MALFORMATIONS AND DEGENERATION OF THE LIVER

DEVELOPMENTAL HEPATOBILIARY ANOMALIES

- most developmental anomalies of the liver and biliary tree are **incidental findings**
  - e.g. agenesis or hypoplasia of individual liver lobes
  - e.g. abnormal lobe fissures
  - e.g. accessory or ectopic hepatic tissue
  - e.g. absent or duplicated gall bladders

- **absence or atresia of extrahepatic bile ducts** is rare but of clinical significance → jaundice and deficiency of fat-soluble vitamins (due to deficiency of bile salts reaching the duodenum); affected animals may develop vitamin D deficiency rickets or vitamin K deficiency (→ haemorrhage)

Congenital Portosystemic Shunts

- in a congenital portosystemic shunt, an anomalous blood vessel allows a proportion of the portal venous blood returning from the abdominal viscera to be shunted away from the liver into the systemic circulation

- most commonly diagnosed in dogs and cats but can occur in any species
- suspected inheritance in breeds such as Maltese and Yorkshire terriers, Irish wolfhounds and Australian cattle dogs

- **cats and small dog breeds** - usually a **single, large, extrahepatic shunt** between the portal vein (or a major tributary such as the left gastric or splenic vein) and the caudal vena cava (portocaval shunt) or the azygous vein (portoazygous shunt)
  - the portal vein distal to the origin of the shunt may be hypoplastic

- **large dog breeds** - usually a **single, large intrahepatic shunt**
  - usually due to persistence of the **foetal ductus venosus** in the left part of the liver but occasionally due to an anomalous vessel elsewhere within the liver

- affected animals are typically stunted in growth (litter runts) and often display signs of hepatic encephalopathy

- the bypassed liver is typically of small size (**hypoplasia**) due to deprivation of hepatotrophic factors (e.g. insulin, glucagon, dietary amino acids)
- microscopically in portal areas, portal vein branches are small or inapparent and there is increased prominence/proliferation of hepatic arteriolar branches due to a compensatory increase in arterial blood flow into the liver; this vascular pattern is a **stereotypical response to a decrease in portal venous blood flow into the liver**

- identical microscopic lesions develop in animals that have **congenital hypoplasia of the portal vein**, **congenital hypoplasia of one or more intra-hepatic branches of the portal vein** (often termed **microvascular dysplasia**) or **acquired portosystemic shunting** (see Lecture 9)
- therefore cannot rely on a hepatic biopsy to confirm the presence of a congenital shunt

Congenital Hepatic and Biliary Cysts

- congenital hepatic or biliary cysts occur in all species
- may be derived from the intrahepatic bile duct system or from the hepatic capsule
- cysts may be single or multiple, and small or large
- cyst content is usually clear and watery and the cyst cavity is lined by epithelium
- large cysts may distend the abdominal cavity but most do not compromise liver function

- single large superficial cysts that protrude from the diaphragmatic aspect of the liver capsule (so-called **serosal inclusion cysts**) are common in young lambs and calves and are thought to be derived from the hepatic capsule
- often involute in the early post-natal period

- **congenital malformations of the intrahepatic bile ducts** (**ductal plate malformations**) – seen in cats (especially Persians), dogs (especially Cairn and West Highland white terriers), pigs and goats
- often associated with **polycystic kidneys** (which may ultimately cause renal failure) +/- **polycystic pancreatic ducts**
- ductal plate malformations are subclassified according to the calibre of the affected bile ducts and also on whether the cysts progressively expand due to fluid accumulation or are eventually obliterated by fibrosis
- ductal plate malformations that arise early are usually large and located centrally towards the hilus of the liver
- ductal plate malformations that develop late are situated at the periphery of the lobes (the latter are common in cats and have been often misdiagnosed in the past when detected in mature cats as tumours of biliary epithelial origin (cholangiocellular cystadenomas)

HEPATIC ATROPHY

- atrophy of hepatocytes is an **adaptive response** to a suboptimal environment
- affected hepatocytes **shrink** in volume and have **decreased metabolic functional activity**
- atrophy may involve the liver **diffusely** or it may be **localised** to one or more regions
- the reduction in size of the organ may reflect not only shrinkage of hepatocytes but also loss of individual hepatocytes

Diffuse Atrophy

- e.g. **nutritional atrophy** - due to catabolism of stored substrates in response to starvation or increased metabolic demand (e.g. starvation, cachexia of malignancy or chronic disease)

- e.g. **congenital** or **acquired portosystemic shunting** - diversion of portal venous blood away from the liver deprives the organ of hepatotrophic factors (e.g. amino acids, insulin, glucagon)

- e.g. **impaired mitotic division of hepatocytes** - e.g. chronic pyrrolizidine alkaloid poisoning
- the liver is reduced diffusely in size and weight
- it may be firmer than normal due to condensation of existing connective tissue +/- fibrosis
- the hepatic capsule may be wrinkled

- the hepatic parenchyma may be darker brown than normal due to accumulation of lipofuscin +/- ceroid pigments (see Hepatic Pigmentation below)
- microscopically, see crowding of small hepatocytes, with portal areas and central veins closer together due to the small size of the lobules/acini
- the plates of hepatocytes appear narrow, with a compensatory increase in prominence of the blood-filled sinusoids

Localised Atrophy

- **local compression → pressure atrophy** (probably involves a local reduction of blood flow, especially reduced portal venous inflow)
  - e.g. atrophy of the right hepatic lobe in horses due to chronic distension of the right dorsal colon and/or caecum
  - e.g. atrophy of hepatocytes immediately adjacent to an expansively growing hepatic mass such as an abscess or tumour

- **local obstruction of bile drainage**
  - e.g. atrophy of the left hepatic lobe in ruminants with chronic fascioliasis in which adult liver flukes are present in the bile ducts
  - e.g. atrophy of the left hepatic lobe in ruminants with chronic facial eczema in which the mycotoxin, sporidesmin, destroys intra-hepatic bile ducts and causes peribiliary fibrosis

HEPATIC DEGENERATION

- a high metabolic rate renders hepatocytes prone to **degeneration** if they are **sublethally injured**
- degenerate hepatocytes may accumulate **water** or **lipid**
- metabolic disturbances or enzymatic deficiencies can cause **glycogen accumulation** within hepatocytes
- hepatocellular degeneration may be of zonal distribution (i.e. hepatocytes within acinar zone 1, 2 or 3 may be targeted) → a grossly obvious **zonal pattern**

HYDROPIC DEGENERATION

- sublethal injury to hepatocytes often leads to loss of control of fluid and ionic movements across cell membranes → influx of sodium ions and water → swelling of endoplasmic reticulum, mitochondria and/or lysosomes
- affected cells appear swollen by light microscopy, with irregular wispy pallor of the cytoplasm
- may see mild hepatomegaly with mild pallor of the parenchyma grossly
- causes include:

  - **sublethal hypoxia**
  - **sublethal toxic injury**
  - **prolonged cholestasis** - with intracellular retention of bilirubin and especially bile salts

GLYCOGEN ACCUMULATION

- **common** in **dogs** with **hyperadrenocorticism** and referred to as **steroid hepatopathy**

- e.g. dogs with *spontaneous hyperadrenocorticism* (due to a functional ACTH-producing pituitary tumour or a functional cortisol-producing tumour in an adrenal cortex) or with *iatrogenic hyperadrenocorticism* (caused by excessive administration of corticosteroids)
- excess glucocorticoids in dogs induce transcription of hepatocellular glycogen synthetase → excessive storage of glycogen in hepatocytes, especially in midzonal hepatocytes (zone 2) but all hepatocytes can be involved in severe and chronic cases
- affected hepatocytes are often markedly swollen with irregular cytoplasmic clearing
- reversible change (but may take weeks to months to resolve)
- liver may be grossly enlarged and pale and may be friable
- glycogen storage in steroid hepatopathy is **usually NOT responsible for hepatic dysfunction**

- glycogen accumulation can also occur in **inherited glycogen storage disorders** (a form of inherited lysosomal storage disease that is rare in domestic animals)

HEPATIC LIPIDOSIS

- **hepatic lipidosis = excessive accumulation of triglycerides (triacylglycerols) in the cytoplasm of hepatocytes**

- also known as **fatty change** or **fatty degeneration**
- **a common degenerative change because of the vital role that the liver normally plays in lipid metabolism**
- some of the fatty acids that enter the liver (chylomicrons derived from dietary lipid, very low density lipoproteins (VLDL) in circulation, low density lipoproteins (LDL) mobilised from body fat depots etc) may be oxidised and used as an energy source in the mitochondria of hepatocytes
- however, most incoming fatty acids are esterified by the hepatocytes to form **triglycerides**
- the triglycerides are then packaged by the hepatocytes with **apoproteins** to form **VLDL** → exported into the sinusoids as a readily available energy source for other tissues

- synthesis and export of VLDL require considerable energy consumption by hepatocytes
- esterification of fatty acids to triglycerides is less energy-dependent

- hepatic lipidosis can result from:

- **diminished hepatocyte energy (ATP) supply** → decreased VLDL synthesis and/or export whilst triglyceride synthesis continues
- **entry of excess fatty acids** - exceeding hepatocyte capacity to process them rapidly
- **inadequate protein supply to permit synthesis of apoproteins**
- **inadequate supply of phospholipids or cholesterol**
- **damage to the hepatocellular organelles in which lipoprotein synthesis and assembly occurs** (e.g. rough endoplasmic reticulum and Golgi apparatus)

- hepatic lipidosis is essentially **reversible** provided it is not associated with fibrosis and hence architectural remodelling (both may occur in chronic hepatic lipidosis)

- fatty livers are highly vulnerable to superimposed insults by toxins or endogenous reactive oxygen species (free radicals)

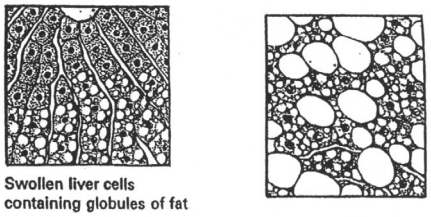
Gross Appearance

- the liver may be enlarged with rounded borders, diffusely pale cream-yellow, soft and friable, with a greasy cut surface
- if lipidosis is severe, pieces of liver may float in water and in formalin
- if fatty change is zonal in distribution (e.g. early stages of hepatic lipidosis), a zonal pattern may be grossly obvious

Microscopic Appearance

- lipid initially accumulates as small clear globules in the cytoplasm of hepatocytes (Figure 1, left), especially in the **periacinar zone (zone 3)**
- periacinar hepatocytes are rich in smooth endoplasmic reticulum in which triglycerides are produced
- this is also **the zone most susceptible to hypoxic and toxic insults**
- in severe lipidosis, most hepatocytes are affected and are distended by a single, large, clear, cytoplasmic vacuole (Figure 1, right)

Figure 1



Reference: "Pathology Illustrated" – A.D.T. Govan, P.S. Macfarlane, R. Callander, 4th edition, Churchill Livingstone, Edinburgh, 1995

Common Conditions Causing Hepatic Lipidosis in Domestic Animals

- **Physiological** - late pregnancy and peak lactation (especially ruminants)
  - neonates receiving fat-rich milk
  - milk-fed vealer calves
- **High energy/high lipid diets** - e.g. cage/aviary birds (especially psittacines) on all-seed diets
- **Fasting of animals** - especially obese animals
- **Starvation**
- **Sublethal toxic injury to hepatocytes**
- **Sublethal hypoxic injury to hepatocytes**
- **Pregnancy toxaemia** - especially in late pregnancy in ewes carrying twins
- **Bovine fatty liver syndrome** - especially obese beef cows a few days prior to parturition and obese dairy cattle a few days after parturition
- **Ketosis** - especially dairy cows in peak lactation
- **Feline hepatic lipidosis** - especially obese cats that develop anorexia

- **Equine hyperlipaemia** - especially anorexic, obese, pregnant or lactating Shetland ponies
- **Endocrine disorders** - especially diabetes mellitus but also hypothyroidism
- **Deficiencies of cobalt or vitamin B_{12}** - sheep and goats (**white liver disease**)
- **Fatty liver haemorrhagic syndrome** - especially caged layer chickens
- **Fatty liver kidney syndrome** - especially young broiler chickens, due to a deficiency of biotin

Tension Lipidosis

- in tension lipidosis, there is a sharply demarcated zone of lipidosis involving superficial hepatic parenchyma
- common in **cattle**
- typically develops deep to the attachment point of a band of scar tissue linking the liver to an adjacent structure (e.g. a chronic fibrous adhesion resulting from a previous bout of hardware disease)
- tension on the capsule is thought to impair blood flow into the affected area → sublethal hypoxia of hepatocytes → localised lipidosis

HEPATIC AMYLOIDOSIS

- amyloid deposition in the liver occurs in cattle, horses, dogs, cats (especially Oriental breeds) and birds (especially captive and domestic waterfowl)
- usually associated with amyloid deposition in other organs

- **amyloid** is an extracellular glycoprotein that may be of variable chemical composition but always forms β-pleated sheets of non-branching fibrils
- in haematoxylin-and-eosin-stained tissue sections, amyloid appears as an amorphous, eosinophilic (pink), homogeneous, **extracellular** material
- stains orange-red with Congo red stain, and thence appears green and birefringent when viewed with polarised light

- amyloid in animals is usually an insoluble fragment of the acute phase protein, **serum amyloid A (SAA)**, which is normally produced by the liver and found in circulating plasma
- deposition of this type of amyloid (**amyloid AA**) is often referred to as **secondary** or **reactive amyloidosis** because increased hepatic synthesis and release of SAA into circulation occurs whenever there is active inflammation and/or tissue damage in the body

- **most animals with increased blood concentrations of SAA do NOT develop amyloidosis**
- amyloid deposition may therefore involve defective enzymatic degradation of SAA by macrophages, or the synthesis of an aberrant SAA protein that is resistant to degradation and prone to forming insoluble deposits in tissues

- a diagnosis of reactive amyloidosis always warrants a hunt for an underlying disease process that might be promoting increased hepatic SAA production
- e.g. in cattle, hepatic amyloidosis is usually attributable to a chronic infection somewhere in the body (e.g. bacterial mastitis or hardware disease)

- however, some forms of AA amyloidosis in animals are instead **inherited** or **familial**
- e.g. amyloidosis in Shar Pei dogs and in Oriental breeds of cats (e.g. Abyssinian and Siamese)

- in hepatic amyloidosis, the amyloid is deposited in the perisinusoidal space (space of Disse) +/- in blood vessel walls → impaired supply of oxygen and nutrients to hepatocytes → hepatocyte atrophy
- affected livers tend to be enlarged, pale, firm or soft, and **prone to rupture** → fatal haemoperitoneum
- in the absence of hepatic rupture, **renal failure** (due to concurrent amyloid deposition in the kidneys) usually develops before clinical signs of hepatic dysfunction/failure emerge

HEPATIC PIGMENTATION

Bilirubin

- in jaundice, the liver and its connective tissues may be grossly discoloured green or orange-yellow
- the degree of discolouration is usually most spectacular when the jaundice is due to extra-hepatic bile duct obstruction

Melanin

- calves and occasionally lambs and piglets may be born with melanin pigment in the liver (**congenital melanosis**)
- the pigment is confined to the capsule and other connective tissues of the liver
- the blue-black foci may be numerous and small or few and large
- the foci fade and become less discrete over time
- an **incidental finding**, **NOT associated with any liver dysfunction**

Iron

- **haemosiderin** is a protein-iron complex (ferritin aggregates) which appears microscopically as a **golden-brown, coarsely granular, intracellular pigment**
- haemosiderin is largely derived from haemoglobin iron after lysis or phagocytosis of red blood cells
- can also accumulate if there is excessive absorption of iron from the gastrointestinal tract, or following multiple iron injections or multiple blood transfusions
- accumulates mainly in Kupffer cells but can also occur in hepatocytes

- **diffuse hepatic haemosiderosis** - e.g. extravascular haemolytic anaemia, copper deficiency, anaemia of chronic disease
- **localised hepatic haemosiderosis** - e.g. areas of haemorrhage and in the periacinar zone (zone 3) in chronic passive congestion of the liver

- haemosiderin rarely causes grossly obvious discolouration of the liver
- however, in extreme cases, the liver may be diffusely dark brown (e.g. in inherited **haemochromatosis** in certain species of birds, in which excess dietary iron is absorbed)

Lipofuscin

- lipofuscin is a yellow-brown, intracellular “wear and tear” or “age” pigment that accumulates in lysosomes of old or atrophic cells as an indigestible residue of oxidation of membrane phospholipids
- common in zone 3 (periacinar) hepatocytes in older animals
- does NOT cause any hepatic dysfunction
- usually insufficient pigment is present to cause gross discolouration of the liver

- **exogenous (or environmental) lipofuscinosis** occurs in sheep and, less often, cattle grazing unimproved pasture in inland eastern Australia
- the liver may be diffusely dull grey to black
- +/- comparable pigmentation of hepatic lymph nodes, lungs and renal cortex
- yellow pigment accumulates initially within hepatocytes and then Kupffer cells and then oxidises to a black pigment that resembles melanin but is histochemically most consistent with lipofuscin
- the pigment is suspected to be an insoluble residue from ingested foliage of the **mulga tree** (*Acacia aneura*)
- therefore sometimes referred to as **“mulga liver”**

Ceroid

- ceroid is very similar histochemically and morphologically to lipofuscin and is also derived from oxidation of membrane phospholipids
- unlike lipofuscin, it can accumulate intra- or extracellularly and can be responsible for cellular dysfunction
- seen in hepatocytes and Kupffer cells in such diseases as **starvation**, **anti-oxidant deficiency** (e.g. vitamin E or selenium deficiency) and **cachexia** (wasting diseases)

Fluke Pigments

- black **iron-porphyrin** pigments are common in hepatic migratory tracks and cysts of some liver flukes
- the pigment also accumulates in Kupffer cells, bile and hepatic lymph nodes

DISPLACEMENT, TORSION AND RUPTURE OF THE LIVER

Displacement of the Liver

- usually caudal displacement with hepatomegaly or space-occupying masses in the thorax
- cranial displacement is common in diaphragmatic hernias
- lobe(s) strangled by a hernial ring undergo congestion and oedema (due to impaired venous drainage) and eventually venous infarction

Liver Lobe Torsion

- especially left lateral hepatic lobe in sows and dogs
- the lobe undergoes venous infarction

Hepatic Rupture

- e.g. blunt abdominal trauma
- e.g. energetic resuscitation attempts in small animals
- e.g. diffuse hepatomegaly with tension on capsule (e.g. hepatic lipidosis, acute hepatitis, severe passive congestion, hepatic amyloidosis, neoplasia)
- rupture of hepatic parenchyma may lead to fatal haemoperitoneum
- parenchymal fissure fractures responsible for haemorrhage may be quite subtle at necropsy