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INFLAMMATORY DISEASES OF THE LIVER AND BILIARY TRACT

The inflammatory response in the liver is unusual for three main reasons. First, *hepatic microvasculature is structurally and functionally different from tissues with capillary vasculature*. Microvascular permeability to plasma proteins, a hallmark of acute inflammation in most tissues, is a normal property of the fenestrated sinusoidal endothelium of the liver. Thus, edema is not a prominent feature of acute parenchymal inflammation, although it can be observed in the capsule, biliary tracts, and gallbladder. Microvascular blood flow in hepatic sinusoids is also less responsive to the actions of various vasoactive mediators that alter blood flow in most other acutely inflamed tissues. Second, *hepatic Kupffer cells have some distinctive properties that enable them to deal with many potentially inflammatory insults in the portal circulation*. While they appear to have a higher threshold for activation, they can release large amounts of potent mediators such as nitric oxide, interleukin-6, and tumor necrosis factor-α that can influence cell populations in the liver and elsewhere. Third, *the liver has central regulatory influences on many proinflammatory insults and inflammatory mediators*. The liver produces most plasma proteins with anti-inflammatory functions, and is also the site of degradation of most soluble plasma proteins. Kupffer cells are the main site of clearance of immune complexes from the circulation, and they have an important role in the development of immunotolerance to potential antigenic substances absorbed from the intestine.

These unusual aspects of the inflammatory response in the liver can make it more difficult to differentiate some degenerative and inflammatory conditions in this organ. Ongoing cell death and repair can appear inflammatory and acute leukocyte responses can cause necrosis and apoptosis in the liver. *The term* "**necroinflammatory**" *is convenient when the underlying pathogenetic mechanisms of necrosis and inflammation are unknown*. Areas of focal hepatitis are commonly found in the liver, particularly in older animals. These usually reflect previous areas of focal infection or necrosis that are of little functional significance because the liver has so much functional reserve and regenerative capacity.

Increased numbers of leukocytes (**sinusoidal leukocytosis**) are observed in hepatic sinusoids in many acute or subacute bacteremias. These changes can be diagnostically useful but they do not constitute evidence of hepatitis unless there is obvious infiltration of granulocytes, monocytes, or lymphocytes into the perisinusoidal space. **Extramedullary hematopoiesis** can also appear as focal aggregates of myeloid cells in the perisinusoidal compartment. These changes (sometimes termed *myeloid metaplasia*) can be distinguished from inflammatory infiltrates by the presence of immature myeloid cells. Occasionally, hematopoietic cells from the splenic red pulp can be artifactually extruded into the portal vasculature and appear in the liver, usually as nucleated cell aggregates in the larger portal veins.

Infectious agents capable of causing hepatitis include viruses, bacteria, fungi, and helminths. Autoimmune and idiosyncratic drug responses are also observed in frequently, but often the etiology of acute or chronic hepatitis cannot be determined.

Acute hepatitis

The liver is subject to infectious and degenerative insults that elicit inflammatory responses in various patterns, for which the general term hepatitis is appropriate. **Cholangiohepatitis** *applies to hepatic inflammation centered on the biliary tract and extending into adjacent hepatic parenchyma*. The term **hepatitis** *is used for focal or diffuse hepatic conditions that are either caused by infectious agents or characterized by a leukocytic infiltrative inflammatory response, irrespective of the cause*. This definition allows us to include viral infections that are hepatotropic, even though the lesions are mainly characterized by hepatocellular necrosis or apoptosis rather than by the inflammatory response to the agent. Demonstration of sufficient amounts of injurious infectious agents within the lesions by inclusion bodies, antigens, or nucleic acids are important in making this diagnosis. The term hepatitis is also used for responses to some hepatic toxicants, metals, or drug metabolic idiosyncrasies in which there is a prominent leukocytic response to damaged cells. However, in responses in which single necrotic hepatocytes elicit a mild neutrophilic or histiocytic response, the term hepatitis is less appropriate because the pattern of injury is primarily degenerative.

Leukocyte infiltrates in diffuse hepatitis tend to accumulate mainly in the vicinity of the portal tracts, around major bile ducts, or sometimes in the capsule and around the central veins. Small but important numbers of neutrophils and mononuclear cells, including lymphocytes, are usually seen in the perisinusoidal space and among hepatocytes, and are often focally concentrated in sites of necrosis. Edema is an unusual feature of acute hepatitis, but is seen in severe injury, for example in infectious canine hepatitis. Grossly, hepatic edema is most obvious in the gallbladder, large extrahepatic bile ducts, hepatic lymph nodes, and sometimes in the capsule. Microscopically, edema is also evident in the portal triads and sometimes by an increase in the perisinusoidal space.

Kupffer cells are key participants in the acute inflammatory responses in the liver. They can enlarge and accumulate vacuoles and lysosomal debris during regular phagocytic removal of microorganisms, cell debris, and extravascular erythrocytes. They can also be activated to secretory histiocytes that release various cytokines and other mediators that induce hypertrophic or proliferative responses of hepatocytes, stellate cells, and endothelium. Activated Kupffer cells are larger and more prominent or numerous in sections, their nuclei are larger and vesicular, and their cytoplasm is basophilic and may contain vacuoles or ingested particulate matter. In overwhelming infections, many of the Kupffer cells and adjacent sinusoidal endothelial cells and hepatocytes undergo necrosis.

Patterns and character of inflammation in hepatitis vary according to causative agent, severity and stage of disease, the route of entry into the liver, and pathogenesis of liver injury. Some viral pathogens such as *Canine adenovirus 1* can cause acute and diffuse hepatitis, with widespread hepatocellular necrosis, mixed leukocyte infiltrates, sinusoidal congestion, and edema. By comparison, most infectious causes of hepatitis, for example toxoplasmosis, various herpesviruses, and various bacteria, produce a more patchy pattern of inflammation with focally intense leukocyte and Kupffer cell responses in the vicinity of areas of necrosis. The distribution, character, and chronicity of these focal lesions are important diagnostically, but they typically do not damage enough functional hepatic parenchyma, ducts, or vasculature to produce systemic signs of liver failure. Foci of hepatitis with necrosis are common incidental findings, and these are assumed to reflect localized responses to bacteria that arrive via the portal system. Occasionally such focal necroinflammatory lesions are large and numerous, for example in cattle with rumenitis.

Chronic hepatitis

Chronic liver disease in domestic animals has historically been classified into several different entities based on morphologic criteria. In human medicine, classification of chronic hepatitis has been simplified, and morphologic divisions such as chronic active hepatitis and chronic persistent hepatitis, originally defined in specific clinical contexts, have been abandoned due to problems of evolving definitions and application, and lack of correspondence with prognosis. The single designation "**chronic hepatitis**" is now used for *chronic necroinflammatory disease lasting more than 6 months*, further modified by specifying the etiology, type, and severity of inflammation and degree and distribution of necrosis (activity or grade), and the degree of fibrosis (chronicity or stage). Systems for *grading and staging chronic hepatitis* have been developed (Tables 2.1 and 2.2). More detailed *histological activity index* scoring systems have also been developed. In human medicine, chronic hepatitis is usually the result of chronic infection with hepatotropic viruses, and, less commonly, autoimmune, drug-induced or associated with inherited metabolic diseases such as Wilson disease. In veterinary medicine, chronic liver disease may develop following chronic bile duct obstruction, infection with hepatotropic infectious agents, familial or hereditary metabolic diseases, or may be toxic, drug-induced, or possibly autoimmune in origin. However, *the majority of chronic liver disease is idiopathic*, reflecting deficiencies in our current level of understanding of the etiological, pathophysiological, and clinical implications of the patterns of inflammation and necrosis seen in domestic animals.

Regardless of the etiology, *initial acute liver damage will not progress to fibrosis or cirrhosis unless the inflammation and damage are protracted*, for example, by ongoing hepatocellular injury mediated by immunological mechanisms, including antibody- and lymphocyte-mediated cytotoxicity, or ongoing oxidative damage. Clinical signs are nonspecific in the early stages, but as the disease progresses to involve more of the liver and impair regeneration, icterus, ascites, and hepatic encephalopathy may develop as typical correlates with hepatic insufficiency.

Chronic hepatitis of humans has several characteristic lesions. These are also evident in animals, although not to the same degree or frequency as described in the various forms of viral, immune-mediated, and idiosyncratic hepatitis in humans. The first is **periportal interface hepatitis**, sometimes referred to as "*piecemeal necrosis*" (Fig. 2.43). *This necroinflammatory change initially destroys the limiting plate of periportal hepatocytes, and may continue to erode into the hepatic parenchyma, expanding the portal areas.* Portal inflammation is variable in intensity, and includes infiltration by lymphocytes and plasma cells. Bridging necrosis, with tracts of necrosis dissecting across the hepatic lobule between portal triads or between portal areas and central veins, may also develop. Degenerative changes affecting hepatocytes in areas of interface hepatitis include cell swelling and apoptosis. Bile duct degeneration, multifocal necrosis, and hepatocellular regeneration in the form of increased numbers of binucleated and trinucleated cells and mitotic figures, may also be seen. Deposition of collagen and basement membrane material in the space of Disse leads to capillarization

Table 2.1 Grading the degree of disease activity in chronic hepatitis

	Lesions and degree of injury			
Category	Portal area inflammation	Periportal (piecemeal) necrosis	Nonzonal necrosis	Bridging and/or multiacinar necrosis
Mild	Mild, patchy	Absent or mild	Mild	Absent
Moderate	Moderate	Moderate	Moderate	Absent
Marked	Marked	Marked	Marked	Absent
Very marked	Marked	Marked	Marked	Present

Adapted from Ishak KG. Pathologic features of chronic hepatitis. Am J Clin Pathol 2000;113:40–55.

Table 2.2 Staging the progression of chronic hepatitis

	Component lesions		
Category	Fibrous expansion of portal areas	Bridging fibrosis (portal to portal, portal to central, central to central)	Bridging with nodules (cirrhosis)
Mild	Absent or mild	Absent	Absent
Moderate	Moderate	Absent (occasional)	Absent
Marked	Marked	Marked	Absent (occasional nodule)
Very marked	Marked	Marked	Present

Adapted from Ishak KG. Pathologic features of chronic hepatitis. Am J Clin Pathol 2000;113:40–55.

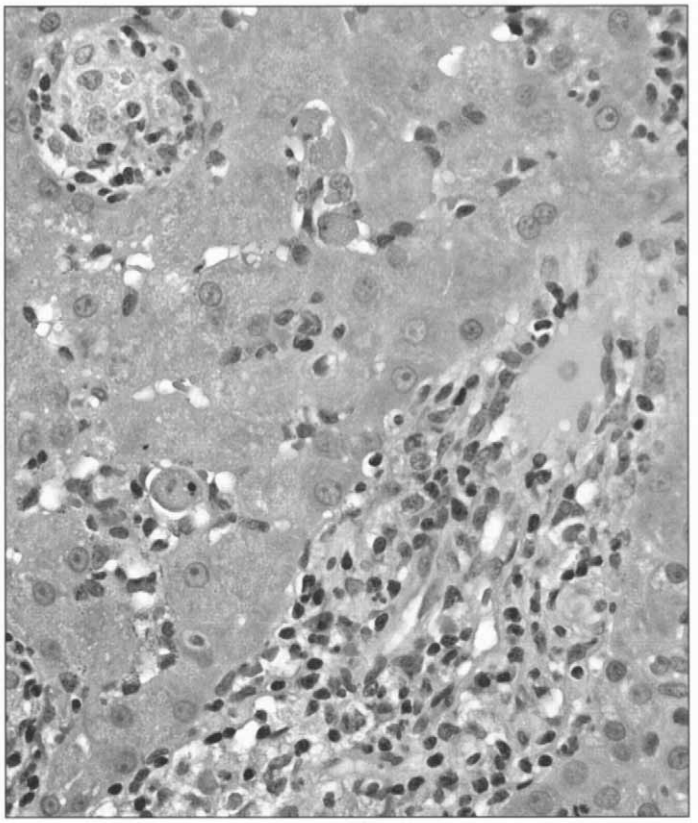

Figure 2.43 Periportal interface hepatitis in chronic hepatitis in a dog.

of hepatic sinusoids. Single or small groups of hepatocytes may be isolated and entrapped in expanded portal areas. Fibrosis may progress to bridge portal tracts, culminating in the development of cirrhosis.

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Chronic hepatitis in dogs

Chronic hepatitis is a relatively common diagnosis in dogs. While infectious etiologies, and drug- and toxin-induced chronic hepatic disease have been described, *the majority remains idiopathic*, although some appear to be breed-associated or familial. *Breeds of dogs* reported to be at increased risk for chronic hepatitis include the Bedlington Terrier, West Highland White Terrier, Doberman Pinscher, American and English Cocker Spaniel, Skye Terrier, Labrador Retriever, and Standard Poodle. Apart from the hereditary hepatic copper accumulation in Bedlington Terriers, the etiology of the breed-related disorders remains unclear.

The pathophysiologic mechanisms of chronic hepatitis in dogs are poorly understood. Given the importance of autoimmune hepatitis in human medicine, several studies have evaluated the role of immune mechanisms in dogs. Peripheral blood mononuclear cell proliferation in response to liver membrane antigens was higher in dogs with chronic hepatitis, supporting the hypothesis of an immune-mediated process, although whether this is primary or secondary to hepatocyte destruction is not known. An immunohistochemical study of the inflammatory infiltrate in 16 dogs with chronic hepatitis identified CD3+ lymphocytes as the most numerous lymphoid cells in liver sections from affected animals. Degenerate hepatocytes were occasionally surrounded by these cells, and necrosis was positively correlated with the numbers of CD3+ lymphocytes, suggesting a role for an immune-mediated process in chronic hepatitis. The number of α-smooth-muscle actin-positive cells (periductular myofibroblasts and activated perisinusoidal stellate cells) in portal triads and fibrous septa was positively correlated with the stage of fibrosis, lending support to the role of these cells in fibrogenesis in the canine liver. Upregulation of major histocompatibility complex class II antigen expression in hepatocytes has been demonstrated in Doberman hepatitis in association with lymphocyte infiltration, and it has been suggested that hepatocytes presenting a putative major histocompatibility complex class II molecule-associated autoantigen could be targets for T-cell-mediated immune attack. However, a primary autoimmune pathogenesis has yet to be demonstrated.

Liver disease associated with increased hepatic **copper** *occurs in various breeds of dogs that develop acute hepatic necrosis, subacute hepatitis, chronic hepatitis, and cirrhosis.* Copper is an essential metal cofactor for cuproenzymes, acting as a redox catalyst for a number of cellular oxidases. However, interaction with cellular hydrogen peroxide can yield highly reactive hydroxyl radicals. Hepatic copper accumulation may result from a primary metabolic defect in hepatic copper metabolism, or possibly as a secondary event resulting from abnormal hepatic function, cholestasis, and altered biliary excretion, a mechanism described in the human literature but not conclusively demonstrated in dogs. *A hereditary, autosomal recessive copper-associated hepatopathy associated with impaired biliary copper excretion and progressive accumulation of copper within hepatocytes has been well documented in Bedlington Terriers, and postulated in other breeds, including West Highland White Terriers and Skye Terriers.* The chromosomal locus of the gene in affected Bedlingtons has been mapped and a mutation in the *MURR1* gene identified, while other defects in the canine homologs of human genes for the copper-transporting ATPase, *ATP7B*, defective in Wilson disease in humans, and *ATOX1*, the copper chaperone delivering copper to *ATP7B*, have been excluded as possible candidates. While its function is unknown, the protein Murr1 has been shown to interact with the copper transporter ATP7B, and may be a copper chaperone involved in directing copper to biliary excretion. The human *MURR1* gene is also polymorphic and one mutation is believed to contribute to the pathogenesis of Wilson disease in a minority of human patients.

The role of copper in the pathogenesis of hepatic disease is less clear in breeds of dogs other than the Bedlington Terrier. Elevated hepatic copper (>400 μg/g dry weight) has been reported in clinically normal dogs, as well as in diseased liver from other breeds. Liver disease with concurrent copper accumulation has been reported in the Doberman Pinscher, West Highland White Terrier, Skye Terrier, Dalmatian, Keeshond, and Poodle, as well as others. *Chronic cholestasis, hepatitis, and cirrhosis of any etiology could increase liver copper concentrations;* secondary copper accumulation occurs in the majority of human patients with primary biliary cirrhosis, prolonged extrahepatic bile duct obstruction, or chronic liver disease. When the hepatic concentration of copper surpasses 400 μg/g dry weight, the excess begins to accumulate within lysosomes in all breeds of dogs, first demonstrable in the hepatocytes of zone 3, later in zone 2, and finally in zone 1 at the highest copper concentrations, a distribution that differs from that of other copper-loaded animal species. At levels exceeding 400 μg/g dry weight, copper-loaded lysosomes become demonstrable by the histochemical stains, rubeanic acid and rhodanine, allowing a qualitative assessment of copper storage. Regardless of the reasons for copper accumulation, lysosomal copper can exceed a threshold or be released when hepatocytes die, and thereby contribute to the development of hepatitis. *Hepatic pathology does not typically occur at concentrations less than 2000 μg/g dry weight*, although higher values can still be found in some dogs with normal liver histology.

Bedlington Terriers *are the only breed to date shown to accumulate copper continuously throughout life,* and hepatic copper concentrations in these animals may be very high; as much as 12 000 μg/g dry weight has been recorded, and levels higher than 5000 μg/g are common. Affected Bedlingtons are usually presented with signs of progressive liver failure, including ill-thrift, wasting, ascites, and signs of encephalopathy. An acute form may occur in some dogs, with acute hepatic necrosis and release of copper into the systemic circulation, where it provokes a hemolytic crisis and rapidly developing anemia and icterus. The most characteristic feature of the histology is the presence of numerous golden-brown refractile granules in hepatocytes, and darker pigment in Kupffer cells. The hepatocellular granules are copper-engorged lysosomes, which preferentially

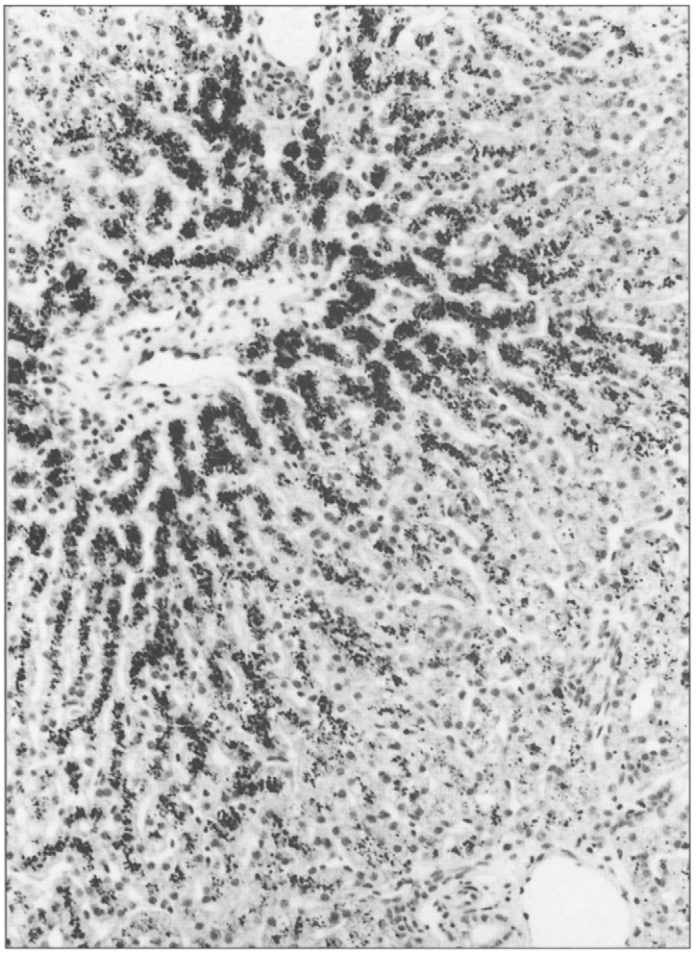

Figure 2.44 Section of liver from Bedlington Terrier, stained with rhodanine for copper to demonstrate the predominantly zone 3 distribution of **lysosomal copper**.

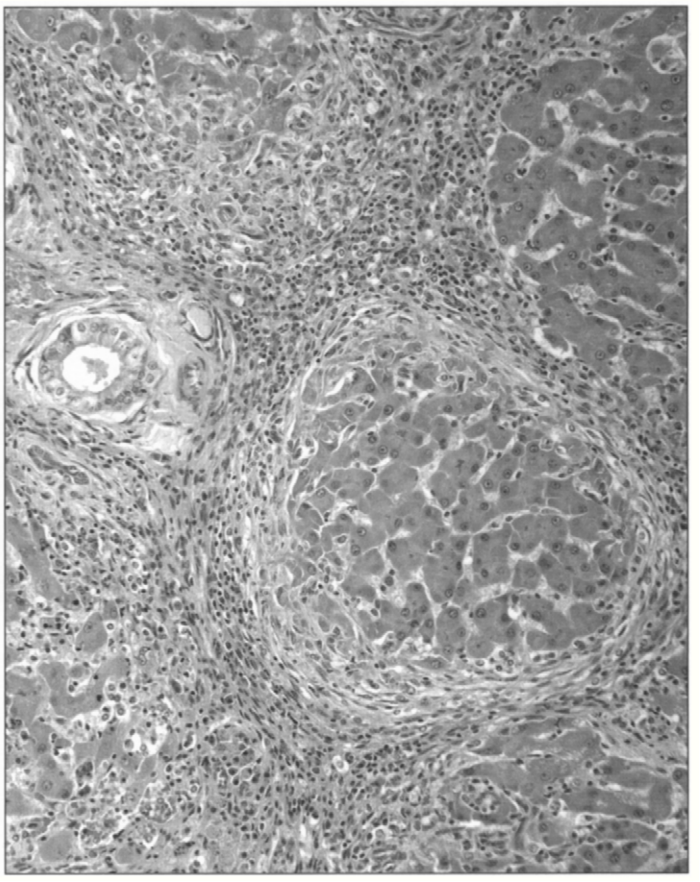

Figure 2.45 Periportal interface hepatitis with mixed inflammatory infiltrates and bridging portal fibrosis in a Doberman Pinscher dog.

accumulate in the cytoplasm of zone 3 hepatocytes. Evidence of hepatitis generally does not develop until levels exceed 2000 μg/g. The initial histologic lesion is multifocal centrilobular hepatitis, with foci of macrophages, lymphocytes, plasma cells, and neutrophils among the copper-laden hepatocytes in zone 3 (Fig. 2.44). Apoptotic hepatocytes, some containing copper granules, appear at the periphery of some foci. Copper levels exceeding 3000 μg/g dry weight result in widespread massive necrosis in some dogs. Survivors may progress to develop postnecrotic cirrhosis. Grossly, the livers in later stages are fibrotic, pale, and finely nodular.

Chronic hepatitis is well documented in **Doberman Pinschers**. The disease is more common in middle-aged female dogs. Histologic changes in the livers of dogs exhibiting clinical signs of advanced hepatic disease include piecemeal necrosis of periportal zone 1 hepatocytes, with a mixed inflammatory cell infiltrate, as well as necrosis of zone 3 hepatocytes with bridging necrosis crossing the lobule. Various degrees of portal fibrosis develop, with bile duct proliferation, bridging fibrosis, and development of cirrhosis in the most severely affected dogs (Fig. 2.45). Accumulation of copper in periportal zone 1 hepatocytes, particularly in areas of degeneration and necrosis, is prominent, although central hepatocytes also have some copper-positive granules (Fig. 2.46). Intrahepatocyte bile pigment accumulation and intracanalicular bile stasis are present in periportal zones, along with iron accumulation in Kupffer cells and macrophages.

Two recent studies, however, document that piecemeal necrosis and marked periportal inflammation are not prominent lesions in early stages of hepatic disease in Dobermans. One retrospective histologic study of the lesions in the livers of 35 Dobermans in the early precirrhotic stages of the disease found a consistently different pattern, with progressive fibrosis, inflammation, and hepatocyte loss beginning in zone 3, affecting hepatocytes around the terminal hepatic vein branches. The earliest changes were inflammation, predominantly small lymphocytes, plasma cells, and individual or clusters of pigmented macrophages often containing iron or copper, collagen deposition around the small hepatic vein branches, and apoptosis of scattered hepatocytes in zone 3. Copper-containing cells were exclusively in zone 3 hepatocytes, contrary to previously published reports. As the disease progressed, collagen deposition increased around the hepatic veins. In some specimens, thin fibrous septa radiated from the hepatic vein branches. In a few dogs, lymphoplasmacytic inflammation was mild and restricted to the connective tissue surrounding smaller branches of the hepatic vein. In the majority of cases, inflammation was distributed equally to the connective tissue around hepatic veins and the connective tissue of the portal tracts. In the most severe cases, infiltrating inflammatory cells were also present in the parenchyma among the hepatocytes. The sinusoids adjacent to the areas of fibrosis were converted to endothelial-lined, thin-walled vessels. Histologic changes were the same regardless of hepatic copper concentration, which appeared to be incidental to the disease progression.

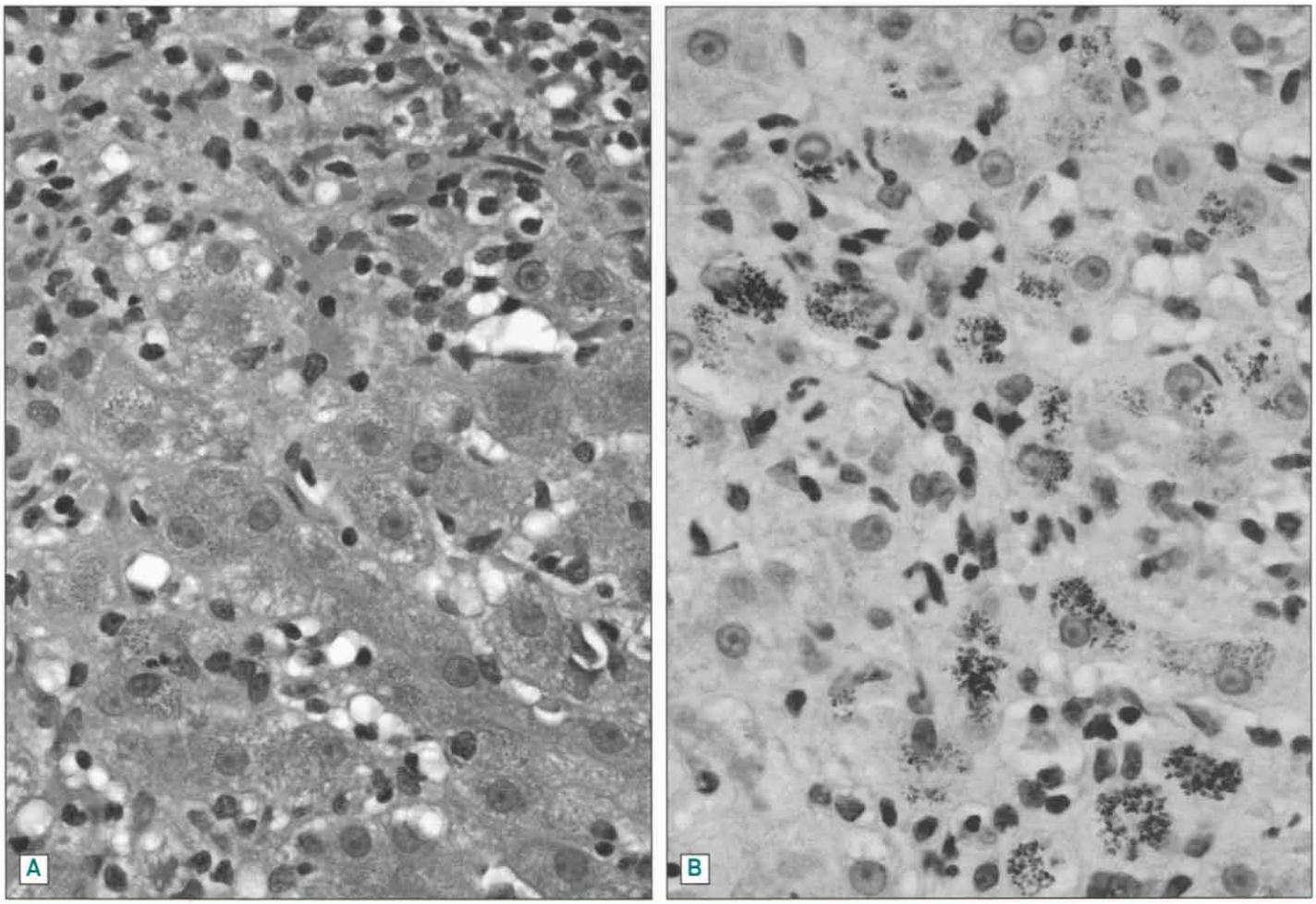

Figure 2.46 **A.** Periportal inflammation and hepatocellular **copper** accumulation in a Doberman Pinscher dog. **B.** Liver in (**A**) stained for **copper** with rhodanine.

The second study of the histologic hepatic lesions in 18 Dobermans suffering from subclinical hepatitis reported that the most significant changes in biopsy samples were multifocal clusters of inflammatory cells in the parenchyma, and portal inflammation. Inflammatory cells were mainly lymphocytes, but neutrophils and macrophages also appeared. Numbers of plasma cells were low. Periportal piecemeal necrosis was usually mild or moderate, and the limiting plate surrounding the portal area was never markedly ruptured. Three dogs had minimal bridging necrosis. Expansion of the portal area, fibrosis, and bile duct proliferation were uncommon, and, if present, mild. Every subclinically affected dog had excessive copper staining in its liver. Five dogs later euthanized for reasons other than liver disease showed progression of hepatic lesions, with at least moderate piecemeal necrosis, and moderate to marked portal expansion. Four dogs were later euthanized because of progressive hepatic disease. All had moderate to marked piecemeal and bridging necrosis, moderate to marked portal expansion, bile duct proliferation, and fibrosis.

Elevated concentrations of hepatic copper have been reported in many, but not all, Doberman Pinschers with chronic hepatitis. *The significance of increased hepatic copper concentration in this breed remains controversial.* It has been reported that clinically normal Doberman Pinschers (with no evidence of liver disease on liver biopsy) are one of several breeds that have higher hepatic copper concentrations than what is considered normal, with a mean hepatic copper concentration of 413 ± 298 μg/g and a range of 140–1500 μg/g. In one report of clinically affected Dobermans, the mean concentration was approximately 2000 μg/g dry weight, sequestered in zone 1 (periportal) hepatocytes. A study of 23 affected Dobermans reported one dog with normal hepatic copper concentration (250 μg/g), 12 dogs with copper levels <2000 μg/g (range from 650 to 1900 μg/g), and 10 dogs with copper levels >2000 μg/g (the highest 4700 μg/g). A study of Dobermans with early precirrhotic hepatitis reported elevated hepatic copper concentrations in 30 of 35 dogs. Of the 22 affected dogs whose liver copper was measured by atomic absorption analysis, 10 dogs had hepatic copper concentrations ≥2000 μg/g dry weight, 3 of which had copper >3000 μg/g, and 12 dogs had copper concentrations ranging from 650 to 1900 μg/g dry weight. In these dogs, the copper-laden hepatocytes were found in zone 3, adjacent to the hepatic vein. The copper accumulation was suggested to be neither the cause nor the effect, but occurred antecedent to the disease, and was incidental to disease progression. However, a recent investigation into the possibility of impaired copper excretion in affected Doberman Pinschers reported that 5 dogs with elevated liver copper and persistent subclinical hepatitis but without demonstrable cholestasis had comparable rates of plasma copper clearance to control dogs, but reduced rates of biliary excretion of ^{64}Cu. This provides additional support for the view that copper

accumulation contributes to chronic hepatitis in Dobermans, and is more likely a cause than a consequence of liver damage in this breed.

West Highland White Terriers *are at increased risk of developing chronic hepatitis and cirrhosis.* There is evidence to support *familial* hepatic copper accumulation in some West Highland White Terriers, although the mode of inheritance is not completely understood. Hepatic copper accumulates in zone 3 hepatocytes, up to about 8 months of age, with concentrations rarely exceeding 2000 μg/g dry weight. Clinical illness directly attributable to copper hepatotoxicity (concentrations >2000 μg/g dry weight) in West Highland White Terriers is, however, apparently uncommon. *Idiopathic chronic hepatitis progressing to cirrhosis does also occur in this breed,* and may be distinguished on the basis of a different zonal location and morphology of the inflammatory lesions. In the idiopathic disease, inflammatory foci are smaller, composed of a single apoptotic hepatocyte or fragments of cells accompanied by a few lymphocytes and plasma cells, and are commonly localized to zone 1, or may be random in distribution. In dogs with copper toxicosis, foci of inflammation and necrosis were larger, always found around the central vein among copper-laden hepatocytes, and were composed of debris-filled macrophages, lymphocytes, plasma cells, and scattered neutrophils, with occasional apoptotic hepatocytes around the periphery. *Distinguishing between copper toxicosis and idiopathic chronic hepatic disease may be difficult in cirrhotic livers,* which, irrespective of the underlying cause, may have reduced copper burdens due to connective tissue displacement of hepatic parenchyma, and typically lower concentrations of copper in regenerative nodules.

Chronic hepatitis been reported in genetically related **Skye Terriers**, accompanied by modest and somewhat inconsistent hepatic copper accumulation. Lesions ranged from hepatocellular degeneration and necrosis with mild inflammation in zone 3, to chronic hepatitis and cirrhosis with marked intracanalicular cholestasis. Hepatic copper concentrations ranged from 800 to 2200 μg/g dry weight, and copper-containing hepatocytes were found predominantly in zone 3. The etiology is unknown, although a defect in bile secretion has been suggested.

Chronic liver disease associated with elevated hepatic copper concentrations has been reported in **Dalmatians**. A range of necroinflammatory changes has been reported, including multifocal, piecemeal, centrilobular to massive hepatic necrosis, and cirrhosis, although, in one study of 10 dogs, various degrees of piecemeal necrosis and bridging fibrosis were the most common histologic change, with either primarily lymphocytic or neutrophilic inflammatory infiltrates. Morphologic or biochemical evidence of cholestatic liver disease was not prominent. Hepatic copper concentrations ranged from 745 to 8390 μg/g dry weight (mean 3197 μg/g) in one report of 10 dogs, aged 2–10 years, with a variable zonal distribution. Three previous cases in young Dalmatians reported hepatic copper concentrations of 7940 μg/g dry weight, 1916 μg/g wet weight, and 2356 μg/g wet weight, and two of these reports describe diffuse positive staining for copper in all hepatocytes, with the strongest staining observed in centrilobular hepatocytes.

Chronic hepatitis has been reported in **Cocker Spaniels**, characterized by a brief clinical illness with ascites, weight loss, and other signs typical of hepatic disease. Affected dogs develop chronic hepatitis and cirrhosis, and, at necropsy, livers are typically small and firm, with multiple small regenerative nodules. Histologically, there is moderate to severe portal hepatitis, with inflammatory infiltrates

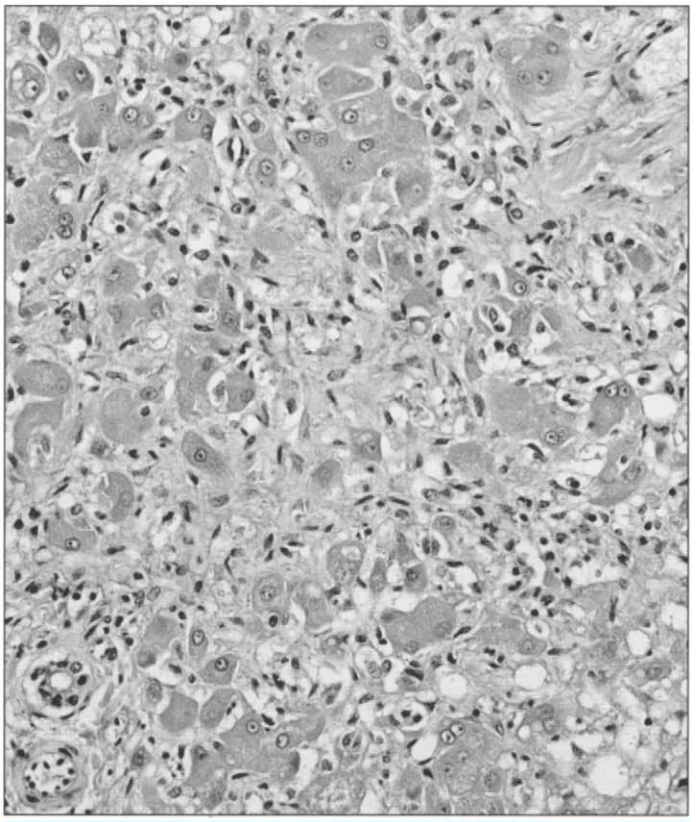

Figure 2.47 Lobular dissecting hepatitis with diffuse fine interstitial fibrosis isolating hepatocytes in a juvenile Golden Retriever dog.

of predominantly lymphocytes, plasma cells, and fewer neutrophils, and variable degrees of portal fibrosis and bridging fibrosis. Piecemeal necrosis and limiting plate destruction have been reported. Biliary hyperplasia is a common feature. Hepatic copper staining is variable, and hepatic copper accumulation does not appear to be a consistent feature. α_1-antitrypsin deficiency *has been suggested to play a role in chronic hepatitis in some dog breeds, including English Cocker Spaniels,* although whether this is an epiphenomenon or cause of chronic liver disease has not yet been proven. α_1-antitrypsin is a member of the serine proteinase inhibitor (serpin) superfamily, and is a potent inhibitor of neutrophil elastase. Hereditary α_1-antitrypsin deficiency in humans is associated with mutations that perturb the protein's tertiary structure and promote polymerization. Accumulation of altered forms of α_1-antitrypsin in the endoplasmic reticulum of hepatocytes, with the formation of inclusion bodies and subsequent cell death has been associated in humans with neonatal hepatitis, juvenile cirrhosis, and adult hepatocellular carcinoma.

Noninflammatory **idiopathic hepatic fibrosis** *has been reported in young dogs,* typically <2 years of age, and is associated with chronic hepatic failure and portal hypertension. Histologically, there are various patterns of hepatic fibrosis, including diffuse pericellular (reticulofibrosis), periportal, and central perivenous (periacinar) fibrosis. Diffuse pericellular fibrosis is characterized by intralobular reticulin deposition that surrounds individual hepatocytes, and alters normal hepatic architecture (lobular dissecting hepatitis). The periportal pattern (hepatoportal fibrosis) has been discussed previously, and has been associated in some cases with congenital hypoplasia of the portal vein. Central perivenous fibrosis resembles hepatic veno-occlusive

disease; however, there is no evidence of intimal damage, and the fibrous tissue is deposited peripheral to the intimal lining of the terminal hepatic veins.

Lobular dissecting hepatitis, *associated with predominantly sinusoidal inflammation and fibrosis, has been described in young dogs with ascites and acquired portosystemic shunts.* The liver is usually small, pale with a predominantly smooth surface, and occasional hyperplastic nodules. The histologic lesion is characterized by dissection of lobular parenchyma by reticulin and fine collagen fibers into individual and small groups of hepatocytes, accompanied by a mixed inflammatory infiltrate of lymphocytes, plasma cells, and lesser numbers of neutrophils and macrophages (Fig. 2.47). Activated fibroblastic cells, likely hepatic stellate cells, may also be prominent along sinusoids. Hepatocytes form rosettes or pseudoductular structures, and regenerative nodules may be present. Portal inflammation and periportal fibrosis are not conspicuous features of this disease. The etiology of this disorder remains unknown.

Granulomatous hepatitis *has been reported in dogs with various systemic parasitic, mycotic, and bacterial infections.* However, granulomatous hepatitis with signs of clinical liver disease, including hepatomegaly, icterus, ascites, and elevated hepatic enzymes, has also been reported in dogs with intestinal lymphangiectasia and inflammatory bowel disease, lymphosarcoma, and histiocytosis. The histologic lesion consists of multifocal infiltrates of histiocytes, often associated with lymphocytes and plasma cells, neutrophils, or eosinophils.

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Miscellaneous inflammatory liver disease

Idiopathic acute hepatic disease, *also known as* **equine serum hepatitis** *or* **Theiler's disease**, *is a common cause of acute hepatic failure in horses.* The disease was originally observed in horses passively immunized against African horse sickness and later in horses passively immunized against anthrax, tetanus, and equine encephalomyelitis. Various injectable biologics of equine origin have been associated with the disease, including *Clostridium perfringens* toxoids, tetanus antitoxin, and equine herpesviral vaccines prepared from equine fetal tissue and pregnant mare serum. However, while such an association holds for the majority of cases, there are many, usually sporadic, cases in horses that have not received any injections.

While the disease remains idiopathic, *a viral cause that is serum-transmissible, similar to hepatitis B in humans, is proposed.* The incubation period of 42–60 days, sometimes up to 90 days, is similar to some other viral causes of hepatitis. The occurrence of equine serum hepatitis among inoculated animals is variable and attempts to reproduce the disease by experimental transmission have rarely been successful. It is unknown how many exposed horses get subclinical disease, because the condition is seldom diagnosed before the onset of hepatic failure. However, some horses do recover after transient illness with jaundice, and some can survive with residual neurologic problems.

The onset of the typical clinical syndrome is sudden, with death occurring in 6–24 hours. Clinically, there is jaundice, hyperexcitability, often with mania, continuous walking and pushing, apparent blindness, and ataxia. Death occurs suddenly without a period of prostration.

At autopsy, icterus is present, with moderate ascites; the spleen is normal or congested, and there may be petechial hemorrhages on serous membranes and renal cortices, and some congestion of the intestine with hemorrhage into its lumen. Grossly, the liver usually appears to be of normal size, although it may be slightly enlarged or atrophic and flabby due to the acute loss of many hepatocytes. The liver may be stained by bile pigments, and its surface mottled with a few strands of fresh fibrin. The mottling is more evident on the cut surface, which appears as if severely congested and sometimes fatty (Fig. 2.48A).

Microscopically, the hepatic lesion is considerably older than the clinical course would suggest (Fig. 2.48B). *There may be a few surviving swollen and vacuolated periportal hepatocytes or sometimes complete depletion of parenchymal cells in the section.* In less affected regions in animals with adequate dietary or adipose reserves to mobilize, there is severe macrovesicular fatty change in most remaining hepatocytes. Acute necrosis is typically not seen, and there is no significant hemorrhage. Variable numbers of apoptotic hepatocytes are expected. In the periphery of the acini, severely ballooned cells undergo dissolution to leave scattered fatty cysts, but most of them disappear to leave either sinusoids that are dilated and filled with blood or a condensed and distorted reticulin framework. Extensive deposits of bile pigments are present in Kupffer cells and hepatocytes. Leukocytes, including lymphocytes, plasma cells, histiocytes, and a few neutrophils, may infiltrate diffusely, but not in large numbers. There is diffuse but very slight fibroplasia, especially in the portal units. In some livers, there are small irregular clusters of proliferating ductular cells in the portal areas, resembling the regenerating cholangiolar or oval cells that replicate in atrophic livers.

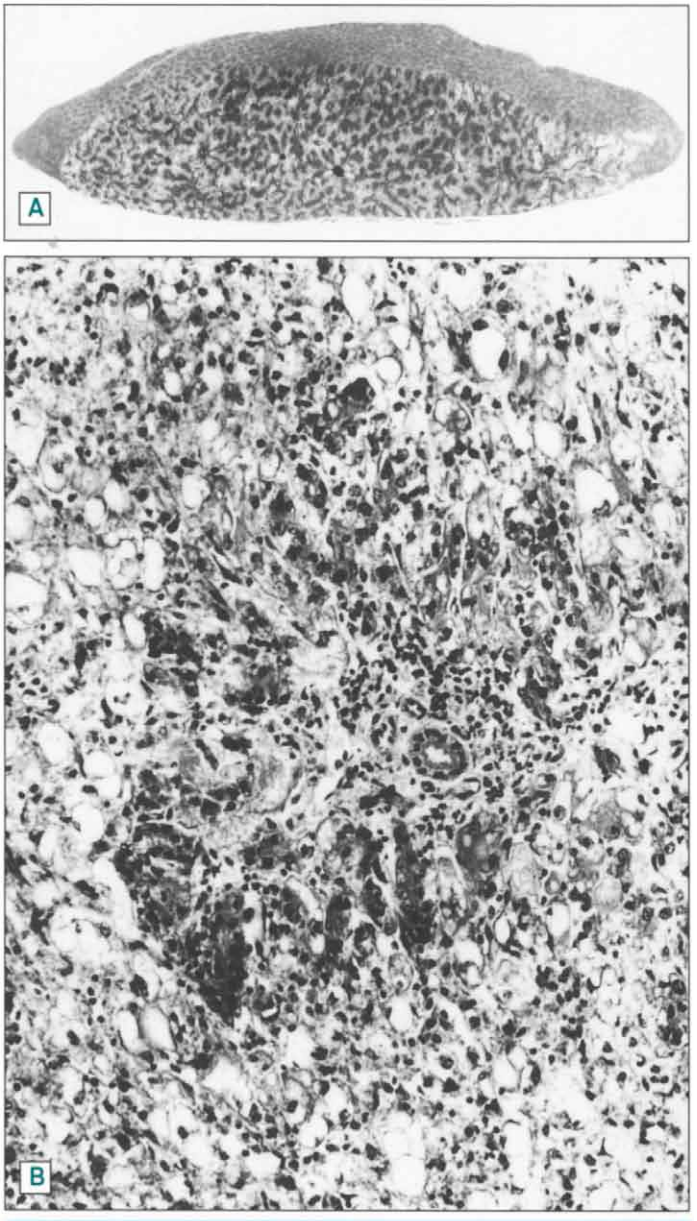

Figure 2.48 Equine serum hepatitis. A. The reticular pattern in this slice of liver suggests **zonal necrosis**. **B.** Section of the liver in (**A**) to show extensive periacinar degenerative changes, cellular infiltration, and periportal survival zone.

Focal or diffuse **fetal hepatitis** *occurs in a number of intrauterine fetal infections.* Whether caused by bacteria or viruses, focal necrosis is often present and bacteria or viral inclusions can often be identified. Frequently, however, the lesions are subtle and diffuse and without necrosis, and the inflammatory process may be difficult to distinguish from hematopoiesis. There is inflammatory edema of the connective tissues of the portal triads with distension of lymphatics there and beneath Glisson's capsule. A preponderance of mature granulocytes in the portal triads and in the adventitia of hepatic veins helps to distinguish inflammatory infiltrates from hematopoietic foci, which are predominantly in sinusoids.

Giant cell hepatitis *is an uncommon lesion in animals, but is recorded in cats, calves, and foals.* There is evidence for maternal leptospirosis in some cases in foals. Two cases are reported in young cats with concurrent thymic lymphomas. The liver is deeply bile-stained. Histologically, the acinar structure is effaced and the blood vessels engorged. Hepatocytes are large and syncytial and may contain 10 or more nuclei. The pale or ballooned cytoplasm contains bile pigments, and cytoplasmic invaginations into hepatocyte nuclei are common. Inflammatory cells are not conspicuous. Liver parenchymal giant cell transformation occurs in humans in a wide variety of congenital and neonatal liver disorders, including bile duct obstruction associated with biliary atresia, viral and bacterial infections, some metabolic disorders such as galactosemia, some cases of Down syndrome and other genetic disorders, as well as in idiopathic neonatal hepatitis, a cholestatic condition of undetermined cause. While giant cells were originally suggested to be a marker of infantile obstructive cholangiopathy, their association with a wide range of disorders supports an *alternative conclusion that giant cell formation represents a nonspecific reaction of the infant's hepatocytes to various types of injury.*

Hypertrophic hepatic cirrhosis in calves is described from Germany and occasionally observed elsewhere. Death may occur in liver failure within a few days to weeks of birth or the disease may be discovered at slaughter for veal. The liver is moderately enlarged with rounded borders, very firm but smooth on the surface, and gray. Histologically, there is some biliary hyperplasia but the lesion is dominated by diffuse fibrosis infiltrated in the early stages by mononuclear inflammatory cells. No cause has been identified. Similar lesions of **congenital hepatic fibrosis** may be found in unborn or aborted calves.

Systemic granulomatous disease has been reported in cattle grazing *hairy vetch (Vicia villosa).* The disease is characterized clinically

by dermatitis, pruritus, diarrhea, wasting, and high mortality. Histologic lesions include infiltration of skin and internal organs, including portal areas of the liver, by monocytes, lymphocytes, plasma cells, eosinophils, and multinucleated giant cells. The pathogenesis is unknown, although the inflammatory reaction has characteristics of a type IV hypersensitivity reaction. Alternatively, vetch lectin may act to activate T lymphocytes directly to initiate the cellular response.

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Inflammatory diseases of the biliary tract

Inflammation of the gallbladder is termed **cholecystitis**. *Inflammation of the large bile ducts is* **cholangitis**, *whereas inflammation of the smallest intrahepatic bile ductules is termed* **cholangiolitis.** Cholangiolitis is uncommon in animals, and occurs mainly in conjunction with inflammation of larger ducts. Destructive cholangiolitis has been observed in dogs, and is associated with adverse drug reactions in humans.

Cholecystitis

Cholecystitis is uncommon, and may occur alone if the neck of the gallbladder is obstructed. More typically, it is associated with concurrent cholelithiasis. *Cholecystitis is thought to be due to reflux of intestinal bacteria into the gallbladder via the bile ducts, or to hematogenous entry of bacteria from the adjacent hepatic circulation.* Aerobic gram-negative bacteria are the most frequent isolates from canine cases, although occasionally anaerobic bacteria such as clostridia have been cultured. *Campylobacter jejuni* has been isolated from two dogs with bacteremia and cholecystitis. Canine cholecystitis has been associated with various disorders, including diabetes mellitus, severe enteritis, biliary stasis, septicemia, as well as with the use of immunosuppressive drugs, each of which may promote bacterial colonization of the gallbladder. In the acute lesion, histologic changes include neutrophilic inflammatory infiltrates in the wall and lumen of the gallbladder, with focal erosion or ulceration, and edema. More chronic stages develop typical mixed inflammatory infiltrates, with fibrosis. Occasionally, the infiltrate may be predominantly lymphoplasmacytic, with formation of lymphoid follicles within the mucosa.

Gallbladder infarction characterized by transmural coagulative necrosis of the gallbladder wall with intravascular fibrin thrombi has been reported in dogs. Predisposing factors have not been identified; however, the lack of significant concurrent inflammatory response suggests that this is not simply a sequela to underlying cholecystitis.

Cholangitis/cholangiohepatitis

Although pure cholangitis does occur, involvement of the periportal hepatic parenchyma by extension of inflammation from the ducts is almost inevitable, and such lesions can quite accurately be regarded as cholangiohepatitis.

Bile contains various antimicrobial factors, including beta defensins and bile acids that are inhospitable to most bacteria, except for some species with particular capsule adaptations. Bacterial cholangiohepatitis is usually caused by common opportunists of enteric origin, such as coliforms and streptococci. Some bacteremic organisms, including some *Salmonella*, can be cultured from the bile, but the mechanism by which they get there is unknown. Salmonellosis is a distinctive cause of fibrinous cholecystitis in cattle, especially calves.

The *pathogenesis of bacterial cholangiohepatitis* depends on various predisposing conditions, similar to those involved in the pathogenesis of pyelonephritis. These include infection by bacteria that reach the ducts hematogenously, facilitated by localization in the peribiliary plexus or by extension from sinusoidal Kupffer cells or foci of necrosis. Descending cholangitis is occasionally observed in cattle with suppurative hepatitis with extension from abscesses directly into the ducts or via the portal lymphatics. Cholangiohepatitis of this origin may be restricted in its distribution to biliary fields, but in some cases it does become quite diffuse in the biliary system. Alternatively, bacteria can extend up the ducts from the intestine, facilitated by bile stasis due to mechanical or functional obstructions. The inflammatory and proliferative responses in cholangitis further interfere with bile flow and exacerbate the ductular spread of bacterial infections once they are established.

The course and pathologic changes in cholangiohepatitis vary greatly, from fulminating suppurative infection to persistent mild inflammation that over a period of months or years leads to hepatic fibrosis of biliary distribution. *Severe suppurative cholangiohepatitis* may follow a short course to death, the effects being those of the infection itself, which may become septicemic, rather than of hepatic injury. At autopsy, the liver is swollen, soft, and pale, and its architecture is blurred. Few or many suppurative foci may be visible beneath the capsule and on the cut surface (Fig. 2.49). They are small, sometimes miliary in distribution, and not encapsulated. Lesions in other organs may be those of septicemia and jaundice. Microscopically, the larger

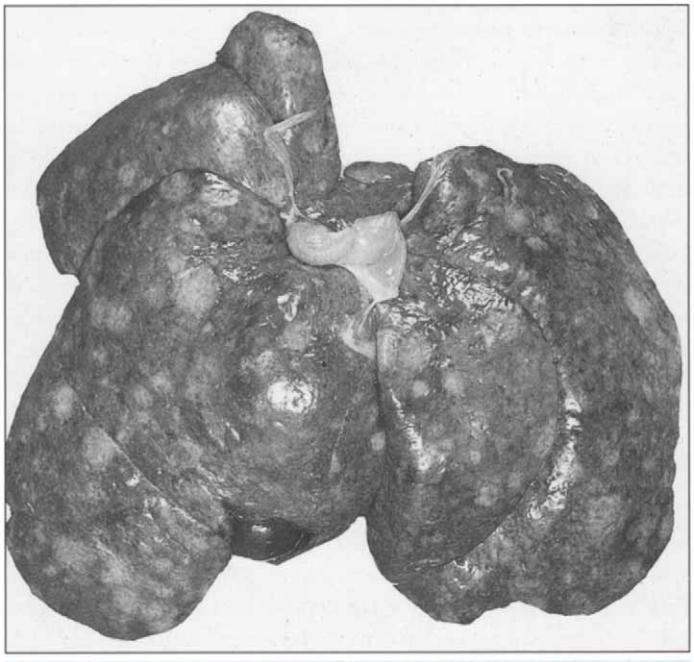

Figure 2.49 Acute **cholangiohepatitis** in a dog.

ducts contain purulent exudate, and the smaller ones are disintegrated. Dense masses of neutrophils, liquefied or not, are present in the portal triads and infiltrate the degenerate parenchyma.

In *subacute and chronic cholangiohepatitis*, the inflammation is more proliferative than exudative. The liver is enlarged and may be of normal shape, or distorted owing to irregular areas of atrophy and regenerative hyperplasia. Its surface may be smooth or finely granular; the capsule is thickened and may bear fibrous villi or be adherent to adjacent viscera. Within areas of duct obstruction, retention of bile pigments can be found in the regions served by the occluded ducts, but systemic icterus (or photosensitization in herbivores) is unlikely unless a very large amount of liver is affected. On the cut surface, the enlarged portal tracts are easily visible and accentuate the architecture of the organ. Eventually, the new fibrous tissue replaces the parenchyma, and in chronic diffuse cases in which the original infection persists, continuous fibroplasia may produce hepatic enlargement, the organ becoming huge, gray, and gristly. This spectrum of liver changes is typical of alsike clover poisoning ("big-liver disease") in horses (discussed in the section on Toxic hepatic disease, below). Alternatively, the chronic fibrosis may occur in wedge-shaped areas oriented to a small bile duct. The enlarged interlobular ducts may be readily visible and frequently contain plugs of inspissated secretion and debris. This lesion may be referred to as *biliary infarction*.

Microscopically, the reaction remains centered on portal tracts. These are expanded in subacute cases by infiltration of leukocytes and macrophages and the proliferation of small ducts and, in chronic cases, chiefly by organizing fibrous tissue and proliferating bile ducts (see Fig. 2.37). Encroachment on the parenchyma is minimal but inevitable. Continued degeneration of the periportal parenchyma is probably an additional stimulus to local fibroplasia, which, as well as thickening the smallest portal triads, extends along their length and links up with neighboring triads, thus subdividing the acini into segments. The hepatic venules and sublobular veins are involved. Regenerative nodules are not a prominent feature of cholangiohepatitis unless large areas of parenchyma have been destroyed, in which case the least damaged lobes are expanded by coarse nodules.

Suppurative or neutrophilic cholangiohepatitis *of ill-defined pathogenesis occurs in mature cats and less commonly in dogs.* The acute stage is characterized by edema and neutrophilic portal infiltrates, inflammation and degeneration of bile ducts with neutrophils in ductular lumens and emigrating through the ductular epithelium, infiltration of inflammatory cells into hepatic lobules and periportal hepatocellular necrosis. Mixed cholangiohepatitis, with neutrophils, lymphocytes, and plasma cells infiltrating portal areas accompanied by bile duct proliferation, biliary epithelial degeneration, and various degrees of periportal to bridging fibrosis, may represent the subacute stage (Fig. 2.50), while concentric periportal fibrosis and pseudolobule formation may represent the most chronic stage of the disease. Suppurative cholangiohepatitis is more prevalent in cats 11–15 years of age, and often occurs in conjunction with other disorders, including acute extrahepatic bile duct obstruction, pancreatitis, or inflammatory bowel disease. *This condition has been suggested to be the result of acute inflammation in the biliary tree associated with ascending bacterial infection.* In the cat, the biliary and pancreatic ducts have a common entry to the duodenum, and simultaneous infectious inflammation of these systems is common. *Escherichia coli* is the most common bacterial isolate; however, *Bacteroides*, hemolytic *Streptococcus*, and clostridia have also been reported.

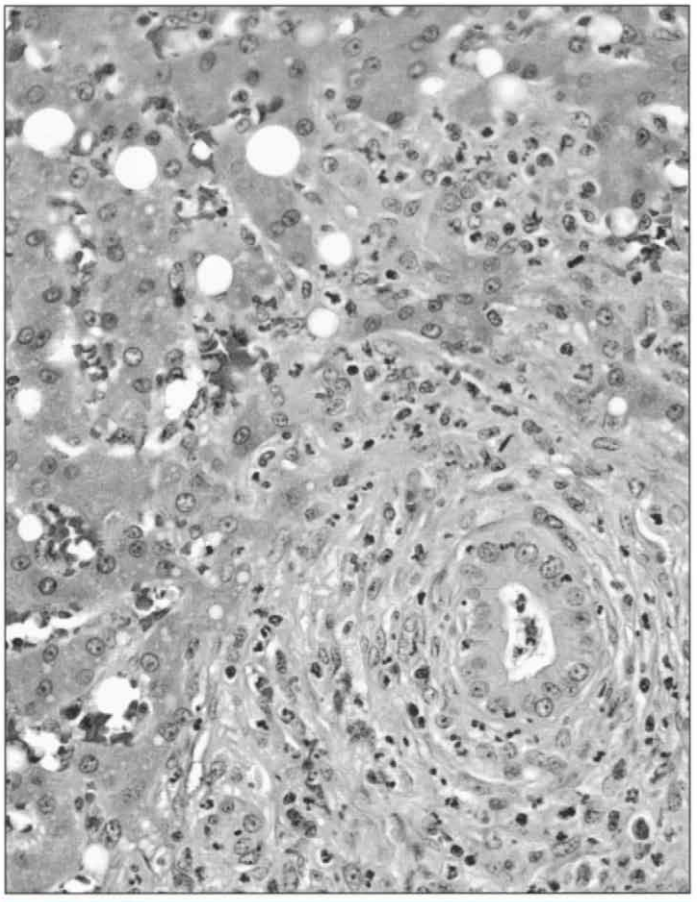

Figure 2.50 Bile duct inflammation with portal edema, mixed inflammation, and early fibrosis in a case of **suppurative cholangiohepatitis** in a dog.

An apparently distinct condition of cats, **lymphocytic portal hepatitis** *is characterized by lymphocytic or lymphoplasmacytic infiltrates confined to the portal area, with no evidence of periportal necrosis or invasion of adjacent hepatic lobules* (Fig. 2.51A). Bile duct proliferation is present, but there is no evidence of bile duct epithelial degeneration or cholangitis. Periportal fibrosis is typically present, but there is no bridging between portal areas and central veins. The condition is seen most often in cats over 15 years of age, and is slowly progressive, but does not result in pseudolobule formation. Lymphocytic portal hepatitis differs from descriptions of **feline progressive lymphocytic cholangitis/cholangiohepatitis**, which has been suggested by some authors to be part of the chronic phase of neutrophilic cholangiohepatitis, as described above (Fig. 2.51B). However, progressive lymphocytic cholangitis/cholangiohepatitis has been reported predominantly in younger cats, is not apparently associated with concurrent intestinal or pancreatic disease, and is postulated to have an immune-mediated pathogenesis. This condition is typified by lymphocytic inflammation of portal tracts, with infiltration of bile ducts, extension into periportal hepatic parenchyma, bile duct proliferation accompanied by small foci of neutrophil and macrophage infiltration, and fibrosis.

Biliary tract obstruction

Cholelithiasis *(gallstone formation) is seldom observed in animals.* The choleliths usually form in the gallbladder and are composed of a

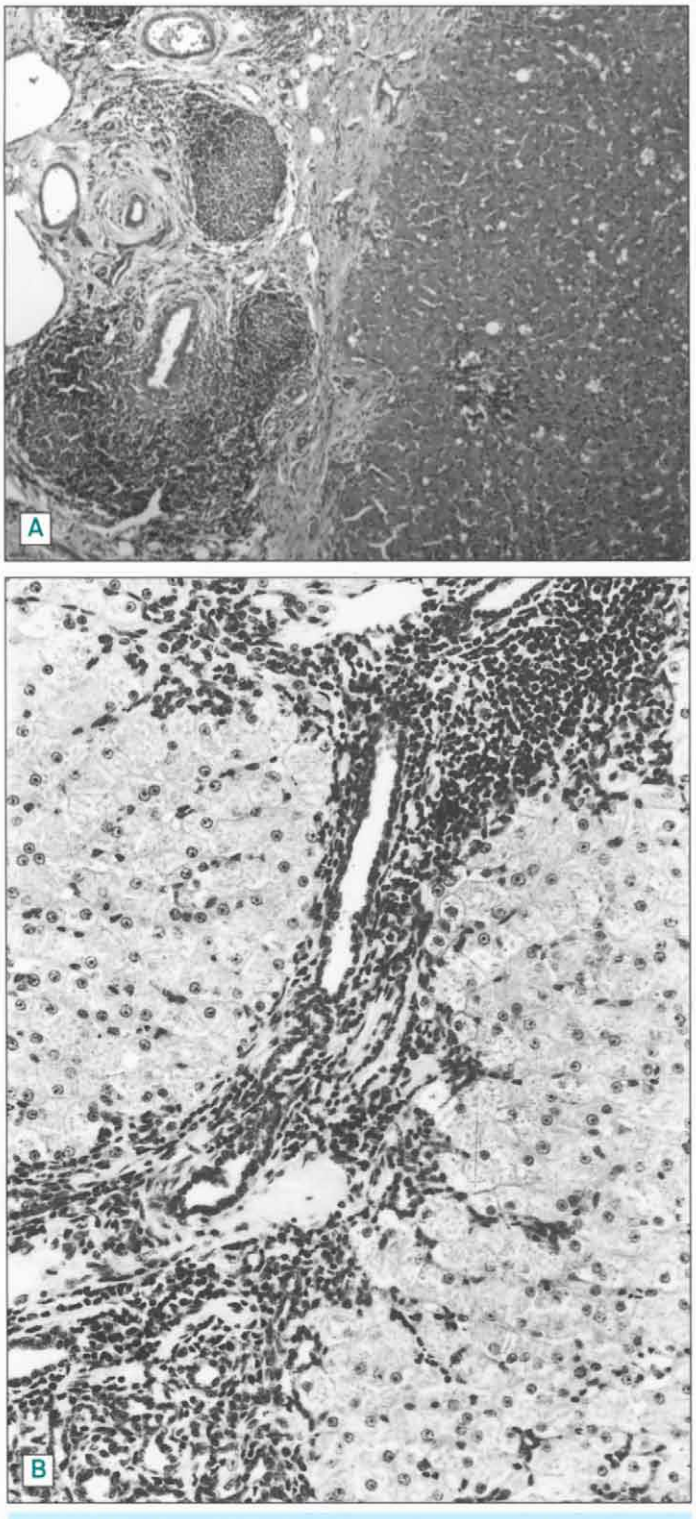

Figure 2.51 A. Lymphocytic portal hepatitis in a cat. **B. Lymphocytic cholangiohepatitis** in a cat.

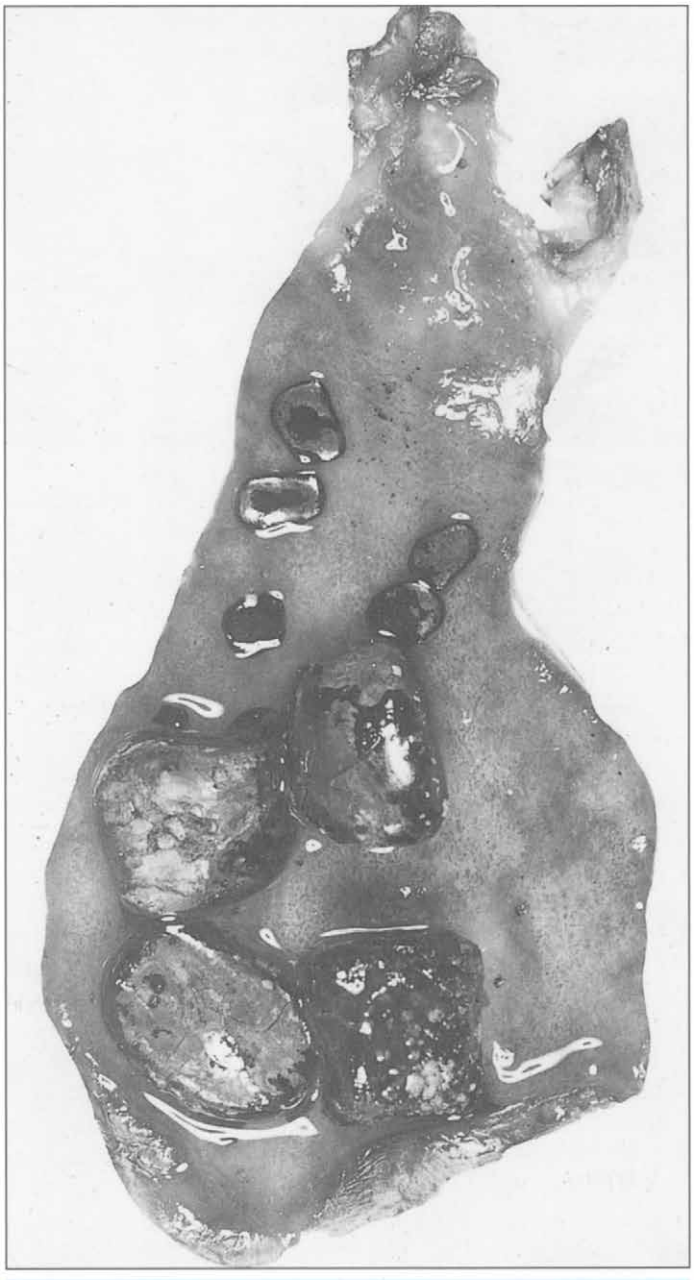

Figure 2.52 Gallstones in the opened gallbladder of a dog.

mixture of cholesterols, bile pigments, salts of bile acids, calcium salts, and a proteinaceous matrix. Choleliths of mixed composition are yellow-black or green-black and are friable. *Pigment stones*, composed of calcium bilirubinate, and *cholesterol stones* have also been reported in dogs. There may be hundreds of small stones or a few large ones (Fig. 2.52). The large stones are usually faceted. The origin of these mixed gallstones is uncertain, but their development is probably secondary to chronic mild cholecystitis and related to disturbances of the resorptive activities of the gallbladder, whereby the bile salts are removed faster than the stone-forming compounds. Gallstones are usually asymptomatic. Occasionally, they lodge in and obstruct bile ducts and cause jaundice. The larger stones may cause pressure necrosis and ulceration of the mucosa, local dilations of the bile ducts, and saccular diverticula of the gallbladder. Calculi seldom form in the ducts, although calcareous deposits often do so in fascioliasis of cattle. Calcium bilirubinate calculi have been reported in the bile ducts of horses (Fig. 2.53), associated with intermittent jaundice.

Occasionally, particles of solid ingesta may find their way into the gallbladder; sand has been seen in sheep, and seeds in pigs.

Biliary obstruction is rarely due to impacted gallstones. Usually it is *due to cholangitis or cholecystitis*, the obstruction being produced

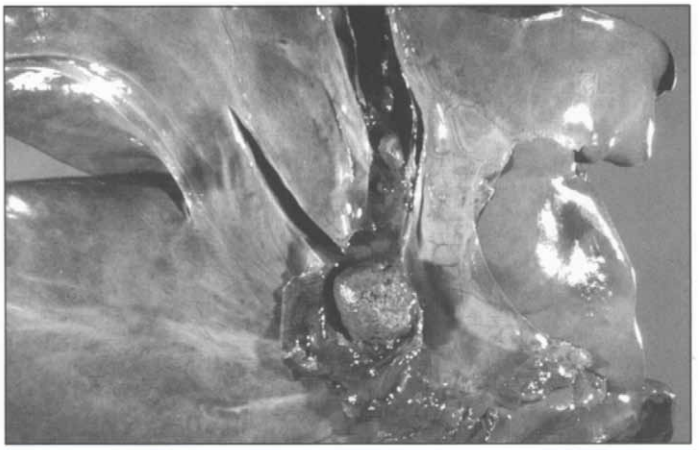

Figure 2.53 Cholelith obstructing the bile duct in a horse.

by masses of detritus and biliary constituents, parasites, or cicatricial stenosis of the ducts. Adult ascarids may cause mechanical obstruction. Inspissated bile-stained friable plugs are occasionally responsible for obstructions in segments of the liver in horses. Tumors of the pancreas and duodenum, and tumors and abscesses of the hilus of the liver and portal nodes, may cause compression stenosis of the ducts. Edematous swelling of the papilla in enteritis may also be of significance. Biliary obstruction by abnormal intraluminal mucoid secretion (*gallbladder mucocele*) has been reported in dogs (see section on Ectopic, metaplastic, and hyperplastic lesions, below).

The consequences of biliary obstruction depend on the site and duration of the obstruction. When the main duct is involved, there is jaundice. When one of the hepatic ducts is involved, there is no jaundice, and depending on the efficiency of biliary collaterals, there may be no pigmentation of the obstructed segments of liver. Increases in serum γ-glutamyltranspeptidase and alkaline phosphatase usually occur when a sufficiently large amount of the duct system is affected. The ducts undergo progressive cylindric dilation, which may be extreme. The smallest interlobular ducts and the cholangioles proliferate. There is inflammation in the walls of the ducts and the portal triads, and this is probably due in part to chemical irritation by bile acids but is largely due to secondary bacterial infections. These infections may be acute and purulent, or low-grade; in these cases, bacteria may not be easily cultured. The cholangiohepatitis that almost inevitably follows has been described earlier.

Inflammatory stenoses of larger ducts may recanalize via mucosal glands, which can proliferate and link to form a tortuous detour around the obstruction.

Rupture of the biliary tract or the gallbladder causes steady leakage of bile into the peritoneal cavity, the omentum being unable to seal even small defects. The bile salts are very irritating and may cause *acute chemical peritonitis*. The peritoneal effusion that follows may remain sterile; more often it is infected by enteric bacteria, and severe diffuse peritonitis ensues. This may be rapidly fatal, particularly if clostridia are involved. Most perforations of the biliary tract are traumatic in origin.

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INFECTIOUS DISORDERS OF THE LIVER

Viral infections

Various systemic viral diseases may affect the liver. Adenoviral infections of lambs, calves, and goat kids can cause multifocal hepatic necrosis and cholangitis, in addition to pneumonia. Lymphohistiocytic hepatitis with single-cell necrosis of hepatocytes and perilobular fibrosis is a frequent histologic lesion in cases of postweaning multisystemic wasting syndrome in pigs, associated with *Porcine circovirus* type 2 infection. Neonatal *Canid herpesvirus 1* infection in puppies causes disseminated focal necrosis and hemorrhages in parenchymal organs, including the liver, with formation of amphophilic intranuclear inclusion bodies in epithelial cells of kidney, lung, and liver. Similar microfoci of hepatic necrosis sometimes occur in aborted or newborn foals with congenital *Equid herpesvirus 1* infections (see Fig. 2.26). *Feline coronavirus* infection can cause granulomatous hepatitis in some infected cats, as part of feline infectious peritonitis.

The viral diseases included below are those in which the liver is the major target organ for viruses that cause substantial hepatic disease that sometimes culminates in hepatic failure. Unlike humans, in which several pathogenic hepatitis viruses from various families are well described, the major domestic mammals are vulnerable to few viruses that target hepatocytes. Some hepadnaviruses have been found in ducks, woodchucks, and herons. Closely related human and swine genotypes of *Hepatitis E virus* (HEV – Caliciviridae) can replicate in porcine hepatocytes wherein antigens and viral nucleic acids can be detected. There is evidence for fecal–oral transmission of HEV in pigs, and zoonotic transmission, but experimental HEV infection has not been reported as a primary cause of hepatitis in pigs.

Infectious canine hepatitis

Canine adenovirus 1 (CAdV-1) infection can cause infectious canine hepatitis, a severe liver disease in dogs and other canids. Vaccination has made the disease rare in many countries in which it was endemic.