Morphological classification of parenchymal disorders of the canine and feline liver

3. Hepatic abcesses and granulomas, hepatic metabolic storage disorders and miscellaneous conditions

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ABSTRACT

Hepatic abscesses and granulomas usually occur by hematogenic spread from the portal vein or in neonates from the umbilical vein and a wide variety of causative organism is given. The various hepatic metabolic storage diseases in dogs and cats mentioned in the literature are summarized including the enzymatic defect, the hepatic cells involved and their morphological aspect. Finally, miscellaneous conditions are presented which include cytoplasmic and nuclear alterations in hepatocytes, Kupffer cells and hepatic stellate cells as well as lipogranulomas and pigment granulomas and extramedullary hemopoiesis.

HEPATIC ABSCESSES AND GRANULOMAS

Hepatic abscesses usually are the result of bacterial infections evoking intense accumulation and subsequent lysis of neutrophilic granulocytes at the infection site (Fig. 1). They can reach the liver via different routes including the portal vein or umbilical vein, ascending infection of the biliary system, and by direct contact and penetration of the liver capsule. Hepatic abscesses in dogs and cats are particularly seen in newborn animals due to umbilical infection (e.g. several Gram-positive and Gram-negative bacteria). In adult animals hepatic abscesses are often the result of infections with *Yersinia spp* (Fig. 2), *Nocardia asteroides* and *Actinomyces spp*.[1, 2] Hepatic abscesses may occur in association with central necrosis of hepatocellular neoplasms.

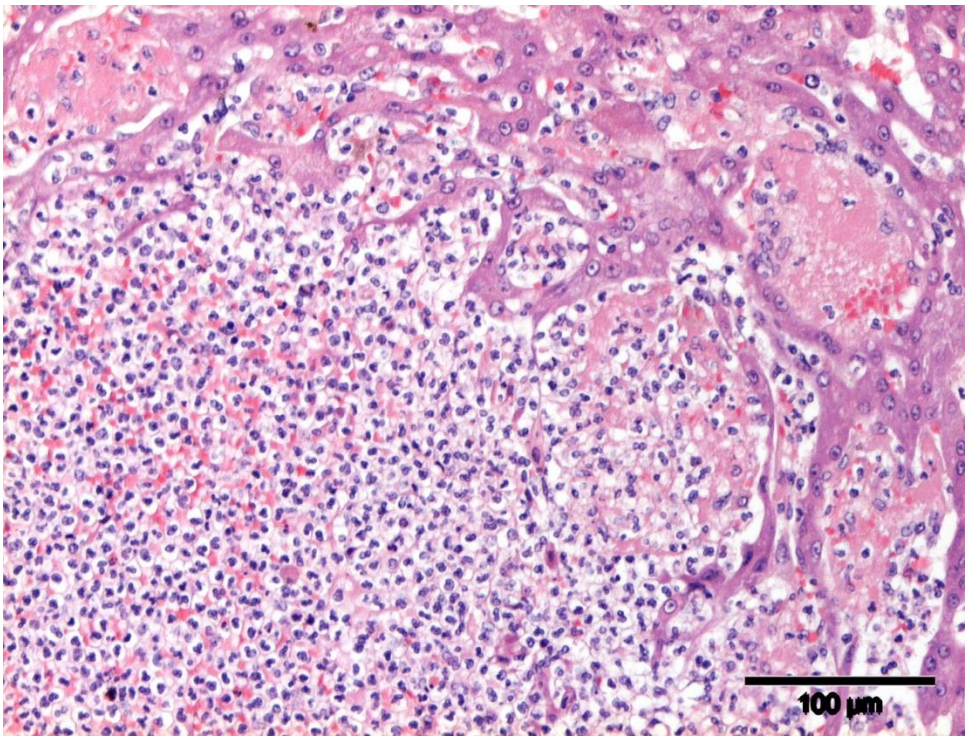

Fig. 1. Dog. Hepatic abscess with fibrinoid deposits at the periphery. HE.

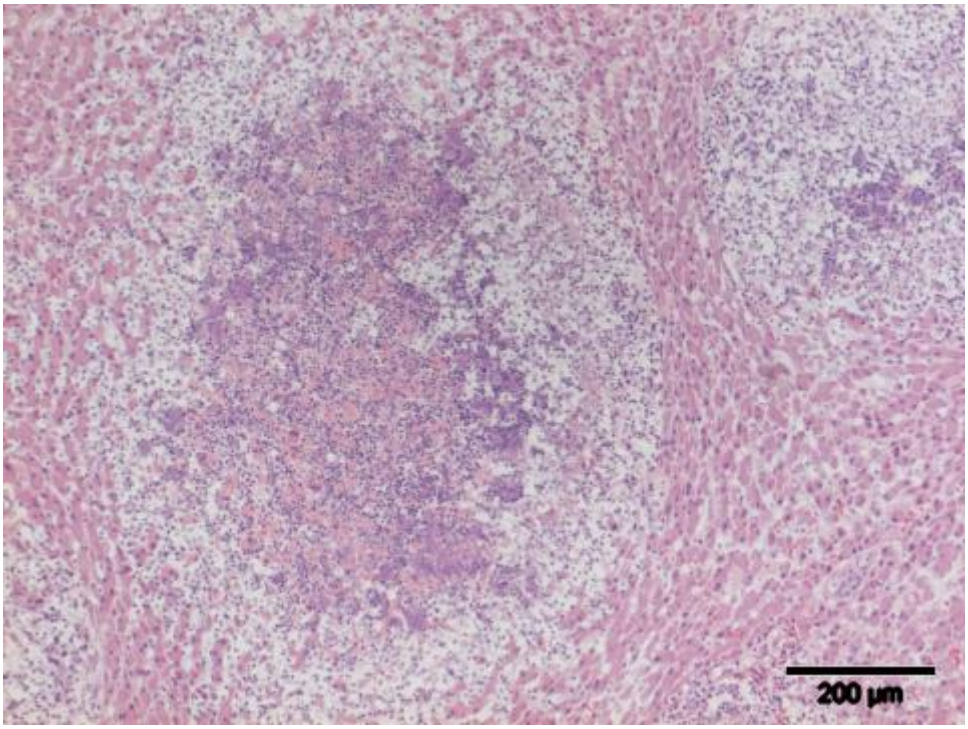

Fig. 2. Cat. Hepatic abscess due to Yersinia spp with centrally located bacteria. HE.

Hepatic granulomas may occur in a wide variety of diseases, some of which are primary in the liver, but most are part of a generalized disease process. They consist of (multi)focal aggregations of activated macrophages with an epithelioid appearance, mostly infiltrated by

lymphocytes and plasma cells and possibly fibroblasts and may be surrounded by collagen fibers. Epithelioid cells may fuse to form multinucleated giant cells; the nuclei may either be arranged peripherally (Langhans-type giant cell) or haphazardly (foreign-body-type giant cell).[3] The classic example of granulomatous disease is tuberculosis. The granulomas, referred to as tubercles, are characterized by the presence of epithelioid cells and Langhans-type giant cells with central caseous necrosis and a peripheral zone of lymphocytes (Fig. 3); in contrast to other domestic animal species giant cells of Langhans type are only rarely observed in both dogs and cats[4].

Infectious causes for hepatic granulomas in dogs and cats include mycobacterial infections (*M. tuberculosis* (Fig. 3), *M. avium intracellulare* (Fig. 5)), systemic mycoses (*Blastomyces dermatitidis, Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis)* and opportunistic fungal infections (Fig. 6), migrating nematode larvae (visceral larva migrans) and schistosomiasis. Alveolar echinococcosis due to *Echinococcus multilocularis* is sometimes seen in dogs in endemic areas and usually presents as one large or multiple neoplastic-like processes in the liver. Histologically the lesion is characterized by the presence of, usually dead, echinococcal cysts embedded and surrounded by chronic granulomatous inflammation. (Fig. 7)

A diffuse granulomatous inflammation of the liver is observed in *Leishmania spp* infection (Fig. 8) in dogs [5] and *Cytauxzoon felis* infection (Fig. 9) in cats [6]; in both cases large numbers of amastigotes respectively schizonts may be observed in Kupffer cells and macrophages. Granulomatous and non-suppurative hepatitis has been reported in the dog in association with *Bartonella* spp. [7]

Granulomas may also be incited by relatively inert foreign material (e.g. crystalline material, sutures, plant material). In neonates, subcapsular hepatocellular necrosis (probably associated with asphyxia) with subsequent mineralization and granulomatous inflammation may be seen at the periphery of the liver lobes (Fig. 10).

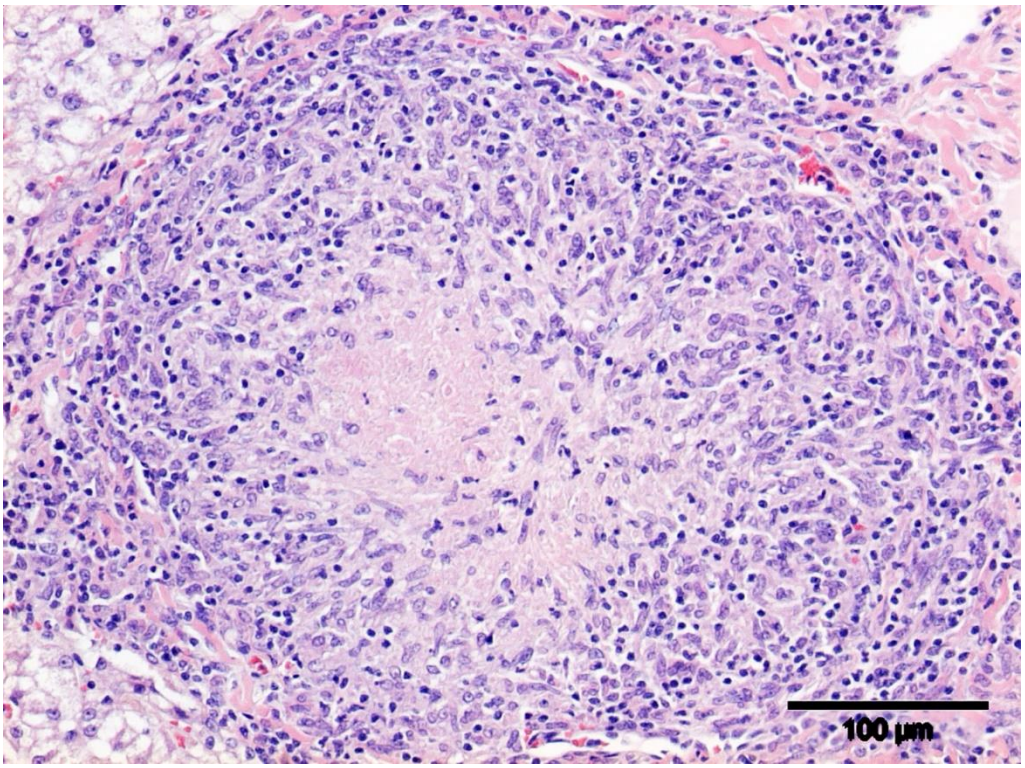

Fig. 3. Dog. Tubercle with epithelioid cells, central caseous necrosis and peripheral lymphocytic infiltrate. Note absence of Langhans type multinucleated giant cells. Mycobacterium tuberculosis. HE.

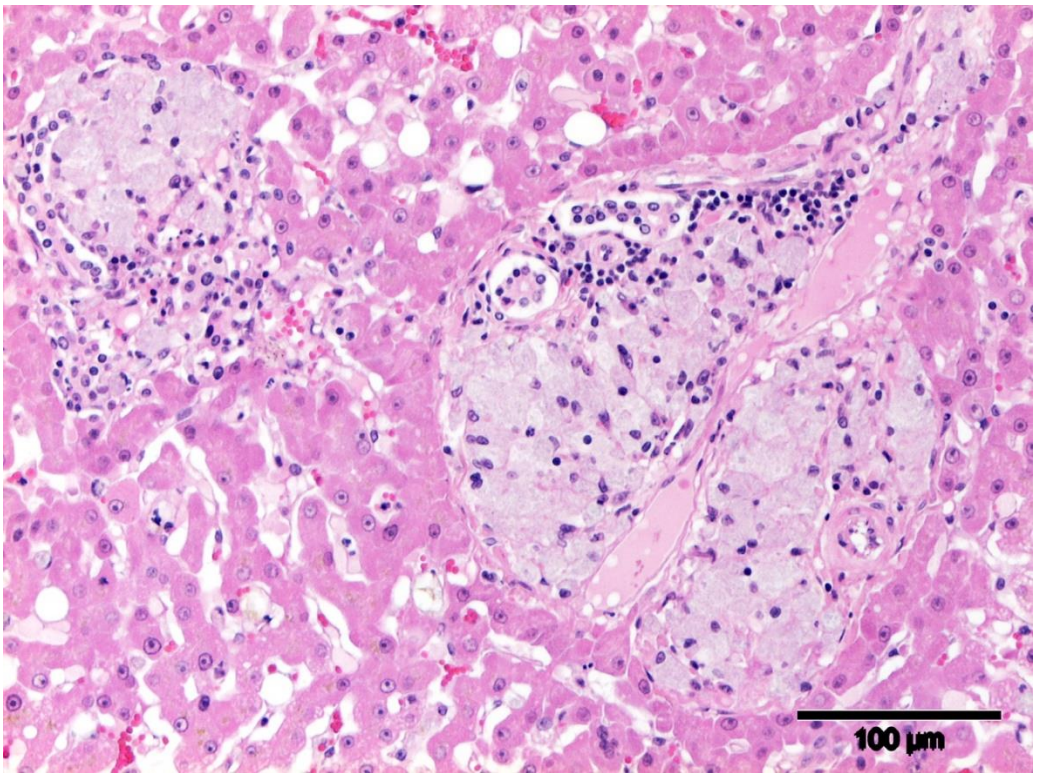

Fig. 4. Cat. Epithelioid granulomas in the portal area and parenchyma. Mycobacterium avium. HE.

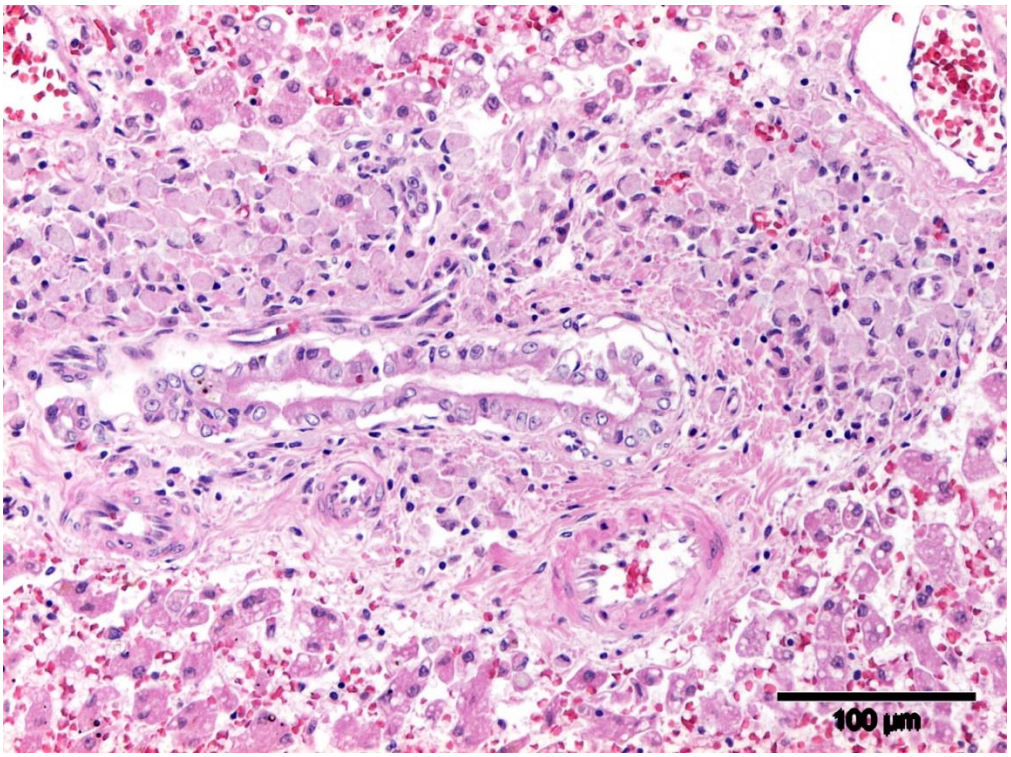

Fig. 5. Dog. Epithelioid granulomatous inflammation in the portal area. Mycobacterium avium. HE.

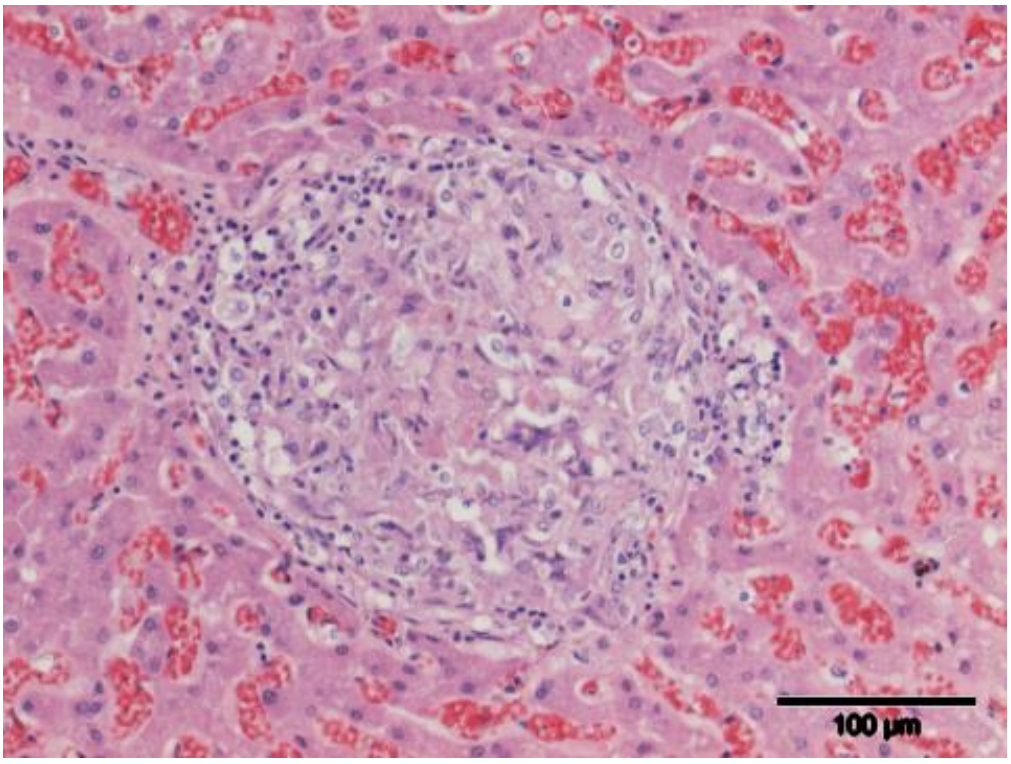

Fig. 6. Dog. Mycotic granuloma with pale irregularly formed fungal organisms. HE.

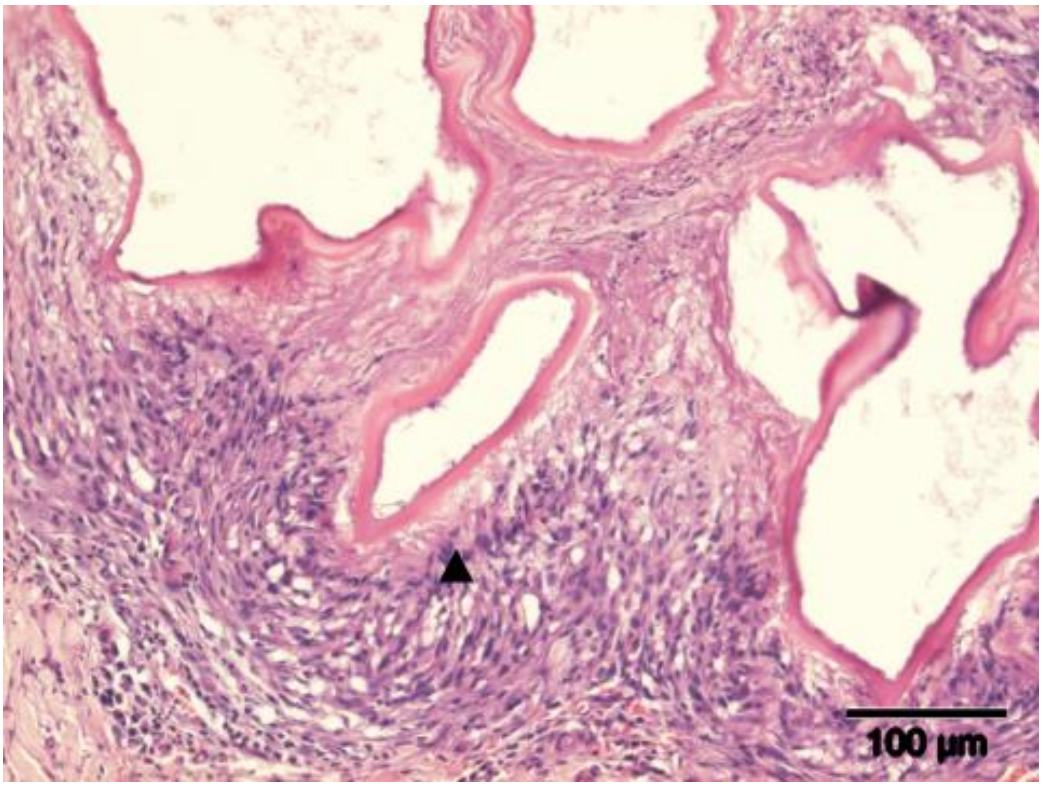

Fig. 7. Dog. Alveolar echinococcosis. Dead echinococcal cysts surrounded by a ring of foreign-body multinucleated giant cells (arrowhead) and chronic inflammation. HE.

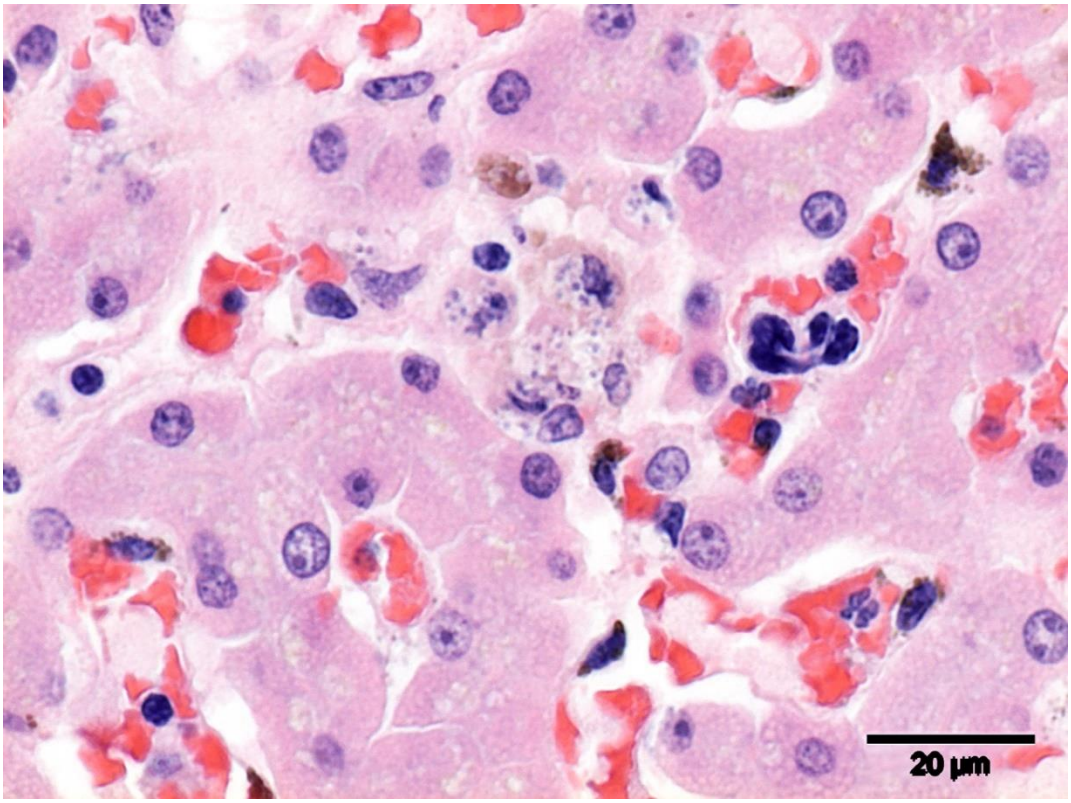

Fig. 8. Dog. Leishmaniasis. Amastigotes in the cytoplasm of Kupffer cells / macrophages. HE.

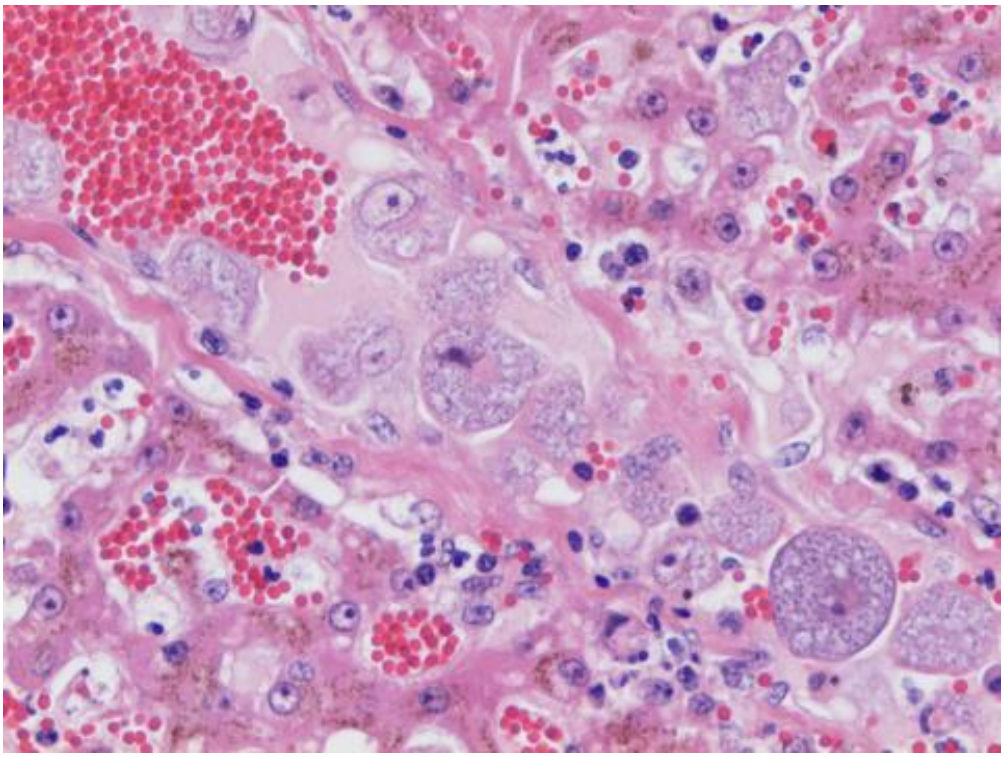

Fig. 9. Cat. Cytauxoon felis infection. Large numbers of schizonts in Kupffer cells and macrophages. HE.

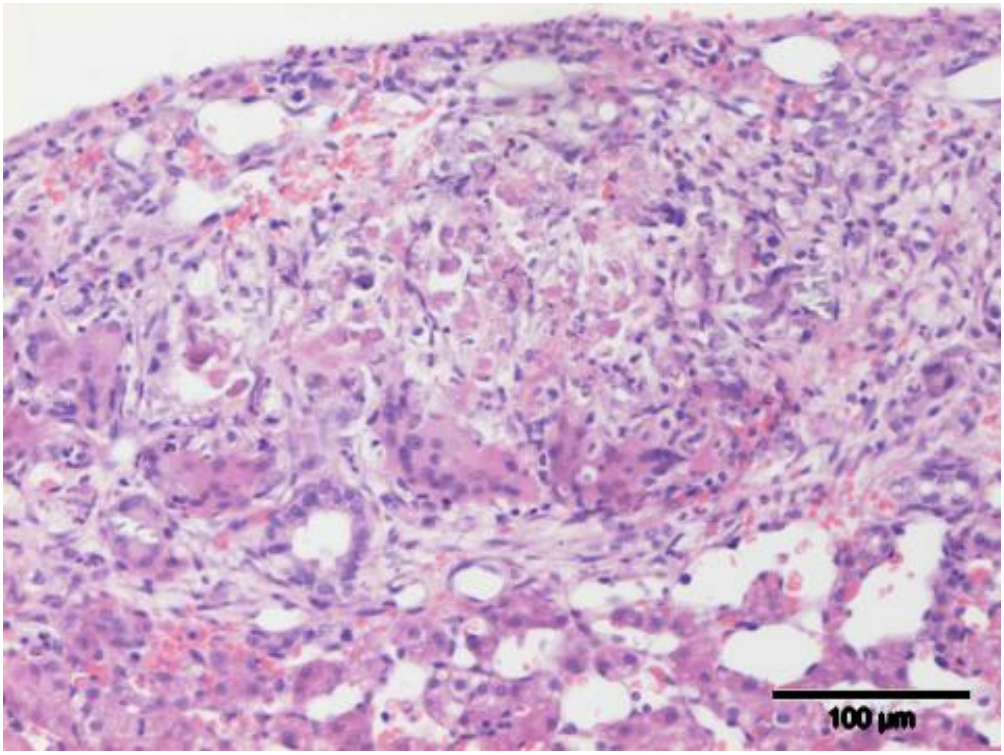

Fig. 10. Dog, neonate. Subcapsular necrosis with dystrophic calcification and subsequent granulomatous inflammation. HE.

HEPATIC METABOLIC STORAGE DISORDERS

General

Hepatic metabolic storage disorders, usually associated with inherited but sometimes acquired metabolic enzyme deficiencies, can have a variety of morphologic appearances (Table 1). The most common finding is the presence of clear vacuoles, vacuoles with granular or hyaline material, or pigmented granules in hepatocytes and, or Kupffer cells and macrophages (Fig. 11, 12). Rarely, as in glycogenosis type I and III, the lesion is characterized by markedly swollen, clear hepatocytes with well outlined cell membranes giving the hepatocytes the appearance of plant cells.

Table 1 Hepatic metabolic storage disorders

Disease name	Stored material	Defective enzyme	Morphology of stored material	Hepatocytes	Kupffer cells / macrophages	Species / breed
Ceroid-lipofuscinosis	ceroid / lipofuscin	Unknown	granules (yellow-brown)		X	Canine [15-17] Feline [17,18]
Cholesterol ester storage disease	cholesterol esters and cholesterol in Kupffer cells and macrophages; neutral lipids and cholesterol in hepatocytes	acid lipase	clear vacuoles and cholesterol crystals	X	X	Canine [19] Fox terrier
Fucosidosis	fucose containing glycolipids, glycoproteins, poly- / oligo-saccharides	alpha-L-fucosidase	clear vacuoles		X	Canine [20,21] English springer spaniel

Galactosialidosis	glycolipids and oligosaccharides	beta galactosidase, alpha-neuraminidase	clear vacuoles	X	X	Canine [22] Schipperke dog
GM 1 gangliosidosis	gangliosides	beta-galactosidase	clear vacuoles	X	X	Canine [22-28] Portugese waterdog, Shiba dog, Alaskan husky, English springer spaniel, Mixed breed dog Feline[29,30] Siamese, Korat
GM2 gangliosidosis	gangliosides	beta-hexosaminidase A / B	clear vacuoles	X	X	Canine [31-33] Japanese spaniel, German shorthaired pointer, Golden retriever, Feline [34] DSH
Glycogenosis type IA	glycogen	glucose-6-phosphatase	swollen clear cells	X		Canine [35] Maltese dog
Glycogenosis Type III	glycogen	amylo-1,6-glucosidase	swollen clear cells	X		Canine[36,37,63,65] German sheperd dog, Curly-coated retriever
Glycogenosis Type IV	abnormally branched glycogen (alpha-1,4-D-glucan)	branching enzyme	pale blue granules	X	X	Feline [38] Norwegian forest cat

Glycosyl ceramide lipidosis (Gaucher's disease)	glycosyl ceramines	acid beta-glucosidase	pale, faintly striated inclusions		X	Canine [39,40] Silky terrier
Inherited Copper Toxicosis	copper	COMMD-1 ATPB-7/ATPA-7	granules (blue-grey, yellow-brown,red-brown	X	X (secondary)	Canine (see Chapter 7 copper associated chronic hepatitis)
Mannosidosis	glycoprotein derived mannose-rich oligosaccharides	alpha or beta mannosidase	clear vacuoles	X	X	Canine German shepherd dog[68] Feline [41-43] Persian, DSH, DLH
Mucolipidosis type II	mucopolysaccharids, lipids, glycoproteins	N-acetyl glucosamine-1-phosphotransferase	clear vacuoles		X (Fibroblasts /endothelial lining cells)	Feline [44] DSH
Mucopolysaccharidosis type I	heparan and dermatan sulphate	alpha-L-iduronidase	clear vacuoles	X	X	Canine [45,46] Plott hound Feline [45,47] DSH
Mucopolysaccharidosis type II	heparan and dermatan sulphate	alpha-L-iduronidase sulphatase	clear vacuoles	X	X	Canine [48] Labrador retriever
Mucopolysaccharidosis type III	heparan sulphate	heparan sulphatase	clear vacuoles	X	X	Canine [49-51] Wirehaired dachshund, New Zealand huntaway dog

Mucopolysaccharidosis type VI	dermatan sulphate	arylsulphatase B	clear vacuoles	X	X	Canine[16,52,64] Miniature schnauzer, Miniature pinscher, Miniature poodle Feline [16,45,53]DSH, Siamese
Mucopolysaccharidosis type VII	chondroitin and dermatan sulphate	beta-glucuronidase	clear vacuoles	X	X	Canine [45,54] Mixed breed Feline [55,56,66] DSH
Primary hyperlipoproteinaemia	lipids	lipoprotein lipase	clear vacuoles	X	X (including xanthomata)	Feline [57,58]
Sphingomyelin-cholesterol lipidosis (Niemann-Pick disease type C)	unesterified cholesterol	acidic sphingomyelinase	clear vacuoles		X	Canine [59,60] Miniature poodle, Boxer Feline [61,62,67] DSH, Siamese,

These changes are usually non-specific and can be better evaluated in frozen or plastic-embedded sections using conventional, lectin- and immunohistochemistry or electron microscopy. However, diagnosis depends on either the identification of the storage product or the enzyme deficiency by biochemical methods, or by identification of the genetic defect. Although the changes may be insufficient to cause hepatocellular or Kupffer cell necrosis, particularly severe hepatocellular storage may result in hepatocellular necrosis and inflammation and even chronic hepatitis and cirrhosis may develop.

Erythropoietic protoporphyria

Erythropoietic protoporphyria is known in dogs as an acquired storage disease following administration of a number of xenobiotics among others griseofulvin and the antiarthritic drug 3-[2-(2,4,6-trimethylphenyl)-thiothyl]methylsydnoneis (TTMS).[8] Drug induced protoporphyria is a result of inhibition of ferrochelatase, compensatory stimulation of the first enzyme in the 5-aminolevulate synthase pathway and massive accumulation of the substrate protoporphyrin. Protoporphyrin is recognized as dark brown pigment in canaliculi and interlobular bile ducts, and in more severe cases also in Kupffer cells and macrophages (Fig. 13). The pigment displays bright red birefringence with a centrally located dark Maltese cross. Occasionally severe deposition of the pigment may result in chronic hepatitis and cirrhosis[9, 10].

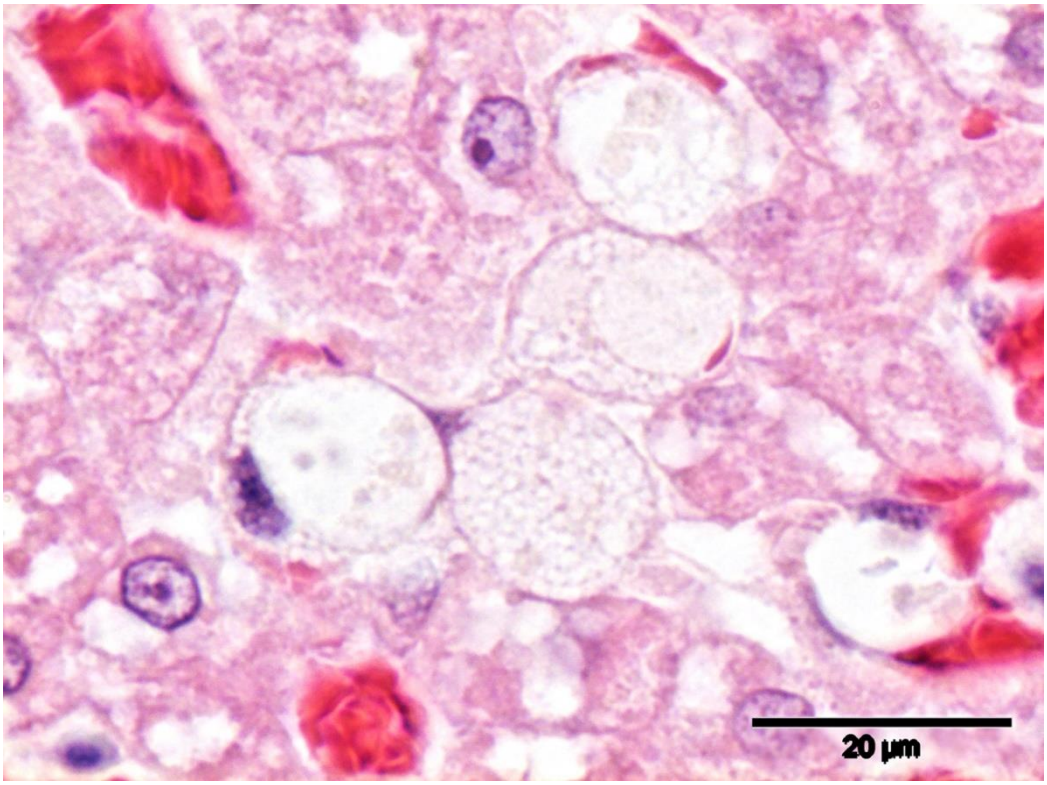

Fig. 11. Dog. Fucosidosis. Swollen Kupffer cells – macrophages with vacuolisation of the cytoplasm. HE.

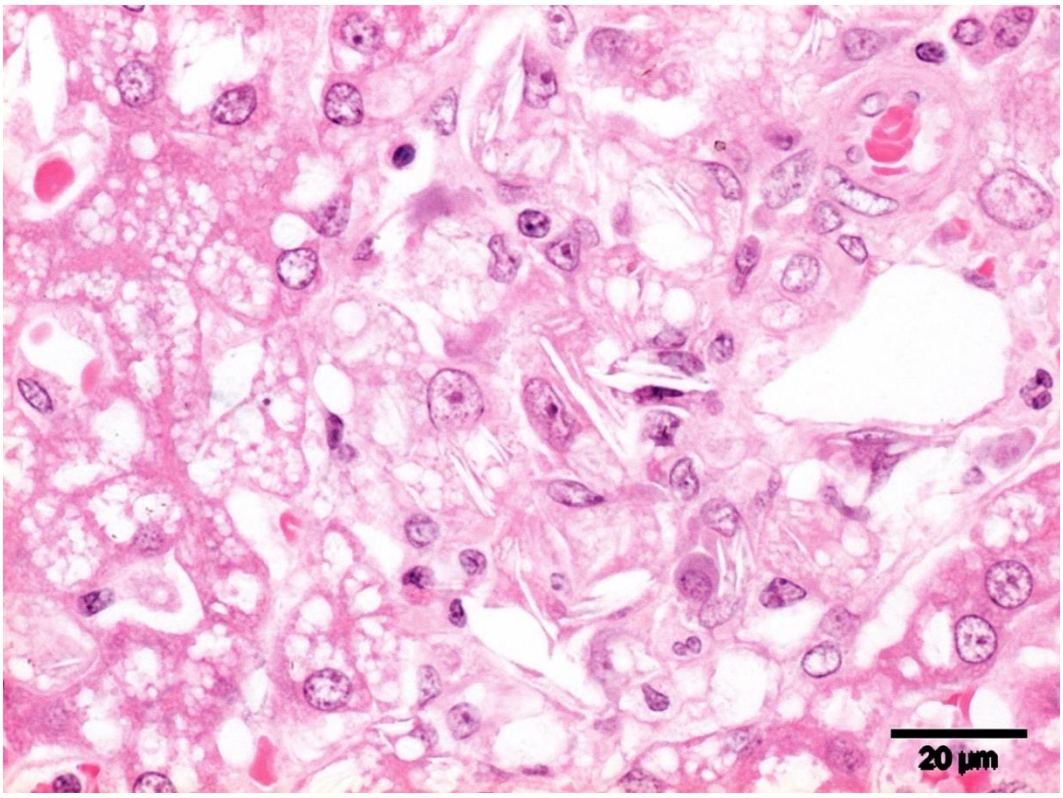

Fig. 12. Dog. Cholesterol ester storage disease (Wolman's disease). Vacuolation of hepatocytes and vacuolation and cholesterol crystals in macrophages in the portal area. HE.

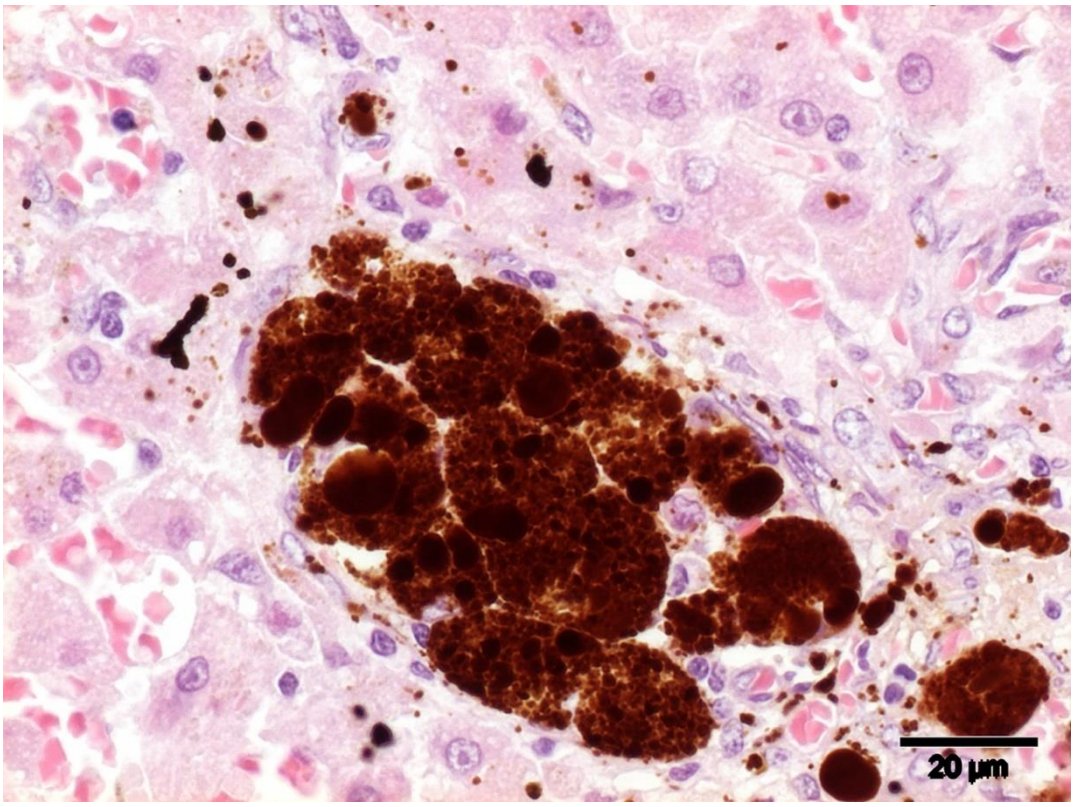

Fig. 13. Dog. Erythropoietic protoporphyria. Darkbrown pigment (protoporphyrin) in canaliculi and in macrophages. HE.

MISCELLANEOUS CONDITIONS

Hepatocytes

Cytoplasmic Alterations

- **Protein droplets** are variably sized eosinophilic (hyaline) droplets in the cytoplasm of hepatocytes (Fig. 14). They may consist of engulfed serum proteins and represent a non-specific and variable finding associated with shock, ischemia, or other acute hepatocellular injury. They also may consist of fibrinogen and acute phase proteins (alpha-1-antitrypsin, haptoglobin, alpha-macroglobulin) retained in the endoplasmic reticulum in hepatocytes as seen in dogs with chronic hepatitis and cirrhosis[11]
- **Eosinophilic cytoplasmic bodies** of variable size may be the result of phagocytosis of apoptotic bodies by hepatocytes
- **'Ground glass' appearance:** swollen hepatocytes with pink finely granular to hyaline cytoplasm (Fig. 15) associated with an increase in the smooth endoplasmic reticulum and induction of the hepatic microsomal drug metabolizing enzymes. Ground glass appearance of hepatocytes may be caused by drugs (e.g. phenobarbital) and other substances that cause induction of cytochrome P450 enzymes
- **Lipofuscin:** brown-yellow pigmented granular material in hepatocytes within lysosomes and most abundant in a pericanalicular location (Fig. 16). It is present in normal livers in varying amount. Increased hepatocellular lipofuscin occurs with age, particularly in cats, and is most prominent in the centrilobular hepatocytes.
- **Accumulation of copper** is seen as gray-yellow to gray-brown or gray-blue granules in the cytoplasm. The color of the granules may vary depending on tissue preparation procedures used by the laboratory (Fig. 17). Copper can be specifically identified by histochemical stains (e.g. rubeanic acid or rhodanine for copper and orcein for copper-binding protein). Storage of copper can be primary due to a genetic defect in one of the genes associated with copper metabolism, such as in inherited copper toxicosis in Bedlington terriers or secondary due to excessive copper intake. Copper accumulation in hepatocytes is also a hallmark of cholate-stasis (Chapter 5); however, with persistent cholestasis such as in chronic extrahepatic cholestasis and chronic hepatitis/cirrhosis the liver has normal copper concentrations and genes related to copper metabolism remain at concentration similar to normal dogs[72].
- **Accumulation of iron** is seen as brown granules in the cytoplasm of hepatocytes (Fig. 18, 19) and may be seen with increased red blood cell turnover, anaemia of chronic disease and after administration of iron.
- **Emperipolesis** is a rare phenomenon of invagination of the cell membrane and engulfement of complete cells. It is particularly seen in epitheliotropic T-cell lymphoma (Fig. 20), where the neoplastic lymphocytes are engulfed by the hepatocytes.[12]

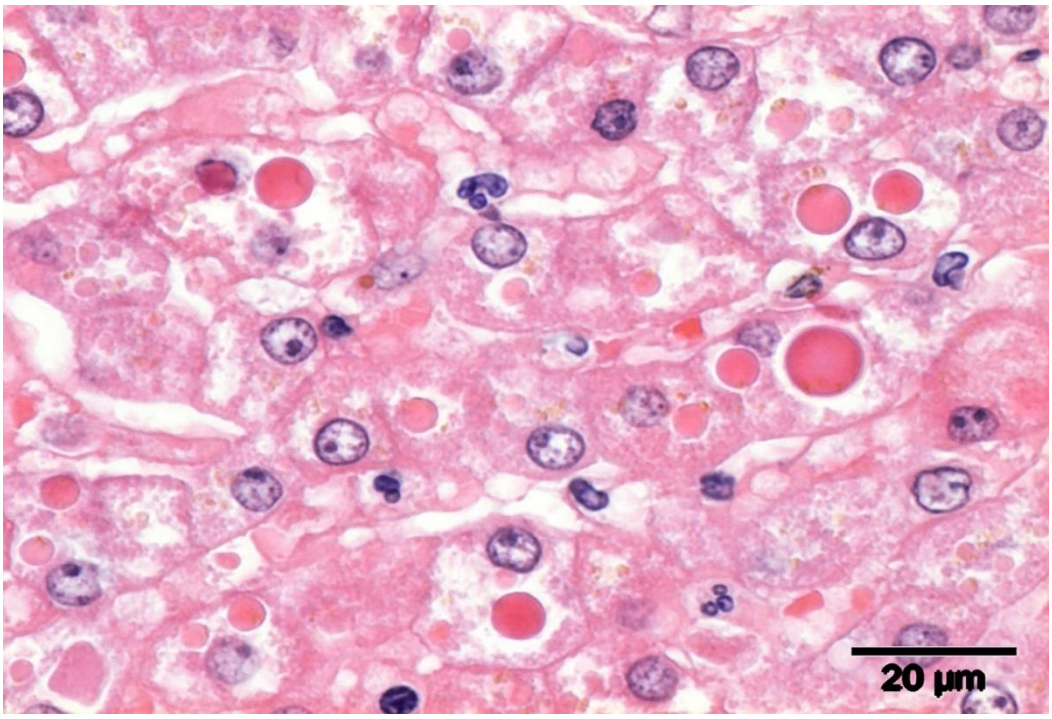

Fig. 14. Dog. Protein droplets (engulfed serum proteins) in the hepatocytic cytoplasm. HE.

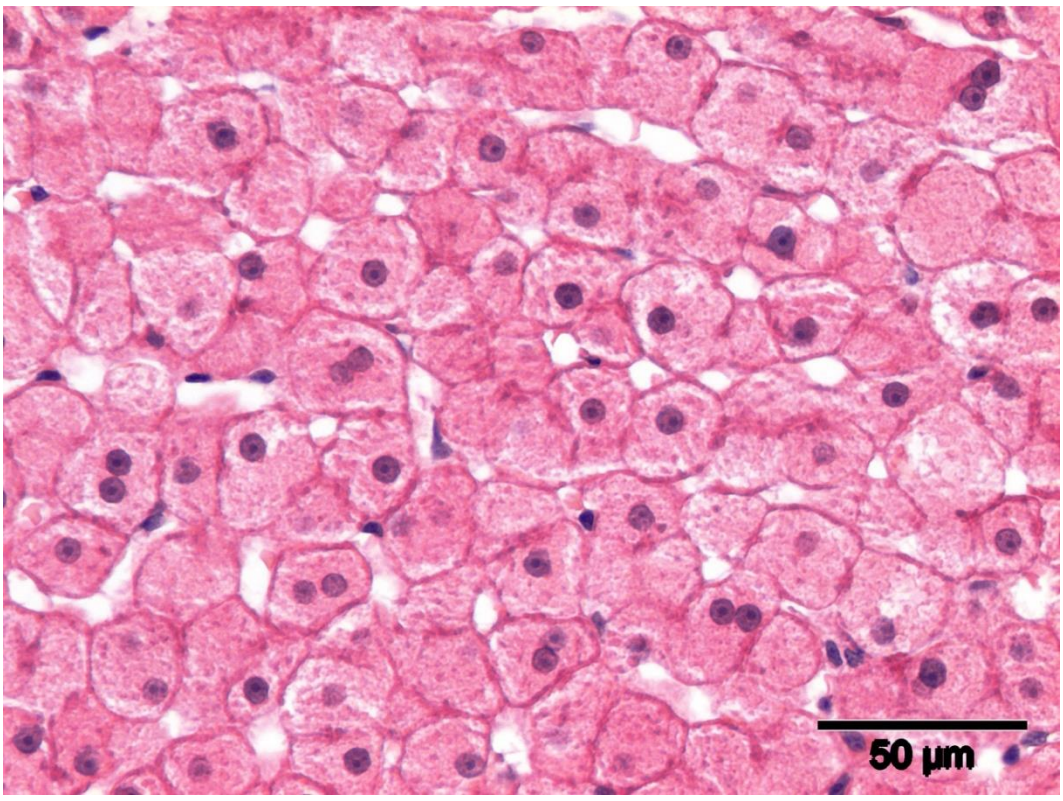

Fig. 15. Dog. Ground glass appearance associated with phenobarbital medication. HE.

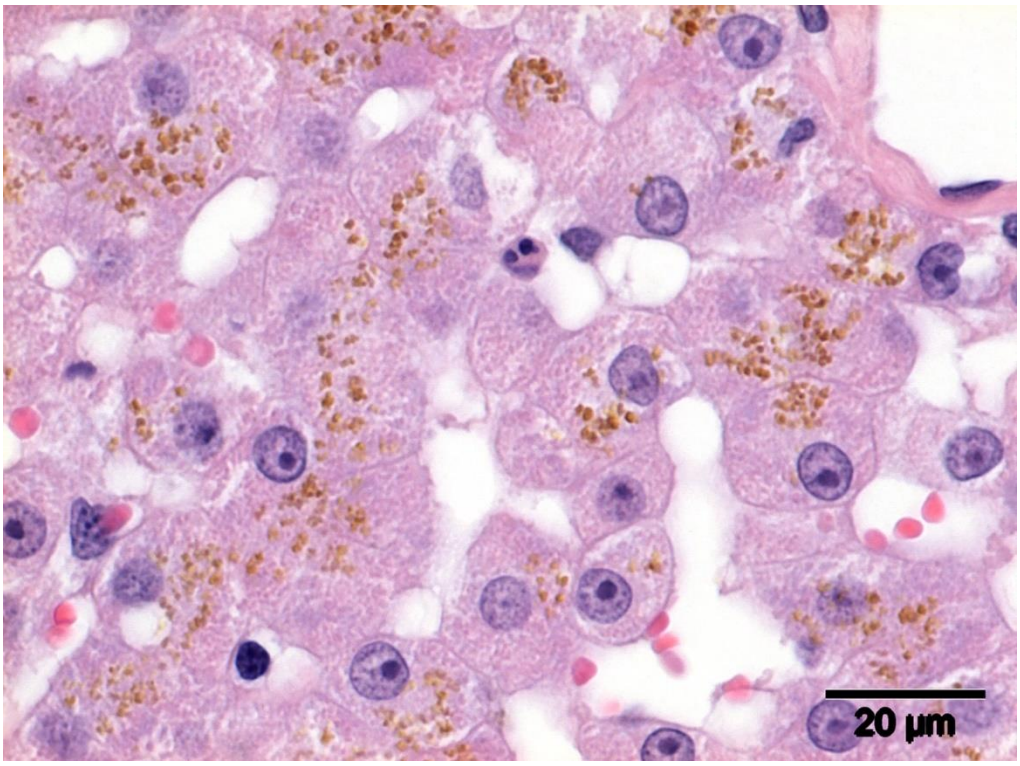

Fig. 16. Cat. Lipofuscin deposition in a pericanalicular location in centrolobular hepatocytes. HE.

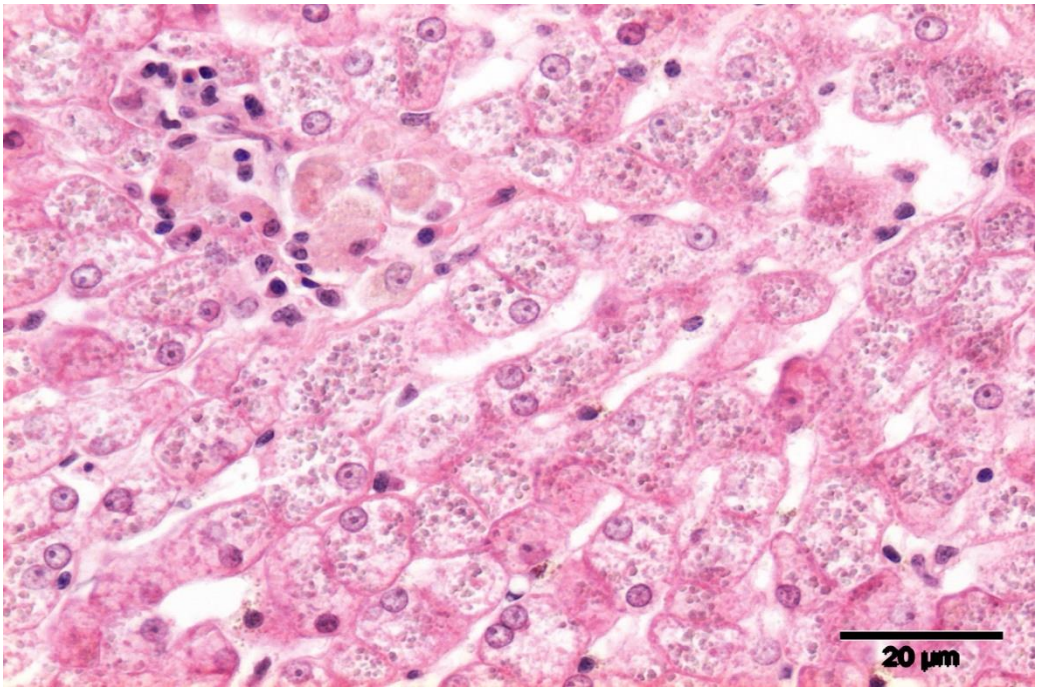

Fig.17. Bedlington terrier. Gray-yellow copper containing granules diffusely dispersed in the hepatocytic cytoplasm. Inherited copper toxicosis. HE.

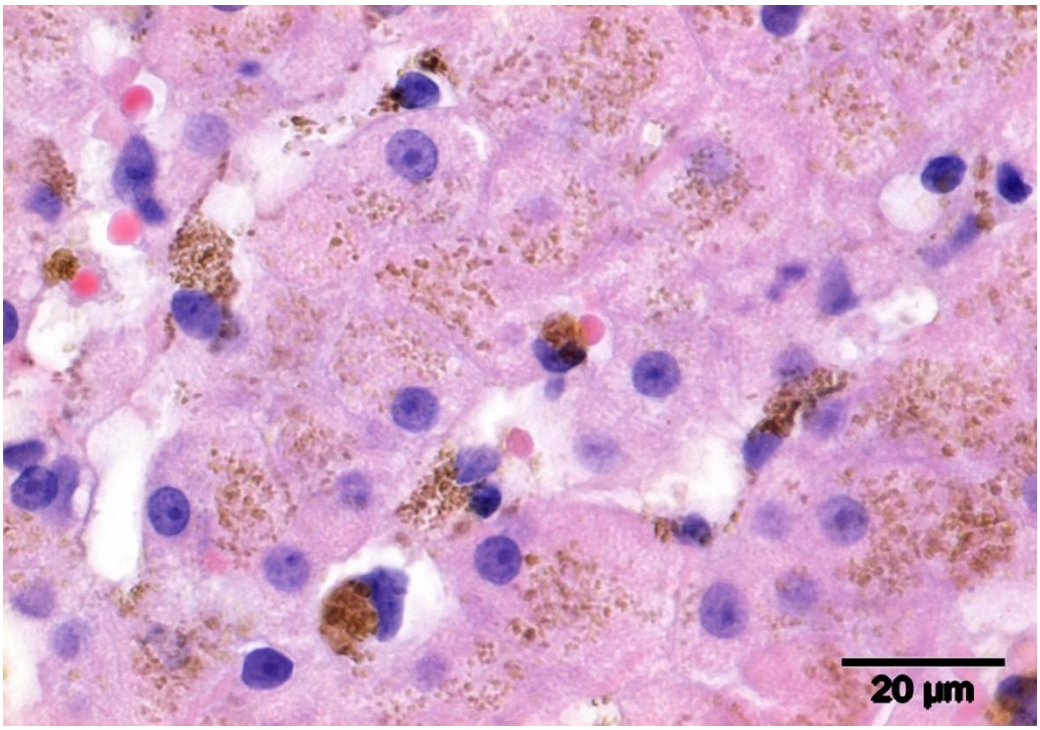

Fig. 18. Cat. Brown iron containing granules in the cytoplasm of hepatocytes and Kupffer cells. Erythremic myelosis. HE.

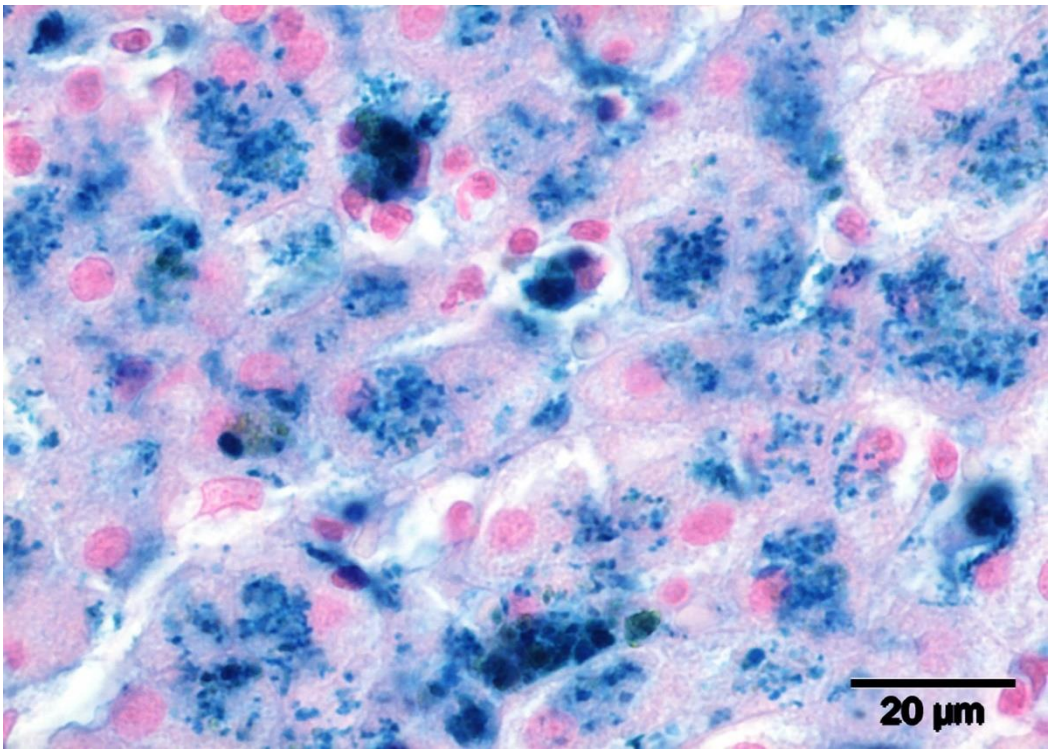

Fig. 19. Cat (same animal as Fig 8.18). Blue staining iron pigment in hepatocytes and Kupffer cells. Prussian blue stain for iron.

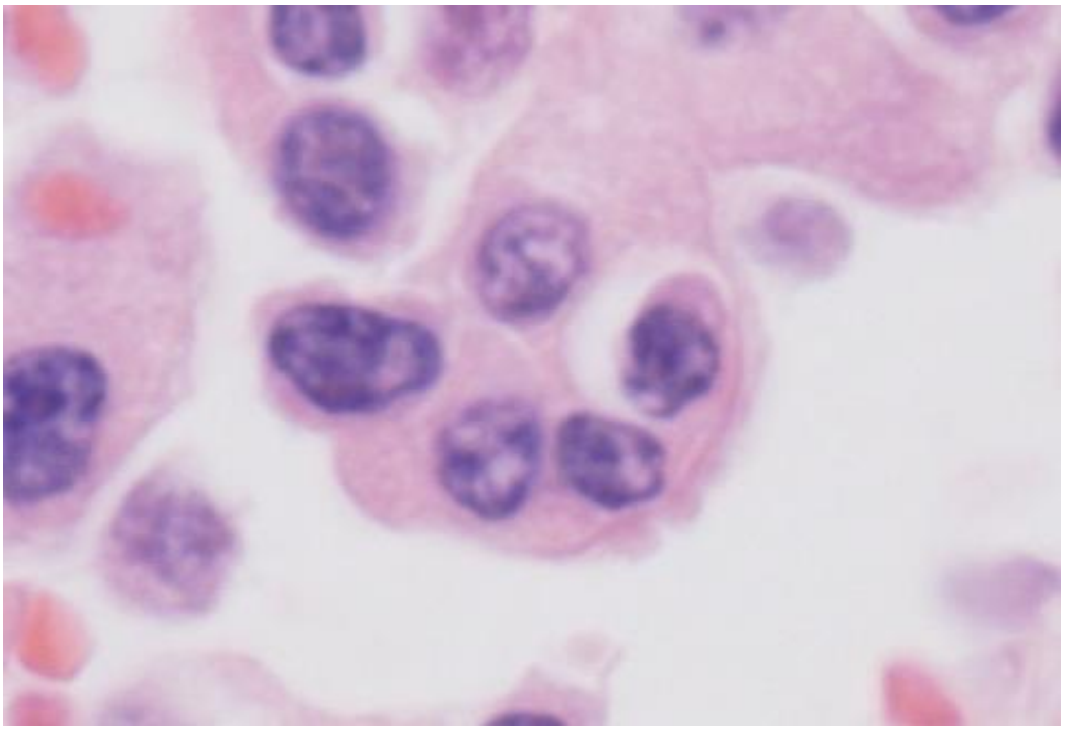

Fig. 20. Emperipolesis. Engulfment of neoplastic T lymphocytes by hepatocytes. HE

Nuclear Alterations

- **'Brick' inclusions** (Fig. 21) are rectangular to rhomboid brightly eosinophilic bodies in the nuclei of hepatocytes in dogs that are of no known cause of significance.
- **Cytoplasmic invaginations** occur as round to oval protrusions of the cytoplasm into the nucleus and are of no known significance
- **Glycogen inclusions** (Fig. 22) occur as clear inclusions in the nucleus and are of unknown significance. They are non-specific and may occur among others in diabetes mellitus and hepatocellular neoplasia
- **Intranuclear viral inclusions** (Fig. 23) may be observed in various viral infections (see hepatitis)
- **Intranuclear acid fast inclusions** have been reported in dogs with lead intoxication but are extremely rare.[13]

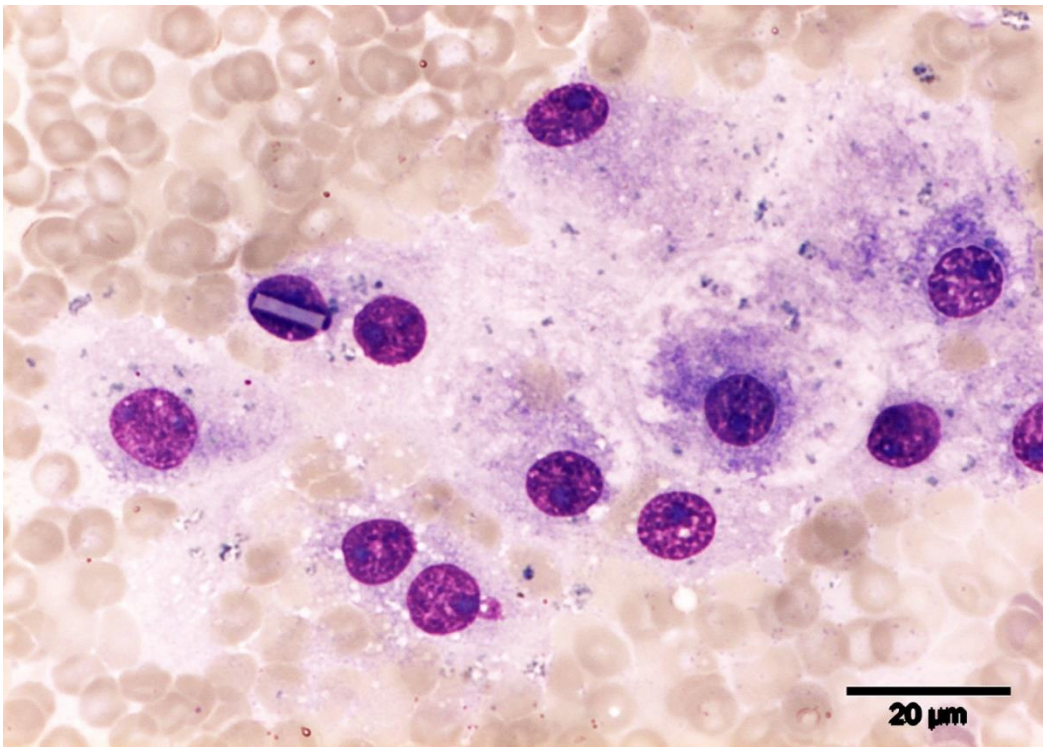

Fig. 21. Dog. Cytological specimen. Intranuclear brick inclusion. May-Grünwald Giemsa stain.

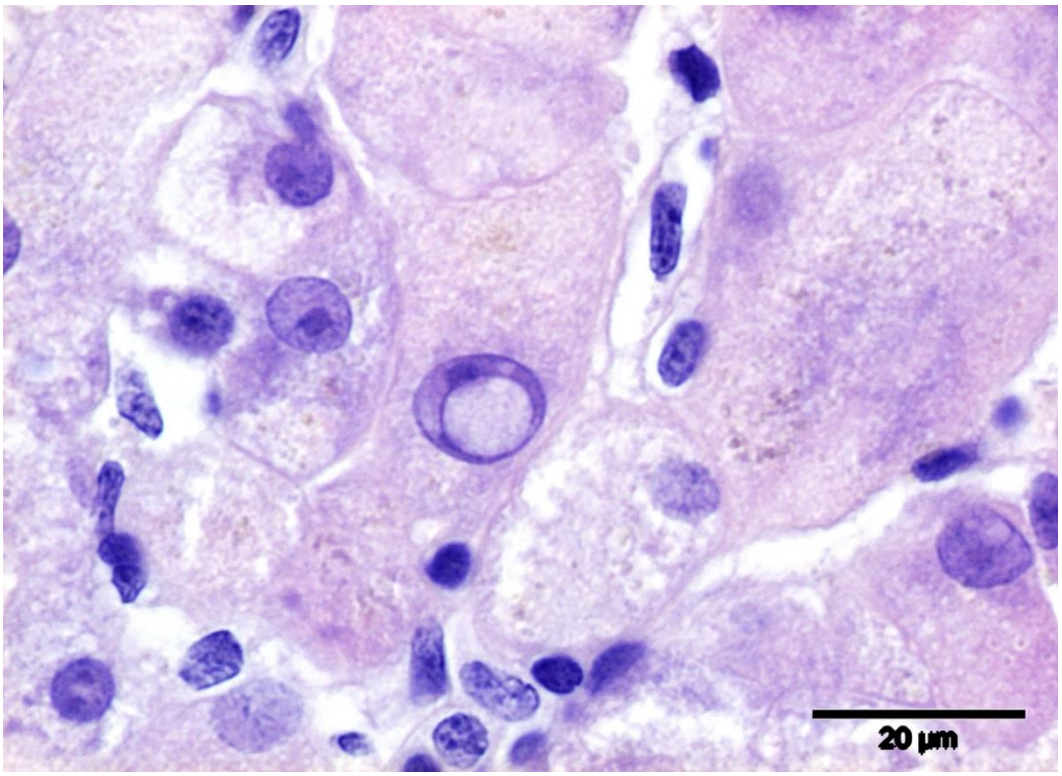

Fig. 22. Dog. Intranuclear glycogen inclusion. HE.

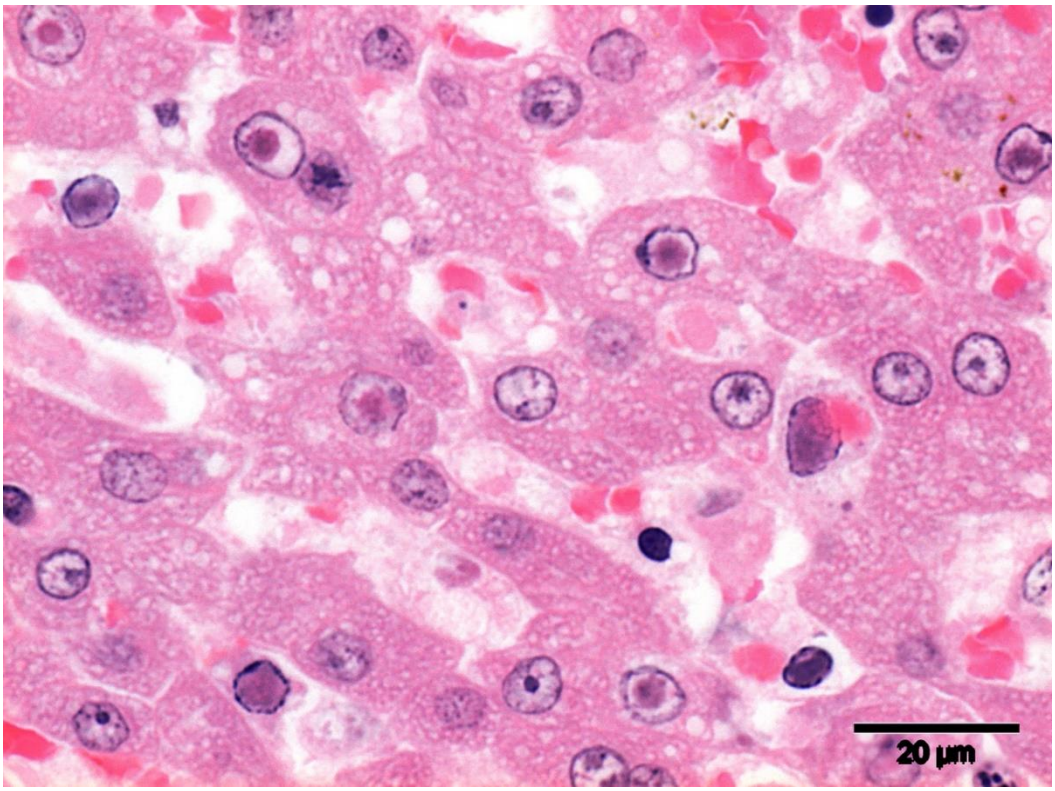

Fig. 23. Dog. Basophilic and amphophilic intranuclear viral inclusions in hepatocytes and endothelial cells. Adenovirus type 1 infection.

Hepatic stellate cells

Hepatic stellate cells have large lipid vacuoles. Increased numbers of hepatic stellate cells are observed in older cats and less pronounced in old dogs. They are recognized as solitary cells with a single large empty vacuole with displacement of the nucleus to the periphery of the cell (Fig. 24). The significance of this change is not known.

Chronic vitamin A intoxication is known in cats and causes hypertrophy and hyperplasia of lipid-laden hepatic stellate cells (Fig. 25), which show specific vitamin A autofluorescence, as well as sinusoidal fibrosis [69,70,71] with or without mild hepatocellular steatosis.

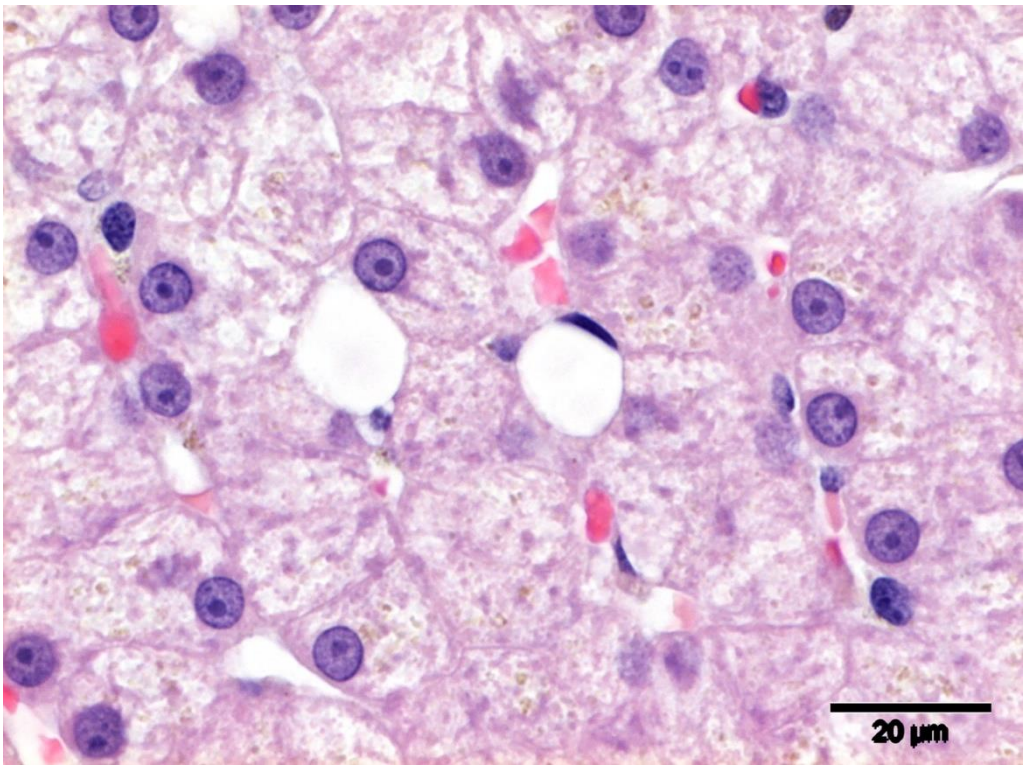

Fig. 24. Dog. Hepatic stellate cell with a large lipid vacuole and displacement of the nucleus to the periphery of the cell. HE.

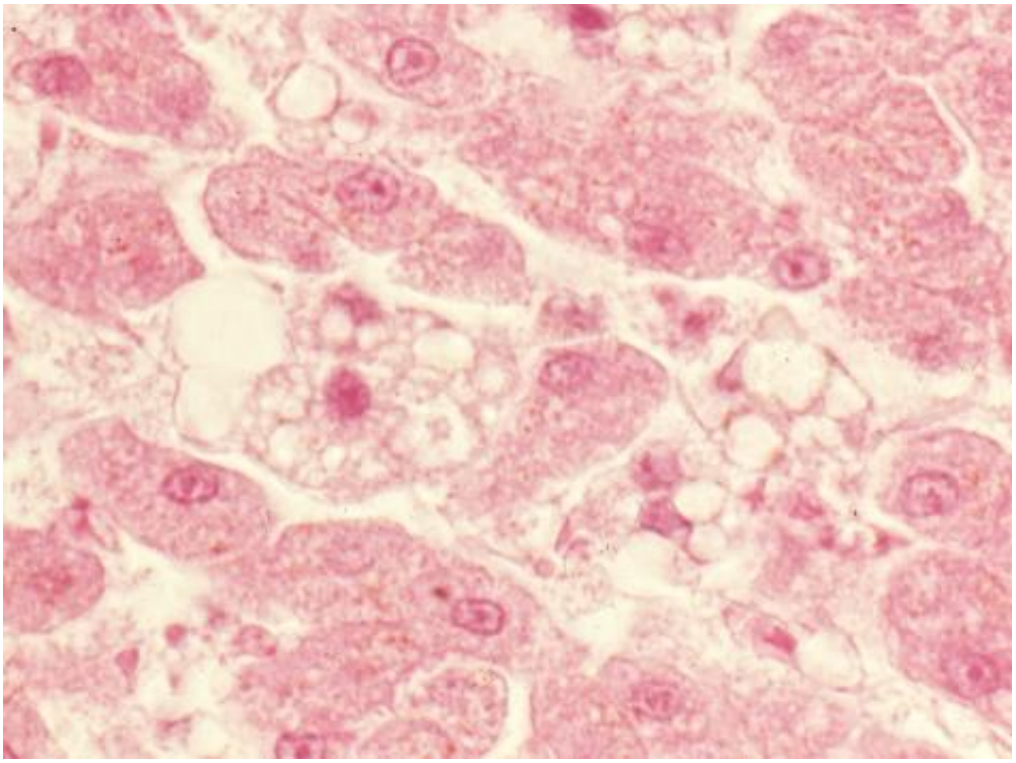

Fig. 25. Cat. Hypertrophy and hyperplasia of lipid laden hepatic stellate cells. Vitamin A intoxication. HE. (From Mouwen JMVM, De Groot ECBM. Atlas of Veterinary Pathology. Utrecht: Bunge; 1982, with permission).

Kuppfer cells

- **Necrosis** of Kupffer cells may be seen in sepsis and toxemia.
- **Erythrophagocytosis / hemosiderosis** (Fig. 26) is observed in conditions with increased red cell turnover, such as hemolytic anemia, anaemia of chronic disease and chronic hepatitis. The Kupffer cells may contain erythrocytes (erythrophagocytosis) and, or increased amounts of iron pigment (hemosiderosis)
- **Bile pigment** (Fig. 27) can be seen in cases with marked cholestasis and will be present as yellow-brown to yellow-green intracytoplasmic granules or bile plugs.
- **Eosinophilic cytoplasmic bodies** of variable size may be the result of phagocytosis of fragments of apoptotic cells by Kupffer cells.
- **Ceroid** is a yellow-brown, PAS positive, lipid breakdown product that accumulates in Kupffer cells and macrophages as a result of increased hepatocyte turnover due to necrosis / apoptosis. (Fig. 28)

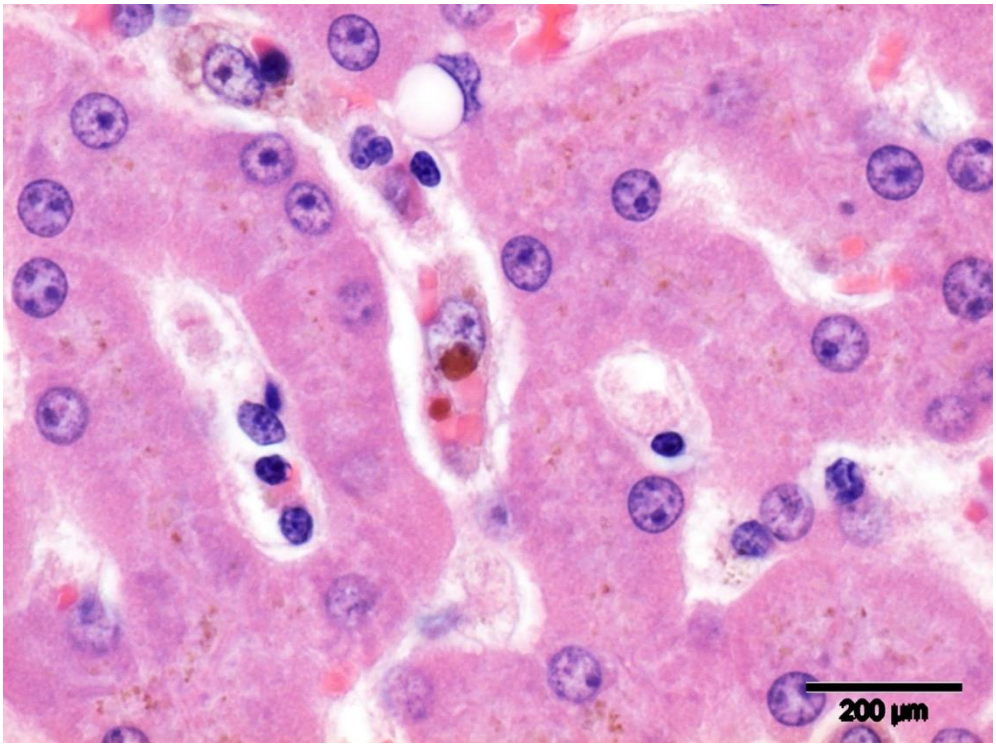

Fig. 26. Dog. Erythrophagocytosis and haemosiderosis of Kupffer cell. Immune-mediated haemolytic anaemia. HE.

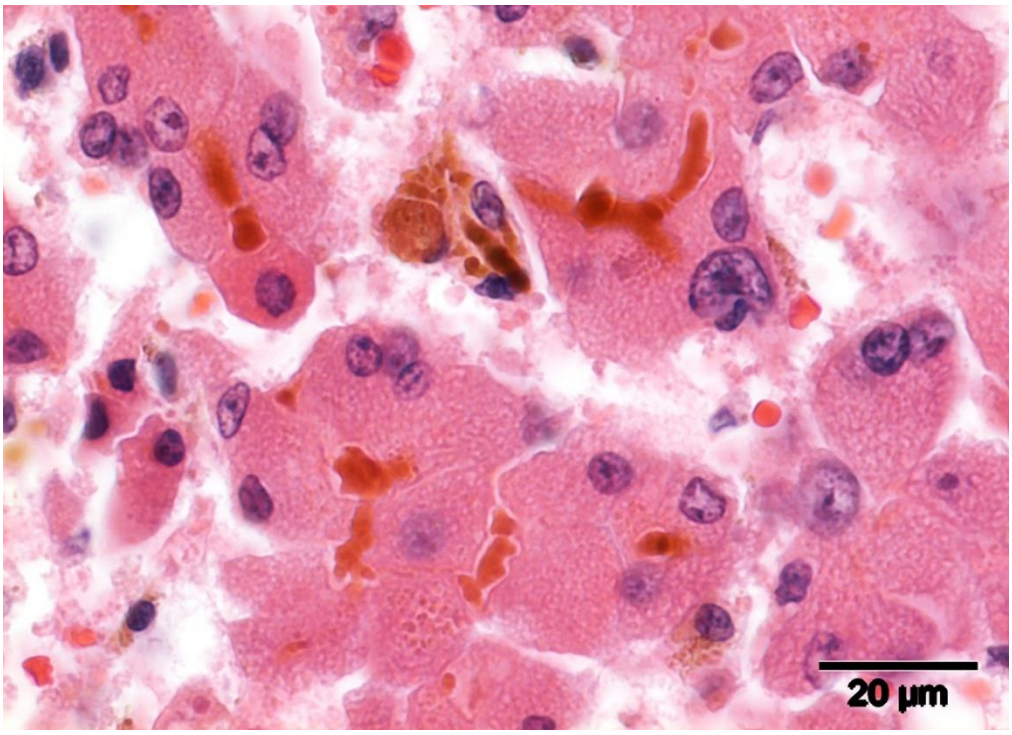

Fig. 27. Dog. Bile plugs in canaliculi and phagocytosed bile plugs in Kupffer cells. HE.

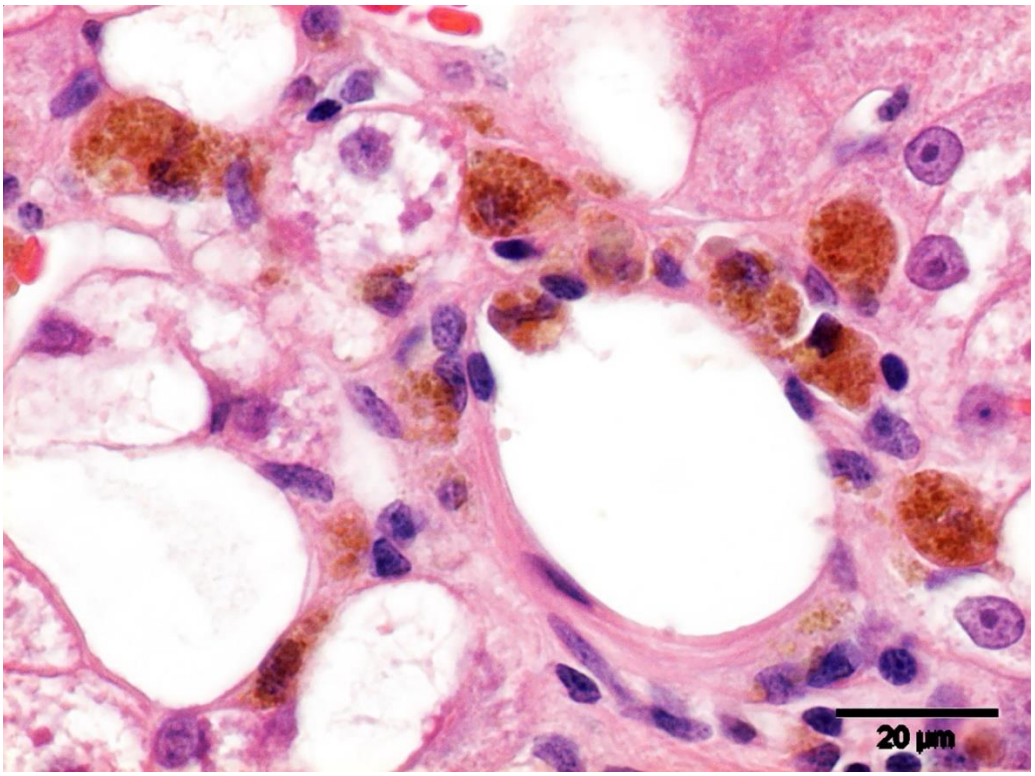

Fig. 28. Dog. Ceroid containing macrophages. HE.

Lipogranulomas and pigment granulomas

Lipogranulomas (syn : fatty cysts[14]) and pigment granulomas are poorly defined lesions of undetermined significance with overlapping features. Lipogranulomas are aggregates of

ceroid-laden, foamy fat-containing macrophages and sometimes also some lymphocytes and plasma cells (Fig. 29). They probably are associated with previous hepatocyte death and occur both in the parenchyma as well as in the portal and perivenular connective tissue. Pigment granulomas generally consist of both ceroid- and iron pigment containing macrophages (Fig. 30); often also lymphocytes or plasma cells are present. They are present throughout the parenchyma and are regularly seen particularly in older animals without known significance.

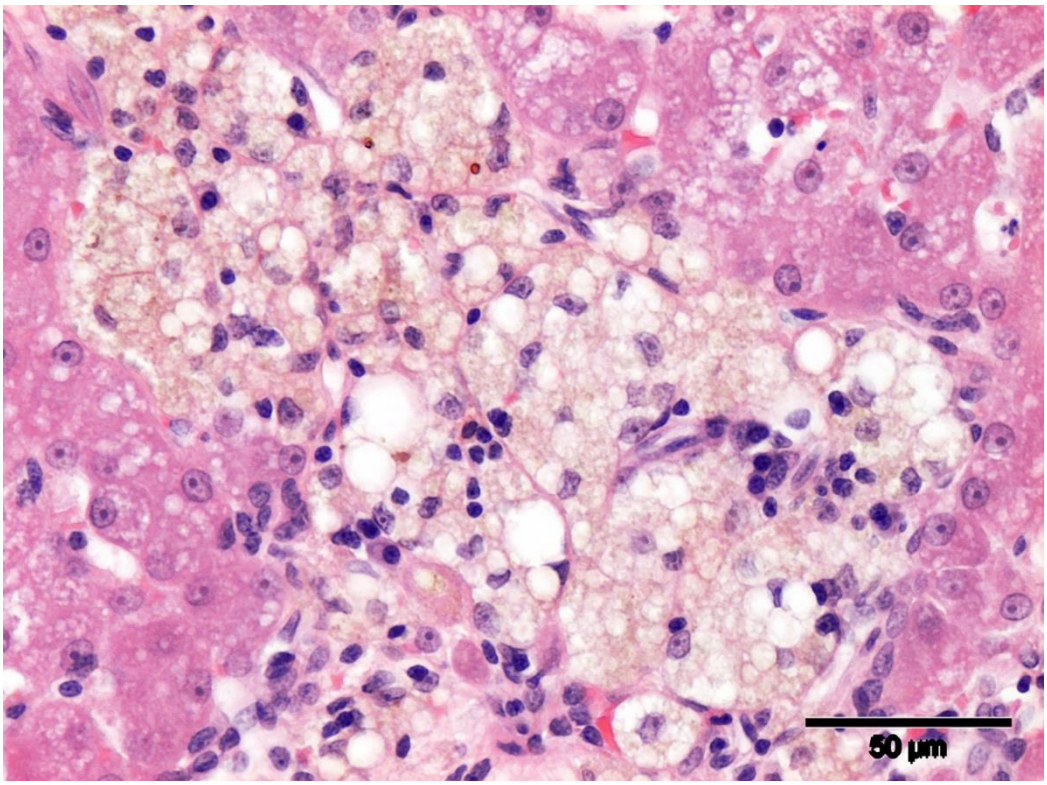

Fig. 29 Dog. Lipogranuloma. HE.

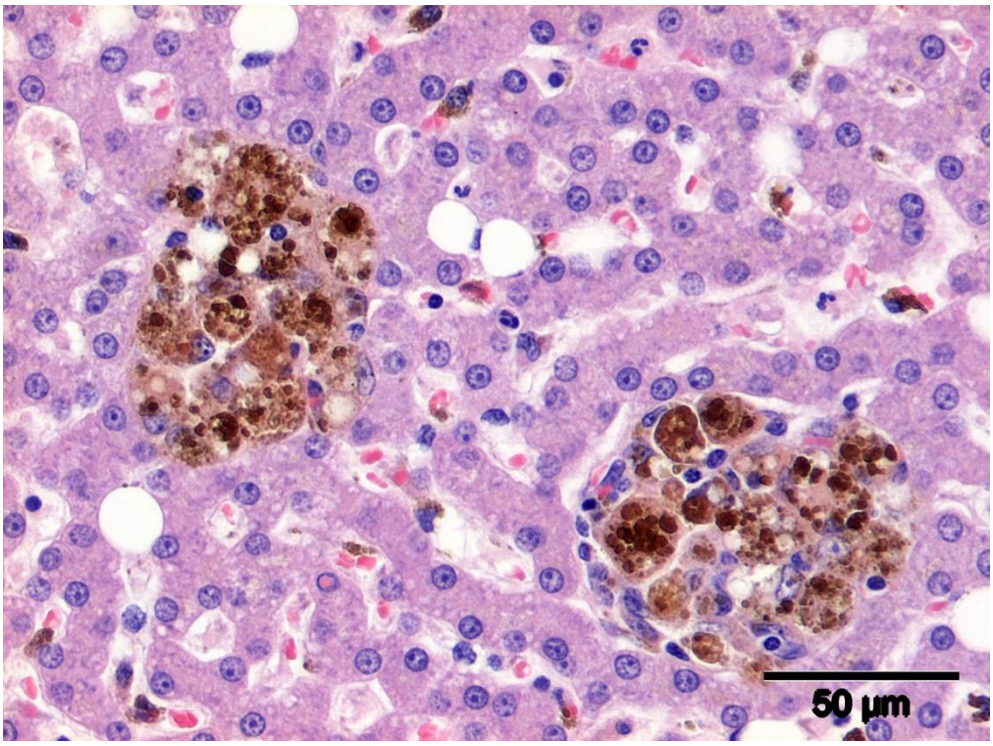

Fig. 30. Dog. Pigment granulomas. HE.

Extramedullary hemopoiesis

In both canine and feline neonates **extramedullary hemopoiesis** of all hematopoietic elements is a normal condition. Whereas the erythropoietic activity (Fig. 31) and megakaryocytes are particularly seen in the parenchyma, the myelopoiesis is mainly seen in the stromal tissue of the portal and perivenular areas. In septicaemic bacterial diseases the myelopoietic activity may be markedly increased.

In older dogs and less frequent in cats **extramedullary erythropoiesis and megakaryocytes** can be observed in immune-mediated haemolytic anaemia and thrombocytopenia. **Extramedullary myelopoiesis** (Fig. 32) is regularly seen as small foci of band and segmented neutrophils in dogs with steroid induced hepatopathy, and in chronic purulent inflammation as pyometra and pleuritis or peritonitis due to nocardiosis or actinomycosis.

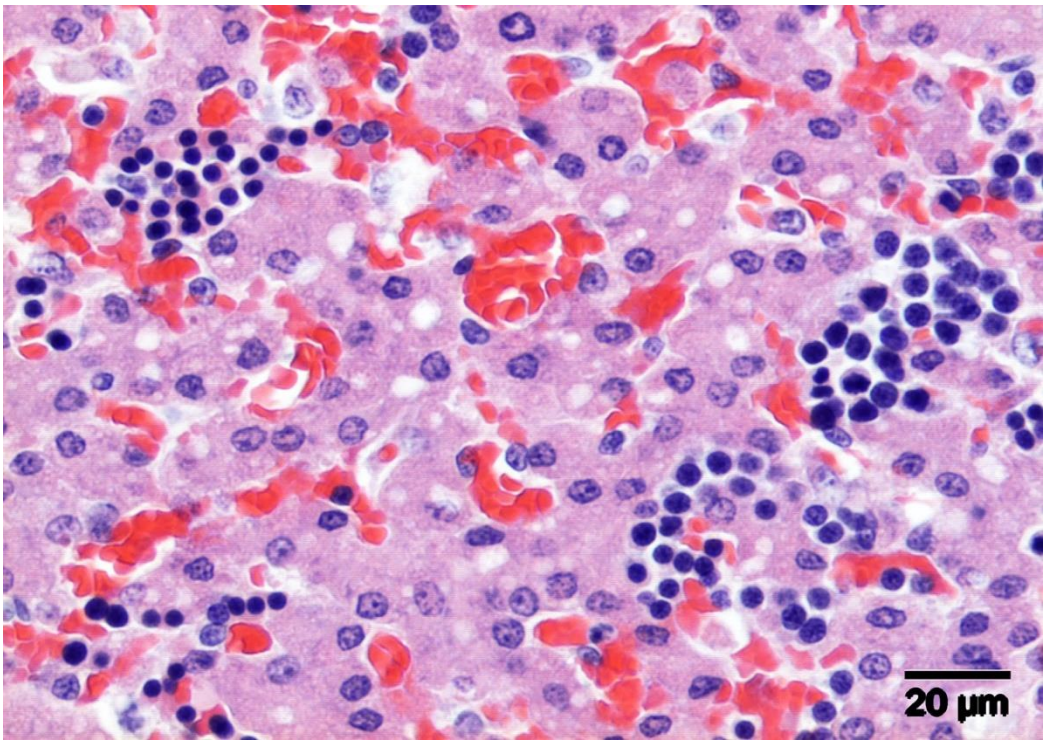

Fig. 31. Dog, neonate. Extramedullary erythropoiesis. HE.

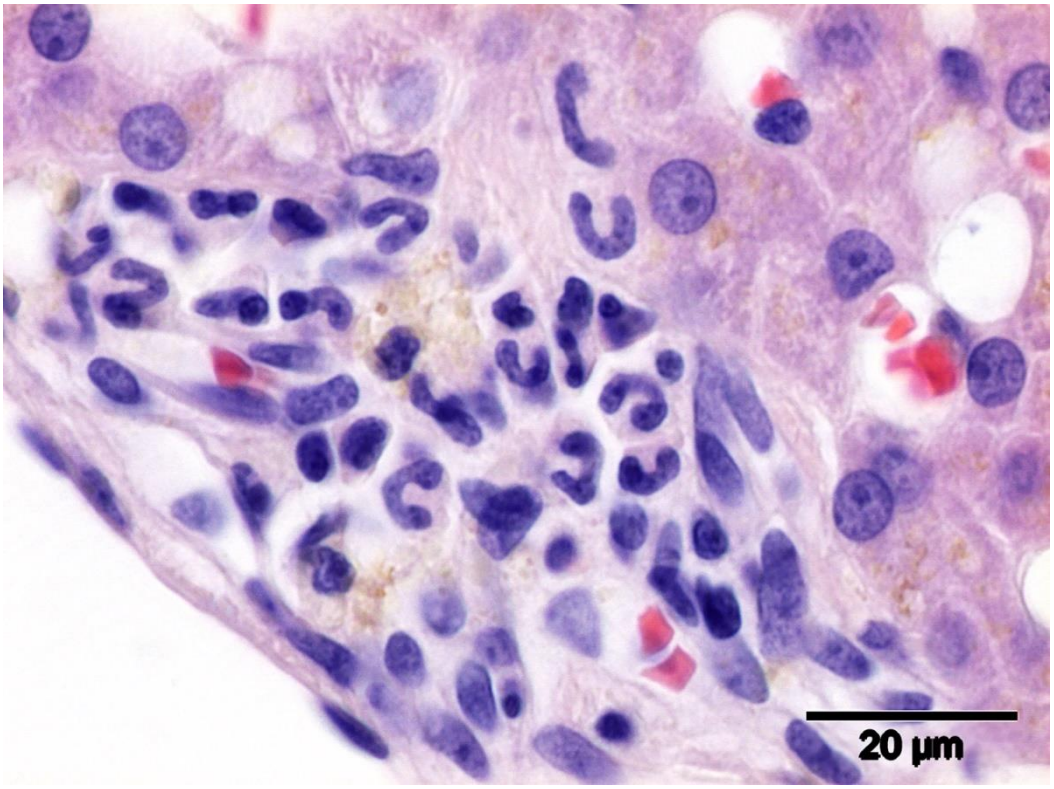

Fig. 32. Dog. Extramedullary myelopoiesis. HE.

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