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Carolien graduated from Utrecht State University and completed an internship at the University of Pennsylvania and a residency and Masters degree at Ohio State University. In between she worked in referral small animal practice. She joined the University of Liverpool in 1985 as a Lecturer in Small Animal Medicine and moved in 1990 to the Royal Veterinary College, where she later became a Senior Lecturer. She is now an independent consultant. Carolien has published more than 100 scientific papers and book chapters, and has lectured widely in the UK and abroad. Her major research interests are in gastroenterology and liver disease. She is a Diplomate of the American College of Veterinary Internal Medicine (ACVIM), a Foundation Diplomate of the European College of Veterinary Internal Medicine - Companion Animals (ECVIM-CA), and a RCVS Diplomate in Small Animal Medicine. Carolien has been a foundation Board member of the ECVIM-CA and a member of the RCVS Small Animal Medicine and Surgery Board, and a Diploma examiner for both.

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Vincent Biourge graduated from the Faculty of Veterinary Medicine of the University of Liège (Belgium) in 1985. He stayed as an assistant in the nutrition department for 2 more years before moving to the Veterinary Hospital of University of Pennsylvania (Philadelphia, USA) and to the Veterinary Medical Teaching Hospital of the University of California (Davis, USA) as a PhD/resident in Clinical nutrition. In 1993, he was awarded his PhD in Nutrition from the University of California and became a Diplomate of the American College of Veterinary Nutrition (ACVN). In 1994, he joined the Research Center of Royal Canin in Aimargues (France) as head of scientific communication and nutritionist. Since 1999, he is in charge of managing the nutritional research program of Royal Canin. Dr. Biourge has published more than 30 papers, and regularly present scientific papers as well as guest lectures at International Veterinary Medicine and Nutrition meetings. He is also a Diplomate of the European College of Veterinary Comparative Nutrition (ECVN).

The liver has many complex functions which is reflected in the multitude of pathophysiological derangements that can occur in liver disease. The liver has however a huge reserve capacity and great potential to regenerate, and clinical signs occur only when this reserve is exhausted by progressive disease.

The liver is essential for the digestion, absorption, metabolism and storage of most nutrients **(Table 1)**. Malnutrition is therefore common in liver disease, and the lack of nutrients can also aggravate it *(Center, 1999b; Laflamme, 1999)*. Nutritional support is the keystone in the management of dogs with liver disease. It is therefore imperative to maintain nutrition status.

In acute liver disease, treatment is mainly aimed at supporting the patient during this process of hepatic regeneration, and patients may fully recover provided there has only been a single sublethal insult to the liver.

In chronic liver disease, the emphasis is on supporting the limited remaining metabolic capabilities of the liver, to minimize complications and to prevent progression of liver disease, e.g. by curtailing oxidative reactions. Early nutritional intervention in the management of malnutrition, ascites, and hepatic encephalopathy (HE) is especially important and can reduce morbidity and mortality.

TABLE 1 - MAJOR HEPATOBILIARY FUNCTIONS

Protein metabolism	Synthesis of albumin, acute phase proteins, coagulation factors Regulation of amino acid metabolism Detoxification of ammonia and synthesis of urea
Carbohydrate metabolism	Glycogen metabolism and storage Glucose homeostasis Gluconeogenesis
Lipid metabolism	Synthesis of triglycerides, phospholipids, cholesterol Lipid oxidation and ketone production Lipoprotein synthesis Excretion of cholesterol and bile acids
Vitamin metabolism	Storage and activation of vitamins B, K Activation of vitamin D Vitamin C synthesis
Hormone metabolism	Degradation of polypeptides and steroid hormones
Storage functions	Vitamins, lipids, glycogen, copper, iron, zinc
Digestive functions	Bile acid synthesis and enterohepatic circulation Digestion and absorption of lipids Absorption of vitamins A, D, E, K
Detoxification and excretion	Ammonia, drugs and toxins

1 - Diagnosis of liver diseases

► History and clinical signs

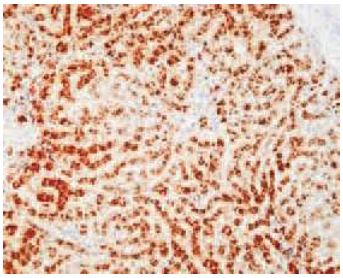
Historical findings in dogs with liver disease are often vague and non-specific, and rarely evident until liver disease is advanced. The onset of clinical signs may be acute, even though this may be the end result of liver disease that has been progressing for many weeks or months.

Physical examination findings are often variable and non-specific. Jaundice, abnormal liver size and ascites are the findings most suggestive of liver disease, but these may also be seen in other diseases not related to the liver. The only sign specific for liver disease is acholic (grey) feces, which may be found in complete extrahepatic bile duct obstruction **(Table 2)**.

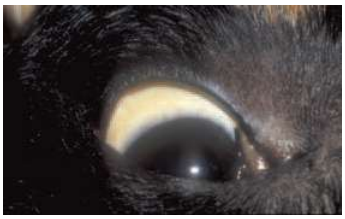
TABLE 2 - CLINICAL FINDINGS IN LIVER DISEASE

Early signs	Anorexia Weight loss Lethargy Vomiting Diarrhea Polydipsia/polyuria
Severe hepatic insufficiency	Jaundice Ascites Hepatic encephalopathy Coagulopathy (excessive bleeding upon blood sampling or liver biopsy, melena)
Major bile duct obstruction	Acholic (pale) feces*

** specific for liver disease, but rarely observed*



Liver biopsy
from a Bedlington Terrier with chronic hepatitis showing extensive copper accumulation (rhodanine stain; the copper grains show up as black).



Jaundice in a Doberman Pinscher with advanced chronic hepatitis.

► Differential diagnosis

> Jaundice

This is not a common sign of liver disease, and signifies severe disease. It may however also be due to hemolysis or post-hepatic causes (such as compression of the common bile duct, commonly seen in acute pancreatitis, or obstruction, due to neoplasia or cholelithiasis) *(Leveille-Webster, 2000)*.

> Altered liver size

In dogs, most chronic liver diseases result in reduced liver size, and even acute diseases may cause little change in size. Hepatomegaly is uncommon but may be seen in hepatic neoplasia and congestion, and with secondary involvement in metabolic disease (e.g. hyperadrenocorticism).

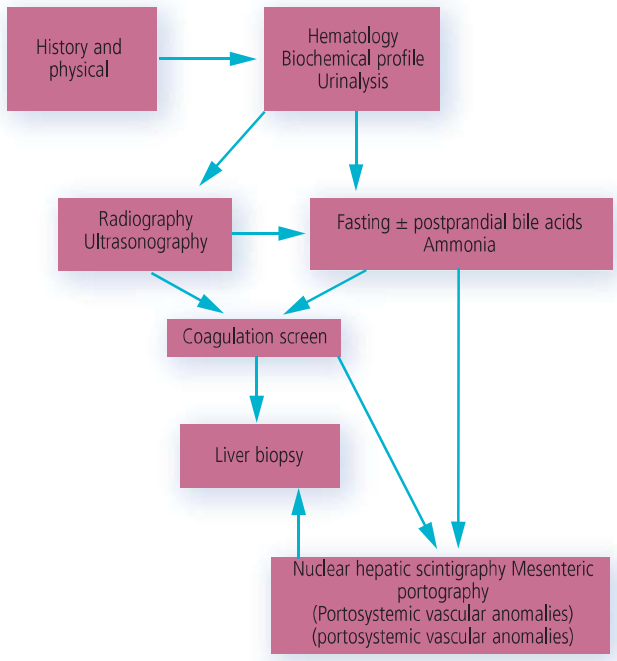
> Ascites

This is a common occurrence in dogs with severe chronic liver disease, and is mostly caused by portal hypertension. It is a modified transudate, as also seen in congestive heart failure and neoplasia. It has to be distinguished from transudate, which may occur in protein-losing enteropathy and nephropathy, and from exudates, as in peritonitis, hemorrhage, and ruptured biliary or urinary tract.

► Laboratory testing

Laboratory assessment is essential to identify hepatic disease, assess severity and monitor progression; however, laboratory tests will not identify specific diseases and may be influenced by non-hepatic disease. Baseline tests (hematology, serum biochemistries and urinalysis) are useful in initial screening to look for evidence of hepatic disease as well as other abnormalities **(Figure 1)**.

FIGURE 1 - DIAGNOSIS OF LIVER DISEASE



Serum bile acid analysis is a sensitive and specific indicator of hepatic function, useful for the diagnosis of subclinical liver diseases and portosystemic shunts. Measurement of fasting serum ammonia can document the presence of HE. Coagulation tests are indicated in animals with a bleeding tendency and prior to biopsy (blind, ultrasound-guided or surgical) or a mesenteric portography if a portosystemic shunt is suspected.

► Diagnostic imaging

Survey abdominal radiographs provide an idea about liver size and shape, but ultrasonography gives more specific information about liver parenchyma, bile ducts and blood vessels. Operative mesenteric portography can visualize vascular anomalies; nuclear hepatic scintigraphy is non-invasive but requires specialized equipment and the use of radioactive tracers.

► Biopsy

Histologic examination of liver tissue is often essential to clarify the cause of abnormal liver tests and/or size, to define whether it is a primary or secondary problem, and determine hepatic copper levels. It may also be used to monitor progression or response to treatment when non-invasive testing is inadequate.

2 - Epidemiology

► Causes

> Non-infectious inflammatory liver diseases

These represent one of the most common manifestations of liver disease in the dog **(Table 3)** *(Center, 1996a; Watson, 2004)*. The liver has a very active reticuloendothelial system and plays an important role in blocking substances from the gastrointestinal tract that have been transported by the portal vein. The liver is also sensitive to endogenous and exogenous toxins, and drugs. Immune-mediated mechanisms may furthermore lead to the perpetuation of inflammation following hepatic damage caused by any agent *(Center, 1999b)*. Primary autoimmune hepatitis, which is an important disease in humans, has however not been conclusively demonstrated to exist in dogs.

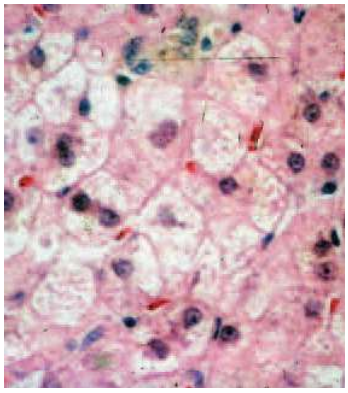
> Infectious inflammatory liver diseases

Viral causes are not important in dogs, in contrast to man. However, infections with 'atypical' leptospires (i.e. those not covered in routine vaccinations) may be a more significant cause of chronic hepatitis than previously assumed *(Adamus et al, 1997; Bishop et al, 1979)*.

> Non-inflammatory liver diseases

Vacuolar hepatopathies are a vague term used to describe a non-inflammatory liver disease that occurs in conjunction with cytoplasmic vacuoles in hepatocytes *(Cullen, 2001)*. Generally, vacuole formation is a nonspecific response to hepatic injury, with glucocorticoid excess (either endogenous or exogenous) the main cause in dogs.

Clinically more important are liver diseases related to vascular anomalies, such as congenital portosystemic shunts and portal hypoplasia (e.g. microvascular dysplasia and juvenile fibrosing liver disease). Neoplasia, commonly secondary, is less frequent.



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Steroid hepatopathy.

TABLE 3 - HEPATOBILIARY DISEASES IN THE DOG

Inflammatory liver disease	Non-inflammatory liver disease	Biliary disease
Non-infectious Chronic hepatitis* Cirrhosis/fibrosis* Toxic and drug-induced*	**Vacuolar hepatopathies** Degenerative/storage Glucocorticoid therapy* Diabetes mellitus Hepatocutaneous syndrome Chronic illnesses*	**Congenital cystic disease** **Cholestasis** - **Intrahepatic** (secondary to hepatocellular disease)* - **Extrahepatic** (bile duct obstruction due to cholelithiasis, neoplasia or compression by pancreatic disease*) **Cholangitis/cholecystitis**
Infectious Bacterial (leptospirosis, abscess, cholangiohepatitis) Viral (ICH Infectious canine hepatitis)	**Portal vascular anomalies** Congenital portosystemic shunts* Portal vein hypoplasia (incl. microvascular dysplasia and juvenile fibrosing liver disease)* Lobular dissecting hepatitis Intrahepatic arteriovenous fistula	
	Neoplasia (primary or metastatic*)	

* *Common diseases in the dog*

TABLE 4 - BREED PREDISPOSITION IN LIVER DISEASE

Copper associated liver disease	
Bedlington Terrier*	
West Highland White Terrier	
Sky Terrier	
Dalmatian	
Doberman Pinscher	
Chronic hepatitis	
Cocker Spaniel	
Doberman Pinscher	
Labrador Retriever	
Standard Poodle	
Congenital portosystemic shunts	
Irish Wolfhound*	
Cairn Terrier*	
Yorkshire Terrier*	
Maltese Terrier	

* *Inheritance proven.*

Chronic hepatitis in Doberman Pinschers is associated with increased liver levels of copper and iron, which is a consequence of reduced biliary copper excretion that has a different genetic basis than the disease in Bedlington terriers (Spee et al, 2005).

► Predisposition and risk factors

> Chronic hepatitis

The cause of chronic hepatitis in dogs is usually unknown. Some breeds are however more likely to suffer from chronic hepatitis than others **(Table 4)**. A familial predisposition has been described in Bedlington Terriers, West Highland White Terriers, Skye Terriers, Doberman Pinschers, Cocker Spaniels and Labrador Retrievers *(Johnson, 2000)*. The increased incidence of chronic hepatitis in certain breeds suggests a possible genetic basis.

So far, the genetic defect has only been demonstrated in copper storage hepatopathy in the Bedlington *(Johnson et al, 1980)*. In this breed, copper storage hepatopathy is autosomal recessive.

Copper accumulates in the liver due to an inherited metabolic defect in biliary copper excretion; the increased hepatic copper content then causes hepatocellular injury, chronic hepatitis and cirrhosis *(Twedt et al, 1979)*. The genetic defect was initially demonstrated via a DNA microsatellite marker *(Yusbasiyan-Gurkan et al, 1997; Holmes et al, 1998; Rothuizen et al, 1999)*, but recently the locus of the abnormal copper toxicosis gene has been identified *(van De Sluijs et al, 2002)*. Biopsy and determination of hepatic copper content are still essential for the diagnosis, although a DNA microsatellite marker test is now available to detect both affected and carrier Bedlington Terriers. This test is not 100% accurate (due to recombination), but offers a simple procedure that can be used by breeders to reduce the incidence of this disease.

It is sometimes difficult to establish whether copper accumulation in the hepatocytes is a cause of hepatic disease or a consequence of reduced biliary excretion of copper *(Rolfe & Twedt, 1995; Thornburg, 2000)*. Copper accumulation in association with liver disease has been especially demonstrated in Doberman Pinschers, Dalmatians, West Highland White Terriers and Skye Terriers *(Rolfe & Twedt, 1995)*. The mode of inheritance in these breeds is as yet unknown *(Rolfe & Twedt, 1995; Webb et al, 2002)*. Chronic hepatitis in Cocker Spaniels is often associated with copper accumulation *(Johnson, 2000)*. The copper-storage hepatopathy that was described in young Dalmatians may share some similarities with the disease in Bedlington Terriers, but this needs further investigation *(Webb et al, 2002)*.

> Portovascular anomalies

Congenital intrahepatic portosystemic shunts are more common in large breed dogs. They have been shown to be autosomal recessive inherited in Irish Wolfhounds *(Rothuizen et al, 2001)*. In contrast, most congenital extrahepatic shunts occur in small dogs. They are inherited via a polygenic trait in Cairn Terriers *(Rothuizen et al, 2001)*, and are likely to be inherited in Yorkshire Terriers *(Tobias, 2003; Tobias & Rohrbach, 2003)*.

Portal vein hypoplasia (microvascular dysplasia) occurs more commonly in small breed dogs *(Van den Ingh et al, 1995)*. Yorkshire and Cairn Terriers are both predisposed to congenital portosystemic shunts as well as microvascular dysplasia.

> Drugs

Certain therapeutic agents may provide a risk factor for development of acute or chronic liver disease. Chronic hepatitis has been most commonly associated with anticonvulsant drugs (primidone, phenobarbital, phenytoin), and diethylcarbamazine oxibendazole. Acute toxic injury has been described with several drugs, including carprofen, mebendazole and potentiated sulfonamides (trimethoprim-sulfadiazine) *(Hooser, 2000; Trepanier et al, 2003)*. In addition, excess glucocorticosteroids, either exogenous or endogenous as in hyperadrenocorticism, frequently cause a typical vacuolar hepatopathy (steroid hepatopathy).

3 - Physiopathology

Hepatocellular dysfunction can cause multiple metabolic disturbances, which are compounded by malnutrition.

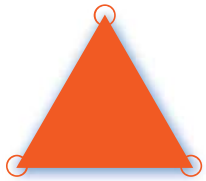
Hepatocellular dysfunction is associated with a number of metabolic disturbances that alter the utilization of nutrients **(Table 5)**. Alterations in protein, carbohydrate and fat metabolism reflect the influence of neuroendocrine mediators and are particularly prominent in the fasting state. Serum concentrations of glucagon and insulin are increased due to reduced hepatic degradation, with the effects of hyperglucagonemia predominating. This causes a more rapid depletion of hepatic glycogen stores, which results in premature protein catabolism to supply amino acids for gluconeogenesis. Fasting hypoglycemia is in many cases prevented by a compensatory decrease in peripheral glucose oxidation and increase in gluconeogenesis. Peripheral lipolysis is also enhanced, generating fatty acids for energy production *(Marks et al, 1994)*. Prolonged inadequate food intake in dogs with chronic liver disease will therefore result in progressive loss of fat and muscle, which contributes to the malnutrition found commonly in liver disease **(Figure 2)**.

TABLE 5 - NUTRITIONAL CONSEQUENCES OF LIVER DISEASE

Substrate	Clinical effect
Carbohydrate metabolism	
Decreased hepatic glycogen storage	Hypoglycemia (acute liver disease)
Increased gluconeogenesis	Muscle wasting, malnutrition
Glucose intolerance and insulin resistance	Hyperglycemia (end-stage liver disease)
Fat metabolism	
Increased lipolysis	Malnutrition
Decreased excretion of bile acids	Malabsorption of fats and fat-soluble vitamins
	Steatorrhea
	Coagulopathy
Protein metabolism	
Increased catabolism	Malnutrition, HE*
Enhanced peripheral utilization of BCAA	Contributory to HE**
Impaired urea cycle	HE*
Decreased albumin synthesis	Hypoalbuminemia
Decreased synthesis of coagulation factors	Coagulopathy
Vitamin metabolism	
Decreased storage	Oxidant damage (vitamin E)
Decreased absorption of vit. A, D, E, K (cholestasis)	Coagulopathy (vitamin K)
Minerals and trace elements	
Increased hepatic copper content (copper hepatotoxicosis)	Oxidative damage, hepatitis
	Decreased zinc levels
	Decreased antioxidant protection
Detoxification and excretion	
Decreased excretion of bilirubin	Jaundice
Decreased detoxification (drugs, ammonia)	HE*

* *HE: hepatic encephalopathy*

FIGURE 2 - ETIOLOGY OF MALNUTRITION IN LIVER DISEASE



Decreased intake
Anorexia, nausea, vomiting
Unpalatable diet

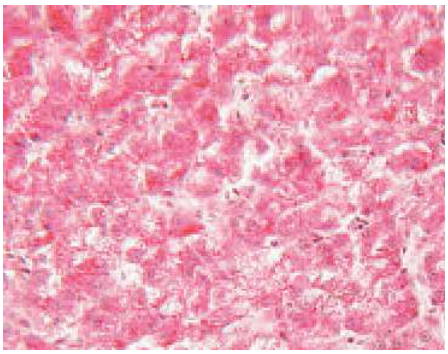
Malabsorption
Cholestasis
Enteropathy (portal hypertension)

Increased requirements
Hypermetabolism
Increased protein breakdown

The liver has a large functional reserve and is able to preserve homeostasis and minimize catabolism for a long time, despite extensive damage. The appearance of metabolic alterations and clinical signs of liver dysfunction usually signify advanced disease.

► Carbohydrate, fat and protein metabolism

Carbohydrate – The liver is responsible for the maintenance of blood glucose levels because it is the primary organ for glucose storage (as glycogen) and provides glucose during fasting (through glycogenolysis). Liver disease results in more rapid depletion of hepatic glycogen stores, and glucose needs are then supplied through catabolism of muscle proteins to amino acids. This causes muscle wasting and increases the nitrogen load, which may potentiate hyperammonemia and hepatic encephalopathy *(Bauer, 1996)*. Fasting hypoglycemia may occur in severe acute liver disease and portosystemic shunts due to inadequate glycogen storage and gluconeogenesis. In contrast, a mild hyperglycemia can occur in cirrhosis due to reduced hepatic clearance of glucocorticosteroids.



Microscopic view of hepatic glycogen reserves (PSA X 40).

Lipid – The liver has an important function in the synthesis, oxidation and transport of lipids. Liver disease causes an increase in peripheral lipolysis in order to generate fatty acids for energy production, resulting in fat depletion, while the rate of hepatic fatty acid oxidation increases *(Bauer, 1996)*.

Through its synthesis of bile acids and secretion of bile, the liver plays an important role in the digestion and absorption of lipids and fat-soluble vitamins (A, D, E, K). Fat malabsorption is nevertheless not common in liver disorders, since some dietary tri glycerides still can be absorbed in the complete absence of bile acids *(Gallagher et al, 1965)*.

In severe cholestatic liver disease, the reduced availability of enteric bile acids can cause malabsorption of fats, fat-soluble vitamins and some minerals. The liver is the only site of cholesterol synthesis. Hypocholesterolemia may occur in acute liver failure and portosystemic shunts, whereas hypercholesterolemia is seen in obstructive jaundice.

Protein – The liver has an essential role in protein synthesis and degradation. It controls serum concentrations of most amino acids, with the exception of branched chain amino acids (BCAA), which are regulated by skeletal muscle. The liver synthesizes the majority of circulating plasma proteins and is the only site of albumin synthesis.

Albumin has a relative priority for synthesis; hypoalbuminemia does not occur until the disease is chronic, and is compounded by malnutrition.

The liver furthermore synthesizes the majority of coagulation factors. Lack of synthesis in liver failure may lead to prolonged coagulation times (↑ PT, ↑ PTT) but only when factors are reduced to less than 30% of normal. Disseminated intravascular coagulation (DIC) is however the most common coagulopathy associated with liver disease, and is most likely to cause spontaneous hemorrhage *(Center, 1999b)*. Decreased absorption of vitamin K in chronic biliary obstruction may also lead to prolonged clotting times, but these can be corrected by parenteral administration of vitamin K1.

In acute disease, functional proteins in skeletal muscle and other tissues are catabolized to meet the demands for synthesis of host defense proteins. In chronic liver disease, the etiology of the catabolic state is multifactorial *(Mizock, 1999)*. Plasma concentrations of aromatic amino acids (AAA) increase in liver disease due to increased peripheral release and decreased hepatic clearance, but BCAA levels decrease because of enhanced utilization as an energy source by muscle. This imbalance between AAA and BCAA has been implicated in the pathogenesis of HE, although its significance is now being questioned *(Mizock, 1999)*.

L-carnitine is an essential cofactor for transport of long-chain fatty acids from the cytoplasm into mitochondria **(Figure 3)**. The liver is a central organ for whole body L-carnitine homeostasis, and its metabolism can be impaired in multiple ways in chronic liver disease. L-carnitine deficiency in liver disease may occur due to insufficient intake of carnitine or its precursors, reduced hepatic synthesis, or increased turnover *(Krahenbuhl & Reichen, 1997)*. L-carnitine supplementation has a protective influence against the development of ammonia-induced HE in experimental animals *(Therrien et al, 1997)* and may be protective against the development of hepatic lipidosis in cats *(Twedt, 2004)*, but its usefulness in dogs is still undetermined.

THE LIVER CONTROLS MANY METABOLIC FUNCTIONS. MOST IMPORTANTLY, IT:

- maintains homeostasis of blood levels of glucose, amino acids and trace elements
- synthesizes albumin and coagulation factors
- detoxifies and excretes endogenous and exogenous waste products (i.e. NH_3, drugs and toxins
- regulates immune function
- regulates hormone balance.

Protein catabolism is increased in all liver diseases. Protein breakdown is augmented in patients with infections or gastrointestinal hemorrhage, which can precipitate hepatic encephalopathy due to increased ammonia production.

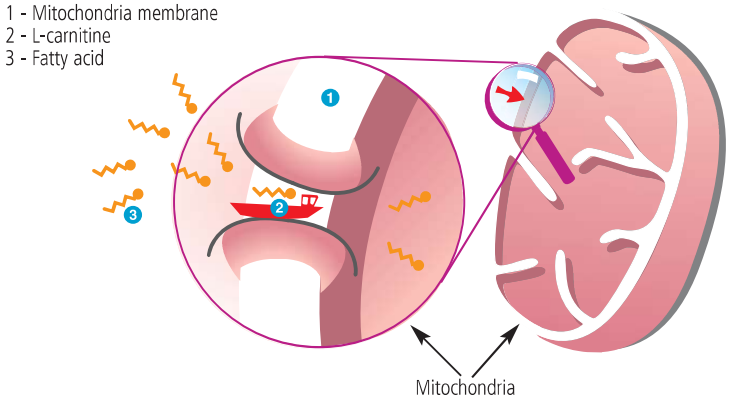
► Micronutrient metabolism

> Vitamins

The liver stores many vitamins and converts them to metabolically active forms. Liver disease can therefore result in deficiency of vitamins stored in the liver, such as B-complex vitamins. Vitamin deficiencies are augmented by increased demands for hepatocyte regeneration, reduced metabolic activation and increased urinary losses. B-complex deficiencies are common in people with liver disease and probably also occur in dogs.

Vitamin C can be synthesized in dogs but is not stored. Its synthesis may be affected by liver disease *(Center, 1996a)*.

FIGURE 3 - MODE OF ACTION OF L-CARNITINE



L-carnitine is incorporated into the enzyme chain needed to convey long-chain fatty acids though the mitochondrial membrane.

This permits the transfer of fatty acids to the interior of the mitochondria. In case of deficiency, the transport system is disturbed and the production of energy is compromised.

Deficiencies of the fat-soluble vitamins A, D, E and K can occur in any condition that impairs the enterohepatic circulation of bile acids or fat absorption. Deficiencies of vitamins E and K are most significant. Vitamin E is an important antioxidant that protects lipoproteins and cell membranes from lipid peroxidation. In addition, Vitamin E deficiency, common in chronic liver disease *(Sokol, 1994)*, causes an increased susceptibility to oxidative stress, which perpetuates ongoing liver injury. Vitamin K deficiency is best recognized in dogs, since it develops rapidly and is readily detectable by measurement of coagulation times *(Leveille-Webster, 2000)*.

> Minerals and trace elements

Iron, zinc and copper are the main trace elements stored in the liver. Both iron and copper can be hepatotoxic in high levels, but only copper appears to be a potential hepatotoxin in the dog.

Zinc deficiency is common in chronic liver disease, due to poor dietary intake, reduced intestinal absorption and increased urinary loss. Deficiency results in low resistance to oxidative stress and reduces ammonia detoxification in the urea cycle, thus promoting hepatic encephalopathy.

The liver is central to the maintenance of copper homeostasis, since it takes up most of the absorbed copper and regulates the amount retained by controlling excretion through the biliary tract. Copper may accumulate in the liver as a result of a primary metabolic defect in copper metabolism, or secondary to decreased hepatic copper excretion associated with longstanding cholestasis *(Thornburg, 2000)*. In dogs with primary copper storage disease, copper accumulates in the liver before the development of hepatic damage or cholestasis. Excessive hepatic copper accumulation in Bedlington Terriers has been shown to result in mitochondrial injury, generation of reactive oxygen species and free radicals, and hepatocellular damage *(Sokol et al, 1994)*.

Zinc is an essential cofactor in many biological processes. It has an antioxidant role, anti-fibrotic properties, and enhances ureagenesis *(Dhawan & Goel, 1995; Marchesini et al, 1996)*.

Manganese is another trace element with antioxidant properties that can become deficient in cirrhosis.

> Antioxidants

There is mounting evidence that free radicals play important roles in many liver diseases. They damage cellular macromolecules via lipid peroxidation and other mechanisms, and can initiate and perpetuate liver injury. Their production is increased in inflammation, cholestasis, immunological events, and exposure to heavy metals and toxins *(Sokol et al, 1994; Feher et al, 1998)*. There is a wide range of both dietary and endogenous enzymatic antioxidant defense systems that hold the generation of free radicals in check. A disruption in this natural defense system results in oxidant stress **(Figure 4)**.

This type of disruption may occur during liver disease **(Table 6)**.

TABLE 6 - ANTIOXIDANT DEFENSES

Dietary antioxidants	Endogenous enzyme systems
Vitamin E Vitamin C Taurine Carotenoids	Superoxide dismutase Glutathione peroxidase Catalase

► Detoxification and excretion

The liver is the primary site of detoxification of both endogenous by-products of the intermediary metabolism (e.g. ammonia) and exogenous substances absorbed from the gastrointestinal tract. All of these may play a role in the etiology of HE. The precise pathogenesis is likely to be multifactorial, and may be based on inter-related changes in reduced hepatic clearance of gut-derived substances such as ammonia, altered amino acid neurotransmission and endogenous benzodiazepines *(Maddison, 2000)*. Ammonia is the substance most commonly linked with HE, although serum ammonia levels correlate poorly with the degree of HE **(Figure 5)**.

FIGURE 4 - ETIOLOGY OF OXIDANT STRESS IN LIVER DISEASE

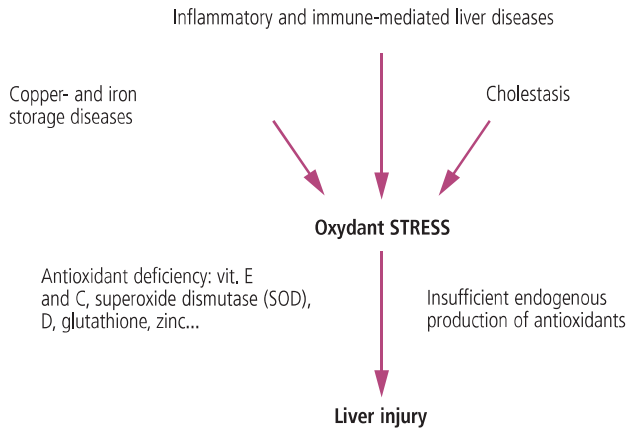
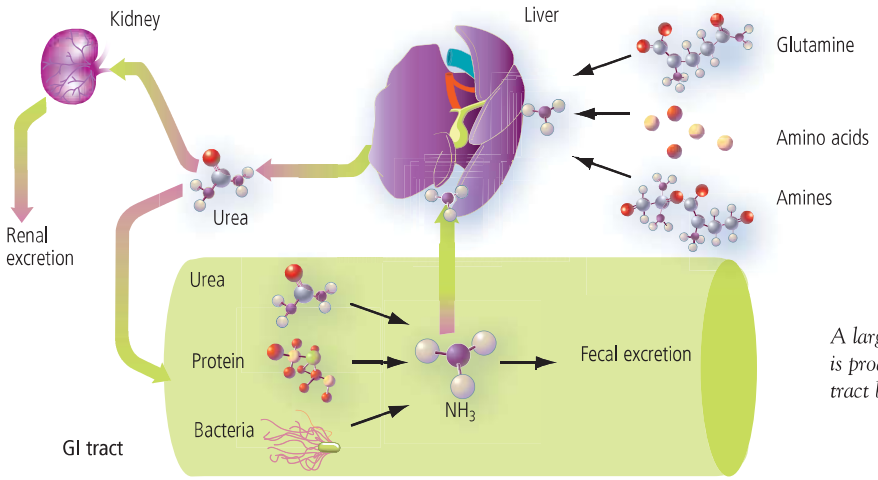


FIGURE 5 - AMMONIA METABOLISM



A large part of ammonia is produced in the gastrointestinal tract by urease-producing bacteria.

4 - Adaptation of nutritional intakes

Diets for animals with liver disease are best formulated on an individual basis, with consideration given to the type and origin of the liver disease and the extent of liver dysfunction (*Laflamme, 1999*). Care must be taken to avoid overwhelming the remaining metabolic capacities of the diseased liver. The diet must be highly palatable and provide adequate energy, protein, fat, and all essential micronutrients. It is furthermore becoming increasingly evident that it is possible to modulate metabolic and pathological processes through the use of specific nutrients and metabolites.

THE AIMS OF DIETARY MANAGEMENT OF LIVER DISEASE ARE:

(1) to supply adequate energy and nutrients to fulfill basic requirements and prevent malnutrition
(2) to limit further liver damage by preventing accumulation of copper and free radicals
(3) to support hepatocellular regeneration
(4) to prevent or minimize metabolic complications, such as hepatic encephalopathy and ascites

Dogs with liver disease are usually catabolic and have increased energy requirements.

Provision of adequate high-quality proteins as well as calories is essential to ensure a positive protein balance and enable hepatic regeneration.

Protein levels are often inappropriately restricted in dogs with liver disease in order to manage possible hyperammonemia. In fact, protein requirements are at least normal or even increased, and many dogs with liver disease do not have hyperammonemia.

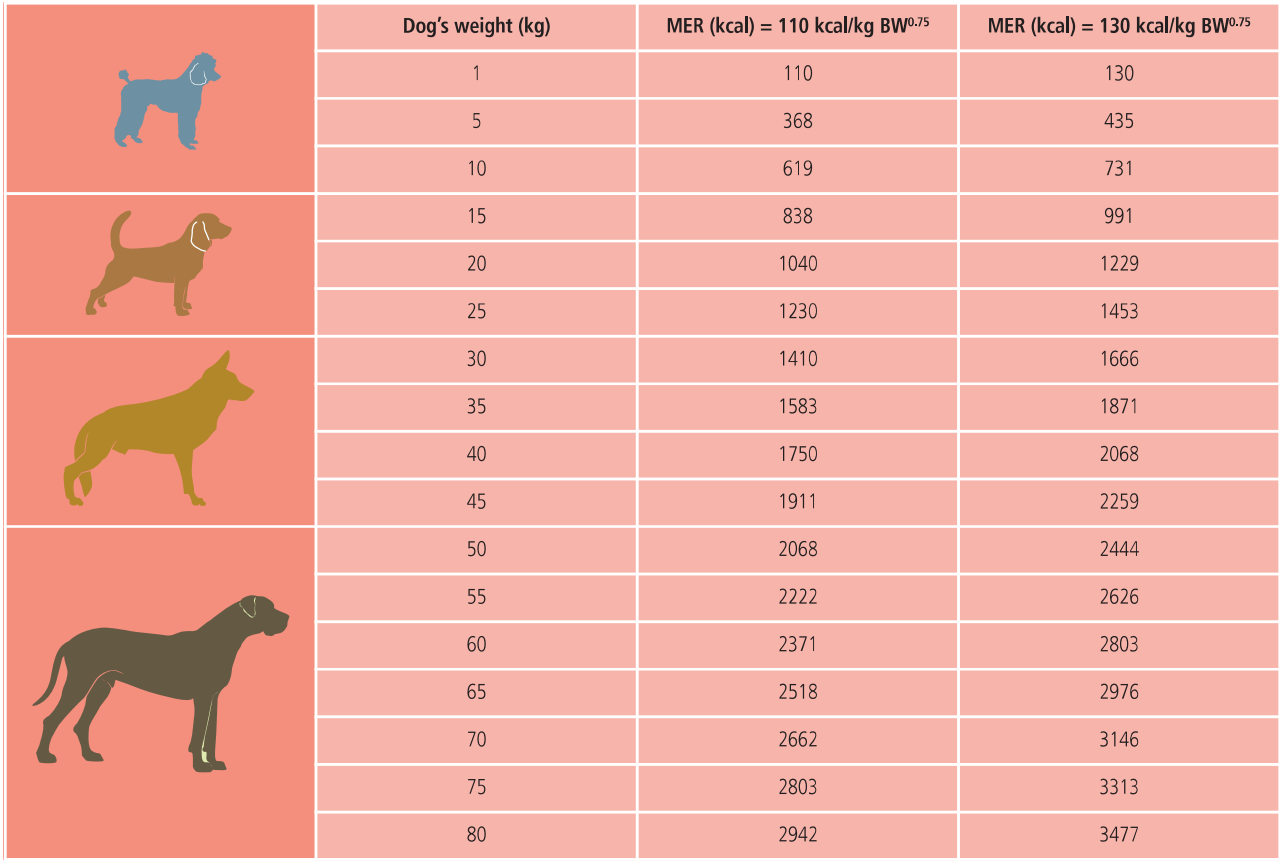
Correction and prevention of malnutrition are essential in the management of dogs with liver disease. Impaired dietary intake, malabsorption associated with severe cholestasis or portal hypertension, and catabolism all contribute to protein-calorie malnutrition, resulting in loss of muscle mass and hypoalbuminemia. Negative protein and energy balance promote HE, reduce immune response and increase mortality (*Center, 1998*). Providing several small meals daily as well as a bedtime snack will improve nitrogen balance and carbohydrate availability. Tube feeding via a nasogastric, esophagostomy or gastrostomy tube may be required in dogs that are anorexic for more than 3-5 days.

► Energy

An adequate supply of both energy and protein is essential to prevent weight loss. The use of non-protein calories is important to prevent the use of amino acids for energy and reduce the need for gluconeogenesis. The diet should have a high energy density, since dogs with liver disease usually have reduced appetites. Normal daily maintenance needs in the dog are 110-130 kcal ME/kg$^{0.75}$ **(Table 7)** (*Bauer, 1996*).

Normally, energy is best supplied in the form of fat since it is a highly palatable and concentrated source of energy. The diet's caloric density is proportional to its fat content. Dogs with liver disease can tolerate larger quantities of fat in the diet (30-50% of calories) than previously assumed (*Biourge, 1997*).

TABLE 7 - INDICATIVE RANGE OF THE MAINTENANCE ENERGY REQUIREMENT OF DOGS BASED ON WEIGHT



Dog's weight (kg)	MER (kcal) = 110 kcal/kg BW$^{0.75}$	MER (kcal) = 130 kcal/kg BW$^{0.75}$
1	110	130
5	368	435
10	619	731
15	838	991
20	1040	1229
25	1230	1453
30	1410	1666
35	1583	1871
40	1750	2068
45	1911	2259
50	2068	2444
55	2222	2626
60	2371	2803
65	2518	2976
70	2662	3146
75	2803	3313
80	2942	3477

Fat restriction should only be considered in the few cases with severe cholestatic liver disease and suspected fat malabsorption, although adequate essential fatty acids must be provided.

Altered carbohydrate metabolism in dogs with liver disease can induce either hyper- or hypoglycemia. Hypoglycemia may be seen in acute fulminant liver disease, whereas hyperglycemia is infrequently seen in dogs with cirrhosis. Carbohydrates should not represent more than 45% of dietary calories, especially in dogs with cirrhosis, which may be glucose intolerant. Boiled white rice, and to a lesser degree pasta, are useful because of their high digestibility. Soluble fibers are useful in dogs with cirrhosis and a tendency to hyperglycemia, because they smoothen the postprandial glycemic response and prolong glucose delivery to the liver *(Center, 1998)*.

► Protein

> Dietary protein level

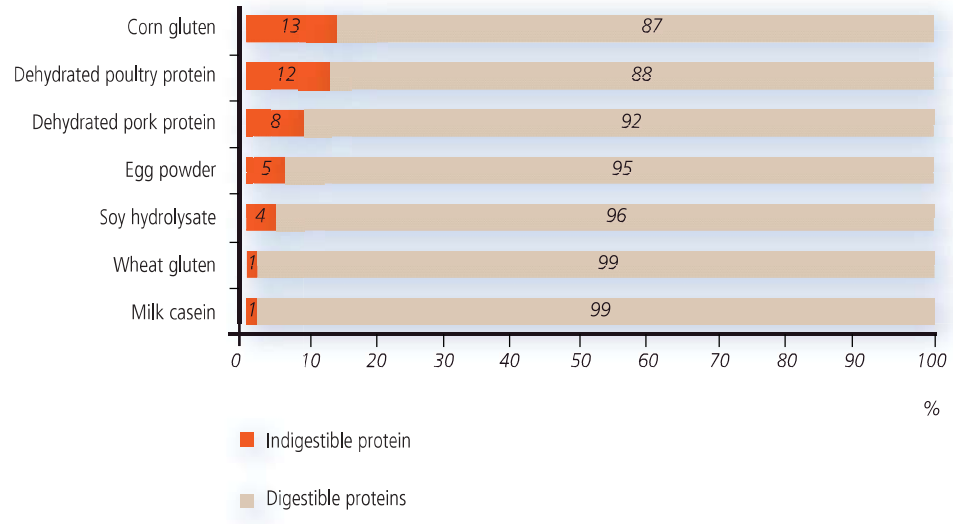
Incorrect protein restriction in dogs with liver disease causes catabolism of endogenous proteins and loss of muscle mass, both of which increase the potential for HE. Feeding of excessive and/or poor quality protein should also be avoided since this may aggravate signs of HE. In dogs, protein should represent as a minimum 10 to 14% of dietary calories, preferably at least 20%, and most dogs can tolerate higher quantities *(Biourge, 1997; Laflamme, 1999)*. The aim is to gradually increase the amount of protein in the diet, keeping the protein intake as close to normal as can be tolerated without precipitating signs of HE *(Michel, 1995)*.

> Protein type

The quality and source of the protein are important. High-quality proteins are better digested **(Figure 6)** and have an amino acid content close to the animal's requirements. Proteins of animal origin used to be considered as having a higher quality than proteins of plant origin, but soy isolates, wheat gluten and dairy products are better tolerated than meat proteins in people with HE, and this is probably also the case in dogs *(Strombeck et al, 1983)*. The potential benefit of vegetable proteins is attributed to their high fiber content, which causes a decrease in transit time and promotes incorporation and excretion of nitrogen in fecal bacteria, whereas the effect of dairy

FIGURE 6 - COMPARABLE QUANTITIES OF INDIGESTIBLE PROTEIN IN DIFFERENT SOURCES OF PROTEIN USED IN DOG FOOD

(Source: Royal Canin)



products is likely due to the influence of lactose on intestinal transit and pH (*Center, 1998*). The benefit of soy and dairy proteins cannot be attributed to their amino acid composition, since this is similar to that of meat and fish proteins. Exclusive use of soybean or lactose-containing dairy protein diets is generally not advocated in dogs, since they have low palatability and can cause diarrhea, although this is less significant when purified proteins are used.

> The role of branched chain amino acids

BCAA supplementation has been used to improve protein and energy utilization and HE in people with advanced liver disease, since a decreased plasma ratio of BCAA to AAA has been considered an important pathogenetic factor in HE. Results however have been mixed (*Als-Nielsen et al, 2003; Marchesini et al, 2003*), and it is now thought that any beneficial effect of BCAA supplementation is mostly related to improvement of the nutritional status, likely due to a stimulating effect on hepatocyte growth factor, favoring liver regeneration (*Bianchi et a, 2005*). A study in dogs showed no efficacy on HE from a diet high in BCAA and low in AAA, and it was concluded that the total protein intake was more important than dietary amino acid profile (*Meyer et al, 1999*). At present, BCAA supplements are unlikely to be of benefit in the management of canine liver disease, in view of their expense and questionable efficacy.

► Fiber

Moderate quantities of dietary fiber can have several beneficial effects in liver disease. Soluble fiber is of particular benefit in managing HE. Colonic fermentation of soluble fibers such as fructo-oligosaccharides, beet pulp and gums lowers the intraluminal pH and thus reduces the production and absorption of ammonia, the effect of which is similar to that of lactulose. Colonic fermentation also favors the growth of acidophilic bacteria that produce less ammonia and promote incorporation and excretion of ammonia in fecal bacteria (e.g. *Lactobacillus spp*). Fiber (both soluble and insoluble) binds bile acids in the intestinal lumen and promotes their excretion. Insoluble fibers (lignin, cellulose, hemicellulose) act by normalizing transit time, whereas they can also prevent constipation and bind toxins. Diets containing soluble fiber and some insoluble fiber should therefore be useful in the long-term dietary management of dogs with HE (*Marks et al, 1994; Center, 1998*).

► Minerals

> Potassium

Hypokalemia is a common precipitating cause of HE in dogs with liver disease (*Center, 1998*). It occurs due to a combination of anorexia, vomiting or diarrhea, or excessive use of diuretics in the management of ascites. Diets for dogs with liver disease should therefore be potassium replete. Anorectic dogs may need supplementation by either intravenous administration of potassium chloride (10-40 mEq/500 ml fluids, depending on serum potassium) or oral potassium gluconate (0.5 mEq/kg once or twice daily). Potassium citrate should be avoided because of its alkanizing properties, since alkalosis can aggravate HE.

> Sodium

Abnormalities in sodium balance are less frequent, but moderate restriction of dietary sodium (less than 0.5 g/1000 kcal) is recommended in dogs with ascites and/or portal hypertension.

► Trace elements

> Zinc

Zinc is an essential trace metal involved in many metabolic and enzymatic functions of the body. Zinc benefits the urea cycle and central nervous system neurotransmission, has clear hepatoprotective effects against a variety of hepatotoxic agents, and has antioxidant functions (*Marchesini et al, 1996*). Diets high in zinc (>43 mg/1000 kcal) are therefore useful for all patients with liver

disease. Additional zinc supplementation may furthermore be useful to prevent hepatic copper accumulation in copper hepatotoxicosis, since dietary zinc induces an increase in the intestinal metal-binding protein metallothionein. Dietary copper then binds to the metallothionein with a high affinity that prevents its transfer from the intestine into the blood. When the intestinal cells die and are sloughed, the metallothionein bound copper passes out through the stool, thus blocking copper absorption *(Sokol, 1996)*.

Dietary supplementation with zinc in patients with severe liver disease is done empirically with doses similar to those used in dogs with copper hepatopathies. Zinc is available as zinc acetate (2-4 mg/kg per day), sulfate, gluconate (3 mg/kg per day) and methionine. It is administered divided into two or three daily doses, and can be used as a dietary supplement *(Brewer et al, 1992)*. Zinc should be given on an empty stomach and should not be given in combination with copper chelators. Toxicity other than occasional vomiting is minimal and the acetate salt may cause fewer GI signs.

Many liver diseases result in increased generation of free radicals and oxidant stress. **Supplementation with antioxidants** will therefore help to reduce oxidative liver injury.

Zinc supplementation may reduce lipid peroxidation, has antifibrotic properties, prevents hepatic copper accumulation, and can reduce the severity of hepatic encephalopathy.

> Copper

Diets low in copper are recommended for dog breeds known to be prone to hepatic copper accumulation, especially Bedlington Terriers, and for dogs with documented increased hepatic copper **(Table 8)**. Restriction of dietary copper in itself does little to lower increased hepatic copper levels, but it is an additional adjunct to decoppering therapy such as d-penicillamine and zinc.

► Vitamins

> B Vitamins

B Vitamins are often empirically supplemented at double maintenance dose, based upon recommendations for people with liver disease.

> Vitamin C

TABLE 8 - FOOD CLASSIFICATION ACCORDING TO COPPER CONTENT

	Food stuffs rich in copper	Food stuffs moderately rich in copper	Food stuffs containing little copper
Animal protein sources	Lamb, pork, duck, organ meats, salmon, shellfish	Turkey Chicken All other fish	Beef Cheese Eggs
Starch sources	Dried beans, dried peas, lentils, soybeans, barley, wheat germ, bran	Whole wheat bread Potatoes	-
Vegetables	Mushrooms, broccoli	Beet, spinach, bean sprout	Fresh tomatoes

The diet should contain adequate levels of vitamin C in order to compensate for failing hepatic synthesis and to take advantage of the antioxidant properties of vitamin C. Most commercial pet foods contain adequate amounts, and additional supplementation should only be necessary in case of severe fat malabsorption *(Laflamme, 1999)*. Mega doses of vitamin C should be avoided in dogs with copper storage hepatotoxicity, since it can function as a pro-oxidant in the presence of high concentrations of heavy metals *(Sokol, 1996)*.

> Vitamin E

Vitamin E is an important endogenous free radical scavenger that protects against oxidative injury. There is evidence that oxidative damage from free radical formation plays an important role in the pathogenesis of liver disease. In particular, abnormal concentrations of bile acids, accumulation of heavy metals such as copper and iron, and inflammation can cause free radical generation and oxidant stress in the liver. Supplementation with vitamin E (400-600 IU/day) is especially indicated in cholestatic and copper-associated liver disease, but is likely also important in other forms of chronic liver disease. In severe cholestatic disease parenteral administration or an oral water-soluble form is preferred, since a certain level of enteric bile acids are required for its absorption.

Vitamin E supplementation can reduce free radical or oxidant injury in many types of liver disease and may prevent progression of disease.

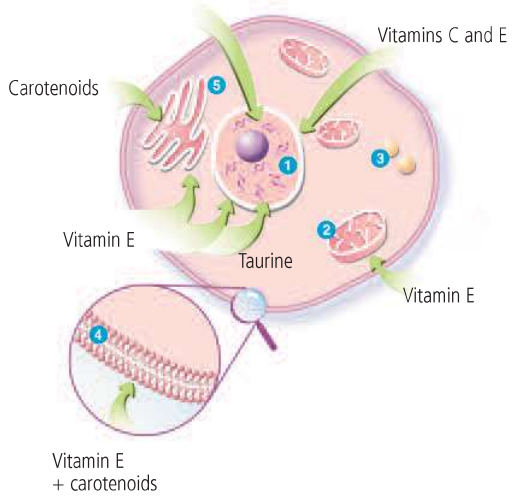
> Vitamin K

Vitamin K deficiency is mostly relevant in cholestatic disorders, although it may also become depleted in severe chronic liver disease. Vitamin deficiency is documented by demonstration of prolonged coagulation times and normalization after parenteral administration of vitamin K1. Coagulopathies secondary to vitamin K deficiency should be treated with two or three doses of vitamin K1 (0.5-1.0 mg/kg subcutaneously every 12 hours) *(Laflamme, 1999)*. The same dose can be given biweekly or monthly in chronic disorders in which continued repletion of vitamin K is required.

► Antioxidants

Chronic hepatitis and fibrosis, cholestatic liver disease and heavy metal hepatotoxicity are all known to be associated with increased generation of free radicals, and this is likely also the case in other types of liver disease *(Britton & Bacon, 1994; Feher et al, 1998)*. Adequate dietary levels of antioxidants such as vitamins E and C, as well as taurine, are essential to minimize oxidative injury. A combination of dietary antioxidants is better than a single one, since they appear to act synergistically **(Figure 7)**. A good balanced diet should also contain nutrients such as zinc, manganese and selenium, which are normally incorporated in enzymatic antioxidant systems *(Sokol, 1996)*.

FIGURE 7 - CELLULAR FREE RADICAL SCAVENGERS



1 - DNA
2 - Mitochondria
3 - Lysosomes
4 - Cell membrane
5 - Endoplasmic Reticulum

The intake of highly diverse antioxidants acting in synergy helps improve the protection of the cell's various sensitive points and optimize protection against oxidation.

S-Adenosylmethionine (SAMe) may also be helpful in reducing oxidative injury *(Davidson, 2002)*. It is a precursor of glutathione, an important hepatic antioxidant enzyme that is often reduced in dogs with liver disease. Oral administration helps to replenish hepatic glutathione stores and may thus improve antioxidant function. In addition, SAMe has anti-inflammatory properties *(Center et al, 2002)*.

Phosphatidylcholine (PC) is a phospholipid that is one of the components of bile required for normal bile acid transport and a building block for cell membranes. Its hepatoprotective actions are thought to be by improvement of membrane integrity and function *(Twedt, 2004)*. Based on its multiple mechanisms of action, this nutrient may be beneficial for chronic liver disease associated with oxidative stress, but it has not yet been validated for use in dogs.

Silymarin is the active component of milk thistle, and is thought to have antioxidant and free radical scavenging properties for various types of liver disease, as well as a protective agent against various hepatotoxicities *(Saller et al, 2001)*. There are currently limited clinical studies evaluating its efficacy in dogs with liver disease. Suggested doses range from 50 to 250 mg/day *(Twedt, 2004)*.

5 - Nutritional management adapted to the type of liver disease

► Acute liver diseases

Acute liver disease is most commonly caused by toxic injury, and less frequently by infection (e.g. infectious canine hepatitis, sepsis), trauma, heat stroke, or vascular compromise *(Center, 1996b)*. The spectrum of disease can range widely, and signs vary from mild to fulminant hepatic failure. Vomiting and diarrhea are common, whereas HE, melena, hematochezia, and DIC may occur in acute liver failure.

Stabilization - Fluid therapy with a balanced electrolyte solution is necessary for initial stabilization. Potassium and glucose should be supplemented as appropriate, and correction may reduce the severity of HE. Vomiting may be controlled by anti-emetics (metoclopramide, 0.2-0.5 mg/kg q 6-8h IV, IM, PO), whereas gastroprotectants (ranitidine 2 mg/kg q 8-12h IV, PO) are indicated in dogs with bloody vomiting and/or diarrhea. Treatment of HE may be needed as outlined below, using lactulose and oral antibiotics.

Dogs with acute liver disease are typically hypercatabolic and need prompt nutritional intervention in order to prevent debilitating malnutrition. The liver has tremendous regenerative capacities, but this is dependent on the availability of sufficient nutrients.

> Enteral nutrition

Enteral nutrition via tube feeding of frequent meals (3-6 hrs) should be instituted when the dog remains anorexic after 48 to 72 hours *(Michel, 1995)*, provided there is no intractable vomiting. Tube feeding is usually first started using a naso-esophageal tube; esophagostomy or gastrostomy tubes may have to be used at a later stage when the dog remains anorexic **(see chapter 14)**.

> Dietary management

Oral feeding should be started gradually with small frequent meals in order not to overload the liver's metabolic capacity. Half of the daily requirements should be fed initially, and this should be increased by 10% every day dependent upon the dog's response. The diet should contain normal amounts of protein (20%) if at all possible, since a positive nitrogen balance is essential for hepatic regeneration. Protein tolerance can be augmented by increasing caloric content (for instance by mixing a hepatic support diet with a convalescence diet) and/or using drugs to counteract hepatic encephalopathy (e.g. lactulose, oral antibiotics). Moderate protein restriction may be necessary in patients with persistent HE. However, in acute liver disease it is especially important not to over-restrict dietary protein, since this could result in endogenous ammonia production from protein catabolism as well as a reduction in the availability of protein for hepatocellular repair. The source of protein is also important, with milk and soy protein being better tolerated than animal protein.

The diet should also include free radical scavengers and antioxidants, such as vitamin E, vitamin C and SAMe. Ursodesoxycholic acid (10-15 mg/kg PO q24h) can be given as a hepatoprotectant in the subacute stage when serum bile acids remain high.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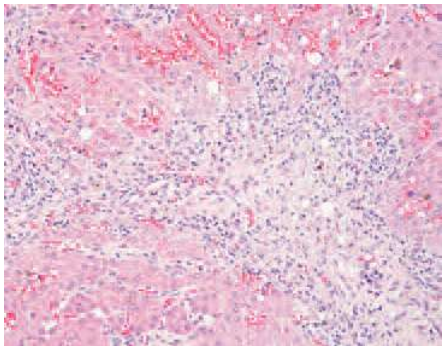
In case of acute liver failure, oral feeding must be reintroduced gradually, with frequent small meals so as not to overload the liver's metabolic capacity.

► Chronic liver disease

Chronic hepatitis includes a diverse group of disorders characterized by mixed inflammatory cell infiltrates, in which lymphocytes and plasma cells predominate *(Center, 1996b; Johnson, 2000)*. The etiology is often never determined. Documented causes include abnormal hepatic copper accumulation and drug- or toxin-induced hepatic injury (anticonvulsants). The presence of lymphocytic-plasmacytic infiltrates may be suggestive of an immune-mediated mechanism, but this is difficult to distinguish from immunological disease that occurs secondary to hepatocellular injury, due to release of liver antigens and subsequent antibody formation. The use of immunosuppressive therapy remains therefore limited to the few cases with clear lymphocytic-plasmacytic inflammation of unknown etiology *(Center, 1996a,b)*, especially since immunosuppressents may have detrimental effects on liver function.

Remember that glucocorticoids can have side-effects that may impact dietary needs, e.g. by aggravating HE, ascites, glucose intolerance and/or gastric ulceration *(Laflamme, 1999)*. This disease is usually in an advanced stage when recognized, and prognosis is guarded.



Liver biopsy of a dog suffering from chronic hepatitis, showing periportal inflammation with mononuclear inflammatory cells (H&E).

Dietary management – Nutritional therapy is particularly important in chronic liver disease. The amount fed should at first be based on an estimation of the patient's energy requirements **(Table 7).**

> Energy

Every effort should be made to get the dog to eat voluntarily. Food should be palatable, at room temperature and be fed in small portions 3 to 6 times daily. Dogs that refuse to eat or consume insufficient amounts to meet minimum requirements may require tube feeding, usually initially via a nasogastric tube, in order to halt the vicious cycle of excessive muscle catabolism and worsening signs of liver dysfunction. If the dog remains anorexic, esophagostomy or gastrostomy tubes may have to be inserted in order to ensure continuing nutritional adequacy **(see chapter 14)**.

> Protein

Dietary protein should ideally represent 17-20% of metabolic energy, be highly digestible and of high biological value. Protein restriction should only be instituted when there are signs of HE. Protein tolerance can be increased by administering lactulose (0.5 ml/kg orally three times daily), which may be combined with oral antibiotics (metronidazole 7.5 mg/kg q 12hr, or ampicillin 20 mg/kg q 8hr). Increasing dietary levels of vegetable, soy or dairy protein may also help to reduce the likelihood of HE.

REVERSIBILITY OF PROBLEMS

Dietary management of dogs with chronic liver disease aims to maintain adequate body condition in order to support hepatic regeneration and reduce signs of hepatic encephalopathy.

Assessment of the protein-calorie adequacy of the diet is generally based upon weekly monitoring of body weight and serum albumin concentrations. Progressive hypoalbuminemia (in absence of proteinuria) is indicative of protein malnutrition and/or progressive liver disease.

> Fiber

The diet should contain both soluble fiber, in order to promote an acidic colonic pH and decrease NH_4^+ absorption, and insoluble fiber, which helps to normalize transit time, prevent constipation and bind toxins. Foods low in fiber can be supplemented with psyllium (1 tsp per 5 to 10 kg bodyweight per meal).

> Minerals and vitamins

It is essential that the diet contains increased zinc levels and a mixture of antioxidants including vitamins E and C. Additional oral zinc supplementation (zinc acetate 2 mg/kg daily) may be helpful because it is an antioxidant that also has antifibrotic properties and can reduce the severity of HE.

► Copper toxicosis

Bedlington Terriers affected with primary copper toxicosis develop progressive liver disease and die within a few years. This disease in Bedlington Terriers has similarities to Wilson's disease in man but differs clinically and genetically *(Brewer, 1998; Muller et al, 2003)*; the treatment is however similar. The role of copper in other breeds is less clear, although it is thought that in some breeds copper accumulation may contribute to the development of liver disease (e.g. West Highland White Terriers, Doberman Pinschers and Dalmatians) *(Rolfe & Twedt, 1995; Webb et al, 2002; Spee et al, 2005)*. Quantitative determination of liver copper levels as well as histopathologic assessment is important in differentiating primary copper storage disease from secondary copper retention due to cholestasis. Dogs with secondary copper accumulates tend to have lower concentrations in the liver, rarely exceeding 2000 ppm, and a different localization of copper within the lobule *(Center, 1996b; Rolfe & Twedt, 1995)*.

Dietary management – Diets for dogs with copper hepatotoxicosis should be low in copper while high in zinc, contain increased vitamin B levels and adequate levels of high quality proteins. Many canine diets contain copper well above the minimum required amount, and it is important to choose a diet with levels as low as possible. Feeding copper-restricted diets slows hepatic copper accumulation but does little to lower liver copper levels in already diseased dogs with large amounts of hepatic copper accumulation.

Dogs with severely increased liver copper levels (> 2000 ppm; normal less than 400 ppm) should be partially decoppered for 2-4 months using a copper chelator such as D-penicillamine (10-15 mg/kg orally q 12hr). Subsequently, treatment with oral zinc, which blocks intestinal copper absorption by induction of copper-binding metallothionein, is continued lifelong *(Brewer et al, 1992)*. Treatment of dogs with secondary copper retention involves addressing the primary cause, as well as measures to reduce the accumulated copper.

Prevention – Diets low in copper are essential in breeds known to accumulate copper or that have increased concentrations on biopsy. Bedlington Terriers that have been genetically assessed as being at risk of developing copper hepatotoxicosis should be fed a low-copper diet from a young age since copper accumulation happens early in life. Other foodstuffs (e.g. shellfish, liver), mineral supplements or water with a high copper concentration should also be avoided **(Table 8)**. DNA testing may help to identify affected and/or carrier Bedlingtons.

► Hepatic encephalopathy (HE)

HE is a metabolic disorder affecting the central nervous system, which develops secondary to hepatic disease *(Maddison, 2000)*. It is usually a result of congenital portovascular anomalies (congenital portosystemic shunts, microvascular dysplasia) and less commonly due to severe hepatocellular disease. Acquired shunts may occur in response to portal hypertension caused by severe chronic hepatitis, cirrhosis and fibrosis, and will also predispose to development of HE. Rarely, HE is due to urea cycle deficiencies as reported in Irish Wolfhounds *(Rothuizen et al, 2001)*. Signs are typically intermittent, may be precipitated by a high-protein meal, and vary from anorexia, vomiting, diarrhea and polyuria/polydipsia to disorientation, apparent blindness and seizures. Stunted growth or failure to gain weight may occur in young dogs with congenital portovascular shunts. A high index of clinical suspicion is important, since appropriate management of HE will greatly improve the patient's demeanor and may restore appetite.

> Dietary modification

- ***Protein quantity***

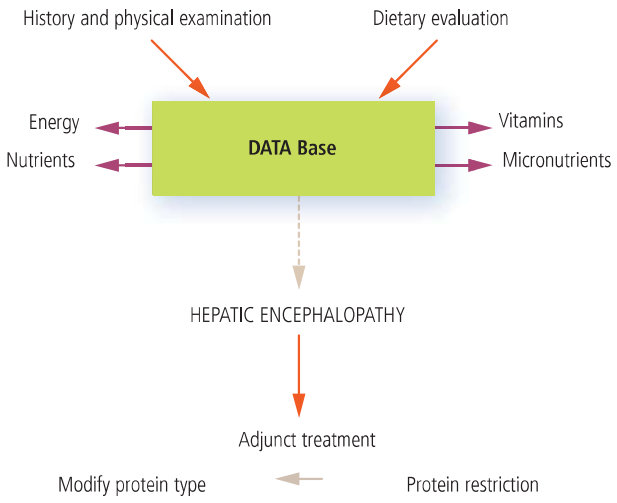
Dogs with HE are initially offered a highly digestible, protein-restricted diet (around 15 % ME), in combination with medication aimed at reducing ammonia production and colonic absorption (lactulose; oral antibiotics such as metronidazole or ampicillin) **(Figure 8)**. High diet digestibility as well as the addition of moderate amounts of fermentable fibers is of added benefit in regulating the intestinal microflora. Frequent, small meals should be fed in order to limit the time between meals, which improves nutritional status and reduces catabolism *(Laflamme, 1999)*. If the patient becomes neurologically asymptomatic, protein quantity is gradually and cautiously increased at weekly or biweekly intervals. Normal or near-normal maintenance protein requirements should be fed unless the animal again becomes encephalopathic, and in that case the medical treatment ought to be reinstituted and/or intensified. Serum proteins should be monitored to prevent hypoalbuminemia, in which case dietary protein content is increased in association with more aggressive adjunctive treatment. In dogs with refractory HE, protein quality may be modified by replacing animal proteins with vegetable (soy) and/or dairy proteins.

Maintenance of muscle mass and a positive nitrogen balance is essential in reducing the risk of hepatic encephalopathy (HE). Dietary protein should be restricted only as needed to prevent HE. Correction of enteric bleeding, constipation, infection, alkalosis, hypokalemia and azotemia is also important in reducing the risk of HE.

- ***Protein quality***

In addition to a protein-restricted diet and adjunct medication, it can be helpful to replace meat proteins with highly digestible vegetable (e.g. soy isolate) and/or milk proteins (e.g. casein, cottage cheese) *(Strombeck et al, 1983; Center, 1998)*.

FIGURE 8 - OVERVIEW OF NUTRITIONAL MANAGEMENT OF LIVER DISEASE



- ***Soluble fiber***

Addition of soluble fiber can be of benefit by acidifying colonic contents and minimizing ammonia absorption. Psyllium (1-3 tsp per 5-10 kg of weight mixed with food daily) also contains some insoluble fiber, which adds bulk to the stool and prevents constipation.

- ***Drug therapy***

Adjunct medical therapy can increase protein tolerance. Lactulose is a synthetic disaccharide that is fermented in the colon, resulting in colonic acidification and reduced ammonia absorption. The starting dose is 0.25-0.5 ml/kg two to three times daily, which is titrated to produce two soft stools daily.

Oral antibiotics (e.g. metronidazole 7.5 mg/kg q 8-12 hr or ampicillin 20 mg/kg q 8hr) are given during severe encephalopathic episodes in order to modify the enteric microbial flora that is responsible for the generation of ammonia and other toxins.

► Homemade versus commercial diets

Commercial diets are preferred above homemade ones because they are nutritionally complete. Veterinary diets formulated for dogs with hepatic insufficiency are now available and meet the specific nutritional requirements of the liver patient. It is difficult to create homemade diets that are balanced enough to be used for prolonged periods *(Laflamme, 1999)*.

In general, diets for dogs with liver disease should be highly digestible with a high energy density provided by fat and carbohydrates **(Table 9)**. Moderate protein restriction may be necessary in dogs with clinically evident HE, but protein quality should be very high. In addition, the diet should contain high normal to increased levels of water-soluble vitamins, enhanced zinc (>43 mg/1000kcal), restricted copper, restricted sodium (<0.5 g Na/1000 kcal) in case of ascites, and a moderate amount of mostly soluble fiber. Protein restriction should be avoided as much as possible, especially in dogs with acute inflammatory hepatic disease or necrosis.

TABLE 9 - DIETARY RECOMMENDATIONS FOR MANAGEMENT OF LIVER DISEASE IN DOGS

Provide adequate energy

Supply sufficient energy (110-130 kcal ME/kg $BW^{0.75}$)
Provide energy as protein as well as non-protein calories
High diet palatability and energy density
Small meals fed frequently
- increases total food intake
- maintains energy and nutrient supply
- prevents overwhelming hepatic metabolic capacity

Fat:
- 30-50 % of dietary calories
- avoid high fat diets in: severe cholestasis, hyperlipidemia or vacuolar hepatopathies

Carbohydrates:
- maximal 45% of dietary calories

in glucose intolerance: avoid simple sugars, increase complex carbohydrates

Provide adequate protein

Protein should be of high quality and digestibility
Avoid inappropriate protein restriction (>14% of dietary calories, preferably >20%)
Feed protein at level of body condition and serum albumin
Restrict protein only as necessary in HE, and even then protein tolerance can be increased by augmenting caloric content (e.g. soy hydrolyzate) and adjunctive medical management

Fiber

Moderate amounts, predominantly soluble fiber

Provide adequate vitamins and minerals

Double maintenance level of vitamin B
Increased vitamin E
Moderate dietary restriction of sodium
Potassium replete
Restricted copper

Include additional antioxidants

Increased zinc (>43 mg/1000 kcal)
Increased vitamin E (10-100 IU/kg)
Increased vitamin C
Taurine

Management of complications

a) Hepatic encephalopathy:
- correct precipitating factors (e.g. hypokalemia, infection, GI bleeding)
- restrict dietary protein (12 to 16%, with a minimum of 2.1 g/kg per day)
- increase dietary protein tolerance with adjunctive treatment:
  - increasing caloric content
  - lactulose 0.25-0.5 mL/kg q 8h po
  - metronidazole 7.5 mg/kp q 12h po
  - ampicillin 20 mg/kg q 8h po
  - soluble fiber
- modify protein quality: vegetable and/or dairy proteins

b) Ascites
- dietary sodium restriction (<0.5 g Na/1000 kcal)
- diuretics (spironolactone 1-2 mg/kg q 12h, furosemide 2-4 mg/kg q8-12h PO)

Frequently asked questions - Nutrition of dogs with liver disease

Q	A
Dogs with liver disease often have a decreased appetite or are anorexic. How can they be stimulated to eat?	The diet must be highly palatable and high in energy, and provide adequate protein, fat, and all essential micronutrients. Feeding small amounts frequently and slightly warming canned food can increase palatability. Tube feeding, initially via a nasogastric tube, may be required in dogs that are anorexic for more than 3-5 days, since correction and prevention of malnutrition are essential to halt the vicious cycle of excessive muscle catabolism and worsening signs of liver dysfunction.
The liver biopsy of a seven-year-old Golden Retriever showed chronic hepatitis and copper accumulation. Is this copper important?	Golden Retrievers are not known to have primary copper hepatotoxicosis, and copper accumulation is probably a consequence of cholestatic liver disease resulting in decreased biliary excretion of copper. Typically, these copper levels are not high enough to result in hepatocellular damage. However, zinc treatment together with measures for chronic liver disease will help to prevent further copper accumulation.
Are antioxidants important in managing liver disease?	**Yes.** There is mounting evidence that free radical production is increased in many liver diseases and it can play an important role in initiating and perpetuating liver injury. Furthermore, endogenous antioxidant systems become depleted during liver disease, which aggravates the problem. Supplementation with antioxidants such as vitamins E, C, and S-adenosylmethionine (SAMe) helps to minimize oxidative injury. A combination of dietary antioxidants is better than a single one, since they appear to act synergistically.
Should dogs with liver disease be fed a protein-restricted diet?	**Not necessarily.** Protein levels are often inappropriately restricted in order to manage possible hyperammonemia. In fact, protein requirements are at least normal or even increased, and many dogs with liver disease do not have hyperammonemia. Provision of adequate high-quality proteins as well as calories is essential to ensure a positive protein balance and enable hepatic regeneration. The aim is to keep the protein intake as close to normal as can be tolerated without precipitating signs of hepatic encephalopathy (HE). Protein restriction should only be instituted when there are signs of HE, and additional treatments such as lactulose and oral antibiotics can help to avoid excessive restriction of dietary protein.
How should I feed a dog with acute liver disease?	A dog with acute liver disease needs an ample supply of energy and protein to allow for hepatic regeneration. Protein should never be restricted; protein tolerance can be enhanced if necessary by increasing caloric content and/or using drugs (lactulose, oral antibiotics). The dog should be fed small frequent meals in order not to overload the liver's metabolic capacity. Tube feeding should be considered if the dog remains anorexic for more than 72 hours.

Q	A
What are the dietary recommendations for dogs with chronic hepatitis?	The diet should have high palatability and energy density, contain normal levels of fat (which provides energy as well as palatability), adequate levels of high quality protein (>14% of dietary calories, preferably >20%), be restricted in copper and sodium, and contain some fermentable fiber. In addition, the diet should have increased vitamin B and zinc levels, and a mixture of antioxidants (e.g. vitamin E, C and S-adenosylmethionine). Zinc supplementation is useful because it is an antioxidant, reduces copper accumulation in the liver, can reduce the severity of HE and has antifibrotic properties.
What are the dietary recommendations for a Bedlington Terrier with copper hepatotoxicosis?	The diet should be low in copper while high in zinc, and contain adequate levels of high quality proteins. Many canine diets contain copper well above the minimum required amount, and it is important to choose a diet with levels as low as possible. Feeding copper-restricted diets slows hepatic copper accumulation but does little to lower liver copper levels in already diseased dogs with large amounts of hepatic copper. Additional treatment with a copper chelator (D-penicillamine) will be needed, followed by life-long zinc therapy to prevent further copper accumulation.
How do I manage a dog with hepatic encephalopathy?	Firstly, determine the cause – congenital portosystemic shunt or severe liver disease. Dietary management should focus on providing adequate energy and adequate protein to support hepatic regeneration while preventing worsening of HE. Patients with signs of HE are initially offered a protein-restricted diet in combination with medication aimed at reducing colonic absorption of ammonia (lactulose, oral antibiotics). Protein quantity is gradually increased at weekly or biweekly intervals when the dog becomes neurologically asymptomatic. Serum proteins should be monitored to prevent hypoalbuminemia, in which case dietary protein content should be increased in association with more aggressive adjunct treatment. When HE persists despite a protein-restricted diet and adjunct medication, it may be helpful to replace meat proteins with highly digestible vegetable and/or milk proteins. Addition of soluble fiber (psyllium 1-3 tsp mixed with food daily) can also help by acidifying colonic contents and minimizing ammonia absorption.

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EXAMPLES OF HOME-PREPARED
THE TREATMENT FOR

Example 1

COMPOSITION
(1000 g diet)

Chicken, breast with skin ..... 220 g
Rice, cooked ..... 680 g
Carrots (boiled, drained) ..... 60 g
Wheat bran ..... 20 g
Rapeseed oil ..... 20 g

Add a low-sodium and low-copper mineral and vitamin supplement.

ANALYSIS		
The diet prepared in this way contains 31% dry matter and 69% water		
	% dry matter	**g/1000 kcal**
Protein	22	50
Fat	12	27
Available carbohydrate	60	136
Fiber	4	10

Key Points

- **Reduce the copper content** to limit the risk of copper accumulation in the liver
- **Reduce the sodium content** to reduce portal hypertension and limit the loss of fluid through the extra-luminal space
- **Increase the energy level** to prevent the risk of excessive protein catabolism and combat hepatic encephalopathy

INDICATIVE RATIONING			
Energy value (metabolizable energy) 1355 kcal/1000 g of diet prepared (2380 kcal/1000 g DM)			
Dog's weight (kg)*	Daily amount (g)**	Dog's weight (kg)*	Daily amount (g)**
2	160	45	1670
4	270	50	1800
6	370	55	1940
10	540	60	2070
15	730	65	2200
20	910	70	2320
25	1070	75	2450
30	1230	80	2570
35	1380	85	2690
40	1530	90	2800

** The rationing is offered in accordance with the dog's healthy weight. In case of obesity, the rationing must be prescribed in accordance with the ideal weight and not the real weight of the dog.*
***The fractioning of the daily amount over two or three meals is recommended to limit the postprandial hepatic load.*

DIETS ADAPTED TO LIVER DISEASES

Example 2

COMPOSITION
(1000 g diet)

Beef, minced meat, 15% fat ..... 100 g
Tofu ..... 400 g
Rice, cooked ..... 440 g
Carrots (boiled, drained) ..... 30 g
Wheat bran ..... 10 g
Rapeseed oil ..... 20 g

Add a low-sodium and low-copper mineral and vitamin supplement.

INDICATIVE RATIONING			
Energy value (metabolizable energy) 1265 kcal/1000 g of diet prepared (1900 kcal/1000 g DM)			
Dog's weight (kg)*	Daily amount (g)**	Dog's weight (kg)*	Daily amount (g)**
2	170	45	1790
4	290	50	1930
6	390	55	2080
10	580	60	2220
15	780	65	2350
20	970	70	2490
25	1150	75	2620
30	1320	80	2750
35	1480	85	2880
40	1630	90	3000

ANALYSIS		
The diet prepared in this way contains 26% dry matter and 74% water		
	% dry matter	g/1000 kcal
Protein	25	51
Fat	21	43
Available carbohydrate	49	100
Fiber	3	6

Contra-indications

Gestation
Lactation
Growth

Examples of home-made diets are proposed by Pr Patrick Nguyen
(Nutrition and Endocrinology Unit; Biology and Pathology Department, National veterinary School of Nantes)

It is important to serve several smaller meals over the day while respecting the daily ration in order to limit the postprandial hepatic load.

Key points
to remember:

Nutrition in the treatment and prevention of liver diseases

The four objectives of nutritional support for liver diseases in dogs are:

- **Treating the malnutrition** by responding to the energy requirements in terms of essential nutrients
- **Favoring the regeneration of hepatocytes** by ensuring the limited intake of nutrients, particularly proteins
- **Limiting hepatic lesions** by preventing the accumulation of copper and capturing free radicals
- **Preventing or minimizing complications**, such as hepatic encephalopathy, portal hypertension and ascites

Anorexia is a frequent consequence of hepatopathies.

Tube feeding can be utilized to ensure an appropriate intake of energy and nutrients.

Highly digestible vegetable or dairy proteins are better tolerated than animal proteins in animals suffering from hepatic encephalopathy.

Nutritional support must be adapted to the case, based on the type of hepatopathy, the degree of hepatic dysfunction, the tolerance to dietary proteins and the animal's nutritional condition.

The length of the nutritional treatment is dependent on the cause of the disease and the regeneration capacity of the liver tissue. A lifelong prescription may prove necessary in case of a chronic disease.

Focus on:
COPPER

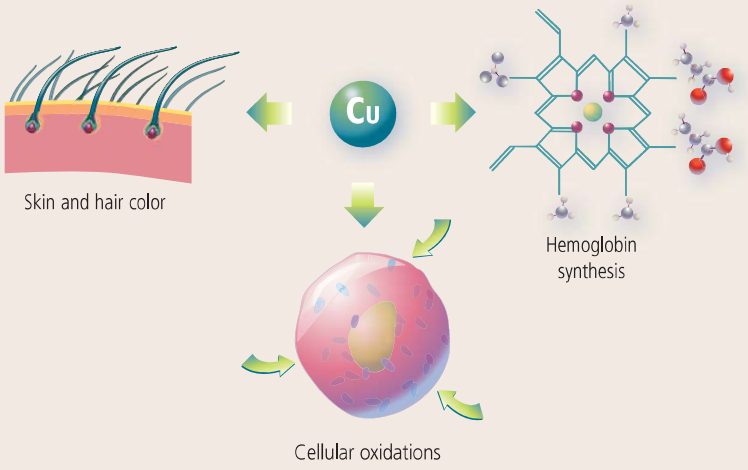
Although it is present in the organism in very low quantities (< 10 mg /kg of body weight), copper plays the role of coenzyme in a great many metabolic reactions.

- Copper is one of the anti-anemic factors that also include folates, vitamin B12 and iron. Copper facilitates the incorporation of iron in hemoglobin.
- Copper helps the synthesis of collagen and myelin.
- Copper also plays a role in the synthesis of melanin, due to its tyrosinase coenzyme function.
- As a cofactor of superoxide dismutase (SOD), copper is an integrative part of the oxidative stress defense mechanisms.

Copper is absorbed and stored by bonding with liver proteins: most of the organism's copper is stored in the liver. This storage capacity is limited and excess copper is eliminated by the bile. Copper may be toxic when accumulation is excessive, as in some predisposed breeds.

The intestinal absorption of copper, zinc and iron is interdependent. An excessive iron or zinc level may reduce the availability of copper. In the enterocytes zinc induces the synthesis of metallothioneine, a metalloprotein that forms a strong bond with copper in the epithelial cells of the intestine and prevents its absorption. Food high in zinc (> 40 mg /1000 kcal) is therefore recommended for dogs with liver failure.

EXAMPLES OF MAJOR FUNCTIONS IN WHICH COPPER PLAYS A ROLE



With pathological accumulation, copper levels in the liver will reach concentrations of several thousand mg/g of dry liver tissue, or ten times that of a healthy liver.

DOG BREEDS PRESENTING INCREASED COPPER IN THE LIVER DURING HEPATOPATHY

(From Johnson, 2000)

Airedale Terrier
Bedlington Terrier*
Bobtail
Boxer
Bull Terrier
Bulldog
Cocker Spaniel
Collie
Dachshund
Dalmatian
Doberman Pinscher
German Shepherd
Golden Retriever
Keeshond
Kerry Blue Terrier
Pekingese
Poodle
Samoyed
Schnauzer
Skye Terrier*
West Highland White Terrier*
Wirehaired Fox Terrier

** accumulation of copper in the liver related to a hereditary mechanism*

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