

STUDIES ON DISTURBANCES OF THE INTRAHEPATIC PORTAL FLOW, AFTER THE LIGATION OF THE HEPATIC ARTERIES

by

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CONTENTS

- I Introduction
- II Interruption of arterial blood supply to the liver and the production of the portal dogs
- III Radiological examination of intrahepatic portal stagnation
- IV Intrahepatic portal circulation after the ligation of the hepatic arteries in normal dogs
- V Intrahepatic portal circulation in the portal dogs
- VI Intrahepatic portal flow after the ligation of the hepatic arteries in the ascitic dogs
- VII Effects of atropine, adrenalin and vagostigmine on intrahepatic portal flow, under the ligation of the hepatic arteries
- VIII Discussion
- IX Conclusion

I INTRODUCTION

Ligation of the hepatic arteries, which has been advocated as a surgical treatment for liver cirrhosis and especially for those with ascites, has not yet been generally accepted because of the probable danger of liver necrosis following the ligation. In fact, the ligation of the hepatic arteries in normal dogs often results in liver necrosis, despite the postoperative administration of antibiotics. According to our experiences, however, the ligation of the hepatic arteries was successfully performed in patients with ascites caused by the liver cirrhosis, and none of them showed a clinical symptom of liver necrosis. No liver necrosis was disclosed even in the necropsy performed in some cases.

TSUCHIYA, in our clinic, reported that the ligation of the hepatic arteries is less mortal to ascitic dogs than to normal ones. In the present study a radiological examination was made of the intrahepatic portal flow after the ligation of the hepatic arteries to reveal the mechanism of the development of liver necrosis, which has a lower incidence in ascitic dogs than in normal ones.

The effect of atropine, adrenalin, and vagostigmine on the impairment of the intrahepatic portal flow caused by the ligation of the hepatic arteries was also studied.

II INTERRUPTION OF ARTERIAL BLOOD SUPPLY TO THE LIVER AND THE PRODUCTION OF THE PORTAL DOGS

Besides the proper hepatic artery, which is the largest artery supplying the liver, the liver is supplied with minor arterial branches originating from the

diaphragmatic artery and the left gastric artery. These minor branches are apt to have a wide range of anatomical variations and a complete surgical interruption of them is almost impossible. The interruption of the arterial inflow at the hilus, however, is enough to bring about liver necrosis. In the present study, for the purpose of complete interruption of arterial inflow to the liver, the author ligated concurrently the right gastric, the gastroduodenal as well as the common hepatic arteries. Hereafter, the ligation of these three arteries will be referred to simply as "ligation of the hepatic artery" (Fig. 1).

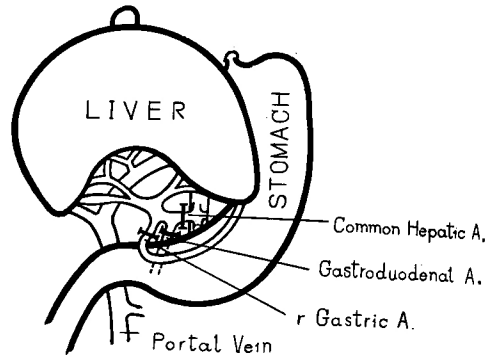


Fig. 1

In several dogs, the cholecystectomy was added to the ligation of the hepatic artery and 100,000 units of crystal penicillin was administered intraperitoneally before the laparotomy wound was closed, and then several hundred thousand units of oil penicillin was intramuscularly injected everyday for two to three postoperative days. In this series of dogs, the mortality was reduced to about 35 per cent. The surviving dogs will be called "portal dogs" in the sense that the liver is supplied practically only by the portal vein.

III RADIOLOGICAL EXAMINATION OF INTRAHEPATIC PORTAL STAGNATION

10cc of 76 per cent urografin was injected into the liver within 5 seconds, by way of the portal vein, at the radix mesenterii. Just before the whole amount was injected, an X-ray picture was taken of the hepatic area to make sure that the injected medium pervaded the intrahepatic portal system. Five minutes later, another picture was taken of the same area to see if the injected medium still remained there.

Hereafter, the above procedure will be called simply "injection of urografin".

It was observed, by the application of an image amplifier, that 10cc of urografin passed through a normal liver within 30 seconds. Therefore, should urografin remain in the liver over 5 minutes after the injection, it is a definitive sign of intrahepatic portal stagnation.

The injection of urografin was performed in dogs before and after the ligation to study the changes of the intrahepatic portal circulation. As control, the same procedure was applied to the dogs which had intraabdominal operations other than the ligation. For example, urografin was injected in a dog after cholecystectomy, and no sign of portal stagnation was observed.

IV INTRAHEPATIC PORTAL CIRCULATION AFTER THE LIGATION OF THE HEPATIC ARTERIES IN NORMAL DOGS

1) Materials and Methods

Table 1

Dog No.	within 1 hour	1 hour after	2 hour after	3 hour after
No. 4	(+)			
No. 5	(+)			
No. 9	(-)	(-)	(-)	
No. 10		(+)	(+)	(+)
No. 12		(-)	(+)	(+)
No. 13			(-)	
No. 14		(+)	(+)	
No. 15		(+)	(+)	(+)
No. 22		(-)	(-)	
No. 30		(-)	(-)	
No. 31	(-)	(-)		

(+) shows a positive portal stagnation.

Adult mongrel dogs, weighing 7 to 15kg. were used. The ligation was performed under intravenous nembutal anesthesia. The injection of urografin was carried out once to three times, between 30 minutes and 3 hours after the ligation of the hepatic arteries. Table 1 shows the times at which the injection was performed, and the presence or absence of the stagnation of the portal flow at these times.

2) Results

As mentioned in the preceeding chapter, the injected urografin leaves the liver within 30 seconds in normal dogs. Here again, four normal dogs had the injection of urografin and in their X-ray pictures none presented any remains of the medium in the liver 5 minutes after the injection.

Eleven dogs had an injection of urografin between 30 minutes and 3 hours after the ligation. Six of them showed a part of the injected urografin still remaining in the liver five minutes after the injection, indicating the disturbance

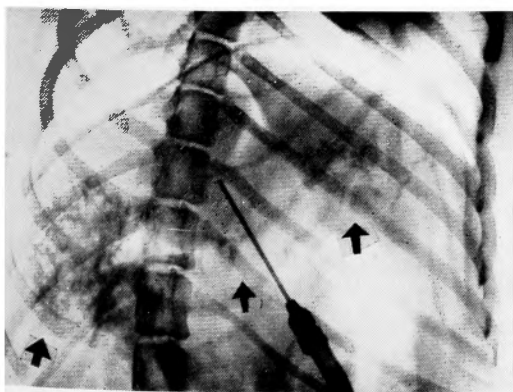


Fig. 2

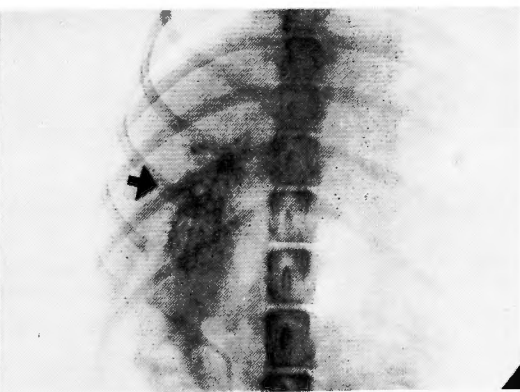


Fig. 3

Fig. 2 Urografin injected 1 hour after the ligation of hepatic arteries. Expansive residue of urografin shown in the liver.

Fig. 3 1hour after the ligation of hepatic arteries. 10cc of urografin injected into portal vein. Trace of urografin shown in the liver 5 minutes after the injection.

of the intrahepatic portal flow (Figs. 2 & 3).

In Fig. 4 is given our conventional nomenclature of the dog's liver lobes (Fig. 4).

Residue of urografen is seen mostly in the left half of the liver, including the left superior and inferior lobes, caudate and quadrate lobes, and in the right inferior lobe.

In one case, urografen was injected three times, one, two, and three hours after ligation. It was observed at each injection that remains of urografen covered a larger area as time went on. These areas correspond to such in which liver necrosis is most likely to occur after the ligation (Figs. 5a, 5b, 5c, 5d, 5e & 5f). From the above findings it is assumed that the ligation lowered the velocity of the intrahepatic portal flow and gave rise to stagnation in those parts of the liver.

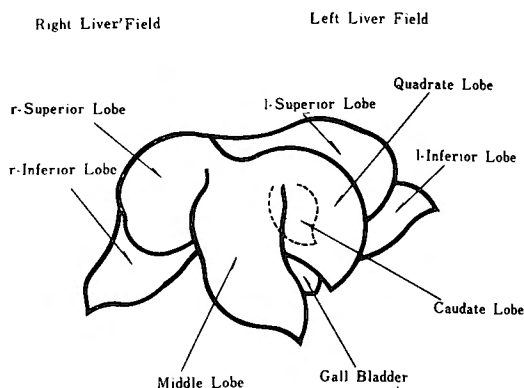


Fig. 4

Fig. 4

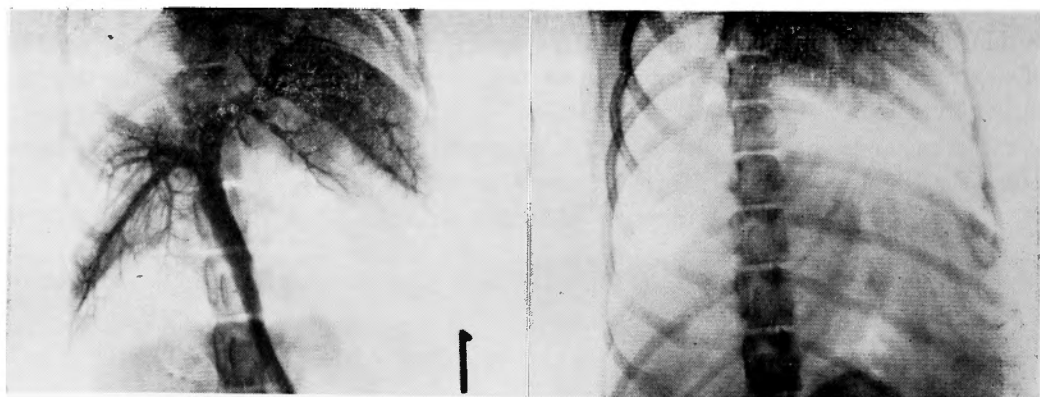


Fig. 5a

Fig. 5b

Fig. 5a Before the ligation of hepatic arteries. 10cc of urografen pervaded the intrahepatic portal system.

Fig. 5b 5 minutes after Fig. 5a. No trace of urografen in the liver.

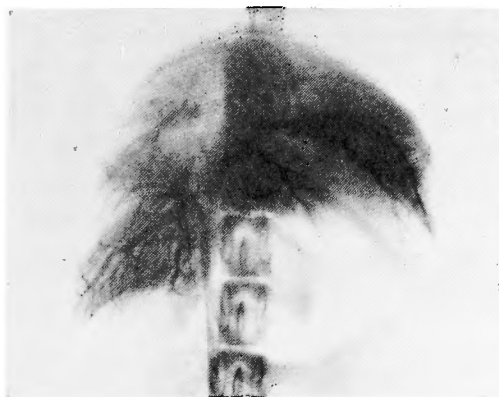


Fig. 5c

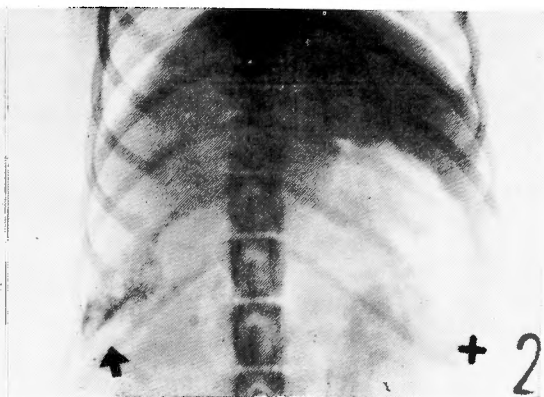


Fig. 5d

Fig. 5c 1 hour after the ligation of hepatic arteries. 10cc of urografin used. Notice spasms of portal veins.

Fig. 5d Taken 5 minutes after Fig. 5c. Trace of urografin in the right inferior lobe.

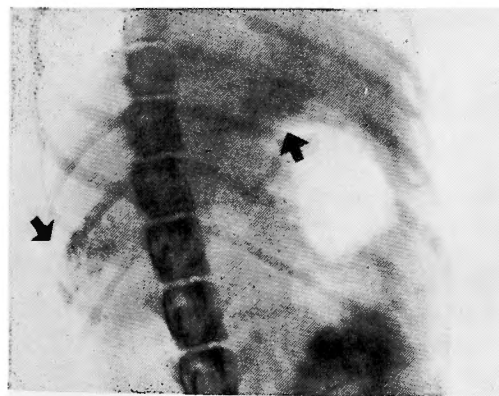


Fig. 5e

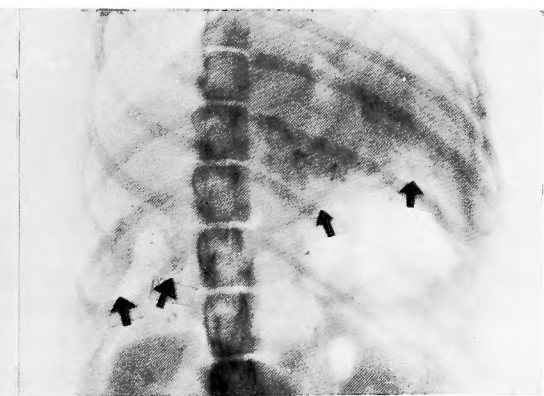


Fig. 5f

Fig. 5e Taken 2 hours after the ligation of hepatic arteries. 10cc of urografin was injected into portal vein. Trace of urografin shown in the right inferior and left liver field.

Fig. 5f Taken 3 hours after the ligation of hepatic arteries. 5 minutes after the injection of 10cc of urografin into portal vein. Residue of urografin seen in larger area.

V INTRAHEPATIC PORTAL CIRCULATION IN THE PORTAL DOGS

1) Materials and Methods

The ligation of the hepatic arteries was performed to produce portal dogs, to which were administered penicillin to prevent postoperative deaths. Four dogs were used in the following experiment 12, 16, 22 days, and one year, respectively after the ligation. Urografin was injected, in the same way as described in Chapter III, to detect probable disturbance of the intrahepatic portal circulation.

2) Results

With the exception of No. 16 dog, no signs of urografin were observed in the liver (Table 2, Fig. 6). No. 16 dog was sacrificed 16 days after the injection and

Table 2

Dog No.	Survival period (all sacrificed)	Stagnation of intrahepatic portal flow.
No. 17	12 days	(-)
No. 16	16 days	(+)
No. 18	22 days	(-)
No. 33	about one year	(-)

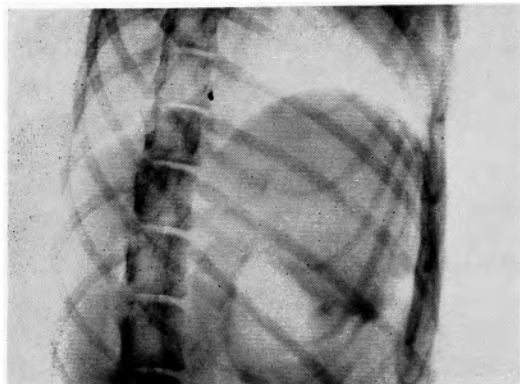


Fig. 6

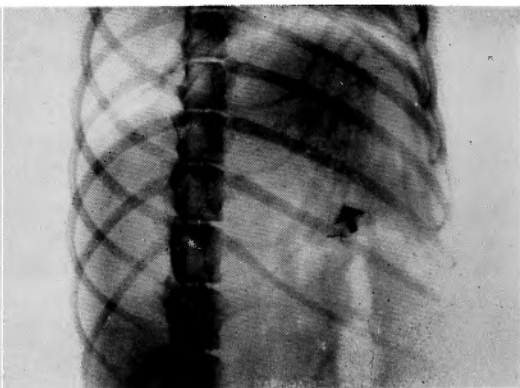


Fig. 7

Fig. 6 Portal dog sacrificed 20 days after the ligation of hepatic arteries. 5 minutes after the injection of urografin. No trace of urografin shown in the liver.

Fig. 7 No. 16 portal dog sacrificed 16 days after the ligation of hepatic arteries. Residue of urografin seen in left liver field 5 minutes after the injection.

the remains of urografin was still observable in the left liver field (Fig. 7).

The postoperative course of these four dogs was favourable and uneventful, and they recovered normal behavior within a few days. except for dog No. 16, which did not quite recover his appetite even two weeks after the injection.

VI INTRAHEPATIC PORTAL FLOW AFTER THE LIGATION OF THE HEPATIC ARTERIES IN THE ASCITIC DOGS

1) Materials and Methods

MACKEE's method was employed for the production of ascitic dogs. Under intratracheal general anesthesia, the thorax was opened at the 6th intercostal space to reach the inferior vena cava, which was freed from surrounding tissues just above the diaphragm, and then constricted with cellophane tape. A considerable amount of ascites was produced a week after the operation.

Two weeks after the operation, three dogs had the following procedure:

In order to avoid shock, the ascites was removed in small fractions, and the rest of it was slowly drained off at the time of laparotomy. Then urografin was injected before and after the ligation to check the state of intrahepatic portal circulatory impairment.

2) Results

Differing from normal, the portal system of the ascitic dogs was only vaguely

visualized on the X-ray pictures, though the ligation of the hepatic arteries and the injection of urografen were performed in the same manner as in normal dogs. It was confirmed by the image amplifier that the contrast medium injected just before the ligation of the hepatic arteries did not remain in the liver 5 minutes after the injection. Urografen was again injected one hour after the ligation. The result was the same -- no trace of urografen was observed in the picture 5 minutes after the injection. This showed a pretty contrast to the same experiment in normal dogs (Fig. 8).

Besides, the spasm of the portal veins, which usually appears after the ligation in a normal dog, was not seen in the ascitic dog.

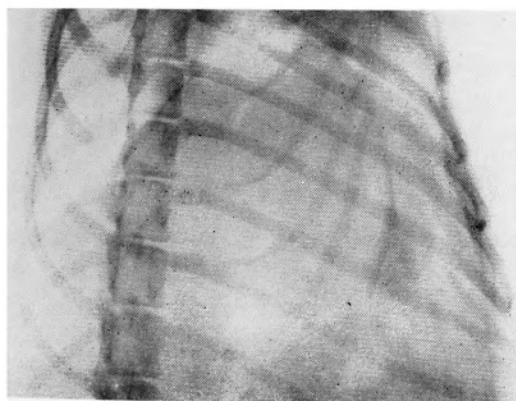


Fig. 8

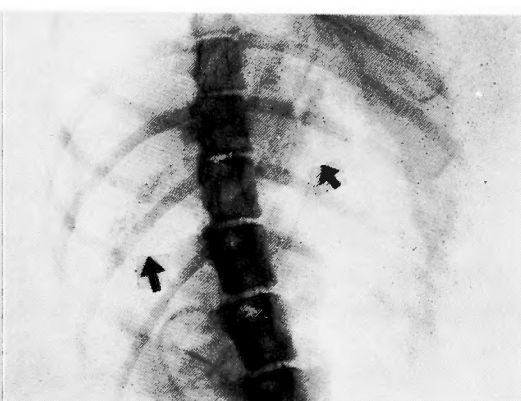


Fig. 9

Fig. 8 Ascitic dog. 1 hour after the ligation of hepatic arteries. 5 minutes after the injection of 15cc of urografen into portal vein. No remain is to be seen in the liver.

Fig. 9 Case given atropine. 1 hour after the ligation of hepatic arteries. Trace of urografen is shown in the liver 5 minutes after the injection.

VII EFFECTS OF ATROPINE, ADRENALIN AND VAGOSTIGMINE ON INTRAHEPATIC PORTAL FLOW, UNDER THE LIGATION OF THE HEPATIC ARTERIES

1) Materials and Methods

Atropine, adrenalin and vagostigmine were given to the dogs before and after the ligation of the hepatic arteries and then the intrahepatic portal flow was observed by the injection of urografen.

2) Results

a) Cases given atropine:

A normal dog received 0.5mg of atropine and the other 1mg. About thirty minutes later, the ligation of the hepatic arteries was done on both dogs. Then urografen was injected one hour in the former, and two hours in the latter respectively after the ligation. 0.5mg of atropine was readministered thirty minutes before each injection of urografen. As shown in Fig. 9, circulatory stagnation took place in the intrahepatic portal system just as in normal dogs (Fig. 9).

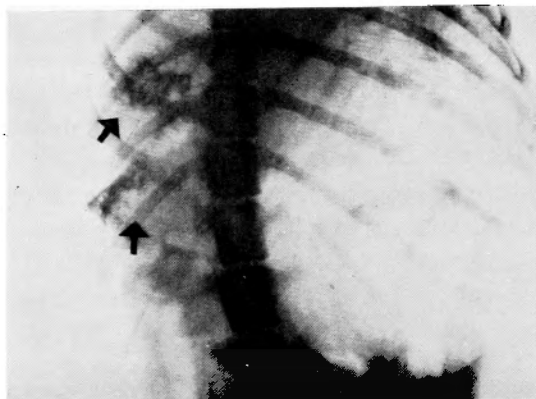


Fig. 10

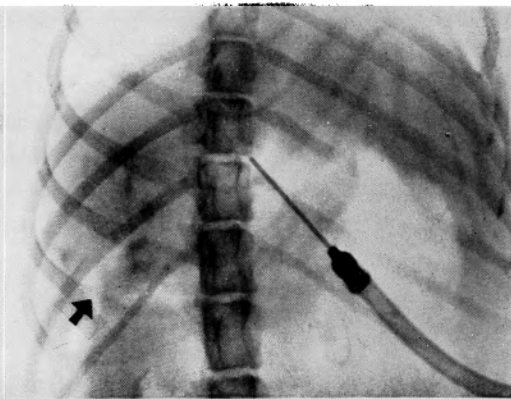


Fig. 11

Fig. 10 Case given vagostigmine. 1 hour after the ligation of hepatic arteries. Residue of urografin shown in the liver 5 minutes after the injection.

Fig. 11 Case given adrenalin. 3 hours after the ligation of hepatic arteries. 5 minutes after the injection of urografin. Trace of which is shown in the liver.

b) A case given vagostigmine :

1mg of vagostigmine was given an hour before the ligation, and the same dose an hour after the ligation. Urografin was twice injected, thirty minutes after each administration of vagostigmine. X-ray pictures revealed no signs of urografin in the liver before the ligation, while the residue of urografin was shown in the second injection (Fig. 10).

c) A case given adrenalin :

The ligation and the injection of urografin were routinely performed and the X-ray picture showed the stagnation of the intrahepatic portal flow. Then 1mg of adrenalin was given and thirty minutes later, three hours after the ligation, urografin was again injected. Urografin was found remaining in the liver showing that the administration of adrenalin did not improve the portal circulatory impairment (Fig. 11).

Besides, the administration of acetylcholine did not also show any demonstrable effects upon the impairment of the intrahepatic portal flow after the ligation of the hepatic arteries.

VIII DISCUSSION

1) Intrahepatic portal circulation after the ligation of the hepatic arteries in normal dogs

Upon the ligation of the hepatic arteries, there is a danger of postoperative liver necrosis. URABE, in our clinic, has reported that in normal dogs, the ligation of the gastroduodenal, the right gastric as well as the common hepatic arteries almost constantly led to liver necrosis followed by death within three days, though the liver was still supplied by small branches coming in from the diaphragmatic, left gastric and other arteries.

In 1949, MARKOWITZ and others successfully performed the occlusion of the

hepatic artery in normal dogs with a survival rate up to 70 per cent with the administration of penicillin. Many experiments by other workers have confirmed this fact. In these cases, the surviving dogs present no histological changes in the liver.

MARKOWITZ, POPPER, and others asserted that the principal physiological significance of the hepatic artery consists in oxygen supply, and the life of a dog after the ligation of the artery depends on the oxygen supply through collateral arteries entering the liver, e. g. the diaphragmatic artery. They also maintain that the development of liver necrosis is accelerated by the growth of anaerobic bacteria in the liver under a decreased amount of oxygen in the blood.

Child and others reported that monkeys do survive the ligation without the administration of antibiotics, and no liver necrosis is detectable by necropsy. This is, as they asserted, due to the absence of anaerobic bacteria in the monkey's liver.

As will be understood from these experiments, the shortage of oxygen supply to the liver and the consequent growth of anaerobic bacteria are the important factors in the development of liver necrosis. Therefore, the suppression of bacterial growth with antibiotics must be an effective means of preventing liver necrosis. According to URABE, in our clinic, however, the amount of penicillin necessary for the purpose is so small as 100,000 units, the effect of which lasts no longer than eight hours. This suggests that the prognosis of the dog after the ligation is decided within a short postoperative period, perhaps ten hours or so.

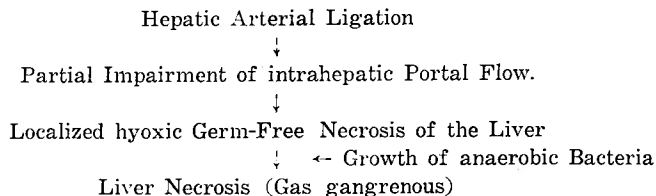
Immediately after the ligation, the color of the liver turns into dark brown, and later some parts of the liver becomes cyanotic. The cyanotic change frequently occurs in those portions of the liver where necrosis is likely to develop, e. g., in the caudate and quadrate lobes. This implies the presence of circulatory impairment in those areas.

The ligation of the hepatic artery is necessarily followed by a decrease of oxygen supply to the liver. Although this is indeed an important factor in the development of liver necrosis, it is regarded that unequal distribution of the decreased oxygen supply is more important. The present experiment has definitely proved that the ligation unevenly disturbs the portal circulation, and in some portions of the liver the stagnation reaches high enough to provoke an hypoxic, germfree necrosis. On the necrotizing liver tissue, as proved by YAMABE, in our clinic, anaerobic bacteria proliferate and accelerate necrosis.

The next problem is whether such portal circulatory impairment is immediately fatal to a dog. One dog survived the ligation for 16 days and then was sacrificed, revealing the existence of a prolonged portal circulatory impairment. As a general, the dogs which survived the ligation of the hepatic arteries, e. g. portal dogs do not show any signs of liver necrosis. In these dogs, however, the liver function is temporarily lowered to a large extent.

In this respect, KURAMOTO, in our clinic, investigated the serum protein and reported that the liver function which declined once after the occlusion of the hepatic arteries, was restored to normal after about two weeks. IZUE also reported

Fig. 12



that restoration of the liver function takes nine days after the ligation. Hence, it may be inferred that the complete restoration of the intrahepatic portal circulatory impairment is brought about two weeks after the ligation, and that the restoration of the circulatory state runs parallel with that of liver function. Of course, the recovery process must vary more or less from one case to another. In dog No. 16, mentioned above, recovery was somewhat prolonged, still the hepatic circulatory impairment would be completely repaired in the due course of time.

The process of events from the ligation of the hepatic arteries to the development of liver necrosis may be summarized as in Fig. 12. An intermediate stage must be added to the generally accepted idea on the development of liver necrosis.

That is the impairment of the portal circulation. The ligation necessarily entails the portal circulatory impairment to some extent and should the impairment be lessened by some means early enough to prevent the growth of anaerobic bacteria, the animal could survive without developing liver necrosis.

2) Intrahepatic portal circulation after the ligation of the hepatic arteries in ascitic dogs

There is a theory that portal hypertension in liver cirrhosis is directly influenced by a hepatic arterial pressure. If this be true, the ligation of the hepatic artery will be a justifiable means of lowering the high portal pressure in cirrhotic patients. There are also reports that the ligation is effective in decreasing the ascites in liver cirrhosis. The ligation has been successfully performed in cirrhotic patients and animals without entailing liver necrosis, and the results were more favorable when cirrhosis was accompanied with ascites. There still remains the question why the ligation of the hepatic artery causes liver necrosis in normal dogs, but not in ascitic dogs. It was shown from my study that the ligation of the hepatic artery in normal dogs necessarily gives rise to the stagnation of the portal flow, but not in ascitic dogs. Therefore, it may be assumed that in ascitic dogs intrahepatic portal circulation is maintained undisturbed after the ligation, and thus liver necrosis is prevented.

This was also confirmed by measuring the velocity of portal flow in ascitic dogs by Hosono, in our clinic. Thus, the question why the intrahepatic stagnation of portal flow does not occur after the arterial ligation in ascitic dogs has not yet been solved. It may be assumed that a cirrhotic liver responds abnormally to certain form of stimulation, namely, the ligation of the hepatic artery.

3) Effects of atropine, adrenalin and vagostigmine on stagnation of the intrahepatic portal flow after the ligation

The portal venous pressure and the volume of its flow changes very sensitively with the body position or the balance of the autonomic nervous system. In this respect, CHILD and others showed that adrenalin affects the portal flow, portal pressure, and the hepatic venous flow in men and monkeys. MARGRAITH and others found a similar effect of adrenalin and acetylcholine on a perfused liver. NAKASE, in our clinic, succeeded in making dogs survive the ligation without penicillin by postoperative administration of atropine, acetylcholine, and dibenamine. Liver necrosis might have been avoided, because the stagnation of the intrahepatic portal flow was lessened by these drugs. The results of the present experiments, however, could not confirm these findings.

IX CONCLUSION

Changes in the intrahepatic portal flow after the ligation of the hepatic arteries were studied by X-ray photographs with urografen injected into the portal vein. Experiments were performed in portal dogs (dogs which has survived the ligation), ascitic ones (dogs with the constricted inferior vena cava), as well as normal dogs.

Results were obtained as follows:

1) In normal dogs, the ligation of the hepatic arteries disturbs the intrahepatic portal flow in some parts of the liver and makes it stagnant. This stagnation is indicated by traces of the urografen which appear in the X-ray pictures.

2) The mechanism of the development of liver necrosis after the ligation of the hepatic arteries may be explained as follows: After the ligation of the hepatic artery the portal circulation is disturbed so much in several parts of the liver that hypoxic liver necrosis takes place. If anaerobic bacteria are harbored in the liver, they accelerate the necrosis. To prevent the development of liver necrosis after the ligation of the hepatic artery, it is urged to take some means as soon as possible to mitigate the disturbance of the intrahepatic portal flow.

3) In the ascitic dogs the ligation does not cause an intrahepatic circulatory impairment. That is why the ascitic dogs survive the ligation without entailing liver necrosis.

4) Positive data were not obtained as to the effects of adrenalin, atropine, and vagostigmine on the portal circulatory impairment induced by the ligation of the hepatic arteries.

In concluding my report, I wish to express my deepest gratitude to Dr. CHISATO ARAKI, professor of Kyoto University, Dr. ICHIO HONJO, professor of Kanazawa University and IKUZO YOKOYAMA, assist. professor of Kyoto University for their kind, continuous guidance, encouragement and supervision.

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肝動脈遮断と肝内門脈血流

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犬を用いて肝動脈遮断後の肝内門脈循環を血管造影剤の使用によるレントゲン撮影法により追求した。

実験方法: 肝動脈遮断前と遮断後30分~3時間を経て, 76%ウログラフィンを門脈より約5秒間で注入し, その後5分を経て肝臓部のレントゲン撮影を行い, 造影剤がなお肝内に残っているか否かを検した。ウログラフィンは普通30秒以内に肝臓を通過し終る。この事はイメジ・アンプリファイアーの透視下で確かめた。

肝動脈遮断に際しては, 総肝動脈, 胃十二指腸動脈右胃動脈を結紮離断し, 肝門部より流入する動脈血を完全に遮断するようにした。そして肝動脈遮断後ペニシリンを投与して生存せしめた犬を門脈犬と呼称した。

腹水犬はMCKEE氏法に従い, 開胸して下大静脈を狭窄することにより作製した。

実験には, 正常犬, 門脈水, 腹水犬を使用した。又別にアトロピン, ワゴスチグミン, アドレナリンを夫々肝動脈遮断後1~2時間を経て投与し, 上記方法により撮影実験を行い, これら薬品の術後肝内門脈に及ぼす影響を検討した。

実験成績: 肝動脈遮断前の実験から, 全例とも注入したウログラフィンは5分以内に肝臓を通過し終ることを知つたが, 肝動脈遮断後では, 正常犬に於て11例

中6例, 門脈犬では4例中1例に於て門脈循環障害を来たしたと思われる造影剤の残留像が証明された。しかし腹水犬3例に於ける実験では肝動脈を遮断しても造影剤の残留像はみなかった。又肝動脈遮断後アトロピン, ワゴスチグミン, アドレナリンを投与した例にも同じくウログラフィンの残留像を証明した。

以上の事より次の結論を得た。

1) 正常犬の肝動脈遮断を行うと, 肝内門脈循環障害が一部におこり, 門脈血の停滞が生ずる。

2) 肝動脈遮断後に起る肝壊死は次のようにして発生すると思われる。即ち肝動脈遮断を行うと肝臓の一部に循環障害を生じ, この部に乏酸素性壊死を来す。この場合嫌気性菌が存在すると壊死はなお高度となり遂に肝壊死を発生する。よつて肝動脈遮断後の肝壊死を防ぐには, 何らかの方法で肝内門脈血流の障害を出来るだけ速かに回復せしめる必要がある。

3) 腹水犬の肝動脈遮断に際しては, 正常犬の場合と異り, 術後に門脈循環障害を起こさない。腹水犬が正常犬に比し肝動脈遮断に耐え易いことはこの事実からも証明される。

4) 自律神経作用薬剤を投与しても, 肝動脈遮断後に発生する門脈循環障害に効果を及ぼすようには考えられない。