GI

Pathology

LEC no.

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CLINICAL SYNDROMES

- The major clinical syndromes of liver disease are:
- 1-hepatic failure
- 2-cirrhosis
- 3-portal hypertension
- 4-cholestasis.

Hepatic Failure

-It results when the hepatic functional capacity is almost totally lost (80 – 90%)

-Causes

1.Massive hepatic necrosis

-Fulminant viral hepatitis

-Drugs & chemicals

acetominophen
halothane
anti TB drugs
CCL4 poisoning
Mushroom poisoning

2-Chronic liver disease

3-Hepatic dysfunction without overt cirrhosis

- **Reye’s syndrome**
- **Tetracyline toxicity**
- **Acute fatty liver of pregnancy**

1-Acute liver failure.

- **This is most often caused by drugs (**acetaminophen, halothane, anti TB drugs, CCL4 poisoning, and mushroom poisoning**) or fulminant viral hepatitis.**
- **Acute liver failure denotes clinical hepatic insufficiency that progresses from onset of symptoms to hepatic encephalopathy within 2 to 3 weeks.**
- **A course extending as long as 3 months is called subacute failure.**

- If the patient born with hepatic failure the cause maybe due to viral hepatitis , if not… it could be due to drugs .

-It is possible that the mother may have had a viral hepatitis infection during pregnancy, which could have been transmitted to the baby.

- Excluding the 2 aforementioned causes, other potential reasons for hepatic failure include hepatic vein obstruction and metabolic disorders such as Wilson disease -which can lead to liver failure- and acute fatty liver of pregnancy (AFLP) , maybe also due to extensive infiltration of the liver by malignant cells cause destruction of hepatocytes and fibrosis .

-In cases of viral hepatitis, particularly hepatitis D (HDV) superimposed on hepatitis B (HBV), there is a heightened risk of severe hepatitis development. This risk is particularly marked in individuals already infected with HBV, as acquiring HDV infection can lead to a more severe form of hepatitis characterized by necrosis and potential liver failure.

- Carrier for HBV won't have symptoms and the liver is normal , once affected with HDV they would develop the liver failure.
- Autoimmune hepatitis can mimic viral hepatitis and induce liver failure due to hepatic necrosis (not common).

- HDV infection only occurs in people who are already infected with HBV.

- Superimposed hepatitis refers to the simultaneous infection of an individual with more than one type of hepatitis virus, most commonly hepatitis D virus (HDV) superimposed on hepatitis B virus (HBV) infection.

- This condition is significant because it can lead to more severe liver damage than infection with a single virus.

- **The histologic correlate of acute liver failure is massive hepatic necrosis.**
- **It is an uncommon but life-threatening condition that often requires liver transplantation.**

2-Chronic liver disease

- **This is the most common route to hepatic failure and is the end point of relentless chronic liver damage ending in cirrhosis.**

3-Hepatic dysfunction without overt necrosis.

- Hepatocytes may be viable but unable to perform normal metabolic function:
- 1- acute fatty liver of pregnancy (which can lead to acute liver failure a few days after onset)
- 2- tetracycline toxicity
- 3- Reye syndrome

Clinical features

1-Jaundice
2-Hypoalbuminemia → edema
3-Hyperammonemia
4-Fetor hepaticus (musty or sweet & sour)
5-Palmar erythema hyperestrogenemia
6-Spider angiomas
7-Hypogonadism & gynecomastia

Consequences:

1-Multiple organ failure kidneys & lung

2-Coagulopathy → bleeding

def. factors II, VII, IX, X

3-Hepatic encephalopathy

↓level of conseiousness

Rigidity

Hyperreflexia

EEG changes

Seizures

Asterixis

4-Hepatorenal syndrome

Renal failure in patients with severe liver disease with no morphologic or functional causes for renal failure

Massive hepatic necrosis

-Fulminant hepatic failure from the onset of symptoms to hepatic encephalopathy (within 2 -3 wks).
Subfulminant (within 3 months).

Causes:

1-Viral hepatitis 50 – 65% (B, B-D, A,C hepatitis)
2-Drugs & chemicals 20 – 30%
3-Heat stroke
4-Hepatic vein obstruction
5-Wilson disease
6-Acute fatty liver of pregnancy
7-Massive malignant infiltration
8-Reactivation of chronic HBV hepatitis on HDV superimposed infection
9-Autoimmune hepatitis

Alcoholic liver disease

Alcohol is a toxic substance that affect the liver and cause injury.

-Alcohol is most widely abused agent

-It is the 5th leading cause of death in USA due to :

1.accidents

2.Cirrhosis

-80 – 100 mg/dl is the legal definition for driving under the influence of alcohol

-44 ml of ethanol is required to produce this level in 70kg person

-Short term ingestion of 80 gms/d of ethanol is associated with fatty change in liver

Excessive ethanol consumption causes more than revil cinorhc fo 60%disease.

- BAC (blood alcohol concentration) >> 80-100 mg/dl is high level of alcohol, below this level would be a minimal effect .

-16In occasional drinkers, bl. Level of 200 mg/dl produces coma & death & resp. failure at 300-400 mg/dl

-Habitual drinkers can tolerate levels up to 700 mg/dl without clinical effect due to metabolic tolerance explained by 5-10X induction of cytochrome P-450 system that includes enzyme CYP2E1 which increases the metabolism of ethanol as well as other drugs as cocaine & acetaminophen

- **The consumption of alcohol and ethanol in quantities leading to an elevation of Blood Alcohol Concentration (BAC) is associated with increased risk of injury. This elevation in BAC correlates with elevated levels of triglycerides, lactic acid, and liver enzymes.**

- Affection and toxicity in the liver by ethanol is determined by the duration and the amount of daily uptake.

- Exposure to ethanol is associated with fatty changes in liver.

- There is a variation between occasional drinkers and habitual drinkers.

- The other determinant of the outcome of exposure to ethanol is the enzymes responsible for metabolism of ethanol mainly cytochrome P450 system .

- Activation of these enzymes will affect the track dosage in patients who use some drugs , they may need to adjust the doses in order to get the benefit of those drugs .

Forms of alcoholic liver disease

1-Hepatic steatosis (90-100% of drinkers)

2-Alcoholic hepatitis (1- 35% of drinkers)

3-Cirrhosis (14% of drinkers)

-Steatosis & hepatitis may develop independently

- Hepatic steatosis occurs almost in all alcoholic drinkers.
- -Cirrhosis is the outcome of chronic uptake of alcohol.
- Steatosis or fatty change occurs even in moderate uptake of alcohol
- However, the severity of fatty infiltration is related to the duration of the uptake.

Hepatic steatosis

-Can occur following even moderate intake of alcohol in form of microvesicular steatosis

-Chronic intake → diffuse steatosis

-Liver is large (4 – 6 kg) soft yellow & greasy

-Continued intake →fibrosis

-Fatty change is reversible with complete abstention from further intake of alcohol

- Initially the uptake of alcohol will cause fatty change, this could be reversible when the patient completely stop the uptake of alcohol and the liver would back to normal state .

- If the patient continue the uptake of alcohol it would progress to irreversible and develop fibrosis .

- Remember that each type of these injuries present or develop by its own so these aren’t stages of the development in injury.

Alcoholic hepatitis

- This is more sever than fatty change.
- There will be inflammatory components and necrosis due to the injury of hepatocytes

Characteristic findings : >> Bilestasis

1 Hepatocyte swelling & necrosis

-Accumulation of fat & water & proteins

-Cholestasis

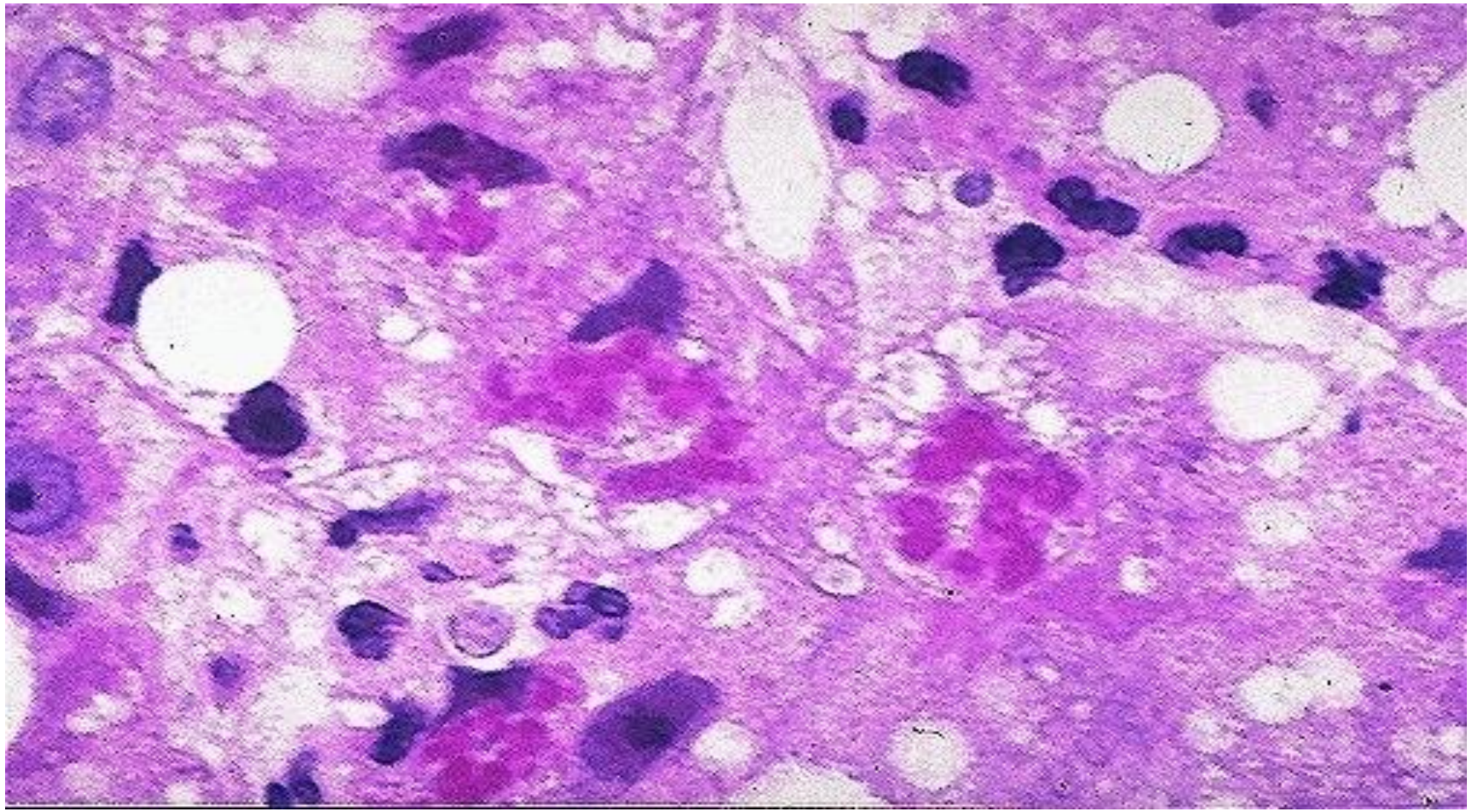
-Hemosiderin deposition in hepatocytocytes & kupffer cells

2 Mallory-hayline bodies

-eosinoplilic cytoplasmic inclusions in degenerating hepatocytes made of keratin intermediate filaments & other proteins

- Ethanol is toxic and cause injury so in Mallory hyaline bodies there will be a collapsing of proteins and accumulation in cytoplasm.
- Cholestasis is a condition in which the flow of bile from the liver is impaired. When bile flow is obstructed or diminished, it can lead to a buildup of bile acids in the liver and bloodstream.

Mallory-hayline bodies



- We have fatty change .
- Cytoplasm is large and eosinophilic .

- Pathognomonic mean a special symptom refer to a special disorder.

-Mallory-hayline inclusions are characteristic but not pathognomonic of alcoholic liver disease, they are also seen in :

1-Primary biliary cirrhosis

2-Wilson disease >> Patients are young in age

3-Chronic cholestatic syndromes >> young in age

4-Hepatocellular carcinoma >> due to cirrhosis

Characteristic findings : (Alcoholic hepatitis)

3-Neutrophilic reaction

4-Fibrosis **(step forward to irreversiblity)**

-Sinusoidal & perivenular fibrosis

-Periportal fibrosis

5 Cholestasis **>> accumulation of bile salts in hepatocytes**

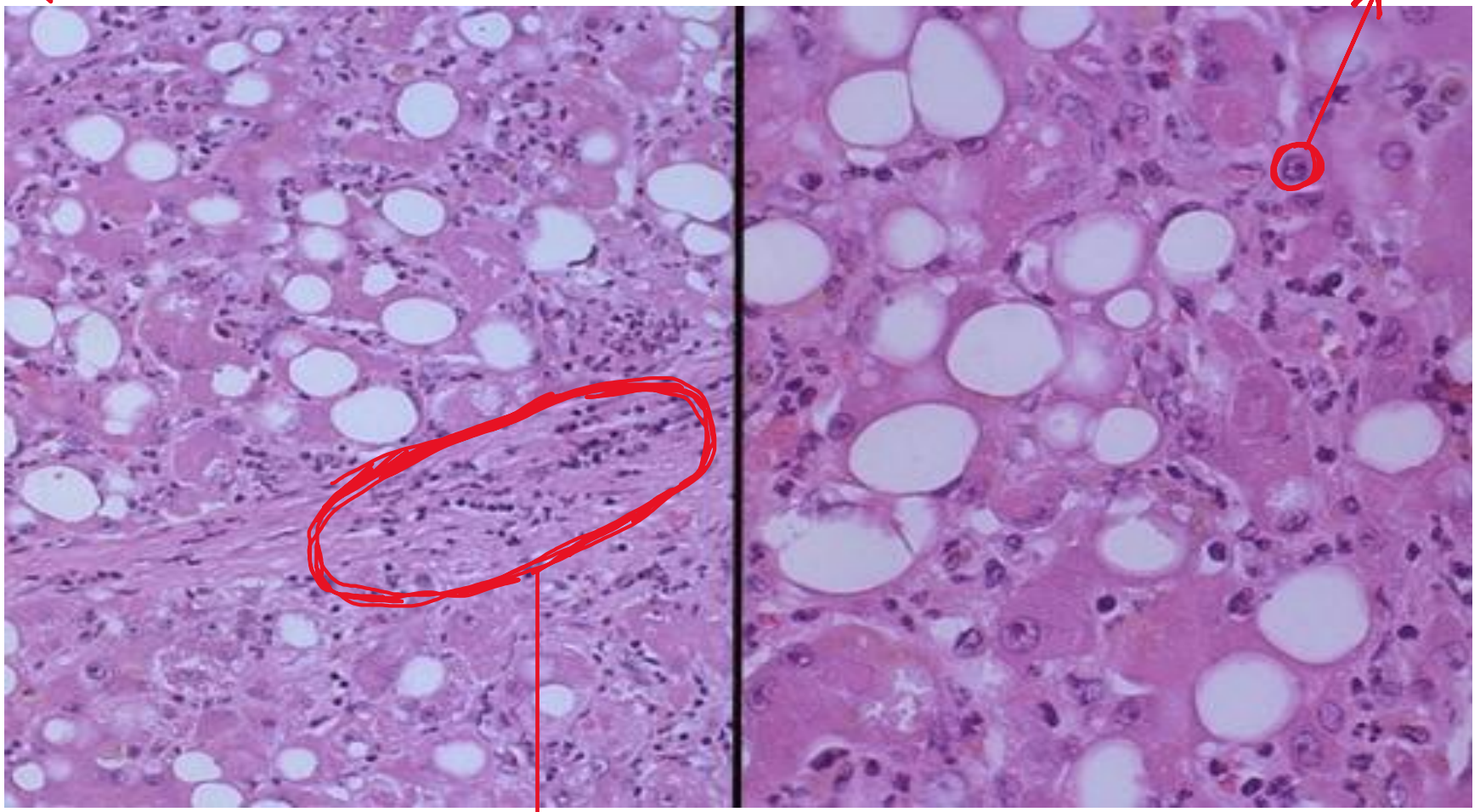
6 Mild deposition of hemosiderin in hepatocytes & kupffer cells

- **Mallory hyaline bodies + fatty infiltration + inflammation + fibrosis >>> we should think firstly of alcoholic hepatitis.**

Alcoholic hepatitis

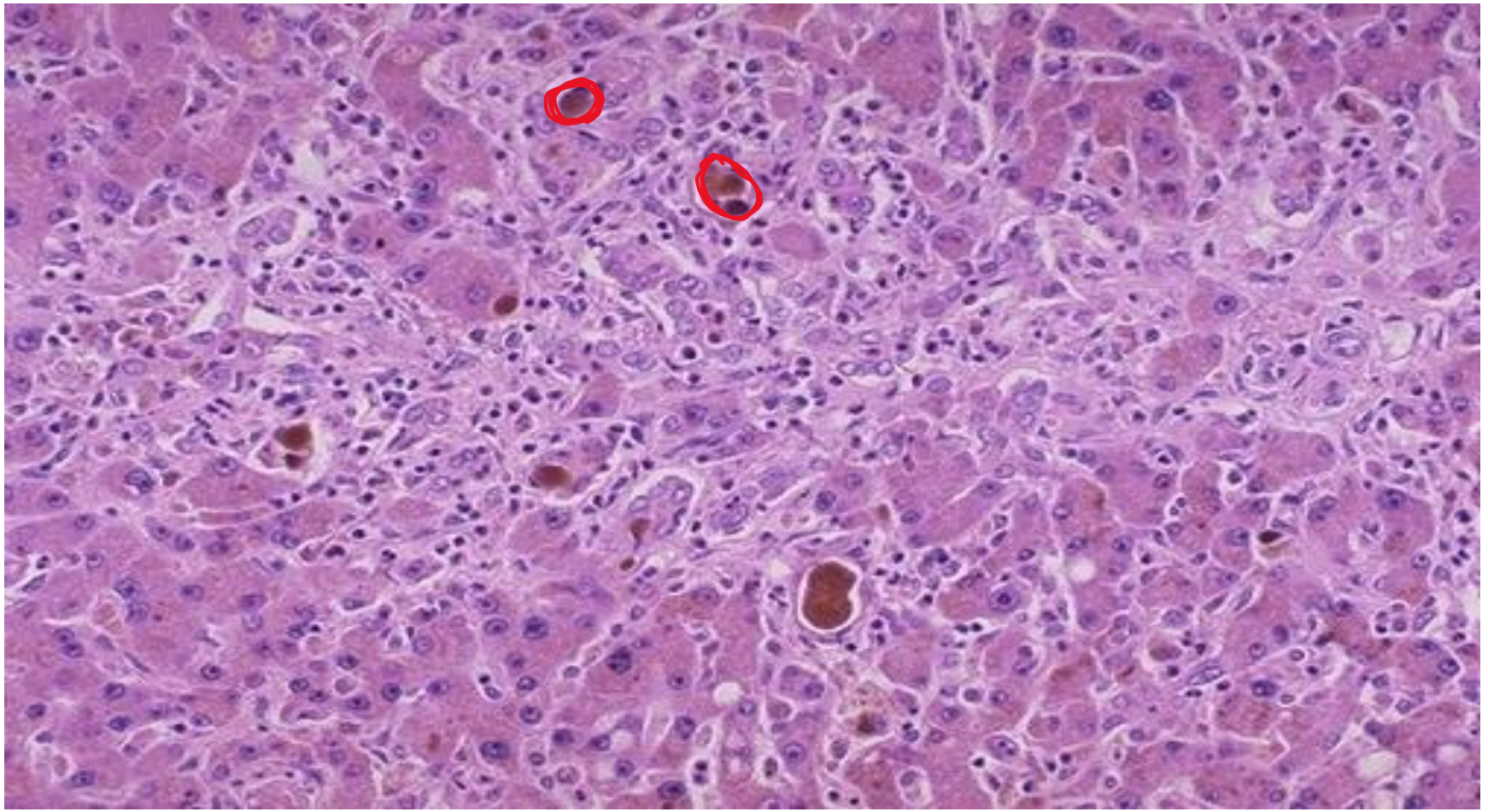
Fatty change

Lymphocytes



Fibrous tissue duo to fibrosis so this is chronic ,(normal liver doesn't have fibrosis) .

Cholestasis



- **Bile salts and hemosiderin are both brown in color .**

- **We can differentiate between them by Staining .**

- **Hemosiderin >> Stains blue with Prussian Blue stain, indicating the presence of iron.**

- **Bile Salts >> Stains green with Hall's bile stain, indicating the presence of bile pigments.**

Alcoholic cirrhosis

-Usually it develops slowly(after years of alcohol consumption).

-Initially the liver is enlarged yellow but over years it becomes brown shrunken non-fatty organ

s.t < l kg in wt.

-Micronodular → mixed micro & macronodular

-Laennec cirrhosis = scar tissue

-Bile stasis

-Mallory bodies are only rarely evident at this stage(rarely evident in all condition, there is **No** comparison between cirrhosis and hepatitis)

-Irreversible

-It can develop rapidly in the presence of alcoholic hepatitis (within 1-2 yrs).

regarding alcoholic cirrhosis, its development and progression are indeed closely tied to time. As individuals continue to consume alcohol excessively over an extended period(years of uptake), the damage to the liver accumulates, eventually leading to cirrhosis. The liver can become enlarged enough to be palpable below the costal margin during a physical examination.

In alcoholic cirrhosis, the liver undergoes significant changes, including the development of nodules within the liver tissue. And these nodules will be small in size , they are referred to as micronodular cirrhosis and it can be mixed(micronodular and macronodular) later on.

Sometimes during over uptake of alcohol, fibrous tissue replaces the liver tissue . As the fibrous tissue continues to accumulate, it can lead to the loss of liver parenchyma and the transformation of the liver into a nodular, scarred organ which is known as Laennec cirrhosis .

-patient will have bile stasis and Malloy bodies .

-remember all these changes particularly fibrosis ,are irreversible .

-Each type of hepatitis is associated with increased risk of cirrhosis .

Liver cirrhosis

This figure to show you the gross appearance of liver which is fibrotic. the surface is irregular , it is replaced by nodules (small in size so it is called micronodular cirrhosis)

Ethanol metabolism

Ethanol → acetaldehyde

CH_3CH_2OH $CH_3C(=O)H$

↑

-Alcohol dehydrogenase

(stomach + liver)

-Cytochrome P-450

-Catalase (liver)

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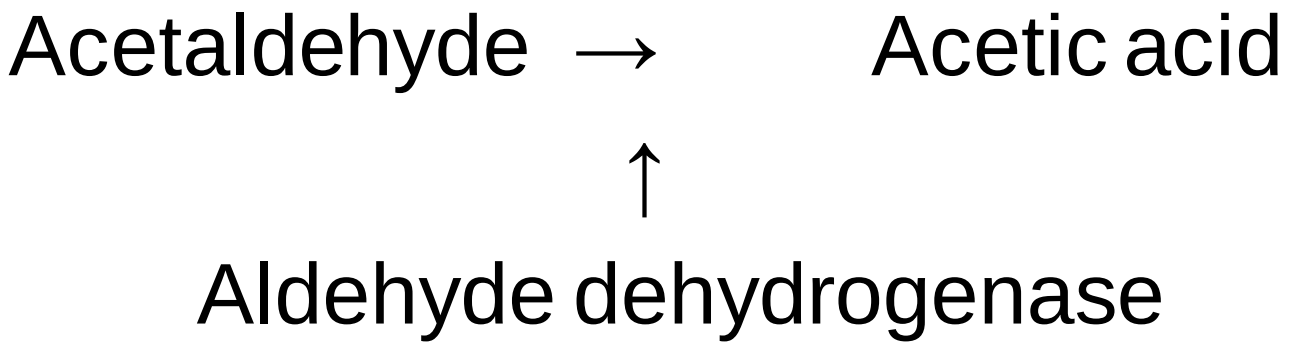

Alcohol is introduced in our body as ethanol, and by the action of different enzymes (the most important is alcohol dehydrogenase which is present in the liver and stomach) ,it metabolized into acetaldehyde. Then, by the action of aldehyde dehydrogenase, it metabolized into acetic acid .
Acetic acid is the form that is distributed in different organs and excreted in all body fluid .

After absorption ethanol is distributed as **Acetic acid** in all tissues & fluid in direct proportion to blood level acetic acid is present in all tissues and fluid in a concentration related to the concentration of the blood.

Women have lower levels of gastric alcohol dehydrogenase activity than men & they may develop higher blood Levels than men after drinking the same quantity of ethanol. women will develop more severe manifestation due to toxicity

- Less than 10% of absorbed ethanol is excreted unchanged in urine , sweat & breathe (we can measure the concentration of ethanol through a person's breath)

-There is **genetic polymorphism** in aldehyde dehydrogenase that affect ethanol metabolism e.g 50% of chinese , vietnamase & Japanese have lowered enzyme activity due to point mutation of the enzyme → accumulation of acetaldehyde → **facial flushing (الوجه احمرار) , tachycardia & hyperventilation.**

ALDH is an enzyme responsible for breaking down acetaldehyde, a toxic byproduct of alcohol metabolism, into acetate. However, genetic variations can affect the activity of this enzyme. When individuals have lower activity of the enzyme, particularly in the cytochrome P-450 system, they retain ethanol metabolites in the bloodstream for a longer duration before they are converted into acetic acid and excreted. This prolonged presence of metabolites can lead to symptoms such as facial flushing, increased heart rate (tachycardia), and high blood pressure (hypertension).

Pathogenesis of alcoholic liver disease

-Short term ingestion of 80gm of ethanol/day (8bears) → mild reversible hepatic changes (fatty liver)
-Long term ingestion (10-20yrs) of 160gm of ethanol per day → severe hepatic injury
-50 – 60gm/day → borderline effect
-Women are more susceptible to hepatic injury due to ↓gastric metabolism of ethanol .
-Only 8 – 20% of alcoholics develop cirrhosis

-In occasional drinkers, bl. Level of 200 mg/dl, coma & death is rare.

- severe manifestations.

Mechanism of ethanol toxicity

1-Fatty change

a-Shunting of lipid catabolism toward lipid bio-synthesis due to excess production of NADH over NAD+ in cytosol & mitochondria

b-

Acetaldehyde forms adducts with tubulin & ↓ function of microtubules → ↓ in lipoprotein transport from liver (Lipoproteins are important because they act as carriers for lipids (fats) in the bloodstream to be metabolized by distant organs)

a. ↑ peripheral catabolism of fat → ↑ FFA delivery to the liver

b. ↓ secretion of lipoproteins from hepatocytes

e. ↓ oxidation of FFA by mitochondria

2-Induction of cytochrome P-450 enhances the metabolism of drugs to toxic metabolites **and free radicals which is part of inflammatory process** (e.g.; acetaminophen)

-short term ingestion of 80 grams of ethanol per day is associated with fatty change, fatty change occurs in older patients .

-over long ingestion of higher amount of ethanol for long duration is associated in development of a significant hepatic injury, women are more susceptible to have injury more than men even with taking same amount due to lower level of metabolism .

-cirrhosis will develop in about 10% to 50% of patients . Why ethanol induced liver toxicity? Because it interferes with fat metabolism (ethanol interferes with all pathways of fat metabolism due to accumulation of free fatty acids) these free fatty acids will get deposited in different organs primarily the liver

3. ↑free radicals production due to activation of cytochrome P-450 leads to membrane & protein damage

4. Alcohol directly affect microtubular & mitochondrial function & membrane fluidity (will affect microtubules and produce damage of hepatocytes and microvilli affecting their function.

5. Acetaldehyde causes lipid peroxidation & antigenic alteration of hepatocytes → immune attack (antigenicity of the cell changes, this stimulates immune cells to recognize these antigens as foreign antigens starting to attack hepatocytes.

6. Superimposed HCV infection causes acceleration of liver injury (HCV hepatitis occurs in 30% of alcoholics)

7. Alcohol → release of bacterial endotoxins into portal circulation from the gut → inflammation of the liver

   ethanol interact with the normal bacterial flora in GIT

8. Alcohol → regional **hypoxia** in the liver due to release of endothelins which are potent vasoconstrictors → ↓ hepatic sinusoidal perfusion
9. Alteration of cytokine regulation TNF is a major effector of injury IL6 IL8 IL18

Clinical features

-Hepatic steatosis (reversible)

↑ liver

↑ liver enz.

Severe hepatic dysfunction is unusual

-Alcoholic hepatitis after years of excessive drinking

- **15-20 yr. of excessive drinking**
- **Non-specific symptoms, malaise, anorexia, wt. loss** although these symptoms are not specific
- **Hepatosplenomegaly**
- ↑ **LFT** (liver function test, it is a multiple tests, bilirubin direct and indirect tests , enzymes and proteins)
- **Each bout of hepatitis →10-20% risk of death→ cirrhosis in 1/3 in few yrs.**

-Cirrhosis

Portal hypertension

Clinical presentations are related to the extent of damage, patients with a fatty infiltration can be asymptomatic or they can have a specific symptoms .
-patient can perform lab tests to measure liver enzymes particularly ***transaminases*** , transaminases synthesized by hepatocytes , an increase in serum transaminase levels indicates that there is damage in hepatocytes, In this stage (hepatic steatosis) liver is not severely damaged only there is fat infiltration.

- **Causes of death in alcoholic liver disease**

  latent period of cirrhosis

1 hepatic failure

2Massive GI bleeding

3-Infections

4-Hepatorenal syndrome

5-HCC in 3-6% of cases (Hepatocellular carcinoma, once tumor develop patient will have all effects of malignancy

"اللهمَّ قد طال أمدُ بلائهم ...
اللهمَّ أظهِر أَمْنَهم ..
وأَزِلْ كربهم ..
وفرِّج همَّهم ..
وعجِّل بنصرِهم"

قالَ اللَّهُ تَبارَكَ وتَعالَى: أنا أغْنَى الشُّرَكاءِ عَنِ الشِّرْكِ، مَن عَمِلَ عَمَلًا أشْرَكَ فيه مَعِي غيرِي، تَرَكْتُهُ وشِرْكَهُ.

الراوي : أبو هريرة | المحدث : مسلم | المصدر : صحيح مسلم

الصفحة أو الرقم: 2985 | خلاصة حكم المحدث : [صحيح]

الشِّركُ الأصغَرُ هو كلُّ ما نَهى عنه الشَّرعُ ممَّا هو ذَريعةٌ إلى الشِّركِ الأكبَرِ، ووَسيلةٌ لِلوُقوعِ فيه، وهو غيرُ مُخرِجٍ مِن مِلَّةِ الإسلامِ، ومِن أنواعِ هذا الشِّركِ: الرِّياءُ، وهو مِن صَنيعِ المنافِقين.

وفي هذا الحديثِ يُخبِرُ النَّبيُّ صلَّى اللهُ عليه وسلَّمَ أنَّ اللهَ تبارَكَ وتعالى قال: «أنا أغنى الشُّركاءِ عن الشِّرك»؛ فاللهُ تَعالى هُو الغنيُّ عن كُلِّ شيءٍ، لا نِدَّ له، ومُعطِيَ إلَّا هو، وأنَّه إذا عَمِلَ الإنسانُ عَمَلًا مِنَ الطَّاعاتِ ممَّا يَختَصُّ به اللهُ، فجَعَله للهِ ولِغيرِ اللهِ، تَرَكَه اللهُ فلم يَقبَلْه منه ولم يُعطِه ثَوابًا عليه، فلَو صلَّى الإنسانُ للهِ ولِلنَّاسِ لم يَقبَلِ اللهُ صَلاتَه؛ فاللهُ سُبحانَه وتَعالَى هو الَّذي خلَقَ الخلَقَ، وهو الَّذي يَرزُقُهم، فكيْف يُقابِلون نِعَمَه وأفضالَه عليهم بإشراكِ غيرِه معه في التَّوجُّهِ إليه بالطَّاعةِ؟! بلِ الواجبُ عليهم إخلاصُ النِّيَّةِ للهِ وإفرادُه بالعبادةِ.

فأخبَرَ اللهُ عزَّ وجلَّ أنَّه يَتبرَّأُ مِنَ العملِ الَّذي لم يُخلِصْ فيه صاحِبُه النِّيَّةَ له سُبحانَه، وشابَتْهُ شائبةُ الشِّركِ؛ فيَرُدُّه على صاحِبِه، ولا يَقبَلُه؛ لأنَّه سُبحانَه لا يَقبَلُ إلَّا ما كان خالِصًا لوَجْهِه لا رِياءَ فيه ولا سُمْعةَ تُخالِطُه.

وفي الحديثِ: أنَّ الرِّياءَ إذا دخَلَ في العِبادةِ؛ فإنَّها لا تُقبَلُ.