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EXPERIMENTAL STUDIES ON THE RESPIRATION OF THE LIVER TISSUE AFTER THE INTERRUPTION OF THE HEPATIC ARTERY IN DOGS

by

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Ⅰ. INTRODUCTION

Since Haberer's[17] report it has been widely confirmed that in the dogs death always results and the liver shows massive necrosis following complete interruption of arterial inflow to the liver.

In 1949, Markowitz, Rappaport and Scott[30)31)] found the fact that almost all their dogs survived if given very large doses of penicillin after the interruption and the liver showed little or no changes. Since then many studies have been performed on changes in the liver following interruption of the hepatic artery and effects of penicillin upon the changes.

And it was reported that both reduced arterial blood supply and bacterial proliferation were the important causes of death as well as of development of liver necrosis after interruption of the hepatic artery, and that penicillin prevented bacterial proliferation and production of bacterial toxin[6)7)10)12)15)30)31)42)50)], and during the period of penicillin administration a small amount of arterial blood, draining into the liver by the enlargement in calibre and increase in number of the collateral arterial vessels via the diaphragm, the bile duct, the inferior vena cava and the

adhesions in the porta hepatis, prevented the augmentation of liver necrosis[16)25)26)27)38)~41)].

MARKOWITZ, RAPPAPORT and SCOTT[30)31)], FRASER and others[12)] administered large doses of penicillin for more than a week postoperatively, and TANTURI, SWIGART and CANEPA[50)], GRINDLAY, MANN and BOLLMAN[16)], however, for 4 to 5 days and CHAU, GOLDBLOOM and GURD[6)] for 2 days. Then EZE[7)] reported that dog survived by administration of a single dose of 100,000 units of penicillin after interruption of the hepatic artery.

HONJO[18)~23)] and his associates, having debated the significance of the hepatic arterial and portal venous blood flow in the intrahepatic circulation, especially, in the pathophysiologic studies on the interruption of the hepatic artery obtained the following results.

Approximately 70 per cent of dogs survived by the intraperitoneal administration of 100,000 units of penicillin immediately after the interruption, and penicillin could prevent bacterial proliferation for about 8 hours following its administration[52)].

Even the penicillin-treated dogs that survived the interruption were unable to be free from some disturbances in liver functions, but did not show any marked liver necrosis. In a dog the arterial branches draining directly into the liver from the diaphragm were hardly perceived and each whole liver lobule was systematically supplied only by the blood flow which were connected with the hepatic artery or its branches at the porta hepatis. These connecting vessels were extremely faint within a short period after interruption of the hepatic artery, and moreover it did not alter the survival rate to interrupt these vessels together with the hepatic artery[24)].

Liver ferritin, in dogs non-treated with penicillin, began to decrease rapidly and markedly after 3 hours following the interruption, and preserved its lowered value for 6 to 12 hours, while, in penicillin-treated dogs, it decreased only slightly[37)].

The blood ammonia level, in dogs non-treated with penicillin, increased progressively after 6 to 12 hours following the interruption, while, in penicillin-treated dogs, it increased slightly immediately after the interruption, and soon returned nearly to the level before the interruption[35)].

As to the activity of lecithinase C in the liver, in dogs non-treated with penicillin, every instance showed positive at the death, while, in penicillin-treated dogs, only 35 per cent of all instances showed positive even at 24 to 48 hours after the interruption[56)].

The oxygen content of portal blood, in dogs non-treated with penicillin, increased temporarily after the interruption and thereafter decreased gradually, while, in penicillin-treated dogs, increased temporarily and then decreased, and thereafter increased again[1)].

By this series of experiments it was demonstrated that in dogs non-treated with penicillin, morphological and metabolic changes in the liver took place after several hours following interruption of the hepatic artery, progressed with time and all instances died within 1 to 3 days, and that in penicillin-treated dogs such changes

after the interruption were slight and approximately 70 per cent of all instances survived.

Thus it came to be clear that the fate of dogs after interruption of the hepatic artery depends upon the degree of the changes taking place within a short time following the interruption.

The hepatic hypoxia results extensive biochemical changes in the liver, and plays a significant role in shock. Energy metabolism has been widely studied in various shock. On the energy metabolism, however, in the liver after the interruption of the hepatic artery any reports can not be seen except WILHELMI and others[55] in eviscerated rats.

In order to clarify the mechanism of penicillin-effects in the interruption of the hepatic artery, the author performed measurements of the rate of respiration of liver tissue before and after the interruption and obtained the following results.

Ⅱ. MATERIALS AND MHTHODS

1) Materials: Adult mongrel dogs of either sex, weighing from 6.0 to 15.5 kg, were used. Each of them was fed a diet containing rice and fish, and fasted for 24 hours before operation. The operation was performed under basal anesthesia with morphine (20 mg per Kg) and local anesthesia with xylocain (0.5 per cent) using aseptic technique.

2) Complete interruption of the hepatic artery: The three arteries of "the common hepatic artery, the gastroduodenal artery and the right gastric artery" were dissected free of their sorrounding tissues through a midline upper abdominal incision, and each of them doubly ligated and divided.

3) Measurement of the rate of respiration of liver slices: By means of the WARBURG respirometer and through the WARBURG "indirect method"[51][53] the coefficients of respiration, aerobic glycolysis and anaerobic glycolysis, which were denoted as $|Qo|$, $Q_L^{O_2}$ and $Q_L^{N_2}$ respectively, were measured.

$|Qo_2|$ = cmm O_2 taken up per mg dry weight of tissue per hour

$Q_L^{O_2}$ = cmm CO_2 given off in an atmosphere of oxygen per mg dry weight of tissue per hour

$Q_L^{N_2}$ = cmm CO_2 given off in an atmosphere of nitrogen per mg dry weight of tissue per hour

(Qo_2 is a minus quantity. Nevertheless, this coefficient was in this paper represented by its absolute value Qo_2 for the sake of convenience for explanation.)

Small masses of the liver used for measurement of the rate of respiration were dissected from the margin of the lower left lobe, then these masses were sliced to about 0.4 mm thickness with a razor blade. After finishing the measurements these slices dried in the water-bath for 2 hours and left in the desiccator all night long, dry weights were determined. Every slice used in these experiments was from 5 to 10 mg in dry weight.

The gas space was filled with gas mixture of 95 per cent oxygen or 95 per cent nitrogen, each containing 5 per cent carbon dioxide. The KREBS-physiological-

salt-solution was used as the suspension, to which 0.2 per cent glucose was added as the respiratory substrate. The temperature was maintained at 37°C in a water bath, in which the flasks were shaken at about 110 double excursions per minute.

4) Measurement of the arterial pressure: Before interruption of the hepatic artery a glass cannula connected to a mercury manometer was inserted into the femoral artery and the arterial pressure was measured continuously.

5) Transfusion: Each dog was injected with physiological salt solution and 5 per cent glucose solution subcutaneously, each in a dose of 100 cc, 12 hours after the interruption, and the survival dogs received the same transfusion twice a day for 3 days after the interruption.

6) Administration of penicillin: In the experiments of penicillin-treated dogs, 300,000 units of procain penicillin G in oil was injected intramuscularly immediately after interruption of the hepatic artery.

Ⅲ. EXPERIMENTAL RESULTS

1) Mortality: Of the 19 dogs that were untreated with penicillin after interruption of the hepatic artery, all instances died within 15 to 51 hours after the interruption, and the average period of survival was 29 hours. Of the 19 dogs that were treated with penicillin, 12 survived the interruption, and the survival rate was approximately 63 per cent. Moreover the average period of survival in the 7 dogs that died was 57 hours, which showed evidently that the survival period was prolonged in penicillin-treated dogs as compared with in dogs non-treated with penicillin.

Grindlay, Mann and Bollman[16], Markowitz, Rappaport and Scott[30][31], Schilling, McKee and Wilt[44], Urabe[72], Fujita[15] and Koshizuka[28] reported that all of dogs without penicillin treatment had died within 70 hours after interruption of the hepatic artery. On the other hand Fraser and others[12] reported that approximately 65 per cent of the dogs survived the interruption by the administration of penicillin and Urabe reported that the survival rate was about 70 per cent.

The results the author obtained were similar to those reports.

2) The rate of respiration of liver slices till 12 hours after interruption of the hepatic artery:

Measurements were made five times — before and 1, 3, 6 and 12 hours after the interruption.

A. Dogs non-treated with penicillin (Tab. 1, Fig. 1): In this experiment 10 dogs were used.

a) Q_{O_2}: The values before the interruption ranged from 6.6 to 13.0 with a mean value of 9.6. The values at the 1st hour after the interruption ranges from 4.8 to 9.0 with a mean value of 7.1. The differences between the values before and 1 hour after the interruption ranged from -8.2 to -0.2 with a mean difference of -2.5. The values at the 3rd hour after the interruption ranged from 5.2 to 12.4 with a mean value of 8.7. The differences between the values before and 3 hours after the interruption ranged from -7.8 to 2.3 with a mean difference of -0.9.

The values at the 6th hour after the interruption ranged from 6.4 to 13.0 with a mean value of 8.9. The differences between the values before and 6 hours after the interruption ranged from −6.6 to 0.9 with a mean difference of −0.7. The values at the 12th hour after the interruption ranged from 5.4 to 10.5 with a mean value of 7.3. The differences between the values before and 12 hours after the interruption ranged from −5.0 to 0.2 with a mean difference of −2.3.

$|Q_{O_2}|$ decreased in every instance at the 1st hour after the interruption, then it increased in 9 instances from 3 to 6 hours, and thereafter decreased again, while in the other one (Dog No. 1) it increased gradually till 12 hours.

b) $Q_L^{2^2}$: The values before the interruption ranged from 0.8 to 6.5 with a mean value of 2.8. The values at the 1st hour after the interruption ranged from 0.6 to 3.6 with a mean value of 1.7. The differences between the values before and 1 hour after the interruption ranged from −2.9 to −0.2 with a mean difference of −1.1. The values at the 3rd hour after the interruption ranged from 0.9 to 4.2 with a mean value of 2.3. The differences between the values before and 3 hours after the interruption ranged from −2.3 to 0.8 with a mean difference of −0.6. The values at the 6th hour after the interruption ranged from 0.5 to 5.3 with a mean value of 2.4. The differences between the values before and 6 hours after

Table 1. The rate of respiration of liver slices till 12 hours after interruption of the hepatic artery in dogs non-treated with penicillin.

1a. $|Q_{O_2}|$

Dog No.	Sex	Weight (kg)	Before interruption	Hours after interruption Result			
				1	3	6	12
1	F	9.5	13.0	4.8 *(−8.2)	5.2 (−7.8)	6.4 (−6.6)	8.0 (−5.0) Died
2	M	15.5	9.2	5.8 (−3.4)	6.9 (−2.3)	8.5 (−0.7)	7.3 (−1.9) Died
3	F	9.5	6.6	6.4 (−0.2)	6.6 (0.0)	7.0 (0.4)	6.8 (0.2) Died
4	F	10.5	7.9	7.7 (−0.2)	9.0 (1.1)	8.0 (0.1)	6.1 (−1.8) Died
5	M	7.5	9.7	6.4 (−3.4)	12.0 (2.3)	11.6 (0.9)	9.0 (−0.7) Died
6	M	9.0	8.4	6.3 (−2.1)	7.1 (−1.3)	7.9 (−0.5)	7.7 (−0.7) Died
7	M	8.5	12.3	8.1 (−4.2)	12.4 (0.1)	13.0 (0.7)	10.5 (−1.8) Died
8	F	8.0	10.2	7.8 (−2.4)	8.6 (−1.6)	10.7 (0.5)	6.3 (−3.9) Died
9	M	8.5	9.6	9.0 (−0.6)	9.0 (−0.6)	7.6 (−2.0)	6.0 (−3.6) Died
10	F	10.5	8.8	8.2 (−0.6)	9.9 (1.1)	8.4 (−0.4)	5.4 (−3.4) Died
		Mean	9.6	7.1 (−2.5)	8.7 (−0.9)	8.9 (−0.7)	7.3 (−2.3)

* Each bracketed value means the difference between the respective value before and every hour after interruption.

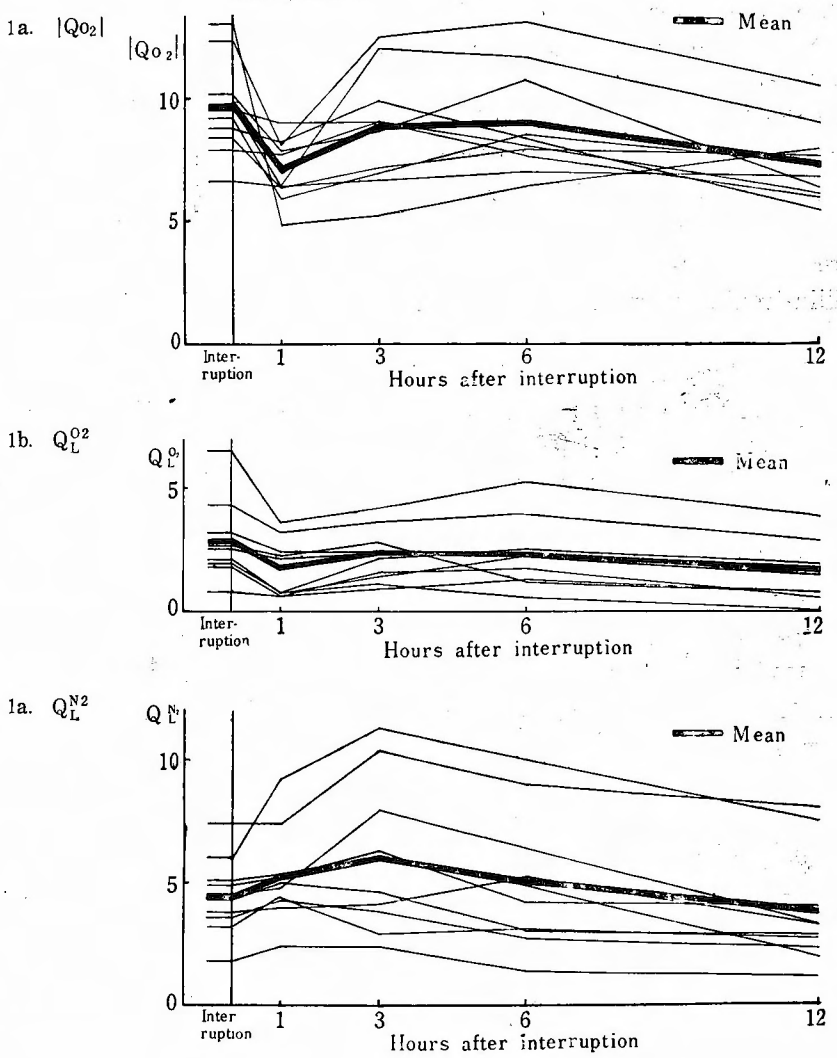
1b. $Q_L^{O_2}$

Dog No.	Before interruption	Hours after interruption			
		1	3	6	12
1	6.5	3.6 (−2.9)	4.2 (−2.3)	5.3 (−1.2)	3.9 (−2.6)
2	3.2	2.4 (−0.8)	2.4 (−0.8)	2.4 (−0.8)	1.5 (−1.7)
3	2.1	0.7 (−1.4)	1.4 (−0.7)	2.3 (0.2)	1.8 (−0.3)
4	0.8	0.6 (−0.2)	1.6 (0.8)	1.7 (0.9)	0.5 (−0.3)
5	1.8	0.6 (−1.2)	0.9 (−0.9)	1.3 (−0.5)	0.8 (−1.0)
6	1.9	0.8 (−1.1)	2.1 (0.2)	2.6 (0.7)	1.9 (0.0)
7	2.1	0.7 (−1.4)	1.1 (−1.0)	0.5 (−1.6)	0.0 (−2.1)
8	4.3	3.2 (−1.1)	3.6 (−0.7)	4.0 (−0.3)	2.8 (−1.5)
9	2.7	2.3 (−0.4)	2.8 (0.1)	1.2 (−1.5)	0.8 (−1.9)
10	2.6	2.1 (−0.5)	2.4 (−0.2)	2.2 (−0.4)	1.5 (−1.1)
Mean	2.8	1.7 (−1.1)	2.3 (−0.6)	2.4 (−0.5)	1.6 (−1.3)

1c. $Q_L^{N_2}$

Dog No.	Before interruption	Hours after interruption			
		1	3	6	12
1	7.4	7.4 (0.0)	10.4 (3.0)	9.0 (1.6)	8.0 (0.6)
2	3.8	4.0 (0.2)	4.1 (0.3)	5.2 (1.5)	3.2 (−0.6)
3	6.0	9.2 (3.2)	11.3 (5.3)	10.0 (4.0)	7.5 (1.5)
4	4.5	4.8 (0.3)	7.9 (3.4)	6.4 (1.9)	3.2 (−1.3)
5	1.8	2.4 (0.6)	2.4 (0.6)	1.4 (−0.4)	1.1 (−0.7)
6	4.9	5.2 (0.3)	6.3 (1.4)	4.2 (−0.7)	4.0 (−0.9)
7	3.2	4.4 (1.2)	2.9 (−0.3)	3.1 (−0.1)	2.7 (−0.5)
8	5.1	5.3 (0.2)	6.0 (0.9)	4.9 (−0.2)	1.9 (−3.2)
9	4.3	5.0 (0.7)	4.6 (0.3)	3.0 (−1.3)	2.8 (−1.5)
10	3.6	4.3 (0.7)	3.9 (0.3)	2.7 (−1.1)	2.3 (−1.3)
Mean	4.5	5.2 (0.7)	6.0 (1.5)	5.0 (0.5)	3.7 (−0.8)

Fig. 1 The rate of respiration of liver slices till 12 hours after interruption of the hepatic artery in dogs non-treated with penicillin.



the interruption ranged from −1.6 to 0.9 with a mean difference of −0.5. The values at the 12th hour after the interruption ranged from 0.0 to 3.9 with a mean value of 1.6. The differences between the values before and 12 hours after the interruption ranged from −2.6 to 0.0 with a mean difference of −1.3.

$Q_L^{O_2}$ in every instance decreased at the 1st hour, then increased from 3 to 6 hours after the interruption, and thereafter decreased again.

c) $Q_L^{N_2}$: The values before the interruption ranged from 1.8 to 7.4 with a mean value of 4.5. The values at the 1st hour after the interruption ranged from 2.4 to 7.4 with a mean value of 5.2. The differences between the values before and 1 hour after the interruption ranged from 0.0 to 3.2 with a mean difference of 0.7. The values at the 3rd hour after the interruption ranged from 2.4 to 11.3

with a mean value of 6.0. The differences between the values before and 3 hours after the interruption ranged from −0.3 to 5.3 with a mean difference of 1.5. The values at the 6th hour after the interruption ranged from 1.4 to 10.0 with a mean value of 5.0. The differences between the values before and 6 hours after the interruption ranged from −1.3 to 4.0 with a mean difference of 0.5. The values at the 12th hour after the interruption ranged from 1.1 to 8.0 with a mean value of 3.7. The differences between the values before and 12 hours after the interruption ranged from −3.2 to 1.5 with a mean difference of −0.8.

$Q_L^{N_2}$ in every instance increased till 1 to 6 hours after the interruption and thereafter decreased gradually.

B. Penicillin-treated dogs (Tab. 2, Fig. 2) : In this experiment 10 dogs were used.

a) Q_O : The values before the interruption ranged from 8.0 to 12.2 with a mean value of 9.9. The values at the 1st hour after the interruption ranged from 7.5 to 11.5 with a mean value of 9.0. The differences between the values before and 1 hour after the interruption ranged from −2.3 to 1.6 with a mean difference of −0.9. The values at the 3rd hour after the interruption ranged from 8.0 to 12.2 with a mean value of 10.8. The differences between the values before and 3 hours after the interruption ranged from −2.7 to 4.1 with a mean difference of 0.9.

Table 2 The rate of respiration of liver slices till 12 hours after interruption of the hepatic artery in penicillin-treated dogs.

2a. $|Q_{O_2}|$

Dog No.	Sex	Weight (kg)	Before interruption	Hours after interruption				Result
				1	3	6	12	
11	F	10.0	9.2	7.9 *(−1.3)	10.1 (0.9)	9.8 (0.6)	9.4 (0.2)	Survived
12	M	7.5	9.9	11.5 (1.6)	11.0 (1.1)	12.7 (2.8)	10.0 (0.1)	Survived
13	M	7.0	10.1	9.9 (−0.2)	11.8 (1.7)	11.0 (0.9)	10.6 (0.5)	Died
14	F	9.0	10.7	10.1 (−0.6)	8.0 (−2.7)	9.3 (−1.4)	10.5 (−0.2)	Survived
15	F	9.0	8.0	7.5 (−0.5)	11.6 (3.6)	10.1 (2.1)	8.5 (0.5)	Died
16	F	9.5	9.6	7.6 (−2.0)	10.4 (0.8)	9.1 (−0.5)	9.5 (0.1)	Survived
17	M	10.0	9.3	8.4 (−0.9)	9.8 (0.5)	11.0 (1.7)	10.7 (1.4)	Died
18	F	8.5	12.2	10.3 (−1.9)	11.0 (−1.2)	13.0 (0.8)	11.8 (−0.4)	Survived
19	M	8.0	11.5	9.2 (−2.3)	12.0 (0.5)	11.2 (−0.3)	10.8 (−0.7)	Survived
20	M	7.0	8.1	8.0 (−0.1)	12.2 (1.1)	10.7 (2.6)	10.5 (2.4)	Survived
	Mean		9.9	9.0 (−0.9)	10.8 (0.9)	10.8 (0.9)	10.2 (0.3)	

* Each bracketed value means the difference between the respective value before and every hour after the interruption.

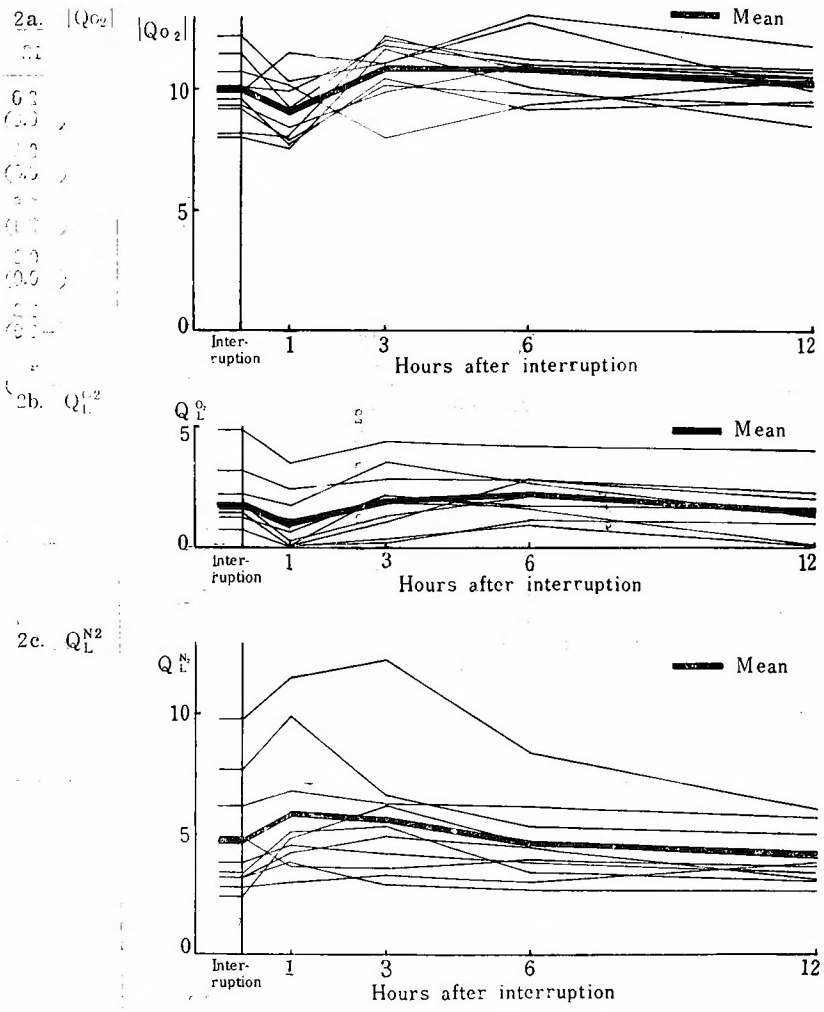
2b. Q_L^{O2}

Dog No.		Before interruption	Hours after interruption			
			1	3	6	12
11		1.4	0.0 (−1.4)	1.0 (−0.4)	2.8 (1.4)	2.0 (0.6)
12		0.0	0.0 (0.0)	0.3 (0.3)	0.9 (0.9)	0.0 (0.0)
13		1.2	0.6 (−0.6)	2.1 (0.9)	1.7 (0.5)	1.6 (0.4)
14		0.0	0.0 (0.0)	2.1 (2.1)	1.6 (1.6)	0.0 (0.0)
15		2.2	1.7 (−0.5)	3.5 (1.3)	2.7 (0.5)	1.2 (−1.0)
16		4.9	3.4 (−1.5)	4.4 (−0.5)	4.2 (−0.7)	4.0 (−0.9)
17		0.7	0.0 (−0.7)	0.2 (−0.5)	1.1 (0.4)	1.0 (0.3)
18		1.8	0.2 (−1.6)	1.2 (−0.6)	2.1 (0.3)	1.3 (−0.5)
19		3.2	2.4 (−0.8)	2.8 (−0.4)	2.8 (−0.4)	2.2 (−1.0)
20		1.5	1.1 (−0.4)	1.8 (0.3)	1.7 (0.2)	1.5 (0.0)
	Mean	1.7	0.9 (−0.8)	1.9 (0.3)	2.2 (0.5)	1.4 (−0.3)

2c. Q_L^{N2}

Dog No.		Before interruption	Hours after interruption			
			1	3	9	12
11		3.2	4.2 (1.0)	5.0 (1.8)	4.5 (1.3)	3.2 (0.0)
12		2.4	5.8 (3.4)	6.2 (3.8)	4.6 (2.2)	4.0 (1.6)
13		2.8	3.0 (0.2)	3.3 (0.5)	3.0 (0.2)	3.9 (1.1)
14		4.9	3.7 (−1.2)	3.6 (−1.3)	4.0 (−0.9)	3.7 (−1.2)
15		7.7	9.9 (2.2)	6.6 (−1.1)	5.3 (−2.4)	5.0 (−2.7)
16		9.8	11.6 (1.8)	12.3 (2.5)	8.4 (−1.4)	6.1 (−3.7)
17		6.2	6.8 (0.6)	6.3 (0.1)	6.2 (0.0)	5.7 (−0.5)
18		3.2	3.9 (0.7)	2.9 (−0.3)	2.7 (−0.5)	2.6 (−0.6)
19		3.4	5.1 (1.7)	5.3 (1.9)	3.4 (0.0)	3.0 (−0.4)
20		3.8	4.5 (0.7)	4.2 (0.4)	3.9 (0.1)	3.4 (−0.4)
	Mean	4.7	5.9 (1.1)	5.6 (0.8)	4.6 (−0.1)	4.1 (−0.7)

Fig. 2 The rate of respiration of liver slices till 12 hours after interruption of the hepatic artery in penicilin-treated dogs.



The values at the 6th hour after the interruption ranged from 9.1 to 13.0 with a mean value of 10.8. The differences between the values before and 6 hours after the interruption ranged from −1.4 to 2.8 with a mean difference of 0.9. The values at the 12th hour after the interruption ranged from 8.5 to 11.8 with a mean value of 10.2. The differences between the values before and 12 hours after the interruption ranged from −0.7 to 2.4 with a mean difference of 0.3.

Qo in 8 of 10 instances decreased at the 1st hour and then increased from 3 to 6 hours after the interruption, and thereafter decreased again. In one instance (Dog No. 14) it decreased till 3 hours after the interruption and thereafter increased gradually and in the other instance (Dog No. 12) it increased till 6 hours after the interruption and thereafter decreased slightly.

b) $Q_L^{O_2}$: The values before the interruption ranged from 0.0 to 4.9 with a

mean value of 1.7. The values at the 1st hour after the interruption ranged from 0.0 to 3.4 with a mean value of 0.9. The differences between the values before and 1 hour after the interruption ranged from −1.6 to 0.0 with a mean difference of −0.8. The values at the 3rd hour after the interruption ranged from 0.2 to 4.4 with a mean value of 1.9. The differences between the values before and 3 hours after the interruption ranged from −0.6 to 2.1 with a mean difference of 0.3. The values at the 6th hour after the interruption ranged from 0.9 to 4.2 with a mean value of 2.2. The differences between the values before and 6 hours after the interruption ranged from −0.7 to 1.6 with a mean difference of 0.5. The values at the 12th hour after the interruption ranged from 0.0 to 4.0 with a mean value of 1.4. The differences between the values before and 12 hours after the interruption ranged from −1.0 to 0.6 with a mean difference of −0.3.

$Q_L^{O_2}$ in 8 instances decreased at the 1st hour after the interruption, then increased from 3 to 6 hours and thereafter decreased again. In the other 2 instances (Dog No. 12 and 14) both the values before and 1 hour after the interruption were 0.0.

c) $Q_L^{N_2}$: The values before the interruption ranged from 2.4 to 9.8 with a mean value of 4.7. The values at the 1st hour after the interruption ranged from 3.0 to 11.6 with a mean value of 5.9. The differences between the values before and 1 hour after the interruption ranged from −1.2 to 3.4 with a mean difference of 1.1. The values at the 3rd hour after the interruption ranged from 2.9 to 12.3 with a mean value of 5.6. The differences between the values before and 3 hours after the interruption ranged from −1.3 to 3.8 with a mean difference of 0.8. The values at the 6th hour after the interrupption ranged from 3.0 to 8.4 with a mean value of 4.6. The differences between the values before and 6 hours after the interruption ranged from −2.4 to 2.2 with a mean difference of −0.1. The values at the 12th hour after the interruption ranged from 3.0 to 6.1 with a mean value of 4.1. The differences between the values before and 12 hours after the interruption ranged from −3.7 to 1.6 with a mean difference of −0.7.

$Q_L^{N_2}$ in 9 instances increased till 1 to 6 hours after the interruption and thereafter decreased gradually. In the other instance (Dog No. 14) the value decreased gradually showing no recognizable temporary increase after the interruption.

3) The rate of respiration of liver slices 24 hours and furthermore after the interruption.

The abdomen was closed after the interruption of the hepatic artery, and the first measurement was made at the 24th hour after the interruption. In the instances that survived thereafter, the measurements were made two times above—at the 48th and the 72nd hour after the interruption.

A. Dogs non-treated with penicillin (Tab. 3, Fig. 3): In this experiment 6 dogs were used. The value at the 24th hour after the interruption in every instance could be measured. In only 2 instances (Dog No. 21 and 26) the values at the 48th hour after the interruption could be measured.

a) $|Qo|$: The values at the 24th hour after the interruption ranged from 5.7 to 10.2 with a mean value of 7.9. The values at the 48th hour after the interr-

uption were 4.1 and 4.3, a mean value was 4.2. The differences between the values 24 and 48 hours after the interruption were −6.1 and −5.2, a mean difference was −5.7.

Q_{O_2} in every instance decreased markedly at the 48th hour after the interruption.

b) $Q_L^{O_2}$: The values at the 24th hour after the interruption ranged from 0.0 to 0.9 with a mean value of 0.3. The values at the 48th hour after the interruption

Table 3 The rate of respiration of liver slices 24 hours and furthermore after interruption of the hepatic artery in dogs non-treated with penicillin.

3a. Q_{O_2}

Dog No.	Sex	Weight (kg)	Hours after interruption		Result
			24	48	
21	M	10.0	9.5	4.3 (−5.2)*	Died
22	F	9.0	6.1	†	Died
23	M	10.0	5.7	†	Died
24	M	8.0	8.6	†	Died
25	F	8.5	7.3	†	Died
26	F	7.5	10.2	4.1 (−6.1)	Died
	Mean		7.9	4.2 (−5.7)	

3b. $Q_L^{O_2}$

Dog No.		Hours after interruption	
		24	48
21		0.0	0.9 (0.9)
22		0.4	†
23		0.9	†
24		0.0	†
25		0.2	†
26		0.0	0.0 (0.0)
	Mean	0.3	0.5 (0.5)

3c. $Q_L^{N_2}$

Dog No.		Hours after interruption	
		24	48
21		3.6	3.8 (0.2)
22		2.3	†
23		2.0	†
24		3.1	†
25		2.4	†
26		3.7	4.1 (0.4)
	Mean	2.9	3.9 (0.3)

* Each bracketed value means the differences between the respective value 24 and 48 hours after the interruption.

were 0.0 and 0.9, a mean value was 0.5. The differences between the values 24 and 48 hours after the interruption were 0.0 and 0.9, a mean difference was 0.5.

c) $Q_L^{N_2}$: The values at the 24th hour after the interruption ranged from 2.0 to 3.7 with a mean value of 2.9. The values at the 48th hour after the interruption were 3.8 and 4.1, a mean value was 3.9. The differences between the values 24 and 48 hours after the interruption were 0.2 and 0.4, a mean difference was 0.3.

B. Penicillin-treated dogs (Tab. 4, Fig. 4): In this experiment 6 dogs were used. In every instance the value at the 72nd hour after the interruption as well as the other two could be measured.

a) $|Q_{O_2}|$: The values at the 24th hour after the interruption ranged from 10.4 to 12.2, with a mean value of 11.1. The values at the 48th hour after the interruption ranged from 7.0 to 10.8 with a mean value of 8.5. The differences between the values 24 and 48 hours after the interruption ranged from −4.4 to −0.1 with a mean difference of −2.6.

Fig. 3 The rate of respiration of liver slices 24 hours and furthermore after interruption of the hepatic artery in dogs non-treated with penicillin.

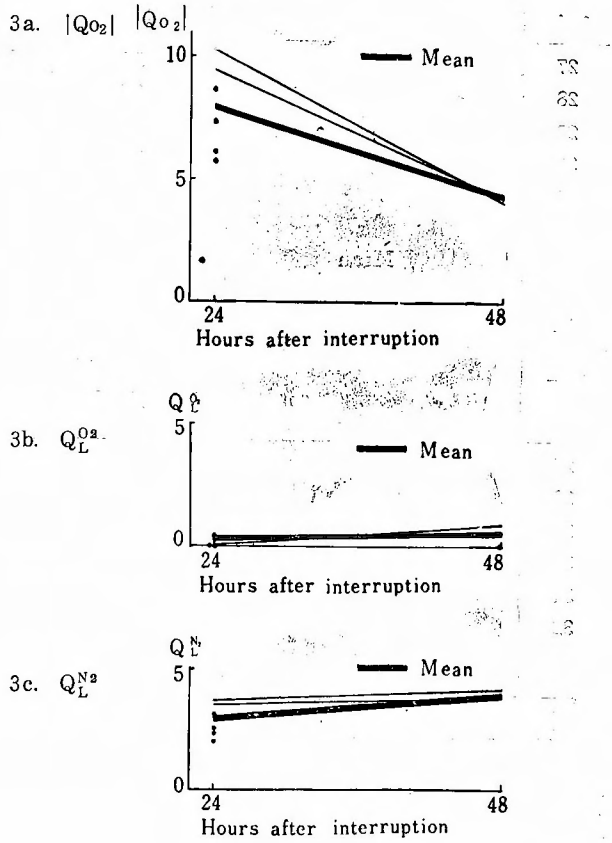


Table 4 The rate of respiration of liver slices 24 hours and furthermore after interruption of the hepatic artery in penicillin-treated dogs.

4a. $|Q_{O_2}|$

Dog No.	Sex	Weight (kg)	Hours after interruption			Result
			24	48	72	
27	M	10.0	12.2	7.8 (−4.4)	6.5 (−5.7)*	Died
28	F	9.0	11.8	8.7 (−3.1)	5.8 (−6.0)	Survived
29	M	10.0	10.9	10.8 (−0.1)	6.4 (−4.5)	Died
30	M	8.0	10.5	7.0 (−3.5)	6.9 (−3.6)	Survived
31	F	8.5	10.8	7.7 (−3.1)	7.6 (−3.2)	Survived
32	M	7.5	10.4	8.9 (−1.5)	6.3 (−4.1)	Died
	Mean		11.1	8.5 (−2.6)	6.6 (−4.5)	

4b. $Q_L^{O_2}$

Dog No.		Hours after interruption		
		24	48	72
27		2.5	0.0 (−2.5)	0.2 (−2.3)
28		0.0	0.0 (0.0)	0.4 (0.4)
29		0.0	0.0 (0.0)	0.0 (0.0)
30		0.0	0.0 (0.0)	0.1 (0.1)
31		1.1	0.0 (−1.1)	0.0 (−1.1)
32		0.0	0.0 (0.0)	0.0 (0.0)
	Mean	0.6	0.0 (−0.6)	0.1 (−0.5)

4c. $Q_L^{N_2}$

Dog No.		Hours after interruption		
		24	48	72
27		3.2	3.8 (0.6)	2.9 (−0.3)
28		2.1	2.7 (0.6)	1.5 (−0.6)
29		2.4	1.8 (−0.6)	2.7 (0.3)
30		1.8	3.1 (1.3)	2.6 (0.8)
31		2.6	3.2 (0.6)	2.9 (0.3)
32		2.5	2.9 (0.4)	2.6 (0.1)
	Mean	2.4	2.9 (0.5)	2.5 (0.1)

* Each bracketed value means the difference between the respective value 24 hours and 48 or 72 hours after the interruption.

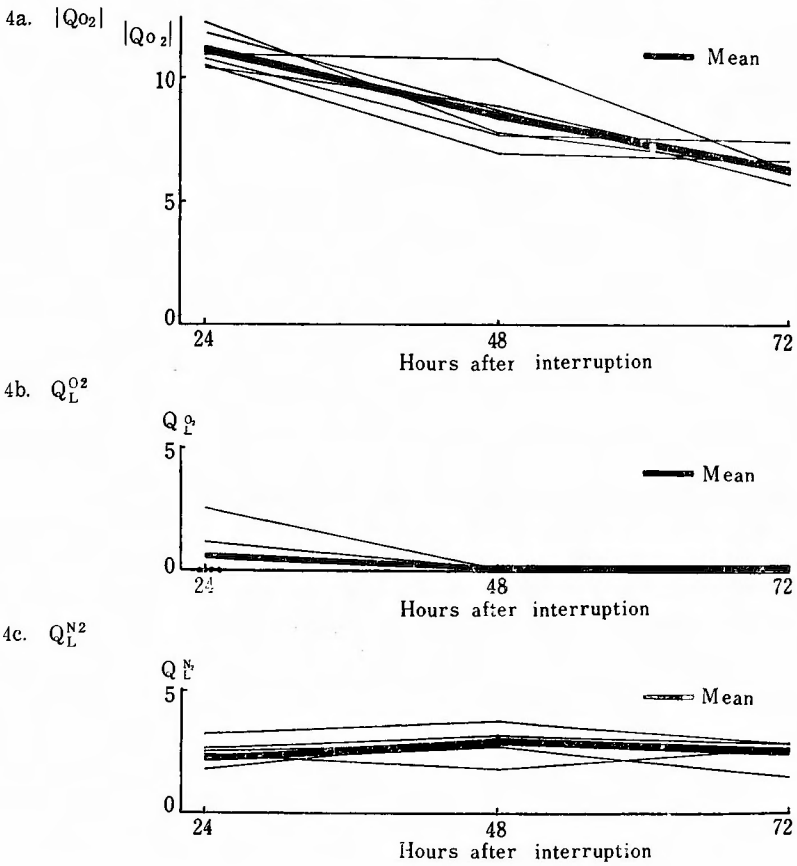
The values at the 72nd hour after the interruption ranged from 5.8 to 7.6 with a mean value of 6.6. The differences between the values 24 and 72 hours after the interruption ranged from −6.0 to −3.2 with a mean difference of −4.5.

Q_{O_2} in every instance decreased gradually since 24 hours after the interruption.

b) $Q_L^{O_2}$: The values at the 24th hour after the interruption ranged from 0.0 to 2.5 with a mean value of 0.6. Every value at the 48th hour after the interruption was 0.0. The differences between the values 24 and 48 hours after the interruption ranged from −2.5 to 0.0 with a mean difference of −0.6. The values at the 72nd hour after the interruption ranged from 0.0 to 0.4 with a mean value of 0.1. The differences between the values 24 and 72 hours after the interruption ranged from −2.3 to 0.4 with a mean difference of −0.5.

c) $Q_L^{N_2}$: The values at the 24th hour after the interruption ranged from 1.8 to 3.2 with a mean value of 2.4. The values at the 48th hour after the interruption ranged from 1.8 to 3.8 with a mean value of 2.9. The differences between the values 24 and 48 hours after the interruption ranged from −0.6 to 1.3 with a mean difference of 0.5. The values at the 72nd hour after the interruption ranged from 1.5 to 2.9 with a mean value of 2.5. The differences between the values 24 and 72 hours after the interruption ranged from −0.6 to 0.8 with a mean difference of 0.1.

Fig. 4 The rate of respiration of liver slices 24 hours and furthermore after interruption of the hepatic artery in penicillin-treated dogs.



Results from these measurements of the rate of respiration of liver slices after the interruption of the hepatic artery were as follows.

Q_{O_2} in dogs non-treated with penicillin decreased at the 1st hour, then slightly increased from 3 to 6 hours after the interruption and thereafter decreased further. This increase, however, was slow-paced and before long followed by a decrease again. Consequently, the values at the 12th hour in 9 of 10 instances decreased below the respective values before the interruption. While Q_{O_2} in penicillin-treated dogs also increased following the temporary decrease after the interruption and since then maintained the level almost without decrease, and the instances in which the values at the 12th hour after the interruption decreased below the respective values before the interruption were only 3 of 10 instances. After 24 hours gradual decrease took place in $|Q_{O_2}|$ in penicillin-treated dogs.

In the differences between the values before and either 3, 6 or 12 hours after the interruption, a significant difference was observed statistically through t-test between penicillin-treated group and non-treated one, and the difference increased whth time. That is to say, the significant levels obtained by t-test at 3,6 and 12

hours after the interruption were 0.1, 0.05 and 0.01 respectively.

$Q_L^{O_2}$ in both groups decreased at the 1st hour after the interruption, then increased and thereafter decreased again. The course of $Q_L^{O_2}$ was similar to that of Q_{O_2}. In addition, the fluctuation of values in Q_{O_2} in penicillin-treated dogs after the interruption were slighter than those in dogs non-treated with penicillin.

Q^{N_2} in both groups temporary increased after the interruption and then decreased gradually. There was no significant difference between the two groups.

4) Effect of basal anesthesia on the rate of respiration of liver slices. (Tab. 5, Fig. 5): The measurements of the rate of respiration of liver slices were made under basal anesthesia with morphine that had been indispensable to perform the interruption of the hepatic artery. In order to obtain the genuine values in the rate of respiration of liver slices due to interruption of the hepatic artery, the following experiment was carried out excluding the influence of morphine.

Table 5 The rate of respiration of liver slices after basal anesthesia in normal dogs.

5a. $|Q_{O_2}|$

Dog No.	Sex	Weight (kg)	Hours after basal anesthesia				
			1	2	4	7	13
33	F	7.0	7.3	9.8 (2.5)	11.3 (4.0)	11.6 (4.3)	11.1 (3.8)*
34	F	8.5	9.7	10.5 (0.8)	10.4 (0.7)	10.8 (1.1)	10.6 (0.9)
35	F	8.5	10.7	12.0 (1.3)	12.9 (2.2)	13.0 (2.3)	12.3 (1.6)
36	M	6.0	7.7	9.2 (1.5)	11.5 (3.8)	11.8 (4.1)	11.6 (3.9)
	Mean		8.9	10.4 (1.5)	11.5 (2.7)	11.8 (3.0)	11.4 (2.6)

5b. $Q_L^{O_2}$

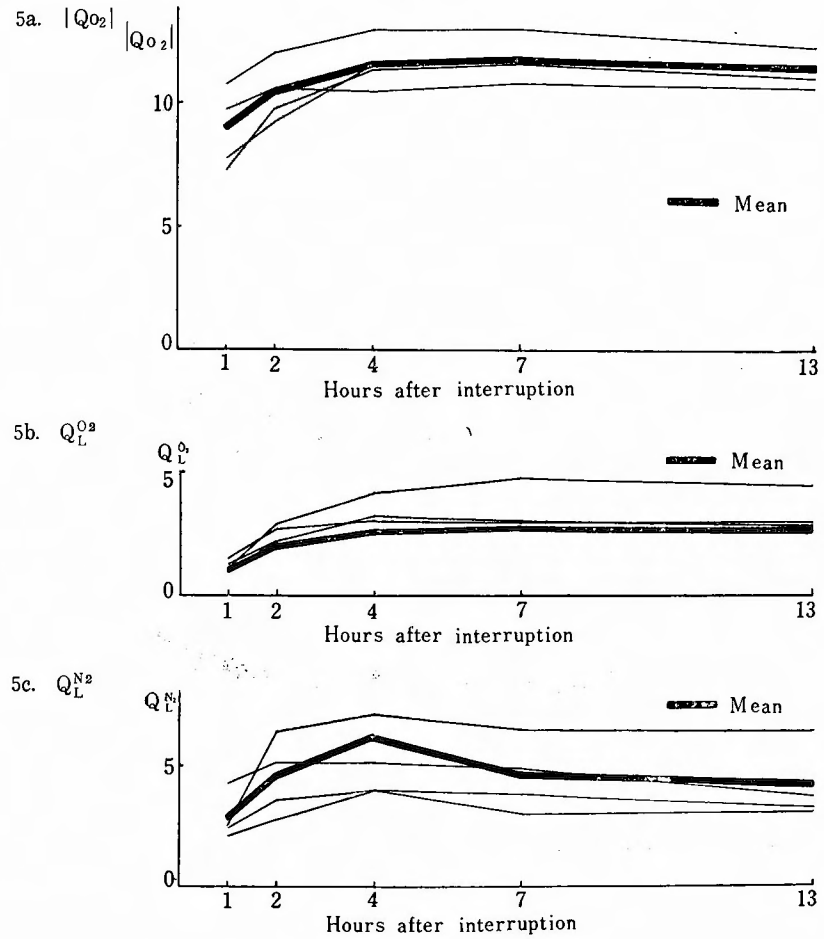
Dog No.		Hours after basal anesthesia				
		1	2	4	7	13
33		1.1	2.9 (1.8)	4.1 (3.0)	4.8 (3.7)	4.5 (3.4)
34		1.2	2.2 (1.0)	3.2 (2.0)	3.0 (1.8)	2.8 (1.6)
35		0.0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
36		1.5	2.8 (1.3)	3.0 (1.5)	3.0 (1.5)	2.9 (1.4)
	Mean	1.0	2.0 (1.0)	2.6 (1.6)	2.7 (1.8)	2.6 (1.6)

5c. $Q_L^{N_2}$

Dog No.		Hours after basal anesthesia				
		1	2	4	7	13
33		2.5	6.4 (3.9)	7.1 (4.6)	6.4 (3.9)	6.4 (3.9)
34		2.4	3.6 (1.2)	1.0 (1.6)	3.8 (1.4)	3.2 (0.8)
35		2.1	2.7 (0.6)	4.0 (1.9)	3.0 (0.9)	3.1 (1.0)
36		1.2	5.1 (0.9)	5.1 (0.9)	4.9 (0.7)	3.7 (−0.5)
	Mean	2.8	4.5 (1.7)	5.1 (2.3)	4.5 (1.7)	4.1 (1.6)

* Each bracketed value means the difference between the respective value 1 hour and 2, 4, 7 or 13 hours after basal anesthesia.

Fig. 5 The rate of respiration of liver slices after basal anesthesia in normal dogs. (administration of morphine)



The rate of respiration of liver slices was measured 1, 2, 4, 7 and 13 hours after the injection of morphine that approximately corresponded respectively before and 1, 3, 6 and 12 hours after the interruption in the experiment on occlusion of the hepatic artery.

a) |Qo| : The values at the 1st hour after the injection ranged from 7.3 to 10.7 with a mean value of 8.9. The values at the 2nd hour after the injection ranged from 9.2 to 12.0 with a mean value of 10.4. The differences between the values 1 hour and 2 hours after the injection ranged from 0.8 to 2.5 with a mean difference of 1.5. The values at the 4th hour after the injection ranged from 10.4 to 12.9 with a mean value of 11.5. The differences between the values 1 hour and 4 hours after the injection ranged from 0.7 to 4.0 with a mean difference 2.7. The values at the 7th hour after the injection ranged from 10.8 to 13.0 with a mean value of 11.8. The differences between the values 1 hour and 7 hours after the injection ranged from 1.1 to 4.3 with a mean difference of 3.0. The values at the 13th hour

after the injection ranged from 10.6 to 12.3 with a mean value of 11.4. The differences between the values 1 hour and 13 hours after the injection ranged from 0.9 to 3.9 with a mean difference of 2.6.

$|Qo_2|$ in every instance increased till 7 hours and then decreased slightly at the 13th hour after the injection.

b) $Q_{N_2}^{O_2}$: The values at the 1st hour after the injection ranged from 0.0 to 1.5 with a mean value of 1.0. The values at the 2nd hour after the injection ranged from 0.0 to 2.9 with a mean value of 2.0. The differences between the values 1 hour and 2 hours after the injection ranged from 0.0 to 1.8 with a mean difference of 1.0. The values at the 4th hour after the injection ranged from 0.0 to 4.1 with a mean value of 2.6. The differences between the values 1 hour and 4 hours after the injection ranged from 0.0 to 3.0 with a mean difference of 1.6. The values at the 7th hour after the injection ranged from 0.0 to 4.8 with a mean value of 2.7. The differences between the values 1 hour and 7 hours after the injection ranged from 0.0 to 3.7 with a mean difference of 1.8. The values at the 13th hour after the injection ranged from 0.0 to 4.5 with a mean value of 2.6. The differences between the values 1 hour and 13 hours after the injection ranged from 0.0 to 3.4 with a mean difference of 1.6.

$Q_{N_2}^{O_2}$ in 3 instances increased till 7 hours and then decreased slightly at the 13th hour after the injection. Every value in the other instance (Dog No. 35) was 0.0.

c) $Q_{N_2}^{N_2}$: The values at the 1st hour after the injection ranged from 2.1 to 4.2 with a mean value of 2.8. The values at the 2nd hour after the injection ranged from 2.7 to 6.4 with a mean value of 4.5. The differences between the values 1 hour and 2 hours after the injection ranged from 0.6 to 3.9 with a mean difference of 1.7. The values at the 4th hour after the injection ranged from 4.0 to 7.1 with a mean value of 5.1. The differences between the values 1 hour and 4 hours after the injection ranged from 0.9 to 4.6 with a mean difference of 2.3. The values at the 7th hour after the iniection ranged from 3.0 to 6.4 with a mean value of 4.5. The differences between the values 1 hour and 7 hours after the injection ranged from 0.7 to 3.9 with a mean difference of 1.7. The values at the 13th hour after the injection ranged from 3.1 to 6.4 with a mean value of 4.1. The differences between the values 1 hour and 13 hours after the injection ranged from -0.5 to 3.9 with a mean difference of 1.6.

$Q_{N_2}^{N_2}$ in every instance increased till 4 hours after the injection and thereafter decreased slightly.

These results showed that the respiration of liver tissue was depressed by basal anesthesia with morphine, and this effect, however, disappeared by 4 hours after the injection. Accordingly, the corrected values in the rate of respiration of liver slices due to the interruption of the hepatic artery can be shown as follows.

(The difference between the values before and after the interruption in the dog occluded the hepatic artery) — (The difference between the value at the 1st hour after the administration of morphine and that estimated later)

As shown in Table 6 and Figure 6 $|Qo_2|$ in both groups of penicillin treated

and non-treated dogs decreased markedly at the 1st hour after the interruption and increased slightly from 3 to 6 hours. Since then it decreased rapidly in dogs non-treated with penicillin, while in penicillin-treated dogs its decrease at the same stage was slight and the degree of the decrease at the 12th hour was equivalent to that at the 1st hour after the interruption. It can be said, therefore, that the disturbance in penicillin-treated dogs after the interruption was slighter than in dogs non-treated with penicillin.

$Q_L^{O_2}$ in both groups decreased at the 1st hour after the interruption, and thereafter in dogs non-treated with penicillin it continued to decrease gradually, while in penicillin-treated dogs it increased slightly at the 3rd hour after the interruption and then decreased again.

$Q_L^{N_2}$ in both groups decreased at the 1st hour after the interruption and thereafter in dogs non-treated with penicillin it increased slightly at the 3rd hour after the interruption and then decreased again, while in penicillin-treated dogs it continued to decrease gradually without increase.

In short, whether penicillin-treated or non-treated, after the interruption the decrease of Qo_2 was quite marked, while the decrease of $Q_L^{N_2}$ at the 1st hour after the interruption was extremely slight. And further, the decrease of either Qo_2 or $Q_L^{N_2}$ after the interruption in penicillin-treated dogs was slighter than that in dogs non-treated with penicillin.

5) The arterial pressure after interruption of the hepatic artery (Tab. 7, Fig. 7): In this experiment 3 of each group of dogs were used.

Table 6 Corrected values in the rate of respiration of liver slices after interruption of the hepatic artery.

6a. $|Q_{O_2}|$

Penicillin	Hours after interruption			
	1	3	5	12
Non-treated group	−4.0	−3.6	−3.7	−4.9
Treated group	−2.4	−1.8	−2.1	−2.3

6b. $Q_L^{O_2}$

Penicillin	Hours after interruption			
	1	3	6	12
Non-treated group	−2.1	−2.2	−2.3	−2.9
Treated group	−1.8	−1.3	−1.3	−1.9

6c. $Q_L^{N_2}$

Penicillin	Hours after interruption			
	1	3	6	12
Non-treated group	−1.0	−0.8	−1.2	−2.4
Treated group	−0.6	−1.5	−1.8	−2.3

Fig. 6 Corrected value in the rate of respiration of liver slices after interruption of the hepatic artery.
..... : Dog non-treated with penicillin —— : Dog treated with peniclin

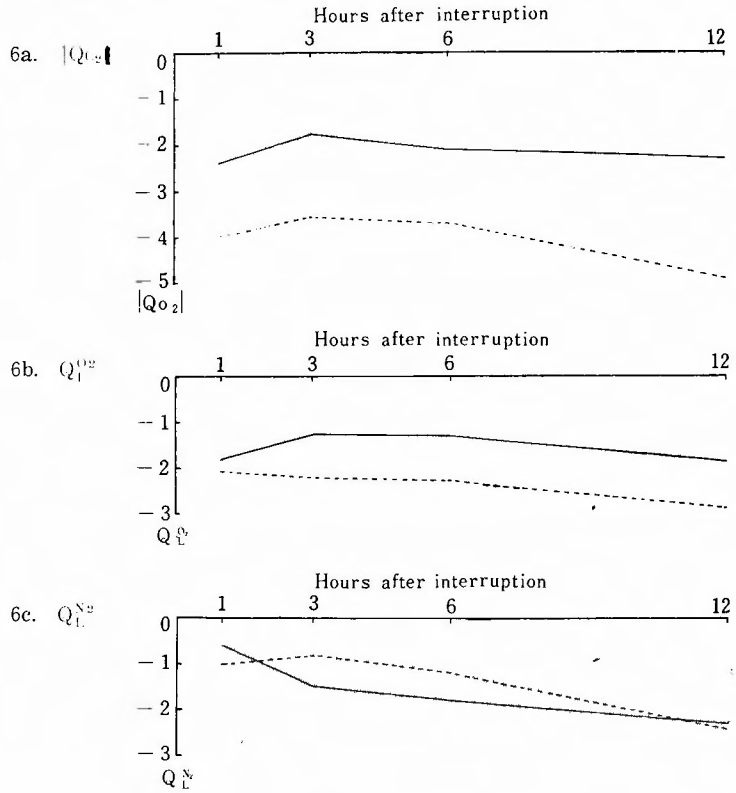
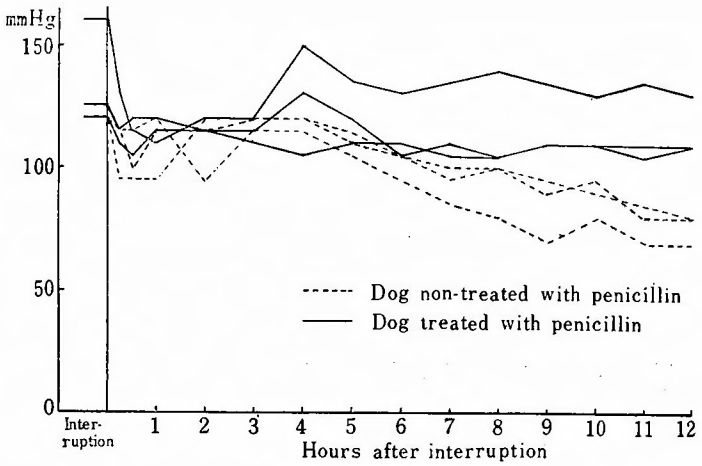


Table 7 Systolic arterial pressure after interruption of the hepatic artery.

Dog No.	Sex Weight (kg)	Before interr-uption	Hours after interruption													
			15m	30m	1h	2h	3h	4h	5h	6h	7h	8h	9h	10h	11h	12h
			Dogs non-treated with penicillin													
37	M 6.0	125	115	115	120	95	115	115	105	95	85	80	70	80	70	70
38	F 7.0	120	95	95	95	120	120	120	115	105	95	100	95	90	85	80
39	F 7.5	120	115	100	115	115	120	120	110	105	100	100	90	95	80	80
			Dogs treated with penicillin													
40	M 7.5	125	115	120	120	115	115	130	120	105	110	105	110	110	110	110
41	F 6.5	120	110	105	115	115	110	105	110	110	105	105	110	110	105	110
42	M 8.5	160	140	115	110	120	120	150	135	130	135	140	135	130	135	130

Fig. 7 Systolic arterial pressure after intierruption of the hepatic artery.



The systolic arterial pressure in both groups decreased 10 to 50 mmHg immediately after the interruption and then increased slightly 3 to 6 hours after the interruption. Since then in dogs non-treated with penicillin it decreased gradually and the values at the 12th hour after the interruption ranged from 70 to 80 mmHg, while the values in penicillin-treated dogs even at the 12th hour were still maintained as high as 110 to 130 mmHg.

Thus, by administration of 300,000 units of penicillin immediately after the interruption the rate of respiration of liver slices was maintained at a high level, and further the arterial pressure was kept stable without showing any decrease, and in consequence the pathophysiologic changes after the interruption in penicillin-treated dogs were slighter than in dogs non-treated with penicillin.

Ⅳ. DISCUSSION

Energy of cell action is obtained by glycolysis and respiration in vital organ, therefore the coefficient of respiration (Qo), the coefficient of aerobic glycolysis ($Q_L^{O_2}$) and the coefficient of anaerobic glycolysis ($Q_L^{N_2}$) measured with the WARBURG respirometer represent not only the degrees of glycolysis and respiration performed by intracellular enzymatic systems, but also interrelation of these two actions.

The fall of free energy entailed by glycolysis to lactic acid amounts to 50 to 60 Kcal per g mol of glucose and in this process two high-energy phosphate redicals are yielded, which corresponds to an energy-capture efficiency of about 40 per cent. While the fall of free energy entailed by complete oxidation of glucose, respiration, to carbon dioxide and water amounts to about 686 Kcal per g mol of glucose, and as a whole 38 high-energy phosphate radicals are yielded in this process, which corresponds to an energy-capture efficiency of about 60 per cent[13)36)]. In such a way by glycolytic reaction only a part of whole utilizable energy can be caught.

Under aerobic conditions lactic acid, the terminal product of glycolysis, decreased by PASTEUR effect and at the same time glycolysis itself is restrained. The regu-

lation between these two systems, however, is not always perfect in every tissue, and when it is imperfect, glycolysis proceeds to some extent even under aerobic coditions and lactic acid produced in this process, therefore, can be observed and summed up as an aerobic glycolysis.

By WAREURG, POSENER and NEGELEIN[54] it was reported that Q_{O_2}, $Q_L^{N_2}$ and $Q_L^{N_2}$ in the liver slices of the rat were approximately 11.6, 0.6 and 3.3 respectively. In normal dog Q_{O_2}, $Q_L^{N_2}$ and $Q_L^{N_2}$ were 11.4, 2.6 and 4.1 respectively showing a higher level in Q_{O_2} and $Q_L^{N_2}$ than those in the rat. (Tab. 5)

Every enzyme composing glycolytic system exists within the cell as a soluble protein and every respiratory enzyme exists, connecting with electron-transporting particles, within the mitochondria. Further, from the point of view of the evolution theory, an old system, the system of anaerobic glycolysis, and a system that is thought of recent origin, the respiratory system, coexist within the cell. Accordingly it is an important problem to investigate how these two systems that have both tectonic and genetic differences, relate functionally each other.

Under hypoxic state the respiration is depressed and the tissue tries to obtain energy by glycolysis and continuance of such a hypoxic state accelerate the pace of glucose consumption, and hence the enzyme activities in the energy metabolism are made tired and lowered in at an earlier stage. Further, a cell on dying from damages, or on changing into a connective tissue by enervation of metabolism, it is the respiration that is disturbed at first. That is, while the glycolysis maintains its function, the respiration become to be enfeebled[14].

The liver, in which the two blood flows through the hepatic artery and the portal vein are draining, performs complicated and important functions.

BARCROFT and SHORE[2], SCHWIEGK[43] and SINODA[47] observed that the liver in normal state utilized oxygen contained not only in hepatic arterial blood but also in portal venous blood.

SCHILLING, MCKEE and WILT[44] reported that dogs could survive by arterialization of portal blood through hepaticportal arterio-venous anastomosis, and then POPPER, JEFFERSON and NECHELES[41] found that a few hours after interruption of the hepatic artery intrahepatic arteriovenous communications were put into action and brought the portal blood to areas of the liver which normally only arterial blood had acess.

In the present experiments, regardless to the administration of penicillin or not, Q_{O_2} decreased earlier and more markedly than $Q_L^{N_2}$ after the interruption. And in penicillin-treated dogs Q_{O_2} continued to decrease since 24 hours after the interruption, while $Q_L^{N_2}$ preserved its value without falling. Therefore it can be said that the respiratory system suffers disturbances at an earlier stage and to a higher degree than the glycolytic system.

Hitherto, lack of arterial blood and anaerobic bacterial proliferation have been enumerated as the causes of death following interruption of the hepatic artery, and small amount of arterial inflow to the liver mainly through collateral vessels from the diaphragm, it has been thought, would prevent the development of these factors.

TANTURI, SWIGART and CANEPA[50], CHAU, GOLDBLOOM and GURD[6] and ISHIGURO[24]

reported that collateral vessels extensive enough to explain survival could not be observed within a short period following the interruption, and HONJO and his associates have been demonstrated that cause of death after interruption of the hepatic artery was hepatic anoxic-necrosis due to the disturbance of the portal blood flow after the interruption followed by proliferation of anaerobic bacillus, and that release of liver ferritin into the blood played a significant role in the disturbance of the portal blood flow.

Although developmental mechanism of the irreversible shock is obscure at present, two theories which have developed since World War Ⅱ, that are, SHORR's VDM[32)45)] theory and FINE's bacteria infection theory[8)9)], become noticed widely.

VDM is identified chemically and immunologically as ferritin and is elaborated by anoxia in the liver or the skeletal muscle. It is released principally from the liver in hemorrhagic shock and from the damaged muscle in traumatic shock, and consequently terminal vessels lose thir constrictor response to topically applied epinephrine, and in area which this process proceed blood stasis is caused and then it develops into irreversible shock. VDM is the only one which is directly related to the vascular phenomena[4)5)], and its biological properties are specifically related to the sulfhydryl groups of ferritin protein and ferrous iron at the surface of ferritin, which are formed by the reduction of ferric-disulfied-ferritin in the prolonged tissue hypoxia[32)].

Liver ferritin decreases to a marked degree not only in a hemorrhagic, a tourniquet and a leg-crushing shock and ileus[34)], but also after the interruption of the hepatic artery[28)27)]. SHORR[45)], moreover, reported that both the formation of VDM and the deterioration of the hepatic VDM inactivating mechanism took place simultaneously with the decrease of oxygen consumption.

FINE reported that in his experiments on hemorrhagic shock hypotension lasting for a long time made clostridium welchii proliferate in the liver, and then, through infection accompanied by metabolic disturbance, developed into irreversible shock and that by administration of a large dose of antibiotics before hemorrhage the occurrence of irreversible shock could be prevented.

The Welch-bacillus produces many kinds of endotoxin, one of which, κ-toxin, with collagenase action induces hemorrhage and necrosis to the tissue. Another of which, α-toxin, with lecithinase action operating upon lipid — a component of the red cell — and destructing it, induces hemorrhage. This α-toxin moreover, it is supposed, operates upon lipoprotein within the mitochondria and destroys the respiratory enzymes so that cellular function may become lowered. It has been demonstrated that the activity of lecithinase C was positive in ascitic fluid[50)] as well as in the liver[56)] of the dog dying after interruption of the hepatic artery.

While BAEZ and others[3)] described that a small amount of aureomycin acted upon enzymatic systems in liver cells in addition to antibiotic action.

It was reported that by administration of penicillin after interruption of the hepatic artery release of liver ferritin into the blood was prevented[28)37)] and further the activity of lecithinase C in the liver and ascites became negative[50)56)].

As mentioned above, bacterial proliferation and release of liver ferritin into the blood, both caused by hepatic hypoxia, are closely related to problems about the developmental mechanism of irreversible shock. And it has been accepted that the prevention of release of liver ferritin by the administration of penicillin may build a bridge over a difference between SHORR's and FINE's theories and as much can be applied well to effect of penicillin administration after the interruption of the hepatic artery.

FRASER and others[12] and EZE[7] observed that in most of the dogs that survived interruption of the hepatic artery by penicillin administration the disturbance in some degree took place in liver function, which recovered to normal state 9 to 14 days after the interruption, and Honjo and his associates also observed much the same result.

FRASER and others[12] as well as CHAU, GOLDBLOOM and GURD[6] had supposed that a certain adaptive mechanism existing during the period of penicillin administration after interruption of the hepatic artery might be related to the fate of those dogs, and in 1952 EZE found that by a single dose of 100,000 units of penicillin administered immediately after the interruption dogs could survive and he emphasized the significance of the defensive mechanism against the changes consequent upon interruption of the hepatic artery. Recently HONJO and his associates, paying their attention to the morphological and metabolic changes in the liver that occurred within a few hours following interruption of the hepatic artery, demonstrated that in dogs non-treated with penicillin after the interruption the disturbance of the intrahepatic portal circulation and elaboration of VDM took place in a way of vicious circle, and consequently hepatic anoxia proceeded to a higher degree and liver necrosis was resulted, and that penicillin administration could cut the chain of this vicious circle, and consequently the changes after interruption of the hepatic artery were reduced.

In such a way, effects of penicillin administered after interruption of the hepatic artery were certified, but it has not yet been demonstrated how penicillin prevents the release of liver ferritin and breaks the vicious circle above mentioned[37].

In order to investigate the active mechanism of penicillin in preventing the release of liver ferritin, the author measured the rate of respiration of the liver following elapse of time after the interruption of the hepatic artery in both groups of penicillin-treated and non-treated dogs.

$|Qo|$ in dogs non-treated with penicillin decreased to a marked degree after 6 hours following the interruption, while $|Qo$ in penicillin-treated dogs decreased slightly at an early stage after the interruption, since then it maintained stable a high level, and after 24 hours it began to decrease gradually. This process in penicillin-treated dogs was in remarkable contrast to that in non-treated dogs, and the difference between these two groups after 3 hours proved to be statistically significant, and increased with time.

$Q_L^{O_2}$ in both groups showed much the same tendency as $|Qo$, though the alteration of $Q_L^{O_2}$ in penicillin-treated dogs was slighter than that in dogs non-treated with

penicillin.

$Q_L^{N_2}$ in both groups decreased scarcely at an earlier stage following the interruption, and after several hours began to decrease gradually in accordance with decrease in Q_{O_2}. The difference between the two groups was not significant to be mentioned.

The experimental results just described reveal that first, the respiratory system becomes depressed to a higher degree and earlier than glycolytic system after the interruption of the hepatic artery, secondly, exygen consumption of liver slices in dogs non-treated with penicillin began to decrease within a short period after the interruption, and this decrease was prevented by the administration of penicillin, thirdly, effects of penicillin could be observed after 3 hours following the interruption. Additionally even in penicillin-treated dogs oxygen consumption of liver slices in the favorite site of the liver necrosis also decreased after 24 hours, but by this time hypoxie area of the liver was extremely localized and lessened, and this decrease of Q_{O_2} did not relate directly to the fate of dogs after the interruption of the hepatic artery.

Accordingly, it is assumed that under hypoxic environment after the interruption of the hepatic artery the liver tissue can maintain energy metabolism of high efficiency by the administration of penicillin, and consequently the liver tissue is exempted from rapid deterioration of metabolic equilibrium being restrained the release of liver ferritin.

V. SUMMARY AND CONCLUSIONS

In 38 normal dogs "the three arteries" — the common hepatic artery, the gastroduodenal artery and the right gastric artery were interrupted, 19 of which were administered with 300,000 units of penicillin intramuscularly immediately after the interruption.

In each of these 38 dogs, the rate of respiration of liver tissue was measueed by means of WARBURG respirometer, and the arterial pressure was also measured. The results were as follows.

1) Of dogs non-treated with penicillin, all instances died within 3 days after interruption of the hepatic artery.

2) Of 19 dogs treated with penicillin after the interruption, 12 dogs survived, and the mortality rate was reduced from 100 per cent to approximately 37 per cent.

3) Q_{O_2} in dogs non-treated with penicillin decreased markedly immediately after the interruption, then increased slightly and after 6 hours it decreased again rapidly. On the other hand, in dogs treated with penicillin the decrease of Q_{O_2} immediately after the interruption was slight and the following increase was rapid and maintained a high level since 3 hours till 24 hours after the interruption with following gradual decrease.

4) $Q_L^{O_2}$ in both groups increased temporarily after the interruption, then increased and thereafter decreased again, showing the similar course to that of Q_{O_2}. The fluctuation of $Q_L^{O_2}$, however, in penicillin-treated dogs was slighter than in non-

treated dogs.

5) $Q_{I}^{O_2}$ in both groups increased immediately after the interruption and after 1 to 3 hours began to decrease gradually, showing no significant difference between the two.

6) The arterial pressure decreased temporarily following the interruption of the hepatic artery and then slightly increased in both groups. Thereafter, in dogs non-treated with penicillin it decreased gradually, while in penicillin-treated dogs it remained stable.

7) Both respiration and glycolysis of the liver tissue were depressed by the interruption of the hepatic artery. The depression, however, in respiratory system took place earlier and to a higher degree, while that of glycolytic system was extremely slight at an early stage following the interruption. Notwithstanding hypoxic environment caused by the interruption of the hepatic artery, the liver tissue can be exempted from the deterioration of metabolic equilibrium by the administration of penicillin.

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肝動脈遮断後の肝組織呼吸に関する実験的研究

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肝流入動脈血流の遮断により犬は死亡し，その際肝に広範な壊死の存在することは Haberer (1907) の報告以来広く確認されてきた．しかるに1949年 Markowitz 等が肋動脈遮断後長期間，大量のペニシリン投与により多くの犬は生存し，肝壊死も軽度であることを発見してより肝動脈遮断後の肝変化，ペニシリン投与の効果につき多くの研究が行なわれてきている．

本邦においても本庄等は肝動脈遮断の病態生理につき系統的研究を行ない遮断後の門脈血行障害と肝フェリチンの血中遊離が肝動脈遮断後の犬の死亡の重要な原因であることを実証し，さらに遮断直後10万単位ペニシリン1回の投与により約70%の犬は生存し，遮断後の諸変化は軽減され遮断後早期よりペニシリン投与犬，無投与犬群間に著明な差が認められることを明らかにした．

著者は肝動脈遮断後のペニシリン投与の効果解明の一端としてワールブルグ検圧計により肝動脈遮断後の肝組織呼吸を経時的に測定しつぎの結果を得た．

実験方法：肝動脈遮断は総肝動脈，胃十二指腸動脈，右胃動脈の三動脈を二重に結紮，切離した．肝組織呼吸の測定は肝動脈遮断後の肝壊死好発部位である左下葉辺縁部より肝小片を逐次切離しワールブルグ新法により呼吸係数（$|Q_{O_2}|$），好気的解糖係数（$Q_L^{O_2}$），嫌気的解糖係数（$Q_L^{N_2}$），を測定した．ペニシリンは肝動脈遮断直後30万単位1回を筋注した．

実験成績

1) ペニシリン無投与犬は19頭にて肝動脈遮断後3

日以内に全例死亡した.

2) ペニシリン投与犬は19頭にて，うち12頭は生存し死亡率は37%であつた.

3) $|Q_{O_2}|$ はペニシリン無投与犬においては遮断後1時間にて著明に低下し，その後軽度に上昇し遮断6時間以後ふたたび急速に低下した．他方ペニシリン投与犬にては遮断後も殆ど低下することなく，ほぼ遮断前値に近い値を維持し24時間以後漸次低下した.

4) $Q_L^{O_2}$ は両群とも肝動脈遮断後一次的低下についで上昇し，その後ふたたび漸次低下した．しかしペリシリン投与犬における遮断後の $Q_L^{O_2}$ の変動は無投与犬の $Q_L^{O_2}$ の変動に比して軽度であつた.

5) $Q_L^{N_2}$ は両群とも遮断後上昇し，1～6時間以後漸次低下した.

6) 動脈圧は両群とも肝動脈遮断後一次的低下についで上昇したが，その後ペニシリン無投与犬においては漸次低下し，遮断後12時間値にて70～80mmHgに低下した．他方投与犬にては遮断後12時間値にても110～130mmHgを維持した.

7) 肝動脈遮断により肝の呼吸系は解糖系に比して早期より高度の障害をうけ，従つて $|Q_{O_2}|$ は著明に低下したが，$Q_L^{N_2}$ は遮断後早期においては殆んど低下することなく経過した．さらにペニシリン投与犬にては無投与犬に比して遮断後の $|Q_{O_2}|$ の低下は極めて軽度であり，従つて犬はペニシリン投与により肝動脈遮断後の急激なる代謝平衡の失調を免かれる.