

An Experimental Study on Partial Drainage of Bile in Obstructive Jaundice

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I. INTRODUCTION

PONFICK¹⁾, FISHBACK²⁾, MIKAMI³⁾, and others have demonstrated that experimental animals can well survive extensive resection of the liver without manifestation of jaundice or other untoward general disturbances, and they clarified that the liver is possessed of a large reserve capacity to compensate the entire function with its relatively small part.

On the other side, it was discovered by MCMASTER, ROUS and others⁴⁾ that jaundice does not appear in dogs and monkeys, even if bile excretion from 75 per cent of the entire liver be obstructed. SHIBAGAKI⁵⁾ also reported that jaundice did not appear when bile was drained from one-sixth of the entire liver. Furthermore, SCHALM⁶⁾⁷⁾, who carried out the same experiments in rabbits, ascertained that ligation of the bile duct from 75 per cent of the entire liver is feasible without manifestation of jaundice, from which observation he postulated that for the manifestation of obstructive jaundice in men, it would be necessary that both right and left bile duct should be occluded, and he further presumed that if the hepatic duct on one side be patent, the duct on the other side can be spared when required.

There can be seen many clinical cases reported by HIJMANS VAN DEN BERGH and SNAPPER⁸⁾ and others⁹⁾¹⁰⁾¹¹⁾, in which jaundice could not be observed at all, despite the occlusion of a large branch of the biliary tract.

As obviously understood from the results of these experiments and clinical observations, it is assumed that the normal liver has the ability to excrete bilirubin in serum adequately, provided a drainage from a certain amount of the parenchyma is maintained.

An establishment of bile drainage from the entire liver is scarcely successful in cases of jaundice with obstructive moment such as malignant neoplasms in the liver hilum. In such cases, drainage of the bile merely from a restricted area of the liver has been attempted based on the results of experiments on the above mentioned reserve capacity of the liver and clinical observations, and favorable results have been obtained such as release of jaundice, improvement of general conditions and prolongation of survival time. However, in cases of long-persisted jaundice with resulting serious impairment of the liver parenchyma, the outcome of the operation is frequently uncertain, the jaundice being hardly improved by the drainage of the bile from some part of the liver, and sometimes postoperative aggravation of jaundice can be observed.

Concerning such cases, it was recently reported by MISTILIS and SCHIFF¹²⁾ that release of jaundice can be enhanced by resection of the hepatic segment where the bile drainage is impossible. This phenomenon is interesting as a measure of mitigating jaundice when the partial release of biliary obstruction demonstrates no remarkable effect. Clinical application of this measure is, however, considered to be threatening in cases of long-persisted obstructive jaundice with impairment of the liver parenchyma because of its too large operative invasion.

It may be interpreted that enhancement of release of jaundice is the result of improvement of bile excretion caused by appearance of functionally active regenerative cells of the liver in the area with bile drainage, being provoked by hepatectomy. If this interpretation be acceptable, some device of provoking hepatic regeneration with less affection, instead of hepatectomy, in the area with bile drainage will have a large clinical value.

At this point, based on the phenomenon, as reported by ROUS and LARIMORE¹³⁾, that active hepatic regeneration can be induced by an interruption of portal blood flow concurrently with marked atrophy in the hepatic segment deprived of portal blood supply, the degree of which amounting to the compensatory hypertrophy of the residual liver after hepatectomy, portal blood flow to the area without bile drainage was interrupted simultaneously with the partial drainage of bile in obstructive jaundice, in the aim of provoking hepatic regeneration in the area with the bile drainage, and the effect of this procedure on the improvement of jaundice was studied.

II. PARTIAL BILE DRAINAGE IN DOGS WITH OBSTRUCTIVE JAUNDICE

1. Animal

Adult healthy mongrel dogs of both sexes were used, in the fasting state for 24 hours. The abdomen was opened under the anesthesia with intravenous injection of Isozol, and the common bile duct was ligated. Experiments were carried out in jaundiced dogs of 5th day after the ligation of the bile duct.

2. Methods

The liver of dog is lobulated in 7 lobes, the bile duct and portal vein bifurcating and entering the each lobe as shown in Fig. 1. Proportion of weight of each lobe and

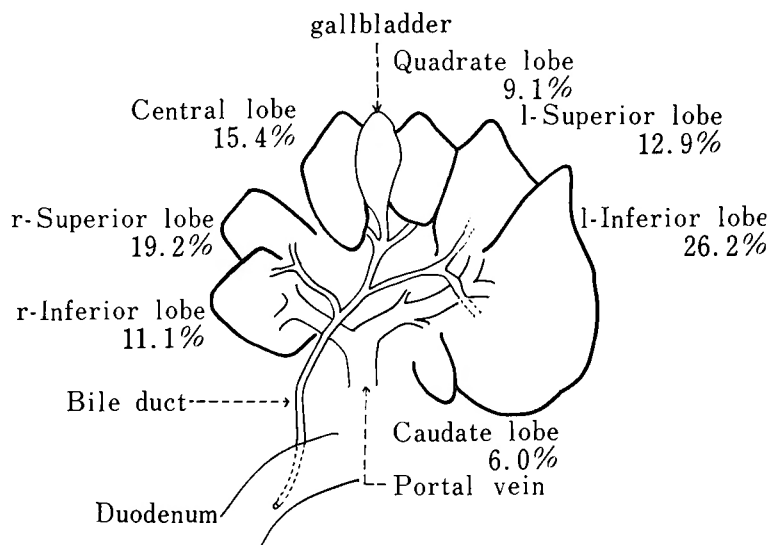


Fig. 1

Table 1.

			Percentages of each lobe to total liver weight.							
	Body weight (kg)	Liver weight (g)	Liver index	r-Super. lobe	r-Infe. lobe	l-Super. lobe	l-Infe. lobe	Cent. lobe	Quad. lobe	Caud. lobe
Means	6.0	179	3.0	22.9	10.6	12.8	25.7	18.4	5.6	4.0
	9.0	280	3.1	19.2	13.3	10.4	25.8	15.0	10.0	6.3
	9.0	271	3.0	19.9	8.2	15.5	27.3	17.3	7.0	4.8
	9.5	304	3.2	16.1	12.5	11.8	27.3	19.4	4.9	7.9
	5.0	140	2.8	17.9	10.7	14.3	25.0	7.1	17.9	7.1
	7.7	235	3.0	19.2	11.1	12.9	26.2	15.4	9.1	6.0

that of the entire liver to body weight are represented in Tab. 1, the latter being represented in the term of liver index, which was calculated from the percentage of liver weight to body weight.

In the present experiment, bile was drained from the right superior and inferior lobes which correspond approximately to 30 per cent of the entire liver.

i. Operative Procedures

Following procedures were carried out in the jaundiced dogs produced as described in the above, the diet being kept away for 24 hours pre- and postoperatively. After the operation, 200 to 300 cc of 5 per cent glucose solution was given subcutaneously, and 30×10^4 units of penicillin was intramuscularly administered everyday for a week.

Group 1: Group of simple partial drainage of bile for the control study (abbreviated to control group, hereafter).

Three branches of the bile duct were doubly ligated at the points as illustrated in Fig. 2, a, in order to check the outlet of bile from 70 per cent of the entire liver.

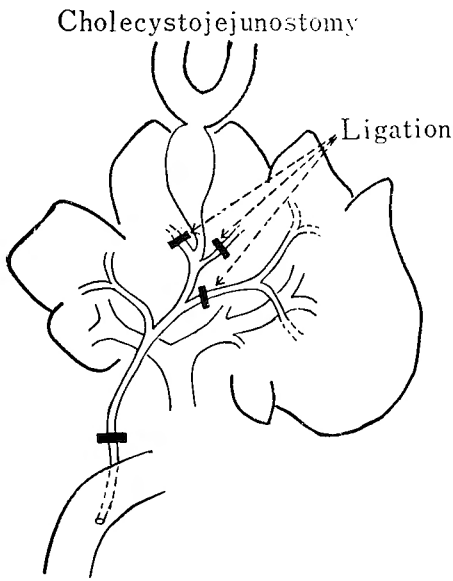


Fig. 2a Group of control of experiment in II.

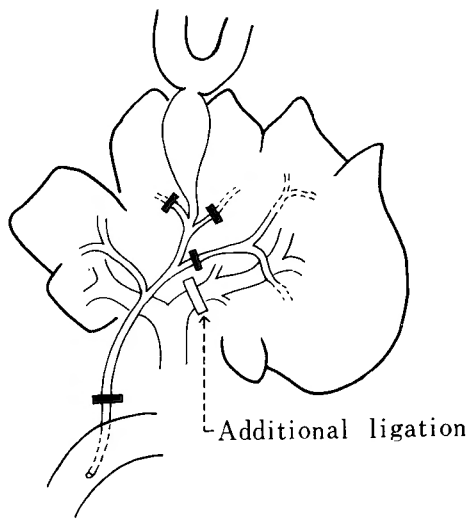


Fig. 2b Group of additional ligation of portal branch.

Then, cholecystojejunostomy was performed to drain bile from 30 per cent area into the jejunum. Braun's anastomosis was placed between both intestinal arms before and after the cholecystojejunostomy.

Group 2 : Group of additional ligation of portal branch to the area having no bile drainage (abbreviated to group of additional ligation of the portal branch, hereafter).

Bile was drained in the same way as in Group 1, and the portal branch to the area having no bile drainage was ligated as shown in Fig. 2, b.

Group 3 : Group of hepatic resection.

The left superior and inferior lobes corresponding to 40 per cent of the entire liver were resected as illustrated in Fig. 2, c. Bile was drained from the residual liver into the jejunum through cholecystojejunostomy. Although resection of the entire area without bile drainage as described in Group 1 and 2 was attempted, this was almost invariably lethal in dogs having obstructive jaundice, and postoperative study could not be continued. Accordingly, bile drainage was carried out from 60 per cent of the entire liver in this group.

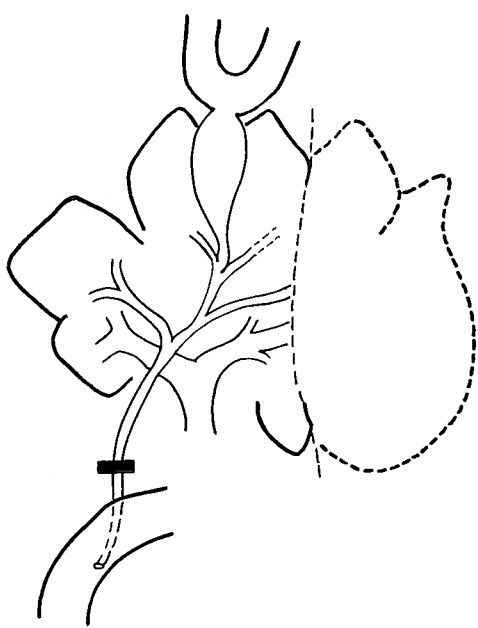


Fig. 2c Group of hepatectomy.

- ii. Examinations
 - a. Determination of total bilirubin

in serum¹⁴⁾.

b. B.S.P. retention test. 5 mg/kg body weight of heptasulphalein was injected into the femoral vein, and blood was taken 15 minutes later for the colorimetry from the femoral vein of the other side.

c. A/G ratio.¹⁵⁾

d. Cholesterin-ester ratio.¹⁶⁾

iii. Histological study

Histological study was routinely carried out in all the experimental animals about 2 months after the operation. Sections were taken from the area both with and without bile drainage, respectively in each animal, which were then fixed in a 10 per cent formalin solution and doubly stained with hematoxylin and eosin.

3. Results

i. Examinations of liver function

a. Total bilirubin in serum

In control animal, total bilirubin level showed temporary increase after the operation which was followed by a tendency of decrease, although hardly returning to normal. In the group of additional ligation of the portal branch, the bilirubin level began to decrease from the day immediately after the operation and returned to normal within 5 days (Fig. 3). Although the level showed slight fluctuation thereafter, it was maintained within the

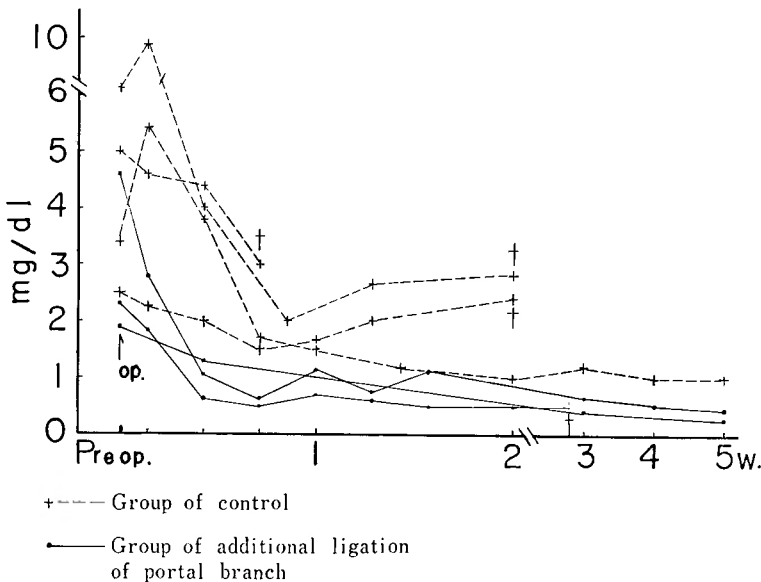


Fig. 3 Serum bilirubin level.

normal range, and the animals survived for long. There were many cases in control group that showed an elevation of total bilirubin level again thereafter finally leading to death, revealing inflammatory changes in the gall bladder and bile duct at necropsy.

Bilirubin excretion in the group of hepatic resection showed the same tendency as in the group of additional ligation of the portal branch (Fig. 4).

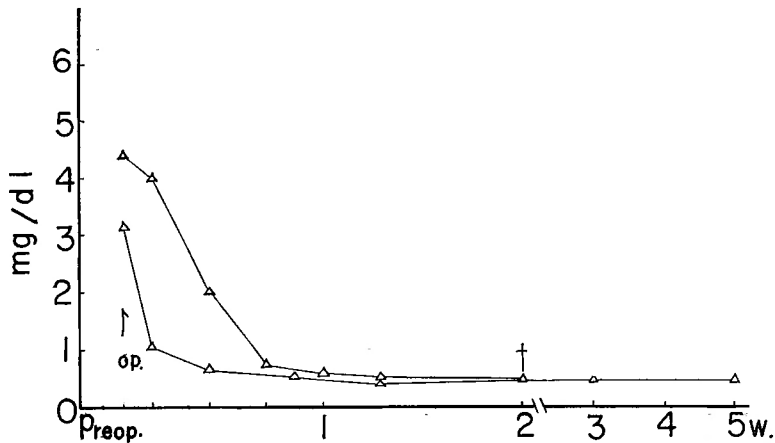


Fig. 4 Serum bilirubin level in group of hepatectomy

b. Other examinations of liver function

In all cases, B. S. P. retention was around 10 per cent, the test being carried out once on 5th day after the operation. A/G ratio and cholesterin-ester ratio in these groups showed no particular difference between them, although slight decrease was observed in these values immediately after the operation in the group of hepatic resection and that of control. (Fig. 5 and 6)

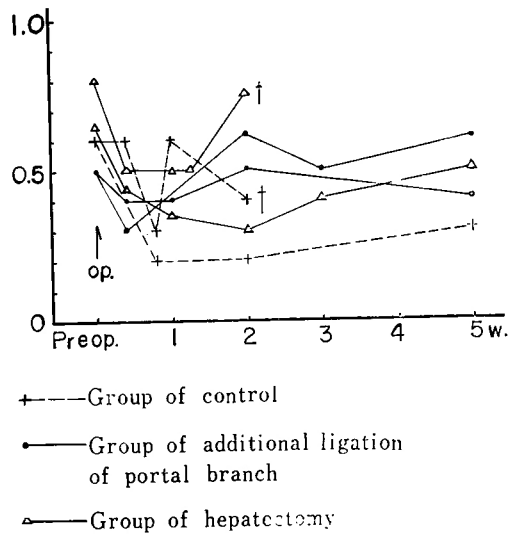


Fig. 5 A/G ratio

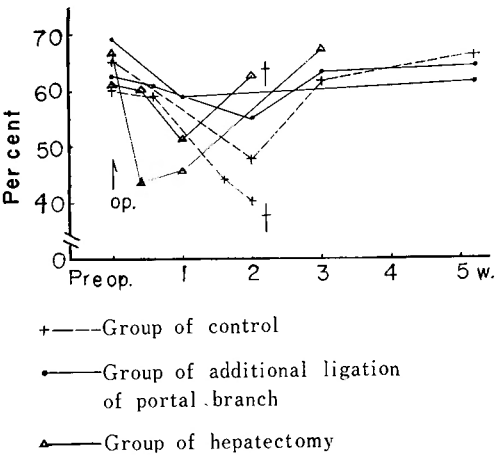


Fig. 6 Cholesterin-ester ratio

ii. Pathological findings

Hypertrophy of the hepatic area with bile drainage was macroscopically observed in all groups, with some variations in its degree. Particularly, it was prominent in the groups of additional ligation of the portal branch and hepatic resection, showing lightly colored tincture compared with normal liver. The hepatic area without bile drainage

showed atrophy on gross observation, with thin and fibrous appearance. The degree of atrophy was more profound in the group of additional ligation of the portal branch.

The hepatic area with bile drainage, which showed hypertrophy on gross observation, revealed an accomplished picture of regeneration histologically, bearing a close resemblance of normal liver (Fig. 20, 22 and 24). An increase in number of Kupffer's cell was generally observed. Slight dilatation of the sinusoids could be observed in the group of additional ligation of the portal branch and that of hepatic resection. In all groups infiltration of polymorphnuclear neutrophiles with a plenty of eosinophiles in some part of the interlobular venules and interlobular spaces, which was presumably due to ascending bacterial contamination.

In the hepatic area without bile drainage, a shrinkage of the acini caused by the atrophy of liver cells could be observed being accompanied by a picture of pericholangitis such as dilated bile ducts with proliferated connective tissue around and leucocytes infiltration (Fig. 21 and 23). Atrophy of the liver parenchyma was outstanding in the group of additional ligation of the portal branch.

III. PARTIAL BILE DRAINAGE IN DOGS WITH OBSTRUCTIVE JAUNDICE AND CARBON TETRACHLORIDE INTOXICATION

In clinical cases, there naturally appears impairment of the liver parenchyma when obstructive jaundice has persisted for long. Since it was difficult to use dogs which survived the ligation of the bile duct for long in the present experiment, jaundiced dogs were used, the liver parenchyma being impaired with carbon tetrachloride simulating the model of clinical cases.

1. Animal

Similarly to the previous experiment in II 1, jaundice was produced by the ligation of the common bile duct, and 0.3 cc/kg body weight of 20 per cent carbon tetrachloride in olive oil was simultaneously injected intramuscularly to induce impairment of the liver parenchyma. For the control study, 4 day aged jaundiced dogs were used.

2. Methods

i. Operative procedures

Since the operative procedure in the previous experiment in II 2 was too much aggressive and there occurred ascending bacterial contamination through cholecystojejunostomy, the method of bile drainage was changed here, and the following operations were carried out. Pre- and postoperative procedures were entirely similar to those in the previous experiment.

Group 1 : Group of simple partial drainage of bile for the control study (abbreviated to control group, hereafter).

In the first place, the thread of ligation of the common bile duct performed 4 days before was carefully removed and the gall bladder was gently pressed so that the lumen of the once ligated common bile duct may be recanalized and the engorged bile may flow out into the duodenum. To make sure, adequate outflow of bile was ascertained by duodenal puncture, and in some cases polyethylene tube was inserted from the gall bladder to the duodenum, in order to ascertain the absence of stenosis in the common bile duct.

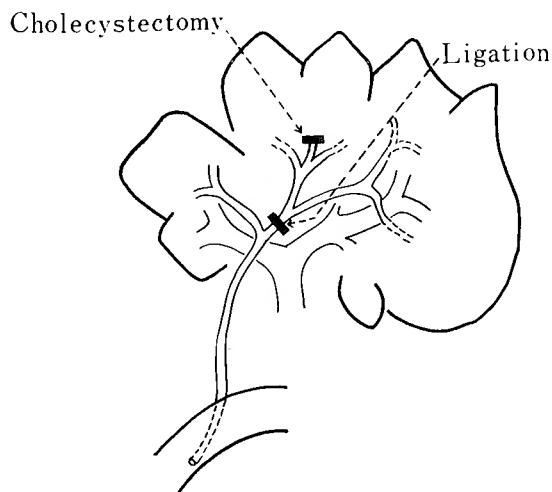


Fig. 7a Group of control of experiment in III

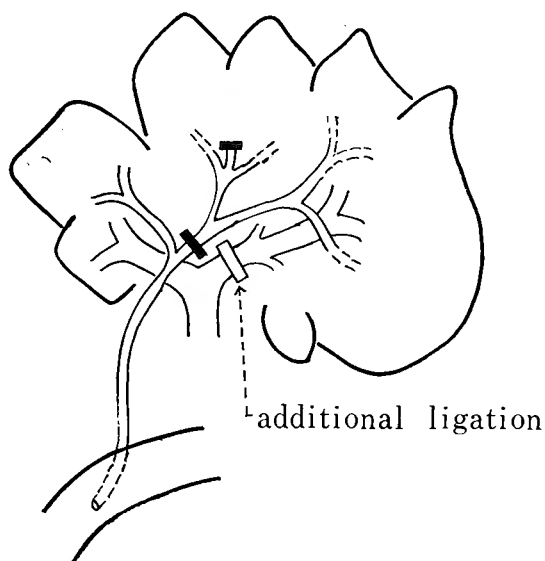


Fig. 7b Group of additional ligation of portal branch

Then the bile ducts were doubly ligated as illustrated in Fig. 7a, leaving the branches of the duct from the right superior and inferior lobes. In addition to these, the gall bladder was extirpated in order to prevent the rupture. By these procedures, the bile exclusively from the right lobes came to be drained into the duodenum through the physiological pathway.

Group 2 : Group of additional ligation of the portal branch to the area without bile drainage (abbreviated to group of additional ligation of the portal branch, hereafter).

In addition to the above mentioned bile drainage in control group, the portal branch to the area without bile drainage was ligated as shown in Fig. 7, b.

ii. Examinations

Besides the examinations in the experiment in II 2, following items were added.

- a. Z. T. T.¹⁷⁾
- b. T. T. T.¹⁸⁾
- c. s-G. O. T. and s-G. P. T.¹⁹⁾

3. Results

i. Preoperative condition of the liver

Owing to the intoxication with carbon tetrachloride, jaundice appear-

ed earlier and the liver itself was also slightly tintured yellow. Histologically, hemorrhage, degeneration of liver cells in the central area of the hepatic lobules and necrotic foci were observed (Fig. 25).

ii. Examinations of liver function

a. Total bilirubin

Although a shorter period as large as 4 days had elapsed after the ligation of the common bile duct, jaundice was more profound as shown in Fig. 8, compared with those in the experiment in II, some animals revealing as high a level as 50 mg/dl.

Notwithstanding the similar procedure of the operation in every case, animals of

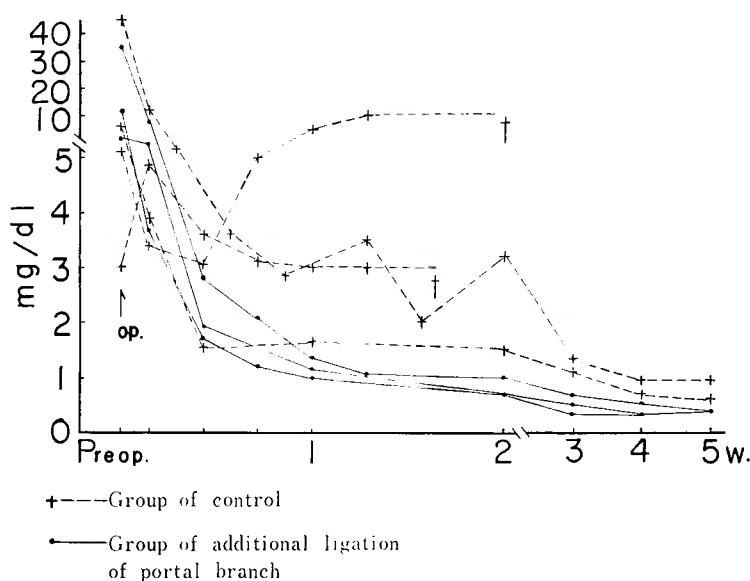


Fig. 8 Serum bilirubin level.

control group showed various course after the operation, without certain tendency. Some of the animals showed favorable decrease in bilirubin level, some showing temporary increase postoperatively, some showing frequent fluctuation on the way of the decrease and the others showing transient decrease which was taken place by the increase in the bilirubin level to final death. From these findings, it is assumed that this method of bile drainage is not reliable. On the contrary, in the group of additional ligation of the portal branch, the bilirubin level decreased rapidly in all cases regardless of the preoperative level, returning to normal within 2 weeks without fluctuation on the way.

b. B. S. P. retention test

The test was repeated 5 times in total 5 days, 2 weeks, 3 weeks, 4 weeks and 5 weeks after the operation. In control group, the retention rate was around 20 per cent

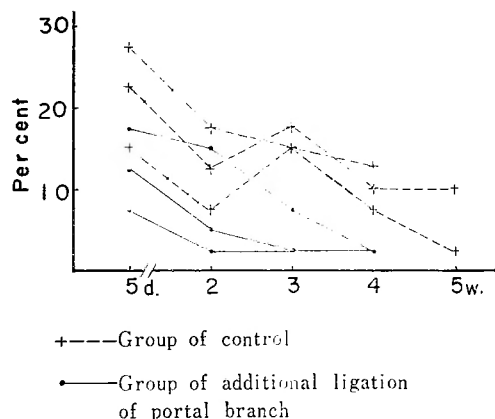


Fig. 9 B. S. P. retention.

as early as 5 days after the operation, and in some animals it continued to be around 10 per cent more than 5 weeks after the operation. On the contrary, in the group of additional ligation of the portal branch, the retention rate showed restoration to normal at earliest within 2 weeks and at latest within 4 weeks (Fig. 9). Restoration of this retention rate was a little delayed than that of total bilirubin level in serum.

c. Cholesterin-ester ratio

Total cholesterin decreased in control animals in parallel with the release of

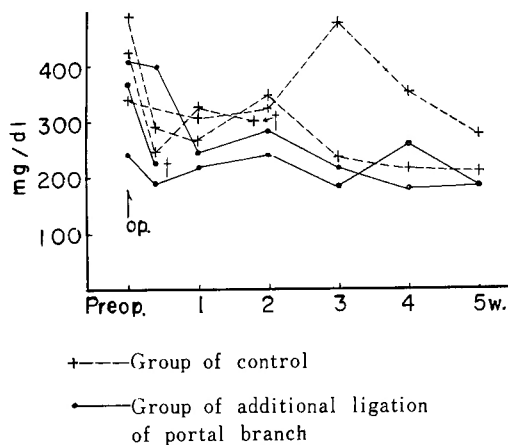


Fig. 10 Total Cholesterolin

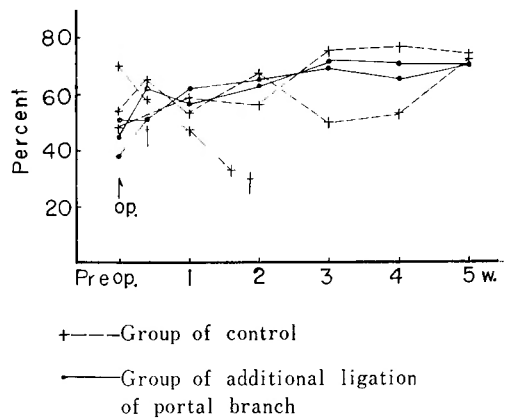


Fig. 11 Cholesterolin-ester ratio.

jaundice, in some cases, however, fluctuating and remaining in a high level even 5 weeks after the operation. In the group of additional ligation of the portal branch, total cholesterolin returned to normal within 5 weeks, showing the same attitude as in control animals, regardless of the preoperative level (Fig. 10).

Cholesterolin-ester ratio in control group showed considerable fluctuation postoperatively, giving an impression as if there remained some disturbance of esterification of cholesterolin in the liver for long, whereas in the group of additional ligation of the portal branch, the ratio gradually improved, showing a value of 60 per cent 2 weeks after the operation and returned to normal thereafter without fluctuation in all cases. (Fig. 11).

d. Z. T. T., T. T. T. and A/G ratio

Significant difference could not be found in Z. T. T. and T. T. T. between both groups (Fig. 12 and 13).

A/G ratio slightly decreased immediately after the operation in the group of addi-

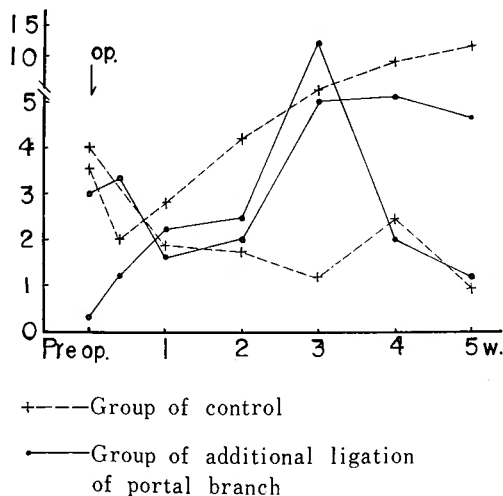


Fig. 12 Z. T. T.

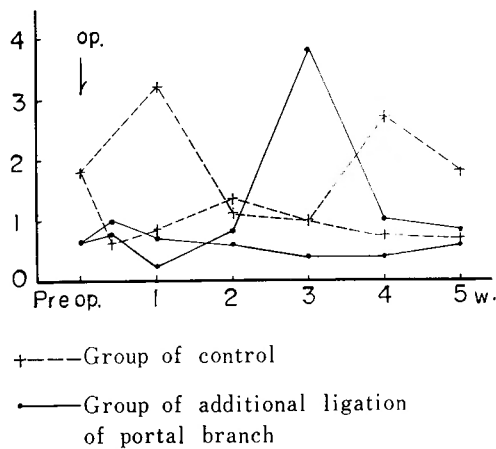


Fig. 13 T. T. T.

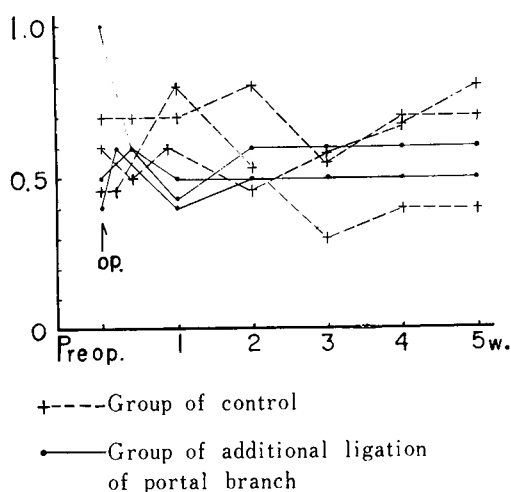


Fig. 14 A/G ratio.

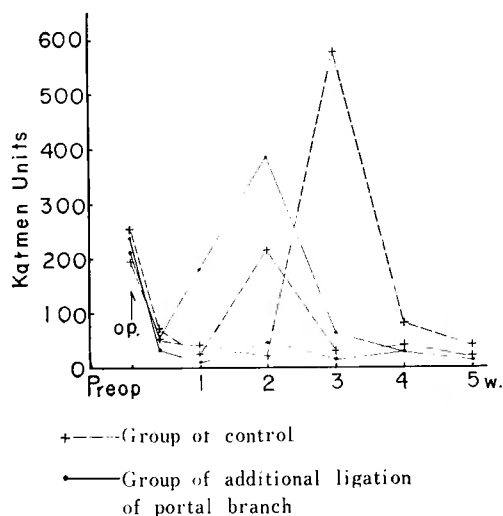


Fig. 15 s-G. O. T.

tional ligation of the portal branch and it increased thereafter to normal, with less fluctuation in individual cases than in control animals and showing a tendency of recovery common to all cases (Fig. 14).

e. s-G. O. T. and s-G. P. T.

Particular difference could not be observed in s-G. O. T. between two groups, returning to normal towards 5 weeks after the operation (Fig. 15). In some cases of the control group, s-G. P. T. showed strange increase 2 to 3 weeks after the operation (Fig. 16).

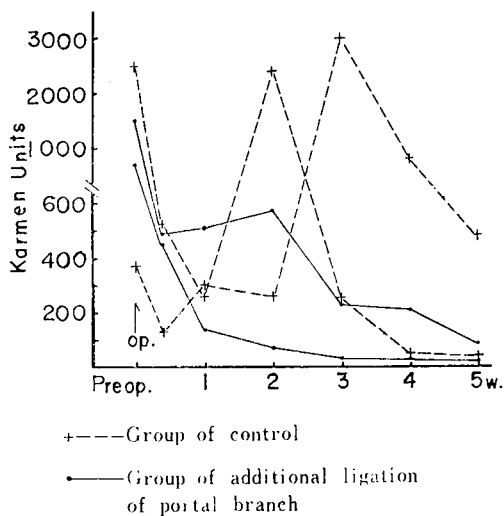


Fig. 16 s-G. P. T.

iii. Pathological and histological findings

a. Gross findings

About 2 months after the operation, autopsy was carried out.

In both groups, the right superior and inferior lobes of the liver with bile drainage showed hypertrophic regeneration, although with some difference in case by case, with watery lightly colored appearance (Fig. 26 and 27). The degree of hypertrophy was more remarkable in the group of additional ligation of the portal branch, as shown in Tab. 2. Namely, average liver weight was 320 g in control group and approximately similar weight of 303 g in the group of additional ligation of the portal branch. Despite this fact, average weight of liver area with bile drainage was 148 g in control group corresponding to 46 per cent of the entire liver, whereas it was 215 g in the group of

Table 2.

Body weight (kg)	Total liver weight (g)	Liver index	Bile drainage area	
			weight (g)	Per cent to total weight
Group of control				
10	360	3.6	170	47
9	270	3.0	135	50
10	330	3.3	140	42
Means 9.5	320	3.3	148	46
Group of additional ligation of portal branch				
10	290	2.9	215	74
10	350	3.5	250	71
9	270	3.0	180	66
Means 9.5	303	3.1	215	70

additional ligation of the portal branch occupying such a large proportion as 70 per cent of the entire liver.

The liver area without bile drainage showed the appearance of thin and fibrous shrinkage with adhesion existing between the lobes. The degree of the shrinkage was more prominent in the group of additional ligation of the portal branch.

b. Histological findings

In the liver area with bile drainage, degeneration, necrosis and hemorrhage could not be observed as was seen preoperatively due to carbon tetrachloride intoxication. The liver tissue showed the picture of regeneration closely resembling the normal one (Fig. 28 and 30). Cell infiltration due to ascending bacterial contamination could not be observed, as was in the experiment of II3.

Marked atrophy of liver cells was observed in the liver area without bile drainage with necessarily resulting shrinkage of liver acini. Dilated bile ducts could be observed with proliferated connective tissue around. The degree of the shrinkage and proliferation of connective tissue were more pronounced in the group of additional ligation of the portal branch (Fig. 29 and 31).

IV. EXPERIMENTS ON THE RELATIONSHIP BETWEEN PORTAL BLOOD FLOW AND BILIRUBIN EXCRETION

In order to clarify the influence of ligation of the portal branch to the area without bile drainage as carried out in the experiments of II and III on bilirubin excretion in the area with bile drainage, following experiments were carried out. Healthy mongrel dogs were used.

1. Ligation of the bile duct branch and concurrent ligation of the portal branch on the non-bile drainage area.

i. Methods

A. Operative procedures

The branch of the bile duct to the right hepatic lobes was ligated as illustrated in Fig. 17, and the portal branch was also ligated except that to the right lobes. Since the

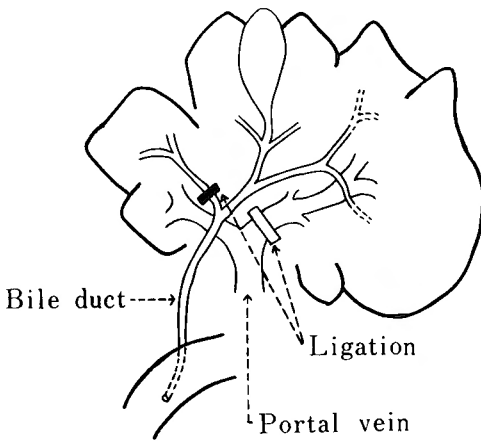


Fig. 17 Ligation of bile duct branch and concurrent ligation of portal branch on non-bile drainage area.

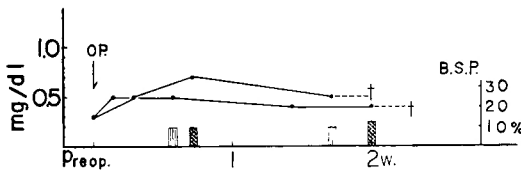


Fig. 18 Serum bilirubin and B. S. P. retention

to 3 weeks postoperatively. At autopsy, intraperitoneal bleeding could be observed in some cases.

2. Determination of Bilirubin in Hepatic Bile

i. Methods

A. Operative procedures

Hepatic bile from the right lobes was extracorporeally drained and bilirubin excreted during 24 hours was determined.

a. Control group

As illustrated in Fig. 19, an incision was laid on the common bile duct, from which a polyethylene tube was so inserted as to have the bile only from the right lobes. In order to prevent the bile from the other lobes to mix, the bile duct draining these lobes was ligated near the gall bladder, and the stagnant bile was drained into the duodenum through cholecystojejunostomy.

b. The group of additional ligation of the portal branch

Bile was drained in the similar way to the control group, and the main portal branch to the hepatic lobes except to the right ones was ligated as shown in Fig. 19.

B. Examinations

Determination of bilirubin in bile¹⁴⁾ was carried out, the bile being diluted 100 to 200 times.

ii. Results

The bile excreted from the right lobe during 24 hours was collected, and bilirubin

bile ducts were occluded in the area with portal blood supply by this procedure, bile excretion should be exerted in the hepatic area deprived of portal blood supply. Manifestation of jaundice was ascertained.

B. Examinations

a. Total bilirubin in serum¹⁴⁾

b. B. S. P. retention test

ii. Results

Postoperative determination of total bilirubin in serum for 2 weeks revealed absence of jaundice, B.S.P. retention rate also being around 10 per cent (Fig. 18).

From this finding, it was disclosed that even though deprived of portal blood supply, the liver parenchyma is possessed of the ability to excrete all the bilirubin including that reabsorbed from the area with bile duct obstruction.

By this operation, however, the dogs gradually lost appetite with frequent vomiting, and the animals ultimately died 2

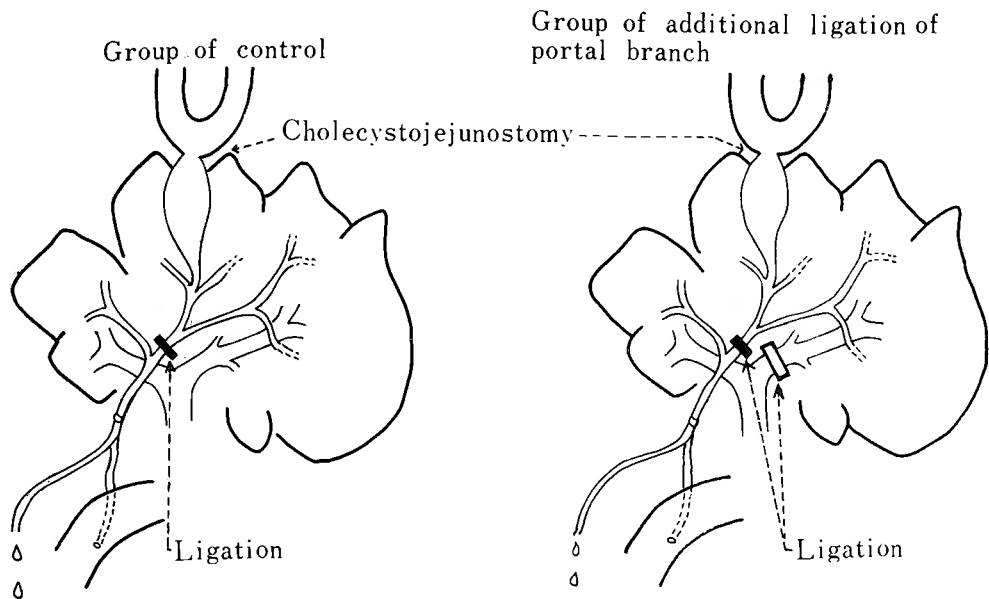


Fig. 19

determined was represented in the term of mg/kg(body weight)/day.

As shown in Tab. 3, when compared with the control group, bilirubin excretion was larger in the group of additional ligation of the portal branch in which bile was collected from the right lobes receiving the entire portal blood inflow.

Table 3.

		Group of control				Group of additional ligation of portal branch			
		Means				Means			
Bilirubin in bile	mg/kg/day	2.4	2.1	2.3	2.3	3.7	3.3	3.0	3.3

From these findings, it is assumed that bile excretion of the liver tissue is increased by dint of the increase in portal blood supply.

V. DISCUSSION

MISTILIS and SCHIFF¹²⁾ observed a remarkable improvement of jaundice following excision of the left hepatic lobe with biliary obstruction in a case of obstructive jaundice in which bile drainage, performed in the right side because of the complete biliary obstruction in the left side, was ineffective for the release of jaundice. They explained this phenomenon that partial bile drainage was ineffective in this case presumably owing to reabsorption of bile once excreted from the area with the biliary obstruction into the blood and excision of the hepatic lobes with the obstruction was significant in removing the source of reabsorption of bile into blood. They further presumed that conjugated bilirubin, which is once produced in the liver parenchyma with biliary obstruction and absorbed reversely into blood, can be hardly excreted in men. In fact, it is justifiably

considered that reabsorption of bilirubin into blood, which is produced in the concurrently existing liver parenchyma with biliary obstruction, would become a great hindrance in the process of improvement of jaundice. This fact is, however, incompatible with the reports of many cases⁸⁾⁹⁾¹⁰⁾¹¹⁾, as mentioned in the introduction, in which there developed no jaundice discernible despite obstruction of the biliary tract belonging to some part of the liver.

It is reported by many researchers⁴⁾⁶⁾⁷⁾ that experimental occlusion of the bile duct from 75 per cent area of the liver does not result in manifestation of jaundice. From the findings of his experiments in rabbits and pigs and further from the clinical observations, SCHALM⁶⁾ made an interpretation of the absence of jaundice in such occasions that excretion of all the bilirubin including that absorbed in the hepatic area with biliary obstruction is fairly excreted by the hyperfunction of the liver parenchyma having no obstruction of the biliary tract.

Concerning the excreta from the hepatic area with biliary obstruction, a possibility can be considered as pointed out by BRAASCH²⁰⁾ that some altered bilirubin might be excreted in this area. However, as presumed from the absence of jaundice in animals with obstruction of the bile duct from 75 per cent of the entire liver or in clinical cases with obstruction of the bile duct from some part of the liver, it is considered that normally healthy liver tissue has the function to excrete such bilirubin also.

Although excretion of conjugated bilirubin has not been clarified in men, ARIAS and others²¹⁾ observed in rats that conjugated bilirubin is swiftly eliminated when injected intravenously. Thus, considering from these facts, it cannot be assumed otherwise than that the effect of portal branch ligation or hepatectomy on the improvement of jaundice is nothing but the results of favorable influence of these procedures on the function of bilirubin excretion in the liver parenchyma with bile drainage. Here, the influence of ligation of the portal branch to the hepatic area with biliary obstruction on the function of liver parenchyma with bile drainage should be studied.

As the influence of the ligation of the portal branch to the hepatic area without bile drainage on the function of liver parenchyma with bile drainage, an increase in portal blood supply and hepatic regeneration in this area must be pointed out.

Concerning the influence of portal blood flow on bile excretion, BAUER²²⁾ carried out studies on bile excretion in isolated liver perfused with blood of various temperatures, pressures and volumes, and observed that bile excretion is rather proportional to the volume of blood flow than to the blood pressure. WHIPPLE²³⁾ observed a decrease in bilirubin excretion in dogs with Eck's fistula compared with normal ones. In the experiment in IV 2 of the present paper also, it was demonstrated that bilirubin excretion in the hepatic bile from the hepatic area with bile drainage increases by confining the portal blood flow in this area.

Concerning the function of regenerative cells in the regenerative liver parenchyma, NAKAMURA²⁴⁾ and OKUMURA²⁵⁾ clarified from tissue respiration study in rabbits and dogs that regenerative hepatic cells appearing after liver resection perform their function so much actively. Concerning this respect, Whipple stated that production of bilirubin is closely related to the activity of liver cells.

KELLY²⁶⁾ observed that necrotic liver, induced with carbon tetrachloride intoxication, is rapidly repaired as the regeneration is provoked in the liver, which was also ascertained by GOTO²⁷⁾ in cirrhotic liver similarly induced in rats.

Judging from these observation, it is assumed that, in the present experiment, the effect of the ligation of the portal branch on the improvement of liver function consisted in increasing portal blood flow to the hepatic area with bile drainage, and in appearance of functionally active liver cells provoked by the hypertrophic regeneration in this area with resulting improvement of bilirubin excretion owing to rapid of impaired liver parenchyma.

Analyzing the effect of the ligation of the portal branch in improvement of jaundice from the aspect of the assertion of MISTILIS and SCHIFF¹²⁾, there is yet a room for a hypothesis that the effect consists in stoppage of bilirubin production in the liver parenchyma with biliary obstruction, similarly to hepatectomy. Although it is assumed from the observations of Whipple and Bauer that withdrawal of portal blood supply certainly decreases production of bilirubin, it can never be said to be so complete as to stop the bilirubin production.

ROUS and LARIMORE¹³⁾ also studied the bile excretion from the liver parenchyma deprived of portal blood flow and reported that such liver parenchyma maintained ability of bile production for considerably long period, though the bile was lightly colored and less in amount. In the experiment in IV 1, manifestation of jaundice could not be observed after the ligation of the bile duct on one side and that of the portal branch on the other side, suggesting that the liver parenchyma deprived of portal blood supply is still possessed of the ability to excrete all the bilirubin, including bilirubin reabsorbed in the liver area with biliary obstruction. In addition, jaundice could not be observed in this occasion, notwithstanding the increased absorption of bilirubin due to the existence of the area of biliary obstruction with the increased portal blood flow.

Accordingly, it is difficult to conceive that enhancement of improvement of jaundice caused by the ligation of the portal branch is brought about by the cessation of bilirubin production in the portal vein ligated area, and, as mentioned in the above, this might be attributable to such factors as hyperfunction of the liver parenchyma caused by the increase in portal blood supply in the area with bile drainage, and appearance of functionally very active liver cells provoked by the liver regeneration and rapid repair of the improvement in bilirubin excretion.

Hereupon, it is necessary to consider about the influence of portal branch ligation on organisms, since the liver encountered the ligation in the present experiment is thought to have had parenchymal impairment in considerable degree.

KOZAKA²⁸⁾ strongly asserted that the ligation of the portal branch to 80 per cent area of the liver could be carried out more safely in normal liver, cirrhotic liver with carbon tetrachloride intoxication and cholangitic liver induced with *E. coli* infection than segmental resection of the same extent of 80 per cent of the liver parenchyma. He further reported that by this procedure hypertrophic regeneration was provoked in corresponding degree to that observed following the hepatectomy, without manifestation of circulatory disturbance³⁰⁾ or profound degeneration^{25) 29)} which appeared temporarily in the residual liver tissue following the hepatectomy. GOTO²⁷⁾ also successfully carried out the

ligation of the portal branch in cirrhotic liver induced with carbon tetrachloride intoxication in rats. Taking these results into consideration together with the favorable results of the ligation in the present experiment, it is assumed that the ligation of the portal branch can be carried out with considerable safety in clinical cases of obstructive jaundice with parenchymal impairment of the liver.

However, as atrophy and hypertrophy were observed, although in a lesser degree, even in control group without additional ligation of the portal branch, atrophy could be provoked by mere ligation of the bile duct concurrently with compensatory hypertrophy of the non-bile duct ligated area.⁶⁾⁷⁾³¹⁾³²⁾ Accordingly, there arises a question if the addition of the portal branch ligation is absolutely necessary. However, the degree of this phenomenon largely differed depending upon the species of the experimental animals, being prominent in rabbits, in which amount of bile excreted is so larger as six times than in rats.²⁷⁾ On the contrary, this phenomenon cannot be observed at all in rats, unless the portal branch is ligated simultaneously with the bile duct. It is said that the amount of bile excretion in dog is in the intermediate degree of these two³⁴⁾, and that in men in the same degree as in rats. From these facts, LAURENCE³⁵⁾ postulated that the ligation of the bile duct would not result in remarkable change of the liver parenchyma in men as well as in rats. Concerning the cause of the phenomenon of atrophy and hypertrophy induced by the ligation of the bile duct, McMASTER and ROUS⁴⁾ insisted that it might be attributable to an impairment of portal blood flow brought about by the pressure of bile ducts dilated with stagnant bile. In other words the ultimate cause consists in the impairment of portal blood flow. Thus, in the present experiment, it is readily comprehended that hypertrophy and regeneration in the liver parenchyma with bile drainage were obtained with more certainty and more conspicuously by the addition of the ligation of the portal branch.

Although the assertion of LAURENCE was cited in the above concerning the ligation of the bile duct in men, some papers can be found in the literatures⁹⁾¹⁰⁾¹¹⁾³⁶⁾³⁷⁾ reporting the clinical observation of atrophy or hypertrophy which was presumably caused by obstruction of the biliary tract. According to GOTO²⁷⁾, however, in most of such cases¹¹⁾¹⁰⁾ revealing hypertrophic regeneration simultaneously with atrophy, compression process on the biliary tract due to neoplasms was frequently demonstrable, suggesting an inevitable influence of the tumor on the portal flow. He further stated that hypertrophic regeneration could not be observed in the occasions⁹⁾³⁶⁾ of intraductal biliary obstruction caused by some mechanisms such as stones.

As has been discussed in the above, judging from the observation in dogs with obstructive jaundice in the present experiment that reliable effect for improvement of jaundice could not be obtained by mere partial drainage of bile, whereas the effects of bile drainage became more prominent by the additional ligation of the portal branch, even in dogs which have more plentiful bile excretion than men, it is considered that the ligation of the portal branch would ensure the effect of partial bile drainage in men, in which the amount of bile excretion is relatively less and the regeneration hardly develops merely by the obstruction of the biliary tract.

VI. SUMMARY AND CONCLUSION

In order to have a more efficacious result in partial bile drainage for improvement of obstructive jaundice, ligation was performed in the portal branch draining into the hepatic area having no bile drainage and the effect of which was experimentally studied.

1. Improvement of jaundice in dogs with obstructive jaundice was observed in the following three groups: -- control group with bile drainage from 30 per cent of the entire liver, group of additional ligation of the portal branch to the area deprived of bile drainage with the same drainage of bile as in control group and group of hepatectomy of 40 per cent of the entire liver with bile drainage from the residual 60 per cent of liver tissue. Improvement of jaundice was as favorable in group of additional ligation of the portal branch as in the group of bile drainage from the 60 per cent area of the liver with hepatectomy, bilirubin level returning to normal towards 5 days after the operation and the animals survived. On the contrary, bilirubin level hardly returned to normal in control group including some cases which showed temporary increase in bilirubin content postoperatively, and sometimes animals died showing the increase in bilirubin level on the way of improvement of jaundice. Significant difference could not be observed among these groups in A/G ratio and cholesterin-ester ratio, although a tendency of temporary decrease was markedly observed immediately after the operation in the group of hepatectomy and that of control.

2. Even in the dogs of obstructive jaundice with carbon tetrachloride intoxication, the additional ligation of the portal branch revealed an excellent effect of improvement of jaundice, bilirubin level returning to normal approximately 2 weeks after the operation. On the contrary, improvement of jaundice was uncertain in control group, fluctuation of bilirubin level being marked in the postoperative course, and in some cases death resulted with the increase in serum bilirubin on the way of improvement of jaundice, though there were some animals which showed favorable improvement. Concerning B. S. P. retention rate and cholesterin-ester ratio, the additional ligation of the portal branch showed favorable effect, the values returning to normal by 4 weeks after the operation, whereas in control group, there were some cases in which the values did not return to normal even 5 weeks after the operation. Particular difference, however, could not be observed in A/G ratio, Z. T. T., T. T. T., s-G. O. T. and s-G. P. T. A remarkable hypertrophic regeneration at 215 g, on the average, corresponding to 70 per cent of the entire liver could be observed at autopsy carried out about 2 months later in the hepatic area with bile drainage in the group of additional ligation of the portal branch, while in control group only 148 g on the average corresponding to 46 per cent of the entire liver was obtained. In both groups, atrophy was observed in the area of liver parenchyma without bile drainage. Histological studies of the regenerative liver tissue in the area with bile drainage revealed almost normal picture, in contrast with atrophy of liver cells and proliferation of connective tissue in the area without bile drainage.

3. Concerning the relationship between portal blood supply and bile production, significance of the ligation of the portal branch to the area without bile drainage was studied.

a. It was clarified by the experiment of bile duct ligation on one side and portal branch ligation on the other side that liver parenchyma, even though deprived of portal

blood supply, is possessed of the ability to excrete all the bilirubin including that reabsorbed from the hepatic area with biliary obstruction.

b. Amount of bilirubin in the hepatic bile produced in 30 per cent of the hepatic area during 24 hours was determined and represented in the term of mg/kg (body weight)/day, which was 2.3 mg/kg/day in the control group, while it increased to 3.3 mg/kg/day in the group of the portal branch ligation in which portal blood flow was confined to the hepatic area with bile drainage.

From these findings, it was clarified that the improvement of jaundice is obtained with more certainty and more rapidly at the partial drainage of bile in dogs with obstructive jaundice, when the ligation of the portal branch to the hepatic area without bile drainage is additionally carried out. This effect of the portal branch ligation presumably consists in hyperfunction of the liver parenchyma with increased portal blood supply appearance of functionally active regenerative cells due to hepatic regeneration and rapid repair of the impaired liver parenchyma with resulting improvement of bilirubin excretion.

At the clinical practice of partial bile drainage in cases of long persisting obstructive jaundice with possibly accompanying impairment of the liver parenchyma, it is expected that additional ligation of the portal branch to the hepatic area without bile drainage will ensure, as observed in the present experiment, more rapid improvement of jaundice with more certainty.

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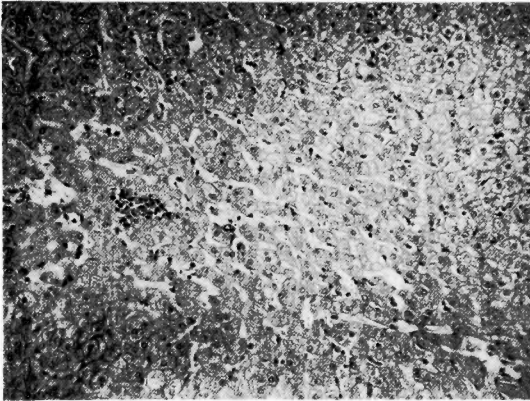


Fig. 20 Liver of control animal in experiment of II. Microscopic section of bile drainage area. ($\times 100$, H-E)

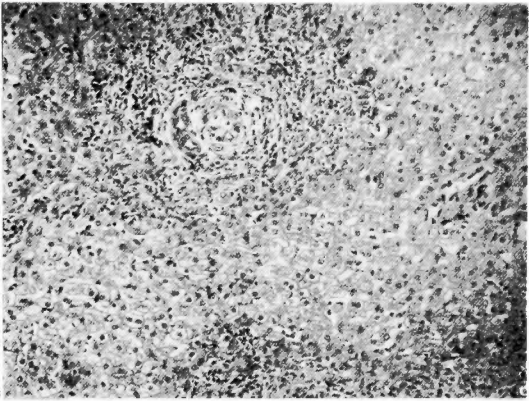


Fig. 21 Liver of control animal in experiment of II. Microscopic section of non-bile drainage area. ($\times 100$, H-E)

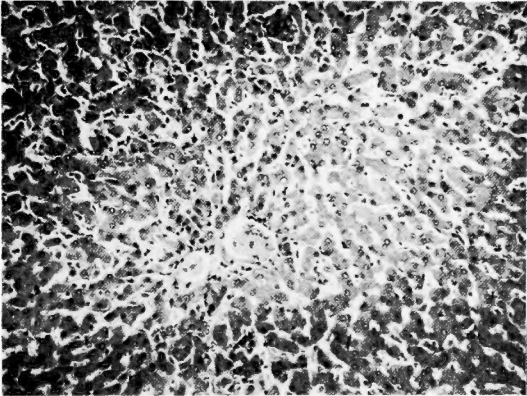


Fig. 22 Liver of animal of additional ligation of portal branch in experiment of II. Microscopic section of bile drainage area. ($\times 100$, H-E)



Fig. 23 Liver of animal of additional ligation of portal branch in experiment of II. Microscopic section of non-bile drainage area. ($\times 100$, H-E)

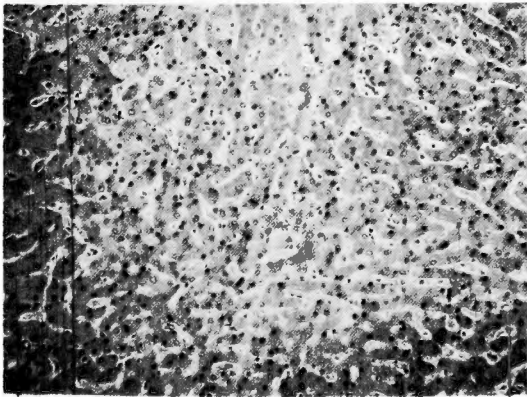


Fig. 24 Liver of animal of hepatectomy of experiment in II. Microscopic section of bile drainage area. ($\times 100$, H-E)

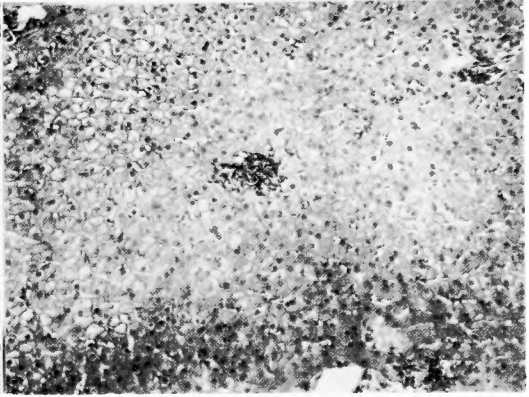


Fig. 25 Preoperative histological picture of liver in animal intoxicated with carbon tetrachloride and obstructive jaundice in experiment of III. ($\times 100$, H-E)

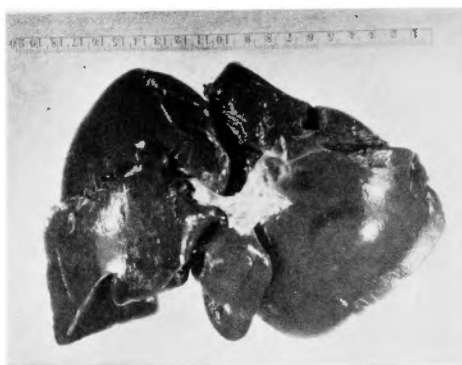


Fig. 26 Liver of control animal in experiment of III.



Fig. 27 Liver of animal of additional ligation of portal branch in experiment of III.

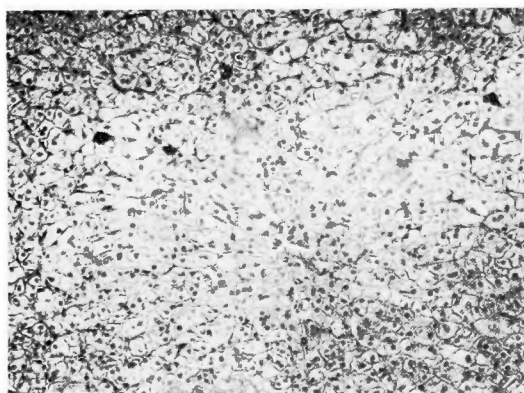


Fig. 28 Liver of control animal in experiment of III. Microscopic section of bile drainage area. ($\times 100$, H.-E.)

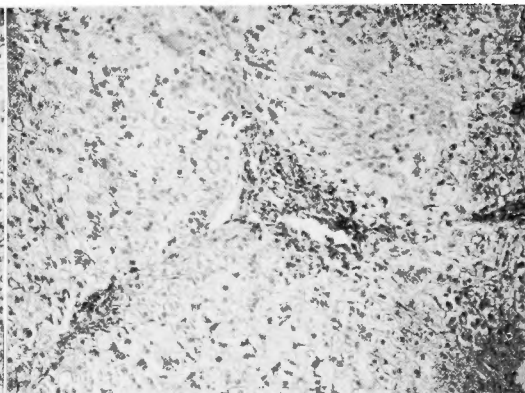


Fig. 29 Liver of control animal in experiment of III. Microscopic section of non-bile drainage area. ($\times 100$, H.-E.)

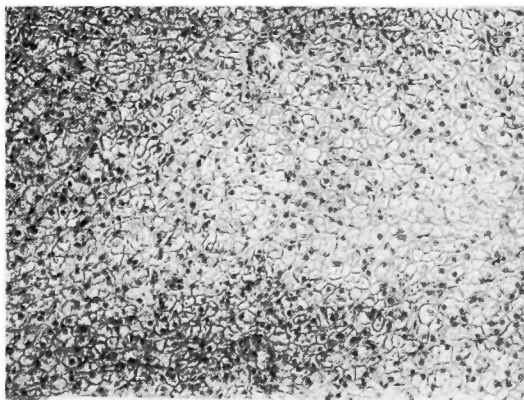


Fig. 30 Liver of additional ligation of portal branch in experiment of III. Microscopic section of bile drainage area. ($\times 100$, H.-E.)

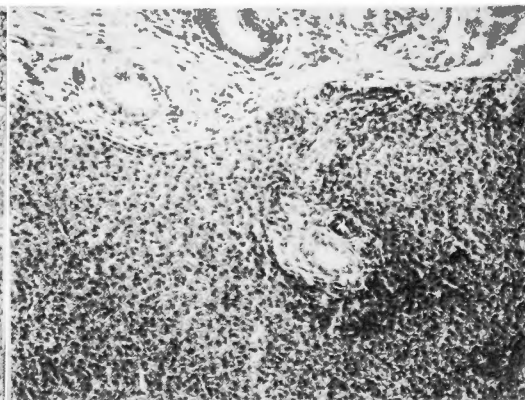


Fig. 31 Liver of animal of additional ligation of portal branch in experiment in III. Microscopic section of non-bile drainage area. ($\times 100$, H.-E.)

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(* in Japanese)

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閉塞性黄疸の部分的解除に関する実験的研究

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肝門部腫瘍等により閉塞性黄疸を呈している症例に対して、外科手術により、全肝領域の bile drainage を実施し得る症例は臨床上至つて少い。そこで肝の優れた予備能力に着目し、一部の領域の bile drainage が行われ、可成りの黄疸軽減効果が得られているが、黄疸が長期に亘つて持続し、肝実質障害の高度な症例では、しばしばその効果が不確実である。

そこで、この様な症例に対して、確実な黄疸軽減効果を得るために、一部の bile drainage に加えて、胆汁非誘導領域の門脈枝結紮を行ない胆汁誘導領域に肥大再生を誘起し、その黄疸軽減効果に及ぼす影響並びにその意義を検討した。

1) 閉塞性黄疸犬において、全肝の30%肝領域から bile drainage を行なつた対照群と、同様の bile drainage に加えて、胆汁非誘導領域に流入する門脈枝結紮を追加した門脈枝結紮追加群及び、40%肝切除を行ない、60%残存肝から bile drainage を行なつた肝切除群の3群を作製し術後の黄疸軽減の経過を比較した。その結果門脈枝結紮追加群において、肝切除群に匹敵する良好な黄疸軽減経過を示し、術後、約5日間で、ビリルビン値が正常化し長期生存し得た。これに対し、対照群では、術後一旦上昇する例もあり、正常値になかなか下降せず、中には下降途中で再び上昇し死亡するものがあつた。

A/G 比、コレステリン・エステル比では、各群間に有意の差はなかつた。

2) 四塩化炭素負荷閉塞性黄疸犬においても門脈枝結紮追加群は優れた黄疸軽減効果を示し、術後、約2週間で全例ビリルビン値が正常化した。これに比し対照群では順調な下降を示す例もあつたが、途中動揺が著しいものや下降途中で再び上昇し死亡するもの等、確実な黄疸軽減効果が得られなかつた。

B. S. P. 試験、総コレステリン、コレステリン・エステル比等においても、同様門脈枝結紮追加群では4

週間迄に全例正常値を示しているのに対し、対照群では5週間でも正常化しない例があつた。但し A/G 比、Z. T. T., T. T. T., s-G. O. T., s-G. P. T. においては有意の差はなかつた。

剖検所見より門脈枝結紮追加群の胆汁誘導領域は平均215g 全肝の70%に達する著明な肥大再生を示しているのに対し、対照群では平均148g、全肝の46%を占めるにすぎなかつた。組織標本では両群とも、胆汁誘導領域は正常肝に近い再生像を示し、胆汁非誘導領域は肝細胞の萎縮と結合組織の増生を認めた。

3) 門脈血流と胆汁分泌に関する実験を行い胆汁非誘導領域門脈枝結紮の意義を検討した。

a) 胆管枝及び門脈交叉結紮を行ない、門脈血を欠除した肝領域でも胆管閉塞部より再吸収されるビリルビンを含めて、全てのビリルビンを排泄する能力を有する事が判明した。

b) 30%肝領域の肝胆汁を採集し、24時間に排泄されるビリルビン量を $\text{mg/kg}(\text{body weight})/\text{day}$ で算出した結果、正常の肝胆汁を採集した対照群では 2.3mg/kg/day であるのに対し、胆汁誘導領域に門脈血の集中した門脈枝結紮追加群では、 3.3mg/kg/day と増加を示した。

以上の所見より部分的胆汁誘導に加えて、胆汁非誘導領域の門脈枝結紮を行なえば、確実により速かな黄疸軽減効果の得られる事が分つた。この様な門脈枝結紮の効果は、胆汁誘導領域への門脈血増加による機能亢進、再生による機能的に壊れた再生細胞の出現及び障害肝の速やかな修復により、ビリルビンの排泄能力が向上した結果と考えられる。

長期の閉塞性黄疸を来した、かなりの肝実質障害を伴っていると考えられる臨床例に応用すれば、実験で示された如く、単なる部分的胆汁誘導にくらべ、確実により速やかな黄疸軽減効果が得られるものと考えられる。