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Author(s)	MAETANI, SHUNZO
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## Experimental Obstruction of Left Hepatic Vein in Dogs

### I. Histopathological Changes and Gross Vascular Alterations

by

SHUNZO MAETANI

From the 2nd Surgical Division, Kyoto University Medical School

(Director : Prof. Dr. CHUJI KIMURA)

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Venous congestion of the liver is usually seen in association with other pathological conditions and rarely occurs as a simple primary lesion or CHIARI disease. Consequently, it is very difficult to accurately evaluate the significance of hepatic congestion in a given clinical case unless some informations are provided by experimental studies.

In experimental animals hepatovenous congestion has been produced either by constricting the thoracic inferior vena cava or by occluding the hepatic veins. The constriction of the thoracic inferior vena cava is technically simple<sup>1)-3)</sup> and has been utilized by many investigators. However, this method seems to be inadequate to study the effects of hepatic congestion alone since other organs drained by the inferior vena cava, including the kidneys and the adrenal glands, are also involved. In this respect occlusion of the hepatic veins is preferable.

During the past fifteen years an increasing number of attempts have been made to produce pure hepatic outflow obstruction by various techniques<sup>4)-14)</sup>. Most investigators thereby aimed at production of portal hypertension and ascites, so that they tried to occlude all or most of the hepatic veins. Although the procedures have been greatly improved and refined in recent years<sup>6)10)12)14)</sup> as compared with the former methods<sup>15)-18)</sup>, they still entail technical complexity, high mortality or variability of results. On the other hand, only a few works have been reported to study pathologic or pathophysiological changes following venous congestion of one side of the liver<sup>10)19)20)</sup>. The author directed attention to the high lobulation of the canine liver which is divided by deep interlobar fissures, and attempted to produce venous congestion in the left hepatic lobes by obstructing the left hepatic vein. The present study was made on pathological changes of the occluded lobes as well as the open lobes following the obstruction. Hemodynamic alterations will be described in the next report.

#### MATERIAL AND METHODS

Adult mongrel dogs weighing 6 to 15 kg were used. After fasted for about 24 hours they were anesthetized with pentobarbital (Nembutal) intravenously in doses of about 30 mg per kg body weight. The animals were placed in a supine position and the anterior abdominal walls were prepared by the usual sterile methods. The abdominal cavity was entered by a median incision beginning from the middle level of the xyphoid process and extending about 15 cm downward. A sufficient operative field was provided by applying

a self-retaining retractor and inserting a pillow under the back.

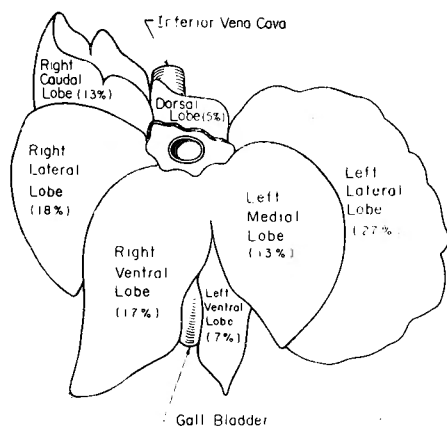
Before proceeding to the method of obstructing the left hepatic vein its relation to the liver lobes is briefly described.

**Anatomical relation of hepatic veins to hepatic lobes** The dog liver is divided into seven lobes and assuming that the gall bladder and the inferior vena cava form the median line each lobe is named according to its anatomical position. The nomenclature conveniently used in this report is illustrated in Fig. 1.

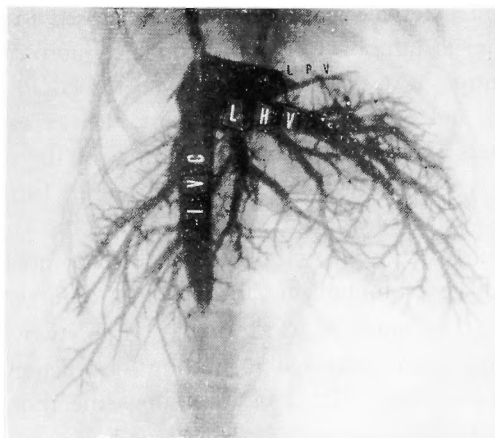
The left hepatic vein is formed by confluence of the veins draining the left lateral lobe, and is joined at the hilus of the latter by one or more veins from the left medial lobe. Along its course it usually receives two more lobar veins: one anteriorly from the ventral lobes and the other posteriorly from the dorsal lobe, thus forming the left hepatic vein trunk. It is also joined cranially by the left phrenic vein and enters the inferior vena cava immediately below the diaphragmatic hiatus where the latter forms the venous sinus. Though there are some variations in the venous drainage of the right ventral lobe and the dorsal lobe the left hepatic vein usually drains blood from the left lateral, medial and ventral lobes as well as the left portions of the dorsal and right ventral lobes, which together make up about 60% of the total liver mass. The remaining portion is drained by several hepatic veins which individually enter the inferior vena cava at different levels (Fig. 2).

**Method of hepatic vein obstruction** The dog was turned slightly to the right and the ligament fixing the posterior edge of the left lateral lobe to the diaphragm was divided as far as the junction of the left phrenic vein with the left hepatic vein. The left side of the dorsal lobe was also freed from the adjoining tissue. Then either one of the following procedures was carried out.

a) *Ligation of the distal portion of the left hepatic vein* By this method venous congestion is restricted to the left lateral lobe amounting to 27% of the total liver mass. When the left medial lobe was raised from the left lateral lobe, the left hepatic vein was



**Fig. 1** Diagrammatic representation of cranial view of dog liver showing the name of each lobe and its mean weight per cent in parentheses.



**Fig. 2** Hepatic venography in a normal dog. LHV, left hepatic vein; IVC, inferior vena cava; LPV, left phrenic vein.

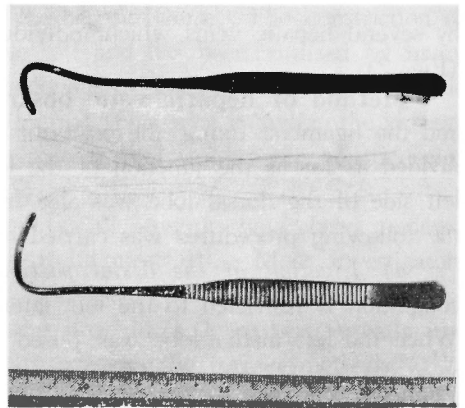
easily seen at the bottom of the interlobar fissure, leaving the latter lobe in parallel with a portal branch, lymphatics and bile ducts of which the hepatic vein takes the most dorsal position. A ligature carrier was inserted between the portal branch and the left hepatic vein, passed around the latter and brought back from the posterior (or dorsal) edge of the lobe. Then the vein was doubly ligated. Thereby the ligatures enclose not only the entire outflow tract of the lobe but also a thin parenchymal bridge and a small portal branch which lies respectively behind and beneath the vein.

*B) Ligation of the left hepatic vein trunk* This method is almost the same as TSUCHIYA<sup>10)</sup> described before and about 60% of the liver is involved. The animal was turned back to the supine position. When the ventral lobes, freed from their attachment to the diaphragm, were depressed the anterior aspect of the left hepatic vein trunk was seen as it joined the inferior vena cava. A ligature carrier was inserted into the hepatic parenchyma between both veins just distal to their junction. By palpating its tip with a finger it was passed under the left hepatic vein trunk and then brought back around the posterior edge of the left lateral lobe. The small parenchymal tissue inclosed in the ligature was cut with the latter before it was tied.

The ligature carrier the author used is shown in Fig. 3. It is blunt-pointed and flexible so that vascular injury by unnecessary force may be prevented. Besides, it can be bent in a desired curvature at each time. When it is advanced the venous wall shows distinctly greater resistance than the parenchymal tissue and can be easily avoided.

In a few instances venous obstruction was accomplished with a balloon (tip of a condom) attached to one end of a catheter which was filled with barium solution. It was inserted from the right external jugular vein and passed to the thoracic inferior vena cava under fluoroscopic control. At this level its tip was turned to the left and pushed slightly forward, then it easily enters the left hepatic vein trunk. If the catheter was too pliable it was armed with a curved elastic stylet. When advanced further it entered the left lateral lobe. After its tip was positioned at a desired level the balloon was inflated with 2 to 3 cc of barium solution (Fig. 4). This method is not applicable for chronic obstruction but has the advantage of minimizing the operative intervention.

The animals were divided into two groups: The first group consisted in 13 dogs which were subjected to outflow obstruction of the left lateral lobe (ligation of the left hepatic vein). In 2 of these dogs the thoracic duct was also ligated at its entrance to the left venous angle. The second group was composed of 25 animals in which the left hepatic vein was obstructed at its trunk. After the operation the dogs were usually given 300 cc of Ringer solution and 100,000 units of penicillin. After varying periods they were reoperated on or sacrificed for further studies.



**Fig 3** Photograph of ligature carrier, taken from two different angles. This partially spiral bent is suited for passing it around the left hepatic vein trunk.

**Histological procedures** Microscopic specimens were obtained during operation, at sacrifice or after death from the left lateral lobe ("occluded lobe") as well as from the right caudal lobe ("open lobe") in both groups. Sections of the formalin fixed specimens were stained with hematoxylin and eosin, Sudan III and by periodic acid-Schiff method with or without amylase digestion. In some specimens Unna's methyl green-pyronin stain or HEIDENHEIN's modification of MALLORY's aniline blue stain were employed.

**Preparation of vascular casts** In six dogs of Group 2 the liver was extirpated with its vessels and perfused with water. The injection material was prepared by TOYOSHIMA's method (polymerization of methyl metacrylate). The liver was injected through the portal vein, the common hepatic artery and in a retrograde manner through the inferior vena cava with differently coloured materials in the above order. Thereafter, the liver was corroded in a caustic soda solution.

**Other studies** Hemodynamic changes were also studied at the same time and will be described in the next paper. In some dogs in Group 2 the weights of the hepatic lobes were measured after sacrifice or death.

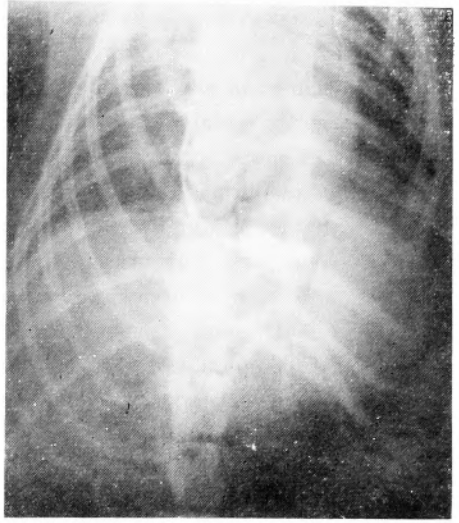


Fig. 4 Roentgenogram showing obstruction of the left hepatic vein trunk with a balloon.

## RESULTS

**Mortality** Three dogs in Group 1 and one in Group 2 were excluded from each series because of incomplete obstruction. Of the remaining 12 dogs in Group 1 two ( $\approx 5$  and  $\approx 15$ ) were sacrificed with Nembutal and another dog ( $\approx 7$ ) was accidentally hanged shortly after operation. The two dogs whose thoracic duct was also ligated expired within 12 hours. Of the remaining 5 animals 2 died within 20 hours and 3 survived more than 43 days. Two dogs ( $\approx 17$  and  $\approx 45$ ) in Group 2 succumbed to pulmonary embolism resulting from accidental rupture of the balloon. Another one ( $\approx 60$ ) was sacrificed several hours after obstruction. Of the remaining 21 animals in Group 2, 5 died within 20 hours and the other 16 survived over 6 days.

Group 1 had a higher operative mortality and animals' conditions in this group appeared worse than those in Group 2. However, if dogs survived the first 24 hours their conditions were progressively improved in either group. After a few days they appeared almost normal unless some complications or other diseases developed.

**Gross change** Shortly after obstruction the occluded lobe (or lobes) became dark red in colour and increased in size. It became firmer in consistency while its capsule was tense and its edge blunted. The surface showed accentuated lobular markings and was shining with exudate. In the hilus of the occluded lobe the lymphatics were dilated and

the periportal connective tissue became edematous. Except for slight congestion the open lobes showed no gross alterations.

The swelling of the occluded lobe subsided within a few days but occasionally its dark colour partly remained. It gradually became atrophic and friable while the right lobes showed compensatory hypertrophy in Group 2 (Table 1). The occluded lobe was adherent to the diaphragm, adjoining lobes, lesser omentum, stomach and duodenum. Its adhesion with the diaphragm and other lobes was separated for the most part by blunt dissection. The portal branch supplying the occluded lobe decreased in size while the lymphatics and lymph nodes were enlarged. The pericardial veins and paraesophageal veins were dilated, serving as collateral channels together with the phrenic veins. There was no noticeable amount of ascites. Simultaneous constriction or occlusion of the inferior vena cava was never encountered at autopsy.

**Histological changes** They are summarized in Tables 2 and 3. There were some individual variations. Fatal dogs showed more severe changes than non-fatal dogs. In general histological pictures in Group 2 were less severe than those in Group 1.

*Acute stage* Shortly after venous obstruction marked changes were seen in the occluded lobe, especially in its centrilobular areas. As a rule two processes were readily recognized: vascular congestion and hydropic degeneration of liver cells. In severe cases there were in addition with necrosis and dissociation of liver cells, extravasation of red cells as well as formation of many PAS-positive inclusions (Fig. 5 and 6). If congestive process predominated, the central vein and the adjoining sinusoids were dilated and filled with blood while liver cells appeared compressed and atrophic. Because of this congestion as well as acidophilic cellular degeneration the central portion of the lobule frequently appeared intensely eosinophilic in contrast to the peripheral portion where liver cells stained more basophilic. However, the picture of congestion was usually combined with and modified by hydropic degeneration which were characterized by vacuolation, reticulation or swelling of cells with rarefaction of cytoplasm. Occasionally sinusoids collapsed between swollen, colourless cells, so that congestive changes were obscured. In more advanced cases hydropic changes and other degenerative processes were followed by necrosis in the central zone and rarely in other areas. As the result of necrosis centrilobular cells disappeared, leaving the reticulum frame work. There appeared a wide perivascular space between the central vein and the surrounding hepatic cells. Extravasation occurred in this space as well as in the GLISSON'S capsule. Occasionally the perisinusoidal space of DISSE was also opened and filled with albuminous debris or with red cells.

**Table 1** Weight Percentage of Left Lateral Lobe and Right Lateral Lobe after Obstruction of Left Hepatic Vein Trunk

Dog No.	66	71	64	61	11	46	69	51	Normal
Time after obstruction	2 h	10 h	12 h	9 d	15 d	31 d	71 d	146 d	
Left lateral lobe	32%*	28%	29%	25%	20%	21%	22%	20%	27%
Right lateral lobe	15%	17%	13%	20%	24%	21%	24%	24%	18%
Ratio of left lateral lobe to right lateral lobe	2.1	1.6	2.2	1.3	0.8	1.0	0.9	0.8	1.5

\* per cent of total liver mass

**Table 2** Histological Changes after Obstruction of Left Hepatic Vein (Group 1)

Dog No.		3*		4†		5		6		7†		8		15		26				36†*		37†*									
Specimens were obtained	Days (d) or hours (h) after occlusion	18 h	14 h	1.5 h	43 d	18 h	345 d	450 d	0.5 h	1.5 h	0.5 h	1.5 h	3 d	32 d	240 d	6 h	4 h														
	During life (B), at sacrifice (S) or after death (D)	D	D	S	B	D	B	S	B	B	B	B	B	B	S	D	D														
Hepatic cell	From occluded lobe (L) or from open lobe (R)	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R								
	Necrosis or disappearance	1	0	2	0	1	0	0	0	2	0	2	0	1	0	2	3	0	2	3	0	1	0	1	0	2	1	1	0		
Hepatic cell	Cytoplasmic inclusions	3	0	2	0	1	0	1	0	3	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	
	Vacuolation	1	0	2	0	3	1	1	0	1	0	0	0	0	0	1	1	1	2	1	0	0	0	0	0	0	0	0	0	1	0
	Swelling	0	0	0	0	0	0	0	0	0	0	0	0	1	1	3	3	1	0	0	0	0	1	0	1	0	0	0	0	0	0
	Irregular arrangement	1	1	0	0	1	1	2	0	0	0	2	0	1	0	2	2	1	1	1	0	2	0	1	0	0	0	0	0	0	0
	Atrophy	3	2	3	1	3	0	0	0	1	0	0	0	0	0	0	0	0	0	3	0	2	0	1	0	3	1	1	1	1	
	Fatty change	0	0							0	1	0	0			0															
	Opening of Disse's space	2	2	1	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	1	0	1	0	3	0	3	1	2	1	1
Sinusoid	Dilatation	3	3	2	2	3	0	0	0	2	1	0	0	0	0	0	0	0	1	2	0	3	0	0	0	1	2	1	1	1	
	Collapse	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	2	0	0	0	0	1	1	1	0	1	0	0	0	0	
Central vein & adjoining area	Dilatation	0	1	0	2	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	
	Fibrinous debris	1	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	1	1	1	1	
	Narrowing or obliteration	1	1	1	0	0	0	1	0	0	0	3	1	2	0	1	0	0	0	3	0	3	0	2	1	0	0	0	0	0	0
	Cellular infiltration	2	1	1	1	1	0	2	1	0	1	2	1	2	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
	Fibrous proliferation	0	0	0	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Glisson's capsule	Ductular proliferation	0	0	0	0	0	0	1	0	0	0	3	0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Cellular infiltration	0	0	0	0	0	0	3	1	0	0	2	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Extravasation	Fibrous proliferation	0	0	0	0	0	1	0	0	0	3	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Extravasation	2	2	1	1	1	0	0	0	2	0	3	0	0	0	2	2	0	1	0	0	2	0	3	0	0	0	0	1	0	1
Pigment deposits		2	2	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	1	0	0	2	0	1	0	2	1	1	1	1	1

The degree of each change is graded 0 to 3.

†Died within 24 hours postoperatively ; \* The thoracic duct was also ligated.

On the other hand the open lobe showed congestion and slight degree of degenerative changes. In the two dogs (# 36 and # 37) in which hepatic vein obstruction was combined with thoracic duct ligation widening of perisinusoidal space with albuminoid precipitation was more marked. Postmortem specimens of fatal dogs showed severe degree of central necrosis, thinning of cells, opening of perisinusoidal space and dissociation of cellular cords. These changes were, though less severe, recognized in the right lobe, too. The agonal and postmortem alterations<sup>21)</sup> were thought to be partly responsible for them.

*Cytoplasmic inclusion* The cytoplasmic inclusion observed in this experiment was a spherical, sharply-defined homogeneous body which was frequently surrounded by a well-demarcated clear zone and embedded in the cytoplasm of the liver cells (Fig. 6). It varied considerably in size ; It may be as small as a nucleolus, but it may glow as large as a hepatic cell, occupying the entire cellular space. Usually a hepatic cell contained a single body, but occasionally multiple smaller ones were found in a single cell.

**Table 3** Histological Changes after Obstruction of Left Hepatic Vein Trunk (Group 2)

Dog No.		17**	41	45**	46		47†		49		51†		52	53		51			
Specimens were obtained	Days (d) or hours (h) after venous obstruction	2.5 h	15 h	1 h	7 d	15 d	21 d	1.5 h	8 d	30 d	100 d	339 d	1.5 h	12 d	39 d	23 d	22 d	62 d	
	During life (B), at sacrifice (S) or after death (D)	D	D	B	B	B	D	B	B	B	B	B	B	B	B	S	B	B	
	From occluded lobe (L) or from open lobe (R)	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
Hepatic cell	Necrosis or disappearance	1	1	3	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0
	Cytoplasmic inclusions	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Vacuolation	3	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Swelling	0	0	0	0	0	1	0	0	0	0	0	0	0	2	2	2	2	0
	Irregular arrangement	1	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Atrophy	0	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	1
	Fatty change		1	2	0	0	0	0	0	1	2	0	0	0	0	0	0	1	0
Opening of Disse's space		1	1	1	2	0	0	1	1	1	1	1	1	0	0	0	0	0	
Sinusoid	Dilatation	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	2	
	Collapse	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	
Central vein & adjoining area	Dilatation	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Fibrinous debris	0	0	3	0	0	0	0	0	0	0	0	0	0	2	1	1	0	
	Narrowing or obliteration	0	0	2	0	0	0	1	1	1	0	1	0	0	0	0	0	0	
	Cellular infiltration	0	0	3	1	0	0	1	1	1	1	0	0	0	0	0	0	0	
Gibson's capsule	Fibrous proliferation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Ductular proliferation	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	
	Cellular infiltration	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	
Extravasation	Fibrous proliferation	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Cellular infiltration	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Pigment deposits		2	1	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	

The degree of each change is graded 0 to 3.

†Died within 24 hours postoperatively; \* A balloon was used for venous obstruction.

This inclusion was commonly associated with vacuolation and karyolysis of hepatic cells, so that it appeared to be the content of the vacuole or substitution for the nucleus. However, not all vacuoles contained PAS-positive material. Rarely it occurred without vacuolar



Table 3 Continued

Dog No.		57				58		60	61		63		61†		66†		67	68	69	70	71†														
Specimens were obtained	Days (d) or hours (h) after venous obstruction	14 d	31 d	106 d	250 d	11 d	3 h	9 d	27 d	196 d	10 h	2.5 h	3.5 h	121 d	6 d	71 d	53 d	12 h																	
	During life (B), at sacrifice (S) or after death (D)	B	B	B	B	B	S	D	B	B	D	B	D	B	D	D	D	S	D																
	From occluded lobe (L) or from open lobe (R)	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R														
Hepatic cell	Necrosis or disappearance	2	0	2	0	0	0	0	0	0	0	0	0	3	0	2	0	1	0	0	0	3	2	3	3	0	0	0	1						
	Cytoplasmic inclusions	0	0	0	0	0	0	0	0	0	0	0	0	3	0	1	0	1	0	0	0	0	0	0	0	0	0	0	2	0					
	Vacuolation	0	0	0	0	0	0	0	1	0	0	0	0	0	2	0	3	1	3	1	0	0	0	0	0	1	2	2	0	2	1				
	Swelling	3	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
	Irregular arrangement	2	0	2	0	2	1	3	0	1	0	0	0	1	1	2	1	1	1	0	0	0	1	0	0	1	1	0	1	0	1				
	Atrophy	1	0	0	0	0	0	0	2	0	0	0	2	1	0	0	0	0	3	0	0	2	1	0	0	0	0	0	3	1					
	Fatty change	0	0	0	0	0	0	0	0	0	0	1	2	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1	0	0	0				
Opening of Disse's space		1	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	1	1	1	1	0	0	3	1					
Sinusoid	Dilatation	0	0	0	0	0	0	0	2	0	0	0	0	2	1	1	0	0	3	2	3	2	3	3	0	0	1	1	1	1	0	0	2	2	
	Collapse	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0		
Central vein & adjoining area	Dilatation	0	0	0	0	0	0	0	2	1	0	0	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	2	1		
	Fibrinous debris	3	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	2	0	2	0	0	1	1	1	3	1	3	3	1	1	2	2		
	Narrowing or Obliteration	1	0	1	0	0	1	1	0	2	0	0	0	0	2	1	1	0	0	0	0	0	0	0	0	0	3	1	3	3	0	0	0	0	
	Cellular infiltration	0	0	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0	1	2	1	0	0	0		
Glisson's capsule	Fibrous proliferation	2	0	2	1	1	0	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	0	1	0	1	0	0	0	0		
	Ductular proliferation	0	0	1	0	0	0	2	0	0	0	0	0	0	0	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Cellular infiltration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Extravasation	Fibrous proliferation	0	0	0	0	0	0	0	0	0	0	0	1	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Pigment deposits	1	0	0	0	0	0	0	1	0	0	0	2	1	0	0	1	0	2	0	3	0	3	1	0	0	0	0	2	2	0	0	1	1	
Pigment deposits		0	0	0	0	0	0	0	0	0	0	0	2	2	0	0	1	1	1	0	1	0	1	0	2	0	0	0	0	2	2	1	1	2	2

degeneration or coexisted with the nucleus, indenting the latter. The inclusion stained with eosin; sometimes so deeply as if it had been erythrocytes trapped in the liver cell, and sometimes so weakly that its differentiation from a vacuole was difficult. However, this inclusion body was readily differentiated from other structures by periodic acid-Schiff method which stained the body deeply pink regardless of amylase digestion. With UNNA'S

stain it took both colours of methyl green and pyronin, but predominantly the latter while treatment with ribonuclease gave ambiguous results. HEIDENHEIN'S modification of MAL-LORY'S aniline blue stain brought out the body golden red. It did not stain with Sudan III.

As for the incidence of the PAS-positive bodies, they were abundantly seen in 8 of 9 dogs which died within 24 hours after operation and were examined more than 1.5 hours after obstruction. Of these 9 fatalities 3 had an episode of respiratory insufficiency: One (♯17) was accidentally hanged, another (♯17) had pulmonary embolism when the balloon placed in the left hepatic vein was ruptured and the third (♯47) showed temporary respiratory arrest following an addition of Nembutal. On the other hand they were absent or scarcely present in those specimens which were taken from 1.5 to 24 hours after occlusion from one fatal, three sacrificed and one survived dogs. No inclusions were found in those dogs which were examined 3 days or more after ligation, except in one (♯6) which died several hours after the second laparotomy. The inclusions were demonstrated not only in postmortem materials but also in biopsy specimens of five dogs, especially abundantly in one (♯51) of them, before the animals showed agonal signs. In 2 dogs they appeared as early as one and half hours after obstruction. Only in one instance considerable number of inclusions were observed in the open lobe specimen. Such cytoplasmic inclusions were also seen in other experiments in which 0.1 cc of 0.1% epinephrine was repeatedly injected into the open and occluded lobes in order to determine the circulation time.

*Chronic stage* In a few specimens obtained one week or more postoperatively from the occluded lobe, many phagocytes were found to fill the necrotic focus, which tended to be demarcated from the surrounding parenchymal tissue, and finally disappeared. Polymorphonuclear leucocyte infiltration which was seen around necrotic cells in a few early specimens was rare in chronic specimens. It was surprising that the extensive necrotic zone had disappeared so completely as if reconstruction ad integrum had occurred. However, when chronic specimens of the occluded lobe were carefully studied in comparison with those of the open lobe, it was found that the lobular architecture especially the relationship of the central vein to the portal triad was more or less distorted or obscured. Also, in the central portion of the lobule liver cells were smaller and stained darker than in the peripheral area. Near the central vein pigment-containing mesenchymal cells and occasionally a ductular structure were recognized. The central vein was occasionally narrowed, thickened or even obliterated, while larger hepatic veins with thick wall were relatively often encountered. Along their courses they were segmentally constricted by the sphincters and were surrounded by several dilated lymphatics. Connective tissue was slightly increased in the occluded lobe, rarely to such a degree that collagen fibers extended from the central portion to the portal tract or neighbouring central veins (Fig. 9 and 10). Though typical cirrhotic picture was observed in no instance there was one specimen (♯8) which showed extremely rich ductular proliferation, severe extravasation as well as extensive disappearance of liver cells (Fig. 7 and 8). There was no demonstrable fatty change except in 5 dogs (♯11, ♯46, ♯53, ♯61, ♯69) which died in malnutrition after having purulent complications or other diseases. In 3 of these dogs fatty change was more marked

in the centrolobular area of the open lobe whereas in the occluded lobe Sudan III was demonstrated in the zone surrounding the necrotic focus.

Except such fatty change the open lobe specimen revealed no marked abnormalities. Nevertheless those changes which were seen in the occluded lobe were also recognized from time to time in the open lobe, though they were less remarkable.

**Gross vascular alterations** In the five vascular casts which were prepared 53 to 330 days postoperatively, similar changes were noted. At a glance the hepatic arterial bed was markedly increased in the occluded lobes, especially in the left medial lobe and in the anterior portion of the left lateral lobe where hepatic arteries were not only larger in caliber but also they were injected to their finer branches (Fig. 11 and 12). Portal trees appeared abruptly narrowed toward the periphery and were occasionally compressed by the accompanying arteries. Their smaller branches were often absent so that the portal trees appeared to be clipped. As the result, in some areas of the occluded lobes hepatic arterial trees were not only larger but extended more peripherally than the corresponding portal trees. As for the hepatic veins, they were seen in both sides of the liver, but they were relatively few and irregularly spaced in some of the occluded area. In the right ventral lobe and the dorsal lobe which had been partly drained by the left hepatic vein and partly by other open veins numerous collateral channels developed, connecting tributaries of the obstructed vein with open veins. These collaterals appeared not only inside the lobes as relatively large arcades, but also in their surface. An entirely new vein of large caliber was found in the interlobular fissure between the left ventral and left medial lobes. Venous collaterals were also noted between the liver and the diaphragm. In the adhesion of the left lobes with the stomach and the lesser omentum collaterals formed were primarily portal but in one instance they were partly filled with injection mass from the hepatic vein. Pre-existing hepatic veins were enlarged in the open side of the boundary lobes.

In the right lateral and right caudal lobes the hepatic venous trees and portal trees were more densely distributed.

Because the injection material used rapidly increased in viscosity during injection no anastomoses were demonstrated between the hepatic veins and the portal veins or between the latter and the hepatic arteries. However, when the liver was perfused either from the hepatic artery or from the portal vein, more water flowed out from each other than from the inferior vena cava. Consequently anastomoses between the hepatic arterial and portal systems were likely to have developed.

## DISCUSSION

Acute obstruction of all the hepatic veins is always fatal in experimental animals<sup>(4) (6) (17)</sup>. Even if the hepatic veins are either gradually or partially obstructed the operative mortality is considerably high. The cause of death may be explained by the following three factors besides the operative intervention and complications:

- a) Pooling of blood in the splanchnic area.
- b) Decrease or loss of normal liver functions.
- c) Production or liberation of toxic substances in the damaged liver.

In the present experiment in which outflow obstruction was restricted to an area of

60% or less of the total liver the first and the second factors seem to be less important than in other experiments in which almost all hepatic veins are occluded: Following the left hepatic vein obstruction the blood pressure did not fall so deeply as to suggest a circulatory collapse from splanchnic pooling. Also, it is unlikely in view of the generous reserve capacity of the liver as demonstrated by experimental liver resection, that metabolic activities of the liver were decreased to a critical level in this experiment. As for the third factor, vaso-depressor material, growth of anaerobic bacteria and breakdown products of the liver have been blamed. No attempt was made in the present experiment to confirm the presence of such materials or organisms. However, it deserves special attention that a higher mortality as well as more severe symptoms than in Group 2 were observed in Group 1 in which only as half as large portion of the liver as in Group 2 was subjected to venous congestion, but to a more severe degree. This difference in mortality may be regarded as suggesting the significance of the third factor. However, the number of dogs used is too small to allow one to draw a final conclusion inasmuch as there are in effect many additional factors contributing to the operative death, such as filariasis, deep anesthesia and bleeding.

It is of interest to know whether obstruction of a hepatic vein produces pathological changes in a selective region. WINTERNITZ<sup>22)</sup> ligated a single hepatic vein in dog and found no changes in the lobe several weeks after operation. He did not clearly mention which vein was ligated. WIDMANN<sup>19)</sup> and his coworkers, using the technique which was originally described by CHILD<sup>4)</sup> et al. and was later modified by ALLEN<sup>8)</sup> et al., placed a tube in the hepatic segment of the inferior vena cava so as to occlude the hepatic veins from inside the cava. In none of the dogs were the ostiums of hepatic veins draining more than 55% of the liver mass occluded. However, microscopic changes in most cases were either absent or observed diffusely in all lobes. In only 2 of the 11 animals slight atrophy and minimal centrilobular fibrosis were seen in the lobes with occluded hepatic venous ostiums. KIMURA<sup>23)</sup> reported five cases of membranous obstruction of the hepatic inferior vena cava. This condition was frequently associated with thrombotic occlusion of the left hepatic vein; no histological difference was noted between the left and right lobes. These results were explained by collateral formations between the occluded and non-occluded veins.

The present investigation has revealed that acute obstruction of the left hepatic vein produces definite pathological changes in the left lateral lobe. Histologically, central necrosis, congestion, hydropic degeneration, extravasation etc. are seen in early specimens of that lobe. However, the most remarkable finding is the development of PAS-positive inclusion in many hepatic cells. It is commonly associated with karyolysis, so that it may be interpreted as indicating necrosis of the cell. The inclusion body contains neither glycogen, nor lipid. The presence of nucleoprotein or mucoprotein is suspected but not confirmed. Though it is impossible in the scope of the present investigation to elucidate the nature of the inclusion, several possibilities may be suggested:

- a) Degenerative process of the protoplasm under anoxic condition.
- b) Accumulation of some substance which is forced into the cell from blood or to be excreted in bile.

c) Aggregate of elementary bodies or some immunological process.

It is noteworthy that about 90% of the animals dying within 24 hours postoperatively showed a considerable number of these inclusions in the occluded lobe, whereas they were absent or scarcely present in other animals sacrificed or survived. In spite of such a high correlation between occurrence of numerous inclusions and acute death of the animals, it is very difficult to clarify their causal relation. Since they were present in some biopsy specimens obtained before the agonal period, it is unlikely that such inclusions represent an agonal or postmortem change.

In the literature cytoplasmic inclusions have been observed by many authors within vacuoles of human or animal livers under different conditions. MALLORY<sup>24)</sup> found them in acute infectious diseases with central necrosis of the liver. PAPPENHEIMER and HAWTHORNE<sup>25)</sup> failed to find any correlation between their presence and general disease. The last authors could not demonstrate such bodies in dogs and cats. Later, inclusion bodies similar to those in the present experiment were observed by ULRICH<sup>26)</sup>, PICHOTKA<sup>27)</sup> and ALTMAN<sup>28)</sup> in experimental animals which were subjected to oxygen deficiency in a hypobaric chamber or in other experimental conditions. The periodic acid-Schiff procedure was not available at that time, and they were referred to as eosinophilic content of the vacuole. Also, similar vacuolar degeneration was demonstrated by MÜLLER<sup>29)</sup> in four airplane crew who died in the air, and by HESSE<sup>30)</sup> in fatal cases of asphyxia, hydrocyanic poisoning, pulmonary embolism, pulmonary stenosis, circulatory insufficiency etc.. These German authors claimed that general oxygen deficiency was the common cause of vacuolar degeneration with or without eosinophilic content. In the present investigation at least 3 of 9 deaths with cytoplasmic inclusions are related to respiratory insufficiency and other fatal dogs may have also suffered oxygen deficiency. Thus, hepatic anoxia due to venous congestion of the liver seems to be a very important factor for the development of such inclusion bodies. On the other hand MÜLLER noted venous congestion of the liver and other organs in all his cases with vacuolar degeneration. Likewise, hepatovenous congestion may have occurred in HESSE's cases with pulmonary stenosis, pulmonary embolism or circulatory insufficiency. It is still uncertain whether liver anoxia alone can produce such a lesion without concomitant stagnation of blood. In this experiment it remains also unanswered whether the selective occurrence of cytoplasmic inclusions in the occluded lobe should be solely ascribed to lower oxygen tension in that lobe and not to blood stagnation. In any case it is reasonable to presume that a combination of hepatovenous congestion and general oxygen deficiency can cause the most severe changes in the liver and may be fatal to the organism.

WALLACH and POPPER<sup>31)</sup> claimed that there were characteristic differences between the central necrosis resulting from venous congestion and that caused by toxic or bacterial factors. The histological findings in the present studies do not always conform to what was claimed to be characteristic of congestive type in man; some of them are rather similar to the findings described by MALLORY<sup>24)</sup> and ALTMAN<sup>28)</sup> in acute bacterial infection and in hypoxic condition respectively. Besides, when the histological picture of gradual constriction of the thoracic inferior vena cava is compared with that of acute hepatic vein obstruction, there seems to be more difference between them than between hepatic lesions due to

different causative factors. In other words the liver seems to respond to a variety of deleterious factors with similar histological changes and yet it may show different histological pictures under the same causative factor according to the degree and rapidity of its action.

As to the open lobe, it is not completely free from the effect of left hepatic vein obstruction. This may be due to the fact that it receives not only portal blood from the splanchnic area but also venous blood from the occluded lobe.

In the chronic survivors the acute histological changes disappear almost completely. The left lateral lobe, however, can be still differentiated from the right caudal lobe; reconstruction ad integrum is not the case. The draining capacity of the collateral circulation seems to limit the extent of reconstruction in the occluded lobe. On the other hand typical cirrhotic pictures or other progressive changes, degenerative or regenerative, are exceptional though fibrosis and slight degree of ductular hyperplasia are occasionally noted. Repeated venous obstruction or other additional factors seems to be necessary for development of cirrhosis.

Regarding the gross vascular alterations the present studies agree well with the observation by WIDMANN<sup>19)</sup> and his colleagues. However, in contrast to the diffuse vascular changes described by them the present investigation reveals rather selective involvement of the occluded lobe, where the most remarkable change is enlargement of the hepatic arteries. Such arterial enlargement was seen in experimental constriction of the thoracic inferior vena cava<sup>32)</sup> and also in human cirrhosis<sup>33) 34) 35)</sup>. The mechanism which underlies this change remains to be investigated.

#### SUMMARY

A simple method is described for obstruction of the left hepatic vein in dog so as to selectively produce venous congestion in the left lobe or lobes of the liver.

Following obstruction histopathological changes of an occluded lobe as well as an open lobe are studied and the following results obtained.

In acute stage central congestion, necrosis, hydropic degeneration, extravasation and dissociation of cells are observed. However, the most remarkable finding is the development of PAS-positive cytoplasmic inclusions in association with vacuolation and karyolysis. A considerable number of them appear almost constantly in the occluded lobe of the dogs which died within 24 hours postoperatively while they are absent or relatively few in the open lobe of these fatal dogs as well as in other dogs sacrificed or survived. Their nature is briefly discussed. It is suggested that if hypoxic condition is superimposed on hepatovenous congestion it may produce the most severe damage to the liver and may be fatal to the organism.

In chronic survivors the acute changes disappear almost completely. However, in the occluded lobe portal triads and central veins are irregularly spaced. The latter are occasionally obliterated in contrast to the usual picture of congestive liver characterized by dilatation of central veins and adjacent sinusoids. The connective tissue is slightly increased but cirrhotic changes are exceptional, for which other factors seem to be necessary.

The open lobe is not free from the effect of left hepatic vein obstruction. In some

of the dogs dying from suppurative infections fatty change is more severe in the centrolobular area of the open lobe.

Vascular casts of chronic specimens revealed that in the obstructed side the hepatic arterial bed is increased and portal trees are narrowed and slightly distorted, while hepatic veins are poorly injected and irregularly arranged. There are numerous collaterals between the occluded and open sides of the liver.

#### ACKNOWLEDGMENT

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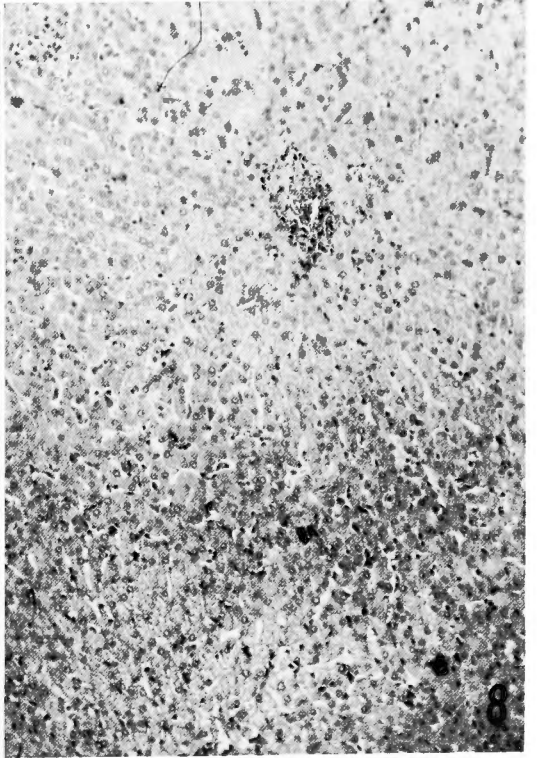
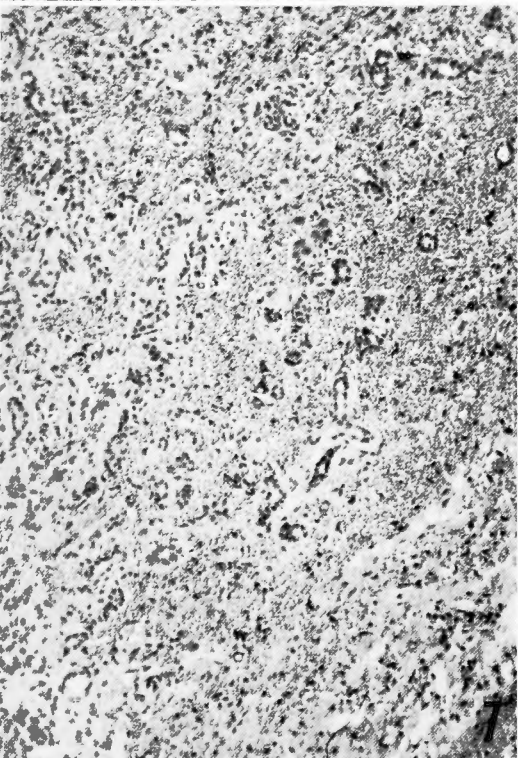
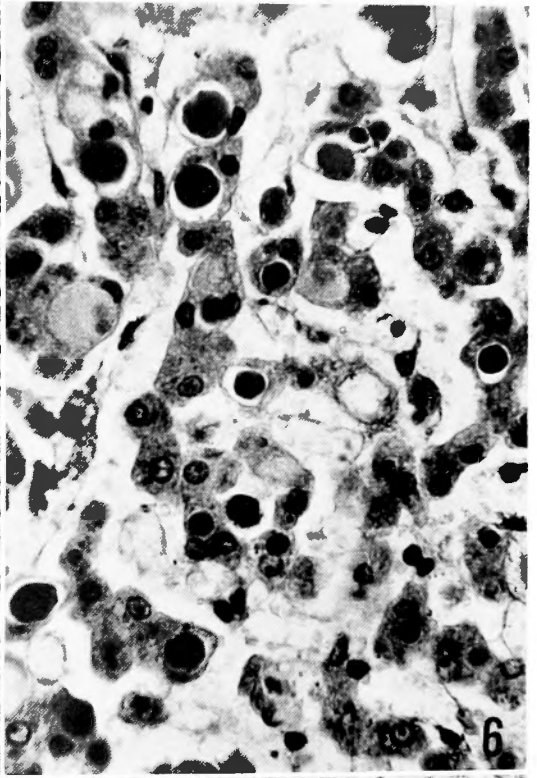
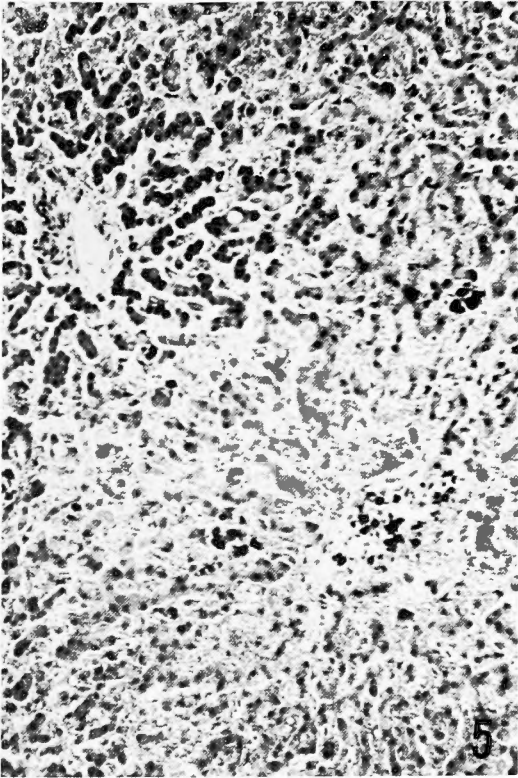
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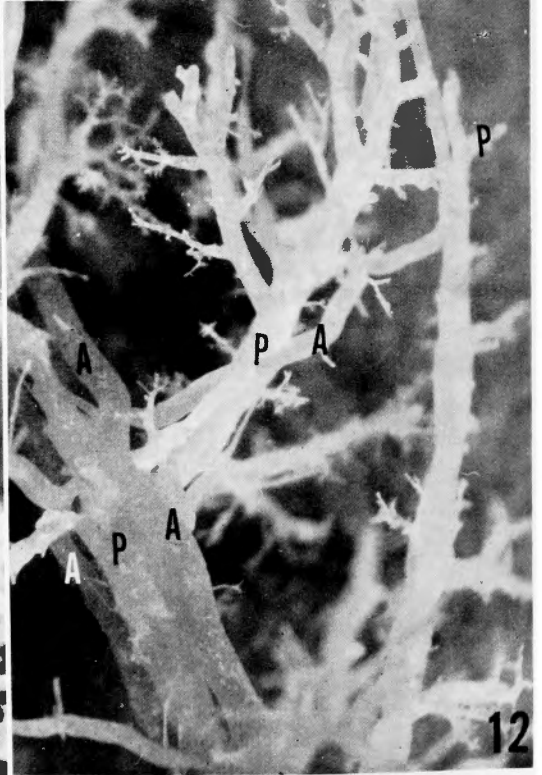
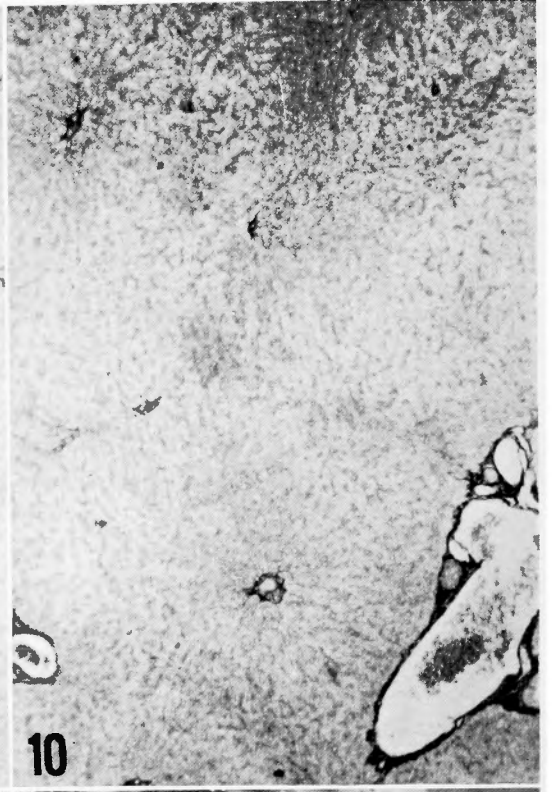
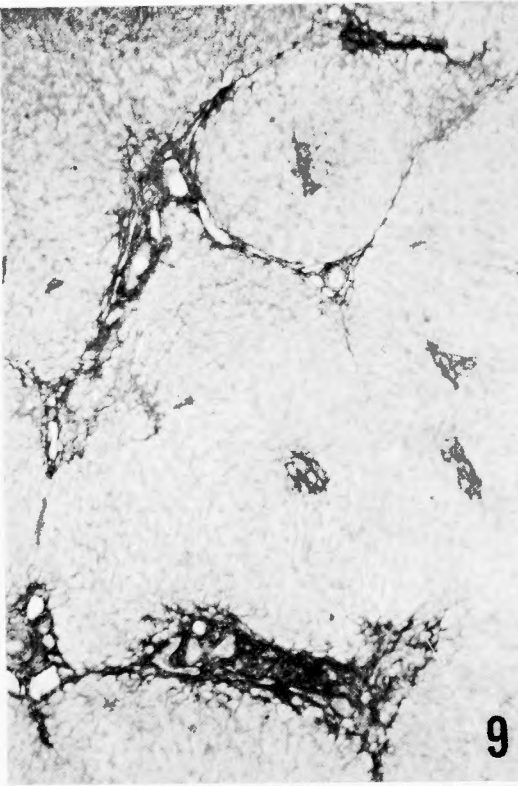
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#### Legends for Fig. 5-12

- Fig. 5** Occluded lobe of dog # 3 dying 18 hours after ligation of the left hepatic vein. There are central congestion and necrosis, thinning of liver cells with opening of perisinusoidal space, cytoplasmic inclusions, extravasation of red cells and pigment deposits. Postmortem specimen. Hematoxylin and eosin stain.  $\times 80$ .
- Fig. 6** Higher magnification of the same specimen as Fig. 5, showing PAS-positive inclusions in hepatic cells. PAS-stain.  $\times 320$ .
- Fig. 7 and 8** Occluded lobe and open lobe of dog # 8, 345 days after ligation of the left hepatic vein. In the occluded lobe (Fig. 7) ductular hyperplasia, disappearance of hepatic cells, cellular infiltration and extravasation of red cells are seen; the open lobe (Fig. 8) shows no remarkable change except for slight cellular infiltration around the central vein. The occluded lobe specimen was obtained from the anterior edge adherent to the diaphragm and the lesser omentum. Biopsy specimens. Hematoxylin and eosin stain.  $\times 80$ .
- Fig. 9 and 10** Occluded lobe and open lobe of dog # 57, 250 days after ligation of the left hepatic vein trunk. In the occluded lobe (Fig. 9) central fibrosis and reversal of lobular architecture are seen. There are dilated lymphatics around the central canal. The open lobe (Fig. 10) shows no abnormality. Biopsy specimens. Mallory's stain.  $\times 80$ .
- Fig. 11 and 12** Vascular casts of the occluded lobe and of the open lobe of dog # 65 sacrificed 99 days after ligation of the left hepatic vein trunk. In some area of the occluded lobe (Fig. 11) portal veins (P) are narrowed and slightly distorted while hepatic arteries (A) are enlarged as compared with those of the open lobe (Fig. 12) which are far smaller than the adjacent portal veins or hepatic veins (V).







## 和文抄録

## 左肝静脈閉塞による実験的肝鬱血の研究

## I 病理組織所見及び血管系の変化について

京都大学医学部外科第2講座(指導:木村忠司教授)

前 谷 俊 三

肝鬱血は臨床上或は病理解剖時屢々見られるが、多くは他の疾患と合併して現われる為各症例につき肝鬱血そのものの意義を知ることは困難である。そこで実験的に純粋な肝鬱血による変化を研究することも重要と思われる。ところが肝静脈全体にわたる狭窄或は閉塞は門脈圧亢進症及び腹水の生成に必要なとは云え、その死亡率も高く又技術的に困難を伴い、その上一定した結果が得られない。そこでより簡単な方法として犬の左肝静脈を完全閉塞して左葉(閉塞葉)に撰択的に鬱血を起させる方法を考え、その際の病理組織学的所見及び血管鑄型の変化を右葉(非閉塞葉)と比較しつつ検討して次の結果を得た。

1) 急性期の閉塞葉には中心性鬱血、壊死、水腫変性、出血、細胞の解離等が見られる。最も特異的な変化はPAS染色陽性の細胞内封入体の出現であり、通常空胞変性、核崩壊を伴っている。このPAS陽性体は術後24時間以内に死亡した犬の殆んど全例に多数出現したが、他方その非閉塞葉及び他の生存犬又は屠殺犬に

は皆無か少数であつた。この出現には肝鬱血に伴い或はこれに加わる酸素欠乏が重要な一因子と思われる。肝鬱血に酸素欠乏が加わると極めて重篤な肝障害を来たし、個体の生命をおびやかすことも考えられる。

2) 慢性生存犬に於ては急性期の変化は殆んど消失する。しかしその閉塞葉では血管の配列が不規則となり、中心静脈は時として消失する。即ち鬱血肝の特徴と云われた中心静脈や類洞の拡張は必ずしも見られない。結合織の増加や時として偽胆管の増生が見られるが定型的な肝硬変様変化は稀であり、その発生には他の因子の関与が必要と思われる。

3) 非閉塞葉も多少共左肝静脈閉塞の影響を受ける。化膿症等を合併して死亡した犬の中には、脂肪化はむしろ非閉塞葉の小葉中心部に強いものもあつた。

4) 血管鑄型では閉塞葉の一部で肝動脈が拡大し、門脈枝はやゝ縮小、変形していた。肝静脈の分布は不規則かつ粗となり、非閉塞葉との間には多数の副血路の発達が見られた。