HEPATOTOXINS

Vulnerability of the Liver to Toxins

- the **liver is the organ most commonly injured by toxins** because:

  - it receives most of its afferent blood from the portal vein draining the gastrointestinal tract and is therefore likely to be exposed to ingested toxins

  - biotransformation of **xenobiotics** (non-polar foreign compounds such as chemicals, drugs, and plant and fungal metabolites) within hepatocytes may produce **intermediate metabolites** (that are more toxic than the parent compound) and **reactive oxygen species** (which can trigger peroxidation of membrane phospholipids)

  - hepatocytes may selectively take up and concentrate certain toxic substances (e.g. copper, phalloidin from toxic *Amanita* mushrooms) or concentrate them in bile (e.g. sporidesmin)

Hepatic Biotransformation Reactions

- the liver performs enzymatic biotransformation of both xenobiotics and endogenous metabolites (e.g. arachidonic acid, steroid hormones, vitamin D)
- typically, hepatic biotransformation reactions are designed to **transform fat-soluble compounds into water-soluble compounds** that can be **excreted in bile or urine**

- the **two stages in hepatic biotransformation** are:

  - **phase 1 reactions**

    - polar groups are added or exposed by oxidation or (less often) reduction or hydrolysis
    - usually performed in the smooth endoplasmic reticulum (SER) of hepatocytes
    - catalysed by the **mixed function oxidase** (MFO) **enzyme system** (of the **cytochrome P450** superfamily of enzymes)
    - phase 1 reactions can generate transient intermediate metabolites (e.g. epoxides and reactive oxygen species) that can bind to and damage hepatocellular components → hepatotoxicity

  - **phase 2 reactions**

    - the products of phase 1 metabolism are **conjugated** to glucuronate, sulphate, reduced glutathione or other molecules to increase their water-solubility
    - these reactions chiefly take place in the cytoplasm of hepatocytes and are mediated by transferase enzymes

    - one important phase 2 pathway involves conjugation with **reduced glutathione** and is catalysed by glutathione *S*-transferase enzymes
    - depletion of hepatocellular glutathione reserves can result in failure of this conjugation pathway → hepatotoxicity
    - reduced glutathione is also important as an **anti-oxidant**
    - depletion of glutathione (e.g. in selenium deficiency) can permit peroxidation of hepatocyte membranes by reactive oxygen species

Primary versus Secondary Poisoning

- in **primary poisoning**, an animal ingests something (e.g. a plant, grain, seed etc.) that contains either a preformed toxin or a compound that can be metabolised by gastrointestinal bacteria or cellular metabolism to a toxin
- **most cases of hepatotoxicity in domestic animals are examples of primary poisoning**

- in **secondary poisoning**, an animal ingests a product derived from an animal that has consumed a toxin

- e.g. there is potential for **pyrrolizidine alkaloid poisoning in humans** consuming honey made by bees eating pollen from viper's bugloss (alpine blue borage) (*Echium vulgare*) or Paterson's curse (*Echium plantagineum*)

- e.g. **indospicine poisoning in dogs in Australia**
- various legumes of the genus *Indigofera* contain a hepatotoxic amino acid, **indospicine** (a structural analogue of arginine), and a neurotoxin, **3 nitroproprionic acid (3-NPA)**
- naturally occurring primary hepatotoxicity has been reported in cattle grazing *I. spicata* (creeping indigo) which contains high concentrations of indospicine
- a chronic neurological disease due to 3-NPA occurs naturally in horses grazing *I. linnaei* (Birdsville indigo) in subtropical and arid parts of Australia ("Birdsville horse disease")
- ingestion of indospicine-rich skeletal muscle from horses with clinical signs of Birdsville horse disease → fatal acute hepatotoxicity in dogs

Predictable Versus Idiosyncratic Hepatotoxins

- a **predictable hepatotoxin = a toxin that in a sufficient dose will predictably cause hepatic injury in virtually all susceptible animals**

  - e.g. carbon tetrachloride
  - e.g. paracetamol in cats
  - e.g. pyrrolizidine alkaloids
  - e.g. aflatoxin B_1

- an **idiosyncratic hepatotoxin = a toxin that causes hepatic injury in a minority of exposed animals, often after prolonged or repeat exposure**

  - susceptibility of individuals may reflect **genetic differences in the competency of the biotransformation enzyme systems** → overproduction of a toxic intermediate or generation of an unusual toxic intermediate
  - alternatively, susceptibility of individuals may involve the binding of drug metabolites to liver proteins → formation of a **hapten allergen** → **immune-mediated hypersensitivity reaction** that damages hepatocytes

  - e.g. **halothane** and **methoxyfluorane**
  - e.g. **mebendazole**, **carprofen**, **sulphamethoxazole-trimethoprim** in dogs
  - e.g. **tetracyclines**, **methimazole**, **glipizide** and **diazepam** in cats

Other Factors That Influence the Outcome of Exposure to Hepatotoxins

- in general, **males** have a greater volume of hepatocellular SER and greater MFO enzyme activity than do females → potentially greater risk of generating toxic metabolites
- in general, **adults** have more hepatocellular SER and MFO enzyme activity than do neonates

- MFO enzyme activity can be up-regulated by prior exposure to non-toxic xenobiotics (e.g. barbiturate drugs) or to endogenous metabolites (e.g. steroid hormones such as testosterone, oestrogen and progesterone)

- conversely, prolonged starvation may cause catabolism of cell proteins and hence MFO enzymes → may afford some protection against toxic injury

- well-nourished animals subjected to a short fast → consumption of hepatic glycogen stores → potentially greater risk of toxic insult because glycogen can trap reactive oxygen species

- as reactive oxygen species are generated in biotransformation reactions, animals that are deficient in anti-oxidants (e.g. vitamin E, reduced glutathione) or those with concurrent hepatic lipidosis are at greater risk of toxic hepatic damage

- **an individual's response to an ingested hepatotoxin is therefore unpredictable**
- the response is influenced by not only the toxin dose but also by such factors as age, gender, diet, nutritional status, endocrine function, genetics, previous drug exposure etc.

Acute Hepatoxicity

Clinical Signs

- especially free-ranging ruminants, ruminants under nutritional stress (e.g. drought, floods) or naive travelling stock
- **sudden death** or a brief period of anorexia, colic (signs indicative of abdominal pain), mental dullness +/- other signs of hepatic encephalopathy immediately prior to death
- **usually insufficient time for development of jaundice or photosensitisation**

Post Mortem Lesions

- liver may be deep red and swollen, with oedema of the gall bladder and hilar connective tissues
- +/- a grossly obvious zonal pattern or mosaic pattern typical of acute massive necrosis
- often a slight excess of clear serous abdominal fluid
- +/- multifocal haemorrhages, especially over serosal membranes and over the endocardium (inner lining of the heart)
- ruminants often have diffuse gut haemorrhage (especially in the duodenum) and into the wall of the gall bladder
- the haemorrhage is a consequence of vascular endothelial injury +/- superimposed **disseminated intravascular coagulation** (with widespread microthrombosis and consumption of platelets and coagulation factors)

- **periacinar necrosis** is the **most common hepatic lesion induced by acute poisoning**
- this is because the highest activity of MFO enzymes is in the **periacinar** (zone 3) **hepatocytes** and they are damaged by the products of biotransformation
- surviving sublethally injured hepatocytes (any zone but especially zones 1 and 2) may undergo

hydropic degeneration or fatty degeneration

- in severe acute intoxications, there may instead be **massive hepatic necrosis** (i.e. destruction of all hepatocytes within individual hepatic acini)

- the following patterns of necrosis seen in acute hepatotoxicity are much less likely but have great diagnostic value when observed:

- e.g. **periportal (zone 1) necrosis** may be seen in:

    - some cases of blue-green algal poisoning
    - some cases of poisoning by *Myoporum* species of plants
    - acute bovine liver disease - possibly caused by a mycotoxin
    - poisoning by metal salts - due to the proximity of periportal hepatocytes to direct-acting toxins arriving via the bloodstream

- e.g. **midzonal (zone 2) necrosis** may be seen in:

    - some cases of blue-green algal poisoning (rarely)
    - most cases of poisoning by *Myoporum* species of plants
    - some cases of aflatoxicosis in pigs and horses

Chronic Hepatotoxicity

Clinical Signs

- often due to long term, low level consumption of a cumulative toxin
- affected animals have sufficient time to develop **jaundice**, signs of **hepatic encephalopathy** and (in herbivores) **photosensitisation** +/- other abnormalities suggestive of hepatobiliary disease (e.g. ascites)

NOTE - Most hepatotoxins that are commonly responsible for chronic poisoning of animals may cause non-specific acute periacinar or massive necrosis at high doses (e.g. aflatoxins, pyrrolizidine alkaloids).

Post Mortem Lesions

- many of the gross and microscopic hepatic lesions in chronic hepatotoxicity may be non-specific and merely indicative of chronicity and attempted repair
- e.g. evidence of cholestasis, hepatic fibrosis, biliary hyperplasia, regenerative nodular hyperplasia of hepatocytes etc.
- other microscopic lesions may emerge that have diagnostic value - e.g. nuclear gigantism (karyomegaly) of hepatocytes due to alkylating toxins that inhibit hepatocyte mitotic division (e.g. aflatoxins, pyrrolizidine alkaloids)

COMMON ACUTE HEPATOTOXINS

Amatoxins

- **amatoxins** are potent hepatotoxins found in several genera of mushrooms (especially *Amanita* species)
- inhibit nuclear RNA polymerase → inhibition of nuclear transcription and protein synthesis → cell death
- ingestion → acute gastroenteritis, hypoglycaemia and acute liver failure in humans, dogs and other animals
- in dogs, see **massive hepatic necrosis**

Blue-green Algae

- especially *Microcystis aeruginosa* but also *Nodularia*, *Anabaena* and *Aphanizomenon* species
- algal blooms may form on dams and stagnant water, especially if receiving run-off water rich in nitrogen or phosphates from fertilised pasture
- especially late summer or early autumn
- can be responsible for heavy mortality in mammals (especially ruminants) and birds that drink the water

- dead and dying algae release preformed toxins
- some algal species contain **neurotoxins** → death within minutes with central nervous system signs (e.g. seizures, hyperaesthesia) and respiratory paralysis
- some contain **hepatotoxins** (e.g. microcystin and nodularin) → phosphatase inhibition → disorganisation of hepatocellular cytoskeletal actin filaments → dissociation of hepatocytes → hypovolaemic shock due to massive disruption of liver and intrahepatic pooling of blood
- usually see **acute periacinar** or **massive necrosis**
- occasionally see periportal or rarely midzonal necrosis

Acute Bovine Liver Disease

- important cause of morbidity and mortality of dairy and beef cattle across southern parts of Australia
- syndrome is also suspected to affect sheep
- clinical signs include sudden death, severe morbidity, drop in condition, decreased milk production, photosensitisation and hepatic encephalopathy
- originally thought to be due to a toxic principle in rough dog's tail (*Cynosurus echinatus*) but now suspected to be caused by a mycotoxin produced by a fungus *(Drechslera biseptata*) growing on the pasture

Paracetamol (Acetaminophen)

- toxicity occurs especially in **cats** but also occasionally in **dogs**
- in most species, low doses of paracetamol are safely conjugated by hepatocytes with sulphate or glucuronate, with only a small proportion being metabolised by the MFO enzymes to produce reactive intermediate metabolites (e.g. N-acetylbenzyoquinonime) which must be conjugated with glutathione to allow excretion

- cats are less effective than other species in conjugating metabolites with glucuronate or sulphate and therefore generate far more of the toxic intermediates → glutathione depletion and failure to scavenge reactive metabolites and reactive oxygen species → **acute periacinar** to **massive hepatic necrosis**
- haemoglobin in the erythrocytes of cats is also prone to oxidative injury if glutathione depletion occurs → intravascular haemolytic anaemia with Heinz body formation and methaemoglobinaemia (may prove fatal in cats before hepatic necrosis develops)

Iron

- **organic iron** occasionally causes severe mortality in marginally vitamin E/selenium-deficient piglets (e.g. following iron-dextran injections to prevent anaemia)
- causes **acute skeletal myonecrosis** and/or **massive hepatic necrosis** (akin to hepatosis dietetica in pigs) → release of intracellular potassium from necrotic cells → cardiotoxicity
- the valency of iron can catalyse the generation of reactive oxygen species → peroxidation of phospholipid membranes of hepatocytes and/or skeletal myocytes

- **acute hepatic necrosis** has also been reported in calves, neonatal foals, young cattle and adult horses after injection or oral administration of supplements containing iron
- the pattern of necrosis has varied from periacinar to periportal to massive

Miscellaneous Poisonous Plants

Cycads

- cycads (genera *Cycas, Zamia, Bowenia, Macrozamia*) are primitive palm-like plants in tropical and subtropical habitats
- contain glycosides that are converted by gut bacteria to toxic metabolites that are further metabolised in the liver
- in sheep, see **acute periacinar necrosis**
- in cattle, see **chronic hepatotoxicity** due to the alkylating effects of the metabolites (may mimic chronic pyrrolizidine alkaloid poisoning or chronic aflatoxicosis)

Ink-berry Plants

- e.g. *Cestrum parqui* (green cestrum) and related species in Australia, Africa and South America
- **acute periacinar to submassive (periacinar + midzonal) necrosis**
- especially cattle but also sheep, goats and birds

Poison Peach

- *Trema aspera*
- contains a toxic glycoside, trematoxin
- responsible for high mortality of cattle in Australia
- **acute periacinar necrosis**

Noogoora Burr

- *Xanthium pungens*
- cotyledons and burrs contain a toxic diterpenoid glycoside, carboxyatractyloside

- responsible for deaths of pigs, sheep and cattle in Australia
- **acute periacinar necrosis**

***Myoporum* Species**

- e.g. *Myoporum tetrandum* (boobialla), *M. laetum* (ngaio), *M. deserti* (Ellangowan poison bush)
- leaves and branchlets contain toxic furanosesquiterpenoid oils (the best known is ngaione)
- responsible for mortality of sheep (and occasionally cattle, pigs, horses and camelids) in Australia, New Zealand and South America
- typically see **acute midzonal necrosis** but can see **periportal** or **periacinar necrosis** if there has been prior induction or suppression respectively of hepatocellular MFO enzymes
- rapid death in some animals reflects direct toxic injury to pulmonary alveolar walls following metabolism of the toxin by MFO enzymes of alveolar type II epithelial cells → pulmonary oedema

COMMON CHRONIC HEPATOTOXINS

Pyrrolizidine Alkaloids

- pyrrolizidine alkaloids are found in many plant families world-wide, especially *Senecio, Crotalaria, Heliotropium, Echium, Amsinckia, Cynoglossum* and *Trichodesma* species

- biotransformation by MFO enzymes → production of highly reactive, alkylating **dihydropyrrolizidine (DHP) derivatives** (**pyrrolic esters**) which can bind covalently to proteins and nucleic acids → inhibition of mitosis and protein synthesis +/- carcinogenesis
- DHP metabolites can be detoxified by glutathione conjugation catalysed by glutathione *S*-transferases

- animal species differ in their susceptibility to pyrrozidine alkaloid toxicity
- in order of increasing resistance: pigs < poultry < cattle and horses < rats < mice, sheep and goats

Acute Poisoning

- acute poisoning is unusual because plants containing pyrrolizidine alkaloids are unpalatable but can occur in starving animals that consume large quantities
- can also occur in pigs and poultry if feed is contaminated (e.g. with toxic *Amsinckia* seeds)
- **periacinar (zone 3) hepatic necrosis** and haemorrhage

Chronic Poisoning

- toxic effects of pyrrolizidine alkaloids are cumulative and **clinical disease usually reflects long term, low grade exposure** (e.g. two seasons of ingestion of the relevant plants in sheep)
- clinical signs may include jaundice, photosensitisation and hepatic encephalopathy

- in severe chronic toxicity, inhibition of DNA synthesis and mitosis → **atrophy of the liver**
- any hepatocytes that have escaped injury undergo mitotic division → formation of regenerative nodules
- biliary hyperplasia in the portal areas and periportal parenchyma probably represents attempted regeneration of hepatocytes by cholangiolar oval cells
- some hepatocytes may be inhibited from undergoing mitosis but may still be able to synthesise DNA → **hepatocellular megalocytosis and karyomegaly** (greatly enlarged hepatocytes with very

large and often convoluted polyploid nuclei) is characteristic of chronic pyrrolizidine alkaloid poisoning
- less often, comparable hepatocytes can be seen with other chronic intoxications (e.g. aflatoxins, nitrosamines, +/- cycads)

- **hepatic fibrosis** also develops (minimal in sheep, moderate in horses, and often marked in cattle)
- cattle with severe bridging or periacinar fibrosis may develop **portal hypertension** and **ascites** (also seen in humans exposed to pyrrolizidine alkaloids in herbal preparations and "bush teas")

- reactive metabolites may also be produced by biotransformation of pyrrolizidine alkaloids by **MFO enzymes in other organs**
- e.g. in the lungs, monocrotaline from *Crotalaria* species can be metabolised to reactive DHP derivatives → injury to the alveolar walls of the lungs → pulmonary oedema, haemorrhage, fibrosis and emphysema
- reported in horses and sheep ingesting *Crotalaria* species
- reported in pigs ingesting *Senecio jacobaea*

Aflatoxins

- aflatoxins are bisfuranocoumarin compounds produced as metabolites by such fungi as *Aspergillus flavus*, *A. parasiticus* and *Penicillium puberulum*
- usually produced during storage of fungus-contaminated feed in moist and warm conditions
- these fungi also grow on legume stubbles, bread and especially peanuts
- **aflatoxin B_1** is the most potent hepatotoxin and carcinogen

- aflatoxins are biotransformed by hepatic MFO enzymes into a variety of toxic and non-toxic metabolites
- the most potent toxic metabolite is the **8,9 epoxide of aflatoxin B_1** → alkylating activity (i.e. it can bind to DNA and RNA) → inhibition of mitosis and protein synthesis, immunosuppression +/- carcinogenic and teratogenic effects

- **birds**, **pigs**, **calves**, **horses** and **dogs** are more susceptible to aflatoxicosis than are adult cattle or sheep
- **young animals** are more sensitive than adults

Acute Poisoning

- mainly **garbage-feeding dogs**, especially young dogs
- sudden death or brief illness with vomiting, anorexia, colic etc.
- **massive** or **periacinar hepatic necrosis** and widespread haemorrhage

Chronic Poisoning

- low-level exposure to aflatoxins → decreased growth rate and hepatic lipidosis
- ultimately, affected livers become atrophic, firm, yellow and multinodular due to hepatic lipidosis, progressive fibrosis, biliary hyperplasia and regenerative nodular hyperplasia
- hepatic microscopic lesions in the chronic phase may closely resemble those of chronic pyrrolizidine alkaloid poisoning, including the presence of **hepatocellular megalocytosis**

Phomopsins (Lupinosis)

- the fungus *Phomopsis leptostromiformis* can grow on green lupins (*Lupinus* species) and becomes saprophytic after the plant wilts and dies
- fungus produces **phomopsin A** or **B** if the lupin stubble is moistened; the stubble then remains toxic for months
- the toxins may also be found in lupin seed

- especially **sheep** but also cattle and horses
- usually subacute to chronic toxicity
- anorexia, weight loss, +/- jaundice, photosensitisation and/or hepatic encephalopathy
- anorexia in poisoned cattle that are heavily pregnant or lactating → **ketosis**

- phomopsin A interferes with formation of hepatocellular cytoplasmic and spindle microtubules (→ arrest of mitosis in metaphase) and damages membranes of cell organelles (→ hepatic lipidosis)
- see progressive hepatic atrophy due to mitotic inhibition and diffuse fibrosis
- unaffected hepatocytes undergo mitotic division → regenerative nodular hyperplasia
- there is also non-specific accompanying biliary hyperplasia

Lantana

- *Lantana camara* is an ornamental shrub that grows in tropical and subtropical climates
- contains toxic pentacyclic triterpenes, especially lantadene A, B and C
- typically cause subacute to chronic disease with **intense jaundice and photosensitisation**
- especially cattle; rarely sheep and goats
- the toxins paralyse the gall bladder and may also disrupt the cytoskeletal support of the canaliculi → **severe intra- and extrahepatic cholestasis**
- poisoning is also responsible for ruminal stasis and nephrosis (renal tubular epithelial necrosis or degeneration) → polyuria, severe dehydration, constipation and anorexia
- +/- severe myocardial necrosis in sheep

Chronic Copper Poisoning

Pathogenesis

- the liver is the major organ responsible for regulating body copper stores, by maintaining a balance between dietary intake and excretion via the bile
- copper is usually complexed with metallothionein in the cytoplasm of hepatocytes and thence incorporated into lysosomes before being **excreted into bile**
- in **cholestasis**, copper accumulates in hepatocytes

- at excess concentrations, copper is toxic because of its valency and its capacity to promote formation of **reactive oxygen species** and hence **peroxidation of membrane phospholipids**

- **sheep are especially prone to chronic copper poisoning** due to the strong avidity of the ovine liver for copper and their limited capacity to excrete it in bile
- **British breeds** are more susceptible than the Merino

- sheep have an increased risk of chronic copper poisoning if there is:

  - **excessive copper intake** - e.g. contamination of pasture or prepared feed, use of cattle mineral preparations in sheep, copper water pipes, $CuSO_4$ footbaths

  - **increased availability of dietary copper** - e.g. low molybdenum, sulphate or zinc

  - **intercurrent disease interfering with hepatocyte mitosis** - especially chronic pyrrolizidine alkaloid poisoning or phomopsin poisoning

- copper is largely sequestered in hepatocellular lysosomes
- when liver [Cu] reaches 200-300 ppm (µg/g) (dry weight), hepatocyte apoptosis begins → released copper is then accumulated by adjacent hepatocytes, Kupffer cells and other macrophages
- apoptosis is matched by increased hepatocyte mitosis

- if hepatocyte loss exceeds hepatocyte mitosis rate → increased plasma [copper] → **acute intravascular haemolysis** → haemoglobinaemia, haemoglobinuria, +/- methaemoglobinaemia (due to oxidation) → **hypoxic damage to hepatocytes** → further copper release → crisis → **sudden death**

Post Mortem Lesions

- deeply jaundiced carcase
- superimposed red colour of haemoglobinaemia +/- brown colour of methaemoglobinaemia
- deep red-brown-black kidneys with red-brown urine (due to bilirubinuria and haemoglobinuria)
- liver may be swollen, orange and soft, with dark granular bile in the gall bladder
- alternatively, the liver may show evidence of concurrent disease (e.g. atrophy, fibrosis and nodular regeneration in chronic pyrrolizidine alkaloid poisoning)
- spleen may be diffusely congested due to portal hypertension

- **liver histopathology** - multifocal hepatocellular apoptosis, +/- increased hepatocellular mitoses, accumulation of faint yellow-pigmented copper-containing macrophages, + superimposed periacinar necrosis due to hypoxia, +/- lesions of chronic pyrrolizidine alkaloid poisoning or lupinosis

HEPATOBILIARY HYPERPLASTIC LESIONS

Idiopathic Nodular Hyperplasia of Hepatocytes

- **common incidental finding in middle-aged and older dogs**
- usually multiple (but not numerous), non-encapsulated, randomly scattered parenchymal nodules, a few mm to several cm in diameter
- composed of slightly enlarged hepatocytes arranged into a modified lobule with a still recognisable central vein and portal areas (c.f. hepatocellular adenoma - see below)
- may be grossly paler than the surrounding liver if the component hepatocytes contain lipid or glycogen
- **arise in an otherwise normal liver**

- **DDx** - **regenerative hyperplastic nodules** that are a compensatory response to hepatocyte loss and that develop in livers that have significant architectural abnormalities and fibrosis

Cystic Mucosal Hyperplasia of the Gall Bladder

- **common incidental finding in older dogs**
- multifocal sessile (broad-based) or protruberant polyps of hyperplastic and distended mucus-secreting glands of the gall bladder mucosa
- may result from chronic inflammation of the gall bladder mucosa but more often idiopathic (i.e. no obvious cause)

HEPATOBILIARY NEOPLASMS

METASTATIC (SECONDARY) TUMOURS

- **metastatic tumours are more common than primary hepatobiliary tumours**
- metastasis to the liver is common due to the anatomic position, rich blood supply and filtering function of the liver
- usually appear as multiple masses scattered randomly throughout the organ
- rarely cause signs of liver dysfunction/failure because of the large hepatic functional reserve capacity

- **carcinomas = malignant tumours of epithelial origin**
- tend to be scirrhous (firm due to host fibroplasia/fibrosis) and may be umbilicate (with a central dimple) if positioned superficially beneath the hepatic capsule
- especially metastases from primary intestinal carcinomas and exocrine or endocrine pancreatic carcinomas

- **sarcomas = malignant tumours of mesenchymal origin**
- tend to be nodular, cream-white, smooth-surfaced and non-umbilicate

- **haemangiosarcoma = a malignant tumour of vascular endothelium**
- more commonly seen in the liver as a metastatic tumour (e.g. from a primary in the spleen) than a primary liver tumour
- usually appears as multiple, soft, dark red, blood-filled nodules

- **malignancies of haematopoietic cells** - e.g. lymphoma, leukaemia of red or white blood cell origin, mast cell leukaemia or metastasising mast cell tumours of skin origin, malignancies of macrophage/histiocyte origin etc.
- often cause **diffuse hepatomegaly** and **pallor**
- can also appear as **multifocal cream-white nodules**, usually of soft consistency
- in diffuse lymphoma of the liver, sometimes see a gross zonal pattern due to homing of the neoplastic lymphocytes to portal areas

PRIMARY HEPATOBILIARY TUMOURS

Hepatocellular Tumours

Hepatocellular Adenoma (Hepatoma)

- a **benign tumour of hepatocytes**
- usually a solitary, sharply demarcated but usually not encapsulated, soft, red-brown to yellow or bile-stained mass
- may reach many cm in diameter
- most common in **ruminants**
- composed of well-differentiated hepatocytes but lacks normal lobular architecture (e.g. portal areas, central vein) (c.f. nodular hyperplasia of hepatocytes)

Hepatocellular Carcinoma

- **a malignant tumour of hepatocytes**
- uncommon
- old dogs, cats, sheep and cattle
- may appear as a solitary mass or there may be a large primary tumour with multiple smaller metastases within the liver +/- other organs
- typically invades veins → haematogenous as well as lymphogenous metastasis
- especially spreads to regional lymph nodes and lungs +/- retrograde spread along veins and lymphatics to abdominal viscera +/- peritoneal implantation

Cholangiocellular (Bile Duct) Tumours

Cholangiocellular Adenoma

- a **benign tumour of bile duct epithelium**
- mainly **old dogs** and **cats**
- composed of well-differentiated bile duct epithelium and contains mucin rather than bile
- can be solid or polycystic (the latter form is termed a **biliary cystadenoma**)
- cystic biliary tumours need to be differentiated from congenital cysts of the intrahepatic bile ducts (ductal plate malformations) (Lecture 7)

Cholangiocellular Carcinoma

- a **malignant tumour of bile duct epithelium**
- especially older dogs and cats
- can be caused by chronic fluke infestation of the biliary tree in carnivores (and humans)
- single or, more typically, multiple masses scattered throughout the liver
- typically firm (scirrhous), cream-white nodules; may be umbilicate where contacting the hepatic capsule
- composed of ductules and acini of biliary epithelium and may contain mucin
- highly invasive growth pattern with metastasis to hepatic lymph nodes and lungs and peritoneal implantation common
- need to differentiate from metastatic adenocarcinomas, especially exocrine pancreatic adenocarcinoma

Other Primary Hepatobiliary Tumours

- rare
- e.g. haemangioma (benign), haemangiosarcoma (malignant) - tumours of vascular endothelium
- e.g. leiomyoma (benign), leiomyosarcoma (malignant) - tumours of smooth muscle
- e.g. fibroma (benign), fibrosarcoma (malignant) - tumours of fibrocytes/fibroblasts
- e.g. osteosarcoma (malignant tumour of osteoblasts, derived from mesenchymal elements of the liver)
- e.g. carcinoids (malignancies of neuroendocrine cells)
- e.g. gall bladder adenoma (benign) and adenocarcinoma (malignant) - tumours of mucus-secreting cells of the gall bladder mucosa