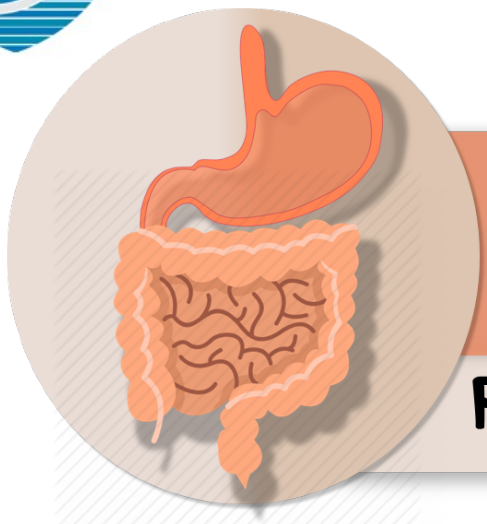


GI system

Pathology

◉Sheet ○Slide

Number:	-1
Done by:	-Ahmad Rawajbeh
Corrected by:	-Omar Eyad
Doctor:	-Maha Shomaf

Diseases of the liver are related to loss of its functions

Functions of the liver:

1-Metabolic: Glucose.

>>metabolism of different substances occurs inside the liver.

2-Synthetic: Albumin, clotting factors

>>Liver dysfunction affects synthesis of albumin which means ***edema***

Reminder: Albumin is the main plasma protein that generates the oncotic pressure back to the plasma of the blood— (osmotic pressure exerted by proteins).

3-Detoxification: Drugs, hormones, NH3.

Most of drugs are detoxified in the liver, some of them affect the liver and exhibit side effects on it.

Always, ask the patients about their history regarding drugs.

4-Storage: Glycogen, TG—Triacylglycerides(fat), Fe, Cu, vitamins.

5-Excretory: Bile *(containing bilirubin from the metabolism of the hemoglobin).*

Features of the liver

- Normal weight of the liver is about 1.5 kg (2.5% of body weight).

>>increase in the weight of the liver is associated with many diseases.

- Blood supply of the liver:

1-Portal vein: 60 - 70%
2-Hepatic artery: 30- 40%

Blood coming from the portal vein is not oxygenated but is filled with nutrients and other stuff coming from the gut that the hepatocytes are required to metabolize, and blood coming from the hepatic artery is oxygenated, they both get mixed in the sinusoid system of the liver, the hepatocytes do their action on the blood in the sinusoids after that blood is discharged to the three hepatic veins draining in the inferior vena cava.

Some diseases of the liver may affect either of the two vessels supplying the liver (the hepatic artery and portal vein) and cause obstruction;

- Microstructure of the liver: the liver consists of hexagonal lobules

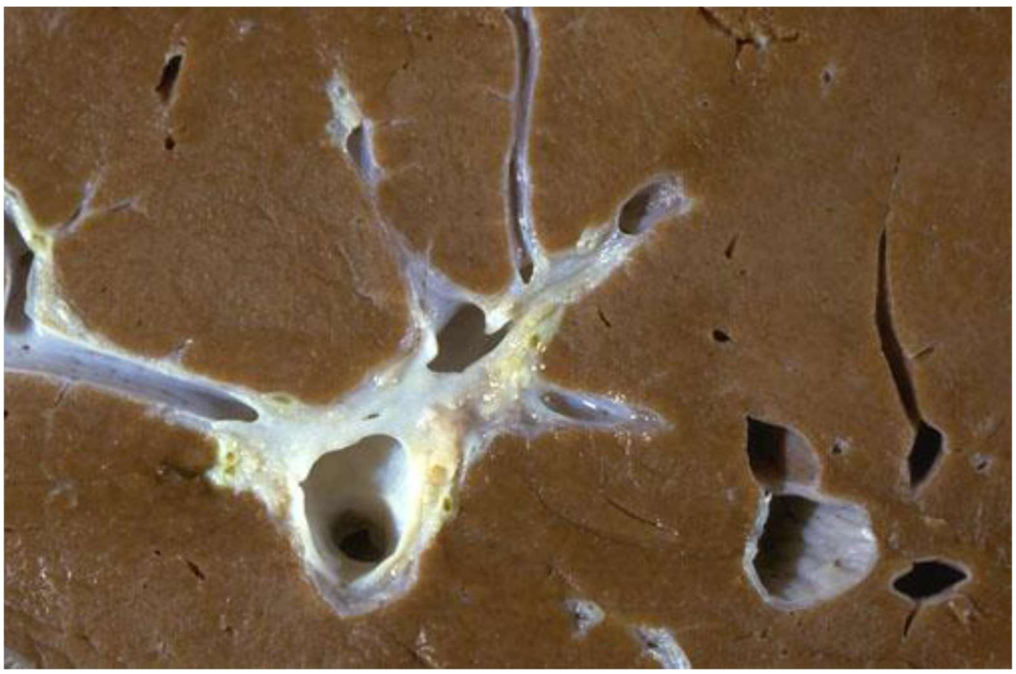
>>angles of each hexagonal lobule are formed by *portal triads or tracts* (bile ductule, hepatic artery, and hepatic portal vein)
>>at the center of the hexagons, there is *central vein*.

- The thickness of the sinusoid system that distributes blood to other hepatocytes is 1-2 cell thickness.

>>If thicker lines present, this means that there is disarrangement

- Hepatocytes surround the vascular sinusoids and are in close contact with blood to uptake drugs and other substances for detoxification and secretion of synthesized substances.

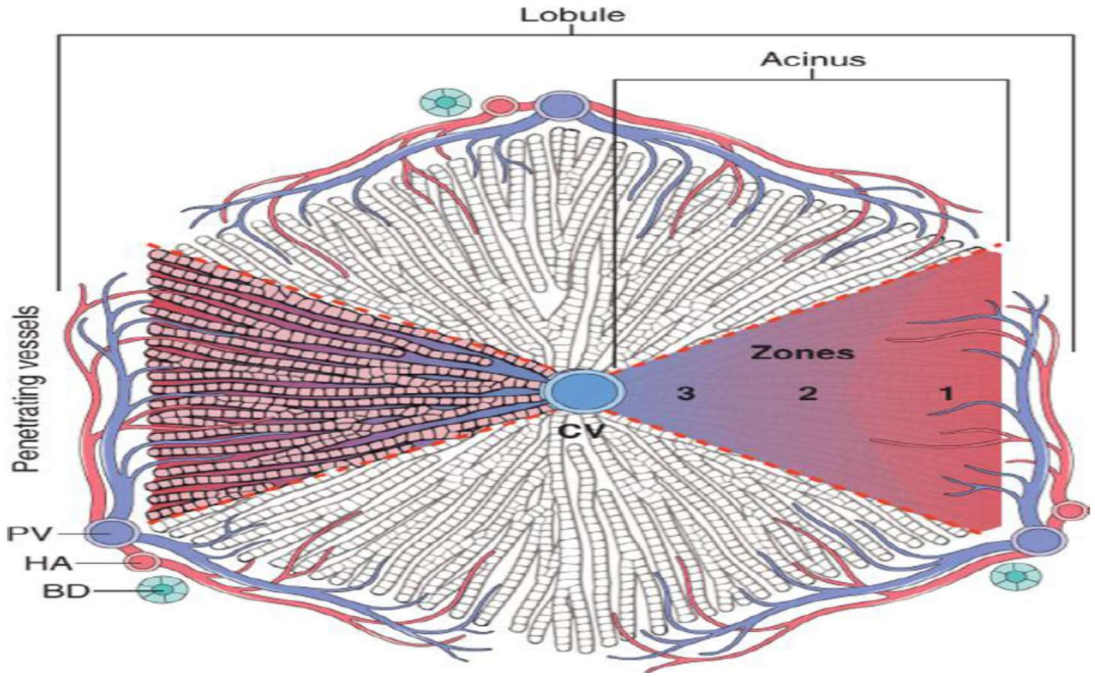
- The normal liver has a nice brownish color and its surface is smooth.



A section in the liver. Shows the homogeneous parenchyma
You can't see sinusoids in gross section, only under the microscope.

- The area between the central vein and the triad is divided into three zones, diseases can develop in each of these three zones:

—Zone 1 Periportal area _ closest to the vascular supply.
—Zone 2 Intermediate area _ between zone 1 and zone 3.
—Zone 3 Pericentral area _closest to the central vein.
#when the severity of a disease increases, all zones will be affected.



Hepatic injury

There are certain features and changes that might point to some underlining causes, but these changes are not specific:

1-Inflammation (**Hepatitis**): infiltration of the liver by inflammatory cells. The infiltration starts in the portal vein (early and mild inflammation) and may extend to the parenchyma (severe inflammation if it does).

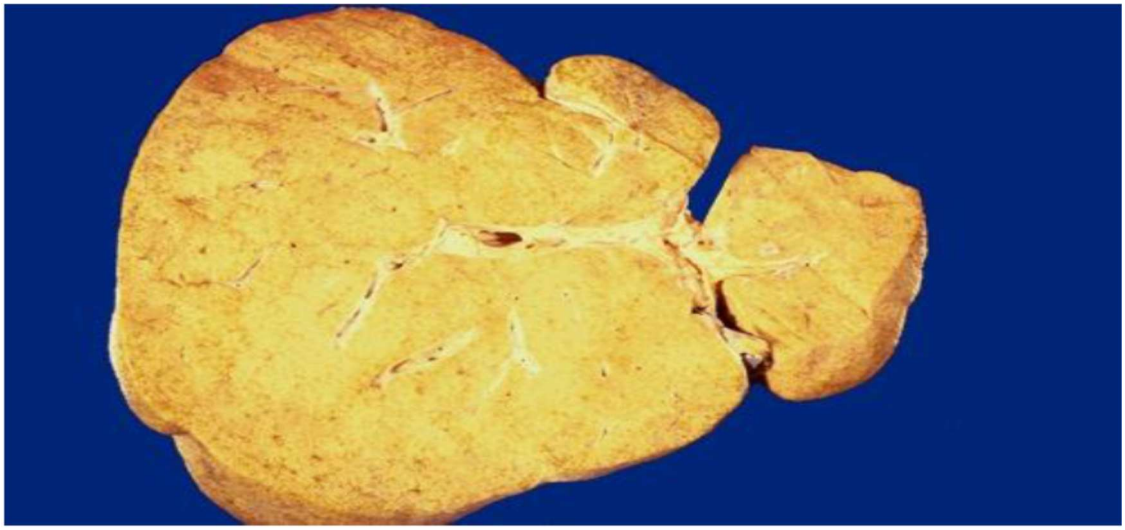
2-Ballooning degeneration:
Caused by disturbances in the permeability of the cell membrane of hepatocytes via certain injury sources.
This causes the hepatocytes to increase in size, and large amounts of water accumulate inside the cytoplasm which in turn causes rupture of the hepatocytes.
also, substances may accumulate in hepatocytes, including fat, iron, copper, and retained biliary material.

3-Steatosis (fatty change):

Normally, there is no fat tissue in the liver. So, any small amount of fat inside the liver indicates a pathological condition.
Previously, this fatty change was thought to be reversible and harmless. Now, it is considered as a disease which may be chronic and damage the liver.

It's totally nonspecific and can be seen in many diseases.

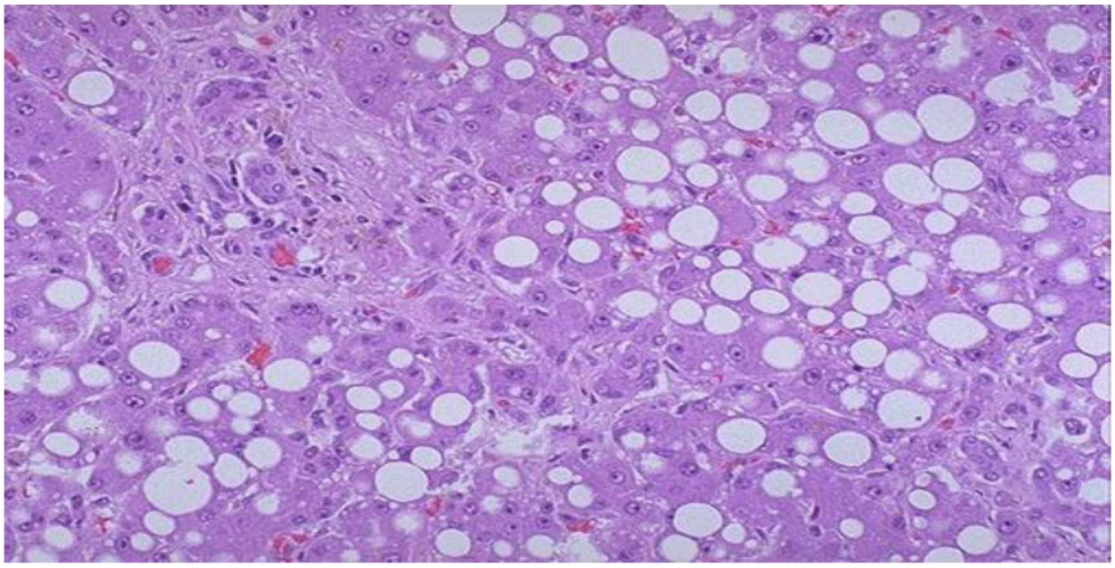
The picture shows enlarged liver with severe fatty change (yellowish color):



the color is yellow

The following examples were not mentioned by the doctor, but they present in the slides:
1-microvesicular steatosis: is characterized by intracytoplasmic fat vacuoles that accumulate in the cell, examples of: ALD, Reye syndrome, acute fatty change of pregnancy.
2- macrovesicular steatosis: is the more common form of fatty degeneration and is caused by oversupply of fat in obese people and diabetic people as well.

*Microscopically, fat appears as empty spaces (vacuoles) within the cytoplasm of the cells.
*Fat that's been accumulated in the cytoplasm affects the integrity of the hepatocytes and inactivates their functions.



4-Necrosis:

The presence of necrosis is very important because it means total loss of cells and loss of function.

Necrosis evaluates the severity of the condition. If a disease causes necrosis, it is a very severe disease.

Necrosis is divided into several types to predict what is the underlying cause. It is not specific but can help.

- Depending on the type:

1-Coagulative necrosis: around central vein.

>>It's related to ischemia

2-Councilman bodies

>>Individual cell necrosis. If we look at a liver tissue specimen from a patient without an active disease and we found councilman bodies, we should know that this liver was exposed to injury previously leaving these globules of cells that are surrounded by parenchymal cells scattered in between hepatocytes.

They are shrunken cells with very eosinophilic cytoplasm and the nucleus is dark

This indicates that the patient is in long term drug use causing this type of injury.

3-Lytic necrosis

>>can be related to infections. Parasitic infections can be related to lytic necrosis.

**Liver injury can also be classified depending on:

—Depending on the cause

1-Ischemic: vascular problem due to obstructions in blood vessels

2-Toxic: exposure to toxic substances like drugs or toxins in mushrooms

—Depending on the location

1-Centrilobular necrosis: necrosis around the central vein

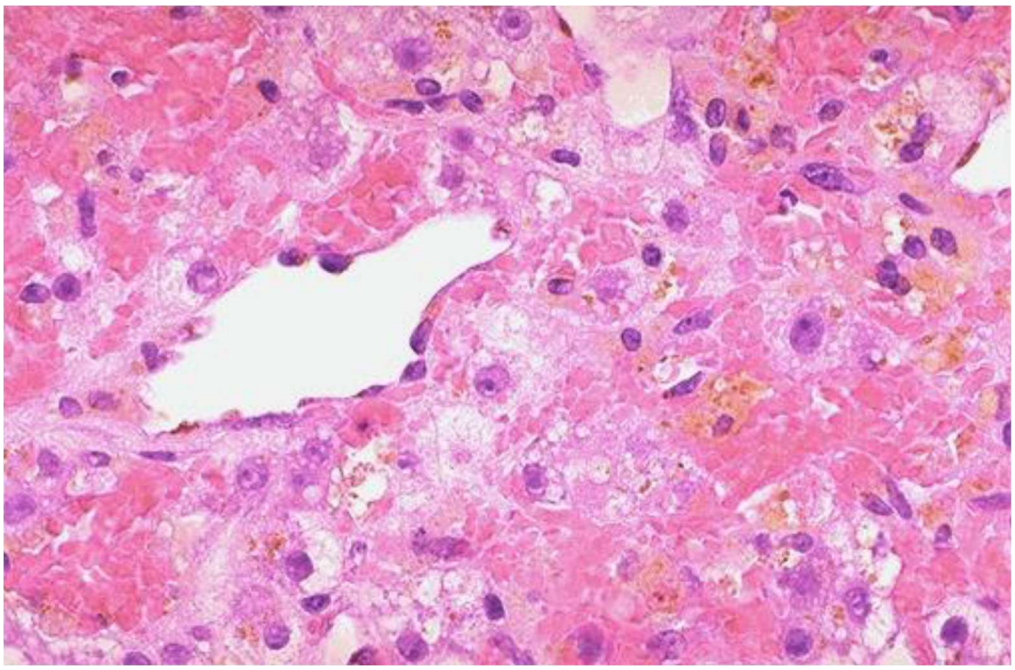
2-Mid zonal: necrosis area in between the central vein and the portal triad

3-Periportal: necrosis around the portal tract (triad), previously called the Piece meal necrosis, now it's called interface hepatitis, because it’s most commonly caused by hepatitis viral infection.

—Depending on the scatter of the inflammation:

1-Focal: necrosis affecting small group of cells like the piece meal necrosis and bridging necrosis which leaves bridging fibrosis. Fibrosis is irreversible and means, if it is found, that the patient has chronic liver disease.

2-Diffuse: massive & submassive necrosis



The specimen above shows unusual color (pigments) within the hepatocytes. These pigments mean accumulation of certain substances (e.g. Bile or iron) within the cells.

Regeneration

Liver is characterized by having high regenerative capacity. Therefore, loss of the liver tissue can be compensated. This is the principle of liver transplant in which part of donor's liver can be regenerated.

Liver failure appears and shows manifestations only when 90% of it has been lost.

It is evidenced by increased mitosis or cell cycle markers.

The cells of the *Canal of Hering* are the progenitor for hepatocytes & bile duct cells (oval cells).

Fibrosis

Again, it is irreversible. And it is very important to evaluate the disease process. It can develop into cirrhosis

Hepatic Failure

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

  1-Massive hepatic necrosis: massive means diffused and most of the liver is involved, commonly:

  -Fulminant viral hepatitis: hepatitis B, hepatitis B-D, hepatitis C, and sometimes even hepatitis A.

  -Drugs & chemicals: after excluding viral hepatitis, think in drugs: acetaminophen (paracetamol), halothane (anesthetic agent), anti TB drugs, CCL4 poisoning, Mushroom poisoning.

  They are acute conditions.

  2-Chronic liver disease: like in cirrhosis

  3-Hepatic dysfunction without overt cirrhosis: Here, there is no obvious necrosis and if we looked at the hepatocytes, they will look normal. So, the failure is due to loss of function

  Examples:

  -Reye's syndrome.

  -Tetracyline toxicity.

  -Acute fatty liver of pregnancy. It occurs suddenly in a pregnant woman and represents severe acute fat infiltration in the liver leading to acute sudden liver failure.

Clinical features of liver failure

1-Jaundice: one of liver's main functions is the excretion of bile containing bilirubin. Loss of this function causes Jaundice.

2-Hypoalbuminemia → edema (collection of fluid in the extravascular tissues).

3-Hyperammonemia: as the ammonia is metabolized in the liver.

4-Fetor hepaticus (musty or sweet & sour)

5-Palmar erythema

6- hyperestrogenemia: defect in the metabolism of estrogen; may manifest as enlargement of the male breast.

8-Spider angiomas.

9-Hypogonadism & gynecomastia

Consequences:

1-Multiple organ failures (kidneys and lungs) because the body can't deal with the toxic substances.

2-Coagulopathy: bleeding because of defect synthesis of clotting factors II, VII, IX, X.

3-Hepatic encephalopathy: liver failure affects the brain (e.g. hyperammonemia) which causes neurological manifestations: decrease the level of consciousness, rigidity, hyperreflexia, EEG changes, seizures, and asterixis.

Hepatorenal syndrome: renal failure in patients with severe liver disease with no morphologic or functional causes for renal failure. And treating the liver disease cures the kidneys.

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), it's the most common cause and the first one you should think of.

2-Drugs & chemicals 20 – 30%

Other causes that are not common:

1-Heat stroke
2-Hepatic vein obstruction
3-Wilson disease
4-Acute fatty liver of pregnancy
5-Massive malignant infiltration
6-Reactivation of chronic HBV hepatitis on HDV superimposed infection
7-Autoimmune hepatitis

Alcoholic liver disease

Alcohol (ethanol) is most widely abused agent and the most common toxin affecting the liver.

Ethanol is metabolized in the liver.

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

1. accidents: 80-100mg/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 mg/d of ethanol is associated with fatty change in liver.

2. Cirrhosis: most common cause of cirrhosis in western countries is the alcoholism. In other countries, it is something else.

Effect of ethanol varies between people and between male and female.

>In occasional drinkers, blood Level of 200 mg/dl produces coma & death and respiratory failure at 300-400 mg/dl.

> In habitual drinkers can tolerate levels up to 700 mg/dl without clinical effect. This is 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. In addition, uptake of ethanol can affect drugs that share with it the same enzyme in their metabolism. Thus, alcoholic patients should increase the doses of these drugs to have effects.

Forms of alcoholic liver disease:

1-Hepatic steatosis: fatty infiltration occurs almost in all patients (90-100% of drinkers).

2-Alcoholic hepatitis (1- 35% of drinkers): inflammation and injury of the liver tissue.

3-Cirrhosis (14% of drinkers)

* Steatosis and hepatitis may develop independently

Hepatic steatosis

Ethanol can affect all the aspects and pathways of fat metabolism, it can increase fatty acids release from the adipose tissue or increase the synthesis de novo. Thus, uptake of ethanol leads to increase in the amount of free fatty acids in the blood. These free fatty acids accumulate in the liver and cause steatosis.

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

Chronic intake → diffuse steatosis and enlargement of the liver (4 – 6 kg) soft yellow & greasy

Continued intake →fibrosis

*Fatty change is reversible with complete abstention from further intake of alcohol, but fibrosis is not.

Alcoholic hepatitis

Characteristic findings:

1-Infiltration of inflammatory cells (neutrophils which cause further damage (necrosis) to hepatocytes.

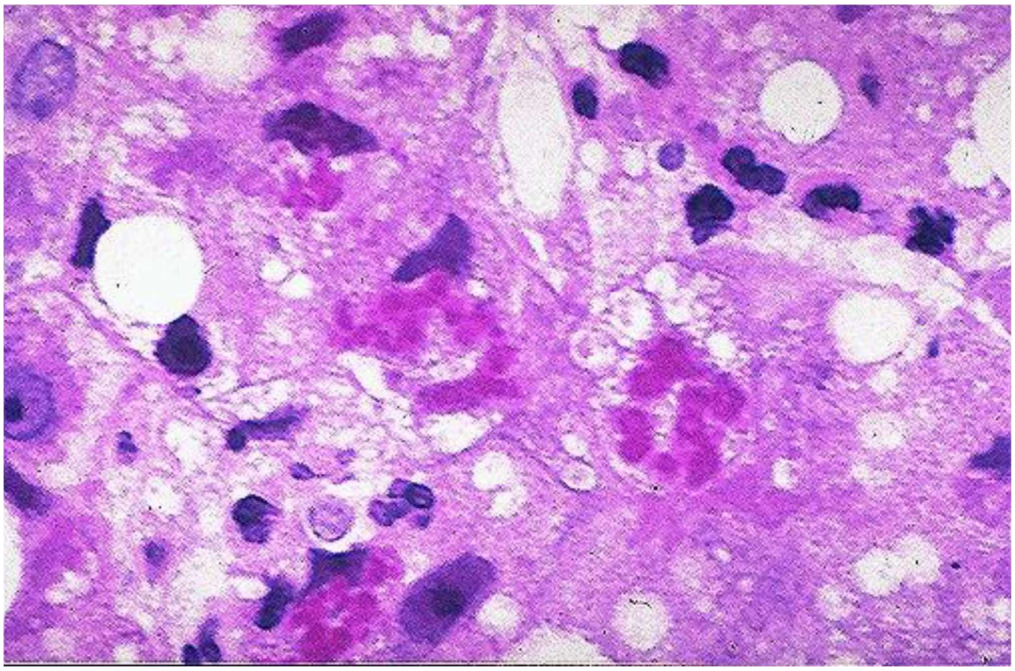
2-Hepatocyte swelling & necrosis

3-Accumulation of fat (steatosis), water, and proteins: structural proteins are damaged and accumulated in the form of Mallory-Hayline bodies.

*Presence of fatty changes and Mallory-Hayline bodies>>> indicating the patient is alcoholic. Although it is not very specific, but if you see these features, ask the patient whether he/she is alcoholic or not.

4-Cholestasis: which decreased flow of bile from the hepatocytes.

5-Hemosidrein deposition (Iron storage complex) in hepatocytes and Kupffer cells.



In this tissue >>Mallory-Hayline bodies which are eosinoplilic cytoplasmic inclusions in degenerating hepatocytes formed of cytokeratin intermediate filaments and other proteins. Also steatosis is present

Again, Mallory-Hayline inclusions are characteristic but not pathognomonic of alcoholic liver disease.

>> they are also seen in: Primary biliary cirrhosis, Wilson disease, Chronic cholestatic syndromes, and Hepatocellular carcinoma.