Morphological classification of circulatory disorders of the canine and feline liver

John M. Cullen, Ted S.G.A.M. van den Ingh, Susan E. Bunch, Jan Rothuizen, Robert J. Washabau, Valeer J. Desmet

Updated 2021: John M. Cullen, Hille Fieten, Guy C.M. Grinwis, Ted S.G.A.M. van den Ingh

ABSTRACT

This chapter describes the nature and morphological characteristics of the normal hepatic circulation, consequences of impaired hepatic perfusion, the histological pattern of portal venous hypoperfusion, and the circulatory disorders of the liver in dogs and cats. Impaired hepatic perfusion can result in reduced portal flow, which leads to atrophy of (the deprived segment of) the liver, or ischaemia and subsequent ischaemic necrosis. Portal venous hypoperfusion causes a stereotypical histological response of the liver. In the portal tracts the profile of the portal vein becomes diminished or absent, the number of arteriolar profiles increases, and sometimes sinusoidal dilatation in the periportal areas; fibrosis and an increased number of ductular profiles may also be present. Circulatory disorders of the liver can be grouped into three major categories: congenital portosystemic shunts, disorders with outflow disturbances resulting in passive congestion of the liver, and disorders associated with deranged inflow of portal blood and portal hypertension. Congenital portosystemic shunts (CPSS) are single large calibre vascular anomalies that directly connect the portal venous system with the systemic venous circulation. The liver histologically shows the typical characteristics of portal venous hypoperfusion. Outflow disturbances of the liver result in acute or chronic passive congestion and usually result from cardiac failure. Portal hypertension with resultant portosystemic collateral circulation and ascites mainly results from chronic primary liver disease, particularly cirrhosis. Portal hypertension may also be the result of a primary vascular lesions as primary hypoplasia of the portal vein, obstruction (thrombosis) of the portal vein, and intrahepatic arterio-venous fistula. Primary hypoplasia of the portal vein histologically shows the typical pattern of portal venous hypoperfusion. Animals with longstanding portal vein obstruction and intrahepatic arterio-venous fistulas, apart from the usually localized primary lesion, often also show this pattern with hypoplasia of the portal vein and an increased number of arteriolar profiles in the portal tracts. Finally, other vascular disorders are described. In addition diagnostic methods required for diagnosis of circulatory disorders of the liver are discussed.

INTRODUCTION

For the recognition of the lesions associated with the various circulatory disorders in dogs and cats, it is essential to understand the normal hepatic circulation, and to know the consequences of impaired hepatic perfusion as well as the histological pattern of portal venous hypoperfusion. The circulatory disorders of the liver in dogs and cats can be categorized as congenital portosystemic shunts, disorders associated with outflow disturbances resulting in passive congestion, and disorders associated with portal hypertension.

The diagnosis of most of the circulatory diseases does not depend on histological evaluation of the liver. For congenital portosystemic shunts, ultrasonography and, or computed tomography are the most important diagnostic tools as explained in detail in Chapter 3. Intrahepatic arterio-venous fistulae are also diagnosed by ultrasonography/computed tomography. Primary portal vein hypoplasia, however, should be diagnosed on the basis of negative ultrasonography/computed tomography of the portal vasculature and the typical but non-specific findings of histology of the liver. Blood tests to find or exclude portosystemic collateral circulation (either acquired due to portal hypertension or due to congenital portosystemic shunts) are the plasma bile acid and ammonia concentrations. Functional testing can be performed by postprandrial bile acid measurement or ammonia tolerance test (rectal or oral), respectively. Finally, there are several scintigraphic techniques using ^{99}mTechnetium to demonstrate or quantify portosystemic shunting. The critical diagnostic steps of the vascular disorders of the liver are summarized in Table 1 at the end of the chapter.

NORMAL HEPATIC CIRCULATION

The liver is supplied with blood by the hepatic artery and the portal vein. The portal vein drains the splanchnic viscera i.e. stomach, intestine, spleen and pancreas, and normally contributes to approximately 70 percent of the total hepatic blood flow.(1) The portal vein is formed by the confluence of cranial and caudal mesenteric veins and receives the splenic and gastroduodenal vein before it enters the liver at the porta hepatis. (2, 3). Here the portal vein divides into a short right branch and a large left branch. The right branch serves the right side of the liver whereas the left branch serves the left and central divisions of the liver. They then subdivide into successively smaller branches.(4) The intrahepatic portal vein branches are situated in the portal areas and represent by far the largest structure in the portal areas (Fig. 1).

The terminal branches, present in the smallest portal areas, finally give rise to the inlet venules which penetrate the periportal limiting plate and open into the sinusoids. The hepatic artery accompanies the portal vein and two or more branches may be present within each portal area. The terminal distribution of the arteries is by three routes, i.e. the periportal plexus, which is characteristically distributed around portal vein branches within the portal area, the peribiliary plexus, which supplies all the intrahepatic bile ducts, and the terminal hepatic artery branches, which have an internal elastic lamina and a layer of smooth muscle cells and open directly into periportal sinusoids.[1] The hepatic artery also supplies the Glisson's capsule and some arteries supply the hepatic venous plexus surrounding the larger draining hepatic veins. From the sinusoids the blood enters directly into the terminal hepatic veins (synonym: central veins) (Fig 2).

Sphincters in the wall of these arterioles, in the inlet venules and at the outlet of the sinusoids to the hepatic veins regulate the lobular microcirculation and hence probably parenchymal

function.[1] The terminal hepatic veins unite to form the intercalated or sublobular veins which in turn anastomose to form the large hepatic veins which finally drain into the caudal caval

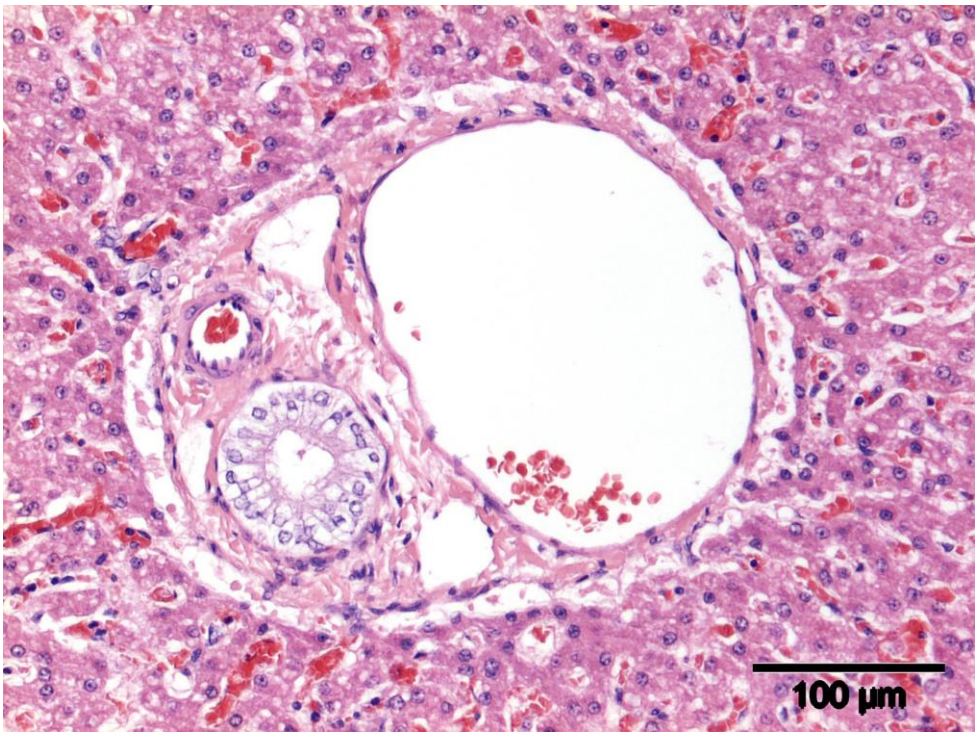

Fig. 1. Dog. Portal area with normal profiles of the portal vein, hepatic artery and bile duct. Dilated lymphatics. HE.

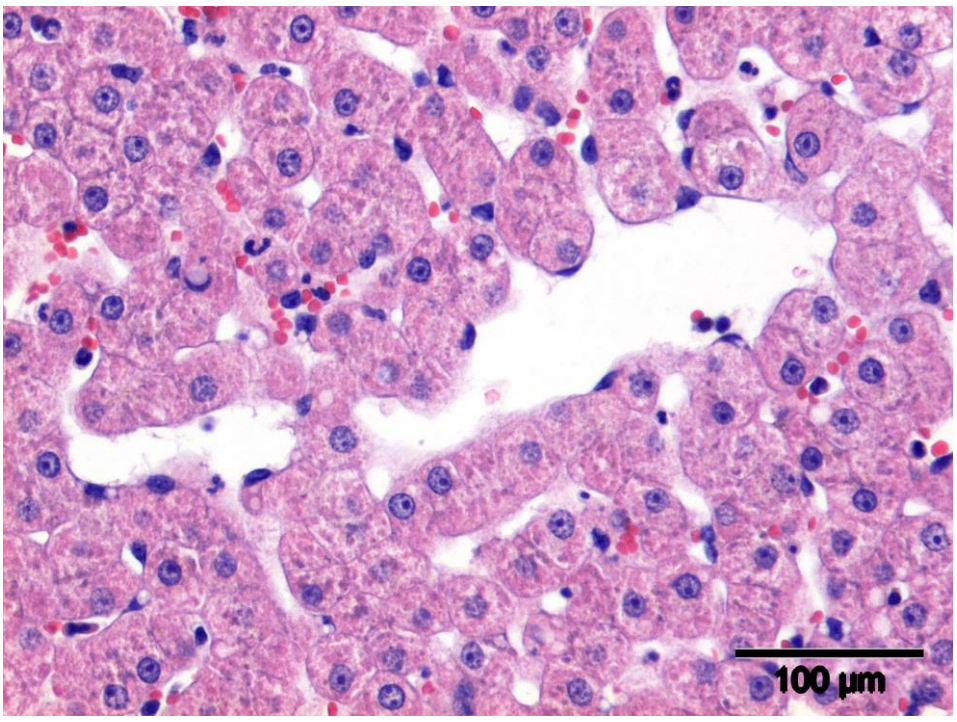

Fig. 2. Cat. Terminal hepatic vein with draining sinusoids. HE.

vein. In dogs, the sublobular or intercalated hepatic veins are characterized by a relatively thin wall with a spiral shaped smooth muscle and are surrounded by loosely structured stromal tissue (Fig.3) [5], whereas in cats they are characterized by a relatively thick fibrous wall (Fig.4).

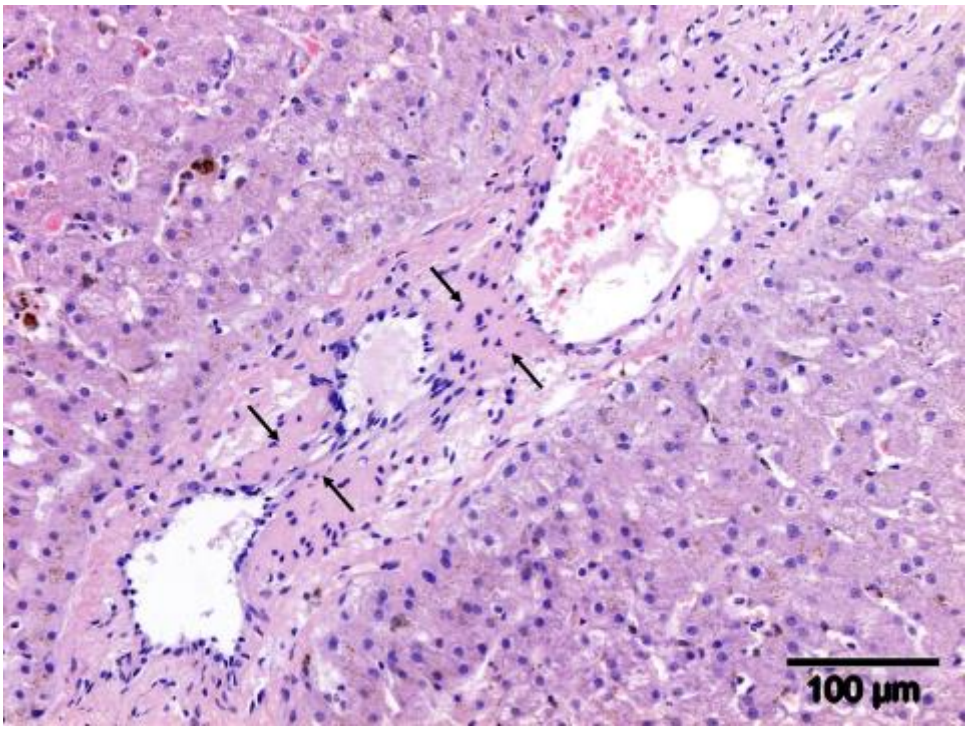

Fig. 3. Dog. Normal sublobular hepatic vein characterized by a relatively thin wall with a spiral shaped smooth muscle (arrows) and surrounded by loosely structured stromal tissue. HE.

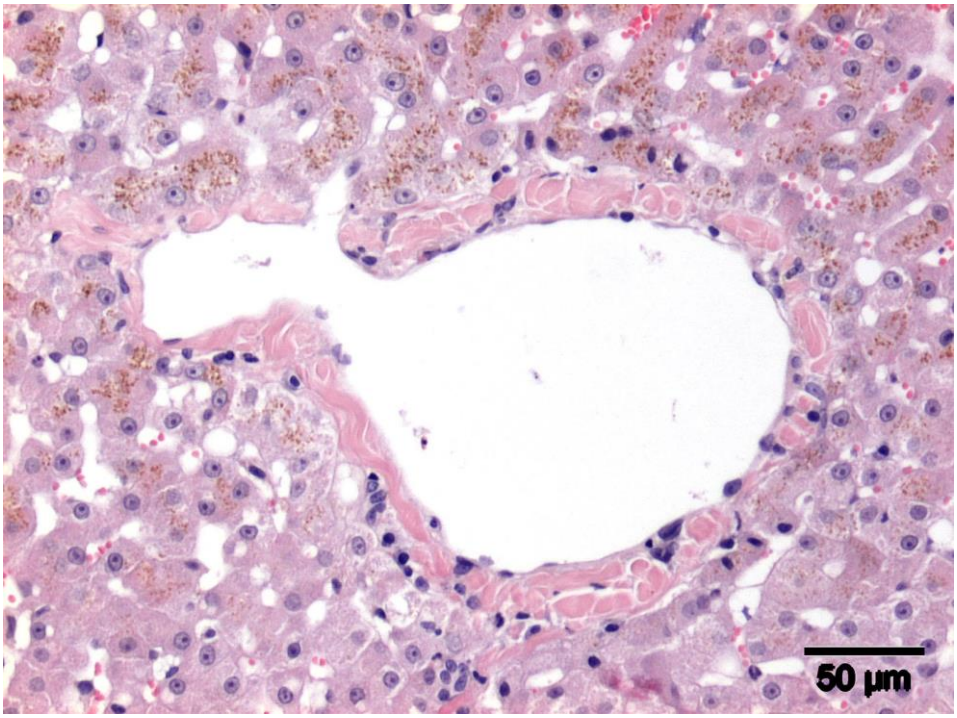

Fig. 4. Cat. Transition of terminal hepatic vein to the sublobular hepatic vein which is characterized by a relatively thick fibrous wall. HE.

While the portal vein supplies the larger amount of blood to the liver, the liver is not capable of directly controlling this flow and changes in flow within the portal vein are largely determined by factors affecting intestinal blood flow. So, hepatic blood flow increases after feeding and decreases during sleep and exercise. Total hepatic blood flow is regulated by hepatic artery autoregulation, which means that if portal flow increases, arterial flow will decrease, and vice-versa.[6, 7]

Although the liver normally produces large quantities of lymph fluid, lymph vessels are hardly observed under normal conditions. With increased lymph production dilated lymphatics can be observed at three possible locations i.e. in the portal areas (Fig. 1), around the larger hepatic veins and in the Glisson's capsule. Lymph vessels, however, do not exist in the hepatic parenchyma due to the peculiar structure of the hepatic sinusoids. [1]

In fetal life the umbilical vein contributes markedly to the afferent hepatic flow; it usually communicates with the portal vein where the portal vein divides into the (intra)lobular) veins of the left central and lateral liver lobes. Most umbilical blood is directed towards the ductus venosus, a fetal connection between the portal vein and the posterior caval vein situated opposite the inflow opening of the umbilical vein. [4] Thus the umbilical blood directly streams into the posterior caval vein, bypassing the sinusoidal vascular bed of the liver. After birth the ductus venosus closes by sphincteric contraction and subsequently disappears. Functional closure occurs within 3 days, whereas structural closure takes 15 to 18 days in the dog. [8]. The umbilical vein obliterates, forming the ligamentum teres hepatis (synonym: round ligament).

CONSEQUENCES OF IMPAIRED HEPATIC PERFUSION

The function of the liver is highly dependent on adequate perfusion and hence malperfusion may cause gross and microscopic pathological changes in the liver and clinical disease.

1 Hepatic atrophy

Maintenance of the mass and function of the hepatic parenchyma is largely determined by hepatic perfusion, particularly by the quantity and quality of the portal blood. This contains many nutrients and specific hepatotrophic factors. Lack of nutrients and hepatotrophic factors in the portal blood e.g. in cachexia, or deprivation of these factors by reduced portal blood flow, leads to atrophy (of the deprived segment) of the liver. Regionally decreased perfusion of the liver (for example thrombosis of the left branch of the portal vein) often results in increased hepatic flow and hypertrophy of the remaining (right) part of the liver (Fig. 5). [9]

2 Peliosis hepatis

Peliosis hepatis is defined as randomly distributed, cystic blood-filled spaces in the liver and occurs rarely in dogs and is more common in cats. [10, 11] These may result from local obstruction of small branches of the portal vein with subsequent focal hepatic atrophy and

sinusoidal dilatation (phlebectatic type, also called teleangiectasis (Fig. 6)), or from focal hepatocytic necrosis (parenchymal type) (Fig. 7).

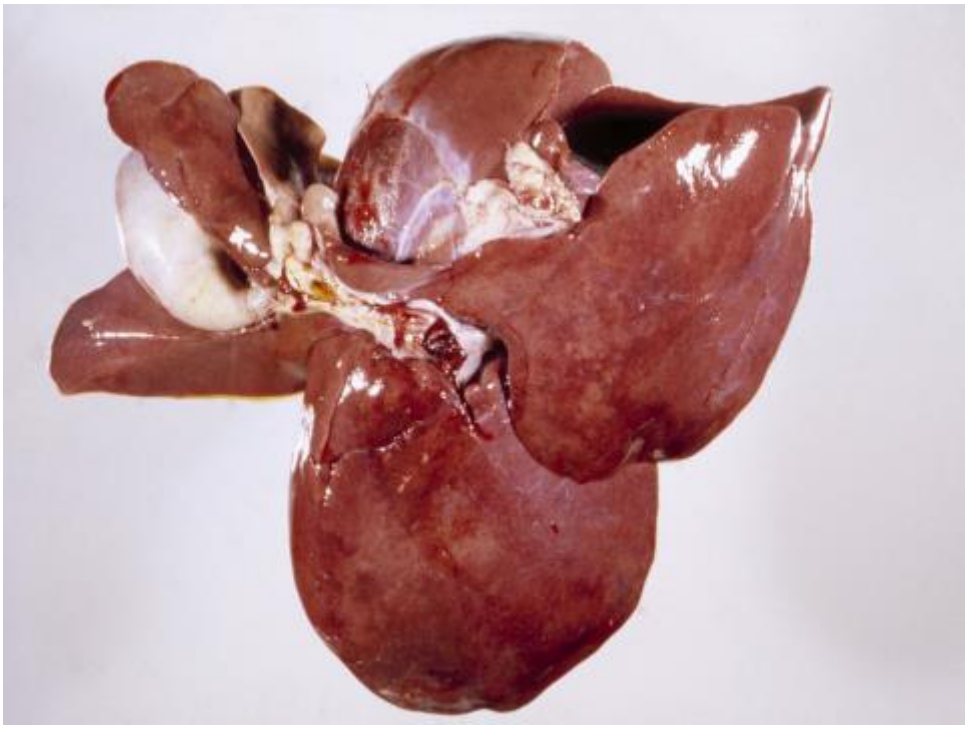

Fig. 5. Dog. Left sided atrophy of the liver due to thrombosis of the left branch of the portal vein and compensatory hypertrophy of the right side of the liver.

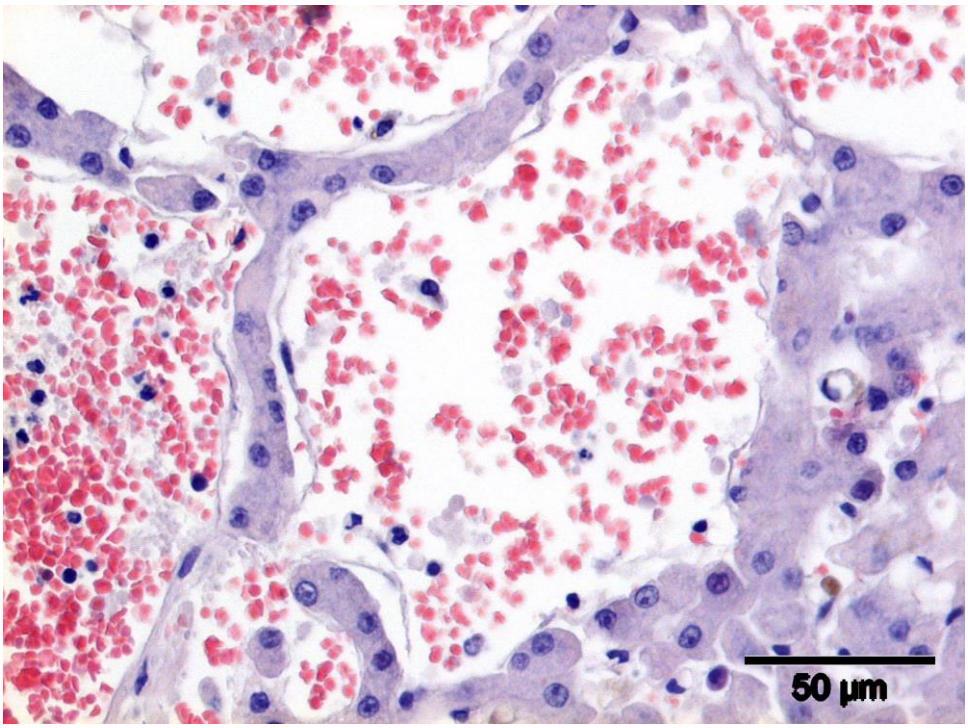

Fig. 6. Cat. Peliosis. phlebectatic type witth intact endothelium. HE.

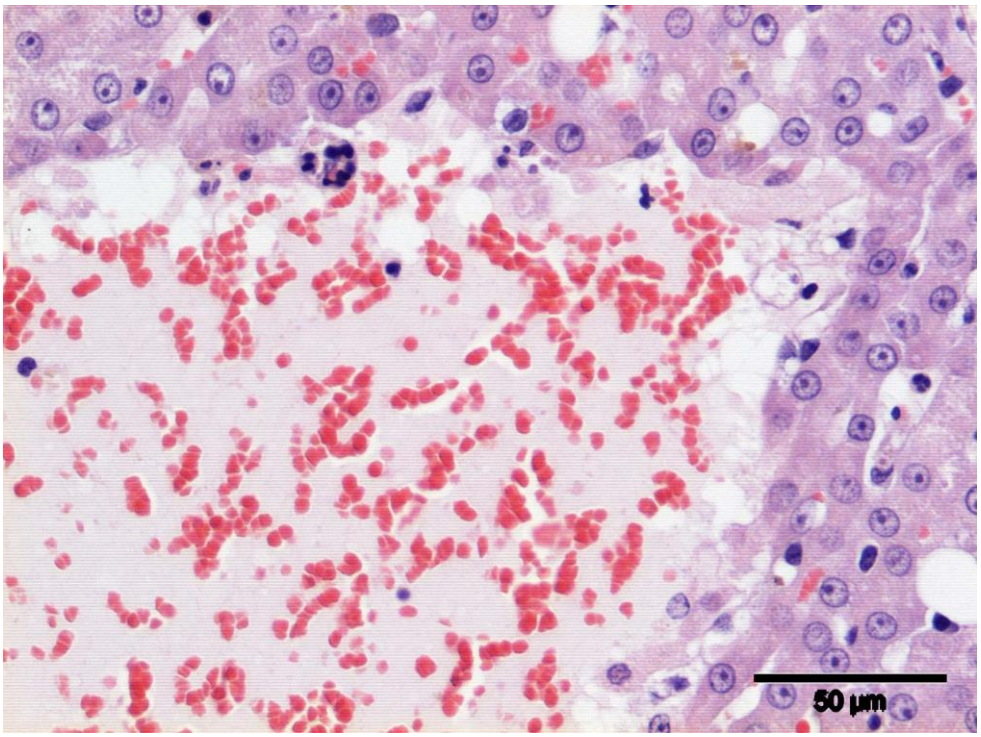

Fig. 7. Cat. Peliosis. parenchymal type, necrosis and absence of endothelium HE.

A strict division in these two types may be not as clear as suggested above as both types can be seen in the same animals. [11] They may even have an identical pathogenesis whereby the phlebectatic type represents a more slowly developing lesion with focal portal venous hypoperfusion and the parenchymal type an acute and more severe obstructive and ischaemic lesion (vide infra). Teleangiectasis associated with prolonged use of steroids, as observed in man, has an unknown pathogenesis and until now has not been observed in dogs and cats.

3 Ischaemic hepatic necrosis

The parenchyma of the liver is protected against ischaemia by its double blood supply and, in the healthy dog, the liver can survive complete loss of perfusion by either the portal vein or the hepatic artery without infarction.

Infarction of the liver

Infarction of the liver occurs infrequently and usually results from combined obstruction of hepatic artery and portal vein or portal vein / hepatic artery obstruction in combination with hepatic vein obstruction, with subsequent acute ischaemia and hepatic necrosis. Infarcts tend to occur at the outer margins of the liver and are grossly recognized as sharply delineated pale or dark red areas (Fig. 8). [12, 13]

Generalized centrolobular ischaemic necrosis

Generalized centrolobular ischaemic necrosis is much more common than other patterns (Fig.9) and occurs with (cardiac) shock when arterial flow and portal vein oxygen saturation are decreased simultaneously or with severe (acute) anaemia. [14]

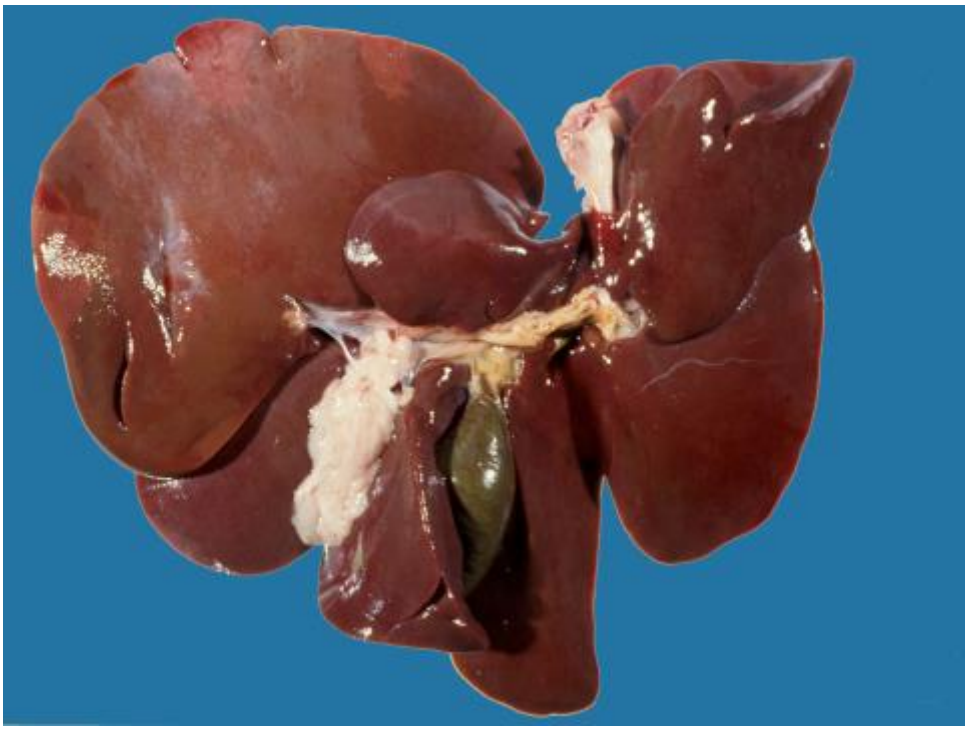

Fig. 8. Dog. Multiple pale well delineated infarcts at the outer margin of the liver.

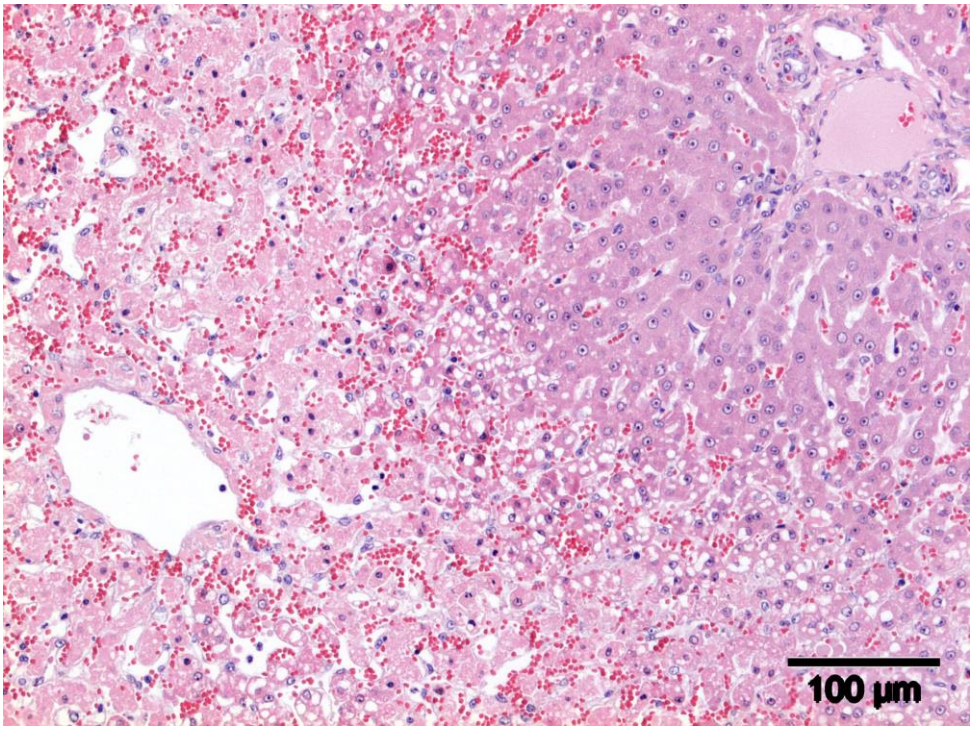

Fig. 9. Cat. Generalized centrolobular ischaemic necrosis associated with acute cardiac decompensation (cardiac shock). HE.

Focal ischaemic necrosis

Focal ischaemic necrosis is particularly associated with disseminated intravascular coagulation and associated focal thrombotic obstruction of sinusoids with subsequent ischaemic necrosis of adjacent hepatocytes (Fig. 10).

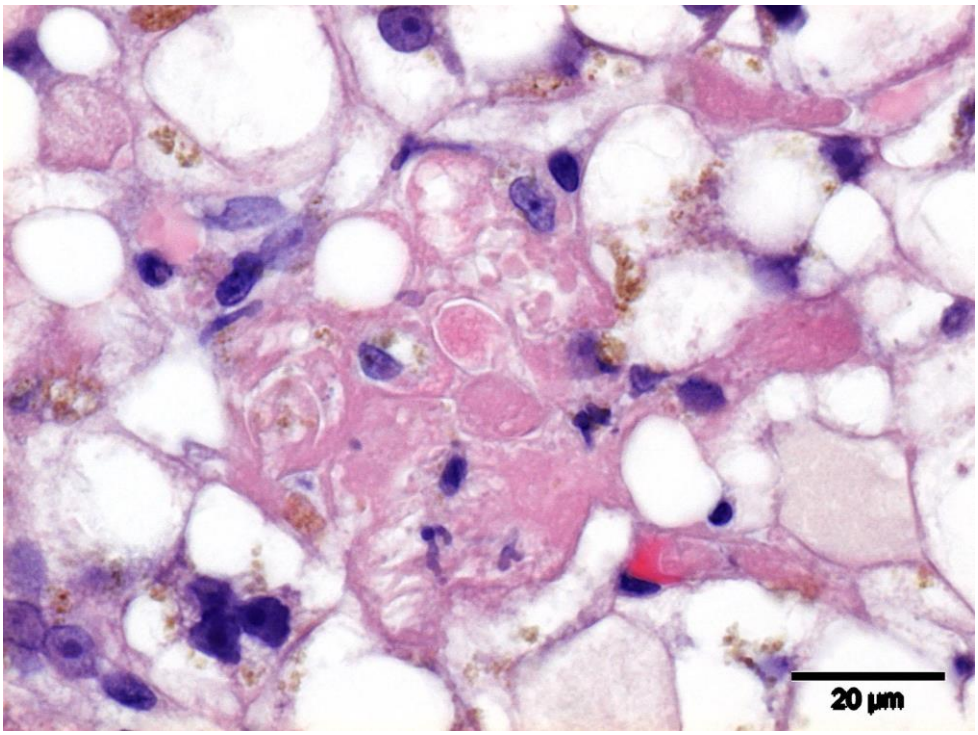

Fig. 10. Dog. Focal ischaemic necrosis associated with disseminated intravascular coagulation and thrombus formation in the sinusoids. HE.

HISTOLOGICAL PATTERN OF PORTAL VEIN HYPOPERFUSION

One of the principal challenges to the pathologists trying to diagnose vascular disorders of the liver is the stereotypical histological response of the liver to inadequate portal vein flow (Fig. 11). With decreased portal blood flow, the profile of the portal vein in the portal tracts becomes diminished or absent. Hepatic arteries respond to hypoperfusion of the liver and increase their blood flow.[6, 7] As a result they become more tortuous and hypertrophied and, or may proliferate. This produces histologically an increased number of arteriolar profiles in the portal tracts and probably makes formerly inapparent intralobular arterioles more prominent. Sometimes, also an increased number of biliary profiles and slight portal fibrosis may occur. Additional changes in the parenchyma which may be seen are hepatocellular atrophy, the presence of lipogranulomas and sinusoidal dilatation particularly in the periportal areas. The latter probably is the result of the increased arterial hepatic flow with focal increased sinusoidal pressure and subsequent sinusoidal dilatation.

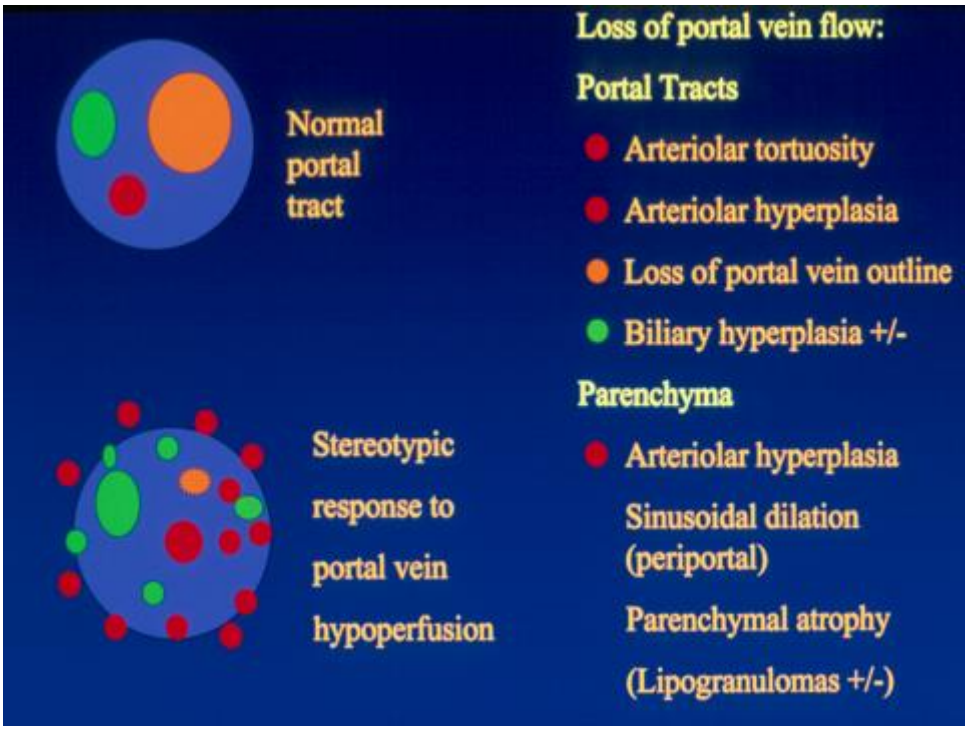

Fig. 11. Schematic presentation of stereotypical response of the liver to portal vein hypoperfusion.

The classic example of this stereotypic reaction of portal vein hypoperfusion in the dog is the Eck's fistula, an experimental surgically produced portocaval shunt (Fig.12). Similar lesions are seen in various circulatory disorders associated with portal venous hypoperfusion like congenital portosystemic shunts, intrahepatic arterio-venous fistulas, primary hypoplasia of the portal vein, and obstruction of the portal vein (vide infra). Some of these characteristics also may be seen in primary chronic liver diseases associated with portal hypertension as cirrhosis or congenital hepatic fibrosis, in which there also exists persistent decreased portal blood flow and increased arterial hepatic flow.

CIRCULATORY DISORDERS OF THE LIVER

Circulatory disorders of the liver can be grouped into three major categories: congenital portosystemic shunts, disorders with outflow disturbances resulting in passive congestion of the liver, and disorders associated with deranged inflow of portal blood and portal hypertension. Histological examination of liver biopsies can aid in the diagnosis of all of these disorders, but due to considerable overlap in the appearance of several of these conditions, additional clinical, biochemical, or imaging information may be needed to formulate a final diagnosis. The relationship of the different procedures needed to make a diagnosis is summarized in Table 1 at the end of the chapter.

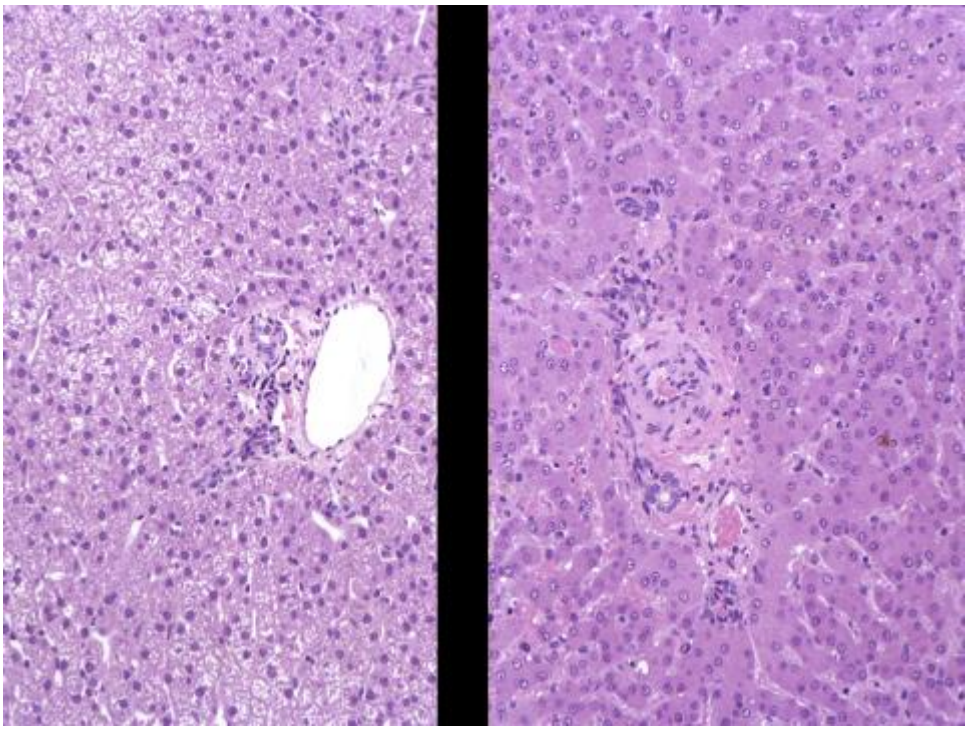

Fig. 12. Dog, Eck's fistula. Preoperative (left) normal aspect of the portal area and postoperative (right) aspect with loss of portal vein profile and proliferation of arterioles. HE.

1 Congenital portosystemic shunts

Congenital portosystemic shunts (CPSS) are single large calibre vascular anomalies that directly connect the portal venous system with the systemic venous circulation. CPSS are more frequently seen in dogs than in cats. They may be intrahepatic or extrahepatic. Intrahepatic shunts result from a failure of the ductus venosus to close after birth. They are mostly originating from the left branch of the portal vein, which is consistent with the normal embryology of the ductus venosus. Sometimes they originate from the right branch of the portal vein and drain directly into the posterior caval vein (Fig. 13).

Extrahepatic shunts represent abnormal functional communications; they may arise from any part of the portal system and may drain in the caudal caval vein or the (hemi) azygos vein. In the dog most extrahepatic shunts originate at the junction of the splenic and the left gastric vein. The shunt may receive its main volume of blood directly from the splenic vein, or from the gastroduodenal vein via the communicating right and left gastric vein. The drainage site at the caudal caval vein is usually situated between the phrenico-abdominal vein and the liver. In the dog, intrahepatic shunts are most often seen in large breeds, whereas in small breeds the shunts are usually extrahepatic. In the cat both intrahepatic and extrahepatic shunts occur; extrahepatic shunts vary widely with respect to their origin and course. [(9)]

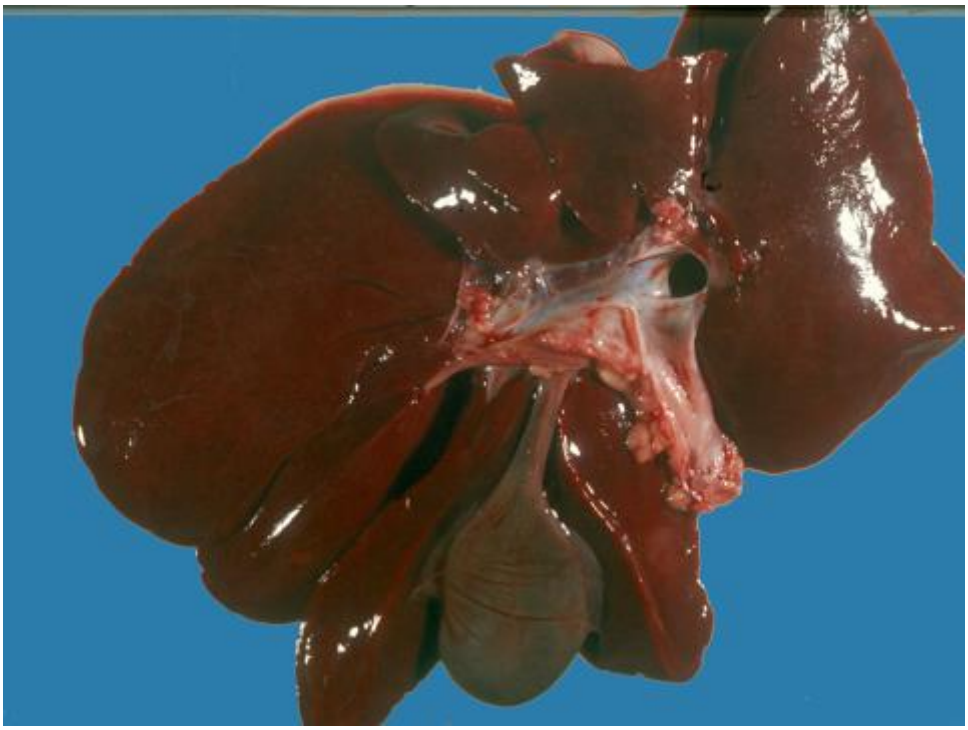

Fig. 13. Dog. Congenital intrahepatic portosystemic shunt originating from the right branch of the portal vein.

The pathological changes of CPSS are secondary to the shunting of blood past the liver. Macroscopic changes are liver atrophy, and when there is an extrahepatic shunt, hypoplasia of the portal vein downstream the origin of the shunt. The degree of change in the hepatic histology is probably a function of the amount of portal blood that is diverted from the liver and may vary between liver lobes depending of the site of the shunt vessel, particularly with intrahepatic shunts. The histological changes are characteristic for portal venous hypoperfusion (vide supra) and consist of loss of portal vein profiles, increased numbers of arteriolar profiles, hepatocellular atrophy with lipogranulomas and sometimes periportal sinusoidal dilatation (Fig. 14, 15). The histologic appearance of affected cats and dogs is similar.

Both intrahepatic and extrahepatic portosystemic shunts are most likely hereditary as a digenic mode of inheritance has been shown in Irish Wolfhounds with intrahepatic shunts and a multigenic or complex mode of inheritance has been shown in Cairn teriers with extrahepatic portosystemic shunts[46].

An important clinical feature of this disorder is that portal hypertension does not occur.

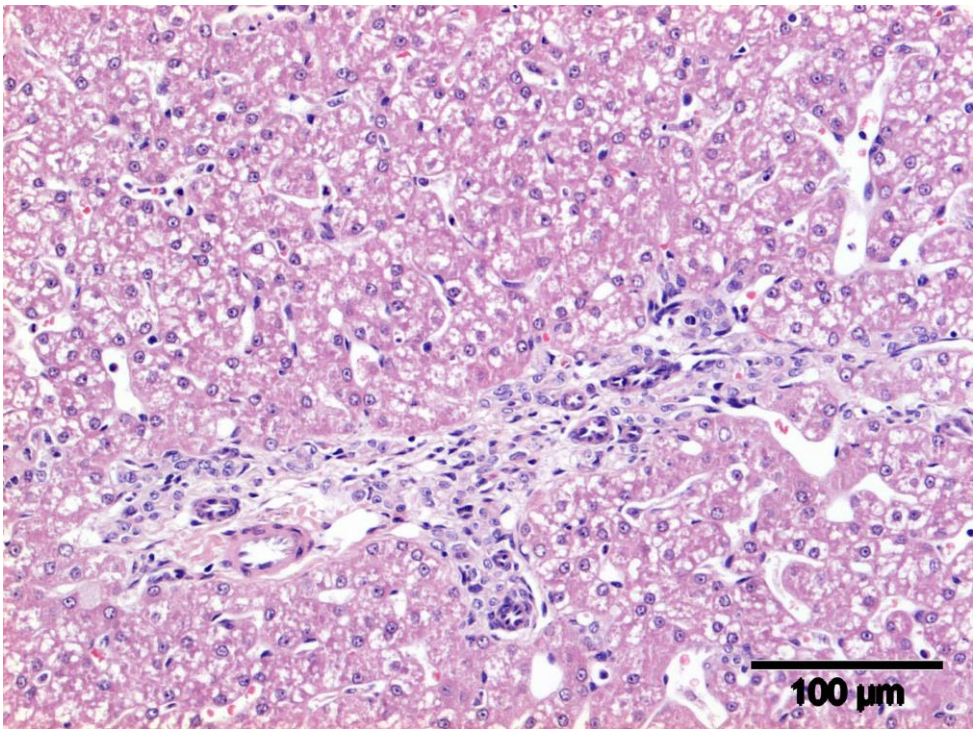

Fig. 14. Dog. Congenital portosystemic shunt. Portal area without recognizable portal vein and arteriolar proliferation. Some dilated sinusoids in the periportal hepatic parenchyma. HE.

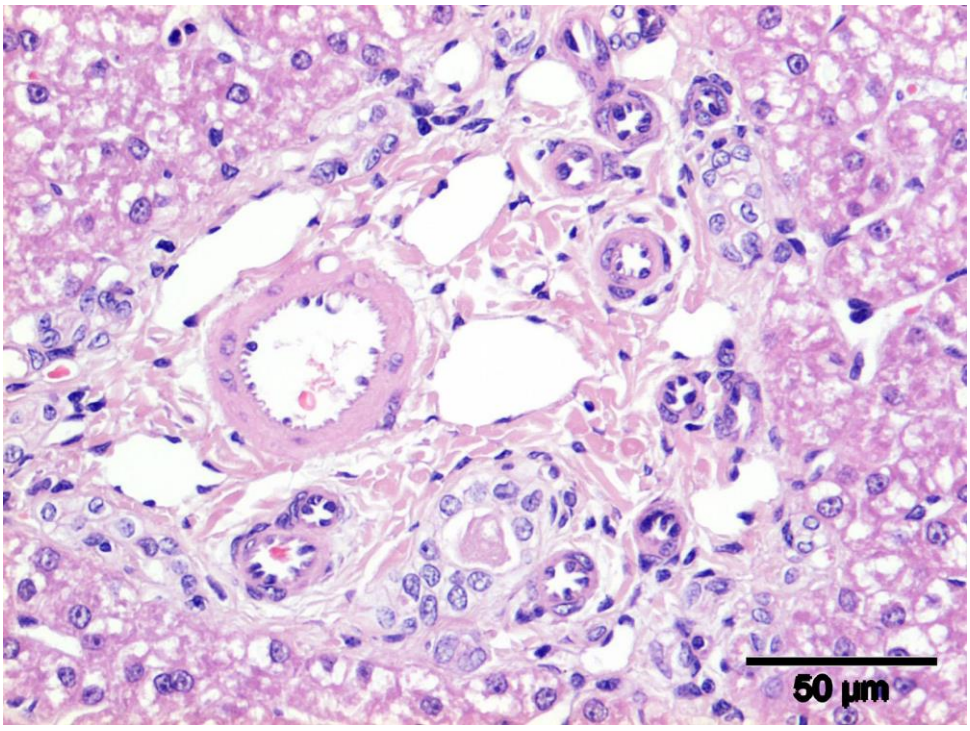

Fig. 15. Dog. Congenital portosystemic shunt. Portal area without recognizable portal vein, arteriolar proliferation, dilated lymphatics. HE

2 Disorders associated with outflow disturbances

Impairment of venous outflow results in passive congestion of the liver. Passive congestion of the liver is characterized by engorgement and dilatation of the hepatic veins and the centrolobular sinusoids (Fig. 16) and sometimes extravasation of erythrocytes in the liver cell plates (Fig. 17). In these areas there will be atrophy and subsequent loss of hepatocytes as well as gradual development of perivenular fibrosis (Fig. 18) and deposition of extracellular matrix in the walls of the affected sinusoids, eventually leading to bridging fibrosis linking hepatic venules, and finally so-called cardiac cirrhosis. In chronic passive congestion hepatocellular regeneration as a consequence of loss of functional hepatic parenchyma, often will be evident by the presence of double layered hepatic cords in the unaffected periportal areas (Fig. 18). In acute or recurrent severe disruptions of the hepatic outflow ischaemic hepatic necrosis is regularly observed (Fig. 19). Passive congestion also causes increased lymph production and dilated lymphatics are seen in the Glisson's capsule, the portal areas and around the larger hepatic veins.

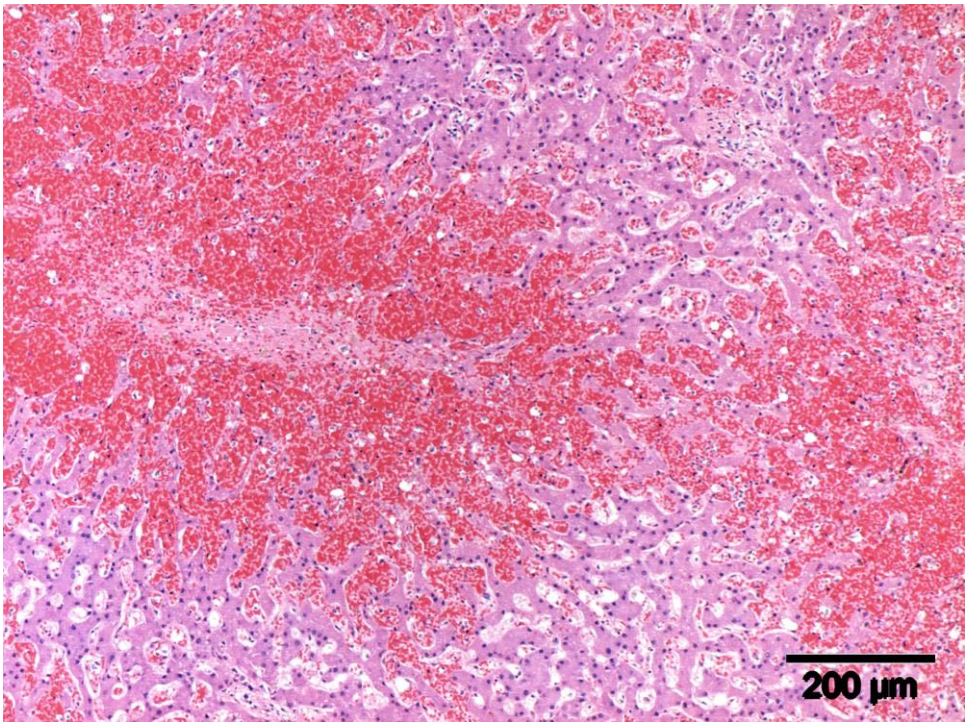

Fig. 16. Dog. Passive congestion. Centrolobular engorgement and dilatation of the sinusoids with atrophy of the hepatic cords. HE.

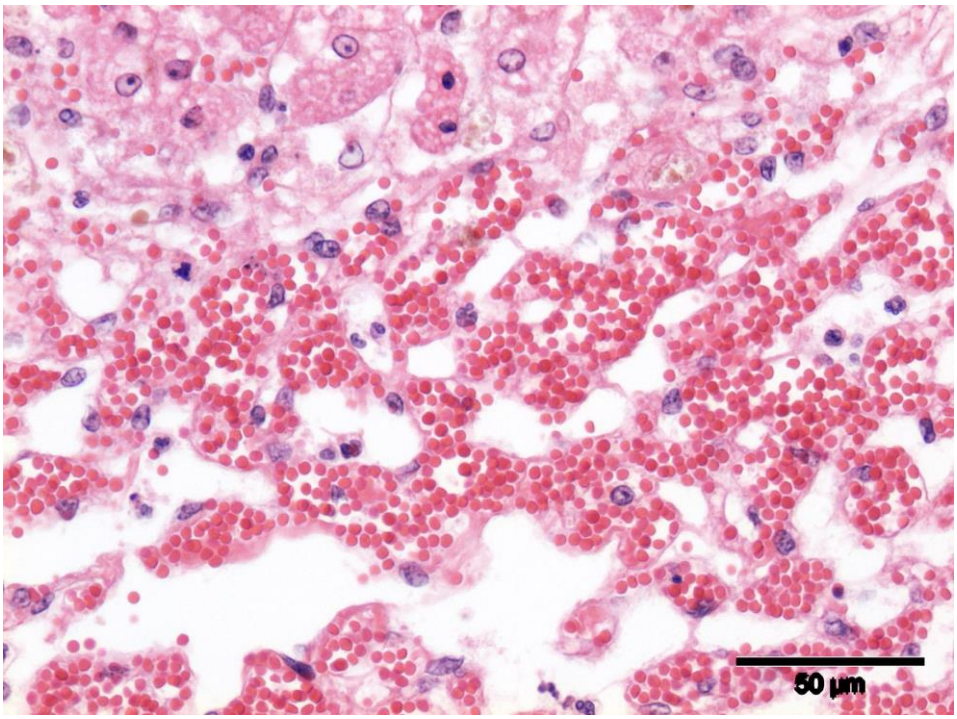

Fig. 17. Cat. Acute passive congestion. Extravasation of erythrocytes in the liver cell plates with loss of the hepatocytes. HE.

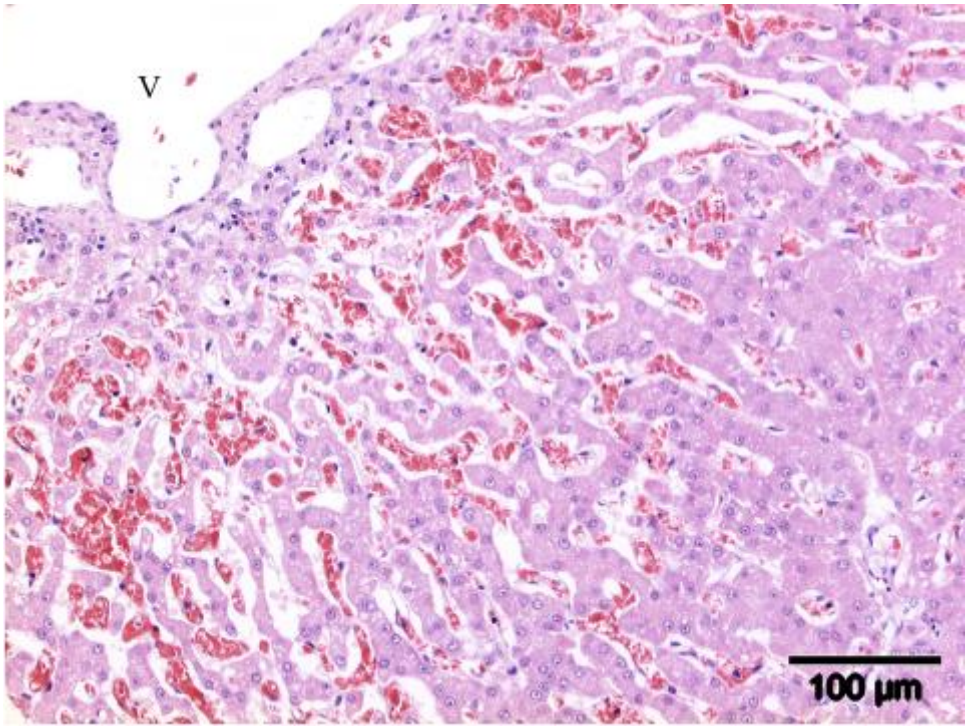

Fig. 18. Dog. Chronic passive congestion. Perivenous fibrosis with dilated lymphatics, centrolobular atrophy of the hepatic cords and hepatocellular regeneration as evidenced by double layered hepatic cords (lower right). HE.
V: Hepatic vein

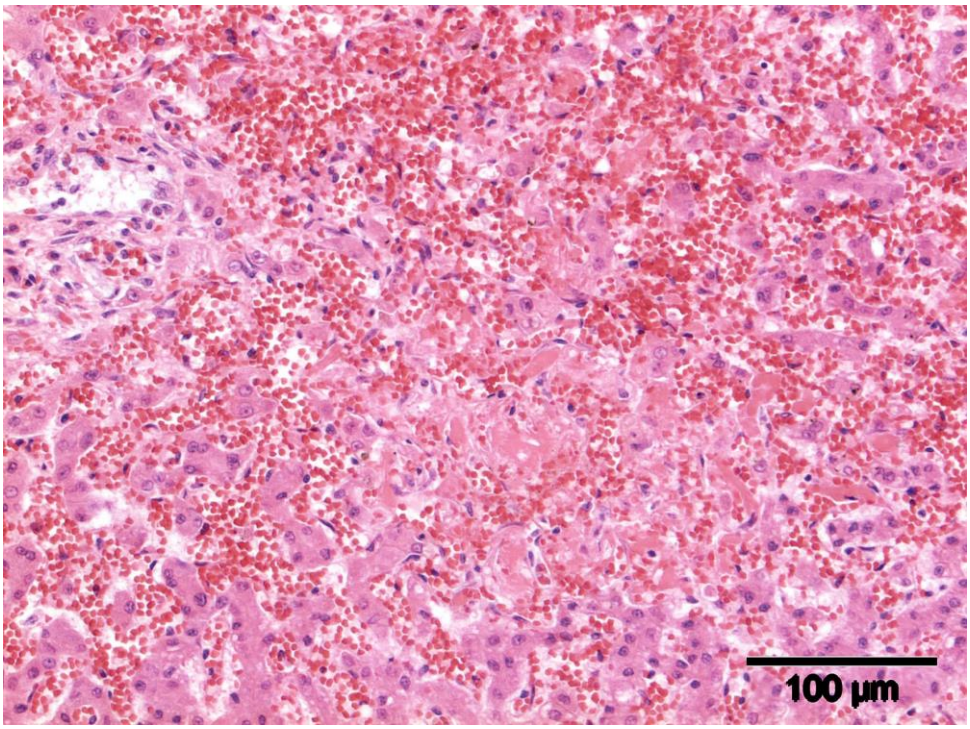

Fig. 19. Dog. Passive congestion and ischaemic hepatocellular necrosis. HE.

Macroscopically the liver becomes swollen, dark and congested, often with an accentuated lobular pattern (nutmeg appearance) caused by centrolobular congestion contrasting with periportal steatosis or hyperplasia of hepatocytes (Fig. 20). The increased venous pressure may also lead to transudation of plasma and erythrocytes through the capsule. As a result, fibrinous plaques may develop on the surface of the liver (Fig. 21) and blood-tinged fluid may accumulate in the abdominal cavity. In chronic stages the capsule becomes thickened by fibrosis as a result of the organisation of the fibrinous placques.

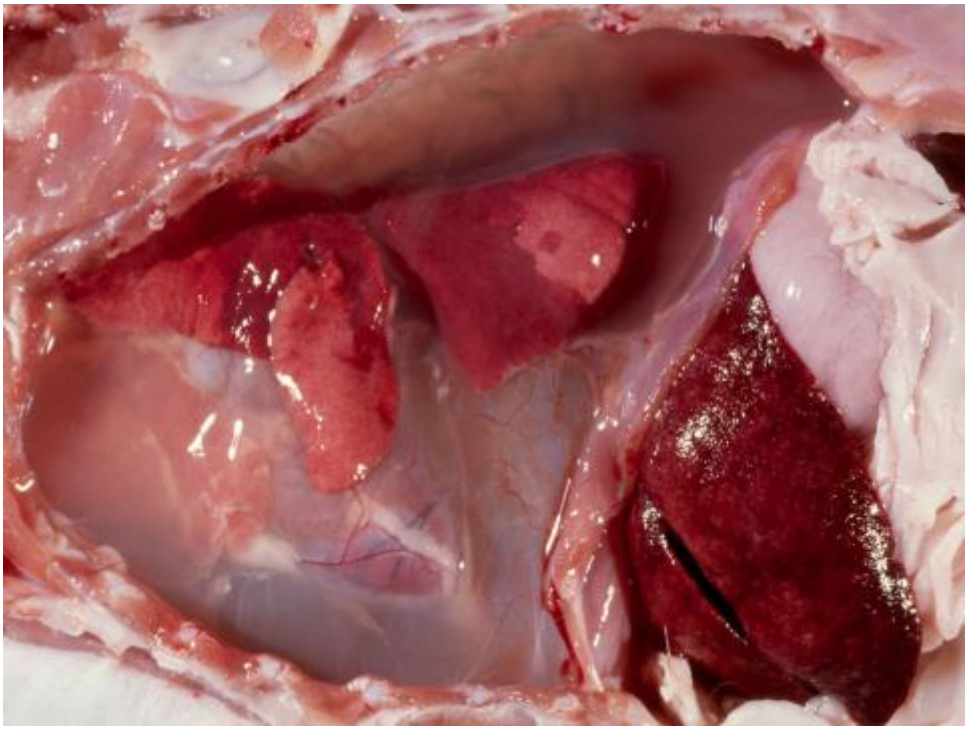

Fig. 20. Cat. Chronic passive congestion with an accentuated lobular pattern due to centrolobular congestion and periportal hepatocellular regeneration. Cardiac pulmonary stenosis.

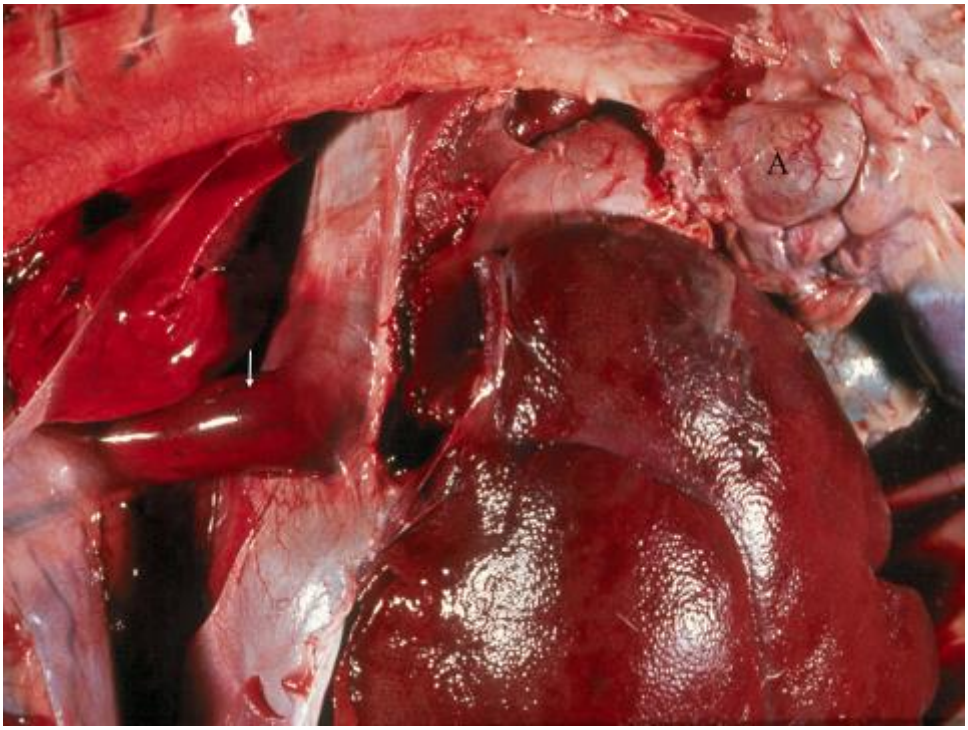

Fig. 21. Dog. Passive congestion of the liver (swollen, dark, fibrin on the surface) due to expansion of an adrenocortical tumour (A) along the posterior caval vein up to the thoracic segment (arrow). (From Van den Ingh, Rothuizen and Meyer(9) with permission)

In dogs and cats passive congestion of the liver is usually the consequence of **cardiac failure** as in congenital cardiac anomalies (Fig. 20), valvular endocarditis or endocardiosis, myocardial damage, and pericardial effusion. Passive congestion may also result from partial or complete **obstruction** (as by thrombosis, neoplasia, Dirofilariosis) **or compression** (as by neoplasia, inflammation) **of the caudal caval vein** downstream from or at the outflow site of the hepatic veins (Fig. 21). Passive congestion due to **intrahepatic outflow disturbances** is associated with obstruction of the hepatic veins. Thrombotic obstruction of the larger hepatic veins, as in human Budd Chiari syndrome has not been conclusively reported in dogs and cats. Canine and feline cases reported as Budd Chiari-like syndrome [15-19], a misleading and in our opinion not preferred terminology, were associated with passive congestion caused by obstruction or compression of the caudal caval vein or perivenular fibrosis of the intrahepatic veins. Veno-occlusive disease i.e. occlusion typically of intercalated (sublobular) and larger hepatic veins by intimal thickening with loosely arranged or dense fibrous connective tissue. occurs in humans and animals (Fig. 22). This syndrome is associated with ingestion of pyrrolizidine alkaloids and, in man, with anticancer therapy such as irradiation and chemotherapy. Veno-occlusive disease does not occur spontaneously in dogs or cats, but it has been produced experimentally in dogs [20] and occurs spontaneously in wild felidae (cheetah and snow leopard). [21, 22]

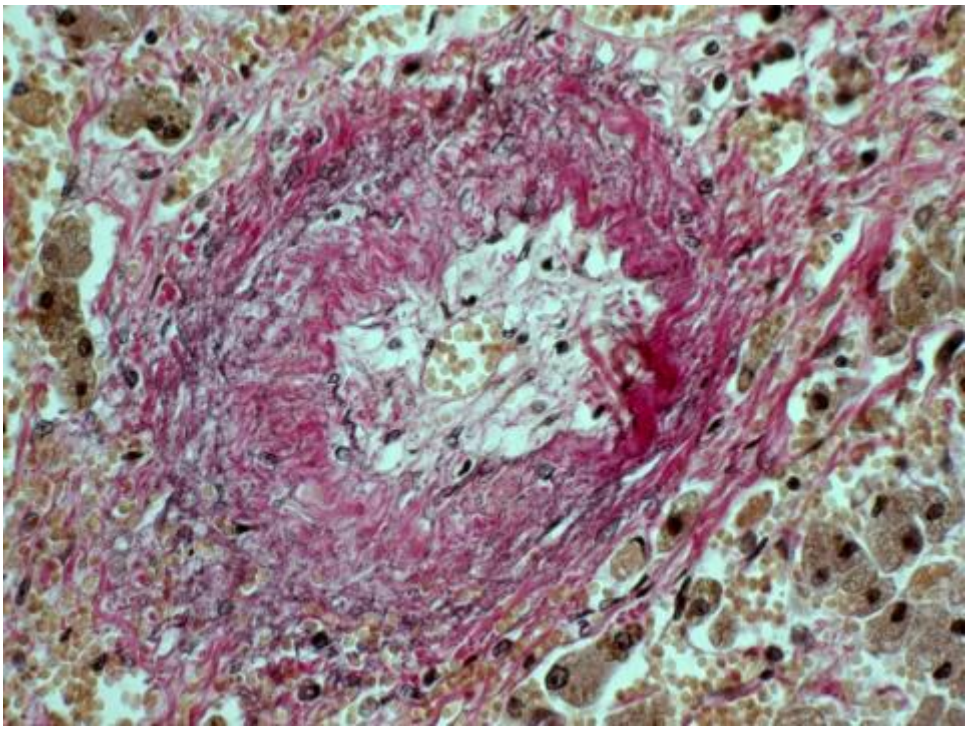

Fig. 22. Cheetah. Veno-occlusive disease (Von Gieson - Elastica stain).

3 Disorders associated with portal hypertension

Portal hypertension is the abnormal state of a persistent increase in pressure in the portal venous system. Consequently, it is often accompanied by ascites and acquired portosystemic shunting via collateral vessels. In contrast to man, congestive splenomegaly is not a feature of portal hypertension in dogs and cats. In the normal dog and cat, these portosystemic collaterals are small and insignificant, but dilatation develops in response to portal hypertension, so that the high pressure is relieved by the patent connection of the portal system with the systemic circulation, in which the pressure is normally low. These vessels become only functional if there is a pressure gradient between the portal and systemic circulation, hence not in case of generalized hypertension. Functional collaterals become visible as multiple, tortuous vessels particularly in the mediastinum along the esophagus originating from the cardia of the stomach (cardio-esophageal anastomoses), in the omentum between the spleen and the left dorsal abdominal wall cranial to the kidney (spleno-renal anastomoses), and in the mesocolon and mesorectum (mesenteric anastomoses). [23, 24] Portal hypertension with portosystemic collaterals is regularly seen in dogs (Fig. 23) but rare in cats (Fig. 24). It may result from primary vascular disorders or primary hepatic diseases. Portal hypertension may also occur in passive congestion of the liver but then it is not associated with acquired portosystemic collaterals due to the absence of a pressure gradient.

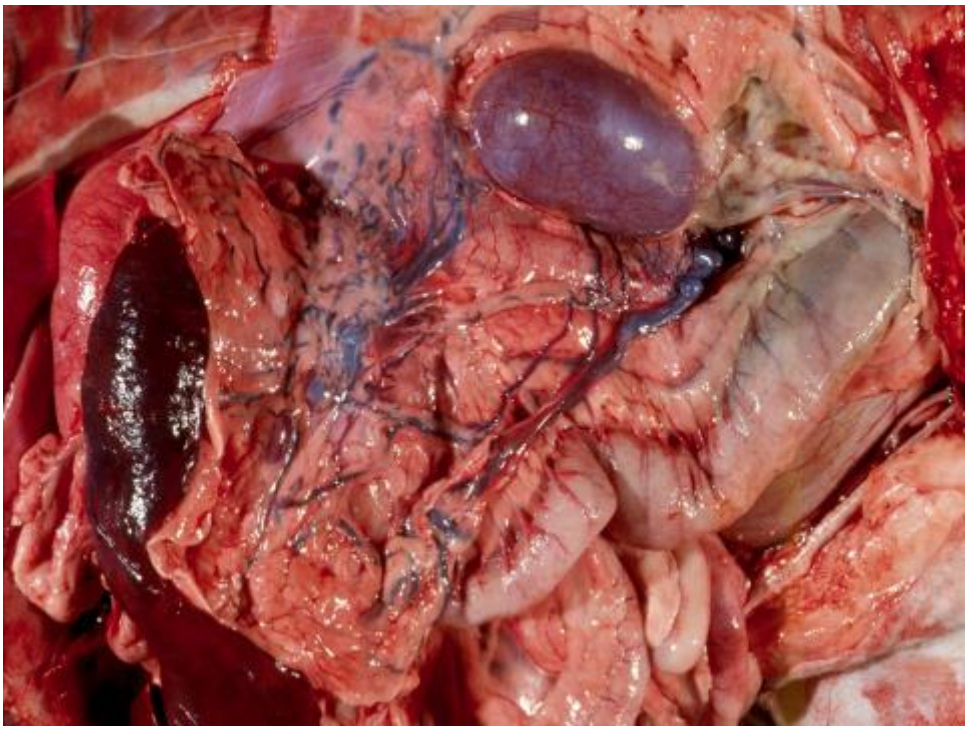

Fig. 23. Dog. Multiple portosystemic collaterals. spleno-renal and mesenteric anastomoses secondary to portal hypertension. (From Van den Ingh, Rothuizen and Meyer(9) with permission).

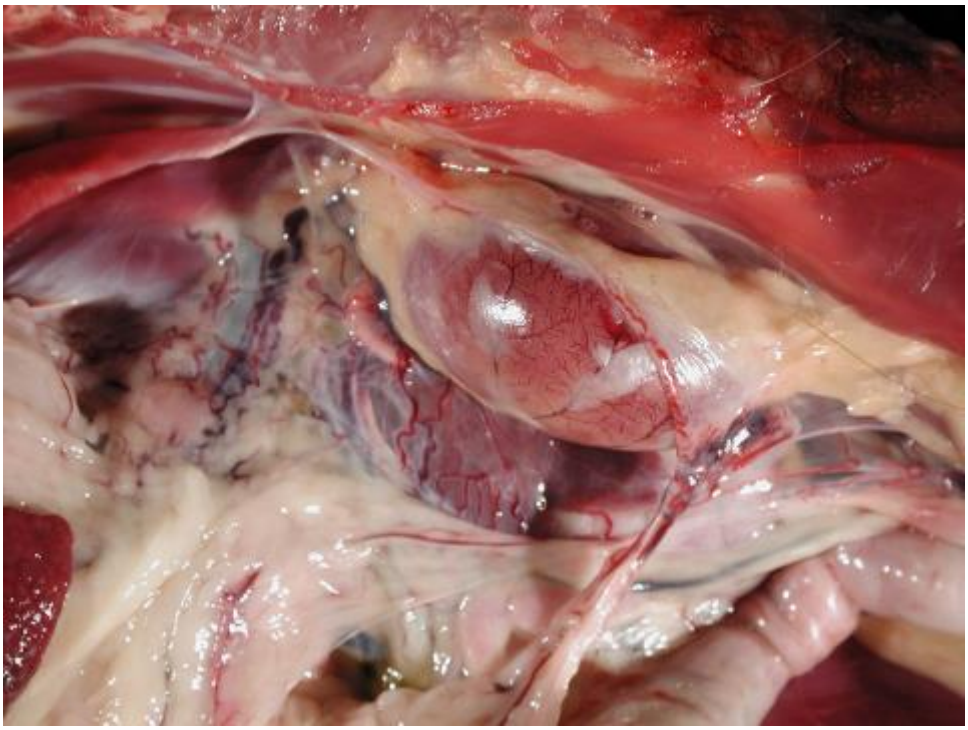

Fig. 24. Cat. Multiple portosystemic collaterals: spleno-renal and mesenteric anastomoses secondary to portal hypertension.

3.1 Primary Vascular Disorders

Portal Vein Obstruction

Portal vein obstruction can occur from intraluminal disorders, such as thrombosis (Fig. .25) induced by damage to the portal vein by local inflammatory processes as in pancreatitis, ascending omphalophlebitis, and focal or diffuse peritonitis, or by hypercoagulable states[9,25]. Neoplasia may occasionally cause obstruction of the portal vein by direct invasion and expansion in the portal vein or by embolization of portal veins.

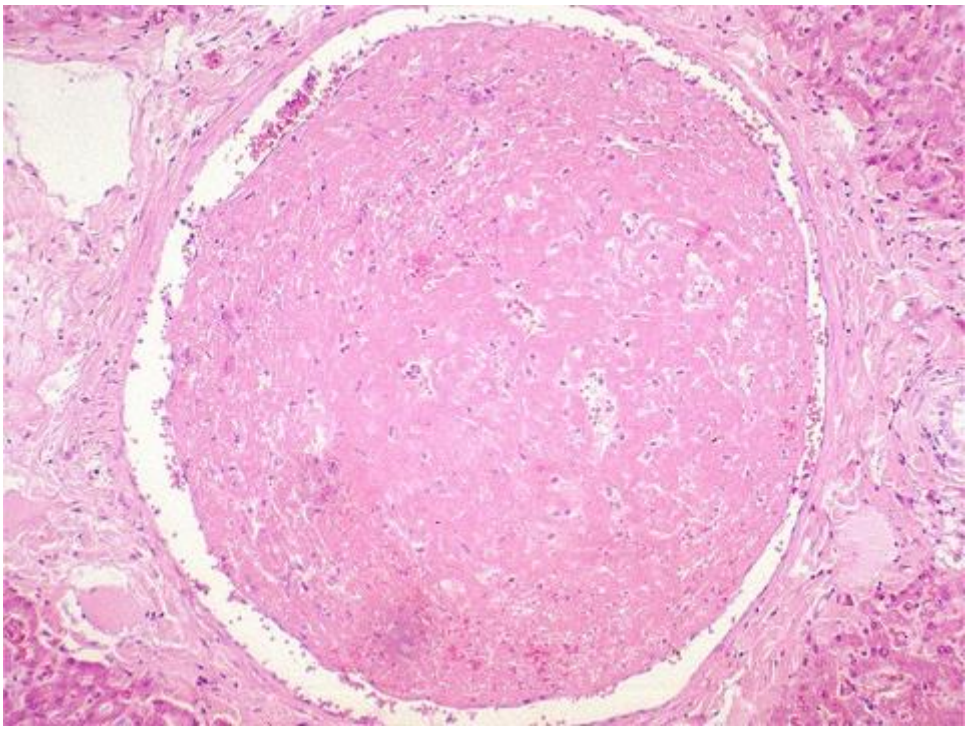

Fig. 25. Dog. Thrombosis of the portal vein. HE.

Circumscribed fibrosis of the wall and constriction of the extrahepatic portal vein [26] or compression of the extrahepatic portal vein due to local inflammatory lesions, such as abscesses or local neoplasms, also can occur and reduce or completely arrest portal blood flow. Histologically, the intrahepatic portal veins may be reduced in size depending on the degree and duration of reduced portal vein flow and this change may occur along with an increase in the number of arteriolar profiles in the portal tracts (Fig. 26). These changes are not specific for portal vein obstruction and additional clinical, biochemical or imaging information may be needed to make a diagnosis. In some circumstances etiologic clues may be present in the liver biopsy such as disseminated tumor emboli or a multifocal distribution of inflammatory foci or thrombi depending on the cause of the portal vein obstruction. These features may help to distinguish portal vein obstruction from other causes of reduced portal vein flow.

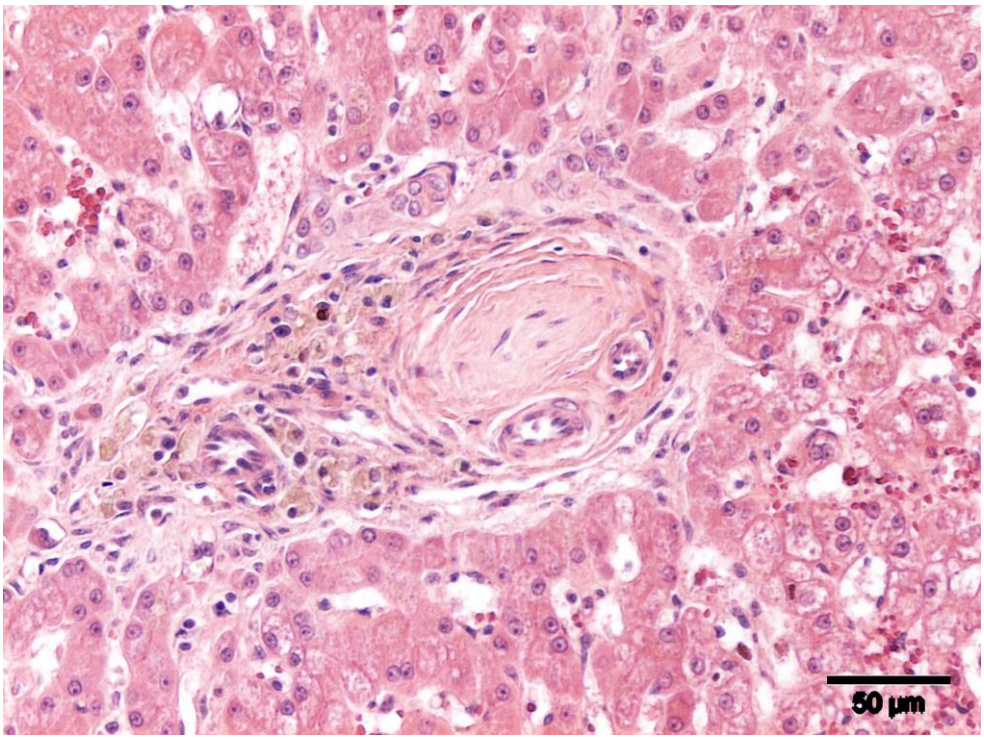

Fig. 26.Dog. Obliteration due to fibrosis of the portal vein and arteriolar proliferation. HE.

A special form of portal vein obstruction and possible subsequent portal hypertension is seen in dogs after parasitic infestation with trematodes of the genus *Schistosoma japonicum* (East Asia) and *Heterobilharzia americana* (North America) [27, 28]. The adult worms live in the mesenteric veins; their ova, which circulate as emboli can lodge in the smaller intrahepatic portal vein branches and, as foreign body, cause a chronic granulomatous inflammation in the portal veins and surrounding portal areas (Fig. 27)

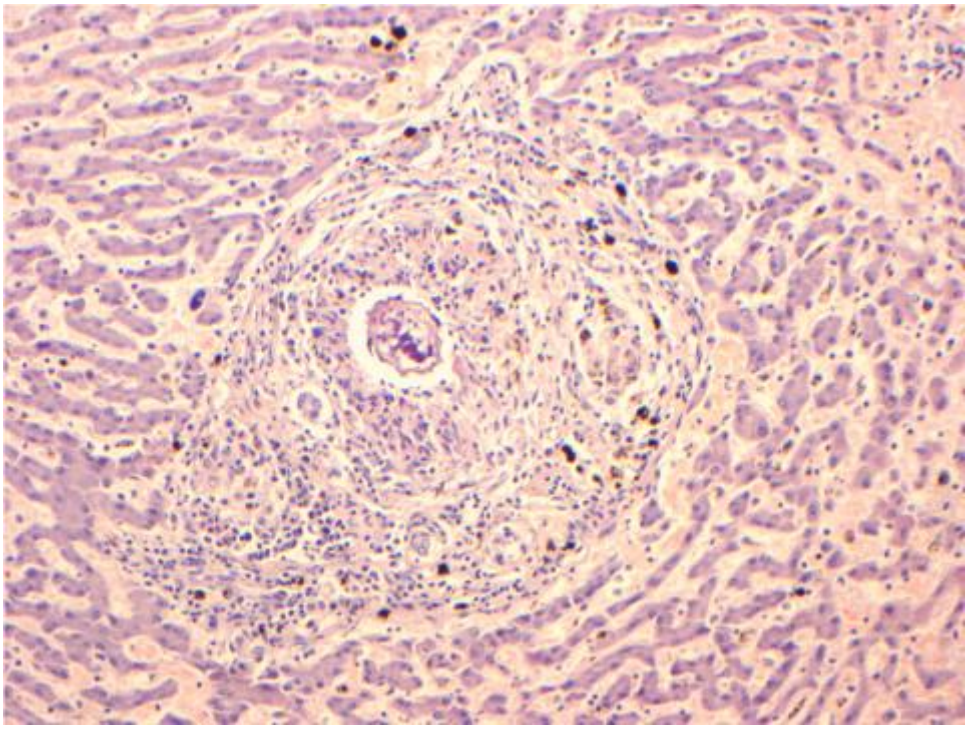

Fig..27. Dog. Portal area with fibrosis and mononuclear inflammation with a granulomatous reaction around ovum. Heterobilharzia infestation HE.

Primary Hypoplasia of the Portal Vein

Primary hypoplasia of the portal vein is a congenital disorder which occurs in dogs and very seldom in cats. [9, 29] Several diagnostic terms have been used until now to identify this congenital condition (non-cirrhotic portal hypertension[30], hepatoportal fibrosis[31]), but our preference is primary hypoplasia of the portal vein. Microvascular dysplasia [32-34] as reported in dogs shows the stereotypical histological picture of portal vein hypoperfusion. In the available literature there have been no clinical or biochemical findings to suggest that this disease is different (mild forms of) from primary portal vein hypoplasia. The authors involved in this standardization effort have therefore decided to abandon the name microvascular dysplasia, since the disease had already been reported before as primary portal vein hypoplasia which gives a better description of the disease.

The disorder has a wide variation in clinical severity and morphology depending on the degree of hypoplasia of the portal vein and consequent acquired portosystemic collateral circulation and loss of hepatocellular function. The hypoplasia most likely affects both the extrahepatic (Fig. 28) and the intrahepatic segments of the portal vein. However, due to lack of objective criteria, hypoplasia of the extrahepatic portal vein may easily be overlooked. Histologically, the disorder shares many histological features with other diseases with hypoperfusion of the portal vein as congenital portosystemic shunts, intrahepatic arterio-venous fistulas (vide infra) and portal vein obstruction.

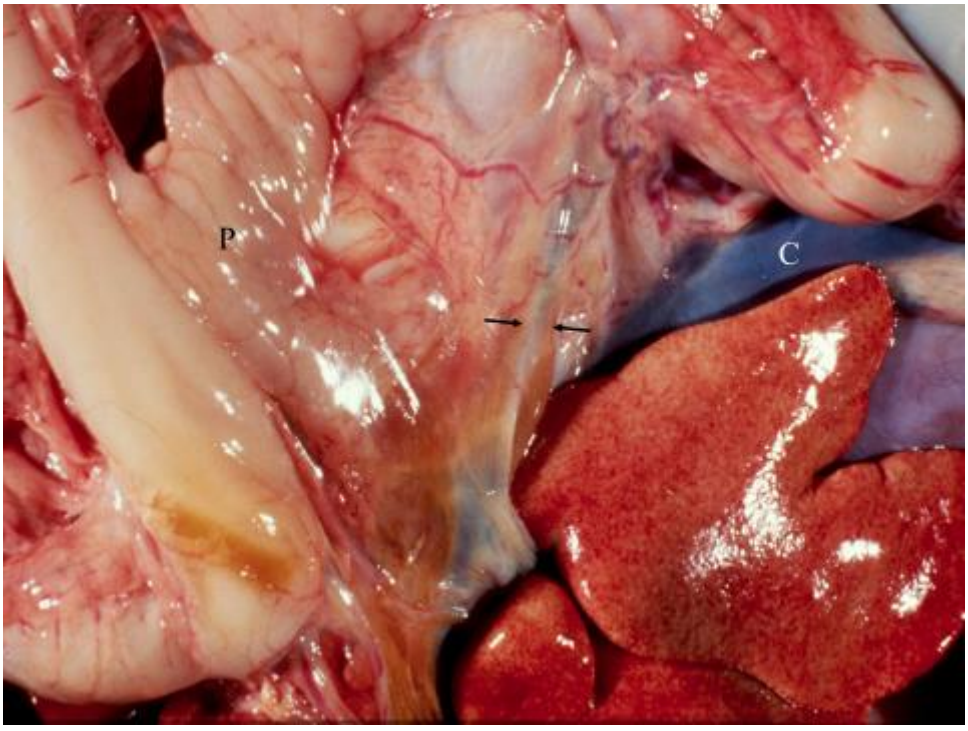

Fig. 28. Dog. Primary hypoplasia of the portal vein. Marked gross hypoplasia of the extrahepatic portal vein (arrows). C. Posterior caval vein. P. Pancreas (From Van den Ingh, Rothuizen and Meyer(29) with permission).

Typically there is a decreased portal vein diameter or absence of the portal vein and an increased number of arteriolar profiles in the portal tracts. In about 30 % of the dogs with primary hypoplasia of the portal vein the vascular changes are mild and there is no evidence of portal fibrosis (Fig. 29) , the other cases are characterized by moderate to marked fibrosis of the portal tracts sometimes resulting in porto-portal fibrosis, hypoplasia or absence of the portal veins, and a varying proliferation of arterioles and bile ductules, particularly at the periphery of the portal areas (Fig. 30).[29] Hepatocytes are usually atrophic and lobules are small. Lymphatics may be distended

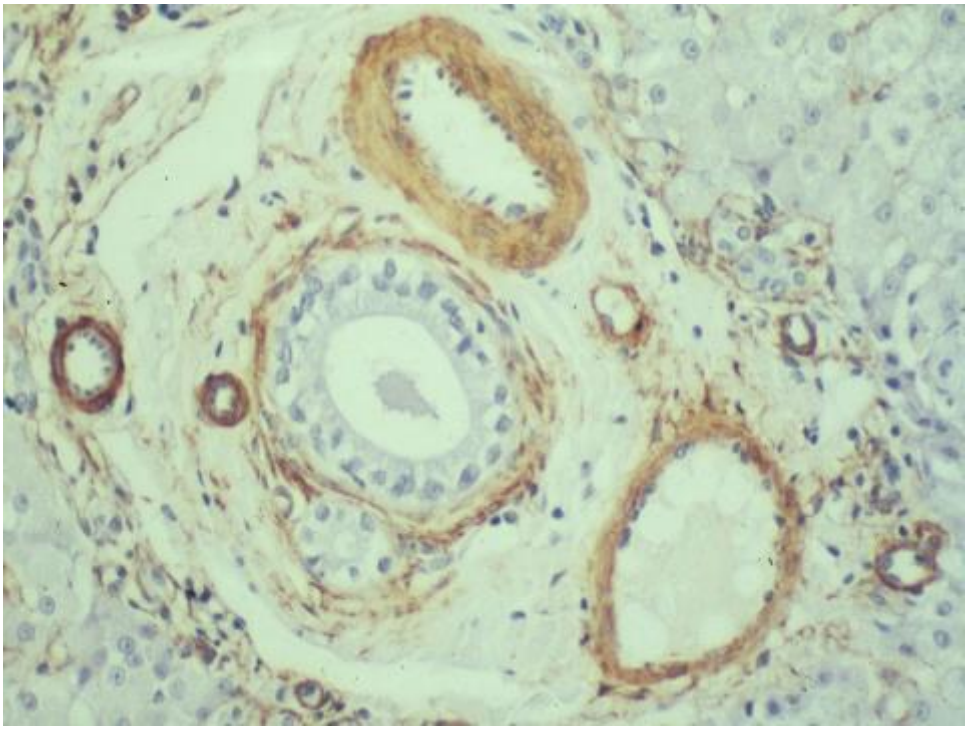

Fig. 29. Dog. Primary hypoplasia of the portal vein. Decreased diameter of the portal vein and slight arteriolar proliferation. Immunohistochemical stain for alpha- smooth muscle actin.

Clinical signs may become manifest between 1 month and 4 years of age and result from portal hypertension with development of multiple portosystemic collaterals and secondary hepatic atrophy. Some animals have ascites and hepato-encephalopathy at presentation while others may develop these signs later in the course of their disease depending on the degree of abnormality in the portal vasculature. The diagnosis is based on histological examination of a liver biopsy in combination with biochemical and ultrasonographic findings regarding the presence or absence of an anomalous portosystemic vessel, retrograde portal flow or the presence c.q. absence of ascites and multiple portosystemic collaterals.

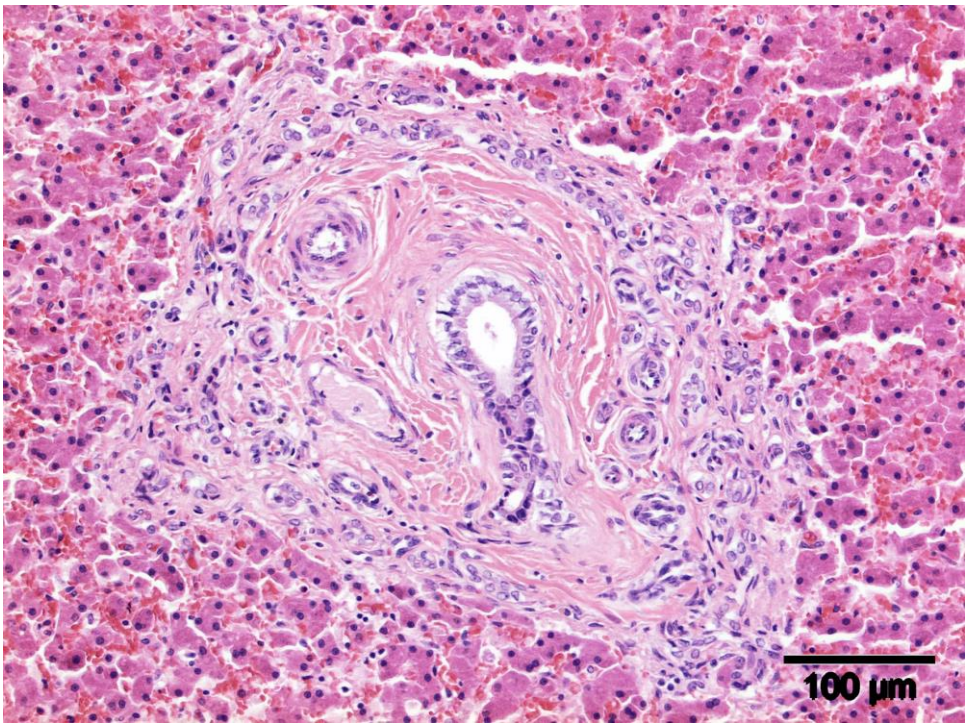

Fig. 30. Dog. Primary hypoplasia of the portal vein. Portal fibrosis, no recognizable portal vein, arteriolar and bile duct proliferation. HE.

Intrahepatic Arterio-Venous Fistula

Intrahepatic arterio-venous fistulas occur in young dogs and cats. [35, 36] In both species the disorder is presumed to be a congenital abnormality and represents communications between the hepatic artery and portal venous radicles with subsequent retrograde flow in the portal vein and portal hypertension. One or more lobes may be affected, which usually reveal aneurysmal distension of pulsating portal veins and are supplied by one or several thick walled tortuous hepatic arteries (Fig. 31). Histologically, the affected lobes show distended portal veins with damaged walls characterized by intimal and medial fibro-elastosis and smooth muscle hypertrophy, multiple cross sections of hypertrophic hepatic arteries and often atrophy and fibrosis of the adjacent hepatic tissue (Fig. 32).

Sometimes secondary portal vein thrombosis and reorganisation may be seen. Portal tracts aside from the primary lesion in the affected lobe(s) and in the non-affected lobes often show hypoplasia of the portal vein with an increased number of arteriolar and sometimes also ductular profiles (Fig. 33).

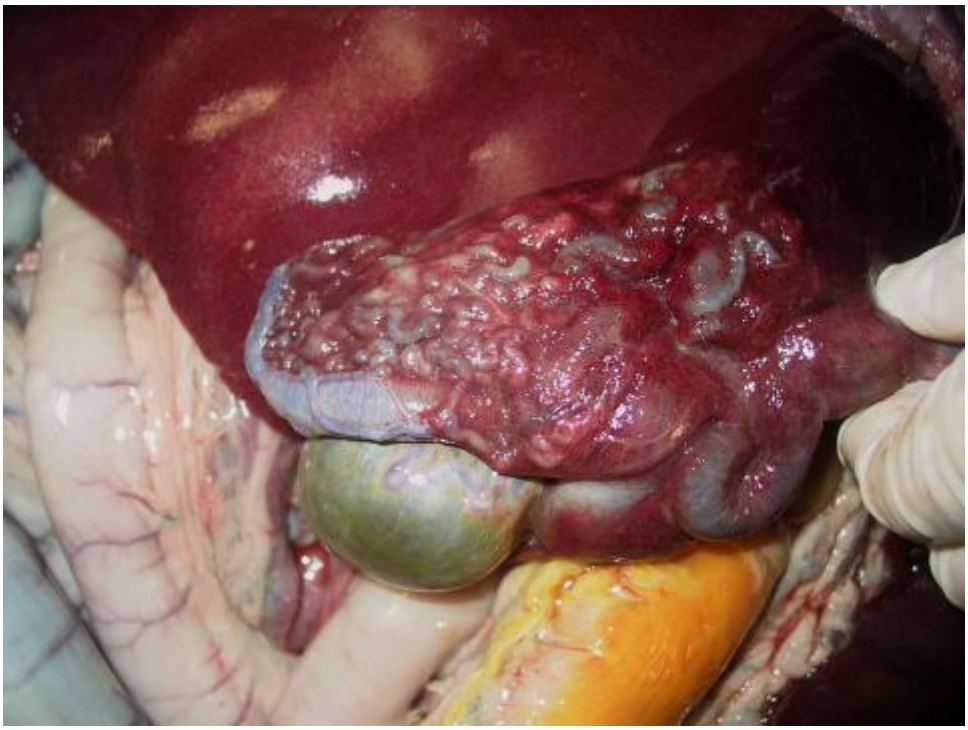

Fig. 31. Dog. Intrahepatic arterio-venous fistula.

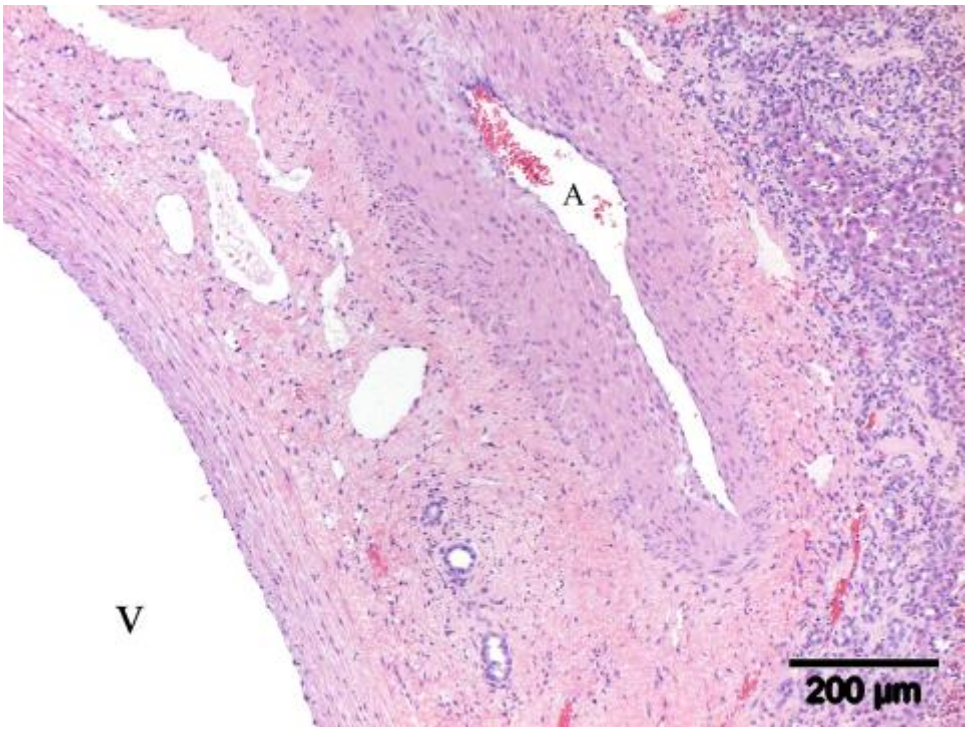

Fig. 32. Dog. Intrahepatic arterio-venous fistula. Markedly distended portal vein (V) with smooth muscle hypertrophy, hyperthropic hepatic artery (A) and fibrosis of the remaining liver tissue (upper right). HE.

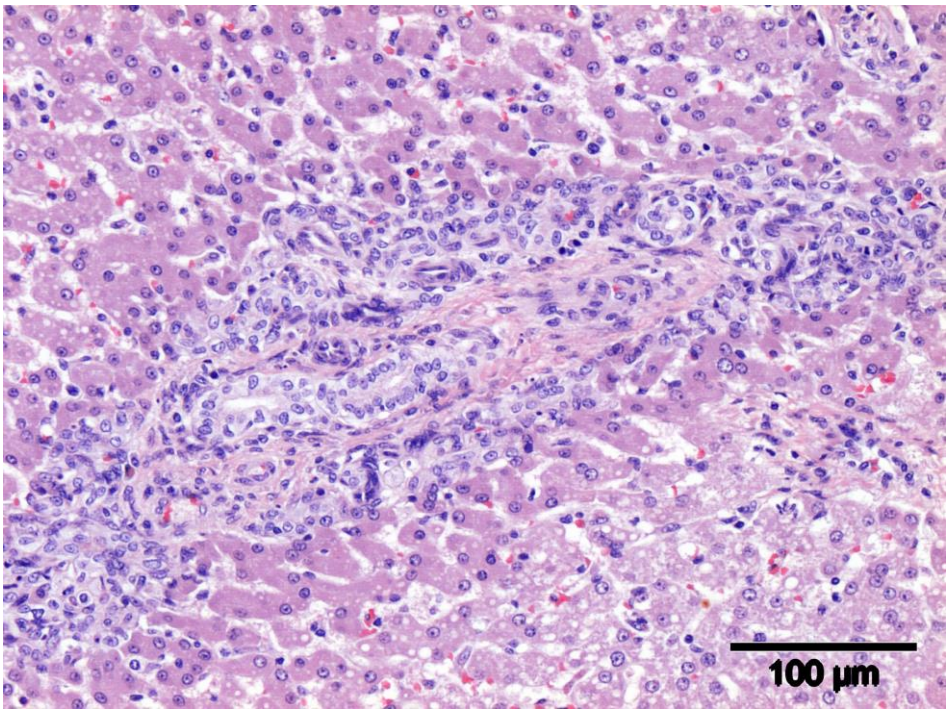

Fig. 33. Dog. Intrahepatic arterio-venous fistula. Portal area aside from primary lesion with hypoplasia of the portal vein and marked arteriolar proliferation. HE.

If the fistula is missed at clinical examination or surgery the histology of this disorder is difficult to distinguish from congenital portosystemic shunts and primary hypoplasia of the portal vein, since the histologic appearance of the portal tracts in the non affected lobes are similar. We have the strong impression that in dogs intrahepatic arterio-venous fistulas are very often associated with the primary form of portal vein hypoplasia. One argument for this is that recovery of portal vein hypoplasia has never been recorded after surgical correction of the fistula by resection of the affected lobe. Arteriovenous shunts in extrahepatic splanchnic or umbilical (own observations) location may also produce portal hypertension.

3.2 Primary Hepatic Disease

Portal hypertension in the dog usually is the result of advanced chronic liver disease such as macronodular and micronodular cirrhosis, lobular dissecting hepatitis and very chronic extrahepatic cholestasis (biliary fibrosis). Portal hypertension in such cases is attributed to compression of the portal and hepatic veins, increased resistance to sinusoidal blood flow, the formation of arteriovenous anastomoses particularly in the fibrous septa of cirrhotic livers, and increased portal flow (hyperdynamic portal circulation). In the cat portal hypertension is particularly associated with chronic biliary inflammatory disease associated with marked biliary fibrosis. In both species also congenital cystic disease of the liver with advanced portal fibrosis may result in portal hypertension

OTHER VASCULAR DISORDERS

Thrombophlebitis of the portal vein and its tributaries can occur as mentioned above in ascending omphalophlebitis (Fig. 34), or in association with focal or diffuse inflammatory processes in the abdominal cavity (pancreas, spleen, stomach, intestine, peritoneum). The

main consequence may be obstruction of the portal vein (vide supra) or extension of the inflammation from the affected portal vein branches into the connective tissue of the portal area or into the liver parenchyma to produce suppurative, necrotizing or granulomatous inflammation.

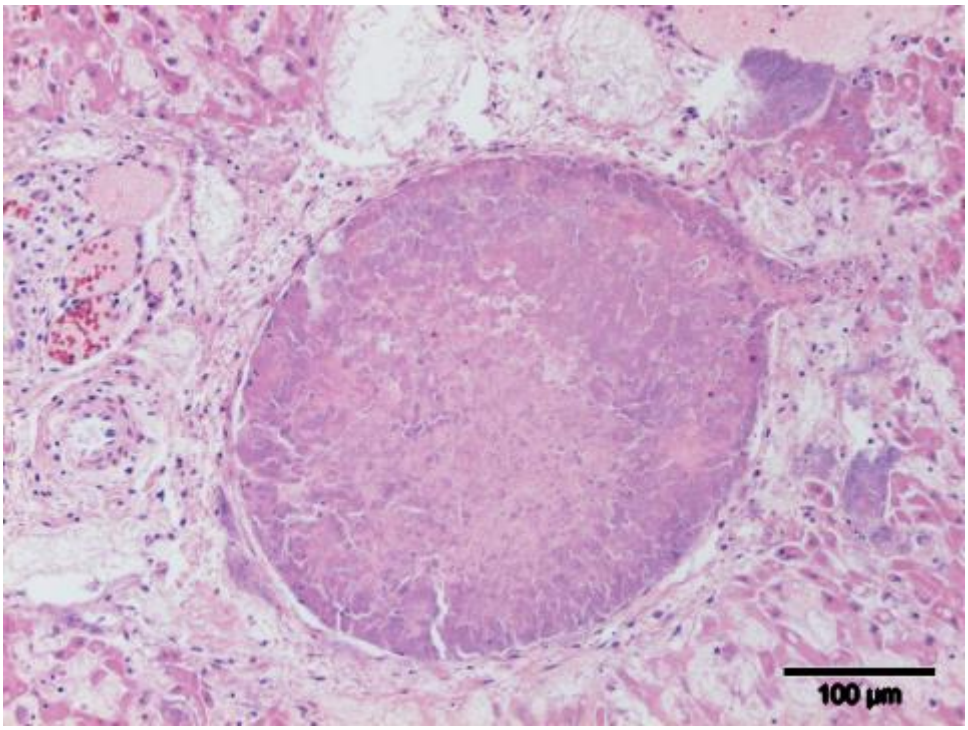

Fig. 34. Kitten. Septic thrombosis of the portal vein with many bacteria. Fibrinous deposition, dilated lymphatics and many bacteria in the surrounding tissue. HE.

The hepatic artery is susceptible to diseases found in other arteries: arteriosclerosis and atherosclerosis, periarteritis nodosa and amyloidosis. The histological appearance is identical to those seen in other tissues, but they are rarely of clinical significance. Particularly in **periarteritis nodosa** (Fig. 35, 36) the inflammation or the secondary ischaemia may affect other structures in the portal tracts or even cause parenchymal necrotic lesions.

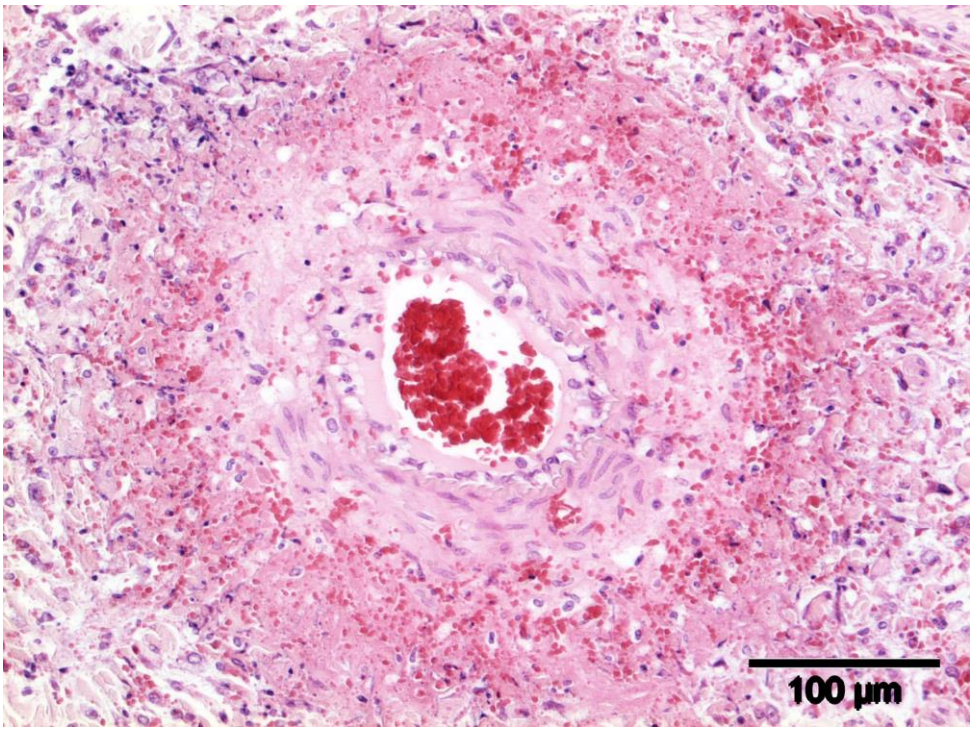

Fig. 35. Dog. Fibrinoid periarteritis hepatic artery. HE

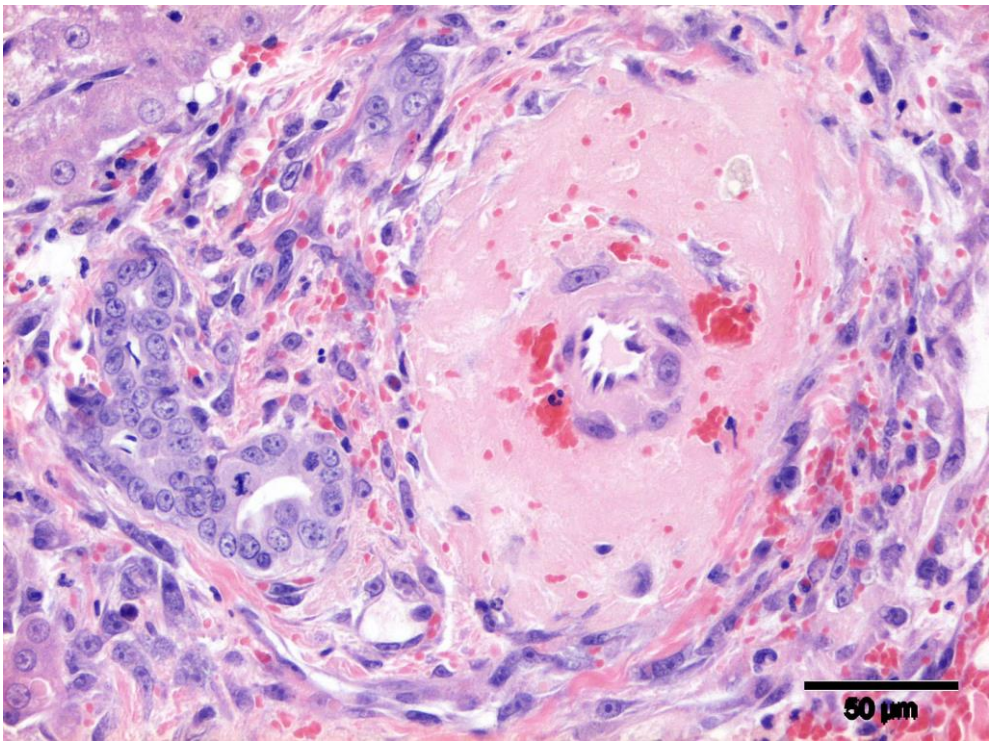

Fig. 36. Cat. Generalized fibrinoid periarteritis with some reactive fibrosis and biliary proliferation. HE

DIAGNOSTIC METHODS REQUIRED FOR DIAGNOSIS OF CIRCULATORY DISORDERS OF THE LIVER

Vascular liver diseases often are associated by portosystemic collateral circulation. In case of congenital portosystemic shunts (CPSS) this causes almost complete shunting of portal blood past the liver and poor growth and development of the liver which stays behind as the animal grows. This discrepancy causes clinical signs usually starting around half a year of age. Also in other congenital diseases of the portal vein, such as primary portal vein hypoplasia and arteriovenous fistulas the liver is poorly perfused and does not grow adequately.

Portal hypertension often leads to acquired collateral shunting of portal blood, and these animals too present symptoms of portosystemic shunting and have a small liver. However, circulatory diseases acquired later in life such as portal vein thrombosis or chronic hepatitis also lead to a decreased liver mass and portal hypertension. Depending on how severe and prolonged portal hypertension is, these diseases may also cause acquired portosystemic collateral circulalation, and again symptoms of that in association with a too small liver. Diseases such as primary portal vein hypoplasia and chronic hepatitis may vary much in their severity and hence clinical presentation.

The liver may be very small or normal in size and portal hypertension and acquired formation of portosystemic collaterals may be pronounced or slight to absent. The principle difference between congenital portosystemic shunts and the other circulatory liver diseases is that animals with CPSS never have portal hypertension, and therefore don't display ascites. The other primary or acquired circulatory diseases are associated with portal hypertension which may, if severe enough, cause ascites.

Tests to demonstrate (or exclude) portosystemic shunting

Portosystemic shunting may be congenital or acquired. In congenital portosystemic shunts nearly all portal blood bypasses the liver; in porta-(hemi)azygos shunts the shunting fraction may be lower because the receiving vessel is relatively small and presents resistance to the shunting blood. The symptoms of hepatic encephalopathy, vomiting and polydipsia/polyuria which are classical for all forms of portosystemic shunting may be less pronounced or nearly absent in dogs with porta-(hemi)azygos shunts. Dogs with porta-azygos shunts may become symptomatic much older than dogs with porta-cava shunts. Dogs with acquired shunts due to portal hypertension may present at any age, naturally depending on the underlying cause. Acquired portosystemic shunting may vary from slight to very pronounced, so that related symptoms and blood changes may also vary. Acquired portosystemic shunting is very rare in cats and is almost exclusively associated with very chronic lymphocytic cholangitis.

The classical blood tests to demonstrate portosystemic shunting are plasma bile acids with post-prandrial bile acid levels as the related challenge test[37], and plasma ammonia which may be extended to the rectal or oral ammonial tolerance test[38,39]. Bile acids concentrations are influenced by decreased clearance by the liver in case of portosystemic collateral circulation, but also by reflux of bile components into the blood stream or via the hepatic lymphatic system. Cholestasis, clinically defined as presence of bile components (conjugated bilirubin, bile acids, cholesterol) in the blood, occurs in nearly all parenchymal hepatic and biliary diseases so that bile acid concentrations (basal and post-prandrially) may be increased in many hepatobiliary diseases. Bile acid measurement is therefore less suitable to demonstrate

portosystemic shunting in a clinical population which contains many patients with liver disease.

Plasma ammonia is much more specific to demonstrate portosystemic shunting, also in a population of patients with liver disease[39]. Apart of the extremely rare inborn errors of ammonia metabolism[41], portosystemic shunting is the only way ammonia can become increased[40]. In case of severe liver dysfunction without portosystemic shunting the reserve capacity of the liver is adequate enough to keep ammonia within the reference limits and to prevent that the ammonia tolerance test becomes abnormal. The only parenchymal disease which may cause hyperammonemia without portal hypertension is fulminant hepatitis. This disease may functionally be considered as a condition with extreme intrahepatic portosystemic shunting due to gross absence of liver parenchyma. The ammonia tolerance test is best tolerated when ammonia is given deep rectally (10-15 cm) via a catheter after a walk to empty the rectum. Oral administration may induce vomiting and requires restraint and administration via a gastric tube. The standard dose is 2ml/kg of a 5% NH_4Cl solution, and blood sampling for ammonia measurement is done before and 20 and 40 minutes after administration.

In case of portosystemic shunting there is at least a doubling of the basal level, but in nearly all cases with pronounced shunting (e.g., congenital portosystemic shunts) the challenged concentration is much higher. The short-lasting temporary increment of the ammonia concentration during the ammonia tolerance test is never hazardous for the patient. Fasting ammonia concentrations exceeding 100 µmol/L (upper reference concentration is around 45-100 µmol/L) are diagnostic for portosystemic shunting and there is no indication for an ammonia tolerance test in such cases. The ammonia tolerance test is preferred over measurement of post-prandrial ammonia, which is less distinct and predictable. Presently there are good and affordable ammonia analyzers for practice[41]. A blood sample for ammonia measurement should be processed immediately, or stored in melting ice until analysis, but never longer than 40 min. Contact with ammonia contaminants such as saliva, sweat and cigarette smoke should be avoided. Haemolysed samples should not be processed because the ammonia concentration is three times higher in the erythrocyte than in normal plasma.

Scintigraphic diagnosis of portosystemic shunting

Portosystemic shunting may be diagnosed by per rectal portal scintigraphy using ^{99m}Technetium pertechnetate[42,43]. In normal dogs, dynamic lateral scintigraphic images of the abdomen sequentially visualise the portal vein and liver, and several seconds later the heart and lungs. In case of congenital portosystemic shunts the heart and lungs are visualised before the liver which receives most activity via the hepatic artery in the second circulation and not via the portal vein. Per rectal scintigraphy gives semi-quantitative information about the fraction of portal blood shunting past the liver. Precise measurement of the shunting fraction may be performed with another method of portal vein scintigraphy, in which suspended ^{99m}Tc-labeled albumin macroaggregate particles are injected in a splenic vein branch under ultrasound guidance[44,45]. The labelled particles are trapped in the first met capillary bed, which normally is the liver, but the lung in case of portosystemic shunting. The ratio (activity in lungs and liver) : (activity in the liver) gives the shunting fraction.

The above mentioned tests to confirm or exclude the presence of portosystemic shunting are usually not diagnostic for the underlying disease, but evaluate shunting irrespective of the cause. For the final diagnosis of the disease causing portosystemic shunting the combination

of different tests and criteria is necessary. Not all circulatory liver disorders are associated with portosystemic shunting (acquired or congenital) or portal hypertension.

Table 1. Summary of pathophysiologic characteristics of vascular diseases of the liver, and role of different diagnostic tests

Disease:	Portosystemic shunting		Portal hyper-tension	Ascites	Histology essential for diagnosis	Ultrasonography / Computed tomography essential for diagnosis
	Congenital, Usually 90-100%	Acquired, all stages from mild to severe				
Congenital PS shunt	+	-	-	-	-*	+
Outflow disturbances	-	-	±	-/+	-	- / +
Portal vein obstruction	-	-/±/+	±/+	±/+	-*	+
Arteriovenous fistula	-	±/+	+	±/+	-*	+
Portal vein hypoplasia**	-	-/±/+	±/+	-/±/+	±	±
Primary hepatic diseases	-	-/±/+	-/±/+	-/±/+	+	±

- = not true; + = essential, * these diseases have identical histopathological changes,
**no single test is diagnostic, combined results should be evaluated.

REFERENCES

1. McSween RNM, Desmet VJ, Roskams T, Scothorne RJ. Developmental anatomy and normal structure. In: McSween RNM, Burt AD, Portmann BC, Ishak KG, Scheuer PJ, Anthony PP, editors. Pathology of the liver. 4th ed. London: Churchill Livingstone; 2002. p. 3-66.
2. Wilkens H, Münster W. Eingeweidevenen der V.cava caudalis. In: Nickel R, Schummer A, Seiferle E, editors. Lehrbuch der Anatomie der Haustiere. Berlin: Paul Parey Verlag; 1976. p. 268-273.
3. Kalt DJ, Stump JE. Gross anatomy of the canine portal vein. Anat Histol Embryol 1993;22:191-197.

4. Payne JT, Martin RA, Constantinescu GM. The anatomy and embryology of portosystemic shunts in dogs and cats. Semin Vet Med Surg (Small Anim) 1990;5:76-82.
5. Yamamoto K. Ultrastructural study on the venous sphincter in the sublobular vein of the canine liver. Microvasc Res 1998;55(3):215-22.
6. Hanson KM, Johnson PC. Local control of hepatic arterial and portal venous flow in the dog. Am J Physiol 1966;211:712-720.
7. Campra JL, Reynolds TB. The hepatic circulation. In: Arias IM, Jakoby WB, Popper H, Schachter D, Shafritz DA, editors. The Liver: Biology and Pathobiology. 2nd ed. New York: Raven Press; 1988. p. 911-930.
8. Lohse CL, Suter PF. Functional closure of the ductus venosus during early postnatal life in the dog. Am J Vet Res 1977;38:839-844.
9. van den Ingh TS, Rothuizen J, Meyer HP. Circulatory disorders of the liver in dogs and cats. Vet Q 1995;17(2):70-6.
10. Inoue S, Matsunuma N, Ono K, et al. Five cases of canine peliosis hepatis. Nippon Juigaku Zasshi 1988;50(2):565-7.
11. Brown PJ, Henderson JP, Galloway P, et al. Peliosis hepatis and teleangiectasis in 18 cats. J Small Anim Pract 1994;35:73-77.
12. Cullen JM, MacLachlan NJ. Liver,biliary system and pancreas. In: McGavin MD, Carlton WW, Zachary JF, editors. Thomson's Special Veterinary Pathology. St. Louis; 2001. p. 81-123.
13. Kelly WR. The liver and biliary system. In: Jubb KVF, Kennedy PC, Palmer N, editors. Pathology of domestic animals. 4th ed. San Diego: Academic Press; 1992. p. 319-406.
14. Wanless IR. Vascular disorders. In: McSween RNM, Burt AD, Portmann BC, Ishak KG, Scheuer PJ, Anthony PP, editors. Pathology of the liver. 4th ed. London: Churchil Livingstone; 2002. p. 539-573.
15. Cohn LA, Spaulding KA, Cullen JM, et al. Intrahepatic postsinusoidal venous obstruction in a dog. J Vet Intern Med 1991;5(6):317-21.
16. MacIntire DK, Henderson RH, Banfield C, et al. Budd-Chiari syndrome in a kitten, caused by membranous obstruction of the caudal vena cava. J Am Anim Hosp Assoc 1995;31(6):484-91.
17. Fine DM, Olivier NB, Walshaw R, et al. Surgical correction of late-onset Budd-Chiari-like syndrome in a dog. J Am Vet Med Assoc 1998;212(6):835-7.
18. Schoeman JP, Stidworthy MF. Budd-Chiari-like syndrome associated with an adrenal phaeochromocytoma in a dog. J Small Anim Pract 2001;42(4):191-4.
19. Cave TA, Martineau H, Dickie A, et al. Idiopathic hepatic veno-occlusive disease causing Budd-Chiari-like syndrome in a cat. J Small Anim Pract 2002;43(9):411-5.
20. Schulman KB, Luk K, Deeg HJ, et al. Induction of hepatic veno-occlusive disease in dogs. Am J Pathol 1987;126:114-125.
21. Gosselin SJ, Loudy DL, Tarr MJ, et al. Veno-occlusive disease of the liver in captive cheetah. Vet Pathol 1988;25(1):48-57.
22. van den Ingh TS, Zwart P, Heldstab A. Veno-occlusive disease (VOD) of the liver in cheetah's and snowleopards. Schweiz Arch Tierheilkd 1981;123(6):323-7.
23. Khan IR, Vitums A. Portosystemic communications in the cat. Res Vet Sci 1971;12:215-218.
24. Vitums A. Portosystemic communications in the dog. Acta Anat 1959;39:271-299.
25. Van Winkle TJ, Bruce E. Thrombosis of the portal vein in eleven dogs. Vet Pathol 1993;30:28-35.

26. Szatmari V, van den Ingh TS, Fenyves B, et al. Portal hypertension in a dog due to circumscribed fibrosis of the wall of the extrahepatic portal vein. Vet Rec 2002;150(19):602-5.
27. Smith HA, Jones TC. Veterinary Pathology. 3rd ed. Philadelphia: Lea and Febiger; 1966.
28. Flowers JR, Hammerberg B, Wood SL, et al. Heterobilharzia americana infection in a dog. J Am Vet Med Assoc 2002;220:193-196.
29. Van den Ingh TS, Rothuizen J, Meyer HP. Portal hypertension associated with primary hypoplasia of the hepatic portal vein in dogs. Vet Rec 1995;137(17):424-7.
30. Bunch SE, Johnson SE, Cullen JM. Idiopathic noncirrhotic portal hypertension in dogs: 33 cases (1982-1998). J Am Vet Med Assoc 2001;218(3):392-9.
31. Van Den Ingh TS, Rothuizen J. Hepatoportal fibrosis in three young dogs. Vet Rec 1982;110(25):575-7.
32. Schermerhorn T, Center SA, Dykes NL, et al. Characterization of hepatoportal microvascular dysplasia in a kindred of cairn terriers. J Vet Intern Med 1996;10:219-230.
33. Christiansen JS, Hottinger HA, Allen L, et al. Hepatic microvascular dysplasia in dogs: a retrospective study of 24 cases. J Am Anim Hosp Assoc 2000;36:385-389.
34. Allen L, Stobie D, Mauldin GN, et al. Clinicopathologic features of dogs with hepatic microvascular dysplasia with and without portosystemic shunts: 42 cases (1991-1996). J Am Vet Med Assoc 1999;214(2):218-20.
35. Moore PF, Whiting PG. Hepatic lesions associated with intrahepatic arterioportal fistulae in dogs. Vet Pathol 1986;23(1):57-62.
36. Legendre AM, Krahwinkel DJ, Carrig CB, et al. Ascites associated with intrahepatic arteriovenous fistula in a cat. J Am Vet Med Assoc 1976;168:589-591.
37. Kerr MG, van Doorn T. Mass screening of Irish wolfhound puppies for portosystemic shunts by the dynamic bile acid test. Vet Rec. 1999;144(25):693-6.
38. Rothuizen J, van den Ingh TS. Rectal ammonia tolerance test in the evaluation of portal circulation in dogs with liver disease. Res Vet Sci. 1982;33(1):22-5.
39. Rothuizen J, van den Ingh TS. Arterial and venous ammonia concentrations in the diagnosis of canine hepato-encephalopathy. Res Vet Sci. 1982;33(1):17-21.
40. Meyer HP, Rothuizen J, Tiemessen I, et al. Transient metabolic hyperammonaemia in young Irish wolfhounds. Vet Rec. 1996;138(5):105-7.
41. Sterczer A, Meyer HP, Boswijk HC, et al. Evaluation of ammonia measurements in dogs with two analysers for use in veterinary practice. Vet Rec. 1999;144(19):523-6.
42. Daniel GB, Bright R, Ollis P, et al. Per rectal portal scintigraphy using 99mtechnetium pertechnetate to diagnose portosystemic shunts in dogs and cats. J Vet Intern Med. 1991;5(1):23-7.
43. Koblik PD, Komtebedde J, Yen CK, et al. Use of transcolonic 99mtechnetium-pertechnetate as a screening test for portosystemic shunts in dogs. J Am Vet Med Assoc. 1990;196(6):925-30.
44. Meyer HP, Rothuizen J, van den Brom WE, et al. Quantitation of portosystemic shunting in dogs by ultrasound-guided injection of 99MTc-macroaggregates into a splenic vein. Res Vet Sci. 1994;57(1):58-62.
45. Meyer HP, Rothuizen J, van Sluijs FJ, et al. Progressive remission of portosystemic shunting in 23 dogs after partial closure of congenital portosystemic shunts. Vet Rec. 1999;144(13):333-7.
46. van Steenbeek FG, van den Bossche L, Leegwater PAJ, et al. Inherited liver shunts in dogs elucidate pathways regulating embryonic development and clinical disorders of the portal vein. Mamm Genome 2012;23:76–84 DOI 10.1007/s00335-011-9364-0