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Clinical and Experimental Studies of the Effect of Vagotomy on the Liver

by

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Introduction

The prevention and alleviation of liver dysfunction after surgery is still an important problem. In surgery of the upper alimentary tract, truncal vagotomy often performed, can become a factor in postoperative liver dysfunction. As the liver has tremendous functional reserves, vagotomy in uncomplicated gastric or duodenal ulcer surgery usually has little effect on its function. However, in cases of poor risk, such as massive bleeding, perforated ulcers and other major surgery, vagotomy may have significant effects on liver function.

In our clinic, a new type of total gastrectomy with preservation of the hepatic and posterior celiac vagi (KIMURA-ISHIGAMI) has been performed in order to reduce the postoperative sequelae of conventional total gastrectomy with truncal vagotomy[23]. It was found that diarrhea and weight loss were less frequent, while fat absorption, carbohydrate metabolism and gallbladder function were markedly improved[14)17)22)53].

In this study, a comparative observation of postoperative liver function in patients receiving total gastrectomy, with and without vagotomy, was made in order to clarify the effect of vagotomy on liver function.

It is known that the liver has a great capacity for regeneration[11)33]. Elucidation of the effect of vagotomy on liver regeneration can be useful in order to better understand liver dysfunction after vagotomy. However, there is a dearth of this kind of information. Therefore, in this study, the effect of vagotomy on liver regeneration in rats was investigated experimentally.

Effect of Vagotomy on Liver Function After Total Gastrectomy

1. Materials and methods

a) Clinical cases

Key words . Vagotomy, Liver dysfunction, Liver regeneration, Total gastrectomy, DNA metabolism
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The cases in this study were 87 patients observed for more than 6 weeks after total gastrectomy for gastric cancer, at Yamaguchi University School of Medicine Hospital (Dec. 1969 to May 1977) and at Tokuyama Central Hospital (Jan. 1975 to Dec. 1976). None of the patients had preoperative liver dysfunction (defined as serum bilirubin over 1.2mg/dl and SGPT over 30 U) or postoperative complications, such as leakage and pneumonia.

The eighty-seven cases consisted of 43 cases with preservation of the hepatic and posterior celiac branches (non-vagotomized group), 38 cases with division of both branches, (vagotomized group), 2 cases with preservation of the hepatic branch and division of the posterior celiac branch, and 4 cases with division of the hepatic branch and preservation of the posterior celiac branch. Large numbers of vagal nerve fibers entering the liver through the posterior celiac branch are probably divided during dissection of lymph nodes around the celiac and hepatic arteries. Therefore, 2 cases with preservation of the hepatic branch were classified as non-vagotomized and 4 cases with division of the hepatic branch and preservation of the posterior celiac branch were classified as vagotomized.

All the paitents underwent R2 or incomplete R3 surgery. After total gastrectomy an end-to-side esophagojejunostomy with jejunojejunostomy of β type (NAKAYAMA) was performed in most cases. Nitrous oxide and Halothane were given for anesthesia, but Droleptan and Fentanest were given in almost half of the cases after 1974.

Two comparative studies were performed as follows.

i) Cases exclusive of absolute non-curative resection.

Out of 87 cases, 78 were studied (9 cases were omitted because of absolute non-curative resection). Table 1 shows the distribution of sex, age, stage, curability, combined resection,

Table 1 Background facters of the cases.

Group	Sex		Age (year)		Stage†				Curability†		Combined resection		Blood transfusion(l)			Anti-cancer drugs	
	M.	F.	<60	≧60	I	II	III	IV	C.	n C.	(-)	(+)	<1	≧1	≧2	(-)	(+)
Non-vagotomized n=40	24	16	21	19	7	7	17	9	28	12	16	24	12	15	13	13	27
Vagotomized n=38	19	19	23	15	11	5	13	9	30	8	16	22	8	19	11	13	25
χ^2	0.7878		0.5106		1.7055				0.8182		0.0358		1.3570			0.0257	

n: Number of patients. †: According to Japanese Research Society for gastric cancer. C: Curative resection. n C: Non-curative resection. (The caces with absolute non-curative resection, preoperative liver dysfuncton and postoperative complication such as leakage and pneumonia were not included.)

blood transfusion and anti-cancer drugs in the non-vagotomized and the vagotomized groups. No significant differences were found between the two groups.

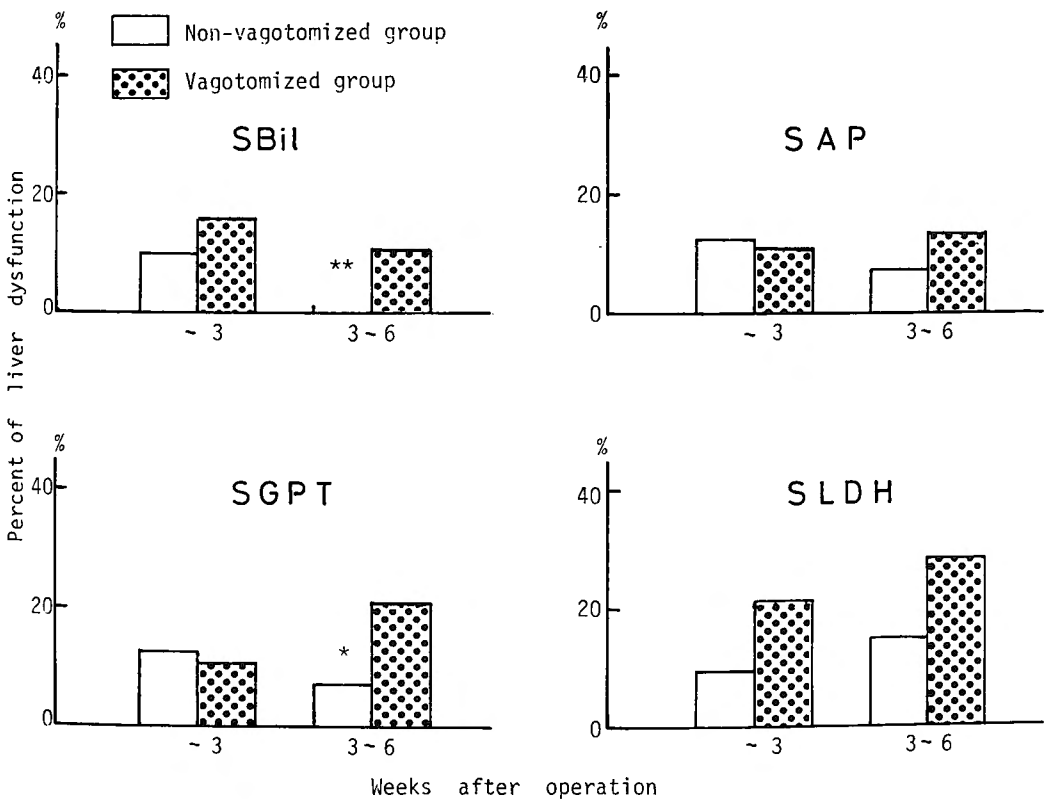
ii) Cases with administration of anti-cancer drugs

Forty-one cases were observed for more than 3 weeks after starting the administration

Table 2 Background facters of the cases with administration of anti-cancer drugs.

Group	Stage †		Curability †		Combined resection		Blood transfusion (l)	
	I + II	III+IV	curative	non-curative	(-)	(+)	<2	≧2
Non-vagotomized n=19	3	16	8	11	8	11	14	5
Vagotomized n=22	5	17	12	10	7	15	14	8
χ^2	0.3125		0.6315		0.4650		0.4753	

n: Number of patients. †: According to Japanese Research Society for gastric cancer.



*, **: Significance, as compared with vagotomized group, students t test ($p<0.10, 0.05$). S Bil : Serum bilirubin. SAP · Serum alkaline phosphatase. SGPT : Serum glutamic pyruvic transaminase. SLDH : Serum lactic acid dehydrogenase. (The cases with absolute non-curative resection, preoperative liver dysfunction and postoperative complication such as leakage and pneumonia were not included.)

Fig. 1 Liver dysfunction after total gastrectomy with or without vagotomy.

of Mitomycin C (MMC) or MMC and 5-Fluorouracil (5FU) with or without cytosine arabinoside (C)－MF(C). There were 19 cases in the non-vagotomized group and 22 in the vagotomized group. Table 2 shows the distribution of stage, curability, combined resection and blood transfusion in the two groups. Anti-cancer drugs were injected intravenously twice a week. In the case of MMC therapy, a continuous infusion of 8mg of MMC or a one-shot injection of 4mg of MMC was given. In the case of MF(C) therapy, 2～4mg of MMC and 250～500mg of 5FU with or without 20～40mg of C were given.

b) Liver function tests

Serum bilirubin, serum glutamic pyruvic transaminase (SGPT), serum alkaline phosphatase (SAP) and, occasionally, serum lactic dehydrogenase (SLDH) were used as indicators of liver function. Serum bilirubin and SAP were measured by a modification of the MICHAELSSON HEIRWEGH method[46] and the BESSEY LOWRY method[41], respectively. SGPT and SLDH were measured by the UV method[41]. Serum bilirubin over 1.2mg/dl, SGPT above 30 U, SAP above 50 U and SLDH over 300 U were considered abnormal. Liver function tests were performed before and once a week after each operation.

2. Result

a) Postoperative abnormality in the values of each indicator.

The occurrence of postoperative abnormality in the values of each indicator in the cases without preoperative liver dysfunction is shown in Fig. 1 and Table 3.

i) Serum bilirubin

In the early postoperative period, within 3 weeks after surgery, abnormal serum bilirubin was found in 4 of the 40 non-vagotomized cases (10.0%) and 6 of the 38 vagotomized ones (15.8%). This difference was not significant. In the later postoperative period, 3 to 6 weeks after surgery, none of the 40 non-vagotomized cases had abnormal serum bilirubin, but in 4 of the 38 vagotomized cases (10.5%) abnormality was found. This difference was statistically significant ($p<0.05$). The serum bilirubin was under 5.0mg/dl in all 4 of the non-vagotomized cases, but was over 5.0mg/dl in 4 of the 10 vagotomized ones.

ii) SGPT

In the early postoperative period, no significant difference was noted between the two groups. In the later postoperative period, abnormality was found in 3 of the 40 non-vagotomized cases (7.5%) and in 8 of the 38 vagotomized cases (21.1%). This difference was significant at the 10% level. SGPT over 100 U was found in only 2 of the vagotomized cases.

iii) SAP

Although there was no significant difference between the two groups in the early postoperative period, abnormal SAP was found in 3 of the 40 non-vagotomized cases (7.5%) and in 5 of the 38 vagotomized cases (13.2%) in the later postoperative period. SAP above 100 U was found in 2 of the vagotomized cases.

iv) SLDH

SLDH over 600 U was found in 2 of the 14 vagotomized cases tested, but in none of

Table 3 Liver dysfunction after total gastrectomy with or without vagotomy.

(Number of patients)

		Non-vagotomized n=40		Vagotomized n=38	
		~3 weeks	3~6 weeks	~3 weeks	3~6 weeks
SBil	1.2 ~ 3.0 (mg/dl)	2		2	1
	3.0 ~ 5.0	2		2	1
	5.0 ~			2	2
SGPT	30 ~ 100 (U)	5	3	4	6
	100 ~ 200				1
	200 ~				1
SAP	50 ~ 100 (U)	5	3	3	4
	100 ~ 150				1
	150 ~			1	
SLDH	300 ~ 600 (U)	2	3	3	2
	600 ~ 1000				2

SBil: Serum bilirubin. SGPT: Serum glutamic pyruvic transaminase. SAP: Serum alkaline phosphatase. SLDH: Serum lactic dehydrogenase n: Number of patients. (SLDH was tested in 21 non-vagotomized and 14 vagotomized patients.)

the 21 non-vagotomized cases tested, but in none of the 21 non-vagotomized ones.

b) Cases with liver dysfunction

Out of the total, 17 of the 40 non-vagotomized cases (42.5%) and 22 of the 38 vagotomized cases (57.1%) had abnormal valves in one or more of the indicators. The abnormal serum bilirubin and SGPT fonud in the early postoperative period were transient and disappeared within 2 weeks. In the later postoperative period, 3 non-vagotomized and 7 vagotomized cases had abnormal serum bilirubin and SGPT. Table 4 shows these cases.

Abnormal SAP persisted in 2 vagotomized cases. Because SAP and serum bilirubin at 15 minutes were normal or only slightly increased, jaundice was judged to be hepatocellular in all cases.

c) Operating time and liver dysfunction

The relationship between operating time and liver dysfunction is shown in Fig. 2. No difference was found between the two groups.

d) Blood transfusion and liver dysfunction

The relationship between blood transfusion and liver dysfunction is shown in Fig. 3. No difference was found between the two groups.

e) Anti-cancer drugs and liver dysfunction

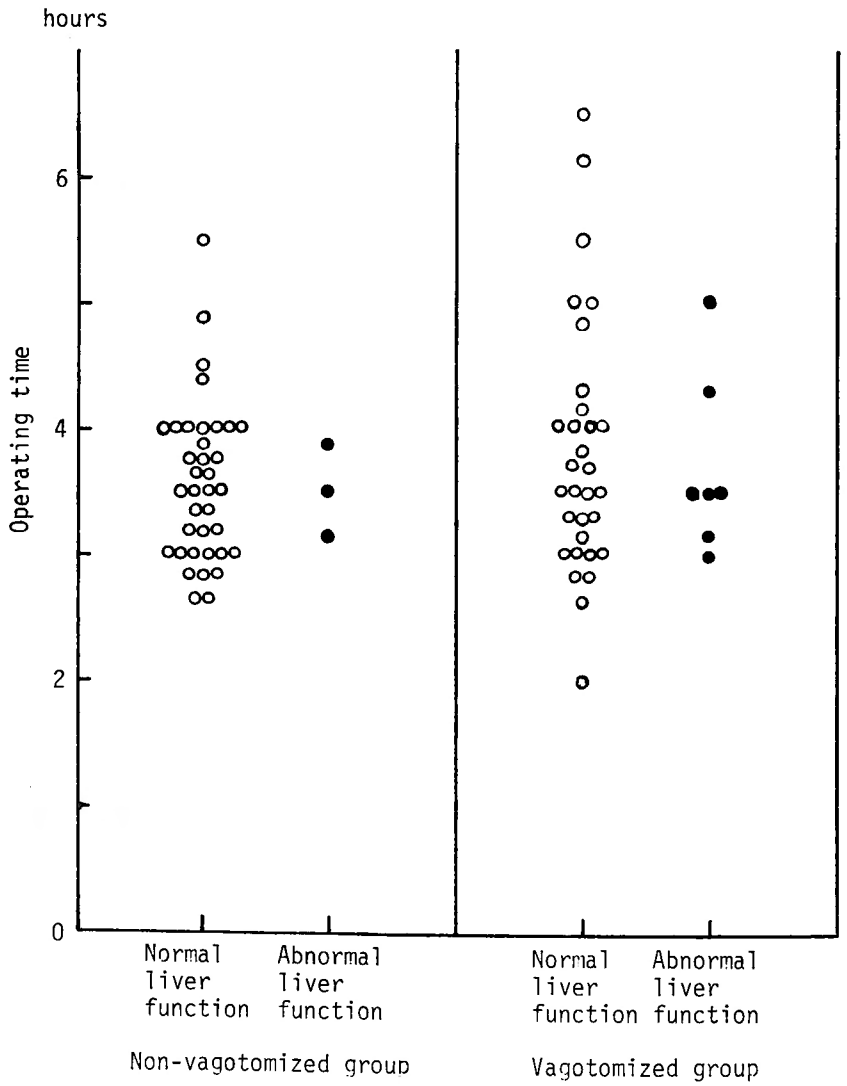


Fig. 2. Operating time and liver dysfunction.

Table 4 The cases with abnormal serum bilirubin and SGPT.

	Case	Liver function									Blood transfusion (ml)	Anti-cancer drugs (mg)
		T-Bil (mg/dl)	15min Bil(%)	A/G	CCFT	Ch-E (ΔpH)	SGPT (U)	SAP (U)	SLAP (U)	SLDH (U)		
Non-vagotomized	A. M. 42 ♀			0.94	0	0.55	82	21		180	600	MMC 20 F 2000
	T. N. 60 ♂			0.76	0	0.37	67	15	22	158	2400	(-)
	S. H. 35 ♀			0.94	0	0.63	35	20		330	1400	MMC 40
Vagotomized	K. Y. 41 ♀	7.7	71.4	0.98	2+	0.25	353	37	27	340	2800	MMC 40
	Z. M. 62 ♂	2.0	45.0	0.56	1+	0.35	60	30			2000	MMC 32
	R. F. 37 ♀	3.2	34.4	0.81	2+	0.47	53	50	20	999	2400	MMC 60
	M. H. 47 ♀	12.3	42.0	1.03	2+	0.46	93	49			1800	MMC 20 F 1250
	T. K. 63 ♀			1.01	0	0.44	50	83			0	(-)
	S. S. 47 ♂			0.90	0	0.42	82	55			0	MMC 40
	S. S. 40 ♀			0.79	0	0.51	133	49			1000	MMC 24 F 1500

MMC: Mitomycin C. F: 5-Fluorouracil. T-Bil: Total serum bilirubin. CCFT: Cephalin cholesterol flocculation test. Ch-E: Cholinesterase. SGPT: Serum glutamic pyruvic transaminase. SAP: Serum alkaline phosphatase. SLAP: Serum leucine aminopeptidase. SLDH: Serum lactic dehydrogenase.

Table 5 Side effects of anti-cancer drugs after total gastrectomy with or without vagotomy.

		Initiation of chemotherapy(weeks)		Liver function			
		<2	2≦	Serum bilirubin	SGPT (U) <100	100≦<200	200≦	SAP
Non-vagotomized n=19	MMC	6	6		2			
	MF(C)	2	5					
Vagotomized n=22	MMC	4	7	3	2		1	1
	MF(C)	7	4			1		

n: Number of patients. SGPT: Serum glutamic pyruvic transaminase. SAP: Serum alkaline phosphatase. MMC: Mitomycin C. MF(C): MMC and 5-Fluorouracil with or without Cytosine arabinoside.

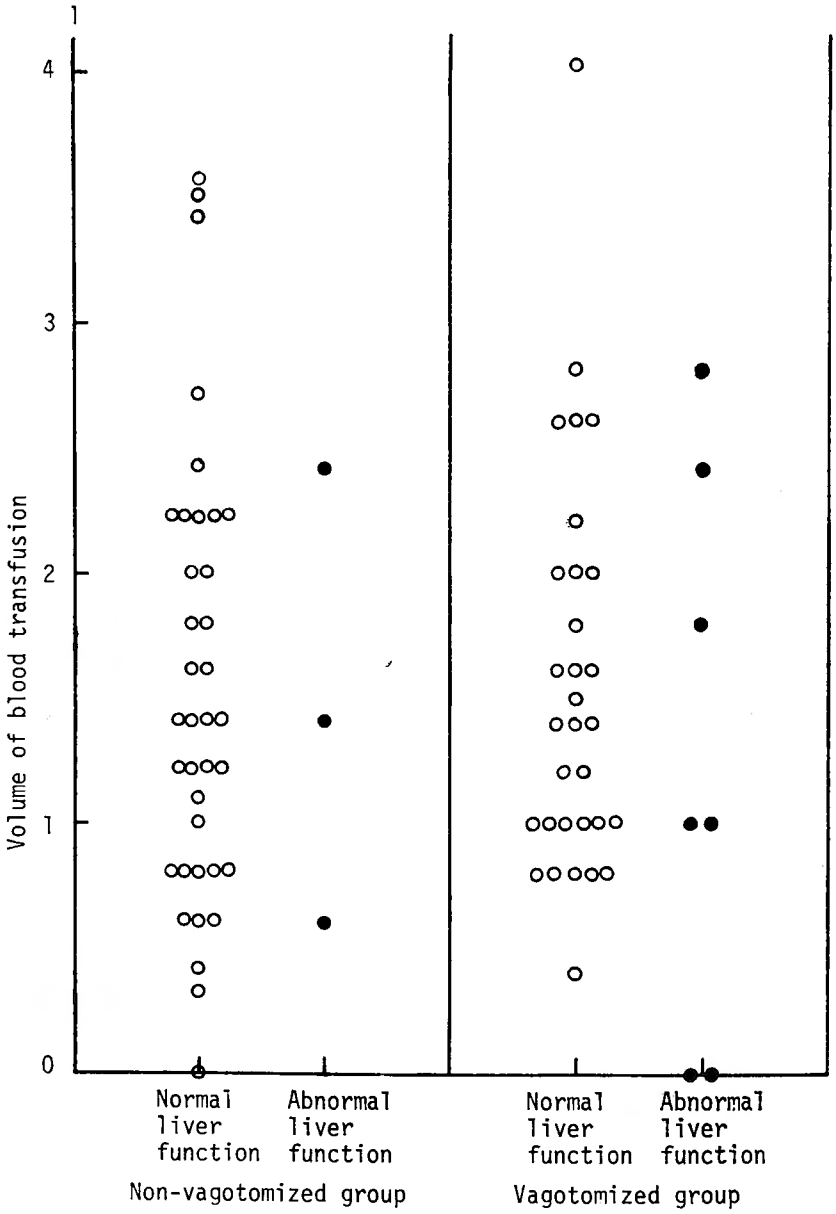
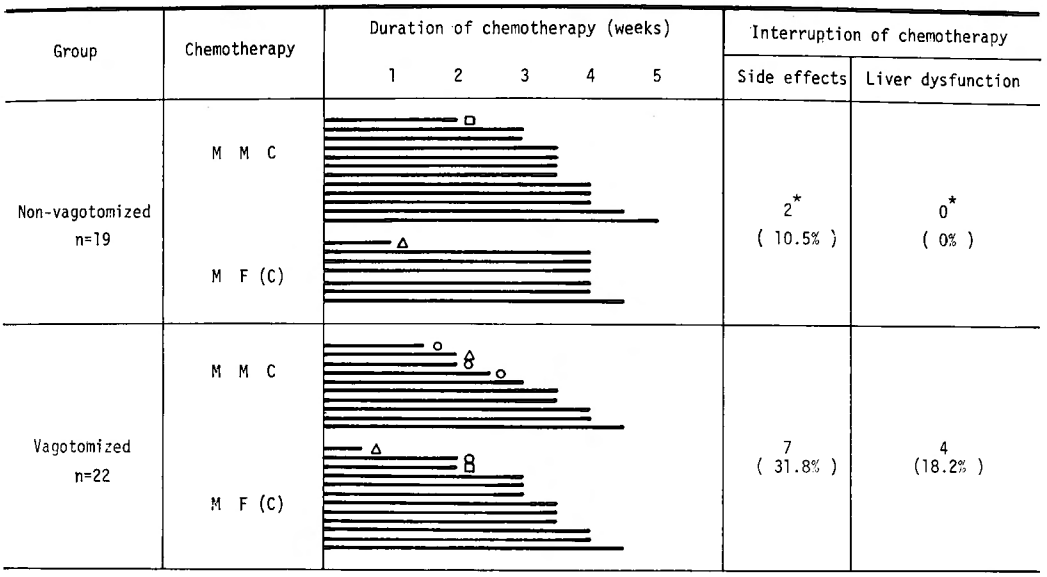


Fig. 3. Blood transfusion and liver dysfunction.

Liver dysfunction in the cases which were observed for more than 3 weeks after starting the administration of anti-cancer drugs is shown in Table 5. Liver dysfunction occurred more frequently and more markedly in the vagotomized groups. Serum bilirubin was abnormally high in 3 of the 4 vagotomized cases with abnormal SGPT. Fig. 4 shows the cases with interruption of adjuvant chemotherapy because of serum bilirubin over 2.0 mg/dl and SGPT over 100 U. Although liver dysfunction did not occur in the 12 cases



n: Number of patients. * : Significance, as compared with vagotomized group, students t test ($p<0.10$). ○: Liver dysfunction. □: Leucopenia. △: Abdominal distress. MMC : Mitomycin C. MF(C): MMC and 5-Fluorouracil with or without Cytosine arabinoside.

Fig. 4. Side effects of anti-cancer drugs after total gastrectomy with or without vagotomy.

with MMC therapy and the 7 cases with MF(C) therapy in the non-vagotomized group, it occurred in 3 of the 10 cases with MMC therapy and one of the 12 cases with MF(C) therapy in the vagotomized group. This difference was significant at the 10% level. Because of liver dysfunction, leucopenia and abdominal distress, adjuvant chemotherapy was interrupted in 2 of the 19 non-vagotomized cases and 3 of the 22 vagotomized cases.

Effect of Vagotomy on Liver Regeneration in Rats

1. Materials and methods

a) Animals and procedures

Male albino rats of the Wister strain weighing 170 ± 20g were used. Under ether anesthesia, laparotomies were performed. According to the method of HIGGINGS & ANDERSON [19], approximately two-thirds of the liver, including the middle and left lobe, was resected. The rats were divided into 3 groups: non-vagotomized group, anteriorly vagotomized group and posteriorly vagotomized group. In the vagotomized groups the anterior or posterior trunk of the vagus was divided under the diaphragm, as shown in Fig. 5. In the two vagotomized groups, no food stagnation was observed and the gastric juice pH average was 2.0 ± 0.31 (anterior) and 2.3 ± 0.20 (posterior), not significantly different from 2.2 ± 0.18 in the non-vagotomized group.

During the experiments, the animals were maintained on Oriental Chow and tap water. Since the vagotomized groups had a tendency toward decreased food intake, each group

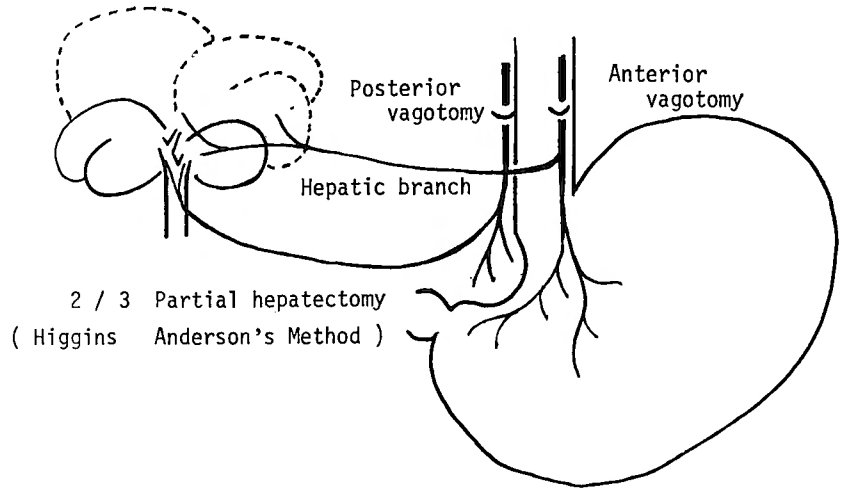


Fig. 5. Diagrammatic representation of partial hepatectomy and vagotomy.

was pair-fed. The animals were killed by venesection.

b) Regeneration ratio of liver weight

The regeneration ratio of liver weight was calculated according to CANZANELLI's formula[8]:

$$\text{Regeneration ratio} = \frac{\text{regenerated liver weight}}{\text{resected liver weight}} \times 100\%$$

where the regenerated liver weight was calculated by subtracting a half of the resected liver weight from the liver weight at the time of killing.

c) Mitotic index

Specimens of the right lobe were fixed in formalin, embedded in paraffin, sectioned and stained with hematoxylin for histological study. The mitotic index was expressed as the number of cells with mitosis in 1000 liver cells. Since identification of each stage of mitosis was difficult, mitosis was judged to be present when the nuclear membrane could no longer be seen.

d) DNA metabolism

i) Liver DNA

Liver DNA was extracted by a modification of the SCHMIDT-THANNHAUSER and the SCHNEIDER method[43]. Sutitable amounts of liver tissue were homogenized with cold physiological saline. DNA was extracted by 0.6 N trichloroacetic acid followed by absolute ethanol. The DNA content was determined by the KISSANE and ROBINS method[26]. The extracted DNA was heated with 3,5-diaminobenzoic acid and 4 N HCl. After the addition of 0.6 N $HClO_4$ and centrifugation, fluorescence of the supernatant fluid was measured by a spectrophotofluorimeter (Hitachi model 512) with activation at 415 mμ and emission at 515 mμ.

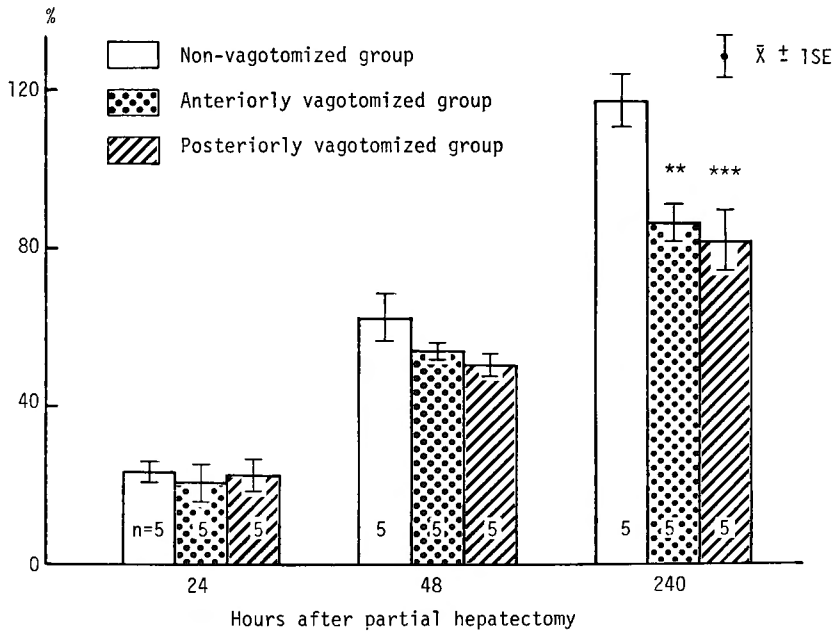
ii) Incorporation of ^{3}H-thymidine into Liver DNA

One hour after an intraperitoneal injection of 25μC of ^{3}H-me thyl thymidine, the animals were killed. After the liver DNA was extracted, radioactivity was measured by a liquid scintillation spectrometer (Packard model 3385). The incorporation of ^{3}H-thymidine into liver DNA

was expressed as cpm/mg DNA.

e) Cell size

According to SCHNEYER & HALL[44], cell size was estimated by counting the number of nuclei per calibrated area of hematoxylin stained sections. In this examination cell size was inversely related to the number of nuclei.



* *, * * *: Significance, as compared with non-vagotomized group, students t test ($p<0.05$, 0.01). n: Number of rats.

Fig. 6. Effect of vagotomy on regeneration ratio of liver weight after partial hepatectomy.

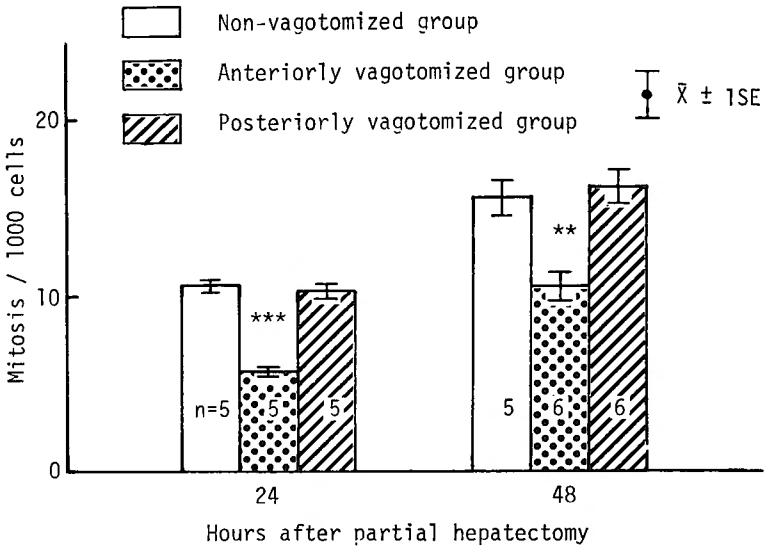
2. Results

a) Regeneration ratio of liver weight

As shown in Fig. 6, the weight regeneration ratio in the non-vagotomized, anteriorly vagotomized and posteriorly vagotomized groups following partial hepatectomy were 24.3 ±3.93%, 20.9±5.62% and 23.3±4.84% at 24 hours, and 62.7±5.7%, 54.8±1.57% and 50.6± 2.52% at 48 hours. No significant difference were found. At 240 hours, however, the regeneration ratio was 117.3±6.15% in the non-vagotomized group, 86.8±5.67% in the anteriorly vagotomized group and 82.7±7.99% in the posteriorly vagotomized group. A significant decrease was noted in both vagotomized groups.

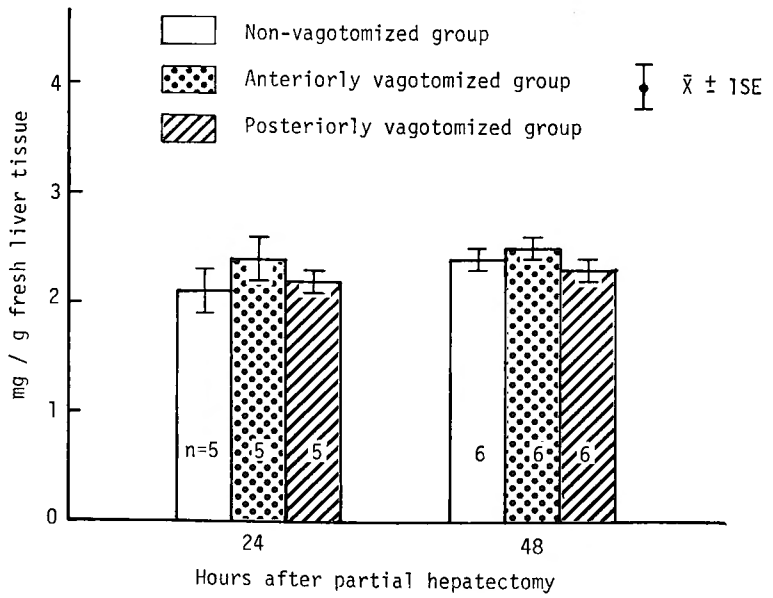
b) Mitotic index

As shown in Fig. 7, mitotic indices in the non-vagotomized, anteriorly vagotomized and posteriorly vagotomized groups following partial hepatectomy were 11.6±0.68, 6.4±0.51 and 10.4±0.87 at 24 hours, and 16.2±1.71, 11.1±1.35 and 17.5±1.69 at 48 hours. A significant decrease was found in the anteriorly vagotomized group. At 240 hours, the mitotic index



* *, * * *: Significance, as compared with non-vagotomized group, students t test ($p<0.05, 0.01$). n: Number of rats.

Fig. 7. Effect of vagotomy on mitotic index after partial hepatectomy.



n: Number of rats.

Fig. 8. Effect of vagotomy on liver DNA levels after partial hepatectomy.

was under 1.0 in all groups.

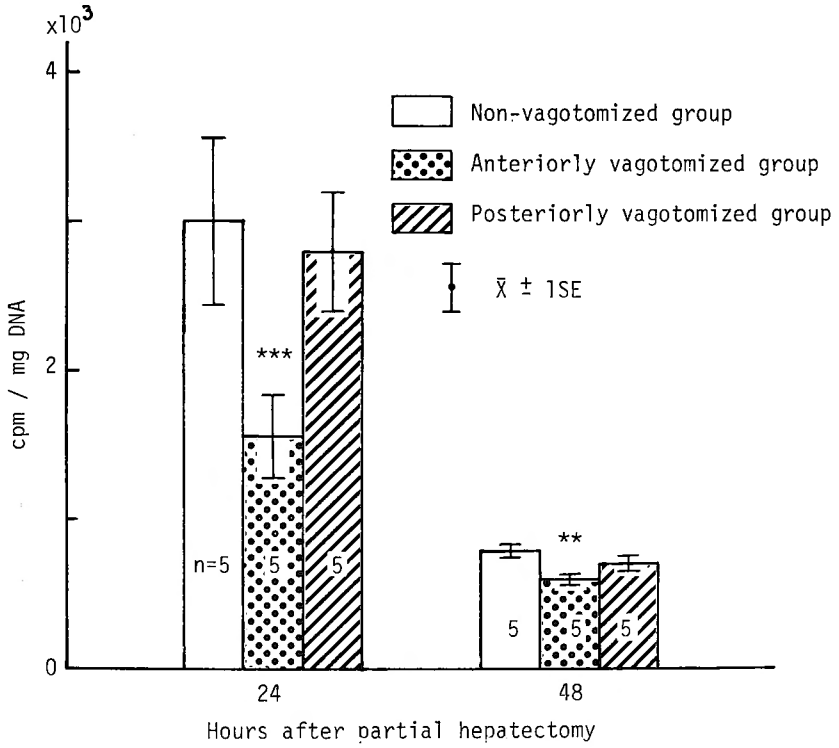
c) DNA metabolism

i) Liver DNA (Fig. 8)

Liver DNA levels in the non-vagotomized, anteriorly vagotomized and posteriorly vagotomized groups following partial hepatectomy were 2.1 ± 0.21mg/g, 2.4 ± 0.25mg/g and 2.2 ± 0.14mg/g at 24 hours, and 2.4 ± 0.14mg/g, 2.5 ± 0.13mg/g and 2.3 ± 0.21mg/g at 48 hours. No significant differences were found.

ii) Incorporation of ^{3}H-thymidine into liver DNA

Fig. 9 shows the incorporation of ^{3}H-thymidine into liver DNA in the non-vagotomized, anteriorly vagotomized and posteriorly vagotomized groups following partial hepatectomy. The values in each group were $(3.0\pm0.56)\times10^3$ cpm/mg DNA, $(1.6\pm0.27)\times10^3$ cpm/mg DNA and $(2.8\pm0.39)\times10^3$ cpm/mg DNA at 24 hours, and $(7.6\pm0.27)\times10^2$cpm/mg DNA, $(6.4\pm0.24)\times10^2$cpm/mg DNA and $(6.9\pm0.47)\times10^2$cpm/mg DNA at 48 hours. A significant decrease was found in anteriorly vagotomized group.

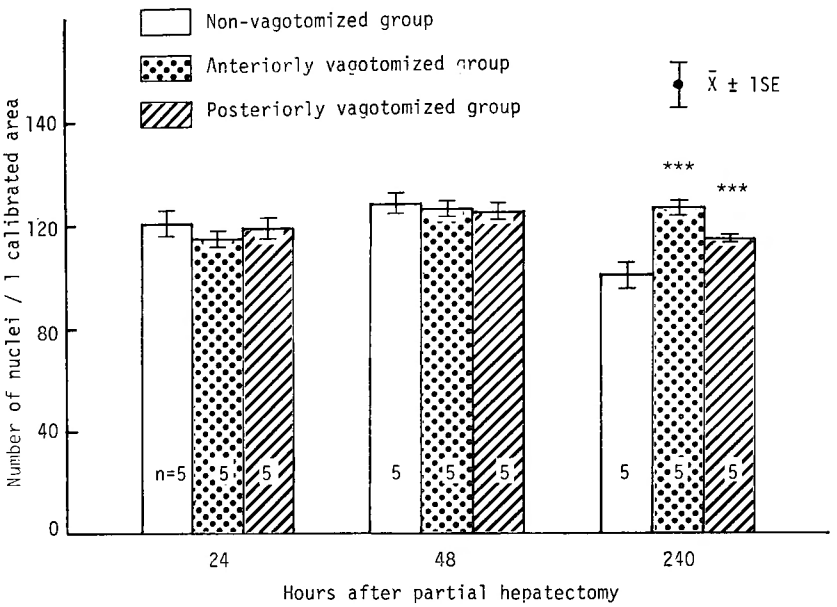


* *, * * *: Significance, as compared with non-vagotomized group, students t test ($p<0.05$, 0.01).

Fig. 9. Effect of vagotomy on incorporation of ^{3}H-thymidine into liver DNA after partial hepatectomy.

d) Cell size (Fig. 10)

No significant differences were seen among the three groups at 24 and 48 hours following partial hepatectomy. At 240 hours, however, the number of hepatic cell nuclei increased significantly in both vagotomized groups; 99.8 ± 4.45 in the non-vagotomized



* * *: Significance, as compared with non-vagotomized group, students t test ($p<0.01$). n: Number of rats. Cell size is inversely related to the number of nuclei.

Fig. 10. Effect of vagotomy on cell size after partial hepatectomy.

group, 126.3 ± 3.70 in the anteriorly vagotomized groups and 114.3 ± 1.04 in the posteriorly vagotomized group. Because of the inverse relationship between number of nuclei and cell size, this finding means that there was a significant decrease in cell size in both vagotomized groups.

Discussion

It is known that the liver is innervated by the hepatic and celiac vagi, and that protein and carbohydrate metabolism, bile secretion and blood flow in the liver are controlled by these vagal nerves[2)14)20)28)29)50)53)]. Therefore, it is though that vagotomy affects liver function.

The experimental studies of OKADA[37)], ODA[36)] and BALDWIN, et al[1)]. showed that the effect of vagotomy on liver function was mild and transient. SUGITANI, et al[49)]. recognized that hepatic uptake and excretion of ^{131}I-BSP following total gastrectomy markedly decreased as compared with other types of gastrectomy. They supposed that the decrease of ^{131}I-BSP clearance was caused by total vagotomy accompaning total gastrectomy.

However, these experimental and clinical observations did not indicate the exact effect of vagotomy on liver function, since some differences in extent of gastrectomy, postoperative gastric acidity and reconstruction mode were found between the non-vagotomized and the vagotomized groups.

In this study, the total gastrectomy with preservation of the hepatic and posterior celiac

vagi (non-vagotomized group) was the same as the conventional total gastrectomy (vagotomized group) except for the preservation of the vagi. In addition, the following factors were held constant for both groups : anesthesia, operative method, operating time, anti-cancer drugs, blood transfusion, stage and curability of the gastric cancer. Therefore, the difference in postoperative liver dysfunction between the non-vagotomized and vagotomized groups can be ascribed to the effect of vagotomy on liver function.

Usually, postoperative liver dysfunction is divided into two groups according to the time of appearance. In one group, signs and symptoms appear in the early postoperative period, within 3 weeks after surgery. In the other group, the dysfunction appears in the later postoperative period, after 3 weeks.[42]

Development of jaundice following major surgery is generally accepted[18][42]. The jaundice is associated with shock, heart failure, multiple transfusion, infection and various drugs[14][18][30]. SATO, et al[42]. studied liver dysfunction following uncomplicated abdominal surgery such as gastrectomy and cholecystectomy, using icteric index, SGPT, SGOT and SAP as indicators. They observed that postoperative liver dysfunction occurred in 60.5% and disappeared within 3 weeks in most cases.

In the present study, liver dysfunction within 3 weeks following total gastrectomy appeared in approximately one-third of each group, (non-vagotomized and vagotomized) with no significant difference between them. However, a more frequent occurrence of abnormally high values for serum bilirubin, SGPT, SAP and SLDH were found in the vagotomized group. There was no case of Halothane hepatitis, which is characterized by high fever, jaundice and eosinophilia 1 to 2 weeks after Halothane anesthesia.

On the other hand, 3 to 6 weeks following total gastrectomy, liver dysfunction occurred more frequently and more markedly in the vagotomized group. Especially, a significant difference was found in the values for serum bilirubin and SGPT.

Liver dysfunction in the later postoperative period is caused by many factors. One is serum hepatitis. Only one case in the vagotomized group satisfied the criteria of serum hepatitis[55]: SGPT above 200 U, or SGPT of 100 to 200 U with more than 10% retention of BSP at 45 minutes, 3 weeks or more following a blood transfusion.

Liver dysfunction is also caused by anti-cancer drugs. Cytosine arabinoside and 5-fluorouracil sometimes produce minor and transient liver dysfunction[56]. The administration of anti-cancer drugs early in the postoperative period has better results but it also produces stronger toxic effects[35]. In the 4 cases with interruption of adjuvant chemotherapy because of liver dysfunction, administration of the drugs was started within 2 weeks after total gastrectomy and the liver dysfunction appeared within 6 weeks. Since all of these cases were in the vagotomized group, it is thought that vagotomy aggravates the liver dysfunction caused by anti-cancer drugs.

In summary, liver dysfunction in the later postoperative period occurred in 9 of the 40 cases (22.5%) in the non-vagotomized group and in 12 of the 38 cases (31.6%) in the vagotomized group and was severe in the latter group. It is interesting that the one case

with serum hepatitis and the 4 cases with liver dysfunction from anti-cancer drugs were in the vagotomized group.

Usually, the effects of vagotomy on liver function are so mild that they can not be detected by conventional liver function tests following minor or uncomplicated abdominal surgery. In total gastrectomy for gastric cancer, however, many hepatotoxic factors such as general anesthesia, blood transfusion and anti-cancer drugs put an extra burden on the liver. Since vagotomy affects metabolism, blood flow and the regeneration process of the liver[31)45)], it is quite possible that vagotomy during total gastrectomy overburdens the liver and resluts in liver damage[15)].

The next area of consideration is the effect of vagotomy on liver regeneration. BILIOTTI, et al[3)] showed that the increase in liver weight after partial hepatectomy was suppressed in vagotomized rats. SEKI[45)] observed in rats that total abdominal vagotomy significantly decreased the weight regeneration ratio, but did not decrease the incorporation of ^{32}p into liver DNA. LAMAR & HOLLOWAY[31)] showed that bilateral vagotomy markedly decreased the incorporation of ^{3}H-thymidine into liver DNA, 24 hours after partial hepatectomy, and suggested that vagal innervation might play a role in the control of liver regeneration.

"Liver regeneration" means that the liver remaining after partial hepatectomy restores itself to its original mass. However, since the first step in the regenaration process is the division of liver cells (induced by liver injury), the mitotic activity and the synthesis of nuclear DNA are usually used as the indices of liver regeneration in its early phase[7)].

In both anteriorly and posteriorly vagotomized rats, the weight regeneration ratio showed a significantly lower value 240 hours following partial hepatectomy. This is consistent with the finding that the size of hepatocytes estimated from the number of nuclei per calibrated area was significantly smaller in both vagotomized groups. On the other hand, the mitotic index and the incorporation of ^{3}H-thymidine into liver DNA, 24 and 48 hours after partial hepatectomy, was significantly decreased in the anteriorly vagotomized rats. But these effects were not found in the posteriorly vagotomized rats.

From the above findings, it may be concluded that anterior vagotomy inhibits cell division and enlargement of hepatocytes, while posterior vagotomy inhibits only enlargement.

The mechanism by which vagotomy suppresses liver regeneration is poorly understood. SEKI[45)] suggested that vagotomy did not act on cell division of hepatocytes but suppressed their enlargement. On the other hand, LAMAR & HOLLOWAY[31)] observed that bilateral cervical vagotomy performed in two stages decreased the synthesis of liver DNA and the activity of ornithine decarboxylase which stimulates the formation of polyamines related to DNA synthesis[10)]. They supposed that these changes were induced by the indirect effects of bilateral cervical vagotomy, since the vagotomy probably caused dysfunction of various organs. However, it seems unreasonable to deny the direct effect of vagotomy on liver regeneration, since the activity of tyrosine transaminase, glycogenolytic enzymes, cyclic AMP and ornithine decarboxylase in the liver are shown to respond to vagal stimulation or adrenergic bloking agents[4)5)47)52)].

In this respect, SCHNEYER & HALL[44] reported a very interesting observation. They showed that an increase of bulk in the diet of rats induced a transient burst of mitosis with increase in total DNA, RNA, weight and cell size of the parotid gland, and that these changes did not occur after the division of the auriculotemporal nerve, a parasympathetic nerve. This effect is identical with that of anterior vagotomy.

Other possible contributing factors to the effect of vagotomy on liver regeneration involve hepatotrophic substances[12)34)38)48] such as insulin and glucagon, and hemodynamics[9)16)51]. As to hepatotrophic substances, it is known that vagal stimulation accelerates the release of insulin[10)13)24]. Vagal release of other hepatotrophic substances is also possible[6)25]. Since the posterior trunk of the vagus innervates the pancreas and small intestine[22)29)39], the release of hepatotrophic substances should be controlled by the posterior trunk. In this study, however, posterior vagotomy did not have a significant effect on DNA synthesis and the mitosis of liver cells. Therefore, it seems unlikely that the effect of posterior vagotomy on liver regeneration is induced by inhibition of the release of hepatotrophic substances.

On the other hand, the effect of vagotomy on hepatic blood flow is poorly understood. GREENWAY, et al[16]. showed in cats that resistance of blood flow in the liver artery and portal vein was increased by electrical stimulation of the vagus. However, it is suggested that simply increasing blood flow through the liver does not stimulate cell division, although it increases organ weight[9)51]. WEINBREN[54] and LEE, et al.[32] disagreed with the suggestion that vagotomy has a significant effect on liver regeneration through an alteration in the regulation of hepatic blood flow.

From the above observations and discussion, it is deduced that the inhibition of liver regeneration by anterior vagotomy is induced mainly by the direct effect of vagotomy on the liver, although the participation of hepatotrophic substances and hepatic blood flow cannot be denied. The mechanism of inhibition of liver regeneration by posterior vagotomy remains to be determined.

In summary, clinical observation showed that the preservation of the hepatic and posterior celiac vagi during total gastrectomy decreased postoperative liver dysfunction, and experimental study showed that liver regeneration was suppressed by vagotomy. Therefore, it may be concluded that, during surgery in the upper alimentary tract area, the vagal nerves should be preserved in order to alleviate the postoperative liver dysfunction.

Summary and Conclusion

The effects of vagotomy on the liver were studied clinically and experimentally. The results obtained were as follows :

1. Postoperative liver function in 45 cases of total gastrectomy with preservation of the vagal nerves (non-vagotomized group) was compared with postoperative liver function in 42 cases of total gastrectomy with vagotomy (vagotomized group), using serum bilirubin, SGPT, SAP and SLDH as indicators of liver function.

i) Postoperative liver dysfunction occurred more frequently and more markedly in the

vagotomized group. Especially, a significant difference was found in the vagotomized group. Especially, a significant difference was found in the levels of serum bilirubin and SGPT, 3 to 6 weeks after surgery.

ii) In comparing the relationship between liver dysfunction and operating time and blood transfusion, no differences were found between the two groups.

iii) Appearance of liver dysfunction due to adjuvant chemotherpy, MMC or MF(C) therapy, was significantly higher in the vagotomized group. Because of toxic effects such as liver dysfunction, leucopenia and diarrhea, this therapy was interrupted more frequently in the vagotomized group.

iv) In a statistical study of the distribution of background factors, no significant differences were noted between the groups. Therefore, the above differences in postoperative liver dysfunction can be ascribed to the effect of vagotomy on liver function.

2. The effect of vagotomy on liver regeneration after partial hepatectomy in rats was investigated.

i) The weight regeneration ratio of the anteriorly and posteriorly vagotomized rats was approximately 30% lower than that of the non-vagotomized rats. This difference was statistically significant.

ii) The mitotic index and the incorporation of ^{3}H-thymidine into liver DNA showed a significant decrease after anterior vagotomy, while posterior vagotomy did not produce these effects.

iii) The size of hepatocytes estimated from the number of nuclei per calibrated area showed a significant decrease in both vagotomized groups.

iv) From the above findings, it may be concluded that anterior vagotomy suppresses the division and enlargement of liver cells, while posterior vagotomy suppresses the enlargement.

In summary, the present clinical and experimental observations showed that vagotomy produced some harmful effects on the liver. Therefore, preservation of the vagal nerves during surgery of the upper alimentary tract is recommended.

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References

1) Baldwin JN, Albo R et al: Metabolic effects of selective and total vagotomy. Surg Gyn Obst: **210** 777-783, 1965.
2) Ballinger WF: The extragastric effects of vagotomy. Surg Clin NA **46** : 455-462, 1966.
3) Biliotti GC, Masi EM : The inhibitory action of vagotomy on hepatic regeneration in rat. Archivio "de Vecchi" per L' Anatomia Pathologica e la Medicine Clinica **51** : 853, 1968.

4) Black IB: Induction of hepatic tyrosine aminotransferase medicated by a cholinergic agent. Nature **225** : 684, 1970.
5) Black IB, Reis DJ : Cholinergic regulation of hepatic tyrosine transaminase activity. J Physiol **213** : 421-433, 1971.
6) Bloom SR, Edwards AV et al: The role of the autonomic innervation in the control of glucagon release during hypoglycaemia in the calf. J Physiol **236** : 611-623, 1974.
7) Bucher NLR : Structural and kinetic aspect of hepatic regeneration in reaction to experimental injury or liver loss, Introduction. In Liver regeneration after experimental injury edited by Lesch R, Reuter W. Strattion Intercontinental Book Corp, 1975, p.1-5.
8) Canzanelli SL et al: Control of liver regeneration and nucleic acid content by the thyroid with observations on the effect of pyrimidine. Am J Physiol **157** : 225-233, 1949.
9) Clarke AM, Thomson RY et al : Vascular factors in liver regeneration. Surg Gyn Obst **126** : 45-52, 1968.
10) Daniel TM, Henderson JR: The effect of vagal stimulation on plasma insulin and glucose levels in the baboon. J Physiol **192** :317-326, 1967.
11) Fishback FC : A morphological study of regeneration of the liver after partial removal. Arch Path **7** : 955 -977, 1929.
12) Fisher B, Szuch P et al: The intestine as a source of a portal blood factor responsible for liver regeneration. Surg Gyn Obst **137** : 210-214, 1973.
13) Frohman LA, Ezdinli EZ et al: Effect of vagotomy and vagal stimulation on insulin secretion. Diabetes **16** : 443-448, 1967.
14) Fuchimoto T, Ishigami K et al : Total gastrectomy with preservation of the hepatic and celiac vagi -A countermeasure against postvagotomy syndrome following total gastrectomy-. Clin Surg **26**: 1023-1029, 1971. (Jpn)
15) Fuchimoto T, Ishigami K et al : [Vagus nerve and liver function-From the view point of total gastrectomy with preservation of the hepatic and celiac vagi-(Author's transl).] Jpn J Clin Exp Med **50** : 2294-2298, 1973. (Jpn)
16) Greenway CV, Lawson AE et al . The effects of stimulation of the hepatic nerves, infusions of noradrenaline and occulusion of the carotid arteries on liver blood flow in the anaesthetized cat. J Physiol **192** : 21-41, 1967.
17) Griffith CA: Significant function of the hepatic and celiac vagi. Am J Surg **118** : 251-259, 1969.
18) Hampel N, Lichtig C et al : Postoperative intrahepatic cholestasis. International Surgery **62** : 51-53, 1977.
19) Higgins GM, Anderson RM : Experimental pathology of the liver-I. Restoration of the liver of the white rat following partial surgical removal. Arch Path **12** : 186-202, 1931.
20) Hori M, Yamasaki Y et al: Surgical physiology of the visceral circulation in relation to perivascular nerve. Clin Surg **21** : 1366-1370, 1966. (Jpn)
21) Ichida F, Inoue K : Postoperative acute liver insufficiency. J Clin Surg **31** : 1421-1425, 1976. (Jpn)
22) Ishigami K, Fuchimoto T et al : [Various problems in vagotomy in the operation of upper digestive tract, especially total gastrectomy with preservation of the hepatic and celiac vagi and intrathoracic esophagogastrostomy with inplantation of the vagus into the wall of gastric tube (Author's transl).] Surgery (Tokyo) **34** : 1122-1474, 1972. (Jpn)
23) Ishigami K, Fuchimoto T et al : Total gastrectomy with preservation of the hepatic and celiac vagi. Arch Jap Chir **43** : 309-325, 1974.
24) Kaneto A, Kosaka K et al : Effects of stimulation of vagus nerve on insulin secretion. Endocrinology **80** :530-536, 1967.
25) Kaneto A, Miki E et al : Effects of vagal stimulation on glucagon and insulin secretion. Endocrinology **95** : 1005-1010, 1974.
26) Kissane JM, Robins E : The fluorometric measurement of deoxyribonucleic acid in animal tissue with special reference to the central nervous system. J Biol Chem **233** : 184-188, 1958.
27) Klion FM, Schaffner F et al : Hepatitis after exposure to halothane. Ann Intern Med **71** : 467-477, 1969.
28) Kuntz A : The autonomic nervous system, Philadelphia, Lea & Febiger, 1953.
29) Kure K et al : The autonomic nervous system, Tokyo, Nihon Ishoshuppan Co. 1950. (Jpn)

30) LaMonto JT, Isselbacher KJ · Postoperative jaundice. N Engl J Med **288** : 305-307, 1973.
31) Lamar C, Holloway LS : The effect of vagotomy on hepatic regeneration in rats. Acta Hepato-Gastoenterol **24** : 7-10, 1977.
32) Lee S, Broelsch CE et al: Liver regeneration after portacaval transportation in rats. Surgery **77** : 144-149, 1975.
33) Mann FC: The portal circulation and restoration of the liver after partial removal. Surgery **8** : 225-238, 1940.
34) Morley CGD, Kingdon HS: The regulation of cell growth-I. Identification and partial characterization of a DNA synthesis stimulating factor from the serum of partially hepatectomized rats. Biochim Biophys Acta **308** : 260-275, 1973.
35) Nakajima T, Ota S : Toxic reaction to MFC and MMC adjuvant chemotherapy after cancer surgery. Jpn J Cancer Clin **19** : 991-996, 1973. (Jpn)
36) Oda N : [The effects of bilateral intrathoracic truncal vagotomy on the liver function (Author's transl).] J Jpn Surg Society **34** : 1628-1641, 1933. (Jpn)
37) Okada K . A study onl iver function after total gastrectomy. Acta Medica **23** : 2093-2111, 1953.(Jpn)
38) Ozawa K, Kitamura O et al: Role of portal blood on the enhancement of liver mitochondrial metabolism. Am J Surg **124** : 16-20, 1972.
39) Pick J : The autonomic nervous system, Lippincott Co, 1970.
40) Russel D, Synder SH: Amine synthesis in rapidly growing tissues : Ornithine decarboxylase activity in regenerating rat liver, chick embryo, and various tumors. Proc Natl Acad Sci **60** : 1420-1427, 1968.
41) Saito M, Kitamura M et al : [Clinical chemical analysis IV, -Enzyme-(Author's transl).] Tokyo kagakudojin, 1970. (Jpn)
42) Sato Y, Koyama K et al : Postoperative liver failure and its preventive measures. J Clin Surg **31** : 165-173, 1976. (Jpn)
43) Schneider WC : Phosphorous compounds in animal tissue III. A comparison of methods for the estimation of nucleic acids. J Biol Chem **164** : 747-751. 1946.
44) Schneyer CA, Hall HD : Neurally mediated increase in mitosis and DNA of rat parotid with increase in bulk of diet. Am J physiol **230** : 911-915, 1976.
45) Seki M : On the effect of autonomic nervous system and portal blood supply to liver regeneration. Jpn J Gastroenterol **68** : 1063-1079, 1971. (Jpn)
46) Shibata S, Sasaki M : [Routine clinical chemistry-chemical method for ultramicroestimation (Author's transl),] Kyoto, Kinhodo Co, 1967. (Jpn)
47) Shimizu T, Amakawa A : Regulation of glycogen metabolism in liver by the autonomic nervous system II, Neural control of glycogenolytic enzymes. Biochim Biophys Acta **165** : 335-348, 1968.
48) Starzl T, Francavilla A et al : The origin, hormonal nature, and action of hepatotrophic substances in portal venous blood. Surg Gyn Obst **137** : 179-199, 1973.
49) Sugitani M, Ogiya I et al: [Effect on the liver after gastrectomy. (Author's transl).] Annual meeting of Jpn J Gastroenterol Surg VI, Kurume, 1976. (Jpn)
50) Tanturi C et al : A study of the effect of vascular change in the liver and the excitation of its nerve supply on the formation of bile. Am J Physiol **121** : 61-74, 1938.
51) Thomson RY, Clark AM : Role of portal blood supply in liver regeneration. Nature **208** : 392-393, 1965.
52) Thrower S, Ord MG : Hormonal control of liver regeneration. Biochem J **144** : 361-369, 1974.
53) Wakabayashi N: Studies on total gastrectomy with preservation of the hepatic and the posterior celiac vagi, especially the relation of the hepatic vagi to gallbladder function and the posterior celiac vagi to dumping syndrome. Arch Jap Chir **42** : 211-228, 1973.(Jpn)
54) Weinbren K : The portal blood supply and regeneration of the rat liver. Brit J Exp Path **36** : 583-591, 1955.
55) Yoshitoshi Y et al : [The criteria of diagnosis of serum hepatitis by a research team of serum hepatitis of the Ministry of Health and Welfare. (Author's transl)] cited from Current Encyclopedia of Medicine, Tokyo, Nakayama Shoten Co, 1967, p. 152. (Jpn)
56) Zimmerman HZ: Liver injury induced by chemicals and drugs. In gastroenterology edited by Bockus HL, Philadelphia, Saunders Co, 1976, p. 328.

和文抄録

迷走神経切離の肝に及ぼす影響に関する臨床的および実験的研究

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迷走神経切離（迷切）の肝に及ぼす影響を臨床的および実験的に検討し，次の成績をえた．

1．胃全摘術後肝障害における迷走神経保存の意義を迷走神経保存例40例と迷切例38例の術後肝機能成績を比較することによって検討した．肝機能障害の示標としては血清ビリルビン，GPT，アルカリフォスファターゼ，LDH を用いた．えられた結果をまとめると次のようである．

i）術後3週以内における肝機能検査では，各示標における異常値の発現頻度にはほとんど差がみられなかったが，重症度は迷切群においてつよかった．術後3～6週においては，迷切群では保存群に比べて異常値の発現頻度が高く，とくに血清ビリルビン，GPTでは有意の差を認めた．また迷切群では高度の異常をきたす例が多かった．

ii）手術時間，輸血量と肝障害との関係については両群で差を認めなかった．

iii）術後抗癌剤投与〔MMC 単独または MF(C) 併用療法〕による肝障害の発現は迷切群では保存群に比べて有意に高く，しかも早期中止例が多かった．

iv）両群において背景因子の均一性に関する推計学的検討で，有意差が認められなかったので，以上の成績は迷走神経保存の有無による差とみなされる．

2．ラットを用いて腹部前幹迷切および後幹迷切の肝再生に及ぼす影響を検討し，次の結果をえた．

i）肝部分切除後240時間における重量再生率は前幹迷切，後幹迷切とも対照の約70%であり，有意の低下を示した．

ii）前幹迷切では24時間，48時間における Mitotic index および ^{3}H-thymidine の肝 DNA へのとりこみが有意の低値を示したが，後幹迷切では有意の低値を示さなかった．一方，DNA 量にはほとんど差が認められなかった．

iii）組織学的検索で，240時間における一視野中の平均肝細胞核数は前幹迷切，後幹迷切ともに有意の増加を示した．この所見は肝細胞の萎縮を示すものである．

iv）以上の成績から，前幹迷切は肝細胞の分裂機構と肝細胞の増大を，後幹迷切は肝細胞の増大を抑制すると結論される．

以上の臨床的および実験的観察から，迷切は肝障害性に働くことが明らかであり，上部消化管手術においては，できるだけ迷走神経を保存することが望ましい．