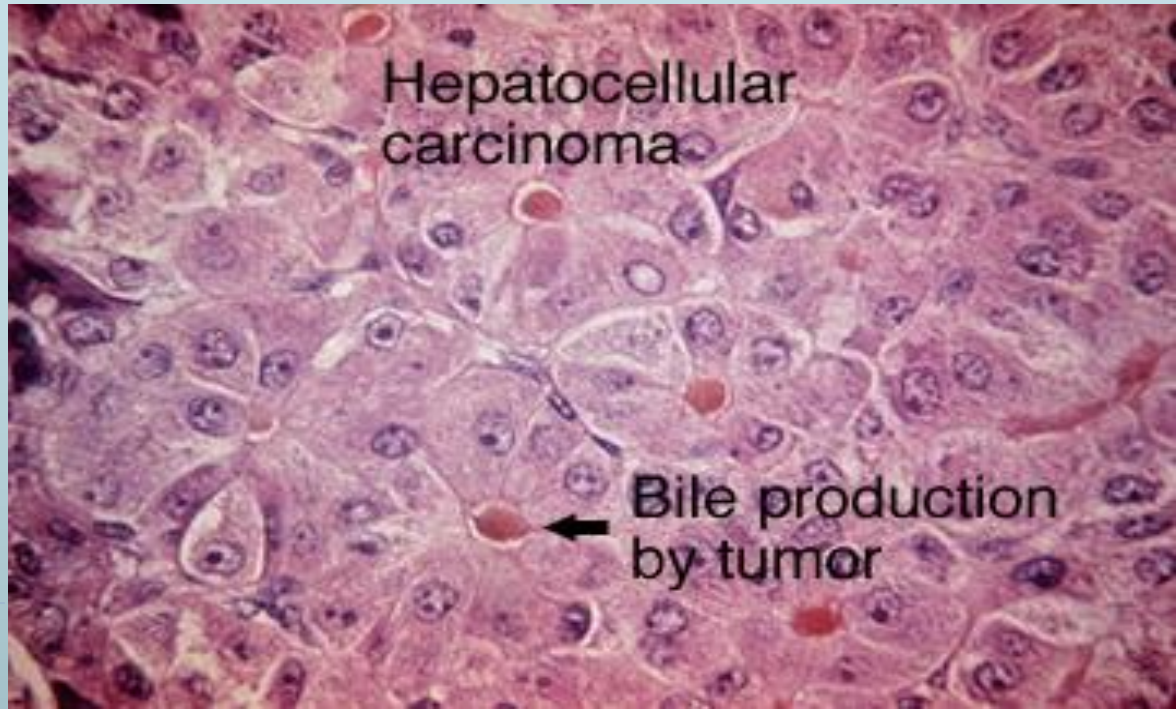



# HISTOPATHOLOGY OF HEPATOCELLULAR CARCINOMA

**Range from well-differentiated to anaplastic.**

**Neoplastic cells of well-differentiated tumors resemble hepatocytes & may show intra-cytoplasmic bile globules**



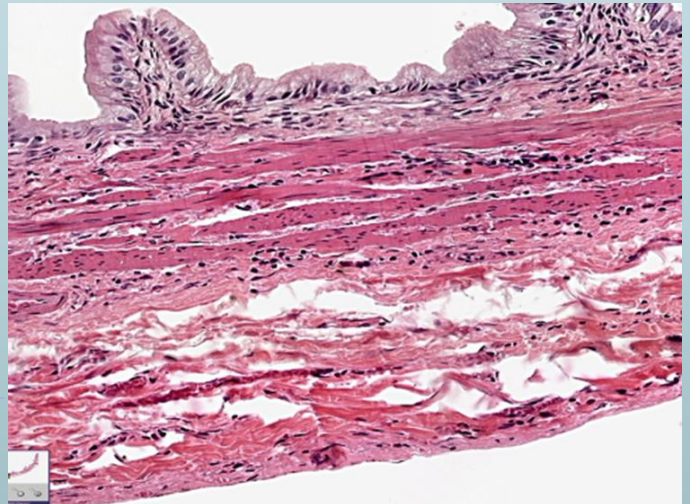



# Gall bladder

**The primary function** :is storage, concentration and release of bile.

The wall of the gallbladder is composed of

a mucous membrane, a muscularis and an adventitia and is covered by a reflection of the visceral peritoneum. The mucosa is thrown into folds and consists of a columnar epithelium and a lamina propria of loose connective tissue



# Gallbladder Pathology

Gall stone(cholelithiasis)

Acute cholecystitis :

acute calculous

acute Acalculous

Chronic cholecystitis

Gall bladder tumors

# Cholelithiasis (gallstones)

Affects 10- 20 % of adults in developed countries.

80% of gallstones are silent

<1% of children have gallstones.

Gall stones result from the constituents of bile (cholesterol, bile pigment, calcium salts & organic material).

Two main types; **80% cholesterol stones** &

**20% of pigmented stones**.


0
1
2 cm 3
4
5

# Pathogenesis of Cholesterol Stones

Cholesterol is insoluble in water

To become soluble in bile it should be aggregated with bile salts and lecithins, both of which act as detergents.

*When cholesterol concentrations exceed the solubilizing capacity of bile (supersaturation), cholesterol can no longer remain dispersed and nucleates into solid cholesterol monohydrate crystals.*

# Four conditions appear to contribute to formation of cholesterol gallstones

(1) Supersaturation of bile with cholesterol;

(2) hypomotility of the gallbladder;

(3) accelerated cholesterol crystal nucleation;

(4) and hypersecretion of mucus in the gallbladder, which traps the nucleated crystals(act as a glue ), leading to accretion of more cholesterol and the appearance of macroscopic stones.

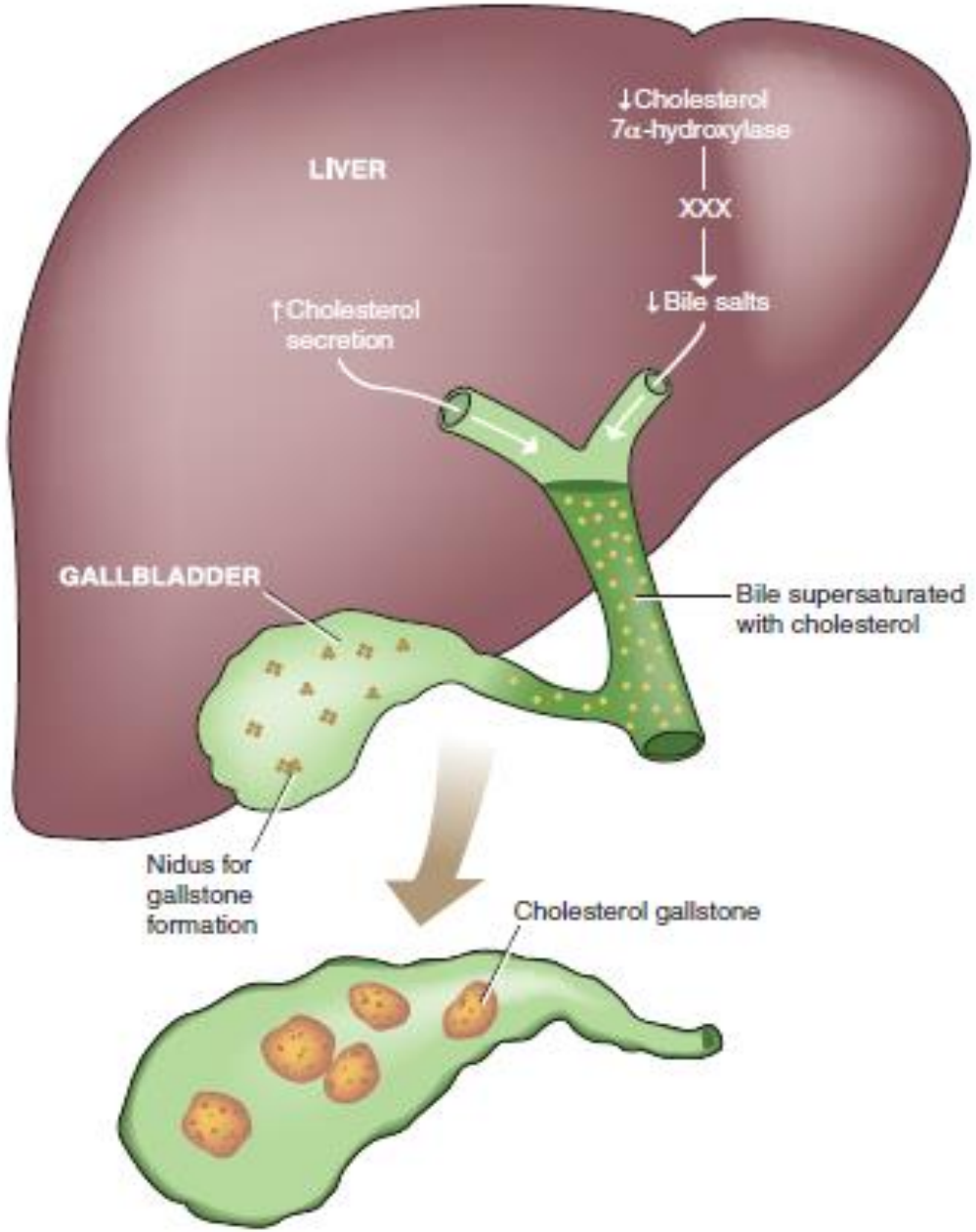



**FIGURE 14-31. Pathogenesis of cholesterol gallstones.**

# Pathogenesis of Pigment Stones

. Pigment gallstones are complex mixtures of insoluble calcium salts of unconjugated bilirubin .

Disorders that are associated with elevated levels of unconjugated bilirubin in bile, increase the risk of developing pigment stones. such as:

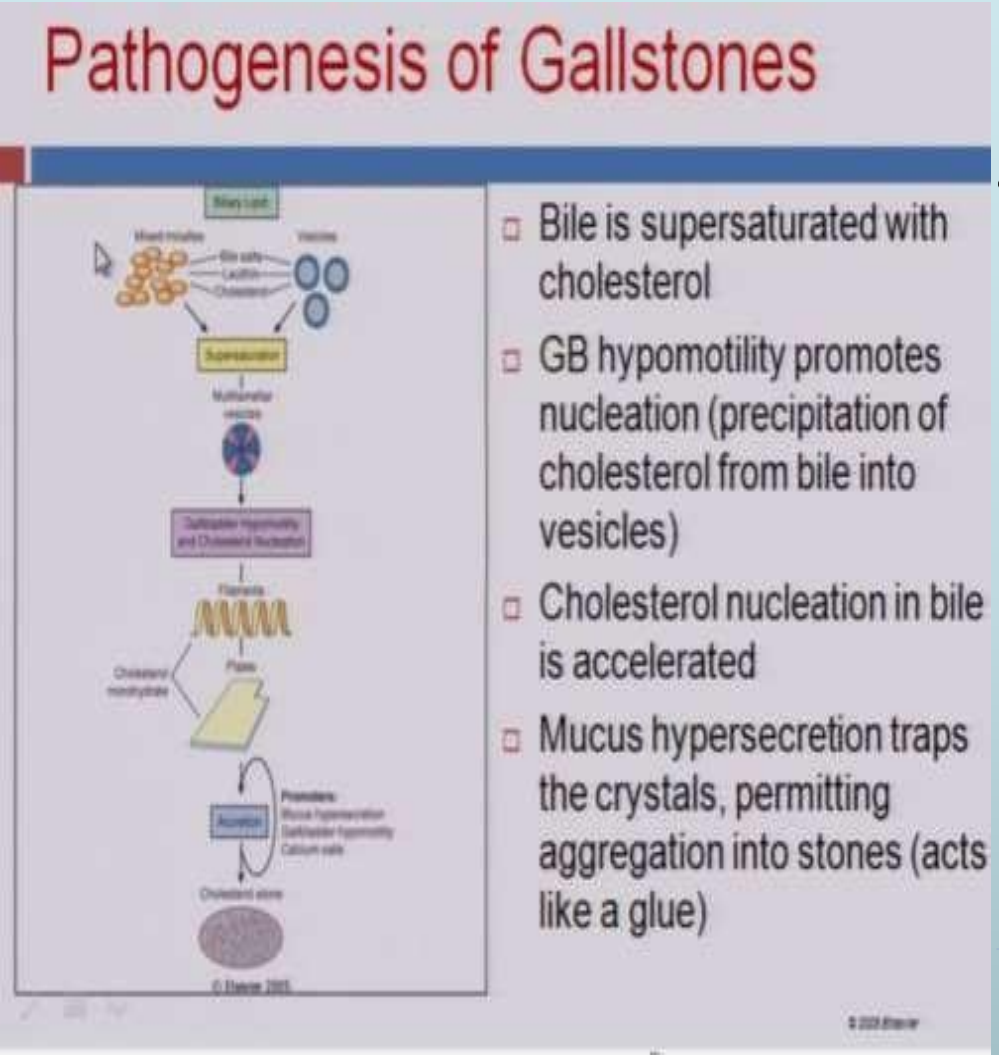
1-chronic hemolytic anemias,

2-severe ileal dysfunction or bypass,

3- bacterial contamination of the biliary tree,

# Pathogenesis

## Cholesterol stone




## Pigment stone

- Pathogenesis of pigment stone:
  - Hemolytic anemias and infections of the biliary tract → increased unconjugated bilirubin in the biliary tree → form precipitates : insoluble calcium bilirubinate salts.

# Cholelithiasis-Risk Factors

| CHOLESTEROL STONES | PIGMENT STONES |
| --- | --- |
| Common in Western/ developed countries | Common in Asians |
| Advancing age | Rural > urban |
| <6% in <40Y | Chronic hemolytic syndromes |
| 30% in >80Y | Biliary infections |
| Female gender | GI disorders |
| OCP | Ileal disease e.g. Crohn's disease or ileal resection or bypass |
| Pregnancy | cystic fibrosis of pancreas |
| Obesity | |
| Rapid weight reduction | |
| Gall bladder stasis | |
| Inborn error of Bile salt metabolism | |
| Hyperlipidemia syndromes | |

# Cholelithiasis Risk factors -

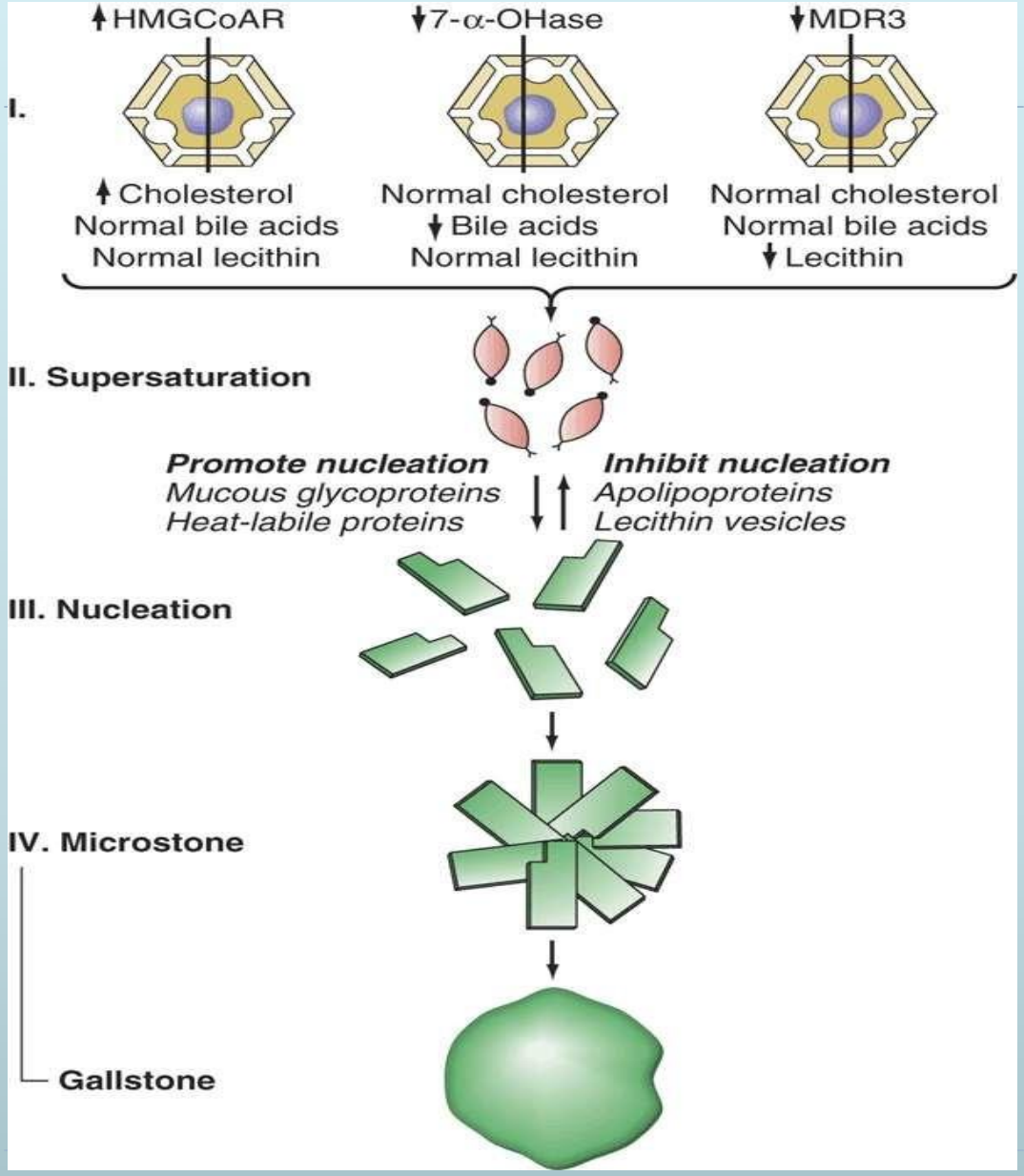
- :
  - Age and sex : Prevalence increase with age – associated with metabolic syndrome and obesity. More common in women (2x)
  - 5 F :female, forty /fifty , fatty, fair, fertile (**multiple pregnancies)**
  - Ethnic and geographic. Cholesterol stone is more common in Native American population, related to biliary cholesterol hypersecretion.
  - **Hereditary :** positive family history of stones, inborn error of metabolism associated with impaired bile salt synthesis and secretion
  - **Environmental factors :**
    - **Estrogenic influence ( OCP and pregnancy) - excess biliary secretion of cholesterol.**
    - Obesity, rapid weight loss also **increase biliary cholesterol secretion.**
  - **Acquired disorders** : gall bladder stasis and reduced gall bladder motility ( in pregnancy, rapid weight loss, spinal cord injury).

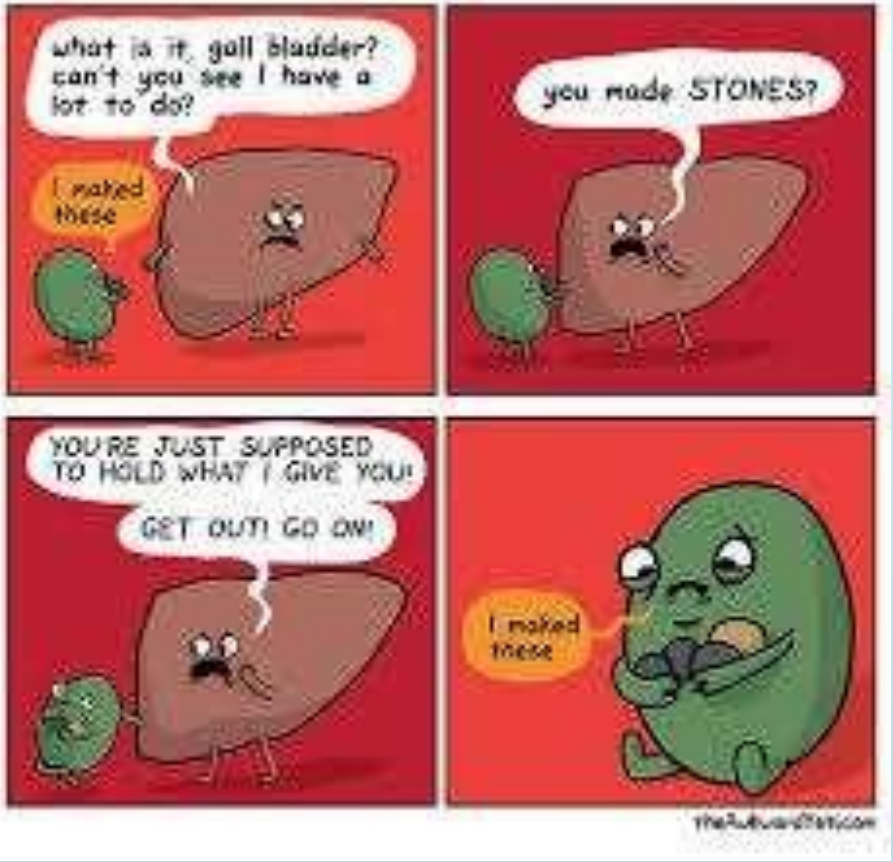
# Risk factors for Pigment stones

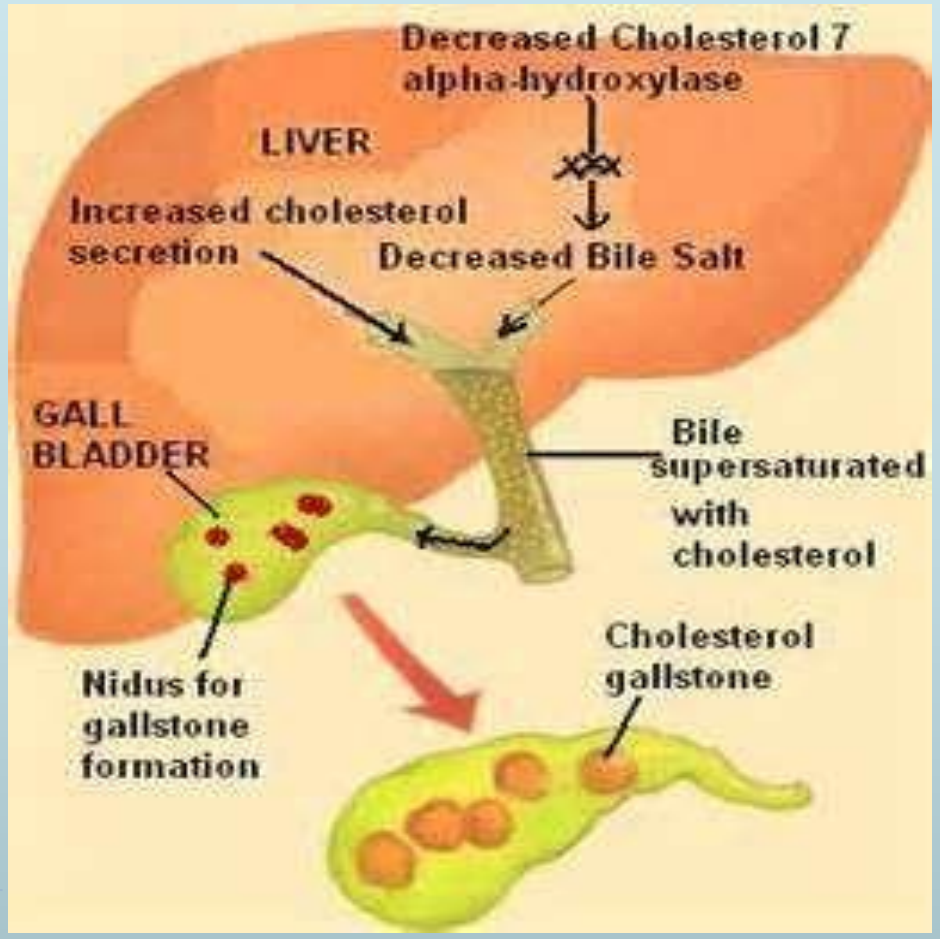
risk factors

The most important cause is increased unconjugated bilirubin (from hemolytic syndromes Like sickle cell anemia, thalassemia, and hereditary spherocytosis)

**Other causes** : biliary infection, , ileal dysfunction/bypass,ileal crohns disease, cystic fibrosis


I.
↑HMGCoAR
↓7-α-OHase
↓MDR3
↑Cholesterol
Normal bile acids
Normal lecithin
Normal cholesterol
↓Bile acids
Normal lecithin
Normal cholesterol
Normal bile acids
↓Lecithin
II. Supersaturation
Promote nucleation
Mucous glycoproteins
Heat-labile proteins
Inhibit nucleation
Apolipoproteins
Lecithin vesicles
III. Nucleation
IV. Microstone
Gallstone


what is it, gall bladder? can't you see I have a lot to do?
I maked these
you made STONES?
YOU'RE JUST SUPPOSED TO HOLD WHAT I GIVE YOU!
GET OUT! GO ON!
I maked these


Decreased Cholesterol 7 alpha-hydroxylase
LIVER
Increased cholesterol secretion
Decreased Bile Salt
GALL BLADDER
Bile supersaturated with cholesterol
Nidus for gallstone formation
Cholesterol gallstone

# Morphology

## *I. Cholesterol stones(80%)*

- ***Pure cholesterol stone:*** yellow, round-ovoid, faceted radiolucent
- ***Mixed type:*** often multiple stones composed of calcium carbonate, phosphates & bilirubine. Radioopaque.

## II. Pigmented gallstones (20%)

- ***Black stone:*** Multiple, Rarely more than 1.5 cm., of sterile bile contain calcium salts, unconjugated bilirubin , calcium carbonate & phosphate with cholesterol crystals.
- ***Brown stone:*** Laminated, soft, soap or greasy like, of **infected bile** contain calcium salts, unconjugated bilirubin & glycoprotein.

# Pathology

## Cholesterol stones :

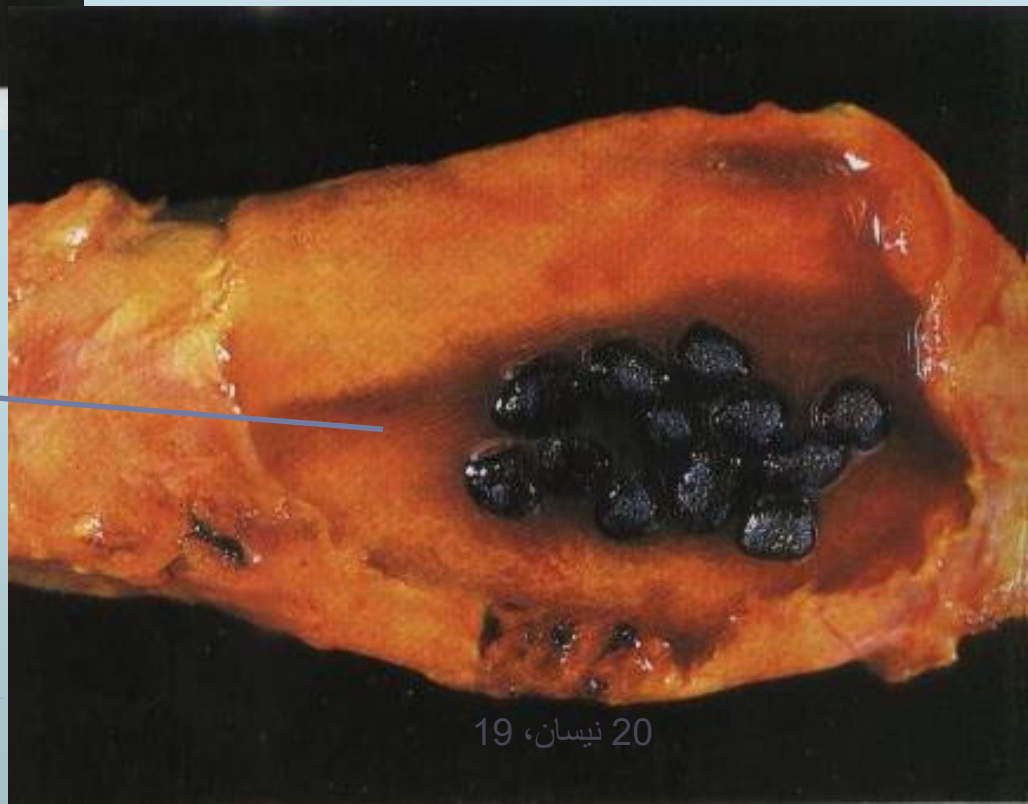
- Gross : pale yellow, ovoid, firm, single to multiple with faceted surfaces
- Mostly radiolucent, 20% is radio opaque due to the presence of calcium carbonate content.

## Pigment stones

- Black stone (in sterile gall bladder bile)- small size, fragile to touch, numerous, 50-70% are radioopaque
- Brown stone (in infected intrahepatic or extrahepatic ducts)- single to a few, soft, greasy, soaplike consistency due to presence of retained fatty acids released by bacterial phospholipases on biliary lecithins, radiolucent.
- Stone content : calcium salts of unconjugated bilirubin, lesser amounts of other calcium salts, mucin glycoproteins and cholesterol.


***Cholesterol stones***

**Pigmented gallstones**



| Cholestrol stone | Pigmented stome |
| --- | --- |
| multiparous women, related to the fact that cholesterol metabolism is altered during pregnancy. | In hemolytic anemia |
| arise exclusively in the gallbladder | anywhere in the biliary tree |
| There is controversial about correlation between the presence of cholesterol stones in the gallbladder & the level of cholesterol in the blood. | Due to increase unconjugated bilirubin |
| Most of cholesterol stones are radiolucent, (only 20% are radiopaque, due to contents of Ca+2).<br><br>single, spherical ,& coarsely nodular, they have translucent bluish white color. | 50% to 70% of pigmented stones are radiopaque.<br><br>These are multiple, small, brown to black |