INFLAMMATION OF THE LIVER AND BILIARY TREE

HEPATITIS

- **hepatitis = inflammation of the hepatic parenchyma**

- inflammatory foci may be acute, subacute, chronic or chronic active in duration
- inflammatory foci may be **focal**, **multifocal**, **zonal** or **diffuse** in distribution
- **the distribution pattern of the lesions provides important clues as to the likely cause**

- hepatitis is **common** in domestic animals
- traces of inflammation are detectable in the livers of most adult animals but most lesions are incidental findings that do not have a significant effect on liver function
- focal or multifocal lesions (e.g. abscesses) usually do not lead to liver failure, even if large
- **severe diffuse hepatitis usually progresses to liver failure**
- **most causes** of hepatitis in domestic animals are **infectious agents** that have arrived in the liver via the bloodstream **(haematogeneous infections)**

FOCAL HEPATITIS

Hepatic Abscesses

- may be single or multiple
- **common** in **cattle**, especially **feedlot cattle**
- occasionally seen in other species

Routes of Entry of Bacteria

- **direct implantation** - e.g. foreign body penetration from the reticulum (hardware disease)
- **direct extension from suppurative lesions in adjacent tissues** - e.g. hardware disease
- **ascending infections up the bile ducts** - e.g. horses, dogs, cats and pigs
- **haematogenous infections** - via the portal vein (common), umbilical vein (neonates) or hepatic artery (rare)

Feedlot Cattle

- hepatic abscesses are usually caused by portal venous embolism of bacteria following **ruminal acidosis/rumenitis (grain overload)**
- the most common bacterium responsible is *Fusobacterium necrophorum* = **hepatic necrobacillosis**
- bacterial endo- and exotoxins produce sharply circumscribed, dry zones of coagulative necrosis with an intense margin of hyperaemia and haemorrhage
- in animals that survive, the centres of these foci liquefy to form conventional abscesses

Adult Cattle

- hepatic abscesses most commonly result from **traumatic reticuloperitonitis** (hardware disease), either via direct inoculation of bacteria into the liver or via extension of infection to the liver from suppurative foci in the cranial peritoneal cavity

- often in the **left hepatic lobe** due to its anatomic position in relation to the reticulum
- the most common bacterial isolate is *Trueperella* (*Arcanobacterium*) *pyogenes* → yellow-green liquid pus

Neonates

- **neonatal omphalogenic abscesses** occur in all species but are especially common in **calves**
- infection of the umbilicus ("navel-ill") → bacteria grow along the physiological thrombus in the umbilical vein to the liver → formation of one or more abscesses (especially in the **left hepatic lobe**)
- usually involve pyogenic (= pus-forming) bacteria such as *T. pyogenes*, streptococci and/or staphylococci → yellow or yellow-green liquid pus

Consequences of Hepatic Abscessation

- **most hepatic abscesses are asymptomatic**
- +/- weight loss and decreased milk production in dairy cattle, slow rate of weight gain in feedlot cattle
- economic loss from liver condemnation at meat inspection

- abscesses may sterilise and heal by resorption and fibrosis or they may become encapsulated
- fibrin exudation over capsular surface → fibrosis +/- adhesions to adjacent viscera

- rarely perforation of the liver capsule → peritonitis
- may erode into hepatic veins → thrombosis and inflammation (thrombophlebitis) of hepatic veins and/or caudal vena cava, vegetative endocarditis (formation of septic thrombi on heart valves), fatal septic pulmonary thromboembolism +/- pulmonary abscessation
- systemic spread is common with omphalogenic abscesses in neonates
- death from toxaemia is possible in adults with multiple acute abscesses, especially if due to *F. necrophorum*

Black Disease

- uncommon due to vaccination of livestock against clostridia
- especially **sheep**
- caused by ***Clostridium novyi* type B**
- spores of *C. novyi* are widely distributed in soil
- ingested spores may persist in macrophages in liver, spleen and bone marrow for many months

- any liver damage that lowers O_2 concentration → spore germination → proliferation of vegetative bacilli and release of potent exotoxins → necrosis and expansion of the original lesion → absorption of toxins into the general circulation → widespread vascular injury
- spore germination is usually triggered by hepatic necrosis caused by **migration of immature liver flukes**
- occasionally triggered by migration of other parasite larvae (e.g. cysticerci), hepatic abscessation, lobe torsion etc.

- sudden death or very brief period of illness prior to death
- rapid carcase putrefaction
- severe subcutaneous congestion (hence the name, "black disease")

- systemic oedema with accumulation of serous fluid in body cavities and pulmonary oedema

- **liver** - lesions of larval fluke migration or other primary problem
- one or more, large (> 2 cm diameter), yellow-white to red zones of coagulative necrosis, with a margin of intense hyperaemia
- large Gram-positive bacilli in zone of necrosis and concentrated at its margin

Bacillary Haemoglobinuria

- mainly **cattle** but occasionally sheep
- similar pathogenesis to black disease but caused by ***Clostridium haemolyticum***
- produces potent exotoxins that cause hepatic necrosis and intravascular haemolysis → anaemia, haemoglobinaemia, haemoglobinuria +/- jaundice
- liver lesions are as per black disease but usually only one large focus of liver necrosis is present

MULTIFOCAL (EMBOLIC) HEPATITIS

- the **most common pattern of hepatitis**
- especially common in **young animals of the large domestic animal species** (i.e. lambs, calves, goat kids, foals and piglets)

- if infectious agents shower the liver from the bloodstream, death may occur before there is a significant inflammatory response to the initial necrosis
- this is more accurately described morphologically as **multifocal hepatic necrosis** but is often referred to as **multifocal hepatitis** as the lesions will evolve into the latter if the animal survives for a day or so after onset

- **causes** include:

  - **most bacteraemias**
  - **some systemic protozoal infections** - e.g. *Toxoplasma gondii*
  - **some viraemias** - e.g. feline infectious peritonitis virus (a coronavirus)
    - e.g. most animal herpesviruses
    - e.g. adenoviruses in ruminants
  - **systemic fungal infections** - e.g. following portal venous embolism from lesions of ruminal acidosis → acute hepatic infarcts and later multifocal granulomas
  - **migrating parasites**

Transhepatic Parasite Migration

- so-called **parasitic hepatitis** is common but rarely fatal
- leads to economic loss from liver condemnation at meat inspection
- can be fatal if large numbers of parasite larvae are migrating simultaneously (→ widespread hepatic necrosis and hepatic failure) or if the parenchymal injury caused by the parasites triggers activation of a clostridial spore (→ **black disease** or **bacillary haemoglobinuria**)

- migration of helminth larvae or adults that have invaded the liver from the peritoneal cavity or from portal venous blood → parenchymal destruction, haemorrhage, necrosis and release of antigens promoting inflammation
- see **linear or sinuous tunnels** containing haemorrhage, necrotic debris and leukocytes

(especially eosinophils) and fibrin exudation wherever the liver capsule is breached
- migratory tracks heal by fibrosis

- most larvae escape the liver to enter bile ducts, efferent blood, retroperitoneal tissues or the peritoneal cavity
- some may be trapped in the liver by granulomatous inflammation and fibrosis → encapsulation +/- caseation and mineralisation

Common Causes of Parasitic Hepatitis

- **cattle** - larvae of *Fasciola hepatica* (common liver fluke) (**acute fascioliasis**)
- **sheep** - larvae of *Fasciola hepatica* (**acute fascioliasis**)
  - immature cysticerci (metacestode stage) of the canine tapeworm, *Taenia hydatigena*
- **pigs** - larvae of *Ascaris suum* (roundworm) → "**milk spots"** (multiple, small, white, superficial scars beneath the hepatic capsule)
  - larvae of *Stephanurus dentatus* (kidney worm)

ZONAL HEPATITIS

- the following two conditions are characterised by a zonal (especially **periacinar** = zone 3/ centrilobular) distribution of hepatic inflammation and necrosis:

  - **canine adenovirus-1** (canine infectious hepatitis)
  - **equine serum hepatitis** (Theiler's disease)

- the lesions therefore mimic those of toxic and hypoxic insults to the liver

DIFFUSE HEPATITIS

Chronic Hepatitis in Dogs

- a **common disease** in **dogs**
- originally referred to as **chronic active hepatitis** in both human and veterinary medicine
- **chronic hepatitis** (CH) is now the preferred terminology in human and veterinary medicine because not all cases are active or progress to end-stage (cirrhotic) liver failure

- characterised by **periportal interface hepatitis** (inflammation of the portal areas and periportal (zone 1) parenchyma, especially involving lymphocytes and plasma cells), apoptosis of periportal hepatocytes (= **piecemeal necrosis**) and frequent **progression to cirrhosis** due to progressive deposition of collagen in the perisinusoidal space by stellate cells

- in **humans**, CH is most often caused by infection with hepatitis viruses A-E, especially hepatitis viruses B and C
- other causes in humans include autoimmune hepatitis, drugs, alcohol, metabolic disorders (e.g. α_1-protease inhibitor deficiency) or storage disorders (e.g. Wilson's disease due to copper storage, haemochromatosis due to iron storage)
- T lymphocyte-mediated or antibody-dependent cellular cytotoxicity is implicated in the pathogenesis of hepatocyte necrosis in CH in humans

- in **dogs**, an immune-mediated pathogenesis of CH is still to be confirmed

- however, aberrant expression of major histocompatibility complex (MHC) class II antigens by hepatocytes has been demonstrated in Doberman pinschers with CH (possibly induced by intra-hepatic lymphocyte release of cytokines, especially interferon-γ) → hepatocytes become targets for T-cell-mediated immune attack

Factors Implicated in the Pathogenesis of Chronic Hepatitis in Dogs

Idiopathic - **most cases of CH in dogs are of unknown cause**

Breed- and/or copper-associated - Bedlington terrier
- West Highland white terrier
- Skye terrier
- Doberman pinscher
- Dalmatian
- Labrador retriever
- American and English cocker spaniel
- standard poodle

Drugs - **anticonvulsant drugs** - especially **primidone** but also **phenobarbital** and **phenytoin**
- antiparasitic combinations of diethylcarbamazine and oxybendazole
- idiosyncratic reactions to various drugs, including chemotherapeutic agents such as azathioprine

Infectious agents - canine adenovirus-1 (rarely)
- *Leptospira interrogans* serovar *grippotyphosa* (rarely)

α_1-protease inhibitor deficiency - rare

- dogs with CH are ill for weeks to months
- usually have a persistent increase in serum activity of alanine aminotransferase (ALT)
- late in the disease course, there is biochemical evidence of liver dysfunction (e.g. low serum urea and albumin concentrations and increased total serum bile acids concentration)
- some dogs with CH respond well to immunosuppressive therapy but **many progress to cirrhosis**

Chronic Hepatic Copper Storage in Dogs

- copper is normally stored in hepatocytes and is gradually excreted via the bile
- due to its valency, excess copper can interact with cellular hydrogen peroxide → generation of hydroxyl radicals (reactive oxygen species) → peroxidative damage to phospholipid membranes → hepatocyte degeneration or necrosis

- the liver of a healthy dog may contain a copper concentration of up to 400 ppm (μg per g) (dry weight)
- above this threshold, the copper begins to accumulate within hepatocyte lysosomes and can be demonstrated with special histochemical stains (e.g. rubeanic acid, rhodanine)
- liver lesions typical of chronic hepatitis do not typically develop until the copper concentration exceeds 2000 ppm (dry weight)

- excess copper accumulation associated with chronic hepatitis +/- cirrhosis is common in several dog breeds
- in some breeds (e.g. Dobermans and cocker spaniels), **copper accumulation is believed to develop secondary to cholestasis** and is chiefly stored in **periportal (zone 1) hepatocytes**

- in breeds with **primary copper storage** (Bedlington terriers, West Highland white terriers, Skye terriers, Labradors and Dalmatians), copper accumulation commences in **periacinar (zone 3) hepatocytes**

- in **Bedlington terriers**, hepatic copper accumulation is inherited as an autosomal recessive defect due to a mutation in the *MURR1* gene
- the Murr1 protein may act as a copper chaperone involved in directing copper into the biliary drainage system
- affected dogs may have liver copper concentrations in excess of 12,000 ppm and continue to accumulate copper throughout life
- clinical signs of hepatic dysfunction develop in homozygotes when middle-aged or older, when the liver [Cu] reaches 2000 ppm and lysosomal rupture and hepatocyte death are occurring; by this stage, the liver lesions are often advanced and irreversible

- a single case of copper-induced chronic hepatitis and cirrhosis has been described in a **cat** (a Siamese)

INFLAMMATION OF THE BILIARY TREE

- **cholangitis** = inflammation of the bile ducts and their supporting connective tissues

- **cholangiohepatitis** = inflammation centred on the bile ducts of the portal areas but spreading to involve the hepatic parenchyma (usually periportal = zone 1)

- **cholecystitis** = inflammation of the gall bladder

- **in domestic animals, cholangitis has usually extended to cause cholangiohepatitis by the time of diagnosis**

- inflammation of the biliary tree can be due to **parasites** (+/- secondary bacterial infection), **ascending bacterial infection**, **toxins** or **autoimmune disease**
- reflux of pancreatic digestive enzymes and bile acids from the duodenal lumen up the bile ducts may also cause cholangiohepatitis in dogs and cats

PARASITIC CHOLANGITIS/CHOLANGIOHEPATITIS

- e.g. **adult liver flukes in ruminants** - *Fasciola hepatica* (common liver fluke) in Australia
- e.g. various genera of flukes in cats and occasionally dogs in endemic areas in Europe, Asia and North, Central and South America
- e.g. **adult roundworms (*Ascaris suum)* in pigs** - may migrate up biliary and pancreatic ducts from the small intestine in heavy infestations
- e.g. **hepatic coccidiosis** - *Eimeria stiediae* in rabbits → pronounced papillary hyperplasia of bile duct epithelial cells containing replicating protozoal schizonts and gamonts

Chronic Fascioliasis in Ruminants

- adult liver flukes lie in lumina of the larger bile ducts
- they suck blood and probably produce toxic and irritating excretions
- suckers and scales cause mechanical irritation

- cause obstruction of ducts and bile stasis → atrophy of the affected hepatic parenchyma
- bile stasis may also predispose to secondary bacterial infection

- lesions occur in both liver lobes but are more severe in the **left lobe** (probably because a greater number of larvae arrive in this lobe after transperitoneal migration)
- the right lobe may undergo compensatory hypertrophy

- in **sheep**, **dilation of thin-walled bile ducts** is typical, due to duct obstruction with only mild catarrhal inflammation of the duct mucosa and little reactive fibrosis (scarring)
- in **cattle**, **bile duct fibrosis** predominates, due to more severe duct mucosal erosion and ulceration → irregular duct stenosis with "pipe-stem" thickening +/- dystrophic mineralisation of the duct walls

BACTERIAL CHOLANGITIS/CHOLANGIOHEPATITIS

- uncommon but seen in **cats** and **horses** and sporadically in other species
- affected cats often have concurrent duodenitis and ascending interstitial pancreatitis

- bacteria may arrive **haematogenously** in the liver and descend the bile ducts (e.g. following hepatic abscessation in cattle) but more commonly they **ascend the bile ducts from the duodenum**
- either way, the bacteria involved are usually intestinal flora, e.g. *E. coli*, streptococci etc

- in **ruminants**, there is normally a continuous low-level **enterohepatic circulation of bacteria**, including salmonellae and *Campylobacter* species
- bile stasis in ruminants can therefore promote bacterial infection of the biliary tree

- the inflammatory reaction induced by bacterial infection is usually suppurative (dominated by neutrophils)

- **acute stage** - liver is swollen and soft with few or many suppurative foci; pus is obvious within the lumina of distended extra- and intra-hepatic bile ducts
- if severe, can be rapidly fatal during the acute stage

- **subacute and chronic stages** - fibrosis develops around the affected bile ducts and may bridge between adjacent portal areas
  - accompanied by biliary hyperplasia, intra- and extra-hepatic cholestasis, parenchymal atrophy +/- mild regenerative nodular hyperplasia of surviving hepatocytes

BACTERIAL CHOLECYSTITIS

- in some bacterial infections, inflammation may be largely restricted to the gall bladder (e.g. because of proliferation of bacteria during storage of bile in the gall bladder or because the neck of the bladder becomes occluded by exudate)

- e.g. fibrinous cholecystitis in acute salmonellosis in cattle (especially calves)
- e.g. fibrinosuppurative cholecystitis in sheep with intestinal *Campylobacter jejuni* infection

LYMPHOCYTIC CHOLANGITIS/CHOLANGIOHEPATITIS OF CATS

- a chronic progressive disease of usually young or middle-aged cats
- chronic inflammation rich in small lymphocytes is centred on the extra- and intra-hepatic bile ducts, with a variable degree of biliary fibrosis (can be severe), biliary hyperplasia and extra- and intra-hepatic cholestasis
- distinction from lymphoma can be difficult if based purely on the histological morphology of the infiltrating lymphocytes

- an **immune-mediated pathogenesis is suspected** and some cats respond well to immunosuppressive therapy
- *Helicobacter* species have been identified by polymerase chain reaction (PCR) in the bile of many affected cats but their role in the pathogenesis is unknown

- affected cats may be intensely jaundiced, especially if there is severe biliary fibrosis
- some affected cats develop a high protein ascites ± hypergammaglobulinaemia (and may therefore clinically resemble cats with feline infectious peritonitis)

TOXIC CHOLANGITIS/CHOLANGIOHEPATITIS

Facial Eczema

- an important cause of chronic liver damage and photosensitisation in **sheep** and, to a lesser extent, **cattle** in Australia, New Zealand and South Africa

- **sporidesmin** = a **mycotoxin** produced by the fungus *Pithomyces chartarum* usually growing on pasture litter (especially dead ryegrass) moistened in warm weather
- the density of the fungal spores in which sporidesmin is concentrated determines the toxicity of the pasture

- sporidesmin is carried to the liver from the gastrointestinal tract via the portal vein and is then excreted unconjugated into bile
- it is a **direct irritant** and in high concentration in bile causes necrosis of intra- and extra-hepatic biliary epithelium and irritation of the peribiliary connective tissues and blood vessels → **obstructive jaundice** and **photosensitisation**
- sporidesmin is also excreted in urine; in high concentrations, it can cause mucosal oedema and haemorrhage in the urinary bladder

- **acute** - swollen jaundiced liver; oedema of the gall bladder and portal connective tissues; oedematous thickening of the extra-hepatic bile ducts; +/- parenchymal "bile infarcts" (focal areas of hepatic necrosis due to release of bile and irritant bile salts)

- **chronic** - firm, fibrotic, atrophic **left lobe** with fibrous thickening of the walls of the intra- and extra-hepatic bile ducts, and compensatory hypertrophy of the right lobe
  - the liver in chronic facial eczema can resemble chronic fascioliasis except for the absence of the thin-walled dilated bile ducts expected in sheep with adult liver flukes

Tribulosis and Related Plant Intoxications

- sheep and goats in Australia and South Africa consuming ***Tribulus terrestris*** (**caltrop**) develop jaundice and hepatogenous photosensitisation (**geeldikkop** = Afrikaans word for "yellow bighead")

- caltrop contains **steroidal sapogenins**
- after metabolism in the rumen and liver, the sapogenins may form salts with calcium ions → precipitation as **fine crystals** within bile ducts → physical obstruction to bile flow
- the plant may also contain toxins that disrupt the membranes of bile canaliculi
- crystals may also be found microscopically in hepatocytes, Kupffer cells and sometimes renal tubules
- hepatic "bile infarcts" and oedema and fibrosis of the bile ducts are less common in geeldikkop than in facial eczema

- similar crystal-associated cholangiohepatitis can be seen in ruminants grazing the following plants:

Agave lecheguilla	*Brachiaria decumbens* (signal grass)
Narthecium species	*Panicum* species (especially *P. coloratum*, kleingrass)
Nolena texana	

MISCELLANEOUS CONDITIONS OF THE BILIARY TREE

CHOLELITHIASIS (GALL STONES)

- gall stones (**choleliths**) usually form in the gall bladder
- occasionally see stones in lumina of bile ducts in cattle with chronic fascioliasis
- usually mixed stones composed of cholesterol, bile pigments, bile salts, calcium salts and a proteinaceous matrix
- often soft, yellow to green-black and friable
- probably develop secondary to chronic mild cholecystitis with supersaturation and precipitation of bile constituents
- may also develop in dehydrated animals, or in anorexic animals in which emptying of the gall bladder occurs infrequently

- **choleliths** are **usually of no clinical significance in domestic animals** (c.f. humans)
- although usually asymptomatic in domestic animals, they may rarely cause obstructive jaundice and/or pressure necrosis with risk of rupture of the gall bladder

GALL BLADDER MUCOCOELE

- **gall bladder mucocoele = accumulation of excess mucin in the gall bladder**

- a common disease of older dogs (average age of 10 years)
- usually small to medium breeds (especially Shetland sheepdogs, cocker spaniels, Pomeranians, miniature schnauzers and chihuahuas)
- clinical signs include anorexia, lethargy and vomiting but some dogs may have jaundice and/or abdominal pain

- there is usually no downstream physical obstruction of the extra-hepatic biliary tree to explain the accumulation of mucus
- however, anything that increases the bile salt concentration in the gall bladder, increases the viscosity of bile or decreases gall bladder contractility (i.e. a functional obstruction) could lead to mucocoele formation
- increased mucus production may be promoted by bile stasis and prolonged mucosal exposure to bile salts, and by inflammatory cytokines, endotoxins and prostaglandins

- dogs with hyperadrenocorticism, hypothyroidism or hyperlipidaemia appear to be at increased risk of developing a mucocoele
- in a study of affected Shetland sheepdogs, administration of imidacloprid (a topical insecticide used to control fleas) was thought to be a contributing or exacerbating factor (possibly via drug metabolites excreted in bile stimulating nicotinic acetylcholine receptors and hence mucus production)
- another study found that many affected dogs have a mutation in the gene that codes for ABCB4, a protein in the hepatocyte cell membrane which is required for the transfer of protective phospholipids into bile

- usually diagnosed by ultrasonography - characteristic radiating echogenic "wagon wheel" appearance of the dilated gall bladder and its contents

- the inspissated mucin and bile may cause marked distension of the gall bladder → +/- ischaemic necrosis (due to collapse of thin-walled mural veins) and rupture → bile peritonitis
- bile stasis resulting from the mucocoele may also promote secondary bacterial infection

EXTRA-HEPATIC BILE DUCT OBSTRUCTION

- may be caused by cholangitis (with obstruction of the extra-hepatic bile ducts by luminal exudate and inspissated bile), intra-luminal parasites, choleliths (rarely), a gall bladder mucocoele, periductal fibrosis, or a pancreatic, bile duct or proximal duodenal tumour
- results in **post-hepatic (obstructive) jaundice**

- grossly see progressive distension of the extra-hepatic biliary tree proximal to the obstruction
- if unrelieved, eventually results in intra-hepatic cholestasis and peribiliary fibrosis

- rarely, and **only if the obstruction is complete**, may see **acholic faeces** (due to the absence of stercobilin derived from intestinal bacterial breakdown of conjugated bilirubin) +/- **steatorrhoea** (due to failure of duodenal lipid digestion in the complete absence of bile salts)

BILE PERITONITIS

- most cases of bile peritonitis result from **traumatic rupture of the extra-hepatic biliary tree**
- can also result from spontaneous rupture of an inflamed/infected or obstructed or infarcted segment of the extra-hepatic biliary tree, especially the **gall bladder**

- the omentum cannot seal even small leaks in the extra-hepatic biliary system → generalised peritonitis

- if the underlying process is caused by bacteria, the bile peritonitis will be septic from the outset → life-threatening bacteraemia/septicaemia and shock

- even if initially sterile, bile peritonitis can become life-threatening
- bile salts are irritating (due to their powerful detergent effect) → sterile chemical peritonitis
- peritoneal damage from bile salts may increase the permeability of the intestinal wall → trans-intestinal seepage of enteric bacteria and/or their toxins → life-threatening septic peritonitis

- the peritoneal exudate in bile peritonitis is characteristically grossly stained orange to yellow or green
- bile pigments can be identified within macrophages and mesothelial cells in cytological smears of peritoneal exudate

VETERINARY BIOSCIENCE: METABOLISM
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