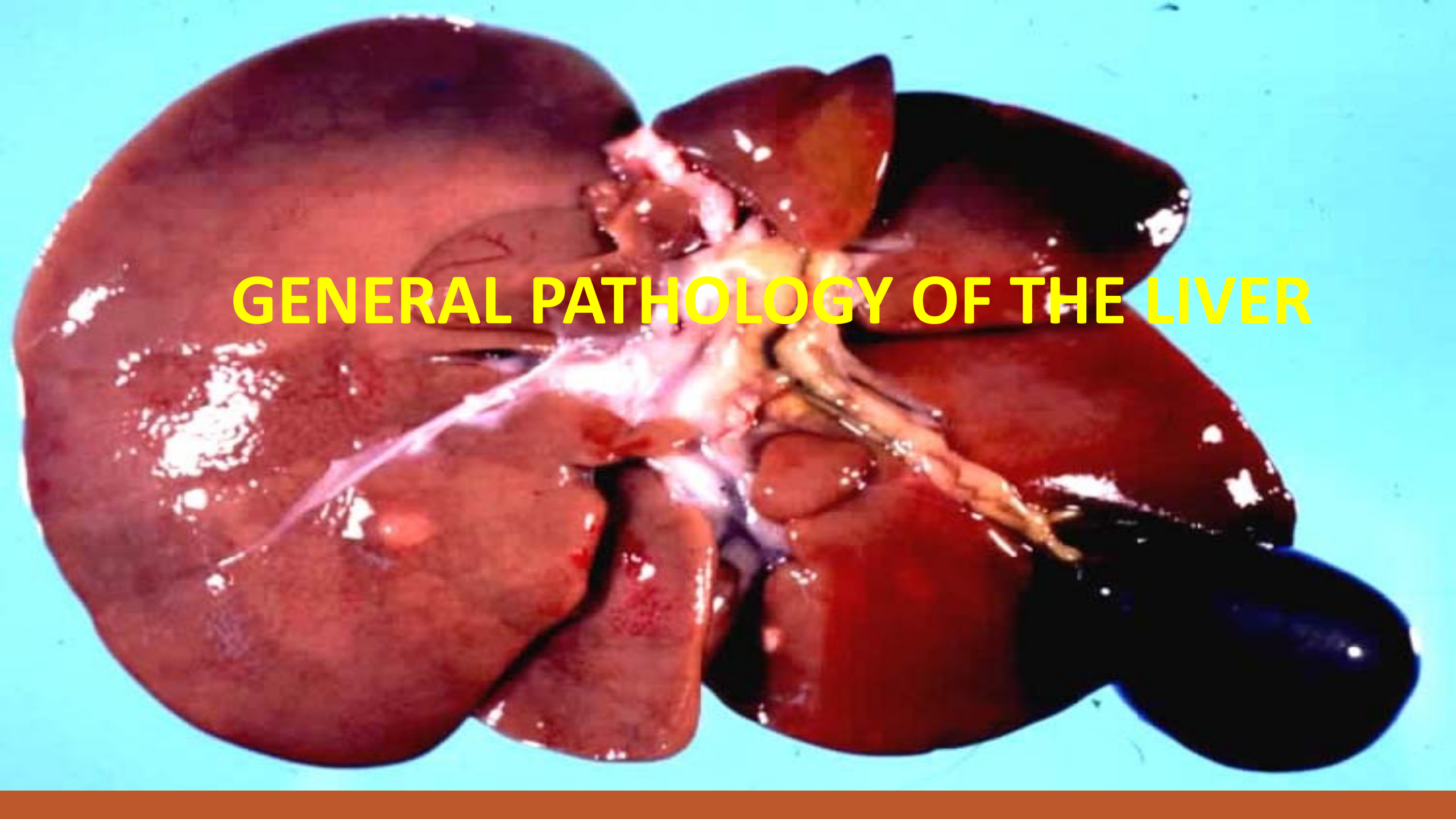
GENERAL PATHOLOGY OF THE LIVER

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Hepatic failure

Implies exhaustion of the large functional reserve and regenerative capacity of the liver

Has implications for many other tissues

May be acute from sudden massive hepatic damage or, more commonly, as an end-stage of chronic liver disease

Cholestasis

Impedance of bile outflow, leading to jaundice (icterus) from excess bile pigments

Divided into prehepatic (in haemolytic disease), hepatic (impaired uptake, metabolism, secretion and transport within liver) and posthepatic (obstruction of bile ducts or gallbladder)

Photosensitisation

Inflammation of non-pigmented skin due to the action of UV light on dermal-bound photodynamic compounds.

Primary from ingestion of photodynamic agents or hepatogenous (especially with cholestasis in ruminants consuming green feed). Photoactive phytoporphrins are metabolites of chlorophyll produced by intestinal microflora in herbivores. Retention of phytoporphrins with cholestasis leads to an increase in blood and eventually photosensitisation

PHOTOSENSITISATION

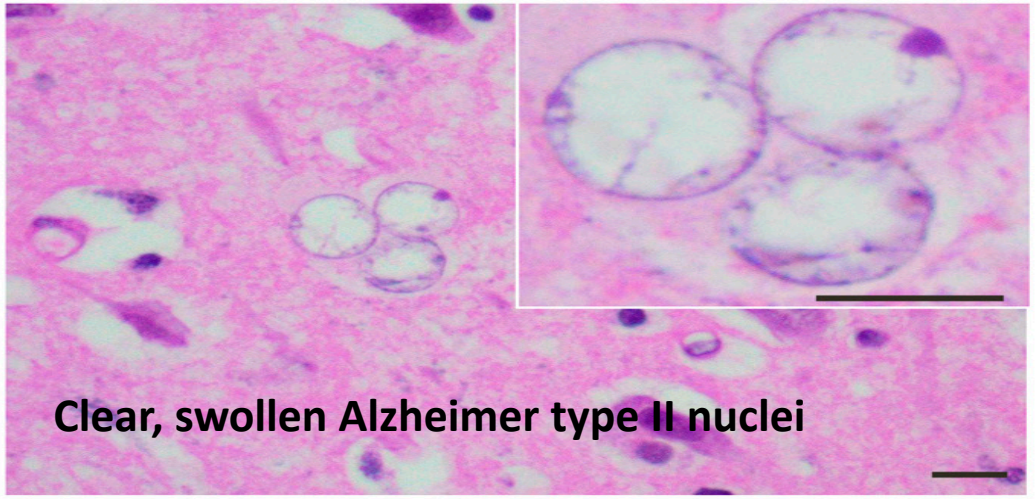
Hepatic encephalopathy

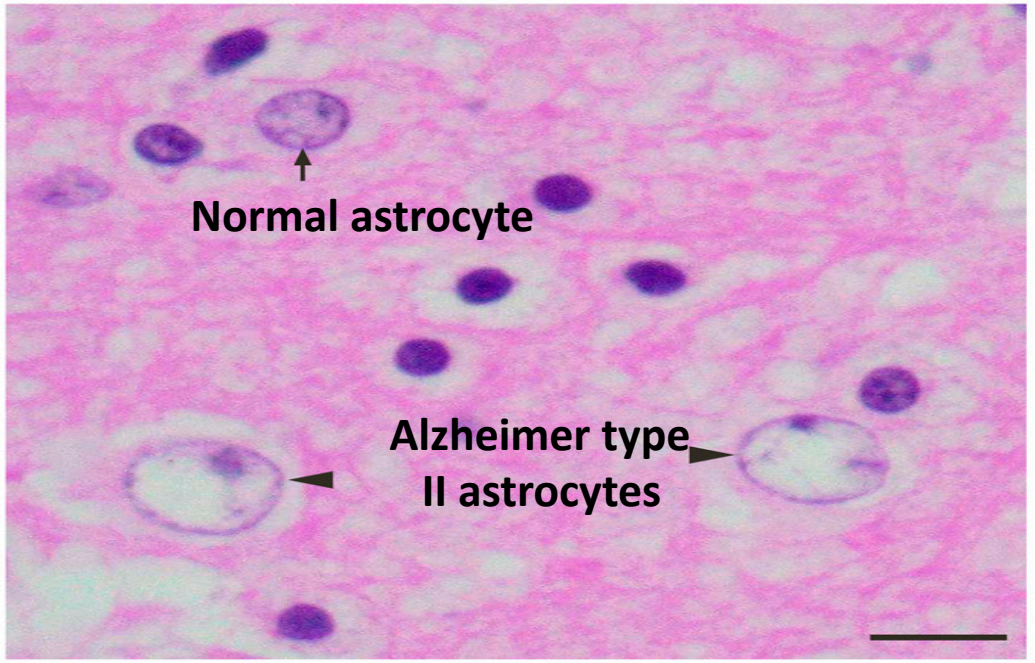
Neurological disorder with an often fatal outcome, largely due to (but also many other noxious compounds probably contributing) hyperammonaemia

Ammonia produced in the gut is normally removed from portal blood by the liver. In severe hepatic disease (or shunting), excess ammonia in circulation crosses the blood-brain barrier (BBB) and overwhelms the ability of astrocytes to break it down to glutamine

Hepatic encephalopathy

Increased glutamine causes Alzheimer type II astrocyte formation (clear, swollen, naked nuclei) and spongiosis of myelinated tracts (intramyelinic oedema)





ALZHEIMER TYPE II ASTROCYTES IN HEPATIC ENCEPHALOPATHY

Haemorrhagic diathesis

Acute liver disease can deplete the production of plasma proteins involved in the clotting cascade and

Cause excessive consumption of clotting factors (consumption coagulopathy) and

A tendency to haemorrhage

Hepatorenal syndrome

Reduced systemic blood volume from liver disease can cause compensatory renal vasoconstriction, oliguria and even renal failure

Ascites

Excess fluid in abdominal cavity

Possibly due to altered blood flow through liver from fibrosis and nodular regeneration

Autolysis

Very rapid in the liver as it is rich in nutrients and is exposed to agonal and post-mortem invasion by bacteria (especially clostridia) in the portal circulation from the intestine

Circulatory diseases of liver

Liver can receive ~25% of cardiac output and ~25% of liver weight is blood

Hepatic artery: 1/3 of afferent blood supply to liver and obstruction can cause infarction, the severity depending on the collateral circulation that develops

Portal vein: blood flow streamed in some species, with that from the stomach and duodenum going to left lobes and that from jejunum and ileum to right lobes, thus determining the location of metastatic tumours and infections

Circulatory diseases of liver

Umbilical vein blood favours the left liver lobes, so umbilical infections tend to localise there

Liver cannot regulate portal blood flow, so hepatic artery flow is increased or decreased in response to portal flows

Obstruction of the portal vein causes rapid death, with large branch occlusion causing infarction and, small branches, necrosis of a variable number of acini

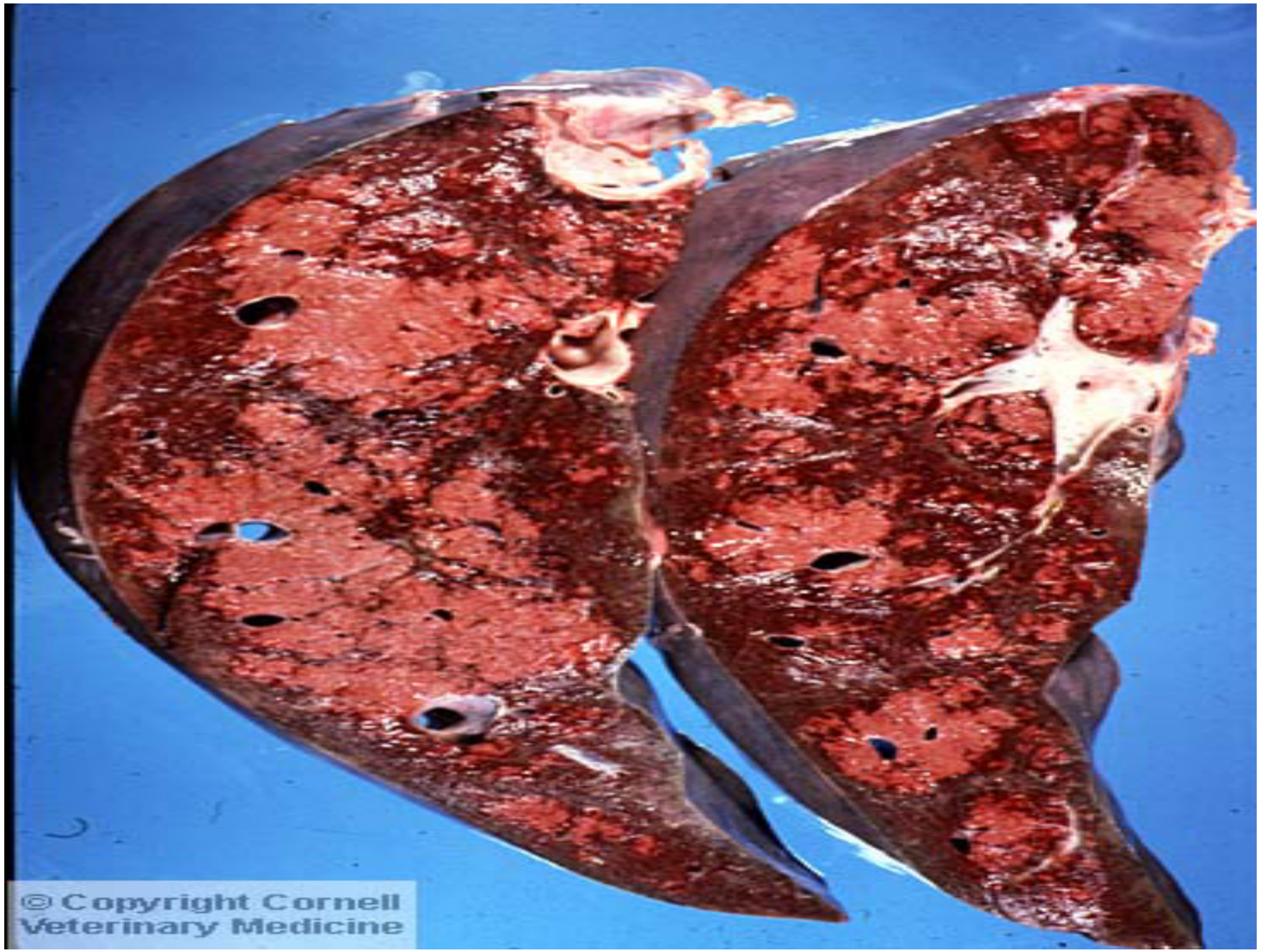
Acute hepatocyte necrosis often causes sinusoidal compression and thrombosis and portal fibrosis with chronic disease sometimes results in portal hypertension

Hepatic congestion

Most commonly due to cardiac failure

Acute – liver swollen, dark and bloody on section with sinusoidal engorgement, fatty change, atrophy of hepatic cords and hypoxic necrosis of periacinar hepatocytes

Chronic – produces a "nutmeg liver" from contrasting red periacinar zones (loss of hepatocytes and resulting sinusoidal dilatation) and yellow periportal zones (fatty change of hepatocytes)

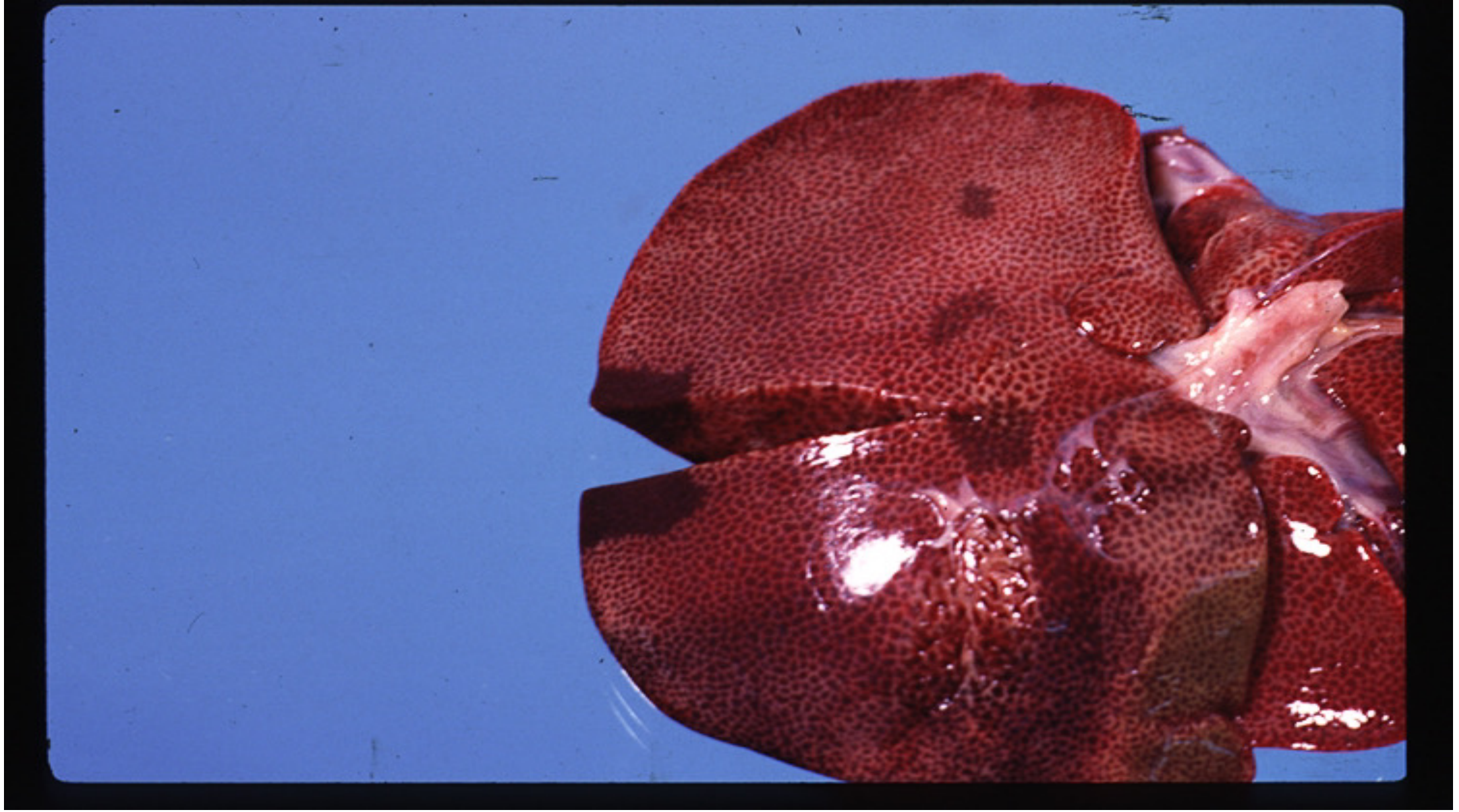


“Nutmeg liver” – mottled pale and dark (congested) areas

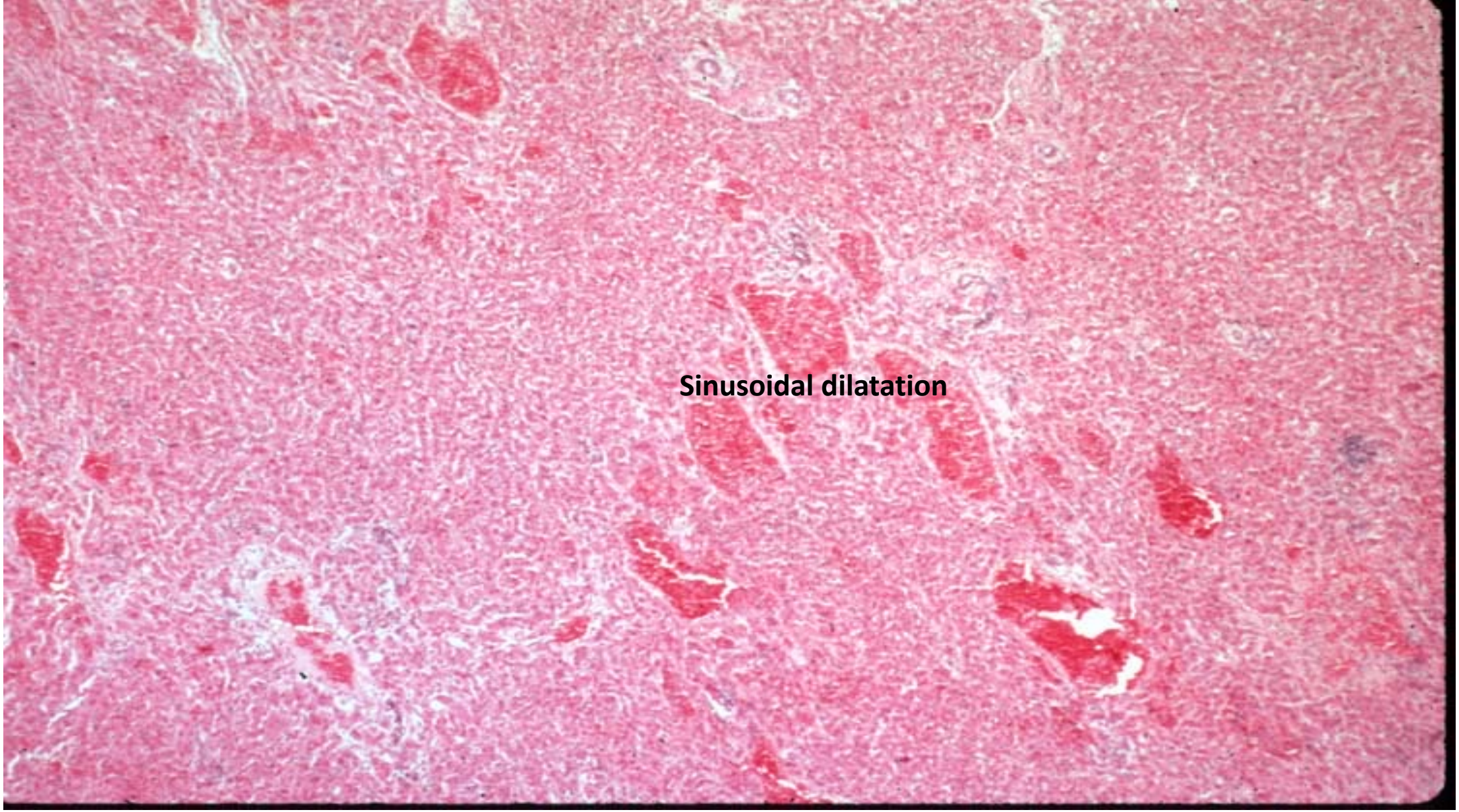
Telangiectasis

Cavernous dilatation (ectasia) of sinusoids visible grossly as dark red, well-circumscribed foci of varying size

Functionally insignificant



Telangiectasis – dark red areas representing marked sinusoidal dilatation



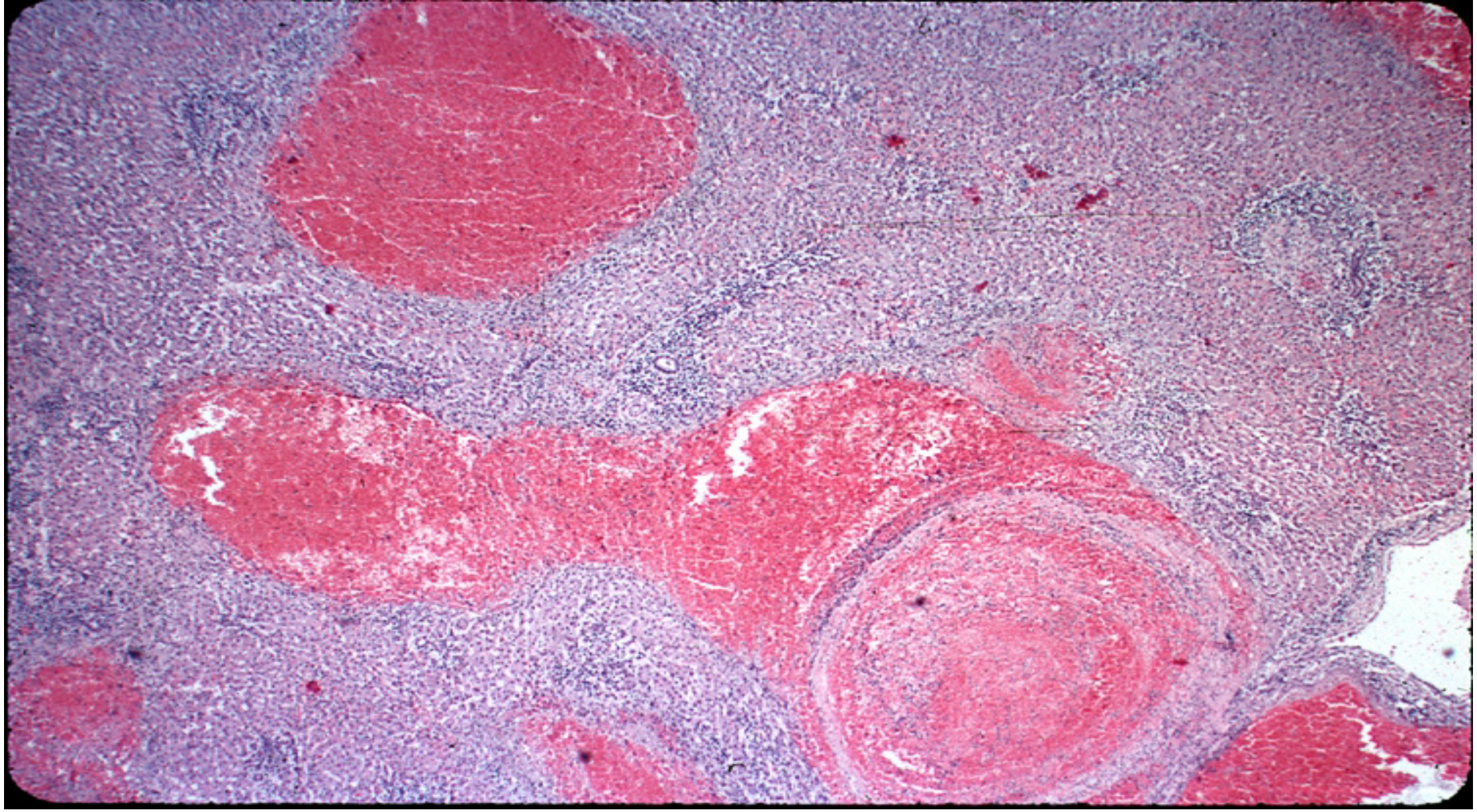
Telangiectasis – marked sinusoidal dilatation

Peliosis hepatis

Formation of large, cystic, blood-filled spaces

Usually of uncertain cause

Ultimately, in severe cases, the liver can resemble a large, blood-filled sponge



Peliosis hepatis – marked, blood-filled, sinusoidal dilatation

Hepatic inflammation

Differs from that in other tissues because:

Unlike capillaries, fenestrated sinusoids are normally permeable to plasma proteins so there is little osmotic oedema from unusual leakage of fluid and sinusoids are less responsive to vasoactive compounds

Kupffer cells can release large amounts of pro-inflammatory cytokines and can more effectively deal with potentially inflammatory insults

Hepatic inflammation

Liver produces most of the plasma proteins with anti-inflammatory properties and Kupffer cells clear immune complexes from the circulation and facilitate immunotolerance to antigens absorbed from the intestine

Kupffer cells are a major factor in acute hepatic inflammation due to their release of cytokines and active phagocytic ability

Hepatitis

Multifocal hepatitis is common and usually clinically silent, being mainly an incidental finding in response to intestinal bacteria arriving in portal blood

But **acute focal hepatitis** with intense leucocytic and Kupffer cell reaction can be diagnostically important

Hepatitis

Acute focal hepatitis does not usually progress to fibrosis and cirrhosis unless the inflammation and resulting damage is prolonged, e.g. immune-mediated

Chronic hepatitis is relatively common in domestic animals, especially dogs, but is usually idiopathic

Cholecystitis

Cholecystitis is uncommon, but believed to be due to reflux of intestinal bacteria into the gallbladder via bile ducts or haematogenously from the adjacent hepatic circulation

Extension to periportal hepatocytes from inflamed bile ducts is almost inevitable (cholangiohepatitis)

Cholelithiasis (gallstones) is rare in animals, unlike humans

VIRAL HEPATITIS

Examples:

Human viral hepatitis

Infectious canine hepatitis

Human viral hepatitis

Most commonly caused by hepatitis A virus (picornavirus), hepatitis B virus (hepadnavirus) and hepatitis C virus (hepacivirus)

All can cause acute diseases with symptoms of nausea, abdominal pain, fatigue, malaise and jaundice

Types B and C can also lead to chronic infection with the development of cirrhosis and hepatocellular carcinoma

Chronic hepatitis carriers remain infectious and may transmit the disease for years

Infectious canine hepatitis

Canine adenovirus-1 (CAdV-1) has a special tropism for endothelium, mesothelium and hepatic parenchyma

This tropism is manifest as oedema, serosal haemorrhages and hepatic necrosis

Large, intranuclear inclusion bodies found in endothelium and hepatocytes are deeply acidophilic with a blue tint

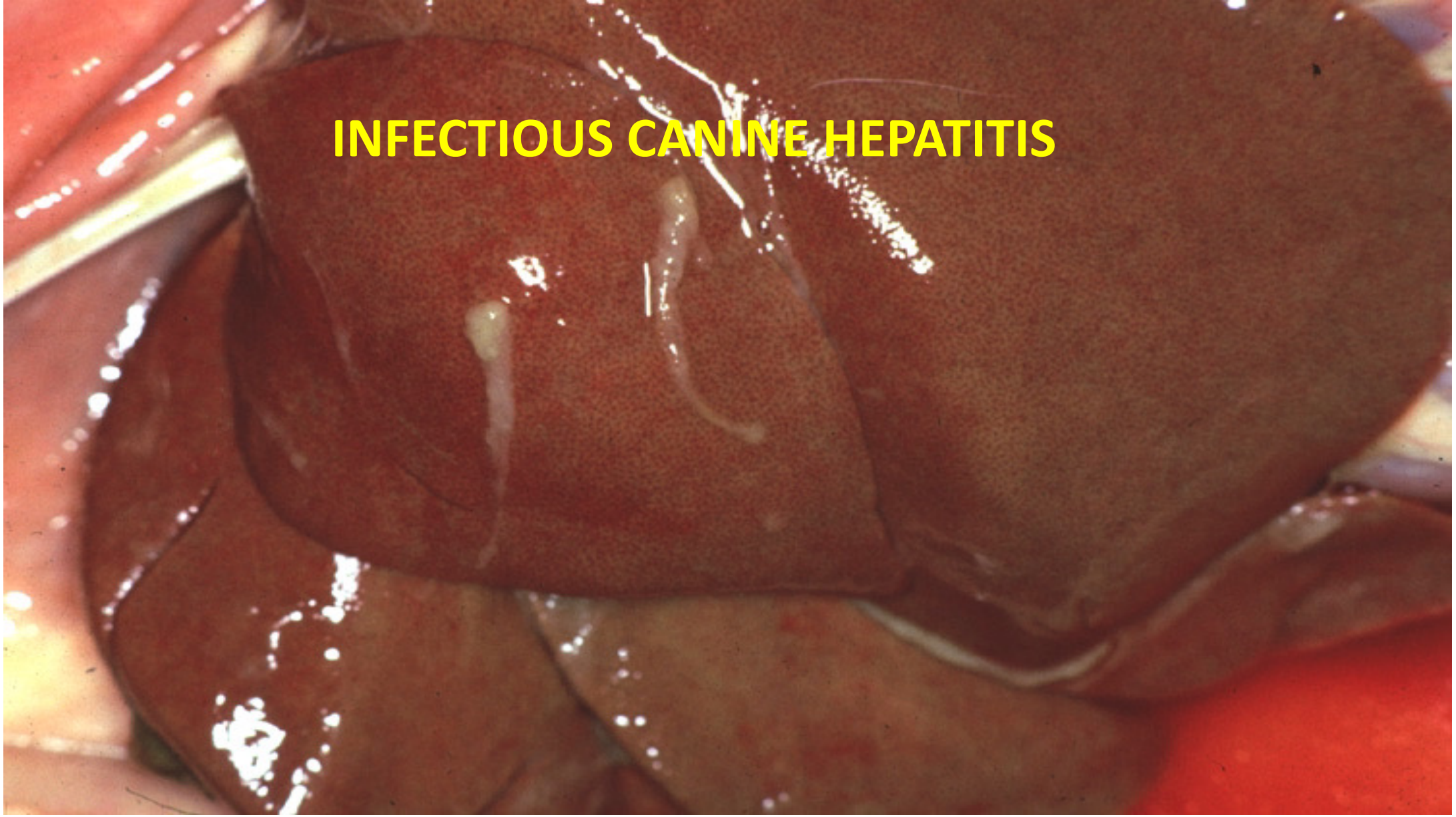
Infectious canine hepatitis

At autopsy, enlarged, friable liver with uniform yellow mottling

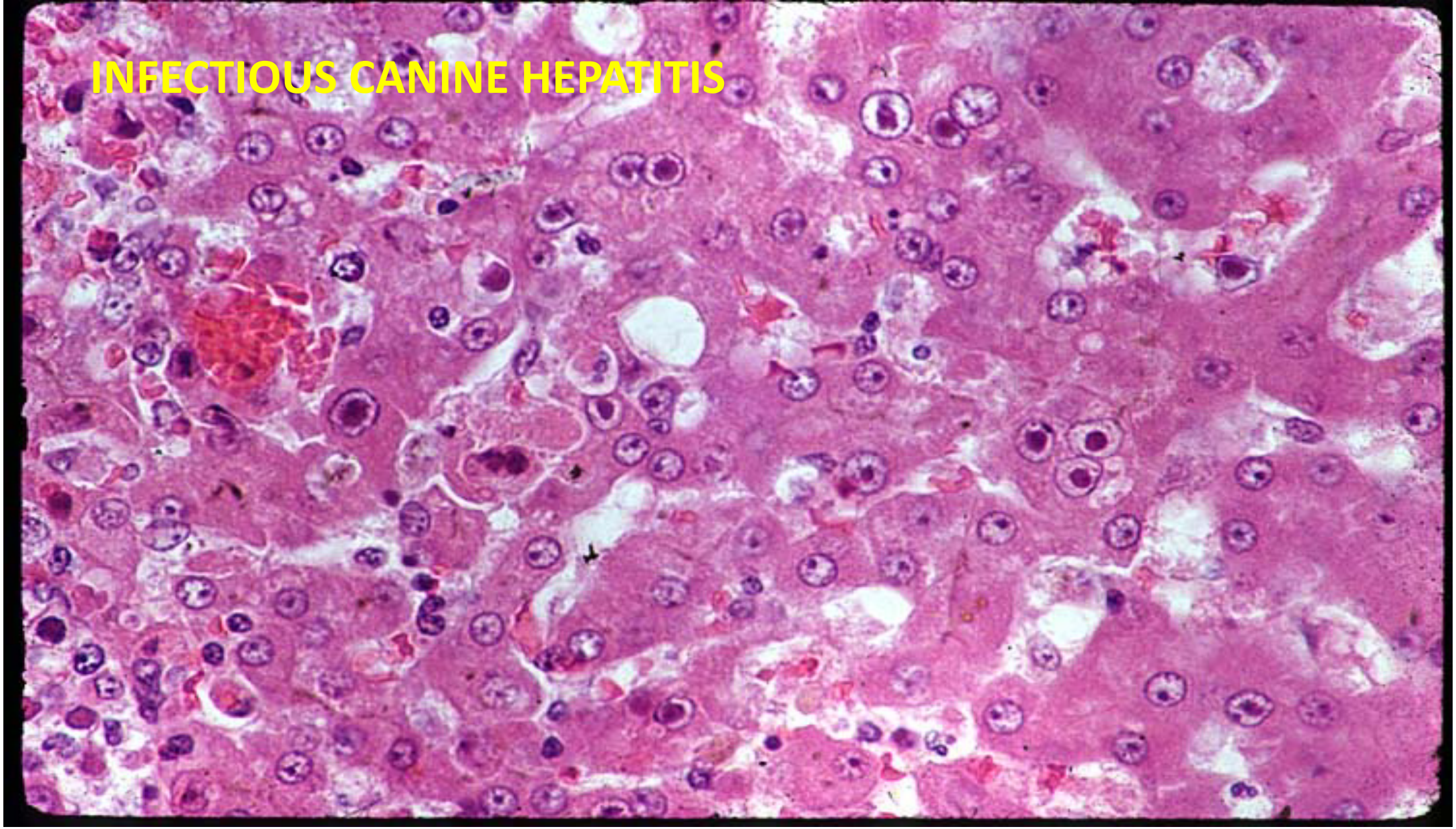
Histologically, periacinar necrosis and loss of hepatocytes with secondary sinusoidal dilatation and engorgement with blood, inclusion bodies in hepatocytes, Kupffer cells and many endothelia

In recovered cases, restitution of the liver can be almost complete because the reticulin framework (scaffolding) remains intact

INFECTIOUS CANINE HEPATITIS



Enlarged liver (hepatomegaly) with yellowish stippling and capsular fibrin tags



Intranuclear viral inclusion bodies in hepatocytes with margination of nuclear chromatin

Bacterial hepatitis

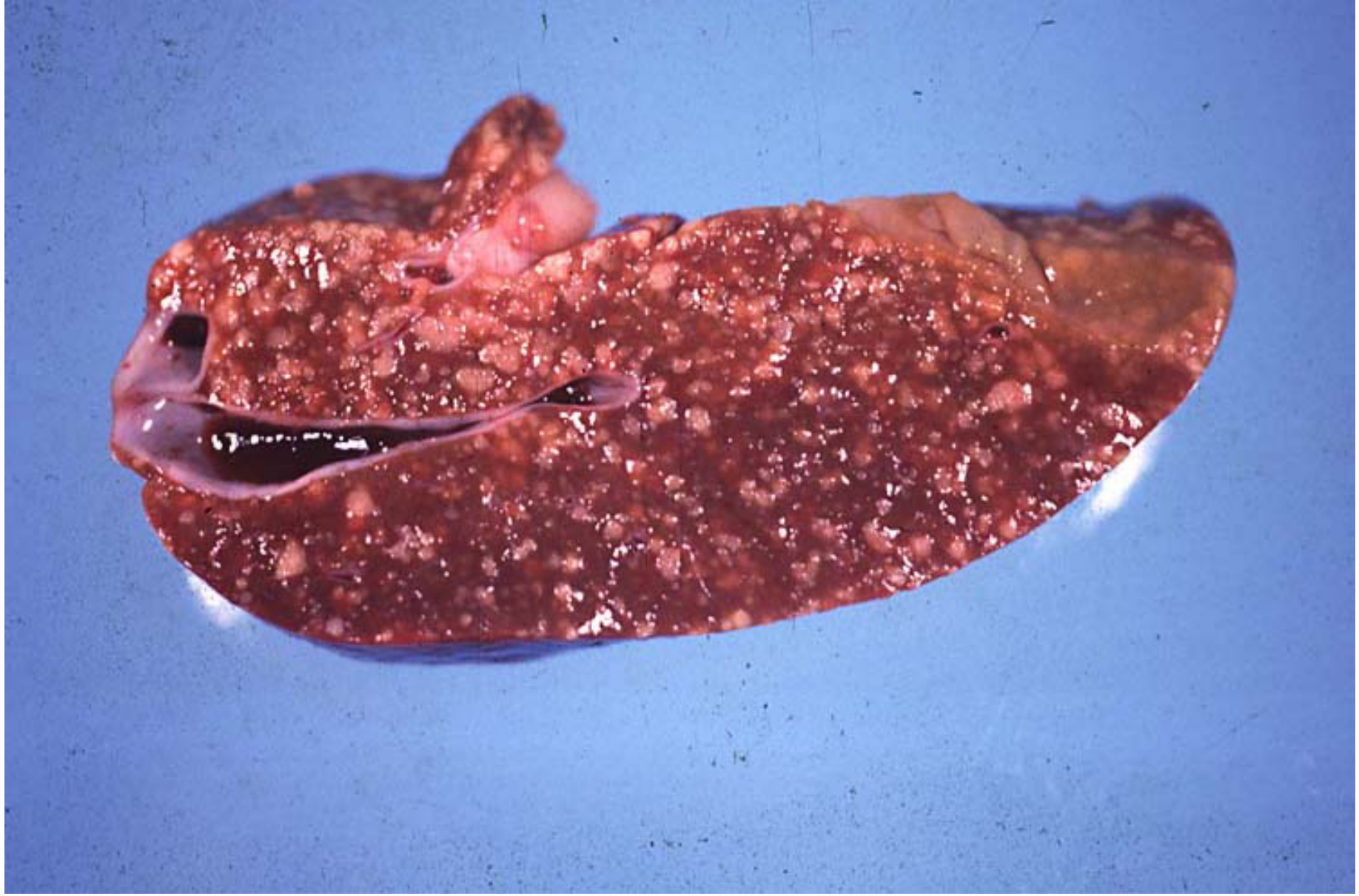
Common, but usually focal (or multifocal) and of scant clinical significance

Bacteria gain entry to the liver by direct implantation, extension from peritonitis, haematogenously, or via bile ducts

Most bacterial infections causing a sustained or repeated bacteraemia produce focal hepatic lesions

Hepatic abscess

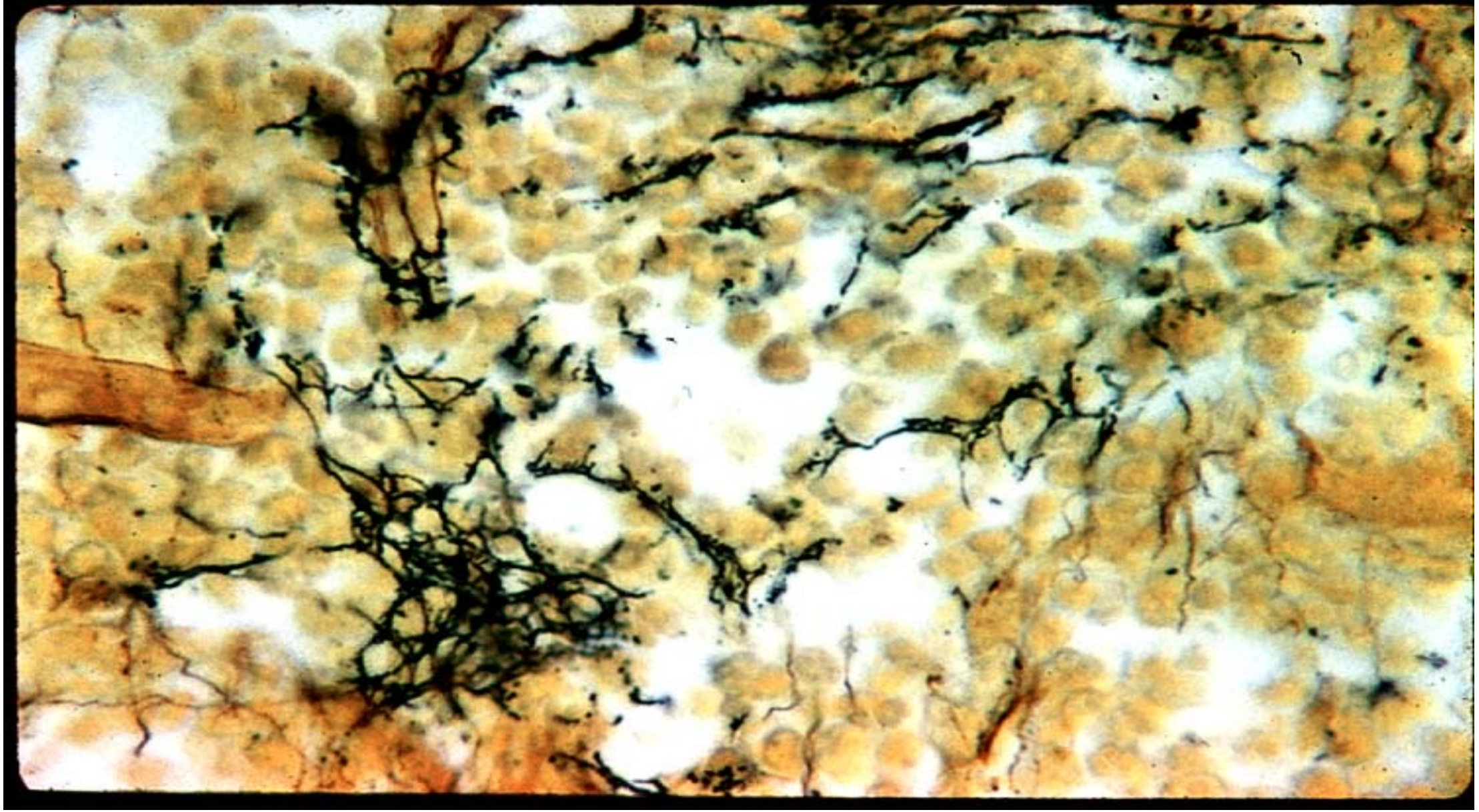
Usually asymptomatic but, if multiple, can cause death from toxaemia and generalised systemic infection



MULTIPLE HEPATIC ABSCESSES

Leptospirosis

Can cause dissociation of hepatocytes, leading to cholestasis and clinical jaundice



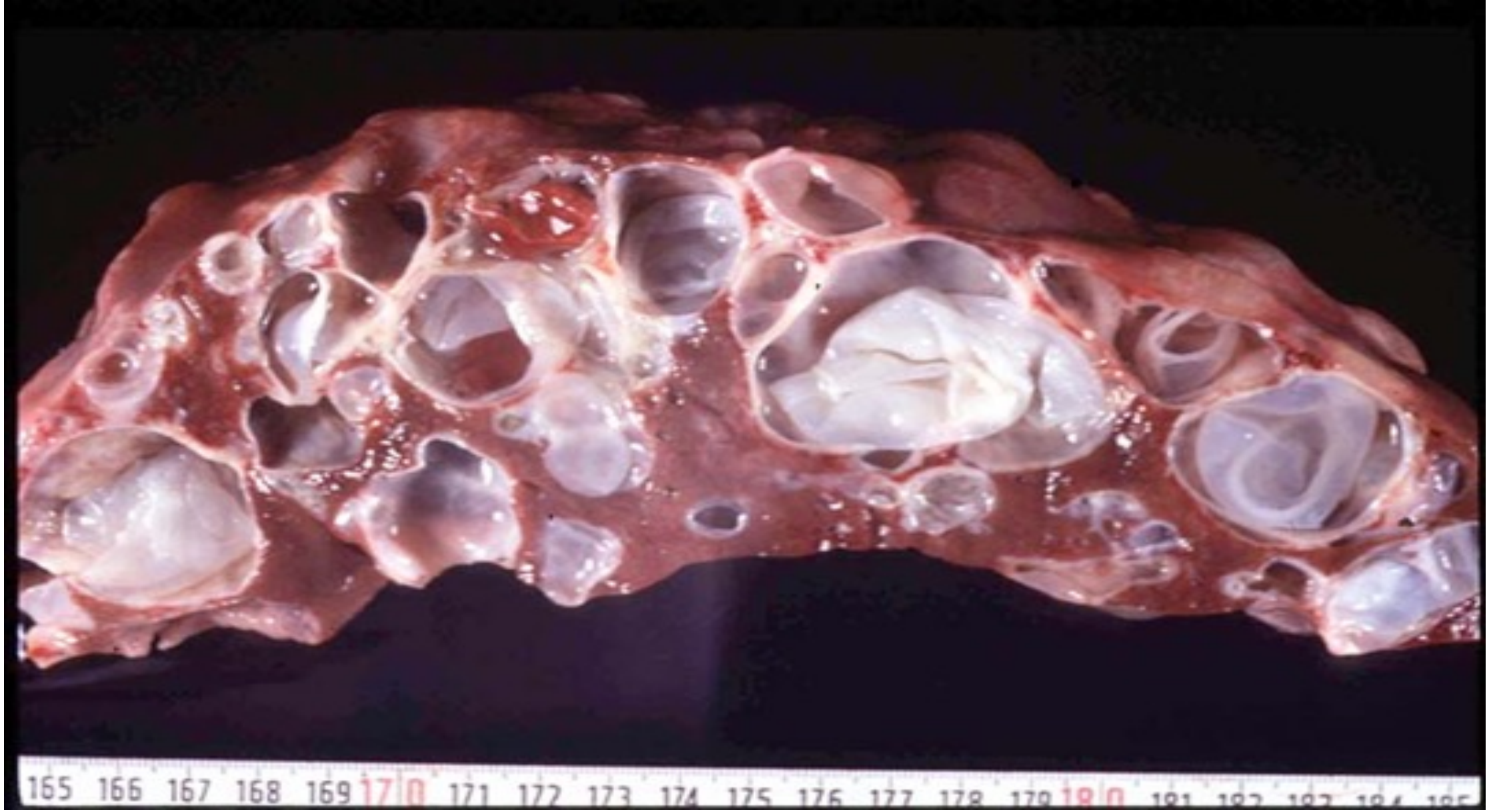
Leptospires demonstrated by silver staining

Parasitic infection

Echinococcus granulosus (hydatid cysts)

In ruminants and humans

MULTIPLE HYDATID CYSTS



MULTIPLE HYDATID CYSTS

Toxic hepatopathies

Mycotoxic (fungal): alflatoxin as an example

Phytogenous (plant-associated): pyrrolizidine alkaloids as an example

Drug-induced (adverse drug reactions)

Metals: copper and iron dextran as examples

Toxic hepatopathies

Hepatocytes are the major site of metabolism of endogenous substances and xenobiotics (ingested foreign chemicals and drugs) and are especially vulnerable to toxic injury because they are exposed to virtually everything that is absorbed

Most xenobiotics are unable to directly enter hepatocytes and require specific transporters to pass through the hepatocyte plasma membrane

Some metabolites may cause hepatocellular injury and others may produce biliary injury when transported in canaliculi

Toxic hepatopathies

Some drug metabolites may be reabsorbed into the enterohepatic circulation resembling the route of bile acids, facilitating repeat exposure of hepatocytes to the drug

Compounds that are hepatotoxic after metabolism tend to be fat-soluble rather than water-soluble and many of the biotransformations are directed to rendering lipophilic substances more water-soluble so as to increase their renal clearance rate in urine

Hepatic enzymatic biotransformation occurs in 3 phases

Phase I reactions are mainly conducted by cytochrome P450 (mixed function oxidase system) in hepatocyte smooth endoplasmic reticulum (SER). Usually involve the addition of oxygen and removal of hydrogen. Important for permitting further detoxification but, in the process, toxic intermediates can sometimes be produced

Highest concentration of cytochrome P450 is in periacinar hepatocytes, which are thus sometimes injured in the detoxification process. Periportal hepatocytes more susceptible to direct-acting toxins such as metals

Toxic hepatopathies

Phase II reaction enzymes are generally located in the cytosol. Typically conjugation reactions. Glutathione and Se/vitamin E help cell membranes cope with toxic free radicals. Hence, livers deficient in these factors are more susceptible to hepatotoxins

In phase III reactions, conjugated molecules are transported across hepatocyte membrane that lines the canaliculus

Toxic hepatopathies

Paradoxically, although the liver has a central role in detoxification and excretion of xenobiotics, it my be severely damaged when other tissues remain unscathed

In an attempt to transform these toxins into excretable metabolites, the liver may convert them into intermediate reactive radicals (which are usually unstable and short-lived and thus damage the cytoplasm of the cell in which they are produced) that are more toxic than the parent compound

Toxic hepatopathies

The outcome of naturally occurring exposure to hepatotoxins is unpredictable

Nutritional status can affect susceptibility – enzymic activity reduction with starvation may be protective and reduced hepatic glycogen may increase vulnerability

Acute hepatotoxic injury

Cytotoxic – damage to hepatocytes manifest as necrosis/apoptosis, steatosis (impaired triglyceride movement through liver, interference with VLDL synthesis or transport, or impaired hepatic usage of fatty acids from mitochondrial dysfunction) or haemorrhage when sinusoidal endothelium damaged

Cholestatic – injury to components essential for bile flow

Acute hepatotoxic injury

Usually periacinar necrosis – rarely mid-zonal or periportal

Clinically, dullness, anorexia and neurological disturbance with convulsions due to hepatic encephalopathy

When fatal, usually widespread haemorrhage due to lack of coagulation factors (lack of production and excessive consumption in liver)

Chronic hepatotoxic injury

Chronic inflammation, steatosis, fibrosis, nodular regeneration, atrophy and potential carcinogenesis

Clinically, jaundice, photosensitisation and hepatic encephalopathy, due to inadequate detoxification and excretion

Hepatotoxic agents

Very wide range of hepatotoxic agents, including metals (Fe, Cu), drugs, plant compounds (phytotoxins), fungal metabolites (mycotoxins), bacterial products (e.g. cyanobacterial microcystin) and industrial products (especially aromatic solvents)

Mycotoxic hepatopathy- aflatoxins

Produced by *Aspergillus* and *Penicillium* spp fungi, especially aflatoxin B1

Fungal strains differ in the quantity of toxin they produce, which is genetically determined, and production varies under different conditions of fungal growth (substrate concentration, temperature, and moisture)

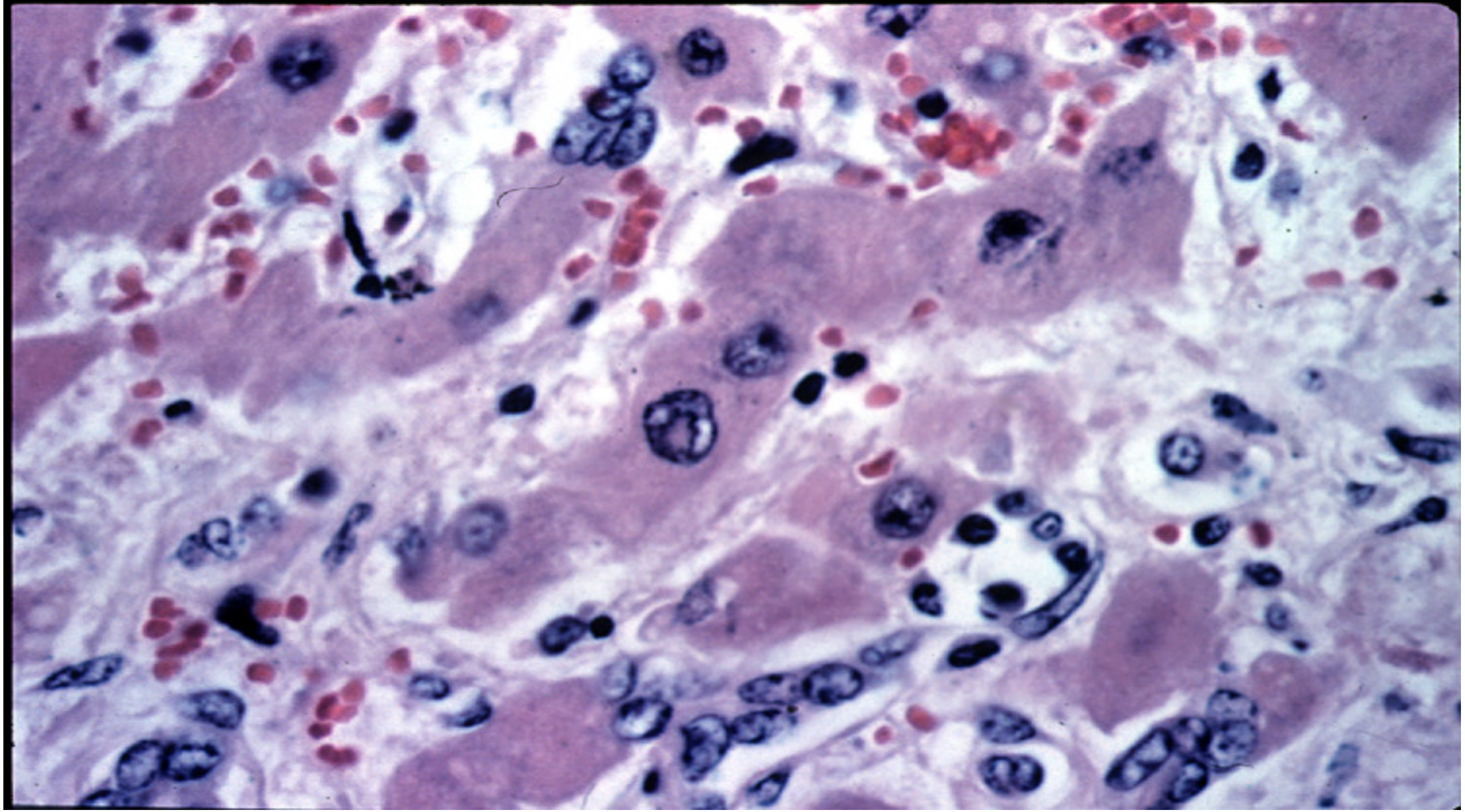
Toxicity occurs especially with stored or unharvested mature grain, particularly if damaged by moisture

Aflatoxins

Aflatoxins are metabolised by the hepatic mixed function oxidative system to toxic metabolites

Sheep and cattle are quite resistant, but dogs, pigs and calves are sensitive

Microscopically, initially hepatocyte enlargement due to SER hypertrophy and fatty change, then increased nuclear (karyomegaly) and cytoplasmic (megalocytosis) size, hepatocyte necrosis/apoptosis, bile ductule hyperplasia, bile stasis and fibrosis



Aflatoxicosis – megalocytosis (enlarged hepatocytes) and karyomegaly (enlarged nuclei)

Aflatoxins

Aflatoxins are carcinogens

Sometimes high toxin doses cause acute, fulminating, massive hepatocyte necrosis in younger dogs

Aflatoxicosis resembles pyrrolizidine alkaloid poisoning as both toxins inhibit hepatocellular regeneration, leading to liver atrophy

Phytogenous hepatopathy – pyrrolizidine alkaloidosis

Majority of phytogeneous hepatopathies in ruminants in Australia are the result of grazing plants containing pyrrolizidine alkaloids

Most commonly *Heliotropium europaeum* (common heliotrope, potato weed) and *Echium plantagineum* (Salvation Jane or Paterson's curse) – widely distributed over mixed wheat-sheep areas of temperate Australia

Also *Senecio* spp, *Amsinckia* spp, *Crotalaria* spp, and *Cynoglossus* spp

Pyrrolizidine alkaloids

PA's must be metabolised to more reactive forms to be hepatotoxic, including by cytochrome P450

These toxins are produced by plants to deter herbivorous grazing and they are unpalatable, therefore unusual for large amounts to be consumed, except under drought conditions

2 main manifestations: (1) acute periacinar necrosis when large amounts ingested (unusual) and (2) hepatic atrophy with fibrosis and regenerative nodule formation after repeated seasonal exposure (most common)

Pyrrolizidine alkaloids

PA's inhibit DNA synthesis and mitosis in hepatocytes

But some hepatocytes can replicate their DNA without undergoing mitosis, producing very large hepatocytes (megalocytosis) with large polyploid nuclei (karyomegaly)

When inhibition is total, DNA is not replicated, but some resistant hepatocytes manage to replicate normally

Megalocytes are long-lived but eventually undergo apoptosis

In chronic poisoning, the liver can become atrophic as hepatocytes are lost faster than they can be replaced

Cyanobacteria (blue-green algae)

Bloom (microcystin-producing *Microcystis aeruginosa* and *Anabaena* sp) on lakes accumulating phosphates and nitrate as runoff from fertilised soils

Can cause high mortality in ruminants

Periacinar to massive hepatocellular necrosis

BLUE-GREEN ALGAL BLOOM

Adverse drug reaction-induced hepatic disease

Due to the liver's role as the primary site of biotransformation of many therapeutic agents

Results in a high concentration of metabolites, which are water-soluble and excreted in bile and urine

Also exposed to high concentrations of orally administered drugs in the portal blood flow, which are then concentrated in the liver

Adverse drug reactions

Intrinsic – dose-related, predictable, reproducible in experimental animals, and mechanism of action known

Idiosyncratic – less dose-related, more unpredictable, occurs in only small proportion of exposed individuals, and mechanism of action often unknown. Reflects an unusual susceptibility of the recipient

Idiosyncratic reactions may be acquired (previous or concurrent exposure to other agents that induce the offending drug-metabolising pathway) or genetic

Idiosyncratic drug reactions can be further subdivided into

Metabolic – excessive generation of a normally mild hepatotoxic metabolite or altered metabolism to unusual hepatotoxic metabolites

Immunological – immune-mediated hypersensitivity responses to drug metabolites

In general, intrinsic hepatotoxins produce zonal necrosis and idiosyncratic hepatoxins cause non-zonal necrosis (diffuse, focal or massive)

Copper hepatotoxicity

Cu levels are regulated by the liver, maintaining a balance between dietary intake and excretion

Sheep are most susceptible due to reduced biliary excretion

Cu hepatotoxicity occurs as an autosomal recessive condition in Bedlington Terriers and a familial hepatopathy in West Highland White Terriers

Vitamin E/Se deficiency predisposes to acute Cu poisoning

Copper hepatotoxicity

In dogs and sheep, toxic amounts of Cu can accumulate in the liver at dietary levels which are not excessive in other species

Chronic Cu poisoning in sheep is due to:

Excess intake

Increased availability when dietary molybdenum is very low (forms complexes with Cu, rendering it biologically inert)

Increased predisposition due to the presence of other hepatotoxins, especially pyrrolizidine alkaloids

Copper hepatotoxicity

- **In sheep, the liver has a great avidity for Cu and a limited biliary excretory capacity**

As Cu levels rise, hepatocyte apoptosis increases, together with a compensatory increase in hepatocyte mitotic rate, but

If hepatocyte loss exceeds the liver's capacity to phagocytose cell debris, Cu is released into the plasma and intravascular haemolysis occurs, the resulting anaemia exacerbating Cu release from damaged, hypoxia-prone periacinar hepatocytes

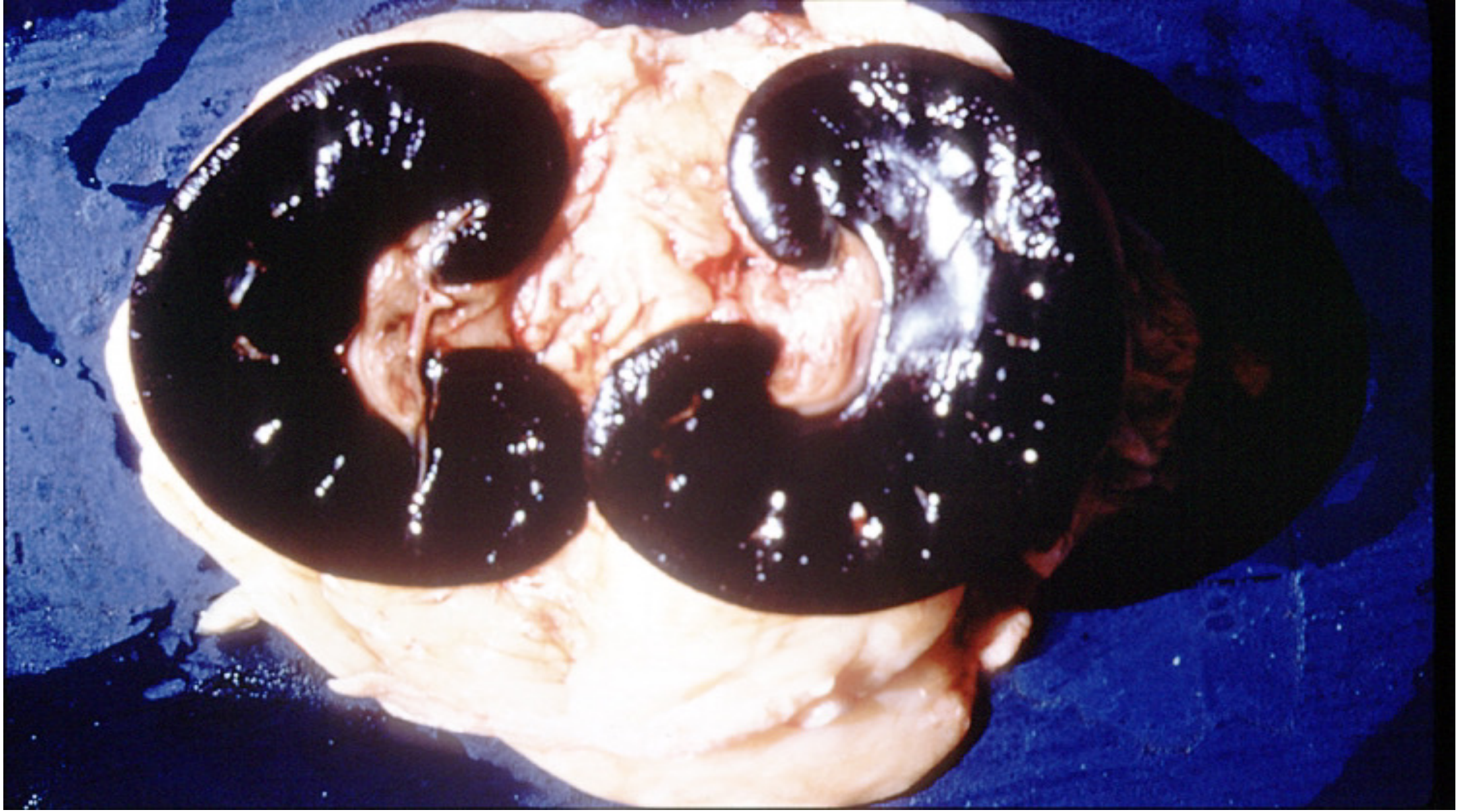
Cu enters the urine and kidney Cu levels rise

Copper hepatotoxicity

At autopsy, the liver is swollen and deep orange in colour (or atrophic/fibrotic if the disease is chronic); kidneys are deep red-brown to black; icterus; and red staining of tissues by free Hb (with some brown staining due to conversion of Hb to MetHb)

Chronic Cu poisoning is also less commonly seen in pigs and cattle

Liver in copper toxicity and haemoglobinuric nephrosis



Copper nephrotoxicity – haemoglobinuric nephrosis

Iron dextran hepatotoxicity

Used for prevention of anaemia in suckling pigs

Rarely, produces massive hepatic necrosis in animals with marginal Se/Vitamin E deficiency and release of large amounts of potassium by liver/muscle can produce cardiac failure

Proliferative liver lesions

Hepatocellular nodular hyperplasia

Not the result or cause of significant hepatic dysfunction

Must be distinguished from regenerative nodules and neoplasms

Proliferative liver lesions

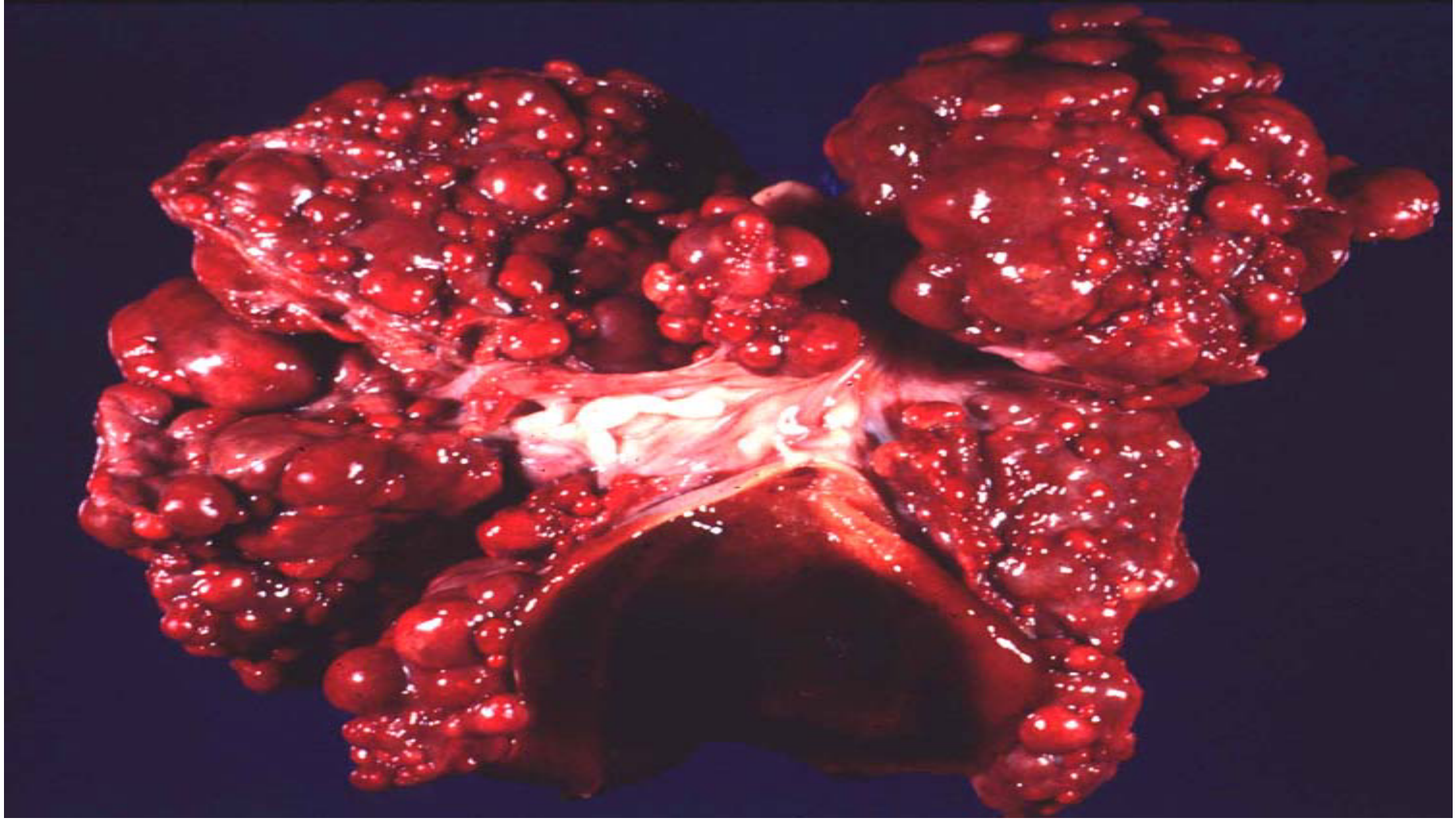
Regenerative nodules

Develop in response to hepatocyte loss

Occur in presence of fibrosis and disruption to normal liver parenchymal architecture

Bile duct (cholangiocellular) hyperplasia

Non-specific response to a variety of hepatic injuries



NODULAR REGENERATIVE HYPERPLASIA

Neoplasia

Primary neoplasms of the hepatobiliary system can arise from epithelial elements (hepatocytes, biliary epithelium) and mesenchymal elements (connective tissue and blood vessels)

Liver and lung are the most common sites for metastatic spread of malignant tumours and, in fact, the majority of neoplasms in the liver are metastases from other organs

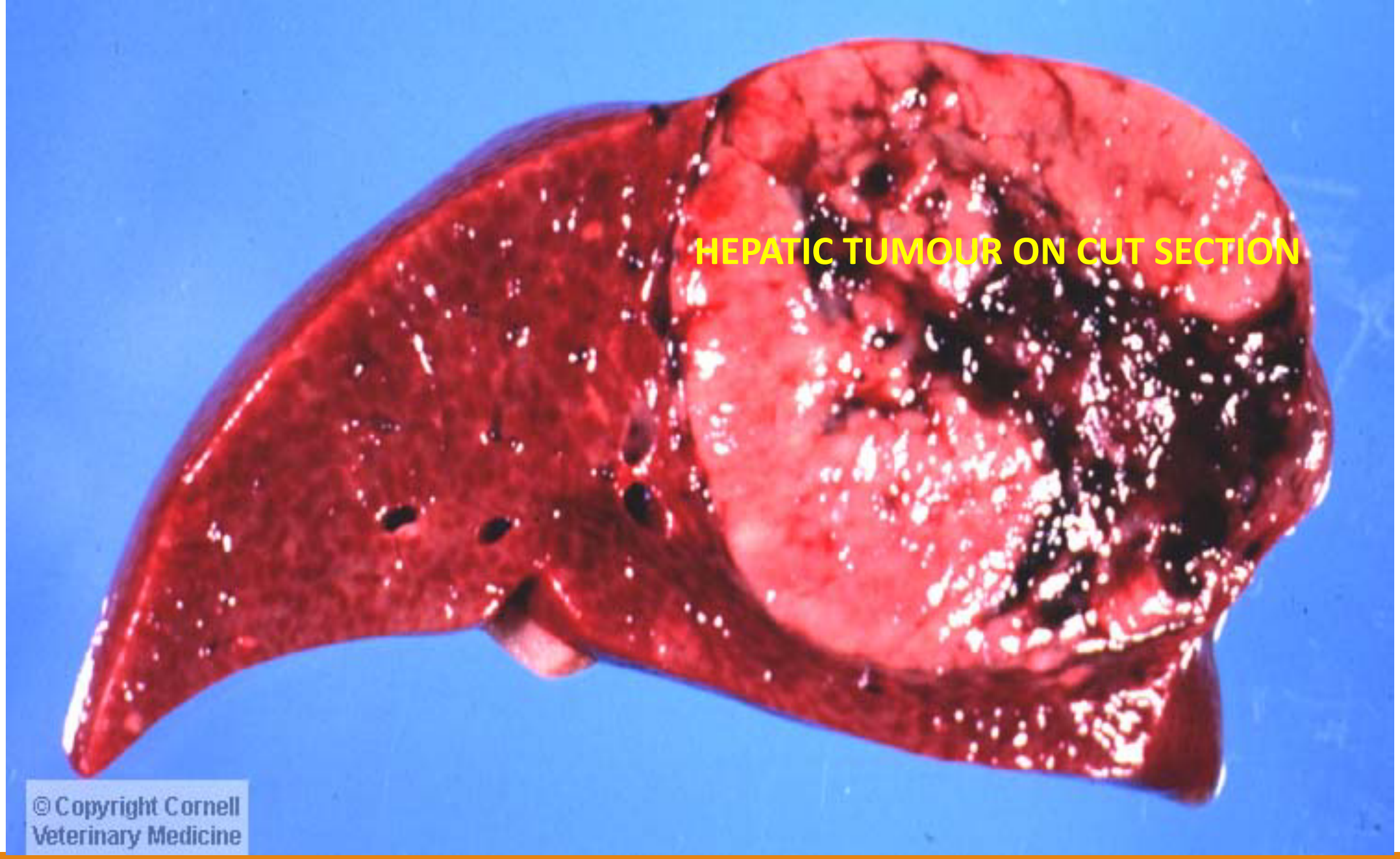
Neoplasia

Hepatocellular adenomas and carcinomas

Cholangiocellular (bile duct) adenomas and carcinomas

Primary haemangiosarcomas

Metastatic neoplasms - lymphoma most common (diffuse infiltration or nodular patterns) in domestic animals


HEPATIC TUMOUR ON CUT SECTION
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Veterinary Medicine

Liver of the laboratory mouse

4 main lobes joined dorsally and, unlike rats, have gallbladders

Hepatocytes frequently show cytomegaly, anisokaryocytosis, polykarya, and karyomegaly

Cytoplasmic invagination into the nucleus is frequent, resembling nuclear inclusions

Hepatocytes often contain cytoplasmic fat vacuoles and some strains (BALB) normally have diffuse hepatocellular fatty change with grossly pallid livers

Liver of the laboratory mouse

Haematopoiesis normally occurs in infant livers but wanes by weaning age, although islands can be found in older mice, particularly in disease states

Foci of cellular alteration are phenotypically altered hepatocellular foci that occur spontaneously in mice (and rats) and must be distinguished from small adenomas. Vary in size from < 1 lobule to several lobules in diameter and usually round to oval in shape. Classified on cytological features as basophilic, eosinophilic, clear, vacuolated or mixed

Hepatic enzyme alterations in disease

Alterations in serum enzymes provide a sensitive method to evaluate liver disease and can be divided 2 categories:

1. **Hepatocellular leakage enzymes**
2. **Induced (cholestatic) enzymes**

Species vary in the activity of enzymes expressed by the liver as well as their enzymatic responses to induction

Magnitude of increase in serum enzyme activity does not necessarily correlate with clinical manifestations of hepatic insufficiency

Clinical chemistry

Magnitude of increase in serum enzyme activity depends on the number of hepatocytes affected, the severity of the injury, and serum half-life of the enzyme

Following hepatic injury, increased serum enzyme activity is evident in hours

Commonly increased enzymes include alanine aminotransferase (ALT), aspartate aminotransferase (AST) and sorbitol dehydrogenase (SDH). These enzymes vary in their concentration in liver and specificity for hepatic disease in different species

Clinical Chemistry

Hepatocellular leakage/necrosis

Altered permeability of hepatocyte cell membranes results in leakage of cytosolic enzymes into the blood

Leakage may occur with either sublethal (reversible) injury or necrosis

Increase in serum enzyme activity depends on number of hepatocytes damaged and serum half-life of enzyme

Following hepatocellular injury, increased serum enzyme ativity is evident within hours

Hepatocellular leakage/necrosis

Hepatocellular injury often accompanied by cellular swelling, inflammation and/or necrosis, which may alter bile flow, resulting in intrahepatic cholestasis

Commonly measured enzymes: alanine aminotransferase (ALT), aspartate aminotransferase (AST) and sorbitol dehydrogenase (SDH)

These enzymes vary in their concentration in the liver and specificity for liver disease in different species

Hepatic enzyme alterations in disease

In chronic, progressive liver diseases, a low proportion of hepatocytes may undergo damage or necrosis at a given time

Hepatic atrophy may result in lower enzyme activity due to reduced numbers of hepatocytes

Increased serum activity of enzymes may originate in other tissues (skeletal or cardiac muscle) and can be distinguished by concurrent measurement of creatine kinase, a specific indicator of muscle injury

Common enzymes evaluated are ALT, AST, SDH, LDH and GDH

Induced hepatic enzymes

Typically membrane-bound and not released into serum with increased membrane permeability

Increased serum activity due to induction, usually from cholestasis, drug, or hormonal effects

ALP and GGT are the commonly induced enzymes measured

Hepatic insufficiency

Due to decreased hepatic functional mass from:

Hepatocellular injury or necrosis

Hepatocyte loss in chronic liver disease with replacement fibrosis (cirrhosis)

Hepatic atrophy (often due to chronic portosystemic shunts)

Cholestasis

Interruption or obstruction of bile flow or excretion

Intrahepatic (within bile canaliculi or ductules) or extrahepatic (in common bile duct or gallbladder)

Can result from physical obstruction of bile flow (inflammation, infection, cholelithiasis or neoplasia) or from metabolic derangements

May cause induction and release of certain membrane-bound hepatic enzymes: alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT)

Cholestasis

Also results in retention or reflux of bile, increasing serum concentrations of bilirubin and bile acids normally excreted in bile

May also cause hepatocellular damage due to bile acid retention, which has a detergent action on cell membranes

Alterations in portal blood flow

Hepatic artery provides oxygenated blood from systemic circulation, portal vein provides blood from intestine and spleen, and hepatic vein returns blood from liver to systemic circulation

Portal blood contains bile acids, amino acids, glucose, ammonia, fatty acids

Largely removed from blood by liver before reaching systemic circulation

Portosystemic shunts bypass the liver and deliver e.g. bile acids, ammonia directly into systemic circulation

Tests of hepatic uptake, conjugation and secretion

Bilirubin

Produced by degradation of haem portion of haemoglobin and myoglobin

1. **Unconjugated – water-insoluble and transported in blood bound to albumin, then taken up by hepatocytes**
2. **Conjugated – formed in hepatocyte and water soluble, secreted into the bile and ultimately the intestine**

Hyperbilirubinaemia

Increased bilirubin production (pre-hepatic) – increased erythrocyte breakdown with haemolysis/internal haemorrhage, overwhelming hepatic uptake, conjugation and secretion capacity

Decreased hepatic uptake or conjugation (hepatic) due to a hepatocyte functional deficit

Cholestasis (post-hepatic) due to decreased secretion of bilirubin into bile, obstruction of bile flow

Hyperbilirubinaemia

Cause determined by relative concentration of unconjugated versus conjugated bilirubin

Unconjugated tends to predominate in pre-hepatic and hepatic forms and conjugated in post-hepatic

However, this is not always the case

Bilirubinuria/bile acids

Bilirubinuria

Conjugated bilirubin passes through the glomerular filter into the urine, but unconjugated bilirubin, being albumin-bound, is too large

Bile acids

Synthesised in the liver from cholesterol, conjugated, and secreted into the bile

Function is to solubilise lipids and aid in intestinal fat digestion

Bile acids

Most are reabsorbed into the portal circulation and recycled (enterohepatic circulation) by hepatocytes

In cholestasis, they can contribute to hepatocellular damage by a detergent action

Increased with portosystemic shunts (by-passing the liver), liver failure, and cholestasis

Ammonia

Produced in the gastrointestinal tract by breakdown of amino acids and urea by gut microflora and transported by the portal vein to the liver, where it is converted into urea

Hyperammonaemia occurs with liver insufficiency due to decreased liver uptake and portosystemic shunting

When severe and chronic, can lead to hepatic encephalopathy