Patterns of fibrosis

- Postnecrotic scarring
  - Single event of widespread hepatocellular necrosis followed by fibrosis
- Biliary fibrosis
- Focal/multifocal fibrosis
- Diffuse hepatic fibrosis (End-stage liver)

“Milk spotted liver”, pig (multifocal fibrosis)

Biliary fibrosis in chronic cholangitis due to *Fasciola hepatica*, cow
Schematic diagram of the effects of hepatic injury leading to fibrosis

Liver. Thick fibrous bands (blue) surrounding regenerative nodules. Trichrome stain
Biliary hyperplasia

Proliferation of new bile ducts within the portal areas

- Bile drainage obstruction
- Often seen in chronic hepatic injury (hepatotoxicity)
  - pyrrolizidine alkaloid
  - aflatoxin poisoning
- Can occur quickly in young animals
- Secondary to liver fibrosis
- An attempt to regenerate hepatocytes?

Biliary duct hyperplasia (arrows) and fibrosis (F)
End-stage liver (Cirrhosis)

Final irreversible result of different hepatic diseases characterized by
- Nodular regeneration
- Fibrosis
- Bile duct hyperplasia

Liver architecture is very distorted so the initial pattern or cause can no longer be determined.
End stage liver II

- Vascular abnormalities (Acquired portosystemic shunts)
- Causes include:
  - Chronic Toxicities
  - Chronic Biliary obstruction
  - Chronic Inflammation
  - Abnormal Storage or Metabolism of metals
  - Widespread necrosis
End-stage (cirrhotic) livers, dogs
Microscopic features of end-stage liver

(nodular regeneration, fibrosis & biliary hyperplasia)
Hepatic failure

Clinical syndrome that results from inadequate liver function

• It indicates massive reduction of the amount of liver cells or decrease in their functionality (when liver’s considerable reserve and regenerative capacity is overwhelmed or when biliary outflow is obstructed).
• Result of either acute or chronic liver damage
• Not all functions lost at the same time
Manifestations of liver dysfunction and failure

Potential consequences of hepatic dysfunction and failure differ somewhat among domestic species. They include:

1. Hepatic encephalopathy
2. Disturbances of bile flow & icterus
3. Metabolic disturbances
4. Vascular and hemodynamic alterations
5. Cutaneous lesions
6. Impaired immune functions – detoxification & phagocytosis
Hepatic encephalopathy

Hepatic Coma

- Signs vary
  - Depression, behavioral changes
  - Mania, convulsions
- Acute liver disease (Horses and ruminants)
- Portosystemic shunts (Dogs and cats)
- Chronic liver disease (Any animal)
Pathogenesis of hepatic encephalopathy

- Blood accumulation of neurotoxic substances bypassing the liver and reaching the brain
- Requires shunting of >10-15% of portal blood
- Main substance is ammonia
- Clinical signs are more severe after feeding
- Other factors implicated are
  - Imbalance of inhibitory & excitatory amino acid neurotransmitters
  - Increased brain concentration of benzodiazepines
**Disturbances of bile flow**

**Cholestasis and Icterus (Jaundice)**

- **Cholestasis** - Abnormal accumulation of bile within the liver (intrahepatic), extrahepatic bile ducts or the gallbladder.
- **Icterus** – Yellow discoloration of tissues and body fluids due to hyperbilirubinemia

Yellow discoloration of the oral mucosa (Icterus)
Elevations in bilirubin

Hyperbilirubinemia (> 2 mg/dl) leads to icterus best seen in tissues rich in elastin (sclera, aorta, etc)

Causes

- Overproduction of bilirubin (prehepatic jaundice)
  - Hemolysis - intra- or extra-vascular
- Decreased uptake, conjugation or secretion of bilirubin (hepatic jaundice)
  - Severe hepatocellular injury
  - Impairment of flow within canaliculi (intrahepatic cholestasis)
- Reduced outflow of bile in extrahepatic bile ducts and gallbladder (post hepatic jaundice)
  - Mechanical obstruction of bile ducts (extrahepatic cholestasis) or gallbladder (cholelithiasis)
Conjugated vs unconjugated bilirubin

Why is this important?

- **Unconjugated bilirubin**
  - Toxic to tissues
  - Not soluble in aqueous solutions
  - Tightly complexed to albumin
  - Cannot be excreted in the urine even when blood levels are high

- **Conjugated bilirubin**
  - Water-soluble
  - Non-toxic
  - Loosely bound to albumin
  - Excreted in urine (bilirubinuria)
Diagnosis of icterus and cholestasis

- **Gross**
  - Generalized yellowish discoloration
  - Yellowish/greenish brown liver

- **Histo**
  - Bile pigment in canaliculi & hepatocytes

- **Clinical chemistry**
  Elevated blood levels of
  - Bilirubin
  - Cholesterol
  - Bile acids

_Icterus, dog. Yellow discoloration subcutaneous (top) and internal fat deposits (bottom) (Icterus)_
Abundant pigment inclusions in hepatocytes. Human with Dubin-Johnson syndrome.

Canalicular (intrahepatic) cholestasis

Illustration of the morphologic features of cholestasis and comparison with normal liver.
Metabolic Disturbances of Hepatic Failure

- Hemorrhagic diathesis or bleeding tendencies
  - Impaired synthesis of clotting factors
  - Reduced clearance of products of clotting and FDPs
  - Impaired platelet function
  - Impaired absorption of vitamin K
  - Disseminated intravascular coagulation (DIC)

- Intravascular hemolysis
  - Mainly in horses

- Hypoalbuminemia
  - Decreased production
  - Loss in ascites or GIT
Vascular and hemodynamic alterations

- Portal hypertension
- Acquired portosystemic shunts
- Ascites (Most common in dogs and cats)
  Secondary to
  - Portal hypertension
  - Decreased colloid osmotic pressure
  - Retention of sodium and water (Hyperaldosteronism)

Ascites (hydroperitoneum), peritoneal cavity, dog.

Acquired portosystemic shunts
Secondary to portal hypertension, dog.
Cutaneous problems in liver disease

- Photosensitization
- Hepatocutaneous syndrome (superficial necrolytic dermatitis)
Photosensitization

Activation of photodynamic pigments by UV light of 290 to 400 nm

- **Primary**
  - St John’s wort (*Hypericum perforatum*)
  - Chlorpromazine
  - Phenothiazine

- **Secondary**
  - Herbivores with impaired excretion of phylloerythrin
  - Most common form

- **Congenital**
  - Abnormal metabolism of heme → Retention of porphyrins
Hepatocutaneous syndrome

- Rare disease in dogs
- Crusting erosions & scaling especially at mucocutaneous junctions and footpads

Superficial necrolytic dermatitis, skin, dog. The epidermis has a trilaminar pattern: (1) parakeratotic layer \((P)\), (2) edema/necrolytic layer \((N)\), and (3) deep epidermal hyperplasia layer \((H)\).

Footpad. Note the fissure (arrow) and crusts. The crusting is due largely to the parakeratosis.
Developmental anomalies
Congenital cysts

Congenital cysts most likely originated from embryonic bile ducts, calves
Hydatid (parasitic) cysts. Larval stage of *Echinococcus granulosus*, livers from pigs
Miscellaneous lesions

- **Displacements**
  - Ventral hernia
  - Diaphragmatic hernia
  - Torsion of lobes
    - Swine and dogs
    - Infarction, shock, death

- **Rupture**
  - Trauma
  - Enlarged liver

Multiple linear lacerations of the hepatic capsule and parenchyma, dog
Incidental lesions

• Tension Lipidosis
  Focal areas in cattle & horses near mesenteric attachments

• Capsular Fibrosis
  • Resolution of peritonitis
  • Parasitic migration??  
    So called *Perihepatitis filamentosa*

*Perihepatitis filamentosa, liver, horse*
Postmortem changes

- Occur rapidly
- Pale, irregular foci
- Greenish black near intestine
- Emphysema
- Soft & putty-like
Liver Autolysis
CIRCULATORY DISTURBANCES

Disturbances of outflow

- Passive congestion
- Hepatic veno-occlusive syndrome
  - Occlusion of central vein due to fibrosis
  - Pyrrolizidine alkaloids
  - Vitamin A toxicity in captive cats

Veno-occlusive disease. A reticulin stain reveals the parenchyma framework of the lobule and the marked deposition of collagen within the lumen of the central vein.
Passive congestion

- Acute congestion
  - Slight enlargement of liver
  - Prominent reticular pattern

- Chronic congestion
  - Nutmeg appearance
    - Centrilobular congestion
    - Midzonal fatty change
    - Periportal areas almost spared
    - Later, centrilobular fibrosis & hemosiderosis
Examples of **chronic passive congestion**

In dogs (top and bottom left) and a cat (bottom). Note the rounded edges (liver expansion) and extensive areas of subcapsular fibrosis due to chronic exudation of lymph.
Microscopic lesions in chronic passive congestion, liver

Centrilobular (periacinar) congestion and midzonal hydropic degeneration, cow.

Centrilobular fibrosis (arrows). Dog.