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EXPERIMENTAL STUDIES ON THE FAVORITE SITE OF LIVER NECROSIS AFTER THE INTERRUPTION OF THE HEPATIC ARTERIAL INFLOW

by

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I. INTRODUCTION

It was observed by Grindlay[17], Markowitz[28][29], Urabe[54], Ishiguro[20] and many others that, when a dog's liver was cut off from arterial blood flow without receiving any antibiotics, the dog would die of liver necrosis. Fraser[15] observed that in more than half of the experimental dogs, liver necrosis after the hepatic artery ligation appeared most severe in the left part of the liver by unknown cause. Urabe[54] and Nakase[31] pointed out that in the dog the favorite sites of liver necrosis after the interruption of hepatic arterial flow were the left, quadrate, middle and caudate lobes. In 1952, Honjo[18][19] confirmed that the cause of liver necrosis after the occlusion of the hepatic artery was the disturbance of the portal circulation which was induced by the arterial occlusion.

On the other hand, since Mautner and Pick[24], many authors have shown that anaphylactic shock phenomena in the dog were characterized by vascular stasis in the liver and intense congestion of the splanchnic area as well. They attributed the stasis to a constriction of the hepatic vein and their branches. Arey and many other workers pointed out that the contraction of the hepatic vein branches was due to the sphincteric activity of smooth muscles arranged in the wall of the hepatic vein.

Being interested in the activity of the sphincteric mechanism which might display itself when the hepatic arterial inflow are interrupted, the present author undertook the following experiment with cast preparations of hepatic blood vessels in order to find out topographical peculiarities existing in the course of the hepatic vein.

II. METHODS OF EXPERIMENT

(1)　Materials

Fifty-two healthy adult mongrel dogs, weighing from 4 to 24 kg, were used.

(2)　Method of the occlusion of the hepatic artery

As a premedication, dogs were administered 20 mg per kg body weight of 4 per cent morphine solution by subcutaneous injection about 30 minutes prior to the operation. At operation, local anaesthesia with about 10 ml of 0.5 per cent xylocain solution was employed.

According to the observations by URABE[54] and ISHIGURO[20], simultaneous ligation of the common hepatic, gastroduodenal and right gastric arteries causes almost complete interruption of the arterial inflow into the dog's liver. Based on this fact, the present operation was carried out by the interruption of these arteries above mentioned. Upper median incision was used to expose the portal triad. At the time of preparation of the arteries, cautious dissection was required not to impair the sympathetic nerve filaments around the common hepatic artery. The common hepatic artery was severed about 1 cm distal from the celiac axis under the double ligation. In the same way, the gastroduodenal and right gastric arteries were cut off respectively about 0.3 cm distal of their bifurcation from the common hepatic artery.

All the dogs to which any antibiotics were not administered died of liver necrosis.

(3)　Injection technique for the cast preparation of the hepatic blood vessels

a)　Perfusion : Directly after the death of liver necrosis or by sacrificing several hours after the interruption of the hepatic artery, the liver was exstirpated with the diaphragm and a certain length of the vena cava inferior adjacent to the liver. The liver is perfused with running water through cannulas inserted into the hepatic artery and the portal vein at the hilum of the liver. Until the irrigated water turns to clear from the bloody red color, the perfusion was continued under the pressure of about 100 mmHg at the hepatic artery and about 40 mmHg at the portal vein.

b)　Injection of the plastics : The material used for the injection mass was acrylic esters. Injections were made into the portal vein with colorless acrylate and in a retrograde direction into the hepatic veins with green-colored one. So far as the patency of the blood vessels were kept well and so far as the perfused water passed through the hepatic venous tributaries, a cast of blood vessel arborization could be obtained as fine as 7th order of ramification. Combination of acrylate and reagents used in the experiment is as follows[32][52] :

Methylmethacrylate monomer	90.0
n-Buthylmethacrylate monomer	10.0
Methylmethacrylate polymer	25.0
Benzoylperoxide	0.2

(Monomers must not contain hydroquinon)

Warming them in a flask for 1 to 2 minutes on a hot water-bath of 80°C until the mixture comes to oily and foamy. Then the followings were added :

Dioctylphthalate	20.0
Dimethylaniline	1.0

On this step, if necessary, oil-paint was added to the mixture as a dyestuff. This oily mixture contained in a large glass syringe was injected into the portal and hepatic veins respectively through the cannulas. To fill the portal venous system 20 ml or more of a colorless acrylate was required, while for the hepatic venous system about 30 ml of green colored one was required for the retrograde injection from the vena cava. Injection had to be done quite slowly and with moderate pressure because heavy push of the syringe might force the closed sphincters to open.

c) Corrosion: Thus injected liver was left at room temperature for 24 hours until the polymerization of acrylic resin was completed. The liver was then placed in glass jar containing concentrated hydrochloric acid for the digestion of hepatic parenchym for 1 to 5 days. It could be hastened by the addition of large amounts of fresh hydrochloric acid.

d) Washing: The specimens were then washed in running water to remove residual hepatic substances not digested by hydrochloric acid and also to wash away the dripping acid.

(4) Histological sections

To observe changes in the state of contraction of the hepatic venous system with the lapse of time, histological specimens were taken successively at a certain time intervals from the right or left lobe of the liver after the hepatic artery occlusion. After the fixation in 10 per cent formol solution for 24 hours, specimens were cut on a freezing microtome, and then stained by hematoxilin eosin.

(5) Measurement of the systemic blood pressure

To observe the effect of the interruption of the hepatic artery on the blood pressure of systemic circulation, the femoral arterial pressure was recorded. After the intravenous injection with 3 mg per kg body weight of heparin, a glass cannula was connected to a mercuric manometer with a vinyl tube filled with physiological saline solution. Before and after the interruption of the hepatic artery, systolic blood pressure was measured at intervals of 15 minutes.

III. RESULTS OF EXPERIMENT

(1) Determination of the favorite site of the liver necrosis

The interruption of hepatic arterial blood flow without administration of antibiotics resulted in fatal liver necrosis in all 27 cases. The survival time after the operation was between 12 and 80 hours, averaging 40 hours. In these 27 cases, gross observation at autopsy performed immediately after the death revealed marked necrosis constantly in certain parts of the liver. In cases in which necrosis developed diffusely all over the liver, more distinguished changes were observed in these parts above mentioned. The favorite sites were found to be as follows (Fig. 1):

1) The lower left lobe: In the peripheral half of the lobe necrotic changes appeared. The nearer to the periphery, the heavier were the tissue injuries. In the ventral margin, the corner adjacent to the upper left lobe showed severer change even in the early stage of the development of necrosis. Also in an ear-shaped protruding area located in the ventral margin of the visceral surface of the lobe, an early attack was commonly observed.

Fig. 1 The favorite sites of liver necrosis after the interruption of the hepatic artery.
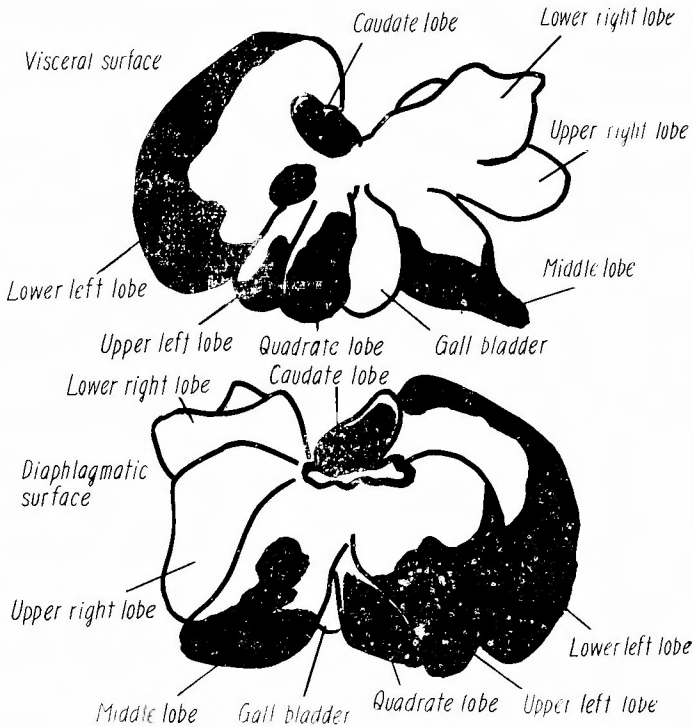
2) The upper left lobe : The favorite site spreads from the central area to the periphery of the lobe. In this lobe also, more marked changes were observed in the marginal area.

3) The quadrate lobe : One of the lobes in which diffuse and highest degree of changes took place from earlier stage. In this lobe also peripheral area was affected more intensely. Moreover, the surface of this lobe as well as that of the middle lobe adjacent to the wall of the gall bladder were observed to assume a congested tone.

4) The middle lobe : The changes were observed universally from central area to periphery. As was found in the other lobes above mentioned, the more distant from the hilum, the more intense was the lesion. In diaphragmatic surface, however, occasionally a marked necrotic zone without distinct demarcation was observed not in periphery but rather in the central area of the lobe. On the other hand, in visceral surface, the adjacent area to the gall-bladder was more markedly damaged.

5) The caudate lobe : As in the middle and quadrate lobes, necrosis of the highest degree appeared constantly in this lobe. Entire lobe was evenly affected with severe necrosis. Above all, the caudate process of visceral surface was observed to sustain the most profound changes throughout the lobe. In addition, tiny foams or hollows which might be formed with metabolic gas produced by anaerobes were frequently demonstrated on the capsule at autopsy (Such foams or hollows were recognized in the cases that survived over 34 hours.).

6) The upper and lower right lobes : There was no favorite site of necrosis. In a

few cases, however, the lobes were dotted with slightly degenerated spots.

2) Observation on cast preparations

A. The hepatic vein system

In intact dogs as well as the hepatic artery ligated ones 30 ml to 50 ml of green colored acrylic resin was injected retrogradely into the hepatic vein through the vena cava inferior. Main tributaries of the hepatic vein until 3rd or 4th order of ramification were verified to assume the same pattern of branching in all experimental dogs. The favorite sites of liver necrosis were found to have some characteristics in the mode of

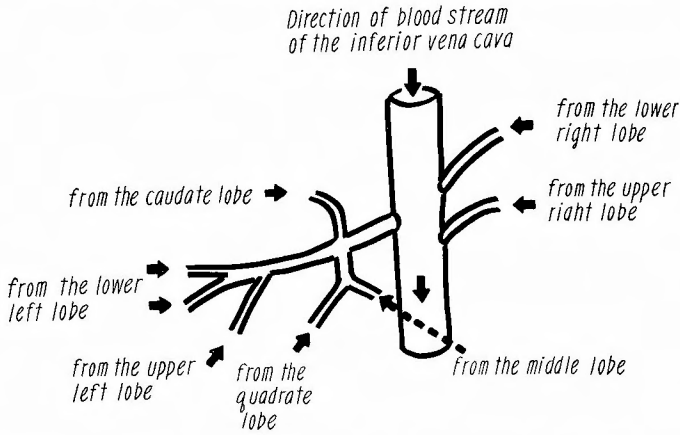**Fig. 2** Schema of the course of the left hepatic vein.
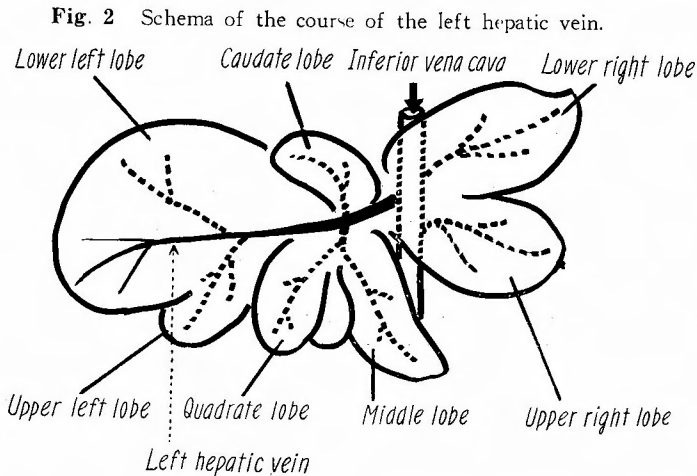
ramification of their hepatic veins.

a) One of the radices of Vena hepatica sinistra originating from the ventral corner of the lower left lobe has the longest course (Fig. 2).

b) Vena hepatica sinistra which brings venous blood together from the lower left, upper left, quadrate, middle and caudate lobes enters into the inferior vena cava with an obtuse angle so that the direction of blood stream within the vessel opposes to that of the inferior vena cava. On the contrary, blood streams from the lower and upper right lobes enter into the inferior vena cava with an acute angle so that the venous return from the right area of the liver is facilitated. In comparison with two or three right hepatic veins, single left hepatic vein is forced to convey far greater amount of blood on account of much greater volume of the left area than the right one. Consequently, drainage from the left area must generally be confronted with some disadvantages (Fig. 3).

c) In almost all cases, in visceral surface of the lower left lobe, a flat ear-shaped protruding is located on ventral margin (Fig. 4). This protruding is subjected to an early attack of necrosis, as was stated above. The course of drainage from this area is quite a circuitous one. Namely, fine radices under 6th order of ramification from this area are gathered together running towards ventrolateral direction coursing away from the hilum. Joining into the venous tributary which arised from the ventral margin of the lower left lobe with an obtuse angle of about 130°, this draining vessel confluences into Radix venae hepaticae sinistrae[11]. Thus, the venous blood from the ear-shaped protruding

Fig. 3　Schema of the outlets of the hepatic veins to the inferior vena cava.

Direction of blood stream
of the inferior vena cava

from the lower
right lobe

from the caudate lobe

from the upper
right lobe

from the lower
left lobe

from the upper
left lobe

from the
quadrate
lobe

from the middle lobe

is forced to flow in an U-shaped route to pour into the inferior vena cava. On account of such a detour, the drainage from this protruding must be impeded considerably (Fig. 4).

Fig. 4　Course of drainage from the ear-shaped protruding on ventral margin of the lower left lobe.

Direction of blood

Left hepatic vein

Ear-shaped protruding
in the lower left lobe
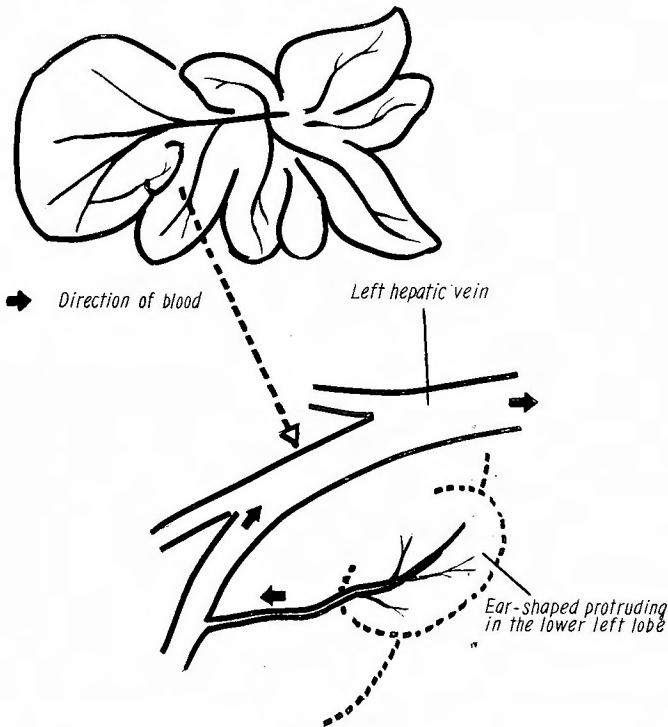
d) The vein from the quadrate lobe and that from the middle lobe join in one vein which pours into the trunk of the left hepatic vein vertically. On the opposite side of this outlet also a venous radix from the caudate lobe pours into the trunk perpendi-

cularly (Fig. 3). Hydro-dynamically, the side pressure of blood stream in the trunk of the left hepatic vein should act as a resistance to the blood flow of these two vertical branches respectively. It is a well known fact that side pressure upon a vessel wall increases inversely proportionate to the speed of blood flow within the vessel[5]. After the interruption of hepatic arterial inflow, as will be elucidated in the following chapter, venous stagnation in the peripheral parts of the hepatic veins must be responsible for the retardation of blood stream in the trunk of the left hepatic vein. In consequence, on account of a gradual rise in the side pressure upon the wall of the trunk, the drainage from both vertical branches must be confronted with an increased resistance after the occlusion of the hepatic artery. This may be the reason why the venous stagnation in the caudate and quadrate lobes although these lobes are favoured by a close situation to the hilum (Fig. 3).

B. Sphincter mechanism

It has been pointed out by many authors that dogs have relatively large amount of smooth muscles which are arranged longitudinally and spirally in the wall of their hepatic veins. Such a muscular apparatus could be observed in cast preparations of the hepatic vein as spiral grooves or as continuously arranged rings like an abacus counter[51]. That is, radices of the hepatic vein under 3rd or 4th order of ramification showed constantly spirals or ring-like folds protruding into the inside of vessel wall uniformly in all lobes. If the sphincter contracts completely, injected resin would not pass through radices farther beyond the closed sphincter. Consequently, in cast preparation, some branches under a certain order of ramification must be missed since the resin failed to fill up the lumen of these radices.

The following preliminary experiments have been performed to confirm ; whether or not the sphincter mechanism is able to function after a surgical stress such as the occlusion of the hepatic artery, and whether the lapse of time can influence upon the release of constriction of the sphincter ; and then, to confirm probable occurrence of localized constriction of the sphincter.

a) Preliminary experiments

In the hepatic vein system, because of the constriction of the sphincter, injected acrylic resin could not enter into peripheral tributaries beyond the contracted sphincter. On the other hand, in the portal vein system, absence of such a mechanism except for sinusoidal level[10][11][12] favoured to fill up the finest end of intrahepatic branches. Therefore, simultaneous injection of acrylic resin into both hepatic and portal vein system will indicate the location of defect in the vascular bed of the hepatic vein.

To study the cast preparation of hepatic vessels made after the interruption of the hepatic artery, some procedures that had been proved to constrict the sphincter were adopted. On the other hand, methods of sacrificing the animals which would have no influences upon the sphincter activity were examined :

(1) KCl

Exp. 1. After a rapid injection with 20 ml of 10 per cent potassium chloride solution into the femoral vein, dogs succumbed within a few seconds with severe convulsions. The color of the whole liver turned to dark purple as a result of rapid congestion. The

dark purplish tone of the liver did not fade after the perfusion through the portal vein except small areas adjacent to the hilum. In the cast preparation, the portal vein could be followed up to 6th or 7th order of ramification, while the hepatic vein was hardly followed up to 4th or 5th order in all cases.

Exp. 2. Ten ml of 10 per cent potassium chloride solution was injected rapidly into the femoral vein. In this case, though a half amount of the substance in the former experiment was used, the same results were obtained. That is, even after a prolonged perfusion, a dark purple tone did not fade in almost all over the lobes except close adjacent areas to the hilum. In the cast preparation, though the portal vein could be followed up to 6th order of ramification, the heptic vein was filled hardly up to 3rd or 4th order (Fig. 5).

(2)　Haemorrhagic shock

It has been well proved by FRIEDMAN[16] et al., DIBLE[8] and by many investigators that the haemorrhagic shock brings forth a contraction of the sphincter of the hepatic vein.

Exp. 1. To produce a state of haemorrhagic shock, the dog was killed by discharging arterial blood all at once from a cannula inserted into the femoral artery. In the cast preparation, the portal vein could be followed up to 6th or 7th order of ramification. On the other hand, radices of the hepatic vein were followed up to 5th order at the most.

Exp. 2. In the former experiment the whole blood was not released from systemic circulation before the death of the dog on account of rapid clot formation in the cannula inserted into the femoral artery. In consequence, it was doubtful whether the state of shock took place before the death of the animal. In the present experiment, to produce a haemorrhagic shock with certainty before the death, an interval of 10 minutes was placed between 1st and 2nd release of the femoral arterial blood. That is, after the intravenous injection with 20 mg of heparin, about 150g of blood was released from the cannula inserted into the femoral artery. Ten minutes later, more 80g of blood was taken from the same cannula and then the dog died. The sixth order of ramification in the portal vein branch and 4th or 5th order in the hepatic venous tributaries were followed up in the cast preparation.

(3)　Barbiturates

In order to represent the state of constriction of the sphincter as it were after the interruption of the hepatic artery, it was necessary to kill dogs with a substance by which the sphincter activity could not be influenced. As was observed in the following experiments, some of the barbiturates were found to be appropriate to this purpose.

Exp. 1. Isozol was first examined as one of the preparation of those barbiturates. A rapid intravenous injection was done to a dog with 0.5g of isozol dissolved in 5 ml saline solution. Five seconds after the injection the respiration, and 5 seconds later the pulsation ceased. By the perfusion of the exstirpated liver, the proper tone of the color faded rapidly all over the lobes. In the cast preparation, both the portal and hepatic vein branches could be followed up to 7th order of ramification.

Exp. 2. In this experiment, 0.3g of isozol dissolved in 5 ml saline solution was
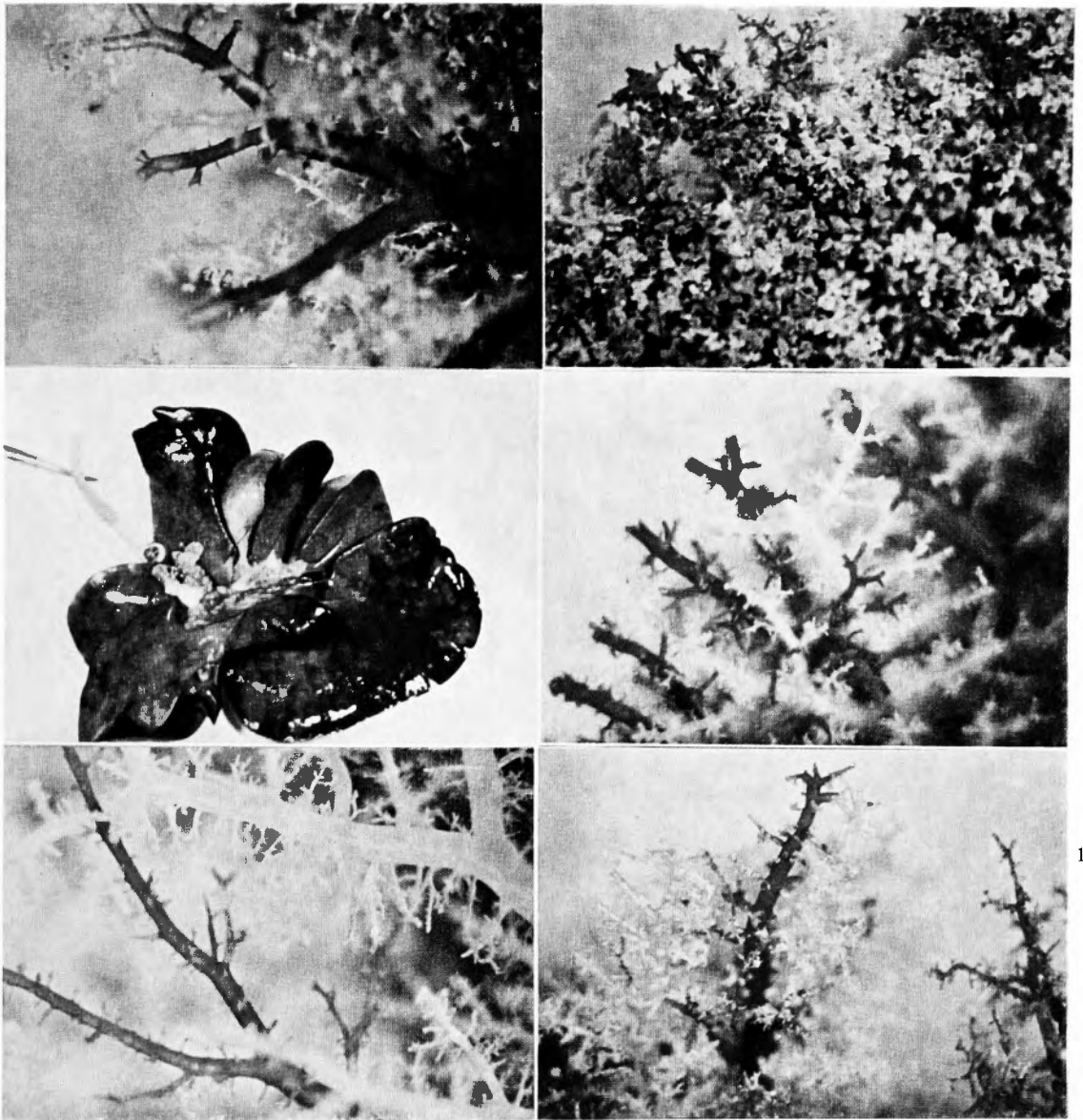
Fig. 5. Cast preparation of hepatic blood vessels of a dog killed by KCl injection.
(Green : the hepatic vein. Colorless : the portal vein)
Note : The portal branches are filled up to 6th order of ramification, while radices of the hepatic veins are filled hardly up to 3rd or 4th order.

Fig. 6. Cast preparation of hepatic blood vessels of a dog killed by isozol injection.
Note : Both the portal and hepatic veins are filled up to 6th or 7th order of ramification.

Fig. 7. Perfusion of a dog's liver exstirpated immediately after the interruption of the hepatic artery.
Note : Coinciding with the favorite sites of necrosis, a dark red tone due to stagnation did not fade away.

Fig. 8. Cast preparation of hepatic blood vessels made 1 hour after the interruption of the hepatic artery.

Note : The seventh order of ramification in the portal vein, whereas 5th order in the hepatic vein can be observed. In addition, abnormally interrupted hepatic venous radices (green) are observed.

Fig. 9. Cast preparation of hepatic blood vessels made 3 hours after the interruption.

Note : The portal veins are filled up to 6th order of ramification, while the hepatic veins up to 5th, occasionally 4th order.

Fig. 10. Cast preparation of hepatic blood vessels made 5 hours after the interruption.

Note : The portal veins are filled up to 7th order of ramification, while the hepatic veins up to 5th, occasionally 6th order.

rapidly injected into the femoral vein of a dog. Similar result as Exp. 1 was obtained. Namely, in the cast preparation, ramification as fine as 6th or 7th order was observed both in the portal and hepatic venous branches (Fig. 6).

Exp. 3. Five ml of 10 per cent ravonal solution was rapidly injected into the femoral vein of a dog. Likewise as in Exp. 1 and 2, 6th or 7th order of ramification was observed in both the portal and hepatic veins in the cast preparation.

The results obtained from those preliminary experiments are presented en bloc in Table 1. From these data following facts were ascertained; When dogs were killed by

Table 1. Results of preliminary experiment

Cause of death	Experimental dog			Orders of ramification of injected vessel tributaries	
	Dog No.	Body weight (kg)	Sex	Portal vein	Hepatic vein
Haemorrhagic shock	C_1	5.5	f	6 or 7	5
	C_2	4.0	f	6 or 7	4 or 5
KCl	A_1	13.5	m	6 or 7	4 or 5
	A_2	9.5	m	5 or 6	3 or 4
Isozol	B_1	6.0	m	7	7
	B_2	6.0	m	6 or 7	6 or 7
Ravonal	B_3	9.5	f	6 or 7	6 or 7

certain means which cause the contraction of the sphincter, the casts of the hepatic vein showed lesser order of ramification than that of the portal vein. On the other hand, when a dog was sacrificed by the injection of isozol or ravonal, branches of both the hepatic and portal veins could equally be followed up to 6th or 7th order of ramification.

Thus, some kinds of barbiturates were demonstrated that they did not affect the activity of the sphincter in the hepatic vein after the death of dogs.

b) Changes observed after the occlusion of the hepatic artery.

Table 2. Changes in ramification observed after the interruption of the hepatic artery.

No. of experiment	Experimental dog			Time after the interruption (hour)	Orders of ramification of injected blood vessels	
	Dog No.	Body weight (kg)	Sex		Portal vein	Hepatic vein
1	40	15.0	f	1/4	6 or 7	5
	46	9.5	m	1/4	6 or 7	5
2	36	4.5	m	1	6	4 or 5
	32	8.5	m	1	6 or 7	5
3	37	11.5	m	3	6	4 or 5
	33	14.5	m	3	7	5
4	34	15.0	m	5	7	5 or 6
	28	9.5	m	5	6	5
5	35	11.5	m	8	6	6
6	38	10.5	m	10	7	5 or 6

Note; All experimental dogs were killed by intravenous injection with 0.3g of isozol.

Does the constriction of the sphincter exist permanently or not? Does the constriction relax wholly or partially after a short duration? To solve these problems, cast specimens prepared at certain intervals of time after the occlusion of the hepatic artery were examined (Table 2).

Fifteen minutes, 1, 3, 5, 8 and 10 hours after the interruption of the hepatic artery, each dog was killed by a rapid intravenous injection with 300 mg of isozol. On each cast preparation, the orders of ramification of the hepatic and portal veins were investigated.

Exp. 1. The dog's liver was exstirpated 15 minutes after the interruption of the hepatic artery. At perfusion through the portal vein, as was shown in Fig. 7, dark tone of the congested liver did not fade in the following parts of the liver; the greater part of the upper and lower left lobes, peripheral one third of the quadrate and middle lobes, and peripheral one half of the caudate lobe. The blood in these areas was not rinsed away from sinusoids and radices of the hepatic vein by perfusing water. In the cast preparation, the portal vein could be followed up to 7th order of ramification, while the hepatic vein to 5th order.

Exp. 2. The liver was exstirpated one hour after the interruption of the hepatic artery. In the cast preparation, 6th or 7th order of ramification in the portal vein could be discriminated grossly, whereas 5th order in the hepatic vein. As is shown in Fig. 8, however, it is interesting that interrupted venous radices of 4th or 5th order of the ramification were found in the peripheral zone of the lower left lobe (Fig. 8).

Exp. 3. The liver was exstirpated 3 hours after the operation. In the cast preparation, the portal venous branches were followed up to 6th order of ramification, while 5th or 4th order in the hepatic venous radices (Fig. 9).

Exp. 4. The liver was exstirpated 5 hours after the interruption of the hepatic artery. At perfusion, dark red tone of the congested liver did not fade away in the peripheral one half of the lower left, upper left, quadrate and middle lobes. In the cast preparation, the portal venous branches were followed up to 7th order, whereas the hepatic venous radices to 5th, occasionally 6th order of ramification (Fig. 10).

Exp. 5. The cast were made 8 hours after the interruption of the hepatic artery. Both portal and hepatic venous tributaries could be followed up to 6th order of ramification.

Exp. 6. At 10th hour after the interruption of the hepatic artery, dogs were killed and the livers were exstirpated. In visceral surface, periphery of the left and quadrate lobes already presented necrosis grossly. At perfusion, in a peripheral half of the upper left, lower left, quadrate and middle lobes as well as at the margin of the upper right lobe congested dark tone did not fade. In the cast preparation 7th order of the portal venous branch and 4th or 5th order of the hepatic venous radices were observed.
The results of this series of experiment are presented in Table 2.

Exp. 7. After the death of liver necrosis, in 12 dogs acrylate was injected into the portal and hepatic venous system, in 6 dogs into the hepatic venous system solely and in 3 dogs into the portal venous system solely. The results obtained from this series of experiment are presented in Table 3.

Table 3 a. Changes in ramification observed after the death of liver necrosis.
(Cast preparations injected into the portal and hepatic veins).

Experimental dog			Survival time (hour)	Orders of ramifications of injected blood vessels	
Dog No.	Body weight (kg)	Sex		Portal vein	Hepatic vein
18	8.5	m	16	6	6
19	11.5	m	27	7	5 or 6
20	7.0	m	25	6	5 or 6
22	10.0	m	24	6	6
24	11.5	f	24	6 or 7	6 or 7
25	9.0	m	32	7	4
27	8.0	f	48	7	7
29	10.0	f	50	6 or 7	6
30	10.0	m	24	6 or 7	4
41	14.0	m	30	5 or 6	4 or 5
43	7.0	f	12	7	5 or 6
45	14.0	m	23	6	6

Table 3b. Changes in ramification observed after the death of liver necrosis.
(Cast preparations injected into the hepatic vein solely)

Experimental dog			Survival time (hour)	Orders of ramification of the hepatic vein
Dog No.	Body weight (kg)	Sex		
5	7.5	m	77	7
6	9.5	f	40	6
10	6.0	m	35	7
11	9.0	m	35	6 (4 or 5)
14	8.5	f	54	6
16	12.0	m	58	6 (3 or 4)
17	10.5	f	39	5

Note ; Each parenthesized value represents the orders of ramification of the hepatic vein at the site of localized filling defect.

Table 3 c. Changes in ramification observed after the death of liver necrosis.
(Cast preparations injected into the portal vein solely)

Experimental dog			Survival time (hour)	Orders of ramification of the portal vein
Dog No.	Body weight (kg)	Sex		
1	11.0	f	80	7
2	9.0	f	62	7
15	4.5	m	13	6

As is shown in Table 3, the orders of ramification of the finest hepatic venous radices in the cast preparations were found to be of varying degree from case to case, so that, after the death of the dog, there could hardly be found a definite tendency in the attitude of the sphincter mechanism.

In one case in which the resin was injected into the hepatic venous system solely,

as is shown in Fig. 11, the degree of ramification of the venous cast was not uniform in each lobe.　Although the greater parts of the most lobes were filled up to 6th order of ramification, the ventral edge of the lower left lobe and the pointed edges of the middle and caudate lobes were observed to be filled up to only 3rd or 4th order in accordance with strongly necrotized areas, thus suggesting an existence of localized constriction of the sphincter (Fig. 11).

Fig.11　Cast preparation injected into the hepatic veins solely
(The dog died of liver necrosis 35 hours after the interruption.)

Note　　Although greater parts of lobes were filled up to 6th order of ramification, the ventral edge of the lower left lobe and the pointed edges of the middle and caudate lobes were filled up to only 3rd or 4th order.

Fig. 12.　A longitudinal section of a hepatic venule
(The liver was exstirpated 8 hours after the interruption.)
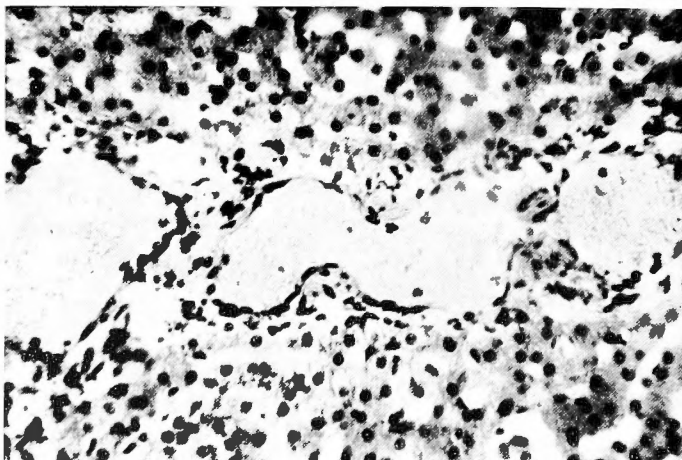
Note :　A conspicuous constriction of the smooth muscle layer is characteristic.

As is shown in Table 3, up to 5th hour after the interruption of the hepatic artery, the sphincter of the hepatic vein was proved to constrict uniformly in all cases from the existence of inperfusable area in the exstirpated liver and from the difference in the order of ramification between the portal and hepatic venous branches in the cast preparations. On the contrary, as the time passes more than 5 hours after the interruption of the hepatic artery, especially in the cast prepared after the death of animals, various degrees of constriction of the sphincter was characteristically observed.

(3)   Histological examinations

After the interruption of the hepatic artery, histological examination of the constriction of smooth muscle layer in the hepatic venous wall was performed. With certain intervals of time after the occlusion of the hepatic artery, tissue specimens of the liver were taken from the parts in the left and right lobes as described below   (Left : ventral margin of the lower left lobe ; Right : ventrolateral edge of the lower right lobe). The specimens thus taken were fixed in 10 per cent formol solution for 24 hours, and then frozen sections were stained with hematoxylin eosin. Tissue specimens were taken before the operation, immediately after the operation, 1, 3, 4, 5, 6, 8, 24 and 48 hours after the operation.

Results : In histological specimens prepared immediately and one hour after the operation, constriction of the sphincter was observed continuously along the hepatic venous tributaries, especially along finer radices in almost all cases. Afterwards, as is seen in Table 4, the degree of the sphincteric constriction seemed to become less prominent with the lapse of time.

Whenever the constriction existed in a specimen taken from the left lobe, the same degree of the constriction was always confirmed in the right lobe, suggesting the existence of uniform constriction of the sphincter mechanism in every section of lobes.

Attention should be given to the fact that widely dilated lymphatic channels were found outside of the muscular layer of strongly constricted venous radices (Fig. 12). Similar dilatation of the lymphatic vessels has been remarked by ELIAS and POPPER[10] (1955) in the dog's hepatic vein on anaphylactic shock.

Table 4. Constriction of the sphincter after the interruption of the hepatic artery observed in histological specimens.

	Whether constricted or not	
	right lobe	left lobe
pre-operative	no	no
immediately after		yes
1 hour after	yes	yes
3 hours after	yes	no
4 hours after		no
5 hours after		no
6 hours after	no	no
8 hours after		yes
24 hours after		no
48 hours after		no

Fig. 13   Changes in blood pressure after the hepatic artery occlusion

Interruption
mmHg

100

50

0

0   6   12

Hours after the interruption

(4)　Measurement of arterial pressure

In five dogs, systolic blood pressure was recorded continuously in the femoral artery before and after the interruption of the hepatic artery.

Results of measurement are summarized in Fig. 13. Following an analogous curve, the blood pressure falls down in all cases.　That is, immediately after the occlusion of the hepatic artery, a sharp precipitation of the blood pressure was observed.　Though a temporary restoration to the pre-operative level was observed 1 to 2 hours after the operation, secondary fall of the blood pressure developed irreversibly until the death of animals.

Ⅳ.　DISCUSSION

Such a primitive circulating system that dual supply with single venous drainage may form some of the characteristics of the hepatic circulation.　Despite the existence of the portal inflow which is capable of conveying almost 70 per cent of oxygen required by the whole liver, the hepatic artery occluded liver falls into necrosis inevitably.　Furthermore, it has been confirmed that this liver necrosis takes place in certain areas of the liver[15)20)31)54)].　As for the main cause of liver necrosis after the occlusion of the hepatic artery, it has been generally accepted that the hepatic tissue anoxia due to the interruption of arterial inflow is responsible.　In this respect, MARKOWITZ and his co-workers[27)28)] suggested that hepatic necrosis which developed after ligation of the hepatic artery was primarily caused by the anaerobic proliferation of organismus which, in turn, caused destruction of liver cells.　FRASER[15)] insisted that the fulminating bacterial proliferation might be secondary to an antecedent ischemic parenchymal necrosis which constituted the primary, though not necessarily the fatal, lesion.

On the other hand, MALLET-GUY[25)] placed great emphasis on the vasomotor unbalance which was produced by the impairment of sympathetic fibres inevitably occurred in the course of the operation of the hepatic artery occlusion, resulting in such a vasomotoric disturbance which may lead the liver to passive congestion.

From an original point of view, HONJO et al[18)19)]. have pointed out the significance of portal circulation after the interruption of the hepatic arterial inflow.　He demonstrated that development of liver necrosis should not be caused by the abolition of arterial oxygen supply itself, but by the temporary disturbance of the portal circulation.

In general, various reactions of animals to anaphylactic shock are dependent on the mode of distribution of smooth muscle in the body.　Namely, as has been demonstrated by AREY and SIMONDS[2)] in guinea pigs, the contraction of the smooth muscle in the bronchioles prevents the egress of air from the lungs and causes marked emphysema of the lung so characteristic of anaphylactic shock in those animals.　The dog, as is seen in SIMONDS'[44)45)] elaborate description, possesses in its hepatic venous wall an analogous histological characteristics as found in the bronchioles of the guinea pig.　That is, a relatively huge mass of smooth muscle is located continuously from the central vein to the outlet of the hepatic vein to the vena cava inferior forming throttle valves, so that its contraction by anaphylactic shock will block venous drainage from one of the largest and most important vascular areas of the body.　An intrahepatic obstruction due to the

contraction of this vein will bring about the impounding of a very large percentage of circulating blood in the liver as well as in the splanchnic area.

Since early recognition of this peculiar arrangement of smooth muscles in the hepatic vein of dogs and seals made by BRISSAUD and SABOURIN[3] in 1888, who described the existence of valves formed from folds of the vessel wall, description of this mechanism has been made by many authors. MAUTNER and PICK postulated that the hepatic veins might serve as a "throttle" mechanism, which resulted in spasm of the finer radices when activated by injection of peptone or histamine or by an anaphylactic shock. Furthermore, Simonds and his co-workers clarified that the intrahepatic stagnation induced by anaphylactic shock or peptone shock was due to the post-sinusoidal blocking. ELIAS and FELLER[9] found out the existence of the sphincter in human liver at the caval end of each hepatic vein. In addition, they demonstrated that the sphincter at hepatic venous outlet could be constricted by injection of hot formaldehyd solution or barium chloride through the vena cava into the hepatic veins. BAUER et al[4]. also studied the influence of adrenalin and histamine on the sphincter mechanism of human liver located in hepatic venous outlet. The existence of the sphincter mechanism in rabbits' liver was confirmed by STARCK[46] and the sphincter mechanism in cats, rabbits, dogs, horses, men and other animals was studied by TISCHENDORF[50].

Being interested in the existence of the sphincter mechnism in the hepatic vein since earlier stage of his studies, H. POPPER also demonstrated the constriction of the sphincter at caval openings in the human liver and also in dog's one by pituitary extract, barium chloride, hot formaldehyd solution, heat, faradisation[33]. Afterwards, he also proved that such stimuli as anaphylactic shock, peptone, histamine, digitoxin, ascaris extract and hydatid cyst fluid was able to put this mechanism into action[35].

On the other hand, DEYSACH introduced a new anatomical concept called "small sluice channels" in his thorough studies concerning the throttle mechanism of various species of animals. These small sluice channels are specially arranged side branches of the sublobular veins which arise from the confluence of many sinusoidal capillaries. By these channels, a certain amount of blood from sinusoidal capillaries may by-pass the central veins and flows directly into the sublobular veins, thus contributing to the regulation of the hepatic circulation. His detailed observations also clarified the activities of these throttle mechanisms on adrenalin and other pharmacodynamics. SNYDER[47] examined autonomic innervations of the sphincter and their reactions to several pharmacodynamics in many vertebrates. The significance of the sphincter mechanism in hepatic circulation, according to this author, consists in the ability to arrest and impound a considerable amount of systemic blood in the hepatic vascular bed, and also to discharge impounded blood suddenly into the vena cava, thus influencing on the systemic circulation. WAKIM and MANN[56][57][58] scrutinized constriction of hepatic veins after the electric stimulation of the hepatic plexus or after the administration of some medicaments by means of the quarts-rod transillumination technic.

It is generally accepted that this sphincter mechanism is responsible for the restriction of hepatic outflow. In this connection, after a thorough follow up of smooth muscle layer in the hepatic vein of seals, dogs, whales and other submergible animals, AREY et al[1].

postulated that the sphincter of the hepatic vein is apparently a mechanism to restrict the return of venous blood from the visceral circulation to the heart during submergence, making the best use of available oxygen in the visceral area. Furthermore, he suggested that the alternate relaxation and contraction of the smooth muscle of the hepatic veins might be a method of controlling the circulation in normal animals. However, according to the observations by the present author, an occurrence of such a rapid repetition of contraction and relaxation was quite doubtful. Considering from the fact that the dog's intrahepatic sphincters possess an ability to arrest[13] blood flow entirely these sphincters seem to differ essentially from the venous valves of extremities in their function. Recently, H. POPPER elucidated on this problem conclusively as follows : The contraction of these sphincters in shock is probably the main cause of the functional and structural damage of the liver.

By means of vinyl cast preparations, THOMAS and ESSEX[51] reported the morphological changes of the hepatic sphincters of dogs in shock induced by the injection of ascaris extract or by the ligation of the hepatic artery. They confirmed no rings of constriction in the portal side, whereas noticed very remarkable changes in the hepatic venous system. According to their observation, a cast of the hepatic vein appeared to be made up only of large vessels, because many of the smaller branches were not filled. The spasm which occurred in the entire hepatic venous vasculature took the form of bands of constriction arranged in a spiral fashion, giving the vessels an appearance of a corkscrew. Although more pronounced in the smaller vessels, constriction was observed also in many of the larger ones. In some instances, the constriction appeared to be more pronounced at the junction of vessels. However, it is evident from the observations by the present author that a corkscrew-formation means the possibility of passage of venous blood through the referred vessels even though augmented resistance may exist. Accordingly, marked portal congestion would never be attained by the constriction of the sphincter to such a degree that smaller radices can be filled with resin. In addition, such a corkscrew-formation can be observed after death even in some conditions other than shock induced by anaphylaxy or hepatic artery ligation.

In other words, it may be needed with utmost certainty the complete blocking of the sphincters in smaller radices to produce an intense portal congestion by which fatal liver necrosis might be attained. Therefore, in cast preparation, such a heavy portal congestion that is responsible for liver necrosis must be manifested as filling defects of smaller venous radices. Because of the successive extension of the sphincteric constriction from the central veins to larger truncus, and also because of a stronger degree of constriction in smaller tributaries, it may be reasonable to represent the intensity of constriction of the sphincter by the order of ramification of venous radices which could be filled with acrylic resin. THOMAS and ESSEX also observed typical rings of constriction 2 hours after the hepatic artery ligation in dogs. They were the first to confirm the constriction of sphincter after the interruption of hepatic arterial inflow. However, none of them remarked the causal relation between the behavior of sphincter and the development of liver necrosis after the ligation of the hepatic artery.

By means of cast preparations, blood pressure measurement and histological specimens,

the present author has demonstrated that the constriction of sphincter of the hepatic venous system could take place after the occlusion of the hepatic artery.

In a curve of blood pressure after the hepatic artery occlusion, as is shown in Fig. 13, the first temporary hypotension is assumed to be due to a constitutional reaction[23] upon such an agression as the hepatic artery ligation. The second gradual downward curve of systemic blood pressure can be interpreted as an exertion of effects of intrahepatic, and then splanchnic pooling upon the systemic pressure. With the lapse of time, the development of liver necrosis must be added to an aggravation of the systemic blood circulation.

In histological specimens of a few cases, distinct contraction of muscle layer in the wall of smaller hepatic venous tributaries was observed after the interruption of the hepatic artery.

Coinciding with that of THOMAS and ESSEX[51], observations by the author in cast preparations and in histological sections showed that intense constriction occurred in entire hepatic venous system after the occlusion of the hepatic artery. Presumably, gradual relaxation of the constricted sphincters must take place more or less corresponding to the intensity of the aggression upon the experimental dog. However, by unknown cause, persistence of the constriction was observed in certain parts of the dog's liver in some cast preparations.

Up to 5th hour after the interruption of the hepatic artery, finer hepatic venous tributaries than 5th order of ramification could not be filled uniformly all over the lobes due to intense constriction of sphincter mechanism, whereas at 8th hour after the interruption and thereafter, similar to the portal branches, 6th or 7th order of the hepatic venous radices were filled in most instances. From the facts described above, it may be accepted that, in the majority of cases, at about 5th hour after the interruption and thereafter the constricted sphincter starts to relax gradually. As the relaxation of the sphincter proceeds, impounded blood in portal vascular bed should be drained to the inferior vena cava by way of the restored hepatic venous circulation. However, on account of some anatomical disadvantages as described above in venous return existed in certain parts of dog's liver, localized portal stagnation may be supposed to persist in these parts of the liver even after the relaxation of the sphincter. It is quite interesting that these areas were identified by the author to be the favorite sites of the liver necrosis. In other words, even after the lessening of generalized portal stagnation provoked by the constriction of the sphincter in the whole liver, continuance of localized stagnation must exist in the periphery of the lower and upper left, quadrate, middle and caudate lobes that are known as the favorite sites of liver necrosis. In consequence, these areas of the liver necessarily fall into an anoxic condition which, in turn, presents favorable media to the proliferation of anaerobes that have been proved to exist[15)28)59)] constantly in dog's liver. Accordingly, it can be postulated that a fulminating proliferation of those bacteria results in the fatal necrosis which develops mainly from these areas.

V SUMMARY AND CONCLUSIONS

Almost complete interruption of arterial blood supply to the liver was achieved by

the occlusion of the common hepatic, gastroduodenal and right gastric arteries. Consequently, all dogs that operated upon died of liver necrosis. Liver necrosis which developed after the interruption of the hepatic artery could be found exclusively in certain parts of dog's liver. By means of cast preparations of intrahepatic vasculatures and of histologic specimens, establishment of the favorite sites of liver necrosis was made.

　　　1)　The favorite sites of liver necrosis after the interruption of the hepatic artery were as follows: Peripheral half of the lower and upper left, quadrate and middle lobes and the entire caudate lobe.

　　　2)　After the interruption of the hepatic artery, marked constriction of the sphincteric apparatus in the hepatic venous tributaries was verified, being accompanied with portal stagnation in all lobes of the liver. At the same time, irreversible hypotension was noted.

　　　3)　Even after the relaxation of the sphincter, on account of some hydrodynamic characteristics existed in hepatic venous system, hepatic venous drainage from the favorite sites of liver necrosis was impeded considerably. Thus, on the basis of the persistence of localized portal congestion in these areas, liver necrosis must develop.

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肝動脈血流遮断後の肝壊死好発部位について

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犬の総肝動脈，胃十二指腸動脈及び右胃動脈を切断すると，肝の一定部位を中心として高度の壊死が起り犬は死亡する．この際の肝壊死の成因に関して，本庄らは肝動脈遮断後に起る一時的な門脈循環障害が重大な要素である事を明らかにした．

著者は，肝動脈遮断術を行つた犬の肝静脈系及び門脈系の血管鋳型標本を作り，組織標本と併せて観察を行つた．之により，肝静脈系には特異な括約筋構造が存在して或種の刺戟により之が収縮して静脈中の血流を全く停止せしめ得る事，及び，一部の肝静脈枝の走行には水力学的見地より血液還流上，不利な条件が存している事等を認めた．

肝動脈遮断後の肝壊死好発部位は，左上葉，左下葉，方形葉及び中葉の夫々半ばより辺縁にかけて，及び，尾状葉全体であるが，これらの好発部位は何れも上記の肝静脈枝の走行上，特殊な条件が存在する為，血液還流が円滑でない領域と一致している事が鋳型標本により確認された．

肝動脈遮断と云う侵襲により，肝静脈系全体の括約筋が収縮し，この為，肝静脈からの血液還流が阻止されるので全葉に亘つて門脈性の鬱滞が惹起される．一定時間後，括約筋収縮が解除されても，上記の好発部位では血液還流はなお円滑を欠くため，依然として門脈性鬱血が残存する事になる．従つて，此処では局部的な低酸素状態が持続するので，これらの部位が肝壊死発生の母地となるのである．