Yamanashi Med. J. 4 (3), 125~132, 1989

Original Article

Quantitative Analysis of Deformed Liver of *Schistosomiasis Japonica* and its Possible Causative Factors

Shingo INOUE, Masayuki YAMAMOTO*, Yuji IIMURO, Hidehisa AOYAMA, Yoshiro MATSUMOTO, and Katsuhiko SUGAHARA

First Department of Surgery, Yamanashi Medical College

Abstract: Carrier rate of calcified ova of *Schistosomiasis japonica* (Sj) was 19.6% among cases at Yamanashi Medical College, Japan. In 45 Sj cases who underwent preoperative CT, possible causative factors inducing deformed Sj livers, such as the numbers of calcified ova, extent of calcification or volume of the spleen, were analyzed with regard to the degree of deformity, and ratio of the right lobe to the left and caudate lobes. A relationship between the degree of deformity and liver function was also studied. Among the 45 cases, 41 cases had liver fibrosis and 4 were accompanied by liver cirrhosis. A negative correlation between the total liver volume and age was observed, but mean total liver volumes were not significantly different from control cases. The degree of deformity of the Sj livers was diverse and showed no significant relation with the spleen volume or the numbers of calcified ova counted microscopically. In Sj cases, the greater the degree of calcification observed via CT images, the more the right lobe tended towards atrophy and the left and caudate lobes towards enlargement. Liver function in the Sj cases was little impaired unless cirrhotic changes occurred, even though the deformity was severe.

Key words: *Schistosomiasis japonica*, Deformity of the liver, Liver-function, Hypersplenism, Calcification of the liver

INTRODUCTION

Schistosomiasis japonica (Sj) had been endemic in the Kofu Basin of Yamanashi Prefecture until 1960s. After continuous efforts to eliminate the intermediate host habitat including the cementing of irrigation ditches, the periodical cleaning of irrigation systems and the treatment of snail infested fields with molluscicides, schistosomes were eradicated from the area. Despite its current lack of prevalency, however, calcified ova of *Schistosoma japonicum* are often detected in surgical specimens of elderly patients.

Moreover, recent preoperative examinations through computed tomography (CT) have revealed more Sj patients, exhibiting no severe clinical symptoms relating to the liver, but showing such typical images (Fig. 1) as liver deformities, that is, atrophy of the right lobe and enlargement of the left and caudate lobes; abnormal shift of the gallbladder toward the right; a dotted, linear or network calcification in the liver; and splenomegaly. The present study was designed in order to calculate the carrier rate of calcified Sj ova in our area and to analyze a possible causal relation of the deformed Sj liver to the numbers of calcified ova in the liver, volume of the spleen, and liver function.

* Correspondence: Masayuki YAMAMOTO, MD, First Dept of Surgery, Yamanashi Medical College, Tamaho, Yamanashi, Japan, 409-38.
Received, April 4, 1989
Accepted, May 11, 1989

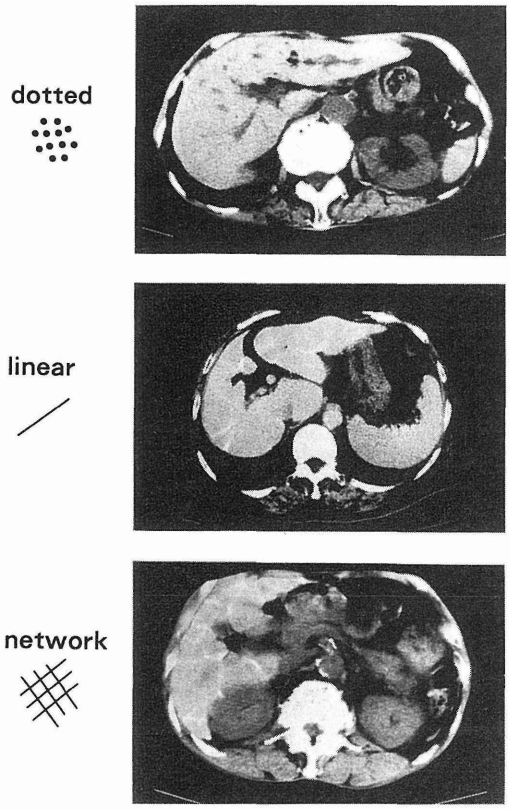

Fig. 1. Calcification in the CT image of the liver. According to its extent, it was divided into three types; dotted, linear and network types.

Patients and Methods

In 560 out of 996 cases who underwent laparotomies in our department during the 4 years and 7 months from October, 1983 to May, 1988, liver specimens were obtained from the edge of the medial segment after preoperative informed consent. Calcified ova of *S. japonicum* were histologically detected in 110 cases, 19.6%. Among the 110 cases, 45 cases whose livers had no space occupying lesions in the preoperative CT were chosen for the present study. Their primary diseases for operation are listed in Table 1. Among them, 41 cases whose livers were not complicated with liver cirrhosis (LC) but with liver fibrosis were classified as Group Sj. The other 4 cases whose livers were complicated with posthepatitic LC were classified as another group, Sj+LC.

Since deformity of the liver and splenomegaly were also observed in LC, 16 cases (Group LC) whose liver had histologically posthepatitic liver cirrhosis without schistosome ova and whose preoperative CT revealed no space occupying lesions in the liver were collected during the same period.

As the normal control group (Group NC), 15 cases were collected at random during the examination period from patients satisfying the following criteria: preoperative normal liver functions, no space occupying lesions in the preoperative CT of the liver, and no pathological changes certified by liver biopsy.

In these 4 Groups the volumes of the total liver, the right, left and caudate lobes of the liver and the spleen were calculated after the integration of liver and spleen areas in each slice, which were scanned at each 1 cm by CT, using a computer [7]. The borders between the lobes were determined by referring to the locations of the inferior vena cava, gallbladder and distribution of Glissonian vessels.

Degree of the deformity was calculated as follows;

Deformity Ratio = volume of the right lobe/(volume of the left lobe + volume of the caudate lobe)

Relationships between the Deformity Ratio and numbers of ova, calcifications in CT, volume of the spleen, or liver functions were analyzed. Calcified ova in the liver were microscopically counted in 3 fields randomly chosen around the sinusoid with a magnification of 100. Calcification of the CT images were divided into 3 types, the dotted, linear and network type according to its extent (Fig. 1). Liver functions examined were total protein (T-P), albumin

Table 1. Liver and spleen volumes in the 4 groups

	Sj (n=41)	Sj+LC (n=4)	LC (n=16)	NC (n=15)
Primary Disease	G ca (24), GU (1) Panc ca (1) Duod ca (1) Colorectal ca (7) Gall ca (1) Gall polyp (1) Chole (4) Diaphragmatic hernia (1)	EV (1) G ca+EV (1) Chole+EV (2)	EV (9) Eso ca (1) Duod ca (1) Gall ca (1) Chole (4)	G ca (10) Colon ca (2) Panc ca (1) Chole (2)
Age	$68\pm10^{***}_{+++}$	66±9	57±12	54±12
Total Liver (cm^3)	1007.6±251.2	874.0±30.0*	1019.1±161.2	1116.2±215.2
TL/BW (cm^3/kg)	19.9±4.6	16.9±1.6	17.7±3.6	19.1±2.2
Spleen (cm^3)	$131.2\pm68.0^{+++}_{\sharp}$	282.4±122.9***	426.6±357.8***	139.6±52.6
Spleen/BW (cm^3/kg)	$2.6\pm1.3^{+++}_{\sharp}$	5.5±2.4***	7.6±6.1**	2.4±0.7
TL/Spleen	$11.2\pm13.3^{+}$	3.6±1.2**	4.4±3.0***	9.1±3.5
RL/TL (%)	52.7±13.3*	51.6±17.4	53.6±9.8**	61.7±5.8
LL/TL (%)	42.8±12.2*	37.9±8.4	42.7±8.9*	35.8±5.8
CL/TL (%)	4.5±2.1***	5.0±1.9**	3.8±1.7*	2.5±1.1
Deformity Ratio	1.30±0.72	1.40±0.84	1.24±0.43**	1.67±0.38

Compared to NC: *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$
Compared to LC: +, $P<0.05$ +++, $P<0.001$
Compared to Sj: ♯, $P<0.001$
Data with no marks showed no significant changes.
G ca, Gastric cancer; GU, Gastric ulcer; Gall ca, Gallbladder cancer; Gall polyp, Gallbladder polyp; Panc ca, Pancreas cancer; Duod ca, Duodenal cancer; Colorectal ca, Colorectal cancer; Chole, Cholelithiasis; EV, Esophageal varices; Eso ca, Esophageal cancer; TL, Total liver; BW, Body weight; RL, Right lobe; LL, Left lobe; CL, caudate lobe; Deformity Ratio, RL/LL+CL,

(Alb), total cholesterol (T-Chol), cholinesterase (Ch-E), total bilirubin (T-Bil), lactic dehydrogenase (LDH), and glutamic oxaloacetic transaminases (GOT), glutamic pyruvic transaminase (GPT) in the serum, and prothrombin time activity (PT-%). Hypersplenism was estimated by numbers of red and white blood cells (RBC, WBC) and platelets (PLT).

Calculated results were expressed as mean±standard deviation (SD). Significant differences between the two groups were calculated by Student's *t*-test.

Results

Age: The mean age of Sj cases was older than that of LC cases (Table 1). There was a negative correlation between age and total liver volume in Groups Sj and Sj+LC ($r=-0.416$, $p<0.05$) (Fig. 2), and no significant difference between age and spleen volume was shown ($r=-0.265$). On the other hand, in Groups LC and NC no significant correlations were observed ($r=-0.037$ and -0.046, respectively).

Mean total volume of the liver (cm^3): that of Sj+LC was smaller ($p<0.05$) than the other 3 groups (Table 1), but there were no significant differences regarding the ratio of total liver volume to body weight.

The degree of liver deformity: the Mean Deformity Ratio (Table 1) of Sj livers was at the same level as the NC livers. However, as to the relationships between the right lobe, and the left and caudate lobes (Fig. 3a), all NC patients except for one were located below the line of Y=X. The correlation rate between the 2 areas of NC

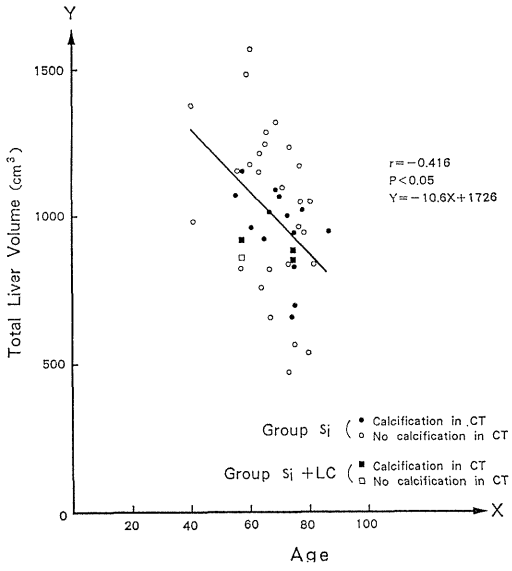

Fig. 2. Age distribution and total liver volume in group Sj and Group Sj+LC. Correlation coefficient is for Group Sj and Group Sj+LC.

livers was r=0.593 ($p<0.05$) and it suggested the existence of a normal ratio of the right lobe to the left and caudate lobes. On the other hand, the distribution of LC livers shifted toward the left (Fig. 3b), indicating atrophy of the right lobe and enlargement of the left and caudate lobes, with a significantly lower Deformity Ratio (Table 1). The distribution of Sj livers, however, was diverse both above and below the line (Fig. 3c).

Calcification in the CT images of the livers: Calcification was recognized in 14 cases of Group Sj and in 3 cases of Group Sj+LC (Fig. 3c). Ten of the 17 cases showing calcification in the CT images were distributed above the line, Y=X. The extent of calcification in the CT images was diverse, showing the dotted, linear and network type of calcification (Fig. 1). The network type of calcification in the CT images of livers was more frequently observed in smaller livers than the former two

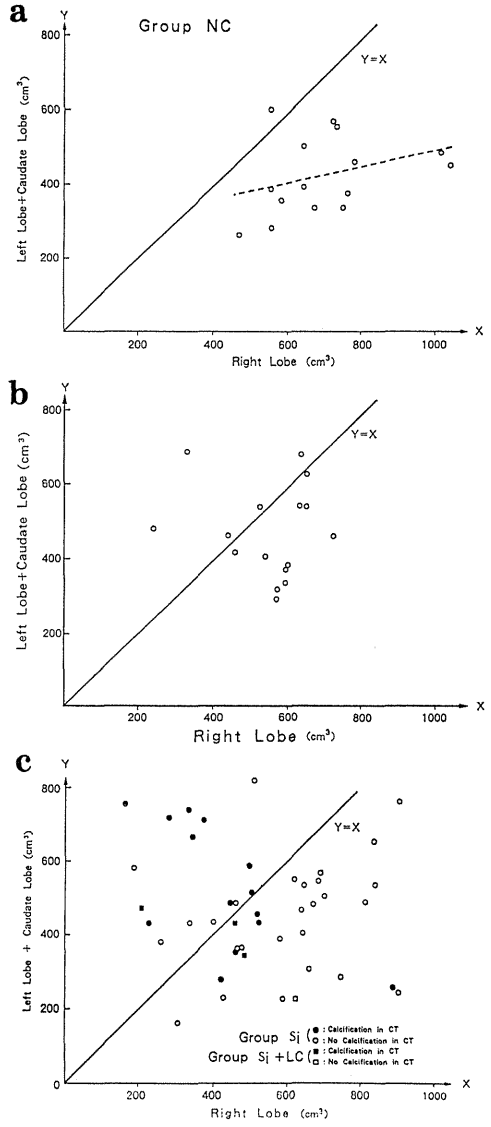

Fig. 3. Deformity of Sj liver. Relationships between the right lobe and the left and caudate lobes in Group NC (a), Group LC (b), and Group Sj and Group Sj+LC (c).

types, but no significant differences were shown (Fig. 4).

Numbers of calcified ova in liver specimens: no significant relationships were observed between the numbers of ova and the volumes of livers and spleens (Fig. 5) or the

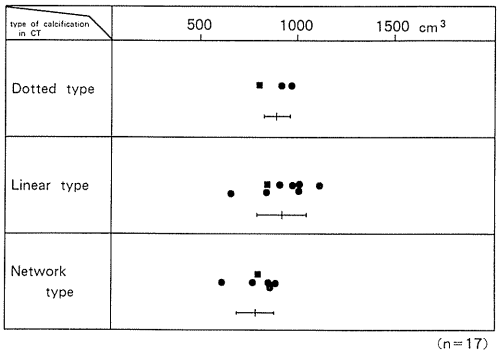

Fig. 4. Three types of calcifications in the CT image of the liver and total liver volumes in Group Sj (●) and Group Sj+LC (■) Bars indicate mean ± SD of the total liver volume in each type.

Deformity Ratio.

Volume of the spleen: splenomegaly was marked in LC and Sj+LC, but not in cases of Sj alone (Table 1). Between the volumes of the spleen and the liver, no significant correlations were found in NC ($r=0.24$) or LC ($r=-0.28$), but a significant correlation ($r=0.38$, $p<0.05$) was observed in Sj and Sj+LC (Fig. 6). Also, between the Deformity Ratio and spleen volume there were no significant correlations among any of the 4 groups.

Liver functions (Table 2): liver functions of Sj cases were in the range of NC, except for slight increases in GOT and GPT. Those of LC were more altered. High levels of T-Bil, LDH, GOT and GPT in Sj+LC reflected acute obstruction of the common bile duct in 2 cases. The state of hypersplenism in Sj+LC was apparently between those of Sj and LC.

Deformity of Sj livers and liver functions (Table 3): the 41 Sj cases were divided into 3 subgroups in terms of Deformity Ratio. The range of subgroup B was between the mean+SD and the mean−SD of the NC

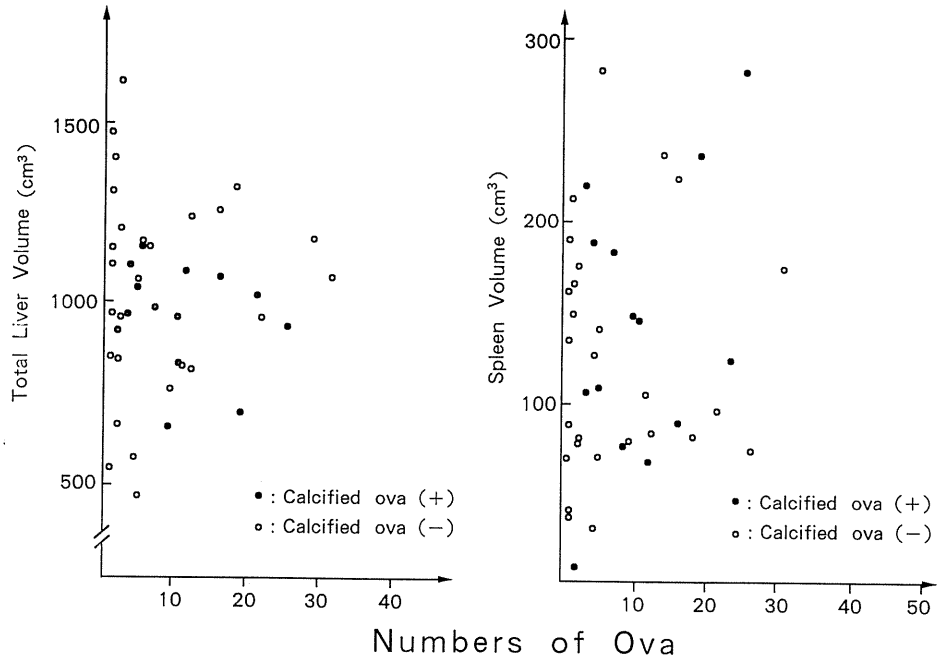

Fig. 5. Relationships between numbers of ova microscopically counted and total liver volume (left) and spleen volume (right). Each number is a mean of counts in 3 fields of the sinusoidal region.

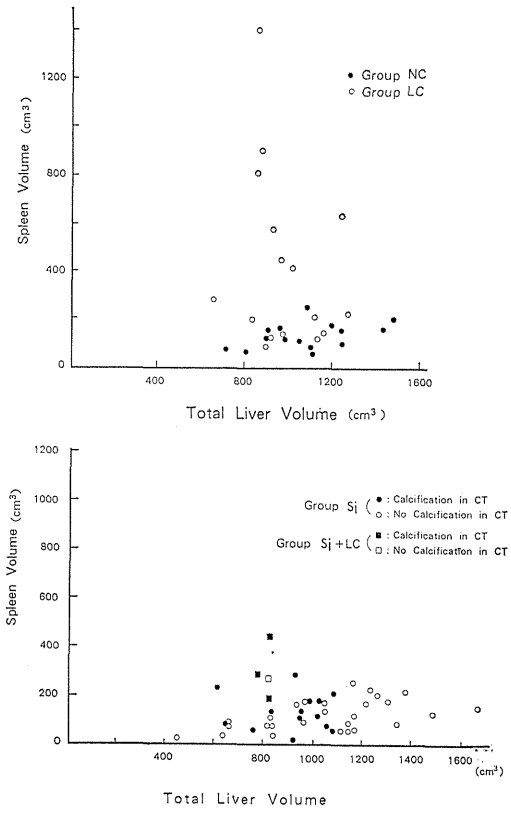

Fig. 6. Relationships between total liver volume and spleen volume. Group NC and Group LC (above), Group Sj and Group Sj+LC (below).

cases (Table 1). Therefore, the Demority Ratio of the 25 SJ cases in subgroup A was smaller than the normal range, while it was greater in subgroup C. No significant changes in the results of the blood examinations were observed in the three levels of deformity of the Sj livers.

Discussion

There are many reports on pathological studies of Sj [2, 3, 4, 10], but few deal with the quantitative analyses of schistosomal changes of the liver in clinical cases [1]. Previous pathological studies reported that these changes are induced by the pathological effects of schistosome itself as well as its ova, but that influences of the latter are more important. A direct influence of ova is obstruction of the portal vein by a lump of ova, and an indirect influence is inflammatory granulation in and around the portal vein induced by immunological responses [9]. Another study reported two types of histological findings about the numbers of ova in the granulation; one type exhibits a few ova in hyalinized nodules

Table 2. Blood examinations of the 4 groups

	Sj	Sj+LC	LC	NC
n	41	4	16	15
T-P (g/dl)	6.7±0.7	7.2±0.8	7.1±0.6	6.7±0.7
Alb (g/dl)	3.9±0.5	3.8±0.7	3.7±0.4*	4.0±0.4
T-Chol (mg/dl)	168.0±42.3+	150±17.6	140.8±28.5**	176.3±33.4
Ch-E (⊿PH)	0.80±0.26+++	0.50±0.14#, **	0.52±0.14***	0.80±0.15
T-Bil (mg/dl)	0.7±0.8##	6.0±6.8###++, **	0.9±0.4***	0.5±0.1
LDH (IU/l)	341.4±107.9	472±136#++, **	309.75±59.92	303.5±69.7
GOT (IU/l)	26.0±13.2++, **	113.1±60.0###+++, ***	40.2±20.4***	15.7±6.7
GPT (IU/l)	23.2±19.2++, *	89.0±50.8###+, ***	42.7±31.6**	12.9±6.2
PT-%	121.4±22.1+++	80.4±25.3##, **	80.1±23.7***	126.0±22.8
WBC ($10^3/\mu l$)	5.7±1.6+++	5.6±1.5	3.9±1.8**	5.8±1.6
RBC ($10^6/\mu l$)	4.15±0.61	3.75±0.62	3.91±1.03	4.28±0.47
PLT ($10^3/\mu l$)	228±87+++	140±72**	101±70***	272±72

Compared to NC: *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$
Compared to LC: +, $P<0.05$; ++, $P<0.01$; +++, $P<0.001$
Compared to Sj: #, $P<0.05$; ##, $P<0.01$; ###, $P<0.001$
Data with no marks showed no significant changes.

Table 3. Results of blood examinations at the 3 deformity levels of Sj liver

Deformity Ratio	A	B	C
	X≦1.29 (n=25)	1.29<X≦2.05 (n=11)	2.05<X (n=5)
Age	70.6±7.8*	62.1±12.0	68.2±8.4
T-P (g/dl)	6.5±0.7	6.9±0.5	7.1±0.6
Alb (g/dl)	3.8±0.4	4.4±0.5	4.2±0.6
T-Chol (mg/dl)	174.1±36.5	152.4±48.4	172.0±46.0
Ch-E (⊿PH)	0.79±0.27	0.79±0.24	0.82±0.24
T-Bil (mg/dl)	0.8±1.0	0.7±0.3	0.6±0.2
LDH (IU/l)	321.6±105.1	348.8±120.0	274.2±58.3
GOT (IU/l)	26.8±13.7	25.6±12.6	23.0±11.8
GPT (IU/l)	22.6±17.8	26.9±24.3	17.8±9.7
PT-%	122.7±20.3	117.5±25.6	123.6±21.4
WBC ($10^3/\mu l$)	4.6±1634	5.6±1.6	6.5±1.5
RBC ($10^6/\mu l$)	4.81±0.65	4.38±0.40	4.38±0.61
PLT ($10^3/\mu l$)	231±95	212±75	253±54

X=DeformityRatio; RL/(LL+CL), ratio of the right lobe to the left and caudate lobes
B, Sj cases whose Defomity Ratio remained in the range between the mean+SD and the mean+SD of the NC cases
A, Sj cases whose Deformity Ratios were smaller than that of NC
C, Sj cases whose Deformity Ratios were greater than that of NC
*, $p<0.05$ between A and B.

and the other shows many ova in the proliferated connective tissues [3].

The present quantitative analyses coincide with these pathological findings. The extent of deformity of Sj livers did not correlate with splenomegaly or the numbers of calcified ova. The diverse deformities of Sj livers can not be explained simply by the direct effect of calcified ova, such as mechanical obstruction of the presinusoidal region. The numbers of calcified ova may be one of the important factors inducing morphological changes, but different humoral and cellular immune responses between hosts in human schistosomiasis [5, 8] may also induce this diversity.

Thus, the deformity was not as simple as our previous clinical impression, described in the Introduction. However, older patients, who supposedly have had longer exposure to schistosome ova, either living or calcified, tend to have smaller livers. It is generally accepted that small liver size and splenomegaly are the most prominent signs in severely damaged Sj livers [6]. But such a tendency for enlarged spleens to be accompanied by smaller livers was not observed in Group Sj. Moreover, although Group Sj+LC showed smaller liver volumes, the degree of deformity and calcification of the livers were not more severe than that in Group Sj. The spleen volume of Sj+LC was not markedly greater than that of Sj. These results also suggest that deformity of the liver and enlargement of the spleen are not induced by a single common cause such as an increase in portal pressure by presinusoidal obstruction.

The number of individuals in Group Sj+LC were only 4. But 11 other livers with Sj and LC observed during the same period had space occupying lesions in the liver, that is, hepatocellular carcinoma. Namely, 73% of the Sj+LC cases in our

study had hepatocellular carcinoma. On the other hand, only one Sj case with no cirrhotic changes was accompanied by hepatocellular carcinoma. It is unclear whether unknown factors inducing LC changes and splenomegaly in Sj cases also play a carcinogenic role. Further study into this problem is necessary.

Since the Sj and LC cases analyzed in the present study were admitted to our surgical department after physicians' selection, it is possible that those patients who had shown poor hepatic functional reserve and who could not have tolerated surgical insult might have been eliminated. Nevertheless, the results suggest that liver function may be maintained within the normal range, despite such peculiar deformities of the liver in cases of Sj, so long as atrophied right lobes are compensated by enlargements of the left and caudate lobes.

References

1. Iio M, Iuchi M, Kitani K, Yamada H, Ishiwa M, Kameda H, and Chiba K: Scintigraphic evaluation of the liver with Schistosomiasis Japonica. J Nucl Med 1971; **12**: 655–659.
2. Mahmoud AA: Current concepts, Schistosomiasis. N Engl J Med 1977; **297**: 1329–1331.
3. Nakashima T: Cirrhosis of the liver due to Schistosoma japonicum. I. Study of human materials. Acta Hepatol Jap 1969; **10**: 485–500.
4. Nakashima T, Okuda K, Kojiro M, Sakamoto K, Kubo Y, and Shimokawa Y: Primary liver cancer coincident with Schistosomiasis Japonica. A study of 24 necropsies. Cancer 1975; **36**: 1483–1489.
5. Ohta N, Nishimura YK, Iuchi M, Sasazuki T: Immunogenetic analysis of patients with post-schistosomal liver cirrhosis in man. Clin exp Immunol 1982; **49**: 493–499.
6. Okada J, Uchiyama G, Hayakawa K, Araki T, Arai T, Iuchi M: Radionuclide study on hepatic blood flow in Schistosomiasis Japonica. Jap Society Nuclear Md 1986; **23**: 1517–1522.
7. Okamoto E, Kyo A, Yamanaka N, Tanaka N, and Kuwata K: Prediction of the safe limits of hepatectomy by combined volmetric and functional measurements in patients with impaired hepatic function. Surgery 1984; **95**: 586–591.
8. Okuda K: Generalized calcification of the liver in advanced schistosomiasis japonica—A case report. Acta Hepato-Gastroenterol 1975; **22**: 98–102.
9. Smithers SR, and Terry RJ: The immunology of schistosomiasis. In: Dawes B, ed. Advances in parasitology vol 14. London, Academic Press, 1976; 399–422.
10. Warren KS: The pathology, pathobiology and pathogenesis of Schistosomiasis. Nature 1978; **272**: 609–612.