# GI
# PATHOLOGY

## #3

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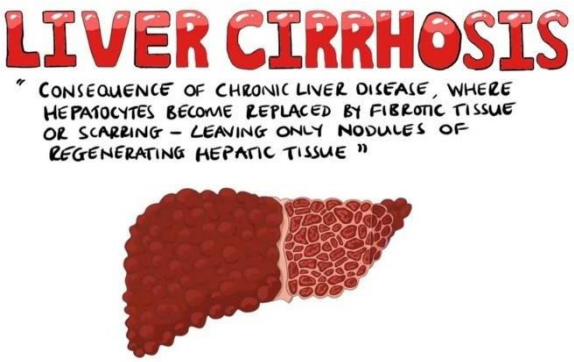
In this lecture we will talk about 3 main liver diseases + some other diseases that are associated with them

The 3 main ones:

1) Cirrhosis
2) Portal Hypertension
3) Drug-Induced Liver Disease




# 1) CIRRHOSIS

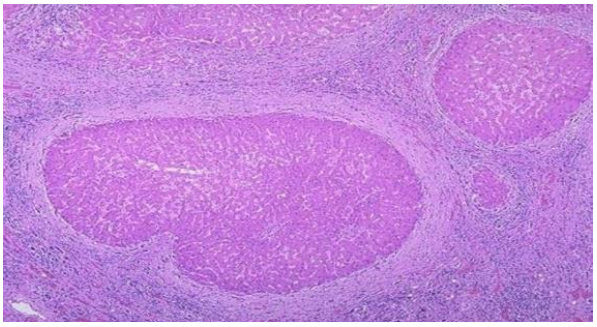
- **It is a diffuse process characterized by fibrosis & the conversion of liver parenchyma into nodules.**

- **Main characteristics:**

**1- Bridging fibrous septae**

**2- Parenchymal nodules encircled by fibrotic bands**

**3- Diffuse architecture disruption (the whole live is involved)**



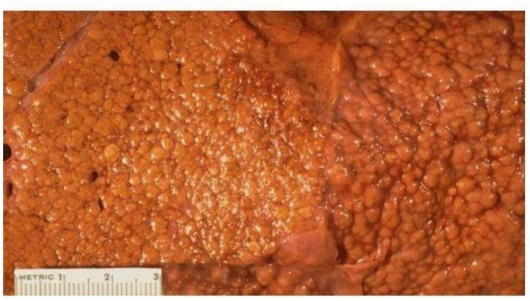
each nodule is formed of parenchyma

- **Types:**

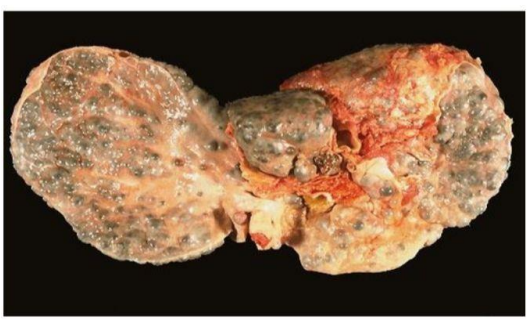
**1- Micronodules <3mm in diameter**

**2- Macronodules >3mm in diameter**

Micronodular cirrhosis



Macronodular cirrhosis



In these pictures we can see a cross section of the gross appecrance of a liver with cirrhosis, the smooth homogenous surface of the liver is replaced by a nodular heterogenous one.

- **Causes of cirrhosis:**

1- **Chronic alcoholism** (most common cause of cirrhosis in developed countries)

2- **Chronic viral infection HBV & HCV** (most common cause of cirrhosis in developing countries)

3- **Biliary disease**

4- **Hemochromatosis (iron build up)**

5- **Autoimmune hepatitis**

6- **Wilson disease (copper build up)**

7- **Alpha-1-antitrypsin deficiency**

8- **Rare causes: galactosemia, tyrosinosis, glycogen storage disease3&4, lipid storage disease, hereditary fructose intolerance, drug induced(eg: methyldopa)**

9- **Cryptogenic cirrhosis 10%**

When a child has cirrhosis it's usually due to a metabolic disorder or it might be inherited

- **Pathogenesis of cirrhosis:**

**The mechanism of cirrhosis involves:**

1- **Hepatocellular death** which stimulates the formation of fibrous tissue

2- **Regeneration**

3- **Progressive Fibrosis**

4- **Vascular changes**

So we have cell death, cell regeneration & fibrosis, and they all make up the nodules that we saw in the histologic image.

- **The development of cirrhosis requires cell death to occur over long periods of time and to be accompanied by fibrosis.**
- **Fibrosis progresses to scar formation when the injury involves not only the parenchyma but also the supporting connective tissue.**

**In normal liver ECM collagen (types 1,3,5,11) is present only in:**

- ✓ **liver capsule**
- ✓ **portal tracts**
- ✓ **around central vein**

**In cirrhosis types 1 & 3 collagen and others are deposited in the space of Disse.**

**Delicate framework of type 4 collagen (the collagen of basement membrane, it supports epithelial cells) & other proteins lies in space of Disse.**

In liver cirrhosis we see an abundance of all these types of collagen.

As a consequence of having fibrosis, vessels will be trapped in the fibrous septae, and that will cause in compression of vessel walls, that will create vascular problems and that's why these patients will suffer from increase in portal hypertension.

**Vascular changes consisting of the loss of sinusoidal endothelial cell fenestrations and the development of portal vein-hepatic vein and hepatic artery-portal vein vascular shunts contribute to defects in liver function.**

The blood vessels are now embedded within a firm fibrous tissue, so the blood flow will go against resistance. The blood flow redirects itself through other channels (connections), portal v.-hepatic v. & hepatic artery-portal v.

**The stimuli for the activation of stellate cells & production of collagen are:**

1- **Reactive oxygen species (toxic substances)**
2- **Growth factors (released from dead cells & inflammatory cells)**
3- **Cytokines, TNF, IL-1, lymphotoxins (chemical mediators)**

- **Clinical features of cirrhosis:**

1- **Silent** (asymptomatic)

Because regenerative nodules can function, patients can survive many years with normal liver function, they will develop sudden liver failure if there were superimposed things (due to an infection or bleeding)

2- **Anorexia, weight loss, weakness** (non-specific symptoms)

- **Complications:**
  1- **Progressive hepatic failure**
  2- **Portal hypertension**
  3- **Hepatocellular carcinoma**

# 2) PORTAL HYPERTENSION

- **↑ resistance to portal blood flow at the level of sinusoids & compression of central veins by perivenular fibrosis & parenchymal nodules**
- **Arterial – portal anastomosis (connection between the arterial system and the portal system) develops in the fibrous bands →increase in the blood pressure in portal venous system**

Because if we connect artery to vein this means that the arterial hyperpressure will be reflected on venous low blood pressure.

- **Causes:**

Cirrhosis is the main causative of portal hypertension

But there are some other causatives and we divide them into 3 groups:

| Prehepatic causes | Post hepatic causes (Related to the heart) | Hepatic causes |
|---|---|---|
| 1-Portal vein thrombosis<br>2-Massive splenomegaly | 1-Severe Rt.- sided heart failure<br>2-Constrictive pericarditis<br>3-Hepatic vein out flow obstruction | 1-Cirrhosis<br>2-Schistosomiasis<br>3-Massive fatty change<br>4-Diffuse granulomatosis as sarcoidosis, TB<br>5-Disease of portal microcirculation as nodular regenerative hyperplasia |

- **Clinical consequence of portal hypertension:**
  i. **Ascitis**
  ii. **Portosystemic shunts**
  iii. **Hepatic encephalopathy**
  iv. **Splenomegaly**

## Ascitis

**-Collection of excess fluid in peritoneal cavity**

**-It becomes clinically detectable when at least 500 ml have accumulated**

**-Features:**

**1-Serous fluid**

**2-Contains as much as 3g/ml of protein (albumin)**

**3-It has the same concentration as blood of glucose, Na+ , & K+**

**4-Mesothelial cells & lymphocytes**

**5-Neutrophils = infection**

**6-RBCs = DISSEMINATED CANCER**

**-Pathogenesis:**

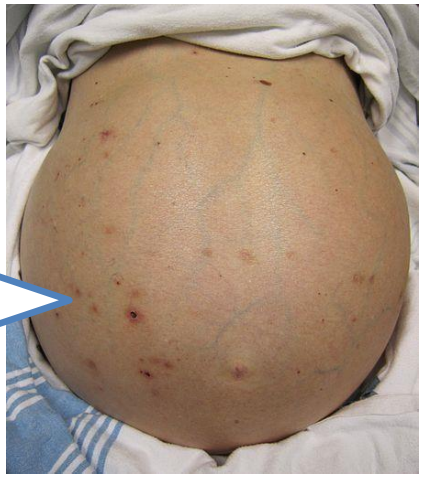
**1-Sinusoidal Bp increases**

**2-Hypoalbuminemia**

**3-Leakage of hepatic lymph into the peritoneal cavity. Normal thoracic duct lymph flow is 800- 1000 ml/d in cirrhosis is 20L /d**

**4-Renal retention of Na+ & water due to secondary hyperaldosteronism**

Ascites



## Portosystemic shunts

**-Because of ↑portal venous pressure bypasses develop wherever the systemic & portal circulation share capillary beds**

**-Sites:**

**1-Around & within the rectum (Hemorrhoids)**

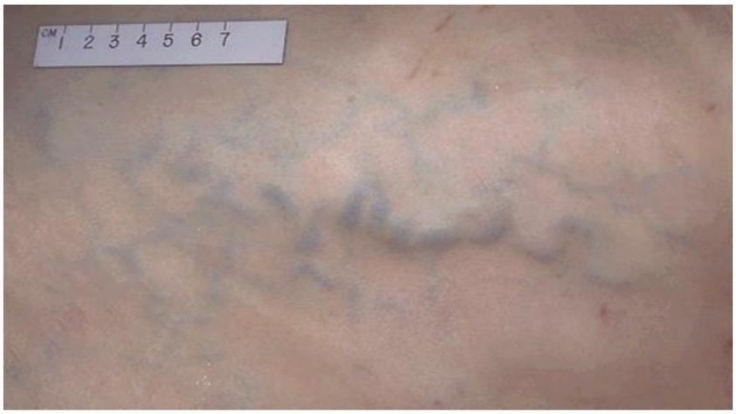
**2-Gastroesophageal junction (varicies)**

**3-Retroperitoneum (where bleeding is rare)**

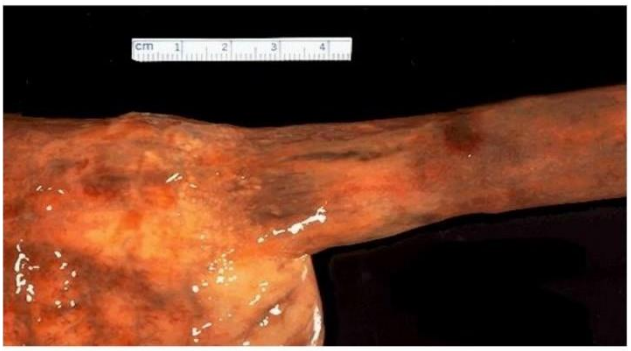
**4-Falciform ligament of the liver (periumbilical & abdominal wall collaterals ) → caput medusae**

**-Gastroesophageal varicies appear in 65% of pts. with advanced cirrhosis & cause death in 50% of then due to UG1 bleeding**

**caput medusae**



Esophageal varicies



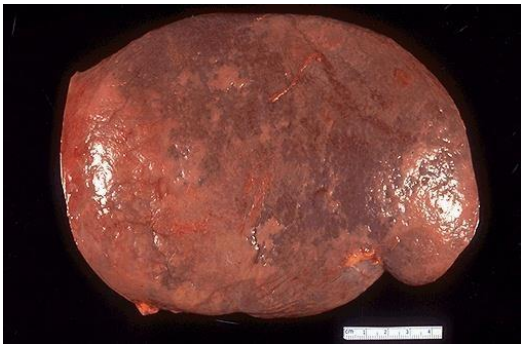
## Splenomegaly

**- Spleen weight can reach 500-1000 grams (Normal spleen <300gms)**

**-Not necessarily correlated with other features of portal increase in blood pressure**

**-May result in hypersplenism**

This spleen is distended with blood, it is engorged, large and extended →



**Hepatic encephalopathy: it's a neurological deficit due a liver problem**

**It is a complication of acute & chronic hepatic failure**

**-Disturbance in brain function ranging from behavioral changes to marked confusion & sutpor to deep coma & death**

**-The changes may progress over hrs. or days**

When the liver fails as an acute process or in the long term, toxic substances (like ammonia) accumulate, when the levels of ammonia increase, it crosses the Blood Brain Barrier and affects the brain causing edema. Because the brain is surrounded by a bony cage (the skull), any increase in its size will result in pressure. This pressure will lead to neurological problems that can progress to coma and death.

**-Neurological signs:**

**Rigidity**

**Hyper-reflexia**

**Non – specific EEG**

**Seizures Asterixis (non-rhythmic rapid extension flexion movements of head & extremities).**

**Brain shows edema & astrocytic reaction.**

**Pathogenesis:**

**Physiologic factors important in development of hepatic encephalopathy :**

**1-Severe loss of hepatocellular function**

**2-Shunting of blood around damaged liver**

**↓↓**

**Exposure of Brain to toxic metabolic products**

**-Acute insult :↑ NH3 level in blood → generalized brain edema impaired neuronal function**

**-Chronic insult: alteration in central nervous system AA metabolism**

Note: patients with cirrhosis can develop secondary renal failure and that's called HepatoRenal Syndrome.

In this case, the patients' kidneys are normal (not exposed to the same toxins as the liver), but they fail secondarily to liver failure.

If the failure of liver is managed or corrected, the renal failure can be reversible, because they weren't diseased in the first place.

**Hepatorenal syndrome:**

- **Appears in individuals with severe liver disease.**
- **Consists of the development of renal failure without primary abnormalities of the kidneys themselves.**
- **Excluded by this definition are concomitant damage to both liver and kidney, as may occur with exposure to CCL4 and certain mycotoxins and the copper toxicity of Wilson disease.**
- **Also excluded are instances of advanced hepatic failure in which circulatory collapse leads to acute tubular necrosis & acute renal failure.**
- **Kidney function promptly improves if hepatic failure is reversed.**
- **The exact cause is unknown.**
- **systemic vasoconstriction leading to severe reduction of renal blood flow particularly to the cortex.**
- **Onset of this syndrome is typically by a drop in urine output associated with rising BUN and creatinine values.**
- **The renal failure may increase the risk of death in the patient with acute fulminant or advanced chronic hepatic disease.**

# 3) DRUG – INDUCED LIVER DISEASE

- **Drug reactions:**

**1-Predictable (intrinsic) outcome**

Predictable because we predict that all drugs can cause liver injury on the long term. (dose-dependent)

**2-Unpredictable (idiosyncratic) outcome**

They can cause liver injury from the first exposure, so they are dose-independent.

- **Predictable drug reactions may occur in anyone who accumulates a sufficient dose (dose-dependent).**
- **Unpredictable reactions depend on idiosyncrasies of the host:**

**1-the host's propensity to mount an immune response to the antigenic stimulus.**

**2-the rate at which the host metabolizes the agent.**

- **The injury may be immediate or take weeks to months to develop.**
- ***drug-induced chronic hepatitis is clinically and histologically indistinguishable from chronic viral hepatitis or autoimmune hepatitis and hence serologic markers of viral infection are critical for making the distinction.***

Drug injury can mimic that of any other disease, particularly viral hepatitis and autoimmune hepatitis. It's important to know the underlying cause of injury, why?

For the treatment

If the drug was the cause, we can stop it & replace it with another drug.

If it was viral hepatitis, we have to treat it by antivirals.

If it was autoimmune, we have to treat it with immune suppressors.

- **Examples :**

  **Predictable drugs:**

  **Acetaminophen (paracetamol precursor)**

  **Tetracycline**

  **Antineoplastic agents**

  **CCL4**

  **Alcohol**

  **Unpredictable drugs:**

  **Chlorpromazine**

  **Halothane**

  **Sulfonamides**

  **Methyldopa**

  **Allopurinol**

- **Mechanism of drug injury :**

**1-Direct toxic damage**

**e.g : acetaminophen, CCl4, mushroom toxins**

Drugs are chemicals, they can cause direct injury to the cell (affecting membranes for example)

**2-Immune-mediated damage**

Drug molecules can sometimes bind to antigens on cell surfaces changing these antigens to foreign antigens, causing an immune response to them and therefor cell damage.

- **Patterns of injury:**

Any sort of liver injury can be induced by drugs

**1-Hepatocellular necrosis**

**2-Cholestasis**

**3-Steatosis (fatty infiltration)**

**4-Steatohepatitis**

## 5-Fibrosis

## 6-Vascular lesions

## 7-Granuloma

## 8-Neoplasms benign & malignant

This table shows us examples of liver pathology and the drugs that can cause them.

We have to memorize them 🔶

| Pattern of Injury | Morphology | Examples |
|---|---|---|
| Cholestatic | Bland hepatocellular cholestasis, without inflammation | Contraceptive and anabolic steroids |
| Cholestatic hepatitis | Cholestasis with lobular necroinflammatory activity | antibiotics; phenothiazines |
| Hepatocellular necrosis | Spotty hepatocyte necrosis | Methyldoya, phenytoin |
| | massive necrosis | Acetaminophen, halothane |
| | chronic hepatitis | Isoniazid |
| Steatosis | Macrovesicular | Ethanol, methotrexate, corticosteroids, total parenteralnutrition |

| | | |
|---|---|---|
| Steatohepatitis | Microvesicular Mallory bodies | Amiodarone, ethanol |
| Fibrosis and cirrhosis | Periportal and pericellular fibrosis | Methotrexate, isoniazid enalapril |
| Granulomas | non-caseating | Sulfonamides |
| Vascular lesions | Sinusoidal obstruction syndrome (veno-occlusivedisease) | High-dose chemotherapy bush teas |
| | Budd-Chiari syndrome | Oral contraceptives(OCP) |
| | Sinusoidal dilatation | Oral contraceptives (OCP) |
| | Peliosis hepatis (blood-filled cavities) | Anabolic steroids tamoxifen |

- Neoplasms

| | |
|---|---|
| Hepatic adenoma | OCP |
| | anabolic steroids |
| HCC | Thorotrast |
| Cholangiocarcinoma | Thorotrast |
| Angiosarcoma | Thorotrast, |
| | vinyl chloride |

- **The most common cause (46% of cases of acute liver failure) is acetaminophen intoxication.**
- **about 60% of these are a consequence of accidental overdosage.**

- **Drugs that may cause acute liver failure:**

**1-acetaminophen (most common)**

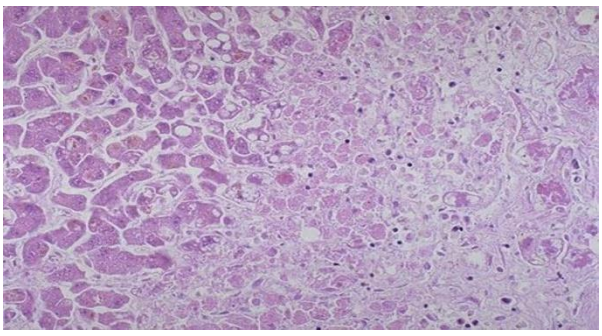
**2-Halothane**

**3-antituberculosis drugs (rifampin, isoniazid)**

**4-antidepressant monoamine oxidase inhibitors**

**5-toxins as CCL4 & mushroom poisoning**

- **Morphology:**



**Massive necrosis → 500 – 700 gm liver**

**Submassive necrosis**

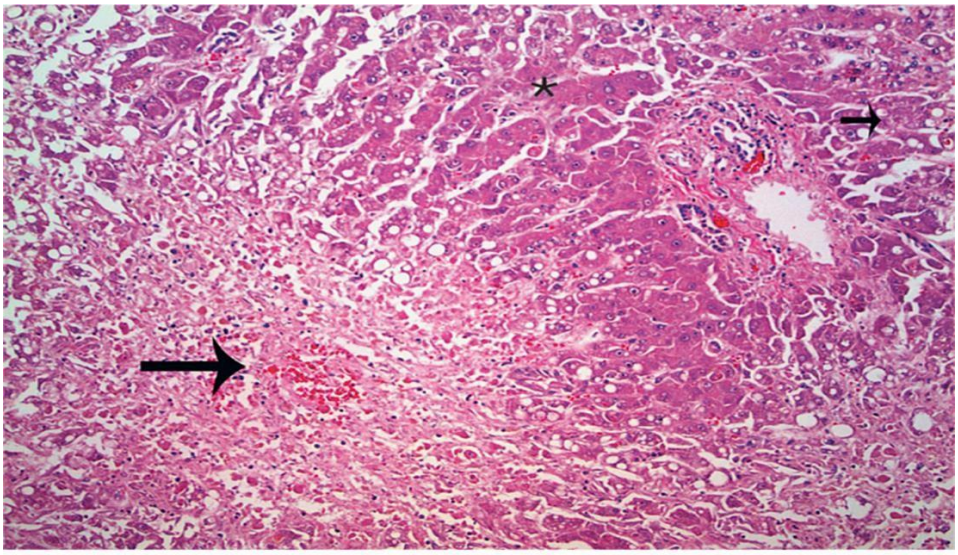
**Patchy necrosis**

As you can see in the area on the right side, the cells are pale & undefined compared to the parenchyma, hepatocytes and sinusoids on the left.

Regeneration, failure & the outcome of the failure depends on the degree of necrosis.

- **Patient survival for more than a week permits regeneration of surviving hepatocytes.**
- **Regeneration is initially in the form of strings of ductular structures which mature into hepatocytes.**
- **If the parenchymal framework is preserved liver architecture is restored.**
- **With massive destruction of lobules leads to formation of nodular masses of liver cells.**
- **Scarring may occur in patients with a protracted course of submassive or patchy necrosis representing a route for developing so-called macronodular cirrhosis**

- **Hepatocellular necrosis caused by acetaminophen overdose. Confluent necrosis is seen in the perivenular region (zone 3 ;*large arrow* .)There is little inflammation. The residual normal tissue is indicated by the *asterisk***



# V2 page 12- the table

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| Hepatocellular necrosis | Spotty hepatocyte necrosis | Methyldoya, phenytoin |
| | Submassive necrosis, zone 3 | Acetaminophen, halothane |
| | Massive necrosis | Isoniazid, phenytoin |
| Steatosis | Macrovesicular | Ethanol, methotrexate, corticosteroids, total parenteralnutrition |

- Hepatocellular necrosis — Spotty hepatocyte necrosis — Methyldoya, phenytoin
- [redacted]massive necrosis, [redacted] — Acetaminophen, halothane
- chronic hepatitis [redacted]necrosis — Isoniazid, [redacted]