WHY IS IT YELLOW AND HEAD-PRESSING?

LIVER DYSFUNCTION AND FAILURE

- due to its anatomic location, blood supply, high metabolic rate and normal functions, the liver is vulnerable to a wide variety of metabolic, toxic, infectious, haemodynamic and neoplastic insults
- liver lesions are often important clues to pathological processes in other organs and systems (e.g. the gastrointestinal tract and the right side of the heart)
- **liver lesions are common** but **seldom cause hepatic failure**

- signs of liver dysfunction/failure usually only manifest if bile outflow is obstructed or if the liver's **large functional reserve** and considerable **regenerative capacity** are exhausted (by which point, lesions may be chronic and irreversible)
- not all functions are lost simultaneously in a diseased liver
- for some functions, clinical signs of dysfunction and/or laboratory test abnormalities may not emerge until 70 to 80% of the hepatic mass is compromised

- hepatic failure is unlikely to result from focal lesions
- hepatic failure may result from **acute massive damage** (e.g. trauma or toxic insult) but most often results from **chronic progressive parenchymal injury**

MANIFESTATIONS OF LIVER DYSFUNCTION/FAILURE

JAUNDICE

- **jaundice (icterus) = yellow discolouration of tissues and body fluids due to an excess of bilirubin in blood** (**hyperbilirubinaemia**)

- do not confuse the terms jaundice and cholestasis

- **cholestasis = reduced flow of bile**
  - may be intrahepatic and/or extrahepatic
  - a common cause of jaundice but not all cases of jaundice are caused by cholestasis

Causes of Jaundice

Haemolysis (Pre-hepatic Jaundice)

- excessive breakdown of erythrocytes (red blood cells) may overwhelm the immediate capacity of hepatocytes to take up and conjugate unconjugated bilirubin

  - e.g. intravascular haemolytic anaemias
  - e.g. extravascular haemolytic anaemias
  - e.g. occasionally see mild jaundice after severe haemorrhage into internal body cavities, following lysis of the extravasated erythrocytes

Hepatocellular Disease (Hepatic Jaundice)

- in hepatocellular disease, jaundice results from **decreased hepatocellular secretion of conjugated bilirubin** and, to a much lesser extent, from decreased uptake and conjugation of bilirubin by hepatocytes
- bile formation/secretion is one of the most sophisticated hepatic functions and is one of the most readily disrupted
- **secretion of conjugated bilirubin into bile canaliculi** is energy-dependent and is the **rate-limiting step** in bilirubin metabolism in most species

- **intrahepatic cholestasis** is common and commences in periacinar zones (zone 3) where bile flow commences
- as bile accumulates, canaliculi become distended and plugged by bile and there is bilirubin discolouration of the cytoplasm of hepatocytes (Figure 1)
- hepatocyte necrosis or canalicular/cholangiolar rupture → local release of bile → inflammation +/- necrosis (so-called "**bile infarcts**"); bile pigments may then be taken up by nearby Kupffer cells (Figure 1)

Figure 1

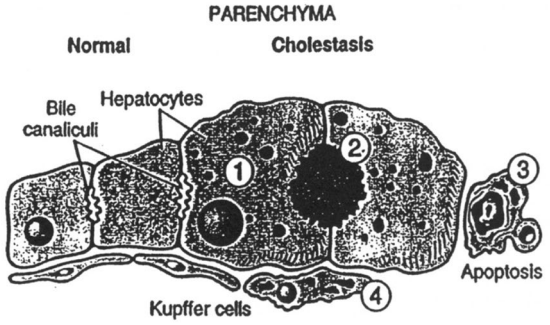


Illustration of the morphologic features of cholestasis (*right*) and comparison with normal liver (*left*). In the parenchyma (*upper panel*), cholestatic hepatocytes (1) are enlarged with dilated canalicular spaces (2). Apoptotic cells (3) may be seen, and Kupffer cells (4) frequently contain regurgitated bile pigments.

Reference: "Robbins Pathologic Basis of Disease" – R.S. Cotran, V. Kumar, T. Collins. 6th edition, W.B. Saunders Company, Philadelphia, 1999

- certain **toxins** may specifically cause intrahepatic cholestasis, e.g. by damaging the smooth endoplasmic reticulum of hepatocytes in which bile conjugation and intracellular bile salt transport occur or by damaging the contractile actin filaments in the pericanalicular cytoplasm of hepatocytes

- intra-hepatic cholestasis can also develop in **anorexia** (especially in horses) and in bacteraemia/septicaemia (**"jaundice of sepsis"**) (mechanisms are incompletely understood)

Extrahepatic Obstruction of Bile Flow (Post-hepatic Jaundice)

- e.g. obstruction of bile ducts by luminal parasites, choleliths (gall stones), inflammatory exudate, fibrosis or neoplasia

- initially see distension of extrahepatic ducts immediately proximal to the obstruction
- ultimately see progressive retrograde distension of the intrahepatic ductal system
- in the liver, extrahepatic cholestasis first becomes obvious in the portal areas where smaller bile ducts dilate and contain luminal bile plugs
- plugging of bile canaliculi and bilirubin pigmentation of hepatocytes develop later
- chronic extrahepatic cholestasis may cause extensive fibrosis around bile ducts

General Comments on Jaundice

- jaundice may be detectable in mucous membranes of small animals when the total serum bilirubin concentration exceeds approximately 35 µmol/L
- intensity of jaundice is greatest when more than one classical mechanism of hyperbilirubinaemia is operating, e.g. chronic copper poisoning in sheep (in which there is both hepatic parenchymal disease and haemolysis)
- intensity of jaundice increases the longer the hyperbilirubinaemia persists
- maximal uptake of bile pigments by tissues takes 1-2 days
- jaundice is most vivid in tissues rich in elastin, e.g. sclera and aorta
- in horses and Jersey and Guernsey cattle, need to distinguish jaundice from the yellow pigmentation of fat caused by dietary carotenoid pigments

PHOTOSENSITISATION

- **hepatogenous photosensitisation** is the most common form of photosensitisation in domestic animals
- photosensitisation almost invariably develops in **herbivores** with intra- or extrahepatic **cholestasis** of several days' duration if eating **green feed** and if exposed to **sunlight**
- **phylloerythrin** = a photodynamic agent produced by the action of herbivore GI bacteria on **chlorophyll** → transported to the liver in portal venous blood → excreted by hepatocytes via the same mechanisms as bilirubin
- in cholestasis, phylloerythrin leaks from hepatocytes into the general circulation and is deposited in tissues
- in the skin, phylloerythrin is activated by absorption of ultraviolet light (290-400 nm wavelength) to produce **reactive oxygen species** (free radicals) that damage nuclei, cell membranes and organelles in adjacent cells

- lesions are usually restricted to hairless or sparsely haired, non- or lightly pigmented skin exposed to sunlight
- see skin hyperaemia (reddening due to increased perfusion of capillary beds with arterial blood), oedema, intense pruritus (itchiness), self-excoriation (self-traumatic damage), exudation and necrosis, desiccation and sloughing

- hepatogenous photosensitisation is usually caused by disease processes that diffusely involve the liver
- especially associated with **toxic hepatic insults** of **plant or mycotoxin** origin
- a classic example is **facial eczema** caused by the mycotoxin, **sporidesmin**

HEPATIC ENCEPHALOPATHY

- common in ruminants and horses with hepatic failure and in dogs with portosystemic shunting and (to a lesser extent) chronic hepatitis
- may rarely result from congenital urea cycle enzyme deficiency or inborn errors of metabolism (organic acidaemias)

- variable and non-specific clinical signs which are often intermittent
- **clinical signs** may include anorexia, depression, dullness, lethargy, compulsive or aimless movement, subtle behavioural changes, mania, seizures (convulsions), circling, head-pressing, central blindness, tremors, ataxia (incoordination), fever, nausea, hypersalivation (ptyalism, especially in cats) and/or intermittent vomiting and diarrhoea

- hepatic encephalopathy (HE) is a complex multifactorial autointoxication due to failure of hepatic detoxification functions or circulatory bypass of the liver
- pathogenesis is incompletely understood but the syndrome is thought to result from cerebrocortical exposure to toxins absorbed from the gastrointestinal tract, from shifts in plasma amino acid concentrations, and from alterations in concentrations of inhibitory and excitatory neurotransmitters

- the following encephalotoxins have been implicated in HE:

  ammonia*
  mercaptans* (derived from methionine)
  short chain fatty acids* (e.g. octanoic acid)
  skatoles*
  indoles*
  aromatic amino acids* (* = absorbed from the gastrointestinal tract)
  octopamine
  tryptophan
  serotonin
  gamma-aminobutyric acid (GABA)*

- **hypoglycaemia** (low blood glucose concentration) may also contribute to seizure activity

- **ammonia is responsible for most of the structural lesions in the brain** → accumulation by astrocytes → cytotoxic oedema → altered gene expression and neurotransmission, and cerebral oedema
- in most species, HE is characterised by swelling of the nuclei of astrocytes (**Alzheimer type 2 cells**) and extensive spongy vacuolation and oedema of myelin, especially at the junction of grey and white matter in the cerebral cortex and in white matter surrounding deep cerebellar nuclei
- in **horses**, typically only see formation of Alzheimer Type 2 cells, without accompanying myelin vacuolation and oedema

OEDEMA

Generalised Oedema due to Hypoalbuminaemia

- the liver is the sole source of albumin
- severe reduction in functional hepatic mass → reduced albumin synthesis
- because albumin has a long half-life, **hypoalbuminaemia only develops late in hepatic disease** when at least 75-80% of functional mass has been lost
- if the hepatic disease results in portal hypertension (see below) and hence congestion of the small intestine, loss of plasma albumin into the bowel lumen can contribute to hypoalbuminaemia

- if the serum albumin concentration falls below 10-15 g/L, water begins to leave the circulation due to decreased plasma oncotic pressure → generalised oedema
- the oedema fluid is typically a **transudate** (low in protein and nucleated cell count) and therefore grossly resembles water
- only chronic hepatic dysfunction, protein-losing nephropathy, protein-losing enteropathy and chronic protein malnutrition are likely to cause severe hypoalbuminaemia (< 20 g/L) in domestic animals

- in most animals with chronic liver disease, serum [albumin] usually exceeds the 10-15 g/L threshold for generalised oedema formation
- hypoalbuminaemia is therefore **NOT** usually the cause of ascites of chronic liver disease (although it may contribute to it)

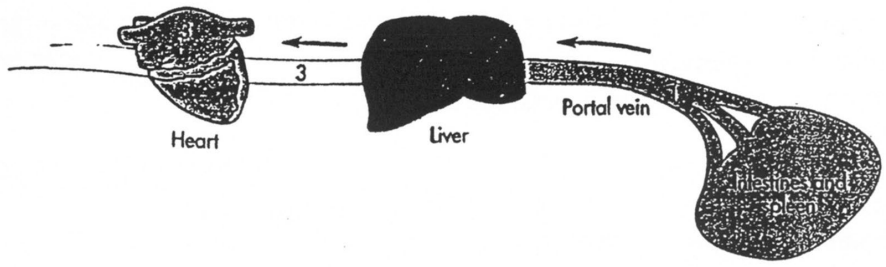
Ascites

- ascites (accumulation of non-inflammatory oedema fluid in the abdominal cavity) associated with hepatoportal pathology develops most commonly in **cats** and **dogs**, occasionally in sheep and rarely in horses and cattle

- the abdominal effusion may be due to **pre-hepatic**, **hepatic** or **post-hepatic** mechanisms (Figure 2)

- **pre-hepatic mechanisms** include any conditions that lead to **portal hypertension** (increased pressure within the portal vein)
- e.g. external compression of the portal vein by a space-occupying mass in the abdominal cavity
- e.g. hepatic diseases with inflammation, fibrosis or neoplastic infiltration of the portal areas and periportal parenchyma; these processes lead to resistance to inflow of portal venous blood
- in portal hypertension, venous blood pools in the veins, venules and capillary beds of the stomach, intestines, spleen, pancreas and mesenteries = **passive congestion**
- the increased blood volume trapped in the microcirculation of these viscera → increased plasma hydrostatic pressure → transudation of low protein fluid from capillaries into the bowel lumen and from other capillaries into the abdominal cavity
- in portal hypertension, the abdominal effusion is typically a **transudate** (low protein, low nucleated cell count)

Figure 2



Mechanisms of abdominal fluid accumulation associated with altered portal and hepatic blood flow. *1*, Prehepatic: arteriovenous fistula or portal vein obstruction; *2a*, hepatic: periportal fibrosis; *2b*, hepatic: sinusoidal cellular infiltrates; *3*, posthepatic: obstruction of hepatic veins or caudal vena cava or right-sided heart failure or pericardial disease (passive congestion). Arrow indicates direction of venous blood flow.

Reference: "Essentials of Small Animal Internal Medicine" - R.W. Nelson and C.G. Couto, 2nd ed., Mosby-Year Book, Inc., St. Louis, 1998

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- the **most common mechanism responsible for ascites in domestic animals = increased hydrostatic pressure in the perisinusoidal space** (the space of Disse) → increased hepatic lymph formation
- e.g. **post-hepatic mechanisms** such as right-sided heart failure, pericardial disease, obstruction of the thoracic caudal vena cava or hepatic veins (i.e. anything that impairs venous outflow from the liver)
- e.g. any process that causes **increased resistance to blood flow through the hepatic sinusoids** (e.g. hepatic parenchymal inflammation, neoplasia, fibrosis or cirrhosis)
- hepatic lymph formation may exceed the drainage capacity of the thoracic duct → leakage of protein-rich lymph from the hepatic capsule and ligaments into the abdominal cavity
- the peritoneal effusion which results from increased pressure in the perisinusoidal space is typically a **modified transudate** with an elevated protein concentration
- this is because hepatic lymph contains the numerous proteins that the hepatocytes normally produce (including fibrinogen)

- **irrespective of the mechanism responsible for ascites**, the kidneys respond to perceived hypovolaemia (low blood volume) by retaining sodium and water, further compounding the ascites

POLYURIA/POLYDIPSIA

- **polyuria** (increased urine volume) and **polydipsia** (increased water consumption) can be a manifestation of severe hepatic dysfunction, especially in **dogs**
- pathogenesis of PU/PD in hepatic disease is multifactorial
- factors which may contribute include:

    - an altered sense of thirst associated with hepatic encephalopathy
    - secondary hyperaldosteronism (including delayed hepatic degradation of aldosterone)
    - delayed hepatic degradation of cortisol
    - persistent hypokalaemia (due to metabolic alkalosis)
    - altered function of portal vein osmoreceptors.

ACHOLIC FAECES

- only a small amount of bile pigment is needed to be converted by intestinal bacteria to **stercobilin** to yield the normal brown colour of faeces
- bile flow must be completely interrupted (e.g. complete extrahepatic bile duct obstruction or transection of the bile duct) to result in acholic (cream or white) faeces
- **steatorrhoea** (due to absence of bile salts required for fat digestion) and interruption of enterohepatic cycling of dietary chlorophyll pigments in herbivores may contribute to the faecal pallor

HAEMORRHAGE AND THROMBOSIS

- **most of the blood coagulation (clotting) factors are synthesised by the liver**
- therefore, advanced liver disease may cause an inability to rapidly seal damaged blood vessels by blood clot formation (**haemostasis**) → **severe haemorrhage**
- although spontaneous haemorrhage due to clotting factor deficiencies is uncommon in hepatic failure, it is routine to run laboratory tests of coagulation function in small animals with suspected liver disease to check for subclinical impairment of haemostasis (especially if you plan to take a liver biopsy!)

- in **complete extrahepatic bile duct obstruction**, inability to absorb fat-soluble vitamin K from the gastrointestinal tract may lead to inactivity of the vitamin K-dependent clotting factors (factors II, VII, IX and X) → **severe haemorrhage**

- conversely, the **liver is the source of most of the anti-coagulant factors in blood** (these are responsible for preventing the circulating blood from clotting)
- the most important of the circulating anti-coagulant factors is **antithrombin III**
- in chronic hepatic disease, the plasma concentration of antithrombin III may decline → predisposition to **thrombosis** (inappropriate intravascular clotting of the blood)

- the enormous sinusoidal vascular bed of the liver means that severe multifocal or diffuse hepatic parenchymal injury will inevitably result in widespread vascular endothelial injury
- this may trigger a potentially fatal condition known as **disseminated intravascular coagulation** (**DIC**), in which widespread thrombosis occurs in the microcirculation (arterioles, capillaries and

venules)

- occasionally see gastroduodenal haemorrhage in hepatobiliary disease (especially in cats and dogs) due to **portal hypertension** and hence congestion of the capillary beds of the gastrointestinal tract

HEPATORENAL SYNDROME

- **acute renal failure** may develop in animals with cirrhosis and ascites
- the renal failure is reversible if the liver function can be improved

- originally ascribed to a putative toxic effect of conjugated bilirubin (which is freely filtered by the renal glomeruli) on renal tubular epithelial cells and hence called **bilurubinuric nephrosis** (or **cholaemic nephrosis**) (nephrosis = degeneration or necrosis of renal tubular epithelium)

- the pathogenesis of hepatorenal syndrome is still incompletely understood but now recognised that **bilirubin is not toxic *per se*** and that the tubular epithelial degeneration/necrosis is really referable to **decreased renal perfusion** (e.g. reduced effective circulating blood volume due to ascites and the diuretic effect of bilirubin; e.g. renal arteriolar vasoconstriction in response to low blood volume and/or pressure)

- in so-called **bilirubinuric nephrosis**, the kidneys are grossly swollen, wet and discoloured orange-yellow or green

AMMONIUM BIURATE CRYSTALLURIA

- dogs with portosystemic shunts or hepatic failure develop **hyperammonaemia** (increased blood ammonia concentration) and hence **hyperammonuria** (increased urine concentration of ammonium ions)
- supersaturation of the urine with ammonium ions promotes formation of **ammonium biurate** (“thorny apple” or “mite”) **crystals**, especially in alkaline urine

MISCELLANEOUS FINDINGS IN LIVER FAILURE

- **drug intolerance** - impaired hepatic biotransformation of administered drugs

- **abnormalities in carbohydrate metabolism** – e.g. prolonged post-prandial hyperglycaemia and hypoglycaemia during fasting periods

- **foetor hepaticus** = a “musty” or “sweet and sour” odour due to retention in circulation of mercaptans (produced in the gastrointestinal tract by bacterial metabolism of methionine)
  - more important in humans than domestic animals

- **impaired hepatic uptake, conjugation and excretion of steroid hormones**
  - can lead to hyperoestrogenism in males with testicular atrophy/degeneration, gynaecomastia (enlargement of mammary glands) and other abnormal secondary sex characteristics

- more important in humans than in domestic animals

- **hepatocutaneous syndrome** (= **superficial necrolytic dermatitis**)
  - especially **dogs**
  - abnormal skin keratinisation → hyperkeratosis and crusting +/- erosion of especially high friction areas (e.g. muzzle and footpads) due to altered plasma amino acid concentrations