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Two cases of liver cirrhosis caused by viral hepatitis : Observations on vascular stereograms of needle liver biopsy tissue

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Two cases of liver cirrhosis caused by viral hepatitis : Observations on vascular stereograms of needle liver biopsy tissue*

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Abstract

Two cases (Case I, 24-year old male, and Case II, 41-year old male) of liver cirrhosis after viral hepatitis have been described with a special emphasis on the distortion of the hepatic lobular architecture induced by hepatic hemodYnamic changes. Careful and precise clinical and laboratory examinations as well as peritoneoscopic examination with liver biopsy, particularly with vascular stereograms of liver biopsy tissue, have been successively carried outfrom stage of normal lobular architecture to early stage of cirrhosis. As the result, it has been found that in the course of these examinations clinical and laboratory features of the patients have remained almost unchanged in spite of gradual aggravation of morphological pictures. It is especially noteworthy that on vascular stereograms of liver biopsy tissue the parenchymal cells under the scarred portal tracts have suffered atrophic changes. Thus, three individual portal tracts of Case I have been gathered in a single connective tissue located on the distributing area of a scarred portal tract, whereas a central vein of Case II has moved from center to side of the scarred portal tract. In the late stage, these two cases ultimately turned to liver cirrhosis.

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TWO CASES OF LIVER CIRRHOSIS CAUSED BY VIRAL HEPATITIS: OBSERVATIONS ON VASCULAR STEREOGRAMS OF NEEDLE LIVER BIOPSY TISSUE

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There are many reports on liver cirrhosis, especially replete are the discussions on causal relations between cirrhosis and antecedent viral hepatitis[1-6]. However, the incidence of initial viral infection to the terminal stage is not clearly elucidated, excepting certain types of the so-called fatal viral hepatitis. Similarly, the intrinsic factors that convert the common type of viral hepatitis to chronic one or liver cirrhosis pose as unresolved problems.

Two cases reported here illustrate the progress of clinical and laboratory findings as well as hepatic hemodynamic and morphological studies, particularly on the stereograms of peripheral branches of portal and hepatic veins, from stage of viral hepatitis to cirrhosis. The main purpose of the present report is to clarify the influence of hepatic hemodynamic changes induced by chronic interstitial inflammatory process involved in the scar formation in portal tracts, on the destruction of hepatic lobular architecture as well as the events of clinical and laboratory features.

METHODS

Measurements of Hepatic Hemodynamics:

Wedged hepatic venous pressure was measured by hepatic venous catheterization methods. Simultaneously, effective hepatic blood flow and intrahepatic shunt flow were measured by means of NAKAMURA's method[7] with constant intravenous infusion of galactose. Au^{198} colloid accumulation rate of the liver was determined by external counting at 3 cm below the lower limits of lungs on the right axillary line (normal range is 0.185 ± 0.035). Indocyanine green (ICG) disappearance rate was decided by the measurements of plasma ICG levels at 5, 10 and 15 minutes after injection of 0.5 mg ICG/1000 g of body weight (normal range is 0.183 ± 0.03). Intrasplenic pressure was measured by means of a modified method of ATKINSON's[8] under the control of peritoneoscopy. This method enables us to estimate the pressure without any danger of bleeding from spleen puncture.

Observation of the Vascular Stereogram Reconstructed with Serial Sections of Liver Biopsy Tissue :

By using Silverman-Boecker's biopsy needle of large size, a considerably big liver tissue (diameter about 2 mm, length about 20 mm) can be obtained under the control of peritoneoscopy. And the stereogram is reconstructed by serial sections of this biopsy material with the aid of Abbe's instrument and vinyl plates. In this stereogram, abnormal changes of peripheral branches of portal and hepatic veins can be observed.

OBSERVATIONS

Case I. T. S.; *The First Hospitalization*

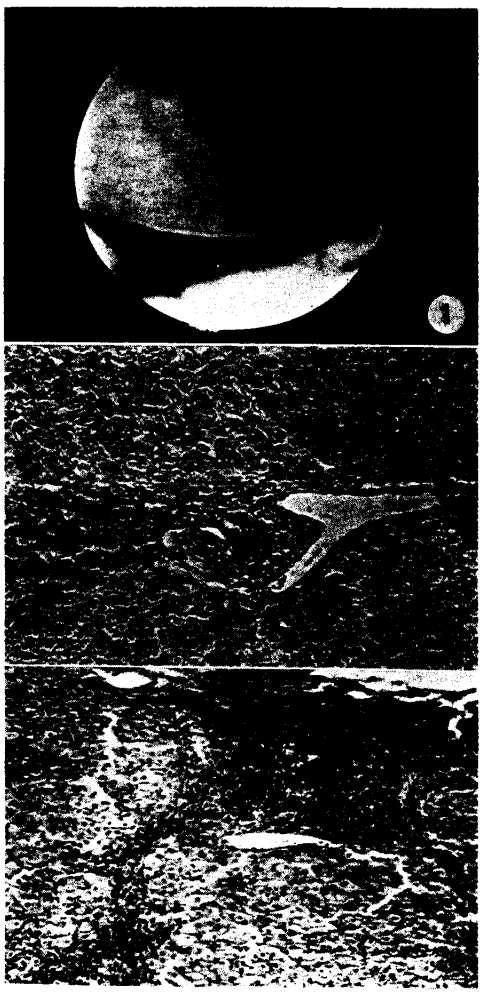
Clinical history: A 24-year old male, a son of wealthy merchant, was admitted to Okayama University Hospital with chief complaints of general fatigue and epigastric pain of ten months' duration, on December 3, 1962. The patient had not experienced any jaundice, fever attacks or anorexia, and he was not alcoholic. The epigastric pain was intermittent but not severe, and was related to overwork, having no association with dietary factors.

Physical examinations: Jaundice and anemia were not noted. Liver was palpable at 1 cm below the costal margin and its consistency was not increased. The spleen was palpable at the costal margin. There were no other apparent signs of liver and gastrointestinal disorders.

Laboratory data: Results of urinalysis were within normal limits. Urine urobilinogen was questionable. The initial blood studies gave the values within normal limits; hemoglobin 99%, red blood cells 5,020,000/mm^3, hematocrit 52%, white blood cells 6,200/mm^3 with a differential count of 54% segmented neutrophils, 4% nonsegmented neutrophils, 32% lymphocytes, 3% eosinophils and 7% monocytes, and thrombocytes 145,000/mm^3. The initial studies of blood chemistry were as follows: total bilirubin 0.92 mg/dl with direct reacting form 0.52 mg/dl, bromsulphalein test (BSP) 14.5% at 45 minutes, serum glutamic oxalacetic transaminase (S-GOT) 42γ of Niitani's method (113 Karmen units in converted value) and serum glutamic pyruvic transaminase (S-GPT) 34γ of Niitani's method (132 K. u. in converted value), alkaline phosphatase 2.5 Bessey-Lowry units, serum total protein 7.3 mg/dl with 36.7% albumin, 5.1% α-globulin, 14.3% β-globulin and 35.7% γ-globulin, cephalin cholesterol flocculation test (CCF) positive (++), thymol turbidity test (TTT) 6.0 units, zinc sulfate turbidity test (ZTT) 10.9 Kunkel units, and total cholesterol 200 mg/dl. The first Au^{198} colloid accumulation rate of liver was 0.169 on February 25, 1963, and the second one was 0.126 which was slightly lower on June 10, 1963. Radiographic examinations of the gastrointestinal tract and biliary tract revealed

normal condition.

Morphological examinations of liver: The first peritoneoscopic examination with liver biopsy was performed on December 18, 1962. Macroscopically, the surface of the liver lobe was found to be smooth and reddish, and neither nodules nor scar formation were observed (Fig. 1). The tip of spleen was visible



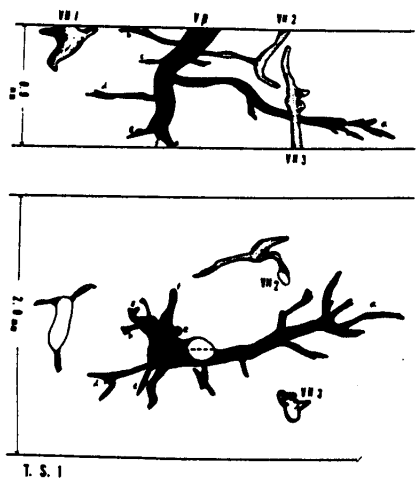
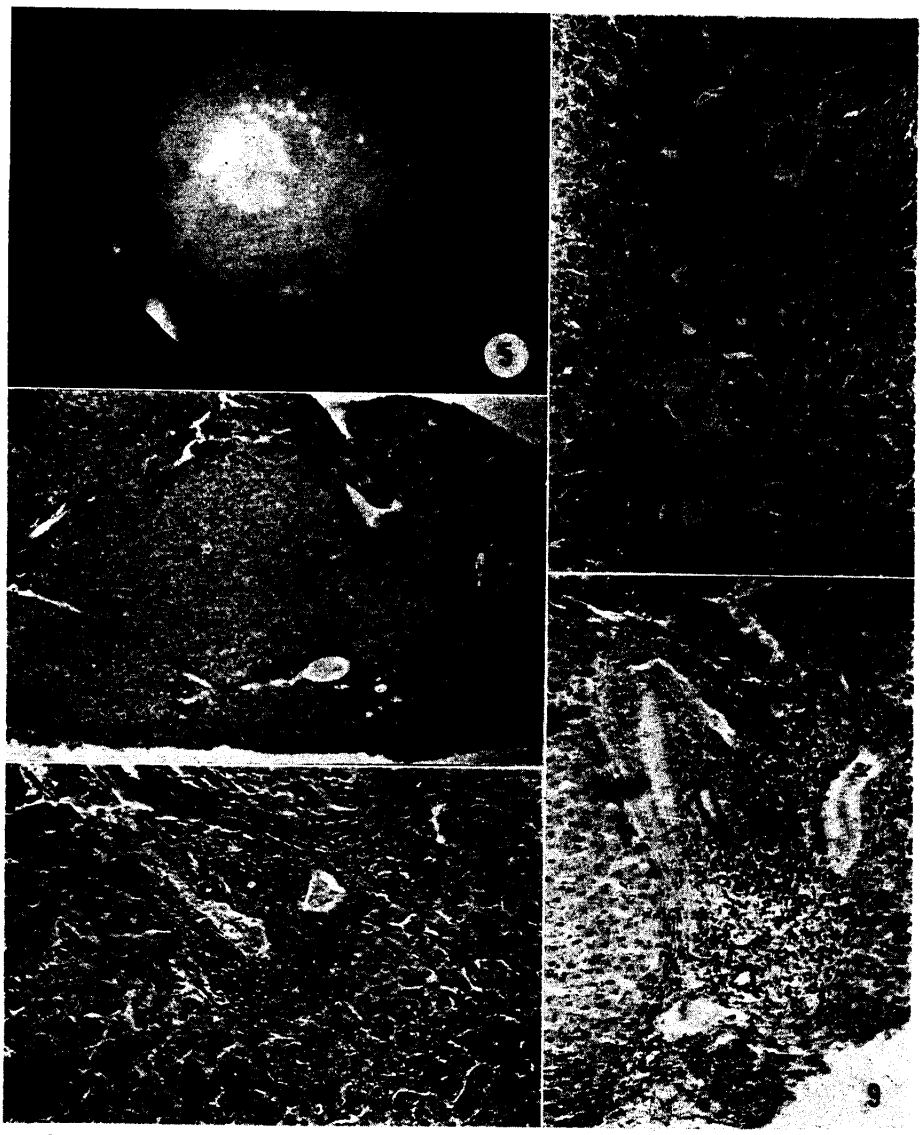


Fig. 4

Figs. 1—4 The results of the first peritoneoscopy with liver biopsy of Case I: Fig. 1 reveals macroscopically the smooth surfaced right liver lobule; Fig. 2 the infiltration of various inflammatory cells around the portal vein in the 75th section, H-E stain, ×100; Fig. 3 scar formation and the infiltration of inflammatory cells in the 67th section, H-E stain; and Fig. 4 illustratrates a vascular stereogram reconstructed with the 31st to the 121st sections (90 sections), showing the portal vein and hepatic veins, a lateral view in the upper picture and the plane view in the lower.

at 3cm inside the costal margin. The observation of the stereograms of portal and hepatic veins revealed normal lobular patterns, and both venous trees presented a shape of interdigitation with each other (Fig. 4). The portal tract, demonstrated by this stereogram, was infiltrated by many inflammatory cells containing fibroblasts, and the limiting plates were destroyed to a certain extent (Fig. 2).



Figs. 5—10 The findings by the second peritoneoscopy with liver biopsy of Case I: Fig. 5 illustrates macroscopically small reddish patches; Fig. 6 is of the 64th section revealing the arrangement of No. 1 to No. 5 portal veins and a central vein, H-E stain, ×50; Fig. 7, the 74th section, showing a narrow portion and it is scarred surrounding area of No. 3 PV, H-E stain, ×100; Fig. 8, the 56th section, showing the manner of approach of No. 3 PV and No. 4 PV, H-E stain, ×100; Fig. 9, the 41st section which reveals PV Nos. 3, 4, 5 gathered and bound up in one strand within a connective tissue, H-E stain, ×100; Fig. 10 reveals a vascular stereogram reconstructed with sections No. 37th to No. 78th (41 sections in all). The lateral view in the upper picture and the plane view in the lower illustrate the manner how the portal veins Nos. 3, 4, 5 are gathered within one connective tissue, marked by dash lines.

The other portal tract not visible on this stereogram due to loss of its radicle from the material, was scarred with collagenous fibers (Fig. 3). Namely, in this stage the case was diagnosed as an active chronic hepatitis on the basis of normal vascular architecture.

The second peritoneoscopic examination with liver biopsy was done on May 31, 1963 (about 6 months after the first one). Macroscopically, the entire surface of the liver lobe was found to be patched with small reddish brown spots on the reddish surface, but no nodular formations (Fig. 5). The tip of spleen was visible at 2 cm inside the costal margin, and the intrasplenic pressure was 210 mm saline. The shapes of portal veins (No. 1 to No. 5 P. V.) and a terminal branch of the hepatic vein were demonstrated on the vascular stereogram (Fig. 10). There were no serious patterns of No. 1 and No. 2 P. V.. A marked

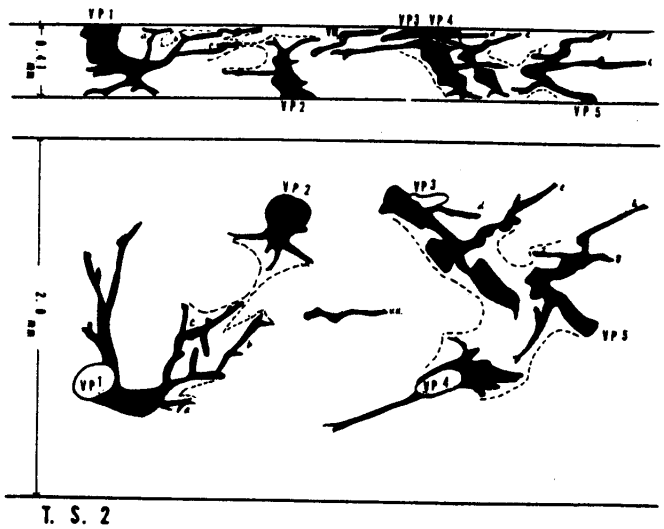
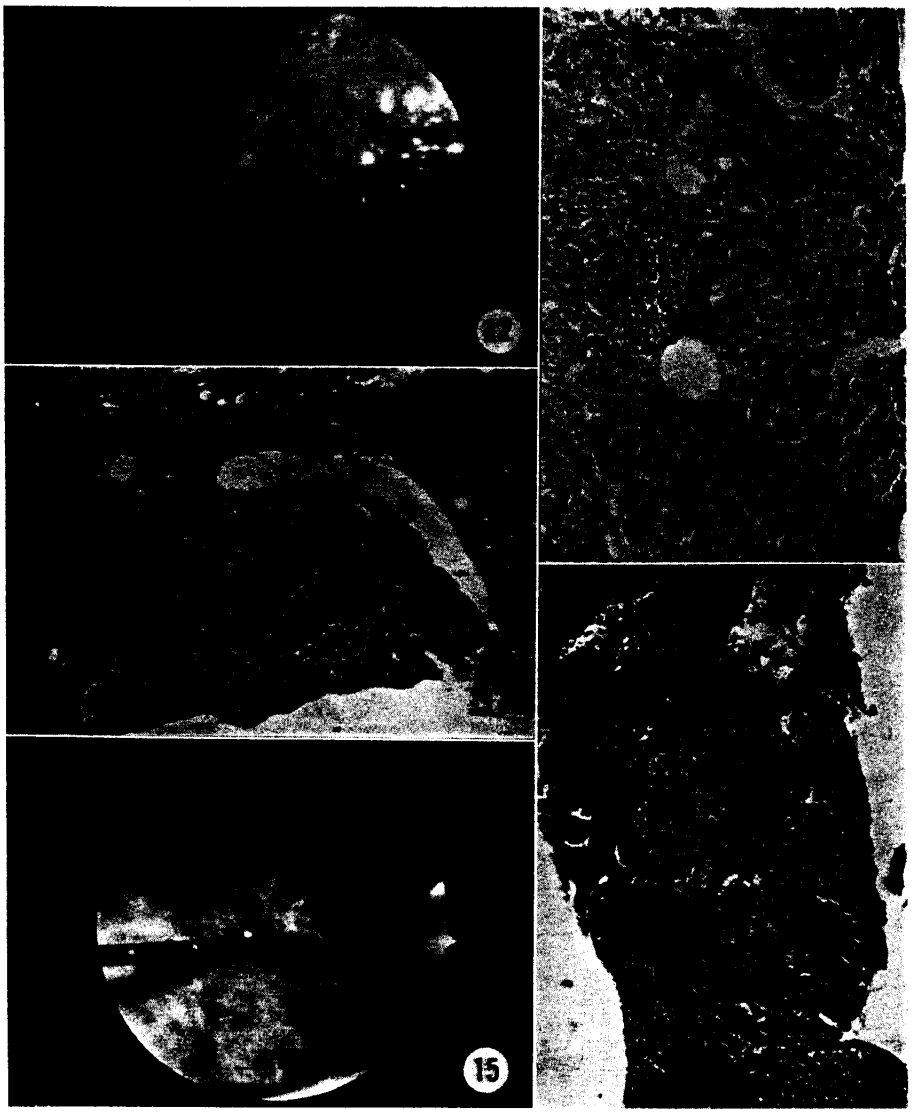


Fig. 10

increase of collagenous fibers was found in the surrounding area of No. 3 P. V. (Fig. 7). Two parts of this vein were evidently narrow, while their upper parts were moderately dilated. On the other hand, the parenchymal zone under the terminal branch of the No. 3 P. V. was found to be very atrophic. Moreover, the extremities of No. 3 and No. 4 P. V. were adjoined and they were involved in a single connective tissue (Fig. 9). The middle part of No. 5 P. V. was contracted inward by this connective tissue, consequently it was curved in the same direction as that of the connective tissue on both plane and side views (Figs. 9, 10).

Clinical course: His clinical course is shown on Table 1. The treatment



Figs. 11—14 The findings of the third peritoneoscopy with liver biopsy: Fig. 11 is the vascular stereogram reconstructed with the sections No. 96 to No. 138 (42 sections), showing an enlarged No. 1 HV attached to the inner wall of a wide connective tissue; Fig. 12 reveals macroscopically unripe nodules which is 2 mm in diameter; Fig. 13 is the picture of the 97th section which shows a dilated No. 1 HV, H-E stain, ×50; and Fig. 14 shows the picture of the 115th section, showing No. 1 HV and No. 5 PV located in the connective tissue a portion of which reveals a large scar and a severe inflammatory reaction in another part, H-E stain, ×100.

Figs. 15 and 16 The findings of the 4th peritoneoscopy with liver biopsy of Case I. Fig. 15 shows macroscopic view of small nodules on the liver surface, and Fig. 16 is the picture of broad scars and pseudolobule formations, H-E stain, ×50.

included continuous high-protein diet and administration of total of 134 mg paramethasone from December 28, 1962 to February 8, 1963. His subjective symptoms had gradually improved, but the clinical and laboratory findings had not changed, in spite of an insidious aggravation of morphologic examinations and hepatohemodynamic data. On December 20, 1963 he left the hospital still not completely recovered.

The Second Hospitalization

Clinical history: The same patient was admitted again on December 19, 1964. He was moderately in poor condition of hepatic damage as revealed by the periodical, physical examinations at our out-patient clinic. However, he complained of no subjective symptoms.

Physical examinations: Jaundice and anemia were not noted. The liver was palpable at 1.5 cm below the costal margin and its consistency was slightly increased. Spleen was palpable at just the costal margin. There were no other signs of liver disease.

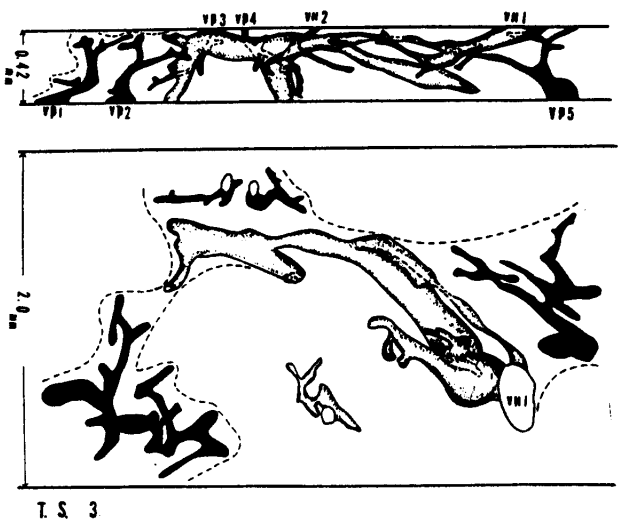


Fig. 11

Laboratory data: The results of urinalysis were within normal limits except for positive (++) urine urobilinogen. The initial blood studies yielded the values within normal limits; hemoglobin 100%, red blood cells 5,240,000/mm^3, white blood cells 7,900/mm^3 with a differential count of 51.6% segmented neutrophils, 4.8% nonsegmented neutrophils, 31.2% lymphocytes, 0.8% eosinophils and 1.6% monocytes, and thrombocytes 162,000/mm^3.

The initial studies of blood chemistry were as follows: Total bilirubin was

0.90mg/dl with direct reacting form 0.52mg/dl, BSP 1.5% at 45min., S-GOT 35 Karmen units and S-GPT 70 Karmen units, alkaline phosphatase 1.1 Bessey-Lowry units, serum total protein 7.6mg/dl with 42.5% albumin, 4.5% α_1-globulin, 7.5% α_2-globulin, 13.5% β-globulin and 32% γ-globulin, CCF questionable, TTT 6.9 units, ZTT 11.5 Kunkel units, and total cholesterol 200 mg/dl. Radioactive Au^{198} colloid accumulation rate of liver was 0.112, which was moderately at a lower level on February 13, 1965, and the second one was 0.182 on July 8, 1965.

Liver catheterization was performed on January 22, 1965. Wedged hepatic venous pressure was 172 mm saline, effective hepatic blood flow 929 cc/min/m^2 and intra-hepatic shunt blood flow 35 cc/min/m^2. These results turned out to be slightly contrary to our expectation.

Morphological examinations of liver: The third peritoneoscopic examination with liver biopsy was performed on December 19, 1964. Macroscopically, the unripe brownish nodules with diameter of about 2 mm were found on reddish liver surface and their nodules were distributed at the distance of about 1 mm to 5 mm from one another (Fig. 12). The tip of spleen was found at 2 cm inside the costal margin, and the intrasplenic pressure was 260mm saline, being at a moderately high level. On the vascular stereogram, the shape of 5 portal veins (No. 1 to No. 5 P. V.) and 2 hepatic veins (No. 1 & No. 2 H. V.) were presented (Fig. 11), but these vessels showed entangled and inarticulate structures. The most prominent finding was a marked dilation of No. 1 H. V. to its peripheral part, and this dilated vein was in contact with the side of the wide connective tissue (Fig. 13). And there were 3 vascular strands tied up with connective tissue; namely, the first one was visible between No. 1 P. V. and No. 2 P. V., the second in between No. 3P. v., No. 4P. V. and No. 1 H. V., and the third in between No. 5 P. V. and No. 1 H. V.. Moreover, many inflammatory cells were found in this connective tissue but the damage of parenchymal cells was rarely observed (Fig. 14).

The fourth peritoneoscopic examination with liver biopsy was done on October 11, 1965, the macroscopic finding of small nodules were clearly more numerous on liver surface than the third one, whereas histological examination revealed broad scars and pseudolobular formations in places (Figs. 15, 16).

Clinical course: His clinical course is shown in Table 1. He was given high-protein diet and oral administration of 75 mg/day of 6-mercaptopurine from January 26, 1965 to the present (for about 8 months) for the treatment of active inflammatory process of connective tissue. His clinical symptoms have been gradually alleviated.

Table 1 Case I, T. S.

Total S-Bilirubin mg% (Direct Reacting F.)	0.92 (0.52)	0.90 (0.33)	0.71 (0.33)	0.90 (0.52)	0.90 (0.52)	0.71 (0.33)	0.85 (0.35)	0.90 (0.52)	0.84 (0.48)	0.69 (0.35)	0.45 (0.30)	0.70 (0.40)	0.85 (0.45)
BSP % retention at 45 min.	14.5	15.5	16.0	6.5	3.0	9.5	2.5	1.5		12.0	5.0		2.0
S-GOT Karmen U.	(42γ) *113	(125γ) *250	(20γ) *37	(38γ) *97	(63γ) *144	41	21	41	64	65	21	28	36
S-GPT Karmen U.	(34γ) *132	(152γ) *560	(20γ) *67	(62γ) *232	(80γ) *268	60	25	48	56	102	42	32	42
CCF	+	−	±	+	±	+	±	±	±	−	−	±	±
TTT Mac. U.	6.0	4.3	4.9	4.8	4.4	6.4	5.2	5.7	5.0	5.0	4.8	6.2	5.9
ZTT Kunkel U.	10.9	9.0	8.6	10.4	10.7	13.9	12.0	10.7	11.0	11.5	9.2	11.8	11.0
Serum Protein Total g/dl	7.3			6.3	6.6		7.0	7.6	7.0	6.6	7.0	8.0	
A/G Ratio	0.58	0.62		0.75	0.75		0.79	0.74	0.89	0.96	0.85	0.77	
γ-Glob. %	35.7	35.8		32.0	33.8		27.5	32.0	28.0	30.0	30.0	34.5	
KL (Au^{198} Colloid)		0.169		0.126					0.112				
KL (Indocyanine Green)													0.144
Wedged Hep. Venous Pressure mm H_2O								170					
Effective Hep. Blood Flow cc/min/m^2								929					
Intrahepatic shunt Flow cc/min/m^2								35					
Intrasplenic Pressure mm H_2O			210				260						
Date Month	12	2	4	6	8	10	12	1	2	4	6	8	10
Date Year	1962	1963					1964	1965					

* Converted from the result obtained by Niitani's method.

Case II S. S.; *The First Hospitalization*

Clinical history: A 41-year old male, a clerk, was admitted to Okayama University Hospital with chief complaints of general fatigue on June 2, 1959. He suffered from epidemic hepatitis with jaundice in the infected portion of virus hepatitis (Takahashi City in Okayama Prefecture) in the summer of 1952 and had recurrent jaundice one year after the onset. Thereafter he experienced continual general fatigue but no other subjective symptoms.

Physical examinations: Jaundice and anemia were not noted. The liver was palpable at 2 cm below the costal margin and its consistency was slightly increased. Spleen was palpable at just the costal margin. No other symptoms of liver disease were observable.

Laboratory data: The results of urinalysis were within normal limits except for positive (+ urine urobilinogen. Initial blood studies gave the values within normal limits; hemoglobin 95%, red blood cells 4,800,000/mm^3, white blood cells 7,200/mm^3 with a differential count of 51.0% segmented neutrophils, 3.5% nonsegmented neutrophils, 40.5% lymphocytes, 2.5% eosinophils and 2.5% monocytes and thrombocytes 154,000/mm^3. The initial studies of blood chemistry were as follows; total bilirubin 0.71 mg/dl with direct reacting form 0 mg/dl, BSP 10% at 45 minutes, S-GOT of 39γ of Niitani's method (80 Karmen units in converted value), and S-GPT 31γ of Niitan's method (116 K. u. in converted value), alkaline phosphatase 4.4 Bodanski units, serum total protein 6.8 mg/dl with 44.8% albumin, 6.6% α_1-globulin, 7.7% α_2-globulin, 13.9% β-globulin and 27.3% γ-globulin, questionable CCF, TTT 3.8 units, ZTT 7.2 Kunkel units, and total cholesterol 160 mg/dl with ester-form 78 mg/dl. Radiographic examinations of the gastrointestinal tract and biliary tract revealed normal conditions.

Morphological examinations of liver: The first peritoneoscopic examination with liver biopsy was performed on June 12, 1959. Macroscopically, the surface of the liver lobe was found to be smooth and whitish brown, and presented several lineal white coats, but there were no nodules and scar formations. The tip of spleen was visible at 3 cm inside the costal margin (Fig. 17). Histological findings showed the portal tract infiltrated with many inflammatory cells and the destruction of limiting plates. In addition, a slight fatty metamorphosis of parenchymal cells was noted (Fig. 18).

By the second peritoneoscopic examination with liver biopsy was done on May 17, 1960, the macro- and microscopic findings were essentially unchanged.

Clinical course: The patient was given a treatment of high-protein diet and oral administration of total of 29.25 mg dexamethasone from June 23, 1959 to July 20, 1959, and total of 385 mg of prednisolone from June 2, 1960 to July

1, 1960. Nevertheless, his clinical symptoms and laboratory findings persisted. He left the hospital on November 18, 1960 still not completely recovered.

The Second Hospitalization

Clinical course: The same patient was admitted again to Okayama University Hospital with chief complaints of general fatigue on May 16, 1964. On returning back to his work, he felt persistent fatigue quite readily but did not suffer from fever attacks and jaundice. The periodical physical examinations in our out-patient clinic revealed that he was sufering from a marked, persistent liver damage.

Physical examinations: Jaundice was not noted; liver palpable at 2 cm below the costal margin; its consistency moderately increased; and spleen palpable at the costal margin; but no other signs of liver disorders.

Laboratory data: Results of urinalysis were normal except for urine urobilinogen (positive ++), and urine sugar was positive. The initial blood studies were as follows: hemoglobin 97%, red blood cells 4,960,000/mm^3, white blood cells 7,750/mm^3 with a differential count of 28% segmented neutrophils, 4% nonsegmented neutrophils, 50% lymphocytes, 12% eosinophils and 5% monocytes, and thrombocytes 158,000/mm^3. The initial studies of blood chemistry were as follows: total bilirubin 0.85 mg/dl with direct reacting form 0.56 mg/dl. BSP was not performed for he was allergic to this dye. It was found that S-GOT proved to be 130 Karmen units and S-GPT 135 Karmen units, alkaline phosphatase 1.8 Bessey-Lowry units, serum total protein 7.2 mg/dl with 42.0% albumin, 7.0% α_1-globulin, 12.0% α_2-globulin, 8% β-globulin and 31.0% γ-globulin, CCF positive (++), TTT 10.3 units, ZTT 20.1 Kunkel units and total cholesterol 195 mg/dl. The fasting blood sugar was 130 mg/dl. The glucose tolerance test showed subsequent levels of 250, 348, 346, 360 and 250 mg/dl at 30, 60, 90, 120 and 180 minutes, respectively. Radioactive Au^{198} colloid accumulation rate of liver was 0.158. ICG disappearance rate was 0.115, which was slightly lower than normal level on August 29, 1964. Liver catheterization was performed on July 4, 1964. Wedged hepatic venous pressure was 205 mm saline, effective hepatic blood flow 702 cc/min/m^2 and intrahepatic shunt blood flow 0 cc/min/m^2.

Morphological examinations of liver: The third peritoneoscopic examination with liver biopsy was performed on July 6, 1964. Macroscopically, the surface of the liver lobe was found to be patched with reddish brown spots and their white outline, and dilated small arteries were visible, but nodular formations were not yet observed (Fig. 20). The tip of spleen was found at 3 cm inside the costal margin. Three portal branches (Ba, Bb, & Bc) diverging from one portal vein and a hepatic vein were demonstrated on the vascular

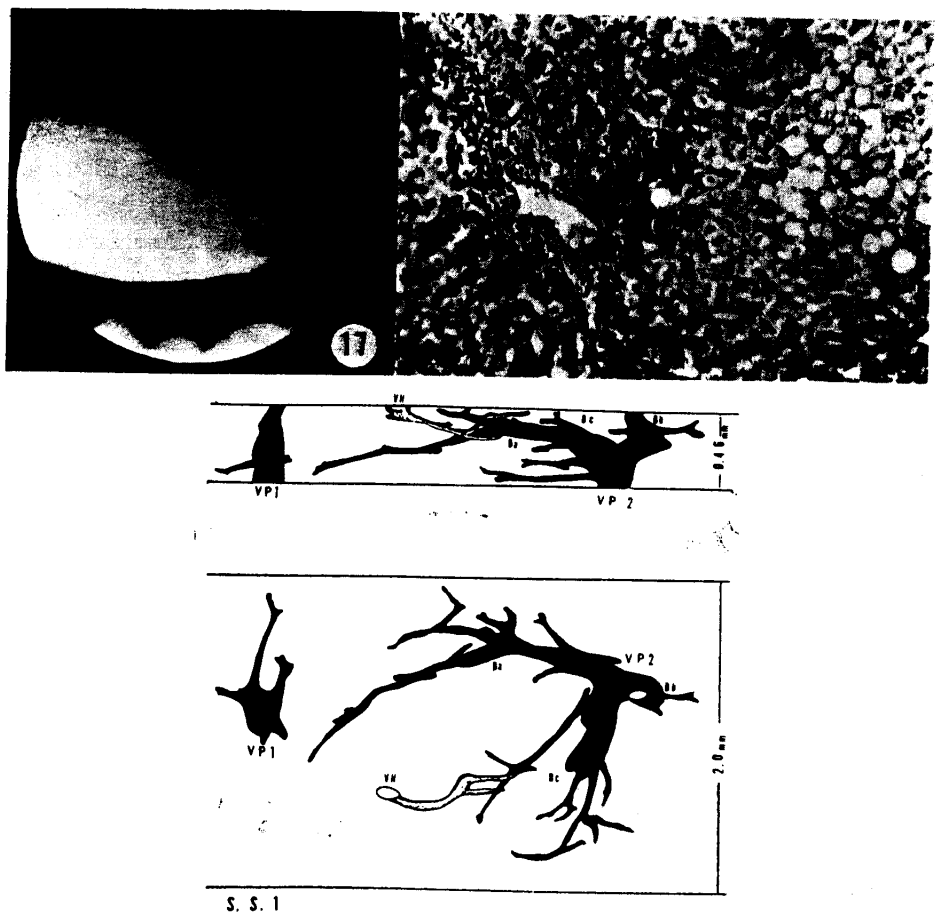
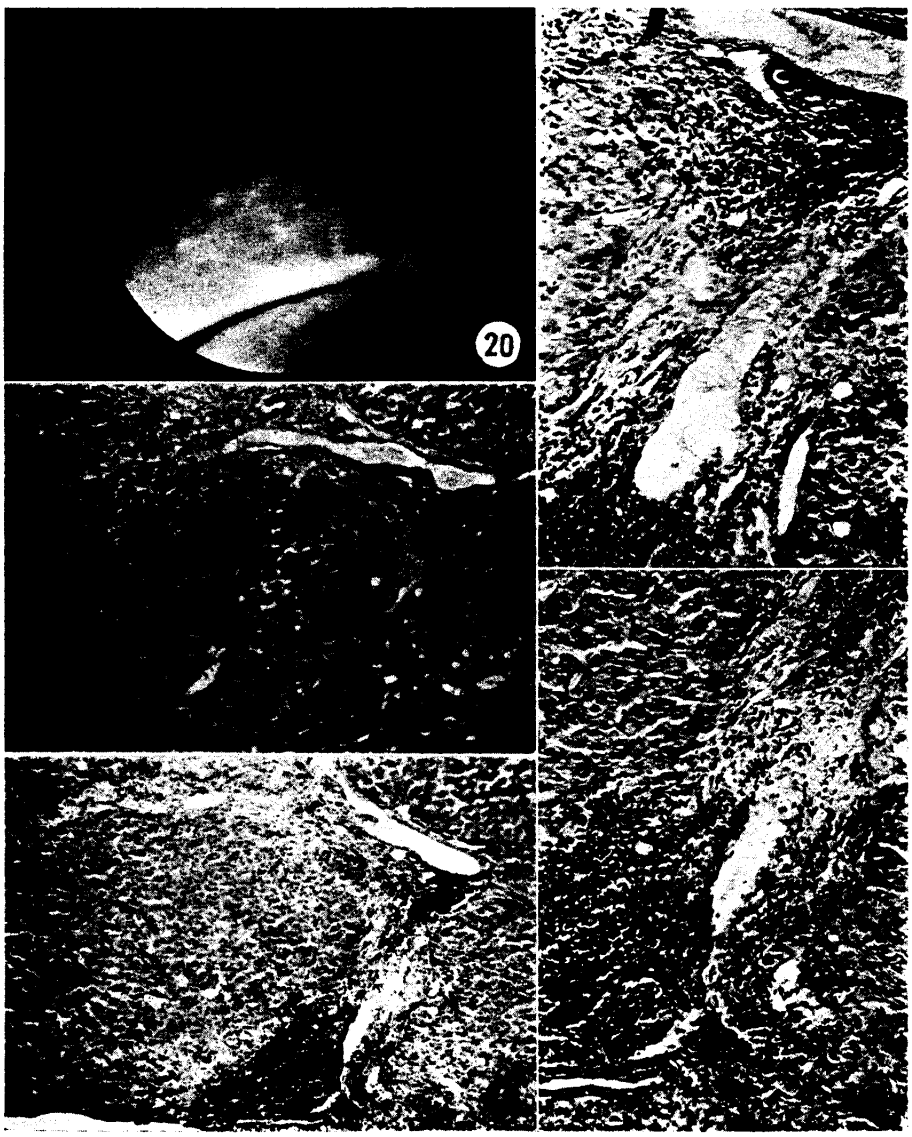


Fig. 19

Figs. 17 and 18 The findings of Case II at the scond peritoneoscopy with liver biopsy: Fig. 17 shows the smooth liver surface with white linear coats, and Fig. 18 infiltration of inflammatory cells in the periportal area, with destruction of limiting plate and a mild fatty degeneration of liver cells.

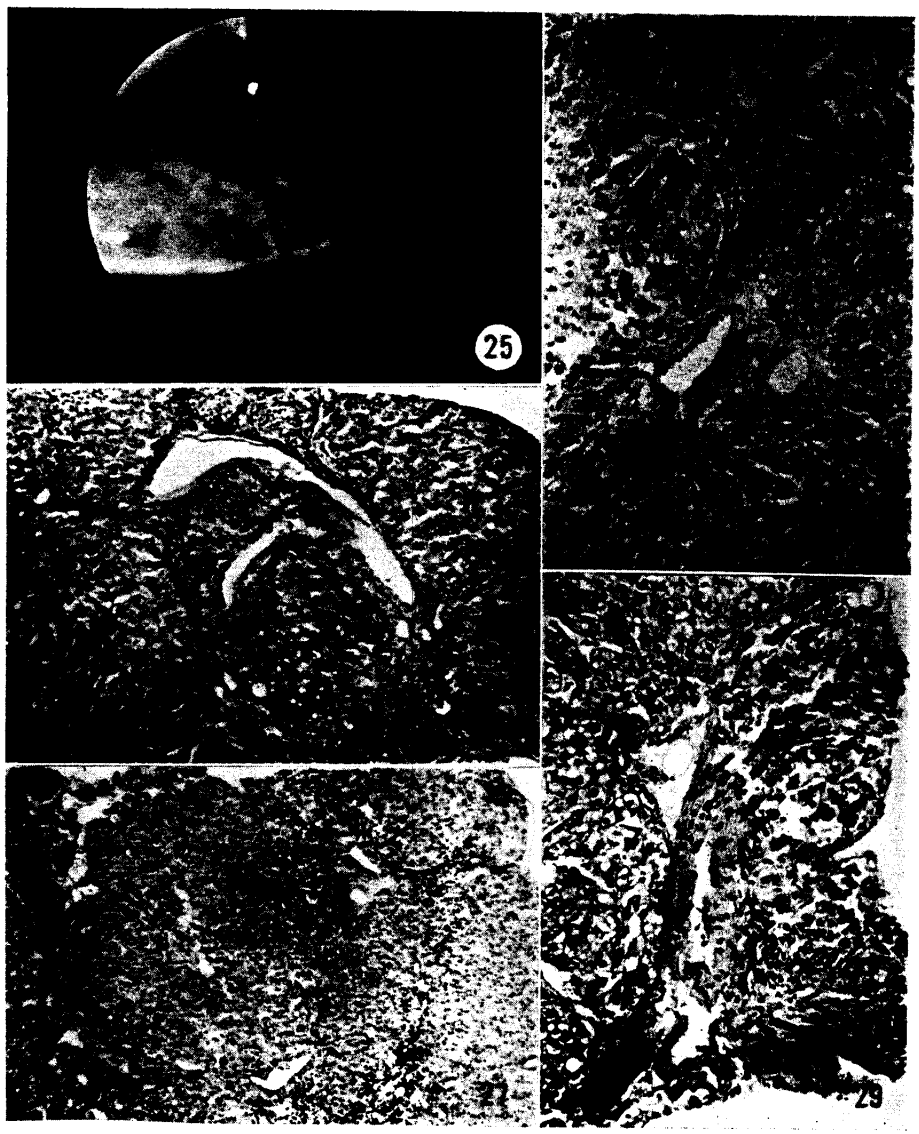
Figs. 19—24 The pictures taken at the third peritoneoscopy with liver biopsy of Case II: Fig. 19 is the vascular stereogram reconstructed with No. 34 to No. 80 sections (46 sections), illustrating the manner how No. 2 PV is diverging into three branches of Ba, Bb and Bc, as shown in the side view of the upper picture and the plane view in the lower. Here the distribution of Ba is normal but there can be recognized an abnormal pattern at the point where Bc further diverges into 3 terminal branches, and HV shifts to the side of Bc. Fig. 20 shows small reddish brown patches macroscopically. Figs. 21 and 22 show the 48th and the 55th sections, respectively, showing the direction of Ba, Bc and HV. H-E stain, ×50. Here HV shows "move" toward Bc, Figs. 23 and 24 are the pictures of the 53rd and the 55th sections, H-E stain, ×100. There can be observed a marked infiltration of inflammatory cells and scar formation in the surrounding area of Bc, which is abruptly narrowed down at the point shown by an arrow (↙). In Figs. 21, 22 and 24 there can be seen the degeneration and atrophy of those liver cells located between HV and Bc.

stereogram (Fig. 19). The Ba diverged again to three terminal branches which appeared to show normal pattern. The course of Bb was not discernible for it protruded out of the material. Bc extended at right angle to Ba, and at the next diverging point of terminal branches it became narrow with a marked increase of inflammatory cells and collagenous fibers (Figs. 21, 22, 23, 24). On the other hand, the central vein located between Ba and Bc was bent toward



the side of Bc. Furthermore, injuries of parenchymal cells on the side of Bc were severer than on the opposite side. Namely, on this side there were many necrotic or degenerated cells, loss of limiting plates and extension of fibers, while on the other side, such histological injuries were rare (Figs. 21, 22, 24).

The fourth peritoneoscopic examination with liver biopsy was done on May 31, 1965. Macroscopically, many unripe reddish nodules were found on the



liver surface, which were located at the distance of about 1 mm from each other, and their diameter measured 2 mm to 4 mm (Fig. 25). The tip of spleen was visible at 2 cm inside the costal margin. Three portal veins (No. 1 to No. 3 P. V.)

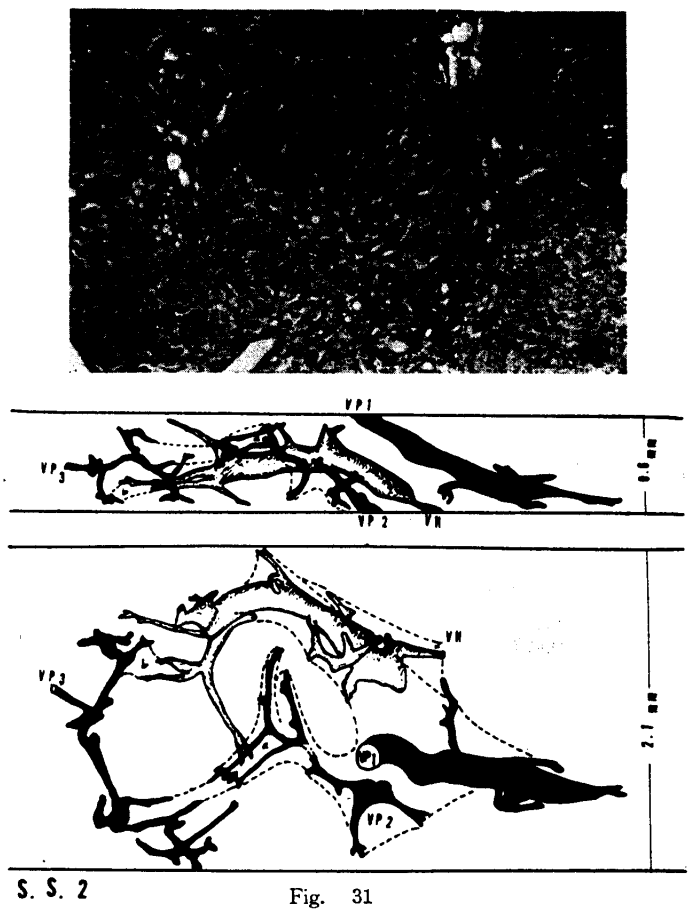


Fig. 31

Figs. 25—31 The findings of Case II at the 4th peritoneoscopy with liver biopsy: Fig. 25 shows macroscopic finding which reveals an unripe nodule and the arrow (↙) points a wire rod 2 mm in diameter with markings at every 5 mm, used to measure the nodule. Figs. 26 and 27 illustrate the 98th and 58th sections, H-E stain, ×50, both of which reveal the same HV pointed out by the arrow (↙). The 98th section shows a distended HV and the 58th section a narrow proximal part of the same vein. Figs. 28 and 29 present the same HV as pointed out by the arrow (↙) in the 58th and the 46th sections respectively, H-E stain, ×100. These pictures show the proliferation of the connective tissue around HV and the thickening of HV wall. Fig. 30 is the picture of the 100th section, H-E stain, ×50, showing a septum formation between No. 2 and No. 3 portal veins. Fig. 31 is the vascular stereogram reconstructed with No. 45 to No. 105 sections (60 sections in all). In this stereogram a complex distortion of hepatic and portal veins can be observed, especially marked is a considerable distenson of the hepatic vein of which the proximal part is distinctly narrow. (Legends: PV=portal vein and HV=hepatic vein)

Table 2 Case II, S. S.

Total S-Bilirubin mg% (Direct Reacting F.)	0.71 (0)	0.90 (0.33)	0.71 (0.33)	0.90 (0.14)	0.85 (0.56)	0.78 (0.40)	0.98 (0.72)	0.75 (0.45)	1.00 (0.60)	1.09 (0.52)	0.68 (0.39)	0.85 (0.52)	0.86 (0.48)
BSP % retention at 45 min	10.0	0	12.5	5.0									
S-GOT Karmen U.	(39γ) *80	(39γ) *100	(40γ) *105	(38γ) *97	130	87	57	105	230	49	80	90	52
S-GPT Karmen U.	(31γ) *116	(27γ) *96	(27γ) *96	(13γ) *42	135	120	125	145	260	145	135	114	33
CCF	−	−	−	−	++	+	+	−	+	±	±	±	±
TTT Mac. U.	3.8	4.2	4.6	4.4	10.3	6.2	4.8	4.7	6.9	7.0	6.8	6.3	5.2
ZTT Kunkel U.	7.2	7.5	9.0	9.0	20.1	14.0	10.2	10.3	14.5	13.9	12.0	11.7	11.8
Serum Protein													
Total g/dl	6.8		8.0	6.4			7.1	7.6	7.6				7.8
A/G Ratio	0.80	1.22	0.89	0.96	0.72		0.85	0.71	0.63				1.04
γ-Glob. %	27.3	26.0	28.9	26.0	31.0		28.5	29.5	33.0				23.0
KL (Au^{198} Colloid)						0.158							
KL (Indocyanine Green)						0.115					0.10		
Wedged Hep. Venous Pressure mm H_2O						205							
Effective Hep. Blood Flow cc/min/m^2						702							
Intrahepatic shunt B. Flow cc/min/m^2						0							
Intrasplenic Pressure mm H_2O													
Date Month	6	12	6	10	5	7	9	11	1	3	5	7	9
Year	1959		1960		1964				1965				

* Converted from the result obtained by Niitani's method.

and one hepatic vein were shown on the vascular stereogram (Fig. 31). A branch of No. 1 P.V. and a proximal part of the hepatic vein were adjoined and the more proximal part of the hepatic vein was moderately narrow with thickened venous wall accompanied by perivascular fibrosis (Figs. 27, 28, 29). Its distal part was markedly dilated (Figs. 26, 27). On the other hand, there were two septa one each in between No. 2 P. V. and No. 3 P. V., and No. 3 P. V. and the peripheral branch of hepatic vein (Fig. 30).

Clinical course: His clinical course is shown in Table 2. He was treated with high-protein diet and lente insulin 10 units/day. Blood sugar level turned almost normal two weeks after the first administration of insulin. These treatments have been continued to the present (for about 15 months), but his symptoms and laboratory findings are practically unchanged.

DISCUSSION

It has been reported[1-3] that liver cirrhosis may follow the common type of acute viral hepatitis, and diagrams of macro- and microscopic findings of such a transition are already shown but etiologic factors of this transition are almost unknown. It is said that in the cases of chronic hepatitis the portal tracts are infiltrated with a variety of inflammatory cells; the limiting plates are already destroyed, and sometimes the portal tracts appear larger and scarred with increased connective tissue. On the incidence of this inflammatory process of periportal area for the progression to liver cirrhosis, many studies have been made, but the etiologic factors are not still established. Furthermore, as regards the subsequent scar formation of portal tracts, there seems to be no discussion whatsoever. Concerning this problem one of the authors has already reported[9] that the intrahepatic portal hypertension is induced by the scar formation in the portal tracts and it seems to persist for a long period of time, judging from such findings as peritoneoscopic examinations, liver catheterization and histological findings, particularly, observations on vascular stereograms of liver biopsy materials. Therefore, it is presumed that the hepatic blood flow decreases in the distributed area of this scarred portal tract and at the point of the supply of oxygen and nutrients, this area being distinguishable from the adjacent area. The patho-physiological studies on hepatic acinar units, especially on hepatic microcirculatory pathways in relation to acinar units, have been discussed, by A. M. RAPPAPORT[10-11], H. POPPER[8], H. ELIAS[12-14], and H. BAGGENSTOSS[15]. And these reports have supported the idea that an insufficient hepatic blood flow is one of the essential factors for the progression to liver cirrhosis.

Case I in the present report may be presumed to have suffered from non-icteric viral hapatitis at the onset. During the first period of 6 months

between the first and the second peritoneoscopies, it has been demonstrated by the foregoing detailed morphological examinations that the liver architecture of this patient was moderately distorted. Moreover, the case shifted to an early stage of liver cirrhosis during the succeeding 18 months between the second and the third peritoneoscopies. In the whole course of the period no outstanding clinical symptoms were noted ; neither fever attacks, jaundice nor ascites, except for mild hepato- and splenomegalias. On the other hand, abnormally high values of ZTT and γ-globulin were continually shown, but the values of S-GOT were gradually normalized. Radioactive Au^{198} colloid accumulation rate of liver gradually diminished at each occasion of measurement, and the intrasplenic pressure showed an identical pattern as in the above findings. Wedged hepatic venous pressure and effective hepatic blood flow were almost normal. Consequently, it may be presumed that such structural alterations have been taking place under subclinical course. Two interesting problems may be pointed out about this cases: 1. the mechanism of progression to cirrhosis, and 2. discrepancies in clinical, laboratory and morphological findings. The main explanation for the former problem is given by the findings at the second morphological examinations. Namely, the parenchymal cells in the dependent area of scarred portal tract were damaged, particularly they all disappeared at the terminal area. As a consequence, three portal tracts, diverging from individual stems, were adjoined in a single connective tissue, by means of the other two portal tracts which had been drawn to this part. These findings indicate two significant facts ; (a) in some cases of viral hepatitis blood flow is partially decreased with chronic inflammatory process, especially with scar formations in portal tracts, and (b) the lobular architecture is distorted due to the above morphological injuries, suspected of a partially decreased supply of oxygen and nutrients from the afferent vessels. These facts have been already discussed thus far. In other words, (a) is based on the author's report[9] and the fact (b) is presumed and supported by these workers. However, it is important to clarify the connection of these two facts in the one and same human case, and to explain the progression from chronic inflammatory process in the portal tracts to distortion of the hepatic lobules on the basis of hepatic circulatory disturbances.

These discrepancies among clinical, laboratory and morphological findings still pose a variety of unresolved elements. At least, the problem might be explained of this case from the fact that the above-morphological partial alterations have been observed at the liver tissue. Furthermore, the above explanation can be supported also by the fact that the number of nodules on the liver surface was sparse in the peritoneoscopic observations.

Case II is remarkable on the point of the initial viral infection at the

infected area. Morphologically, 7 years after the onset of disease his histological findings showed a moderate infiltration of inflammatory cells in the portal tracts with slight fatty metamorphosis under normal liver architecture. In the subsequent five-year period his morphological examinations revealed precirrhotic stage of liver and one year later it was clearly demonstrated that the case had shifted to cirrhosis. However, his clinical symptoms remained unchanged, only with slightly high values of BSP, S-GOT, S-GPT, TTT, ZTT and γ-globulin that have persisted to the present. On the other hand, slightly high level of wedged hepatic venous pressure is noted, but effective hepatic blood flow and Au^{198} colloid accumulation rate are almost within normal limits.

Many interesting findings have also been demonstrated on the vascular stereograms, particularly these are found on the second stereogram showing the position of central vein being deviated from center to side of the scarred portal tract. The fact of this "move" of the central vein from a central to a peripheral position is as serious as the fact of the "gathering" of the portal tracts, being demonstrated in Case I, with respect to the distortion of the lobular architecture.

SUMMARY

Two cases (Case I, 24-year old male, and Case II, 41-year old male) of liver cirrhosis after viral hepatitis have been described with a special emphasis on the distortion of the hepatic lobular architecture induced by hepatic hemodynamic changes.

Careful and precise clinical and laboratory examinations as well as peritoneoscopic examination with liver biopsy, particularly with vascular stereograms of liver biopsy tissue, have been successively carried out from stage of normal lobular architecture to early stage of cirrhosis. As the result, it has been found that in the course of these examinations clinical and laboratory features of the patients have remained almost unchanged in spite of gradual aggravation of morphological pictures. It is especially noteworthy that on vascular stereograms of liver biopsy tissue the parenchymal cells under the scarred portal tracts have suffered atrophic changes. Thus, three individual portal tracts of Case I have been gathered in a single connective tissue located on the distributing area of a scarred portal tract, whereas a central vein of Case II has moved from center to side of the scarred portal tract. In the late stage, these two cases ultimately turned to liver cirrhosis.

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