AN EXPERIMENTAL STUDY ON THE INTERRUPTION OF THE HEPATIC ARTERY UNDER HYPOTHERMIA

by

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CONTENT

I. INTROLUCTION

An application of local hypothermia was first achieved in surgery in 1812 by BELL who intended to get rid of pain. In 1942, SMITH and FAY employed hypothermia in patient of breast cancer in late stadium in the aim of preventing tumor growth. Earlier than this, there have been made experiments to weaken responses of organism by lowering body temperature. SIMPSON and HERRING studied, in 1905, physiological changes caused by descension of body temperature in cats. In 1941, DILL and FORBES employed hypothermia as a treatment in psychatrics. On the other hand in our country, YANAGI made experiments on the influence of low temperature on organisms. Application of hypothermia to surgery as excuted nowadays, however, largely owe to BIGELOW[1,2,3] (1950), SWAN (1953), LEWIS (1953) and others. They succeeded in open heart surgery by the aid of hypothermia wich was employed in order to interrupt the circulation, and published numerous reports concerning the changes in organism under hypothermia, expressing that the aim of hypothermia consists essentially in protecting organs against interruption of circulation which is achieved by reducing oxygen consumption and consequently lowering various metabolism.

Concerning the method of reducing oxygen consumption, it is possible to reduce it below basal metabolism by pharmacological hibernation as was asserted by LABORIT.[4] In general, however, physical cooling is employed in hypothermia, since the reduction of oxygen consumption caused by pharmacological hibernation is often inadequate.

Practically it is required to initiate cooling down after responses of organism are completely blocked by deep anesthesia, because shivering, as a defence response of organism, is observed at initial stage in descension of body temperature, which causes rather temporary increase of metabolism. In this respect, the author of the present experiment employed method of cooling down of ice-water immersion under deep anesthesia with ether.

Concerning the temperature of hypothermia, BIGEGOW[1] observed an increase of mortality when animals were cooled below certain limit, and he explained that this is attributable to irreversible changes such as circulatory distrubance, above all occurrence of ventricular fibrillation. This point is generally called critical temperature, which has been highly discussed and today it is assumed to be 15 to 20°C in general.

The author of the present paper also carried out the experiments under hypothermia of 25 to 28°C. When the temperature was kept above this, it was difficult to execute experiment favorably being accompanied by defence response such as shivering even under deep anesthesia. When the temperature was kept below 25°C, it was likewise difficult to carry on the experiment owing to the occurrence of eventual cardiac arrest.

It has been widely known from early days that by the interruption of the hepatic artery animals are all led to death, cause of which is attributed to liver necrosis. In 1949, MARKOWITZ[5] reported that animals can survive the interruption of the hepatic artery, by the administration of antibiotics, and he explained that this is because proliferation of anaerobic bacteria, which cmmonly exist in the liver of dogs, is depressed by antibiotics. The effect of antibiotics in this direction was ascertained thereafter by TANTURI.[6] Thence, the interruption of the hepatic artery was recommended by RIENHOFF, BERMAN for a treatment of ascites in liver cirrhosis, which was followed by many investigations on the problem. Particularly, HONJO[7,8] made widely extended studies on this point, and he clarified above all that liver necrosis scarcely develops after the interruption of the hepatic artery in ascitic dogs produced by a constriction of the hepatic vein.

The author of the present paper made a series of experiments on the influence of the interruption of the common hepatic, gastroduodenal and right gastric arteries under hypothermia and obtained some informations, that is, under normothermic condition almost all the animals died, while under hypothermia prolongation of survival time was observed and in some cases, it was observed that animals, although few, could be set free from death.

Ⅱ. MATERIALS AND METHODS

1. Experimental animals

Adult mongrel dogs, weighing 8 to 16 kg, were used, which were subjected to operation after starving of preoperative 12 hours. After the operation, RINGER's solution and glucose solution of 5 per cent were administered subcutaneously or intravenously, until the animals have recovered from the operation enough to take feed. Careful attentions were paid postoperatively on prevention of dampness and preserve of heat using the blanket particularly for at least 24 hours. The dogs were moved to the kennel after they walked and showed adequate appetite.

2. Anesthesia and method of cooling

As premedication, atropin sulfate of 0.3 to 0.4 mg was administered. Anesthesia was introduced by the intravenous injection of thiamylal sodium of 10 mg per kg body weight and after intubation of a intratracheal tube, anesthesia was maintained by closed circulating method with ether. Cooling was interrupted when the temperature reached 28°C and the animal was placed on operating table as mentioned in the below. After

drop of rectal temperature was observed to be 0.5 to 3°C.

3. Operative procedures

Dog was laid on the operating table on its back. Abdomen was shaved and disinfected. The abdomen was opened with upper median incision and transverse incision was added. The gastroduodenal ligament was exposed and the common hepatic, gastroduodenal and right gastric arteries were ligated and cut after the method of ISHIGURO.[9] By these procedures, almost complete interruption of arterial blood supply into the liver is achieved. Cholecystectomy was added and after-bleeding was prevented by attaching local hemostatics to the liver wound. Neither antibiotics nor disinfectant was administered pre-and postoperatively.

4. Method of rewarming

Hypothermia was continued for certain duration (30, 60, 90, 120, 150, 180, 240 minutes respectively) after the interruption of the hepatic artery. For the maintenance of constant body temperature, careful attention was paid, by cooling with sacks of icewater or warming by photographic lamps, at the same time, depth of anesthesia being adjusted, when fluctuation of the temperature was observed.

After above mentioned certain duration of hypothermia, the animals were wrapped with vinyl sheet and dipped in hot water of 45°C, for rewarming.

As the rectal temperature arose to 35°C, anesthesia was interrupted and the animals were kept warm in blanket after extubation. At cooling, body temperature fell down 1°C every 10 minutes, and at rewarming it arose 1°C every 15 minutes. No abnormality of impulse originating site of the heart and no disturbance in impulse conducting system were observed. Complications such as circulatory disturbance could be minimized, stroke volume being kept in normal level.

5. Examinations

a. Body temperature

Temperature was measured with the lapse of time with a thermister (Hitachi-Seiki) which was inserted 5 cm from the anal ring.

b. Blood pressure

Blood pressure was measured with mercurial manometer connected to a vinyl tube which was inserted and fixed in the exposed femoral artery, the tube being filled with heparinized saline.

c. Portal pressure

Portal pressure was determined with aqueous manometer connected to a polyethylene tube of internal diameter of 4 mm which was inserted to the portal trunk from the superior mesenteric vein.

d. Liver temperature

Since there exist in the liver after the interuption of the hepatic artery favorite site and non-favorite site of necrosis, liver temperature in the favorite site of necrosis was measured continuously in peripheral portion of the quadrate lobe and marginal portion of the left inferior lobe, and the temperature in the nonfavorite site of necrosis was measured also continuously in middle portion of the left superior and left inferior lobes, by inserting a thermister.

e. Volume of liver blood flow

There have been various method for estimation of volume of liver blood flow. The author of the present experiment estimated the volume of liver blood flow with the lapse of time in order to explore the appearance of intrahepatic circulation after the interruption of the hepatic artery after the method of VETTER,[10] which is essentially based on the fact that radioactive gold is remarkably eliminated from the blood stream in the liver. The method of the determination is summarized as follows.

i. Suspension of radioactive gold of 25 to 50 uC/cc was injected into the femoral vein and 1.5 cc blood was drawn within 1 minute repeatedly for 10 minutes with an interval of 1 minute, with the syringe placed previously in the femoral vein of another side. The blood of accurately 1cc was then put in test tubes using OSTWALD pipette, and radioactivity was measured with scintillation counter (Kobekogyo Co.) for 1 minute. Counts of radioactivity was plotted on a section paper having logalithmic scale in the vertical axis, radioactivity being taken in vertical axis and time in horizontal axis. Lineal decrease was observed in concentration of radioactive gold in the blood. Hence following relationship can be settled, where half time T 1/2 is read from above mentioned curve;

$$1/2\,Co = Coe^{-kT1/2}$$

This is solved as

$$K = \frac{\log_e 2}{T\,1/2} = \frac{0.693}{T\,1/2}$$

K, in this formule, represents coefficient of ^{198}Au disappearance from the blood stream, in other words this represents the percentage of blood volume passing through the liver, that is, volume of liver blood flow to circulating blood volume of the whole body.

ii. Circulating blood volume. Evans blue solution was injected intravenously immediately after the injection of ^{198}Au. 10 minutes later, blood was drawn and circulating plasma volume was estimated following the method of GREGERSON, at the same time Ht ratio being determined. Circulating blood volume was calculated from following formnla;

$$C.\ B.\ V. = \frac{C\ P.\ V. \times 100}{100 - Ht}$$

iii. Volume of liver blood flow was given as multification of two factors of circulating blood volume and K, i. e. coefficient of ^{198}Au disappearance from the blood stream in the liver. In the present paper, K is called hereafter liver blood flow index.

f. Histological examination.

Double staining of hemaraun and eosin was performed.

III. RESULTS

1. Survival rate

According to the result of the author of the present experiment, almost all the dogs died 8 to 48 hours after the interruption of the hepatic artery under normothermic condition. Findings at autopsy disclosed a development of outstanding liver necrosis, which corresponds to the report of other researchers.

On the other hand, marked prolongation of survival time and some cases, although

few, relieved from death were observed in hypothermic group, in which the interruption of the hepatic artery was performed under hypothermia of 25 to 28°C in rectal temperature and hypothermia was continued for certain duration after the interruption and then rewarming was initiated. Autopsy of the dead animals revealed only the finding of stagnation in the liver, and the cause of death could be found in the other than the liver, such as postoperative pneumonia, lung edema or peritonitis.

No anbormality was observed in the life of dogs survived the interruption. Thus it was clarified that in the animals underwent the interuption of the hepatic artery, the liver shows after the interruption entirely different appearance compared with those underwent the interruption under normothermic condition.

Namely, in the hypothermic group, only 2 animals out of 10, which were rewarmed within 1 hour and a half after the interruption, could survive for more than 48 hours and these two, however, also died shortly later, whereas in the animals which were rewarmed after hypothermia of more than 2 hours, 14 animals out of 19, that is, 74 per cent of animals survived for more than 48 hours and 6 animals, that is 31 per cent, could still survived a week after the interruption (Tab. 1, Tab. 2).

Tab. 1 Survival rate (Normothermic group)

No. of case	No. of survivals	No. of deaths
82	3	79

Tab. 2 Survival rate (Hypothermic group)

Duration of hypothermia	No. of case	No. of survivals	No. of deaths
0.5	2	0	2
1	4	1	3
1.5	4	1	3
2	6	4	2
2.5	4	3	1
3	5	4	1
4	4	3	1
Total	19	14(74%)	5 (26%)

Accordingly, it is clarified that it is necessary to continue hypothermia at least for 2 hours after the interruption of the hepatic artery, when the interruption is performed under hypothermia of 25 to 28°C. At the same time it is revealed that the time of 2 hours after the interruption of the hepatic artery has particular significance in the development of liver necrosis, judging from the finding that there was no difference in survival rate even if hypothermia was continued for more than 2 hours.

2. Blood pressure

In the normothermic group, elevation of 5 to 10 mmHg in systolic blood pressure was observed for a few minutes immediately after the interruption of the hepatic artery, which shortly returned to the level before the interruption and then gradually descended on until final death of the animal (Fig. 1).

On the other hand, in the hypothermic group, blood pressure descended in parallel with the fall of body temperature. However, in some cases, temporary rise of around 10 mmHg was observed when body temperature came near 35°C. This is interpreted that at this stage circulation is not completely stabilized and the blood pressure thereafter changed in parallel with body temperature. Furthermore, blood pressure was not influenced by the interruption in this group, and restored to the preoperative level by rewarming. From these studies it is assumed that at the interruption of the hepatic artery

Fig. 1

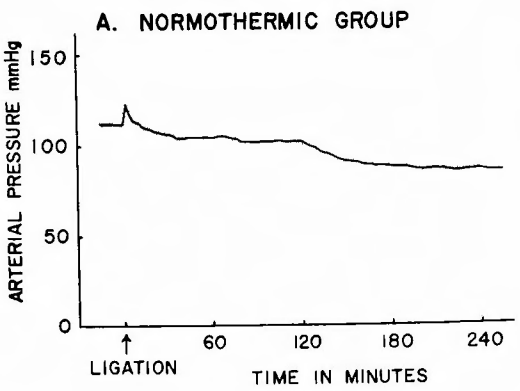
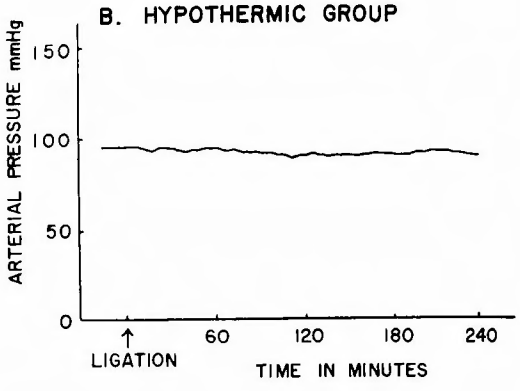


Fig. 2



under hypothermia, no significant change, particular fall, could be observed in the blood pressure (Fig. 2).

3. Portal pressure

In the normothermic group, portal pressure was observed before the interruption to be 140 mmH_2O, on the average, which showed rapid elevation of 50 to 60 mmH_2O within 10 to 20 minutes following the interruption and then tended to fall gradually. This, however, remained to be 10 to 15 mmH_2O higher than that before the interruption and further descended by and by as animals became exhausted (Fig. 3).

Fig. 3

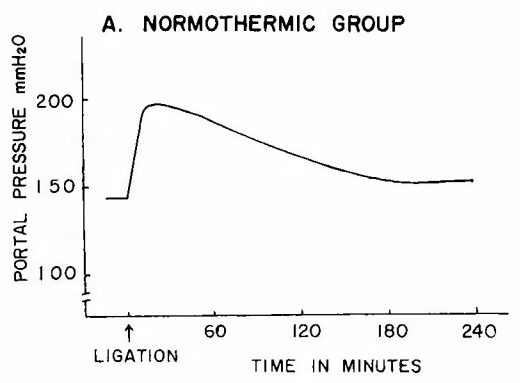
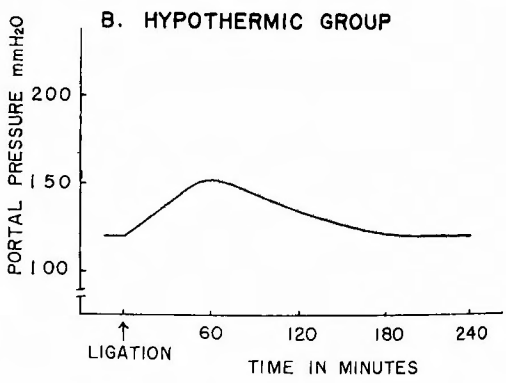


Fig. 4



In the hypothermic group, portal pressure was observed to be 120 mmH_2O on the average before the interruption, which showed similar tendency of elevation after the interruption, although extremely slow, that is, the elevation of portal pressure after the interruption was restrained within 30 to 40 mmH_2O 1 hour after it. The pressure tended to fall gradually since this stadium, restoring to the level before the interruption 3 hours after it, which remained in a stabilized state without showing any elevation above the level before the interruption (Fig. 4).

From these findings, it was disclosed that congestion of the portal flow is more slight in the interruption of the hepatic artery under hypothermia than performed under

normothermic condition.

4. Liver temperature

By an observation on the development of liver necrosis after the interruption of the hepatic artery, two different areas are distignishable, that is, an area of remarkable liver necrosis macroscopically observed and the other in which necrosis is not observed. Favorite site of liver necrosis are situated in the marginal area of the left superior, left inferior and middle lobes and the quadrate and caudate lobes. Liver temperature in these two areas was measured continuously both before and after the interruption with thermister inserted into these two area.

It was clarfied in the normothermic group, that liver temperature was 0.5°C lower on the average in the favorite site of necrosis compared with that in the other area before the interruption, and after the interruption the temperature in both areas showed a tendency of fall which, however, was more remarkable in the favorite site of necrosis. Difference in the temperature between both areas began to increase 30 minutes after the interruption, reaching 2.5°C 1 hour after it.

There was observed temporaily a certain stadium of decrease in difference in the temperature, which was 120 minute after the interruption, followed by little change in the temperature in non-favorite site and gradual fall in the temperature in favorite site, the difference further reaching as far as 3°C, 3 hours after the interruption. Little change was observed in the temperature in the both sites thereafter (Tab. 3, Fig. 5). On the other hand in the hypothermic group, the temperature in the favorite site of necrosis was 2.5°C lower on the average than in the non-favorite site before the interruption. After the interruption of the hepatic artery, little change was observed in the temperature in the non-favorite site of necrosis, whereas the temperature in the favorite

Tab. 3 Difference of liver temperature between favorite and non-favorite site of liver necrosis (Normothermic group)

	Before	15	30	45	60	75	90	105	120	135	150	165	180	195	210	225	240
23	0.4	0.5	0.9	1.9	2.3	2.0	1.2	0.9	0.6	1.0	2.2	2.2	3.1	3.0	3.0	3.0	3.5
25	0.6	0.6	0.8	1.7	2.2	1.9	0.9	0.9	0.4	0.6	2.3	2.3	3.2	3.0	2.9	3.0	3.0
30	0.4	0.6	0.7	2.0	2.6	1.7	1.0	1.0	0.5	1.0	2.7	2.6	2.5	2.7	3.0	2.9	3.0
33	0.4	0.6	0.6	2.3	2.7	2.1	1.4	1.2	0.7	0.7	2.6	2.7	3.1	3.0	2.8	2.8	3.0
34	0.7	0.7	1.0	2.1	2.7	2.3	1.5	1.0	0.3	1.3	2.7	2.7	3.1	3.3	2.3	2.3	2.5
mean	0.5	0.6	1.0	2.0	2.5	2.0	1.2	1.0	0.5	1.2	2.5	2.5	3.0	3.0	2.8	2.8	3.0

Tab. 4 Difference of liver temperature between favorite and non-favorite site of liver necrosis (Hypothermic group)

	Before	15	30	45	60	75	90	105	120	135	150	165	180	195	210	225	240
35	2.7	3.0	3.0	2.8	1.9	0.8	0.5	0.2	0	0.3	0.2	0.3	0	0	0	0.2	0
39	2.1	3.1	2.1	2.0	0.9	1.0	0.7	0.1	0	0.4	0.1	0.1	0	0	0	0	0
40	2.8	2.9	3.0	2.7	2.2	1.2	0.6	0.3	0	0	0.2	0.1	0	0	0	0.1	0
41	2.0	3.0	3.0	2.9	2.1	1.0	0.6	0.1	0	0.3	0	0	0	0	0	0.2	0
45	2.9	3.0	2.9	2.1	2.9	1.0	0.6	0.3	0	0	0	0	0	0	0	0	0
mean	2.5	3.0	2.8	2.5	2.0	1.0	0.6	0.2	0	0.2	0.1	0.1	0	0	0	0.1	0

Fig. 5

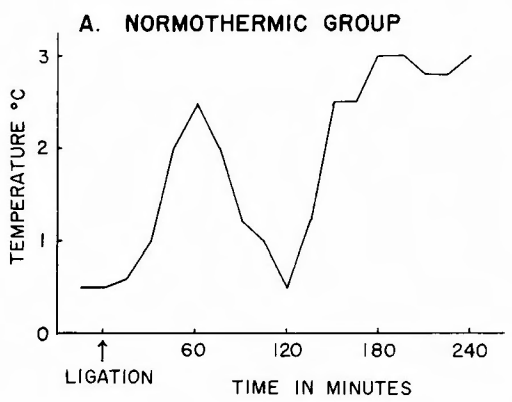
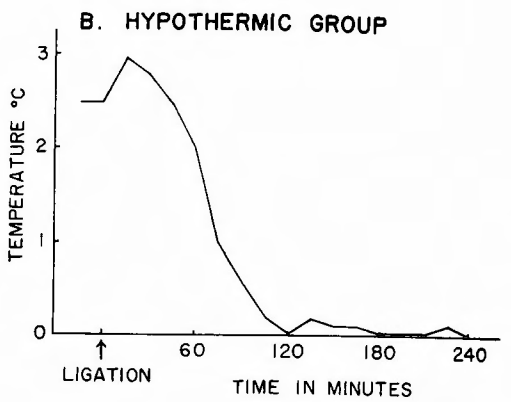


Fig. 6



site showed gradual fall, the difference in temperature in the both areas reaching 3°C on the average, already 15 to 20 minutes after the interruption. The temperature in the favorite site of necrosis showed a tendency of gradual elevation thereafter and the difference in the temperature of the both areas almost disappeared 2 hours after the interruption, showing fluctuation in parallel with body temperature (Tab. 4, Fig. 6). These findings are summarized that, in the normothermic group, the difference in the temperature between the favorite site and non-favorite site showed a tendency of increase after the interruption of the hepatic artery, while in the hypothermic group, the difference showed slight increase shortly after the interruption, being accompanied by a tendency of decrease and disappearing 120 minutes after it.

5. Volume of liver blood flow

Liver blood flow index was estimated with the lapse of time both before and after the interruption, in order to explore the change in the volume of intrahepatic blood flow after the interruption of the hepatic artery.

The index was observed before the interruption to be 0.28 on the average in the normothermic group, which inclined to decrease after the interruption reaching 0.1, 30 minutes after it, which corresponds to 36 per cent of the level before the interruption. The index increased gradually thereafter, restoring up to 0.23, 150 minutes after the interruption, which corresponds to 82 per cent compared with the level before the

Tab. 5 Liver blood flow (Normothermic group)

	Before	30	60	90	120	150	180	210	240
23	0.25	0.07	0.15	0.18	0.20	0.28	0.27	0.27	0.27
25	0.29	0.08	0.13	0.19	0.23	0.22	0.22	0.21	0.20
30	0.27	0.13	0.15	0.20	0.19	0.23	0.21	0.20	0.20
33	0.29	0.10	0.11	0.18	0.17	0.16	0.16	0.17	0.18
34	0.30	0.12	0.21	0.25	0.26	0.26	0.24	0.30	0.30
K mean	0.28	0.10	0.15	0.20	0.21	0.23	0.22	0.23	0.23
C. B. V. mean	82.5	80.3	76.5	79.2	80.4	81.6	70.3	65.2	66.0
L. B. F. mean	23.1	8.0	11.6	15.4	16.9	18.8	15.2	15.0	15.2

Tab. 6 Liver blood flow (Hypothermic group)

	Before	30	60	90	120	150	180	210	240
35	0.28	0.12	0.18	0.18	0.20	0.27	0.26	0.21	0.22
39	0.27	0.23	0.24	0.24	0.27	0.26	0.26	0.29	0.28
40	0.26	0.26	0.28	0.28	0.27	0.29	0.29	0.27	0.25
41	0.23	0.20	0.20	0.23	0.25	0.25	0.27	0.26	0.25
45	0.31	0.19	0.20	0.22	0.31	0.28	0.27	0.27	0.26
K mean	0.27	0.20	0.22	0.23	0.26	0.27	0.27	0.26	0.25
C. B. V. mean	73.5	72.9	74.0	73.2	73.0	70.0	69.5	72.5	72.7
L. B. F. mean	19.8	14.6	16.3	16.8	18.9	18.9	18.8	18.8	18.2

Fig. 7

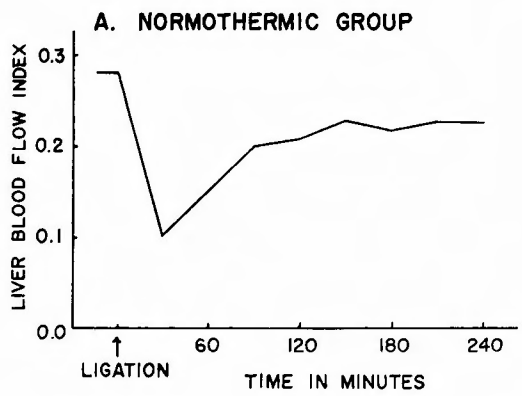
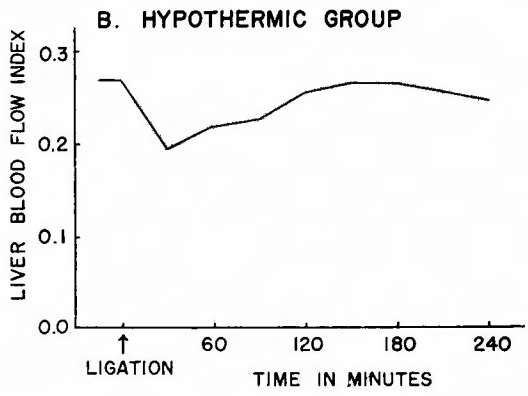


Fig. 8



interruption. No particular change of the index was observed thereafter, being maintained within the range of about 80 per cent of the index of liver blood flow (Tab. 5, Fig. 7).

On the other hand, the index was observed to be 0.27 on the average before the interruption in the hypothermic group, which is slightly lower compared with that of the normothermic group. Thirty minutes after the interruption, the index decreased to 0.2, which corresponds to 74 per cent of the level before the interruption, and it increased gradually thereafter restoring to the preoperative level 150 minutes after the interruption (Tab. 6, Fig. 8).

Namely, 30 minutes after the interruption, the index decreased to 36 per cent of the level before the interruption in the normothermic group, whereas in the hypothermic group the decrease in the index was well maintained within the extent of 74 per cent of the level before the interruption, which is interpreted that the volume of liver blood flow is maintained twice as much in the hypothermic group, compared with that of normothermic. In addition, it was observed that the decrease of the index retored to the level before the interruption 150 minutes after it, in hypothermic group.

6. Macroscopic and microscopic findings

Macroscopic observation of the liver was carried out with the lapse of time since immediately after the interruption of the hepatic artery, and liver tissue was doubly stained with hemaraun and eosin for histological examination.

In normothermic group, color of the liver surface changed uniformly into violet immediately after the interruption. The discoloration of the liver began to fade out gradually 3 hours after the interruption, however, persisting exclusively in the favorite site of liver necrosis. Histological examination of the area, in which discoloration remained, revealed congestion in the sinusoids and central vein, and tortuousity and congestion of the portal branches. About 3 hours after the interruption, dilatation of the sinusoids, tortuousity of the cell cords and partial degeneration of the parenchymal cells due to congestion were observed, which is afterwards to develop necrosis (Photo. 1, 2).

On the other hand, in the hypothermic group, color of the liver surface also turned slightly into violet after the interruption, which was, however, much more slight compared with the normothermic group, being followed by a tendency to fade as early as 2 hours after the interruption. Persistent discoloration was not observed all over in this group. Histological examination in this group showed only slight congestion observed 3 hours after the interruption in the central vein. Appearance of the liver cord was observed to be almost normal and degeneration of the parenchymal cells was not to be found (Photo. 3, 4). In short, both macro-and microscopic changes in the liver were far slight in the hypothermic group compared with that of normothermic, merely revealing temporary and reversible change of congestion.

Ⅳ. DISCUSSION

Origin of experimental studies to check the arterial blood supply into the liver by the interrubtion of the hepatic artery can be traced back to old days. In various animals, experiments have been made in this field, by SIMON de METZ in 1828 and afterwards KOLLMAN (1857), COHNHEIM (1876) and others. Reports on the changes of organism caused by the interruption of the hepatic artery are, however, diversified. BETZ[11] (1863) reported that almost all the animals died when the hepatic artery was ligated and cut at the distal point of the bifurcation of the gastroduodenal artery. HABERER[12] (1909), NAEGELI[13] (1938) and others reported that both in human beings and dogs the interruption of the proper hepatic artery always resulted in death. WOLBACH[14] (1909) and BOYCE[15] (1935) observed proliferation of anaerobic bacteria in the liver after the interruption of the hepatic artery. Lately, MARKOWITZ[5] (1949) observed that animals could survive the interruption of the hepatic artery by the administration of antibiotics, and he attributed the cause of survival to the hindrance of intrahepatic proliferation of anaerobic bacteria. Concerning the effect of antibiotics, TANTURI[6] et al. reported that only 65per cent of animals could survive even if antibiotics were administered, which coincides approximately to the report of KUBOTA.[16] There exists no correlation between dosis of antibiotics administered and survival rate, and accordingly it is impossible to improve survival rate only by the administration of large dosis of antibiotics. According to URABE,[17] penicillin, administered immediately after the interruption of the hepatic artery, is preserved in the liver no longer than 8 hours, when administered 10×10^4 u., and it is difficult to presume that small branches draining into the liver that do not undergo the interruption swiftly come within this period to compensate the adequate arterial blood supply to the liver. Nevertheless, the fact that the liver necrosis caused by the interrup-

tion of the hepatic artery is prevented by the administration of penicillin, makes us presume some other important mechanism of penicillin other than bacteriocidal effect. In this respect, NAKASE,[27] KUBOTA[16] and YOSHITOMI[24] have made significant experiments.

Application of hypothermia to the interruption of the hepatic blood supply was studied by RAFFUCCI[18] in 1953, in which the portal vein, celiac, superior mesenteric and hepatic arteries were all simultaneously interrupted in dogs for 1 hour under hypothermia of 26 to 28°C. He reported favorable result of mortality of 27 per cent, which is far excellent when compared with that of 98 per cent under normothermic condition which is still as high as 50 per cent even if ACTH is administered. BERNHARD[19] (1955) reported the results of his experiment, in which all the vessels draining into the liver were interrupted for 1 hour under hypothermia of 24 to 27°C, that all the animals died in normothermic condition whereas mortality was as little as 7 per cent in hypothermic group, with favorable general condition during the operation and normal findings of liver function, revealing no particular change, except stagnation, in histological studies. HARADA[20] (1956) also reported that permissible time of the interruption of the liver blood flow was much prolonged under hypothermia compared with that under normothermic condition. GOODALL[21] (1957) succeeded in 50 per cent hepatectomy by the interruption of the liver blood flow performed under hypothermia of 28°C for 60 minutes, which was further accompanied by the ligation of the celiac axis and administration of hibernating drugs. SHIMIZU [20] (1959) recognized prolongation of permissible time of the interruption of the portal vein by the aid of hypothermia. TAKAMATSU[23] (1962) also reported that the interruption of the portal vein can be safely performed at least for one hour under hypothermia.

Above mentioned all these studies are concerned with the temporary interruption of all the hepatic vessels or that of the portal vein alone. In the present experiment, things are somewhat different as the hypothermia was applied to the permanent interruption of the only arterial blood supply to the liver, which was performed by ligating and cutting of the common hepatic, gastroduodenal and right gastric arteries.

Seventy-four per cent of the animals survived even 48 hours and still 68 per cent even 72 hours after the interruption performed under hypothermia of 25°C to 28°C which was further maintained for more than 2 hours after the interruption. It is possible to presume that initial two hours of the interruption has an important significance in the development of liver necrosis and hence some correlation is inferred between liver necrosis preventing effect of penicillin and the hypothermic effect of 2 hours, because if these findings are compared with the result that only 20 per cent of the animals could survive for 48 hours when rewarming was initiated within 2 hours after the interruption.

After the interruption, no particular fluctuation of blood pressure was observed in both normothermic and hypothermic groups as well as no particular difference in it between these two. On the contrary, outstanding difference could be observed in portal pressure between these two groups. Namely, portal hypertension caused by the interruption was maintained even 3 hours after the interruption in normothermic group, which in hypothermic group portal pressure showed merely slight elevation after the interruption and restored to the level before it in 3 hours. Similar tendency was also observed in a group in which hypothermia was maintained for more than 4 hours after the interruption.

Accordingly it was clarified that portal hypertension i. e. circulatory disturbance in the portal vein following the interruption of the hepatic arterial flow becomes to be slight under hypothermia, which is presumably because the contraction in the small branches of the hepatic vein observed obviously following the interruption of the hepatic artery under normothermic condition as was demonstrated by Yoshitomi[24] happens to occur very slightly.

The liver receives oxygen supply from both the portal vein and the hepatic artery. As to the proportion of blood flow from these two, BURTON-OPITZ postulated that 22 to 44 per cent is supplied by the hepatic artery in dogs, McLead and Pearce reported to be 26 to 32 per cent, according to BLALOCK it is 19.5 per cent and the latest report of Grindlay tells that blood flow of the hepatic artery is 30 per cent of the portal flow. At present it is generally accepted that the hepatic artery involves 20 to 40 per cent of the total flow to the liver. However, there is some difference in oxygen content between arterial blood and portal blood. Concerning the proportion of oxygen supply from the blood of these vessels, MARKOWITZ[5], RAPPAPORT, KIMOTO and others insisted that oxygen is mainly supplied to the liver by the hepatic artery, whereas according to McMICHAEL, MINABE and others the oxygen supply is chiefly performed by the portal blood. Although there are many contradictions on the problem, it is widely accepted that the liver receives oxygen mainly from the hepatic artery as was shown in the result of experiments of TANTURI[9] and POPPER.[25] Accordingly, it is a matter of fact that the application of hypothermia has an advantage at least in the respect of reducing oxygen consumption in the liver. Hypoxia caused by redution of the organ blood flow plays an important role as a factor of shock formation. Many a studies have been carried out concerning the mechanism of shock. SHORR[26] asserted that the cause of irreversible shock consists in VDM and he demonstrated VDM effect of ferritin. According to his study, ferritin is a kind of chromoprotein which has an effect of paralysing capillary response. NAKASE[27] observed an increase in ADS in serum towards 3 hours after the interruption of the hepatic artery when the diffuse congestion, which develops all over the liver, comes to localize, and he further observed a decrease in ferritin in the favorite site of liver necrosis. He could not find such changes in the areas macroscopically observed to be normal. On the other side, decrease in liver ferritin was not to be observed even in the favorite site of necrosis within 6 hours after the interruption in dogs treated with penicillin, not to say about increase in serum ADS. KUBOTA[13] observed in his experiments on tissure respiration of favorite site of liver necrosis performed with the lapse of time after the interruption of the hepatic artery that there occurs earlier conspicuous impairment in oxydative process of the liver compared with glycolysis, showing marked decrease in Q_{O_2} and little fluctuation in $Q_L^{N_2}$ in early stadium of the interruption. He further clarified that decrease in Q_{O_2} following the interruption is much slighter in dogs treated with penicillin than those without administration of it, and he concluded that penicillin has an effect to hinder the development of disturbance in metabolic balance of the liver which occurs abruptly following the interruption of the hepatic artery.

Namely, it is assumed that immediately after the interruption of the hepatic artery there develops a stagnation of intrahepatic portal flow which gradually decreases thereafter,

but marked hypoxia exists in certain area where the circulatory disturbance persists topically. Subsequently, ferritin is mobilized and since the ferritin acts as a vasodepressor, the liver undergoes the stagnation to an irreversible one, which develops hypoxic liver necrosis and cause to explosive proliferation of anaerobic bacteria. Accordingly it is presumed that hypothermia lessens the degree of stagnation in the initial stadium, and in addition hypothermia shortly eliminates it, owing to which above mentioned vicious cycle is prevented and development of liver necrosis is prevented which is necessarily caused by the interruption of the hepatic artery.

Although very few reports are seen concerning liver temperature, result of the present experiments showed that in normothermic group difference of the temperature between favorite and non-favorite sites of the liver necrosis and although there was some fluctuation, the difference was maintained on showing to increase with the lapse of time after the interruption. On the contrary in hypothermic group it was found that the temperature in the favorite site of liver necrosis fell temporarily after the interruption of the hepatic artery which then promptly restored. Then, the difference of the temperature between favorite and non-favorite sites of liver necrosis showed a marked tendency of decrease, almost disappearing 2 hours after the interruption. As these findings are considered together with the change in intrahepatic blood flow, increase in the difference of liver temperature, i. e. fall of liver temperature in the favorite site was observed roughly corresponding to a stadium of decrease of the index of liver blood flow, i. e. decrease of liver blood flow, and, elevation of the temperature in the favorite site of liver necrosis, i. e. disappearance of the difference of the liver temperature was observed 150 minutes after the interruption when the intrahepatic blood flow restored, which once decreased by the interruption, revealing an intimate correlation between increase in liver blood flow and decrease in the difference of the liver temperature. BIRNIE[8] also recognized in his experiments upon rats that both intrahepatic blood flow and liver temperature are decreased by inhalation of ether, and these two show a tendency of restoration following cessation of ether inhalation, the rise of liver temperature being preceded by the increase of intrahepatic blood flow. Similar findings were observed after the interruption of the hepatic artery also in the present experiment. This is interpreted to suggest an important role of intrahepatic blood flow in the metabolism of heat production is depressed owing to the decrease in blood flow. On the other hand, the fact that little fall of liver temperature in the favorite site is observed even after the interruption under hypothermia

Fig. 9

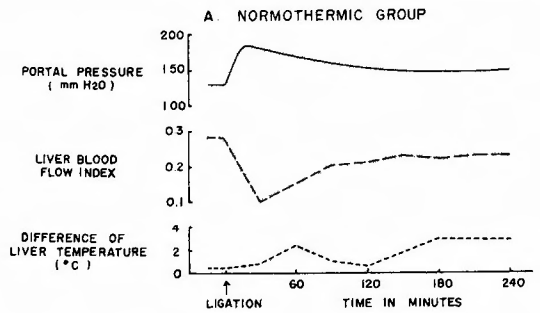
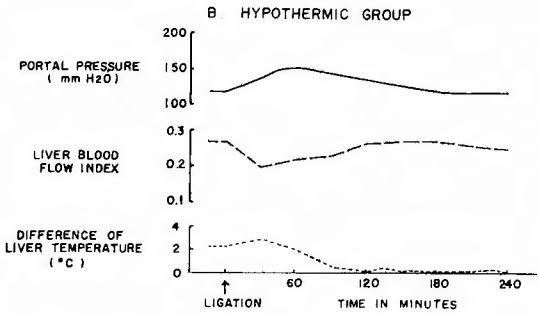


Fig. 10



is accepted to reveal that decrease in blood flow does not result in this site (Fig. 9, Fig. 10).

As mentioned already in the above, propotion of blood flow between the portal vein and hepatic artery is believed roughly to be 7 : 3. It suggests an abrupt decrease in portal blood flow in normothermic group that the index of liver blood flow decreases to 36 per cent 30 minutes after the interruption of the hepatic artery. On the contrary, the index was well kept within the extent of 74 per cent 30 minutes after the interruption, which, in addition, was observed to restore to the level before the interruption 150 minutes after the interruption. This finding is assumed to show that under hypothermia little change results in portal blood flow after the interruption compared with that before it, portal blood flow rather increasing thereafter.

It was, furthermore, clarified by macroscopic and microscopic studies of liver after the interruption that changes are extremely slight in hypothermic group.

By these studies it was demonstrated that prolongation of survival time is expected in experimental dogs of permanent interruption of the hepatic artery under hypothermia and some aminals, althongh few, could be set free from death without administration of any antibiotics such as penicillin, when the interruption is performed under hypothermia and it is maintained at least for 2 hours.

V. CONCLUSION

The common hepatic, gastroduodenal and right gastric arteries were ligated and cut in dogs under hypothermia of 25 to 28°C. The results obtained are as following;

1. It was clarified that 74 per cent of animals could survive for 48 hours after the interruption by maintaining hypothermia for more than 2 hours after it. Only 20 per cent of animals could survive for 48 hours when rewarming was initiated within 2 hours after the interruption and there was no difference in mortality between a group in which hypothermia was maintained for more than 2 hours and that in which it was maintained for 2 hours. When the interruption was performed under normothermic condition, all the animals died within 48 hours.

2. Elevation of portal pressure after the interruption was far slighter in hypothermic group compared with that in normothermic group, which promptly restored to the level before the interruption in the former.

3. The difference in temperature in the favorite and non-favorite site of liver necrosis that develops following the interruption increased in normothermic group, while it decreased in hypothermic group. This is mainly due to the change in the temperature of the favorite site of liver necrosis.

4. Liver blood flow was determined by the use of ^{198}Au, which revealed in normothermic group a decrease of 64 per cent 30 minutes after the interruption, being followed by increase to 82 per cent 150 minutes after the interruption. On the contrary, the blood flow in hypothermic group decreased slightly to 74 per cent 30 minutes after the interruption which, in addition, restored to the level before the interruption 150 minutes after it.

As obvious from these findings, it was clarified that application of hypothermia has

definite advantage in the interruption of the hepatic artery.

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Plate. 1 Normothermic group (H. E.×100)

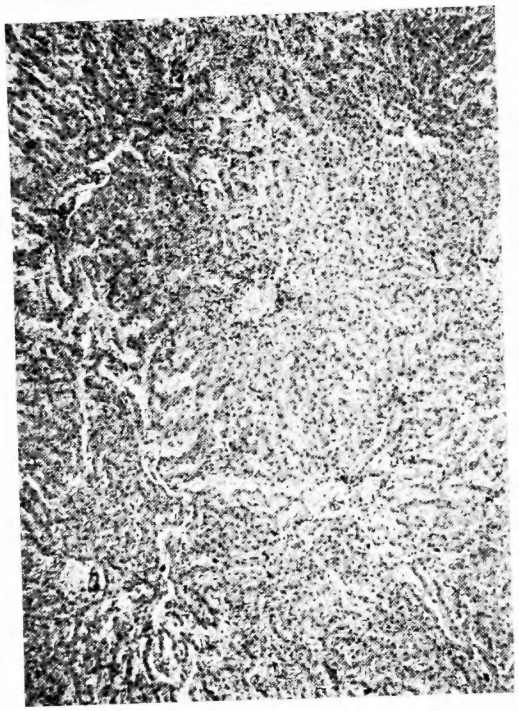


Plate. 2 Normothe mic group (H. E.×300)

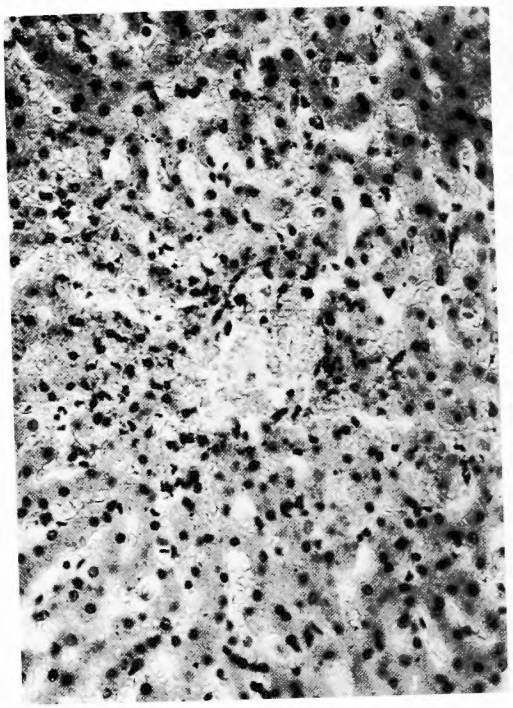


Plate. 3 Hypothermic group (H. E.×100)

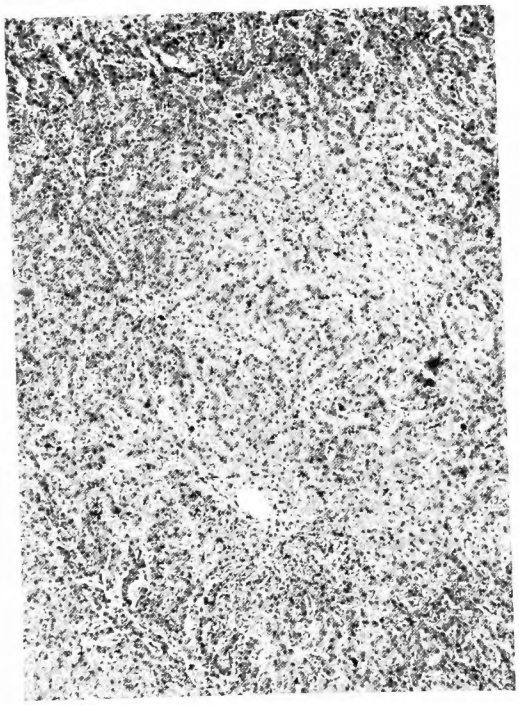
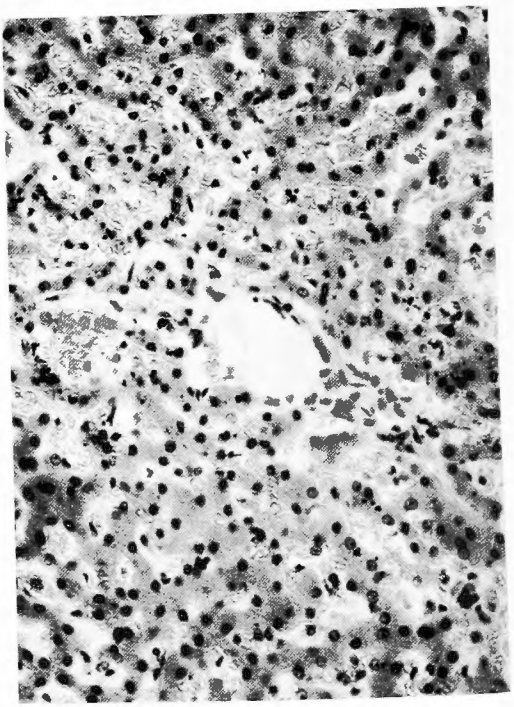


Plate. 4 Hypothermic group (H. E.×300)



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和 文 抄 録

低体温法下肝動脈遮断に関する実験的研究

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肝流入動脈血の遮断により，犬は殆ど全例死亡し肝には広汎な肝壊死発生が認められる事実は，Haberer (1907)の報告以来一般に確認されている．しかるに遮断後抗生物質を使用する事によつて大部分の犬は生存し，肝壊死は軽度にとどまる事実がMarkowitz (1949)によつて発見され，この事はTanturiによつても確認された．以来Rienhoff, Bermanが肝硬変症の治療に本法を提唱して，その後諸家により追試されて来たが一般には肝壊死発生の危懼の故にその実施は躊躇されて来た．本邦においては，本庄により広汎な肝動脈遮断の病態生理が検討され，遮断後の肝壊死発生は随伴する門脈循環障害に起因すること，又肝静脈狭窄による腹水犬は肝動脈遮断後肝壊死の起り難い事実が明らかにされた．著者は低体温法下に肝動脈遮断を行なつた場合の犬の態度につき若干の検索を試みた．実験動物は10kg前後の雑犬を用い，常温遮断，低体温遮断の2群に分ち，遮断後の生存率，血圧，門脈圧，肝温，肝血流量，組織学的所見につき検索した．低体温法に際してはエーテルによる全麻を用い，25～28℃に体温を降下せしめた．なお肝動脈遮断は総肝動脈，胃十二指腸動脈，右胃動脈を結紮切離した．

実　験　成　績

1．遮断後2時間以上低体温に維持する事によつて48時間後に74%生存する事実を知り得た．遮断後2時間以内に復温を行なつた群の48時間後の生存率は20%に止まり，又2時間以上低体温下に維持した群の生存率は，2時間のものと何等変らない．常温下では遮断群は48時間以内に殆ど全例死亡する

2．遮断後の門脈圧は低体温群は常温群に比しその上昇は極めて軽度であり，速かに遮断前値に復する．

3．遮断後発生する壊死の好発部と非好発部の肝温差は，常温群は増加するが低体温群は減少する．これは主として遮断後の壊死好発部の温度差に起因するものである．

4．Au^{198}を使用して肝血流量を測定した結果，常温群は遮断30分後36%に減少し，その後増加して2.5時間後82%の値を示す．一方低体温群は遮断30分後74%に減少するにとどまり，2.5時間後には遮断前値に復している．

5．遮断後の肝の変化を，肉眼的ならびに組織学的に観察した結果，低体温群は常温群に比して遙かに軽度であり，単に一時的に可逆性の鬱血所見を認めたに過ぎなかつた．

6．即ち低体温法下において肝動脈の永久的遮断を行なつた場合，すくなくとも2時間低体温に維持する事により，抗生物質を何等使用する事なく実験犬は生存期間の延長を示し，少数では死を免かれる例のある事が証明された．

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