“PATHOLOGY OF LIVER & HEPATOBILIARY SYSTEM”

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PATHOLOGY OF LIVER & HEPATOBILIARY SYSTEM

- Kumar, Abbas and Fausto (2005): Robbins & Cotran Pathologic Basis of Disease, 7th edition, chapter 18
Outline of Lectures

- Introduction
  - Normal structure and function
  - Hepatobiliary injury & responses
  - Manifestations of hepatic failure
- Developmental anomalies & Miscellaneous lesions
- Circulatory disturbances
- Metabolic & nutritional disturbances
- Infectious diseases of the liver (hepatitis)
- Toxin-induced liver diseases
- Diseases of uncertain cause
- Hepatic injury as a consequence of systemic disease
- Proliferative lesions of the liver
- Diseases of the Gallbladder
General considerations

- Largest visceral organ
- 25% cardiac output
  - 67% portal vein
  - 33% hepatic artery
- Functions – multiple
- Injurious agents: myriads
- Clinical signs: variable
- Size
  - Carnivores 3-4% body weight
  - Omnivores 2% body weight
  - Herbivores 1% body weight
Micro-Anatomy

- Traditional Structural Unit
  - Hexagonal structure 1-2 mm wide
  - Central vein (terminal hepatic vein) at the centre
  - Portal triads
    - Bile ducts
    - Branches of portal vein
    - Hepatic artery
    - Nerves and lymphatics
  - Limiting plate
Schematic view of microscopic organization of the liver

- Sinusoids
- Bile canaliculi
- Central vein
- Bile duct
- Branch of portal vein
- Branch of hepatic artery
- Hepatic plate

Liver, hepatic lobules, normal dog

Higher magnification
Normal portal area of the liver

Portal tract. The normal portal tract contains the hepatic artery (HA), bile duct (BD), portal vein (PV), and several lymphatic vessels (LV). These structures are surrounded by a collagenous extracellular matrix that forms an abrupt border with a circumferential row of hepatocytes, termed the limiting plate (LP—*dotted line*).
Normal liver (trichrome stain). Note the blood-filled sinusoids and cords of hepatocytes; the delicate network of reticulin fibers in the subendothelial space of Disse stains light blue.
**Zone 1** or centroacinar (periportal) surrounds the portal triads
**Zone 2** or midzone is the intermediate or midlobular area
**Zone 3** or periacinar (centrilobular) surrounds the central veins
Functions of the liver

- Bilirubin metabolism
- Bile acid metabolism
- Carbohydrate metabolism
- Lipid metabolism
- Xenobiotic metabolism
- Protein synthesis
- Immune function
Bilirubin metabolism

- Formation of bilirubin mostly from heme
- Binding to albumin
- Hepatocellular uptake
- Conjugation with glucuronic acid
- Secretion into intestine
- Deconjugation & degradation to urobilinogens by gut bacteria
- Excretion & reabsorption of urobilinogens

Schematic diagram of Bilirubin metabolism and elimination
Bile acid metabolism

- Bile acids are produced in the liver, secreted into the intestine and largely reabsorbed into the liver (enterohepatic circulation)

- Main functions
  - Maintenance of cholesterol homeostasis
  - Stimulation of bile flow & digestion
  - Absorption of fats & fat soluble vitamins
Other liver functions

• Carbohydrate metabolism
  – Conversion of glucose to glycogen & back
• Lipid metabolism
  – Production & degradation of plasma lipids
• Xenobiotic metabolism
  – Inactivation of toxins (cytochrome p450 enzymes)
• Protein synthesis
  – Albumin, transport proteins, lipoproteins, etc
• Immune functions
  – Kupffer cells, production of acute phase proteins, recirculation of IgA
Clinical Signs and Symptoms
- Similar in all species
- Clinical signs occur only with severe liver disease or biliary outflow obstruction

Liver has considerable reserve and regenerative capacity

Liver failure - Clinical syndrome resulting from inadequate liver function

Liver lesions are fairly common
- Usually not significant enough to result in hepatic failure
- Interpretation of the location and type of liver lesions may help to identify the presence and cause of disease
- Histopathology is most helpful to make diagnosis
For the clinician, “hepatic biopsy specimen analysis is the only way to accurately diagnose and classify hepatic disease.” (Tams, 2003)
Portals of entry of injurious agents & Liver defense mechanisms

- **Portals of entry**
  - Hematogenous
  - Retrograde through biliary & pancreatic ducts
  - Direct extension through liver capsule
    (Penetrating trauma through the abdominal wall, rib cage, lumen of the GI tract)

- **Defense mechanisms**
  - Structural & functional
  - Immunologic
Mechanisms of liver injury

- Metabolic bioactivation of chemicals to reactive species
- Stimulation of autoimmunity
- Stimulation of apoptosis
- Disruption of calcium homeostasis
- Canalicular injury
- Mitochondrial injury
Patterns of hepatocellular degeneration & necrosis

- **Random**
  - Single cell necrosis
  - Multifocal necrosis
  - Piecemeal necrosis
Multifocal hepatic necrosis, foal with equine herpes virus infection

Multifocal hepatic necrosis and inflammation, pig, salmonellosis

Multifocal hepatic necrosis, tularemia (higher magnification)
Patterns of hepatocellular degeneration & necrosis - II

- **Zonal**
  - Centrilobular
  - Paracentral
  - Midzonal
  - Periportal
  - Bridging

Enhanced lobular pattern
Centrilobular necrosis, pig
C = central vein

Paracentral degeneration/necrosis, cow.
C = central vein

Midzonal necrosis, pig
C = central vein, P = portal area

Periportal necrosis, horse
P = portal area
Bridging necrosis & hemorrhage (central to central).

P = portal areas

Diagrammatic representation of chronic hepatitis. Bridging necrosis (and fibrosis) is portal to central.
Patterns of hepatocellular degeneration & necrosis - III

- Massive necrosis
  Involves entire lobule or contiguous lobules
Morphologic classification of hepatobiliary disease

Based on

- Pattern of involvement
- Types of inflammatory cells
- Evidence of degeneration or necrosis
- Severity of process
- Evidence of regeneration
- Presence of etiological agent
Broad types of inflammation of the hepatobiliary system

- Acute hepatitis
- Chronic hepatitis
- Nonspecific reactive hepatitis
- Cholangitis
- Cholangiohepatitis

Acute, multifocal, necro-suppurative hepatitis

Chronic, multifocal, granulomatous hepatitis (Mycobacteriosis)
Diagrammatic representations of the morphologic features of acute and chronic hepatitis. Bridging necrosis (and fibrosis) is shown only for chronic hepatitis; bridging necrosis may also occur in acute hepatitis (not shown).
Acute, suppurative *cholangitis*, horse

Acute, suppurative *cholangiohepatitis*, rat

Chronic, lymphocytic *cholangiohepatitis*, cat
General responses of liver to injury

- Three ways:
  - Regeneration of parenchyma
  - Replacement by fibrosis
  - Biliary hyperplasia

- Outcome of injury depends upon type and severity of insult
  - Requires 75% damage to functional liver before clinical signs appear
  - Liver enzymes can be elevated earlier (AST, ALT, LDH, alkaline phosphatase, gamma-glutamyl transpeptidase)
Regeneration

- **Conditions for regeneration (without scarring)**
  - Intact framework
  - Good blood supply
  - Patent bile ducts

- **Regeneration**
  - Stimulated by growth factors
  - 60% of liver will regenerate within a week
  - Oval (stem) cells can differentiate into hepatocytes or bile duct epithelium
  - If chronic, regeneration can result in nodular proliferations with impaired flow of blood and bile

Black reticulin fibers (reticulin stain), hepatic extracellular matrix, liver, normal dog.

Oval cell proliferation, liver, rat
Fibrosis

- Increased amount of connective tissue within the liver
- Ito (stellate) cells also proliferate
- Significance is dependent upon effects on normal hepatic function and type of collagen (i.e., can it be removed and remodelled?)