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Incomplete septal cirrhosis: histopathological aspects

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We have reviewed 60 liver specimens from 47 patients with the diagnosis of incomplete septal cirrhosis observed between 1968 and 1987. In reaching this diagnosis evaluation of the following histological features appeared to be helpful: parenchymal nodularity, thin incomplete septa, hypoplastic portal tracts, increased number of venous channels, abnormal spacing between portal tracts and veins, crowding of reticulin fibres between adjacent zones of hyperplastic parenchyma, hyperplasia of hepatocytes and dilated sinusoids. These histological features were not specific for incomplete septal cirrhosis as they were also present—although less evident and less frequent—in a series of 87 non-cirrhotic liver specimens. Reticulin stains were an essential adjunct to assess the architectural disturbance, which was often inconspicuous in needle biopsies. Histological features indicating a specific aetiology were lacking in the great majority of cases. On histological and clinical grounds, incomplete septal cirrhosis resembles idiopathic portal hypertension, nodular regenerative hyperplasia and partial nodular transformation; in these entities an obliterative portal venopathy with non-uniformity of portal blood supply to the parenchyma has been suggested as a pathogenic mechanism. In the present study phlebosclerotic lesions of the portal vein were found in only two cases. This might be explained by sampling error or, alternatively, the hypoplastic portal tracts observed might be a functional equivalent of obliterative portal venopathy resulting in a deficient portal blood supply. Non-uniformity of blood supply to the parenchyma may explain the similarities between incomplete septal cirrhosis and the diseases mentioned.

Keywords: cirrhosis, incomplete septal, histopathology

Introduction

Liver cirrhosis is a diffuse process characterized by fibrosis and the conversion of the normal liver architecture into structurally abnormal nodules (Anthony *et al.* 1978).

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Morphologically, different patterns have been described (micro-macronodular) which depend on the interplay between necrosis, regeneration and fibrosis (Scheuer 1970, Anthony *et al.* 1978). In 1966, Popper introduced the term incomplete septal cirrhosis which represents a type of macronodular ('variform') cirrhosis in which slender and often incomplete septa demarcate larger, rather inconspicuous nodules. This corresponds approximately to the 'post-hepatitic' type of cirrhosis, or type III cirrhosis, proposed by Gall (1960, 1966) and to Miyake's type B cirrhosis (Nakashima *et al.* 1983). Since 1966, incomplete septal cirrhosis has not been studied in detail, nor have its clinical correlations been the subject of study in any large series. This prompted us to investigate this apparently underestimated entity.

Materials and methods

Between 1968 and 1987, 98 liver specimens were diagnosed as, or as suggestive of incomplete septal cirrhosis. In this period about 13 300 liver biopsies were seen. After withdrawal of 38 cases because of the absence of clinical information (n=31), or evidence of another diagnosis (n=7), 60 liver specimens from 47 patients were available for study (38 percutaneous needle specimens, 20 operative wedge biopsies and two autopsy specimens). The evaluation of the clinical features of these cases is the subject of a separate report.

From each biopsy, haematoxylin and eosin, reticulin and Masson's trichrome stains of Bouin-fixed paraffin sections were studied. Additional indirect immunoperoxidase staining for HBsAg and HBcAg (Dakopatts a/s Copenhagen, Denmark) was performed. A preliminary study of all biopsies was performed in order to determine the morphological features which were most frequently observed. These are listed in Table 1 and illustrated in Figures 1–4. After this preliminary study, these morphological features were rated semiquantitatively in each biopsy (0, absent; 1, inconspicuously present; 2, clearly present) and tabulated (Table 2). All biopsies were divided into three categories according to the subjective appreciation of the histological features: I—incomplete septal cirrhosis with high probability; II—suggestive of incomplete septal cirrhosis; III—compatible with incomplete septal cirrhosis (Table 3).

Table 1. Morphological features observed in incomplete septal cirrhosis

1	More or less evident parenchymal nodularity (Figure 1)
2	Thin incomplete septa (Figures 1 & 2)
3	Hypoplastic 'mini' portal tracts (Figure 4)
4	Increase in venous channels (Figures 2 & 3)
5	Abnormal spacing between portal tracts and veins, with veins often near portal tracts or septa (Figures 2 & 3)
6	Crowding of reticulin fibres between adjacent zones of hyperplastic parenchyma with different respective orientation of their sinusoids (Figure 1)
7	Hyperplasia of hepatocytes—two or three cell-thick liver cell plates (Figure 4)
8	Dilated sinusoids (Figure 3)

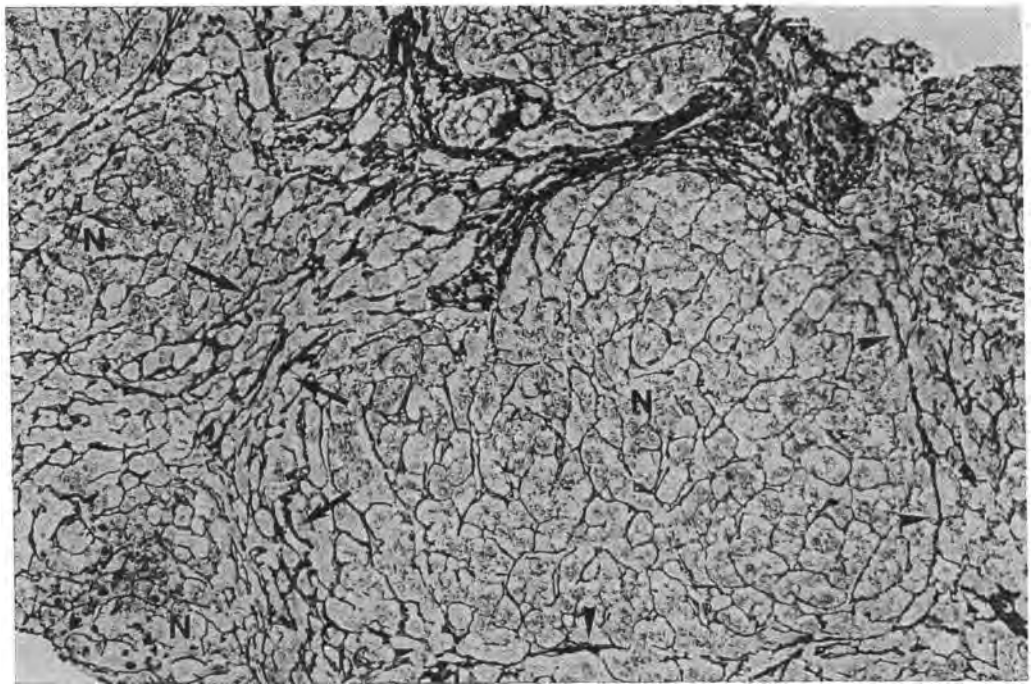

Figure 1. Regenerative parenchymal nodules (N) are surrounded by thin, incomplete septa (arrowheads) and crowded reticulin fibres (arrows). Gordon & Sweets' reticulin stain. ×160.

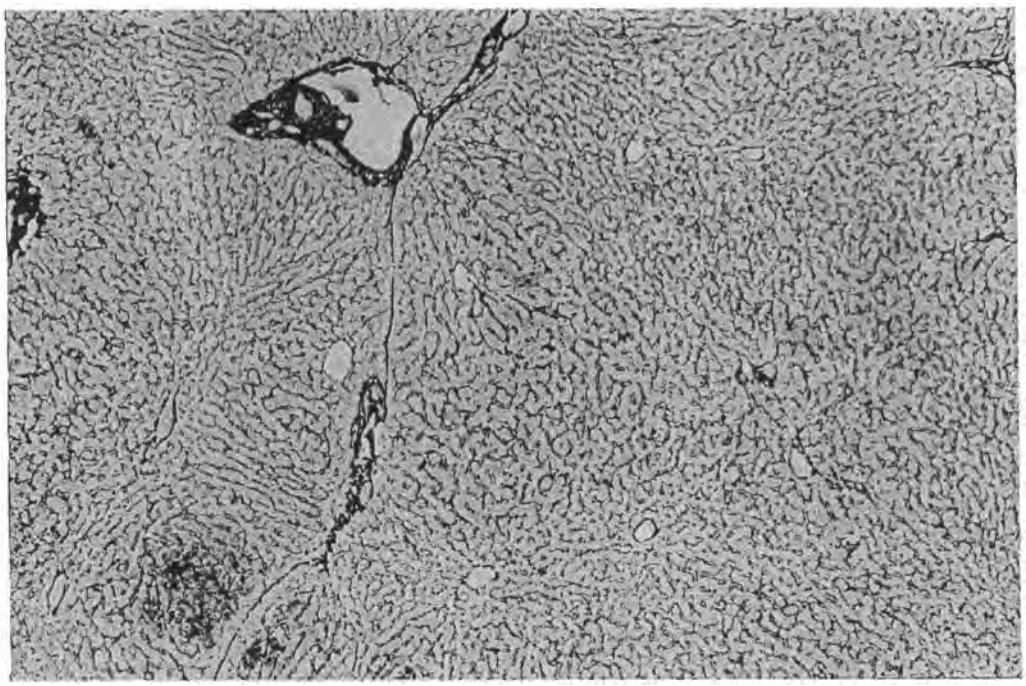

Figure 2. Increased number of veins in the parenchyma and next to a thin septum. Note the irregular orientation of the sinusoids. Gordon & Sweets' reticulin stain. ×60.

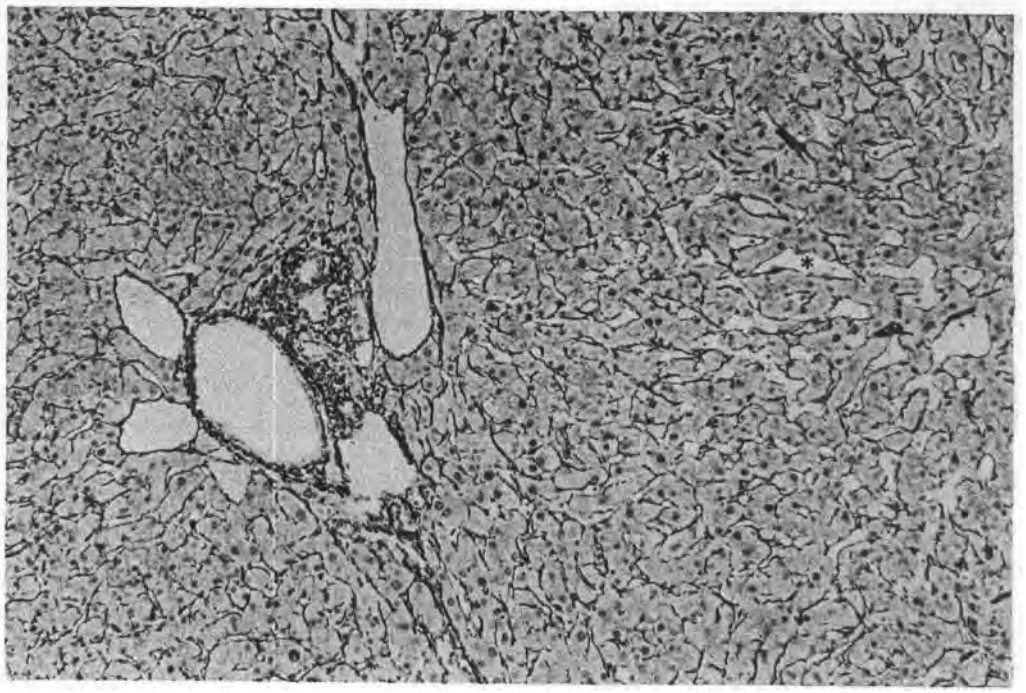

Figure 3. Periportal angiomatosis. Numerous small and larger venous structures are present in the vicinity of a portal tract. The asterisks indicate dilated sinusoids near a terminal venule. Gordon & Sweets' reticulin stain. ×160.

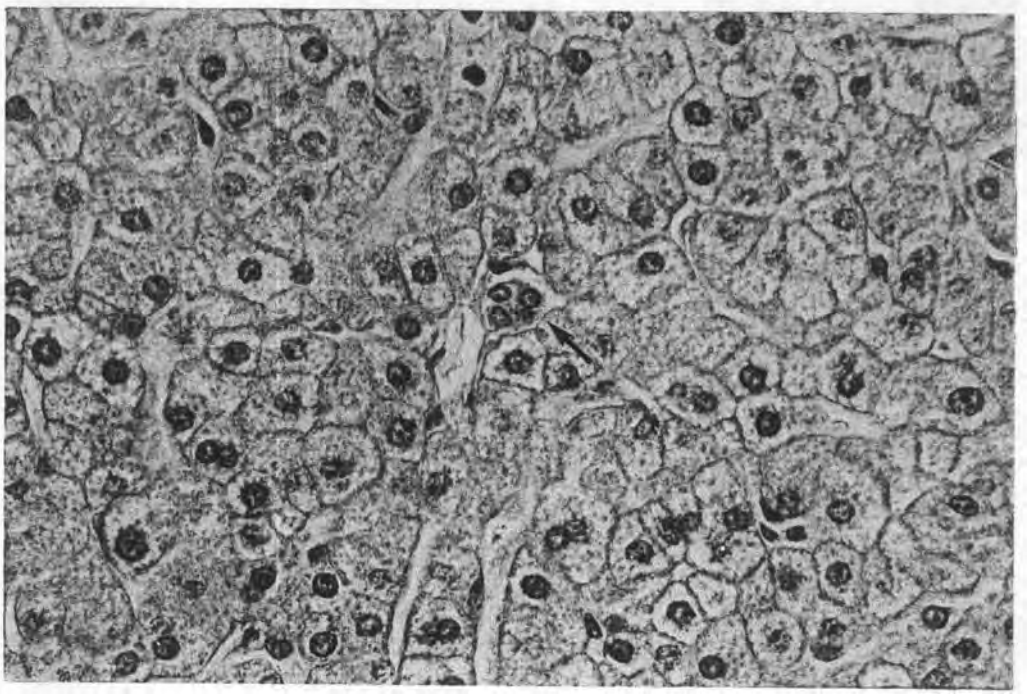

Figure 4. 'Mini' portal tract (arrow) surrounded by hyperplastic liver parenchyma. H & E. ×640.

Table 2. Frequency of morphological features in incomplete septal cirrhosis and controls

		Incomplete septal cirrhosis						Controls		
	Score†	Category I* (n=34)	Category II* (n=20)	Category III* (n=6)	S (n=22)	N (n=38)	Total (n=60)	Total (n=87)	N (n=83)	S (n=4)
Nodularity	0	0	6	4	1	9	10	77	73	4
	1	6	13	2	4	17	21	8	8	0
	2	28	1	0	17	12	29	2	2	0
Incomplete septa	0	0	2	0	0	2	2	60	56	4
	1	4	9	6	2	17	19	19	19	0
	2	30	9	0	20	19	39	8	8	0
'Mini' portral tracts	0	7	3	3	4	9	13	27	27	2
	1	9	3	0	5	7	12	34	32	2
	2	18	14	3	13	22	35	24	24	0
Increase in veins	0	14	13	5	5	27	32	74	71	3
	1	5	3	0	4	4	8	9	8	1
	2	15	4	1	13	7	20	4	4	0
Abnormal spacing	0	6	10	5	0	21	21	69	65	4
between portal	1	6	2	0	4	4	8	14	14	0
tracts and veins	2	22	8	1	18	13	31	4	4	0
Crowding of	0	3	6	4	2	11	13	78	74	4
reticulin fibres	1	3	6	0	3	6	9	9	9	0
	2	28	8	2	17	21	38	0	0	0
Hyperplasia of	0	1	2	2	1	4	5	61	59	2
parenchyma	1	4	7	1	3	9	11	22	20	2
	2	29	11	3	18	25	43	8	4	4
Dilated sinusoids	0	5	7	3	3	12	15	60	57	3
	1	10	2	1	7	6	13	22	22	0
	2	19	11	2	12	20	32	5	4	1

*Categories: I=high probability; II=suggestive of; III=compatible with (see text).

†Scores: 0=absent; 1=inconspicuous; 2=clearly present.

S=surgical+autopsy specimens; N=needle biopsy.

For comparison, we investigated the occurrence of these same morphological features in 87 consecutive non-cirrhotic liver biopsies (Table 2). These biopsies included 12 with alcoholic liver damage, 49 with non-specific changes, seven with hepatitis, eight with chronic biliary pathology, eight with drug-induced liver damage, two with haemochromatosis and one with extramedullary haematopoiesis.

Results

In the 20 surgical biopsies and two autopsy specimens the following histological features were most frequent (Table 2): thin incomplete septa, abnormal spacing between draining veins and portal tracts, hyperplasia of the parenchyma, nodularity and crowding of reticulin fibres. Nineteen of 22 (86%) surgical and autopsy specimens were classified in category I (Table 3). All histological features were usually clearly present—rated as score 2 (Table 2). In the 38 needle specimens the following morphological features were most frequently useful for the diagnosis of incomplete septal cirrhosis (Table 2): incomplete septa, hyperplasia of hepatocytes, 'mini' portal tracts and nodularity. Several criteria were rather inconspicuous—rated as score 1 (Table 2). Only 15/38 (39%) biopsies were classified in category I (Table 3). Inflammation was minimal or absent in the portal tracts and/or parenchyma in all the biopsies. In the 87 control biopsies the frequency of occurrence of some morphological features was relatively high (e.g. 'mini' portal tracts—66%, hyperplasia of parenchyma—34%). However, all the features were rather inconspicuous—rated as score 1 (Table 2).

In 12 patients more than one biopsy with a diagnosis of incomplete septal cirrhosis was available (Table 4). The time lapse between first and second biopsy ranged from 6 days to 17 years. In 9/12 patients the consecutive biopsies were classified in the same category, i.e. there were no major differences between the sequential biopsies. Of the three remaining patients the latest biopsy was a surgical specimen in two, and a needle biopsy in one. They revealed to better advantage the architectural disturbances and

Table 3. Distribution of specimens in categories according to the histological evidence of incomplete septal cirrhosis

Category*	S	N	Total
I	19	15	34
II	3	17	20
III	0	6	6
Total	22	38	60

*Categories: I=high probability; II=suggestive of; III=compatible with (see text).

S=surgical + autopsy specimens; N=needle biopsy.

Table 4. Classification of consecutive liver specimens from patients with incomplete septal cirrhosis

Patient no.	First biopsy	Second biopsy*
1	N—I	S—I (3 years)
2	N—I	N—I (3.2 years)
3	S—I	S—I (5.5 years)
4	N—II	S—II (2.5 months)
5	N—I	A—I (5.2 years)
6	S—I	A—I (20 days)
7	N—I	N—I (13.5 years)
8	N—II	N—I (1.5 years)
9	N—II	S—I (7 days)
10	N—II	N—III (6 days)†
11	S—I	S—I (5.5 years)
12	N—I	N—I (17 years)

*Time between first and second biopsies in parentheses.

†Small fragmented biopsy; a third biopsy (surgical) 7 days after the second was placed in category I.

S=surgical; A=autopsy; N=needle.

Categories: I=high probability of; II=suggestive of; III=compatible with incomplete septal cirrhosis.

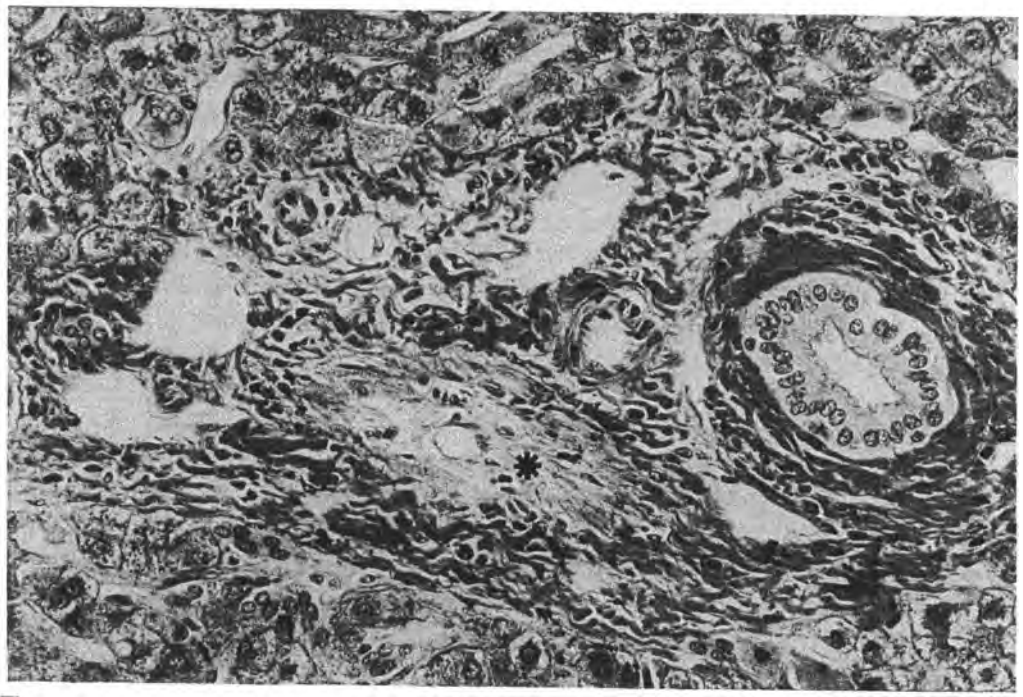

Figure 5. Patient treated with arsenic. In the portal tract phlebosclerotic narrowing of the portal vein branch is seen (asterisk). Masson's trichrome. ×400.

were classified in category I, in contrast to the first biopsies (all needle) classified in category II.

The presence of HBsAg-containing hepatocytes in four biopsies pointed towards a hepatitis B viral infection. HBcAg was demonstrable in two cases. One of these patients developed a hepatocellular carcinoma. In one biopsy chronic liver damage of the alcoholic type was observed. Phlebosclerotic changes in portal vein branches were seen in a few portal tracts of two surgical specimens (Figure 5).

Discussion

The diagnosis of incomplete septal cirrhosis can be difficult for the pathologist because of the often very vague parenchymal nodularity and the very thin blindly ending septa. It is clear from the present study that, indeed, in needle biopsies the evidence for incomplete septal cirrhosis is often only suggestive (60.5% of biopsies were classified in category II or III). None of the histopathological features discussed is by itself specific for the diagnosis but it is the combination of rather inconspicuous pathological features which leads to the diagnosis of the cirrhosis. In the surgical biopsies the architectural disturbance (nodules, septa and abnormal vascular relationships) was usually much more conspicuous, causing less difficulty in diagnosis. Whatever the type of biopsy, reticulin stains were an extremely useful, if not essential, adjunct to assess the architectural disturbance. The comparison of consecutive biopsies from the same patient revealed no major differences (even after 17 years) except for a more 'established' picture of incomplete septal cirrhosis in the later biopsy in three cases; however, two of these were surgical specimens. On review of the clinical records, it was found that two patients had a previous needle biopsy showing a picture of 'post-necrotic' or 'post-collapse' type of macronodular cirrhosis. A second needle biopsy, performed 3 months and 4 years later, pointed towards an incomplete septal cirrhosis of category II and category I respectively. A third patient's first biopsy showed a mixed micro-macronodular cirrhosis; 1 year later a second needle biopsy revealed a clear-cut category I incomplete septal cirrhosis. Sampling variability in a liver where features of incomplete septal as well as 'post-collapse' macronodular cirrhosis co-exist, probably accounts for these findings. This observation supports the concept that the morphological categories in cirrhosis do not necessarily represent different diseases, but correspond to different stages in the development of a single disease process (Popper 1966, Scheuer 1970, MacSween & Scott 1973, Anthony *et al.* 1978, Fauerhold *et al.* 1983). One patient developed a well-differentiated hepatocellular carcinoma 8 years after the first liver biopsy which showed category III incomplete septal cirrhosis. Histological and/or cytological features indicating a specific aetiology for the cirrhosis were only found in five biopsies, four hepatitis B infections and one alcoholic liver damage. Incomplete septal cirrhosis seems to be a burnt-out and rather hyper-regenerative form of cirrhosis in which it is difficult, and most often impossible, to ascertain the aetiology on histological grounds.

The main presenting symptoms of the patients (to be published in a separate report) were bleeding oesophageal varices and splenomegaly with only minor or no

liver function disturbances. At laparotomy or peritoneoscopy the liver surface was nearly normal. Taking into account the pathological and clinical aspects, incomplete septal cirrhosis shows a striking resemblance to several other liver diseases. These include: idiopathic portal hypertension, arsenic or vinyl chloride intoxication, chronic schistosomiasis, nodular regenerative hyperplasia and partial nodular transformation. In these entities the major presenting symptoms are also signs of portal hypertension with only mild liver function abnormalities (Okuda & Omata 1983, Lebrec & Benhamou 1986).

Idiopathic portal hypertension, also termed non-cirrhotic portal fibrosis (Kama *et al.* 1971), is found mainly in Japan and India, although it has also been reported in other areas (Mikkelsen *et al.* 1965, Levison *et al.* 1982). Occasional surface nodularity is seen, but a varying degree of portal fibrosis and phlebosclerotic obliterating lesions of the terminal portal vein branches with an uneven distribution throughout the liver are the most striking features (Okuda *et al.* 1982). The presence of dilated veins, (peri-) portal angiomatosis, mainly in and around portal tracts but sometimes also in the parenchyma is another characteristic finding (Fukuda *et al.* 1985). Recently, Fukuda *et al.* (1985) demonstrated that these vessels are portal in nature and not abnormally located hepatic veins. It seems that intrahepatic collateral vessels develop in order to compensate for the portal circulatory disturbance caused by obliteration of terminal portal vein branches. The same feature is seen in chronic schistosomiasis, a disease that most closely resembles idiopathic portal hypertension in its pathological features, and where the ova obstruct portal vein branches accompanied by periportal angiomatosis (Fukuda *et al.* 1985).

Histologically, nodular regenerative hyperplasia and partial nodular transformation are characterized by a diffuse, respective focal nodularity of the liver without septa in between the nodules (Anthony 1987). Obliterative portal vein lesions have also been described in these conditions and formation of collaterals as a result of the obliteration of portal vein radicles may explain the periportal angiomatosis described in nodular regenerative hyperplasia (Boyer & Gautam 1983, Peters 1983). Lesions of the portal vein branches have also been described in arsenic or vinyl chloride intoxication (Wanless *et al.* 1980, Boyer & Gautam 1983). In the present study, periportal angiomatosis was not studied as such, since it is not strictly defined, but it was noted (Table 1) as 'veins often near portal tracts' (Figure 3). Lesions corresponding to such periportal angiomatosis (Okuda *et al.* 1982, Peters 1983, Fukuda *et al.* 1985) were seen in about 40% of the cases. However, in only two of the 60 specimens studied were phlebosclerotic portal vein lesions observed. One of these patients had been treated with arsenic for psoriasis for 15 years. The absence of portal vein occlusions in 58 of 60 biopsies might be explained by sampling error, since needle biopsies were mainly studied. Alternatively, the 'mini' portal tracts might represent a functional equivalent of an obliterative portal venopathy in that they are deficient for adequate supply of portal blood to the parenchyma. However, 'mini' portal tracts were also relatively frequent in 87 non-cirrhotic biopsies. This is not surprising since they represent the terminal branches of portal tracts. Nevertheless, they were less frequent and less conspicuous than in the incomplete septal cirrhosis group.

In this regard, idiopathic portal hypertension, nodular regenerative hyperplasia,

partial nodular transformation and incomplete septal cirrhosis may be a spectrum of diseases in which non-uniformity of blood supply to the parenchyma plays an important role in their pathogenesis and could explain the clinical and pathological similarities between the four of them. However, other factors in addition to non-uniformity of blood supply seem to determine the final pattern. One such factor must be the distribution of the vascular lesions: partial nodular transformation involves a focal disturbance in blood supply whilst the other three may represent diseases with more diffuse involvement of smaller vessels. Furthermore, the presence and extent of necrosis probably also play a role. Extensive necrosis and collapse, especially when repetitive, with subsequent parenchymal regeneration lead to the 'post-collapse' type of macronodular cirrhosis (Popper 1966). Minimal collapse or collapse after single-hit necrosis is more likely to result in the incomplete septal type of macronodular cirrhosis (Popper 1966); in the other three diseases there is no evidence for loss or damage of liver cells (Wanless *et al.* 1980, Okuda *et al.* 1982, Anthony 1987) and the vascular abnormalities are probably the major pathogenic factor (Boyer *et al.* 1983). Finally, the extent of a collateral circulation, the aetiological agent (chemical toxin, drug, alcohol, virus, etc.) and other unknown factors probably also influence the final pattern of the lesion.

Overlap between these diseases is illustrated by the fact that, on liver biopsy, idiopathic portal hypertension, nodular regenerative hyperplasia and incomplete septal cirrhosis may be difficult to differentiate. The simultaneous presence of morphological characteristics of two of these diseases in one patient has also been described (Sheldofsky *et al.* 1980, Terao *et al.* 1981). Furthermore, the phlebosclerotic lesions observed in two biopsies in the present series might have led to a diagnosis of idiopathic portal hypertension. Nevertheless, this study indicates that incomplete septal cirrhosis can be regarded as a relatively characteristic pathological and clinical entity found within the broad definition of liver cirrhosis.

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