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Studies on the Elimination of Catecholamine in the Dog's Liver in Vivo after the Administration of Adrenaline and Noradrenaline

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In dogs anesthetized with sodium pentobarbital, adrenaline and noradrenaline in the portal and hepatic vein were estimated by using a fluorimetric method after the administration of mixed each 100μg/kg of adrenaline and noradrenaline. Four groups of experiments were performed in the present study as follow; (1) Intact dogs (2) Carbon tetrachloride intoxicated dogs (CCl_4-dogs) (3) Chloroform intoxicated dogs ($CHCl_3$-dogs) (4) Dogs with obstructive jaundice due to common bile duct ligation (Jaundice dogs)

In intact dogs, the reduction rate of catecholamine in the liver 1 minute after the administration of adrenaline and noradrenaline was over 70.1% for adrenaline and 56.1% for noradrenaline. Then the reduction rate of adrenaline was higher than that of noradrenaline. The content of catecholamine was markedly reduced at 3 minutes, and the reduction rate was less at 3 minutes than at 1 minute.

In dogs with severe damaged liver such as CCl_4-dogs and $CHCl_3$-dogs, the reduction rate of catecholamine in the liver was lowered markedly about 10 to 30%, and a highly significant difference was found between this group and intact group. In jaundice dogs with the moderate damaged liver, the figure was between the above two groups.

Levels of S-GOT and S-GPT were inversely proportional to the reduction rate of adrenaline and noradrenaline in the liver.

In intact dogs the glucose from the liver began to release between 1 and 3 minutes after the catecholamine infusion and showed as peak at 7 minutes. On the other hand, in CCl_4-dogs and $CHCl_3$-dogs the glucose output from the liver was not occured. In jaundice dogs the glucose output from the liver was found, but less than in intact dogs.

It is concluded that the liver would reduce a large amount of adrenaline and noradrenaline and the reduction rate would vary in proportion to the degree of damage to the liver.

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INTRODUCTION

Many investigators have studied the liver as an important organ to inactivate catecholamine, since ATHANASIU and LANGLOIS[1] showed that the effect of intravenously injected extract of suprarenal medulla on the blood pressure was prolonged considerably when the liver was excluded from the circulation.

PHILPOT and CANTONI[14] demonstrated that adrenaline injected into the portal vein raised the blood pressure to a much smaller degree than when injected into the jugular vein. In order to achieve a rise of blood pressure when making the injection into the portal vein, a 4 to 5 times larger amount of adrenaline is needed if it is injected into the femoral vein, while a 10 times larger amount is required in TANI's[19] early experiment.

Recently, in order to study the role of the liver in the metabolic inactivation of circulating adrenaline and noradrenaline, HERTTING et al.[11] and HAZELRIG et al.[10] observed the metabolites of dl−7− epinephrine-H^3 and dl-norepinephrine-C^{14} in the bile and urine of rats following their administration.

However, there have been no investigations with relation to the elimination of catecholamine in the liver by means of the determination of the content of adrenaline and noradrenaline in portal and hepatic venous blood after the administration of catecholamine in vivo.

In the present study, the amount of adrenaline and noradrenaline in plasma of portal and hepatic venous blood after the administration of a large amount of adrenaline and noradrenaline was fluorimetrically determined at timed intervals, in order to find the amount of adrenaline and noradrenaline before and after passing through the liver, and the reduction rate of these two substances in the intact and damaged liver.

MATERIALS AND METHODS

47 adult mongrel dogs of both sexes, weighing from 10 to 15 kg, were used in the present study. The animals were anesthetized by intravenous injection of 25mg/kg of sodium pentobarbital (Nembutal, Abbott).

In order to collect the blood samples, the catheterization of the portal vein was done by using a small polyethylene tube through an abdominal approach, and the catheterization of the hepatic vein was

done in the left common hepatic vein by the method of Shoemaker et al.[18]. Heparin solution in a dose of 1000 U/1 ml was used as an anti-coaglant. As a rule, observations were started about one hour after the operation.

Mixed each 100μg/kg of adrenaline and noradrenaline (Sankyo-Seiyaku Co,) was injected into the femoral vein in 5 to 7 seconds. 5 to 8 ml of portal and hepatic venous blood for estimation of adrenaline and noradrenaline were taken in the portal and hepatic vein at 1 minute and 3 minutes intervals following the administration of catecholamine.

Blood samples were immediately centrifuged for 10 minutes at 3000 r. p. m., and 1 ml of plasma was mixed with 1 ml of sodium fluolide-sodium thiosulphate solution according to WEIL-MALHERBE and BONE.[20] Then, the fluorimetric method of EULER and LISHAJKO[6] was applied for determination of adrenaline and noradrenaline. Fluorometry was carried out using a Farrand Fluorometer (Model A).

The following caluculation was made to obtain an approximate value for the reduction rate of adrenaline and noradrenaline in the liver;

$$\text{P-H \% decrease} = \frac{(P-H)}{P} \times 100$$

P; Plasma catecholamine content in the portal vein.
H; Plasma catechlamine content in the hepatic vein.

The concentration of glucose in portal and hepatic venous blood before and 1,3,7,10, and 15 minutes after the injection of adrenaline and noradrenaline was estimated by the method of HAGEDORN and JENSEN.[9]

Hepatic temperature before and after the injection of catecholamine was measured at timed intervals by using Jintan Electro Clinical Thermometer (Model H-1).

Experiments were performed on four groups of dogs in the present study; (1) Intact dogs (2) Carbon tetracloride intoxicated dogs which had been injected 3 times with 1 ml/kg body weight of 50% CCl_4 olive oil solution at 3 day intervals intramuscularly and used in expriments at 2 days after the last injection (CCl_4-dogs). (3) Chloroform intoxicated dogs which had been injected 2 times with 1 ml/kg of 25% $CHCl_3$ olive oil solution at 3 day intervals intramuscularly and used in experiments on the day after the last injection ($CHCl_3$-dogs). (4) Jaundice dogs which had been used in experiments 10 days after the common bile duct ligation (Jaundice dogs).

Levels of serum glutamic oxalacetic transaminase (S-GOT) and serum glutamic pyruvic transaminase (S-GPT) were estimated by the method of REITMANN and FRANKEL[15] with Hitachi Spectrophotometer.

After the experiments the liver was fixed with 10% formaline, stained with hematoxylin-eosin, then the grade of the damaged liver was confirmed.

RESULTS

Intact dogs

After the administration of mixed each 100 μg/kg of adrenaline and noradrenaline the content of adrenaline and noradrenaline in plasma of portal venous, hepatic venous and femoral arterial blood and levels of S-GOT and S-GPT in 15 dogs are summarized in Table 1.

Plasma catecholamine content in portal venous blood 1 minute after the administration of catecholamine was 31～109 μg/dl for adrenaline and 31～125 μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 55.7±5.9 μg/dl (mean±standard error of the mean) and 73.5±7.4 μg/dl respectively. Plasma catecholamine content in hepatic venous blood 1 minute after the administration of catecholamine was 2～29 μg/dl for adrenaline and 11～53 μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 15.5±1.8 μg/dl and 32.0±3.3 μg/dl respectively. The average value of P-H% decrease was 70.1±2.9% for adrenaline and 56.1±2.3% for noradrenaline and there was statistically a highly significant difference between those of adrenaline and noradrenaline ($p<0.01$) (Fig.3). On the other hand, plasma catecholamine content in femoral arterial blood 1 minute after the administration of catecholamine in 5 cases was 37～121 μg/dl for adrenaline and 46～142 μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 70.0±15.3 μg/dl and 91.4±18.9 μg/dl respectively. Plasma content of adrenaline and noradrenaline in the femoral artery was higher than those of the portal vein in all cases.

At 3 minutes after the administration of catecholamine, plasma catecholamine content in portal venous, hepatic venous and femoral arterial blood was remarkably decreased, and plasma catecholamine content in portal venous blood was 7～25 μg/dl for adrenaline and 9～38 μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 13.0±1.3 μg/dl and 20.2±2.1 μg/dl respectively. In the hepatic vein, plasma catecholamine content was 1～12 μg/dl for adrenaline and 3～20 μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 4.2±0.9 μg/dl and 9.8±1.3 μg/dl respectively. The average value of P-H% decrease was 63.8±6.6% for adrenaline and 51.6±4.7% for noradrenaline.

As a typical experiment is shown in Fig. 1, the glucose concentration in portal and hepatic venous blood was changed following the administration of adrenaline and noradrenaline. The glucose output from the liver was not found within 1 minute after the catecholamine infusion,

Table 1. Summary of plasma catecholamine content in portal venous, hepatic venous and femoral arterial blood of intact dogs after the administration of mixed each 100 μg/kg of adrenaline and noradrenaline.

Exp.No. and sex	Body weight (kg)	Plasma catecholamine content (μg/dl) after the administration of adrenaline and noradrenaline.										S-GOT	S-GPT
		1 min.						3 min.					
		F		P		H		F		P		H			
		A	N	A	N	A	N	A	N	A	N	A	N		
1 ♂	11.5	45	79	44	60	13	22	18	25	13	17	3	10	25	27
2 ♀	13.5	121	142	80	105	26	50	26	34	12	30	11	12	5	36
3 ♀	15.0	86	61	65	93	21	27	23	16	11	13	3	7	18	50
4 ♂	14.8	37	46	36	38	18	18	8	10	7	9	1	3	36	39
5 ♂	10.2	61	129	48	92	11	42	18	21	15	17	4	12	23	9
6 ♂	12.3			51	57	16	20			7	10	1	4	20	44
7 ♂	14.0			54	73	19	28			12	18	5	12	38	25
8 ♀	12.6			60	77	16	47			18	31	2	15	25	10
9 ♀	12.0			31	60	9	28			13	15	1	4	1	30
10 ♂	11.3			38	54	10	25			11	18	3	4	30	19
11 ♀	10.8			96	121	20	47			10	22	8	11	8	35
12 ♂	13.0			40	48	11	29			11	38	3	13	18	17
13 ♂	10.5			43	69	12	33			25	22	2	20	38	6
14 ♀	11.0			41	31	2	11			8	15	4	6	17	27
15 ♂	14.1			109	125	29	53			22	28	12	14	3	13
Mean±s.e	A	70.0±15.3		55.7±5.9		15.6±1.8		18.6±3.1		13.0±1.3		4.2±0.9			
	N	91.4±18.9		73.5±7.4		32.0±3.5		21.2±4.7		20.2±2.1		9.8±1.3			
P-H% decrease	A			70.1±2.9						63.8±6.6					
	N			56.1±2.3						51.6±4.7					

A; Adrenaline
N; Noradrenaline
F; Femoral artery
P: Portal vein
H; Hepatic vein

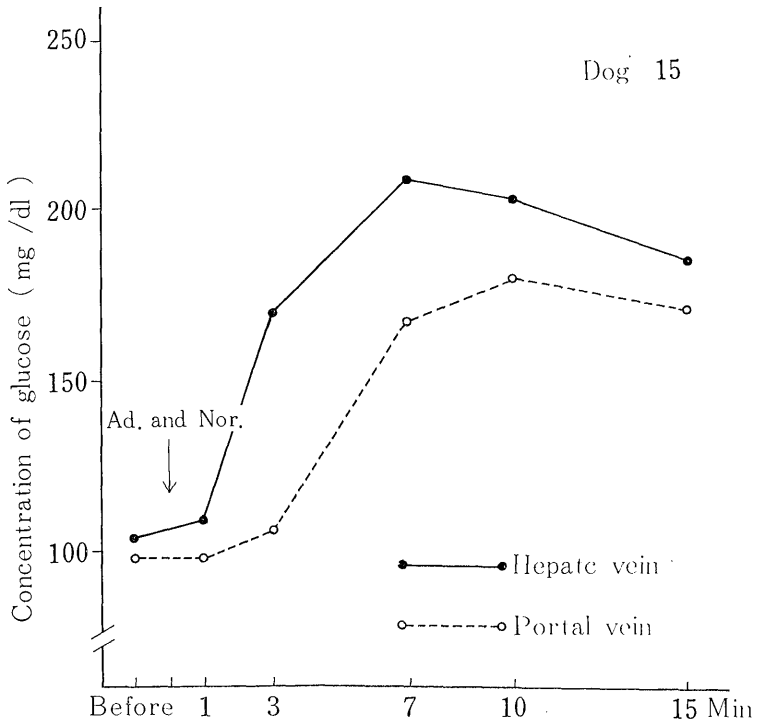
s.e; Standard error of the mean

$$\text{P-H \% decrease} = \frac{(P\text{-}H)}{P} \times 100$$

but the liver began to release the glucose 1 minute later. The glucose concentration in hepatic venous blood was 104 mg/dl before injection. It was rapidly increased to 170 mg/dl at 3 minutes and 208 mg/dl as peak at 7 minutes. On the other hand, the elevation of the glucose concentration in portal venous blood was later than that of hepatic venous blood and reached its peak at 180 mg/dl 10 minutes after the catecholamine infusion.

In all cases liver temperature was between 37.1°C and 39.3°C, showing an increase of 0.5°C within 3 minutes after the catecholamine infusion. Levels of S-GOT and S-GPT were observed under 50 U in all intact dogs.

Fig. 1. The glucose output from the liver after the administration of mixed each 100μg/kg of adrenaline and noradrenaline in the intact dog.



Carbon tetrachloride intoxicated dogs (CCl_4-dogs)

After the administration of mixed each 100 μg/kg of adrenaline and noradrenaline the content of adrenaline and noradrenaline in plasma of portal and hepatic venous blood and levels of S-GOT and S-GPT in 13 CCl_4-dogs are summarized in Table 2.

Plasma catecholamine content in portal venous blood 1 minute after the administration of catecholamine was 27～96 μg/dl for adrenaline and 40～144 μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 58.8±6.5 μg/dl and 79.8±2.2 μg/dl respectively. Plasma catecholamine content in hepatic venous blood 1 minute after the administration of catecholamine was 21～96μg/dl for adrenaline and 26－123 μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 47.3±6.3 μg/dl and 65.5±8.1μg/dl respectively. The average value of P-H% decrease was 20.7±3.1% for adrenaline and 18.7±3.1% for noradrenaline and a highly significant difference was found between P-H % decrease of intact dogs and CCl_4-dogs (adrenaline; $P<0.01$, noradrenaline; $P<0.01$) (Fig. 3).

At 3 minutes after the administration of catecholamine, plasma catecholamine content in portal venous blood was 6～40 μg/dl for adrenaline and 10～54 μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 19.9±2.7 μg/dl and 25.5±3.7 μg/dl

Table 2 Summary of plasma catecholamine content in portal and hepatic venous blood of CCl_4-intoxicated dogs after the administration of mixed each 100 μg/kg of adrenaline and noradrenaline.

Exp. No. and sex	Body weight (kg)	Plasma catecholamine content (μg/dl) after the administration of adrenaline and noradrenaline.								S-GOT	S-GPT
		1 min.				3 min.					
		P		H		P		H			
		A	N	A	N	A	N	A	N		
16 ♂	11.0	66	82	39	60	13	25	17	22	640	800
17 ♂	10.5	53	79	48	80	19	19	10	16	1600<	1200<
18 ♀	12.8	90	113	74	98	24	28	24	27	1600<	1200<
19 ♂	13.6	63	130	51	104	30	42	31	38	1040	1200<
20 ♂	12.0	72	99	68	66	22	36	18	36	1600<	1200<
21 ♀	10.2	29	43	23	34	7	13	7	10	1400	1200<
22 ♀	10.5	27	70	21	60	20	25	11	13	800	960
23 ♂	11.2	40	57	34	56	16	36	6	30	1600	1200<
24 ♂	10.0	49	50	31	38	14	20	13	29	656	1080
25 ♂	13.8	84	77	61	68	19	11	19	9	720	1200<
26 ♂	13.7	31	40	23	26	6	10	4	10	920	880
27 ♀	13.5	65	53	47	38	10	12	8	9	840	1056
28 ♂	10.3	96	144	96	123	40	54	23	51	1600<	1200<
Mean±s.e A		58.8±6.5		47.3±6.3		19.9±2.7		14.7±2.2			
N		79.8±9.2		65.5±8.1		25.5±3.7		23.1±3.7			
P-H% decrease A		20.7±3.1				24.5±6.3					
N		18.7±3.1				10.2±5.8					

A; Adrenaline
N; Noradrenaline
P; Portal vein
H; Hepatic vein

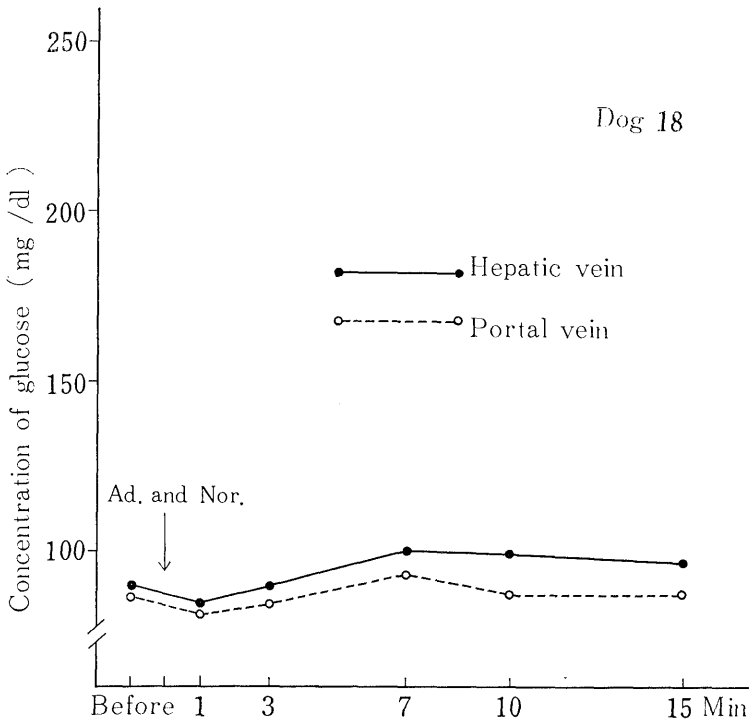
s.e; Standard error of the mean

$$\text{P-H \% decrease} = \frac{(P-H)}{P} \times 100$$

respectively. In hepatic venous blood, plasma catecholamine content was 4~31μg/dl for adrenaline and 95~51 μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 14.7±2.2 μg/dl and 23.1±3.7 μg/dl respectively. The average value of P-H% decrease was 24.5±6.3% for adrenaline and 10.2±5.8% for noradrenaline and there was a highly significant difference between P-H% decrease of intact dogs and CCl_4-dogs (adrenaline; $P<0.01$, noradrenaline; $p<0.01$) (Fig. 4).

As a typical experiment is shown in Fig.2, the glucose output from the liver was not almost found after the catecholamine infusion. In CCl_4-dogs liver temperature was between 37.5°C and 39.6°C, showing the increase of 0.4°C within 3 minutes after the catecholamine infusion. Serum transaminase levels were remarkably increased; S-GOT was over 640 U and S-GPT was over 800 U. Histologically the liver cell showed central fatty degeneration and slight necrosis(Photo.1).

Fig. 2. The glucose output from the liver after the administration of mixed each 100μg/kg of adrenaline and noradrenaline in the CCl_4-intoxicated dog.



Chloroform intoxicated dogs ($CHCl_3$-dogs)

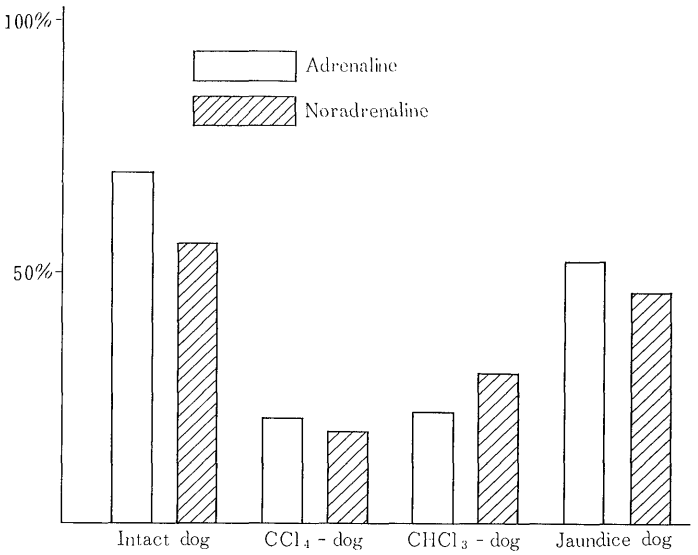
Results in $CHCl_3$-dogs were almost similar to those of CCl_4-dogs.

After the administration of mixed each 100μg/kg of adrenaline and noradrenaline the content of adrenaline and noradrenaline in plasma of portal and hepatic venous blood and levels of S-GOT and S-GPT in 10 $CHCl_3$-dogs are summarized in Table 3.

Plasma catecholamine content in portal venous blood 1 minute after the administration of catecholamine was 32~100 μg/dl for adrenaline and 46~114 μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 60.8±6.5μg/dl and 74.5±5.8μg/dl respectively. Plasma catecholamine content in hepatic venous blood 1 minute after the administration of catecholamine was 21~95 μg/dl for adrenaline and 30~102 μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 46.5±7.0μg/dl and 53.2±6.6 μg/dl respectively. The average value of P-H% decrease was 22.5±6.9% for adrenalinie and 30.0±3.7% for noradrenalne. There was a highly significant difference between those of intact dogs and $CHCl_3$-dogs (adrenaline; $P<0.01$, noradrenaline; $P<0.01$) (Fig. 3).

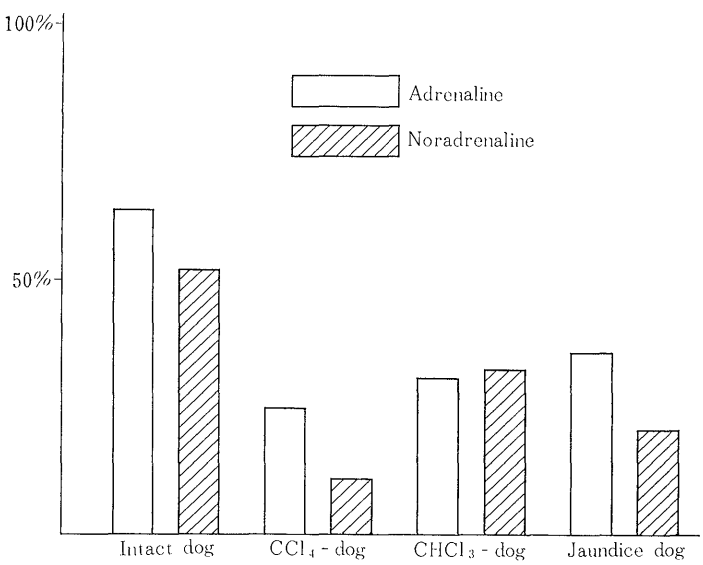
At 3 minutes after the administration of catecholamine, plasma catecholamine content in portal venous blood was 7~42 μg/dl for adrenal-

Fig. 3. P−H% decrease of adrenaline and noradrenaline in the liver of dogs 1 minute after the administration of mixed each 100μg/kg of adrenaline and noradrenaline.



Difference between Ad. and Norad.	P < 0.01								
Difference between Intact group and other groups	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.05			

Fig. 4. P−H% decrease of adrenaline and noradrenaline in the liver of dogs 3 minutes after the administration of minxed each 100μg/kg of adrenaline and noradrenaline



Difference between Intact group and other groups	P < 0.01	P < 0.01	P < 0.01	P < 0.01	N. S	N. S

Table 3. Summary of plasma catecholamine content in portal and hepatic venous blood of $CHCl_3$-intoxicated dogs after the administration of mixed each 100μg/kg of adrenaline and noradrenaline.

Exp. No. and sex	Body weight (kg)	Plasma catecholamine content (μg/dl) after the administration of adrenaline and noradrenaline.								S-GOT	S-GPT
		1 min.				3 min.					
		P		H		P		H			
		A	N	A	N	A	N	A	N		
29 ♀	10.0	100	114	95	102	42	48	39	40	1600<	1200<
30 ♀	10.2	46	60	42	42	18	31	12	24	1600<	1200<
31 ♂	11.5	82	89	59	64	29	35	24	28	1136	1120
32 ♀	14.0	68	64	63	36	16	20	14	16	1600<	1200<
33 ♂	13.6	42	72	21	36	24	24	11	15	936	792
34 ♂	12.2	74	72	30	48	16	19	13	13	856	760
35 ♀	12.4	32	46	32	30	7	10	3	6	1600<	1200<
36 ♂	12.0	56	68	54	58	12	13	7	7	1600<	1200<
37 ♂	14.5	58	75	27	54	10	13	6	5	800	848
38 ♂	10.8	50	85	42	62	8	22	6	16	1600<	980
Mean±s.e A		60.8±6.5		46.5±7.0		18.2±3.4		13.5±3.4			
N		74.5±5.8		53.2±6.6		23.5±3.7		17.0±3.5			
P-H% decrease A		22.5±6.9				30.7±5.5					
N		30.0±3.7				32.3±4.5					

A; Adrenaline
N; Noradrenaline
P; Portal vein
H; Hepatic vein

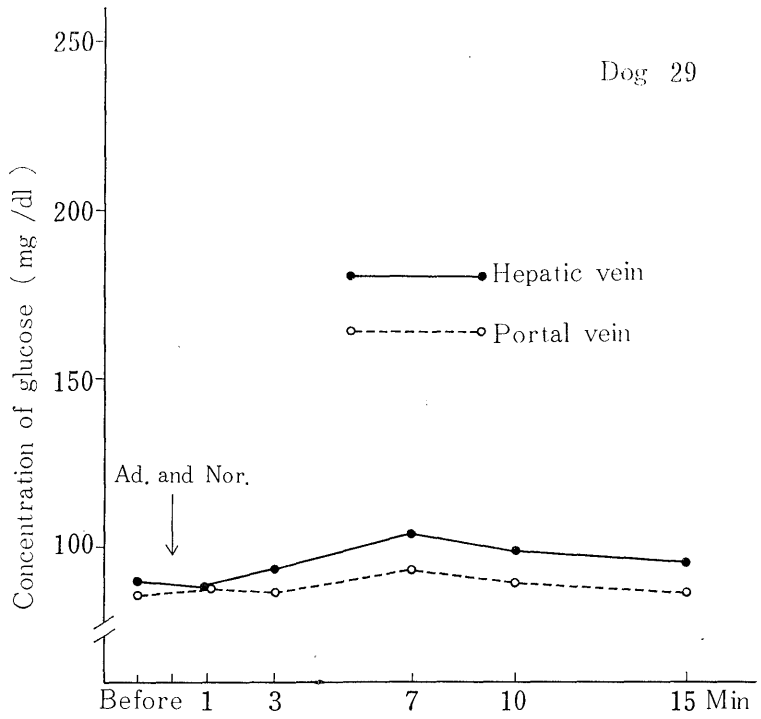
s.e; Standard error of the mean

$$\text{P-H \% decrease} = \frac{(P-H)}{P} \times 100$$

ine and 10~48 μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 18.2±3.4μg/dl and 23.5±3.7μg/dl respectively. Plasma catecholamine content in hepatic venous blood was 3~39μg/dl for adrenaline and 5~40 μg/dl for noradrenline, the average values of adrenaline and noradrenaline being 13.5±3.4μg/dl and 17.0±3.5μg/dl respectively. The average value of P-H% decrease was 30.7±5.5% for adrenaline and 32.3±4.5% for noradrenaline and there was a highly significant difference between P-H% decrease of intact dogs and $CHCl_3$-dogs (adrenaline; $P<0.01$, noradrenaline; $P<0.01$) (Fig. 4).

As a typical experiment is shown in Fig.5, the glucose output from the liver was almost not found after the catecholamine infusion as in CCl_4-dogs. Liver temperature in $CHCl_3$-dogs was between 37.7C° and 40.5 °C, showing the increase of 0.3°C within 3 minutes after the catecholamine infusion. Serum transaminase levels were remarkably increased; S-GOT was over 800 U and S-GPT was over 760 U. Histologically the liver cell showed central fatty degeneration and slight necrosis (Photo.2).

Fig. 5. The glucsse output from the liver after the administration of mixed each 100μg/kg of adrenaline and noradrenaline in the $CHCl_3$-intoxicated dog.



Dogs with obstructive jaundice due to common bile duct ligation (Jaundice dogs)

After the administration of mixed each 100μg/kg of adrenaline and noradrenaline the content of adrenaline and noradrenaline in plasma of portal and hepatic venous blood and levels of S-GOT and S-GPT in 9 jaundice dogs are summarized in Table 4.

Plasma catecholamine content in portal venous blood 1 minute after the administration of catecholamine was 26~92μg/dl for adrenaline and 45~129μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 58.2±7.8 μg/dl and 82.7±8.8μg/dl respectively. Plasma catecholamine content in hepatic venous blood 1 minute after the administration of catecholamine was 11~51 μg/dl for adrenaline and 19~72μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 28.2±4.7μg/dl and 44.1±5.1μg/dl respectively. The average value of P-H% decrease was 52.3±3.3% for adrenaline and 46.6±2.7% for noradrenaline and a highly significant difference was found between P-H% decrease of intact dogs and jaundice dogs ($P<0.01$, $P<0.05$, respectively) (Fig. 3).

At 3 minutes after the administration of catecholamine, plasma catecholamine content in portal venous blood was 5~31μg/dl for adrenaline and 5~36 μg/dl for noradrenaline, the average values of ad-

Table 4. Summary of plasma catecholamine content in portal and hepatic venous blood of dogs with obstructive jaundice after the administration of mixed each 100μg/kg of adrenaline and noradrenaline.

Exp. No. and Sex	Body weight (kg)	Palasma catecholamine content (μg/dl) after the administration of aerenaline noradrenaline.								S-GOT	S-GOT
		1min.				3min.					
		P		H		P		H			
		A	N	A	N	A	N	A	N		
39 ♂	13.2	26	49	14	28	5	28	1	9	1032	1200<
40 ♀	10.8	85	89	46	55	22	36	18	36	1560	600
41 ♂	11.5	51	99	17	44	9	18	2	16	288	568
42 ♂	14.0	75	78	31	40	15	9	21	9	488	460
43 ♀	10.4	37	99	22	49	17	5	11	1	760	1200<
44 ♀	10.1	34	45	11	19	—	—	—	—	540	698
45 ♂	12.6	92	129	51	72	31	8	18	8	632	880
46 ♀	12.3	66	91	35	46	19	23	12	26	816	632
47 ♂	12.6	58	65	27	44	—	—	—	—	640	810
Mean±s.e A		58.2±7.8		28.2±4.7		16.9±3.2		11.9±3.0			
N		82.7±8.8		44.1±5.1		18.1±4.4		15.0±4.6			
P-H% decrease A		52.3±3.3				35.7±15.3					
N		46.6±2.7				20.9±14.0					

A; Adrenaline
N; Noradrenaline
P; Portal yein
H; Hepatic vein

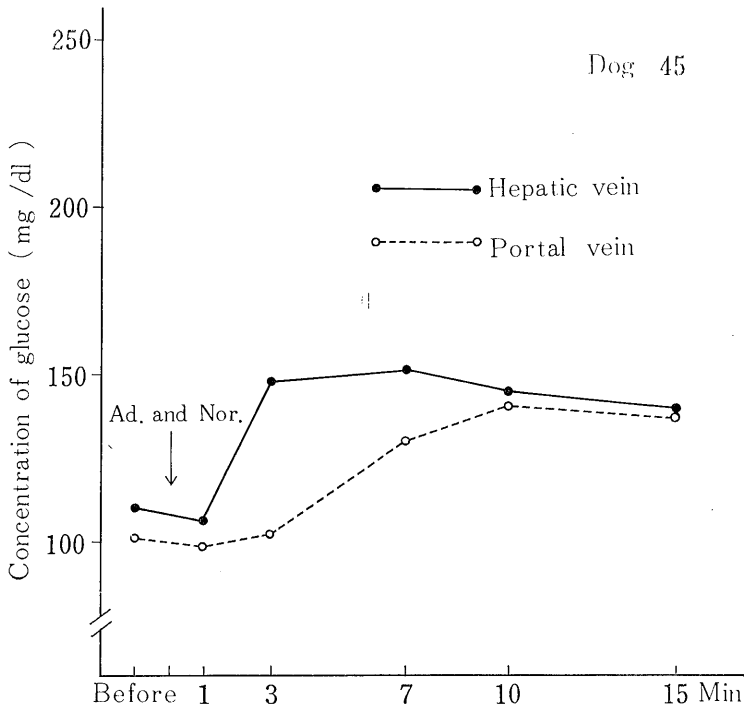
s.e; Standard error of the mean

P-H % decrease $= \frac{(P-H)}{P} \times 100$

renaline and noradrenaline being 16.9±3.2 μg/dl and 18.1±4.4μg/dl respectively. In hepatic venous blood, plasma catecholamine content was 1~21 μg/dl for adrenaline and 1~36μg/dl for noradrenaline, the average values of adrenaline and noradrenaline being 11.9±3.0μg/dl and 15.0± 4.6μg/dl respectively. The average value of P-H% decrease was 35.7 ±15.3% for adrenaline and 20.9±14.0% for noradrenaline.

As a typical experiment is shown in Fig. 6, the glucose output from the liver was not found within 1 minute after the catecholamine infusion, but the liver began to release the glucose 1 minute later. It showed a similar pattern to intact dogs, but the glucose concentration in portal and hepatic venous blood of jaundice dogs was less elevated than that of intact dogs. Liver temperature was between 37.1°C and 38.8°C, showing the increase of 0.5°C within 3 minutes after the catecholamine infusion, which was the same pattern of change as in the above two groups. Histologically the liver showed congestion in the sinusoid, but the degeneration and necrosis in the liver cell could not clearly be found (Photo.3).

Fig. 6. The glucose output from the liver after the administration of mixed each 100μg/kg of adrenaline and noradrenaline in the dog with obstructive jaundice.



Correlation between P-H% decrease and serum transaminase levels

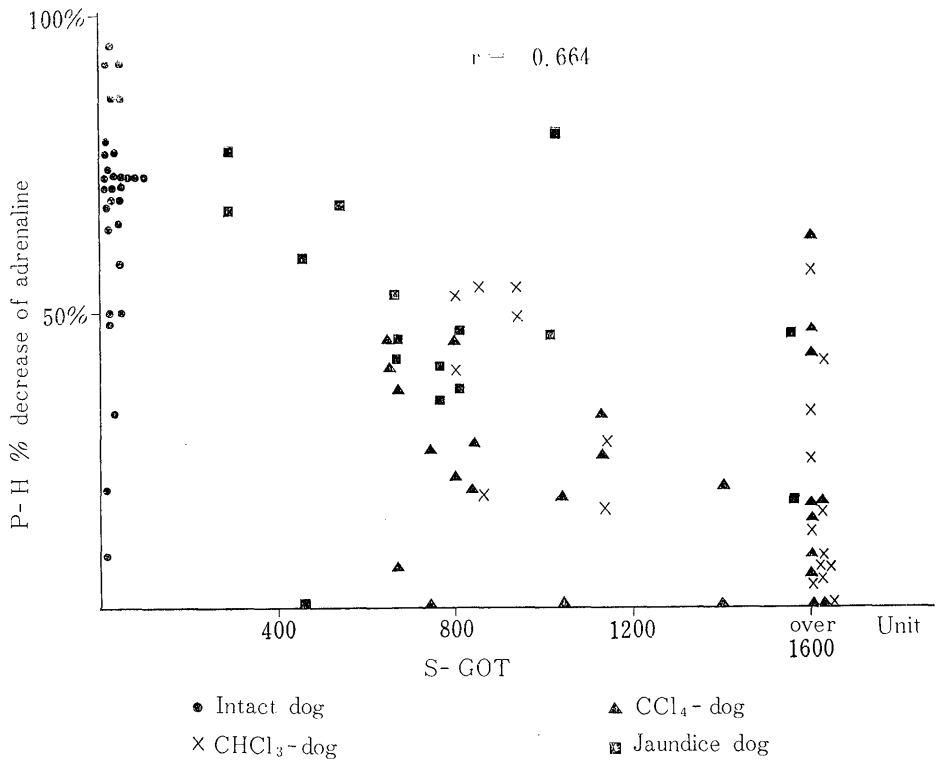
Correlation between P-H% decrease and serum transaminase levels as in Fig. 7~10, such as S-GOT levels and P-H% decrease of adrenaline, S-GOT levels and those of noradrenaline, S-GPT levels and those of adrenaline, and S-GPT levels and those of noradrenaline, were shown in inverse correlation in the present study ($r=-0.664$, $r=-0.555$, $r=-0.672$, $r=-0.563$,) (Fig. 7,8,9,10.).

DISCUSSION

It has been well established that the liver is an important organ to inactivate catecholamine[1,2,3,4,5,7,10,11,13,14,19]. This was confirmed in vivo more directly in the present study by using a fluorimetric method.

In this study, neither the content of catecholamine in the hepatic artery nor blood flow of portal vein and hepatic artery was measured, but the catecholamine content of femoral arterial blood was not less than that of portal venous blood. It is assured that, when the amount of adrenaline being 55.7 ± 5.9μg/dl and noradrenaline being 73.5 ± 7.4μg/dl in plasma of portal venus blood, adrenaline and norad-

Fig. 7. Correlation between P−H% decrease of adrenaline after the administration of catecholamine and S-GOT

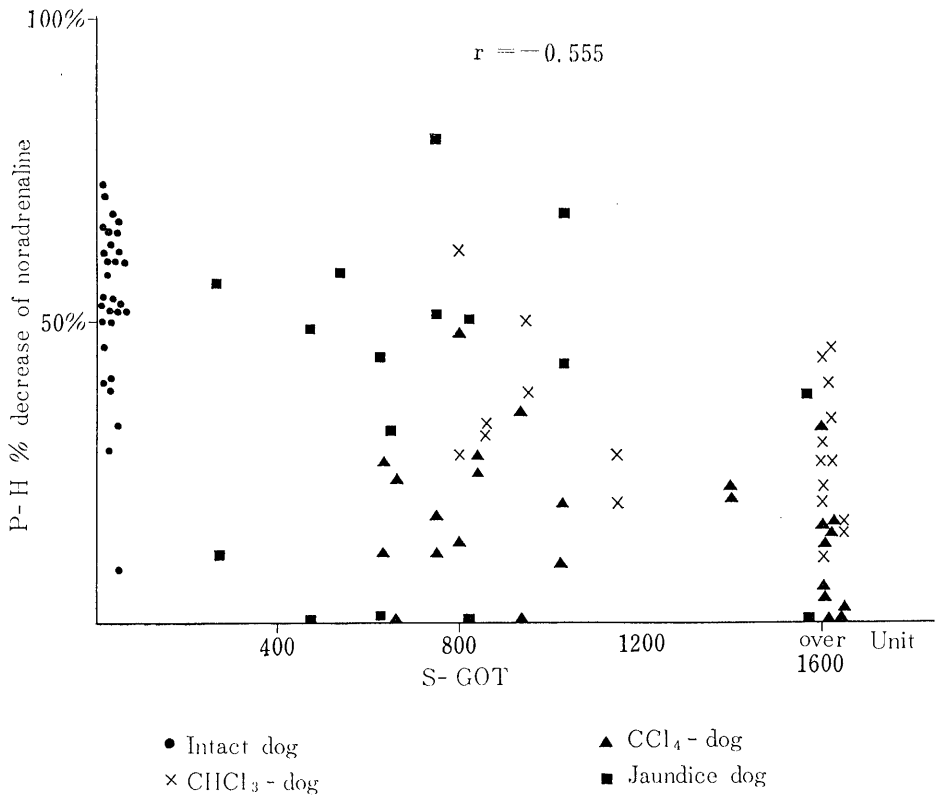


renaline are eliminated over 70.1±2.9% and 56.1±2.3% respectively through the liver in the intact dog at 1 minute after the administration of mixed each 100μg/kg of adrenaline and noradrenaline, and a difference between the reduction rate of adrenaline and noradrenaline is statistically highly significant. The content of cetacholamine in portal venous blood at 3 minutes after the catecholamine infusion was reduced to about 1/3 times of that in 1 minute, and the reduction rate of catecholamine in the liver would be varied in accordance with the content of circulating catecholamine.

BAIN and BATTY[3] studied, in vitro, the half-inactivation times of adrenaline and noradrenaline by human liver slices, which were 15.5 minutes for adrenaline and 12.25 minutes for noradrenaline, being against to my present study. On the other hand, the result of the present study harmonized with that of Blaschko et al.[4] who experimented with extract of the liver of guinea-pig.

By perfusing an isolated liver of rabbit, LUND[13] showed that blood containing 400μg % of adrenaline and 1 mg % of noradrenaline was almost completly cleared passing through the liver, showing a higher inactivation function of the liver than in this study.

Fig. 8. Correlation between P−H % decrease of noradrenaline after the administration of catecholamine and S-GOT

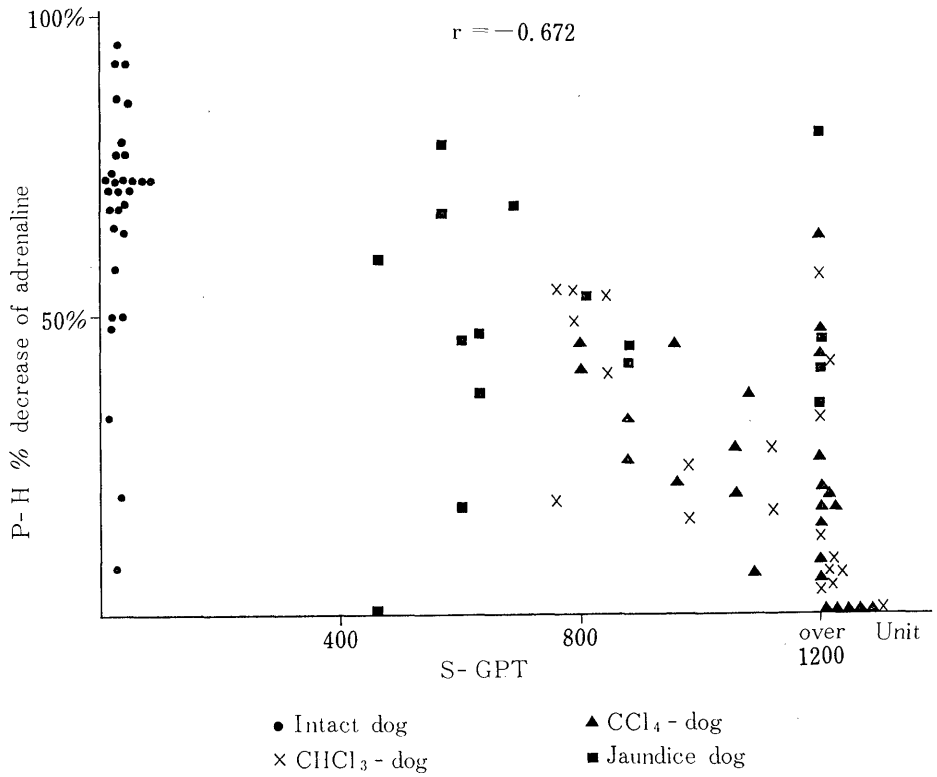


The result of the present study is similar to CARLSSON and WALDECK[5] who investigated the uptake of noradrenaline in the heart and skeletal muscle after the administration of H^3-noradrenaline intraperitoneally and C^{14}-noradrenaline intravenously. The uptake of intraperitoneally administered noradrenaline in the heart and skeletal muscle was about 30% of the intravenons route.

HERTTING and LABROSSE[11] concluded that the liver plays a very important role in the metabolic inactivation of circulating epinephrine following the administration of dl-epinephrine-7-H^3 to rat with biliary fistulas, in which 10% of the injected tritium after intrajugular infusion and 31% after intraportal infusion was excreted in the bile.

More recently, HAZELRIG et al[10]. administered dl-norepinephrine-C^{14} to rat with biliary fistulas via the tail vein or the portal vein. When it was injected into the tail vein, only 10% of the injected C^{14} was excreted in the bile in contrast to 22.3% after the intraportal infusion. The study of HERTTING and LABROSSE[11], HAZELRIG et al[10]., and this experiment indicate that the reduction rate of adrenaline in the liver is higher than that of noradrenaline.

Fig. 9. Correlation between P−H% decrease of adrenaline after the administration of catecholamine and S-GPT



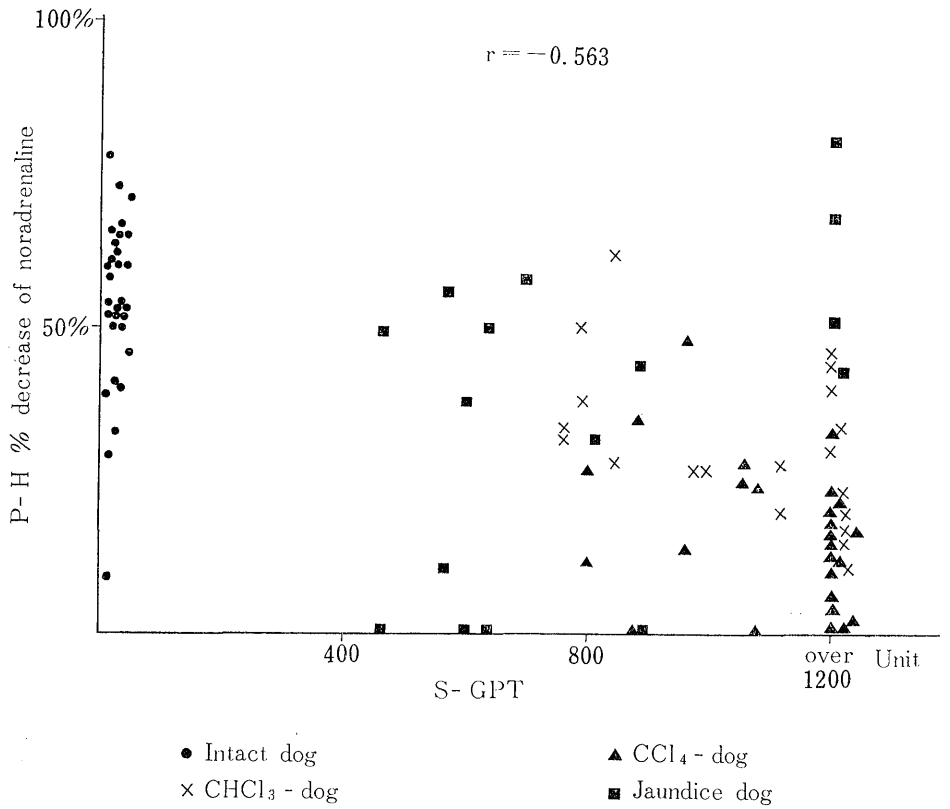
Other investigators showed that adrenaline injected into the portal vein has a much smaller effect in raising blood pressure than when injected into the femoral vein. Thus, all the other studies mentioned above, using the indirect method, suggest that the liver is a most important organ to inactivate catecholamine. The result of the present study using the direct method demonstrated clearly the role of the liver to inactivate catecholamine after the administration of catecholamine, agreeing well with the other findings mentioned above.

The glucose from the intact liver after the administration of adrenaline and noradrenaline began to release between 1 and 3 minutes and reached a maximum at 7 minutes. This was slightly late in comparison with the result of SHOEMAKER and FINDER[17] who injected only adrenaline.

Since there is no available information on the reduction of catecholamine in the damaged liver, the second series of this experiment was carried out to follow up the reduction rate of catecholamine in the damaged liver.

In our previous study [16], it was suggested that the reduction

Fig. 10. Correlation between P−H% drecrease of noradrenaline after the administration of catechloamine and S-GPT



rate of catecholamine in the damaged liver decreases in proportion to the degree of damage. In CCl_4-dogs, the reduction rate of adrenaline and noradrenaline 1 minute after the administration of mixed each 100 μg/kg of both was remarkably lowered to 20.7% and 18.7% respectively, and a difference between intact dogs and CCl_4-dogs was highly significant.

In $CHCl_3$-dogs, the reduction rate of catecholamine was also lowered to 22.5% for adrenaline and 30.0% for noradrenaline, the figure being similar to that of CCl_4-dogs. It would then appear that the degree of damage to the liver in both groups was equally severe.

In jaundice dogs, the figure was between the intact group and the above two groups, the reduction rate of adrenaline being 52.3% and norderenaline being 46.6%, with the degree of damage to the liver being moderate.

JOLY et al[12]. determined catechloamine levels in portal and hepatic venous blood in portal hypertension. They reported that hepatic venous blood contained significantly less noradrenaline than portal venous blood, and strongly suggested a hepatic clearance of noradrenaline in

their conclusion. In contrast, there was no difference between adrenaline levels in portal venous blood and in hepatic venous blood. As their experiments were done with very low catecholamine levels, their findings were slightly different from the results of the present study. In the present study which was done with exceedingly high catecholmine levels, it seems to be the same fate of circulating adrenaline and noradrenaline in the liver. These findings are supported by many other workers who have reported the fate of circulating catecholamine in the liver.

GOODALL et al[8]. studied the metabolic product of noradrenaline in the urine after the intravenous injection of dl-noradrenaline-C^{14} in 4 patients with portal (alcoholic) cirrhosis, and their results seemed to indicate that noradrenaline metabolism is altered in the patient with portal cirrhosis. They suggested that catecholamine metabolism in the liver is changed in the patient with liver disease. This was confirmed clearly in the present study.

Levels of S-GOT and S-GPT and the reduction rate of catecholamine in the liver showed an inverse correlation in the present study. Thus, it is concluded that adrenaline and noradrenaline are reduced significantly in the liver, the reduction rate changing in proportion to the degree of damage to the liver

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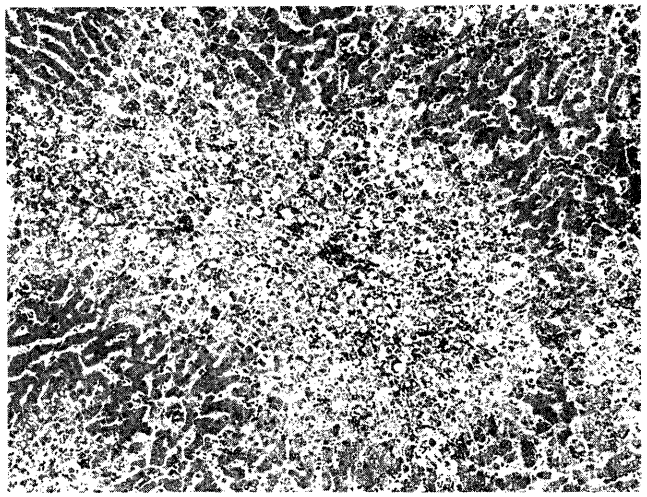

Photo 1.
Tne liver of CCl_4-dog, showing central fatty degeneration and slight necrosis. (Dog 18, H-E stain)

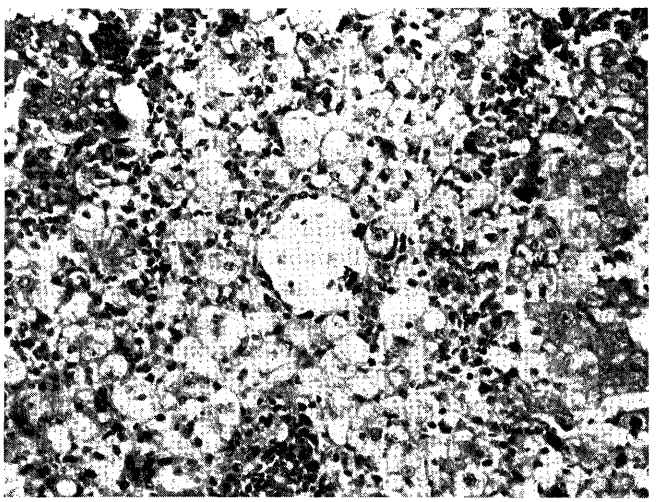

Photo 2.
The liver of $CHCl_3$-dog, showing central fatty degeneration and slight necrosis. (Dog 29, H-E staih)

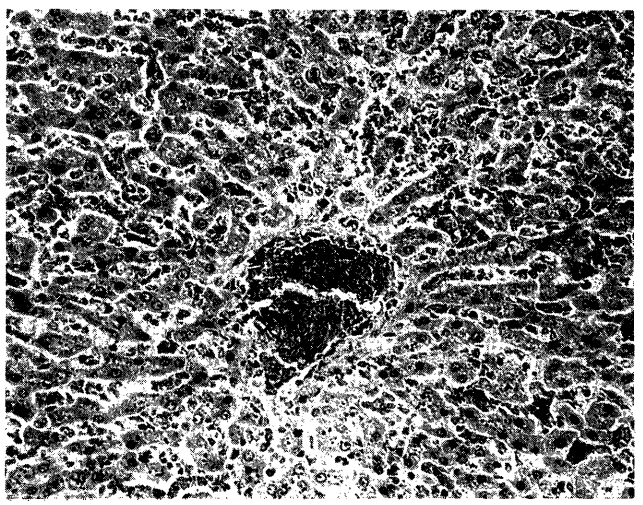

Photo 3.
The liver of Jaundice dog, showing congestion in the sinusoid. (Dog 45, H-E stain)