

HEPATIC MICROCIRCULATION OF LIVER CIRRHOSIS STUDIED BY CORROSION CAST/SCANNING ELECTRON MICROSCOPE EXAMINATION

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Changes of hepatic microcirculations in 22 autopsy cases of liver cirrhosis were analyzed by corrosion cast/scanning electron microscope (SEM) examination. By this method, the site of arterioportal (A-P) communication in liver cirrhosis was clearly demonstrated between proliferated portal venules and arterial capillaries. The communications were observed at the same site as in the normal liver and were not at larger arterial and portal vein branches. The findings indicate that the increase of A-P communication in liver cirrhosis may be called "capillary shunting". On the basis of the findings, it was postulated that the A-P shunt could not assist in the development of portal hypertension by the transmission of high arterial pressure to the portal vein but could only compensate for decreased portal flow and/or elevate the oxygen concentration in the sinusoids to improve the hypoxic state of the liver parenchyma. It was also demonstrated that the arterial capillarization of the interstitial septa in micronodular wide septal cirrhosis was more prominent than that in macronodular thin septal cirrhosis. A grade of portal vein reduction and compensatory arterIALIZATION in a fibrous septum have been regarded as an index to estimate the advancement of liver cirrhosis. Therefore, if alcoholic micronodular cirrhosis could change into macronodular, the process should have occurred at least before the establishment of micronodular wide septal cirrhosis. ACTA PATHOL. JPN. 36 : 375~387, 1986.

Introduction

Many investigations concerning vascular architecture of the liver have been accumulated over the past hundred years.^{4,5,10,18,21,29,33} Especially, recent advance of the three dimensional approach to corrosion cast/SEM examination technique has clearly demonstrated the hepatic microcirculations among arterioles, capillaries, portal venules, and sinusoids.^{8,14,23,24,26} Whereas, the distribution of terminal hepatic arter-

Accepted for publication June 15, 1985.

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oles in liver cirrhosis has not yet been sufficiently clarified.³⁷

Past studies of the vasculature have been made using techniques which require the injection of colored plastic or gelatin^{9,16,20,22,28,34} and reconstruction of the serial tissue sections.¹⁵ However, they have some limitations of resolution in the discrimination of

microvessels, and could frequently mistake the colored material mixture caused by artefactual backflows through sinusoids or capillaries as that caused by a shunt. For this reason, the past injection method is considered to be impossible in accurately discriminating proliferated terminal portal venules from arterioles.

In this study, we applied the method of corrosion cast/SEM examination for investigating the microcirculation in human cirrhotic liver with special attention to the terminal distribution of arterial branches. Attempts to clarify the site of A-P shunt and to reassess the relation of arterial branches to the microcirculations around the regenerative nodules were also made.

Materials and Methods

Twenty-two autopsy cases of liver cirrhosis were collected in the Department of Pathology, Chiba University during the period of 1982-1984. They were classified into the following three types (a) micronodular, (b) mixed nodular, (c) macronodular, according to the predominant size and structural features of the regenerative nodules. In micronodular cirrhosis, regenerative nodules were 5 mm or less in size and contained no portal tracts or terminal hepatic venules. In macronodular cirrhosis, regenerative nodules were larger than 5 mm in diameter and contained portal tracts and/or terminal hepatic venules. Nodules in the mixed nodular type were variable in size with or without containing portal tracts and/or terminal hepatic venules. The grade of the interstitial septum was classified into the following three types 1+ : less than 0.5 mm in mean width, 2+ : 0.5-1.0 mm in mean width, 3+ : more than 1.0 mm in mean width (Fig. 1). All

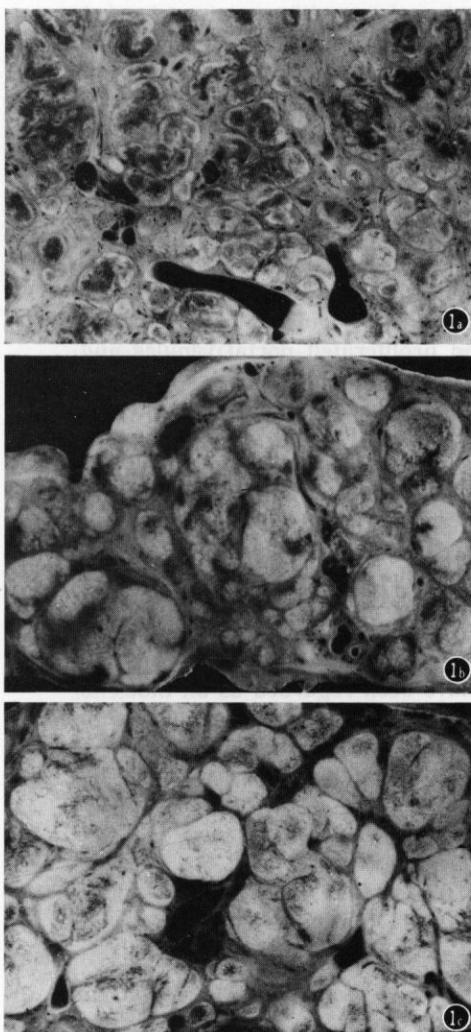


Fig. 1a. Photomicrograph showing a case of micronodular cirrhosis. Regenerative nodules are predominantly less than 5 mm in diameter. $\times 4$. 1b. Photomicrograph showing a case of mixed nodular cirrhosis. Regenerative nodules are variable in size. $\times 4$. 1c. Photomicrograph showing a case of macronodular cirrhosis. Regenerative nodules are predominantly larger than 5 mm in diameter. $\times 4$.

Table 1. Clinical and Gross Anatomical Findings in 22 Cases of Liver Cirrhosis

Case	Age	Sex	HB sAg	HB sAb	HB cAb	BTF	History of alcohol intake	Fibrosis*	Size of nodules**
1.	58	M	—	—	—	—	75 g/D, 33 Y	3+	S
2.	47	M	—	?	?	?	90 g/D, 20 Y	2+	S
3.	46	M	—	+	?	—	210 g/D, 25 Y	3+	S
4.	57	M	—	—	—	—	150 g/D, 37 Y	2+	S
5.	59	M	—	?	?	?	75 g/D, 41 Y	3+	S
6.	72	M	—	—	—	—	150 g/D, 50 Y	3+	S
7.	37	M	+	—	+	—	300 g/D, 18 Y	1+	S
8.	71	M	—	—	+	+	90 g/D, 40 Y	2+	S
9.	51	M	—	+	—	—	150 g/D, 50 Y	1+	M
10.	66	M	—	?	?	+	60 g/D, 30 Y	2+	M
11.	58	M	—	+	+	—	120 g/D, 30 Y	1+	M
12.	51	M	—	?	+	—	80 g/D, 30 Y	1+	M
13.	52	M	—	?	?	—	30 g/D, 28 Y	1+	M
14.	53	F	—	?	?	—	(—)	1+	M
15.	47	M	—	+	+	—	(—)	2+	M
16.	51	M	—	?	?	?	150 g/D, 25 Y	1+	L
17.	64	M	—	?	?	+	(—)	1+	L
18.	44	M	—	+	?	?	(—)	1+	L
19.	60	F	—	+	+	—	(—)	1+	L
20.	65	M	+	—	+	—	(—)	2+	L
21.	67	M	—	+	?	—	(—)	1+	L
22.	35	M	+	—	+	+	(—)	2+	L

* interstitial fibrosis: 1+ ; less than 0.5 mm in mean width

2+ ; 0.5-1.0 mm in mean width

3+ ; more than 1.0 mm in mean width

** size of nodules: S; predominant size of nodules less than 5 mm in diameter, almost equal in size.

M; intermediate, variable in size.

L; predominant size of nodules larger than 5 mm in diameter, almost equal in size.

the cases of micronodular cirrhosis were historically alcoholic with a consumption history of more than 75 g of ethanol (sake) per day for more than 10 years. Except for one case, all were HBsAg negative with no history of hepatitis. Six of the seven cases of macronodular cirrhosis were non-alcoholic with or without history of hepatitis (**Table 1**).

At autopsy three blocks of the liver tissue were excised from the edges of each liver, and capsular injury or tears were sealed with a binding agent (Alon-alfa). After cannulating one selected vessel from the hepatic artery, portal vein, and hepatic vein in the cut-surface, the blocks were rinsed in a normal saline solution. After washing the blood from the blocks, methyl-methacrylate (Mercox) was infused by hand at a regular flow rate of about 3 ml/minute through the cannula nearly measured at the pressures of 100-200 mmHg for the hepatic artery, and 20-50 mmHg for the portal vein and the hepatic vein. The blocks were then fixed in a 10% formaldehyde solution over 2-3 days. After the

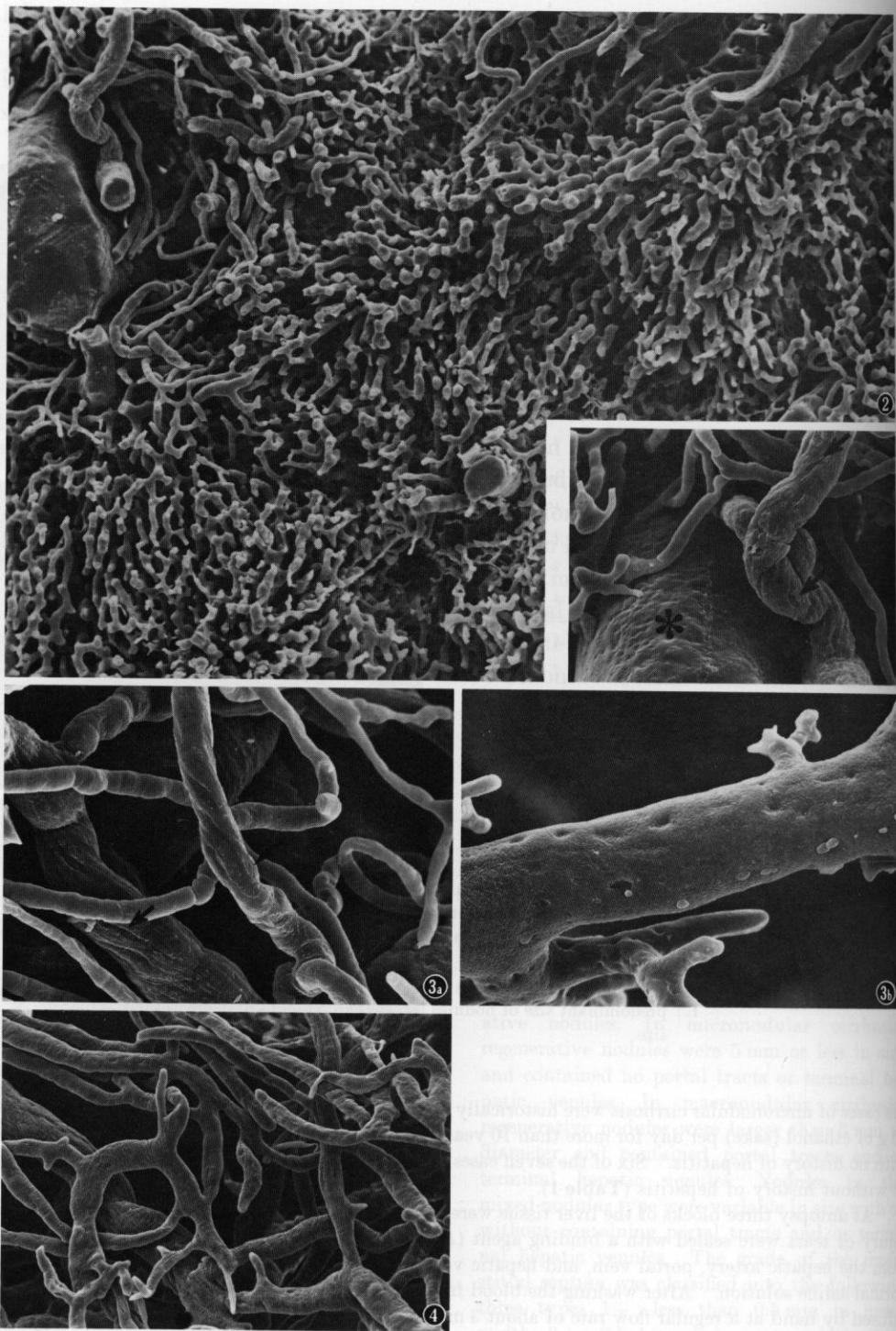


Fig. 2. Corrosion cast of the liver of a patient with primary biliary cirrhosis. The representative nodules were 5 mm in diameter and contained no portal tracts or normal liver tissue. Fig. 3a. Corrosion cast of the liver of a patient with primary biliary cirrhosis. The nodules were 5 mm in diameter and contained no portal tracts or normal liver tissue. Fig. 3b. Corrosion cast of the liver of a patient with primary biliary cirrhosis. The nodules were 5 mm in diameter and contained no portal tracts or normal liver tissue. Fig. 4. Corrosion cast of the liver of a patient with primary biliary cirrhosis. The nodules were 5 mm in diameter and contained no portal tracts or normal liver tissue.

methacrylate was completely polymerized, the blocks were sliced into pieces of $10 \times 10 \times 2$ mm, and their cut-surfaces were recorded as photographs, and they were macerated in hypochloride (Heiter, Kao Sekken Co. Japan). The casts obtained were dried sequentially in ethanol and in air. After coating them with gold by ion-coater (Giko-IB3), they were examined by SEM (JSM-25S2) with an accelerating voltage of 25 kV.

Results

Identification of Hepatic Vessels

(1) *Hepatic artery* : A cast of the hepatic artery is characterized by longitudinal grooves on the surface carved by protruded endothelial cells^{1,12,37} (Fig. 2). Even the cast of pre-capillary terminal arterioles have the longitudinal grooves on the surface (Fig. 3). This finding is very important when using the casting method for differentiation of peripheral arterioles from terminal portal venules at the site of their communications. By looking for this characteristic nature, we can easily clarify the origin of small tributaries of the hepatic vessels without using colored material. Moreover, this may be the only way to make real identification of the distorted arterial or portal microvessels in liver cirrhosis (Fig. 4).

(2) *Portal vein* : In the normal liver, the bifurcation angle of the portal vein is more obtuse than that of the hepatic vein. Besides, the former has trigeminal branching in contrast to bigeminal in the latter. But these features are blurred in cirrhosis and

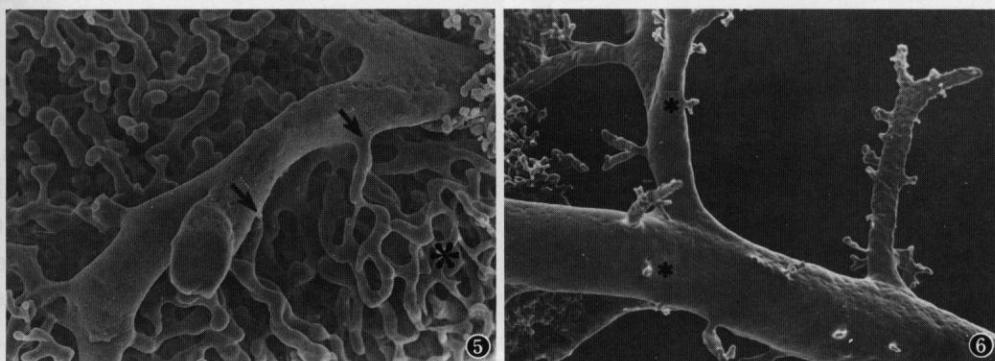


Fig. 5. Inlet venules (arrows) of the portal vein which intervene between portal vein and sinusoids (*). $\times 117$.

Fig. 6. A branch of hepatic vein which receives direct connection of sinusoids (*). $\times 55$.

Fig. 2. A cast of normal liver. Methacrylate was injected only through the hepatic artery. $\times 62$. Inset: A part of the portal area which contains portal vein (*) and several arterial branches which have longitudinal grooves (arrows) on its surface.

Fig. 3a. Several branches of terminal arterioles and capillaries are seen. $\times 350$. Terminal arterioles have longitudinal grooves (arrows) on the surface, but capillaries do not. 3b. A branch of terminal portal venules. No longitudinal grooves are seen on the surface. $\times 350$.

Fig. 4. A plexus of portal venules around the regenerative nodules in cirrhosis that looks like arteriolar plexus in low power magnification, but lacks longitudinal grooves on the surface. $\times 117$.

appear not to be useful for vascular identification. The most prominent characteristic of the portal vein branches is that they have inlet venules connecting terminal portal venules to sinusoids (Fig. 5). The second important feature is that the walls are more resistant to fibrogenic contraction than those of the hepatic veins. These characteristics seem to be useful for differentiating portal venules from hepatic venules even in cirrhosis.

(3) *Hepatic vein* : An important characteristic of the hepatic veins is that they have a direct connection with sinusoids without interposition of inlet venules (Fig. 6). But for discrimination of the distorted hepatic veins around the regenerative nodules, it is sometimes necessary by tracing observation to prove continuity with the apparent branches.

Vascular Changes in Micronodular Cirrhosis

(1) *Arterial branches* : In micronodular cirrhosis, remarkable proliferation of pre-capillary arterioles was noted around the regenerative nodules (Fig. 7). The degree of the arteriolar proliferations was variable according to the thickness of the fibrous septum. This was characteristically seen in every case of micronodular cirrhosis. The portal veins were never observed unless the injected material flowed into the perinodular capillaries or sinusoids (Fig. 8). Moreover, direct connections between the branches larger than arterioles and portal veins were never found. So it was considered that the A-P communication in micronodular cirrhosis occurred between terminal arterioles or capillaries and sinusoids (Fig. 9).

(2) *Portal vein branches* : Such changes of the portal veins as tortuosity, irregularity in calibre, multiramification, or interconnections were more remarkable in the areas with a broad scar of connective tissue (Fig. 10). Around the regenerative nodules, portal veins with a calibre less than 100 μm in diameter, ran separately from arterial branches, so their capillary connections almost disappeared, and it was very difficult to differentiate irregularly deformed portal veins from the hepatic veins. But a close tracing observation could make it possible to discriminate their mutual connections

Fig. 7. A cast in a case of micronodular cirrhosis made by injecting only through the hepatic artery. $\times 40$. Inset: Every branch is composed of arterioles with longitudinal grooves. $\times 264$.

Fig. 8. A cast in a case of micronodular cirrhosis injected only through the hepatic artery. In this specimen, sinusoids(*) are fully injected and some portal veins (arrows) are seen around the regenerative nodules. $\times 35$.

Fig. 9. A site of A-P shunt in micronodular cirrhosis. Sinusoids(*) are supplied with arterial capillaries. $\times 234$.

Fig. 10. A cast of portal veins in micronodular cirrhosis. Changes such as tortuosity, irregularity in calibre, interconnections are remarkable, but flattening or compression by regenerative nodules is unremarkable. $\times 78$.

Fig. 11. A P-V shunt seen around the regenerative nodules. As the wall of the hepatic vein is susceptible to fibrogenic contraction, the hepatic vein (short arrow) is relatively flattened and contracted compared with the portal vein (long arrow). $\times 117$.

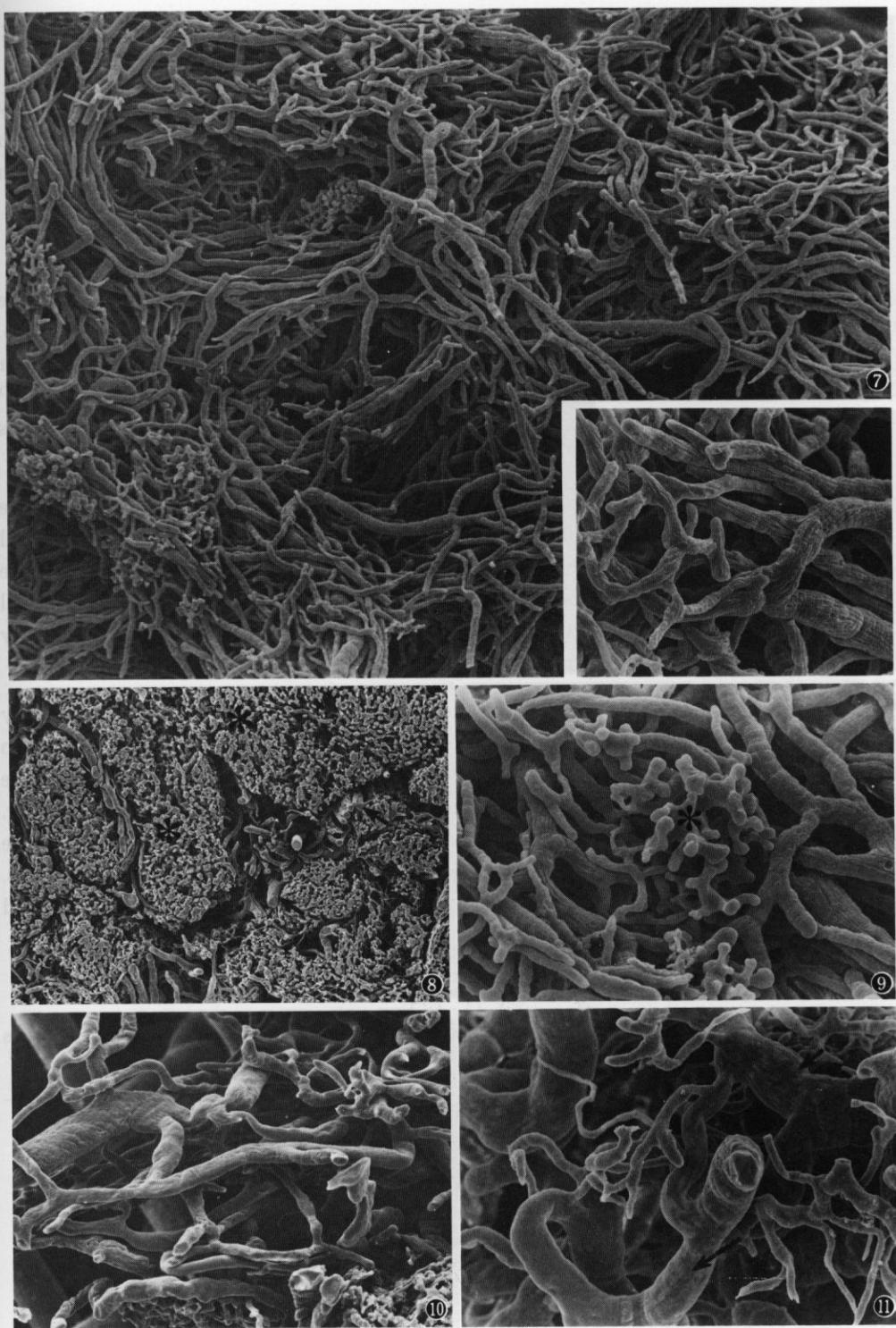


Fig. 7-11. Scanning electron micrographs of *Lamellaria* based on columnar base.

which form portal-hepatic venous (P-V) shunts around the regenerative nodules (Fig. 11).

(3) *Hepatic vein branches* : As changes of the hepatic veins, tortuosity, irregularity in calibre, and interconnections were seen. Hepatic arterioles were often filled with the injected material from the hepatic vein. But, no direct connections between hepatic veins and arterial branches could be demonstrated.

Vascular Changes in Macronodular Cirrhosis

(1) *Arterial branches* : In macronodular cirrhosis, cast material injected from the hepatic artery frequently flowed back into the portal vein branches (Fig. 12). Nevertheless, arterioportal connection was not found at the levels of pre-arteriolar larger arterial branches even on close observation. So it was considered that A-P shunt in macronodular cirrhosis was located between terminal arterioles or capillaries and portal venules (Fig. 13).

(2) *Portal vein branches* : Proliferation of the terminal portal venules seemed to be more remarkable in macronodular cirrhosis. The course of the proliferated portal venules was almost smooth, even though they were compressed or flattened at the periphery of the regenerative nodules. In and around the regenerative nodules, portal vein with a calibre less than $100\ \mu\text{m}$ in diameter, was occasionally accompanied by hepatic artery similar to that in the normal liver triads (Fig. 14).

(3) *Hepatic vein branches* : As changes of the hepatic veins, tortuosity, irregularity in calibre, and multiramifications were also seen. They were essentially similar to those of the micronodular cirrhosis. Flattening of the veins around the regenerative nodules, however, was more remarkable than that in the micronodular cirrhosis (Fig. 15). Several branches with a calibre of about $20-100\ \mu\text{m}$ in diameter were seen in the nodules and they received sinusoids to join the perinodular larger hepatic veins. Connections between portal and hepatic venous branches were also observed around the nodules.

Vascular Changes in Mixed Nodular Cirrhosis

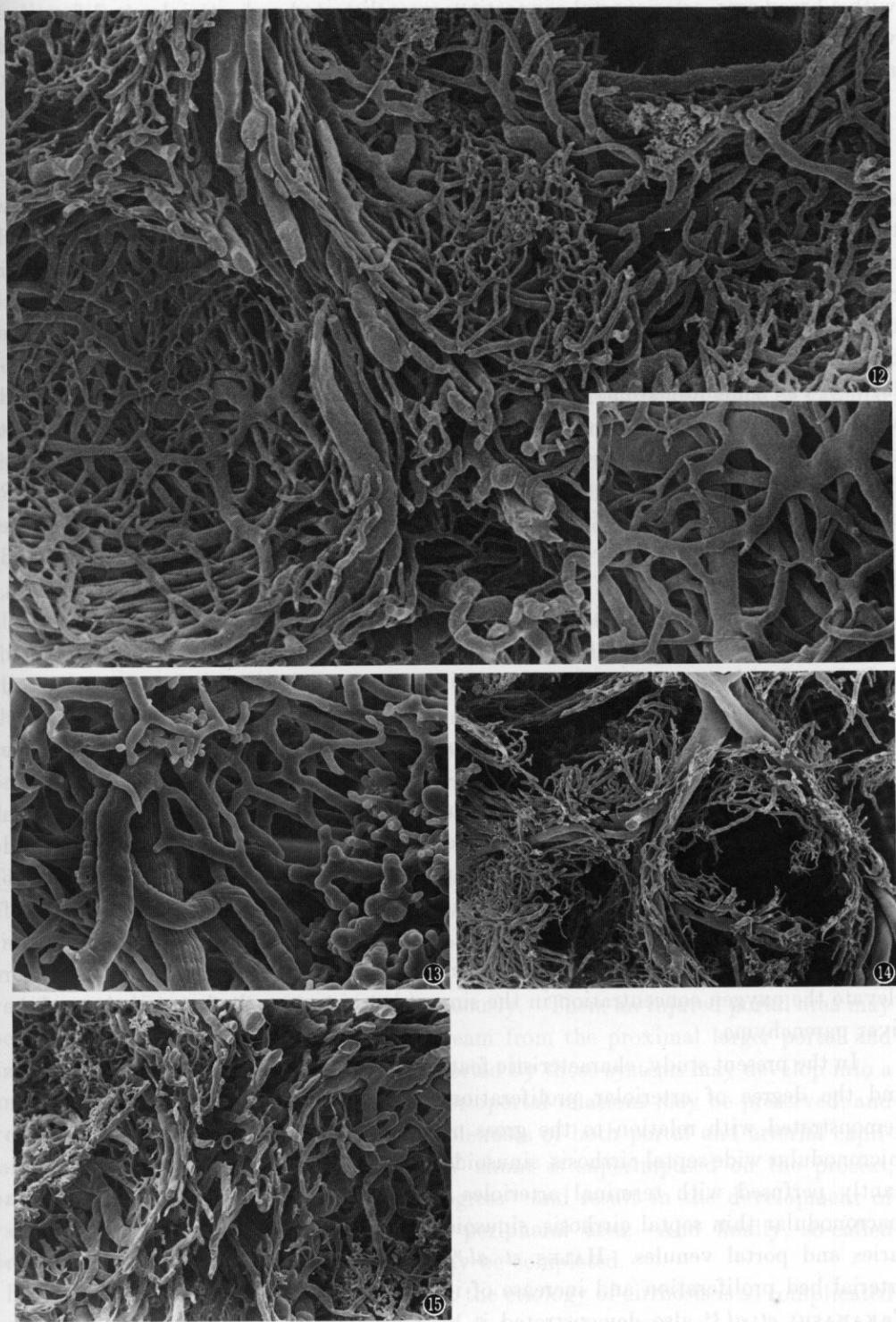
The vascular changes were variable according to the nodules examined. In cases

Fig. 12. A cast in a case of macronodular cirrhosis injected only through the hepatic artery. $\times 40$. Inset: Capillary plexus around the regenerative nodules is composed of both arterial capillaries and portal venules.

Fig. 13. A site of A-P communication around the regenerative nodules in macronodular cirrhosis. $\times 234$.

Fig. 14. A cast in a case of macronodular cirrhosis made by injecting only through the hepatic artery. Note the parallel paths of the portal vein branches (long arrows) with arterial branches (short arrows) in and around the regenerative nodules. $\times 16$.

Fig. 15. A cast of hepatic vein in macronodular cirrhosis. Remarkable compression of proliferated venules is noted around the regenerative nodules. $\times 35$.



with a broad scar, arterioportal connections were distorted and arteriolar proliferations were noted around the regenerative nodules as was frequently observed in the cases of micronodular wide septal cirrhosis.

Discussion

Increased arterioportal (A-P) communication in liver cirrhosis has been demonstrated by many investigators.^{9,11,19,22,28,36} But because of the methodological limitations of the old injection method, the morphologic background of the increased communication has not yet been satisfactorily demonstrated. In this study, vascular communications were investigated by the new method of corrosion cast/SEM examination. As a result, the site of A-P communications was clearly demonstrated at the branches between proliferated portal venules and terminal hepatic arterioles or capillaries. The communications were observed at the same site as in the normal liver and were not at larger arterial and portal vein branches. The finding thus indicates that the A-P shunt in liver cirrhosis is a different pathological entity from that in the hepatocellular carcinoma, post-traumatic A-P shunt, or congenital A-P malformation.^{6,13,27} This is further supported by the results of other studies that the A-P shunt was rarely observed in liver cirrhosis by angiographic demonstration²⁷ and frequently in the others.^{6,13,27} So, increase of A-P communication in liver cirrhosis, derived from increase of capillary connections, may be called "capillary shunting".

Pathophysiological significance of the A-P shunt is still uncertain. Previously, A-P shunt had been considered to play an important role in the development of portal hypertension by the transmission of high arterial pressure into the portal vein.^{11,19} However, the present findings on the site of A-P shunt may suggest that this may be unlikely to occur, because at the site of A-P shunt, proliferated arterioles and capillaries could be considered to work as a kind of circulatory buffer system, where high arterial pressure might be sufficiently reduced near the levels of normal arterial capillaries. Of course, we must be cautious to extrapolate morphological findings to the functional phenomenon occurring in the liver. To prove this hypothesis, more of the hemodynamic study must be necessary. Although, if that might be true, increase of A-P communication may only act to compensate decreased portal flow^{2,25,32} and/or elevate the oxygen concentration in the sinusoids to improve the hypoxic state of the liver parenchyma.

In the present study, characteristic features in the manner of A-P communications and the degree of arteriolar proliferations around the regenerative nodules were demonstrated with relation to the gross morphological types of liver cirrhosis. In micronodular wide septal cirrhosis, sinusoids of the regenerative nodules were predominantly perfused with terminal arterioles and capillaries. On the other hand, in macronodular thin septal cirrhosis, sinusoids were perfused with both arterial capillaries and portal venules. HALES *et al.*⁹ first described the relationship between arterial bed proliferation and increase of interstitial fibrosis in liver cirrhosis. And TAKAHASHI *et al.*³⁴ also demonstrated it by morphometrical analysis. The present

findings of the predominant arteriolar proliferations in the cases of micronodular cirrhosis correspond to their results, because wide septal cases were predominant in the group of micronodular cirrhosis. The findings of less remarkable arteriolar proliferations around the nodules in macronodular cirrhosis with thin septum was also relevant with the results of TAKAHASHI *et al.*

RUBIN *et al.*^{17,31} demonstrated that alcoholic micronodular cirrhosis may change into post-necrotic or macronodular cirrhosis by the process of repeated liver cell necrosis and regeneration. But it is not clear whether all alcoholic micronodular cirrhosis could change into macronodular. In general, the process of the advance of liver cirrhosis can be regarded as a transitional process of blood supply to the parenchyma from portal to arterial predominance.^{20,30,34,36} Therefore, micronodular cirrhosis with wide septum, in which remarkable arteriolar proliferations were noted around the nodules, may be estimated as being in a more advanced stage of vascular reconstruction than macronodular cirrhosis with thin septum. Therefore, considering the vascular reconstruction, alcoholic micronodular cirrhosis with wide septum would be unable to change into macronodular cirrhosis with thin septum. So if alcoholic micronodular cirrhosis could change into macronodular, this process should have occurred at least before the establishment of wide septal cirrhosis.

All the present cases of micronodular cirrhosis were etiologically considered alcoholic and most of macronodular cirrhosis were non-alcoholic. It thus appeared that the differences of microcirculations between them might be based on the etiological differences. Recent evidence to show the development of alcoholic cirrhosis in the absence of alcoholic hepatitis^{3,7,35} may support the possibility. In alcoholic micronodular cirrhosis, circulatory disturbances of venous systems or sinusoids represented by perivenular or pericellular fibrosis may play an important role in the developmental process of fibrosis in alcoholics.³⁵ Consequently, it may affect afferent branches of the weak portal venules more severely than the resistant arterial branches. Then, dissociation of the damage between portal and arterial systems may progress and fibrosis accompanied by arteriolar proliferations may develop remarkably in alcoholic cirrhosis. On the other hand, in non-alcoholic and hepatitis associated liver injury, inflammation and fibrosis of the portal areas may disturb microcirculation of the portal venules and the arterial capillaries simultaneously. Then, an injured portal area may be perfused by the compensatory blood stream from the proximal larger portal and arterial systems. So, the regeneration supported by those systems may develop into a macronodular pattern. In this process, arterioportal relations may be preserved, and vessels of affected triads may change into plexuses of both portal and arterial capillaries. If circulatory disturbance like P-V shunt is superimposed on the process, parenchymal necrosis and fibrosis may progress²⁸ and result in the development of vascular reconstruction in the circulatory peripheral area. And finally, so-called post-necrotic cirrhosis with a broad scar may be completed.

These speculations may be possible, but the etiology of cirrhosis is so complicated and the process of the histological changes is also variable according to the period and

degree of the affecting causes. In order to determine the real process of the pathological changes in cirrhosis, more investigations especially on the changes of interstitial fibrosis are necessary.

Acknowledgement : The authors thank Dr. Masao OHTO, 1st Department of Internal Medicine, Chiba University, for his helpful suggestions.

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Accepted for publication June 12, 1986.

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The contents of this paper were presented partly at the Third Annual Meeting of the Japanese Pathological Society (April, 1984).