THE EFFECTS OF LEFT HEPATIC VEIN LIGATION ON HEPATIC CIRCULATION, FUNCTION AND MICROANATOMY

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(ABSTRACT)

Eighteen healthy dogs were divided into three equal groups. All dogs were evaluated at the beginning of the experiment with complete physical examination, complete blood count, serum alanine aminotransferase, serum alkaline phosphatase, serum bilirubin, serum albumin, sulfobromophthalein excretion test, ammonia tolerance test, glucagon response test, portal and intraparenchymal pressures, operative mesenteric portography, and histologic assessment of hepatic tissue.

The left hepatic vein was ligated in the chronic and acute dogs. The dogs had a ligature placed loosely around the left hepatic vein. Acute and control dogs were evaluated 24 hours postoperatively with the hematologic and biochemical tests listed above. Acute dogs were evaluated with portal and intraparenchymal pressure, operative mesenteric portography

and histologic evaluation of hepatic tissue at 48 hours postoperatively. Chronic and control dogs were evaluated at 4 weeks postoperatively with all of the tests listed above.

The results of all tests performed supported a transient hepatic congestion which resolved by the fourth postoperative week. No longstanding effect on hepatic function was found.

The conclusion of this experiment was that, in normal dogs, left hepatic vein ligation does not cause severe or permanent liver damage. These findings support a clinical trial of this procedure in patients with patent ductus venosus.

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I. INTRODUCTION

Ia. Hepatic Anatomy and Circulation.

The canine liver is situated in the cranial abdomen where it is attached to the diaphragm by the left and right triangular ligaments. The liver is attached to the stomach by the gastrohepatic ligament and to the duodenum by the hepatoduodenal ligament.[1] There are six lobes of the canine liver, namely the right lateral and medial, left lateral and medial, caudate and quadrate lobes. These lobes are arranged in hepatic divisions based upon blood supply in which the caudate and right lateral lobes make up the right division, the right medial and quadrate lobes make up the central division and the left lateral and medial lobes make up the left division (Fig 1).[1] The papillary process of the caudate lobe is considered part of the left hepatic division because of its blood supply.[1]

The vascular network of the liver consists of portal veins, hepatic arteries and hepatic veins. The portal vein receives venous blood from the entire gastrointestinal tract and spleen. The major contributors to the portal vein include the cranial and caudal mesenteric veins, the splenic vein, the gastroduodenal vein and the left gastric vein. The portal vein is relatively constant and predictable in its course. There are two main branches of the portal vein which supply the liver. The right main branch supplies the right hepatic division while the left branch supplies the left and central hepatic divisions. The papillary process is supplied by a vessel from the left main portal branch.

Portal blood, comprising the majority of total hepatic blood flow, determines the environment of the hepatocyte by its hormone and metabolite content. It has been shown that nutrients and hormones (particularly insulin) in portal blood are essential for hepatocellular health.[2] The exception to this is the oxygen content of sinusoidal blood which is regulated primarily by the hepatic arterial blood.[3]

The hepatic artery originates from the celiac artery, and passes dorsal to the portal vein and common bile duct within the hepatoduodenal ligament. While within the hepatoduodenal ligament, the hepatic artery forms an arch before becoming the gastroduodenal artery. The arteries which supply blood to the liver originate from this arch. There are typically 2-3 branches of the hepatic artery supplying the liver.[1,4] The branching patterns are quite variable for hepatic arteries, however each hepatic division tends to have a separate arterial supply in spite of a variation in number of main hepatic artery branches.[1,4]

Hepatic veins are also variable in number and position. There are typically 6-8 major hepatic veins present.[1] The largest and most consistent of these is the left hepatic vein which is the most cranially located. This vein always drains the left hepatic division and may partially drain the central hepatic division.[1] Other hepatic veins are less predictable in size and location. Occasionally the left hepatic vein is joined by the central hepatic vein.[3] The hepatic veins all empty into the caudal vena cava before it passes through the diaphragm.

The biliary drainage of the liver is by way of the common bile duct. The common bile duct receives each of 3-4 divisional ducts which

drain the individual hepatic divisions into the hepatic bile duct or gallbladder.

Intrahepatically, the afferent blood supply of the liver (portal vein and hepatic artery) arborizes, and the liver can be divided into gross and microscopic segments according to afferent and efferent blood vessel distribution.[3,5] Major hepatic arterial vessels do not parallel portal vessels although smaller arterioles do.[3] The hepatic arterial branches have numerous sphincter areas which are used to control vascular flow.[3] Hepatic veins originate in the sinusoids and drain hepatic sinusoids into the caudal vena cava. They are generally named after the segments of liver they drain and, like the portal vein, contain no valves.[3] There are no functional communications between hepatic veins and portal veins in the adults except by way of the sinusoids.[3] The terminal portal and hepatic venules are arranged spatially so that afferent vessels run precisely between and perpendicular to efferent vessels.[3] This accomplishes efficient drainage of the liver and allows the tissue between two hepatic venules to be designated as an acinus, the functional liver unit. The central veins are at the periphery of the acinus they drain.[3]

At the level of the acinus, hepatic circulation becomes quite complex because blood from a low pressure system (portal) and a high pressure system (hepatic arterial) mix in the sinusoids without the portal system becoming stagnated. Terminal hepatic arterioles and arterial capillaries join terminal portal venules in the periportal area.[3] The mechanism of mixing of these separate blood supplies is thought to be controlled by sphincters on the arterial side which equalize

pressure differences.[3] The junction of hepatic arterial capillaries and terminal portal venules is called the arterioportal junction. There is some evidence to further classify portal venules into conducting and axial vessels.[7] Conducting portal venules regularly send out smaller venules to supply periportal cuffs of tissue.[3] Axial portal venules are terminal and show sphincter-like activity which regulates portal blood flow.[3]

The sinusoids are the true hepatic capillaries and contain the Kupffer cells (reticuloendothelial cells) as well as Ito cells (fat storage cells).[3] The lining of the sinusoids have many fenestrations between endothelial cells which facilitates transfer of hepatic nutrients and intestinal toxins into the Disse's spaces (perisinusoidal spaces). The sinusoids empty abruptly into the terminal hepatic venules (central veins).

Anatomically the liver has a relatively straight-forward blood supply. The regulation of this blood flow is complicated and is a result of both local and systemic factors.[3,5,7] Changes in total hepatic blood flow and regulation of total hepatic blood flow depend upon alterations in hepatic arterial and portal blood flow. In simple terms, there is a reciprocity of flow existing between the afferent vessels (hepatic arterioles and portal venules).[5] This control is dependent mainly on changes in hepatic arterial flow since the portal flow relies on the splanchnic circulation flow and is not subject to significant autoregulation unlike the arterial flow.[3,6] Changes in splanchnic circulation, and thus portal flow, have an important effect on total hepatic blood flow. As portal flow decreases, the hepatic arterial flow will increase through a decrease

in hepatic arterial resistance (vasodilation). If the hepatic arterial flow is decreased, portal resistance will decrease, however, portal flow stays unchanged because its flow is dependent upon prehepatic vasculature.[5]

The mean hepatic artery pressure is 100 mmHg.[3] The resistance to flow within the hepatic arterioles is mediated through a series of muscular resistance vessels. Arterial resistance is 30-40 times higher than portal resistance.[3] In the sinusoids, arterial blood and portal blood mix, and flow together from the hepatic artery to the terminal portal venule.[3] The hepatic artery normally provides only 20% of total hepatic flow. Under some circumstances (e.g. portosystemic shunting) it may provide 65% of the total flow.[3] Increasing portal pressure causes a marked constriction in hepatic arterioles.[3] Increases in hepatic vein pressure also lead to increases in arterial vasoconstriction. In order to maintain a relatively constant total hepatic blood flow the arterial system reacts to increases in pressure of the hepatic artery, hepatic vein or portal vein with vasoconstriction and a decrease in arterial flow.[3]

Approximately 25% of the cardiac output is directed through the hepatic circulation. Normally 75-80% of this is through the portal system and 20-25% is arterial.[7] Normal fasting portal and arterial blood flow in the dog has been reported as 31.9 ± 3.4 ml/min/kg and 10.4 ± 1.2 ml/min/kg respectively.[9] All of this afferent blood comes together as a high pressure (arterial) and a low pressure (portal) system in the central acinar area where the sinusoids exist. Direct observation shows an oscillation of flow in sinusoidal circulation which suggests sphincteric control of terminal afferents and possibly efferents at either end of a sinusoid.[7]

This sphincteric control allows two systems with differing pressures to mix and flow into the same space. The sphincters are thought to be composed of specialized reticuloendothelial cells.[7] The acinus is centered around terminal portal venules and hepatic arterioles, and pressure and flow are under the sole control of the hepatic arterioles.[3] The sinusoids form a tuft of tissue around terminal hepatic arterioles and portal venules before emptying into the peripheral hepatic venules. The single layer of smooth muscle in terminal arterioles is richly supplied with unmyelinated nerve fibers.[3]

The hemodynamics of hepatic microcirculation are made possible by valved arteriovenous (AV) anastomoses.[9] There are multiple AV anastomoses in which blood flow is always unidirectional from hepatic arteriole to portal venule.[9] These anastomoses are presinusoidal. The hepatic arterial circulation ends as arterial capillaries and terminal arterioles. The arterial capillaries originate in the periductular arteriolar plexus while the terminal arterioles branch off larger vessels and empty directly into sinusoids through the terminal portal venules.[3] The low pressure portal blood is able to enter into the sinusoids in spite of competition from the hepatic arterial blood which is under pressure 8 times higher. This is possible because of an arterial pressure reduction in the periductular capillary plexus. There is also a drop of arterial pressure to match portal venous pressure immediately at the opening of the arterial capillaries into the sinusoid.[3] The pressure energy is converted into velocity and acceleration energy for the blood flow.[3] Finally, it has been demonstrated that periodic closure of the arterioles and arterial capillaries

is regulated by their sphincters. Portal flow enters sinusoids unabated during hepatic arterial closure. When the arterial sphincters open blood flow is accelerated rapidly.[3] This autoregulation leads to a rhythmic blood flow through hepatic sinusoids. The sinusoids have arterioles entering at various angles which can rapidly change flow direction and velocity. This arrangement minimizes concentration gradients and, along with the pulsatile motion, leads to a thorough mixing of arterial and portal venous blood. In the dog, sphincter control is also present in terminal portal venules and terminal hepatic venules (central veins).[10]

Hepatic microcirculation regulation is accomplished almost exclusively through hepatic arterial changes. The arterioles are responsive to neurogenic control, bile salts, hormones and metabolic by-products. The portal vein plays practically no role in the autoregulation of flow because the terminal portal venules are devoid of smooth muscle.[3] Stimulation of the hepatic plexus causes a transient vasoconstriction and is probably of little importance.[3] The most important control of hepatic microcirculation is a local myogenic control through smooth muscle in the arteriole walls. Hepatic arterioles are responsive to changes in flow and pressure primarily, and bile salt concentration secondarily. There is a difference in circulatory patterns and behavior between the hepatic arterial capillaries which are associated with the periductular network and the hepatic arterioles which enter the sinusoid directly. The periductular capillary plexus is responsive to bile salt levels. This is a poorly understood mechanism but it does show a relation-

ship between blood flow and biliary excretion.[3] Many drugs, particularly vasoactive drugs, have effects on hepatic microcirculation.

Much of this evidence is indicative of intrinsic autoregulation of hepatic blood flow which is mediated through the hepatic artery. This is the most important factor in hepatic blood flow autoregulation, however, extrinsic factors can also affect hepatic blood flow. The hepatic artery is richly supplied with nerve fibers from the celiac plexus and vagus nerve.[3] Electrical stimulation of sympathetic fibers will result in marked but transient arterial constriction. Stimulation of vagal fibers supplying the liver causes little response.[3,10]

Metabolic factors may also play a role in hepatic blood flow, however, like neural control, this is of minimal importance. Hypoxia leads to no change in hepatic arterial flow, unlike hypocapnia which causes arteriolar constriction.[3] Hypercapnia has a vasodilatory effect on the hepatic artery and increases portal flow by 43% through mesenteric vasodilation.[3,10] There are also reports that some bile acids increase hepatic arterial flow.[3,11] Some drugs, such as barbiturates increase activity and production of hepatic enzymes and secondarily increase hepatic blood flow.[10] Increases in portal osmolality may also increase hepatic blood flow by vasodilation of hepatic arterioles.[10]

Hormones also have an influence on total hepatic blood flow. Glucagon, epinephrine, secretin and gastrin all increase hepatic arterial flow which improves oxygen availability in the liver.[10] Epinephrine and secretin cause hepatic arteriolar dilation with relaxation of precapillary sphincters. Glucagon increases portal flow and inhibits reflex arterial

vasoconstriction causing a considerable increase in total hepatic blood flow. Glucagon increases portal flow through intestinal vasodilation. Conversely, norepinephrine causes a profound vasoconstriction in arterioles. Thus, epinephrine increases total hepatic blood flow, and norepinephrine decreases total hepatic blood flow. Cholecystokinin increases intestinal and portal blood flow and may be important in postprandial increases in hepatic blood flow. Vasopressin causes a decrease in portal pressure and flow with a resultant increase in hepatic arterial flow.[3,11] Gastrin, vasoactive intestinal polypeptide and insulin probably have little physiologic effect on total hepatic blood flow.[11]

The portal system flow is not appreciably autoregulated, and is dependent on splanchnic flow. The greatest changes in total hepatic blood flow are caused by extrinsic factors which change the portal blood flow. Increases in segmental and tonic contractions of the bowel loops will increase the flow of portal blood.[3] Food intake volume and quality affect splanchnic circulation and secondarily affect portal circulation.[3,10] Portal pressure and flow normally depend upon the dilation or constriction of mesenteric and splenic arterioles, and portal pressure is also affected by intrahepatic resistance.[3] Hepatic arterial pressure has little effect on portal pressure or flow.[3] Hormones which increase or decrease splanchnic flow have a corresponding effect on portal flow. Hepatic parenchymal disease causes an increase in portal pressure and a decrease in portal blood flow.

The ductus venosus (DV) is a vascular shunt which allows the hepatic sinusoids to be bypassed by blood from the umbilicus. The ductus venosus

is a direct continuation of the umbilical vein and passes through the hepatic parenchyma without branching, to terminate by draining into the left hepatic vein or the caudal vena cava.[12] At birth, the ductus venosus blood flow in the dog decreases, and full functional closure is completed by the second or third day of life.[12] The ductus venosus will close anatomically at 15-18 days to form the ligamentum venosum.[12] The ductus venosus develops early in the embryo as a vascular shunt connecting the subhepatic and subdiaphragmatic anastomoses of the left and right omphalomesenteric veins (Fig 2).[13] During this early stage of development, blood from the yolk sac passes through the liver by the omphalomesenteric veins (similar to splanchnic blood in the adult) while the blood from chorionic villi (placenta) bypasses the liver to empty into the sinus venosus by way of the umbilical veins.[13] At a later stage of development, the right umbilical vein disappears, and the remnant of the right omphalomesenteric vein becomes the portal vein. The left omphalomesenteric vein also disappears except for the cranial part which becomes the caudal vena cava. The left umbilical vein remains and empties into the ductus venosus which continues to empty into the left hepatic vein. The ductus venosus varies in length depending on species, in the human newborn it is 12 cm. long, whereas in the sheep fetus, it is 3 cm. long.[13,14] The wall of the ductus venosus contains little smooth muscle, and some workers have identified a muscular sphincter at its origin.[13,14]

In the fetus, both portal and umbilical blood must pass through the liver. The amount of blood which bypasses the liver through the ductus venosus is variable. Typically 36-64% (mean 53%) of umbilical flow will

pass through the ductus venosus, whereas only 9% of portal blood flow passes through the DV. Umbilical blood flow comprises 98% of total ductus venosus blood flow.[13] Ductus venosus blood flow also correlates positively with umbilical blood flow. There remains considerable controversy as to whether neural control is important in ductus venosus blood flow. The origin of the ductus venosus contains a smooth muscle sphincter which is innervated by sympathetic and parasympathetic nerve fibers.[13] Vagal stimulation does not affect ductus venosus blood flow.[13] A portion of the innervation of the ductus venosus may originate from the right phrenic nerve, and both parasympathetic and sympathetic fibers are probably responsible for control of the ductus venosus sphincter.[13] The adrenergic fibers are probably responsible for most of the neural control.[13]

Chemical regulation of ductus venosus blood flow is controversial. Norepinephrine, epinephrine and acetylcholine have been shown experimentally to cause a reduced fetal hepatic blood flow and to secondarily increase ductus venosus blood flow.[13] The blood flow through the ductus venosus is pulsatile mainly due to the changing pressure in the vena cava during systole and diastole. There are major changes in ductus venosus flow associated with decreasing the umbilical vein flow. As umbilical vein flow decreases, so does ductus venosus flow; however, the proportion of umbilical flow which bypasses the liver increases.[13] This is caused by an increase in hepatic resistance secondary to the decrease in umbilical venous flow.[13] This proportionately greater ductus venosus blood flow serves to ensure adequate venous return to the heart during periods of umbilical venous flow fluctuations.[13] These mechanical factors are

major regulators of ductus venosus blood flow. In summary, the ductus venosus probably responds passively to most mechanical factors ensuring venous return to the heart. There is little evidence to support a role of the ductus venosus in regulating hepatic, umbilical venous or portal venous flow.

At birth, the umbilical circulation ceases, and the ductus venosus blood flow decreases substantially.[13] Various amounts of portal venous blood continue to flow through the ductus venosus until functional closure by 2-3 days of age.[12] Closure of the ductus venosus may be entirely a mechanical phenomenon. The umbilical vein pressure drops from 20-30 mmHg to 7 mmHg at birth, and portal vein pressure slightly exceeds this. Theoretically this causes a collapse of the ductus venosus and leads to rapid functional closure (Fig 3).[13] Some authors have shown that thromboxane A_2 analog causes immediate closure of the ductus venosus sphincter, whereas prostaglandin I_2 (PGI_2) causes relaxation of the ductus venosus sphincter mechanism (Fig 4).[14] Since thromboxane is produced by the liver, this may be an important mediator for ductus venosus closure.[14] The ductus venosus closes structurally at 15-18 days in the dog.[12] This begins in the connective tissue at the junction of the ductus venosus and the umbilical sinus.[13] This connective tissue proliferates and expands from the umbilical sinus to the termination of the ductus venosus at the left hepatic vein.[13] No thrombosis occurs in the ductus venosus at the time of closure.[13]

Ib. Hepatic Health and Function - Assessment.

There are many serum biochemical and clearance tests which have been designed to assess hepatic health and function. Among them are alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, bilirubin, ammonia tolerance test (ATT), sulfobromophthalein retention test (BSP), bile acids, and glucagon response test (GRT).

Alanine aminotransferase is one of the most common enzymes assayed in order to determine hepatic health.[15-17] ALT is found in several tissues throughout the body, but only the hepatocytes contain amounts significant enough to raise serum ALT levels.[15] ALT increases whenever there are alterations in hepatocellular membranes.[16] The half-life of ALT may be as short as 2-4 hours,[15] and levels rise quickly after hepatocellular injury.[16] ALT will also increase secondary to biliary stasis or to drug inductions.[15-17] This enzyme is specific to the liver, however its levels are increased by a multiplicity of causes. Thus ALT elevations do not lead to a specific diagnosis. Significant hepatic dysfunction, as in portosystemic shunts or cirrhosis, can be associated with normal ALT levels.[15]

Alkaline phosphatase is another enzyme commonly used to determine hepatic health.[15-17] ALP increases typically are associated with biliary stasis, and it is thought that bile salt stasis induces hepatocyte alkaline phosphatase production.[15] ALP production is sensitive to biliary stasis, however it is not liver specific since it has 8 isoenzymes. These isoenzymes are produced from liver, bone, renal tubular epithelium, placenta, intestinal epithelium, leukocytes and various tumors.[15] One of the liver

isoenzymes is steroid induced. Only the liver, bone, steroid-induced and tumor isoenzymes have long enough half lives to affect serum levels of ALP.[15] Both intra- and extrahepatic cholestasis lead to increases in ALP.[15]

Albumin is the most plentiful protein in blood and is produced by the liver. Eighty percent or more of the liver mass must be non-functional before hypoalbuminemia occurs.[15] Hypoalbuminemia is seen in chronic end-stage hepatic failure.[15]

Bilirubin is a bile pigment produced as an excretion product in heme and cytochrome catabolism.[18] Bilirubin is produced in macrophages and released in an albumin-bound (unconjugated) form into the blood. Unconjugated bilirubin is removed from blood by hepatocytes and bound to ligandin, a carrier protein. Bilirubin is conjugated in the hepatocyte to glucuronide and excreted into the bile canalicular system. Bile empties into the gastrointestinal tract in response to meals (cholecystokinin induced), and conjugated bilirubin is reduced by bacteria to stercobilinogen or urobilinogen. Ten to twenty percent of urobilinogen is reabsorbed into the blood, and most is re-excreted by the liver. Some urobilinogen is filtered by the kidneys and excreted in the urine. Hyperbilirubinemia may be caused by primary hepatocellular disease, hemolysis, or biliary obstruction, and these are differentiated by comparing serum conjugated and unconjugated bilirubin levels and testing for the presence of urine urobilinogen and urine bilirubin.[18] Typically with primary hepatocellular disease, there is an increase in conjugated and unconjugated bilirubin with relatively normal enterohepatic bile pigment circulation.[18]

Blood ammonia determinations and the ammonia tolerance test are reliable in detecting generalized hepatic disease as well as portosystemic shunting.[19,20] Ammonia is produced as a by-product of protein metabolism and from the deamination of endogenous urea and other amines by microorganisms in the intestinal tract.[20] Following absorption from the bowel, ammonia is carried to the liver by the portal system where normally hepatocytes remove greater than 90% of the ammonia.[20] Ammonia is increased in dogs with portosystemic shunts because ammonia laden portal blood bypasses the hepatic parenchyma and because there is inefficient removal of ammonia because of hepatocellular dysfunction.[20] In some dogs, resting ammonia levels are normal even in the presence of a significant portosystemic shunt, and in these dogs the ammonia tolerance test is nearly always abnormal.[19]

The sulfobromophthalein retention test is a dye retention test which relies on vascular integrity and hepatocellular function.[15,21] BSP is albumin-bound in the blood and removed and bound to ligandin by the normal hepatocyte.[15,21] Following binding, it is conjugated and excreted in the bile. BSP is an extremely sensitive indicator of hepatic disease, however 55% of the liver mass must be non-functional before abnormalities are seen in BSP retention.[15] Normal dogs show <5% retention at 30 minutes. This is a nonspecific test in that several liver abnormalities can alter BSP excretion.[15] Increases in BSP retention may be seen when hepatocellular disease leads to a failure to excrete BSP. Portosystemic shunting allows blood to bypass the liver, thus BSP doesn't reach the hepatocyte and is not excreted.

Serum bile acid concentration is a sensitive indicator of hepatic dysfunction.[22,23] It has been shown to be equal in sensitivity to the ammonia tolerance test in dogs with known portosystemic shunts.[22] Fasting or postprandial serum bile acid levels have been reported to be elevated in 85-100% of dogs with portosystemic shunts.[22,23] Bile acids are synthesized from cholesterol by hepatocytes at a constant rate, and there is an efficient enterohepatic circulation of bile acids.[15] In the liver, cholic acid and chenodeoxycholic acid are formed from cholesterol as primary bile acids. In the intestinal tract, secondary and tertiary bile acids are produced by bacterial action on primary and secondary bile acids respectively (Fig 5).[24] Bile acids have several functions within the body including cholesterol regulation. Bile acids represent the only mechanism for elimination of cholesterol in the feces.[24] Bile acids also regulate their own rate of synthesis from cholesterol by biofeedback mechanisms, and this indirectly affects the rate of cholesterol synthesis.[24] Bile acids also function as a detergent in the intestinal tract and aid in absorption of fats, fat soluble vitamins, and fat soluble drugs.[24] Bile acids function as cofactors in some enzymes including human breast milk lipase and minor pancreatic lipase.[24] The enterohepatic circulation of bile acids is extremely efficient with greater than 95% of secreted bile acids being reabsorbed from the distal intestinal tract.[24] The vast majority of these bile acids (> 80%) are extracted from portal blood on first pass by hepatocytes.[24] Bile acids are thus an endogenous recirculating substance which can be measured in blood and used as an indicator of hepatic circulatory integrity and

hepatocellular health. In dogs, this assay is much easier to perform and less subject to error than many of the other hepatic function tests.[22]

The glucagon response test is a sensitive indicator of hepatic function and mass. Hepatocellular integrity is necessary to produce, store, and break down glycogen. The liver provides glucose to other tissues of the body by two principal mechanisms, glycogenolysis and gluconeogenesis. Gluconeogenesis is accomplished by the synthesis of glucose from lactate, pyruvate, glycerol, propionate and alanine.[25] In glycogen production, glucose is first converted to glucose-6-phosphate in the hepatocyte by glucokinase. Glucose-6-phosphate is converted to glucose-1-phosphate with the conversion catalysed by phosphoglucomutase. Glucose-1-phosphate is converted to uridine-diphosphate glucose which is the building block of glycogen.[25] Many sugars and amino acids can ultimately be converted to glucose-6-phosphate and may contribute to glycogen stores. Following a meal, the liver may convert glucose equalling up to 7% of its own weight into glycogen.[25] After a 24 hour fast less than 1% of hepatic weight is glycogen.[25] Storage of glycogen allows the redistribution of glucose to the body for a prolonged period of time after a meal. It also protects the liver from the high oncotic pressure which would be present if glucose were stored in its monomeric form.[25] Glycogenolysis is the breakdown of glycogen into glucose-6-phosphate. Debranching enzyme and phosphorylase catalyse this reaction. There are several hormones which can promote glycogenolysis. Glucagon acts to promote glycogenolysis by binding to surface receptors on the hepatocyte. When bound to hepatocytes, glucagon activates the cyclic AMP cascade within

the cell which activates enzymes (phosphorylase) which cause glycogenolysis.[25] Secretin and vasoactive intestinal polypeptide probably act similarly.[25] Epinephrine, vasopressin, angiotensin II and oxytocin also promote glycogenolysis.[25]

The glucagon response test has been shown to be a sensitive diagnostic test in dogs with portosystemic shunts. This test also has been shown to be a good indicator of improved hepatic function following surgical correction of portosystemic shunts.[26]

In addition to biochemical evaluation of hepatic function, radiographic techniques may be helpful in the evaluation of hepatic disease. Survey radiographs of the abdomen may give the impression of a small or large liver, but positive contrast angiography remains the standard technique for the diagnosis of hepatic vascular anomalies.[27] There are many techniques available (see following discussion) for positive contrast portography, however operative mesenteric portography remains the best technique for the diagnosis and evaluation of portal system anomalies.[27] In addition, radiocolloid scintigraphy has been used as an aid in the diagnosis of portal system anomalies. This technique is useful in differentiating dogs with portosystemic shunts from dogs with other liver disease.[28] Quantitative hepatic scintigraphy allows estimation of total hepatic blood flow and may be useful in determining a prognosis and in evaluating the response to surgical therapy.[29]

Ic. General Introduction to Portosystemic Shunts.

Congenital portosystemic shunts have been reported in dogs, cats, horses, cattle, and man (extremely rare) and are the most common cause of hepatic encephalopathy in young dogs.[30-35] Portosystemic shunts are characterized as congenital or acquired.[36] Congenital shunts may be intrahepatic or extrahepatic and are typically singular.[30] These shunts represent persistent fetal vessels which communicate between the portal and systemic circulation.[30] Acquired shunts are typically multiple and represent previously nonfunctional fetal vessels which have enlarged and become functional because of chronic portal hypertension.[30] These shunts serve to relieve splanchnic congestion associated with portal hypertension.[30] Acquired shunts are typically extrahepatic.

Congenital portosystemic shunts have no known breed or sex predilection, however, a higher incidence is reported in purebred dogs.[30] In some studies Schnauzers, Yorkshire Terriers and German Shepherd dogs are over-represented.[30] Single congenital intrahepatic shunts tend to be seen in large breed dogs whereas single extrahepatic shunts typically are seen in small breed dogs.[36]

Portosystemic shunts generally are diagnosed at an early age with 65% being diagnosed before 1 year of age and 80% being diagnosed by 2 years of age.[30] Acquired portosystemic shunts tend to be diagnosed later in life, however age alone does not differentiate congenital and acquired shunts.[30] Porto-azygous shunts are diagnosed later in life than the other congenital shunts.[37] It is important to differentiate between acquired and congenital

shunts because single congenital shunts often are amenable to surgical correction.[36]

The diagnosis of portosystemic vascular shunts typically is based on a variety of presenting signs and laboratory data. The most common presenting complaints are related to hepatic encephalopathy with over 90% of patients showing some degree of neurologic dysfunction.[30] Commonly seen neurologic abnormalities include depression and apathy.[30] A significant number of patients show more severe neurologic signs such as ataxia, circling, head pressing and salivation.[37] Neurologic dysfunction tends to be episodic in most animals and may be related to meals. A large meal will cause rapid absorption of amino acids and often intestinal toxins which can lead to exacerbation of the neurologic dysfunction. The neurologic signs lead to anorexia which causes less toxin absorption, and this allows the neurological signs to abate.[32]

In people, hepatic encephalopathy is divided into 5 grades based on severity of dysfunction.[38] Grade I patients demonstrate mild mental dysfunction with hypocapnic hyperventilation. Grade II patients demonstrate lethargy, confusion, asterixis, and hypocapnea. In grade III, patients have progressed to an arousable stupor while maintaining normal pupillary reflexes. These patients have deep tendon reflex increases and demonstrate hypocapnic hyperventilation. The grade IV patient has progressed to unarousable coma but continues to maintain pupillary and oculocephalic reflexes. There is motor hypertonicity with decerebrate responses. These patients continue to show hypocapnic hyperventilation. In grade V, the patient has progressed to unarousable coma with loss of pupillary

and oculocephalic reflexes. Motor function has vanished by this stage, and deep tendon reflexes are depressed. Patients frequently demonstrate metabolic or respiratory acidosis.[38] These stages have not been described in animals, however they allow for categorizing increasingly severe neurologic dysfunction and could be applied to veterinary patients with some modification.

Many abnormalities contribute to hepatic encephalopathy. A decreased oxygen use is noted in brains of individuals with hepatic encephalopathy.[38] This is related to an impairment in cerebral vascular autoregulation such that the total cerebral blood flow is subnormal. These patients typically have alkalosis in earlier stages of encephalopathy followed by acidosis in the terminal stages. The acid/base abnormalities cause a further derangement in cerebral function through impairment of neurosynaptic transmission and changes in cerebral oxygen consumption.[38]

The cause of hepatic encephalopathy is not entirely known. Failure of the liver to process and release cerebral nutrients and cofactors and a failure of the liver to detoxify circulating neurotoxins have both been hypothesized to play a role in the pathogenesis of hepatic encephalopathy.[38] No specific cerebral nutrient has been identified as lacking in the blood of patients with hepatic encephalopathy, but many substances known to be neurotoxic have been identified as increased in their blood.

Ammonia is an important neurotoxin that commonly is increased in the blood and spinal fluid of patients with hepatic encephalopathy.[38] Blood ammonia concentrations do not accurately reflect brain ammonia levels and may not always reflect degrees of encephalopathy.[38] It is

suspected that there is an increased permeability to ammonium ion in the brains of patients with hepatic encephalopathy.[38] In hepatic encephalopathy, the main source of ammonia is the intestinal tract where bacteria deaminate dietary protein and hydrolyse glutamine.[39] Ammonia intoxication may cause brain dysfunction through inhibition of the chloride pump, thus interfering with the repolarization/ depolarization process.[38]

Amino acid concentration abnormalities are also present in patients with hepatic encephalopathy.[39] Aromatic amino acids (methionine, phenylalanine, tyrosine, and unbound tryptophan) typically are increased, and branched chain amino acids (leucine, isoleucine and valine) typically are decreased.[38] It is suspected that an increase in skeletal muscle catabolism (secondary to hyperinsulinism) and a failure of hepatic degradation of aromatic amino acids leads to the amino acid abnormality. The abnormal ratio of aromatic to branched chain amino acids may cause cerebral dysfunction through the competitive inhibition of essential branched chain amino acids by the high concentrations of aromatic acids. It is known that amino acid abnormalities are not as important as ammonia toxicity in hepatic encephalopathy, but branched chain amino acid therapy may aid in the treatment of hepatic encephalopathy by helping neurons detoxify ammonia.[38]

Neurotransmitter and false neurotransmitter abnormalities are also implicated in hepatic encephalopathy, and there are increased levels of serotonin in the brain of encephalopathic patients.[38] False neurotransmitters such as octopramine, tyranine, and ß-phenylethanolamine may be produced in the bowel or synthesized in the brain itself as a result

or a cause of hepatic encephalopathy. It has been suggested that these false neurotransmitters play a major role in hepatic encephalopathy, and many patients respond favorably to L-DOPA therapy. L-DOPA therapy raises true neurotransmitter levels in brain, and this may override the response to false neurotransmitters.[38] L-DOPA also increases renal clearance of ammonia, thus providing another potential explanation for its therapeutic effectiveness.[38] Other substances may play a role in hepatic encephalopathy. Acetylcholine levels may be lowered which may alter neurosynaptic transmission.[39] Mercaptans (bacterial methionine metabolism byproducts) also may play a role if they are not degraded in the liver prior to entering the general circulation.[38] Short chain fatty acids may be toxic by themselves or may potentiate the neurotoxicity of ammonia.[39]

Gastrointestinal dysfunction occurs in over 40% of dogs with portosystemic shunts. Signs seen may include anorexia, vomiting, diarrhea, or rarely, ascites.[30] Vomiting is probably centrally mediated in dogs with hepatic disease but may be related to gastritis caused by increased plasma gastrin levels. Diarrhea may be centrally mediated or related to fat malabsorption or alteration in bile acids.[40] These signs as well as lethargy and depression often are responsible for a poor nutritional status resulting in a stunted, underweight patient.[30]

Urinary tract abnormalities commonly are associated with dogs having portosystemic shunts. Uric acid and ammonium urate calculi have been reported in a high percentage of dogs with portosystemic shunts (up to 64%).[41,42] Hematuria may be the major complaint causing owners to seek

veterinary advice.[41] Ammonium urate calculi are typically seen only in hyperammonemic diseases. Both cystic and renal radiolucent calculi have been reported.[32,41,42] In the normal dog, colonic bacteria metabolize urea from dietary protein into ammonia. Ammonia is absorbed by the colon and is transported to the liver by the portal circulation.[41] In portosystemic shunt dogs, the liver is small and is not able to remove the ammonia from the portal blood. This hepatic hypofunction and the shunting of blood past the liver leads to a hyperammonemia which predisposes to ammonium biurate crystalluria.[41] This crystalluria, as well as a potential failure of the hypofunctional liver to convert uric acid to allantoin, leads to a high incidence of ammonium urate calculi.[41] Allantoin is the excretion product in the degradation of purines (Fig 6). Dogs with portosystemic shunts also exhibit a primary polydipsia with a secondary polyuria. This may be caused by changes in portal vein osmoreceptors or may be psychogenic secondary to hepatic encephalopathy.[43]

A final historical finding which is commonly associated with portosystemic shunt patients is drug sensitivity.[30] Animals with portosystemic shunts may be intolerant of barbiturates or tranquilizers and have been reported to have delayed recoveries from general anesthetic agents.[30] Hepatocellular dysfunction and decreased hepatic blood flow result in reduced hepatic clearance of these drugs.

The physical examination of the portosystemic shunt patient is not diagnostic. These patients are typically smaller than littermates and may have weight loss (42%).[30] The clinician may observe any of the aforementioned neurologic deficits or abnormalities, and the patient may be

depressed. Urinary calculi may be palpated in the urinary bladder or urethra. In many cases, the physical examination is relatively normal. Cryptorchidism has been associated with portosystemic shunts in a large number of male dogs.[41]

Radiographic examination of the abdomen in these patients is also nondiagnostic, the only abnormal finding usually being a small liver. Urinary calculi, even when present, are generally radiolucent and are not visible on survey radiographs. Contrast studies of the urinary tract will demonstrate ammonium urate stones when present.[41,42] A small percentage of patients have renal enlargement which may be caused by increased renal blood flow or by increased renal metabolic activity.[37]

The diagnosis of portosystemic shunts typically is strengthened by the results of laboratory testing. The CBC is abnormal in many cases of portosystemic shunts. Common findings include anemia which probably is caused by impaired hepatic cholesterol metabolism.[30] Many cases also show a microcytosis for which no cause has been demonstrated. This is usually associated with normochromasia. Microcytosis typically is associated with impairment in iron metabolism. In cases of portosystemic shunt, however, serum iron and total iron binding capacity are normal, suggesting that iron availability is not a problem.[44] Mechanisms suggested for the microcytosis include impaired heme synthesis or globin synthesis because of ammonia toxicity, oxidative damage to red blood cells with Heinz body formation, and abnormalities in red blood cell lipid metabolism.[44]

Hypoproteinemia is present in most portosystemic shunt patients. Hypoalbuminemia is seen in approximately 50-93% of patients, but many

have a panhypoproteinemia attributed to a reduced functional liver mass.[30,41,44]

Serum levels of hepatic enzymes such as alanine aminotranferase (ALT) and alkaline phosphatase (ALP) are typically normal to increased.[41,44] They tend to be only slightly increased when above normal, and this is explained by an absence of active hepatocellular disease.[44] Serum bilirubin is normal to slightly increased and, along with ALT and ALP, is increased the most in patients with acquired shunts secondary to chronic hepatic disease.

Sulfobromophthalein dye (BSP) retention is a very sensitive, although nonspecific, test for portosystemic shunt. It is increased in 88-97% of cases.[30,41,44,45] BSP retention is correlated with total hepatic blood flow and hepatocellular integrity. In young dogs with congenital portosystemic shunts, BSP elevation is caused primarily by altered hepatic circulation and is not markedly elevated in many cases.[30]

Resting ammonia determination and the ammonia tolerance test (ATT) are also valuable in the diagnosis of portosystemic shunt. They are abnormal in 88% of cases.[44] Unlike BSP, the ATT correlates with portal blood flow and not simple total hepatic circulation.[30] The ammonia tolerance test should not be performed on patients with high resting ammonia levels which are experiencing neurological problems because the additional ammonium load exacerbates the hepatic encephalopathy. Because of the decreased conversion of ammonia to urea, some dogs with portosystemic shunts have decreased serum urea levels.

Urinalysis in dogs with portosystemic shunts is typically normal with the exception of the presence of ammonium biurate crystals in some urine samples and the presence of secondary urinary tract infections. Urine samples may be concentrated poorly secondary to polydipsia.[43]

Hepatic biopsy can also be used to assist in the diagnosis of portosystemic shunt although it is rarely necessary. The most common findings are hepatic atrophy, vacuolization and lipidosis (Fig 7).[30] Mild portal fibrosis and inflammation are occasionally seen.

A definitive diagnosis of portosystemic shunt is made by demonstrating the shunt by portography. Portography may be done in a variety of ways, and, aside from visualization of a shunt at surgery, remains the only definitive method of diagnosis.[30]

Splenoportography is a method of visualizing the portal system in the dog. This technique is performed by introducing a polypropylene intravenous catheter percutaneously into the splenic pulp. Once the catheter is in place, 1-2 ml/kg of iodinated intravenous contrast medium is injected for each exposure made. Typically, all portograms involve ventrodorsal and lateral views. Splenoportography frequently leads to unsatisfactory results because there is positional variation in portal vein filling and fixating the spleen and needle placement are difficult.[27]

Operative mesenteric portography frequently is used in veterinary medicine. It is performed intraoperatively by catheterizing a mesenteric vein during laparotomy with a large bore (14 or 16 ga) through the needle catheter. The contrast medium injection is identical to splenoportography,

however operative mesenteric portography generally results in good visualization of the portal system in all radiographic views.[27]

Cranial mesenteric arteriography is also used occasionally to diagnose portosystemic shunts.[27] This technique is performed by injecting contrast medium into the cranial mesenteric artery by way of a catheter introduced into the femoral artery. This catheter is passed to the level of the cranial mesenteric artery under fluoroscopic control. The venous phase of the arteriogram is recorded to demonstrate portal anomalies. This technique is not consistently successful because of contrast medium dilution in the portal vein.[27]

Percutaneous transhepatic portography and transjugular transhepatic portography have also been described in the dog, however these are difficult techniques to master and require fluoroscopic control. Both techniques result in excellent visualization of the portal system.[27]

Portosystemic shunts can be diagnosed by ultrasonography, and under ideal conditions, 67% can be detected definitively using this method.[46] Hepatic scintigraphy may also be performed to estimate total hepatic blood flow and relative portal blood flow.[29] Hepatic scintigraphy in dogs with portosystemic shunts demonstrates small liver size and prominent uptake of radiocolloid by the lungs.[28] These features are absent in normal dogs.

Id. Portosystemic Shunts: Anatomy and Pathophysiology.

Portosystemic shunts have been reported to occur in a variety of locations. Extrahepatic shunts occur most commonly as gastrosplenic vein

to caudal vena caval communications. This type of shunt was present in 6 of 16 dogs in one report and in 16 of 19 dogs in another.[37,47] Other reported extrahepatic shunts include shunts from portal vein to azygous vein or portal vein to hemiazygous vein.[37] Occasionally, portosystemic shunts are associated with multiple congenital vascular anomalies as in one case of a portal vein to azygous vein shunt with atresia of the pre and post renal vena cava.[48] Intrahepatic shunts most typically are in the form of a patent ductus venosus. These usually enter the left hepatic vein but can enter the caudal vena cava directly.[36] In one series of 12 dogs with intrahepatic shunts, 5 had a shunt located in the left medial lobe, 3 had the shunt located in the right medial lobe, and 4 dogs had the shunt located in the left lateral lobe.[49] The left lateral lobe shunts typically were not located entirely intraparenchymally and were thought to represent a remnant of the left umbilical vein.[49] A single report describes a shunt located in the right lateral liver lobe which was thought to represent an atypical patent ductus venosus.[50] In all of these anatomic variations, the central theme is that splanchnic blood bypasses the liver to enter the systemic circulation.

Hepatic blood flow has been studied extensively in experimental, surgically constructed portocaval shunts. It has been found that following a portocaval shunt, there is an immediate sustained increase in hepatic arterial blood flow.[51] The amount of increase depends upon the type of shunt established with a 54% increase in end-to-side portocaval shunts and a 100% increase in side-to-side shunts.[51] It has further been observed in people with cirrhosis that an inability in some patients to

further increase arterial blood flow leads to a worsening of hepatic insufficiency following surgically created shunts.[51] In spite of arterial compensation, it is impossible for the hepatic artery to compensate for portal blood flow either in volume or quality of blood. Total hepatic blood flow following total portocaval shunt is reduced approximately 70%, and this along with a loss of trophic factors always leads to atrophy of the liver.[51] It is reported that a left gastric to inferior vena cava anastomosis in people (selective portocaval shunt) results in greater total hepatic blood flow.[51] In an attempt to compensate for the reduction in total hepatic blood flow, some researchers have arterialized the portal system following portocaval shunt. This results in prolonged survival in patients and better hepatic function.[52] This also has been shown to result in nearly normal total hepatic blood flow and no noticeable liver atrophy.[52]

There are a number of normal portosystemic communications in dogs. These include branches from the esophageal veins and cardiac (stomach) veins to the azygous (precaval) communications.[53] The postcaval communications include venous communication between the left gastric vein and the left phrenic vein. Splenorenal branches commonly are seen along with branches from the caudal pancreaticoduodenal vein to the left gonadal vein.[53] There are many other smaller "normal" communications described, however, none of these communications are functional in the adult dog. These branches can become functional under the influence of chronic portal hypertension.[53] It is reported that 1-2 months of chronic portal hypertension is necessary to cause formation of collateral shunts.[53]

Ie. Surgical Correction of Portosystemic Shunts.

There are many reports in the literature describing surgical correction of extrahepatic and intrahepatic shunts. Once identified, extrahepatic shunts are far easier to correct surgically than intrahepatic shunts. When correcting extrahepatic portosystemic shunts, the patient is placed in dorsal recumbency and a standard midline laparotomy is performed. The abdominal cavity is entered and a loop of jejunum is exteriorized to allow for mesenteric vein catheterization. A mesenteric vein is catheterized with a large bore (16 or 14 ga) through the needle catheter. This is used to monitor portal venous pressure as well as to inject contrast medium for portography. Extrahepatic shunts most commonly will pass through the epiploic foramen and can be identified by medial retraction of the duodenum with identification of the epiploic foramen or by opening the omental bursa and identifying the contributing branches of the portal vein.[36] Once the shunt vessel is identified, temporary occlusion will cause portal pressure to rise rapidly. If the vessel cannot be identified in this manner, intraoperative portography will assist in the identification of the shunt vessel.

Most authors recommend ligature attenuation of single extrahepatic shunts to a degree which increases portal pressure by 10 cm. H_2O, not to exceed a total portal pressure of 20 cm. H_2O.[30,36,54] One report used vessel diameter to determine degree of shunt attenuation, and all shunts were attenuated to a known diameter.[55] A recent report of a series of cases of surgical correction of single extrahepatic shunts recommended the use of gross observation of small bowel and colon motility and color

as well as observation of pancreas and splenic color to determine an appropriate degree of attenuation.[47] This group of cases led to the postulation of an equation (pressure after = 4.4 + 1.5 x pressure before) which may be used as a predictor of degree of attenuation.[47] Although perioperative mortality has been reported as high as 50%, this report only had a 25% mortality.[47] Other reports suggest that a 14-21% overall mortality is expected following surgical attenuation of congenital portosystemic shunts.[41]

Intrahepatic portosystemic shunts are more technically difficult to correct, and there have been a number of techniques published describing their correction. Classically, the preferred technique has been attenuation of the shunt vessel itself. Preferably this is accomplished posthepatically by ligating the shunt prior to its entering the left hepatic vein or caudal vena cava.[49] This technique usually involves some intraparenchymal dissection. Intracaval closure of intrahepatic portosystemic shunts have also been reported.[49,56] This is accomplished by temporary occlusion of hepatic blood flow or by bypassing hepatic flow with temporary shunts.[45,56] Both of these techniques are technically difficult. Mortality was nearly 50% in one study.[49] Two case reports describe simplified techniques for attenuation of intrahepatic portosystemic shunts.[50,57] One report suggests the use of intraoperative ultrasound scanning to locate shunts and to aid in attenuation.[50] Many surgeons do not have intraoperative ultrasound capability. The other report suggests ligating the extrahepatic left hepatic vein once it has been demonstrated through portography or temporary occlusion that the ductus venosus

empties into this vein.[57] This report presumes that this technique does not harm overall liver function. Both of these case reports led to good clinical results, and follow-up portography demonstrates good liver perfusion. Portal pressure dictates the degree of intrahepatic shunt attenuation, and recommended parameters for post attenuation portal pressure are identical to those for extrahepatic shunts.

It is clear that left hepatic vein attenuation is the simplest of these techniques, however the effect on overall hepatic function must be documented. Left hepatic vein attenuation nonselectively closes the shunt and compromises the venous drainage of the left and central hepatic divisions.

In addition to the above therapeutic vascular manipulation, there have been a number of experimental vascular manipulations performed on the liver in order to study human hepatic disease. Perhaps the most common vascular alteration performed has been to anastomose the portal vein and the caudal vena cava. This is referred to as an Eck fistula and is of interest because portal hypertension is relieved in this manner in people.[3] Portocaval anastomosis may be performed directly or may be performed by anastomosis of a portal contributing branch (e.g., left gastric vein) to a systemic vein (renal vein).[51] Hepatic de-arterialization has been performed on dogs experimentally both by itself and in combination with portosystemic shunt.[3,6,58] These procedures have been done in order to study hepatic blood supply and the relative importance of its various contributors. De-arterialization of the liver is also recommended in cases of massive liver trauma with uncontrollable hemorrhage.

In the only previously published studies in which hepatic vein ligation has been performed, hepatic outflow obstruction was caused in order to study the pathophysiology of ascites. In most cases, this outflow obstruction has been accomplished by banding the caudal vena cava.[59] In another report of ascites research, the hepatic veins were all ligated except for the left (superior) hepatic vein which was ligated gradually by means of a "Hepatic Vein Choker."[60]

II. JUSTIFICATION AND HYPOTHESIS.

It is clear from the previous discussion that portosystemic anomalies are a relatively complex problem in small animal medicine and surgery. Patent ductus venosus remains a difficult surgical problem, and most published techniques for correction require considerable surgical skill or specialized equipment which may not be universally available.[49,50,56] One published case report describes left hepatic vein attenuation in lieu of intracaval manipulations or intraparenchymal dissections.[57] This procedure is far easier than other published techniques, however the physiologic changes in the liver caused by ligation of the left hepatic vein are not known.[57] It is expected that the patient will survive this procedure, and the purpose of this research is to determine the effects of left hepatic vein ligation on hepatic function. The hypothesis of this project is that left hepatic vein ligation will not adversely affect hepatic function and that the left hepatic division will atrophy or develop collateral venous drainage.

III. METHODS AND MATERIALS.

Eighteen adult (1-6 years old estimated ages) mixed breed dogs of either sex were vaccinated (DA_2 PL-Parvovirus, rabies vaccine), dewormed and quarantined for two weeks. Complete physical examinations were performed on each dog. Dogs were divided into three equal groups; I, II, and III. All dogs were evaluated for hepatic function prior to surgery by means of a complete blood count (white and red blood cell counts, hemoglobin, hematocrit, differential white blood cell count), serum biochemical profile (total protein, total bilirubin, calcium, phosphorus, urea nitrogen, glucose, albumin, creatinine, alanine aminotransferase, alkaline phosphatase, sodium, potassium, chloride, and bicarbonate), sulfobromophthalein dye retention test, ammonia tolerance test, and a glucagon response test.

Sulfobromophthalein dye (BSP) retention test was performed by injecting 5 mg/kg BSP intravenously and measuring the percentage of dye retained in plasma at 30 minutes by standard technique. Blood for this test was collected in heparinized tubes, and plasma was separated within 15 minutes. The ammonia tolerance test was performed by determination of resting ammonia levels by standard technique.[19] Following this, 100 mg/kg ammonium chloride was administered by means of an orogastric tube, and post-challenge plasma ammonia concentrations were determined at 30 minutes. Plasma was separated and frozen within 15 minutes for blood ammonia determinations as previously recommended.[61]

The glucagon response test was performed by determining resting serum glucose levels followed by the intravenous administration of 0.03 mg/kg glucagon. Follow-up serum glucose determinations were made at 5, 10,

15, 30, 60, and 90 minutes post-administration. Serum for glucose determinations was separated from red blood cells within 15 minutes of drawing the blood.

Following biochemical assessment of hepatic health and function, each dog was premedicated with 0.05 mg/kg acepromazine intramuscularly. An intravenous catheter was placed in the right or left cephalic vein, and anesthesia was induced with 3-5 mg/kg thiopental sodium. Each dog was intubated with an appropriate sized endotracheal tube, and anesthesia was maintained with 2-3% halothane in oxygen at a flow rate of 1-2 l/min. Lactated ringers solution was administered intravenously at a rate of 10 ml/kg/hr throughout the anesthetic period.

Each dog was positioned in dorsal recumbency, and their abdomens were clipped from 5 cm. cranial to the xiphoid process to the pubis. The abdominal area was scrubbed with 10% povidone/iodine scrub solution and rinsed with isopropyl alcohol three times. Following the scrub, the abdominal area was painted with 10% povidone/iodine solution.

An incision was made from the cranial aspect of the xiphoid process to the umbilicus. The linea alba was identified and incised for this same distance. The falciform ligament and fat pad were excised, and the abdominal cavity was exposed. Moistened laparotomy sponges were placed over the incision edges, and a balfour retractor was used to retract the abdominal wall.

The right medial liver lobe was identified and retracted caudally, and a ligature of 2-0 dexon was placed around the distal centimeter of the lobe. This ligature was used to guillotine this portion of the right

medial liver lobe, and this portion of the liver was excised with metzenbaum scissors as a preligation liver biopsy. The representative liver sample was preserved in 10% neutral buffered formalin.

Following hepatic biopsy, a 12-15 cm. section of mid-jejunum was exteriorized, and a jejunal vein with a relatively straight course was identified. The connective tissue of the mesentery was dissected carefully from this vein, and a 14 or 16 gauge through-the-needle catheter[a] was placed into this vein until the tip rested in the proximal portion of the portal vein. This catheter was secured by 2-3 dexon ligatures. Resting portal pressures were measured by attaching this catheter to an extension tube attached to a pressure transducer. The pressure transducer was placed at a standardized height throughout the experiment. The pressure transducer was attached to a physiograph which gave a digital readout of portal pressure. Intraparenchymal pressures were measured by attaching the same pressure transducer and extension tube to a 1 inch, 18 gauge hypodermic needle which was inserted into the left medial liver lobe. The abdomen was closed by suturing the linea alba with 3/0 nylon in a simple continuous pattern, and the skin was closed with 3/0 nylon in a simple continuous pattern.

Following abdominal closure, an operative mesenteric portogram was performed. For portography, 1 ml/kg of prewarmed sodium iothalamate[b] was injected by hand by rapid bolus through an extension set connected

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[a]Venocath-14 or Venocath-16, Abbott Laboratories. North Chicago, Illinois 60064.

[b]Conray 400, Mallinckrodt, Inc. St. Louis, Missouri 63134.

to the mesenteric vein catheter. Radiographic exposures were made during injection of the last ml. Exposure factors were determined by an abdominal technique chart. Dorsoventral and right lateral recumbent views were made using high speed film in high speed screen cassettes.

Each dog was returned to surgery, and the abdomen was prepared for surgery and reopened through the previous incision line. The liver was retracted caudally, and the left hepatic vein and caudal vena cava were identified. The left triangular ligament was incised, and a plane of dissection was established between the caudal vena cava and the left hepatic vein. A right angle forcep was used to isolate the left hepatic vein, and a ligature of 2-0 polypropylene was passed around the vein. The left hepatic vein was ligated completely in groups I and II. In group III the ligature was not tightened. Immediate post ligation portal and intrahepatic pressure determinations were made using the previously described technique. The abdominal cavity and skin were closed as previously described, and a postoperative mesenteric portogram was performed as previously described. Dogs were returned to surgery, reprepped and abdomens reopened through the previous incision. Portal and intraparenchymal pressures were determined using the same technique. The mesenteric vein catheter was removed, and the mesenteric vein was ligated with 2/0 dexon suture.

The abdomen was closed using 3-0 nylon in a simple continuous pattern, and the skin was closed using 3-0 nylon in a simple continuous pattern. The dogs were recovered from anesthesia and received a single dose of 0.1 mg/kg butorphenol intramuscularly and 0.1 mg/kg xylazine epidurally for

pain control. Ampicillin (5 mg/kg IV) was given at anesthetic induction, and amoxicillin (22 mg/kg PO BID) was continued for 7 days postoperatively.

Dogs in group I had the CBC, serum biochemical profile, BSP retention test, ammonia tolerance test, and glucagon response test repeated 4 weeks postoperatively. A second laparotomy was performed using the same methods as described previously, portal and intraparenchymal pressures were determined by the previously described technique, and an operative mesenteric portogram was repeated using the previously described technique. The dogs were killed with sodium pentobarbital, and complete necropsies were performed.

The liver from each dog was weighed, and any gross abnormalities were noted. A 1½ cm. by 1½ cm. section of liver was taken from the visceral surface of the left lateral, quadrate, and right lateral lobes as representative samples of the left, central, and right hepatic divisions. These samples and those taken before ligation were fixed in 10% neutral buffered formalin, trimmed, and embedded in paraffin. Sections were cut at 8 μm and stained with hematoxylin and eosin.

Dogs in group II were handled identically to group I except the follow-up time was 24-48 hours post ligation. Group III (control) dogs had CBC, serum biochemical profile, BSP retention test, ammonia tolerance test and glucagon response test at 24 hours and at 4 weeks postoperatively. A determination of portal and intraparenchymal pressures as well as portography were performed only at 4 weeks postoperatively, and complete necropsies were performed following euthanasia as described previously. The results of white blood cell counts, ALT, ALP, albumin, bilirubin and

hepatic function tests were compared to controls and to preoperative values in groups I and II using the student's paired T test or the two sample T test. Portogram results were evaluated for circulatory abnormalities by a veterinary radiologist, and necropsy and biopsy findings were evaluated for gross and histologic abnormalities by a veterinary pathologist.

IV. RESULTS.

All dogs had normal physical examinations prior to surgery except dog 4 which had a grade 3/6 holosystolic heart murmur. This murmur had a point of maximum intensity over the left apex and probably had mitral valve endocardiosis. There were no clinical signs of cardiac failure such as exercise intolerance or coughing.

All dogs survived the experimental period. Immediately following ligation of the left hepatic vein, the lobes of the left and central hepatic divisions became severely swollen and darkly discolored suggesting acute hepatic congestion. During the terminal surgical procedure, the swelling and discoloration of these lobes had reversed and the lobes appeared grossly normal in all acute and chronic group dogs. There were no surgical complications encountered in any dog.

Recovery from anesthesia was uneventful in all groups and all dogs ate and drank spontaneously the day following surgery. There were no signs attributable to portal hypertension such as abdominal pain, bloody feces, or ascites in any dog. Ascites evaluation was based upon observation for abdominal distension and abdominal ballottement for fluid waves. There were no episodes of vomiting. Icterus did not develop at any time during the experiment. Rectal temperatures were normal to slightly elevated on the day following surgery, but temperatures did not exceed 103.5 F. All incisions healed by first intention although one dog in the control group (17) developed an incisional seroma. There was a slight serosanguinous discharge from the incision in all dogs in which the left hepatic vein was ligated. This phenomenon was not observed in the control dogs. The anesthetic protocol and drug dosages required to

produce the same level of anesthesia for the terminal surgical procedure were identical in all cases with the first anesthetic episode.

Hemograms (Table I) were normal in all dogs preoperatively and were still normal in the chronic and control dogs 4 weeks postoperatively. White blood cell counts were not statistically different ($P < 0.05$) between these groups. Hemograms in the control dogs 48 hours postoperatively demonstrated a leukocytosis without left shift, and this was significantly elevated ($P < 0.025$) when compared to preoperative values. Hemograms in the dogs (acute group) which had left hepatic vein ligation showed a severe neutrophilic leukocytosis at 48 hrs. This was characterized by a left shift in every case. The acute group's leukocyte counts were significantly different from preoperative values ($P < 0.025$), but the absolute counts were not significant when compared to control dogs.

Hepatic enzymes (ALT and ALP) (Tables II and III) were normal in all dogs except two preoperatively, and were still within normal limits in both chronically ligated and control dogs at 4 weeks postoperatively. One chronic group dog (8) had a preoperative ALT of 606. This was not associated with other signs of liver disease and the results of other hepatic tests were normal. One control group dog (4) had a preoperative ALP of 211 which was not associated with any signs of hepatic disease. Both of these dogs had normal values for these tests at 4 weeks. These groups were not significantly different from each other or from preoperative values. The control dogs demonstrated a slight increase in both ALT and ALP at 24 hours postoperatively, but only the ALP was significantly ($P < 0.025$) increased. The acute group of dogs demonstrated a massive increase

in ALT values and a milder increase in ALP similar to the control group, and both of these enzymes were significantly increased when compared to preoperative values but were not significantly different from controls.

Total bilirubin (Table IV) determinations were within normal limits in all dogs throughout the experiment. There was a significant increase in values in the control group at 4 weeks ($P < 0.05$) and the acute group at 24 hours ($P < 0.05$).

Albumin levels (Table V) were normal and statistically similar in all dogs preoperatively and were normal postoperatively in all groups except the acute group at 24 hours postoperatively. This group demonstrated a 1 gm/dl mean drop in albumin, and this was significantly lower than the preoperative value ($P < 0.0005$) and the control group values ($P < 0.01$). The control group dogs also had a significant decrease in albumin 24 hours postoperatively ($P < 0.05$), but values remained within the normal range.

Sulfobromophthalein retention tests (Table VI) were normal in all dogs preoperatively. These values were not statistically different postoperatively in the control group at 48 hours or 4 weeks. Chronic group dogs had normal BSP values at 4 weeks postoperatively, and these were not statistically significant when compared to preoperative or control values. The acute group demonstrated an increase in BSP retention to a mean value of 8.2% which was statistically significant when compared to both preoperative values ($P < 0.01$) and controls ($P < 0.05$).

Ammonia tolerance tests (Tables VII and VIII) were normal in most dogs pre- and postoperatively. Dog 8 had an increased preoperative

ammonia, however, challenge ammonia was normal at 30 minutes. Dogs 1 and 4 had normal resting ammonias, but had high challenge values. Dogs 4 and 8 were subsequently normal on all follow-up ammonia challenge tests. Dog 1 was normal 4 weeks after surgery. Ammonia determinations were somewhat erratic, and the only significant difference seen was in the control group resting values at 4 weeks. There was no significant difference between any of the groups on ammonia challenge values.

Glucagon response tests (Table IX) were extremely predictable, and all dogs preoperatively showed a large increase in blood glucose level at 5, 10, 15, and 30 minutes. Glucose levels typically returned to normal by 60-90 minutes. The chronic and control dogs demonstrated a normal glucagon response test postoperatively with few time intervals showing statistical difference (Figs. 8,9) The acute group of dogs all demonstrated a depressed glucagon response at 48 hours postoperatively, and there was statistical difference at 5, 10, 15, and 30 minutes when compared to both preoperative values and control values (Fig 10).

Radiography revealed normal portograms (Fig 11) in all dogs preoperatively with contrast medium filling all liver lobes evenly. Immediately following ligation of the left hepatic vein, portography consistently showed an absence of contrast medium in the left lateral and left medial liver lobes as well as in the papillary process of the caudate lobe (Fig 12). In all cases, the right lateral and caudate lobes showed increased amounts of contrast medium in portal veins. The right medial and quadrate lobes were variable with 4 dogs (2, 7, 10, 14) showing no contrast medium filling in the right medial lobe and 9 dogs (2, 3, 6, 7, 10, 11, 12, 13,

14) showing lack of contrast medium in the quadrate lobe. The other dogs showed normal amounts of contrast medium in these two lobes. In the control group of dogs, portography revealed normal hepatic circulatory patterns immediately following left hepatic vein dissection. One control dog (9) showed an extrahepatic portosystemic shunt four weeks postoperatively. The shunt originated at the left gastric vein and emptied into the left phrenic vein. The shunt was not visible in preoperative portograms. All other control dogs had normal portograms 4 weeks postoperatively. The acute group of dogs had repeat portograms 48 hours postoperatively. Two of six dogs (10,11) had re-established normal hepatic circulation with normal contrast medium filling of all lobes. Portograms of the remaining acute group dogs (Fig 13) were unchanged or only slightly improved from the immediate postoperative portogram showing contrast medium in the right hepatic division and only small amounts of contrast medium in the left hepatic division. Variability remained in contrast medium filling in the central hepatic division with 5 of 6 dogs showing contrast medium in the right medial lobe and 3 of 6 dogs showing contrast medium in the quadrate lobe. In the chronic group of dogs, normal hepatic circulation had been re-established at four weeks postoperatively in five of six dogs with contrast medium filling in all hepatic lobes (Fig 14). The final dog in this group (8) continued to show poor contrast medium filling in the peripheral areas of the left hepatic division with normal circulation in the right and central hepatic divisions.

Portal and intraparenchymal pressures (Tables X and XI) were obtained in all dogs prior to ligation, immediately after ligation, and prior to

euthanasia. Preligation portal pressures ranged from 3 to 8 mmHg in all groups of dogs. Intraparenchymal pressures ranged from 1 to 7 mmHg in all dogs prior to ligation of the left hepatic vein. There was no statistically significant change in portal or intraparenchymal pressures in the control group of dogs at any time after dissection.

The acute group of dogs showed an immediate intraoperative rise in mean portal pressure from 4.8 mmHg to 8.3 mmHg, and this was significant when compared to preoperative ($P < 0.025$) and control ($P < 0.05$) values. The mean portal pressure was still elevated at 9.5 mmHg 48 hours post ligation but was not statistically different from preoperative values or from immediate postligation values. Intraparenchymal pressures showed an immediate increase in mean pressure from 1.8 mmHg to 7.3 mmHg in the acute group of dogs, and this was significant when compared to preoperative values ($P < 0.0005$) and control values ($P < 0.0025$). The mean intraparenchymal pressure 48 hours post ligation was 5.8 mmHg. This was significant when compared to preoperative values ($P < 0.0025$), but not significant when compared to immediate postligation values.

The chronic group of dogs showed a similar immediate rise in mean portal pressure from a preligation value of 6.7 mmHg to 10.2 mmHg postligation, and this was significant when compared to preoperative values ($P < 0.025$). This pressure had dropped to 7.2 mmHg four weeks postligation, and this was statistically insignificant when compared to immediate preligation and immediate postligation values. Intraparenchymal pressures rose similarly from a preligation mean value of 2.5 mmHg to 8.5 mmHg postligation, and this was significant at $P < 0.001$. This pressure had dropped to 5.2

mmHg at four weeks postligation. There was no significant difference between control and experimental values, however there was a significant decrease from immediate postligation values.

All dogs had a complete necropsy performed (Table XII). Livers were weighed, and gross observations were noted. All control dogs had livers which were judged to be grossly normal. The hepatic size as a percentage of body weight ranged from 3.3-4.5% (normal 2.5-5.0%)[62] with a mean value of 3.9%. The mean postmortem liver weights were similar, and no statistical differences were found between any group. In the acute dogs, only 2 of 6 dogs were noted to have grossly enlarged livers. The hepatic size as a percentage of body weight ranged from 3.2-4.9% with a mean value of 4.3%. One dog (14) was noted to have a hydronephrotic right kidney as an incidental finding. The chronic group of dogs had hepatic sizes as a percentage of body weight ranging from 3.5-5.7% with a mean value of 4.4%. Three of these dogs had livers which were grossly considered enlarged, however only one liver exceeded the upper limit of normal (5%) in liver size as a percentage of body weight.

Histopathology of all preligation liver biopsies revealed normal hepatic architecture (Fig 15), but portal veins within the triads often varied in lumenal diameter. In two dogs (6, 14) nearly all portal veins had small lumens. Seven livers (8, 10, 12, 13, 14, 16, 18) had large and prominent lymphatics surrounding sublobular veins and portal triads, while in the remaining livers these lymphatics were collapsed. Several incidental findings were noted in these biopsies. One dog (1) had moderately severe centrilobular lipidosis, and another had centrilobular fibrosis,

congestion and hemosiderosis consistent with chronic passive congestion. This dog (4) had a grade 3/6 heart murmur consistent with atrioventricular valve disease. Two dogs (6, 17) had a mixed eosinophilic lymphocytic inflammation in a few portal areas consistent with parasite migration.

Livers from dogs killed two days following ligation had moderate to severe congestion of centrilobular regions in the left and central hepatic vein circulations. The change was always more severe in the left circulation than the central, and the right circulation was not affected. In one dog the lesion in the left circulation was so extensive that centrilobular hepatocellular necrosis was also present (Fig 16). Two dogs had random multifocal areas of hepatocellular necrosis (Fig 17), one involving the right circulation, the other involving the right and central circulations. These lesions are consistent with an acute bacterial infection entering from the portal circulation, however no bacterial cultures were performed.

Livers from three dogs killed four weeks following ligation had significant microscopic changes, while the other dogs in this group had normal livers (Fig 18). The three affected livers had scattered portal triads containing small, nearly collapsed portal veins and proliferation of endothelial-like cells forming vessels with no lumens (Fig 19). These vascular growths also occurred occasionally within the parenchyma. The left and central circulations were affected in each dog while the right circulation was unaffected. The liver section from the left circulation of one dog had a large affected area surrounded by normal liver.

The centrilobular lipidosis and chronic passive congestion seen in the preligation liver biopsies from two dogs were also seen in the liver sections taken at necropsy from these two dogs. The distended lymphatics surrounding sublobular and portal veins that were seen in many of the preligation liver biopsies were also seen in several experimental and two control dogs at necropsy.

V. DISCUSSION.

Intrahepatic portosystemic shunts are difficult to correct. The majority of these shunts can be managed successfully by the experienced veterinary surgeon, however the correction of intrahepatic shunts has been limited largely to referral centers with access to surgeons capable of advanced techniques such as hepatic circulatory bypass.[49] These shunts may also be managed by ultrasound-guided ligation techniques, but require expensive equipment and training. In the fetus of all species studied, the ductus venosus is the continuation of the left umbilical vein and usually empties into the left hepatic vein and subsequently into the caudal vena cava.[12-14,49] In patients with a patent ductus venosus, this blood flow pattern is continued postnatally, and in the majority of patients, the patent ductus venosus empties into the left hepatic vein. The shunt itself is usually located in the left or central hepatic division. Because of this relatively consistent pattern, left hepatic vein ligation has been postulated as a treatment for this anomaly. This technique requires no specialized equipment and is technically easier to perform than other published techniques. It has been successfully performed in one canine patient.[57] There are some dogs in which intrahepatic shunts do not empty into the left hepatic vein or in which the shunt travels through the right hepatic division, and these dogs are not candidates for this technique. The question raised by this proposed technique was that the effect of left hepatic vein ligation on the hepatic health of normal dogs was not known.

The left hepatic vein is the largest of the hepatic veins and is responsible for venous drainage of the left hepatic division and partially

drains the central hepatic division. The liver can respond in one of four ways to this venous outflow obstruction. The first response would be for the left and central hepatic divisions to become acutely congested and then atrophy with the right lobe becoming hyperplastic. The second response would be acute hepatic congestion, necrosis and death of the patient. The third possible response would be acute hepatic congestion followed by the development of collateral interlobar venous drainage and restoration of normal hepatic function. The fourth possibility is that extrahepatic or intrahepatic collateral portosystemic shunts could develop in response to portal or sinusoidal hypertension. The purpose of this experiment was to determine the response of the liver to left hepatic vein ligation.

The acute and long term clinical response of dogs to left hepatic vein ligation was favorable. Immediately following the ligation of the left hepatic vein, the left hepatic division lobes enlarged to approximately twice normal size, and the color darkened to a dark reddish black. This same response was noted to a lesser extent in the central division lobes while the right division lobes remained normal in size and color. This immediate response probably was caused by acute hepatic congestion secondary to the outflow obstruction.

Following recovery from anesthesia, all dogs in all groups ate and drank spontaneously. There was no abdominal pain exhibited in any dog. No dog exhibited icterus or hepatic encephalopathy at any time during the experiment. This suggests that enough functional liver mass remains after left hepatic vein ligation to support the unstressed animal.

Histopathology showed that acute hepatic necrosis generally did not result from the surgery, and this correlated well with the postoperative physical examinations. No patient exhibited clinically detectable ascites. This suggests that sustained portal hypertension did not occur as a sequel to the surgical procedure. The clinical response to the surgical procedure in normal dogs supports the use of this procedure for the treatment of clinical cases of congenital intrahepatic portosystemic shunts.

Complete blood count (CBC) results were normal on all dogs prior to surgery. Values for leukocytes ranged from 8,000-16,000 cells/cm^3 with normal distributions. Following surgery, the control group's leukocyte count 24 hours postoperatively rose to a mean value of 18,750 with an absolute neutrophilia. These dogs did not have a left shift. These results were statistically significant and are consistent with published data detailing the hematologic response to any major surgical procedure.[63] At 4 weeks postoperatively, the control group had a normal CBC. The acute group of dogs had an increase in leukocytes to a mean of 29,717 cells/cm^3. The absolute white blood cell count was not significant when compared to controls, however the differential leukocyte counts were characterized by an absolute neutrophilia with a left shift. This extreme rise in leukocytes with a left shift is not consistent with surgery alone and reflects a focus of necrosis or inflammation consistent with hepatic necrosis or inflammation.[63] The chronic group of dogs had a normal CBC at 4 weeks postoperatively with a mean leukocyte count of 9,016 cells/cm^3 and a normal cell type distribution. The CBC results

support an acute inflammatory response or acute hepatic necrosis as a result of left hepatic vein ligation. Another possible explanation is that the acute hepatic congestion led to a bacterial hepatitis which was subclinical because of the use of postoperative amoxicillin. Whichever the cause of the inflammatory leukogram postoperatively, it is clear that the condition resolves by the fourth postoperative week.

Serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP) are enzymes commonly used to assess hepatic health. ALT is used largely as an indicator of hepatocellular leakage. ALT will increase in response to any hepatic insult which alters hepatocyte membrane permeability such as hepatic necrosis, inflammation or congestion.[15] ALT is essentially liver specific in the dog. ALP is principally used in small animals as an indicator of biliary stasis. ALP is an induced enzyme which is produced in response to increased intracellular levels of bile salts. ALP is nonspecific and may be increased in response to bone or hepatic disease or as a result of increased cortisone levels in the blood. Hepatic disease of many types can increase ALP levels including biliary stasis, hepatic necrosis, hepatic lipidosis or hepatic congestion.[15] In this experiment, nearly all dogs had normal preoperative values for ALT and ALP. Those with slightly increased values had no other indication of hepatic disease, and values were normal at 4 weeks. The acute group of dogs showed a dramatic increase in ALT postoperatively. The mean value of 1,044 IU is consistent with severe hepatic inflammation, congestion, surgical manipulation or necrosis.[63] The acute group did not differ significantly from controls at 24 hours postoperatively, and it cannot be

concluded that the left hepatic vein ligation contributed to the increase in ALT. There was tremendous variability within groups in postoperative ALT values at 24 hours in both the control and acute groups (Table II).

The ALP in the acute group increased slightly but not as dramatically as ALT values. Increased ALP values also indicate hepatic inflammation, necrosis, or mild biliary stasis.[17] The chronic group had normal values 4 weeks postoperatively for ALT and ALP which were nearly identical to preoperative values. The control group of dogs had an increase in ALT 24 hours postoperatively. The mean value was 322 IU which is consistent with values seen after any major surgical procedure.[63] The ALP also showed a statistically significant rise which is consistent with any major surgical procedure.[63] The control group ALT and ALP values were normal at 4 weeks postoperatively. ALT and ALP values support an initial hepatic necrosis or inflammation, possibly secondary to acute congestion or surgical manipulation, with resolution by four weeks postoperatively. Statistically, these hepatic enzymes did not differentiate between dogs with left hepatic vein ligation and controls at 24 hours or 4 weeks postoperatively.

Bilirubin values were evaluated pre- and postoperatively in all groups, and there were no abnormal values in any dog in any group at any time interval. Bilirubin levels can increase in response to hemolysis, biliary obstruction or diffuse hepatocellular disease. Bilirubin levels correlated well with the clinical lack of icterus in any dog. The information provided by this test suggests that hepatocellular function remained active enough to prevent serum elevations in bilirubin. The control

group at 4 weeks and the acute group at 24 hours showed statistically significant increases in bilirubin levels within the normal range. These increases probably were the result of normal variability in bilirubin levels.[18] This may be indicative of a mild biliary stasis in these dogs.

Albumin is a plasma protein which is produced by the liver. Albumin levels will decrease in response to end stage hepatic disease, overhydration, gastrointestinal disease, renal disease, or blood loss. In the experimental dogs, the albumin values were within the normal range in all groups of dogs at all time intervals. The only significant differences seen were a decrease in albumin to low normal levels 24 hours postoperatively in the acute group of dogs and a decreased albumin in control dogs at 24 hours. The acute dogs decreased to a mean value of 2.5 g/dl as compared to a preoperative mean level of 3.4 g/dl and control mean of 3.1 g/dl. This decrease was possibly because of blood loss during surgery, however neither the control dogs nor the chronic dogs showed this decrease in values. The blood loss was similar in all dogs. This decrease was too rapid to be caused by hepatocellular disease and renal or gastrointestinal disease is not supported in the laboratory data or by physical examination findings. Since albumin's half life is 7-10 days, it is not possible that hepatocellular dysfunction led to this decrease in albumin.[15] It is speculated that the left hepatic vein ligation caused protein exudation through the liver capsule because of congestion within the left and central hepatic divisions. This conclusion is supported by the observation that only dogs with left hepatic vein ligations had exudation from their

incisions and sinusoidal pressures were known to be elevated immediately following left hepatic vein ligation. This is also supported by the acute swelling noted in left and central division liver lobes which resolved by 48 hours in the acute group dogs. Transcapsular fluid exudation is known to be a major compensatory mechanism in sinusoidal hypertension.[64] The decrease in albumin in the control dogs was probably caused by hemodilution secondary to intravenous fluid administration during surgery.

The above tests are all non-specific in that they will not differentiate the types or extent of hepatic damage. ALT and ALP are very sensitive tests but are not specific. Bilirubin and albumin measurements are not sensitive since they are only abnormal when hepatic disease is nearly end stage. The CBC is not specific for hepatic disease.

The sulfobromophthalein dye retention test evaluates not only hepatocellular function but also vascular integrity. Sulfobromophthalein dye (BSP) excretion requires that hepatic circulation be normal. BSP is tightly albumin-bound and will be abnormally low if a dog is hypoalbuminemic.[15,65] BSP is truly a function test since it requires circulation to the liver, uptake by the hepatocyte, binding to hepatocellular cytosolic transport proteins, biotransformation, passage through the canalicular network, and biliary excretion.[21] BSP has been shown to be a very sensitive test for clinical patients with portosystemic shunts. In the experimental dogs, BSP was normal in all cases preoperatively. The acute group had a mild rise in BSP 24 hours postoperatively to a mean value of 8.2%. This value may be falsely decreased because of the decreased albumin values

and was significantly increased over control values. This abnormal BSP retention may represent hepatocellular dysfunction or the development of collateral shunts. The latter possibility is unlikely based upon the inability of collateral shunt formation in such a short period of time and the fact that shunts were not visible radiographically.[53] The chronic dogs had normal BSP values 4 weeks postoperatively. The control dogs had normal BSP values at 24 hours and 4 weeks postoperatively. These results support an acute hepatocellular dysfunction following left hepatic vein ligation which resolves within 4 weeks. It is also possible that the right hepatic division could not extract normal amounts of BSP from blood because the left and central divisions were undercirculated and not contributing to BSP excretion.

The ammonia tolerance test is a provocative hepatic function test which has been used extensively in small animal medicine to identify animals with hepatic dysfunction. Increased blood ammonia levels are indicative of hepatocellular dysfunction or portosystemic shunting. In our experimental animals, a wide variation of resting values was identified in all three groups. The challenge values were similarly variable. Variability is probably caused by the technical difficulties known to affect blood ammonia tests.[61] The ammonia determination is a very sensitive test with a number of outside influences such as serum separation and storage techniques causing variability in the test.[61] There were few significant differences seen in any of the three groups in the pre- and postoperative values. The challenge values tended to be increased more than values previously reported (about 30%), but were within normal

limits for the laboratory where the samples were evaluated.[20] Blood ammonia values tend to increase in samples which are not processed promptly because of adenyl pyrophosphate or adenylic acid breakdown.[20] Normal resting ammonia concentrations have been reported as 45.8 ± 13 μg/ml, with normal challenge levels being 116.5 ± 50.6 μg/ml. The blood ammonia levels seen in all groups of dogs in this study were normal or slightly increased for the resting values, with slightly increased values for some of the challenge values. This suggests that even though this is a sensitive test for the diagnosis of portosystemic shunts and hepatocellular dysfunction, it was not a sensitive test in the diagnosis of the acute hepatic congestion with necrosis seen in our experimental dogs.

The glucagon response test reflects hepatocellular function as well as functional hepatic mass. This test has not been used extensively in veterinary medicine. The control group of dogs showed normal glucagon response curves pre- and postoperatively. The acute dogs showed a normal curve preoperatively with a very attenuated response curve postoperatively with statistically significant differences at many times (Table IX). The chronic group of dogs showed a normal glucagon response pre- and 4 weeks postoperatively. This test correlated well with the histologic and radiographic impressions in the three groups of dogs. The results demonstrated a poor hepatic glycogen breakdown in response to a glucagon challenge at 24 hours post hepatic vein ligation. An abnormal glucagon response curve denotes an inability of the hepatocytes to effectively raise blood glucose through glycogen breakdown. Alternatively, this may be interpreted as an inability of the liver to store normal amounts of

glucose in the form of glycogen, denoting a loss of functional hepatic mass. It is possible that hypoperfusion through the left and central division lobes prevented glucagon from reaching hepatocytes in these lobes preventing a normal response to increased glucagon levels. Despite the interpretation, it appears that the left and central division liver lobes are functionally impaired during this time period. Interpreted in the face of a normal ammonia tolerance test and only mildly increased BSP values, the glucagon response test appears to be the most sensitive and discriminating of the hepatic function tests detecting acute hepatic congestion as well as being the most accessible hepatic function test for most practitioners. The blood glucose test is also relatively insensitive to laboratory error as long as serum is separated soon after the blood is drawn.

Portal pressures are used frequently as an indicator of acute portal hypertension in the surgical management of portosystemic shunts. Normal portal pressures are $\leq$ 10 mmHg with values > 20 mmHg being considered dangerous because of the possibility of acute splanchnic congestion and death. Resting portal pressures in all dogs were below a value of 8 mmHg. With left hepatic vein ligation there was an acute rise in portal pressure seen to a mean value nearing 10 mmHg. However individual values never approached 20 mmHg. The increase in portal pressure tended to stabilize within the first hour following hepatic venous ligation. Injected contrast medium has been reported to cause mild increases in portal pressure, however control dogs showed no increase in portal pressures following left hepatic vein dissection and mesenteric vein

portography.[61] At 48 hours postoperatively the acute dogs tended to have portal pressures similar to immediate postligation pressures . At 4 weeks postoperatively the chronic dogs' portal pressures were similar to preligation values. It is not expected that acute portal hypertension would develop following left hepatic vein ligation because left and central division lobes could drain through the right hepatic division which acts as a "pressure valve." This would imply hepatofugal flow in the left branch of the portal vein. There would be some indirect influence of systemic arterial blood pressure on portal pressure because systemic hypotension could result in decreased splanchnic perfusion and this could decrease portal flow. However, if acute portal hypertension was the result of this process in normal dogs, it would have been manifested as abdominal pain, ascites, bloody diarrhea, or death. Portal pressures tended to correlate well with histology and portography, and it is presumed that the portal pressures were not significantly influenced by systemic hypotension secondary to general anesthesia.

Intraparenchymal pressure is used as a crude determinant of sinusoidal pressure.[66] Normal values are typically lower than portal pressure and greater than caudal vena cava pressure (normal values 4-6 mmHg). Immediately postligation, a slight rise in intraparenchymal pressure was seen in the chronic and acute dogs, however these values tended to return to normal even by 48 hours postoperatively. The mild intraparenchymal pressure elevations did not correlate with the degree of hepatic lobular swelling observed grossly. The method to measure these values was crude, and tissue plugging the needle or systemic hypotension secondary to general

anesthesia may have influenced recorded values. This measurement did not appear to be a useful parameter because of the number of causes of variation. Another method of estimating portal and sinusoidal pressure is hepatic wedge pressure, however this was not used because of access to direct measuring techniques.

Mesenteric vein portography was used to evaluate hepatic blood flow patterns. All dogs had normal mesenteric vein portograms before hepatic vein ligation or dissection. Two dogs were used initially to determine if right lateral or left lateral recumbent views were superior in evaluating the portal system and to determine if the ventrodorsal (VD) radiographic view was superior to the dorsoventral (DV) view. There were no visible differences between the lateral views or between the VD and DV views. Immediately after ligation all dogs evaluated had excellent flow in the right hepatic division which would be expected since the left hepatic vein plays no role in drainage of the right hepatic division. The left lobes had no contrast medium immediately after ligation since the left hepatic vein typically is the only source of drainage for this division. The variability seen in central division circulation after ligation corresponds to the variable role the left hepatic vein plays in central division drainage. Since the hepatic artery continues to supply the left and central divisions, it is suspected that hepatofugal flow is present in the left division immediately following ligation.

All but one of the control group of dogs had normal portograms at 4 weeks postoperatively. In one control dog, a left gastric vein to left phrenic vein shunt was identified. This shunt was probably missed on

pre and postdissection portograms because the mesenteric vein catheter was advanced proximal to the shunt vessel. This was possible because of minor variations in the position of the catheter tip in the portal vein. This shunt was probably not clinically significant since this dog showed no biochemical or histologic evidence of portosystemic shunt. It also presents the likelihood that subclinical but functional portosystemic shunts exist in dogs. This dog was included in the study because the shunt was not discovered until immediately prior to the dog's death, and there was no laboratory evidence that this was a clinically functional shunt. Since contrast medium is injected under pressure, this shunt may not have been functional at normal portal pressures.

The circulation was normal in chronic dogs at 4 weeks postoperatively, and this must be through the establishment of interlobar collateral venous drainage. This is known because necropsy confirmed the ligation of the left hepatic vein in all acute and chronic group dogs and direct inspection showed no visible lumens in these veins. The interlobar veins are probably nonfunctional in the normal animal. This conclusion is drawn because the hepatopedal portal circulation was almost nonexistent to the left hepatic division immediately after ligation based on portography, and normal circulation was noted in only 2 of 6 acute dogs 48 hours after ligation. If these veins were immediately functional, no hepatic congestion would occur immediately after ligation. The increase in intraparenchymal pressure may open existing but previously nonfunctional interlobar veins. Alternatively, the liver may undergo neovascularization and form new vessels to drain the left division. The mechanism

by which alternative drainage developed is an area which requires further investigation. One potential method of clarifying this mechanism would be to inject the individual hepatic divisional veins with color coded methyl methacrylate or latex and examining corrosion casts of the hepatic efferent system. It is clear that by whatever route, the left hepatic lobes must drain through other divisions since there was no recanalization seen at necropsy in the area of the left hepatic vein. There is no evidence in the literature supporting the ability of the liver to form collateral venous drainage other than by portosystemic shunts, and this observation may be important because of its implications in the further development of portosystemic shunt surgery or in liver transplantation.

Histology was normal in nearly all dogs prior to ligation and remained normal in control dogs after ligation. Surgically all livers had a grossly normal appearance at the second laparotomy. At necropsy, all control dogs' livers were grossly of normal size and were normal size on a percentage of body weight basis. The acute group livers were judged to be enlarged grossly, however no dog had a liver exceeding 5% of body weight (the upper limit of normal).[62] Likewise, the chronic group livers were judged to be grossly enlarged 50% of the time, but these livers were also less than 5% of body weight in all but one case. It is unclear why these livers were judged to be enlarged based upon clinical impression, because no significant differences were found with hepatic weights. The extrahepatic shunt seen in the control dog on portography was identified at necropsy.

Histologically, the acute group had severe centrolobular congestion present in the left and central division lobes which are the lobes

drained by the left hepatic vein. The hypoxia which is produced by congestion may be severe enough to cause acute hepatic necrosis as seen in one dog. Centrolobular necrosis would be likely with severe posthepatic congestion since the central vein area of the acinus (Zone 3) is the area of lowest oxygenation.[67] Four weeks following ligation, the hepatic congestion and necrosis resolved, and the chronic dogs' livers showed proliferation of small venules or capillaries which represents an attempt to re-establish hepatopedal circulation.

Histologically, centrolobular lipidosis was seen in one dog preoperatively. Hepatic lipidosis can be caused by overnutrition, starvation, or other metabolic diseases (Cushing's disease, diabetes mellitus, hypothyroidism). Neither dog had evidence of systemic disease and it is likely that these dogs were in a poor nutritional plane prior to the experiment since they were strays prior to being impounded. This histologic lesion was considered incidental in this dog. The one dog with preexisting centrolobular hepatic congestion probably had early cardiac insufficiency because a cardiac murmur was present. This dog was a control dog and had no increase in congestion at necropsy. The dogs with parasitic migration were also asymptomatic for generalized hepatic disease. The only other abnormalities in any of these dogs were an increased ALP in dog 4 and increased challenge ammonia values in dogs 1 and 4. Both of these dogs had normal values at 4 weeks. Preoperative biopsies were evaluated at the same time as the necropsy specimens such that these preexisting lesions were unsuspected at the time of the

experiment, however all of these lesions were considered incidental and probably had no influence on the experimental results.

The random pattern, multifocal necrosis seen in two dogs was consistent with bacterial hepatitis. No cultures were taken at necropsy because this condition was not suspected. Bacterial stains of histologic sections were negative for bacteria, however, this is not a sensitive test. Bacterial hepatitis is known to occur in the dog secondary to hepatic injury or vascular stasis. Prophylactic antibiotic use is encouraged with hepatic or biliary tree surgery in the dog, and antibiotics were used in this experiment.[49] The assumed bacterial hepatitis in these two dogs was subclinical and probably resulted from venous stasis and hypoxia following left hepatic vein ligation.

When all the data is considered as a whole, a distinct progression of events is established. Immediately following ligation of the left hepatic vein, acute passive hepatic congestion ensues. This congestion is confined to the left and central hepatic divisions with all portal blood filtering through the right hepatic division and to a variable extent through the central hepatic division. Reversal of portal flow probably occurs in the left division because of the continued flow in the hepatic arteries, however further studies are necessary to prove this. Doppler flow ultrasound studies would possibly clarify the blood flow patterns. This congestion may be accompanied by acute centrolobular hepatic necrosis which is probably caused by the hypoxia which accompanies congestion. This congestion and necrosis is evidenced in the laboratory data by the observed neutrophilia with a left shift. Hepatic function was also

impaired as evidenced by a poor response to glucagon in the glucagon response test and by elevated BSP values. This congestion and necrosis resolved by the fourth postoperative week in all cases. Evidence for this progression of events is also supported by portography and histopathology. There are several ways in which the liver can respond to chronic congestion. The first way would be to develop multiple extrahepatic portosystemic shunts. These typically are formed in response to sustained portal hypertension and are formed through predetermined normally non-functional vessels.[68] This response was not seen on portography, and the portal pressures measured were never high enough to cause this type of response.

A second response would be for the liver to undergo extensive necrosis acutely with resultant death of the animal. This acute necrosis may be secondary to congestion and hepatic circulatory insufficiency or secondary to bacterial overgrowth. This was not seen in any animal although there was histologic evidence of bacterial hepatitis with random necrosis in the right hepatic division of one acute group dog and one control dog. Bacterial hepatitis would be likely if dogs were not treated with antibiotics following surgery. A third possibility would be for the left and central hepatic divisions to undergo atrophy secondary to vascular insufficiency as reportedly occurred in one patent ductus venosus patient secondary to left hepatic vein attenuation.[57] This response did not occur as evidenced by the histology.

Another response is for the left and central hepatic divisions to re-establish normal circulation through alternative drainage pathways.

This was the response seen at four weeks postoperatively. Since the left hepatic vein was still ligated completely at necropsy, the venous drainage probably was through the development of interlobar drainage alternatives. These vessels were not identified at gross necropsy, probably because they are very small.

VI. CONCLUSIONS.

Left hepatic vein ligation does not result in permanent hepatic functional or anatomic derangements. It does cause an acute hepatic congestion which lasts at least 48 hours but clearly resolves by the fourth postoperative week. It appears that this technique could be an uncomplicated alternative treatment for dogs with left or central hepatic divisional patent ductus venosus.

It is clear that further investigations are needed in two areas. The first area would be to define whether and how collateral venous drainage forms. This experiment did not define the alternative drainage pattern which developed and the pathway can only be speculative at this point. The second area which needs definition is the pattern of blood flow immediately after ligation. It is thought that hepatofugal flow must occur. Hemodynamic observations are needed to confirm this hypothesis.

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TABLE I

Total White Blood Cell Counts (cells/mm^3)				
Dog Number		**Preoperative**	**Postoperative - 24 hours**	**Postoperative - 4 weeks**
Control Group	1	8,400 A	11,200 B	6,500 C
	4	8,900	9,700	3,100
	9	10,900	17,500	6,300
	16	12,300	23,400	
	17	13,200	22,700	15,200
	18	11,200	28,000	13,500
Acute Group	10	12,900 D	32,500 E	
	11	9,000	25,200	
	12	15,900	55,000	
	13	8,000	17,500	
	14	9,700	28,000	
	15	11,900	20,100	
Chronic Group	2	12,900 F		5,500 G
	3	8,400		7,500
	5	15,300		10,100
	6	13,900		11,200
	7	15,800		11,800
	8	11,100		8,000

Mean ± S.D.

A: 10817 ± 1873
B: 18750 ± 7256
C: 8920 ± 5172
D: 11233 ± 2926

E: 29717 ± 13506
F: 12900 ± 2781
G: 9017 ± 2424

Statistical Analysis

A:B - * ($P < 0.025$)
B:C - NS
A:D - NS
A:F - NS

D:E - * ($P < 0.025$)
E:B - NS
F:G - NS
G:C - NS

* = Statistically significant

NS = Not significant

TABLE II

Alanine Aminotransferase (U/1)				
Dog	Number	Preoperative	Postoperative - 24 hours	Postoperative - 4 weeks
Control Group	1	48 A	34 B	44 C
	4	24	24	17
	9	46	103	27
	16	30	102	
	17	40	215	28
	18	40	1450	22
Acute Group	10	27 D	252 E	
	11	29	478	
	12	38	2070	
	13	22	1030	
	14	33	86	
	15	28	2150	
Chronic Group	2	26 F		25 G
	3	26		20
	5	26		27
	6	19		18
	7	23		29
	8	606		45

Mean ± S.D.

A: 38 ± 9
B: 322 ± 557
C: 28 ± 10
D: 30 ± 5

E: 857 ± 981
F: 121 ± 238
G: 27 ± 10

Statistical Analysis

A:B - NS
A:C - NS
A:D - NS
A:F - NS

D:E - * (P < 0.025)
E:B - NS
F:G - NS
G:C - NS

* = Statistically significant

NS = Not significant

TABLE III

Serum Alkaline Phosphatase (U/1)				
Dog Number		Preoperative	Postoperative - 24 hours	Postoperative - 4 weeks
Control Group	1	35 A	125 B	106 C
	4	211	196	81
	9	48	183	93
	16	32	150	
	17	58	62	70
	18	43	131	20
Acute Group	10	30 D	134 E	
	11	44	90	
	12	53	162	
	13	39	266	
	14	78	125	
	15	39	144	
Chronic Group	2	108 F		88 G
	3	81		100
	5	38		86
	6	101		87
	7	27		114
	8	52		107

Mean ± S.D.

A: 71 ± 69
B: 141 ± 48
C: 74 ± 33
D: 47 ± 17

E: 154 ± 60
F: 68 ± 34
G: 97 ± 12

Statistical Analysis

A:B - * (P < 0.025)
A:C - NS
A:D - NS
A:F - NS

D:E - * (P < 0.01)
E:B - NS
F:G - NS
G:C - NS

* = Statistically significant NS = Not significant

TABLE IV

Total Bilirubin (mg/dl)				
Dog	Number	Preoperative	Postoperative - 24 hours	Postoperative - 4 weeks
Control Group	1	0.07 A	0.17 B	0.07 C
	4	0.02	0.36	0.15
	9	0.08	0.18	0.19
	16	0.16	0.13	
	17	0.03	0.49	0.43
	18	0.17	0.14	0.31
Acute Group	10	0.02 D	0.60 E	
	11	0.12	0.18	
	12	0.21	0.30	
	13	0.11	0.24	
	14	0.06	0.14	
	15	0.06	0.25	
Chronic Group	2	0.05 F		0.08 G
	3	0.02		0.11
	5	0.05		0.17
	6	0.09		0.15
	7	0.30		0.06
	8	0.16		0.03

Mean ± S.D.

A: 0.09 ± 0.06
B: 0.25 ± 0.15
C: 0.23 ± 0.14
D: 0.10 ± 0.07
E: 0.29 ± 0.16
F: 0.11 ± 0.10
G: 0.10 ± 0.05

Statistical Analysis

A:B - NS
A:C - * ($P < 0.05$)
A:D - NS
A:F - NS
D:E - * ($P < 0.05$)
E:B - NS
F:G - NS
G:C - NS

* = Statistically significant NS = Not significant

TABLE V

Serum Albumin (g/dl)				
Dog Number		Preoperative	Postoperative - 24 hours	Postoperative - 4 weeks
Control Group	1	3.1 A	3.1 B	3.4 C
	4	3.3	3.3	3.3
	9	3.2	3.1	2.9
	16	3.8	3.3	
	17	3.3	2.7	3.0
	18	3.4	2.9	2.7
Acute Group	10	3.5 D	2.8 E	
	11	3.0	2.0	
	12	3.2	2.3	
	13	3.5	3.0	
	14	3.3	2.6	
	15	3.8	2.5	
Chronic Group	2	2.9 F		3.0 G
	3	3.1		3.5
	5	3.0		3.3
	6	2.8		3.0
	7	3.1		3.3
	8	3.1		3.3

Mean ± S.D.

A: 3.4 ± 0.24
B: 3.1 ± 0.23
C: 3.1 ± 0.29
D: 3.4 ± 0.28
E: 2.5 ± 0.36
F: 3.0 ± 0.13
G: 3.2 ± 0.20

Statistical Analysis

A:B - * ($P < 0.05$)
A:C - NS
A:D - NS
A:F - * ($P < 0.01$)
D:E - * ($P < 0.0005$)
E:B - * ($P < 0.01$)
F:G - NS
G:C - NS

* = Statistically significant

NS = Not significant

TABLE VI

Sulfobromophthalein (% retention)				
Dog Number		Preoperative	Postoperative - 24 hours	Postoperative - 4 weeks
Control Group	1	2.3 A	0.5 B	6.2 C
	4	1.0	0.6	6.0
	9	2.5	2.1	3.7
	16	4.0	9.5	
	17	2.9	3.8	3.4
	18	3.0	3.3	1.6
Acute Group	10	1.6 D	4.5 E	
	11	1.5	4.5	
	12	4.6	16	
	13	3.3	7.5	
	14	2.8	6.7	
	15	4.6	10.2	
Chronic Group	2	4.1 F		4.8 G
	3	5.3		3.0
	5	2.5		3.5
	6	3.8		2.8
	7	5.1		3.2
	8	1.5		2.2

Mean ± S.D.

A: 2.6 ± 0.99
B: 3.3 ± 3.3
C: 4.2 ± 1.9
D: 3.1 ± 1.4

E: 8.2 ± 4.4
F: 3.7 ± 1.5
G: 3.3 ± 0.88

Statistical Analysis

A:B - NS
A:C - NS
A:D - NS
A:F - NS

D:E - * ($P < 0.01$)
E:B - * ($P < 0.05$)
F:G - NS
G:C - NS

* = Statistically significant

NS = Not significant

TABLE VII

Resting Ammonia (µg/dl)				
Dog Number		Preoperative	Postoperative - 24 hours	Postoperative - 4 weeks
Control Group	1	79 A	62 B	70 C
	4	18	13	26
	9	22	18	79
	16	18	104	
	17	18	88	70
	18	31	119	88
Acute Group	10	44 D	92 E	
	11	97	62	
	12	88	35	
	13	66	84	
	14	57	35	
	15	97	110	
Chronic Group	2	18 F		26 G
	3	31		32
	5	97		20
	6	62		35
	7	18		13
	8	189		4

Mean ± S.D.

A: 31 ± 24
B: 67 ± 44
C: 67 ± 24
D: 75 ± 22
E: 70 ± 31
F: 69 ± 66
G: 22 ± 12

Statistical Analysis

A:B - NS
A:C - * $(P < 0.05)$
A:D - * $(P < 0.01)$
A:F - NS
D:E - NS
E:B - NS
F:G - NS
G:C - NS

* = Statistically significant

NS = Not significant

TABLE VIII

Post-Challenge Ammonia (μg/dl)				
Group	Dog Number	Preoperative	Postoperative - 24 hours	Postoperative - 4 weeks
Control Group	1	317 A	242 B	114 C
	4	246	31	92
	9	31	57	102
	16	88	158	
	17	75	207	101
	18	158	141	105
Acute Group	10	128 D	189 E	
	11	158	110	
	12	136	75	
	13	114	128	
	14	101	102	
	15	141	149	
Chronic Group	2	62 F		62 G
	3	141		114
	5	31		163
	6	88		147
	7	57		118
	8	53		9

Mean ± S.D.

A: 153 ± 110
B: 139 ± 82
C: 103 ± 8
D: 130 ± 20
E: 126 ± 40
F: 72 ± 38
G: 102 ± 57

Statistical Analysis

A:B - NS
A:C - NS
A:D - NS
A:F - NS
D:E - NS
E:B - NS
F:G - NS
G:C - NS

* = Statistically significant NS = Not significant

TABLE IX

Glucagon Response Test (mg/dl)							
Time (min)		Control Group - Dog Number					
		1	4	9	16	17	18
A	0	99	91	102	105	96	104
	5	199	155	169	173	159	180
Pre-	10	261	186	162	224	126	236
operative	15	268	194	124	209	118	254
	30	243	169	69	130	307	227
	60	149	98	109	91	278	133
	90	102	87	116	89	83	115
B	0	106	102	95	95	76	91
	5	150	139	122	157	133	186
Post-	10	197	174	141	160	146	205
operative	15	225	201	131	159	141	217
24 hours	30	223	184	91	117	107	179
	60	97	96	86	101	88	119
	90	86	85	92	96	96	105
C	0	106	81	93		96	96
	5	185	137	123		152	159
Post	10	210	154	137		181	193
operative	15	256	176	130		208	223
4 weeks	30	223	184	113		155	153
	60	108	78	87		78	76
	90	93	71	79		81	76
Time (min)		Acute Group - Dog Number					
		10	11	12	13	14	15
D	0	95	86	83	97	99	90
	5	172	183	188	163	162	155
Pre-	10	174	232	218	207	200	197
operative	15	153	226	222	229	199	202
	30	101	162	120	190	139	106
	60	93	80	98	107	92	95
	90	92	94	105	90	95	99
E	0	92	92	55	89	113	87
	5	118	128	87	112	132	106
Post	10	122	139	91	123	133	105
operative	15	120	142	96	125	129	111
24 hours	30	107	133	76	108	106	96
	60	99	113	83	87	114	95
	90	95	112	78	80	110	90

TABLE IX, continued...

Glucagon Response Test (mg/dl)							
Time (min)		Chronic Group - Dog Number					
		2	3	5	6	7	8
F	0	98	104	90	90	89	85
	5	155	166	164	109	149	107
Pre-	10	176	189	229	115	202	123
operative	15	174	178	238	114	225	128
	30	149	161	176	105	195	121
	60	104	111	96	75	86	117
	90	90	96	89	76	78	106
G	0	88	100	86	87	114	107
	5	129	145	146	127	152	148
Post-	10	141	182	204	149	212	199
operative	15	133	181	197	131	228	199
4 weeks	30	85	144	151	83	239	160
	60	70	116	96	72	138	99
	90	75	101	79	80	93	73

Means ± S.D.

A: 0 min: 100 ± 5
5 min: 173 ± 16
10 min: 199 ± 50
15 min: 195 ± 63
30 min: 191 ± 85
60 min: 143 ± 70
90 min: 99 ± 15

B: 0 min: 94 ± 10
5 min: 149 ± 22
10 min: 171 ± 26
15 min: 179 ± 40
30 min: 150 ± 52
60 min: 98 ± 12
90 min: 93 ± 7

C: 0 min: 94 ± 9
5 min: 151 ± 23
10 min: 175 ± 29
15 min: 199 ± 48
30 min: 166 ± 41
60 min: 85 ± 13
90 min: 80 ± 8

D: 0 min: 92 ± 6
5 min: 171 ± 13
10 min: 205 ± 20
15 min: 205 ± 28
30 min: 136 ± 35
60 min: 94 ± 9
90 min: 82 ± 36

E: 0 min: 88 ± 19
5 min: 114 ± 16
10 min: 119 ± 18
15 min: 121 ± 16
30 min: 104 ± 19
60 min: 99 ± 13
90 min: 94 ± 14

TABLE IX, continued...

Group	Time	Value	Time	Value
F:	0 min:	93 ± 7	30 min:	151 ± 34
	5 min:	142 ± 27	60 min:	98 ± 16
	10 min:	172 ± 45	90 min:	89 ± 11
	15 min:	176 ± 50		
G:	0 min:	97 ± 12	30 min:	144 ± 58
	5 min:	141 ± 10	60 min:	99 ± 26
	10 min:	181 ± 30	90 min:	84 ± 11
	15 min:	178 ± 39		

Statistical Analysis

Comparison	Result
A:B	0 min - NS
	5 min - * (P < 0.05)
	10 min - * (P < 0.05)
	15 min - NS
	30 min - NS
	60 min - NS
	90 min - NS
A:C	0 min - NS
	5 min - * (P < 0.01)
	10 min - NS
	15 min - NS
	30 min - NS
	60 min - NS
	90 min - * (P < 0.025)
A:D	0 min - * (P < 0.05)
	5 min - NS
	10 min - NS
	15 min - NS
	30 min - NS
	60 min - NS
	90 min - NS
A:F	0 min - NS
	5 min - * (P < 0.05)
	10 min - NS
	15 min - NS
	30 min - NS
	60 min - NS
	90 min - NS
D:E	0 min - NS
	5 min - * (P < 0.005)
	10 min - * (P < 0.0005)
	15 min - * (P < 0.005)
	30 min - * (P < 0.025)
	60 min - NS
	90 min - NS
E:B	0 min - NS
	5 min - * (P < 0.01)
	10 min - * (P < 0.005)
	15 min - * (P < 0.005)
	30 min - * (P < 0.05)
	60 min - NS
	90 min - NS
F:G	0 min - NS
	5 min - NS
	10 min - NS
	15 min - NS
	30 min - NS
	60 min - NS
	90 min - NS
G:C	0 min - NS
	5 min - NS
	10 min - NS
	15 min - NS
	30 min - NS
	60 min - NS
	90 min - NS

*Statistically significant

NS = Not significant

TABLE X

Portal Pressures (mmHg)					
	Dog Number	Pre Ligation	Immediate Post Ligation	Post Ligation - 48 hours	Post Ligation - 4 weeks
Control Group	1	6 A	6 B		10 C
	4	7	8		5
	9	6	6		3
	16	6	6		
	17	7	7		7
	18	8	7		3
Acute Group	10	8 D	7 E	8 F	
	11	3	10	7	
	12	7	9	8	
	13	4	8	6	
	14	3	6	22	
	15	4	10	6	
Chronic Group	2	6 G	16 H		7 I
	3	7	10		4
	5	8	10		6
	6	7	8		6
	7	5	10		15
	8	7	10		5

Mean ± S.D.

A: 6.7 ± 0.8
B: 6.7 ± 0.8
C: 5.6 ± 3.0
D: 4.8 ± 2.1
E: 8.3 ± 1.6
F: 9.5 ± 6.2
G: 6.7 ± 1.0
H: 10.7 ± 2.7
I: 7.2 ± 4.0

Statistical Analysis

A:B - NS
A:C - NS
A:D - NS
A:G - NS
B:C - NS
D:E - * (P < 0.025)
D:F - NS
E:B - * (P < 0.05)
E:F - NS
G:H - * (P < 0.025)
G:I - NS
H:B - * (P < 0.005)
H:I - NS
I:C - NS

* = Statistically significant   NS = Not significant

TABLE XI

Intraparenchymal Pressures (mmHg)					
	Dog Number	Pre Ligation	Immediate Post Ligation	Post Ligation - 48 hours	Post Ligation - 4 weeks
Control Group	1	3 A	3 B		8 C
	4	5	4		3
	9	5	4		1
	16	3	5		
	17	5	2		0
	18	7	5		2
Acute Group	10	1 D	6 E	6 F	
	11	3	8	5	
	12	3	7	7	
	13	2	7	3	
	14	3	7	8	
	15	2	9	6	
Chronic Group	2	3 G	12 H		5 I
	3	2	4		2
	5	2	7		10
	6	2	9		4
	7	4	11		2
	8	2	11		6

Mean ± S.D.

A: 4.7 ± 1.5
B: 3.8 ± 1.2
C: 2.8 ± 3.1
D: 2.3 ± 0.8
E: 7.3 ± 1.0
F: 5.8 ± 1.7
G: 2.5 ± 0.8
H: 9.0 ± 3.0
I: 4.8 ± 3.0

Statistical Analysis

A:B - NS
A:C - NS
A:D - * ($P < 0.01$)
A:G - * ($P < 0.02$)
B:C - NS
D:E - * ($P < 0.0005$)
D:F - * ($P < 0.0025$)
E:B - * ($P < 0.0005$)
E:F - NS
G:H - * ($P < 0.001$)
G:I - NS
H:B - * ($P < 0.01$)
H:I - * ($P < 0.05$)
I:C - NS

* = Statistically significant
NS = Not significant

TABLE XII

Gross Necropsy Observations				
Dog No.	Group	Liver Weight (g)	Liver weight / Body weight x 100 (%)	Gross Observations
1	Control	387	4.5 **A**	Normal liver, no ligature
4	Control	452	3.3	Normal liver, loose ligature
9	Control	250	4.0	Normal liver, loose ligature
17	Control	706	3.9	Normal liver, loose ligature
18	Control	594	3.8	Normal liver, loose ligature
10	Acute	990	4.9 **B**	Enlarged liver
11	Acute	796	4.5	No comments
12	Acute	546	3.2	Normal liver
13	Acute	876	4.5	Normal liver
14	Acute	800	4.6	Enlarged liver, right hydronephrosis
15	Acute	661	4.3	No comments
2	Chronic	480	4.6 **C**	Enlarged liver
3	Chronic	410	3.5	Normal liver
5	Chronic	404	3.9	Normal liver
6	Chronic	472	4.1	Enlarged liver
7	Chronic	286	4.6	Normal liver
8	Chronic	272	5.7	Slightly enlarged liver

Means ± S.D.

A: 3.9 ± 0.43
B: 4.3 ± 0.59
C: 4.4 ± 0.76

Statistical Analysis

A:B - NS
A:C - NS
B:C - NS

NS = Not significant

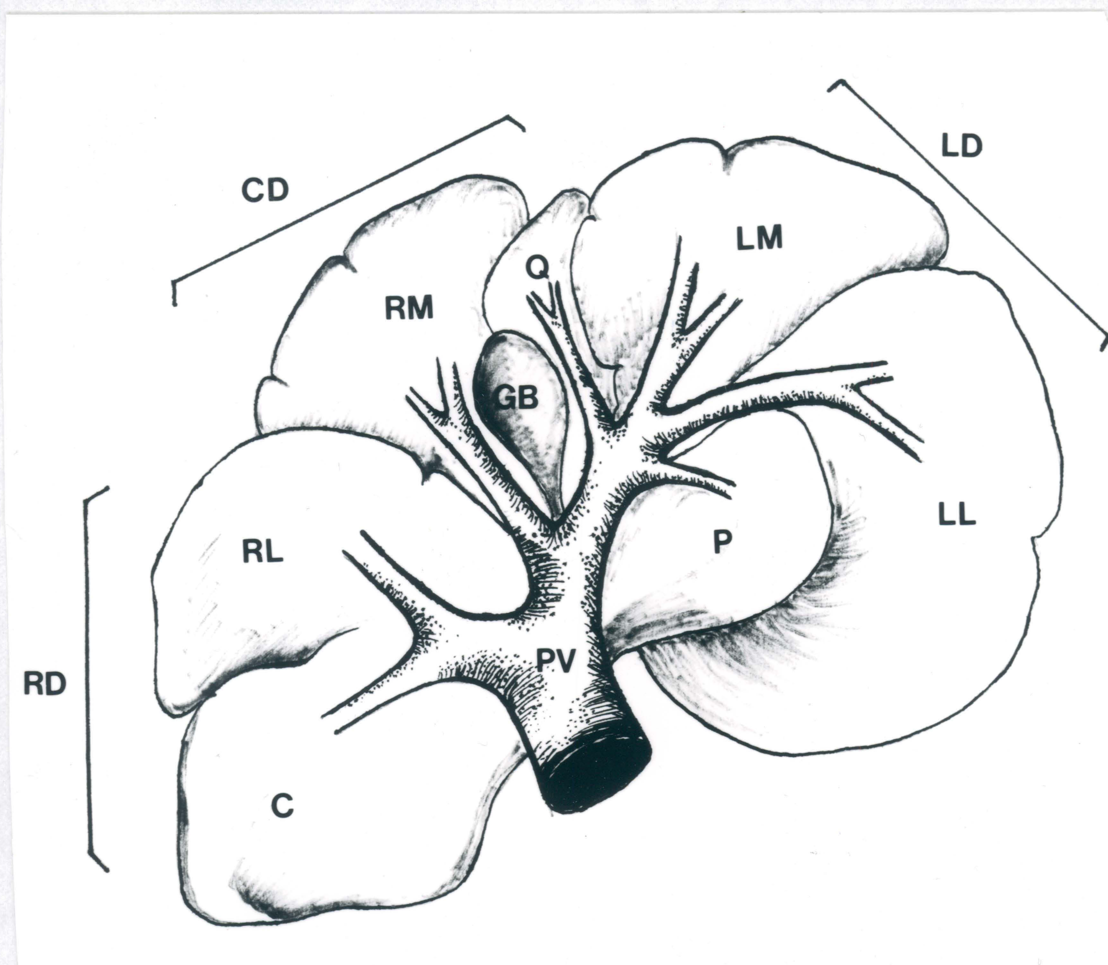

Figure 1: Hepatic lobar anatomy demonstrating lobes and divisions. PV = portal vein; LL = left lateral lobe; LM = left medial lobe; Q = quadrate lobe; RM = right medial lobe; RL = right lateral lobe; C = caudate lobe; P = papillary process of caudate lobe; RD = right division; CD = central division; LD = left division; GB = gallbladder.

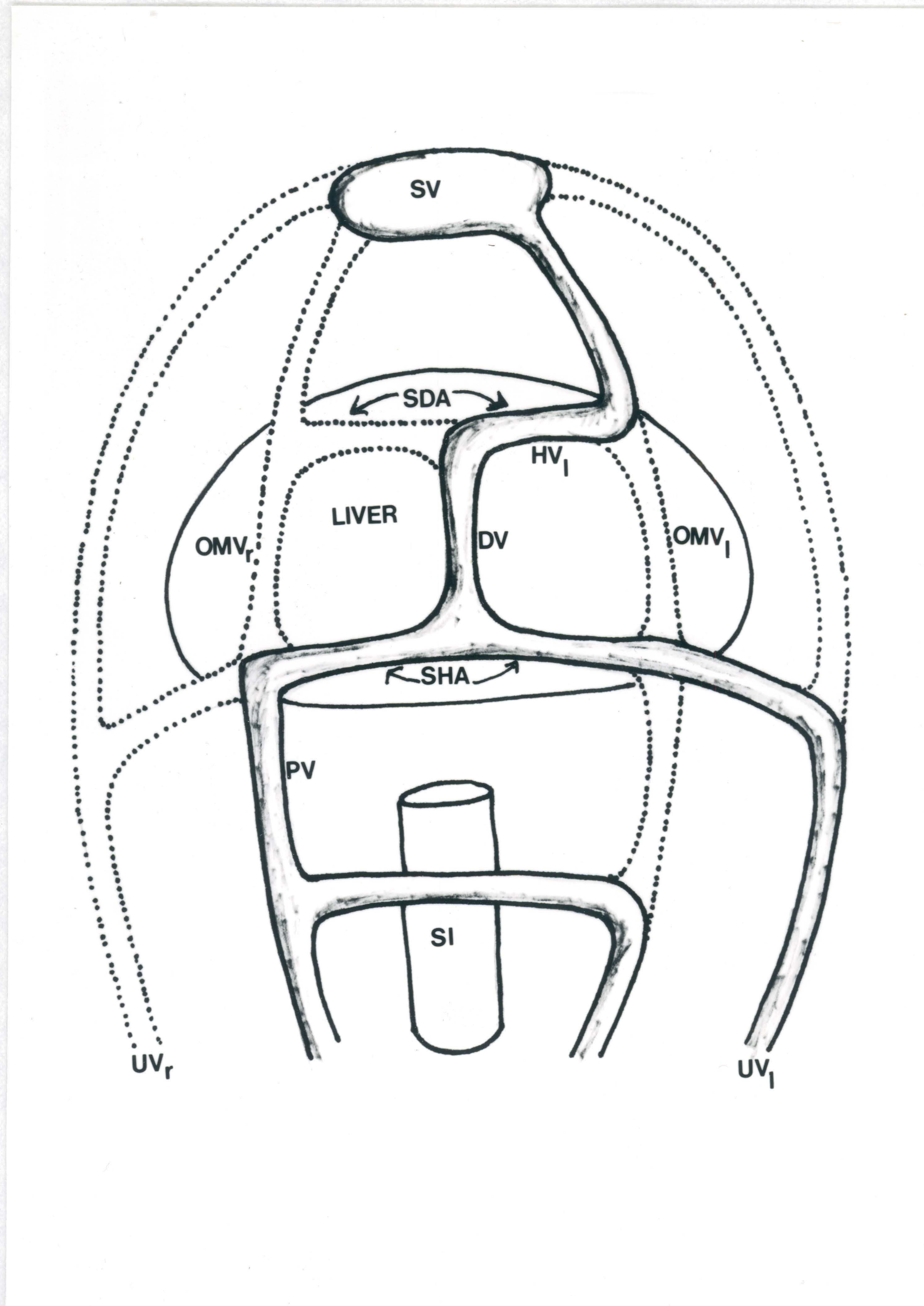

Figure 2: Embryological development of ductus venosus. All vessels present in 5 mm human embryo but only solid vessels present in 9 mm embryo. Note ductus venosus empties into left hepatic vein. SI = small intestine; PV = portal vein; UV_L = left umbilical vein; UV_R = right umbilical vein; OMV_L = left omphalomesenteric vein; OMV_R = right omphalomesenteric vein; DV = ductus venosus; HV_L = left hepatic vein; SDA = subdiaphragmatic anastomosis; SHA = subhepatic anastomosis. Adapted from Edelstone D.I. Regulation of blood flow through the ductus venosus. J Dev Phys 1980; 2:219-38.

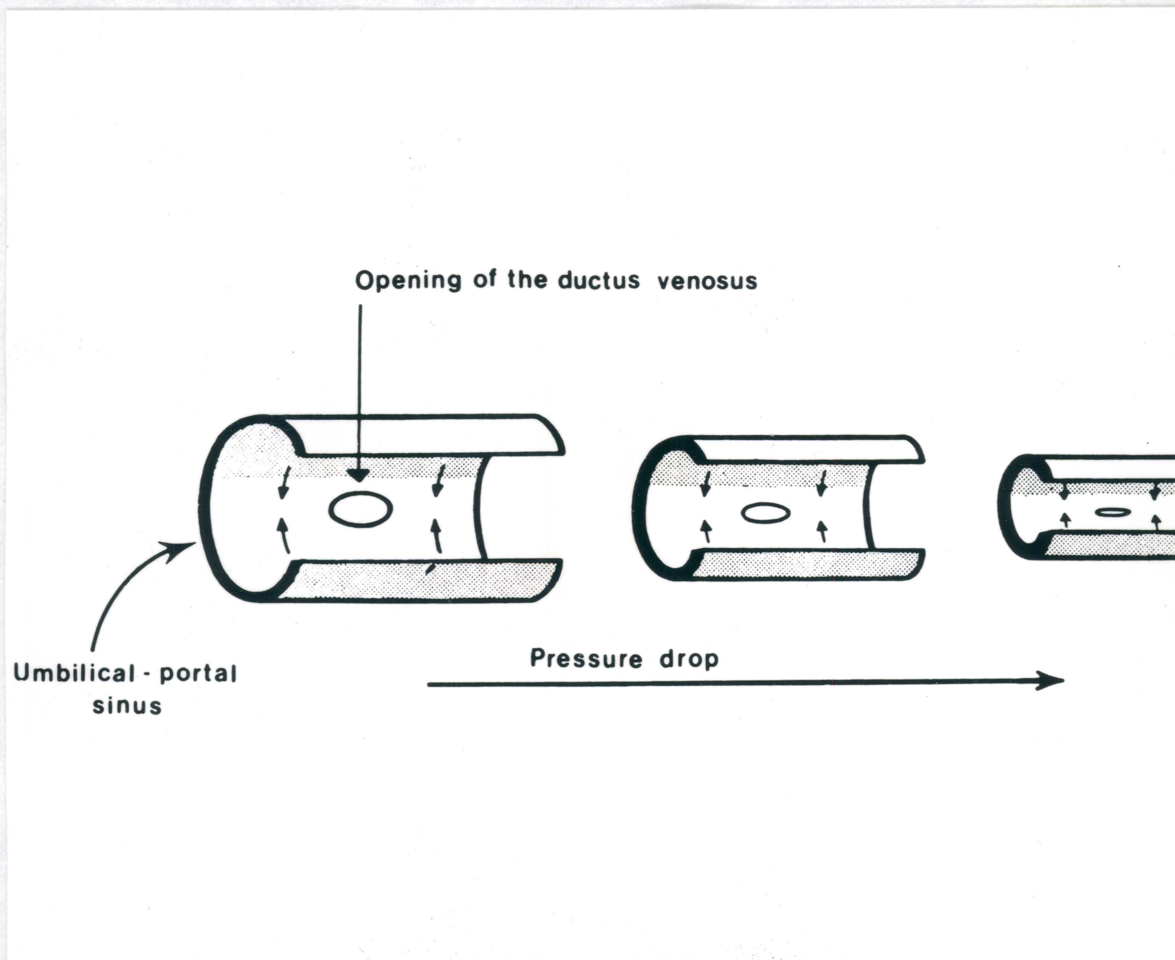

Figure 3: Ductus venosus closure mechanism. As umbilical portal pressure falls, the origin of the ductus venosus becomes smaller. From Edelstone D.I. Regulation of blood flow through the ductus venosus. J Dev Phys 1980; 2:219-38.

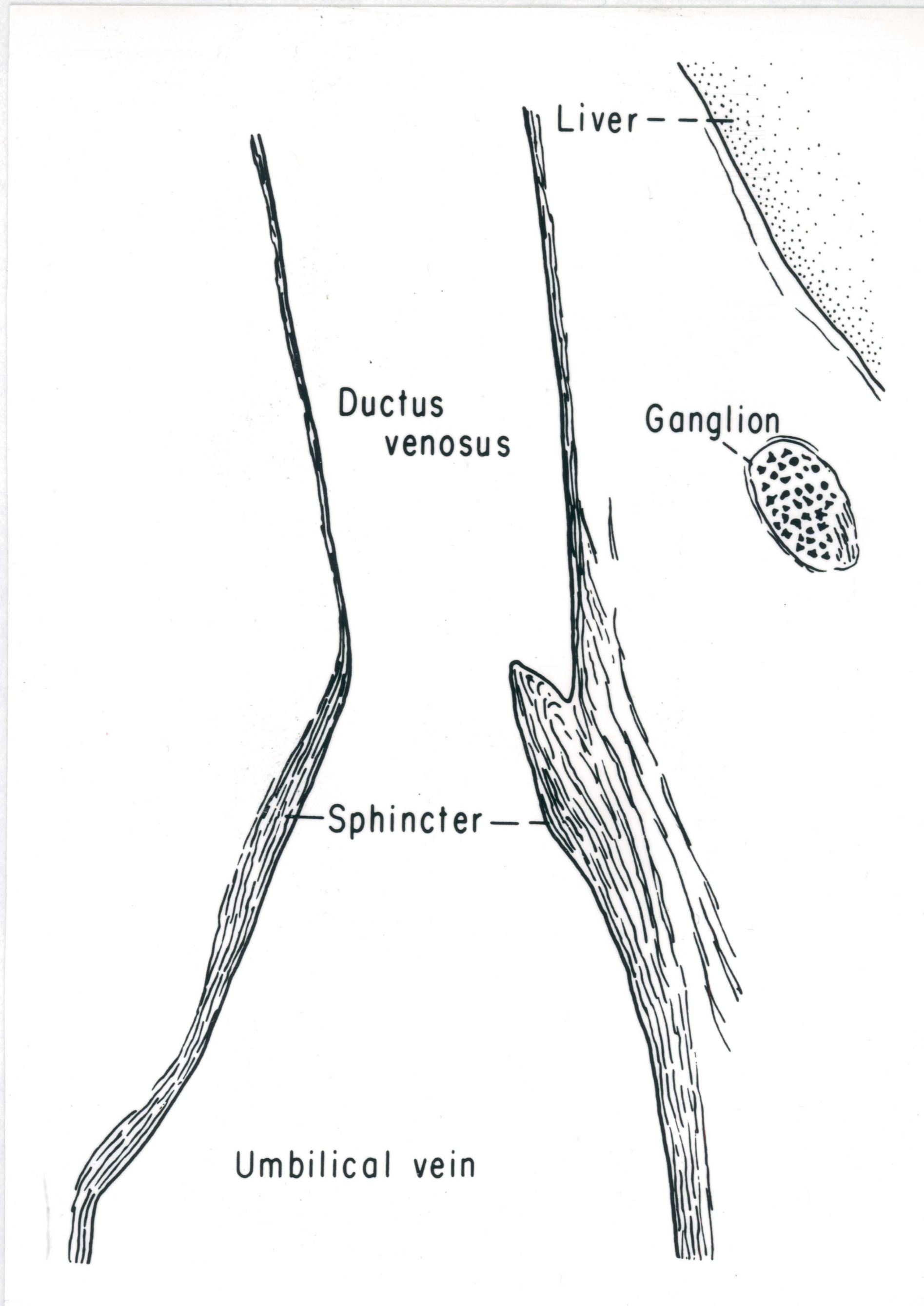

Figure 4: Origin of ductus venosus demonstrating sphincter. From Edelstone D.I. Regulation of blood flow through the ductus venosus. J Dev Phys 1980; 2:219-38.

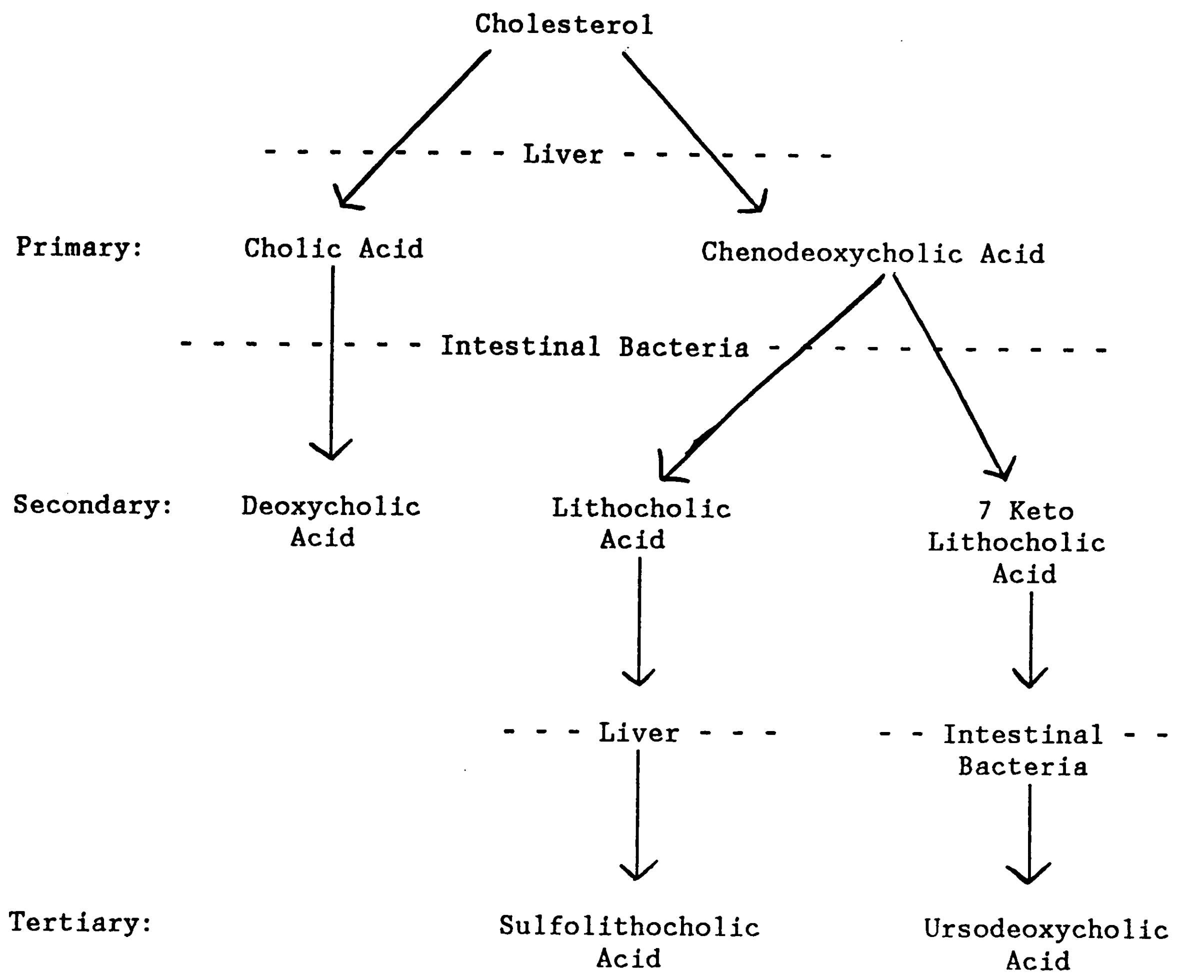

Figure 5. Bile acid metabolism showing sites of synthesis and metabolism.[26]

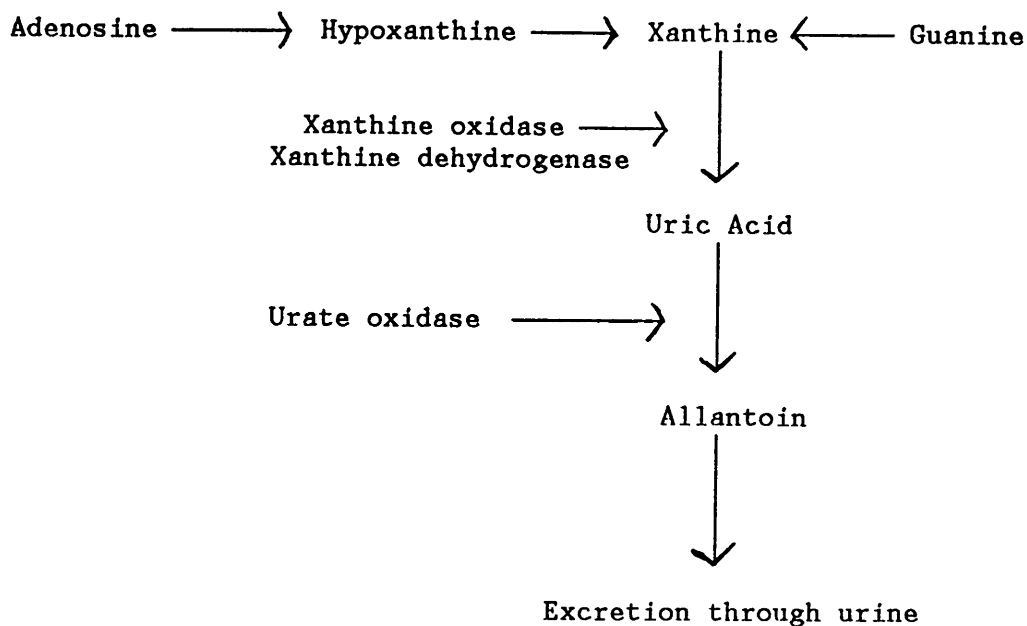

Figure 6: Purine metabolism in the liver (Adapted from Anas IM, Popper H, Schacter D, Shafritz DA. In: The Liver, Biology and Pathobiology. New York; Raven Press: 1982.

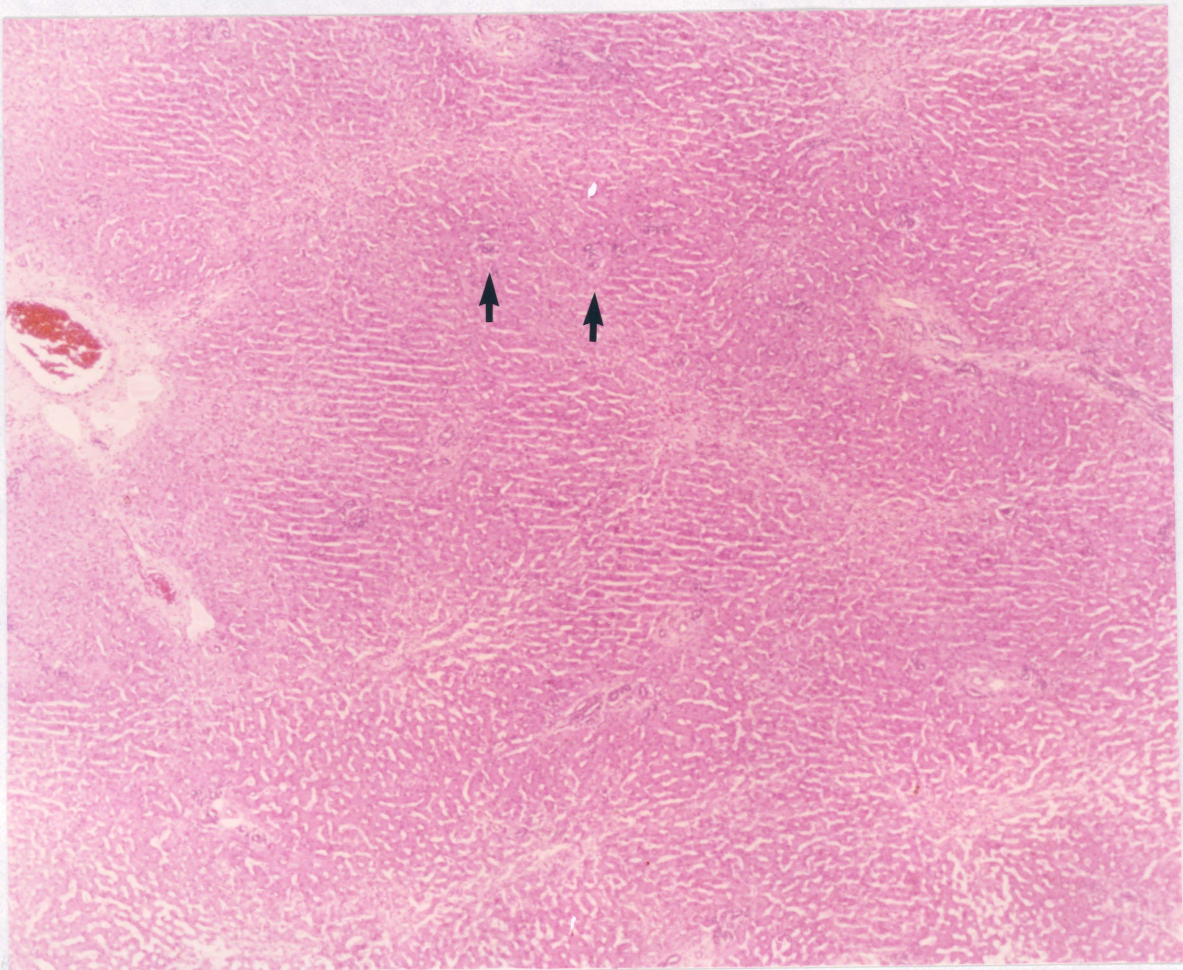

Figure 7: Histologic section from dog with naturally occurring congenital extrahepatic shunt. Small portal areas (arrows) are numerous and too close together suggesting hepatic atrophy. No fibrosis of inflammation is seen. (H and E, x 100).

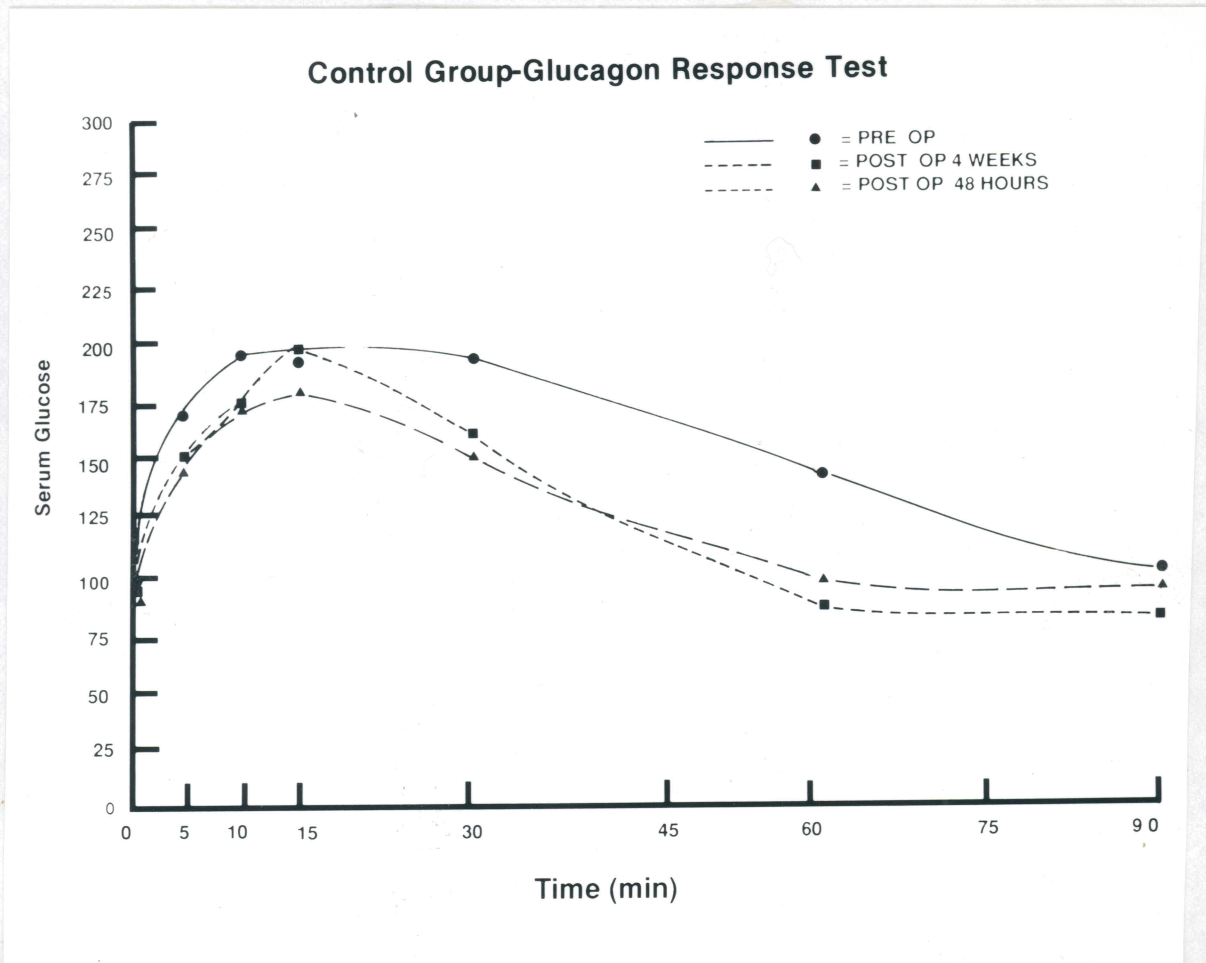

Figure 8: Glucagon response test on control group dogs demonstrating normal response to glucagon preoperatively, at 24 hours and 4 weeks postoperatively. Significant differences noted at 5 and 10 minutes at 24 hours and at 5 and 90 minutes at 4 weeks postoperatively (See Table IX).

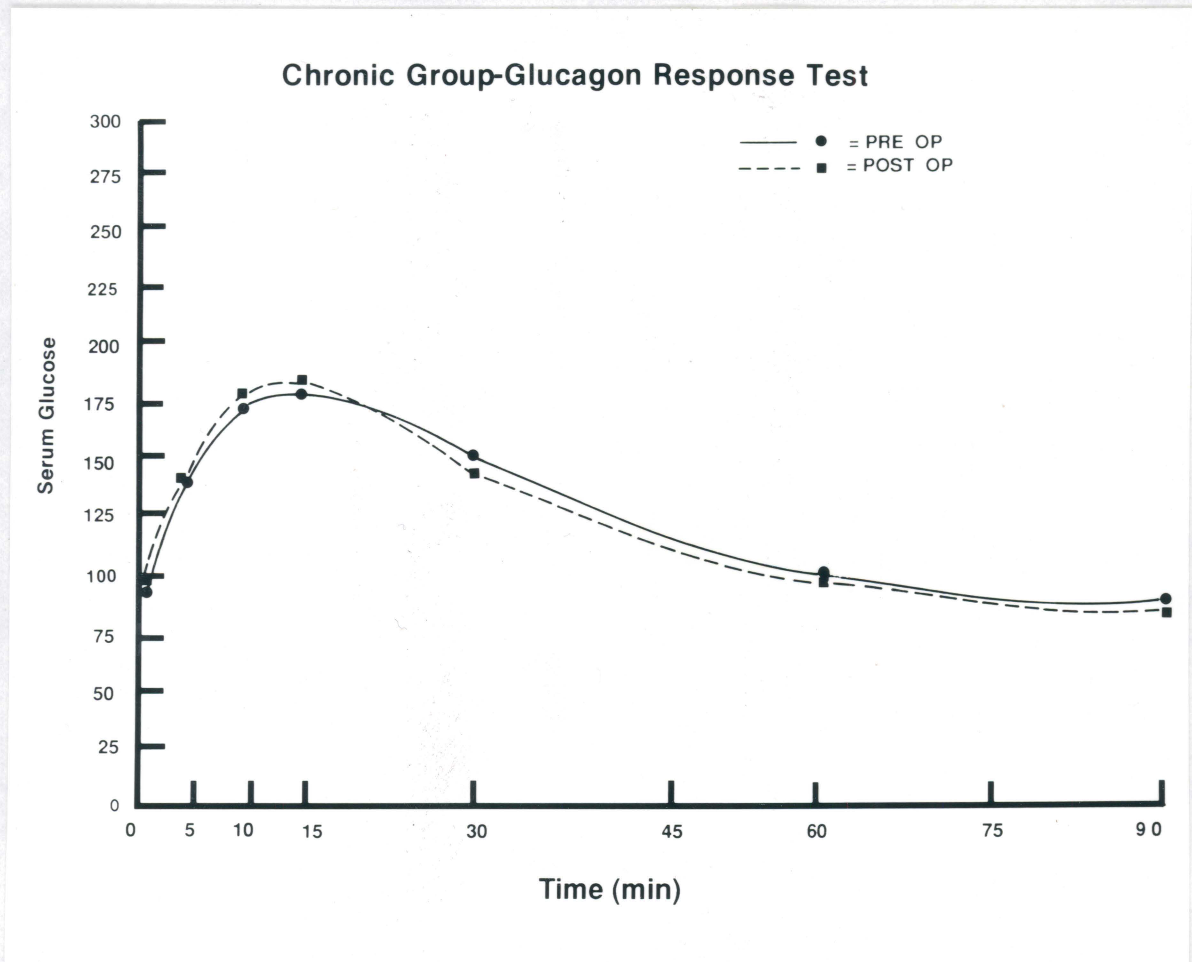

Figure 9: Glucagon response test on chronic group dogs demonstrating normal response to glucagon preoperatively and at 4 weeks postoperatively. No signifanct differences noted (See Table IX).

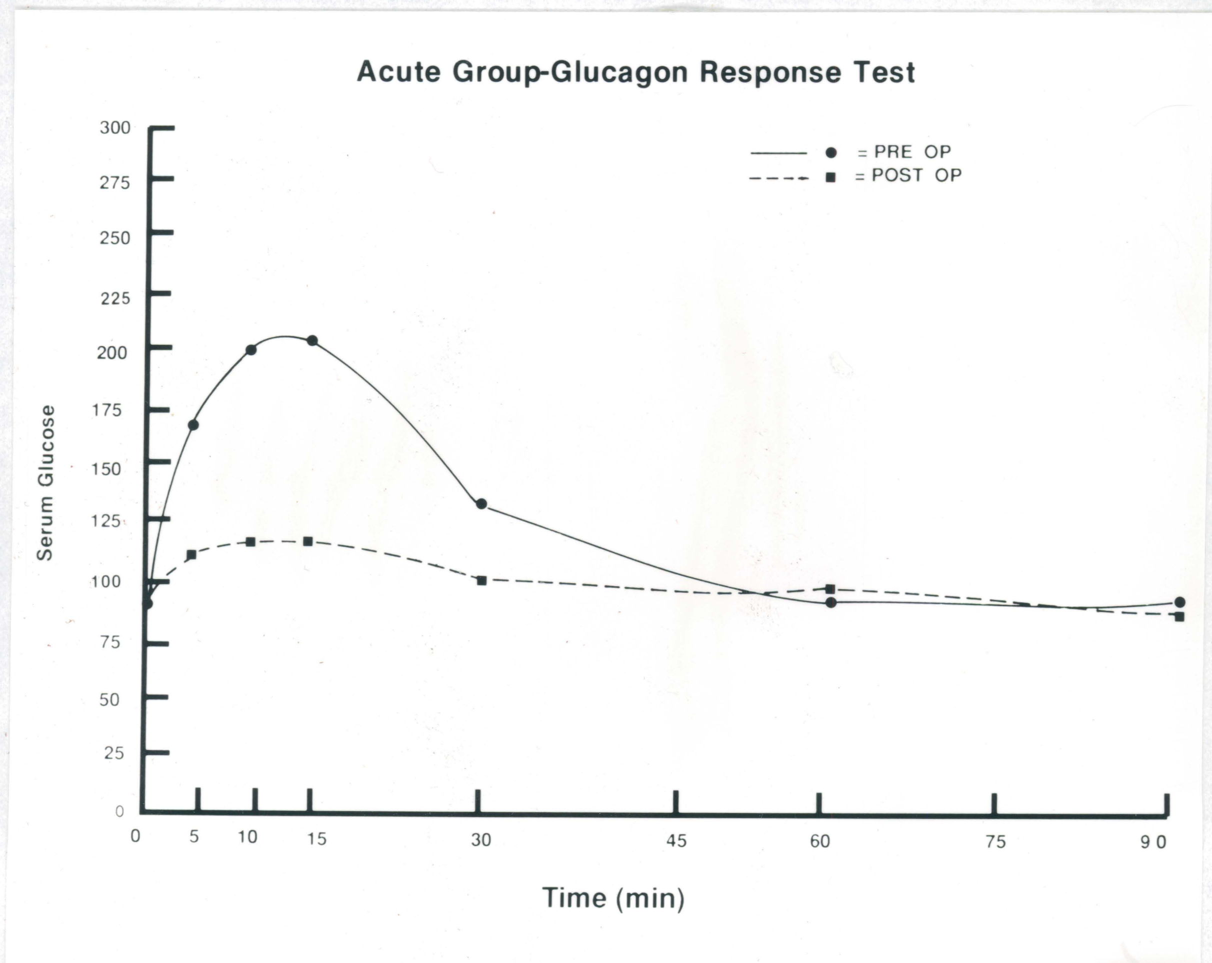

Figure 10: Glucagon response test on acute group dogs demonstrating normal preoperative glucagon response with depressed response 48 hours post-operatively. Statistical difference is noted at 5, 10, 15 and 30 minutes (See Table IX).

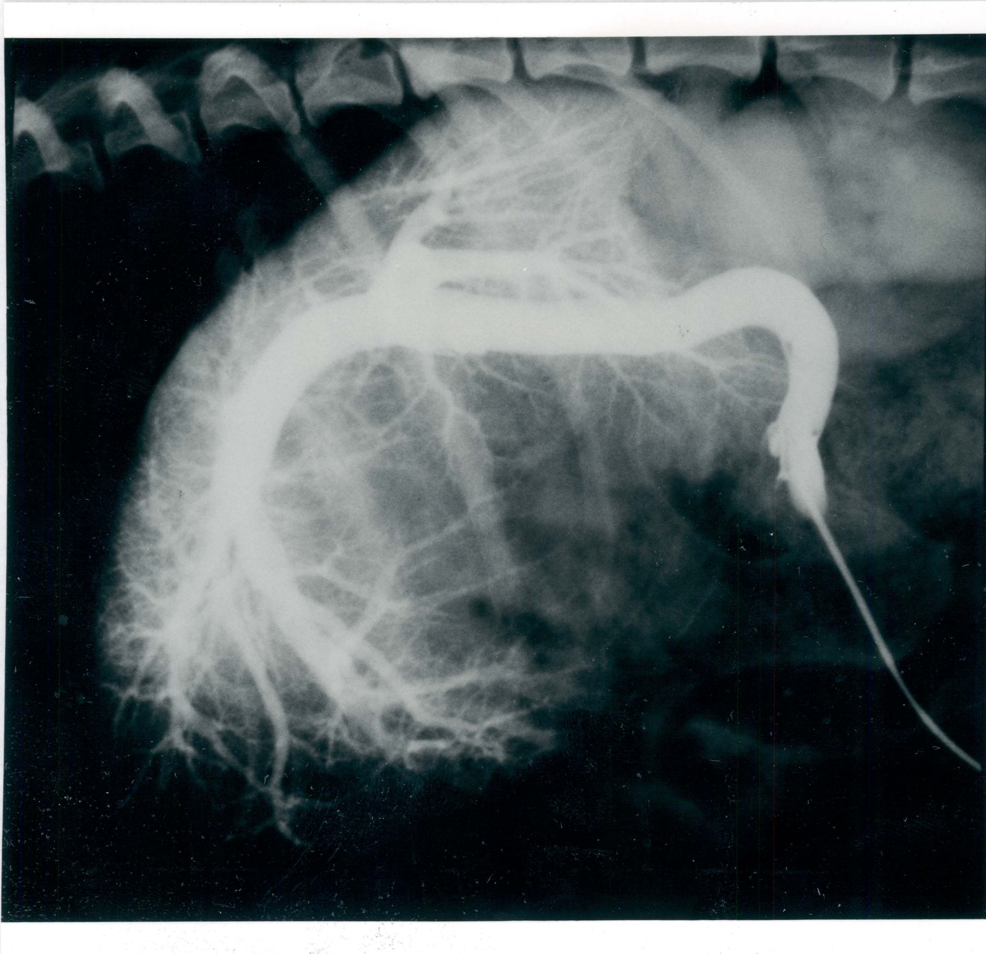

Figure 11: Lateral abdominal radiograph of dog 1 demonstrating normal portogram. Note extent of peripheral filling with contrast medium.

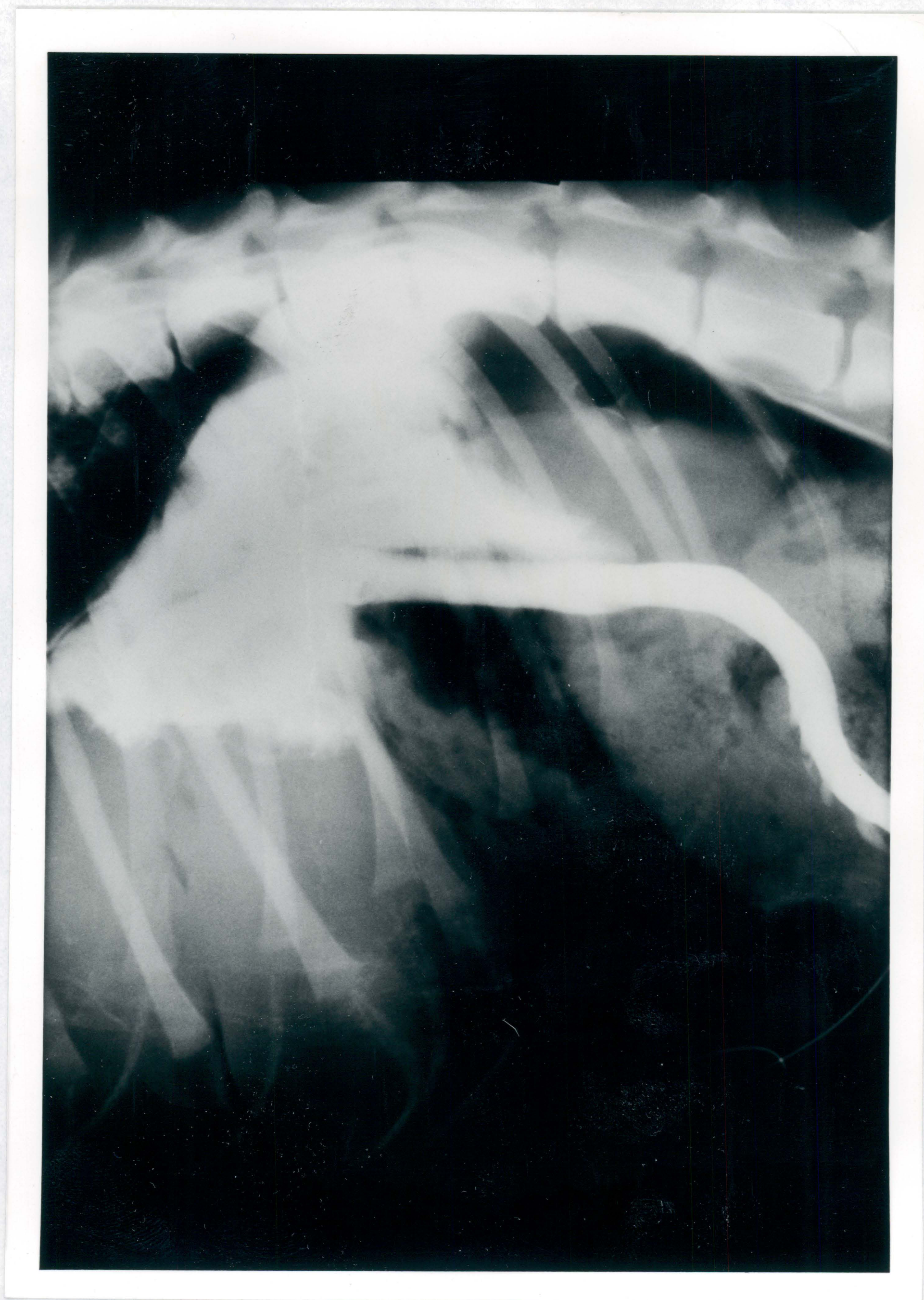

Figure 12: Lateral abdominal portogram of dog 10 immediately post ligation demonstrating overcirculation to right hepatic division with no contrast medium evident in central or left hepatic divisions.

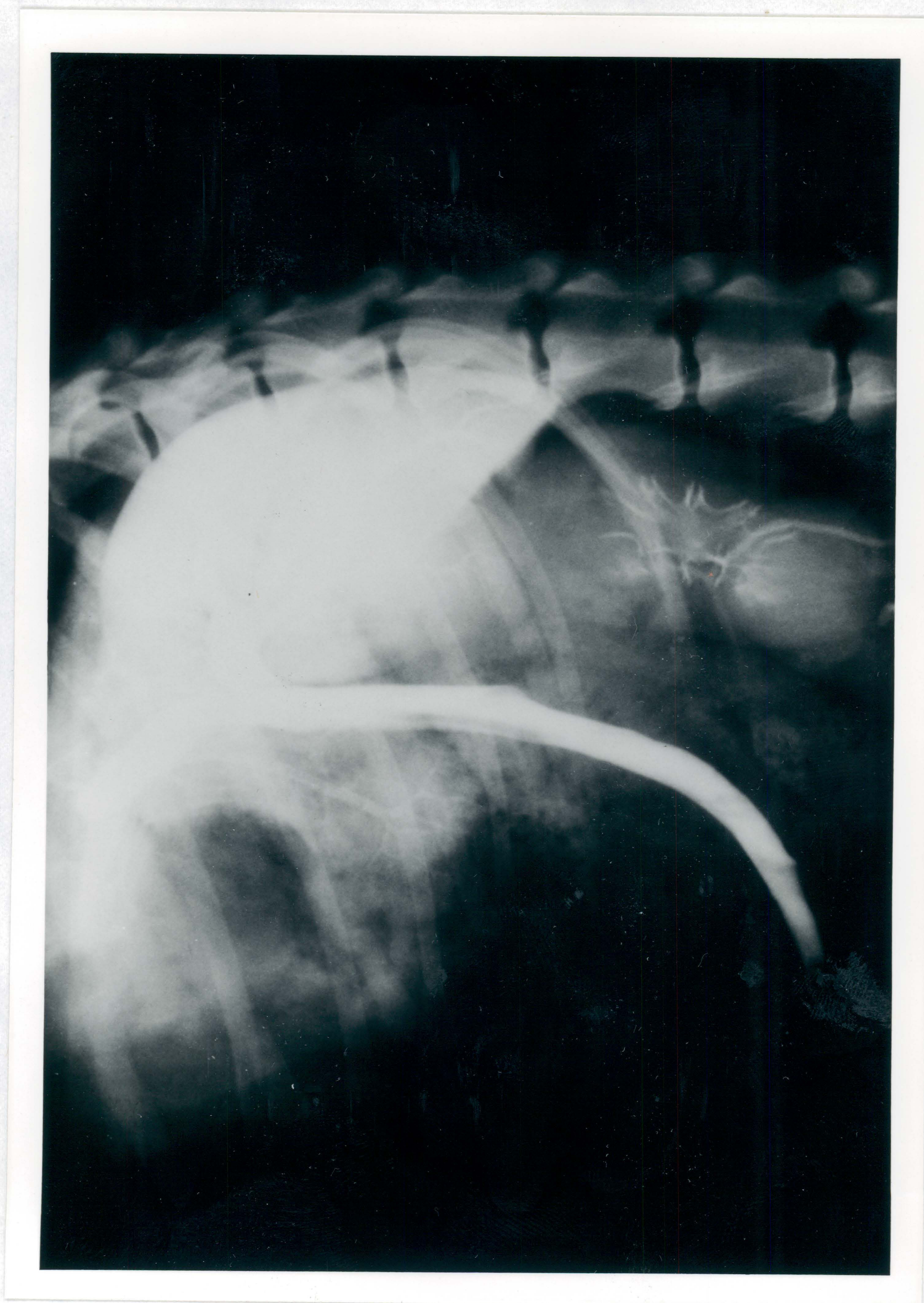

Figure 13: Lateral abdominal portogram of dog 11 48 hours post ligation demonstrating early revascularization in left and central hepatic divisions.

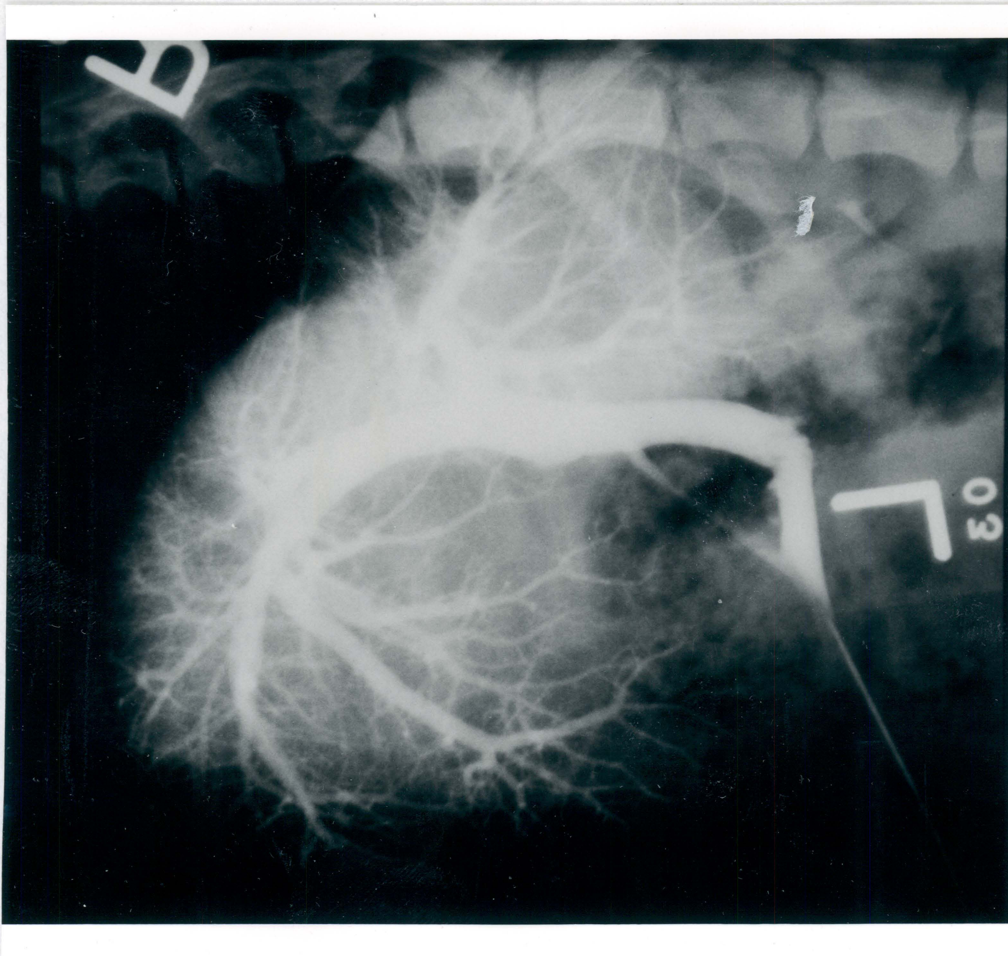

Figure 14: Lateral abdominal portogram of dog 3 4 weeks post ligation demonstrating normal portal flow with no evidence of portosystemic shunting.

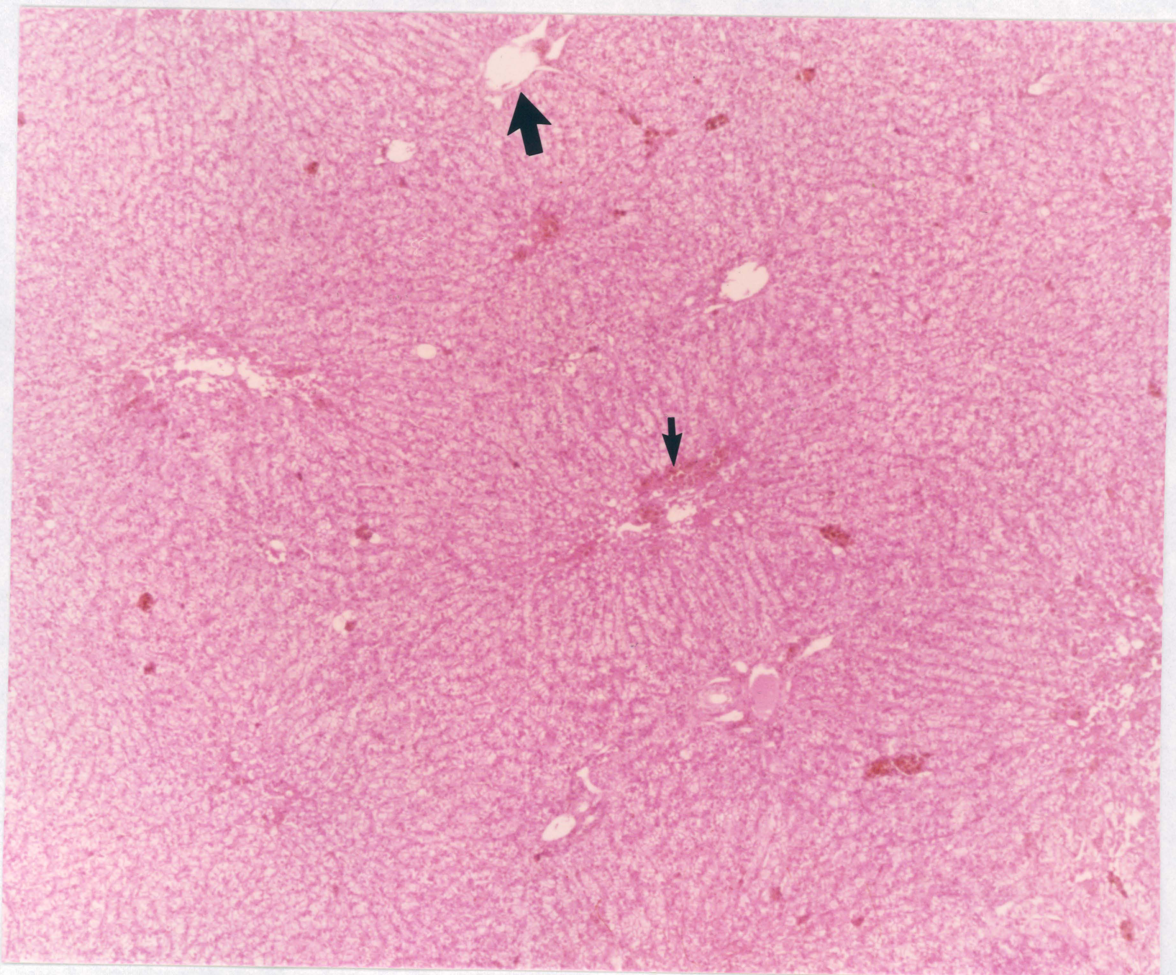

Figure 15: Normal preligation from the right medial lobe hepatic biopsy of dog 9 demonstrating large normal portal areas (small arrow) and central veins. An interlobar vein is seen in lower right (bold arrow). (H and E, x 100).

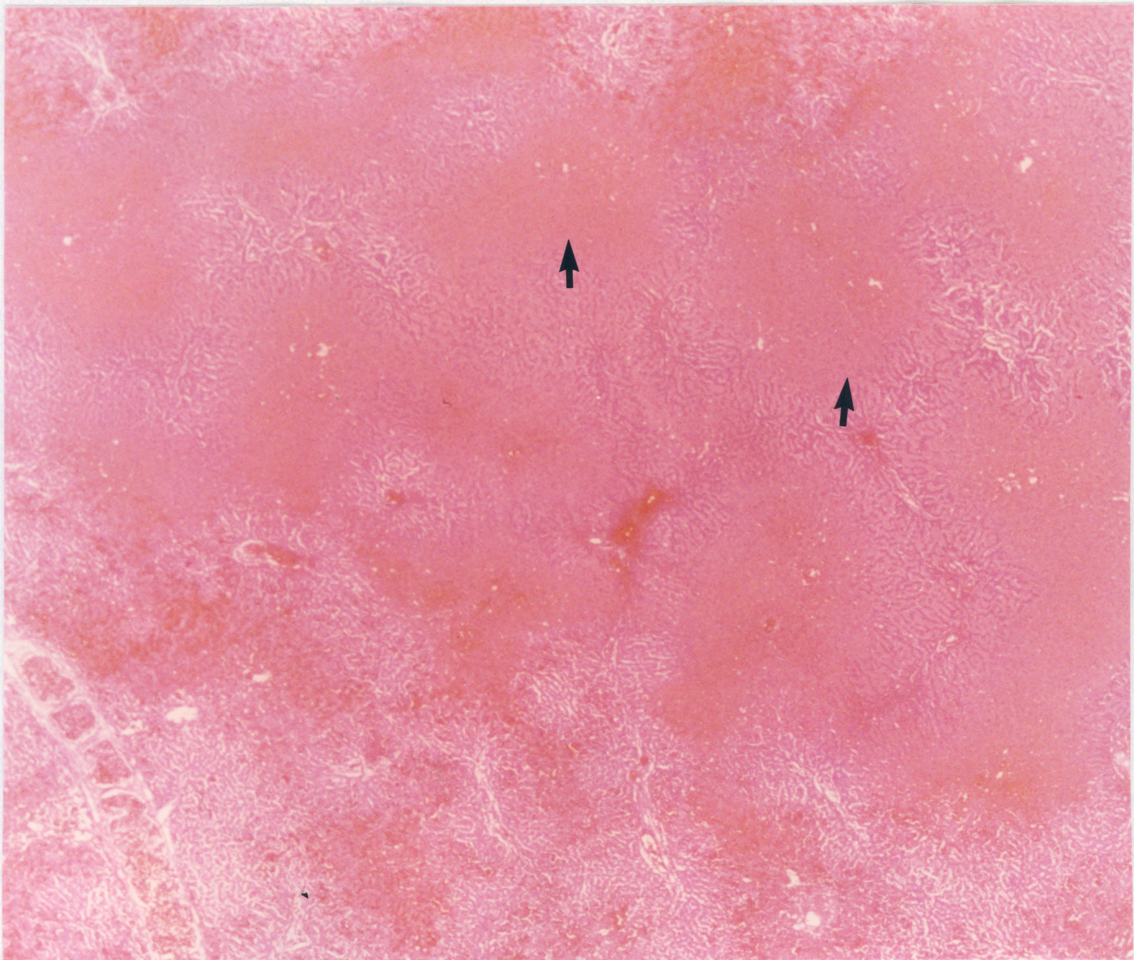

Figure 16: Hepatic biopsy from the left medial lobe of dog 15 48 hours post left hepatic vein ligation demonstrating severe centrolobular congestion and necrosis (arrow). Liver was grossly normal in this dog. (H and E, x 100).

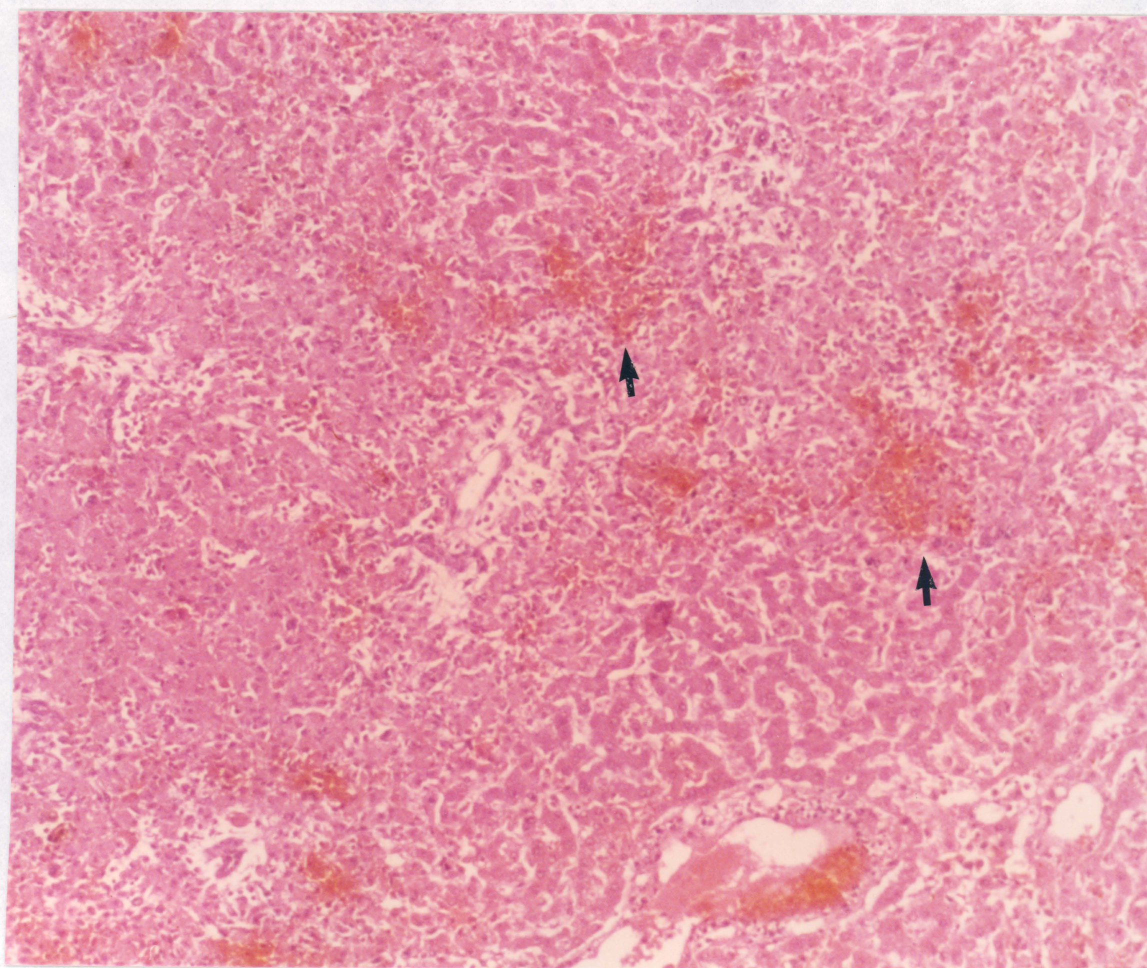

Figure 17: Hepatic biopsy from the right lateral lobe of dog 12 48 hours post left hepatic vein ligation demonstrating random areas of hepatic necrosis and congestion (arrows) suggestive of bacterial hepatitis. (H and E, x 100).

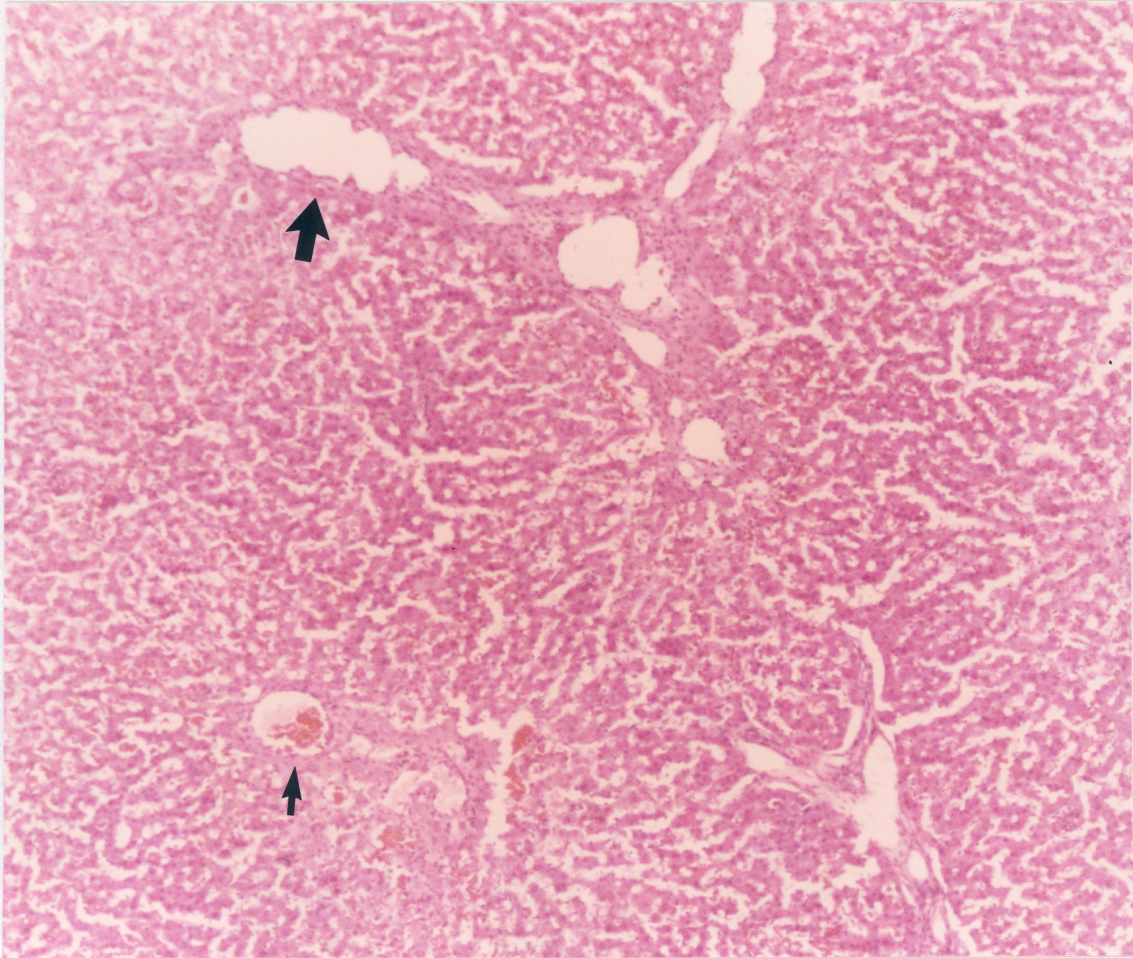

Figure 18: Hepatic biopsy from the left medial lobe of dog 7 4 weeks post left hepatic vein ligation. Normal hepatic architecture with normal portal area seen (arrow). Also present is a large interlobar vein (bold arrow). (H and E, x 400).

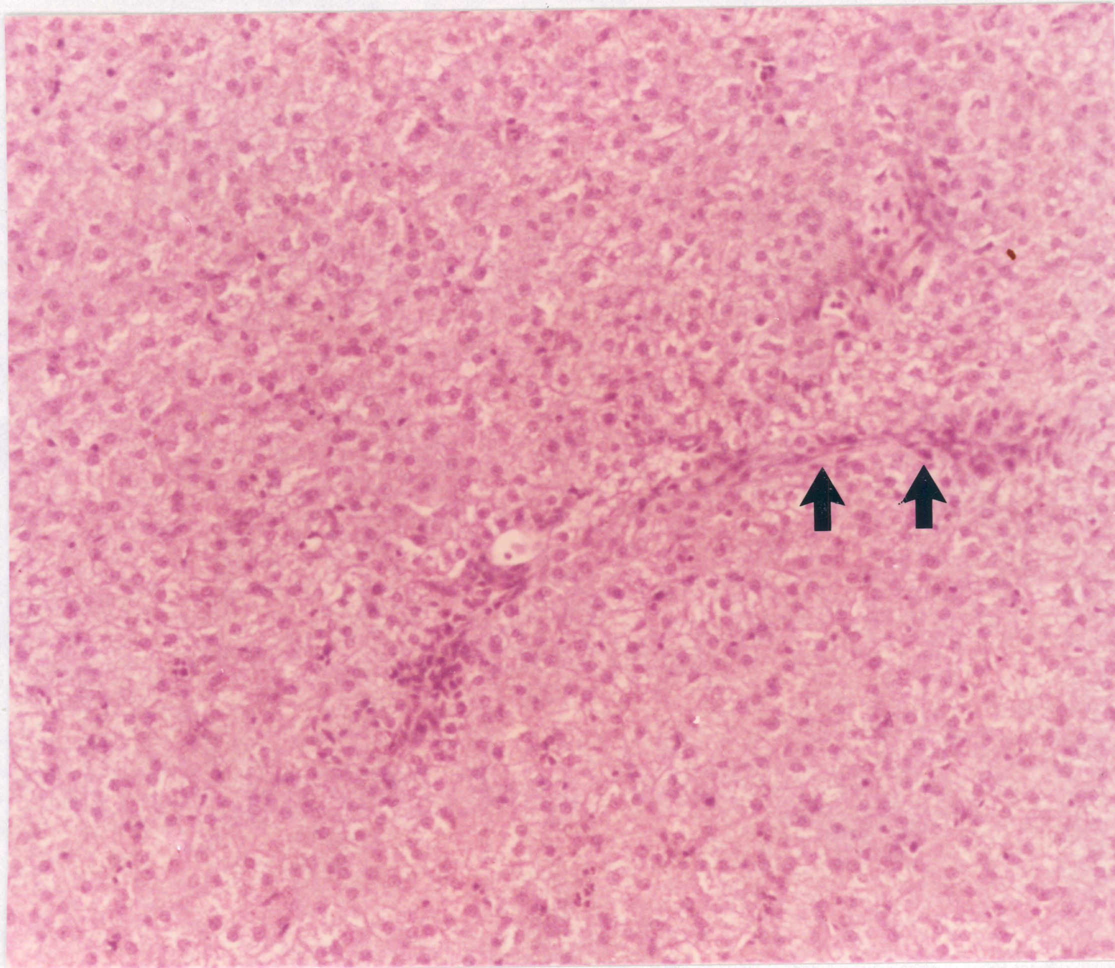

Figure 19: Normal hepatic biopsy from the left medial lobe of dog 7 4 weeks post hepatic vein biopsy showing linear accumulation of endothelial cells with no lumen suggestive of neovascularization (arrows). (H and E, x 400).

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