

Effect of Segmental Interruption of Portal Venous Blood Supply on Implanted Tumor in the Liver of Rats

by

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I. INTRODUCTION

As a technical advancement of hepatic surgery, hepatic resection has come to be performed positively for a treatment of malignant tumors in the liver. Many successful cases of total right hepatic lobectomy²⁹⁾³⁸⁾⁴¹⁾⁴⁸⁾ have been reported since HONJO²⁰⁾²¹⁾. However, despite an increasing desire of extensive hepatectomy for the hepatic tumors, there are few cases of hepatic tumor which permits resection of early stage in which the tumor is localized relatively. In addition, not a few cases are experienced in which an attempt for extensive hepatic lobectomy is rejected due to more or less associated hepatic insufficiency. Particularly, in the cases in which reserve capacity of the liver is reduced markedly owing to accompanied cirrhosis or cholangitis, it has often been experienced that an extensive hepatectomy of more than a half results in severe disturbance of liver function with subsequent fatal liver insufficiency.

In the present study, it was intended to establish some surgical maneuver instead of hepatic resection for such cases of unresectable hepatic cancer.

ROUS and LARIMORE⁴²⁾ have shown that the ligation of portal venous branch to a part of the liver leads to a remarkable atrophy of the liver parenchyma of the referred region and to a progressive regenerative hypertrophy of the remaining hepatic tissue, and they emphasized that portal venous blood plays an important role in such atrophy and regenerative hypertrophy.

HONJO and KOZAKA²²⁾ divided "extensive hepatectomy in two stages" for a safe performance of hepatic resection, in which the portal venous branch to the segment destined to the resection is ligated in the first operation and the resection of the atrophied segment is performed after adequate hypertrophy of unligated region of the liver. At the same time, they demonstrated that the ligation of the portal venous branch to the extensive segment of the liver can be carried out without particular danger. KOZAKA²³⁾ also reported that the occlusion of the portal venous branch to a part of the liver has little influence on animals, even in the diseased liver, and an improvement of previously impaired liver function is observed in the unligated lobes, which is attributable to the regenerative hyper-

trophy of the referred region.

Being interested in such phenomenon as mentioned in the above, the author expected that the interruption of portal venous blood supply might have some influence on the intra-hepatic tumor growth. KRAUS and BELTRAN²⁵⁾ have demonstrated that complete devascularization of a portion of the liver containing tumor results in tumor regression in a high frequency with infarction of that region and a tendency of inhibition of the tumor growth is observed to a certain degree even in the ligation of only a branch of the portal vein or of the bile duct.

The present study was undertaken in order to investigate the effect of segmental interruption of portal venous blood supply on the hepatic tumor using implanted tumor in the liver of rats, moreover to explore the influence of ligation of the hepatic arterial branch to the tumor-bearing lobe of the liver. Possibility of application of this maneuver as a surgical treatment for unresectable carcinoma of the liver was considered, based upon the results of the present experiment.

II. MATERIALS

1. Animals.

Five hundred and twenty-six random-bred adult albino-rats of Gifu-strain, weighing 90 to 200 g, were used in the present experiment. All the animals were fed by water and a standard mixed diet.

2. Tumors.

Ascites hepatoma AH 66* (following 429 th to 435 th generation; abbreviated to AH 66 hereafter), Yoshida sarcoma* (following 1113 th to 1115 th generation) and Walker carcinoma 256** (following 109 th to 114 th generation; abbreviated to Walker 256 hereafter) were used. AH 66 and Yoshida sarcoma were maintained by weekly inoculation in the peritoneal cavity of the rats, and Walker 256 was inoculated subcutaneously every 2 weeks in the right or left axillar region of the rats.

III. METHODS

1. Anatomy of the rat liver.

The rat liver is lobulated as illustrated in Fig. 1 and 6, being consisted of two leaf-shaped diaphragmatic lobes (the left lobe and the central lobe), the right lobe and two small caudate lobes. Rats have no gallbladder. Ramification of the portal vein and hepatic artery to the lobes are accomplished at the liver hilum, and each lobe is supplied by one portal venous branch and one or two hepatic arterial branches (Fig. 1).

Proportion of liver to body weight in 16 normal rats was 4.54 % on an average, though showing slight difference in each animal depending on their body weight (Tab. 1). The left and central lobes occupied 68.1 % of total liver weight on an average as shown in Table 1. This percentage corresponded nearly to the report of HIGGINS and ANDERSON¹⁹⁾ (70.6%) or BRUES⁵⁾ (68.4%).

2. Method of implantation in the liver.

* From Sasaki Institute, Tokyo.

** From Takeda Institute, Osaka.

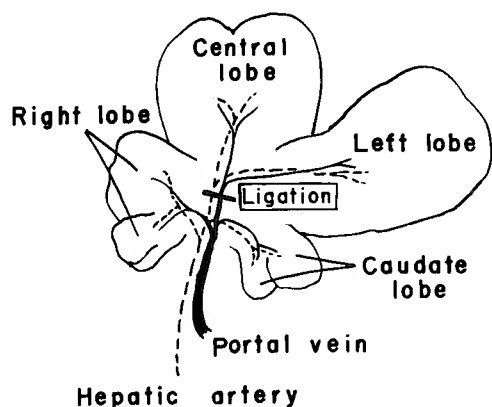


Fig. 1. Anatomy of the rat liver.
(Caudal aspect)

i. Subcutaneous inoculation for production of nodular tumor.

In AH 66 and Yoshida sarcoma, ascitic tumor cells of 500×10^4 of 7 day intraperitoneal growth were inoculated subcutaneously in the right gluteal region. In Walker 256, tumor cell suspension of 0.2 cc, containing 250×10^4 cells, was inoculated subcutaneously in the right or left axillar region. The subcutaneous nodular growth was extirpated 7 to 10 days after inoculation, capsula and necrotic mass were removed in saline solution and the tumor mass was cut into small pieces of approximately 1.5 mm^3 for intrahepatic implantation.

Tab. 1. Proportion of liver to body weight and proportion of the left and central lobes to total liver weight in normal rats.

Rat No.	Body weight (g)	Total liver weight (g)	Proportion of liver to body weight (%)	Left and central lobes	
				Weight (g)	Proportion to total liver weight (%)
1	90.7	4.4	4.85	3.0	68.9
2	92.6	3.9	4.21	2.6	66.7
3	100.5	4.5	4.48	3.1	68.9
4	101.8	4.1	4.03	2.7	65.9
5	102.6	4.8	4.68	3.2	66.7
6	103.2	4.4	4.26	3.0	68.2
Average			4.42		67.6
7	108.3	5.1	4.71	3.3	64.7
8	110.5	4.9	4.43	3.4	69.4
9	121.6	5.8	4.77	4.0	69.0
10	123.7	6.2	5.01	4.4	71.0
11	130.6	6.1	4.67	4.3	70.5
Average			4.72		68.9
12	151.2	7.0	4.63	4.8	68.4
13	155.6	6.4	4.11	4.3	67.2
14	161.4	7.3	4.52	5.2	71.2
15	172.0	7.2	4.19	4.8	66.7
16	180.3	9.1	5.05	5.9	64.8
Average			4.50		67.7
Average of three groups			4.54%		68.1%

ii. Implantation in the liver.

The rats were anesthetized with intraperitoneal isozol injection of 45 mg/kg. The abdomen was opened by an upper middle incision. The left lobe of the liver destined to the implantation was drawn out from the abdominal cavity and was wrapped up with sterile gauze to avoid scattering of tumor cells into the peritoneal cavity. Then the small piece of tumor previously prepared was bluntly inserted into the liver parenchyma with a small pincette and the stab wound was immediately cauterized and clotted with a heated probe to prevent hemorrhage and prolapse of the implanted piece. After the inoculation, the implanted lobe was retracted gently and the abdomen was closed with double layer suture. The procedure of transplantation was performed under aseptic condition within 2 hours after extirpation of subcutaneous tumor.

3. Operative procedure.

In the present experiment, the ligation of portal venous branch or hepatic arterial branches to the left and central lobes of the liver was performed in normal animals and those of tumor implantation. All the inoculated animals were divided into two groups of ligation of the portal venous branch or hepatic arterial branches to the implanted lobe (portal vein or hepatic artery ligation group) and simple laparotomy (control group). In these two groups, survival time, tumor growth and appearance of metastasis were observed.

Ligation of hepatic arterial branch was performed 7 days after the inoculation, and ligation of portal venous branch was performed 7, 10 and 14 days after inoculation respectively in animals of AH 66 inoculation, 7 days after in animals of Yoshida sarcoma inoculation and 7 and 14 days after in animals of Walker 256 inoculation. Among animals of tumor inoculation, animals of obvious intrahepatic growth as ascertained at laparotomy for the operative procedure were subjected to the experiment, and those deprived of tumor growth were excluded from the experiment. Following operations were performed under sterile condition with ether anesthesia.

i. Ligation of portal venous branch.

The abdomen was opened with upper middle incision. The portal trunk was separated with blunt dissection carefully not to injure the hepatic arteries or the bile duct and was ligated with a fine silk ligature just above the branches to the right and caudate lobes (Fig. 1). By such ligation, portal venous blood supply to the left and central lobes which occupy about 70% of total liver weight was interrupted and the whole portal flow perfused the remaining liver lobes. The abdomen was closed with double layer suture.

ii. Ligation of hepatic arterial branch.

Hepatic arterial branches to the left and central lobes were ligated in the same manner as in ligation of the portal venous branch (Fig. 1).

iii. Simple laparotomy.

As control of above mentioned ligations, simple laparotomy with liver manipulation was performed with the same technique as in ligations for observation of intrahepatic implant.

4. Method of India ink infusion into the vessels of the liver.

i. Material of infusion.

Gelatin of 10 g was dissolved in 50 cc of distilled water at 100°C with stirring and

50 cc of commercial India ink was added to this solution. With a few thymol crystals as preservative, the solution was preserved at 37°C to 38°C. Prior to infusion, it was heated to about 50°C.

ii. Method of infusion.

Infusion of India ink was performed in animals of Walker 256 inoculation and the animals were divided into three groups; group of portal vein ligation, group of hepatic artery ligation and control group. In each group, India ink-gelatin solution was injected into the portal vein or hepatic artery.

The abdomen and the chest were opened under intraperitoneal anesthesia of isozol. Then, the hepatic vein was left open and the portal trunk in the abdomen and the descending aorta in the chest were separated and cannulated. From both cannulated vessels saline solution of 35°C to 37°C was injected by dripping in order to perfuse the liver. As the perfusion was performed enough, India ink-gelatin solution was slowly infused into the portal vein or the aorta with clamping of the vessel at the hepatic hilum into which India ink was not infused.

After the infusion of India ink-gelatin solution was completed, all the vessels of the liver were occluded to prevent leakage of infused solution and the liver was extirpated with exquisite care not to injure the parenchyma. The specimen extirpated was fixed in formalin solution and kept in an ice-room for 2 or 3 hours to make the gelatin solidify.

5. Investigations.

i. Weighing of liver.

Measuring the body weight and the weight of each lobe of the liver in normal animals, those of portal venous branch ligation and those of hepatic arterial branch ligation, proportion of liver to body weight and that of the left and central lobes to the total liver weight were calculated to observe the degree of atrophy or hypertrophy of the liver lobes.

ii. Transplantability in the liver.

Transplantability was obtained from macroscopic observation of the implanted tumors within the liver, at laparotomy for simple observation or operative procedure.

iii. Survival time.

In the present experiment, an average survival time was determined in animals of each group died of tumor growth within 6 weeks. The animals survived more than 6 weeks were sacrificed 7 to 8 weeks after the inoculation to observe appearance of tumor growth.

iv. Macroscopic observation of intrahepatic tumor growth.

The maximum diameter of intrahepatic tumor was measured by callipers in all the animals at autopsy or by slaughter.

v. Appearance of metastatic spread.

In all the animals used in the present experiment, spread of extrahepatic metastases was studied, being graded as (+) in which metastases spread to only perihepatic lymphnodes, (++) in which metastases were seen in the area of the mesentery or the retroperitoneum, and (+++) in which metastatic spread extended more widely. At the same time, appearance of ascitic fluid was examined.

vi. Histological study.

Intrahepatic tumor, liver, lung and lymphnodes were examined histologically in all the experimental animals by following stainings at autopsy or sacrifice.

- a. Hematoxylin-eosin double staining.
- b. van Gieson's staining.

IV. RESULTS

- 1. Ligation of portal venous branch or hepatic arterial branch in normal rats.
- i. Group of portal vein ligation in normal rats.

In 16 normal rats, the portal venous branch to the left and central lobes of the liver was ligated. Three to five rats were killed respectively at weekly intervals to observe liver changes following segmental interruption of portal venous blood supply. After a week, the ligated lobe showed atrophy and came to occupy only 36.8% of the total liver weight, showing harder and darker appearance with coarse surface. At the same time in the unligated lobes, a remarkable hypertrophy was observed. This atrophy and hypertrophy

Tab. 2. Proportion of liver to body weight and proportion of the left and central lobes to total liver weight in rats with ligation of portal venous branch.

Rat No.	Weeks after portal vein ligation	Body weight (g)	Total liver weight (g)	Proportion of liver to body weight (%)	Left and central lobes	
					Weight (g)	Proportion to total liver weight (%)
20	1	113.5	4.9	4.32	2.2	44.9
21		121.0	5.6	4.63	2.4	42.9
22		135.5	6.4	4.72	2.1	32.8
23		140.6	6.1	4.34	1.9	31.1
24		171.9	7.4	4.30	2.4	32.4
Average				4.46	36.8	
25	2	121.3	5.0	4.12	1.3	26.0
26		143.2	6.3	4.40	1.8	28.9
27		168.5	7.1	4.21	2.1	29.6
Average				4.24	28.2	
28	3	169.1	6.9	4.08	1.0	14.5
29		178.3	7.4	4.15	1.8	24.3
30		237.7	9.8	4.12	1.5	15.4
Average				4.12	18.1	
31	4	150.3	6.1	4.05	1.0	16.4
32		156.3	1.7	3.01	1.1	23.4
33		172.0	6.7	3.90	0.9	13.4
34		189.0	7.3	3.86	0.9	12.3
35		193.5	7.2	3.72	0.8	11.1
Average				3.71	15.3	
Average in normal rats				4.54%	68.1%	

became more pronounced gradually (Fig. 7). After 4 weeks, the lobe deprived of portal venous blood tarnished and became thin, and occupied only 15.3 % of total liver weight owing to marked atrophy (Tab. 2). On the other side, the unligated hypertrophied lobes occupied 84.7 % of the total liver weight.

In microscopic sections of the ligated lobe, liver cells atrophied remarkably 2 weeks after the operation, the cell cords became thin and a comparatively proliferated connective tissue was seen in liver parenchyma. However, structure of lobules remained almost uniform (Fig. 10). On the other hand, in unligated lobes a marked hypertrophy of liver cells was observed and a large number of binucleated cells appeared in the peripheral zone of the lobules (Fig. 9).

ii. Group of hepatic artery ligation in normal rats.

In 11 normal rats, hepatic arterial branches to the left and central lobes were occluded. All the animals remained apparently healthy until they were slaughtered weekly after the operation for examination of liver changes following the ligation.

After a week, the ligated lobe deprived of arterial blood appeared darker with red tincture and softer (Fig. 8), but no change was seen in the size or the weight (Tab. 3). Histologically, though hemorrhage and degenerative change of liver cells were observed being scattered in a part of the lobules, atrophy of the liver cells was not observed (Fig. 11). There was no change in unligated lobes either macroscopically or microscopically compared with the finding before the operation. Arterial collaterals were observed in a few cases 3 weeks after the ligation of hepatic arterial branches.

Tab. 3. Proportion of liver to body weight and proportion of the left and central lobes to total liver weight in rats with ligation of hepatic arterial branch.

Rat No.	Weeks after hepatic artery ligation	Body weight (g)	Total liver weight (g)	Proportion of liver to body weight (%)	Left and central lobes	
					Weight (g)	Proportion to total liver weight (%)
40	1	114.6	5.2	4.54	3.5	67.3
41		138.4	5.9	4.26	4.0	67.8
42		150.1	6.5	4.33	4.4	66.2
43		170.1	7.1	4.17	4.8	67.6
44		198.8	9.7	4.93	6.8	70.1
Average				4.45	67.8	
45	2	143.8	6.1	4.24	1.0	65.6
46		161.0	6.7	4.16	1.8	71.7
47		180.2	8.3	4.05	5.7	68.7
Average				4.15	68.7	
48	3	153.4	6.4	4.17	4.4	68.8
49		181.7	8.1	4.38	5.5	67.9
50		202.0	8.4	4.16	5.8	69.0
Average				4.24	68.6	
Average in normal rats				1.51%	68.1%	

2. Growth of transplanted tumor in the liver.

i. Group of AH 66 inoculation.

In 31 rats, AH 66 was implanted in the left lobe. The take rate was 81.0% (25/31) as determined by laparotomy 4 days after implantation. Excluding 8 rats sacrificed weekly to examine tumor growth among 25 animals in which tumor grew, the remaining 17 rats died of the invasion and metastasis of the tumor revealing no spontaneous regression and the average survival time was 17.9 days. After 4 days, implanted tumor developed larger to be 3 to 4 mm in diameter in the liver lobe, but scarcely invaded into the liver parenchyma. After 7 days, intrahepatic metastatic invasion was markedly observed, and after 14 days, metastases spread to extrahepatic lymphnodes and bloody ascitic fluid was constantly observed. After 3 weeks, the majority of the animals died of tumor growth and frequently lung metastases were found (Tab. 4, Fig. 12).

ii. Group of Yoshida sarcoma inoculation.

In 22 rats, Yoshida sarcoma was implanted and in 20 rats, intrahepatic tumor growth was observed by laparotomy performed 4 days after the inoculation. Except 5 animals slaughtered weekly, all of 15 animals died of invasion of tumor and the average survival time was 11.2 days. As the enlargement and metastasis occurred exceedingly rapidly in Yoshida sarcoma compared with AH 66, the invasion in the liver parenchyma was already seen after 4 days and after 7 days, extrahepatic metastases, dissemination in the peritoneal cavity and frequently lung metastases were observed (Tab. 5, Fig. 33).

iii. Group of Walker 256 inoculation.

Transplantability of tumor piece was 91.2 % (31 animals out of 34 of Walker 256 inoculation), which was ascertained by laparotomy 4 days after the inoculation. Except 11 animals sacrificed weekly among 31 animals in which tumor grew, the remaining 20 animals all died of tumor growth and the average survival time was 22.9 days. Animals inoculated with Walker 256 showed almost similar tendency as seen in AH 66 inoculation in growth and metastasis, but size of tumor was larger in Walker 256 in general, and the accumulation of ascitic fluid and lung metastases were less than in the other tumor (Tab. 6, Fig. 34).

3. Effect of segmental interruption of portal venous blood supply on implanted tumor in the liver (Tab. 7).

i. Group of AH 66 inoculation.

a. Group of 7 th day operation.

Tab. 4. Growth of Ascites hepatoma AH 66 inoculated in the liver.

Days after inoculation	Diameter of tumor (mm)	Intrahepatic metastasis	Extrahepatic metastasis	Metastasis of lung	Ascites
4	3~ 4	(-)~(+)	(-)	(-)	(-)
7	5~ 7	(+)	(-)	(-)	(-)
14	10~12	(+)	(+)	(-)~(+)	(-)~(+)
21	20~25	(++)~(+++)	(++)	(+)	(++)~(+++)
25	30	(+++)	(+++)	(+)	(+++)
Transplantability in the liver				81.0%	
Average survival days of 17 rats				17.9 (14~25)	

Tab. 5. Growth of Yoshida sarcoma inoculated in the liver.

Days after inoculation	Diameter of tumor (mm)	Intrahepatic metastasis	Extrahepatic metastasis	Metastasis of lung	Ascites
4	4~5	(-)~(+)	(-)~(+)	(-)	(-)
7	7~10	(+)~(++)	(+)	(+)	(-)~(+)
14	11~15	(+++)	(+++)	(+)	(+++)
Transplantability in the liver				90.9%	
Average survival days of 15 rats				11.2 (9~16)	

Tab. 6. Growth of Walker carcinoma 256 inoculated in the liver.

Days after inoculation	Diameter of tumor (mm)	Intrahepatic metastasis	Extrahepatic metastasis	Metastasis of lung	Ascites
4	5~7	(-)	(-)	(-)	(-)
7	7~10	(+)	(-)~(+)	(-)	(-)
14	10~15	(++)	(++)	(-)~(+)	(-)
21	15~25	(++)~(+++)	(+++)	(-)~(+)	(+)
28	30~35	(+++)	(+++)	(+)	(++)
Transplantability in the liver				91.2%	
Average survival days of 20 rats				22.9 (17~34)	

AH 66 was implanted into the left lobe of 70 animals, which was followed by laparotomy 7 days later. In 12 animals, no growth was seen, and they were excluded from the present experiment. The remaining 58 animals, in which tumor grew, were divided into two groups. In 32 cases ligation of the portal venous branch to 70% region of the liver containing the implanted tumor was performed and in the remaining 26 cases simple laparotomy was made as control group. Five animals of ligation group died of technical error during or shortly after the operation.

Control group: All 26 animals died within 11 to 25 days revealing no spontaneous tumor regression, and the average survival time was 16.5 days. In the examination of all these cases at autopsy, enlargement and metastases of the tumor were remarkably observed. Intrahepatic implanted tumor enlarged to be 15 to 30 mm in diameter (Fig. 13). Metastatic spread was invariably seen not only in the other lobes of the liver and perihepatic lymph-nodes, but also in retroperitoneal, mesenteric or perirenal lymphnodes (Fig. 25). Lung metastases were found in 18 cases (Fig. 24). Bloody and muddy ascitic fluid was usually observed in the peritoneal cavity.

Histologically, tumor cells proliferated markedly within the implant being deprived of reactive cell infiltration around (Fig. 17, 18) and invaded directly in the circumferential liver parenchyma (Fig. 19). Frequently, embolus of tumor cells was observed in the small portal venous branches around tumor tissue (Fig. 23). In addition to these, no proliferation of connective tissue was seen in or around tumor tissue as observed with van Gieson's staining (Fig. 26).

Portal vein ligation group: Although 12 animals out of 27 animals died of tumor development within 18 to 31 days, but the average survival time was 24.2 days, showing a prolongation of 7.7 days compared with control group (Fig. 2). Though enlargement

Tab. 7. Effect of segmental interruption of portal venous blood supply on implanted tumor in the liver of rats.

Implanted tumor	Time of* operation	No. of inoculat.	Trans-** plant. (%)	Groups (No. of rats)	No. of tumor death	Average survival days	No. of*** survival (%)	No. of regression (%)
AH 66	7	70	82.9	P.V.L.**** (27)	12	24.2 (18~31)	15 (55.6)	7 (25.9)
				Control (26)	26	16.5 (11~25)	0	0
	10	40	80.0	P.V.L. (16)	9	23.2 (18~30)	7 (43.8)	4 (25.0)
				Control (13)	13	16.4 (13~21)	0	0
Yoshida sarcoma	14	38	81.6	P.V.L. (15)	10	23.1 (19~29)	5 (33.3)	2 (13.3)
				Control (12)	12	17.1 (15~23)	0	0
	7	36	88.9	P.V.L. (14)	14	13.7 (10~19)	0	0
				Control (14)	14	10.1 (8~15)	0	0
Walker 256	7	53	92.5	P.V.L. (23)	15	27.1 (19~39)	8 (34.8)	6 (26.1)
				Control (24)	24	19.6 (15~31)	0	0
	14	39	92.3	P.V.L. (18)	14	21.1 (18~37)	4 (22.2)	3 (16.7)
				Control (15)	15	17.8 (16~25)	0	0

* Days after inoculation
 ** Transplantability in the liver
 *** Animals survived more than 6 weeks
 **** Group of portal vein ligation

and metastases of tumor occurred as seen in control group, lung metastases were found in only 4 cases in these animals died of tumor growth, the accumulation of ascitic fluid was slight generally, and the unligated lobes hypertrophied moderately with no metastasis. The remaining 15 animals (55.6 %) survived apparently healthy more than 6 weeks after inoculation until slaughter. In these long survivors, the unligated lobes which occupied previously only 30 % of total liver weight hypertrophied to reach nearly the total liver weight before the operation. On the other side, the ligated lobe deprived of portal venous blood, which included the tumor-bearing lobe, atrophied remarkably and transplanted tumor nodule became harder and smaller to be about 5 mm in diameter. Furthermore, in 7 cases only slight trace of the implant was found in the part of the atrophied left lobe in which tumor had been previously implanted (Fig. 14). Additionally, no metastasis was observed, excluding 2 cases which had a few enlarged lymphnodes in the hilum of the liver, and

ascitic fluid was not seen in all the survivors.

Histological findings of 12 cases of tumor death revealed slight infiltration to peripheral portal venous system and degeneration or destruction of nuclei of tumor cells in a part, although accompanied by direct invasion of tumor cells in parenchyma of the liver (Fig. 20). Especially, in 9 cases the connective tissue proliferated moderately around or in the tumor tissue (Fig. 27). On the other hand, as examined in the animals survived more than 6 weeks, the connective tissue proliferated remarkably and few tumor cells were scarcely found in the ligated lobe of tumor implantation (Fig. 28). In 7 cases (25.9%), tumor cells disappeared completely and were replaced by the connective tissue or infiltration of histiocytes or other round cells (Fig. 21, 22). These findings were interpreted to reveal an occurrence of tumor regression.

b. Group of 10 th day operation.

AH 66 was implanted in the left lobe of 40 rats and 32 animals in which tumor growth was ascertained by laparotomy 10 days after inoculation were used in the experiment. Excluding 3 animals died of technical error, remaining 29 animals were divided into two groups; one for ligation of portal venous branch in 16 rats and another for simple laparotomy as control in 13 rats.

Control group: All the animals died 13 to 21 days after inoculation, showing remarkable enlargement and extensive metastasis of implanted tumor with a marked accumulation of ascitic fluid (Fig. 15). Survival time was 16.4 days on the average. Lung metastases were found in 9 cases. Histological finding revealed a similar tendency as seen in control of 7 th day operation.

Portal vein ligation group: The average survival time of 9 animals which died within 6 weeks was 23.2 days, with prolongation of 6.8 days compared with control group. The remaining 7 animals (43.8 %) survived more than 6 weeks (Fig. 2). By macroscopic and microscopic examination of these animals of portal vein ligation, a remarkable atrophy of ligated lobes and a tendency of inhibition of tumor growth were observed as seen in the animals of 7th day portal vein ligation (Fig. 16). In addition, tumor regression was observed in 4 cases (25.0 %).

c. Group of 14th day operation.

Intrahepatic tumor growth was ascertained 14 days after the implantation in 31 animals out of 38 of AH 66 inoculation. In most of these animals, implanted tumor already enlarged to be about 10 mm in diameter and extrahepatic metastatic spread or ascitic fluid was observed. Excluding 4 animals of operative death, 27 animals were divided into two groups of portal vein ligation and control.

Control group: All of 12 animals died of enlargement and metastases of tumor and the average survival time was 17.1 days.

Portal vein ligation group: Ten animals out of 15 died of tumor growth, average survival time being 23.1 days with prolongation of 6.0 days compared with that of control group (Fig. 2). The remaining 5 animals (33.3 %) survived more than 6 weeks, revealing a remarkable atrophy of the ligated lobe and a tendency of inhibition of tumor growth and metastases. Histologically, tumor regression was observed in 2 cases (13.3 %).

ii. Group of Yoshida sarcoma inoculation. (Group of 7th day operation).

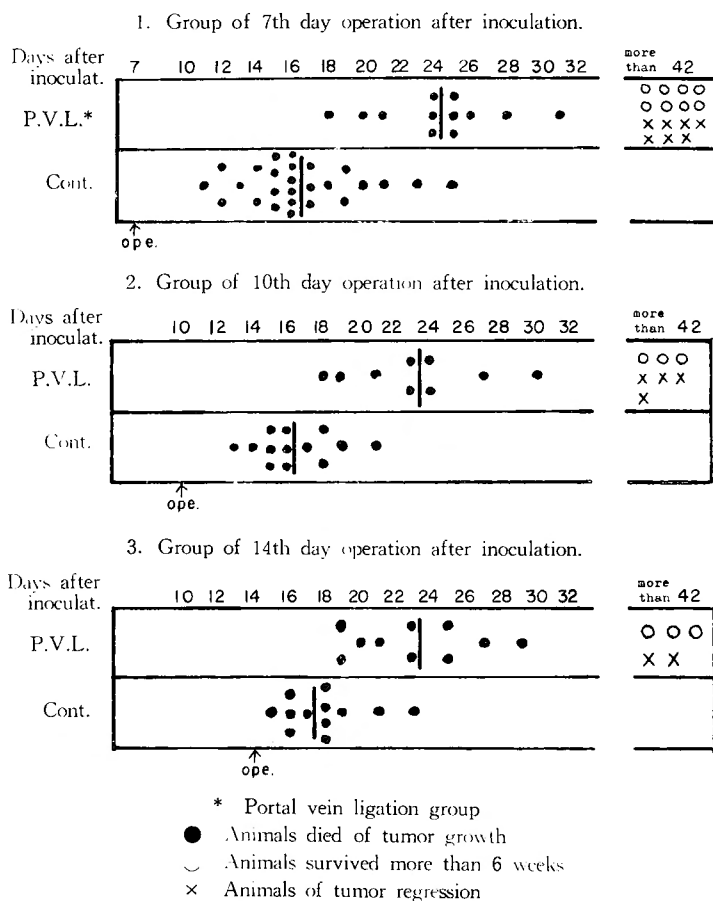


Fig. 2. Survival days of animals with ligation of portal venous branch after Ascites hepatoma AH 66 inoculation.

Yoshida sarcoma was implanted in the left lobe of 36 rats and tumor growth was ascertained by laparotomy 7 days later in 32 animals. Excluding 4 animals lost by technical error, 28 animals were divided into two groups of portal vein ligation in 14 animals and control in 14 animals.

Control group: Fourteen animals all died within 8 to 15 days and the average survival time was 10.1 days. Enlargement of implanted tumor was marked at autopsy in parallel with extensive spread of metastases not only in the perihepatic lymphnodes but also in more distant lymphnodes. Lung metastases were obviously observed in all the cases (Fig. 32). Bloody ascitic fluid was constantly seen in a large amount. Microscopic observation revealed marked proliferation and invasion of tumor cells in the parenchyma, the entire left lobe being replaced with proliferating tumor cells (Fig. 29, 31). Often embolus of tumor cells were detected in the small portal venous branches around the tumor tissue.

Portal vein ligation group: All of 14 animals died within 10 to 19 days and the average survival time was 13.7 days, showing prolongation of only 3.6 days compared with control group (Fig. 3). In all cases, enlargement and metastasis of tumor were

observed as in control group, excluding 2 animals of 18 day and 19 day survival, in which no lung metastasis was found and slight proliferation of connective tissue in the tumor tissue was observed (Fig. 30). Generally, atrophy of ligated lobe was inadequate.

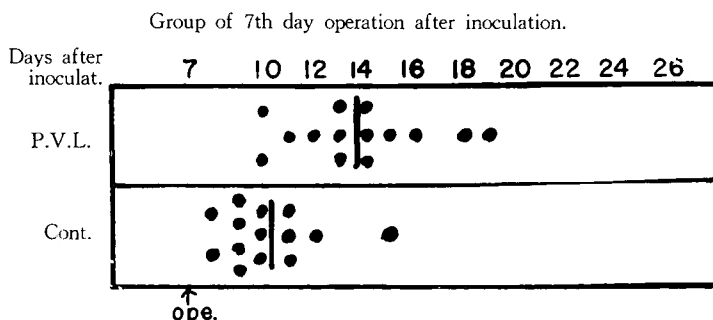


Fig. 3. Survival days of animals with ligation of portal venous branch after Yoshida sarcoma inoculation.

iii. Group of Walker 256 inoculation.

a. Group of 7th day operation.

Walker 256 was implanted in the left lobe of 53 rats, which was followed by laparotomy after 7 days. Four animals with no growth of the implant were excluded from the present experiment. The remaining 49 animals, in which tumor grew, were divided into two groups of portal vein ligation in 25 cases and simple laparotomy in 24 cases. Two animals of ligation group were lost by hemorrhage shortly after the operation.

Control group: All 24 animals died within 15 to 31 days, revealing no spontaneous tumor regression and the average survival time was 19.6 days. In these cases, the implanted tumors enlarged to be 20 to 40 mm in diameter and protruded from the surface of the left lobe (Fig. 35). Metastatic spread was invariably seen in perihepatic, mesenteric, retroperitoneal and perirenal lymphnodes and in a half of the cases metastatic foci were found in the subcutaneous tissue of the abdominal wall caused by continuous spread through the peritoneum. Lung metastasis was comparatively rare, being found in only 7 cases (Fig. 39). Though slight, bloody and muddy ascitic fluid was observed in all the cases.

Histologically, proliferation of tumor cells and invasion into liver parenchyma were marked and many islets of tumor cells were scattered in parenchyma of the left lobe (Fig. 38, 40). In most cases, tumor cells embolus in the small portal venous branches was observed. Furthermore, proliferation of connective tissue was relatively slight in or around the tumor (Fig. 43).

Portal vein ligation group: Fifteen animals out of 23 animals died within 19 to 39 days and the average survival time was 27.1 days, revealing prolongation of 7.5 days compared with control group (Fig. 4). In these animals of tumor death, development and metastasis of tumor were similarly observed as in control group, but no metastatic focus was found in the lung and hypertrophied lobes of the liver (Fig. 35). The ligated lobe including implanted tumor showed moderate atrophy.

The remaining 8 animals (34.8 %) survived more than 6 weeks. Autopsy finding of these cases 8 weeks after inoculation disclosed that the ligated lobe deprived of portal

venous blood and containing the implanted tumor encountered marked atrophy with hypertrophy of unligated lobe, and only a small trace of tumor remained in the site of the implantation in the left lobe (Fig. 37). Metastasis was not observed. Histologically, tumor regression was observed in 6 cases (26.1 %) (Fig. 42), and tumor cells were entirely replaced by the connective tissue with infiltration of histiocytes and other round cells around the site of previous tumor growth (Fig. 44). In addition to these, even in the 15 animals died within 6 weeks, a tendency of inhibition of tumor growth was observed in 11 cases with degenerative change of tumor cells and proliferation of connective tissue within the tumor tissue (Fig. 41).

b. Group of 14th day operation.

Intrahepatic tumor growth was observed in 36 animals out of 39 of Walker 256 inoculation. Excluding 3 animals died from technical error during operation, the remaining 33 animals were divided into two groups of portal vein ligation and control group.

Control group: All 15 animals died and the average survival time was 17.8 days. At autopsy, remarkable proliferation and metastasis of implanted tumor were similarly observed both macro- and microscopically as in control group of 7th day operation after Walker 256 inoculation. Bloody ascitic fluid and lung metastasis were invariably observed in all the cases (Fig. 36).

Portal vein ligation group: Although 14 animals out of 18 died of tumor growth, the average survival time was 24.1 days, revealing prolongation of 6.3 days compared with control group (Fig. 4). Histologically, proliferation of connective tissue into tumor mass was observed in 8 cases. The remaining 4 animals (22.2 %) survived more than 6 weeks, autopsy finding of which revealed atrophy of the ligated lobe including the implant being accompanied by hypertrophy of the unligated lobe. The tumor was observed to be a small node and metastasis was not observed (Fig. 37). Moreover, tumor regression was histologically ascertained in 3 cases (16.7%).

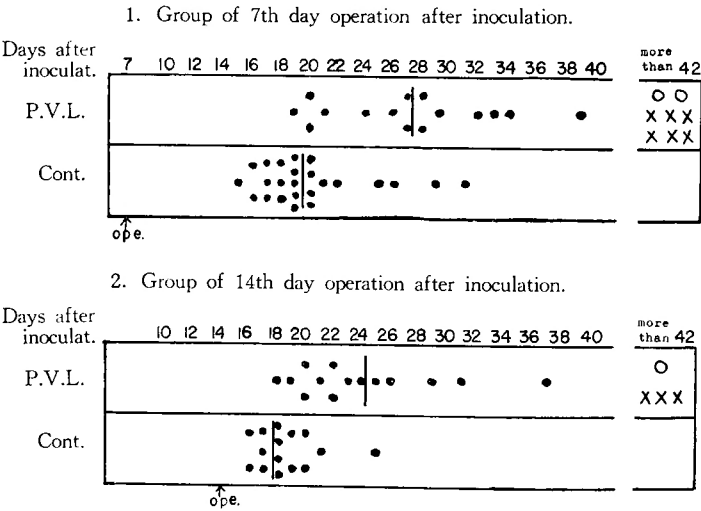


Fig. 4. Survival days of animals with ligation of portal venous branch after Walker carcinoma 256 inoculation.

4. Effect of segmental interruption of hepatic arterial blood supply on implanted tumor in the liver (Tab. 8).

Tab. 8. Effect of segmental interruption of hepatic arterial blood supply on implanted tumor in the liver of rats.

Implanted tumor	No. of inoculation	Transplant.* (%)	Groups (No. of rats)	No. of tumor death	Average survival days
AH 66	43	79.1	H.A.L.** (15)	15	16.9 (13~25)
			Control (16)	16	17.2 (14~21)
Yoshida sarcoma	30	90.0	H.A.L. (12)	12	10.8 (8~14)
			Control (11)	11	10.3 (8~15)
Walker 256	31	90.3	H.A.L. (13)	13	19.5 (16~25)
			Control (13)	13	19.2 (15~29)

* Transplantability in the liver

** Group of hepatic artery ligation

i. Group of AH 66 inoculation.

AH 66 implantation was performed in the left lobe of 43 animals, which was followed by laparotomy 7 days after inoculation. Both 9 rats with no take of the implant and 3 rats died from technical error were excluded from the experiment. The remaining 31 animals in which the tumor grew were divided into two groups of ligation of hepatic arterial branch in 15 animals and simple laparotomy as control in 16 animals.

Control group: All the animals died of tumor growth and metastasis, and the average survival time was 17.2 days.

Hepatic artery ligation group: Fifteen animals all died similarly as in control group, the average survival time being 16.9 days with little difference from control group (Fig. 5). At autopsy, atrophy was not observed in the ligated lobe and the implanted tumor enlarged markedly in the liver with wide-spread metastasis. Microscopically, tumor invasion into liver parenchyma was constantly observed and no proliferation of connective tissue was observed in or around tumor tissue (Fig. 47). Thus, tendency of inhibition of tumor growth and that of metastasis were not observed similarly as in control group.

ii. Group of Yoshida sarcoma inoculation.

Intrahepatic tumor growth was ascertained in 27 rats out of 30 intrahepatic implantation. Excluding both 3 animals of no take and 4 animals died of technical error, remaining 23 animals were divided into two groups of hepatic artery ligation in 12 cases and control in 11 cases.

All the animals died of tumor growth in both groups of the ligation and control. The average survival time was 10.3 days in control group and 10.8 days in ligation group

(Fig. 5). There was no significant difference in survival time, tumor growth and metastatic spread between these two groups (Fig. 48).

iii. Group of Walker 256 inoculation.

Intrahepatic tumor growth was ascertained in 28 rats out of 31 intrahepatic implantation 7 days after inoculation. Excluding 2 animals of operative death, the remaining 26 animals were divided into two groups of hepatic artery ligation in 13 cases and simple laparotomy for control in 13 cases.

All the animals of both groups died of tumor development and metastasis, average survival time being 19.2 days in control group and 19.5 days in ligation group (Fig. 5). There was no significant difference in macro- and microscopic findings between control and ligation group (Fig. 49).

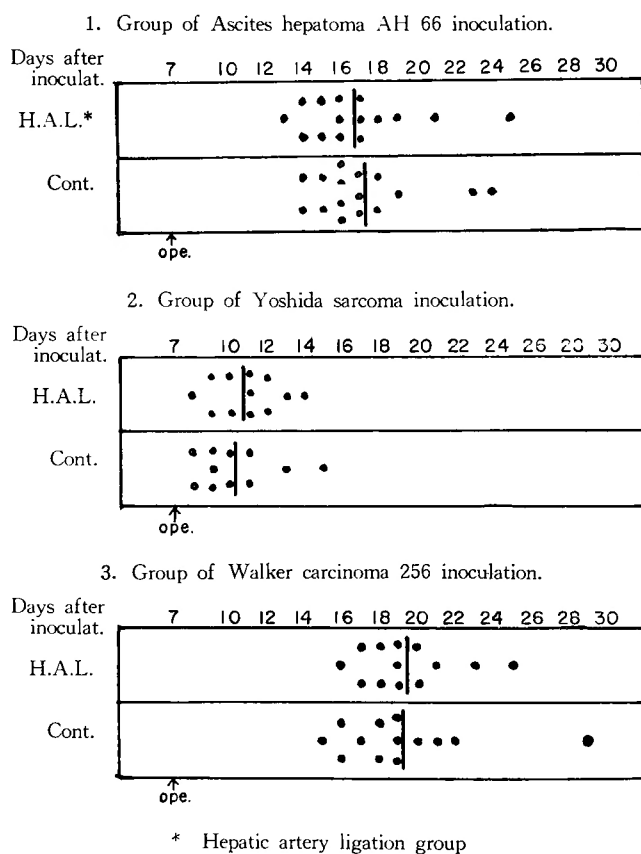


Fig. 5. Survival days of animals with ligation of hepatic arterial branch after tumor inoculation.

5. Infusion of India ink to the intrahepatic implant through the blood vessels.

Intrahepatic tumor growth was ascertained 7 days after the implantation of Walker 256 in the left lobe in 24 animals out of 26. These 24 animals were divided into 3 groups of 7th day ligation of the portal venous branch to the lobe of implantation in 8 cases, ligation of hepatic arterial branch in 8 cases and simple laparotomy in the remaining 8

cases. India ink was injected from the portal vein or hepatic artery in 4 animals of each group, respectively 7 days after the operation, and appearance of blood supply to intrahepatic implant was studied.

i. Infusion from the hepatic artery.

Intrahepatic tumor tissue was stained with India ink in all of 4 cases of control. Although similar finding was obtained in the group of portal vein ligation as in control group, proliferation of connective tissue into tumor tissue was observed in 2 cases out of 4, suggesting inhibition of tumor growth (Fig. 50). On the other hand, India ink was not found within tumor tissue in 2 cases of hepatic artery ligation as was expected, whereas in the remaining 2 cases India ink was found in tumor tissue by way of arterial collaterals.

ii. Infusion from the portal vein.

In portal vein ligation group, India ink was not seen in the ligated lobe as a matter of course. On the other side, in both control and hepatic artery ligation group, both of which showed marked tumor development, abundant vascular net of portal vein around tumor mass was stained with India ink (Fig. 51, 52), while India ink was hardly seen within the tumor.

V. DISCUSSION

It is well known that the liver has a great reserve capacity and the function is well compensated by regenerative hypertrophy of the remaining liver tissue even when a large segment of the liver is resected¹⁰⁾¹⁹⁾⁴⁰⁾. On the other hand, it has been demonstrated that even in normal liver an extensive resection of exceeding 80% of the total liver results in a serious damage of parenchyma of the remaining liver such as watery vacuolation¹⁾, decay of liver function³⁴⁾ or disturbances of systemic and portal circulation⁴⁵⁾ at an early stage, which finally lead animals to death. Moreover, in the clinical cases of hepatic cancer more or less associated with functional insufficiency, obviously there appears a possibility of increase in such disturbances following hepatic resection, which firmly rejects the attempt for extensive hepatic lobectomy.

Since FRERICH¹⁶⁾ (1860), there are numerous clinical reports of observation of marked atrophy in the hepatic lobe following occlusion of the portal venous branch to the lobe³⁾⁸⁾. It has been also observed experimentally that the ligation of the portal venous branch leads to progressive atrophy of the region of the liver deprived of portal venous blood and at the same time to hypertrophy of the unligated region of the liver in dogs⁷⁾, cats⁸⁾, rabbits⁴²⁾⁴⁴⁾ and rats²⁸⁾. It is widely accepted that intrahepatic portal venous blood flow plays an important role in such phenomenon³⁰⁾⁴²⁾.

KOZAKA²³⁾ devised "extensive hepatectomy in two stages" in the intention of establishing a safe extensive hepatic lobectomy applying this phenomenon and demonstrated that ligation of the portal venous branch to 80 % region of the liver in rabbits similarly results in above mentioned regenerative hypertrophy of unligated lobe as seen in hepatic lobectomy with little influence on the portal and systemic circulation and on liver function. In the present experiment, ligation of the portal venous branch to 70 % region of the liver could be performed with comparative safety in rats and followed by remarkable atrophy of ligated lobes with progressive hypertrophy of the remaining lobes. It has been demonstrated that

the portal venous branch to a large part of the liver can be ligated safely and previously impaired liver function is improved more or less owing to regenerative hypertrophy of the unligated lobes even in diseased liver^{18) 23)}.

As mentioned in the above, ligation of the portal venous branch can be performed fairly safely even in the impaired liver with resulting in remarkable atrophy of the ligated lobe and hypertrophy of the remaining liver. Hereupon, it is a problem of interest what influence would be brought about on tumor growth by interruption of portal venous blood supply to the lobe of tumor lesion.

In the present experiment, interruption of portal venous blood supply to 70 % region of the liver lobe including implanted tumor in rats was undertaken using AH 66, Yoshida sarcoma and Walker 256 to investigate this problem (Tab. 7). In group of 7th day operation after intrahepatic inoculation of AH 66, more than a half of the animals of portal vein ligation survived more than 6 weeks. On the contrary, all the animals of control group died of tumor growth within 6 weeks. Even in the animals of portal vein ligation which died within 6 weeks, average survival time was prolonged more than a week compared with control group. Furthermore, tumor regression was observed histologically in 25.9 % of portal vein ligation group. In the group of 10th day operation after AH 66 inoculation, animals of portal vein ligation revealed a similar tendency of inhibition of tumor growth and metastasis as in the above mentioned group. In group of 7th day operation after Walker 256 inoculation, 34.8 % of animals of portal vein ligation similarly survived for more than 6 weeks showing tumor regression in 26.1 %. Prolongation of average survival time exceeding a week was observed compared with control group even in animals of tumor death. In addition, even in two groups of 14th day operation after respective inoculation of AH 66 and Walker 256, 20 to 30 % of animals survived more than 6 weeks in portal vein ligation group and tumor regression was found in about 15% of these groups.

In these experiments, control animals invariably died of remarkable enlargement of the implanted tumor and extensive metastatic spread, whereas in the animals of portal vein ligation, degeneration and destruction of tumor cells and proliferation of connective tissue into tumor mass were observed even in animals of ultimate tumor death and in animals of long survival in this group, marked atrophy of the ligated lobes and regenerative hypertrophy of the remaining lobes were observed, the tumor mass becoming a small node, some of which were ascertained to be tumor regression histologically. Growth of tumor and its metastatic spread were obviously inhibited by interruption of portal venous blood supply compared with control animals.

In animals of 7th day portal vein ligation after Yoshida sarcoma inoculation, although tumor regression was observed in no cases and prolongation of survival time was short, degeneration of tumor cells and proliferation of connective tissue into tumor tissue were observed in several cases.

KRAUS and BELTRAN²⁵⁾ also observed tumor regression in 31.2 % of animals of portal vein ligation performed in the portal venous branch draining into 30 % region containing the lobe of implantation 7 days after Walker 256 implantation in the right lobe.

Differences in the effect of interruption of portal venous blood supply on the implanted

tumor might be attributed to the difference of growth and metastatic spread at the time of ligation depending upon the individuality. Furthermore, there might exist some cases in which extrahepatic metastasis is already established regardless of macroscopic finding. On the other hand, the degree of atrophy following portal venous branch ligation also differs depending on individuality of animals. In the present experiment, the later the time of ligation was, the slighter the inhibition of growth and metastatic spread of tumor. It is probably due to the fact that such cases had already enlargement of the implant and extrahepatic metastatic spread before the portal vein ligation. In addition to these, no particular prolongation of survival time was observed in animals of portal vein ligation after inoculation of Yoshida sarcoma, and this is presumably due to rapid intrahepatic growth and rapid metastatic spread in Yoshida sarcoma, and moreover due to loose connection of tumor cells in non-epithelial Yoshida sarcoma different from AH 66 and Walker 256²⁷⁾⁵²⁾.

Although there exist some difference depending upon the strain of tumors and time of the ligation, above mentioned inhibition of growth and metastatic spread of tumor and a tendency of tumor regression were observed in the ligation groups, whereas the animals invariably died of tumor in control groups, which is interpreted that interruption of portal venous blood supply to the region of tumor growth has an important significance in this phenomenon.

In animals of portal vein ligation, particularly in those of long survivals, atrophy of the liver parenchyma of the ligated region was marked, which was also microscopically ascertained as a marked atrophy of liver cells accompanied by prominent proliferation of connective tissue. From this finding, atrophy of liver parenchyma and proliferation of connective tissue of the ligated lobe are assumed to be important factors to prevent growth and invasive infiltration of tumor. FISHER¹⁵⁾ observed pseudopodal cytoplasmic extension of tumor cells to the surrounding hepatic cells by electron microscopic studies of Walker 256 inoculated in the liver and presumed that there might exist some tumor cells in the marginal area of hepatic tumor which directly receive nutritional supply from the hepatic cells around the tumor. From this point of view also, an atrophy of liver cells surrounding the tumor might bring an unfavorable condition to the tumor growth.

Intrahepatic metastatic spread through the intrahepatic portal venous system can well be prevented by the ligation of the portal venous branch to the lobe of tumor lesion. WILLIS⁵⁰⁾ pointed out in clinical cases of hepatic cancer that tumor embolus in the portal vein around tumor tissue can be observed frequently at an initial stage of tumor cell invasion to the surrounding liver parenchyma. In the present experiment, embolus of tumor cells in the portal vein was often observed in the area of vigorous tumor growth in control group, whereas such finding was hardly observed in portal vein ligation group.

Concerning the blood supply to hepatic tumor, many studies have been attempted both clinically and experimentally employing infusion method³¹⁾³⁶⁾ or vascular cast preparation technique³⁵⁾. Recently, FISHER¹²⁾ reported that intrahepatic tumor which is produced by tumor cell injection either from the portal vein or hepatic artery is invariably supplied by arterial blood. BREEDIS and YOUNG⁴⁾ also observed the similar finding in liver tumor of rabbits and mice, but according to their clinical observations on hepatoma, 15 % of the

cases revealed portal venous blood supply to the tumor more or less. On the other hand, WRIGHT⁵¹⁾ studied vascularization of metastatic hepatoma and presumed that hepatoma receives nutritional supply from the portal vein or directly from liver cells at the initial stadium of tumor proliferation, and he maintained participation of portal venous blood, to some extent, in tumor growth. MATSUMURA³²⁾, in our clinic, investigated blood supply of several implanted tumors in the rat liver by vital staining with infusion method and observed existence of abundant vascular nets of portal venous system around tumor tissue, and the tumor tissue was partly stained by vital pigment infused from the portal vein, although tumor tissue was mainly stained by the pigment infused from the hepatic artery.

Based upon the concept that hepatic tumor receives arterial blood supply, BREEDIS and YOUNG⁴⁾ performed interruption of hepatic artery in several rabbits having Vx₂ carcinoma in the liver, and reported that regression of implanted tumor could not be observed. They attributed the cause of this finding to the early establishment of the collaterals to intrahepatic tumor. However, FISHER¹²⁾ failed to demonstrate inhibition of tumor growth by a complete interruption of arterial blood supply to hepatic tumor, in spite of the absence of significant arterial collaterals, and asserted that complete devascularization of the region of tumor was indispensable for the regression of tumor.

In the present experiment, ligation of hepatic arterial branch to intrahepatic growth of AH 66, Yoshida sarcoma and Walker 256 did not result in atrophy of the ligated lobe as was observed following the ligation of the portal venous branch, consequently without prolongation of survival time and inhibition of tumor growth and the animals similarly died as in control animals (Tab. 8). Furthermore, by the investigation of blood supply to intrahepatic tumor using India ink infusion method, India ink infused from the portal vein was widely scattered in the marginal area of actively growing tumor tissue in the animals of hepatic artery ligation. On the contrary, India ink infused by way of the hepatic artery was found within the intrahepatic tumor tissue of portal vein ligation animals, despite the tendency of inhibition of tumor growth. From these facts, it cannot be readily denied that portal venous blood may play an important role in tumor growth in the peripheral area of the implanted intrahepatic tumor where the growth and metastatic invasion are principally achieved. The fact that inhibition of tumor growth could not be observed following the interruption of arterial blood to the implanted lobe may be explained to be due to absence of atrophy of liver parenchyma or proliferation of connective tissue in the region of the interruption of hepatic arterial blood supply as was observed following the interruption of portal venous blood supply.

It has been already demonstrated that complete devascularization of hepatic segment of tumor implantation results in tumor regression in a high incidence in rats²⁵⁾. Although rats can well survive devascularization of 70 % region of the liver²⁶⁾, this procedure is life-threatening in other species of animal⁹⁾ and clinical application of this procedure involves so much danger.

There have been many experimental reports that ligation of the branch of the bile duct also results in hypertrophy of the unligated lobe and atrophy of the ligated lobe²⁾⁴³⁾⁴⁴⁾. Such atrophy as caused by bile duct occlusion, however, has been accepted to be brought about by compression of dilated bile duct to the intrahepatic portal system³³⁾. It is moreover

reported that the degree of atrophy caused by bile duct ligation is slight in rats¹⁸⁾. Accordingly, it is presumed that the effect of bile duct ligation is not so large as in ligation of the portal venous branch, sometimes being accompanied by unfavorable complications such as leakage of bile from the dilated bile duct due to the ligation. Thus, bile duct ligation has less significance to be recommended clinically.

Many studies have been employed in the relationship between hepatic regeneration and humoral factor⁶⁾¹⁷⁾⁴⁹⁾, and some reseachs insist that enhancing factor for hepatic regeneration prompts growth of certain subcutaneous transplantable tumor on the other side³⁹⁾. However, TROTTER⁴⁷⁾ asserted that such a factor has no influence upon tumor already exists.

FISHER investigated several factors possibly influencing hepatic metastasis of tumors¹¹⁾ and observed that it is immediate damage to the liver such as hepatic resection that enhances hepatic metastasis of tumors¹³⁾¹⁴⁾. Ligation of the portal venous branch as studied in the present experiment has less damage to the liver compared with that of hepatic resection, accordingly with less dissemination of tumor cells within the liver parenchyma.

There exists a possibility of enhancement of tumor growth at the ligation of the portal venous branch for hepatic tumor in parallel with the regenerative hypertrophy if the metastatic spread has already invaded the unligated lobe destined to hypertrophy. Concerning this problem, NAGATA³⁷⁾, one of our co-workers, observed that enlargement of intrahepatic Walker 256 in regenerating liver was not so marked compared with that in control group after regenerative hypertrophy of the region containing the tumor. TAKITA⁴⁶⁾, also, observed less frequent metastasis to regenerated liver, and demonstrated relatively delayed growth of tumor in regenerated liver lobe, using Yoshida sarcoma.

In addition to these, HONJO and KOZAKA²²⁾²⁴⁾ performed "extensive hepatectomy in two stages" for a case of stomach cancer with hepatic metastases to the right lobe 3 weeks after the ligation of portal venous branch to the region of tumor, and reported that the tumor enlargement and metastasis were not so advanced at the 2nd laparotomy with remarkable atrophy of the right lobe deprived of portal venous blood, and microscopically, proliferation of connective tissue was found in the tumor tissue (Fig. 45, 46). Considering from these findings of clinical and experimental observation, it is possibly presumed that growth and metastasis of tumor can be inhibited to some extent also in human hepatoma by interrupting portal venous blood supply to the region including the tumor growth.

From the results of the present experiment, it is expected that clinical application of segmental interruption of portal venous blood supply on hepatic tumor can be recommended as a surgical treatment for unresectable hepatic cancer which promises therapeutic effect of certain extent, effect of which would be further improved by simultaneous use of anti-cancer drugs.

VI. SUMMARY AND CONCLUSION

Effect of segmental interruption of portal venous blood supply to the region of tumor growth on hepatic tumor was studied using several strains of transplantable tumor in the liver of rats, and influence of ligation of hepatic arterial branch to the liver lobe containing implanted tumor was investigated similarly, and the results obtained are summarized as

follows ;

1. In normal rats, ligation of the portal venous branch to 70 % region of the liver could be performed with relative safety, resulting in a remarkable atrophy of the hepatic region deprived of portal venous blood, and a hypertrophy of the unligated lobe. Neither atrophy nor hypertrophy could be observed after the ligation of the hepatic arterial branch.

2. Ascites hepatoma AH 66, Yoshida sarcoma and Walker carcinoma 256 were implanted in the left lobe of rat liver and ligation of the portal venous branch to 70 % region of the liver containing the tumor growth was performed at several periods after intrahepatic inoculation. Results are summarized as follows ;

i. Group of AH 66 inoculation in the liver.

Group of 7th day portal vein ligation : All the control animals died of tumor growth and the average survival time was 16.5 days. On the other hand, in portal vein ligation group 55.6 % of the animals survived more than 6 weeks, revealing a tendency of inhibition of tumor growth and metastatic spread with a remarkable atrophy of the ligated lobe including tumor. Histologically, tumor regression was observed in 25.9 % of portal vein ligation group. Even in the animals died within 6 weeks, the average survival time was 24.2 days, showing prolongation of 7.7 days compared with control group.

Group of 10th day portal vein ligation : All the control animals died and the average survival time was 16.4 days. In ligation group, 43.8 % of animals survived more than 6 weeks and 25.0 % of animals revealed tumor regression. The animals of ligation group died within 6 weeks showed prolongation of 6.8 days in the average survival time compared with control group.

Group of 14th day portal vein ligation : In ligation group, 33.3 % of animals survived more than 6 weeks and tumor regression was observed in 13.3 %. The average survival time of the animals died within 6 weeks was prolonged 6.0 days compared with that of control group.

ii. Group of Yoshida sarcoma inoculation in the liver.

Group of 7th day portal vein ligation : All the animals of both control and ligation groups died of tumor growth and metastases, the average survival time being 10.1 days in control group and 13.7 days in ligation group. Two cases of ligation group showed a tendency of inhibition of tumor growth microscopically.

iii. Group of Walker carcinoma 256 inoculation in the liver.

Group of 7th day portal vein ligation : All the animals of control group died of tumor growth with the average survival time of 19.6 days. On the contrary, in ligation group 34.8 % of animals survived more than 6 weeks being apparently healthy, and the animals which died within 6 weeks revealed prolongation of 7.5 days in the average survival time compared with control group. Histologically, animals of ligation group showed a similar tendency of inhibition of tumor growth as in group of 7th day ligation after AH 66 inoculation, and tumor regression was observed in 26.1 %.

Group of 14th day portal vein ligation : In ligation group, 22.2 % of animals survived more than 6 weeks, 16.7 % showed tumor regression and the animals died within 6 weeks revealed prolongation of 6.3 days in the average survival time compared with control group.

3. Ligation of hepatic arterial branches to the hepatic lobe containing tumor was performed 7 days after AH 66, Yoshida sarcoma or Walker 256 inoculation in the liver. In each group of tumor inoculation, all the animals of both control and ligation groups died of tumor growth. No difference in survival time, tumor growth and metastases was observed in these two groups.

4. With an attempt to investigate blood supply of implanted Walker 256 in the liver, India ink was infused from the both portal vein and hepatic artery. In hepatic artery ligation group and non-ligation group in which the implanted tumor grew remarkably in the liver, India ink infused from the portal vein was observed constituting a network around the tumor tissue. On the other side, India ink infused from the hepatic artery was observed within the tumor tissue even in portal vein ligation group in which a tendency of inhibition of tumor growth was observed.

5. From the results of the present experiment, it was ascertained that tumor growth and metastatic spread can be inhibited by segmental interruption of portal venous blood supply to the region of implanted tumor. Accordingly, certain therapeutic effect can be expected by clinical application of this measure, under exquisite selection of cases, as a surgical treatment for unresectable malignant tumor in the liver.

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Fig. 6 Liver of normal rat (caudal aspect)

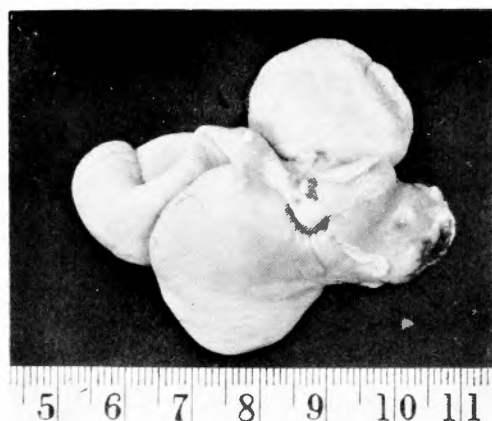


Fig. 7 Liver of rat 3 weeks after portal ligation, showing an atrophy of left and central lobes and a hypertrophy of the unligated lobes.

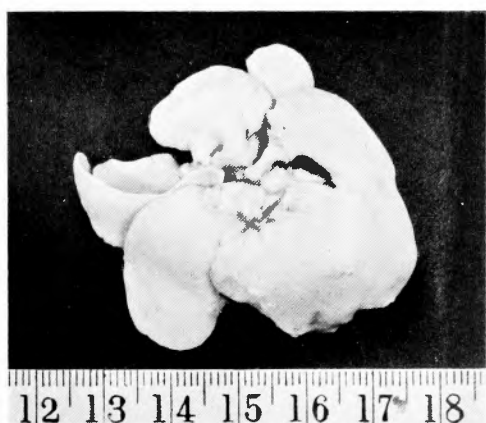


Fig. 8 Liver of rat 3 weeks after hepatic arterial ligation.

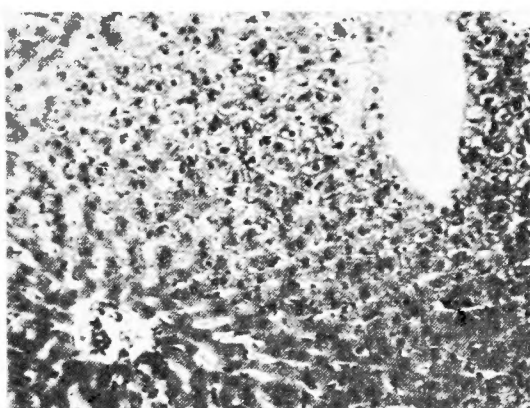


Fig. 9 The unligated lobe of liver 2 weeks after portal ligation. H-E $\times 100$

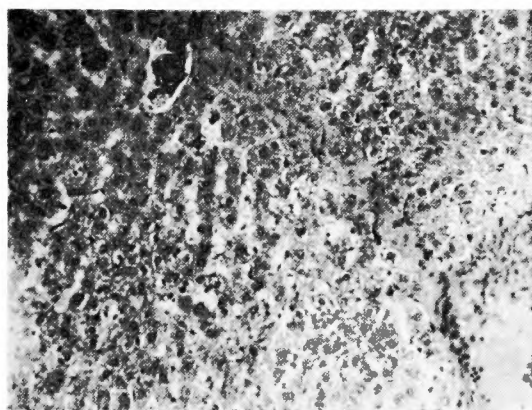


Fig. 10 The ligated lobe of liver 2 weeks after portal ligation, showing an atrophy of liver cells. H-E $\times 100$

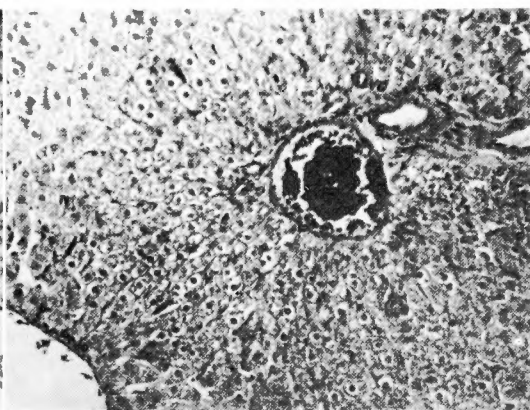


Fig. 11 The ligated lobe of liver 2 weeks after hepatic arterial ligation. H-E $\times 100$

PLATE 2 Rats inoculated with AH 66 in the liver

after inoculation

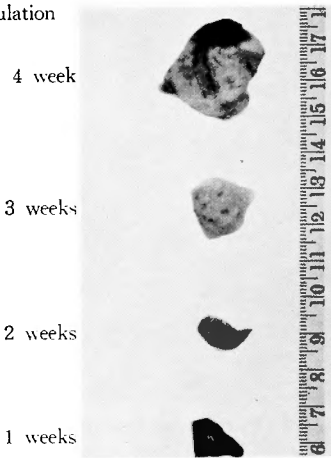


Fig. 12 Growth of AH 66 in the liver.



Fig. 13 The hepatic tumor of control animal died 19 days after inoculation. (Group of 7th day operation.)

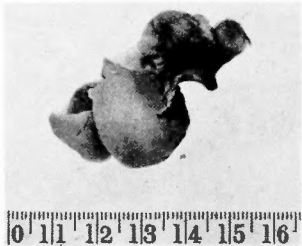


Fig. 14 The liver of portal ligation animal survived more than 6 weeks, showing an atrophy of ligated lobe and a tendency of tumor regression. (Group of 7th day operation.)



Fig. 15 Macroscopic aspect of control animal died 21 days after inoculation. (Group of 10th day operation.)



Fig. 16 Macroscopic aspect of portal ligation animal survived more than 6 weeks. (Group of 10th day operation.)

PLATE 3 Rats inoculated with AH 66 in the liver (Group of 7th day operation)

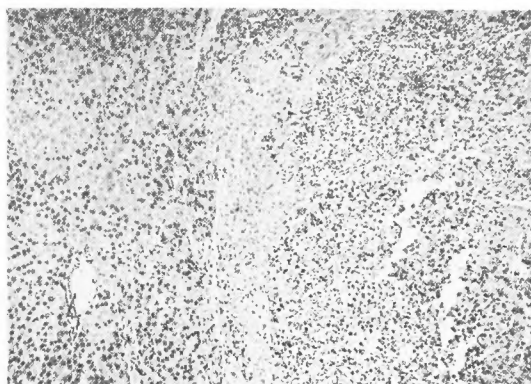


Fig. 17 Tumor growth in the left lobe of control animal died 18 days after. H-E $\times 100$

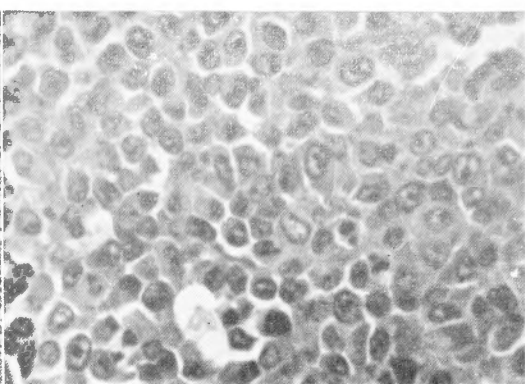


Fig. 18 Hepatic tumor growth of control animal. H-E $\times 400$

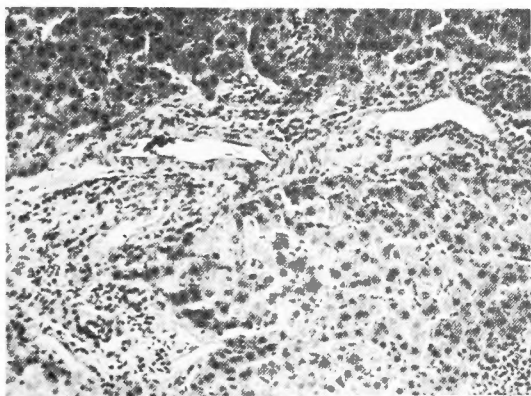


Fig. 19 Metastatic invasion of tumor cells in liver parenchyma of control animal died 17 days after. H-E $\times 150$

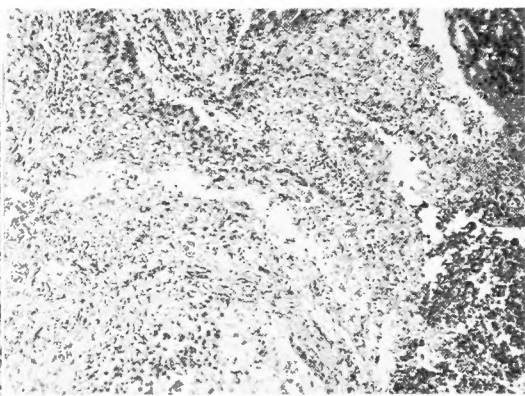


Fig. 20 The ligated lobe of portal ligation animal died 28 days after, showing proliferated connective tissue in hepatic tumor. H-E $\times 100$

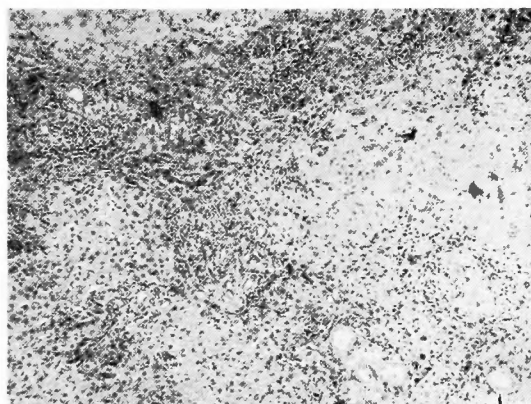


Fig. 21 The ligated lobe of portal ligation animal survived more than 6 weeks, showing tumor regression. H-E $\times 100$

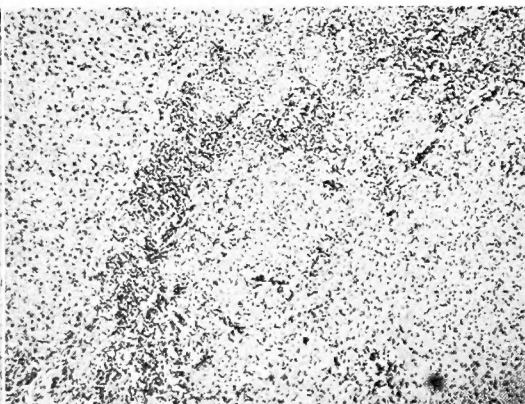


Fig. 22 The ligated lobe of portal ligation animal survived more than 6 weeks, showing tumor regression with histiocytes infiltration. H-E $\times 100$

PLATE 4 Rats inoculated with AH 66 in the liver (Group of 7th day operation)

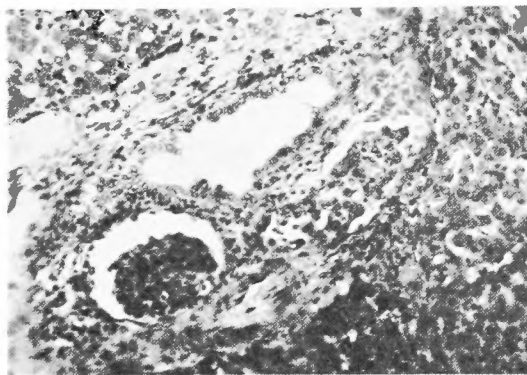


Fig. 23 Embolus of tumor cells in portal branches of control animal died 19 days after.
H-E $\times 100$

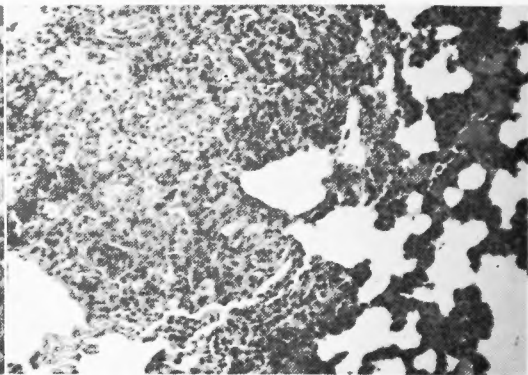


Fig. 24 Lung metastasis of control animal died 14 days after.
H-E $\times 100$

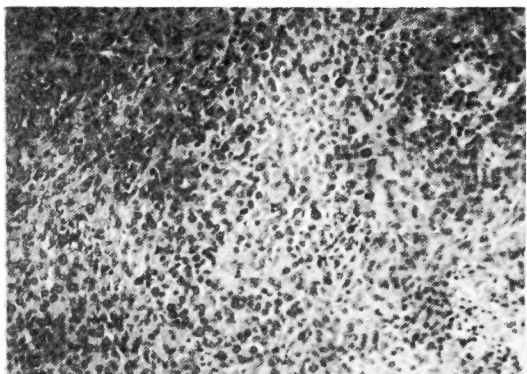


Fig. 25 Metastasis of perihepatic lymphnode of control animal died 16 days after. H-E $\times 100$

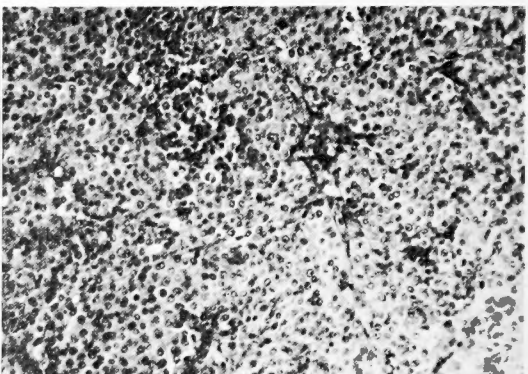


Fig. 26 Hepatic tumor growth of control animal died 23 days after, showing no proliferated connective tissue in the tumor.
van Gieson $\times 100$

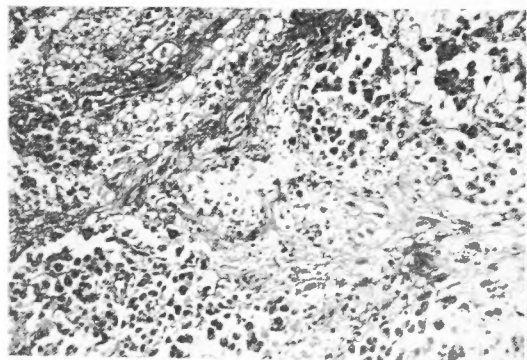


Fig. 27 The ligated lobe of portal ligation animal died 24 days after, showing proliferated connective tissue in the tumor.
van Gieson $\times 100$

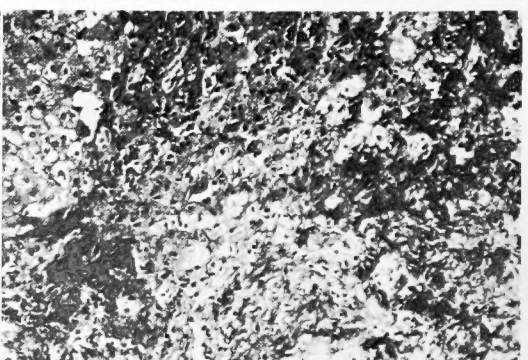


Fig. 28 The ligated lobe of portal ligation animal survived more than 6 weeks, showing tumor regression with proliferated connective tissue.
van Gieson $\times 100$

PLATE 5

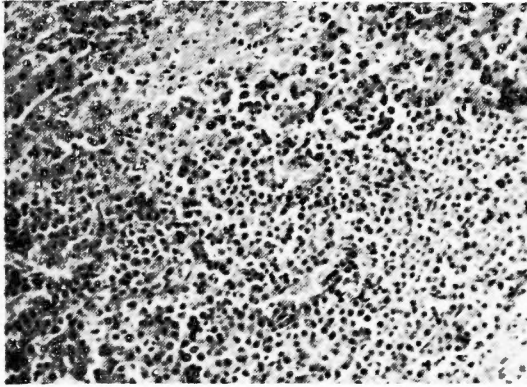


Fig. 29 Hepatic tumor growth of control animal died 10 days after Yoshida sarcoma inoculation.
H-E $\times 100$

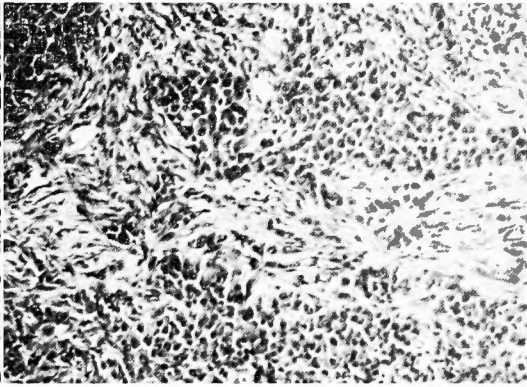


Fig. 30 The ligated lobe of portal ligation animal died 18 days after Yoshida sarcoma inoculation.
H-E $\times 100$

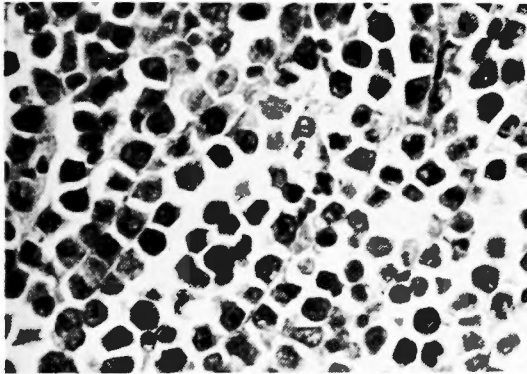


Fig. 31 Hepatic tumor growth of control animal inoculated with Yoshida sarcoma.
H-E $\times 400$

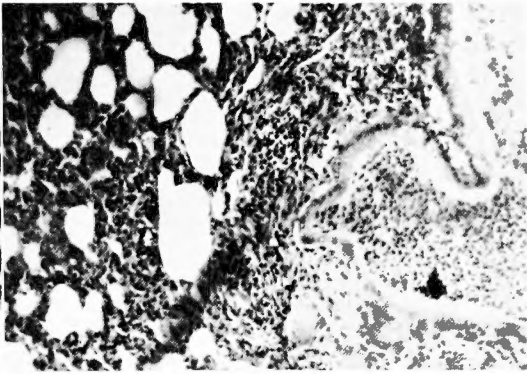


Fig. 32 Lung metastasis of control animal died 8 days after Yoshida sarcoma inoculation.
H-E $\times 100$

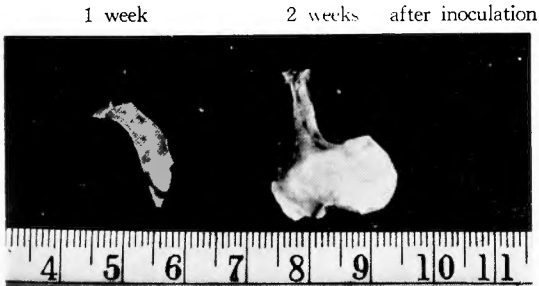


Fig. 33 Hepatic growth of Yoshida sarcoma.

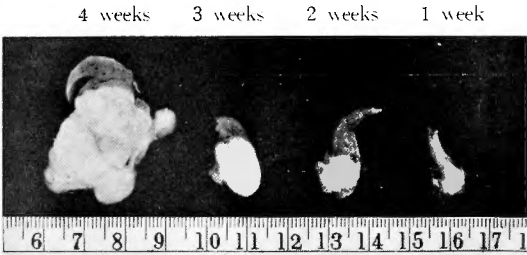


Fig. 34 Hepatic growth of Walker carcinoma
256.

PLATE 6 Rats inoculated with Walker 256 in the liver

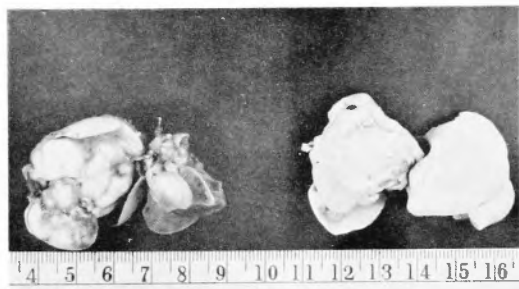


Fig. 35 Liver of portal ligation animal died 24 days after (right), and hepatic tumor of control animal died 22 days after (left). (Group of 7th day operation).



Fig. 36 Liver, lung (left) and kidney (right) of control animal died 18 days after. (Group of 14th day operation).

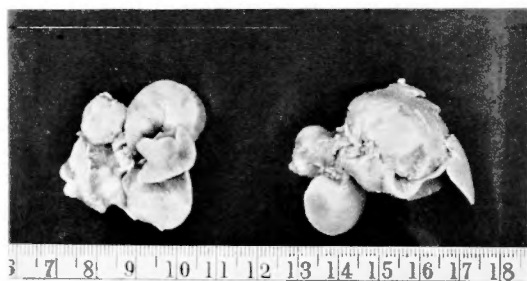


Fig. 37 Liver of portal ligation animal survived more than 6 weeks. (Left: Group of 7th day operation, Right: Group of 14th day operation).

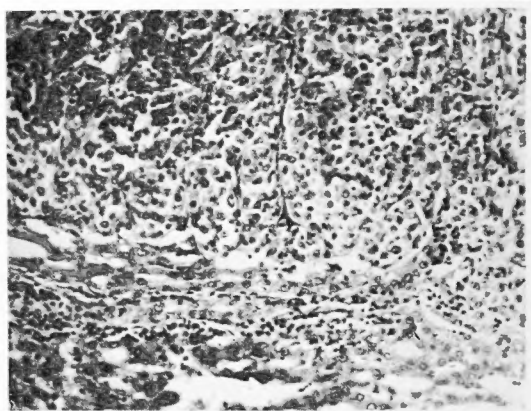


Fig. 38 Hepatic tumor growth of control animal died 19 days after. H-E $\times 000$ (Group of 7th day operation).

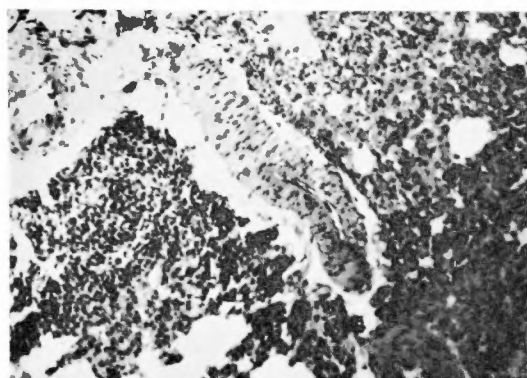


Fig. 39 Lung metastasis of control animal died 16 days after. H-E $\times 100$ (Group of 7th day operation).

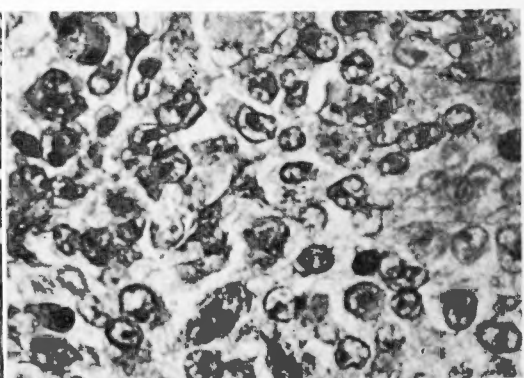


Fig. 40 Hepatic tumor growth of control animal. H-E $\times 400$

PLATE 7 Rats inoculated with Walker 256 in the liver (Group of 7th day operation)

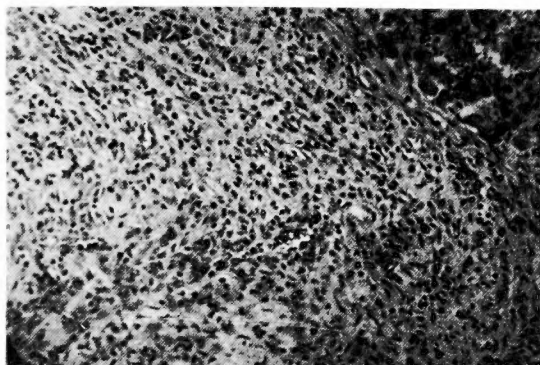


Fig. 41 The ligated lobe of portal ligation animal died 32 days after, showing proliferated connective tissue in the tumor. H-E $\times 100$

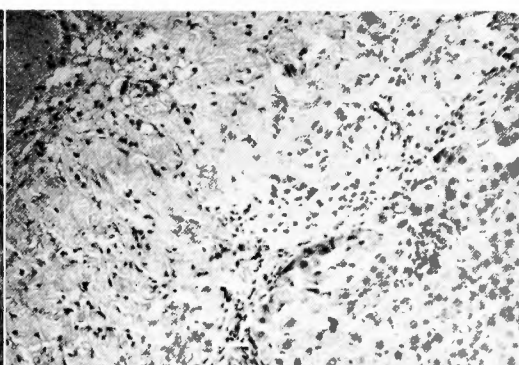


Fig. 42 The ligated lobe of portal ligation animal survived more than 6 weeks, showing tumor regression. H-E $\times 100$

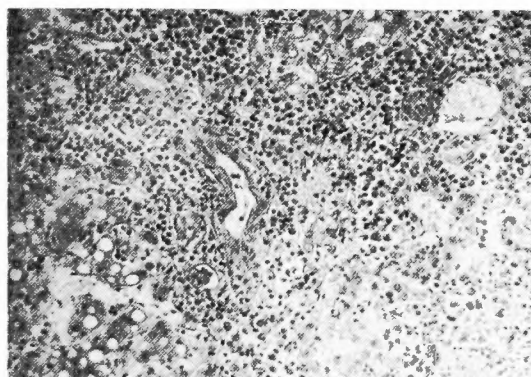


Fig. 43 Hepatic tumor growth of control animal died 26 days after, showing no proliferation of connective tissue in the tumor. van Gieson $\times 100$

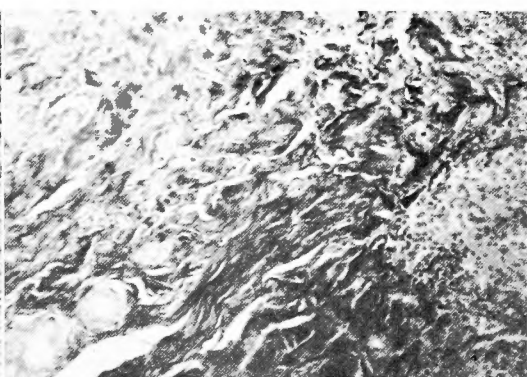


Fig. 44 The ligated lobe of portal ligation animal survived more than 6 weeks, showing tumor regression with proliferated connective tissue. van Gieson $\times 100$

Clinical case . 39 year old woman having metastatic cancer of hepatic right lobe.

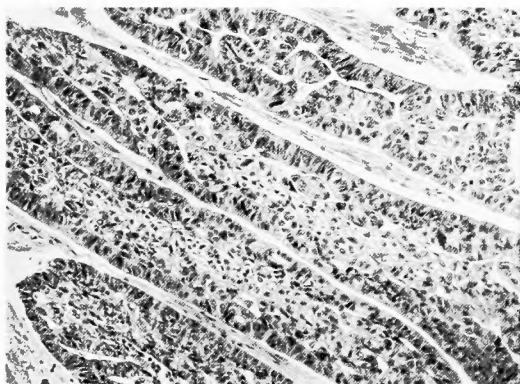


Fig. 45 Hepatic tumor growth prior to portal ligation. H-E $\times 100$

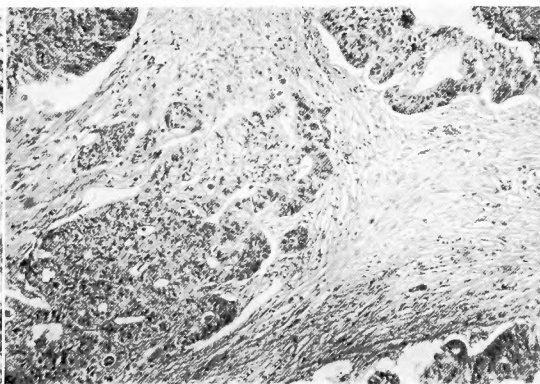


Fig. 46 The ligated lobe 3 weeks after ligation of right portal branch, showing proliferation of connective tissue in the tumor. H-E $\times 100$

PLATE 8

Rats with hepatic arterial ligation after tumor inoculation.

Rats of infusion of India ink to the tumor through the blood vessels.

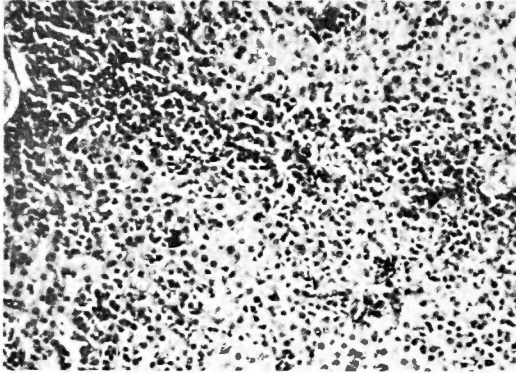


Fig. 47 The ligated lobe of animal died 17 days after AH 66 inoculation. H-E $\times 100$

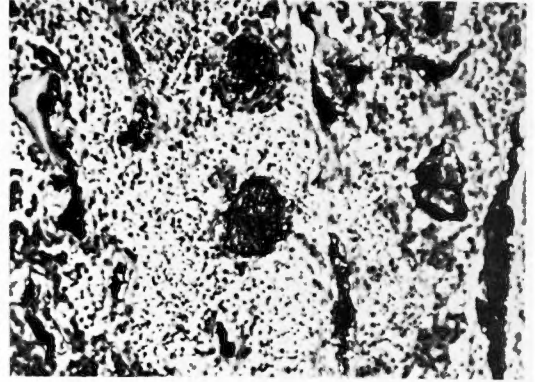


Fig. 50 Intrahepatic tumor tissue of portal ligation animal, stained with India ink injected from the hepatic artery. H-E $\times 100$

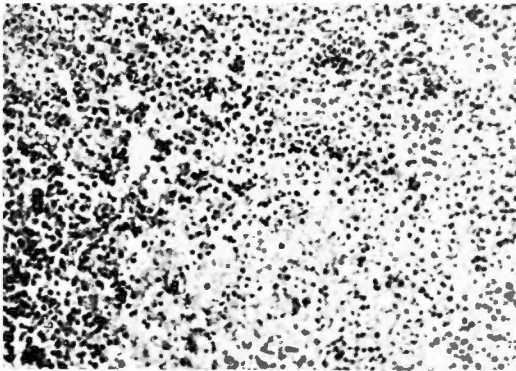


Fig. 48 The ligated lobe of animal died 11 days after Yoshida sarcoma inoculation. H-E $\times 100$

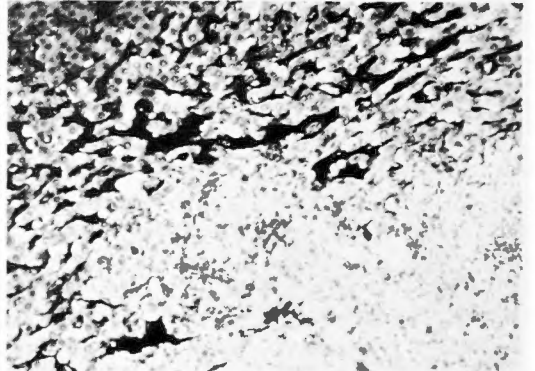


Fig. 51 Vascular net of portal vein around the hepatic tumor, stained with India ink injected from the portal vein. H-E $\times 100$ (Control animal).

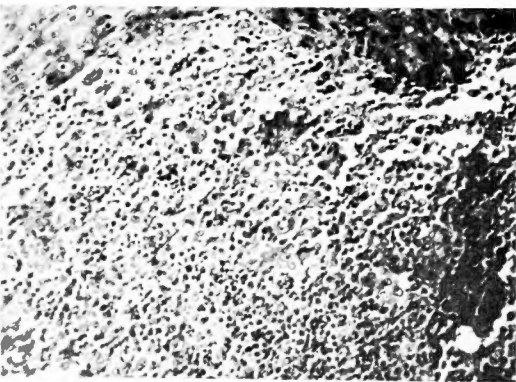


Fig. 49 The ligated lobe of animal died 20 days after Walker 256 inoculation. H-E $\times 100$

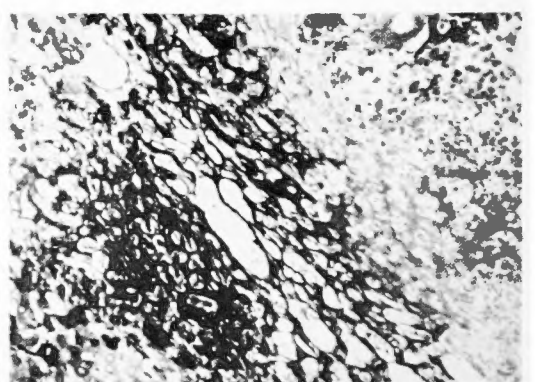


Fig. 52 Abundant vascular net of portal vein around tumor tissue, stained with India ink injected from portal vein. H-E $\times 100$ (Hepatic arterial ligation animal).

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- 46)* Takita, S. et al : Hepatic metastasis in injured and regenerating liver. *Gann*, **53** (Suppl.): 240, 1962.
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- (* in Japanese)

和 文 抄 録

ラッテ移植肝腫瘍に対する区域的門脈血遮断の効果

金沢大学医学部 第2外科学教室

(指導: 本庄一夫教授)

広 野 禎 介

肝切除法が技術的には著しい進歩をとげたが、肝臓の悪性腫瘍を対象とする場合には、限局した初期に手術しうる症例が少なく、加えて、多少とも肝機能障害を随伴しているため、充分な肝広汎切除を実施しえない症例が少なくない。かかる切除不能肝癌症例に対して何らかの外科的治療を行ないたいと考え、門脈枝を結紮すると、肝の門脈血遮断領域が萎縮し、非遮断領域が肥大再生を営む現象に着目し、著者は、種々なラッテ肝内移植腫瘍を用いて、肝腫瘍に対する区域的門脈血遮断の効果を検討し、併せて、肝動脈枝結紮の影響についても追究した。その結果の要約は次の通りである。

1. 正常ラッテにおける70%肝領域流入門脈枝の結紮は、比較的安全に実施し得、門脈血遮断肝領域の著明な萎縮と、非遮断領域の肥大が認められた。肝動脈枝の結紮では、かかる萎縮及び肥大はみられなかった。

2. 腹水肝癌AH66, 吉田肉腫及びWalker carcinoma 256 を肝左葉に移植後、種々なる時期に腫瘍移植葉を含む70%肝領域へ流入する門脈枝の結紮を行なった。

i 腹水肝癌AH66移植群

7日目門脈枝結紮群: 単純開腹にとどめた対照群は全例腫瘍死し、その平均生存日数は16.5日であつた。これに反し、結紮群の55.6%は6週以上生存し、門脈血遮断肝領域の高度な萎縮と、腫瘍の発育及び転移の抑制傾向がみられ、組織学的にも25.9%に腫瘍のregressionが認められた。又、腫瘍死した例でも、その平均生存日数は24.2日で対照群に比べ7.7日の延長が認められた。

10日目及び14日目門脈枝結紮群: 結紮群はいずれも、7日目結紮群と同様に腫瘍の発育の抑制傾向と生存期間の延長を示し、10日目結紮群で13.3%に腫瘍のregressionが認められた。

ii 吉田肉腫移植群(7日目門脈枝結紮群)

対照群は平均10.1日、結紮群は平均13.7日で全例腫瘍死したが、結紮群の数例に腫瘍の発育及び転移の抑制傾向が認められた。

iii Walker carcinoma 256 移植群

7日目門脈枝結紮群: 対照群は平均19.6日で全例腫瘍死したが、結紮群の34.6%は6週以上生存し、腫瘍死した例でも、対照群に比べ7.5日の平均生存日数の延長がみられた。組織学的にも、略、腹水肝癌AH66移植群に見られると同様な腫瘍の増殖及び転移の抑制傾向があり、26.1%に腫瘍のregressionがみられた。

14日目門脈枝結紮群: 7日目結紮群と同様な傾向を示し、結紮群の22.2%は6週以上生存し、16.7%に腫瘍のregressionがみられた。

3. 腹水肝癌AH66, 吉田肉腫及びWalker carcinoma 256を用い、腫瘍肝内移植後7日目に、腫瘍を含む肝領域へ流入する肝動脈枝の結紮を行なった。各腫瘍移植群はいずれも、対照群、肝動脈枝結紮群とも全例腫瘍死し、両群の間には、生存期間、腫瘍の発育及び転移の状態に、大した差異は認められなかった。

4. 肝内移植腫瘍について、その血管支配を検討するため、門脈及び肝動脈より墨汁注入を行なったところ、肝動脈枝結紮群及び対照群では、門脈より注入した墨汁が腫瘍周辺部に網目状に分布している所見をえた。一方、門脈枝結紮群で肝動脈より注入した墨汁が腫瘍内へ入っているにも拘らず、腫瘍の発育が抑制されている例もあつた。

5. 以上の実験成績から、肝内移植腫瘍に対して、腫瘍の存する肝領域の区域的門脈血遮断を行なうことにより、腫瘍の発育及び転移の抑制傾向が認められ、本法は、臨床的に応用しても、適応を厳にすれば切除不能肝癌症例に対して、ある程度の治療効果が期待しうるものと考えられる。

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