GIS 11

PATHOLOGY

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Hepatic encephalopathy

- It is a decline in brain function, which occurs as a result of severe liver disease.
- In this condition, the liver is unable adequately remove toxins from the blood.
- This causes a buildup of toxins in your bloodstream, which can lead to brain damage.

✓ It is a complication of acute & chronic hepatic failure
✓ Disturbance in brain function, ranging from: Behavioural changes to marked confusion & sutpor to deep coma & death
✓ The changes may progress over **hours**, **days**, **weeks** or **months** after acute injury
✓ It's a terminal stage of portal hypertension and may lead to the death of the patient.

❖ Neurological signs:

- ✓ Rigidity
- ✓ Hyper-reflexia
- ✓ Non – specific EEG
- ✓ Seizures
- ✓ Asterixis (Non-rhythmic, rapid extension-flexision movements of the head & extremities) .
- ✓ Brain shows edema & astrocytic reaction.

❖ Pathogenesis:

Physiologic factors that are important in the development of hepatic encephalopathy:

1- Severe loss of hepatocellular function
2- Shunting of blood around the damaged liver

→ **↑ NH3 level and other toxic material in the blood** →Exposure of the Brain to toxic metabolic products → Leads to generalized **brain edema**, **and impaired neuronal function** alteration in *central nervous system AA metabolism.*

Drug – Induced liver disease

- The liver is directly associated and connected to the drugs taken, since most drugs are metabolized in the liver itself → **They could cause damage to the liver**

❖ Drug reactions:

1- Predictable (**intrinsic**)
2- Unpredictable (**idiosyncratic**)

- **Predictable drug reactions**: Affects individuals in a (**dose-dependent**) fashion.
- **Unpredictable drug reactions:** Does not depend on the dose (**Dose-independent**), but depends on *idiosyncrasies* of the host:

1. The **immune response** of the host to the antigenic stimulus -*the drug*-
2. The **rate** at which the host metabolizes the agent

- **Both classes** of injury could either be immediate or could take weeks-months to develop.

Note: Drug-induced chronic hepatitis is clinically & histologically **indistinguishable** from **chronic viral** and **autoimmune hepatitis.**

❖ Drugs that affect the liver:

Predictable drugs (intrinsic):

1. **Acetaminophen**: -used in suicide attempts- (*The toxic agent is not Acetaminophen itself but rather toxic metabolite produced by cyt-p450 system)*
2. **Tetracycline**.
3. **Antineoplastic agents**.
4. **CCL4**.
5. **Alcohol**.

Unpredictable drugs (idiosyncratic):

1. **Chlorpromazine** → **Slow metabolizers** that cause cholestasis.
2. **Halothane** → **Immune mediated** hepatitis after repeated exposure.
3. **Sulfonamides.**
4. **Methyldopa**.

❖ Mechanism of drug injury:

- **Direct toxic damage** **e.g** acetaminophen, CCl4, mushroom toxins
- **Immune-mediated damage**: By a drug or metabolite acting as **Hapten**, to convert a cellular protein into an immunogen.

Further explanation: drugs are known to cause antigenic changes. Certain drugs -**called Haptens-** can attach themselves to a protein present on the surface of a cell, changing the antigenicity of the cell itself→This will stimulate the immune response, which will attack the hepatocytes→causing their damage.

❖ Patterns of drug injury:

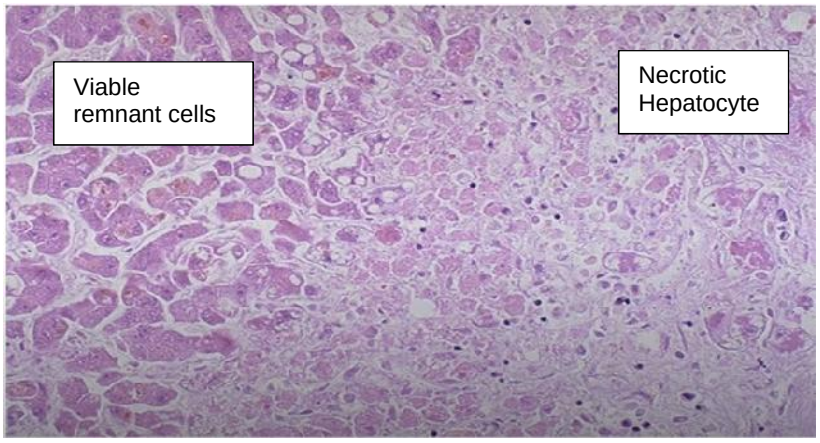
1- Hepatocellular necrosis
2- Cholestasis
3- Steatosis
4- Steatohepatitis
5- Fibrosis
6- Vascular lesions
7- Granuloma
8- Neoplasms benign & malignant

❖ Drugs that may cause acute liver failure:

1- Acetaminophen ***most common and can be used in suicidal attempts***
2- Halothane
3- Anti-tuberculosis drugs (**rifampin, isoniazid**)
4- Antidepressants: **Monoamine oxidase inhibitors**
5- Toxins: **CCL4 & mushroom poisoning**

❖ Morphology:

- Massive necrosis → 500 – 700 gm liver
- Submassive necrosis
- Patchy necrosis



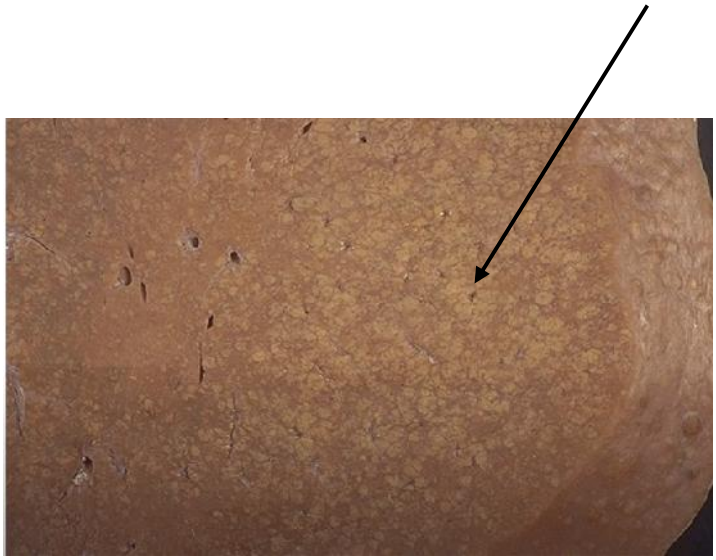
*Microscopic appearance of the **liver with necrosis** (**The right sided hepatocytes**: Necrotic hepatocytes. **The Left sided hepatocytes**: Remnant viable hepatocytes)*

Fulminant hepatitis:

- **Hepatic insufficiency** that progresses from onset of symptoms to hepatic encephalopathy in 2-3 weeks.
- Subfulminant (up to 3 months)

Causes :

1- Viral hepatitis (50 – 65% of cases) **(HBV 2x > HCV) Hepatitis B and C.**
2- Drays & chemical (25- 50%) **e.g**: **Isoniazid , halothane , methyldopa & acetominophen**
3- Obstruction of hepatic vein
4- Wilson's disease
5- Acute fatty change of pregnancy.
6- Massive tumor infiltration
7- Reactivation of chronic hepatitis B
8- Acute immune hepatitis



***Gross appearance** of **fulminant hepatitis;** the **pale yellowish areas** are sites of necrosis.* If you look at the image, notice the small size of the liver. This decrease in size indicates that it it necrotic, **which is the main feature of fulminant hepatitis.**

- Morphology
  - ↓ liver size (500 – 700 gm) ***main feature***
  - Necrosis of hepatocytes
  - Collapsed reticulin tissue
  - Inflammatory infillrate
  - Regenerative activity of hepatocytes -Fibrosis

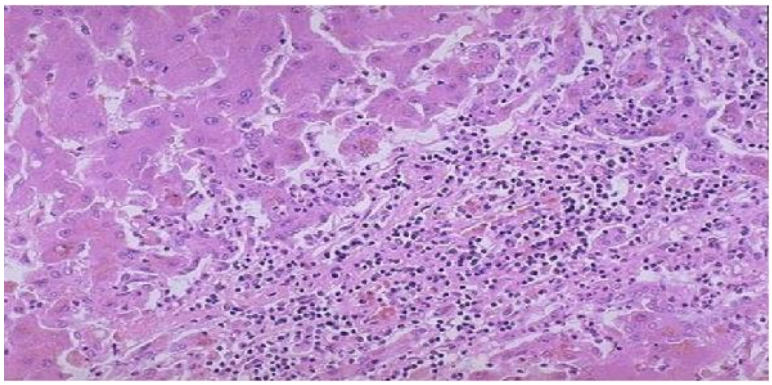
Chronic Hepatitis:

- ✓ Symptomatic, biochemical or serelogic evidence of continuing or relapsing hepatic disease for **more than 6 months**, with histologically documented ***inflammation*** & ***necrosis***.
- ✓ It can be Progressive or non progressive commonly it's caused by HBV, HCV or HBV-HDV (co-infection).

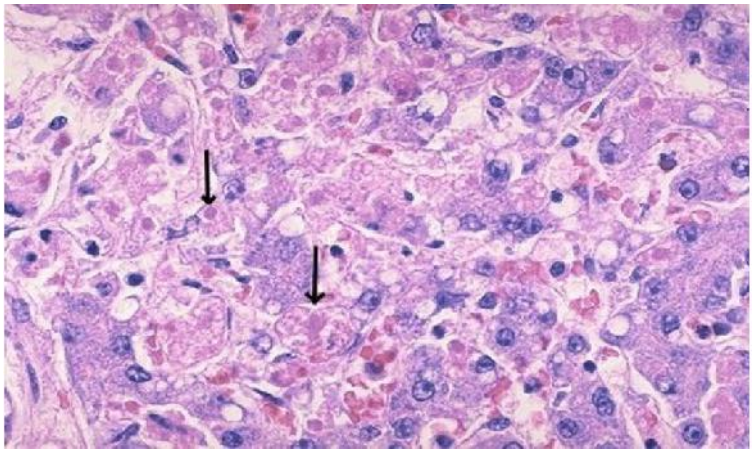
Morphology of chronic hepatitis:

Mild to severe

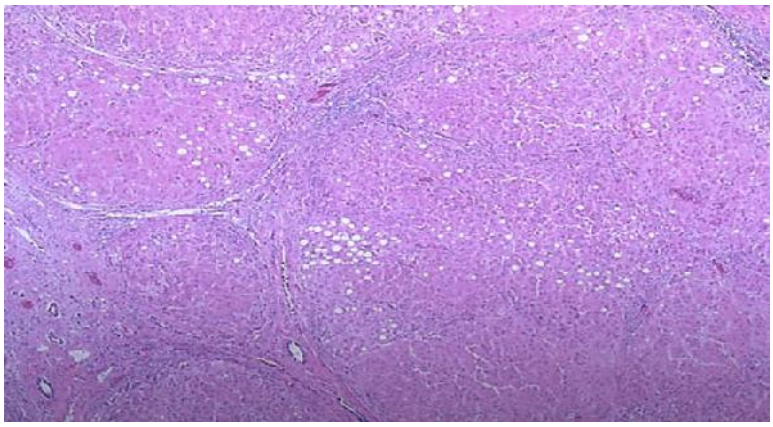
1. Portal inflammation
2. Lymphoid aggregate
3. Necrosis of hepatocytes-councilman bodies
4. Bile duct damage
5. Steatosis
6. Interface hepatitis
7. Bridging necrosis & fibrosis
8. Fibrosis
9. Ground-glass appearance
10. Sanded nuclei
11. Lobular disarray



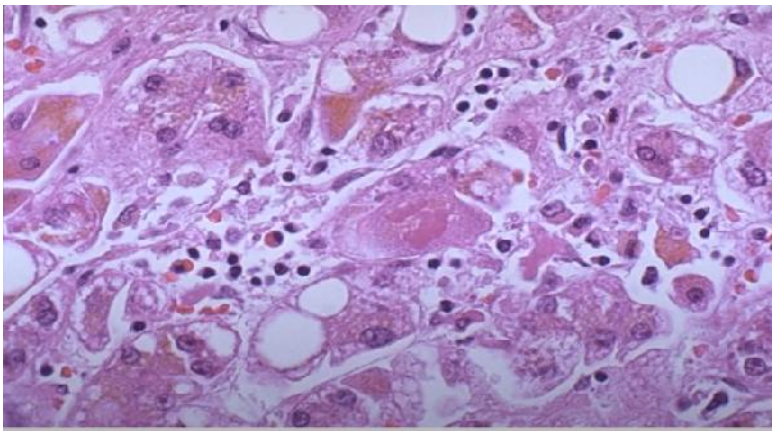
This section shows **chronic hepatitis** features (**inflammatory cell** infiltrate within the parenchyma, with prominent **background fibrosis**)



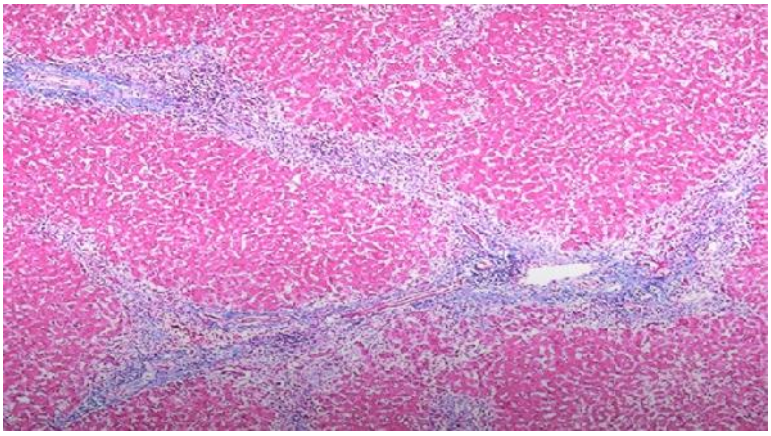
This microscopic image shows scattered necrotic hepatocytes. The arrows are pointing to the **council's bodies** which are **eosinophilic** small **necrotic hepatocytes** with dark nucleus, and are scattered amongst healthy hepatocytes. ***This is an indication of a previous chronic injury***



Chronic hepatitis is characterized by the ***presence of fibrosis***. Here, **bridging fibrosis** is separating the **parenchyma into islands of hepatocytes**, with the presence of **-fatty change** and **inflammatory cells infiltration.**



Higher magnification of the parenchyma with **chronic hepatitis.**



This is a special stain used to visualize **fibrous tissue (Blue)** ***Notice the blue-stained bridging fibrosis*** the fibrous tissue has started to form **nodules** separating the pinkish hepatocytes.

❖ Carrier state of hepatitis has 3 scenarios:

1. Serelogical evidence of viral infection, but **no clinical** or **histological** effects
2. Serelogical evidence of viral infection, chronic liver disease, but **no clinical symptoms**
3. Clinically symptomatic chronic disease

- **Causes of carrier state:**
  1. **Vertical transmission** →**90 – 95%** of carrier state
  2. **Immune deficiency**: Increases the risk of **development of carrier state.**
  3. HBV, HCV, and **possibly** HDV.

Best of luck..