

Experimental Studies of Hepatorenal Relationship from the Sugical Point of View

The Influence of Ligation of the Hepatic Artery and that of Obstructive Jaundice on the Kidney

by

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I INTRODUCTION

It is said that the concept of hepatorenal syndrome as a critical condition following the operation on the liver or biliary tract was first introduced by HEYD¹⁴⁾¹⁵⁾ (1924,1937). Since World War II, the studies of shock have become remarkably animated, and the problem of acute renal insufficiency following shock has also attracted concern of many investigators. On the other hand, it has been reported one after another that the similar clinical pictures to the hepatorenal syndrome can be observed also following the operation of the other organs than the liver and bile duct, and the concept of this syndrome has become obscure gradually.

Nowadays, it has come to be accepted that the hepatorenal syndrome is nothing but an acute renal insufficiency.²⁵⁾ But some investigators⁴⁵⁾⁴⁶⁾ pointed out a difference between clinical picture following damage of the liver or bile duct and that of acute renal insufficiency, and classified the hepatorenal syndrome into two types. They postulated that type I is of toxic and infectious nature and observed chiefly after the biliary tract operation in cases without an obvious renal damage and type II, which covers 80% of the hepatorenal syndrome, is identical with acute renal insufficiency. SANBE et al.³⁸⁾ surmised that in the

presence of jaundice the kidney has already a predisposition to acute renal insufficiency. WILLIAMS et al.⁵²⁾ also demonstrated, using dogs, that in the presence of the obstructive jaundice the kidney is more sensitive to hypotension. As for shock, the liver together with the kidney is one of the most important organs which relate to the irreversible phase of shock.

Among the theories that the liver plays the principal part on the irreversibility of shock, V.D.M.-V.E.M. theory by SHORR et al.⁴⁷⁾ and endotoxin theory by FINE et al.⁸⁾⁹⁾ are most famous. On the other hand, HIRSH¹⁶⁾ and the others²⁾¹⁰⁾ emphasized the brain anoxia, YOKOTA and KURUSU²³⁾ put great importance on congestion in the portal area, and LILLEHEI et al.²⁶⁾²⁷⁾ pointed out the effects of lethal bowel ischemia and sympatomi-metic action of endotoxin in the bowel rather than brain and liver anoxia.

It is easily surmised, however, that the centrilobular necrosis of the liver, which is often observed during prolonged shock, may play an important role in the irreversibility of shock, even if an establishment of an irreversible shock is not simply caused by a hepatic impairment.

Since VON HABERER (1905)¹²⁾ demonstrated that interruption of the hepatic artery in dogs, cats and rabbits leads always to extensive liver necrosis and death, similar results have been confirmed by many investigators.¹⁾ However, MARKOWITZ and the others²⁸⁾²⁹⁾ succeeded in reduction of mortality rate to about 35% by an administration of penicillin during and after the interruption in dogs.

HONJO et al. (1957)¹⁷⁾¹⁸⁾³¹⁾³¹⁾ reported that the mortality in those dogs can be lowered to about 30% by the administration of only 100,000 units of penicillin or by the administration of atropin or dibenamin without any antibiotics before and after the interruption of the hepatic artery, and proved that the disturbance of the intrahepatic portal circulation due to the interruption of the hepatic arterial flow is the principal factor in the development of liver necrosis. They named the survival dogs "portal dog", which have only the portal blood flow through the liver without accompanying lethal liver necrosis after the interruption of the hepatic arterial flow.

On the other side, SVEN RAMSTRÖM in Sweden (1953)³⁷⁾ is firmly convinced that the ligation of the hepatic artery is utterly dangerous, for it is definitely associated with renal insufficiency, and the ligation of the hepatic artery is the factor causing the hepatorenal syndrome.

In view of the presence of the diversified theories, the author tried to investigate the influence of hepatic artery ligation upon the kidney, and also studied the relationship of surgical jaundice to the hepatorenal syndrome.

II EXPERIMENTS

1) Experimental materials and methods

The experiments were done on healthy mongrel adult dogs weighing 7 to 17 kg which were divided into five groups as follows :

- Group I Ligation of the hepatic artery, without penicillin treatment
- Group II Ligation of the hepatic artery, with penicillin treatment
- Group III Measurement of renal blood flow in normal dogs

Group IV Measurement of renal blood flow in jaundiced dogs

Group V Production of hemorrhagic shock in jaundiced dogs

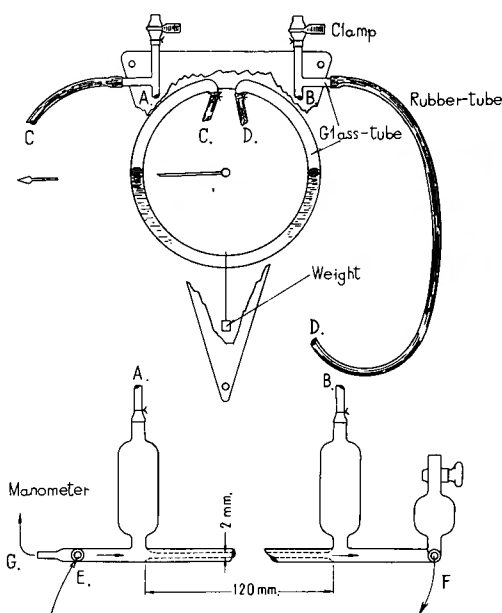
In Group III and IV, the changes of systemic arterial blood pressure and renal blood flow caused by the interruption of hepatic arterial flow were also observed.

2) Blood flowmeter

The differential pressure flowmeter devised by NAKASAWA and UENO³²⁾ was modified and used (Fig. 1).

Fig. 1

Differential Pressure Flowmeter.



A looped manometer is fixed with the disk which is able to rotate freely, and raises a certain rotation due to the differential pressure of a blood stream between the inlet and outlet of the orifice. This movement is recorded on a kymograph.

This blood flowmeter, which has a resistance orifice and calculates blood flow from the differential pressure of a stream between the inlet and outlet of the orifice, indicates somewhat lower value than the theoretical one.

Although this method using the differential pressure flowmeter, as all the direct methods for blood flow measurement, has the disadvantage that direct injury to the organism cannot be avoided and the blood flow is interrupted even if it is transient during the setting of the flowmeter, it is highly evaluated by the following reasons.

- 1) Simplicity of the apparatus.
- 2) No special technique is required.
- 3) The amount of blood flow can be estimated automatically and continuously.
- 4) The instantaneous and successive changes of blood flow can be investigated and

compared easily.

The glass tube, 12 cm in length and caliber of 2 mm, was used as the resistance orifice. And a mercury manometer was connected to one of the inlets of the glass tube to estimate systemic arterial blood pressure. Then, changes in blood pressure and blood flow were recorded on a kymograph. It is said, generally, that the duration of time in which exact measurement can be performed with this apparatus extends within one hour. After the experiment of each cases the blood flow was calculated in the purpose of accuracy by the shed blood of these dogs respectively.

3) Operative procedure

The dogs were anesthetized with sodium pentobarbital of 25 mg/kg of body weight injected into the femoral vein.

A) Interruption of the hepatic artery

Concerning the arterial distribution to the liver, the common hepatic, the gastroduodenal, and right gastric arteries are deemed to be most important. Besides these, the liver is supplied with minor arterial branches originating from the diaphragmatic artery and the left gastric artery. URABE³¹⁾ and ISHIGURO,²⁰⁾ in our clinic, have proved that almost all of the experimental dogs died of liver necrosis after the interruption of the common hepatic, gastroduodenal and right gastric arteries.

Therefore, in the present study, these three arteries were cut under the double ligation. In Group II, 100,000 units of crystal penicillin was administered intraperitoneally before the closure of the abdomen, and 300,000 units of oil penicillin was injected intramuscularly immediately after the operation.

B) Production of surgical jaundice

An upper median abdominal incision was made and the common bile duct was cut under the double ligation at the point of 1 cm distant from the duodenum. After the operation, 100,000 units of crystal penicillin was administered intraperitoneally and 300,000 units of oil penicillin intramuscularly. Each of these dogs was used for the experiment after a certain period of time.

In Group V, the experiment of hemorrhagic shock was performed three to four weeks after ligation of the common bile duct. In Group IV, concurrently with the ligation of the common bile duct, the right gastric and gastroduodenal arteries were ligated and cut, and the common hepatic artery was hanged by a silk-thread which was left in the abdominal wall near by the incision's wound. Renal blood flow was measured about two weeks after the ligation of the common bile duct considering the following facts---Maximal value of blood bilirubin may be attained about two weeks after the operation,^{19) 33) 41)} and at that time, emaciation may not be so remarkable.

C) Measurement of renal blood flow

The unilateral femoral artery and vein were dissected, and through this vein a constant intravenous drip of 5 per cent solution of dextrose was given at the rate of 0.5cc/kg of body weight per minute.

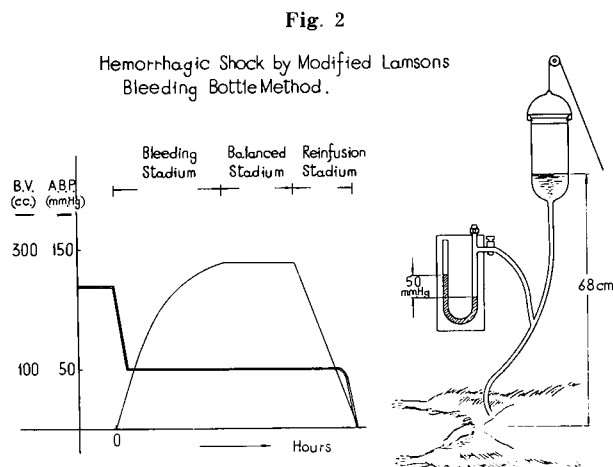
An upper median abdominal incision was made and the right gastric and gastroduodenal arteries were ligated. The common hepatic artery was hanged by a silk-thread (in the case of jaundice, those procedures were done previously).

The renal artery was exposed cautiously. Then, the animal was heparinized by the intravenous injection of heparin of 5 mg/kg of body weight. A thin-walled plastic tube attached to the inlet side of the flow tube was introduced through an incision in the femoral artery and fixed. The plastic tube of the outlet side was inserted into the renal artery towards the kidney at the point as near as possible the juncture with the aorta and fixed.

At the time when the catheter was inserted into and fixed to the renal artery, in order to avoid the injury to the kidney, it was necessary that the time required for the interruption of renal arterial blood flow was as short as possible and the blood flow was reopened gradually lest the kidney should be impaired.⁴⁹⁾ Usually, it took about 30 seconds for this procedure in the present experiment. After the blood pressure and blood flow were stabilized, the influence of the ligation of the femoral artery and the common hepatic artery was studied.

D) Experimental hemorrhagic shock

Hemorrhagic shock was induced by a modification of LAMSON's bleeding bottle method²⁴⁾ (Fig. 2). Heparin was given intravenously in a dose of 5 mg/kg of body



weight. A canula of 3 mm in diameter, which was connected with a steril receptacle by a rubber tube, was inserted into the femoral artery. Blood was allowed to flow rapidly into the receptacle and its level was regulated at the height of 68 cm from the heart of the experimental dog. In this way, the mean arterial pressure was kept at 50 mm Hg.

As for production of experimental hemorrhagic shock, the method of WIGGERS is more popular, but it has a weak point that comparison of the individual animals with each other, at the same phase of hemorrhagic shock, is difficult. By LAMSON's method, the course of the hemorrhagic shock was observed to be divided in the following three phases ; 1) Bleeding stadium. 2) Balanced stadium. 3) Reinfusion stadium.

FINE et al.⁸⁾ confirmed that the irreversible phase begins at the time when the blood volume which returned spontaneously back to the experimental dog in the reinfusion sta-

dium reaches about 40% of the maximal bleeding volume.

In Group V, the bleeding volume was recorded following the lapse of time and at 20% reinfusion stadium when spontaneously retransfused blood volume reaches 20% of maximal bleeding volume, all shed blood in the receptacle were pumped back into the vascular system carefully. And the mortality of the experimental dog was investigated.

4) Microscopic observation

The postmortem changes develop so rapidly in both the liver and kidney, particularly. Hence, in Group I and II, histologic specimens were taken immediately after cessation of heart beat. Also biopsy was performed in Group IV after the observation of both blood pressure and blood flow and in Group V about 20 minutes after all shed blood were retransfused at the time of 20% reinfusion stadium.

Moreover, in Group I, II and V, a piece of the small intestine and spleen together with that of liver and kidney were taken.

All these specimens were put into a 10% formalin solution and stained with EHRlich's hematoxylin and eosin.

III RESULTS

Group I. (Ligation of the hepatic artery, without penicillin treatment)

As a supplementary study of the present experiment, the difference between the group which was cholecystectomized concurrently with interruption of hepatic arterial flow and those without it was investigated.

The gall bladder necrosis and bile peritonitis were observed in all dogs without cholecystectomy, though the severity of the findings was not uniform.

As the studies of hepatorenal relation were thought to be more complicated in those cases which had gall bladder necrosis and bile peritonitis, they were excluded from the present experiment. The histological studies were made on 10 dogs with additional cholecystectomy at the interruption of the hepatic arterial flow. The mean survival time of both groups (14 cases) was 6.1 days (Table 1).

Table 1 Group I. Without Penicillin Treatment.

Number of Dogs.	Cholecystectomy.	Survival Days.	Comments.
1	—	7	
2	—	3	
3	—	4	
4	—	4	
5	+	7	Serious panperitonitis.
6	+	7	Laparotomy immediately after cessation
7	+	3	of heart beat.
8	+	8	Serious panperitonitis.
9	+	4	Laparotomy immediately after cessation
10	+	5	Serious panperitonitis. of heart beat.
11	+	10	
12	+	4	
13	+	14	
14	+	7	
Average		6.1	

1) The liver

In all cases of the present experimental group, though there was a difference in degree, massive liver necrosis was observed. ISHIGURO²¹⁾, in our clinic, has reported in detail about the liver changes after the interruption of hepatic arterial flow. YOSHITOMI⁵³⁾ has studied regarding the favorite site of liver necrosis after the same procedure. In the present experiment also, necrotic change was most likely to occur in the edge of the middle lobe, in the quadrate and caudate lobes and in the periphery of the left superior lobe, while the right lobe showed comparatively less changes. In the areas where the changes are severe macroscopically, the framework of the liver lobule was destructed completely, and only atrophied fragments of the liver cell cords were observed here and there (Fig. 4). Moreover, there was degeneration of various degree, accompanied by necrosis and necrobiosis (Fig. 4.5.6.7). But the sign of bacterial infection (marked infiltration of leucocytes and so forth) was hardly observed in the necrotic area.

2) The kidney

In the severe cases complicated by peritonitis of a manifest degree, the cortical layer of the kidney showed a turbidity in its architecture and was darkly tintured, showing a sharp demarcation from the medulla (Fig. 9). In the other cases in which peritonitis was not demonstrated, only a slight change was observed (Fig. 10), showing an almost normal appearance (Fig. 8). Microscopically, the cortical layer was somewhat ischemic and any changes were not demonstrated in the glomeruli, particularly, the presence of protein like substance which is the product of increased permeability of the glomerular basement membrane for protein and is said to be often found in shock state, was hardly observed.

In the tubules, particularly in the proximal convolution, the epithelium showed chiefly swelling and cloudiness, and also slight vacuolar degeneration and nuclear pyknosis here and there. On the other hand, dilatation of the lower nephron and the tubular casts, including the pigment ones, which are characteristic findings in lower nephron nephrosis, were not observed (Fig. 12, 13).

The portion injured markedly by various toxins or poisons, such as carbon tetrachloride, mercury bichloride, and diethylene glycol, is situated in the entire proximal convoluted tubule where these toxins or poisons are discharged.

The renal change of this experimental group was similar to that of early stage caused by renal toxins or poisons, rather than the renal ischemic change which is observed usually in a shock state.

Furthermore, in contrast with the lethal extensiveness of liver necrosis, the renal changes of this group were unexpectedly slight.

On the other hand, in the cases complicated by severe peritonitis, hemorrhagic foci in the glomeruli and the interstitium of the renal cortex, small round cell infiltration in the interstitium and degeneration of a more marked degree in the nephron, were observed (Fig. 14).

3) The intestine and spleen

At autopsy, the small and large bowels were almost normal, and mucosal congestion, hemorrhage, and necrosis of the bowels were not noticed both macro- and microscopically,

though they seemed to be somewhat ischemic (Fig. 15, 17).

However, in the cases complicated by severe peritonitis, mucosal congestion and hemorrhage were observed from the middle portion of the small intestine to the ileocecal portion (Fig. 16). Though grossly the spleen seemed to be normal, microscopically slight congestion and a decrease in population or size of lymph follicles were observed (Fig. 18).

Group II. (Ligation of the hepatic artery, with penicillin treatment)

Two of 6 experimental dogs died five and eight days respectively after interruption of the hepatic artery. At autopsy, findings of both animals were macroscopically and microscopically identical to those in Group I.

Four surviving animals, which appeared almost healthy for several days after the operation, presented the following features at autopsy 2 weeks after the operation.

1) The liver

Though the liver showed no remarkable changes macroscopically, there were localized small spots here and there in the favorite site of liver necrosis. Microscopically, although the extent and the severity were various, a disturbed arrangement of hepatic cell cords and degeneration of hepatic cells around the central vein still remained. However, these areas of such changes became limited in spread already. And the hepatic cells themselves showed a tendency to regeneration. Moreover, blood congestion was not observed any longer in peripheral portal spaces or sinusoids (Fig. 19).

2) The kidney

The kidney of this group showed neither macroscopical nor microscopical abnormalities (Fig. 11, 12).

Group III. (Measurement of renal blood flow in normal dogs)

The systemic arterial pressure and renal blood flow were recorded simultaneously on a kymograph, then, changes due to the ligation of the hepatic arteries or the femoral artery were observed (Table 2). The mean systemic pressure was 120 mm of mercury and the unilateral renal blood flow was 8.5 cc per kg per minute on the average before

Table 2 Renal Blood Flow and Its Response Immediately after Ligation of the Hepatic Artery.

Number of Dogs	Normal Dogs							Jaundiced Dogs									Average
	4	5	6	8	10	11	Average	14	16	17	19	20	24	26	29		
Body Weight (kg.)	12.0	11.0	9.0	13.0	13.5	9.0		8.5	12.0	12.0	11.5	9.0	10.5	8.0	15.5		
Mean Systemic Arterial Blood Pressure (mm.Hg)	116	124	122	132	104	120	120	80	74	68	90	118	92	110	86	90	
Renal Blood Flow (cc./kg./min.)	9.0	8.5	8.7	7.4	7.5	9.6	8.5	7.5	6.0	4.5	1.1	5.3	1.4	8.3	1.8	5.7	
Icterusindex (Meulengracht)								84	42	16	66	104	64	64	68		
Days after Ligation of the Common Bile Duct								13	14	8	14	14	13	14	21		
A Response of Renal Blood Flow & Systemic Blood Pressure Immediately after Ligation of the Hepatic Artery																	
Elevated Value Continuously								+			+	+	+		+		
Temporarily	+	+	+	+	+	+	+		+	+				+			

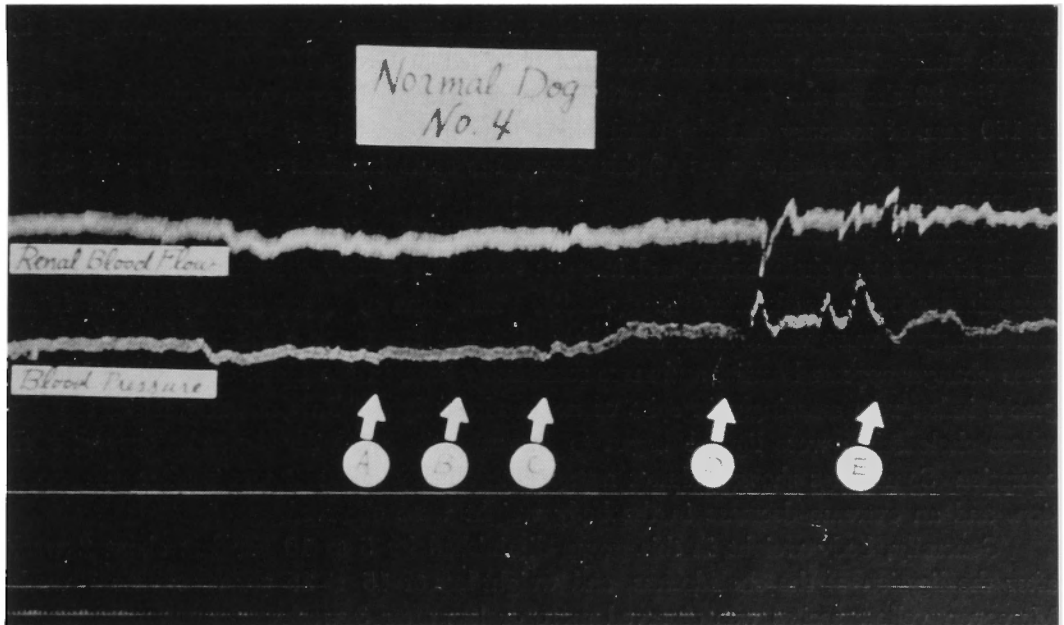
interruption of the hepatic or femoral artery.

Regarding the changes of systemic arterial pressure and renal blood flow after the ligation of the femoral artery, a half of cases showed no changes and the other half showed slight and transient elevation of both values. By the ligation of the common hepatic artery, both values increased reflexively and transiently in all the cases; the systemic arterial pressure increased by 15 to 25 mm of mercury and the renal blood flow by 5 to 10 cc per minute than the initial values (Fig. 21). This increase was more remarkable than in the values when the femoral artery was ligated. From the celiac plexus, a thick bundle of nervous branches courses along the common hepatic artery, coiling itself around the artery. In the cases of the supplemental examination also in which the nerves were carefully stripped off from the artery, there was no difference in the response to the ligation of the common hepatic artery. On the other hand, the same changes were also observed by pulling of this artery. From the above facts, it is surmised that the appearance of these reflexive and transient responses are ascribed to the stimulation of the sympathetic which is never completely eliminated by stripping from the wall of artery.

Group IV. (Measurement of renal blood flow in jaundiced dogs)

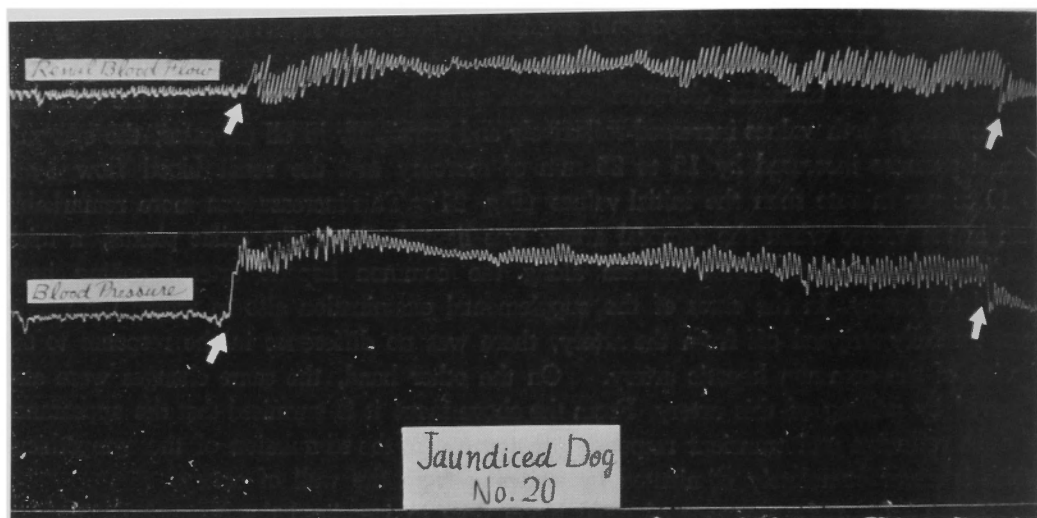
The surgical aggression of the procedures for measurement of renal blood flow in this group was almost of the same grade as in Group III. The mean systemic arterial pressure was 90 mm of mercury and the average blood flow of the unilateral renal artery

Fig. 21



- A : Ligation of the femoral artery.
- B : Reopening of the femoral artery.
- C : Opening of the abdomen.
- D : Ligation of the hepatic artery.
- E : Closure of the abdomen.

Fig. 22



was 5.7 cc per kg per minute; these values were markedly lower than those of normal dogs (Table 2).

In 5 out of 8 jaundiced dogs of this group, arterial pressure and renal blood flow increased continuously together with their increased amplitude after the ligation of the hepatic artery and returned to the initial values simultaneously with reopening of the hepatic artery. These phenomena were not observed in Group III.

Fig. 22 shows the typical case; the systemic arterial pressure was elevated from 118 to 150 mm of mercury and the renal blood flow increased by 5 cc per minute than the initial value. In the other cases of this group, the same transient responses as in Group III were observed.

Generally, experimental dogs began to excrete deep yellow urine 2 to 3 days after the ligation of the choledochus, and in most cases, the yellow conjunctiva and skin were recognized about a week after the operation. The time of appearance of visible icterus and its degree were various and somewhat different from one another; in white dogs, these changes appeared earlier and more remarkably than in the black ones whose Meulengracht index rose amazingly in spite of no manifest sign. On the other hand, the dogs whose choledochus were ligated began to lose appetite gradually several days after the operation. Some dogs showed almost no appetite already about 2 weeks after the operation, and an extreme decrease in the body weight were observed.

Generally, body weight in this group diminished by 5 to 10 per cent about 2 weeks after the ligation of the choledochus, and weight loss of 15 to 25 per cent after 3 weeks. Moreover, yellow ascites was observed more or less after 3 weeks.

1) The liver

Although the Meulengracht index was almost in a resembling value in experimental dogs 2 weeks after ligation of the common bile duct, the microscopical changes of the liver at autopsy showed a considerable difference from each other after the interruption

of the hepatic artery.

In mild cases, there were a slight swelling and round cell infiltration in GLISSON'S sheath, a turbid swelling of parenchymal cells in the periphery of the liver lobules, and slight degeneration around the central vein.

Though bile thrombus was not found at all, the stellate cells of KUPFFER were observed to be taking up the bile pigment vigorously.

However, the influence of the ligation of the hepatic artery was not manifest; congestion in sinusoids and in portal spaces was not demonstrated, although this finding was usually observed at an early stage after the ligation of the hepatic artery (Fig. 23, 24).

In moderately severe cases, small round cell infiltration, edema and fibrosis in the periportal or periductular spaces became remarkable, with a higher degree of centrilobular parenchymal degeneration, and the formation of bile thrombus and accumulation of bile pigments in the KUPFFER'S cells chiefly around the central veins were manifest, together with the occasional occurrence of central hemorrhage (Fig. 25, 26, 27).

In severe cases, interlobular fibrosis was so remarkable that it was similar to or identical with biliary cirrhosis (Fig. 28).

In these cases, it was very difficult to discriminate the effects of the hepatic artery ligation on the histological findings, particularly centrilobular hemorrhage and degeneration from those of obstructive jaundice.

In 2 cases in Group IV complication of cholangitis and microabscess in the liver were observed in spite of the administration of penicillin. In these cases degenerative changes or necrosis were most conspicuous (Fig. 29, 30).

2) The kidney

Though the kidney did not show abnormalities in the cases of only slight liver changes (Fig. 31). In the cases in which more of the liver changes were found, slight dilatation of the tubules and nuclear pyknosis were recognized together with the presence of the protein-like substances in the tubular lumen sporadically.

Occasionally, a bit of the bile pigment was found in the proximal convoluted tubular epithelium, but the bile casts were not recognized anywhere (Fig. 32). The kidney of those with liver microabscess exhibited degenerative changes of the tubular epithelium (Fig. 33). However, any specificity of the affected part of the tubules was not found.

Then, contrasting the microscopical changes of the liver and kidney with the changes of renal blood flow due to the ligation of the hepatic artery, it was found that all the cases that showed the continuously elevated value of the systemic arterial pressure and renal blood flow by the ligation of the hepatic artery had the more severe changes in the liver and kidney. On the other hand, these changes had no correlation to the period of time after the ligation of the choledochus, initial arterial pressure and Meulengracht index. From the above facts, it seems justifiable to conclude that the severity of the liver changes after the ligation of the hepatic arteries plays a leading role.

Group V. (Hemorrhagic shock in jaundiced dogs)

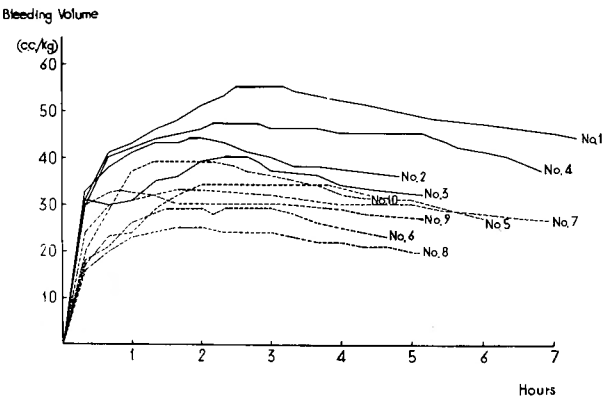
Six jaundiced dogs surviving 3 to 4 weeks after the ligation of the choledochus and 4 normal dogs of the control were studied (Table 3, Fig. 3).

Initial (prehemorrhagic) arterial pressure was lower in the jaundiced dogs than in

Table 3 Hemorrhagic Shock at 50 mm.Hg Mean Arterial Blood Pressuse
by Modified Lamson's Bleeding Bottle Method.

Number of Dogs		Control					Jaundiced Dogs						
		1	2	3	4	Average	5	6	7	8	9	10	Average
Body Weight (kg.)		9.5	8.0	7.0	12.0		7.5	9.0	13.0	11.0	11.5	9.5	
Initial Arterial Blood Pressure		116	110	120	140	131	96	88	118	124	118	88	106
Maximal	Hours after Hemorrhage (min.)	150	110	140	130	134	120	90	100	90	50	80	88
Bleed-out	Bleeding Volume (cc./kg.)	55	44	40	47	46.5	33	29	33	25	33	39	32
20% Spontaneous Reinfusion of the Maximal Bleeding Volume	Hours after Hemorrhage (min.)	435	290	305	415		360	280	420	310	305	270	
	Bleeding Volume (cc./kg.)	44	36	32	37		27	23	27	20	27	31	
Icterusindex (Meulengracht)							74	68	82	64	64	86	
Days after Ligation of the Common Bile Duct							28	21	24	21	28	24	
Comments		Survived		Sacrificed			Died		Sacrificed				

Fig. 3



normal dogs; 106 mmHg on the average in the former, 131 mmHg on the average in the latter.

The period of time to reach the balanced stadium was shorter in the jaundiced dogs than in normal dogs; 80 min. on the average in the jaundiced dogs and 134 min. on the average in the normal dogs. The maximal bleeding volume was less in the jaundiced dogs than normal dogs; 32 cc/kg of body weight on the average in the former and 46.5cc/kg of body weight on the average in the latter. Thus, the jaundiced dogs reached the balanced stadium more swiftly and with less blood removal than normal dogs. The jaundiced dogs tended to be led to hypotension easily.

Furthermore, what was outstanding was that 3 jaundiced dogs all died and 2 control dogs survived by pumping back all the removed blood into the vascular system at the stage of 20% reinfusion. The microscopical findings in 2 normal and 3 jaundiced dogs

at the time of 20% reinfusion stadium were as follows.

1) The liver

The microscopical findings of the liver of jaundiced dogs (Group V), in which all the removed blood were pumped back into the vascular system at the time of 20% reinfusion stadium, were severer than those of jaundiced dogs in Group IV. And there was a single case in which liver showed a typical biliary cirrhosis (Fig. 34). Also in other two cases, it was supposed that the histological findings of the liver were those on the way to biliary cirrhosis.

In addition, it was of interest that the microscopical changes around the central veins involving hemorrhage in these jaundiced dogs resembled to those in some jaundiced dogs with ligation of the hepatic artery in Group IV (Fig. 36). In the liver of normal dogs in which all the removed blood was pumped back into the vascular system at the time of 20% reinfusion stadium, only a slight congestion in sinusoids and central veins, and cloudiness of hepatic cells were observed (Fig. 38).

2) The kidney

Microscopically the kidney of jaundiced dogs in which all the removed blood was pumped back at 20% reinfusion stadium presented considerably unique findings; dilatation of the lower part of the tubules and principally vacuolar degeneration of upper tubular epithelium were noticed.

Bile casts and the pigment casts seen often in shock state were not observed at all, though bile pigment was seen here and there in the proximal convoluted tubules (Fig. 35, 37).

The kidneys in the normal dogs at the same stadium showed a high degree of cloudy swelling of the tubular epithelium and narrowing of the tubular lumen (Fig. 39).

3) The intestine and spleen

In the jaundiced dogs in which all the removed blood was pumped back into the vascular system at 20% reinfusion stadium, a slight congestion and remarkable deposition of hemosiderine were recognized in the spleen, and the intestinal tract was somewhat ischemic but revealing macroscopically as well as microscopically no hemorrhagic changes, as is said to be observed usually in a state of irreversible shock in the intestinal tract. In normal control dogs, on the other hand, both intestine and spleen did not show any noticeable changes histologically. Although there were no remarkable changes in the intestinal tracts of the jaundiced dogs which were sacrificed about twenty minutes after pumping back of all the removed blood at 20% reinfusion stadium, the extensive congestion and hemorrhage were observed at autopsy in intestinal tract after death.

IV DISCUSSION

There have been two terms suggesting the intimate relationship between the liver and kidney; hepatonephropathia and hepatorenal syndrome. In our country, the former is used in internal medicine and the latter in surgery.

MATSUO³⁰⁾ (1927) emphasized the anatomical and functional similarities between the liver and kidney, and named the syndrome in which the liver and kidney are injured simultaneously by some single cause (toxic or infectious), hepatonephropathia. Afterwards,

he recognized that hepatonephropathia is synonymous with hépatonéphrite in French (RICARDIÈRE, 1890. DÉROT, 1934).

On the other hand, it is said that the term "hepatorenal syndrome" is a clinical concept introduced by HEYD in 1924¹⁴⁾¹⁵⁾.

SHIBUSAWA et al.⁴⁴⁾⁴⁵⁾⁴⁶⁾ accepted this term entirely as a surgical one and expressed that about 80 per cent of hepatorenal syndrome are identical to acute renal insufficiency.

Furthermore, LASSEN & THOMSEN²⁵⁾ (1958) asserted that hepatorenal syndrome is nothing but acute renal insufficiency itself. However, POPPER et al.³⁶⁾ gave more flexible interpretation to this term, including hepatonephropathia, and classified it as follows;

- (1) paralleled injury to both organs in toxic conditions;
- (2) the renal damage encountered in obvious hepatic diseases;
- (3) acute renal insufficiency with anuria following either trauma or surgery on the biliary tract.

SANBE et al.³⁸⁾ (1961) postulated that the impairment of the kidney in the presence of jaundice also belongs to hepatorenal syndrome.

Thus, the term "hepatorenal syndrome" has been interpreted variously.

It is in the case in which development of shock, particularly irreversible shock is concerned that the liver and kidney attract great attention simultaneously in the field of surgery.

The postulation that the principal cause of irreversibility of shock is ischemic injury of the liver has been presented by many investigators; SHORR⁴⁷⁾, FINE⁷⁾⁸⁾, COHN⁴⁾, DELORME⁵⁾, FRANK⁹⁾, HAY¹³⁾ and the others.

On the other hand, since World War II, the concept of acute renal insufficiency or shock kidney, in which chief symptom consisted of anuria following traumatic shock in battle, has been postulated and debated tremendously in England and U. S. A., and the terms "Crush syndrome" and "Lower nephron nephrosis" have been often used.

Though there were various opinions on the localization of tubular injury, these renal changes in shock state have been understood as combination of both nephrotoxic damage and tubulorhexis due to renal ischemia, which was clarified by OLIVER's pathohistological study³⁴⁾ (1951) using microdissection method.

POPPER et al.³⁶⁾ also stated that the term "acute nephrosis" is preferable to "lower nephron nephrosis" for such condition, since other parts of the nephron are also involved. On the other hand, KURUSU²⁸⁾ (1949), EDWARDS²⁶⁾ (1954), PARKINS³⁵⁾ (1955), LILLEHEI²⁶⁾²⁷⁾ and others put great importance on mesenterial circulatory insufficiency regarding irreversibility of shock.

A) Influence of the liver injury caused by the interruption of the hepatic artery on the kidney

HARTL¹¹⁾ (1952) stated that the important fact in hepatorenal syndrome is that the hepatocellular degeneration is always accompanied by renal injury, and also diffused peripheral fatty metamorphosis is usually found in the epithelial cells of the thin limb of HENLE and the distal convolution. Very few literatures are found concerning the renal changes in the cases in which the injury is comparatively confined to the liver, as in the present experiment using the method of ligating the hepatic artery. SHIBUSAWA et al.⁴²⁾⁴³⁾

(1955) stated that the renal changes, in the experiments using RAPPAPORT's dogs in which the common hepatic artery was ligated with the establishment of ECK's fistula, were of no more than the same degree of those shown by HARTL et al. as mentioned in the above, and presumed the participation of antidiuretic substances, since the anuria cannot be explained adequately only by these renal morphological changes.

They⁴⁴⁾⁴⁵⁾ divided the hepatorenal syndrome into two types, i. e. type I is chiefly brought about in toxic and infectious conditions after the operation of the liver and biliary tract, and type II is identical with the acute renal insufficiency, and discussed the differences between these 2 types.

Moreover, on type I, they expressed that such renal changes as so called lower nephron nephrosis are not observed in the typical cases, nonprotein nitrogen levels are low, and even if there is a disturbance of consciousness, it is not due to uremia. And they stated that, for these reasons, the artificial kidney which is effective in type II is ineffective in type I.

SVEN RAMSTRÖM³⁷⁾ (1953) using rabbits described also that in spite of the presence of liver necrosis amounting to 20 to 80 per cent of its total volume after the ligation of the hepatic artery, the animals died without showing an elevation in nonprotein nitrogen level.

In the present experiment using dogs, after the liver was injured primarily by ligating the hepatic artery, the renal changes were similar to the early renal changes by nephrotoxins such as mercury or bichloride of mercury, and they were of slight degree and rather nephrotoxic damages than tubulorhexis which is chiefly observed in shock kidney. Though they belong to type I of SHIBUSAWA et al. from the point of view of extensiveness of liver necrosis, it is more suitable and concise to conceive that the death in these cases is so called liver death than to conceive that it is brought about by acute renal insufficiency or shock kidney.

ISHIGURO²¹⁾ (1961), in our clinic, followed up the histological changes of the liver after hepatic arterial interruption and noted that the growth of anerobic bacteria is not the direct cause of liver necrosis, but the result of it — an explosive growth of anerobic bacteria takes place in ischemic necrotic area.

And in the experiments of Group I and II, interstitial cell infiltration of the kidney and severe tubular degeneration were found in only those dogs which were complicated by severe peritonitis after ligation of the hepatic artery regardless of administration of penicillin.

From these facts, it is surmised that those severe renal changes were not inherent to primary liver injury due to the ligation of the hepatic artery.

Furthermore, the influence of the ligation of the hepatic artery on renal blood flow was transient as observed in Group III, and in the cases in which liver necrosis was limited in space by the administration of penicillin, no histological change in the kidney was observed and the animals survived as described in the results of Group II.

Hence, the theory that the ligation of the hepatic artery leads to renal insufficiency inevitably is hardly acceptable.

In addition, the animals having lethal extensive liver necrosis due to ligation of the

hepatic artery showed congestive or hemorrhagic change in the bowel macro- and microscopically except the cases complicated by severe peritonitis.

These findings suggest that these cases in which the liver was injured primarily are not so concerned with the bowel factor as suggested by LILLEHEI.

B) Jaundiced dogs due to ligation of the common bile duct

In dogs, the renal clearance of bilirubin is greater than in man and other experimental animals, and consequently, after ligation of the common bile duct, it is said that appearance of icterus is retarded and bilirubinemia does not develop so high and biliary cirrhosis is not induced^{33) 36)}.

In the jaundiced dogs of Group IV and V, although the intervals of time after the ligation of the common bile duct were almost similar and Meulengracht indices reached almost the same level, a considerable difference in microscopical changes of the liver was observed. Furthermore, there was a case which showed a typical biliary cirrhosis 4 weeks after ligation of the common bile duct and in the other dogs the findings suggesting to be on the way to biliary cirrhosis were noticed.

Furthermore, no bile casts in tubular lumens and rare bile pigment in the epithelium of the proximal convoluted tubules were found in these jaundiced dogs. And there was even a case in which the kidney showed almost normal findings 2 weeks after ligating the common bile duct.

POPPER et al.³⁶⁾ insisted that urinary bile pigment does not seem to cause renal functional disturbances in man, and morphological impressive finding of dark green kidney has little significance in renal function, never causing renal insufficiency clinically. From these facts, there is an advantage in dogs that the theory of renal insufficiency caused by bile casts or bile pigment can be excluded.

The average blood flow through unilateral kidney of jaundiced dogs in the present experiment was so low as 5.7 cc per kg body weight per minute. But BOUNOUS²⁾ and his associates, using dogs, concluded that a perfusion rate through bilateral kidney at a rate of about 7 cc per kg body weight per minute was sufficient to maintain renal function without causing tubular damage.

In the jaundiced dogs in which arterial pressure and renal blood flow were elevated continuously by ligation of the hepatic artery (Group IV), the microscopical changes of the liver and kidney were more severe than those in the other dogs in Group IV which showed transient increase in blood pressure and renal blood flow. It may be supposed that these jaundiced dogs are more apt to be led to shock as compared with the latter jaundiced dogs and normal ones.

The reason why arterial pressure and renal blood flow were elevated continuously by ligation of the hepatic artery in some jaundiced dogs is not clarified at present time but the following facts may be considered.

(1) Biliary acid has acetylcholine like action (SAITO)^{39) 40)}.

(2) Generally, it is said that, in liver cirrhosis, total blood flow through the liver is decreased but hepatic arterial blood flow is increased than in normal state^{36) 50)}.

(3) In severe hepatic failure, cardiac output is increased, and in one third of the cases of cirrhosis, the resting cardiac output is increased; with a shortened circulation time and

an increased stroke volume (POPPER)³⁶⁾.

(4) The liver of these jaundiced dogs showed microscopically more severe changes than that of the other jaundiced dogs; finding of biliary cirrhosis or that on the way to it.

According to the experiment in Group V, jaundiced dogs have a tendency to be easily led to hypotension, in other words, these animals have a decreased tolerance to hemorrhage.

Moreover, after pumping back all the removed blood into the vascular system at the time of 20% reinfusion stadium, all of jaundiced dogs died, whereas normal dogs all survived.

Although FINE et al.⁸⁾, using essentially the same method in experiment, reported that the irreversible phase begins at the time when the blood volume of spontaneous return to the experimental dogs reaches around 40% of the maximal bleeding volume, the irreversible phase begins obviously at most before 20% reinfusion stadium in the jaundiced dogs of the present experiment. The jaundiced dogs in which all the removed blood was pumped back at the time of 20% reinfusion stadium showed the findings suggesting an abrupt ischemic changes in tubules together with those brought about by jaundice itself. These tubular ischemic changes were severe extraordinarily compared with those in the control animals

Though ANLYAN and SUDO⁴⁸⁾, using the same method on normal dogs, found that there is no remarkable change in various organs except the liver, it is surmised from these renal histological changes in the jaundiced dogs in the present experiment that there is a decreased tolerance of the kidney to shock in the presence of jaundice as SANBE³⁸⁾ and his associates have pointed out.

WILLIAMS et al.⁵²⁾, using a modification of the method of WIGGERS in jaundiced dogs, have reported that the same degree of hypotension occurs in jaundiced dogs with approximately one half the blood loss as required in normal dogs. Their results are identical with those of the present experiment in the point that jaundiced dogs have a decreased tolerance to hemorrhage.

On the other hand, ELLISON⁶⁾ and his associates have reported that blood volume deficit runs in parallel with weight loss in jaundiced patients. Accordingly in the present experiment, it is supposed that there exists a considerable hypovolemia, since 5 to 25% of weight loss was observed 2 to 4 weeks after ligation of the common bile duct.

From all the above mentioned facts, it is probable that the ligation of the hepatic artery in jaundiced dogs does not ensue the state of shock immediately, and findings of the kidney are various. However, jaundiced dogs have less tolerance to hemorrhagic shock, being accompanied by considerable injury in the kidney.

V SUMMARY AND CONCLUSIONS

For the purpose of studying surgical hepatorenal relationship, the influence of the ligation of the hepatic artery on the kidney was studied in normal dogs and jaundiced ones in which the common bile duct was ligated and cut, and also the experiment of hemorrhagic shock was carried out, using modified LAMSON's bleeding bottle method in jaundiced dogs. The results are;

(1) In those dogs which died after the ligation of the hepatic artery, regardless of administration of penicillin, some renal changes together with the extensive liver necrosis were noticed, and the essential renal change was not of tubulorhexic nature as is observed often in so-called shock kidney, but of nephrotoxic.

(2) In those dogs which could survive with the administration of penicillin, some degree of centrilobular degeneration in the liver was observed, but these areas were localized and hepatic cells in these areas showed a tendency to prosperous regeneration. In such cases no renal change was observed.

(3) The dogs which died after the ligation of the hepatic artery showed no congestion and hemorrhagic necrosis in the bowel except the dogs with complication of severe peritonitis.

(4) In the normal dogs, the arterial pressure and renal blood flow increased only reflexively and transiently by ligation of the hepatic artery.

(5) It was not considered that the ligation of the hepatic artery itself had an immediate pathological influence upon the kidney in normal dogs.

(6) In the jaundiced dogs, the arterial pressure and renal blood flow were generally lower than in normal dogs and there were many cases in which arterial pressure and renal blood flow increased continuously after ligation of the hepatic artery.

But it was difficult to find out an explanation of this phenomenon through the present experiment.

(7) The jaundiced dogs whose common bile duct was ligated and cut, showed less tolerance to hemorrhage.

(8) Immediately after pumping back of the total removed blood at the time of 20% reinfusion stadium, kidney of the jaundiced dogs showed remarkable changes such as vacuolar degeneration of the upper part of the nephron together with the enlargement of the lower nephron.

In concluding my report, I wish to express my deepest gratitude to Dr. CHISATO ARAKI, professor of Kyoto Univ. and Dr. ICHIO HONJO, professor of Kanazawa Univ. for their kind and continuous guidance, encouragement and supervision. At the same time I am greatly indebted to Dr. RYOICHI TSUCHIYA in the Surgical Division of Kyoto Univ. Medical School for his kind guidance.

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和 文 抄 録

外科的肝腎関係に就いての実験的研究

(肝動脈遮断, 胆道閉塞の腎への影響)

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内 山 輝 美

肝, 及び腎は, 共にショックに関して重要な臓器とされている。一方, 肝腎相互の密接な関係を表現して, 従来, 肝腎症候群と云う臨床概念があるが, 近年, ショックに就いての研究が進むにつれ, 次第に当症候群の存在価値も揺れ, 解釈の仕方も多様で, 曖昧なものになって来た。しかし尚, 腎臓特性に, 急性腎下全の惹起因子として, 肝傷害を重要視する学者がある。以上に鑑み, 臥は, 犬を用い, 腎動脈血流遮断, 又は, 総胆管閉塞によつて, 比較的, 一次的且つ単独の形の肝傷害を作成し, かかる肝傷害がどの程度腎に影響するかを検し, ショック問題と関聯して, 所謂, 肝腎症候群に就いての考察を試みた。

即ち, 正常犬, 及び総胆管結紮による黄疸犬に就いて, 肝動脈血流を遮断し, 或は, 出血ショック実験を行ない, 主として肝, 腎変化を組織学的に追究すると共に, 腎血流量を視察する事によつて, 次のような結果を得た。

1) Penicillin投与の有無に拘らず, 肝動脈血流遮断によつて, 死の転帰をとる犬では, 肝の広汎な壊死と共に腎にも或る程度の変化が見られるが, 其の基調をなすものは, nephroticであり, ショック腎に見られるような tubulorhexic な変化を主とした劇しい所見は

認められなかつた。

2) Penicillin投与により生存する犬でも肝にやはり, 小葉中心性変性像が認められるが, これらは, 限局化され, 又, 旺んな再生像を呈する。このような例では, 腎に変化を証明出来なかつた。

3) 肝動脈血流遮断により死に至る犬でも腹膜炎併発例以外の例では, 腸管に Congestionや, 出血性壊死所見は, 全く認められなかつた。

4) 正常犬では, 肝動脈血流遮断によつて, 血圧, 並びに腎血流量は, 一時的, 反射性に増量するのみであつた。

5) 正常犬では, 肝動脈血流遮断それ自体が直接腎に悪影響を与えるとは思われない。

6) 黄疸犬では, 一般に, 血圧, 腎血流量が低値で, 肝動脈血流遮断により, 血圧, 腎血流量の持続的上昇を示す例が多いが, 本実験からその理由を明らかにする事は出来なかつた。

7) 総胆管結紮による黄疸犬は, 正常犬に比し, 出血に対する抵抗性が低い。

8) 出血ショック実験に於ける20%還血期に全返血した黄疸犬の腎には, 上部尿管の空腔変性, 下部尿管の拡張等顕著な変化が認められた。

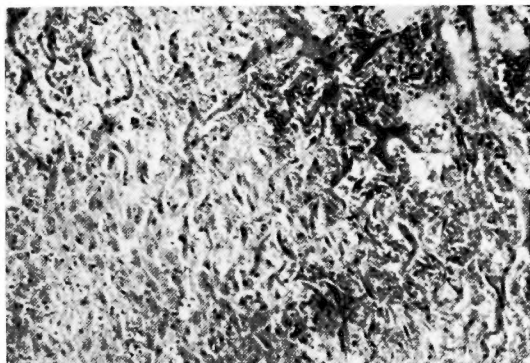


Fig. 4

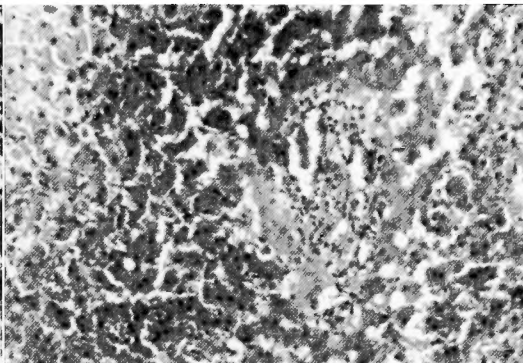


Fig. 5

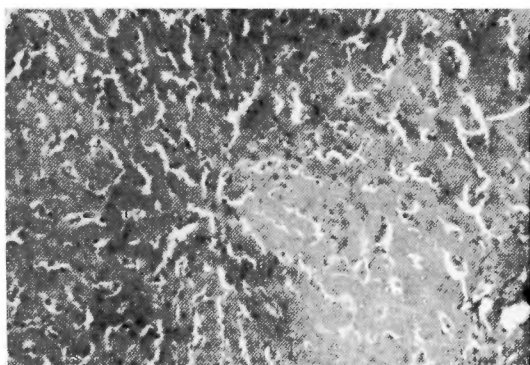


Fig. 6



Fig. 7



Fig. 8



Fig. 9



Fig. 10

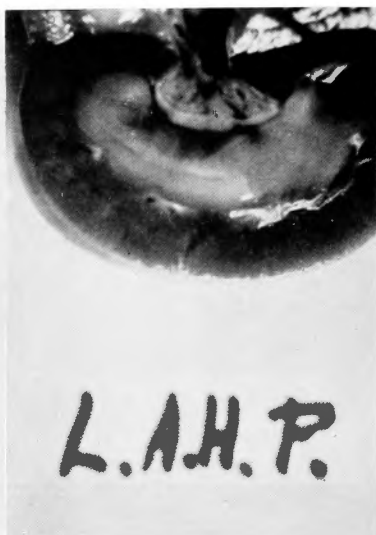


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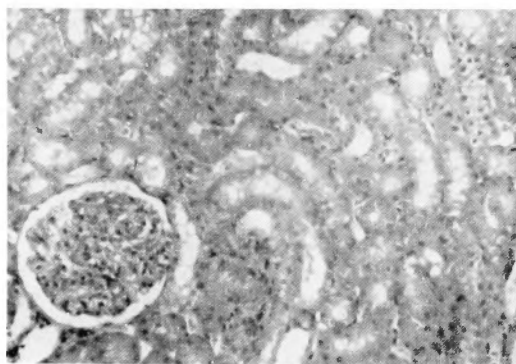


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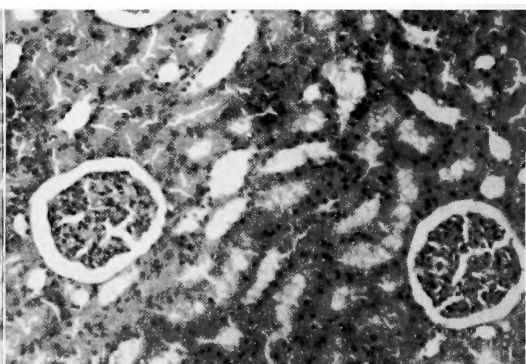


Fig. 13

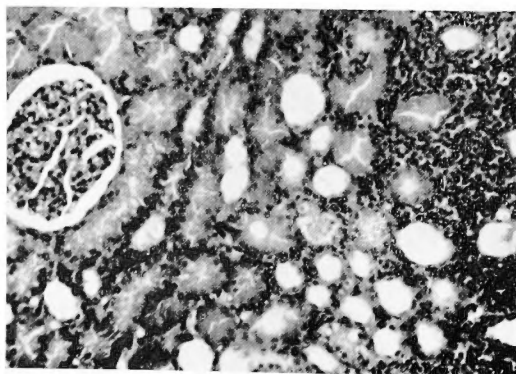


Fig. 14



Fig. 15



Fig. 16

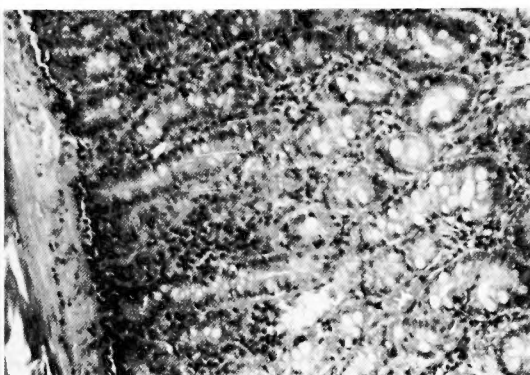


Fig. 17



Fig. 18

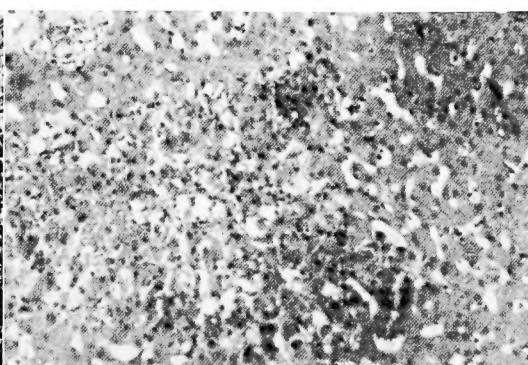


Fig. 19

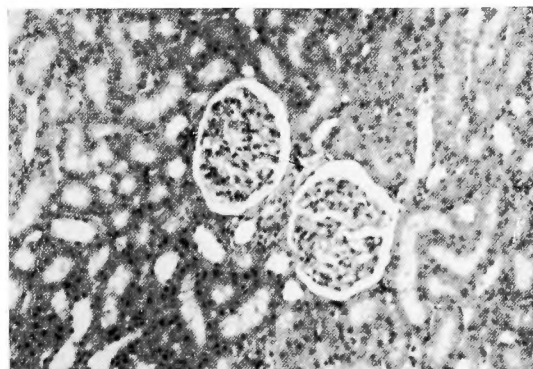


Fig. 20

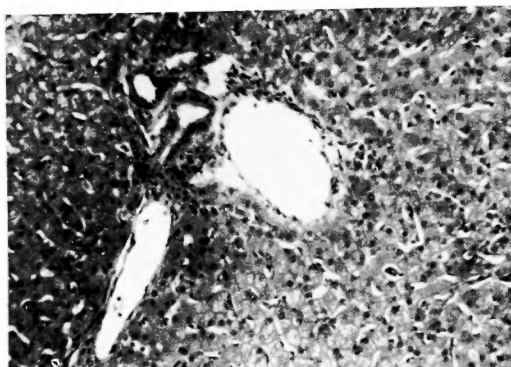


Fig. 23

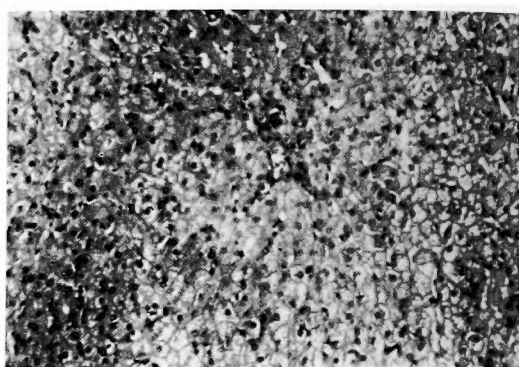


Fig. 24

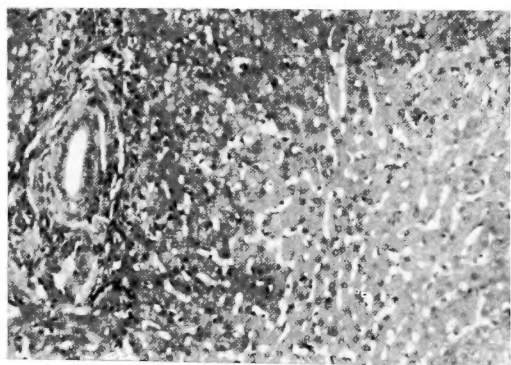


Fig. 25



Fig. 26

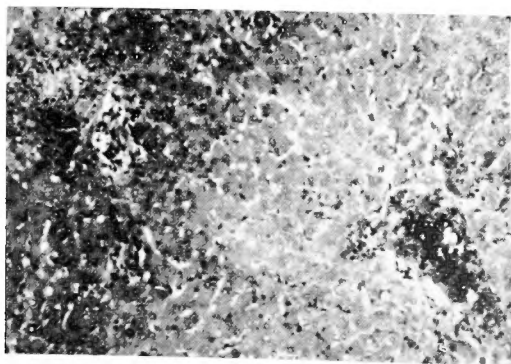


Fig. 27

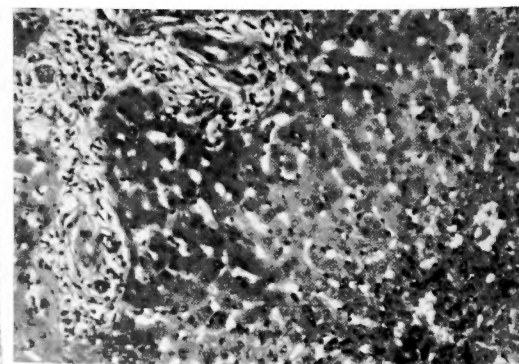


Fig. 28

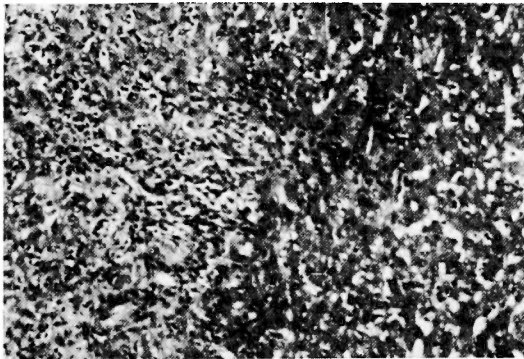


Fig. 29

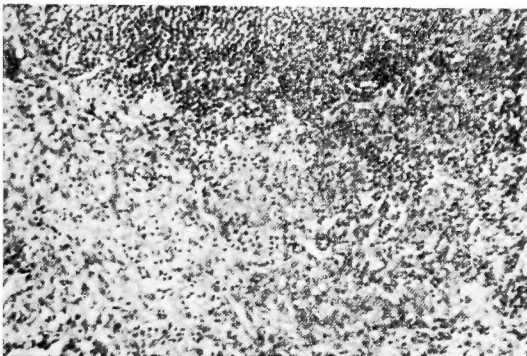


Fig. 30



Fig. 31

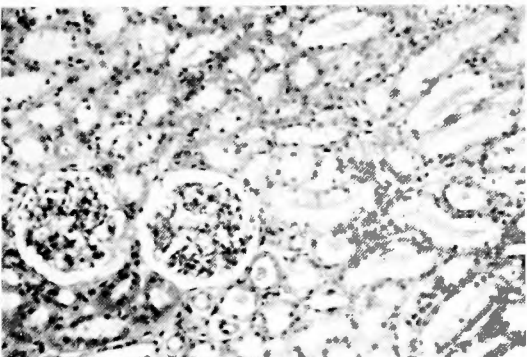


Fig. 32

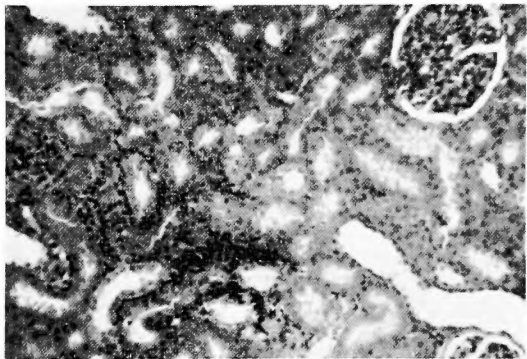


Fig. 33

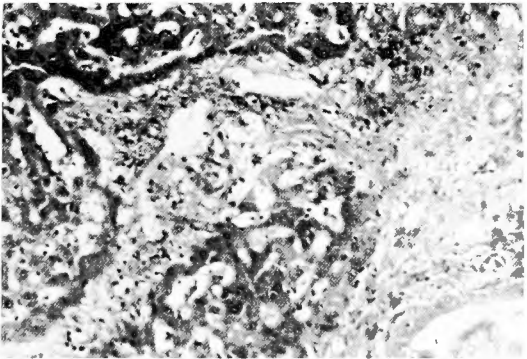


Fig. 34

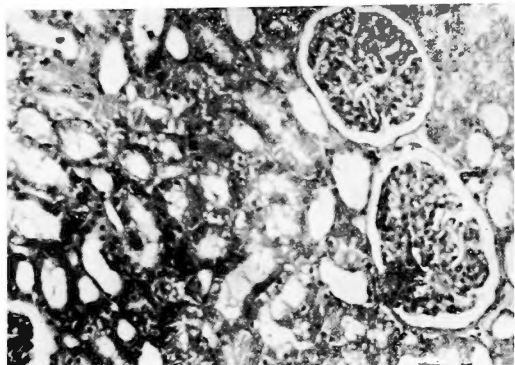


Fig. 35

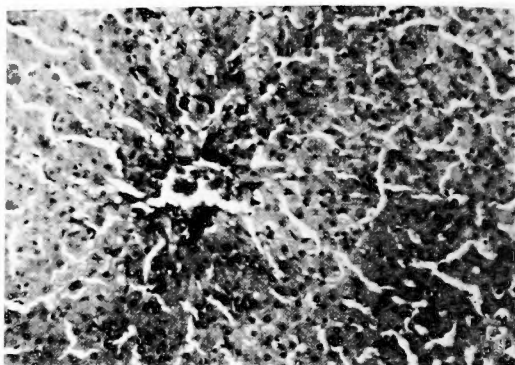


Fig. 36

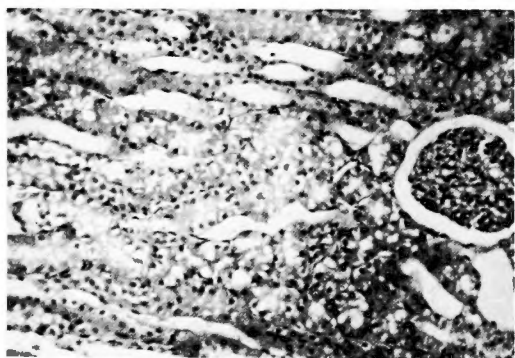


Fig. 37

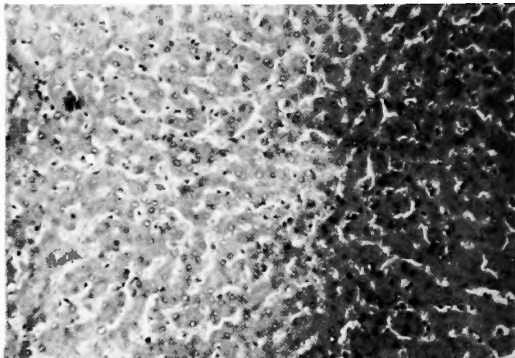


Fig. 38

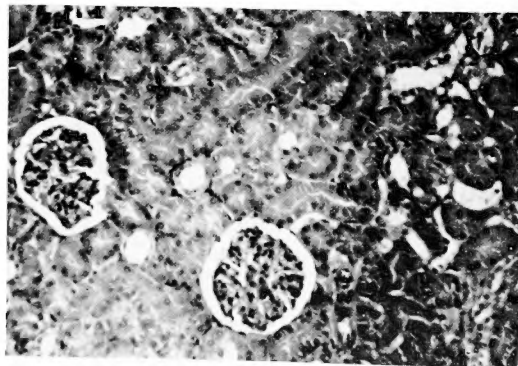


Fig. 39