GI Pathology Verbatim Study Guide (Liver Diseases - Lectures 1-3)

Color Guide

- **Black Text:** Represents the original, verbatim text extracted directly from the provided PDF document.
- Blue Text: Indicates explanatory additions provided by the AI, such as definitions, clarifications, context, image captions, and this guide itself, intended to aid understanding of the original material.

Introduction

This document contains the verbatim text from the Liver Diseases section (Lectures 1-3) of your GI Pathology PDF. Alongside the original text, you will find explanations, definitions, and context provided in blue to help clarify the material for a first-year medical student, while preserving the exact wording you need for exam preparation.

Original Text: Liver Diseases 1

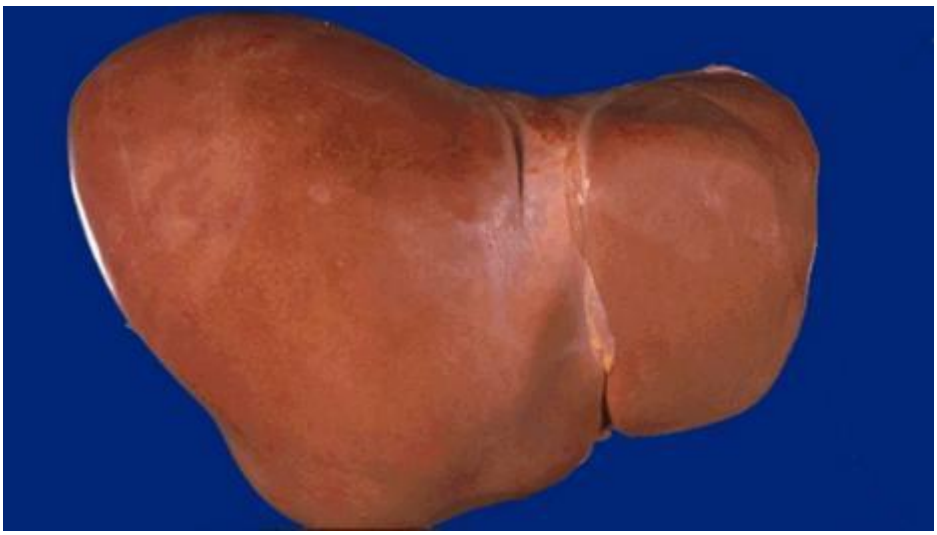
Liver:

* Due to multiple functions, manifestations are variable.
* Liver diseases manifestations are not only confined to the liver, sometimes they can have extrahepatic manifestations.

Explanation: This introduces the liver, highlighting that because it does so many different things, liver diseases can show up in many ways (variable manifestations). These problems aren't always just in the liver;

they can affect other parts of the body too (extrahepatic manifestations).

1. Functions:



(Image: Gross view of a normal human liver.)

- Metabolic: Glucose
- Synthetic: Albumin, clotting factors …
- Detoxification: Drugs, hormones, NH3
- Storage: Glycogen, TG, Fe, Cu, vit
- Excretory: Bile

Explanation: Lists the key jobs of the liver:
* **Metabolic:** Managing blood sugar (glucose).
* **Synthetic:** Making important proteins like albumin (maintains fluid balance) and clotting factors (stop bleeding).
* **Detoxification:** Breaking down or neutralizing harmful substances like drugs, excess hormones, and ammonia (NH3).
* **Storage:** Storing energy (glycogen, triglycerides/TG), iron (Fe), copper (Cu), and vitamins (vit).
* **Excretory:** Producing and releasing bile (helps digest fats).

2. Net weight:
* 1400 – 1600gm (2.5% of body wt.)

Explanation: States the typical weight of an adult liver.

3. Blood supply:

* Portal vein: 60 – 70%
* Hepatic artery: 30 - 40%

Explanation: The liver gets blood from two sources:

* **Portal Vein:** Brings nutrient-rich, deoxygenated blood from the intestines and spleen (majority of blood flow).
* **Hepatic Artery:** Brings oxygenated blood from the heart.

4. Microstructure: (structure fits function)

* Hexagonal lobules → 6 acini

➢ Acinus is divided into 3 zones:

➢ Some diseases prefer certain zones.

1- Zone 1

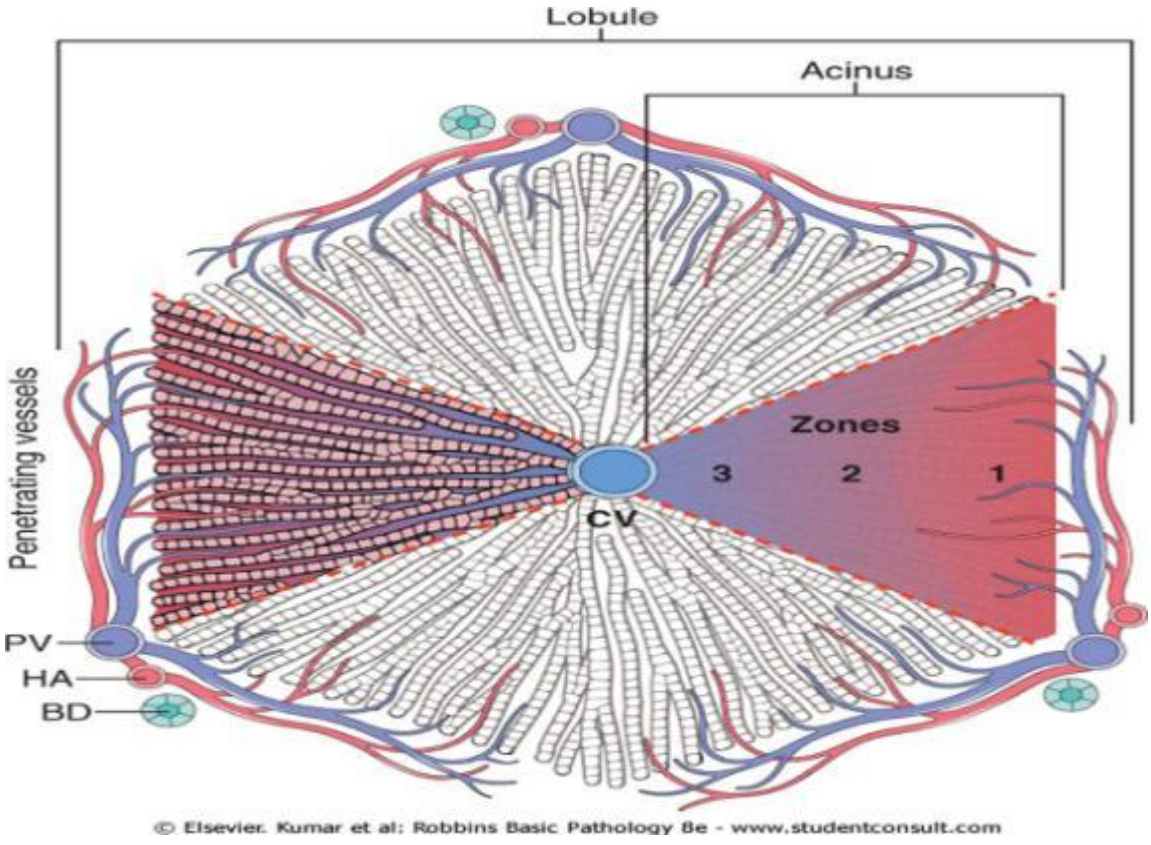
o Periportal areas – close to the vascular supply

2- Zone 3

o Pericentral area

3- Zone 2

o Intermediate between Zones 1&2

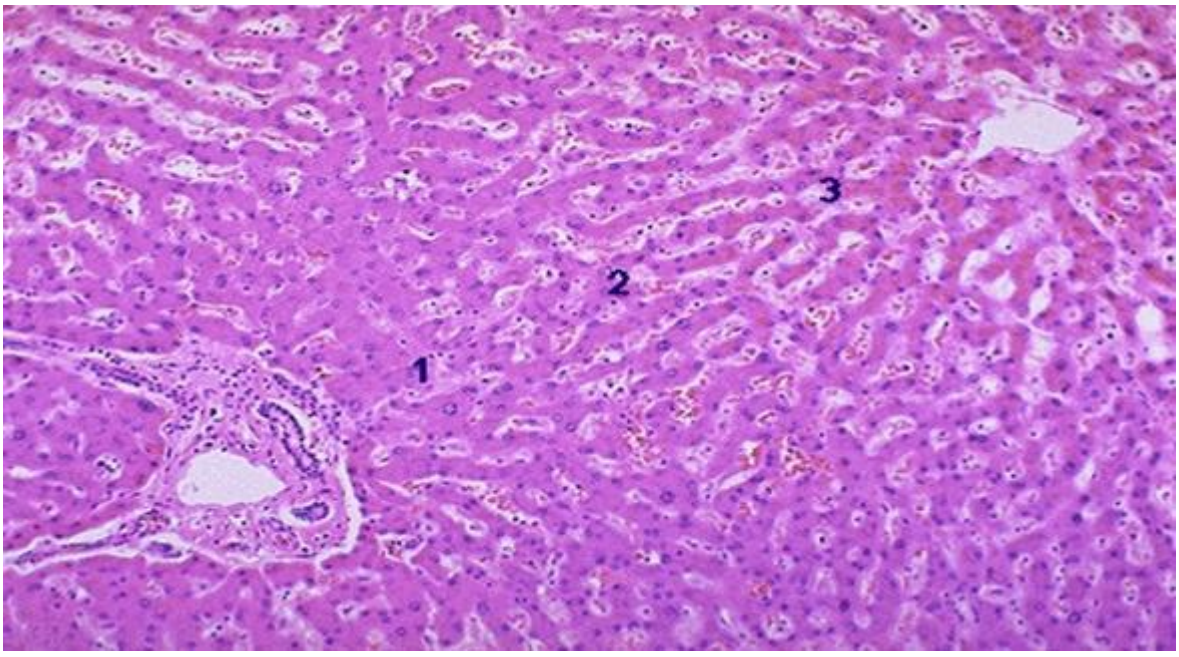


(Image: Diagram illustrating the hexagonal liver lobule centered on the

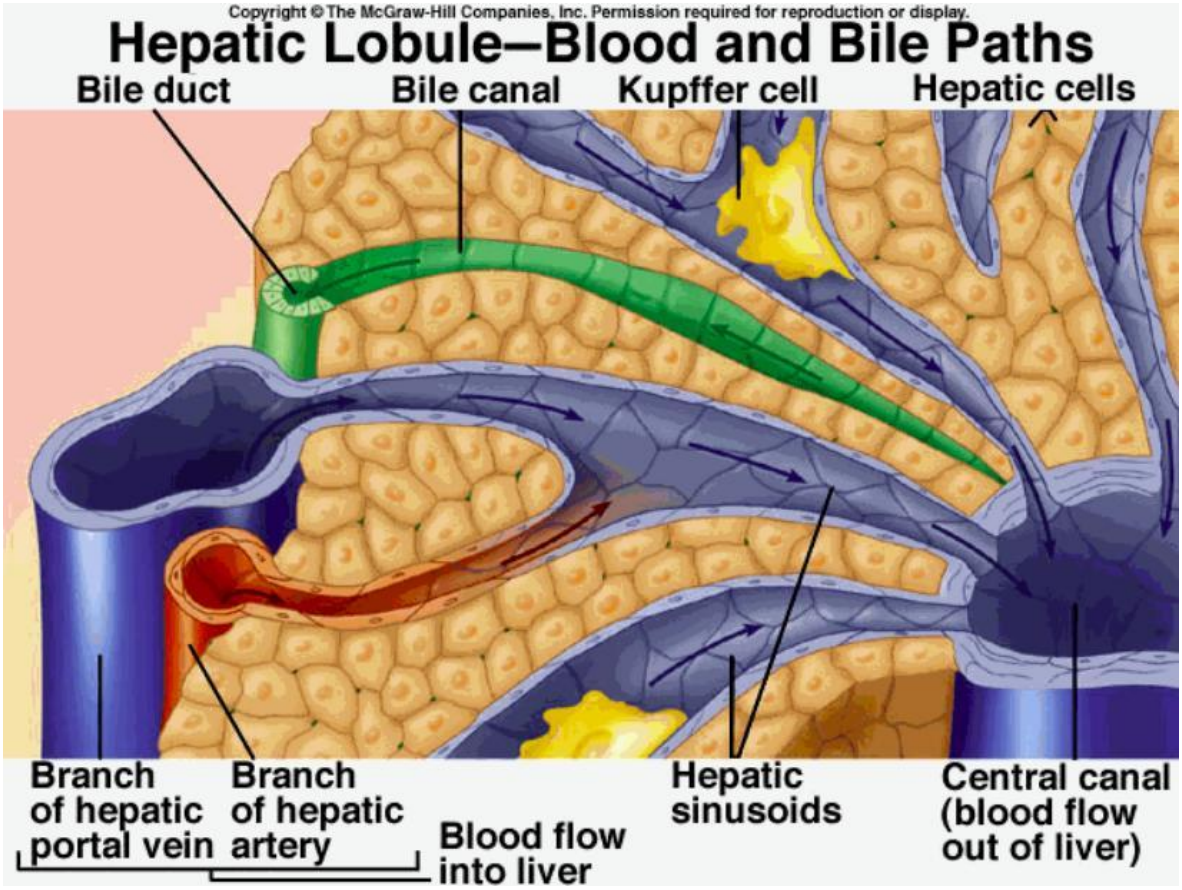
central vein (CV) and the diamond-shaped acinus showing Zones 1, 2, and 3 relative to the portal triad (PV, HA, BD) and central vein.)

Explanation: Describes the microscopic organization:
* **Lobule:** The classic view is a hexagon shape with a central vein in the middle and portal tracts (containing portal vein, hepatic artery, bile duct branches) at the corners.
* **Acinus:** A functional view, diamond-shaped, focused on blood supply zones. Zone 1 is closest to the incoming blood supply (portal tract), gets the most oxygen and nutrients, and is often the first affected by toxins entering via blood. Zone 3 is furthest from the portal tract and closest to the draining central vein, gets the least oxygen, and is most vulnerable to low oxygen (ischemia) and certain drug toxicities metabolized there. Zone 2 is in between. Knowing these zones helps understand why some diseases affect specific areas.

5. The liver parenchyma:
* The parenchyma is organized into plates of hepatocytes.
* Hepatocytes are radially oriented around terminal hepatic vein (central v.)
* Hepatocytes show only minimal variation in the overall size, but nuclei may vary in size, number & ploidy esp. with advancing age
* Vascular sinusoids (bigger capillaries) present between cords of hepatocytes



(Image: Microscopic view (histology) showing liver tissue. The numbers indicate Zone 1 (near portal tract, lower left), Zone 2 (intermediate), and Zone 3 (near central vein, upper right), highlighting the different microenvironments within the acinus.)



(Image: Diagram showing the path of blood flow (from portal vein and hepatic artery through sinusoids to the central vein) and bile flow (from hepatocytes into bile canaliculi, towards the bile duct in the portal tract) within a liver lobule.)

Explanation: Describes the main functional tissue (parenchyma):
* **Hepatocytes:** The main liver cells, arranged in plates or cords.
* **Orientation:** These plates radiate out from the central vein.
* **Cell Appearance:** Hepatocytes are generally similar in size, but their nuclei (containing DNA) can vary, especially as people age (ploidy refers to the number of sets of chromosomes).
* **Sinusoids:** These are special, leaky capillaries that run between the hepatocyte plates, allowing close contact between blood and liver cells for processing.

Extra images showing the parenchyma (the main functional tissue of the liver) that is divided into plates of hepatocytes, hepatocytes are arranged into 2 layers (or into Cords), each layer is facing a vessel, one is facing the sinusoid which drains into a central structure called the central vein, eventually toward the IVC. While the other is facing a bile canaliculus.

Explanation: This note adds detail about the arrangement: hepatocyte plates are often described as being one or two cells thick (cords). One side faces the blood-filled sinusoid, the other side faces a tiny channel called a bile canaliculus where bile produced by the hepatocyte is secreted. Blood flows towards the central vein (which drains to the inferior vena cava - IVC), while bile flows outwards towards the bile ducts in the portal tracts.

Original Text: 6. Liver injury:

1. Can be due to Inflammation (Hepatitis).
2. Ballooning degeneration:
    - Irregularly clumped cytoplasm showing large, with clear spaces.
    - Many Substances may accumulate in viable hepatocytes, including fat, iron, copper, and retained biliary material

Explanation: Describes basic ways the liver shows injury:
* **Inflammation (Hepatitis):** The liver tissue becomes inflamed, often due to infection (like viral hepatitis) or other causes.
* **Ballooning Degeneration:** A specific type of hepatocyte injury where the cells swell up and look pale or clear inside. This is a sign of reversible or irreversible damage.
* **Accumulations:** Injured or overloaded liver cells can accumulate substances like fat (steatosis), iron (hemochromatosis), copper (Wilson disease), or bile components (cholestasis).

1. Steatosis (Fatty change) - (steato always refers to fat)
    - Microvesicular: Alcoholic liver disease (ALD), Reye syndrome, acute fatty change of pregnancy.
    - Macrovesicular: Diabetes mellitus (DM), obese.

Explanation: Focuses on fat accumulation (steatosis):
* **Microvesicular:** Many tiny fat droplets fill the cell but don't push the nucleus aside. Seen in specific conditions like severe ALD, Reye syndrome (rare, often affects children after viral illness + aspirin), and acute fatty liver of pregnancy.
* **Macrovesicular:** Large fat droplets that push the nucleus to the edge of the cell. More common, seen in obesity, diabetes, and typical ALD.

1. Necrosis
Depending on the type	Depending on the cause	Depending on location
Coagulative necrosis: around central v.	Ischemic: caused by ischemia (maybe due to low blood supply).	Zonal necrosis:
   ■ Centrilobular necrosis: around central vein (zone 3)
   ■ Mid zonal: in zone 2
   ■ Periportal: involves zone 1 and linked to interface hepatitis.
   Councilman bodies | Toxic: caused by toxins (ex. acetaminophen overdose). | Focal:
   ■ Piece meal necrosis.
   ■ bridging necrosis.
   Lytic necrosis (liquefactive) | | Diffuse:
   ■ Massive necrosis.
   ■ Submassive necrosis.

Explanation: Describes different patterns of hepatocyte death (necrosis):
* **Types:** Coagulative (cell outline preserved initially), Lytic (cell dissolves), Apoptosis (programmed cell death, often seen as **Councilman bodies** - small, pink, dead cells).
* **Causes:** Ischemic (lack of oxygen), Toxic (drugs, poisons).
* **Location/Pattern:**
* **Zonal:** Affecting specific acinar zones (Centrilobular/Zone 3 is common due to low oxygen/drug metabolism; Periportal/Zone 1 often seen with toxins entering via portal blood or in interface hepatitis; Midzonal/Zone 2 is less common).
* **Focal:** Scattered spots of necrosis.
* **Piecemeal Necrosis (Interface Hepatitis):** Necrosis right at the

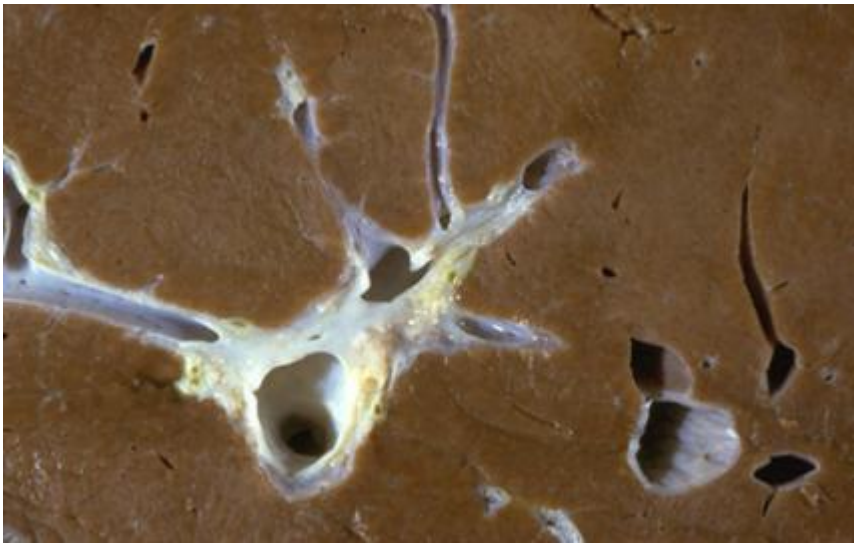
edge of portal tracts (discussed more under chronic hepatitis).
* **Bridging Necrosis:** Bands of dead cells connecting structures (e.g., central vein to portal tract, or portal tract to portal tract). This is serious as it disrupts architecture and predicts worse outcomes.
* **Diffuse:** Widespread necrosis (Massive or Submassive, seen in acute liver failure).

1. Regeneration
    - 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).

Explanation: The liver's ability to repair itself:
* Hepatocytes can divide (mitosis) to replace lost cells.
* Stem cells (progenitors) located in the smallest bile ductules (Canals of Hering), sometimes called oval cells, can also differentiate into new hepatocytes or bile duct cells if needed.

1. Fibrosis
    - portal or periportal fibrosis
    - pericentral- around the central vein.
    - pericellular fibrosis or fibrous tissue may be deposited directly within the sinusoids around single or multiple hepatocytes
    - bridging fibrosis

      ➢ 5 and 6 are related to injury, but not hepatic injuries themselves, they’re repair mechanisms in response to injury.



(Image: Microscopic view showing fibrous scar tissue (pale areas, often stained blue with special stains like Trichrome) forming around liver structures, indicating chronic injury.)

Explanation: Scarring in the liver:
* **Location:** Fibrosis can start around portal tracts (portal/periportal), around central veins (pericentral), or even around individual cells within the sinusoids (pericellular).
* **Bridging Fibrosis:** Scar tissue connecting portal tracts and/or central veins. This is a key step towards cirrhosis.
* **Note:** Regeneration (5) and Fibrosis (6) are the liver's responses to injury, not the initial injury itself. Fibrosis becomes pathological when it's excessive and disrupts function.

1. Cirrhosis (تشمع الكبد)
    - Micronodular.
    - Macronodular.

Explanation: The end-stage of chronic liver disease, characterized by diffuse fibrosis and the formation of regenerative nodules (clumps of liver cells trying to regrow, surrounded by scar). It can be classified by nodule size (Micronodular <3mm, often ALD; Macronodular >3mm, often viral). The Arabic term is provided.

1. Ductular proliferation.

Explanation: An increase in the number of small bile ductules, often seen as a reaction to injury, especially cholestasis or biliary obstruction.

Original Text: 7. Hepatic Failure: (فشل الكبد)

✓ Results when the hepatic functional capacity is almost totally lost (80 – 90%).

Explanation: Defines liver failure as occurring when the liver loses the vast majority (80-90%) of its ability to function. The Arabic term is provided.

- Causes:
  1. Massive hepatic necrosis: (To be explained in p.7)
     - Fulminant viral hepatitis
     - Drugs & chemicals:
     - Acetaminophen.
     - Halothane.
     - CCL4 poisoning.
     - Mushroom poisoning.
     - Anti TB drugs.
  2. Chronic liver disease.
  3. Hepatic dysfunction without overt cirrhosis
     - Reye's syndrome.
     - Tetracycline toxicity.
     - Acute fatty liver of pregnancy.

Explanation: Lists the main causes of liver failure:
1. **Massive Hepatic Necrosis:** Widespread death of liver cells, often happening quickly (acute). Causes include severe viral hepatitis (fulminant means rapid and severe), drug/chemical toxicity (acetaminophen overdose, halothane anesthetic, carbon tetrachloride, certain mushrooms, anti-tuberculosis drugs).
2. **Chronic Liver Disease:** Long-term liver damage eventually progressing to failure (e.g., cirrhosis from chronic hepatitis or alcohol).
3. **Dysfunction without Cirrhosis:** Sometimes the liver fails functionally without the typical scarring of cirrhosis. Examples include Reye's syndrome, tetracycline antibiotic toxicity, and acute fatty liver of pregnancy.

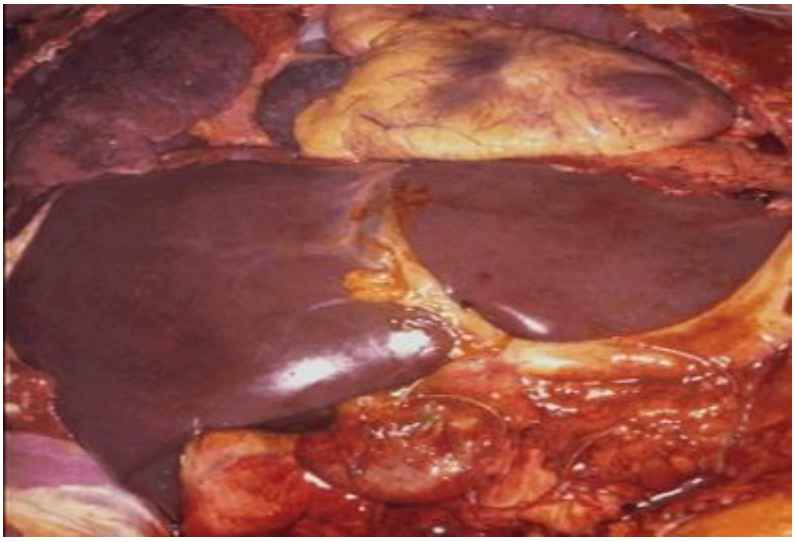
✓ Clinical features:
1. Jaundice (yellowing of the skin and eyes) - (Remember bilirubin metabolism in liver)
2. Hypoalbuminemia → edema. (Remember, liver makes albumin (maintains water in BVs), so low osmotic pressure of blood forces water to move toward the interstitial space (high osmotic pressure), causing edema).

3. Hyperammonemia.
4. Fetor hepaticus (musty or sweet & sour).
➢ A musty or sweet-sour smell on the breath, due to volatile substances like dimethyl sulfide accumulating.
5. Palmar erythema linked to hyperestrogenemia. (redness of the palm)
6. Spider angiomas.
7. Hypogonadism (dec. testosterone) & gynecomastia (breast enlargement in men).

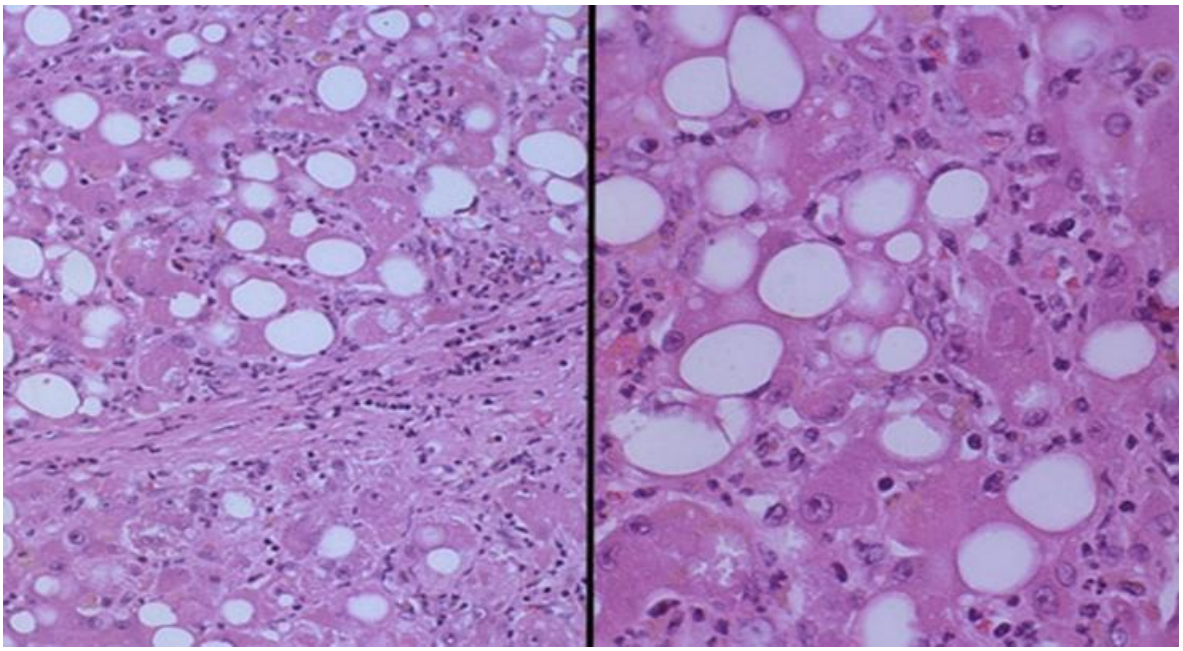
Explanation: Describes the signs and symptoms of liver failure:
1. **Jaundice:** Yellowing due to buildup of bilirubin (a waste product the liver normally processes).
2. **Hypoalbuminemia & Edema:** Low levels of albumin protein (made by the liver) in the blood. Albumin helps keep fluid inside blood vessels. Low levels cause fluid to leak into tissues, causing swelling (edema).
3. **Hyperammonemia:** High levels of ammonia in the blood because the failing liver can't detoxify it.
4. **Fetor Hepaticus:** A distinctive bad breath smell associated with liver failure.
5. **Palmar Erythema:** Redness of the palms, thought to be related to altered hormone metabolism (excess estrogen).
6. **Spider Angiomas:** Small, spider-like blood vessel formations on the skin, also linked to excess estrogen.
7. **Hypogonadism/Gynecomastia:** Reduced sex hormone function (testosterone) and breast development in men, due to altered hormone metabolism.

✓ Consequences:
1. Multiple organ failure: kidneys & lung.
2. Coagulopathy → bleeding due to defective coagulative factors.
➢ II, VII, IX, X
3. Hepatic encephalopathy (The liver fails to detoxify substances like ammonia, which accumulate and affect the brain, remember the clinical feature hyperammonemia.)
➢ Leads to (associated signs):
− ↓level of consciousness.
– Rigidity.
– Hyperreflexia.

− EEG changes.
– Seizures.
– Asterixis.
4. Hepatorenal syndrome (if the multiple organ failure(1) includes kidneys)
* Renal failure in patients with severe liver disease with no morphologic or functional causes for renal failure.



(Image: Gross view showing a severely damaged liver, likely from acute failure, appearing shrunken and discolored due to widespread necrosis.)



(Image: Brain section showing swelling (edema), a potential complication of severe hepatic encephalopathy in liver failure.)

Explanation: Describes the serious outcomes of liver failure:
1. **Multiple Organ Failure:** The liver failure can lead to failure of other organs, especially kidneys and lungs.
2. **Coagulopathy:** Bleeding problems because the liver isn't making essential clotting factors (Factors II, VII, IX, X are vitamin K-dependent factors synthesized by the liver).
3. **Hepatic Encephalopathy:** Brain dysfunction due to toxin buildup (especially ammonia). Signs include decreased consciousness, muscle rigidity, exaggerated reflexes (hyperreflexia), abnormal brain waves (EEG changes), seizures, and **Asterixis** (the characteristic "liver flap" tremor).
4. **Hepatorenal Syndrome:** Kidney failure that develops specifically as a complication of severe liver disease, even though the kidneys themselves may look structurally normal.

Quiz on this lecture

Note: This indicates a link to a quiz related to the lecture content in the original source.

Original Text: 8. Massive hepatic necrosis:

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

Explanation: Defines the timeframe for acute liver failure (ALF) based on how quickly hepatic encephalopathy develops after symptoms start:
* **Fulminant:** Very rapid, within 2-3 weeks.
* **Subfulminant:** Still relatively rapid, but takes longer, up to 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.

Explanation: Lists causes of massive liver cell death leading to ALF. Note the overlap with general causes of liver failure, but emphasizing acute/rapid causes:
1. **Viral Hepatitis:** Especially Hepatitis A, B, or B with D co-infection. Hepatitis C is less likely to cause fulminant failure.
2. **Drugs/Chemicals:** As mentioned before (acetaminophen, etc.).
3. **Heat Stroke:** Severe overheating can damage the liver.
4. **Hepatic Vein Obstruction:** Blockage of veins draining the liver (e.g., Budd-Chiari syndrome).
5. **Wilson Disease:** Genetic copper overload disorder, can present acutely.
6. **Acute Fatty Liver of Pregnancy:** A rare but serious complication of pregnancy.
7. **Massive Malignant Infiltration:** Widespread cancer invasion of the liver.
8. **HBV Reactivation/HDV Superinfection:** Flare-up of chronic Hepatitis B, especially if Hepatitis D virus is also acquired.
9. **Autoimmune Hepatitis:** Can sometimes present acutely and severely.

Original Text: 9. Alcoholic liver disease

✓ Alcohol is the most widely abused agent.
✓ It is the 5th leading cause of death in USA due to:
1. Accidents
2. Cirrhosis

Explanation: Introduces alcoholic liver disease (ALD), highlighting alcohol abuse prevalence and its contribution to mortality, both directly via cirrhosis and indirectly via accidents.

✓ 80 – 100 mg/dl is the legal definition for driving under the influence of alcohol.
➢ 44 ml of ethanol are required to produce this level in 70kg person.

Explanation: Provides context on legal blood alcohol limits and the amount needed to reach it. (Note: 100 mg/dL = 0.10% BAC).

✓ Short term ingestion of 80 gms/d of ethanol is associated with fatty change in liver (steatosis).

Explanation: Even short-term heavy drinking (around 8 standard drinks per day) can cause fatty liver.

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

Explanation: Highlights the dangers of acute alcohol poisoning in non-tolerant individuals.

✓ 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.

Explanation: Explains tolerance in chronic drinkers. Their liver enzymes, particularly the **Cytochrome P450 system** (specifically **CYP2E1**), increase significantly (induction). This speeds up alcohol breakdown, allowing them to tolerate higher blood levels. However, this enzyme induction also affects the metabolism of other drugs (like acetaminophen), potentially increasing their toxicity.

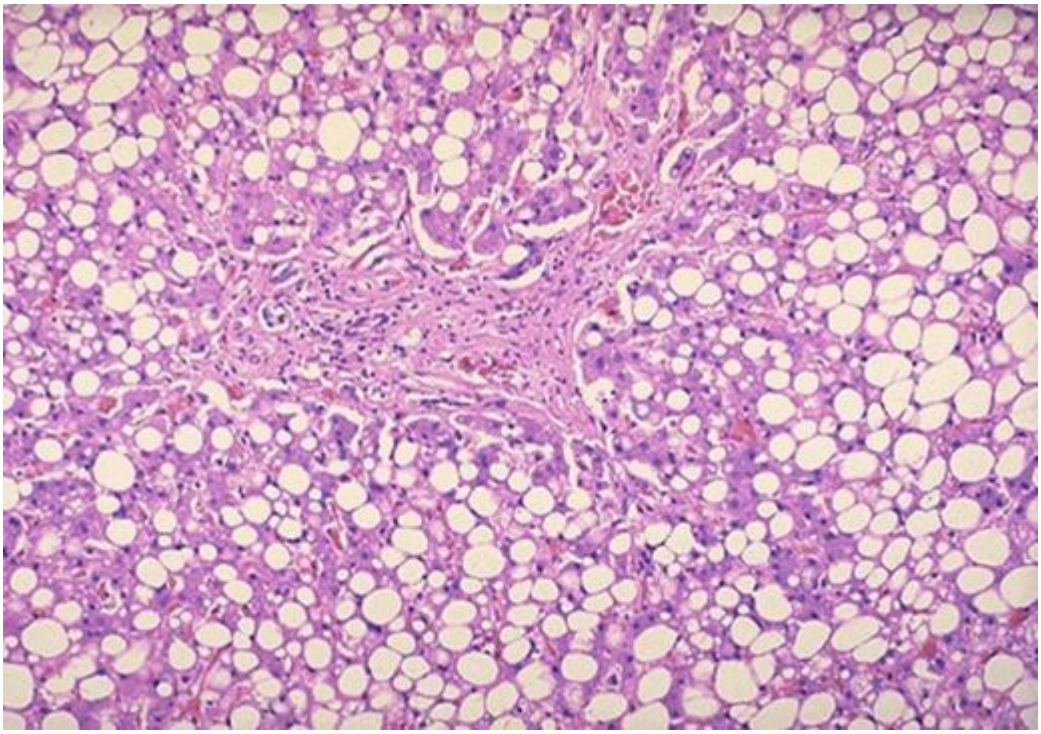
✓ Forms of alcoholic liver disease:
* Hepatic steatosis (90-100% of drinkers).
* Alcoholic hepatitis (1- 35% of drinkers).
* Cirrhosis (14% of drinkers).
✓ Steatosis & hepatitis may develop independently.

Explanation: Lists the main types of ALD:
* **Hepatic Steatosis (Fatty Liver):** Most common, fat buildup.
* **Alcoholic Hepatitis:** More severe inflammation and cell death.
* **Cirrhosis:** End-stage scarring.
Note the percentages: almost all heavy drinkers get fatty liver, but fewer

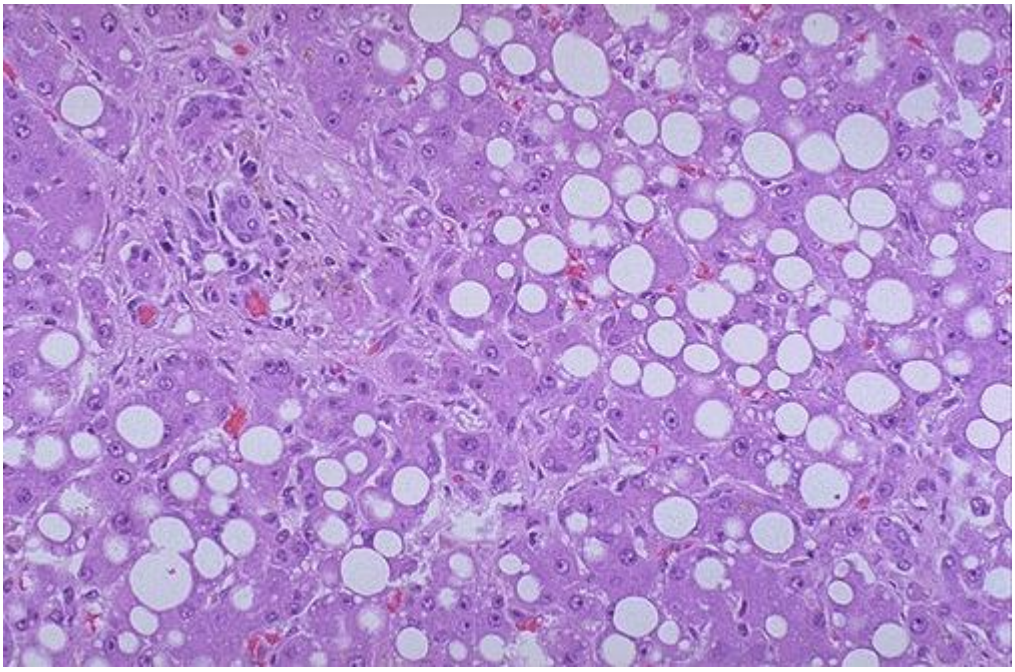
progress to hepatitis or cirrhosis. Fatty liver and hepatitis can occur separately.

Hepatic steatosis	Alcoholic hepatitis	Alcoholic cirrhosis
■ This can occur following even moderate intake of alcohol in the form of microvesicular steatosis.	Characteristic findings:	Usually, it develops slowly.
■ Chronic intake → diffuse steatosis.	1- Hepatocyte swelling & necrosis ■ Accumulation of fat & water & proteins ■ Cholestasis	- Initially the liver is enlarged yellow but over years it becomes brown shrunken non-fatty organ s.t < l kg in wt.
■ Liver is large (4 – 6 kg) soft yellow & greasy	2- Mallory-hyaline bodies (see next page) ■ eosinophilic cytoplasmic inclusions in degenerating hepatocytes formed of cytokeratin intermediate filaments & other proteins.	- Micronodular → mixed micro & macronodular - Laennec cirrhosis = scar tissue - Hemosiderin deposition in hepatocytes & Kupffer cells. - Bile stasis - Mallory bodies are only rarely evident at this stage
■ Continued intake → fibrosis	3- Neutrophilic reaction	- Irreversible
■ Fatty change is reversible with complete absention	4- Fibrosis • Sinusoidal &	It can develop rapidly in the presence of

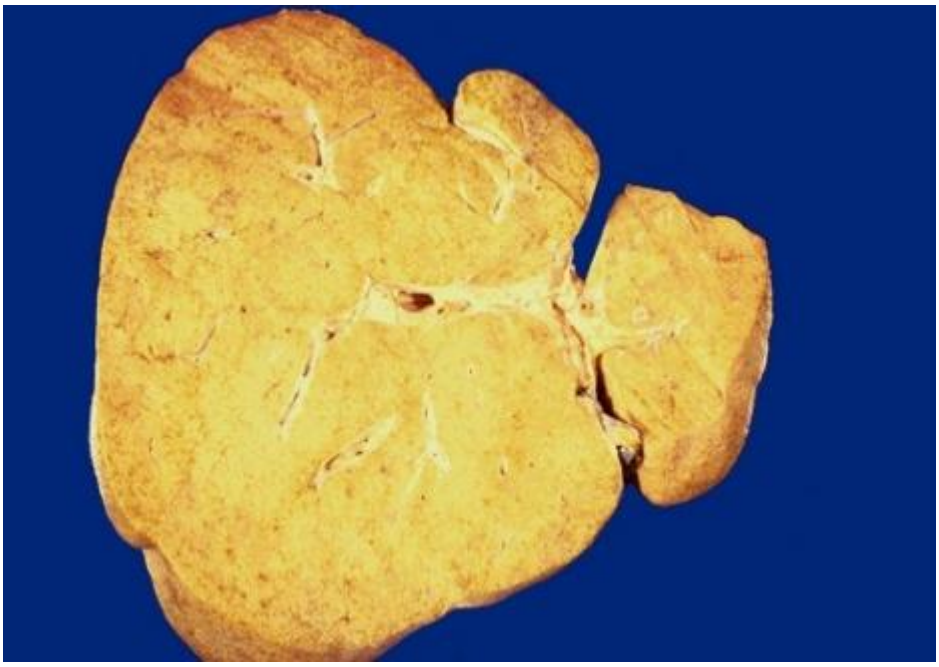
Hepatic steatosis	Alcoholic hepatitis	Alcoholic cirrhosis
from further intake of alcohol	perivenular fibrosis • Periportal fibrosis	alcoholic hepatitis (within 1-2 yrs).
	5- Cholestasis	
	6- Mild deposition of hemosiderin in hepatocytes & Kupffer cells	



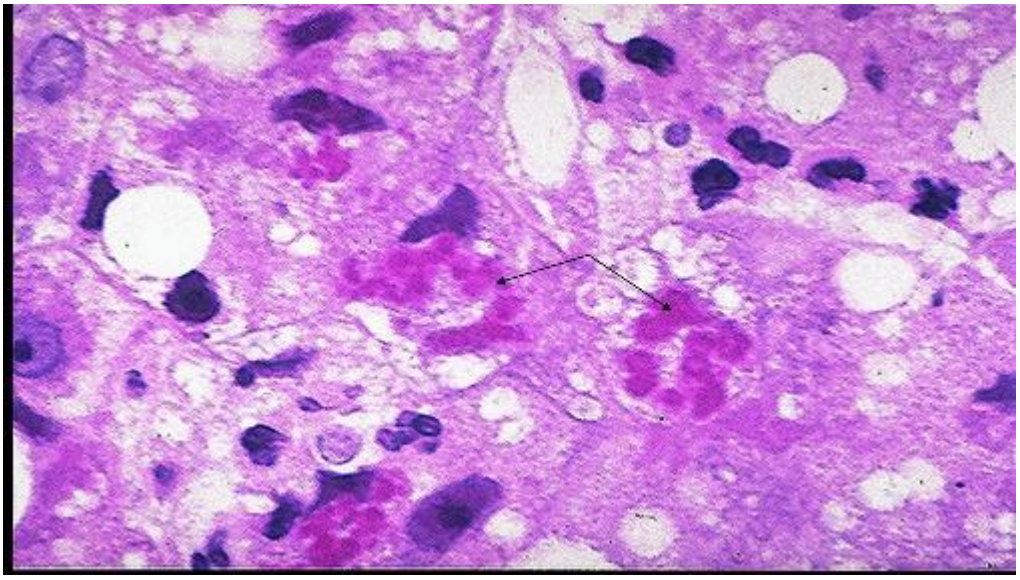
(Image: Microscopic view showing hepatocytes filled with large, clear fat droplets (macrovesicular steatosis), characteristic of alcoholic fatty liver.)



(Image: Another microscopic view of alcoholic steatosis, highlighting the widespread accumulation of fat within liver cells.)



(Image: Gross view of a liver with severe steatosis (fatty change), appearing enlarged and yellow.)



(Image: Microscopic view of alcoholic hepatitis. Note the swollen hepatocytes, inflammatory cells (neutrophils), and the dense, pink, irregular clumps within some cells - Mallory-Denk bodies (indicated by arrows).)

Explanation: Compares the features of the three forms of ALD:
* **Steatosis:** Fat accumulation (micro or macrovesicular), enlarged yellow/greasy liver, generally reversible if drinking stops.
* **Alcoholic Hepatitis:** More severe injury with hepatocyte swelling/necrosis, **Mallory-Denk bodies** (characteristic pink clumps in cells), **neutrophil** inflammation, and early fibrosis (often around central veins - perivenular). Cholestasis (bile flow blockage) can occur.
* **Cirrhosis:** End-stage scarring, liver often shrinks and becomes hard/brown, nodules form (initially micronodular - Laennec cirrhosis), irreversible. Can develop faster if alcoholic hepatitis is present. Mild iron deposition (hemosiderin) can be seen.

2- Mallory-hyaline inclusions are characteristic but not pathognomonic of alcoholic liver disease, they are also seen in:
1- Primary biliary cirrhosis
2- Wilson disease
3- Chronic cholestatic syndromes
4- Hepatocellular carcinoma

Explanation: Important point: While Mallory-Denk bodies are typical of ALD, they aren't unique (**not pathognomonic**). They can be found in other liver conditions too.

❖ Pathogenesis of alcoholic liver disease: (refer to toxicity by ethanol in the next seg.)

- Short term ingestion of 80gm of ethanol/day (8 beers) → 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.

Explanation: Discusses factors influencing ALD development:
* **Dose/Duration:** Short-term heavy drinking causes fatty liver; long-term very heavy drinking causes severe injury. There's a borderline dose.
* **Sex Differences:** Women are more prone to liver damage, partly because they metabolize less alcohol in the stomach, leading to higher blood levels reaching the liver.
* **Individual Susceptibility:** Not everyone who drinks heavily gets cirrhosis, suggesting genetic or other factors play a role.

❖ Clinical features:
* Hepatic steatosis (reversible with alcohol cessation)
  Enlarged liver (hepatomegaly).
  ↑ liver enzymes.
  Severe hepatic dysfunction is unusual.
* Alcoholic hepatitis
  Occurs after 15-20 years of excessive drinking.
  Non-specific symptoms, malaise, anorexia, wt. loss.
  Enlarged liver & Spleen.
  ↑ liver function test (LFT), increase levels of liver enzymes (AST and ALT, etc.).
  Each bout (episode) of hepatitis → 10-20% risk of death.

→ cirrhosis in 1/3 in few yrs.
* Cirrhosis
  Causes Portal hypertension.

Explanation: Describes the clinical presentation of ALD stages:
* **Steatosis:** Often asymptomatic or mild symptoms like enlarged liver and elevated liver enzymes on tests. Usually not severe dysfunction.
* **Alcoholic Hepatitis:** Develops after long-term drinking. Symptoms are often vague (malaise, poor appetite, weight loss). Liver and spleen may be enlarged. Liver function tests (LFTs) are elevated. Each episode carries a significant risk of death and increases the chance of progressing to cirrhosis.
* **Cirrhosis:** Leads to complications like portal hypertension (discussed later).

❖ Causes of death in alcoholic liver disease
1- Hepatic Failure.
2- Massive GI bleeding.
3- Infections.
4- Hepatorenal syndrome.
5- Hepatocellular carcinoma (HCC) in 3-6% of cases.

Explanation: Lists the common ways patients with severe ALD die:
1. **Liver Failure:** The liver stops functioning.
2. **GI Bleeding:** Often from ruptured esophageal varices (a complication of portal hypertension).
3. **Infections:** Liver disease impairs the immune system.
4. **Hepatorenal Syndrome:** Kidney failure secondary to liver failure.
5. **Liver Cancer (HCC):** Cirrhosis significantly increases the risk of developing primary liver cancer.

Original Text: 10. Ethanol metabolism:

- Ethanol → acetaldehyde → Acetic Acid
  $CH_3CH_2OH \rightarrow CH_3C{=}OH$

Explanation: Shows the two main steps in breaking down alcohol (ethanol):

1. Ethanol is converted to Acetaldehyde.
2. Acetaldehyde is converted to Acetic Acid (acetate), which can then be used for energy or excreted.

- The first conversion is catalyzed by:
  Alcohol dehydrogenase (stomach + liver).
  Cytochrome P-450.
  Catalase (liver).

Explanation: Lists the enzymes that perform the first step (Ethanol → Acetaldehyde):
* **Alcohol Dehydrogenase (ADH):** The main enzyme, found in the stomach lining and liver cells.
* **Cytochrome P450 (specifically CYP2E1):** Part of the Microsomal Ethanol Oxidizing System (MEOS). Its activity increases with chronic drinking (induction).
* **Catalase:** A minor pathway located in peroxisomes.

- The second conversion is catalyzed by: Aldehyde dehydrogenase.

Explanation: The enzyme for the second step (Acetaldehyde → Acetic Acid) is **Aldehyde Dehydrogenase (ALDH)**, primarily found in liver mitochondria.

✓ After absorption ethanol is distributed as Acetic acid in all tissues & fluid in direct proportion to blood level.

Correction/Clarification: This sentence seems slightly inaccurate as written. Ethanol itself distributes throughout body water in proportion to blood level. The product, acetic acid, enters general metabolism. The distribution relates to ethanol concentration.

✓ 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.

Explanation: Repeats the point about lower stomach ADH activity in women, leading to less first-pass metabolism and higher blood alcohol levels for the same amount consumed compared to men.

✓ less than 10% of absorbed ethanol is excreted unchanged in urine sweat & breathe.

Explanation: Most alcohol is metabolized; only a small fraction is eliminated directly via kidneys, skin, and lungs (this is the basis for breathalyzer tests).

✓ There is genetic polymorphism in aldehyde dehydrogenase that affect ethanol metabolism, for example:
50% of Chinese, Vietnamese & Japanese have lowered enzyme activity due to point mutation of the enzyme → accumulation of acetaldehyde → facial flushing, tachycardia & hyperventilation.

Explanation: Explains genetic variations (**polymorphism**) in the ALDH enzyme. A common variant, especially in East Asian populations, results in much lower ALDH activity. This causes **acetaldehyde** (the toxic intermediate) to build up after drinking alcohol, leading to unpleasant symptoms known as the "flush reaction" (facial redness, rapid heartbeat, rapid breathing).

❖ Mechanism of ethanol toxicity:
1. Fatty change:
a) Shunting of lipid catabolism toward lipid biosynthesis due to excess production of NADH over NAD in cytosol & mitochondria.
b) Acetaldehyde forms adduct with tubulin and decrease function of microtubules, therefore a decrease in lipoprotein transport from liver.
c) Increased peripheral catabolism of fat, thereby increased FFA delivery to the liver.
d) Decreased secretion of lipoproteins from hepatocytes.
e) Decreased oxidation of FFA by mitochondria

Explanation: Details how alcohol causes fatty liver (steatosis):
a) **Metabolic Shift:** Alcohol metabolism generates excess NADH (relative to NAD+). This imbalance pushes liver metabolism away from breaking down fats (catabolism) and towards making fats (biosynthesis).
b) **Transport Issues:** Acetaldehyde (toxic byproduct) binds to tubulin (part of the cell's transport system - microtubules), impairing the liver's ability to package and export fats as lipoproteins.
c) **Increased Fat Delivery:** Alcohol can increase the breakdown of fat

in peripheral tissues (like adipose tissue), leading to more free fatty acids (FFA) arriving at the liver.
d) **Decreased Export:** Related to (b), the liver's secretion of lipoproteins (the packages used to export fat) is reduced.
e) **Decreased Fat Burning:** The liver's ability to burn fatty acids for energy in the mitochondria is also reduced.

1. Induction of cytochrome P-450 enhances the metabolism of drugs to toxic metabolites (e.g. acetaminophen).

Explanation: As mentioned before, chronic alcohol use increases CYP450 enzymes (especially CYP2E1). This can speed up the conversion of other drugs (like acetaminophen/paracetamol) into their toxic forms, increasing the risk of liver damage even at normally safe doses of the drug.

1. Increased free radicals production due to (+) of cytochrome P-450, this leads to membrane & protein damage.

Explanation: The increased activity of CYP450 also generates more harmful **reactive oxygen species (ROS)** or free radicals, which damage cell membranes and proteins through oxidative stress.

1. Alcohol directly affects microtubular, mitochondrial function, and membrane fluidity.

Explanation: Alcohol itself, not just its byproducts, can directly harm cell structures like microtubules (transport), mitochondria (energy production), and cell membranes.

1. Acetaldehyde causes lipid peroxidation & antigenic alteration of hepatocytes → immune attack

Explanation: Acetaldehyde damages cell membranes (lipid peroxidation) and can alter liver cell proteins, making them look foreign (**antigenic alteration**). This can trigger an immune response against the body's own liver cells.

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

Explanation: Having both ALD and Hepatitis C virus (HCV) infection is much worse than having either alone; the liver damage progresses faster. HCV is common among alcoholics.

1. Alcohol causes the release of bacterial endotoxins into portal circulation from the gut, thus inflammation of the liver.

Explanation: Alcohol can damage the gut lining, allowing bacterial toxins (**endotoxins**) to leak into the portal blood flowing to the liver. These endotoxins activate immune cells (like Kupffer cells) in the liver, promoting inflammation.

1. Alcohol causes regional hypoxia in the liver due to the release of endothelins, which are potent vasoconstrictors, causing a decrease in hepatic sinusoidal perfusion.

Explanation: Alcohol can trigger the release of **endothelins**, substances that constrict blood vessels. This can reduce blood flow (**perfusion**) through the liver sinusoids, leading to localized oxygen deficiency (**hypoxia**), especially in Zone 3 which already has the lowest oxygen supply.

1. Alteration of cytokine regulation
   - TNF is a major effector of injury.
   - IL6, IL8, IL18.

Explanation: Alcohol disrupts the balance of chemical messengers (**cytokines**) involved in inflammation. It increases pro-inflammatory cytokines like **Tumor Necrosis Factor (TNF)**, Interleukin-6 (IL-6), IL-8, and IL-18, which contribute significantly to liver damage.

QUIZ on this lecture

Note: Indicates a link to a quiz in the original source.

Original Text: 11. Cirrhosis:

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

Explanation: Defines cirrhosis as a widespread (**diffuse**) liver condition involving two key features: extensive scarring (**fibrosis**) and the replacement of normal liver tissue (**parenchyma**) with abnormal lumps (**nodules**) of regenerating cells.

✓ Main characteristics:
1. Bridging fibrous septae.
2. Parenchymal nodules encircled by fibrotic bands.
3. Diffuse architecture disruption.

Explanation: Lists the defining histological features of cirrhosis:
1. **Bridging Fibrous Septa:** Thick bands of scar tissue connecting different parts of the liver lobule (e.g., portal tracts to central veins).
2. **Parenchymal Nodules:** Clumps of liver cells (hepatocytes) trying to regenerate, but trapped and surrounded by the scar tissue bands.
3. **Diffuse Architecture Disruption:** The normal, organized structure of the liver is completely distorted by the scarring and nodules throughout the entire organ.

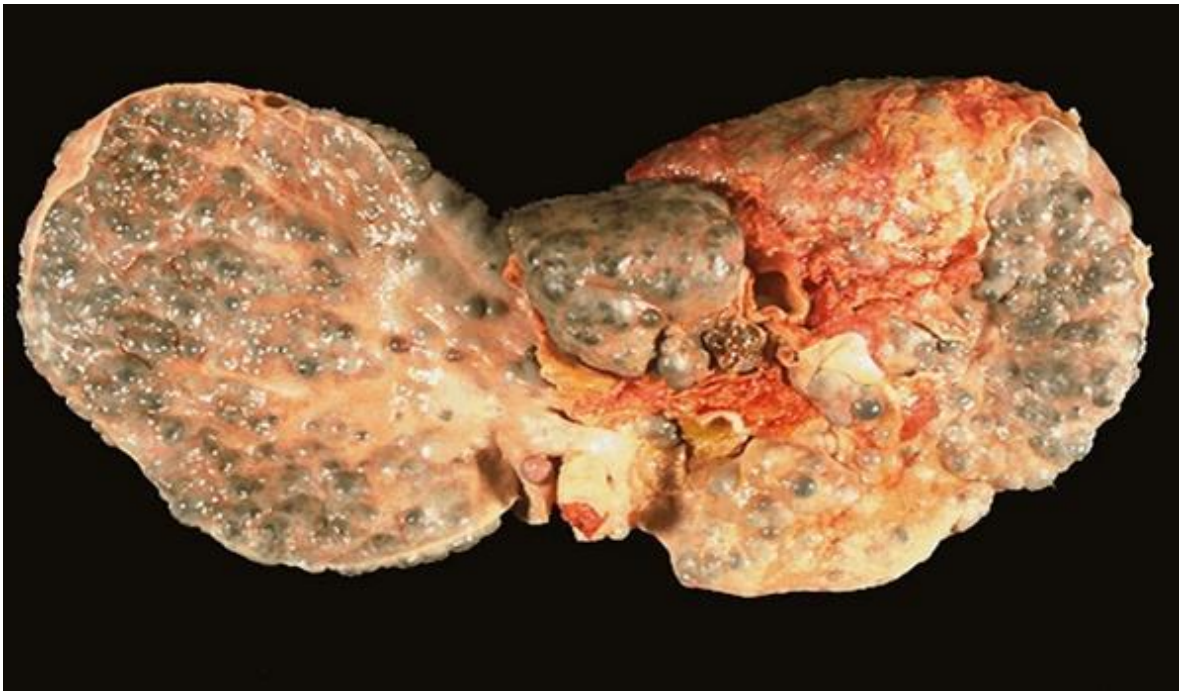
✓ Types:
■ Micronodules < 3mm in diameter.
■ Macronodules > 3 mm in diameter.
Micronodular cirrhosis.
→ Macronodular cirrhosis.

(Image: Gross view of a cirrhotic liver showing the characteristic nodular surface due to extensive fibrosis and regeneration.)

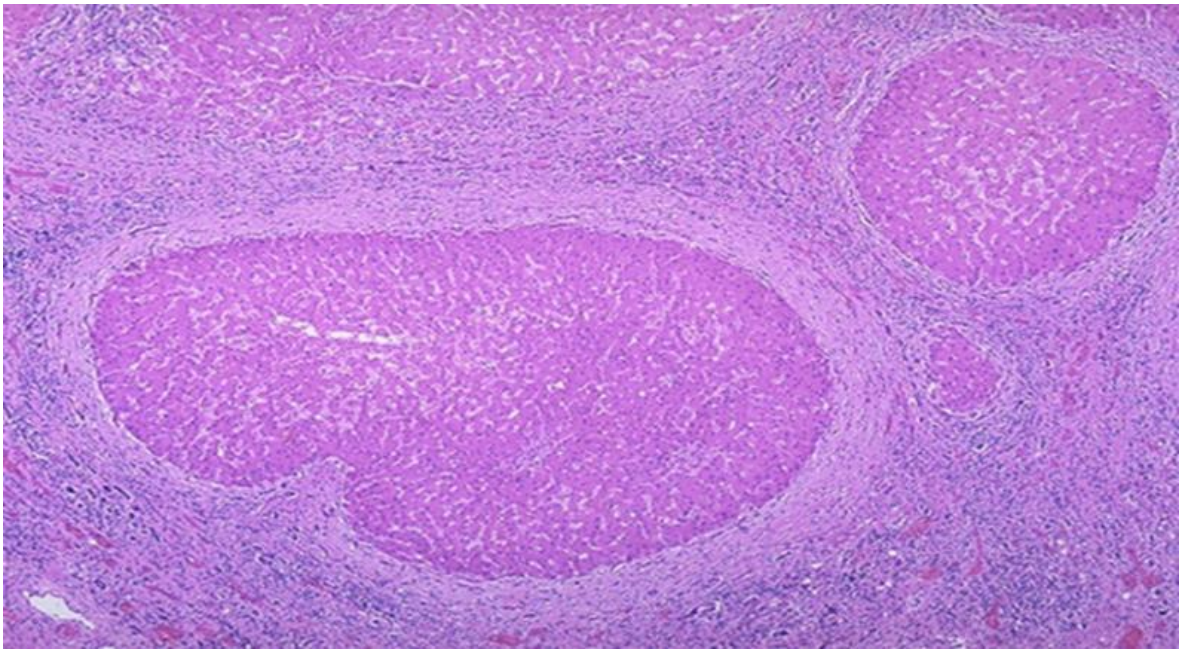
Explanation: Cirrhosis can be classified based on the size of the nodules:
* **Micronodular:** Nodules are small (<3mm). Often associated with alcoholic liver disease or biliary diseases.
* **Macronodular:** Nodules are larger (>3mm). Often associated with chronic viral hepatitis.
(The arrows likely pointed to examples in the original document).

✓ Histology of cirrhosis:

Cirrhosis appears microscopically as regenerating hepatocyte nodules surrounded by fibrous tissue containing blood vessels and inflammatory cells. These regenerative nodules can maintain liver function, which may allow patients to remain asymptomatic for years.



(Image: Microscopic view using Trichrome stain, which highlights fibrous tissue in blue. Note the thick blue bands of collagen surrounding nodules of liver cells.)



(Image: Microscopic view using standard H&E stain showing regenerative nodules of hepatocytes separated by pink fibrous bands.)

Explanation: Describes the microscopic appearance: nodules of liver cells surrounded by scar tissue (fibrosis), which often contains blood vessels and inflammatory cells. While the liver is damaged, these nodules can sometimes provide enough function for the patient to have no symptoms for a long time.

✓ Causes of cirrhosis:
1. Chronic alcoholism.
2. Chronic viral infection HBV & HCV.
3. Biliary disease.
4. Hemochromatosis.
5. Autoimmune hepatitis.
6. Wilson disease.
7. α-1- antitrypsin deficiency.
8. Rare causes
– Galactosemia.
– Tyrosinosis. – Glycogen storage disease III &IV.
– Lipid storage disease.
– Hereditary fructose intolerance.
– Drug induced e.g. methyldopa.
9. Cryptogenic cirrhosis 10%

Explanation: Lists the many causes of cirrhosis:
* **Common:** Chronic alcohol abuse, chronic Hepatitis B (HBV) and C (HCV), diseases affecting bile ducts (Biliary disease), iron overload (Hemochromatosis).
* **Less Common:** Autoimmune hepatitis, copper overload (Wilson disease), Alpha-1-antitrypsin deficiency (a genetic disorder).
* **Rare:** Various inherited metabolic disorders (Galactosemia, Tyrosinosis, certain Glycogen and Lipid storage diseases, Hereditary fructose intolerance), certain drugs (like methyldopa, an old blood pressure medication).
* **Cryptogenic:** Cirrhosis where the cause cannot be identified (about 10% of cases). Many of these are now thought to be related to non-alcoholic fatty liver disease (NAFLD).

✓ Pathogenesis of cirrhosis:
* The mechanism of cirrhosis involves:
1. Hepatocellular death.
* Cell death should occur over a long period of time & accompanied by fibrosis(3).
2. Regeneration.
3. Progressive fibrosis.
4. Vascular changes.

Explanation: Outlines the key processes driving cirrhosis development:
1. **Hepatocyte Death:** Ongoing, long-term death of liver cells.
2. **Regeneration:** Surviving liver cells try to divide and replace the dead ones, forming nodules.
3. **Progressive Fibrosis:** Continuous formation and deposition of scar tissue.
4. **Vascular Changes:** Alterations in blood vessel structure and flow within the liver.

✓ In normal liver the ECM collagen (types I, III, V& XI) is present only in:
* Liver capsule.
* Portal tracts.
* Around the central vein.
✓ Delicate framework of type IV collagen & other proteins lies in the space of Disse (tiny gap found between hepatocytes and sinusoids).

* In cirrhosis types I & III collagen & others are deposited in the space of Disse.

Explanation: Describes the location of collagen (scar protein) in the liver:
* **Normal Liver:** Tougher collagens (Type I, III etc.) forming the extracellular matrix (ECM) are normally restricted to the outer capsule, portal tracts, and around central veins.
A delicate scaffold of Type IV collagen exists in the **Space of Disse** (the crucial gap between hepatocytes and blood sinusoids where exchange happens).
* **Cirrhosis:** The key pathological change is the deposition of the tough, scar-forming collagens (Type I and III) within the Space of Disse, replacing the delicate Type IV scaffold. This severely impairs the exchange between blood and liver cells.

✓ The major source of collagen in cirrhosis is the perisinusoidal stellate cells (Ito cells), which lie in the space of Disse.
* Perisinusoidal stellate cells normally act as storage cells for vitamin A and fat.
* Upon stimulation, they transform into myofibroblast-like cells under the influence of transforming growth factor β (TGF-β).

Explanation: Identifies the main cell responsible for producing scar tissue in cirrhosis:
* **Hepatic Stellate Cells (also called Ito cells):** These cells reside in the Space of Disse.
* **Normal Function:** They store Vitamin A.
* **Activation:** Chronic liver injury activates these cells (influenced by signaling molecules like **TGF-β**). Activated stellate cells transform into cells resembling muscle/fibroblast cells (**myofibroblasts**) and start producing large amounts of collagen (scar tissue).

✓ The stimuli for the activation of stellate cells & production of collagen are:
1. reactive oxygen species
2. Growth factors
3. cytokines TNF, IL-I, lymphotoxins

Explanation: Lists the signals that trigger stellate cell activation and scar production: inflammation-related signals like reactive oxygen species (free radicals), various growth factors, and inflammatory cytokines (TNF, IL-1, lymphotoxins).

✓ The vascular changes include:
1. Loss of sinusoidal endothelial cell fenestration
2. Development of vascular shunts, such as:
Portal v - hepatic v
Hepatic a - portal v

Explanation: Describes changes to blood vessels in cirrhosis:
1. **Loss of Fenestrations:** Normal liver sinusoids have tiny pores (**fenestrations**) in their lining endothelial cells, allowing easy passage of substances between blood and hepatocytes. In cirrhosis, these pores are lost, making the sinusoids more like regular capillaries and hindering exchange.
2. **Shunts:** Abnormal connections (shunts) form between blood vessels within the scar tissue, allowing blood to bypass the functional liver tissue (e.g., portal vein blood flowing directly to hepatic vein, or hepatic artery blood flowing into the portal vein system).

✓ Defect in liver function.
✓ Loss of microvilli from hepatocytes, causes a decrease in the transport capacity of the cells.
✓ Collagen deposition converts sinusoids with fenestrated endothelial channels that allow free exchange of solutes between plasma and hepatocytes to higher-pressure, fast-flowing vascular channels without such solute exchange.
✓ The movement of proteins (e.g., albumin, clotting factors, lipoproteins) between hepatocytes and plasma is markedly impaired.
✓ These functional changes are aggravated by the loss of microvilli from the hepatocyte surface, which diminishes the transport capacity of the cell.

Explanation: Summarizes the functional consequences of the structural changes in cirrhosis:
* The combination of scar tissue deposition in the Space of Disse, loss of sinusoidal fenestrations, and loss of **microvilli** (tiny projections on the

hepatocyte surface that increase surface area for transport) severely impairs the liver's ability to exchange substances with the blood.
* This hinders the uptake of nutrients/toxins and the secretion of proteins (like albumin, clotting factors) made by the liver.
* The sinusoids become less like low-pressure exchange vessels and more like higher-pressure channels, contributing to portal hypertension.

✓ Clinical features of cirrhosis:
* Silent
* Anorexia, wt. loss, weakness

Explanation: Cirrhosis can be asymptomatic (**silent**) for a long time, or present with non-specific symptoms like poor appetite (**anorexia**), weight loss, and weakness.

✓ Complications:
1. Progressive hepatic failure
2. Portal hypertension
3. Hepatocellular carcinoma

Explanation: Lists the major serious complications of cirrhosis: eventual liver failure, increased pressure in the portal vein system (**portal hypertension**), and the development of primary liver cancer (**hepatocellular carcinoma**).

Original Text: 12. Portal Hypertension:

Increased resistance to portal blood flow at the level of sinusoids and compression of central veins by perivenular fibrosis and parenchymal nodules

Explanation: Defines portal hypertension as high blood pressure in the portal vein system. It's caused by increased resistance to blood flowing through the liver. This resistance happens at the sinusoids (due to fibrosis in the Space of Disse, loss of fenestrations) and because the central veins get squeezed by surrounding scar tissue (perivenular fibrosis) and regenerative nodules.

✓ Arterial–portal anastomosis develops in the fibrous bands → increase in the blood pressure in the portal venous system

Explanation: Abnormal connections (**anastomoses**) form between branches of the hepatic artery and the portal vein within the scar tissue (**fibrous bands**). This forces higher-pressure arterial blood into the normally low-pressure portal system, further increasing portal pressure.

✓ ■ These changes disrupt the normal low-resistance circulation within the liver, leading to increased pressure in the portal vein. As a result, blood is forced to bypass the liver through alternative vessels, contributing to complications such as varices, splenomegaly, and ascites.

Explanation: This note summarizes the effect: the scarring and vascular changes stop the liver from being a low-resistance pathway for blood. Pressure builds up in the portal vein, forcing blood to find detours (**alternative vessels** or **collaterals**) around the liver, leading to complications like swollen veins (varices), enlarged spleen (splenomegaly), and fluid buildup in the abdomen (ascites).

✓ Anastomoses between the arterial and portal systems in the fibrous bands also contribute to portal hypertension by imposing arterial pressure on the normally low-pressure portal venous system.

Explanation: Reinforces the point that the abnormal artery-to-portal vein connections worsen portal hypertension.

❖ Causes of portal hypertension:
The most common cause of portal hypertension is liver cirrhosis. However, it can also result from other, less common causes divided into three categories:
1. Prehepatic:
■ Portal vein thrombosis
■ Massive splenomegaly
2. Posthepatic:
■ Severe right-sided heart failure
■ Constrictive pericarditis
■ Hepatic vein outflow obstruction
3. Hepatic

■ Cirrhosis
■ Schistosomiasis
■ Massive fatty change
■ Diffuse granulomatosis (e.g., sarcoidosis, TB)
■ Disease of portal microcirculation (e.g., nodular regenerative hyperplasia)

Explanation: Categorizes the causes of portal hypertension based on where the blockage/resistance occurs relative to the liver sinusoids:
* **Prehepatic:** Problem before the liver sinusoids (e.g., a clot in the portal vein itself - thrombosis, or massive spleen enlargement increasing flow).
* **Posthepatic:** Problem after the liver sinusoids, blocking outflow (e.g., severe heart failure backing blood up, inflammation constricting the heart - pericarditis, blockage of the hepatic veins draining the liver).
* **Hepatic (Intrahepatic):** Problem within the liver itself. Cirrhosis is the most common cause here. Others include parasitic infection (Schistosomiasis), severe fatty liver, widespread inflammatory nodules (granulomas like in Sarcoidosis or Tuberculosis - TB), or diseases affecting the small vessels within the liver.

❖ Clinical consequence of portal hypertension:
1. Ascites.
2. Portosystemic shunts.
3. Hepatic encephalopathy.
■ Hepatic encephalopathy, also called portosystemic encephalopathy, happens when your liver isn’t filtering toxins as it should. These toxins build up in your blood and affect your brain, causing confusion, disorientation and other changes. Hepatic encephalopathy can get better with treatment, but it can be life-threatening without.
4. Splenomegaly

Explanation: Lists the major complications resulting from portal hypertension:
1. **Ascites:** Fluid buildup in the abdomen.
2. **Portosystemic Shunts:** Development of collateral blood vessels bypassing the liver.
3. **Hepatic Encephalopathy:** Brain dysfunction due to toxins (like ammonia) bypassing liver detoxification via the shunts and reaching the

brain.
4. **Splenomegaly:** Enlargement of the spleen due to blood backing up from the portal vein.

Original Text: 13. Ascites (1st clinical consequence of portal hypertension)

- Collection of excess fluid in the peritoneal cavity
- It becomes clinically detectable when at least 500 mL have accumulated
- Features:
    1. Serous fluid
    2. Contains as much as 3 g/mL of protein (albumin)
    3. Has the same concentration as blood of glucose, Na^+, and K^+
    4. Mesothelial cells and lymphocytes (Mesothelial cells are normally lining the cavity)

Extra image:

5. Neutrophils → infection
6. RBCs → disseminated cancer

Explanation: Describes Ascites:
* **Definition:** Fluid buildup in the abdominal (peritoneal) cavity.
* **Detection:** Usually noticeable only after about half a liter (500 mL) accumulates.
* **Fluid Characteristics:**
* It's typically clear, yellowish (**serous**).
* Contains protein, mainly albumin (Note: 3 g/mL seems extremely high, likely a typo in the original, should probably be 3 g/dL or less. Typical ascitic fluid protein is < 2.5-3 g/dL).
* Has similar levels of glucose, sodium (Na+), and potassium (K+) as blood plasma.
* Contains cells normally found lining the cavity (**mesothelial cells**) and some immune cells (**lymphocytes**).
* **Abnormal Cells:** Finding neutrophils suggests infection (spontaneous

bacterial peritonitis - SBP). Finding red blood cells (RBCs) might suggest cancer spread within the abdomen.

❖ Pathogenesis:
1. Increased sinusoidal blood pressure.
2. Hypoalbuminemia
3. Leakage of hepatic lymph into the peritoneal cavity.
✓ Normal thoracic duct lymph flow is 800–1000 mL/day.
✓ In cirrhosis, it can reach up to 20 L/day.
4. Renal retention of Na^+ and water due to secondary hyperaldosteronism.

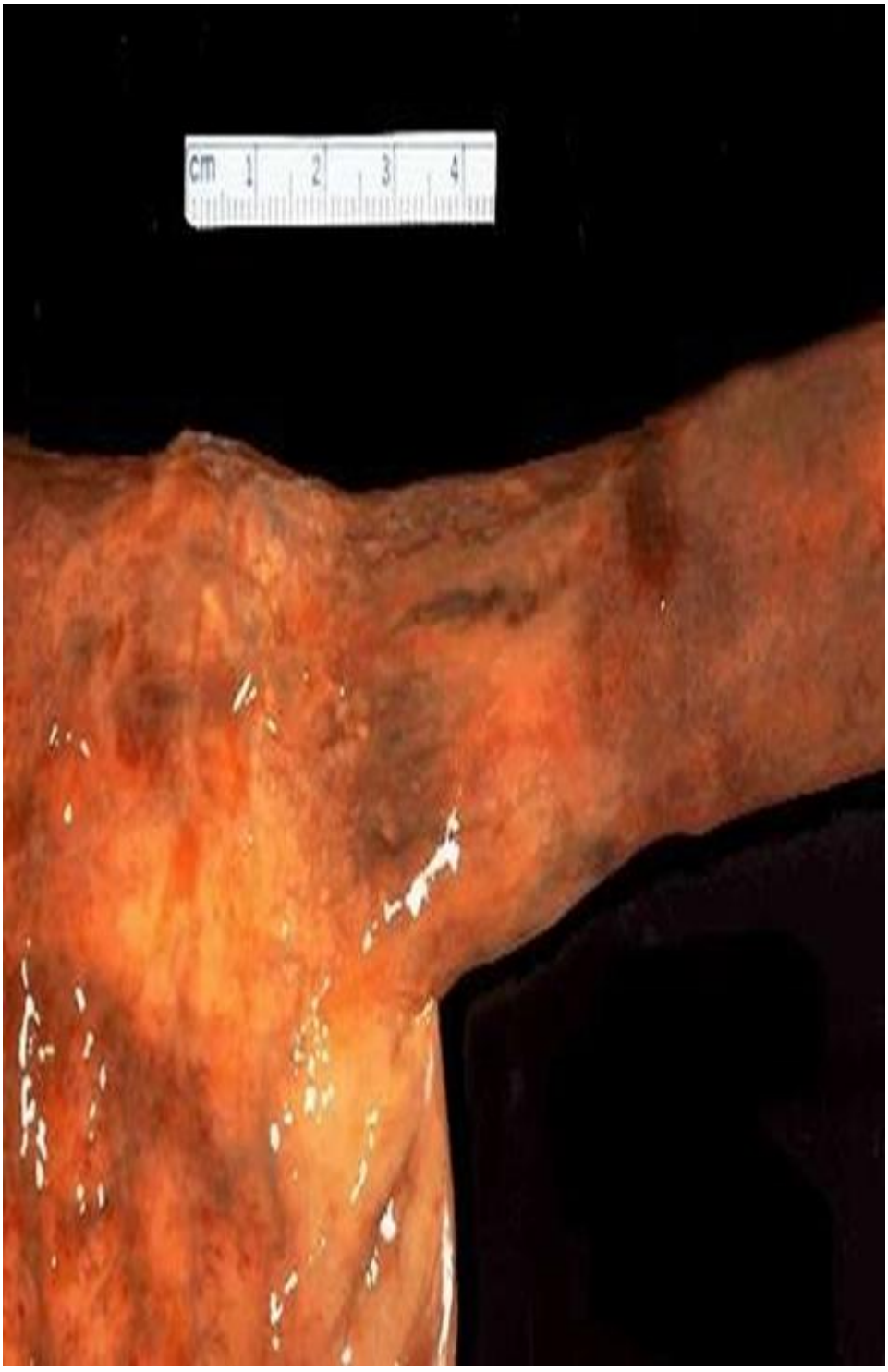
Explanation: Explains why ascites develops in liver disease/portal hypertension:
1. **Increased Sinusoidal Pressure:** High pressure in the liver sinusoids forces fluid out into the Space of Disse and eventually into the abdominal cavity.
2. **Hypoalbuminemia:** Low albumin in the blood (due to poor liver synthesis) reduces the osmotic pressure holding fluid inside blood vessels, allowing it to leak out.
3. **Hepatic Lymph Leakage:** The liver produces much more lymph fluid when congested. This excess lymph can overwhelm the lymphatic drainage system (thoracic duct) and weep directly from the liver surface into the abdomen.
4. **Sodium/Water Retention:** Complex mechanisms involving hormones (like aldosterone, leading to **secondary hyperaldosteronism**) cause the kidneys to retain salt (Na+) and water, increasing overall body fluid volume and worsening ascites.

Original Text: 14. Portosystemic Shunt (2nd clinical consequence of portal hypertension)

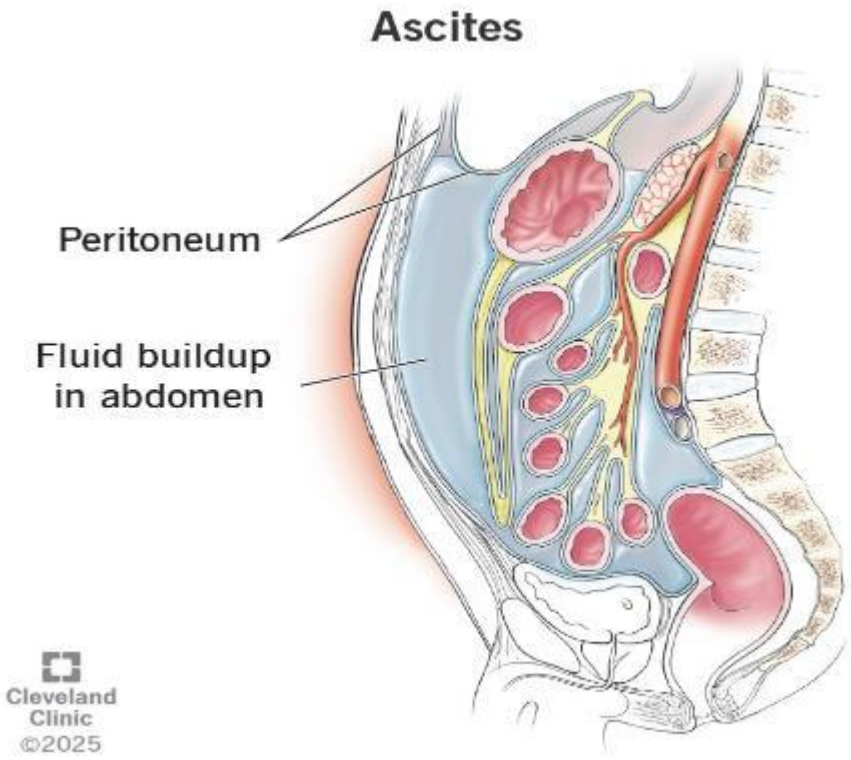
- Because of ↑ portal venous pressure, bypasses develop wherever the systemic and portal circulation share capillary beds

Explanation: Defines portosystemic shunts as alternative pathways (bypasses) that blood takes to get from the portal system back to the main (systemic) circulation, avoiding the high-pressure liver. These form at locations where portal and systemic veins are naturally close.

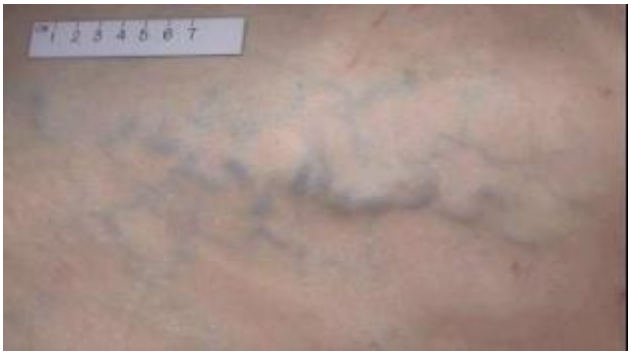
❖ Sites:
1- Around and within the rectum (hemorrhoids)
2- Gastroesophageal junction (varices) – (the most important)
3- Retroperitoneum
4- Falciform ligament of the liver (periumbilical and abdominal wall collaterals) → caput medusae (a cluster of swollen veins in your abdomen.).
* Gastroesophageal varices appear in 65% of patients with advanced cirrhosis and cause death in 50% of them due to upper GI bleeding.



(Image: Endoscopic view inside the esophagus showing large, dilated veins (varices) bulging into the lumen. These are at high risk of rupture.)



(Image: Gross view of an esophagus cut open, revealing markedly dilated submucosal veins (varices).)



(Image: Clinical photo showing dilated superficial abdominal veins radiating from the umbilicus (caput medusae), a sign of portal hypertension.)

Explanation: Lists the common locations where these shunts form:
1. **Rectum:** Leading to hemorrhoids (though hemorrhoids are common for other reasons too).
2. **Gastroesophageal Junction:** Where veins from the stomach/ esophagus (portal) meet veins draining into the systemic circulation.

This leads to **esophageal varices** (swollen veins in the esophagus), which are very dangerous because they can rupture and cause life-threatening bleeding. This is highlighted as the most important site clinically.
3. **Retroperitoneum:** Deep veins behind the abdominal cavity.
4. **Falciform Ligament/Umbilicus:** Re-opening of fetal veins around the belly button, leading to visible swollen veins on the abdominal wall called **caput medusae**.

caput medusae (at the anterior abdominal wall).
Esophageal varices

Note: These appear to be labels reinforcing the image captions or points above.

Original Text: 15. Splenomegaly (3rd clinical consequence of portal hypertension)

- Usually 500–1000 g (normal < 300 g).
- Not necessarily correlated with other features of increased portal blood pressure.
- May result in hypersplenism.

(Image: Gross view of a massively enlarged spleen (splenomegaly), a common consequence of blood backing up due to portal hypertension.)

Explanation: Describes spleen enlargement (**Splenomegaly**) due to portal hypertension:

* **Size:** The spleen becomes significantly larger than normal.
* **Correlation:** The degree of enlargement doesn't always match the severity of other portal hypertension signs.
* **Hypersplenism:** An enlarged, congested spleen can become overactive (**hypersplenism**), destroying blood cells (red cells, white cells, platelets) faster than normal, leading to anemia, increased infection risk, or bleeding tendencies.

Original Text: 16. Hepatic Encephalopathy (4th clinical consequence of portal hypertension)

- It is a complication of acute and chronic hepatic failure.
- Disturbance in brain function ranging from behavioral changes to marked confusion and stupor, to deep coma and death.
- The changes may progress over hours or days.

Explanation: Introduces Hepatic Encephalopathy (HE):
* **Context:** A complication of both acute and chronic liver failure.
* **Definition:** Brain dysfunction caused by liver failure.
* **Spectrum:** Ranges from subtle personality/behavior changes to severe confusion, lethargy (**stupor**), coma, and potentially death.
* **Progression:** Can develop quickly.

❖ Neurological signs:
1. Rigidity
2. Hyperreflexia
3. Non-specific EEG
■ “Non-specific EEG” means that the electroencephalogram (EEG) findings in hepatic encephalopathy do not show a unique pattern that definitively diagnoses the condition. Instead, the EEG may show generalized slowing of brain activity, which is common in many types of encephalopathy or brain dysfunction.
4. Seizures.
5. Asterixis (non-rhythmic rapid extension-flexion movements of the

head and extremities).
6. The brain shows edema and astrocytic reaction.

Explanation: Lists the neurological signs seen in HE:
1. **Rigidity:** Muscle stiffness.
2. **Hyperreflexia:** Overactive reflexes.
3. **Non-specific EEG:** Brain wave tests (EEG) show general slowing, not a pattern unique to HE.
4. **Seizures:** Can occur in severe cases.
5. **Asterixis:** The characteristic "flapping tremor" when the patient tries to hold their hands outstretched.
6. **Brain Changes:** Swelling (**edema**) and changes in brain support cells (**astrocytic reaction**) can be seen pathologically.

❖ Pathogenesis
* Physiological factors important in the development of hepatic encephalopathy:
1. Severe loss of hepatocellular function
2. Shunting of blood around the damaged liver
↓↓
Exposure of the brain to toxic metabolic products
* Increased NH_3 level in blood, thereby generalized brain edema, impaired neuronal function.
* Alteration in central nervous system amino acid metabolism

Explanation: Explains why HE happens:
* **Two Main Factors:** 1) The liver cells themselves aren't working well enough to detoxify blood. 2) Portosystemic shunts allow blood from the gut (containing toxins absorbed there) to bypass the liver entirely and go straight to the brain.
* **Result:** The brain is exposed to toxins it normally wouldn't see.
* **Key Toxin:** Ammonia (NH_3) is considered a major culprit. High ammonia levels contribute to brain swelling and disrupt nerve cell function.
* **Other Factors:** Changes in the balance of amino acids in the brain also play a role.

Original Text: 17. Drug-Induced Liver Disease:

- Drug reactions:
    1. Predictable (intrinsic)
        ➢ Predictable drug reactions depend on the dose (dose-dependent)
        ➢ Predictable drugs:
        – Acetaminophen.
        –Tetracycline.
        – Antineoplastic agents.
        – CCl_4.
        – Alcohol.
    2. Unpredictable (idiosyncratic) – (dose independent)
        ➢ 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.
        ➢ Unpredictable drugs:
        – Chlorpromazine. – Halothane. – Sulfonamides.
        – Methyldopa.
        – Allopurinol.

Explanation: Introduces Drug-Induced Liver Injury (DILI) and its two main types:
* **Predictable (Intrinsic):** Damage is expected if enough drug is given (dose-dependent). Examples include acetaminophen (paracetamol), tetracycline (antibiotic), some chemotherapy drugs (antineoplastic agents), carbon tetrachloride (CCl4 - solvent), and alcohol.
* **Unpredictable (Idiosyncratic):** Damage occurs rarely, isn't related to the dose, and depends on individual factors like the person's immune system reaction or how they specifically metabolize the drug. Examples include chlorpromazine (antipsychotic), halothane (anesthetic), sulfa drugs (antibiotics), methyldopa (antihypertensive), and allopurinol (gout medication).

- The injury may be immediate or take weeks to months.

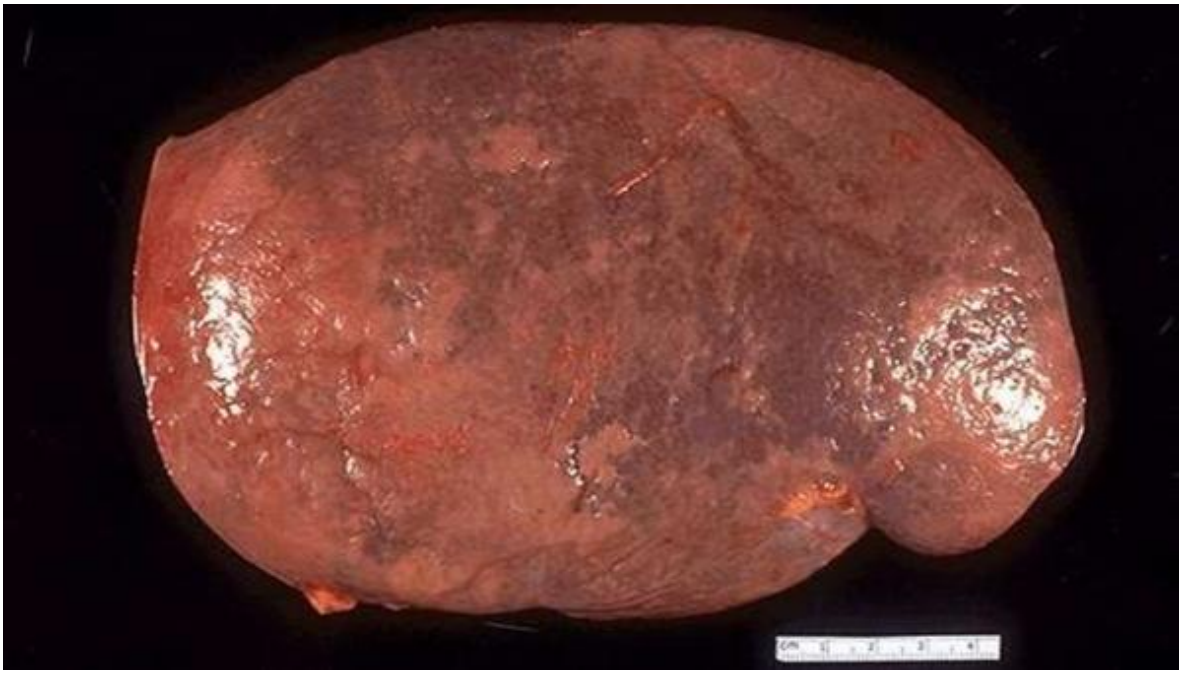
- Drug-induced chronic hepatitis is clinically and histologically indistinguishable from chronic viral or autoimmune hepatitis.

Explanation: DILI can appear quickly or be delayed. Chronic liver inflammation caused by a drug can look identical (clinically and under the microscope) to chronic hepatitis caused by viruses or autoimmune disease, making diagnosis challenging.

❖ Mechanism of drug injury:
1. Direct toxic damage
■ e.g., acetaminophen, CCl_4, mushroom toxins
2. Immune-mediated damage

Explanation: How drugs cause damage:
1. **Direct Toxicity:** The drug or its breakdown products directly poison liver cells (e.g., acetaminophen overdose).
2. **Immune-Mediated:** The drug triggers an immune reaction that attacks the liver cells.

❖ Patterns of Injury:
1. Hepatocellular necrosis
2. Cholestasis
3. Steatosis
4. Steatohepatitis
5. Fibrosis
6. Vascular lesions
7. Granuloma
8. Neoplasms (benign and malignant)



(Image: Microscopic view showing features of cholestasis (bile plugs in canaliculi, yellow-brown pigment) and inflammation, likely caused by a drug reaction.)

Explanation: DILI can manifest in many different ways under the microscope, mimicking almost any other type of liver disease:
1. **Necrosis:** Liver cell death.
2. **Cholestasis:** Impaired bile flow.
3. **Steatosis:** Fatty liver.
4. **Steatohepatitis:** Fatty liver with inflammation.
5. **Fibrosis:** Scarring.
6. **Vascular Lesions:** Damage to blood vessels.
7. **Granuloma:** Collections of inflammatory cells.
8. **Neoplasms:** Some drugs can rarely induce liver tumors (benign or cancerous).

❖ 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 such as CCl_4 and mushroom poisoning

Explanation: Lists specific drugs/toxins known to potentially cause rapid, severe acute liver failure. Acetaminophen overdose is a very common cause.

❖ Morphology:
* Massive necrosis → 500–700 g liver
* Submassive necrosis
* Patchy necrosis
■ Left side: shows preserved hepatocytes without necrosis.
■ Right side: shows necrosis, pallor, and loss of nuclei.

Explanation: Describes the appearance of the liver in severe DILI leading to necrosis:
* **Massive/Submassive Necrosis:** Widespread cell death, often causing the liver to shrink.
* **Patchy Necrosis:** Areas of dead cells scattered among living ones. The note describes a microscopic field showing both preserved and necrotic areas.

Original Text: 18. Fulminant Hepatitis

- Hepatic insufficiency that progresses from the onset of symptoms to hepatic encephalopathy within 2–3 weeks
  Subfulminant: up to 3 months

Explanation: Defines Fulminant Hepatitis as liver failure (insufficiency) developing very rapidly, with brain dysfunction (hepatic encephalopathy) appearing within 2-3 weeks of the first symptoms. Subfulminant hepatitis is similar but develops over a slightly longer period (up to 3 months). This overlaps significantly with the definition of Acute Liver Failure.

❖ Causes:
1. Viral hepatitis (50–65%)
HBV is 2x more common than HCV
2. Drugs and chemicals (25–50%)
e.g., isoniazid, halothane, methyldopa, and acetaminophen
3. Obstruction of the 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

Explanation: Lists causes, largely mirroring those for massive hepatic necrosis / acute liver failure. Viral hepatitis (especially B) and drugs/ chemicals are major causes. Note the comment that HBV is twice as likely as HCV to cause fulminant hepatitis, even though HCV is a common cause of chronic hepatitis.

❖ Morphology:
1. Decrease in Liver size (500–700 g)
2. Necrosis of hepatocytes
3. Collapsed reticulin tissue
4. Inflammatory infiltrate
5. Regenerative activity of hepatocytes
6. Fibrosis

This is the appearance of the liver with necrosis. The pale areas are the necrotic regions. The degree of necrosis is variable; there is also loss of homogeneity. All these are indications of necrosis.

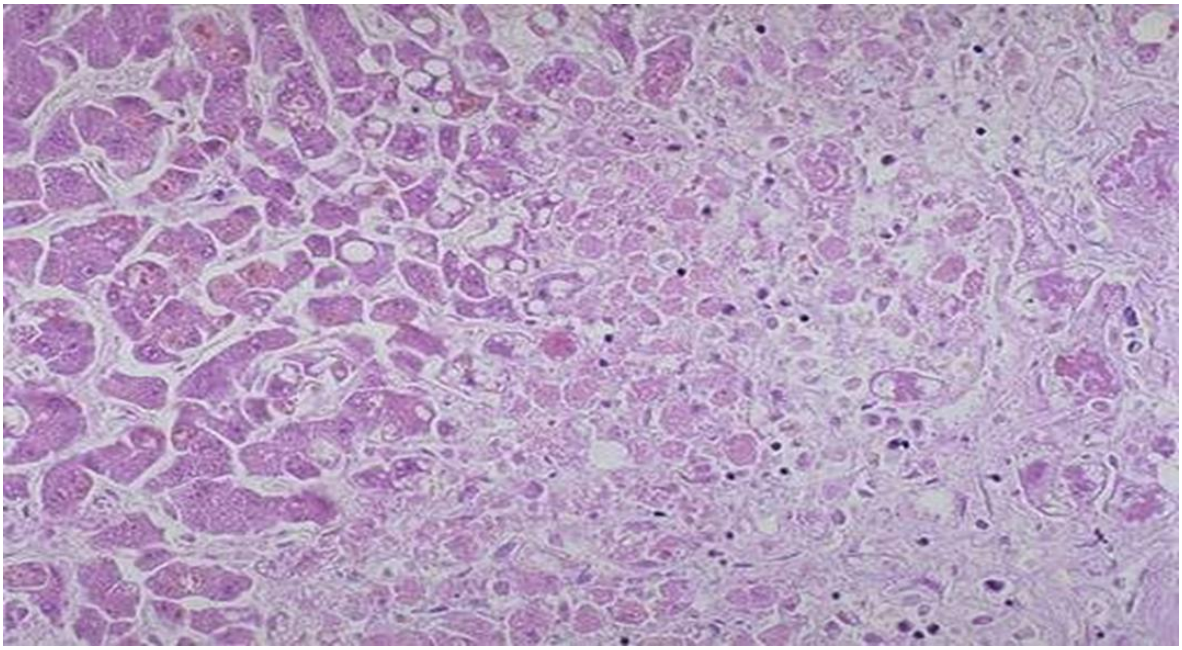
Explanation: Describes the appearance of the liver in fulminant hepatitis:
1. **Size:** The liver often shrinks due to massive cell death.
2. **Necrosis:** Widespread death of liver cells.
3. **Collapsed Reticulin:** The supporting connective tissue framework (reticulin) collapses where cells have died.
4. **Inflammation:** Inflammatory cells are present.
5. **Regeneration:** Surviving hepatocytes may show signs of trying to regenerate.
6. **Fibrosis:** Scarring may begin, especially if the process is subfulminant.
The note describes the visual appearance of necrosis (paleness, loss of uniform texture).

Original Text: 19. Chronic Hepatitis

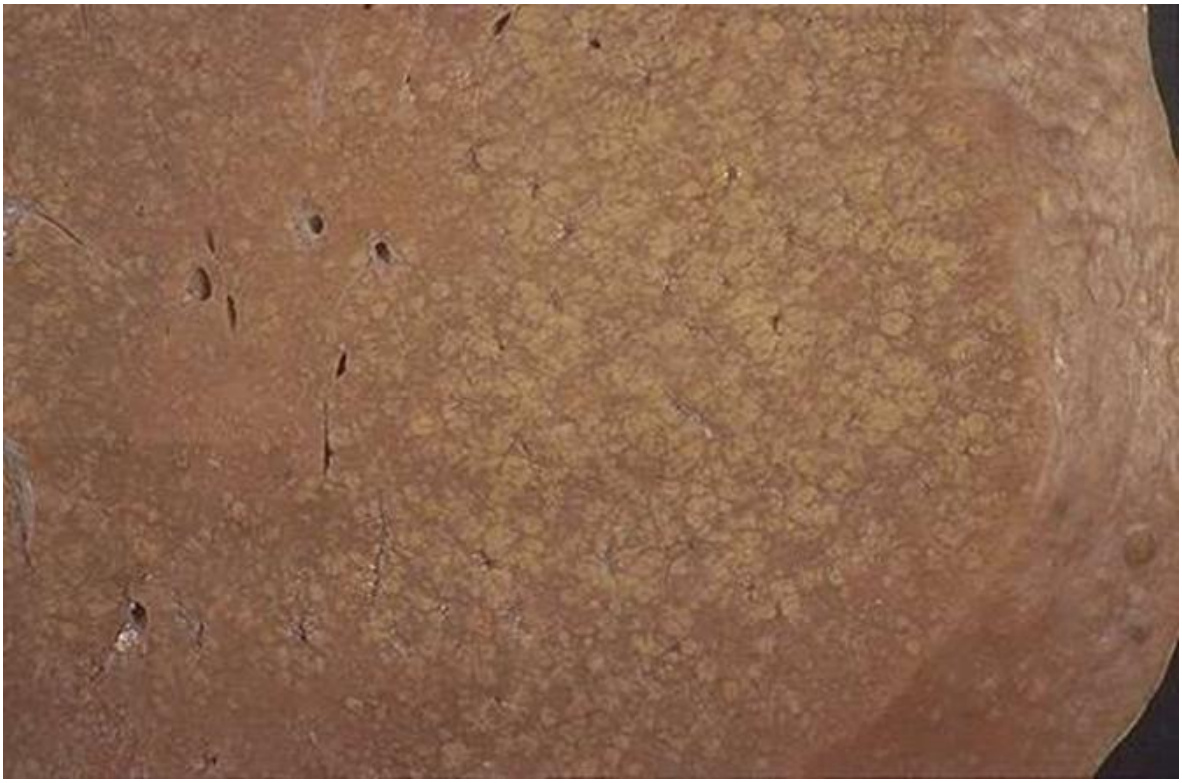
- Symptomatic, biochemical, or serologic evidence of continuing or relapsing hepatic disease for more than 6 months, with histologically documented inflammation and necrosis
- May be progressive or non-progressive
- Causes: HBV, HCV, HBV-HDV
- The other outcome of viral hepatitis, and the most feared one, is chronic hepatitis. It is very important to recognize the causative agent of the viral hepatitis, and we need to follow up with the patient to predict whether they will develop chronic hepatitis.

Explanation: Defines Chronic Hepatitis:
* **Duration:** Liver inflammation and damage lasting longer than 6 months (based on symptoms, blood tests/serology, or liver biopsy).
* **Progression:** Can either worsen over time (progressive) or remain stable (non-progressive).
* **Viral Causes:** Hepatitis B (HBV), Hepatitis C (HCV), or HBV combined with Hepatitis D (HDV) are major causes.
* **Significance:** Developing chronic hepatitis after an acute viral infection is a major concern, hence the need for follow-up.

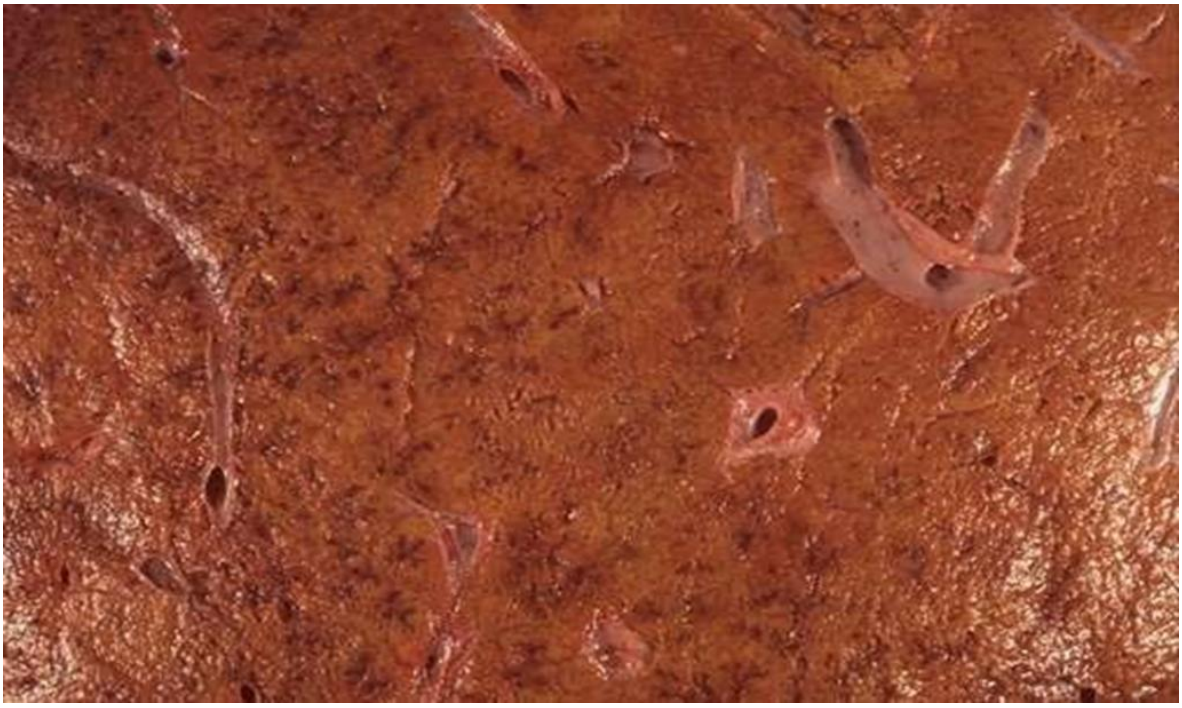
❖ Morphology of chronic hepatitis:
Mild to severe
1. Portal inflammation
2. Lymphoid aggregate
3. Necrosis of hepatocytes-councilman bodies
4. Bile duct damage
5. Steatosis
6. Interface hepatitis
7. Bridging necrosis & fibrosis
8. Fibrosis
9. Ground-glass appearance
10. Sanded nuclei
11. Lobular disarray



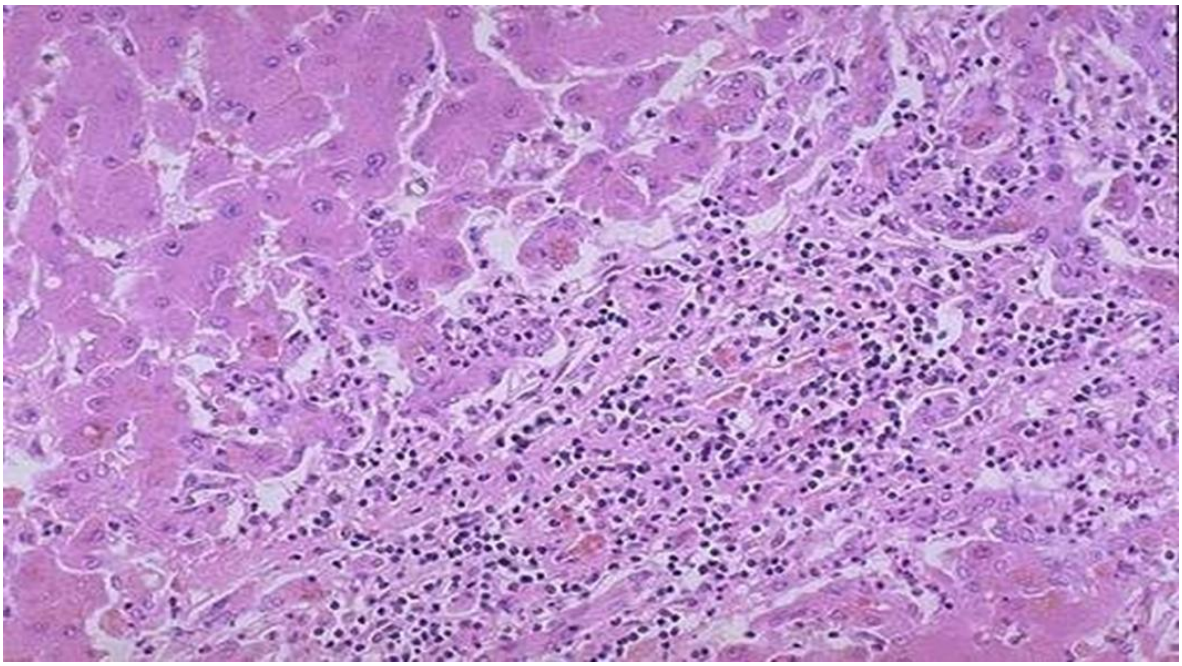
(Image: Microscopic view showing a portal tract densely infiltrated with inflammatory cells (lymphocytes, plasma cells), characteristic of chronic hepatitis.)



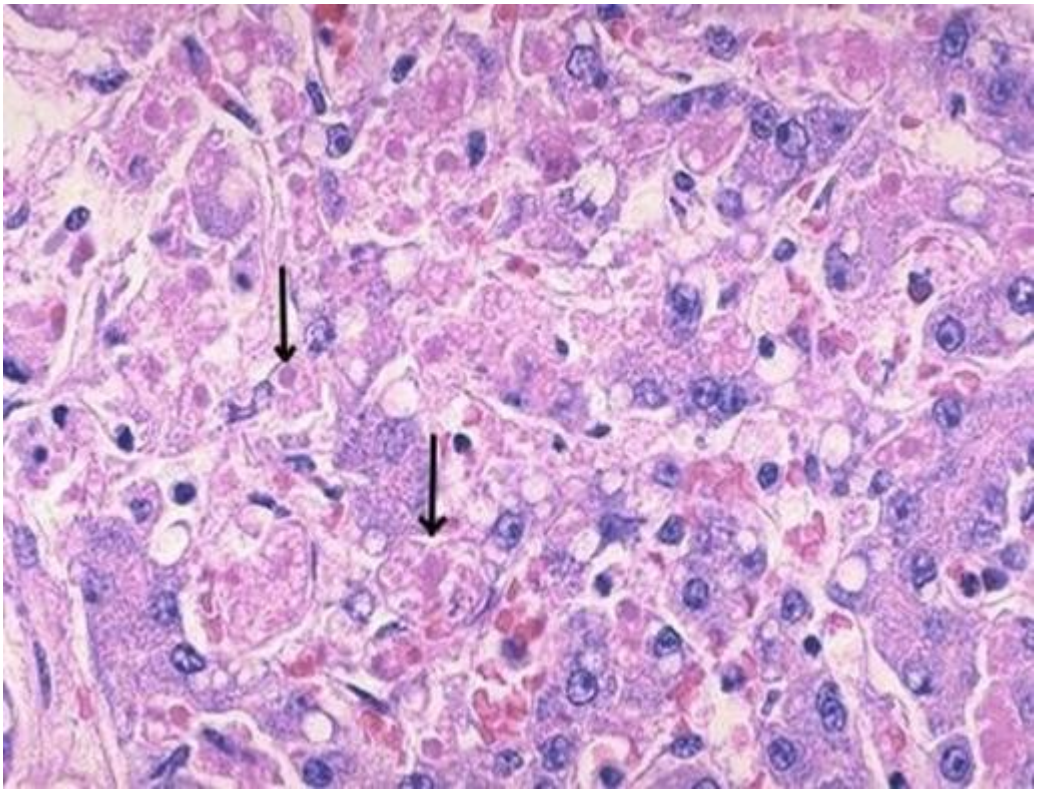
(Image: Microscopic view highlighting interface hepatitis, where inflammatory cells from the portal tract (right) are eroding the limiting plate and damaging adjacent hepatocytes (left).)



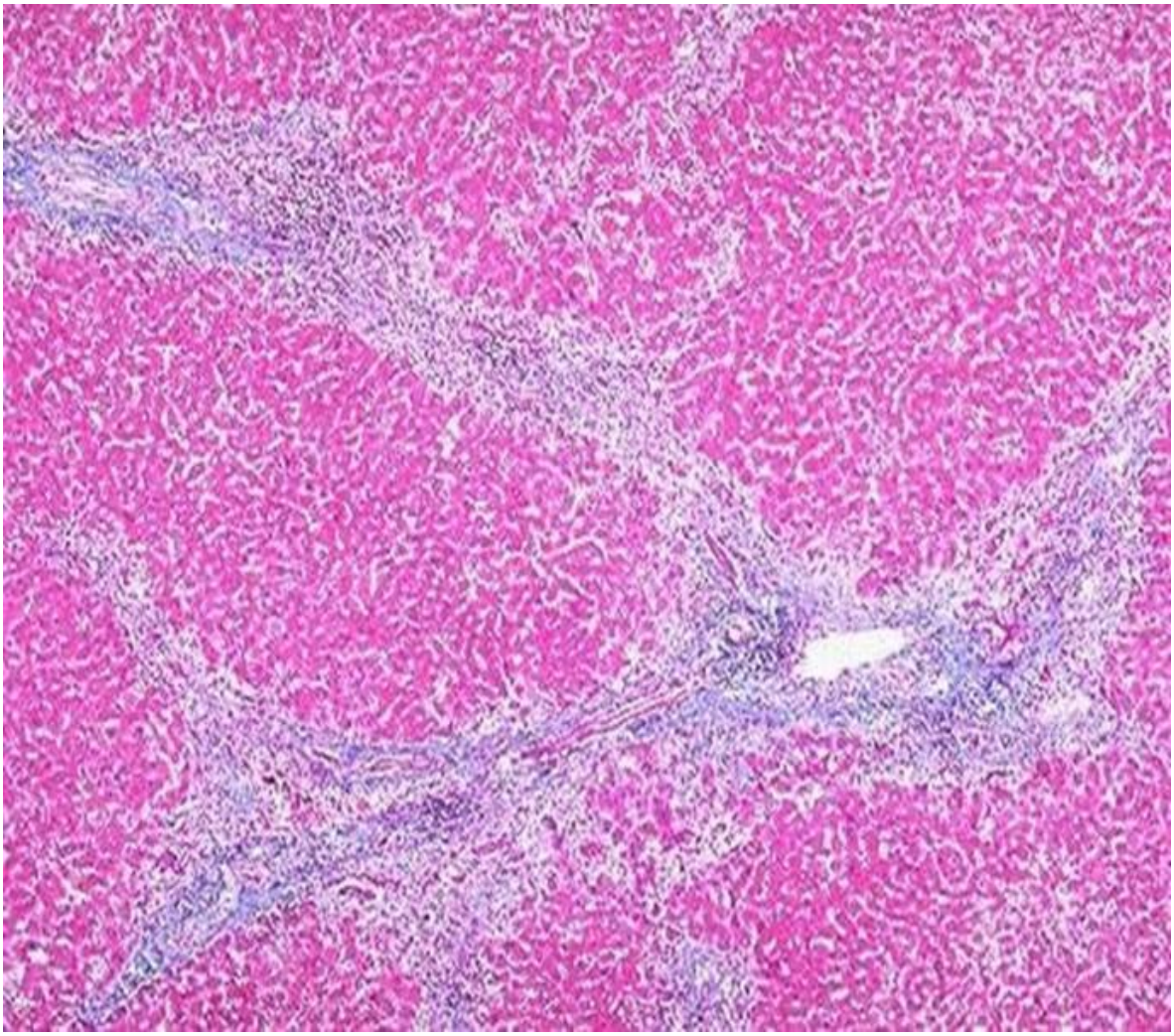
(Image: Trichrome stain showing blue fibrous tissue expanding from the portal tract, indicating early fibrosis in chronic hepatitis.)



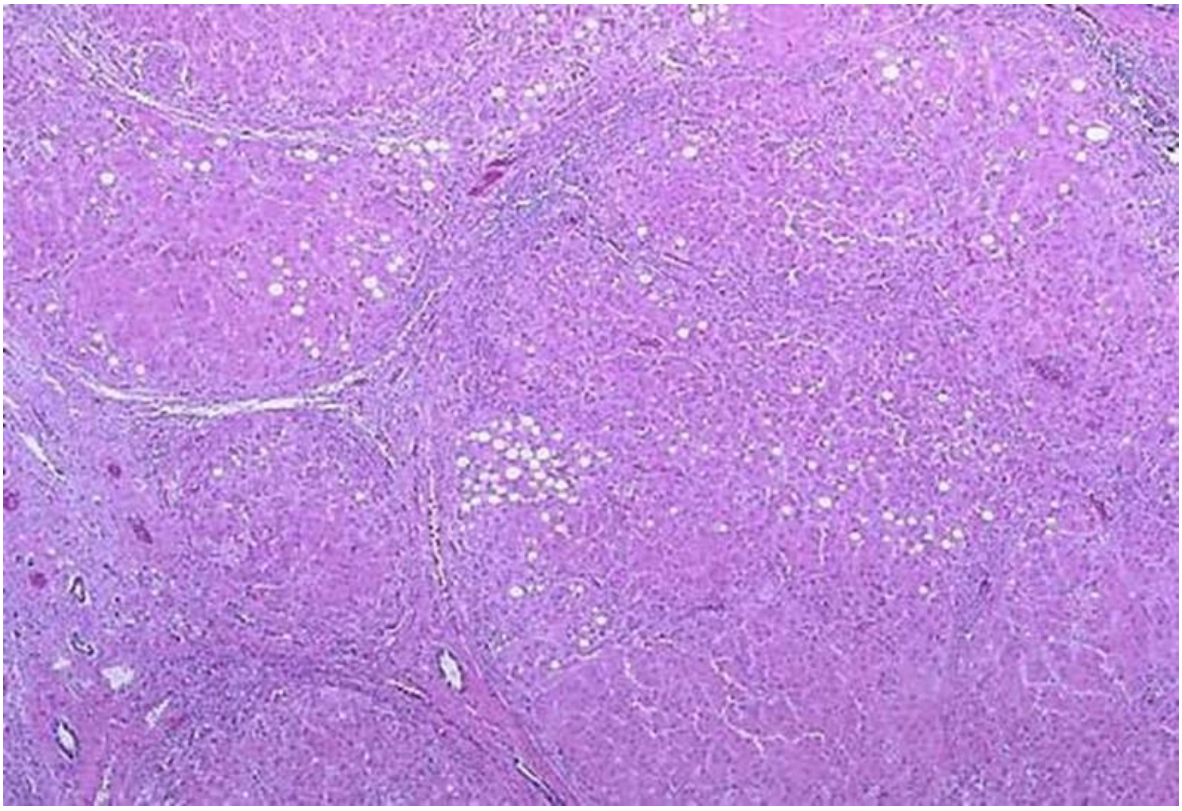
(Image: Microscopic view showing hepatocytes with a hazy, eosinophilic cytoplasm ("ground glass" appearance), characteristic of chronic Hepatitis B infection due to accumulation of HBsAg.)



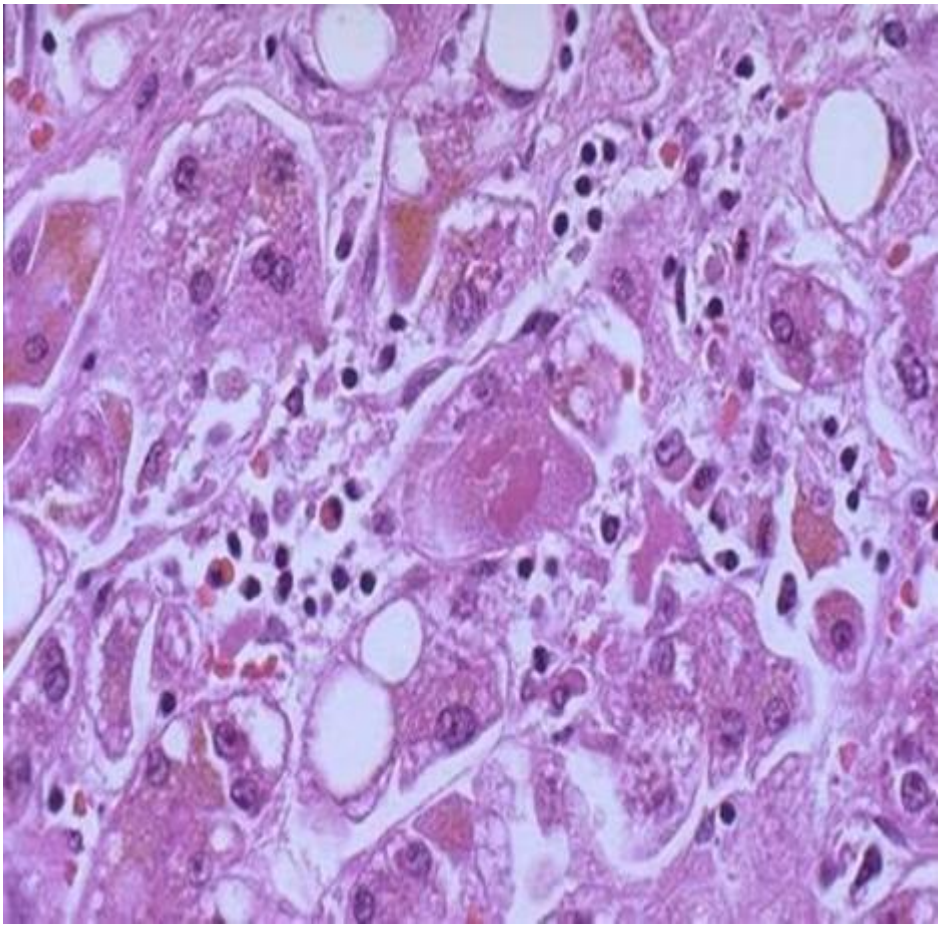
(Image: Microscopic view showing a dense lymphoid aggregate within a portal tract, a feature often seen in chronic Hepatitis C infection.)



(Image: Microscopic view showing fatty change (steatosis) in hepatocytes, which can sometimes accompany chronic Hepatitis C.)



(Image: Microscopic view highlighting numerous plasma cells within the inflammatory infiltrate, a common feature of autoimmune hepatitis.)



(Image: Microscopic view showing advanced chronic hepatitis with bridging fibrosis forming nodules, indicating progression towards cirrhosis.)

Explanation: Lists the various microscopic features seen in chronic hepatitis (severity varies):
1. **Portal Inflammation:** Inflammatory cells (lymphocytes, plasma cells) gather in the portal tracts.
2. **Lymphoid Aggregate:** Dense collections of lymphocytes, sometimes forming follicle-like structures, often seen in HCV.
3. **Necrosis:** Death of individual hepatocytes (may appear as Councilman bodies).
4. **Bile Duct Damage:** Inflammation can damage the bile ducts within the portal tracts.
5. **Steatosis:** Fatty change, particularly common with HCV.
6. **Interface Hepatitis (Piecemeal Necrosis):** Inflammation spilling out from the portal tract and attacking the adjacent layer of hepatocytes (the limiting plate).
7. **Bridging Necrosis & Fibrosis:** Bands of dead cells or scar tissue connecting portal tracts and/or central veins.
8. **Fibrosis:** Scarring, typically starting in portal tracts and potentially progressing to cirrhosis.
9. **Ground-Glass Appearance:** Hazy pink cytoplasm in hepatocytes due to accumulation of Hepatitis B surface antigen (HBsAg), characteristic of chronic HBV.
10. **Sanded Nuclei:** Hepatocyte nuclei filled with Hepatitis B core antigen (HBcAg), appearing granular.
11. **Lobular Disarray:** The normal orderly arrangement of hepatocyte plates within the lobule is disrupted by inflammation and cell death/ regeneration.

There is loss of homogeneity, as seen by the color changes: pale areas with darker surrounding regions. This is due to the presence of fibrosis. There is also some nodule formation.

Explanation: Describes the gross or low-power microscopic appearance where scarring (fibrosis) causes texture and color variations, and early nodule formation might be visible.

This is the microscopic appearance of a severe form of chronic hepatitis. There are some bridging fibrosis, which is an indication of cirrhosis development, along with extensive lymphocytic infiltration.

Explanation: Describes a specific image showing severe inflammation and bridging fibrosis, indicating progression towards cirrhosis.

This image displays hepatocyte necrosis, indicated by the presence of Councilman bodies (highlighted by arrows). Additionally, it demonstrates fibrosis and features consistent with chronic hepatitis.

Explanation: Describes another image showing individual cell death (Councilman bodies) alongside scarring (fibrosis).

- Fat deposition
- Nodules
- Bridging fibrosis (connecting one structure to another)
- This shows extensive fibrosis, but not cirrhosis, because there is no complete nodule formation

Explanation: Describes features potentially seen in another image: fat, early nodules, and bridging fibrosis, noting it hasn't yet met the full criteria for cirrhosis (diffuse nodule formation surrounded by fibrosis).

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

Explanation: Describes an image showing disruption of the normal liver structure and collapse due to cell loss, with associated scarring.

■ Quiz on this lecture
■ Overall quiz
■ Feedback form
■ V1
■ P4; adrenoleukodystrophy → alcoholic liver disease
■ P5; with E and F it was meant to be 5 and 6.

Note: These appear to be links or administrative notes from the original document source (quiz links, version info, possibly corrections to previous slides/pages).

Glossary

(The glossary terms from the previous simplified version can be inserted here, potentially reviewed against the verbatim text for any missing terms)

Conclusion

This document has presented the verbatim text concerning Liver Diseases (Lectures 1-3) from your source material. Explanations and definitions have been added in blue to aid comprehension while preserving the exact original phrasing crucial for your exam preparation. Key topics included liver structure, patterns of injury and repair, liver failure, alcoholic liver disease, cirrhosis, portal hypertension, drug-induced liver injury, and chronic hepatitis. Reviewing the original text alongside these explanations should provide a solid foundation for understanding this complex subject.
