Pathology of Liver and biliary system

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objectives

- By the end of this session students will able to determine and explain
  - Pathology of liver
  - Postmortem changes in liver,
  - Degenerative changes in liver and hepatitis
  - Pathology of gall bladder and bail ducts

- The liver is the largest solid visceral organ in the body and the most important "chemical factory," with functions that cannot be replaced by any artificial means.
- Functions of the liver can essentially be divided into three major groups: synthetic, metabolic, and exocrine.
- Among its function, the more prominent of these functions are the
  - Synthesis of plasma proteins,
  - Catabolism and maintenance of carbohydrate storage,
  - Mobilization of body fat,
  - Detoxification and
  - The formation and elimination of bile.

- The liver has a great reserve power and it has enormous ability to recover from injury.

- So, the tests are not adequate clinically to evaluate the correct state of the health of liver and hence it is not wise to put too much reliance on these tests.

- Damage to the liver may not be detected until the late stage, and it is practically impossible for the anatomic pathologist to state exactly how much of the liver parenchyma must be destroyed before liver failure occurs.

- **Effects of liver failure**
  - With severe hepatic diseases, a great many vital processes will be affected. More important pathological conditions met with are:
  - Jaundice due to retention of bile pigments.
  - Bleeding be due to
    - Lack of absorption of Vitamin K
    - Failure of prothrombin formation
    - Lack of formation of fibrinogen
  - Hypoglycemia due to impairment of glucose metabolism making the animal weak and irritable.

Effects of liver failure

Cont…

- Hypoproteinemia due to failure to synthesize plasma proteins results into generalized edema and emaciation.
- Anemia due to iron and protein deficiencies: liver stores iron and so in liver diseases iron stores are depleted. In liver diseases protein synthesis also does not occur.
- Toxemia due to failure of detoxication of proteins and intestinal toxins.
- Renal failure – Hepatorenal syndrome: In severe hepatic injury, the toxins that are not detoxified are excreted through kidneys resulting into toxic nephrosis. Renal dysfunction leads to uraemia .
- Pyrexia: The thermoregulatory center is affected by the circulating toxins since they are not detoxified.

- Blood supply to and from the liver (**two nutrient supplies):-**
  - Hepatic artery- which divides into fine branches → to the fine bile ducts.
  - Portal vein- carries nutrients from the stomach and intestine to the liver (also from spleen).
    - Portal vein divides into fine branches → into sinusoids.
    - Although the portal blood is incompletely saturated with oxygen (80%), it supplies **50 to 60%** of the oxygen requirement of the hepatocytes because of its **greater flow.**
  - Blood leaves sinusoids via hepatic vein to heart.

- **The liver lobule** Is just large enough to be distinguishable with the naked eye
- At its center is a **central vein** from which cords of liver cells radiate out to the periphery of the lobule.
  - The outer boundaries of the lobule **(periphery)** are incompletely demarcated by the portal triads.
  - Portal triads are connective tissue septa which contain a branch of the **hepatic artery, portal vein,** and **bile duct.**
- The term **hepatosis** is sometimes used to refer to necrotic or degenerative diseases of the liver, and hepatitis refers to inflammation of the liver.

1. Degenerative and necrotic lesions of hepatocytes

Patterns of hepatocellular degeneration and necrosis

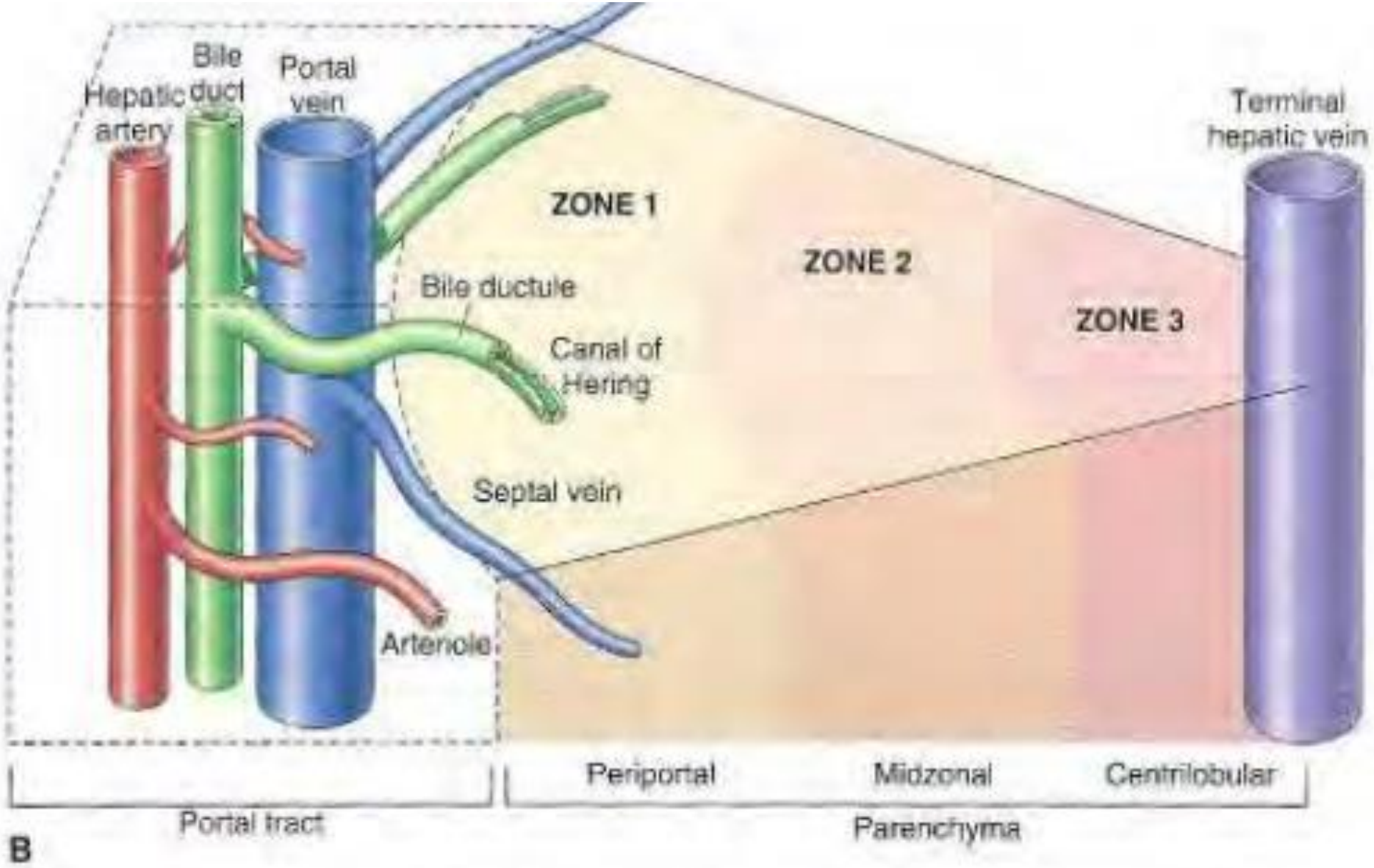
- Occurs in one the 3 morphologic patterns:
  1. Random hepatocellular degeneration and necrosis
  2. Zonal hepatocellular degeneration and necrosis
  3. Massive hepatocellular degeneration and necrosis

1) Random hepatocellular degeneration and necrosis

- Is characterized by the presence of either single cell necrosis or multifocal necrotic areas
  - These areas are scattered randomly and there is no predictable location
  - This pattern is typical of many infectious agents
  - Grossly as discrete, pale or less often dark red foci that are sharply delineated
  - Hepatocytes in affected areas are either degenerated or necrotic

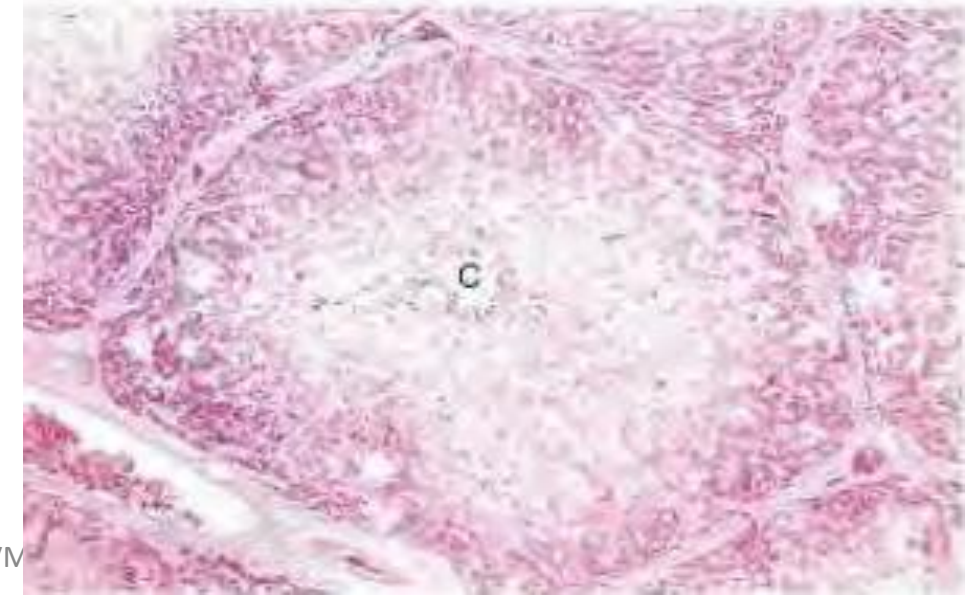
2) Zonal hepatocellular degeneration and/or necrosis

- Affects hepatocytes within defined areas of hepatic lobules
- The zones are:
  I. Centrilobular **(periacinar) (zone 3)**,
  II. Midzonal (between centrilobular & periportal areas) (**zone2)**
  III. Periportal (centroacinar) areas (**zone 1**)


Bile duct
Hepatic artery
Portal vein
Terminal hepatic vein
ZONE 1
ZONE 2
ZONE 3
Bile ductule
Canal of Hering
Septal vein
Arteriole
Periportal
Midzonal
Centrilobular
Portal tract
Parenchyma
B

I) Centrilobular (zone3) degeneration and necrosis

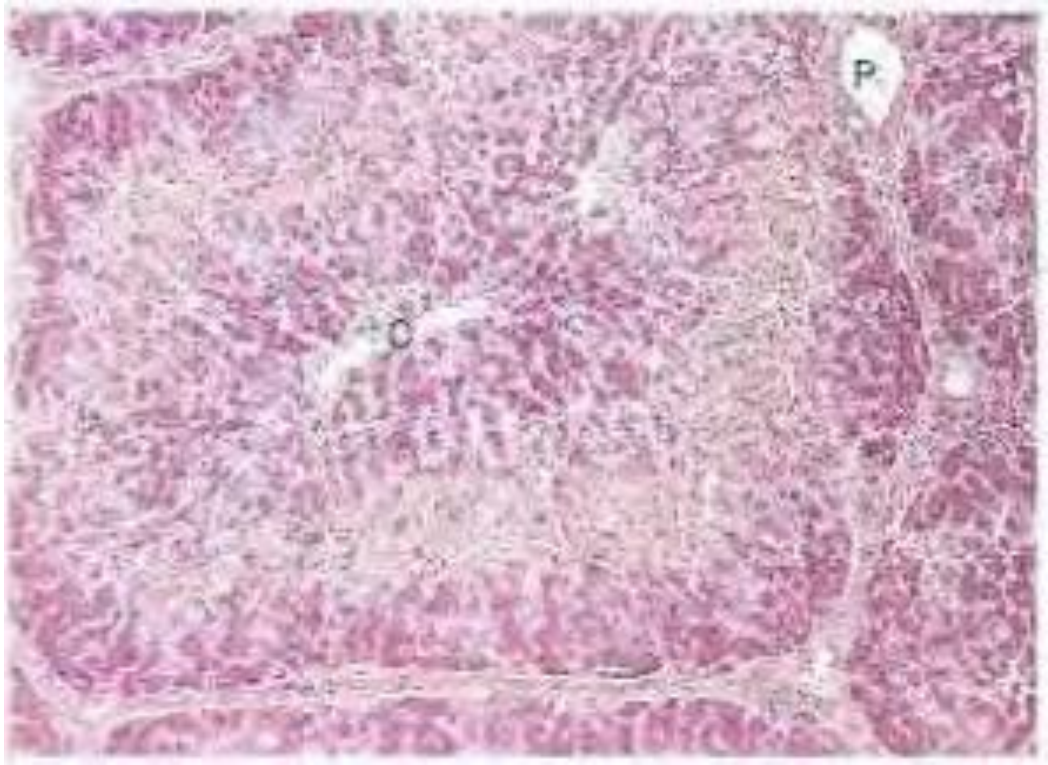
- In this condition, the **cells nearest to the central vein are affected.**
- Is particularly common as this portion of the lobule receives the least oxygenated blood and it is susceptible to hypoxia.
- it has the greatest enzymatic activity (mixed function oxidase) capable of activating compounds into toxic form



- Gross pathology
  - The liver is enlarged and paler than normal.
  - In severe cases the organ may be dark red due to venous stasis.
  - if necrosis of the cells in the center occurs, then the center will be pale while the periphery is darker.
- Histopathology
  - The cells round about the central veins have disappeared, blood taking up their places.
  - In area nearer to the periphery of lobule, the cells may show fatty changes or cloudy swelling.
  - Infiltration of the periportal connective tissue by lymphocytes is seen after some days.

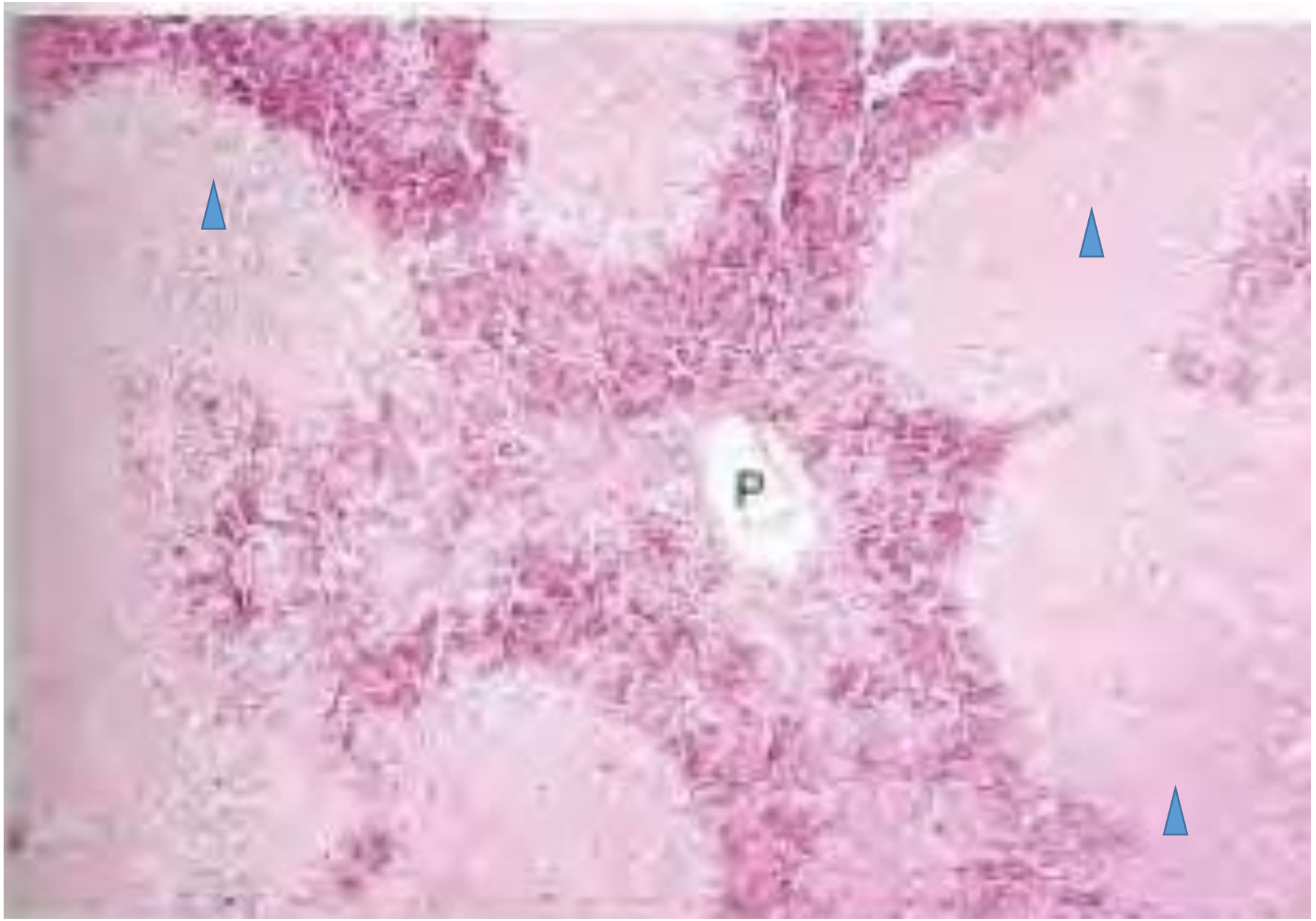
II) Midzonal degeneration and necrosis

- This lesion is found in mid-way between the central vein and the periphery of hepatic lobe.
- Unusual in domestic animals but have been reported in pigs & horses (aflatoxicosis)
- Mid-zonal necrosis is seen in yellow fever of man.



III) Periportal degeneration and necrosis

- In this condition the cells adjoining the portal tract become necrotic.
- Also uncommon but may occur following exposure to toxins that do not require mixed oxidase function (most active in centrilobular hepatocytes).
- This is more commonly seen in phosphorus poisoning.
- Here the toxins should have been conveyed by the portal vein.
- Microscopically Inflammation of the portal triads results in cirrhosis similar to portal cirrhosis.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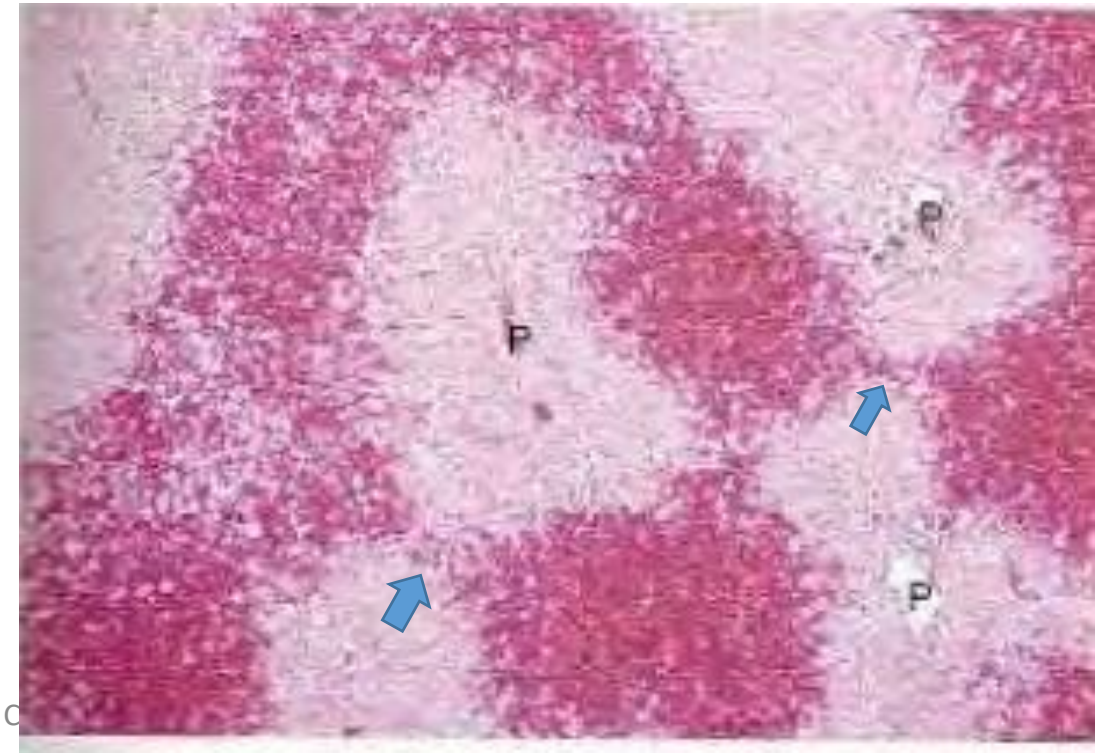
❖ Bridging necrosis

- Refers to a pattern characterized by connection of areas of necrosis between different lobules
- Three patterns of bridging necrosis are recognized (central-central, portal-portal and central-portal)



3) Massive Necrosis / Acute Yellow Atrophy

- In this condition, there is necrosis of considerable number of the cells in a lobule. This may be a severe manifestation of various types of necrosis described above.
- Etiology
  - Dietetic: Deficiency of sulphur-containg amino acids, Tocopherols and Selenium.
  - Poisons: Carbon tetrachloride, chloroform, phosphorus.

- **Grossly**: The liver is yellow and smaller in size.
- **Microscopically**: There is fatty change and necrosis of hepatocytes with loss of parenchyma.
- Sequelae: Since whole parenchyma of the lobule is dead no regeneration occurs.
  - Collapse, condensation, and subsequent scaring are characteristic →post necrotic scarring

Fatty Change:

- Some imbalance in fat production, utilization, or mobilization reflects accumulation of fat within hepatic cells . Thus fat may accumulate in the cytoplasm of injured cells.
- **Microscopically**, fatty change is first manifested by the appearance of small vacuoles within the cytoplasm of hepatocytes.
- **Grossly,** the liver is enlarged, friable, tan to yellow in color, and the cut surfaces bulge when incised. In severe cases, liver sections will float when placed in water or formalin

- *Reading Assignment on different types of degeneration of liver*
  - Cloudy swelling
  - Hydropic degeneration

2. Inflammatory diseases of the hepatobiliary diseases

- Hepatitis is an alterative inflammation of liver in which the various degenerative processes like cloudy swelling, fatty change and necrosis are caused by irritants which also produce inflammation.
- Hepatitis is classified as alternative inflammation because the inflammatory process is caused by the same etiological agents that also produce degeneration and so alteration in the parenchymatous cells is produced.

- Besides, in liver, these degenerative changes are accompanied by lymphocytic or leucocytic infiltrations typical of an inflammatory reaction.

- Hepatitis may be either infectious, non-infectious or toxic. This may again be acute or chronic.
  - The chronic variety is usually called **Cirrhosis.**

✓The nature and distribution of inflammatory lesions in the liver are usually detected by:

- Route of entry
- Host inflammatory response
- The nature of infectious agent

❖ Liver injury should be characterized by:

- Type of inflammatory cells involved (neutrophils, lymphocytes, plasma cells, eosinophils or macrophage)
- The pattern of involvement (random, multifocal, zonal, massive)
- Evidence of necrosid or fibrosis

1. Acute hepatitis

- In acute hepatitis of bacterial and protozoal infections neutrophils accumulate.
- Random foci of neotrophilic hepatitis, as a consequence of embolic localization of bacteria are relatively common in all species
- Acute hepatitis produced by viral infections is more characterized by random distribution of necrosis with minimal inflammation or infiltration of lymphocytes

2. Chronic hepatitis

- Results when there is continued inflammation.
- Is characterized by fibrosis; accumulation of mononuclear inflammatory cells (lymphocytes, macrophages, plasma cells).
- Fibrossis is one of the common manifestation of chronic liver disease.
- Fibrosis itself causes no symptoms but can lead to
  - Portal hypertension: scarring distorts blood flow through the liver
  - Cirrhosis: the scaring results in disruption of normal hepatic architecture and liver dysfunction

- Hepatic fibrosis is potentially reversible if:
  - The underlying insult is effectively treated
  - Apoptosis of hepatic stellate cells → Reduced expression of metalloproteinase inhibitors → slow production of extracellular matrix and allow degradation immature collagen by matrix metaloproteinases.

- The distribution of fibrosis in the liver reflects the pathogenesis of necroinflammatory disease
  - **Biliary fibrosis**- inflammation and fibrosis remains largely in the portal triads
  - **Post necrotic scaring**-occurs after massive necrosis, where a large area of parenchyma are destroyed
  - **Diffuse hepatic fibrosis**-is out come of chronic parenchymal injury (multiple episodes of zonal necrosis)

3. Hepatic failure

- It implies that a less than normal level of organ function exists, and it results from damage to the hepatic parenchymal cells of sufficient magnitude to cause abnormalities in clinical or biochemical findings.
- causes are **massive necrosis** and **chronic liver disease.**

a) **Massive Necrosis (acute liver damage):** may be caused by a variety of etiologic factors **(bacteria, viruses, chemicals, etc.)**

- liver is usually reduced in size, jaundice is a prominent feature, and the necrosis is progressive. Both **conjugated** and **unconjugated hyperbilirubinemia** is found

b) chronic liver disease

- The second major mechanism of hepatic failure is encountered in **end stage liver disease or cirrhosis**.
- **Cirrhosis** refers to generalized involvement of the liver by **concurrent hepatic cell necrosis, regeneration,** and **diffuse fibrosis** resulting in disorganization of the lobular architecture.

4. Cirrhosis

- Used for the end-stage of diffuse hepatic disease characterized by nodular regeneration with fibrovascular bridging scars
- Regeneration of hepatic tissue between fibrous bands leads to the formation of variable sized regenerative nodules
- The entire liver is thus distorted and consists of nodules of regenerative parenchyma separated by fibrous bands, which appears as depressions on the surface


Healthy


Cirrhosis

Inflammatory diseases of the biliary tract

- Inflammation of
  - Gallbladder → cholecystitis
  - Large bile duct →cholangitis
  - Small intrahepatic ductulus → cholangiolitis
- **Cholecystitis** –may occur alone if the neck of the gallbldder affected
- **Cholecystits** ← reflux of intestinal bacteria/ hematogenous

✓ In the acute lesion, histologic changes include:

- Neutrophilic inflammatory infiltrates in the wall & lumen of the gallbladder
- Focal necrosis, ulceration and edema

✓ More chonic stages- mixed inflammatory infiltrates with fibrosis

- Occasionally, the infiltrate may be predominently lymphoplasmcytic

Cholangitis / cholangohepatitis

❖ pathogenesis: portal duct inflammation → periportal inflammation →Pure cholangitis

❖ There are several patterns of inflammation of the biliary trees

- **Neutrophilic (suppurative)** choloengitis: is most common type
  - ❖ Characterized by presence of neutrophils within lumen or epithelium
  - ❖ Rupture of affected bile ducts → hepatic abscess
    - Most neutrophic cholengitis ← ascending (SI)

❖ Persistent mild inflammation → hepatic fibrosis of biliary distribution

Biliary tract obstruction

- **Cholelithiasis** (gallstone)-mixture of cholestrol, bile pigments, calcium salts and proteinecious matrix
  - Obstruction → icterus
  - Large stones → pressure necrosis/ulceration of the mucosa
  - local dilation of bile duct → saccular diverticula of gallbladder
  - Many gallstones are silent (**no symptoms produced).** Occasionally, however, they lodge within and obstruct bile ducts, and in doing so, they produce jaundice.

- Marked cholestasis with intrahepatic bile duct proliferation, fibrosis, and cirrhosis. This liver was rock hard. The dark green color comes from formalin acting on bile pigments in the liver from marked cholestasis, turning bilrubin to biliverdin.

Overview of the Biliary System

Bilirubin:

- a yellow-colored by-product of (RBC)hemoglobin metabolism,
- It is the major bile **pigment.**
- the cells of the **reticuloendothelial system** degrade hemoglobin, and
  yielding bilirubin →is carried in blood bound to albumin
  in the liver extracts bilirubin from blood

conjugates it with **glucuronic acid** to form **bilirubin glucuronide,**

is secreted into bile and accounts for bile's yellow color.

• Abscesses of The Liver

- Infection by pyogenic bacteria cause abscesses in liver.
- The bacteria enter the liver by way of portal veins and hepatic arteries mostly.
- Infection may also occur from the umbilical vein in the young animal.
- In the adult and older cattle, infection may occur from traumatic reticulitis.
- In these animals, highly concentrate diet produces ruminal disturbances, resulting into ulcers. From infected ulcers, *Fusobacterium necrophorum* reaches the liver, where it produces first coagulative necrosis and subsequently abscess on liquefaction.

• Neoplasms of Liver

- Tumours of the liver may be primary (arising from the liver parenchyma and bile ducts) or secondary metastases from elsewhere.
- The most common primary tumours are hepatomas, hepatocellular carcinomas and cholangiocellular carcinoma.
- In chicken, lymphoid leucosis and Marek's disease primarily affect liver.
- Metastases of any malignant tumor may be found in the liver.
- Metastases of lymphocytoma and pancreatic carcinoma are mostly seen
- In the cow, metastases of uterine carcinoma are common.


QUESTIONS