INTRODUCTION
The liver is the largest visceral organ in the body and receives about 25% of cardiac output through the portal vein (2/3) and the hepatic artery (1/3). Blood from the stomach, intestines, spleen, and pancreas drains into the liver via the portal vein. Therefore, oxygen is carried to the liver by both the portal vein and the hepatic artery. The liver is the central organ for the metabolism of carbohydrates, proteins, lipids, vitamins and hormones as well as for detoxification, excretion, storage and digestion. Its size and location expose it to a myriad of injurious agents but it has a remarkable functional reserve and regenerative capacity. Consequently, an injury must be severe or strategically located to result in clinical signs or altered laboratory tests. Hepatic failure is associated with retention of ammonia, bile salts and pigments and failure of synthetic functions. Clinical signs of liver disease are often variable and nonspecific but most commonly include jaundice, ascites and/or hepatomegaly.

I. NORMAL ANATOMY & FUNCTION
NORMAL STRUCTURE
The normal relative size of the liver varies in different species. It comprises 3-4% body weight in adult carnivores, about 2% body weight in omnivores, and about 1% body weight in herbivores. The location of the organ and the number of liver lobes vary with species.

The traditional structural unit of the liver is a lobule – a hexagonal structure containing a central vein at the center and portal triads at the angles (periphery). Within the portal triads there are bile ducts, branches of portal vein, hepatic artery, nerves and lymphatics. The limiting plate, a discontinuous border of hepatocytes, forms the outer boundary of portal areas.

The functional unit is the acinus which is centred around the portal triad with the central vein at the periphery. The functional unit is used when the liver is viewed as a bile-secretory gland. Hepatocytes located near portal triads receive the highest concentrations of oxygen, nutrients and hormones. The acinus is divided into three zones:

- **Zone 1** or centroacinar surrounds the portal triads (periportal)
- **Zone 2** or midzone is the midlobular area
- **Zone 3** or periacinar surrounds the central vein (centrilobular)

Within the lobules or acini, hepatocytes are arranged into branching cords separated by sinusoids lined by fenestrated endothelial cells, Kupffer cells and Ito cells. Perisinusoidal space (of Disse) separates hepatocytes from sinusoids while canaliculi are formed by apposed lateral surfaces of contiguous hepatocytes.

Kupffer cells belong to the monocyte-macrophage system and their primary roles are phagocytosis and clearance of immune complexes. These cells can produce inflammatory mediators of which transforming growth factor β is important in hepatic injury. TGFβ is a potent inhibitor of mitosis of hepatocytes.

Ito cells (lipocytes, hepatic stellate cells) are located beneath the endothelial cells in the space of Disse. They have specialized storage capacity, especially vitamin A. They are associated with hepatic fibrosis since they are able to alter their morphology into myofibroblast conformation and secrete extracellular matrix components such as laminin, collagen, proteoglycans and fibronectin.

Blood from the portal triads (portal vein and hepatic artery) mix in the sinusoids and flow into the central veins whereas bile flows in the opposite direction from the canaliculi and bile ductules (cholangioles or canals of Hering) into bile ducts. Hepatocytes in Zone 1 (periportal) are most resistant to nutritional or circulatory insults whereas those around the central vein (Zone 3) are least resistant. Following injury, regeneration starts from the portal areas (Zone 1).

NORMAL FUNCTIONS OF THE LIVER (for your information only)
The broad range of hepatic functions include metabolism, synthesis, storage, catabolism, excretion, filtration and immunity. The critical functions are:
Bilirubin metabolism: Bilirubin, a major component of bile, is produced from the metabolic degradation of mainly hemoglobin from senescent erythrocytes. The process of bilirubin metabolism and elimination involves:
(a) formation of bilirubin from heme derived from senescent erythrocytes,
(b) binding of bilirubin to albumin and transport to the liver (unconjugated bilirubin)
(c) hepatocellular uptake of bilirubin
(d) conjugation of bilirubin with glucuronic acid so that it becomes water soluble and less toxic (=conjugated bilirubin)
(e) excretion/secretion into bile in canaliculi → bile ducts → intestine where gut bacteria deconjugate and degrade the bilirubin to colorless urobilinogens. The urobilinogens & residual pigments are excreted in feces, with some reabsorption and excretion in urine.
Derangement of this process results in jaundice (icterus), a common clinical sign of liver disease (to be discussed later).

Bile acid metabolism: Bile acids (e.g. cholic acid and chenodeoxycholic acid) are important constituents of bile. Their principal functions are maintenance of cholesterol homeostasis, stimulation of bile flow and digestion, and absorption of fats and fat-soluble vitamins. The acids are synthesized in hepatocytes from cholesterol, conjugated to glycine or taurine and actively secreted into canaliculi by specific intramembranous molecular pumps. The acids flow into the intestine to aid lipid digestion and up to 95% of secreted bile acids are recycled to the liver through the enterohepatic circulation (up to 15 times a day). Interruption of this process results in fat malabsorption and deficiency of fat-soluble vitamins.

Carbohydrate metabolism: The liver responds to changes in the concentration of blood glucose. After eating, excess carbohydrates are stored in the liver as glycogen or fatty acids and during fasting glucose levels are maintained by glycolysis of stored glycogen or by gluconeogenesis.

Lipid metabolism: The liver is involved in the production and degradation of plasma lipids such as cholesterol, triglycerides, phospholipids and lipoproteins.

Xenobiotic metabolism: The cytochrome p450 enzymes of the smooth endoplasmic reticulum of hepatocytes serve as the major site of metabolism of foreign substances (xenobiotics) and endogenous lipophilic substances such as steroids that require conversion to water-soluble forms before elimination in bile or urine. Hence the liver renders inactive many toxins absorbed into the portal circulation.

Protein synthesis: A majority of plasma proteins are produced in the rough endoplasmic reticulum of hepatocytes. The proteins include albumin, transport proteins, lipoproteins, clotting factors, etc. The liver is responsible for synthesis of approximately 15% of body proteins. Highly toxic ammonia generated through the catabolism of amino acids is converted to urea mainly in the liver.

Immune function: The liver is involved in systemic, local and mucosal immunity, e.g. production of acute phase proteins; presence of Kupffer cells responsible for phagocytosis...
of particulate matter and removal of endotoxin; and recirculation of secretory IgA into the biliary tree and intestine.

II. HEPATOBIATORY INJURY AND RESPONSES

Background
In each species and irrespective of cause, all hepatic derangements tend to produce similar signs and symptoms. Clinical signs manifest only when the liver’s considerable reserve and regenerative capacity is overwhelmed or when biliary outflow is obstructed. Liver lesions are fairly common, but only those that affect the majority of the hepatic parenchyma are likely to produce signs and symptoms of hepatic failure. The interpretation of the location and type of liver lesions often helps to identify the presence and cause of disease. This routinely involves histopathology.

Portals of entry of injurious agents
The three main routes are:
- Hematogenous (mostly from portal vein)
- Biliary and pancreatic ductular transport (retrograde)
- Direct extension from peritoneum or digestive tract

PATTERNS OF HEPATOCELLULAR DEGENERATION & NECROSIS
Cellular degeneration and/or necrosis in the liver occurs in one of two morphologic patterns -random and zonal.

Random hepatocellular degeneration & necrosis
The change occurs in one of three forms:
- Single cell necrosis or apoptosis throughout the liver, not visible grossly.
- Multifocal necrosis (scattered randomly throughout the liver). There is no predictable location within liver lobules. It is typical of many infectious agents (viruses, bacteria, certain protozoa). Grossly the lesions appear as discrete, pale or dark-red foci, sharply delineated from normal parenchyma. The size varies from less than 1 mm to several mm. Microscopically, affected cells are degenerate or necrotic and there may be inflammation.

Zonal hepatocellular degeneration & necrosis
Zonal change affects hepatocytes within defined areas of the hepatic lobule and leads to enhanced lobular pattern on the capsular and cut surfaces. Extensively affected livers are pale, friable, and modestly enlarged with rounded margins. Enlargement and pallor are due to swelling of degenerate hepatocytes. When the hepatocytes become necrotic, adjacent sinusoids become dilated and congested and the area appears red. Specific forms of zonal change include:
- Centrilobular degeneration and necrosis. This is a common lesion because zone 3 hepatocytes receive the least oxygenated blood and are therefore more susceptible to hypoxia. Secondly, they have the greatest enzymatic activity (mixed-function oxidases) capable of activating compounds into toxic forms. The main causes of centrilobular zonal change are severe anemia, right heart failure and hypoxia.
• **Midzonal degeneration and necrosis.** This is an uncommon change affecting hepatocytes in the middle portion of the lobule (zone 2). It has been reported in pigs and horses with aflatoxicosis.

• **Periportal degeneration and necrosis.** This is also an uncommon change and it involves zone 1 hepatocytes. It is caused by toxins which do not require metabolism to cause injury (e.g. phosphorus) and thus damage hepatocytes in the first zone encountered, or those that can be metabolized by enzymes in zone 1 hepatocytes.

• **Bridging necrosis.** This is the result of confluence of areas of necrosis and implies severity of the lesion. The links can be central to central, portal to portal, or central to portal.

• **Massive necrosis.** It involves necrosis of all hepatocytes within a lobule or contiguous lobules but not necessarily necrosis of the whole liver. In the acute stage, the liver has a mosaic appearance of dark red areas (necrosis and hemorrhage) intermingled with greyish or yellow areas (surviving hepatocytes). If the animal survives to a chronic stage, the necrotic areas collapse and are replaced by fibrous tissue; the liver becomes smaller and has a wrinkled capsule (postnecrotic scarring). Massive hepatic necrosis is seen in hepatitis dietetica of pigs (vitamin E/Selenium deficiency), migrating helminth parasites in several species, algae poisoning, and iron-dextran poisoning in piglets.

### PATTERNS OF HEPATIC INFLAMMATION

The broad types of inflammation include:

• **Acute hepatitis** as seen in several bacterial, protozoal and viral infections. Neutrophils predominate in bacterial and protozoal hepatitis whereas in viral hepatitis, it is mostly necrosis with or without lymphocytes.

• **Chronic hepatitis** when there is persistence of the injury. It is characterized by fibrosis, accumulation of mononuclear cells (lymphocytes, plasma cells and macrophages) with or without neutrophils, and frequently, regeneration. Lesions may be focal/multifocal in the form of abscesses or granulomas, or they may be diffuse with loss of hepatic parenchyma, fibrosis and nodular regeneration. It can lead to end-stage liver.

• **Cholangitis** is inflammation targeting the biliary ducts. It can be acute or chronic.

• **Cholangiohepatitis** involves the biliary ducts and hepatic parenchyma.

### GENERAL RESPONSES OF THE LIVER TO INJURY

Responses of the liver to different noxious insults that cause destruction of hepatic parenchyma include (1) regeneration of parenchyma, (2) replacement by fibrosis, and (3) biliary hyperplasia. The outcome of any given hepatic insult reflects the nature and duration of the insult.

1. **Regeneration.** The liver has a very good regenerative ability. Regeneration involves mostly the replication of mature hepatocytes adjacent to areas of cell loss. Oval cells (stem cells) also participate in regeneration. The process is stimulated by growth...
factors, including transforming growth factor alpha (TGFα) and hepatocyte growth factor. Regeneration without scarring occurs if the original fibrous and reticulin framework is intact, there is adequate supply of blood, and there is free drainage of bile. As much as three-quarters of the functional mass of the liver must be removed before signs of dysfunction appear, and the liver can quickly (within 6-7 days!) regenerate as much as 60 percent of its mass without apparent ill-effect. Even when necrosis of hepatocytes is continuous, the liver will attempt to regenerate its functional mass, along with bile ducts and vessels. However, prolonged regenerative effort often results in nodular proliferations of parenchyma that produce an architecturally distorted liver. Flow of blood to such nodules and bile from them is abnormal and hepatic function is impaired.

Oval cells are stem cells which reside in the portal areas and have the ability to differentiate into hepatocytes or bile duct epithelium. Histologically, they appear as small basophilic cells with an oval shape. Oval cells can replace hepatocytes in certain (usually toxic) conditions.

2. Fibrosis is a common manifestation of chronic liver injury. Hepatic fibrosis involves an overall increase in the extracellular matrix within the liver. Normally, connective tissue is present in the portal areas, around the central veins, and around the sinusoids of the liver. With mild injury, the immature collagen is removed and replaced by regenerating hepatocytes. However, severe fibrosis will affect liver function and can be lethal. Fibrosis has been associated with growth factors that stimulate Ito cells and myofibroblastic cells in the connective tissue to proliferate and differentiate into collagen-secreting fibroblasts. The pattern of fibrosis can help identify the type of insult early in fibrosis (focal, multifocal, diffuse, and biliary fibrosis). In late stages, there is no distinctive pattern (end-stage liver).

3. Biliary hyperplasia. A variety of insults to the liver can result in the proliferation of new bile ducts within the portal areas. The mechanism for this proliferation is not known. Biliary hyperplasia occurs in any disease which obstructs bile drainage, usually associated with chronic hepatic injury but can occur quickly in young animals. It is seen in hepatotoxicity (pyrrolizidine alkaloid, aflatoxin poisoning), biliary obstruction and secondary to liver fibrosis. It may be an attempt to regenerate hepatocytes.

END-STAGE LIVER (Cirrhosis). Cirrhosis has been defined as "a diffuse process characterized by fibrosis and the conversion of the normal liver architecture into structurally abnormal lobules" but a better term is "end-stage liver". It is the final, irreversible result of different hepatic diseases and it usually involves severe nodular regeneration, fibrosis and bile duct hyperplasia often occurring together but in varying proportions. Grossly, the entire liver is distorted and consists of nodules of regenerating parenchyma separated by fibrous bands, which appear as depressions on the surface. Profound vascular abnormalities in the form of shunts occur in an end-stage liver. Depending on the duration of the disease and type of injury, cirrhosis may be micronodular, macronodular or mixed. The potential causes are numerous and include chronic toxicity, chronic cholangitis and/or obstruction, chronic
congestion (right side heart failure), inherited disorders of metal metabolism (copper or iron), chronic hepatitis, and a variety of poorly defined disease entities (idiopathic).

III. MANIFESTATIONS OF LIVER FAILURE

Hepatic (or liver) failure refers to a clinical syndrome that results from inadequate liver function. It indicates massive reduction of the amount of liver cells or decrease in their functionality. Loss of normal liver function can occur as a consequence of either acute or chronic liver damage; however, all hepatic functions are not usually lost at the same time. The potential consequences of hepatic dysfunction and failure differ somewhat among the domestic species, they include hepatic encephalopathy, disturbances of bile flow resulting in hyperbilirubinemia (icterus), a variety of metabolic disturbances, vascular and hemodynamic alterations, cutaneous manifestations, and impaired immune response.

1. Hepatic encephalopathy

This term refers to a variety of neurologic signs and symptoms in patients who suffer liver failure as a consequence of either acute or chronic liver dysfunction. The signs vary but often include depression, other behavioural changes, mania and convulsions. The condition is seen especially in horses and ruminants with acute liver failure, dogs and cats with portosystemic shunts, and any animal with chronic liver disease.

Several factors have been implicated in contributing to hepatic encephalopathy. Most of these factors relate to an accumulation of neurotoxic substances that have bypassed the liver or have not been metabolized properly by the liver. The main substance implicated is ammonia derived from amines absorbed from the GIT. Other possible causes of hepatic encephalopathy are altered balance of inhibitory and excitatory amino acid neurotransmitters, and increased brain concentrations of endogenous benzodiazepines. The clinical signs may be more severe after feeding.

2. Disturbances of bile flow and hyperbilirubinemia (icterus, jaundice)

Bile is composed of water, bile acids, bilirubin (a yellow pigment), cholesterol, inorganic ions and other materials. It is an excretory product which also facilitates digestion. Bile acids are produced from cholesterol metabolism and they act as detergents; their rate of synthesis is low and approximately 95% occurs via enterohepatic circulation.

Elevated levels (> 2 mg/dl) of bilirubin in blood (hyperbilirubinemia) can produce icterus which is yellow discoloration of tissues and body fluids caused by accumulation of bilirubin. It is especially evident in white tissues or those rich in elastin (eg; fat, sclera, aorta). Causes of hyperbilirubinemia can be prehepatic, hepatic and post hepatic as follows:

i. Prehepatic – Overproduction of bilirubin as a consequence of hemolysis, particularly severe intravascular hemolysis, which overwhelms the liver’s ability to remove bilirubin from plasma and to secrete conjugated bilirubin into.

ii. Hepatic - Decreased uptake, conjugation or secretion of bilirubin, as in severe hepatocellular injury. Often seen with hepatotoxins which inhibit membrane bound
and cytoplasmic enzymes.

iii. Posthepatic - Reduced outflow of bile (cholestasis) following mechanical obstruction of bile ducts (extrahepatic cholestasis) or impairment of flow within canaliculi (intrahepatic cholestasis). In severe cholestasis the liver has a yellowish or greenish brown discoloration. Histologically, the canaliculi are distended with bile which may also be present in Kupffer cells and as extracellular bile lakes. The clinical diagnosis of cholestasis is based on the accumulation in blood of materials normally transferred to the bile, including bilirubin, cholesterol, and bile acids.

Diagnosis of Icterus and cholestasis:
- Gross Findings: Yellowish discoloration of the tissues and yellow-green tinge to the liver
- Histologic Findings: Bile plugs in the canaliculi/bile ducts and granular bile pigment within hepatocytes.
- Clinical Chemistry: Increased blood levels of bilirubin, cholesterol and bile acids

3. Metabolic disturbances
   i. Hemorrhagic diathesis (bleeding tendencies) can accompany liver failure. Normal clotting can be affected in liver disease by:
      a) impaired synthesis of clotting factors, fibrinogen, prothrombin, etc
      b) reduced clearance of products of the clotting process including fibrin degradation products (FDP)
      c) metabolic abnormalities affecting platelet function.

      Obstruction of bile flow leads to impaired absorption of fat which limits vitamin K absorption which leads to inactivity of factors II, VII, IX and X. Acute liver failure may also precipitate disseminated intravascular coagulation (DIC) that can itself lead to hemorrhagic diathesis.

   ii. Intravascular hemolysis is sometimes seen especially in horses with acute liver disease but the exact cause is undetermined.

      iii. Hypoalbuminemia can occur in association with chronic liver disease as a consequence of both decreased hepatic production of albumin and, because of portal hypertension, increased loss of albumin in ascitic fluid or into the intestinal tract. More commonly seen in chronic liver disease because of the long half-life of albumin (dog - 8 days, cattle 21 days).

4. Vascular and hemodynamic alterations
   Chronic damage to the liver and fibrosis can produce an increased amount of vascular resistance through the liver. This results in hemodynamic alterations such as portal hypertension, acquired portosystemic shunts, and ascites. The shunts are collateral vascular channels open to allow blood in the portal vein to bypass the abnormal liver (see pages 12-14).

   Ascites: In some species, the increased hydrostatic pressure within the hepatic
vasculature causes transudation of fluid into the peritoneal cavity to produce ascites. Transudation of fluid into the peritoneal cavity is enhanced by the decreased colloid osmotic pressure of plasma resulting from hypoalbuminemia (due to accelerated loss and reduced hepatic synthesis of plasma proteins). Retention of sodium and water resulting from reduced metabolism of aldosterone (hyperaldosteronism) by a chronically affected liver, may also lead to ascites. Ascites associated with chronic liver disease (end-stage liver) occurs most commonly in the dog and cat, occasionally in sheep, and rarely, in the horse and cattle.

5. **Cutaneous Problems associated with Liver Disease**
   
i. **Photosensitization**: Injury to the skin resulting from activation of photodynamic pigments by ultraviolet light (of 290 to 400 nm) from sun rays is called photosensitization. The pigments are in circulation and become bound to dermal cells. The mechanism of tissue damage is believed to involve oxidative injury and the damage is usually in unpigmented or hairless areas of skin. The lesions display hair loss, erythema, and necrosis especially in the face. Sources of photodynamic agents include:
   - **a) Primary photosensitization**: Preformed photodynamic agent is ingested, absorbed and deposited in tissues e.g. St John's wort (*Hypericum perforatum*), buckwheat, tetracycline and phenothiazine. Not common.
   - **b) Secondary photosensitization (Hepatogenous photosensitization)**: This is the most common and most important form of photosensitization. It occurs in herbivores when hepatic dysfunction or biliary obstruction impairs normal excretion of phylloerythrin in bile. Phylloerythrin is a photodynamic agent, derived from microbial breakdown of chlorophyll in the gastrointestinal tract. Hepatogenous photosensitization usually occurs when about 80% of the normal hepatic function is lost or if the biliary tree is damaged. There will be jaundice as well. Mutant Southdown and Corriedale sheep develop photosensitization as soon as they begin to ingest plant material - an abnormality in the uptake of bilirubin and phylloerythrin inhibits normal excretion of these substances.
   - **c) Congenital porphyria**: Occurs in cattle, cats and other species as a result of an abnormal metabolism of heme, leading to abnormal excretion of porphyrins which are themselves photodynamic. It is rare.

   ii. **Hepatocutaneous syndrome** (superficial necrolytic dermatitis). This is a rare disease of middle-age or older dogs characterized by crusting, erosions, and scaling of the skin. Lesions are distributed symmetrically over the face, footpads and inguinal area especially at mucocutaneous junctions. It is most commonly associated with chronic liver disease and thought to represent an amino acidopathy, but the mechanism of cutaneous injury is not understood.

6. **Immunologic manifestations of hepatic failure** *(For your information only)*
   Chronic liver failure leads to impairment of normal hepatic immune function - detoxification and phagocytosis by Kupffer cells. The affected animal frequently develops endotoxemia and systemic infection primarily a result of shunting which allows the injurious agents to
bypass the liver and its Kupffer cells.

IV. DEVELOPMENTAL ANOMALIES AND MISCELLANEOUS CHANGES

The most important developmental anomaly in dogs is **congenital portosystemic shunts**, a vascular anomaly (see page 12). Most other anomalies are incidental lesions.

**Congenital cysts** occur in all species. They probably arise from embryonic bile ducts or hepatic capsule. They are usually incidental findings and should be distinguished from parasitic cysts, particularly *Cysticercus* (larvae of *Taenia* spp). Congenital polycystic disease occurs in humans, dogs (Cairn terriers) and cats (Persian and Persian X). Multiple cysts in the kidney and liver may be incidental or they may result in renal or hepatic disease.

**Hepatic displacement** *(for your information only).* May be congenital or acquired. Displacements in ventral and diaphragmatic hernias are common.

**Rupture** of the liver is rapidly fatal. It occurs commonly as a result of trauma (hit by car). Diffuse hepatic disease with enlargement, in which the substance is friable and the capsule taut, provides a predisposition to rupture, which may occur spontaneously. Predisposing lesions include acute hepatitis, amyloidosis, severe congestion, fatty degeneration, and neoplasms.

**Tension lipidosis** *(for your information only).* This is a discrete pale area of hepatic lipidosis on the liver, usually adjacent to the insertion of the mesenteric attachment (occurs in cattle and horses). It is proposed that these attachments impede blood supply to the subjacent hepatic parenchyma by exerting tension on the capsule. Hepatocytes in the affected areas most probably undergo fatty degeneration as a consequence of hypoxia.

**Capsular fibrosis** is the presence of discrete fibrous tags or plaques on the diaphragmatic surface of the liver and on the adjacent diaphragm of the horse. The tags most likely represent resolution of nonseptic peritonitis rather than parasitic migration. Also referred to perihepatitis filamentosa.

**Postmortem changes** *(for your information only)* occur rapidly because liver is rich in nutrients for bacteria and is freely exposed to agonal invaders from the intestine. Postmortem changes must be distinguished from antemortem changes. Post mortem changes may appear as:
1. Enlarging pale foci with no evidence of inflammation
2. Greenish black areas adjacent to intestine
3. Brownish and green staining with bile
4. Gas bubbles from bacterial fermentation
5. Loss of normal consistency: the substance of the organ becomes soft and putty-like and the formation of putrefactive gases may make it foamy
V. CIRCULATORY DISTURBANCES

Given the enormous flow of blood through the liver, it is not surprising that circulatory disturbances have considerable impact on the liver. In most instances, however, clinically significant abnormalities of liver function do not develop, but hepatic morphology may be strikingly affected. These disorders can be grouped according to whether blood flow into, through, or from the liver is impaired. Many of these disorders may lead to portal hypertension, which is increased pressure within the portal vein. Persistent portal hypertension can lead to acquired portosystemic shunts composed of numerous thin-walled veins that link the mesenteric veins and the vena cava. Persistent portal hypertension can also lead to ascites.

1. **Impaired blood flow into the liver**
   Any condition that may impair the blood flow through the portal vein, or hepatic artery, before it enters the liver. Uncommon, but seen with hepatic artery compromise (arteritis, thrombosis, embolism), portal vein hypoplasia, portal vein thrombosis or external compression by tumours or abscesses. These conditions may induce prehepatic portal hypertension or liver infarcts.

   - **Portal vein hypoplasia (= microvascular dysplasia)** in dogs and cats. Microscopic liver lesions are similar to those of congenital portosystemic shunts (see below), but affected animals often have portal hypertension and ascites.

2. **Impaired blood flow through the liver**
   It is the most common abnormality and includes any condition able to increase the resistance of blood flow to, or within, the sinusoids. Seen in several chronic liver diseases such as cirrhosis, diffuse fibrosis, amyloidosis, and intrahepatic arteriovenous shunts (congenital malformation or acquired). These conditions may cause intrahepatic portal hypertension.

   - **Intrahepatic arteriovenous shunts** *(For your information only)* may be congenital or acquired in dogs and cats, and are direct communications between the hepatic artery and branches of the portal vein. Affected portions of the liver contain convoluted thick walled arteries and distended portal vein branches.

3. **Impaired blood drainage from the liver - Hepatic venous outflow obstruction**
   Conditions that lead to increased resistance to venous outflow in the hepatic vein or adjacent vena cava. Uncommon, but seen in partial or complete thrombosis of hepatic veins (Budd-Chiari syndrome), veno-occlusive disease, passive congestion (due to congestive heart failure or cor pulmonale). These conditions may cause posthepatic portal hypertension.

   - **Passive Congestion**: Passive congestion of the liver is almost always the consequence of right side heart failure which produces elevated pressure in the caudal vena cava and in hepatic veins and its tributaries. It can be acute or chronic. Passive congestion can also be due to compression of larger
hepatic veins or posterior vena cava by abscess or neoplasm.

**Chronic congestion** leads to persistent hypoxia in centrilobular areas, and because of oxygen and nutrient deprivation, hepatocytes within these areas undergo atrophy, degenerate, or eventually undergo necrosis. The sinusoids in these areas are dilated and congested. Grossly, the liver shows pronounced lobulation (nutmeg liver) due to centrilobular sinusoidal congestion and midzonal fatty degeneration. Fibrosis may be prominent around central veins and in the liver capsule. Portal regions are relatively normal.

**Acute congestion** produces slight enlargement of the organ with pronounced lobular pattern due to marked centrilobular congestion.

- **Hepatic veno-occlusive disease** (*For your information only*): This is intimal thickening and occlusion of the central vein by fibrous tissue. It leads to passive hepatic congestion and may lead to hepatic failure. The lesion can follow pyrrolizidine alkaloid poisoning and aflatoxicosis. High incidence is reported in captive exotic cats fed high vitamin A.

### Other vascular and circulatory disorders

**Congenital portosystemic shunt**: This is an abnormal vascular channel that allows blood within the portal venous system to bypass the hepatic sinusoids and drain into the systemic circulation. It occurs in all species but most often in dogs and cats. The shunt is either intrahepatic or extrahepatic in location but usually limited to a single large-caliber vessel. Typically, intrahepatic shunts involve failure of closure of the ductus venosus at birth and they are often located on the left side of the liver (large breeds of dogs). On the other hand, extrahepatic shunts such as portal vein to caudal vena cava anastomosis, occur more often in smaller breeds of dogs. Affected animals are typically stunted and frequently develop signs of hepatic encephalopathy. The liver is small and is characterized histologically by lobular atrophy and portal areas which lack a portal vein and contain several arterioles. The portal vein pressure will be normal, unlike in acquired portosystemic shunts.

**Telangiectasis** is the presence of focal areas in which sinusoids are dilated and filled with blood where hepatocytes have been lost. Telangiectasia is common in cattle and old cats and has no clinical significance.

- **Gross**: irregular small, 1-5 mm, circumscribed, dark-red foci.
- **Histo**: Cavernous ectasia of sinusoids.

**Anemia**: Anemia first affects the centrilobular regions which receive blood last. Affected livers have an enhanced lobular pattern.

**Infarction** of the liver is uncommon because of the dual blood supply to the liver (from the hepatic artery and portal vein). However, thrombosis or compression of an
intrahepatic branch of the hepatic artery caused by embolism, neoplasia, or sepsis can result in a localized infarct. In ruminants, hemorrhagic infarcts can be secondary to mycotic rumenitis. Torsion of individual lobes, usually the left lateral, occurs in swine and dogs (and mink, rabbits), and the resultant infarction can cause death due to shock and hemorrhage.

VI. METABOLIC DISTURBANCES & NUTRITIONAL DISEASES

FATTY LIVER (HEPATOCELLULAR LIPIDOSIS, STEATOSIS)

Lipids are normally transported to the liver from adipose tissue and the gastrointestinal tract in the form of either free fatty acids or chylomicrons respectively. Within hepatocytes, free fatty acids are esterified to triglycerides that are complexed with apoproteins to form low-density lipoproteins, and these are released into the plasma as a readily available energy source for use by a variety of tissues. With the exception of ruminants, the liver also actively produces lipids from amino acids and glucose. Some oxidation of fatty acids for energy production occurs within hepatocytes, and some fatty acids are converted to phospholipid and cholesterol esters. Fatty liver or hepatic lipidosis occurs when the rate of triglyceride accumulation within hepatocytes exceeds the rate of their metabolic degradation or release as lipoproteins.

Potential Mechanisms of fatty liver include one or more of the following:

1) Excessive entry of fatty acids into the liver as a consequence of excessive dietary intake of fat or increased mobilization of fat from adipose tissue due to increased demand (lactation, starvation, and endocrine abnormalities).
2) Excessive dietary intake of carbohydrates - results in enhanced fatty acid synthesis leading to excessive formation of triglycerides.
3) Abnormal hepatic function - results in accumulations of triglycerides because of decreased energy for oxidation of fatty acids within hepatocytes.
4) Increased esterification of fatty acids to triglycerides - response to increased amounts of glucose and insulin, or from prolonged increase in dietary chylomicrons.
5) Decreased apoprotein synthesis and subsequent decreased production and export of lipoproteins from hepatocytes.
6) Impaired secretion of lipoprotein from the liver – results from hepatotoxins or drugs.

Morphologic changes:

Gross appearance: Enlarged, uniform light yellow or orange liver that cuts with ease and has a greasy texture. The edges are rounded and the surface is smooth. In advanced cases, the tissue will float in water or fixative.

Histological appearance: Single large or multiple small distinct clear cytoplasmic vacuoles within hepatocytes. Large vacuoles may displace the nucleus. Oil red O may be used to demonstrate fat in the vacuoles. Centrilobular location suggests anoxic or toxic damage whereas periportal location may indicate direct injury caused by a toxic agent that do not require metabolic activation by hepatocytes.

Significance: Depends on the cause, severity and duration. The lesion is reversible in mild
cases, but could lead to hepatic necrosis, fat embolism and liver rupture with internal hemorrhage. Fatty livers are also more susceptible to toxic damage.

**Specific causes and syndromes of hepatocellular lipidosis:**

- **Dietary causes:** eg simple dietary excess. Fasting in obese animals is followed by a heavy demand on fat stores since the liver must provide lipoproteins to other tissues. Deficiencies of cobalt and vitamin B₇ have been implicated as causes of fatty liver (white-liver disease) in sheep and goats but the pathogenesis is unknown.

- **Toxic and anoxic injury** to hepatocytes can lead to accumulation of fat because of decreased formation and/or export of lipoproteins by hepatocytes and decreased oxidation of fatty acids within hepatocytes.

- **Ketosis** is a disease resulting from impaired metabolism of carbohydrates and volatile fatty acids. Ketone bodies are derived from fatty acyl CoA - an intermediate in the oxidation of fatty acids. In pregnant and lactating animals, there is a continuous demand for glucose and amino acids, and ketosis results when fat metabolism (which occurs in response to the increased energy demands) becomes excessive. Common in dairy cattle during peak lactation, or pregnancy in ewes - usually twins - known as pregnancy toxemia.

- **Bovine fatty liver syndrome** is usually encountered in obese animals a few days before or after parturition and is often precipitated by an event that causes the cow to go off feed, such as retained placenta, metritis, mastitis, abomasal displacement, or parturient paresis. Accumulation of lipids within the liver is the result of both increased mobilization of adipose tissue (which results in increased influx of fatty acids to the liver) and defective hepatocyte function - resulting in decreased export of lipoproteins from the liver.

- **Feline fatty liver syndrome:** The causes of this disease syndrome are poorly defined, but affected cats often are obese and anorectic and have no other disease that could cause hepatic lipidosis. Poor regulation of intermediary metabolism during starvation is presumed. Obese cats are at risk if food intake drops for more than a few days. Histologic evidence of hepatic lipidosis is seen within 2 weeks of the onset of fasting (it may start after 2 days). Severe cases may show icterus and other signs of hepatic failure, including hepatic encephalopathy.

- **Hepatic lipidosis in horses** occurs especially in obese ponies and miniature breeds. Shetland ponies are predisposed. Usually occurs in pregnant or lactating mares. The pathogenesis is unknown. These ponies may develop signs of hepatic failure such as hepatic encephalopathy and terminal DIC.

- **Endocrine disorders**, especially diabetes mellitus and hypothyroidism. In diabetes, insulin is deficient or inactive due to lack of functioning receptors. The increased lipolysis results in over-supply of fatty acids, coinciding with shortage of ATP (due to reduced glucose availability), and these lead to reduced lipoprotein synthesis.

**GLYCOGEN ACCUMULATION**

Glucose is normally stored within hepatocytes as glycogen, which is often present in large
amounts after feeding. Excessive glycogen accumulation occurs in diabetes mellitus, hyperadrenocorticism and in glycogen storage diseases.

**Glucocorticoid-induced hepatocellular degeneration (steroid induced hepatopathy)** occurs when excessive levels of endogenous or exogenous glucocorticoids cause increased accumulation of glycogen in hepatocytes. Glucocorticoids induce glycogen synthetase and so enhance hepatic storage of glycogen. The disease occurs in dogs and is frequently iatrogenic (due to treatment with steroids). In severe cases, the liver is enlarged and pale, but otherwise grossly unremarkable. Glycogen accumulation leads to pronounced swelling of hepatocytes, particularly those in the midzonal areas. Microscopically, affected hepatocytes are swollen and have extensive cytoplasmic vacuolation.

**AMYLOIDOSIS**
Amyloidosis occurs in most species of domestic animals. As previously discussed (see General Pathology lecture notes) amyloidosis is not a single disease entity but a term used to describe the deposition of amyloid - proteins that are composed of β pleated sheets of non branching fibrils. Hepatic amyloidosis frequently occurs as a consequence of prolonged inflammation such as chronic infection or tissue destruction - 2° amyloidosis. Less commonly, amyloidosis can be due to a plasma cell tumor (primary amyloidosis), or as an inherited condition (familial amyloidosis) as in Shar-Pei dogs and Oriental breeds of cats. The amyloid usually accumulates in vessel walls, portal connective tissue or in the space of Disse where it impairs normal access of plasma to hepatocytes which then undergo atrophy. Severe cases may be accompanied with clinical signs of hepatic dysfunction or failure, or hepatic rupture with exsanguination. The kidneys are usually affected as well.

**COPPER ACCUMULATION**
Copper is an essential trace element of all cells but can be life threatening when present in excess. Following absorption from the intestine copper enters the liver where it is bound to cytosolic metallothionein and stored in lysosomes of hepatocytes. It can then be excreted in bile or bound to ceruloplasmin for transport to peripheral tissues. Biliary excretion is the most important step that regulates copper homeostasis. While in lysosomes, copper is innocuous. Once the lysosomal storage capacity is exhausted, copper breaks into the cytoplasm where it is cytotoxic by causing membrane damage and necrosis. This can result in massive release of copper from damaged hepatocytes, which when taken up in circulation, can lead to a hemolytic crisis.

In domestic animals, copper toxicosis usually occurs as a consequence of one of the following:

1. **Simple dietary excess in ruminants**
   - Overcorrection for copper deficiency
   - Contamination of pasture with copper from sprays or fertilizer
   - Sheep that have access to copper-containing mineral blocks formulated for cattle.

When some event triggers sudden release, there is acute hepatic necrosis, usually centrilobular and midzonal, but can be massive, followed by severe, intravascular hemolysis. Affected sheep are icteric with dark urine and dark red to black (gun metal) kidneys (hemoglobinuric nephrosis).
2. **Grazing on pasture low in molybdenum** (which antagonizes copper uptake).

3. **Predisposing hepatic (cholestatic) conditions**
   - Grazing on fields containing hepatic phytotoxins such as pyrrolizidine alkaloids (as in *Heliotropium, Crotalaria, Senecio*) which prevent hepatocellular mitosis to replace dead cells.
   - Any hepatic disease that results in cholestasis (canine chronic hepatitis).

4. **Hereditary disorders of copper metabolism**
   This occurs in Bedlington terriers as an autosomal recessive disease (an equivalent of Wilson’s disease in humans). The defect is thought to lead to impaired biliary excretion of copper which results in progressive accumulation within the liver. Excess copper can be detected as early as 6 months of age and progresses with time. Liver levels can be 5 to 30 times above normal (< 400 ppm dry weight is the reference upper limit; > 600 ppm are consistent with liver disease). Associated liver lesions are progressive necrosis, chronic inflammation, replacement fibrosis and eventually end-stage liver disease. Copper accumulation leading to necrosis and inflammation also appears to be familial in the West Highland white terrier, Skye terrier, Dalmatian and Labrador retriever. Chronic hepatitis associated with elevated copper concentrations has been reported in Doberman pinchers and American and English cocker spaniels but it remains to be determined whether this copper accumulation is primary or secondary to chronic inflammation, fibrosis and cholestasis.

**PIGMENT ACCUMULATION**
- **Bile**: Excess bile (cholestasis) imparts an olive-green colour to the liver parenchyma. Histologically, conjugated bile pigments may distend bile canaliculi and form bile lakes.

- **Hemosiderin**: The organ will be dark brown (or black if severe). Histologically the pigment is golden brown and granular. It can be demonstrated by staining with Prussian blue. Clusters of macrophages containing iron pigment (pigment granulomas) are often seen in chronic liver disease. Iron accumulation within Kupffer cells usually represents breakdown of erythrocytes and when it accumulates within hepatocytes, it usually represents accumulation of tranferrin.
  - **Hemosiderosis**: excessive systemic load of iron characterized by abundant hemosiderin in a variety of tissues without impairment of organ function.
  - **Hemochromatosis**: abnormal increase of storage of iron within the body that can cause hepatic dysfunction.

- **Lipofuscin (ceroid)** is a brown pigment, particularly common in old cats. It is the wear and tear pigment resulting from incomplete lipid oxidation.

- **Melanin** produces a black discoloration.

- **Parasite hematin** is a dark excreta of liver flukes (fascioliasis) containing iron and porphyrin. It is seen particularly in the migratory tracks of *Fascioloides magna* in bovine
NUTRITIONAL DISEASES OF THE LIVER
The two main conditions are hepatosis dietetica in pigs and white liver disease in sheep.

- **Hepatosis dietetica** is a syndrome of acute hepatic necrosis in young, rapidly growing pigs. While the pathogenesis is not completely understood, the condition is responsive to vitamin E and/or selenium supplementation. Therefore, it is believed that oxidative injury leads to hepatocyte necrosis. The lesion is characterized by centrilobular to massive hepatic necrosis and hemorrhage.

- **White liver disease** is caused by insufficiency of cobalt intake. Cobalt is a necessary cofactor in the synthesis of vitamin B\(_{12}\) and other enzymes, and deficiency of the vitamin leads to anemia. Affected livers are pale and fatty most likely due to anemia.

VII. INFECTIOUS DISEASES OF THE LIVER (HEPATITIS)

Agents causing hepatitis may be blood-borne (most common) or reach the liver by ascending the biliary system or by direct extension from the peritoneum. Terms used include hepatitis, cholangitis, pericholangitis, perihepatitis, portal hepatitis, cholangiohepatitis and cholecystitis depending on the location. They may be acute, subacute, chronic. Neutrophilic cholangitis is mostly an ascending infection from the intestine, whereas lymphocytic cholangitis probably has an immunologic basis. Specific agents causing hepatitis include viruses, bacteria, spirochetes, fungi, protozoa and helminths.

**VIRAL INFECTIONS OF LIVER:**

**Infectious Canine Hepatitis (ICH):** The etiology of ICH is canine adenovirus 1 (CAV-1). It may occur in dogs, foxes and coyotes. The disease is now less common because of widespread vaccination. It is most severe in young dogs where it can be fatal. Mortality is uncommon in older dogs but these may continue to shed virus in urine long after recovery. Infection is mostly via oral exposure to urine. The virus then multiplies in the tonsils before becoming viremic. The organism has tropism for hepatocytes, vascular endothelium, and renal epithelium, producing acute necrosis, minimal inflammation, and characteristic large intranuclear inclusion bodies. Vomiting, diarrhoea, abdominal pain, petechia on mucous membranes, pharyngitis and tonsillitis are the usual signs. Severe endothelial damage may lead to DIC and hemorrhagic diathesis.

**Gross appearance** includes blotchy or paint-brush hemorrhages on serous membranes. The liver is enlarged, turgid, friable and finely mottled. The wall of the gall bladder is markedly edematous and the kidney may have hemorrhagic infarcts. Hemorrhages often occur in the brain and lung. Some dogs recovering from the disease develop transient immune complex uveitis (type III hypersensitivity) and corneal edema (blue eye).
Histological appearance:
- Centrilobular hepatic necrosis (due to ischemia).
- Individual hepatocellular necrosis (single cell necrosis).
- Large intranuclear inclusion bodies in hepatocytes, vascular endothelium and Kupffer cells.
- Congested liver but intact reticulin framework, hence liver regeneration is possible if the animal recovers.
- Endothelial damage and hemorrhages in other organs.

Herpesvirus infections. Herpesvirus infections of the liver typically occur in neonates and fetuses. The abortigenic herpesviruses include equine herpesvirus 1 (EVR), bovine herpesvirus 1 (IBR), canine herpesvirus 1, and pseudorabies virus. The characteristic lesion is multifocal, randomly distributed, small (<1 mm) gray to white foci in several organs including the liver. Histologically, there is multifocal hepatic necrosis and acidophilic intranuclear inclusion bodies and scant inflammation.

Other viral infections. Rift valley fever in ruminants and Wesselsbron disease in sheep are two mosquito-borne viral diseases that cause abortion and multifocal hepatic necrosis in East Africa. They are zoonotic. Other viral diseases that may affect the liver are feline infectious peritonitis, equine infectious anemia, adenoviruses of ruminants and porcine circovirus type 2.

BACTERIAL INFECTIONS OF THE LIVER:
As with viruses, multifocal hepatitis is seen with many bacterial septicemias, especially in fetuses and neonates e.g. salmonellosis, listeriosis, campylobacteriosis and actinobacillosis. Other agents cause abscesses or granulomas.

Liver abscesses are seen in all species but most commonly in cattle as a complication of chemical rumenitis or traumatic reticulitis. Abscesses may be few or many and are usually caused by mixed bacterial flora including Fusobacterium necrophorum, Corynebacterium pseudotuberculosis, Trueperella pyogenes, Streptococcus sp, Staphylococcus sp and Rhodococcus equi. These abscesses more frequently affect the left lobe because of the selective distribution of portal blood.

Significance of hepatic abscesses
- Could be incidental finding at abattoir or necropsy
- May heal, become encapsulated and sterile
- May cause focal adhesive peritonitis
- May break into a hepatic vein or vena cava, leading to thrombophlebitis, septic thromboembolism or fatal septic embolization of the lungs.
- Generalized infection in young animals
- Toxemia if numerous.

Bacillary hemoglobinuria: Etiology is Clostridium hemolyticum (which produces a β toxin). It occurs in cattle and sheep when their livers are injured e.g. by migrating liver flukes, to create an area of low oxygen tension for latent spores of the organism to germinate and elaborate toxins. Toxins (particularly phospholipase C) induce
hepatocellular necrosis and intravascular hemolysis with anemia and hemoglobinuria. A single large area of necrosis is seen in the liver. Autolysis is rapid.

**Black disease** (infectious necrotic hepatitis): Etiology is *Clostridium novyi* (type B). Disease occurs mainly in sheep and other species in circumstances similar to those of bacillary hemoglobinuria. The areas of necrosis are smaller and more numerous. The disease is named after the dark coloration of flayed skins, due to severe subcutaneous venous congestion. Lesions of fluke infestation or other migrating parasites are present in the liver.

**Tyzzer's disease** is caused by *Clostridium piliforme* (previously known as *Bacillus piliformis*) especially in rodents and immunocompromised or very young animals (foals, calves, kittens and puppies). The lesions are multifocal necrotic hepatitis and colitis. Diagnosis is by demonstrating bundles of large, long gram-negative bacilli in hepatocytes (readily seen with Warthin-Starry stain).

**Leptospirosis:** Lesions are more likely due to ischemic injury following a hemolytic anemia. *Leptospira grippotyphosa* has also been associated with some cases of chronic hepatitis in dogs.

Other bacterial infections: Many bacteria reach the liver during sepsis causing hepatitis. These include *Yersinia pseudotuberculosis*, *Francisella tularensis*, *Actinobacillus equuli*, *Brucella* spp, *Salmonella* spp, *Campylobacter fetus subsp fetus* (in fetuses), *Mycobacterium bovis*, etc.

**Fungal Infection of the Liver - Mycotic Granulomatous Hepatitis**
It occurs as part of systemic fungal infections (blastomycosis, histoplasmosis) in dogs and cats. In cattle, mycotic hepatitis is usually secondary to mycotic rumenitis and grain overload but it could be part of any systemic mycosis.

**Parasitic Diseases of the Liver**

**Nematodes**
*Ascaris suum* larvae cause "milk spotted livers" in pigs. These are multiple areas of fibrosis (capsular scars) following migration of larvae through the liver. A tunnel is first formed followed by hemorrhage, eosinophilic infiltration and surrounding coagulation necrosis. As healing occurs, the fibrous tissue and eosinophils are incorporated into the portal units and are most prominent on the capsular surface.

*Stephanurus dentatus* in pigs and *Strongylus vulgaris* in horses also migrate through the liver.

*Capillaria hepatica* affects rodents and less often dogs (adults and eggs in liver)

*Dirofilaria immitis* (heartworm), when present in large numbers, can occasionally cause fatal vena cava syndrome in dogs. It is characterized by disseminated intravascular coagulation,
intravascular hemolysis and acute hepatic failure.

**Cestodes**
Cestodes of clinical significance develop encysted forms within the liver of the intermediate hosts, including humans, hence of zoonotic importance in many parts of the world e.g. hydatidosis due to *Echinococcus granulosus*. The adult cestodes live in the intestine of carnivores whereas the hydatids develop in many other species, including humans. The larval stages (cysticerci) of many *Taenia* species can form parasitic cysts in the liver. In some species of cestodes, including *Stilesia hepatica* and *Thysanosoma actinoides*, the adult lives in the bile ducts of ruminants.

**Trematodes**
Flukes are a major cause of liver disease in human beings and animals throughout the world. Agents responsible include:
- *Fasciola hepatica*, *F. gigantica*, *Fascioloides magna* and *Dicrocoelium spp*. in ruminants.
- *Opisthorchis spp*. and *Platynosomum spp*. in dogs and cats.

Their life cycles require snails in which larvae develop into cercaria. Cercaria leave the snail, encyst and become metacercaria which are infective to the definitive host. In ruminants, infestation is by ingestion of metacercarias which unsheathe in the duodenum and migrate to the liver. *Fasciola hepatica* eventually matures in bile ducts causing chronic fibrosing cholangitis whereas *Fascioloides magna* resides in cysts within liver parenchyma and deposits black excretory pigment.

Immature flukes cause traumatic lesions (hemorrhagic tracts of necrotic liver parenchyma) which may predispose to bacterial infections in the liver. *Fasciola hepatica* adults cause damage due to mechanical irritation and physical obstruction of ducts. Adults and larvae cause blood loss from sucking and produce toxic and irritative metabolites. All these factors lead to chronic cholangitis or cholangiohepatitis, manifested as pipestem liver especially in cattle.

**Protozoa**
- Coccidiosis in rabbits (*Eimeria stiedae*) causes proliferative cholangitis
- Leishmaniasis (*Leishmania donovani*)
- Toxoplasmosis
- Neosporosis
- Histomoniasis in turkeys (*Histomonas meleagridis*)

**VIII. TOXIN-INDUCED LIVER DISEASE**

The liver is the most common site of toxic injury because: a) any toxic substance ingested and absorbed through the GIT is carried directly to the organ via the portal vein, and b) the liver is capable of biotransformation of various endogenous and exogenous substances for excretion and in the process may bioactivate compounds to be more toxic. The main hepatotoxic agents include plant toxins, mycotoxins and chemicals. Most hepatotoxins are predictable, that is, they affect several species and induce predictable lesions. However, the severity of injury is influenced by age, sex, diet, endocrine function, and genetic constitution. A smaller group of hepatotoxins induce idiosyncratic drug reactions (e.g., carprofen in Labrador retrievers and diazepam in some cats). They affect only a small minority of individuals and in circumstances that are not entirely clear.
The lesions of acute toxicity usually include swelling of hepatocytes, fatty degeneration and necrosis. Chronic lesions include fibrosis, biliary hyperplasia and regeneration. All cell types in the liver can be affected by toxins.

**Classification of hepatotoxic liver injury:**

1. Biotransformation by the cytochrome p450 system for excretion. This is the most common pattern of hepatic injury. Lesions are most severe in the centrilobular area. It is a three-step process:
   - Phase I: Bioactivation of chemicals to high-energy reactive intermediates
   - Phase II: Conjugation (e.g. with glucuronic acid) to form water soluble metabolites.
   - Phase III: Excretion into canaliculi by molecular pumps.
2. Stimulation of autoimmunity
3. Stimulation of apoptosis
4. Disruption of calcium homeostasis
5. Canalicular injury leading to cholestasis
6. Mitochondrial injury

**SOME HEPATOTOXIC AGENTS**

Numerous plants contain compounds that are toxic to the liver. In addition, there are certain therapeutic agents that can cause liver injury. Only a few of these will be discussed to illustrate toxin-induced liver disease.

**TOXIC PLANTS**

1. **Pyrrolizidine alkaloids** are found in many plant families. The most common genera are *Senecio, Crotalaria, Amsinckia, Trichodesma, Echium* and *Heliotropium*. They occur worldwide and contain a variety of alkaloids which are converted to toxic pyrrolic esters by hepatic cytochrome p450 system. Pigs, cattle, horses, goats and sheep are susceptible (decreasing order). Human beings are also affected. The toxic esters are eliminated in milk and may poison nursing animals. High doses cause centrilobular necrosis but in usual doses, there is chronic liver damage and fibrosis especially in cattle. Such livers are often small, firm and finely nodular.

The main histological features of pyrrolizidine alkaloid toxicity include:
   - Giant hypertrophy of hepatocytes (**megalocytosis**)
   - Proliferation of bile ducts and ductules
   - Fibrosis which may be centrilobular or extensive
   - Minimal parenchymal regeneration.

In swine, pulmonary and renal lesions are often more severe than hepatic lesions and they include megalocytic interstitial pneumonia and interstitial nephritis.

**Megalocytes** are the result of antimitotic effects of pyrrolizidine alkaloids, which prevent cell division but not DNA synthesis as the hepatocytes attempt to divide to replace those that have undergone necrosis. Megalocytosis is more marked in young animals and in livers damaged from another cause. The cell volume is increased several times, cytoplasm is basophilic and the nucleus is large (karyomegaly) with scanty chromatin and prominent nucleolus. Megalocytosis is not pathognomonic for pyrrolizidine alkaloid poisoning - it can also occur with aflatoxins and nitrosamines.
2. **Cycads** are primitive palmlike plants that are occasionally kept as houseplants. They contain a nontoxic glycoside (cycasin) which is deconjugated by bacteria in the intestine and bioactivated in the liver. Lesions are similar to those of pyrrolizidine alkaloid poisoning in cattle, sheep and goats. Dogs are also susceptible.

3. **Alsike clover** (*Trifolium hybridum*): Horses consuming Alsike clover develop a chronic liver disease characterized by fibrosis, bile duct hyperplasia and portal hepatitis. Photosensitization is common. Unlike cases of pyrrolizidine alkaloid toxicity, megalocytosis is not a feature of this condition. The toxic principle of alsike poisoning has not yet been isolated. It is possible that the plant itself is not toxic; the toxic principal may be an unidentified mycotoxin produced by a fungus (“sooty blotch” or “black blotch”) that is visible on leaves. White clover, red clover and alfalfa can also be affected by the fungus.

**MYCOTOXINS**

Mycotoxins are secondary metabolites of fungi, that is, their production is not necessary for survival of the fungus. The amount of toxin produced is due to a variety of genetic and environmental factors.

1. **Aflatoxins** are produced by *Aspergillus flavus* and *A. parasiticus*. The 4 major aflatoxins are B₁, B₂, G₁ & G₂. B₁ is the most common and also the most potent toxin and carcinogen in the group. They are ingested in mouldy feed (such as corn, peanuts, cottonseed) and are converted to toxic intermediates by hepatic cytochrome p450 enzymes. Warm humid temperatures favour the growth of mould. All species may be affected (including humans), but it’s most common in pigs, poultry, cattle and dogs. Aflatoxins can be incorporated into commercial dog food leading to outbreaks.

   - **Acute intoxication** is rare except in dogs and typically causes centrilobular to massive hepatic lipidosis and hemorrhagic necrosis (lesions are periportal in ducklings). Hemorrhagic diathesis may be seen.

   - **Chronic intoxication** is most common and causes severe fatty degeneration, centrilobular to bridging fibrosis, biliary hyperplasia and megalocytosis. Aflatoxins have been associated with hepatomas and cholangiocellular tumors.

2. **Sporidesmin** is a mycotoxin produced by *Pithomyces chartarum*, a fungus which grows in dead rye grass in warm climates (New Zealand and Australia). Liver lesions are due to excretion of unconjugated sporidesmin in bile which is toxic to the bile epithelial cells. It is characterized by acute to chronic cholangiohepatitis and cholestasis which frequently leads to photosensitization (facial eczema) especially in sheep (due to retention of phylloerythrin). A similar disease in South Africa has now been shown to be due to a toxic plant rather than a mycotoxin.

3. **Phomopsin** is produced by *Phomopsis leptostromiformis* which grows on lupines. The disease affects cattle, sheep, and horses and produces chronic liver damage characterized by small and finely nodular livers due to fibrosis and mitotic inhibition of
hepatocytes, respectively. Fatty change and photosensitization may also occur.

4. **Poisonous Mushrooms** (eg. *Amanita phalloides*, “death cap”) can produce fatal hepatic necrosis (centrilobular to massive), lipidosis and hemorrhage. Toxic cyclopeptides (amatoxin and phalloidin) cause necrosis by inhibition of RNA polymerase II function.

**BLUE-GREEN ALGAE**
These microalgae (*Microcystis*, *Anabaena*, etc) are closely related to bacteria. They grow as blooms on lakes and ponds under optimal conditions such as high light, abundant nutrients, and calm weather (late summer and early fall). Their toxins (*microcystin*) are preformed in dead and dying algae and are lethal to livestock and also dogs and cats. Lesions include hemorrhagic gastro-enteritis and centrilobular to massive hepatic necrosis and hemorrhage. Animals that survive the acute stage of the disease can develop chronic liver disease.

**HEPATOTOXIC CHEMICALS**

1. **Xylitol** – artificial sweetener. Innocuous in humans but highly toxic to dogs. Causes hyperinsulinemia, hypoglycaemia, icterus and acute centrilobular to massive hepatic necrosis.

2. **White Phosphorus** - used as a rodenticide; causes periportal lipidosis and necrosis (does not require metabolic transformation).

3. **CCL₄** - pesticide, anthelmintic, cleaning solvents, in refrigerants, research, etc.; causes hepatocellular lipidosis and necrosis.

4. **Metals** (copper and iron) - Iron-dextran injection in piglets may cause massive hepatic necrosis.

**HEPATOTOXIC THERAPEUTIC DRUGS**

- Many drugs have potential to cause hepatic injury in some animals
- Usually centrilobular hepatocytes are affected (suggesting biotransformation)
- Species susceptibility and individual variations occur.
  - Cats are more sensitive than dogs due to a relative deficiency in glucuronyltransferase activity (phase II enzyme), e.g. intoxication with acetaminophen.
  - Many of these toxicities are idiosyncratic:
    - Trimethoprim-sulfonamide antibiotic preparations in Dobermans and other breeds
    - Carprofen, anti-inflammatory drugs in some dogs - especially Labrador retrievers
    - Cats with the tranquilizer diazepam
  - Anticonvulsants: prolonged use of primidone, phenytoin and phenobarbital cause chronic liver toxicity in dogs:
    - Mechanism unknown
    - Small liver with widespread hepatic fibrosis and nodular regeneration (cirrhosis)
IX. DISEASES OF UNKNOWN OR UNCERTAIN ORIGIN

**Equine serum hepatitis (Theiler’s disease).** The cause is not known, but thought to be a virus. The disease usually occurs 1-2 months after injection with a biological of equine serum origin (e.g., pregnant mare serum gonadotropin or tetanus antitoxin). Clinical signs are acute with rapid progression to death. Typically, there is hepatic encephalopathy and jaundice due to severe hepatic fatty degeneration, necrosis, cholestasis, mononuclear infiltration and slight fibrosis and regeneration. The liver is dark green-brown, small and flabby and shows centrilobular to massive necrosis. Intravascular hemolysis occurs in the terminal stages.

**Idiopathic Canine Chronic Hepatitis** (Synonym: chronic active hepatitis)
The cause is unknown but various agents and factors have been implicated. They include:

- Copper-associated in 36% of cases (see page 15)
- Canine adenovirus 1 infection (ICH)
- Leptospirosis
- Progression from acute hepatitis (within 6 weeks)
- Drug administration
- Immune mediated disease
- Toxic injury

*Clinical features:* anorexia, lethargy, weakness, vomiting, diarrhea, weight loss, jaundice +/- coagulopathies, ascites and hepatic encephalopathy in advanced disease. May see increased ALT, AST, ALP and GGT.

*Gross:* Small liver with accentuated lobular pattern, coarsely nodular.

*Histology:* Mononuclear cell inflammation of portal tracts extending through the limiting plate to the portal parenchyma (“piecemeal necrosis” or interface hepatitis”), portal fibrosis, bile duct proliferation and intrahepatic cholestasis.

**Lymphocytic portal hepatitis** (LPH)
This is a common finding in liver biopsies of older cats (up to 82% of cats greater than 10 years old). The lesion appears to progress slowly with varying degrees of portal fibrosis and bile duct proliferation but no pseudolobule formation. It has been speculated that LPH is an immune-mediated disorder - possibly reflecting a reaction to antigen from the alimentary tract. As opposed to cats with lymphocytic cholangitis (see page 27), there is a lack of neutrophilic inflammation, bile duct involvement, infiltration of inflammatory cells into the hepatic parenchyma, or periportal necrosis. This condition is not associated with inflammatory bowel disease or pancreatitis.

X. PROLIFERATIVE LESIONS OF THE LIVER

NON-NEOPLASTIC PROLIFERATIONS

**Hepatocellular nodular hyperplasia** is common only in dogs. Typically, the nodules are yellow to
tan, raised, 0.5 to 3 cm in diameter and well demarcated from normal parenchyma; they may be single or multiple. They contain all the elements of normal liver; the lobular pattern is preserved but slightly distorted. They are of no clinical significance, except to be distinguished from regenerative nodules and neoplasms.

**Regenerative nodules**, unlike nodular hyperplasia, occur in the presence of significant fibrosis and disruption of normal hepatic parenchyma. Each regenerating nodule usually contains a single portal tract.

**Cholangiocellular (bile duct) hyperplasia** is a nonspecific response to hepatic insult.

**HEPATIC NEOPLASIA**

Secondary tumours: The majority of malignant neoplasms within the liver are metastases from other organs including mammary glands, gastro-intestinal tract, urogenital tract, skin, etc. Primary hepatic tumours: May arise from hepatocytes (hepatocellular), bile ducts (cholangiocellular), gallbladder or mesenchymal tissue such as fibrous connective tissue and blood vessels.

- **Hepatocellular Adenoma** is a benign neoplasm of hepatocytes. It is most often reported in young ruminants. This tumour is characterized by the presence of a single, unencapsulated, red to brown nodule which may be pedunculated. Histologically the tumour is composed of cords or trabeculae of well differentiated hepatocytes that lack portal tracts and bile ducts. Differentiation from nodular hyperplasia in old dogs may be a challenge.

- **Hepatocellular Carcinoma** is a malignant neoplasm which is occasionally diagnosed in dogs. It may be difficult to distinguish from an adenoma because it is often solitary and may involve an entire lobe. The cut surface is multilobulated and grey-white to yellow-brown. Histologically, malignant hepatocytes are arranged in a trabecular pattern (3 or more cells thick), and individual hepatocytes may exhibit atypical and bizarre forms and may infiltrate adjacent normal hepatocytes. In the absence of metastasis, it can be difficult to differentiate well differentiated hepatocellular carcinoma from an adenoma. Some hepatocellular carcinomas metastasize extensively within the liver.

- **Cholangiocellular (biliary) adenoma** is a benign tumour arising from bile ducts. It is fairly common in cats and rare in other species. Grossly, the mass is usually discrete, firm, grey or white and multilobulated. There are cystic variants (biliary cystadenoma) which are difficult to distinguish from a congenital cyst, particularly in cats (in which these lesions may be multiple).

- **Cholangiocellular (biliary) carcinoma** is relatively common and has been described in all species. Grossly, it is usually multilobulated, pale grey to white, firm, raised, with central areas of depression (umbilicated). Multiple intrahepatic masses (representing metastasis) are typical and widespread metastasis to extrahepatic sites is common. Histologically, the tumours are composed of cells that retain a resemblance to the biliary epithelium. Cats with these tumours may develop a cutaneous paraneoplastic syndrome of symmetrical alopecia of the ventral trunk and limbs.
Others:
- Hepatic carcinoids are rare neoplasms in domestic animals, but have been reported in dogs, cats, and a cow. These tumours are presumed to originate from neuroendocrine cells that reside in the bile ducts or gall bladder.

- Myelolipomas, hemangiomas and hemangiosarcomas are the most common primary mesenchymal tumours of the liver.

- Common secondary tumours of the liver include, lymphoma, leukemia, histiocytic sarcoma or malignant histiocytosis, mast cell tumor, and pancreatic carcinoma.

XI. DISEASES OF THE BILIARY TRACT

STRUCTURE AND FUNCTION:
- Gallbladder stores, concentrates and releases bile.
- Hepatic bile ducts carry bile from different lobules of the liver. They unite with the cystic duct from the gallbladder to form the common bile duct.
- Bile consists of water, cholesterol, bile acids, bilirubin, inorganic ions and a variety of other constituents.
- Secretion provides:
  - Bile acids - necessary for digestion of dietary fats
  - Excretory route for various metabolites and drugs
  - Buffers - neutralize acid pH from the stomach

LESIONS OF THE BILIARY TRACT

Gallbladder stones (choleliths)
Gallstones or choleliths are concretions of normally soluble components of bile. They are composed of a mixture of cholesterol, bile pigments, salts of bile acids, calcium salts and a proteinaceous matrix. Stones form when bile components become supersaturated and precipitate, probably secondary to chronic mild cholecystitis. Gallstones usually do not become clinically significant until they obstruct the biliary system.

Biliary obstruction
Severe cholangitis, fibrosis, parasites or cholelithiasis (gall stones) can each lead to obstruction of the biliary system. The consequences include jaundice, hepatic atrophy and biliary fibrosis.

Gallbladder distention
It is a common result of fasting in all species that have gallbladder. Lantana camara poisoning in grazing animals induces subacute to chronic cholestasis, severe icterus and photosensitization. The gall bladder is greatly distended with pale mucoid bile. Gall bladder distention may also be secondary to biliary obstruction caused by choledoliths, inflammation or tumors.
**Gallbladder mucocele** is the dilation of the gall bladder with accumulated mucoid secretion. It is a common disorder affecting mostly small breeds of dogs; Shelties and cocker spaniels are commonly affected. The etiology of this condition is unknown, and may be related to decreased gallbladder motility, bile stasis, and altered bile composition and motility. Cystic mucinous hyperplasia of the gall bladder (see page 38), may be associated with mucocele. Bile-laden mucus may extend into the cystic, hepatic, and common bile ducts, resulting in variable degrees of extrahepatic biliary obstruction. Severely affected gall bladders may undergo ischemic necrosis and rupture.

**Rupture of the biliary tract or gallbladder**

Rupture is usually traumatic in origin and causes steady leakage of bile into the peritoneal cavity. Bile salts are very irritating and may cause acute chemical peritonitis. The resulting peritoneal effusion may remain sterile or, more commonly, it is infected by enteric bacteria. This may be rapidly fatal, particularly if clostridia are involved.

**Gallbladder edema**

Edema of the wall is seen in right heart failure and in infectious canine hepatitis in dogs and with Rift Valley fever and Salmonellosis in cattle.

**Thrombosis and infarction of the Gall Bladder:**

Occasionally thrombosis of the arteries in the wall of the gall bladder may occur in dogs. Resultant infarction (necrosis) of the wall may result in rupture of the organ. The cause is unknown.

**Cholangitis / Cholangiohepatitis**

Inflammation of the intra- and extrahepatic bile ducts is often chronic and non-specific. Although pure cholangitis does occur, involvement of the periportal hepatic parenchyma by extension of inflammation from the ducts is almost inevitable, and such lesions can quite accurately be regarded as cholangiohepatitis. Bacterial cholangiohepatitis is usually caused by common opportunists of enteric origin, such as coliforms and streptococci. Some bacteremic organisms can also reach the bile ducts. Therefore, the portal of entry for bacterial cholangiohepatitis can be hematogenous (descending), or ascending, in which bacteria can extend up the ducts from the intestine, facilitated by bile stasis due to obstructions. The course and pathologic changes in cholangiohepatitis vary greatly, from fulminating suppurative inflammation to persistent mild inflammation that over a period of months or years leads to biliary fibrosis (and bile duct hyperplasia). There are two apparently distinct entities in companion animals characterized by significant inflammation of the biliary tract:

- **Suppurative or neutrophilic cholangiohepatitis** occurs in mature cats and less commonly in dogs. It has been suggested to be associated with ascending bacterial infection. In the cat, the biliary and pancreatic ducts have a common entry to the duodenum, and simultaneous infectious inflammation of these systems is common. The condition is very often associated with inflammatory bowel disease or pancreatitis.

- **Lymphocytic cholangitis** (Feline progressive lymphocytic cholangitis / cholangiohepatitis). It is an important cause of hepatic disease in cats in the United Kingdom. It occurs in cats 4 years and under. Persian cats appear to be over-represented. The most common clinical features are ascites (which is a rare
manifestation of liver disease in cats), jaundice and hypergammaglobulinemia. There are two stages: The **active stage** is characterized by marked lymphocytic inflammation within and around bile ducts, with occasional extension to the periportal hepatic parenchyma. In the **chronic stage**, there is considerable reduction in the intensity of lymphocytic infiltration, and distortion of liver architecture due to porto-portal bridging fibrosis. Concurrent pancreatic or intestinal inflammation is not a feature of the disease. It is postulated to have an immune-mediated pathogenesis.

**Cholecystitis**

Inflammation of the gallbladder can be acute or chronic.

- **Fibrinous cholecystitis** occurs in calves with acute salmonellosis (*S Dublin*) and yersiniosis.
- **Hemorrhagic cholecystitis** is seen in salmonellosis in cattle and in arsenic toxicosis.

**Cystic mucinous hyperplasia of gallbladder**

Cystic hyperplasia of the mucus-producing glands in the walls of the gallbladder and large bile ducts is occasionally observed in old dogs and sheep. The cause is not known, but some cases may be the result of chronic inflammation. It may result in the formation of a mucocele within the gallbladder.

**Neoplasia**

- **Adenomas** of the gallbladder are rare in all species with the exception of cattle.
- **Carcinomas** of the gall bladder may occur more often than adenomas, but are uncommon.