الجهاز الهضمي

علم الأمراض

رقم المحاضرة :

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Drug – Induced liver disease

-Drug reactions:-

1-Predictable (intrinsic)

2-Unpredictable (idiosyncratic)

-Predictable drug reactions depends on the dose (dose-dependent)

Unpredictable drug reactions depend on :

a-The immune response of the host to the antigenic stimulus

b-The rate at which the host metabolizes the agent

-The injury m.b immediate or takes weeks to months

-Drug-induced chronic hepatitis is clinically & histologically indistinguishable from chronic viral or autoimmune hepatitis

we should always include the drugs in our differential diagnosis (ask the patient if he is taking any drug), as they can cause injury to liver and to exclude other causes of liver injury – like viral hepatitis -

Additional (just to understand) :

" Unpredictable drug reactions depend on :

a-The immune response of the host to the antigenic stimulus "

But how this happens? Here are some causes

1. **Individual Variation in Immune System Function: The immune system's response to drugs can vary significantly among individuals due to genetic differences**
2. **Formation of Drug-Protein Complexes: Some drugs can bind to proteins in the blood, forming a complex that is recognized as foreign by the immune system. This can stimulate an immune response & antibodies**
3. **Cytokine Release**

Predictable drugs:

Acetaminophen
Tetracycline
Antineoplastic agents
CCL4
Alcohol

Unpredictable drugs (dose independent)

Chlorpromazine (antipsychotic)
Halothane (anesthetic)
Sulfonamides
Methyldopa
Allopurinol

-Mechanism of drug injury :

1-Direct toxic damage

e.g acetaminophen
CCl4
mushroom toxins

2-Immune-mediated damage

drugs are chemicals, and chemicals can interact with antigens which are found on cell surface of hepatocyte, this will lead to immune system activation as they recognize them as foreign then they will start attacking hepatocytes
Check next slide

Just to understand (not from Dr.)

1-Direct toxic damage

This type of injury occurs when a drug or its metabolites directly harm the liver's cells, either by causing direct cytotoxicity or through metabolic stress. such as:

Acetaminophen: When taken in excessive amounts, acetaminophen can deplete the liver's stores of glutathione, a critical antioxidant. Once glutathione is depleted, the metabolite N-acetyl-p-benzoquinone imine (NAPQI) accumulates and causes direct damage to liver cells. This damage can lead to severe hepatocellular necrosis.

2-Immune-mediated damage

This form of injury occurs when a drug induces an immune response that mistakenly targets the liver. This can happen through several mechanisms such as:

Drugs or their metabolites can bind to liver proteins, forming a complex that is recognized as foreign by the immune system. The result is an adaptive immune response against it, causing liver inflammation and injury.

-Patterns of injury

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

-

The Dr said "we expect anything to happen"
However memorize the ones mentioned in the slide :)
+ Gently check next slide

Just for better understanding for previous slide :) .. Not from Dr

1. **Hepatocellular Necrosis**: This type of injury involves the death of liver cells, often resulting from a direct toxic effect of a drug or its metabolites. It can lead to an abrupt increase in liver enzymes and severe liver dysfunction.
2. **Cholestasis**: This is characterized by impaired bile flow, which can be due to drug-induced damage to the bile ducts or liver cells. Symptoms may include jaundice, itching, and elevated alkaline phosphatase levels.
3. **Steatosis**: Also known as fatty liver, steatosis involves the accumulation of fat within liver cells. This can be caused by drugs that disrupt the normal metabolism of fats or by direct toxic effects leading to cellular stress and fat accumulation.
4. **Steatohepatitis**: This condition combines steatosis with inflammation of the liver. Drug-induced steatohepatitis can lead to more severe liver damage and is often associated with drugs that cause metabolic disturbances.
5. **Fibrosis**: Repeated or chronic liver injury can lead to fibrosis, where normal liver tissue is replaced with scar tissue. This process can be driven by persistent inflammation or direct stimulation of fibrogenic cells by drugs or their metabolites.
6. **Vascular Lesions**: Certain drugs can cause damage to the liver's blood vessels, leading to conditions such as sinusoidal obstruction syndrome or peliosis hepatis. These vascular changes can compromise blood flow within the liver and cause additional injury.
7. **Granuloma**: Some drugs can provoke an immune response leading to the formation of granulomas, which are small areas of inflammation consisting of clustered immune cells. These are usually a reaction to chronic immune stimulation by the drug.
8. **Neoplasms (Benign and Malignant)**: Long-term exposure to certain drugs can increase the risk of liver tumors, both benign (like adenomas) and malignant (like hepatocellular carcinoma). These are thought to arise either from direct mutagenic effects of drugs or chronic proliferative stimuli.

Drugs that may cause acute liver failure

this happens when there is extensive damage to hepatocytes, all these drugs cause cells to necrosis which can lead then to liver failure

1-Acetaminophen (most common) especially if it's taken as suicidal agent

2-Halothane

3-Antituberculosis drugs (rifampin, isoniazid)

4-Antidepressant monoamine oxidase inhibitors

5-Toxins as CCL4 & mushroom poisoning

Morpholagy:

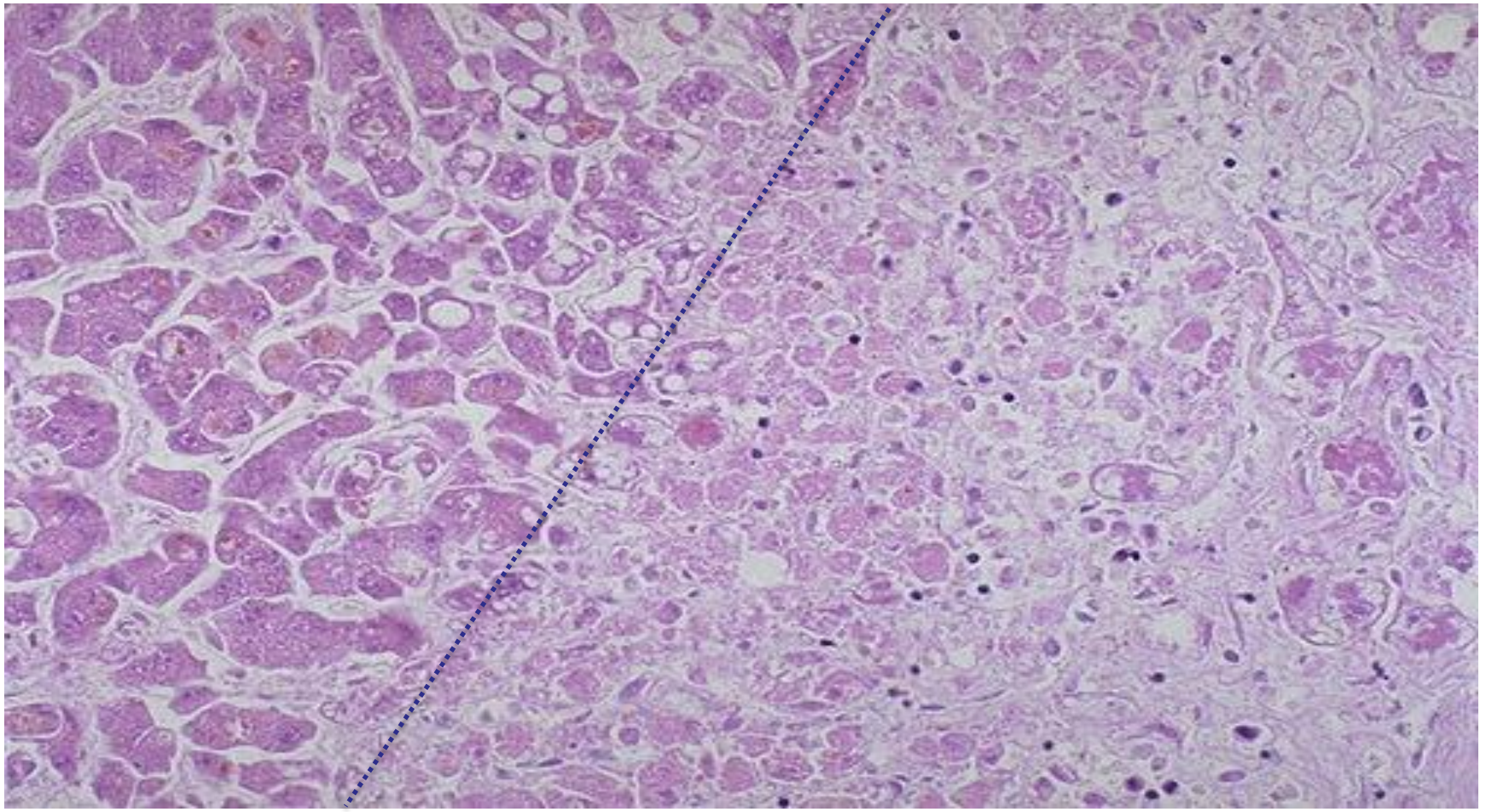
Massive necrosis → 500 – 700 gm liver Shrinking!

Submassive necrosis

Patchy necrosis

the **left side** presents preserved Hepatocytes without necrosis

Right Side: shows necrosis,Pale, nuclei loss



Fulminant hepatitis

Hepatic in sufficiency that progresses from onset of symptoms to hepatic escepholopathy in 2-3 wks short period

Subfulminant (up to 3 months)

Causes :

1-Viral hepatitis 50 – 65%
HBV 2x > HCV

2-Drugs & chemical 25- 50%
e.g Isoniazid , halothane , methyldopa & acetominophen

3-Obstruction of hepatic vein (such as bec. Of thrombi there)

4-Wilson's disease

5-Acute fatty change of pregnancy.

6-Massive tumor infiltration

7-Reactivation of chronic hepatitis B

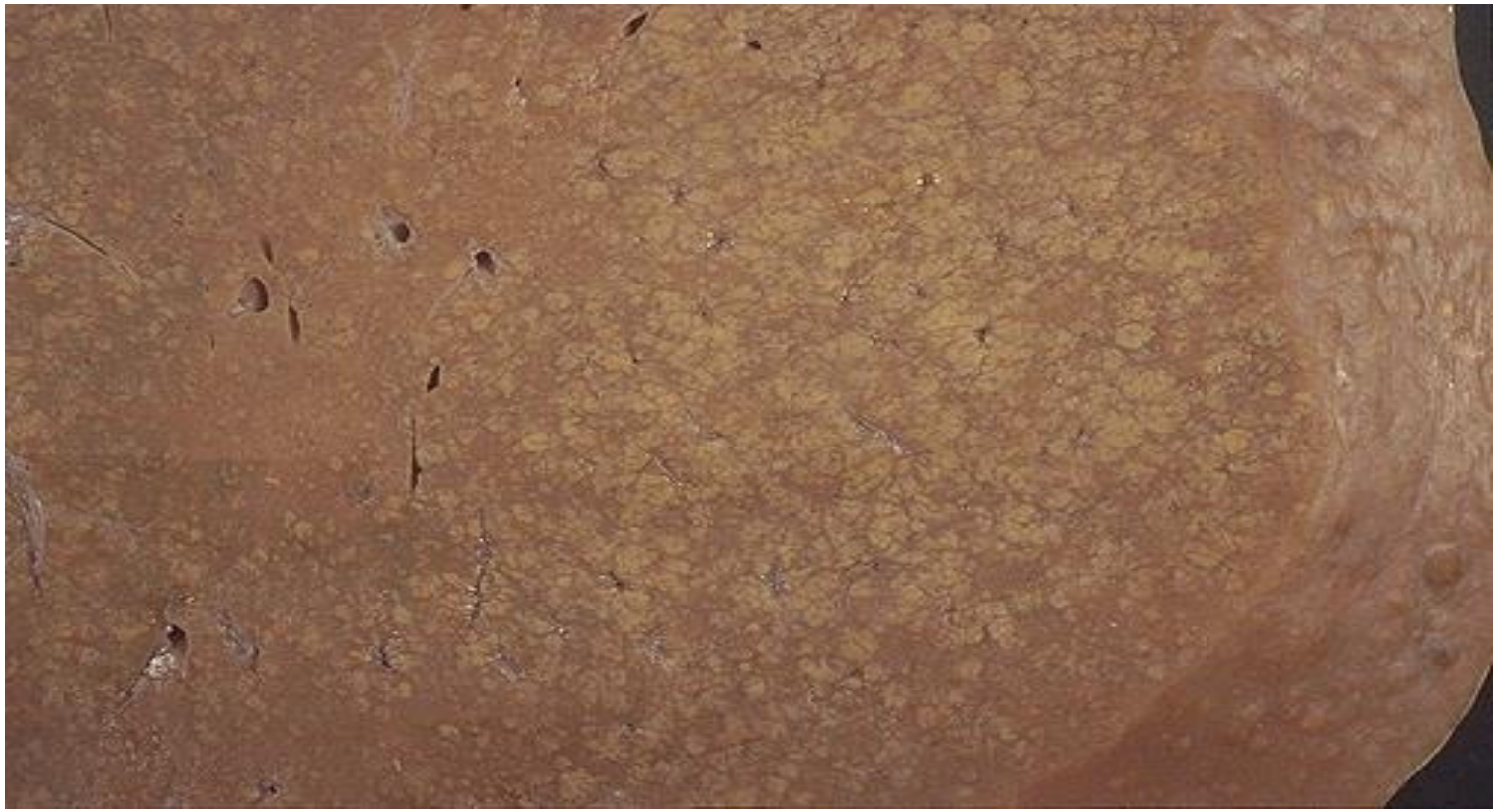
8-Acute immune hepatitis (Auto-immune)

Always remember :
When talking about areas where viral Hepatitis is endemic, it would be the cause for fulminant hepatitis, especially hep B and C or B-D

- **<u>Morphology</u>**

-↓ liver size (500 – 700 gm)
-Necrosis of hepatocytes
-Collapsed reticulin tissue
-Inflammatory infiltrate
-Regenerative activity of hepatocytes
-Fibrosis

this is the appearance of the liver with necrosis, the pale areas are the necrotic areas . the degree of necrosis is variable; there are also loss of homogenicity , all these are indications of necrosis



Chronic Hepatitis

-Symptomatic, biochemical or serologic evidence of continuing or relapsing hepatic disease for more than 6 months with histologically documented inflammation & necrosis And the development of Fibrosis.

-Progressive (This happens when inflammation reaches the parenchyma, then it can lead to fibrosis and cirrhosis) or non progressive (when inflammation limited to portal area)

-HBV , HCV, HBV-HDV

The other outcome of viral hepatitis and it is the most feared one is the Chronic Hepatitis. It is very important to recognize the causative agent of the viral hepatitis and we need to follow up the patient to predict if he will be infected with chronic hepatitis.

Chronic hepatitis can be of 2 types: progressive OR non-progressive.
Progressive hepatitis is when it reaches the parenchyma, can lead then to fibrosis and cirrhosis. And they have high risk of developing chronic hepatitis.
While non-progressive is when inflammation limited to portal area.
As we know inflammation of liver starts in portal area; so if it stayed localized it will be referred as non-progressive. But if the inflammatory cells got diffused through the parenchyma, we refer them as progressive hepatitis.
What are their causative agents?
HBV, HCV (most prominent these days), HBV-HDV.

- **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

Morphology: it depends on the severity but usually they have same symptoms of liver injury.

1. Portal inflammation
2. Lymphoid aggregate: the inflammatory cells are extensive forming follicles in the parenchyma; it is an indication of severe chronic hepatitis.
3. Necrosis of hepatocytes-councilman bodies:
4. Bile duct damage
5. Steatosis

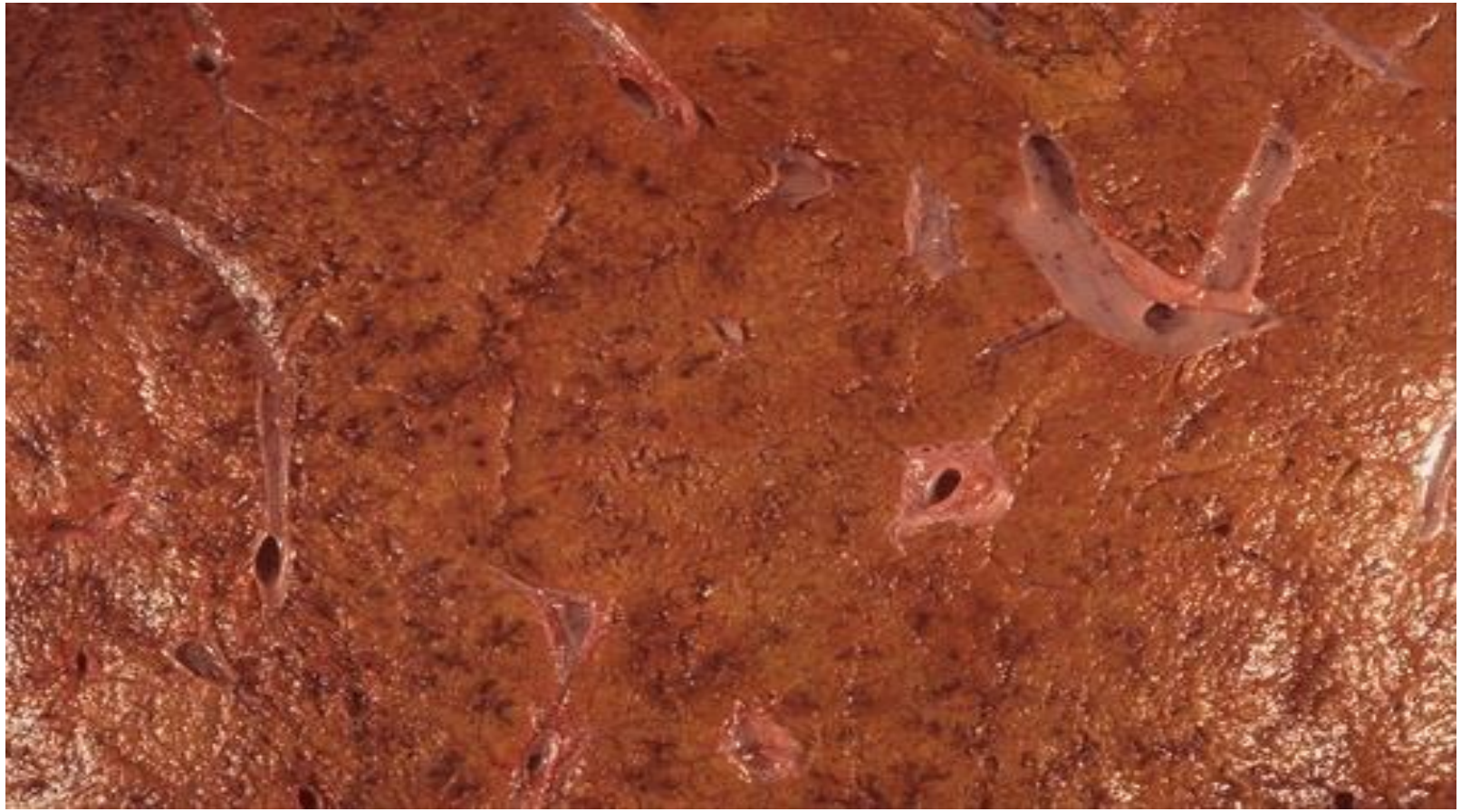
} Caused mainly by HCV

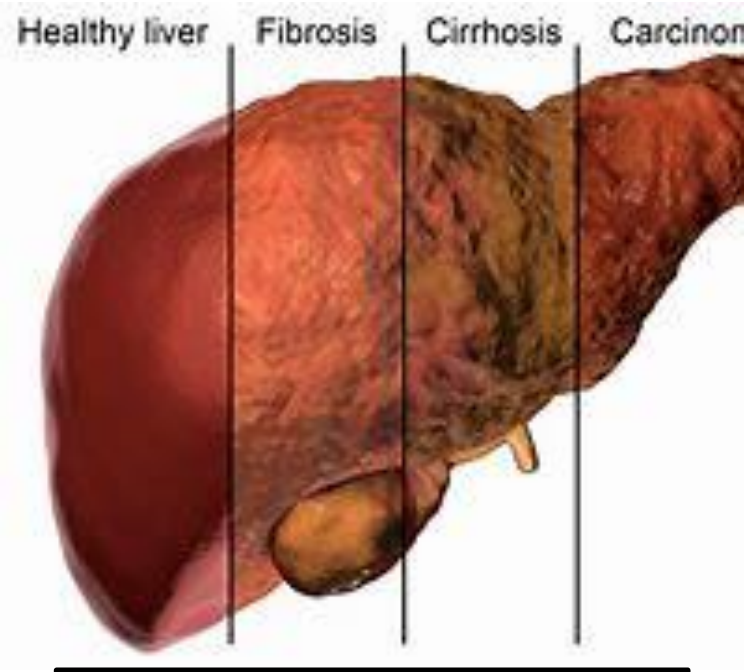
6. Interface hepatitis
7. Bridging necrosis
8. Fibrosis
9. Lobular disarray

} Depends on the severity

10. Ground-glass appearance
11. Sanded nuclei

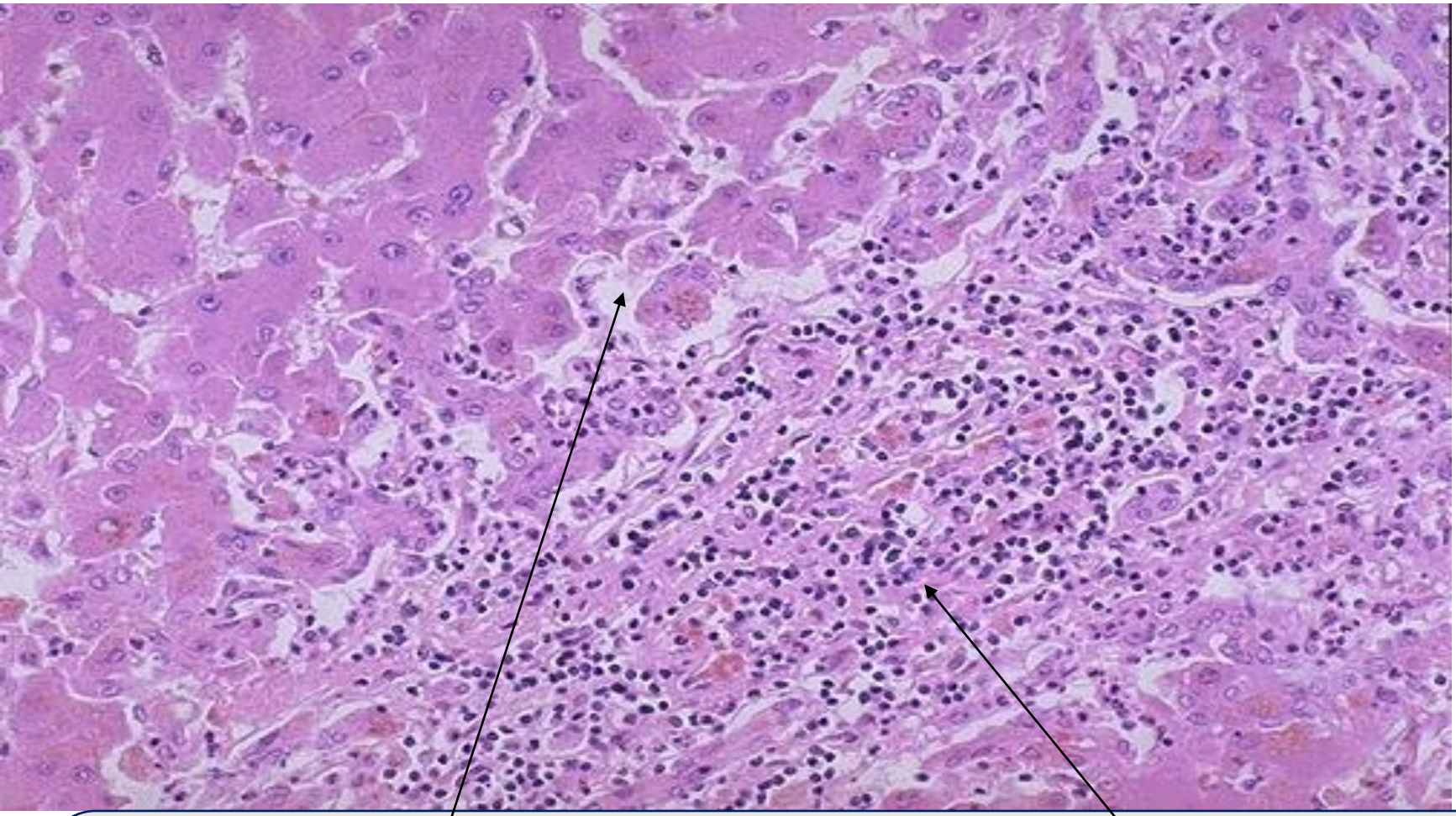
} HBV is a DNA virus, so it enters cell and causes cytoplasmic changes in hepatocytes observed under a microscope. The cytoplasm will abnormal accumulation of proteins, lipids, or viral components.





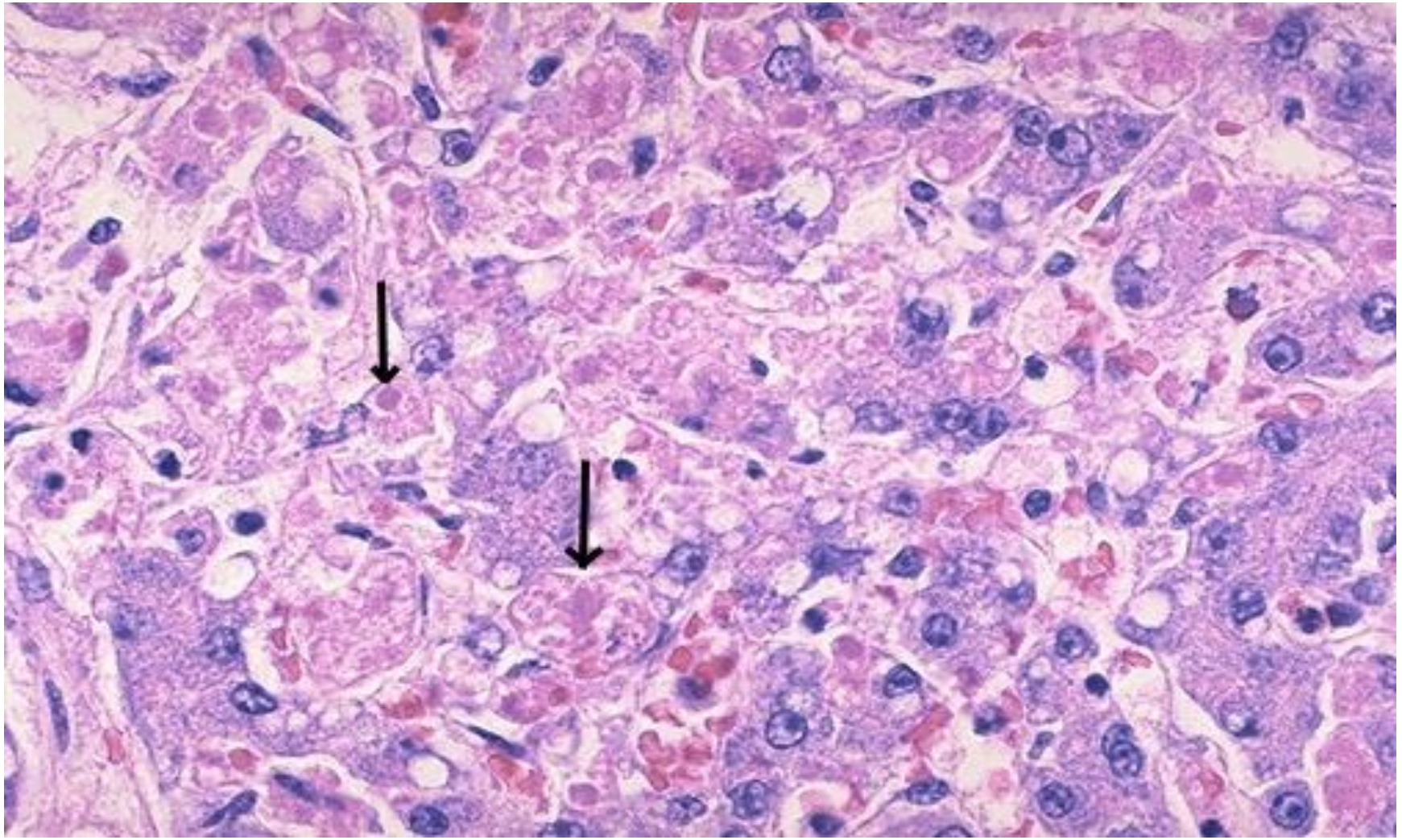
Extra image to distinguish between Normal and other types of liver injury

There is loss of homogeneity as seen by color changes, pale areas and surrounding is darker. This due to presence of fibrosis. There are some nodule formation

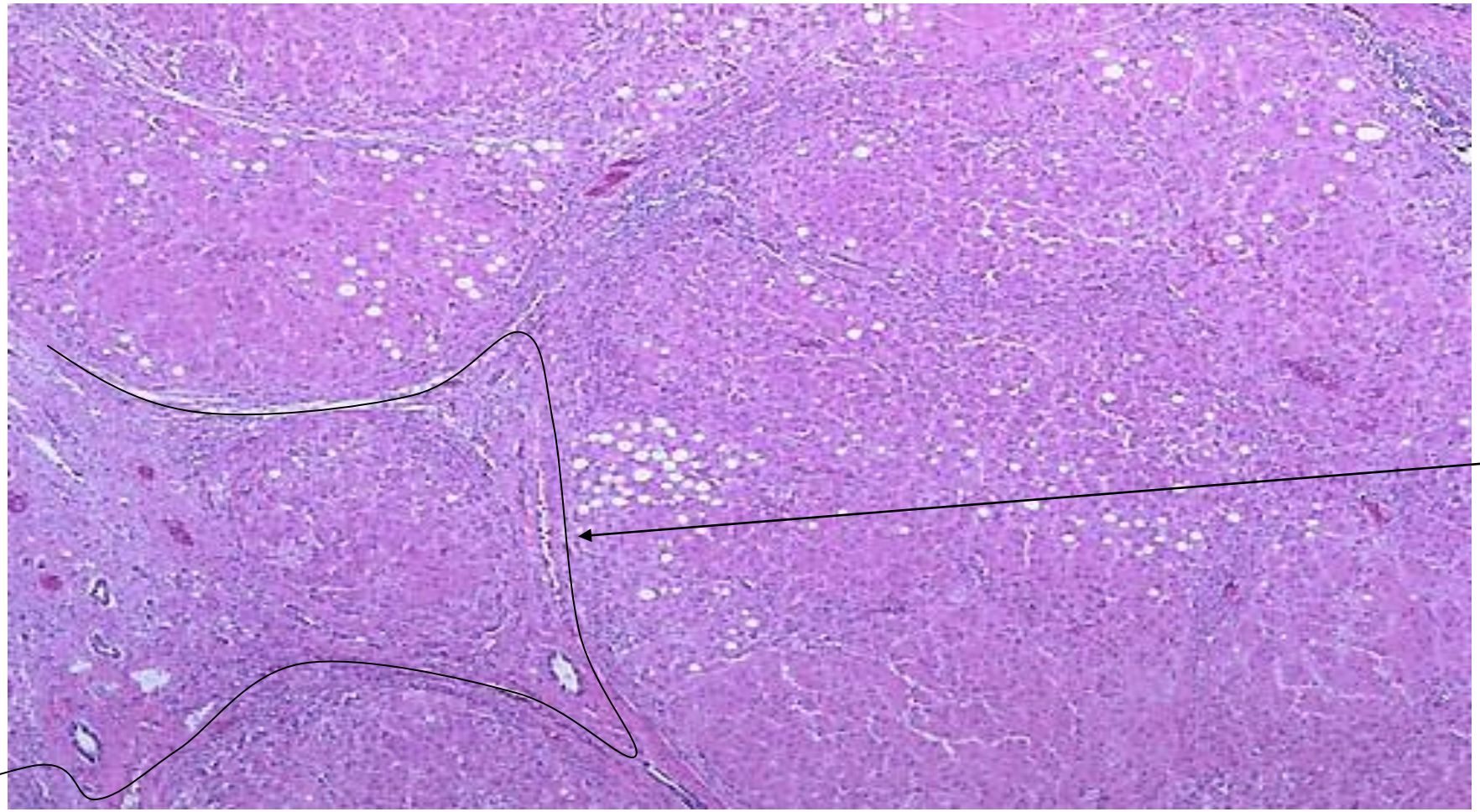


It is microscopic appearance of severe form of chronic hepatitis: there are some bridging fibrosis – follow the arrow -
(indication of cirrhosis development) and extensive lymphocytes--> النقاط السوداء

Necrosis of hepatocytes-councilman bodies (arrows)
Pic shows fibrosis and chronic hepatitis



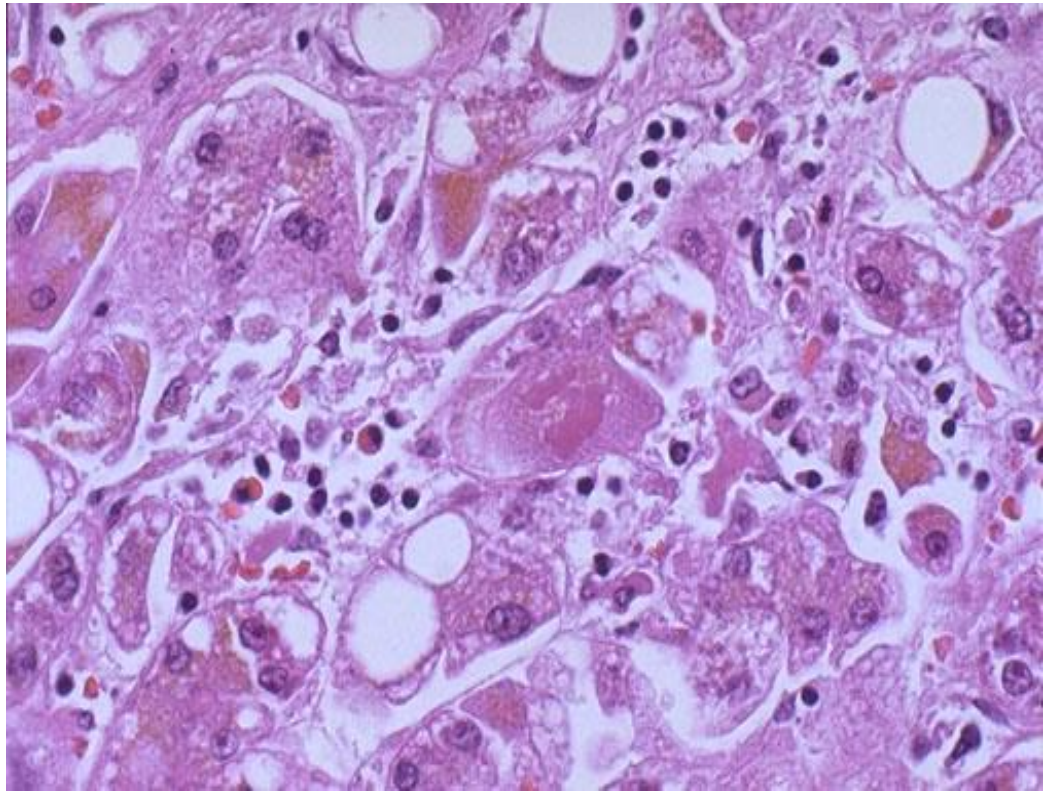
External: hepatitis B can result in a fulminant hepatitis with extensive necrosis. A large pink cell undergoing "ballooning degeneration" is seen below the right arrow. At a later stage, a dying hepatocyte is seen shrinking down to form an eosinophilic "councilman body" below the arrow on the left.

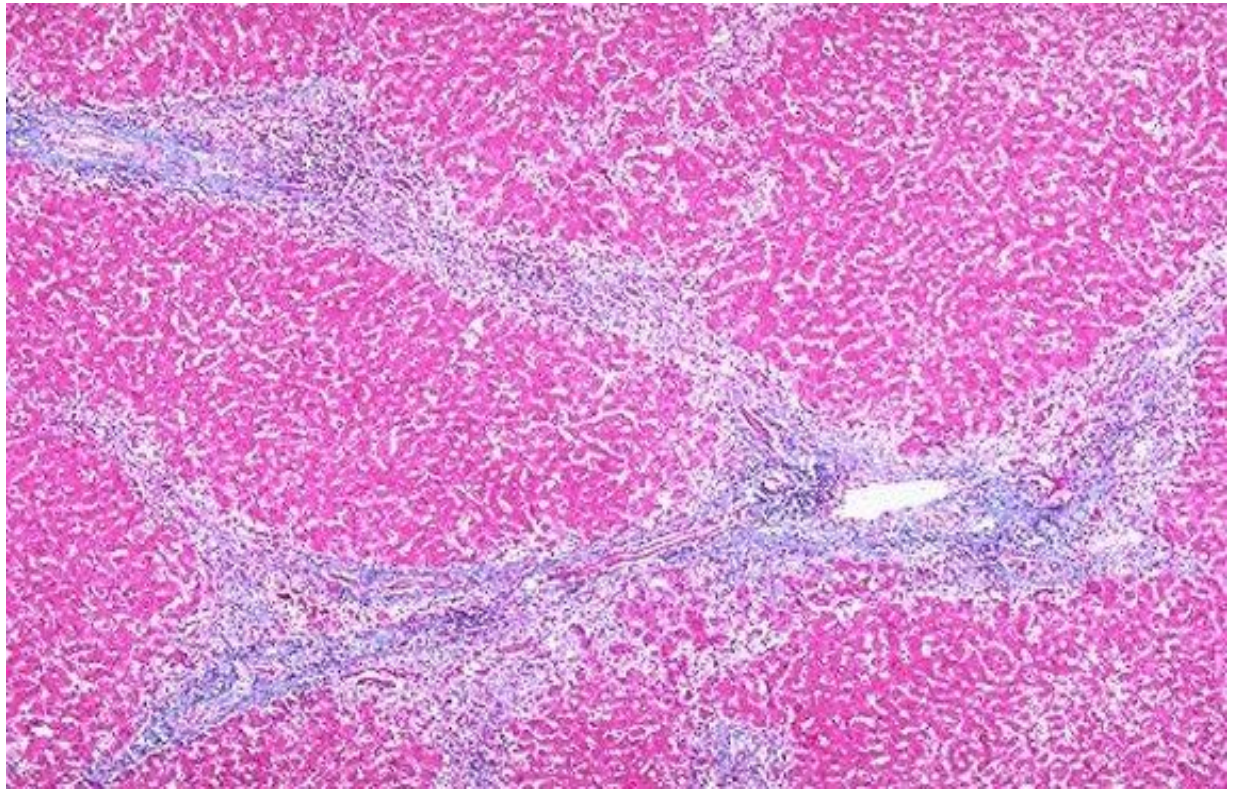


-fat deposition
-nodules
-bridging fibrosis (connecting structures with another)

- **It's showing extensive fibrosis but not cirrhosis**; because there is no complete nodule formation.

we can see loss of hepatocytes architecture and the collapse of the liver parenchyma with viral hepatitis + fibrous tissue on it





Additional Questions

;) Exam Questions will be easier, but just in case

A 37-year-old man has a long history of chronic alcohol abuse. On physical examination his liver edge is firm on palpation of the abdomen, but liver span does not appear to be increased. An abdominal CT scan reveals a cirrhotic liver. He joins a support group for persons with chronic alcohol abuse and he stops drinking. Despite his continued abstinence from alcohol, he most likely remains at risk for development of which of the following disease

A Hepatic adenoma
B Focal nodular hyperplasia
C Cholelithiasis
D Angiosarcoma
E Hepatocellular carcinoma

Answer: E

A 22-year-old woman has had progressive malaise for the past year. She has become increasingly obtunded over the past week. On physical examination she is afebrile. Laboratory studies show a plasma ammonia of 55 micromol/L along with serum total bilirubin of 5.8 mg/dL, direct bilirubin 4.6 mg/dL, AST 110 U/L, and ALT 135 U/L. Her serum ceruloplasmin is 14 mg/dL. The antimitochondrial antibody test is negative. A liver biopsy is performed and microscopic examination reveals increased copper deposition. Which of the following ocular findings is most likely to be present in this woman?

A Bilateral papilledema
B Macular degeneration
C Proliferative retinopathy
D Crystalline lens cataract formation
E Corneal Kayser-Fleischer rings

Answer: E

A 28-year-old woman with recent onset of a major depressive disorder ingests an entire bottle (100 capsules, 500 mg each) of a medication containing acetaminophen. She becomes progressively obtunded over the next 8 hours. Which of the following microscopic findings is most likely to be present in her liver 3 days following this ingestion?

A Normal histology

B Extensive necrosis

C Bridging fibrosis

D Severe steatosis

Answer : B

A 64-year-old postmenopausal woman on estrogen therapy has noted worsening swelling of her feet during the past 5 months. She has had increasing dyspnea at night for the past 2 months. She also has chronic arthritis. Her skin has become more darkly pigmented in the last 2 years without sun exposure. On physical examination there is no joint deformity. She has 2+ pitting edema to her thighs. A chest radiograph shows bilateral pleural effusions and pulmonary edema. Laboratory findings include a serum glucose of 196 mg/dL, creatinine 1.7 mg/dL, **ferritin 9079 ng/mL**, AST 25 U/L, ALT 38 U/L, alkaline phosphatase 49 U/L, total bilirubin 1.2 mg/dL, total protein 5.9 g/dL, and albumin 3.3 g/dL. **Which of the following therapeutic approaches is most appropriate for this patient**?

A Begin corticosteroid therapy

B Stop estrogen therapy

C Give interferon therapy associated with chemotherapy

D Control her diabetes mellitus

E Start regular treatment to reduce iron in her body

Answer E

A 45-year-old man is found in an obtunded state and taken to the hospital. On admission physical examination he is icteric. His abdomen is enlarged with a fluid wave. An abdominal CT scan shows extensive intraperitoneal fluid and a uniformly enlarged liver that has decreased attenuation (decreased brightness). Laboratory studies show total protein 6.5 g/dL, albumin 2.8 g/dL, total bilirubin 4.8 mg/dL, **AST of 563 U/L, ALT 317 U/L**, alkaline phosphatase 55 U/L, and ammonia 91 micromol/L. A liver biopsy is performed and microscopically demonstrates abundant **Mallory hyaline**, neutrophilic infiltrates, hepatocyte necrosis, portal fibrosis, and extensive macrovesicular steatosis. Which of the following is the most likely diagnosis?

A) Autoimmune hepatitis

B Sclerosing cholangitis

C Alcoholic hepatitis

Answer : C

THE END

عَنْ ابْنِ عَبَّاسٍ قَالَ كُنْتُ خَلْفَ رَسُولِ اللَّهِ ﷺ يَوْمًا فَقَالَ:

«يَا غُلَامُ إِنِّي أُعَلِّمُكَ كَلِمَاتٍ احْفَظْ اللَّهَ يَحْفَظْكَ احْفَظْ اللَّهَ تَجِدْهُ تُجَاهَكَ إِذَا سَأَلْتَ فَاسْأَلْ اللَّهَ وَإِذَا اسْتَعَنْتَ فَاسْتَعِنْ بِاللَّهِ وَاعْلَمْ أَنَّ الْأُمَّةَ لَوْ اجْتَمَعَتْ عَلَى أَنْ يَنْفَعُوكَ بِشَيْءٍ لَمْ يَنْفَعُوكَ إِلَّا بِشَيْءٍ قَدْ كَتَبَهُ اللَّهُ لَكَ وَلَوْ اجْتَمَعُوا عَلَى أَنْ يَضُرُّوكَ بِشَيْءٍ لَمْ يَضُرُّوكَ إِلَّا بِشَيْءٍ قَدْ كَتَبَهُ اللَّهُ عَلَيْكَ رُفِعَتْ الْأَقْلَامُ وَجَفَّتْ الصُّحُفُ».رواه الترمذي