Histological Progression of the Hepatic Lesions in Idiopathic Portal Hypertension (Banti's Disease)
—Observations from 25 Autopsies—

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Summary: Pathomorphological changes in the liver were studied in 25 Japanese autopsy cases of idiopathic portal hypertension (IPH), and the cause of histological progression of the hepatic lesion was discussed. The morphological changes in the IPH livers differed markedly from case to case, probably because of the different stages and/or different degrees of severity of the lesion. Most of the patient who had died of hepatic failure were elderly or had an advanced stage of the disease. The livers from these patients were usually atrophied. Parenchymal atrophy of the IPH livers is caused by an insufficiency of the portal blood supply, which is accelerated by progression of phlebosclerotic changes, secondary thrombi of the portal vein branches, and a decrease in the intrahepatic collateral vasculature. Although it is possible that aging and a prolonged duration of the clinical course are contributory factors in the progression of portal lesions, the pathogenesis of portal phlebosclerosis cannot be explained by passive congestion, alone. In the IPH liver, parenchymal atrophy and regeneration seem to exist together. It therefore appears that failure of compensatory parenchymal regeneration due to insufficient blood supply is a major factor in liver atrophy and deterioration of liver function.

Key words: idiopathic portal hypertension — Banti's disease — hepatoporal sclerosis — liver fibrosis — liver cirrhosis.

Introduction

In 1894, Banti described a syndrome characterized by marked splenomegaly, anemia, and delayed hepatic disease. This was called Banti's disease (or syndrome) and is a poorly defined clinical entity of obscure etiology. Its existence has long been disputed (Whipple, 1945; Tisdale et al. 1959; Polish et al. 1962).

Recently, it has been generally accepted that Banti's disease is synonymous with a noncirrhotic portal hypertension of unknown etiology with marked splenomegaly and hypersplenism. A large number of cases have been reported from various parts of the world using different names (Mikkelson et al. 1965; Boyer et al. 1967; Nayak and Ramalingaswami, 1969; Aikat et al. 1979; Levison et al. 1982). "Idiopathic portal hypertension (IPH)" is the term currently used to denote this disease in Japan (Okuda et al. 1982). Although the clinical and histological features of IPH livers vary from case to case, varying degrees of periportal fibrosis with phlebosclerotic changes of the portal vein system are considered to be the basic mor-

Banti (1910) described the course of this disease, which eventually develops into atrophic cirrhosis leading to death from hepatic failure with increasing jaundice and anemia. Little is known concerning the natural history and the cause of the histological progression of the hepatic lesions in IPH.

The purpose of this study was to present observations based on a review of autopsy materials from 25 Japanese IPH patients and to clarify the significance of portal phlebosclerosis in the genesis of the histological and functional deterioration of the liver.

Materials and Methods

This study utilized autopsied livers from 25 authenticated cases of IPH from various institutes throughout Japan. All cases fulfilled the clinical and pathological criteria proposed by the Japan IPH Study Group (Ministry of Health and Welfare Research Committee; Okuda, 1980). The diagnostic criteria were: splenomegaly, anemia and signs of portal hypertension clinically, and pathological absence of cirrhosis, blood disease, parasitic disease, congenital hepatic fibrosis, granulomatous liver disease, occlusion of the hepatic or extrahepatic portal veins, and other known causes of portal hypertension. Cases with early cirrhosis in which fibrous extensions from the portal tracts were about to fuse to form pseudonodules, B'-cirrhosis according to Miyake's nomenclature which is commonly used in Japan (Miyake, 1960), were excluded.

Of the 25 cases, 20 had a splenomegaly with hypersplenism and had died from various causes related to this disease. In the remaining 5 cases, the initial symptom was bleeding from ruptured esophageal varices and death was due to postoperative complications after surgery for the esophageal varices.

Multiple sections taken from whole-cut liver slices containing the hilar region were examined histologically by staining with hematoxylin and eosin, elastica Van Gieson, Silver impregnation and Mallory-Azan methods. Particular attention was paid to the histological changes in the portal venous system.

To elucidate the cause of the histological changes in the hepatic lesions among the IPH livers, 8 representative livers (4 normal weight and 4 markedly atrophied) were studied in detail. In these 8 cases, histometrical examination of portal veins was carried out. For medium and large-sized portal veins which were cut horizontally, the luminal area ($S_1$) and the area circumscribed by the external edge of the tunica intima ($S_2$) were measured using a computer-assisted image analysis system (NEC, PC 8001). The ratio of the luminal area ($S_1/S_2 \times 100\%$) was calculated for each portal vein as an index of luminal stenosis (Fukuda et al. 1985).

Results

1. Clinical and autopsy data

The male to female ratio was 6:19; and the age at autopsy ranged from 44 to 82 years with a mean of 62 years. The causes of death were: upper gastrointestinal bleeding usually due to variceal rupture, 14 cases; postoperative complications, 5 cases; hepatic failure, 4 cases; intestinal infarction caused by a portal thrombus, 1 case; and liver cell carcinoma, 1 case. Splenomegalies had been performed in 8 cases. The livers weighed from 520 to 1700 g with a mean of 893 g. About half of the livers had some degree of atrophy. Most of the cases with marked liver atrophy were aged patients or pa-
patients who had had a long clinical course (Fig. 1 and 2).

2. Histological differences in the cases with and without liver atrophy

Varying degrees of periportal fibrosis with obliteration of the small portal veins and phlebosclerotic changes in the portal venous system were observed in all livers. However, there were wide variations in the severity of the liver lesions, and the clinical courses were also variable.

a) Livers of normal weight

Fig. 3 shows the gross appearance of a normal liver from a 56-year-old female, who died from postoperative complications 3 months after surgery for esophageal varices. Preoperative liver function was normal. The liver weight was 1200 g, and the proportion of liver weight to body weight was 2.7%. The surface of the liver was smooth, and there were no nodular formations. However, focal depression and wrinkles were observed in

Fig. 1. Relationship between liver weight and age in autopsy cases with IPH. The normal range (mean±S.D.) of liver weight for Japanese females is the control.

Fig. 2. Relationship between liver weight and clinical duration.

Fig. 3. Cut surface of an IPH liver with a normal weight. Thickening and sclerosis of the wall of the main portal vein branches were observed.

Fig. 4. Histology of the liver shown in Fig. 3. Periportal fibrosis and obliteration of small portal vein branches were observed. (Elastica Van Gieson stain, ×80).
some areas. The large portal vein branches were dilated and the walls were thickened. Histologically, the portal tracts were slightly fibrotic and the peripheral portal vein branches were frequently obliterated (Fig. 4). Focal parenchymal disappearance or atrophy were observed mainly in the subcapsular region. In the hilar region, however, parenchymal cells were not atrophic, but instead were hyperplastic.

b) Livers with marked atrophy

Cut surfaces of livers in this group had conspicuous parenchymal atrophy in various parts of the liver. In several livers the relative size of one lobe was markedly reduced (Fig. 5). The portal tracts were markedly fibrotic with massive elastoses (Fig. 6). The entire portal vein system was involved in the thrombo-phlebosclerosis and the portal vein lumen was markedly reduced.

Fig. 5. Cut surfaces of livers with conspicuous liver atrophy.
(a) The large portal vein branches had walls that were markedly sclerotic. Occlusive thrombi were present in the main portal vein branches (arrow).
(b) The left lobe was markedly atrophied (arrow).

Fig. 6. Histology of a liver with severe portal sclerosis. The portal tracts were markedly fibroed with a dense collagen accompanied by a massive elastosis. Obliteration of the intrahepatic portal veins was conspicuous. (Elastica Van Gieson stain, ×16).

Fig. 7. Subcapsular region of an IPH liver with marked parenchymal atrophy. (Elastica Van Gieson stain, ×16).
narrowed. Parenchymal disappearance or atrophy, which was indicated by an approximation of the portal tracts, was conspicuous (Fig. 7). Focal hyperplastic nodules or areas were observed mainly in the hilar region, but were not sufficiently developed to compensate for the parenchymal atrophy in the subcapsular region. These cases typically had deteriorating liver function with jaundice and ascites, and had died from hepatic failure or variceal bleeding.

3. Cause of parenchymal atrophy in IPH livers

Parenchymal atrophy observed in the IPH liver was characterized by an approximation of the portal tracts and hepatic veins, shown in Fig. 7. Fig. 8 presents schematic drawings of the area of parenchymal disappearance and atrophy in a typical liver with or without a decrease in weight. As a rule, the basic morphological changes were the same in both groups, and the difference was a matter of degree. Although the variation between each patient was great, portal veins with marked luminal narrowings due to advanced portal

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**Fig. 8.** Schematic drawings of the cut surface of representative livers with and without a conspicuous decrease of liver weight. The dotted areas are the regions with parenchymal atrophy and the solid black area are the regions from which the parenchyma had disappeared.

**Fig. 9.** The ratios of the luminal areas of large and medium-sized portal vein branches. Each plot represents the ratio of the luminal area, which was calculated as follows, $S_1/S_2 \times 100\%$: $S_1$ is the area of the venous lumen and $S_2$ is the area encircled by the external edge of the tunica intima.
Fig. 10. A large Glisson's sheath in the lobe of a liver with conspicuous parenchymal atrophy. A marked fibrous intimal thickening with elastosis and luminal narrowing was present in the portal vein (curved arrow), whereas no remarkable changes were observed in the hepatic artery (straight arrow). (Elastica Van Gieson stain, ×32).

Fig. 11. A transverse section of the portal trunk of an IPH liver. The lumen was narrowed by mural thrombi. (Elastica Van Gieson stain, ×3.3).

sclerosis tended to be more frequently observed in livers with marked parenchymal atrophy (Fig. 9). On the other hand, there were no significant abnormalities in the hepatic arteries, even in areas with marked parenchymal atrophy (Fig. 10).

In general, intrahepatic collateral vessels, such as the angiomatous vasculature in the portal tract and the aberrant vasculature around the portal tract, played an important role in supplying blood to the hepatic parenchyma in livers of normal weight. However, these collateral vessels were poorly developed in livers with marked parenchymal atrophy.

In the majority of cases (21 of the 25 cases), red thrombi were present in the main portal vein branches (Fig. 11). Most of these occlusive or mural thrombi were relatively fresh. However, some showed partial organization and recanalization, and there was one death due to an intestinal infarction caused by a portal thrombus.

4. Relationship between portal sclerosis and the clinical features

The cases were divided into 5 groups, according to the degree and extent of thrombo-phlebosclerosis, as presented in Fig. 12. The gross clinical and histological data for each group are summarized in Table 1. Group 1 included 2 cases with death from postoperative complications, 1 and 3 months after surgery for esophageal varices, respectively. Both patients were relatively young in comparison to the other groups. The livers were normal in weight, and the degree of periportal fi-
brosis was relatively slight. Among the cases classified as group 2a, there were variations in the clinical course and liver lesions, however the clinical course tended to be relatively short. On the other hand, the majority of patients with severe portal sclerosis or marked atrophy (Group 2b, 3a, 3b) were over 60 years of age or had had a long clinical course.

**Discussion**

It is known that Banti's syndrome develops from a variety of hepatic disorders, such as liver cirrhosis, extrahepatic portal obstruction, schistosomiasis, etc. This syndrome has become synonymous with congestive splenomegaly caused by portal hypertension (Rousselot, 1936; Imanaga et al., 1946).

**TABLE 1**

*Summary of the clinical and histological data from 25 autopsies of IPH classified according to the degree of portal phlebosclerosis as shown in Figure 12*

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr.)</th>
<th>Sex</th>
<th>Clinical duration</th>
<th>Cause of death</th>
<th>Liver wt. (g)</th>
<th>Spleen wt. (g)</th>
<th>Fibrosis of portal tract</th>
<th>Collateral vessels</th>
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<tr>
<td>1</td>
<td>44 M</td>
<td>4 m</td>
<td>Postop. a</td>
<td>1120</td>
<td>(600) d</td>
<td>± e</td>
<td>+ f</td>
<td>+ ++</td>
</tr>
<tr>
<td></td>
<td>56 F</td>
<td>3 m</td>
<td>Postop.</td>
<td>1200</td>
<td>(980)</td>
<td>±</td>
<td>±</td>
<td>± ++</td>
</tr>
<tr>
<td></td>
<td>51 M</td>
<td>4 m</td>
<td>GI bleed b</td>
<td>1050</td>
<td>390</td>
<td>+</td>
<td>±</td>
<td>± ++</td>
</tr>
<tr>
<td></td>
<td>52 M</td>
<td>4.5 y</td>
<td>GI bleed</td>
<td>930</td>
<td>1000</td>
<td>+</td>
<td>+</td>
<td>+ ++</td>
</tr>
<tr>
<td></td>
<td>53 F</td>
<td>4 y</td>
<td>GI bleed</td>
<td>1500</td>
<td>(530)</td>
<td>+</td>
<td>+</td>
<td>+ ++</td>
</tr>
<tr>
<td></td>
<td>54 F</td>
<td>4 y</td>
<td>Postop.</td>
<td>1700</td>
<td>(940)</td>
<td>+</td>
<td>+</td>
<td>+ ++</td>
</tr>
<tr>
<td></td>
<td>55 F</td>
<td>1 m</td>
<td>Postop.</td>
<td>1130</td>
<td>(510)</td>
<td>+</td>
<td>+</td>
<td>+ ++</td>
</tr>
<tr>
<td>2a</td>
<td>57 F</td>
<td>2 y</td>
<td>GI bleed</td>
<td>800</td>
<td>330</td>
<td>+</td>
<td>+</td>
<td>+ ++</td>
</tr>
<tr>
<td></td>
<td>58 M</td>
<td>1 y</td>
<td>GI bleed</td>
<td>1130</td>
<td>470</td>
<td>+</td>
<td>+</td>
<td>+ ++</td>
</tr>
<tr>
<td></td>
<td>60 F</td>
<td>5 y</td>
<td>GI bleed</td>
<td>730</td>
<td>320</td>
<td>+</td>
<td>+</td>
<td>+ ++</td>
</tr>
<tr>
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<td>Postop.</td>
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<td>640</td>
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<td>+</td>
<td>+ ++</td>
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<tr>
<td></td>
<td>67 F</td>
<td>4 y</td>
<td>GI bleed</td>
<td>595</td>
<td>490</td>
<td>++</td>
<td>±</td>
<td>± ++</td>
</tr>
<tr>
<td></td>
<td>68 F</td>
<td>2.5 y</td>
<td>Hepatic failure</td>
<td>860</td>
<td>380</td>
<td>++</td>
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<td>+ ++</td>
</tr>
<tr>
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<td>70 F</td>
<td>2.5 y</td>
<td>GI bleed</td>
<td>660</td>
<td>360</td>
<td>+</td>
<td>±</td>
<td>± ++</td>
</tr>
<tr>
<td></td>
<td>78 F</td>
<td>1.5 y</td>
<td>GI bleed</td>
<td>750</td>
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<td>+</td>
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<td>+ ++</td>
</tr>
<tr>
<td>2b</td>
<td>56 F</td>
<td>3 y</td>
<td>Hepatic failure</td>
<td>570</td>
<td>490</td>
<td>+</td>
<td>−</td>
<td>− ++</td>
</tr>
<tr>
<td></td>
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<td>20 y</td>
<td>GI bleed</td>
<td>870</td>
<td>560</td>
<td>+</td>
<td>+</td>
<td>+ ++</td>
</tr>
<tr>
<td></td>
<td>66 F</td>
<td>13 y</td>
<td>Intest. infarct. c</td>
<td>680</td>
<td>330</td>
<td>+</td>
<td>+</td>
<td>+ ++</td>
</tr>
<tr>
<td>3a</td>
<td>59 F</td>
<td>17 y</td>
<td>Hepatoma</td>
<td>660</td>
<td>(? )</td>
<td>+</td>
<td>±</td>
<td>± ++</td>
</tr>
<tr>
<td></td>
<td>79 F</td>
<td>39 y</td>
<td>Hepatoma</td>
<td>890</td>
<td>(? )</td>
<td>+</td>
<td>±</td>
<td>± ++</td>
</tr>
<tr>
<td></td>
<td>82 F</td>
<td>40 y</td>
<td>GI bleed</td>
<td>840</td>
<td>450</td>
<td>+</td>
<td>+</td>
<td>+ ++</td>
</tr>
<tr>
<td>3b</td>
<td>57 M</td>
<td>4 y</td>
<td>GI bleed</td>
<td>640</td>
<td>740</td>
<td>+</td>
<td>+</td>
<td>+ ++</td>
</tr>
<tr>
<td></td>
<td>68 F</td>
<td>16 y</td>
<td>GI bleed</td>
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<td>700</td>
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<td>+ ++</td>
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<tr>
<td></td>
<td>69 F</td>
<td>5 y</td>
<td>Hepatic failure</td>
<td>940</td>
<td>(740)</td>
<td>+</td>
<td>−</td>
<td>− ++</td>
</tr>
<tr>
<td></td>
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<td>6 m</td>
<td>GI bleed</td>
<td>520</td>
<td>280</td>
<td>+</td>
<td>+</td>
<td>+ ++</td>
</tr>
</tbody>
</table>

a : Postoperative complications.

b : Gastro-intestinal bleeding usually due to variceal rupture.

c : Intestinal infarction caused by a portal thrombus.

d : ( ) Splenectomized.

e.f : Degree of fibrosis of the portal tract and development of intrahepatic collateral vessels were evaluated as none (−), slight (+), moderate (++), or marked (+++).
al. 1962), however, the existence of portal hypertension with marked splenomegaly in the absence of cirrhosis or demonstrable portal obstruction (Banti’s disease) has long been the subject of controversy (Polish et al. 1936; Tisdale et al. 1959).

Mikkelsen et al. (1965) described a series of cases of noncirrhotic portal hypertension in which distinct phlebosclerosis was observed, and proposed the term “hepatoportal sclerosis”. Similar clinicopathological features have been reported in India as “noncirrhotic portal fibrosis” (NCPF), and in Japan as IPH. Although intrahepatic presinusoidal block due to obliteration of terminal portal vein branches is believed to be capable of leading to portal hypertension (Fukuda, 1968; Nayak and Ramalingaswami, 1969; Okuda et al. 1982), the pathogenesis and clinical significance of portal phlebosclerosis remain elusive.

Banti (1910) described three stages of Banti’s disease based on 50 cases: the anemic stage in which hypersplenism was the only findings; the transitional stage characterized by jaundice and disturbed gastro-intestinal function; and finally, the ascitic stage characterized by ascites together with increasing jaundice and anemia. Little is known concerning the natural history of IPH, particularly with regard to the cause of the histological progression of hepatic lesions.

Many clinical investigations have demonstrated a favorable prognosis in patients with IPH as compared to those with cirrhosis (Mikkelsen et al. 1965; Basu et al. 1969; Zeegen et al. 1970; Okuda et al. 1984). It is generally accepted that IPH is stable and that the liver function does not deteriorate in the majority of cases for many years (Imai et al. 1983). Most of the autopsy cases, except for those who died from postoperative complications, were aged patients, in an advanced stage of the disease, or had livers which were atrophied.

The basic morphological changes in the IPH cases were the same. The differences in hepatic lesions were just a matter of degree. Since the preservation of liver parenchyma depends on an adequate blood supply, it is likely that the progression of the portal phlebosclerosis and the decrease of intrahepatic collateral vessels are responsible for the decrease in liver weight (Fukuda et al. 1985).

Although the change of intrahepatic circulation in IPH is as yet unestablished, there is much clinical and histological evidence suggesting that intrahepatic portal blood perfusion is well maintained in IPH (Villeneuve et al. 1976; Kitani et al. 1983; Fukuda et al. 1985). Kitani et al.
(1983) demonstrated that the total splenic flow was 3 to 10 times that in control subjects which is approximately in proportional to the enlargement of the spleen. The IPH liver was well perfused by the portal blood flow despite the presence of a portal-systemic shunt and an increased intrahepatic vascular resistance. It was also suggested that the arterial blood supply cannot compensate for the reduction in portal blood supply because of the blood steal phenomenon due to the increased splenic blood flow. This concept has been confirmed by a study involving celiac arteriography, which demonstrated nondilated hepatic arteries in IPH which were obviously different from the dilated hepatic arteries in cirrhosis (Fukasawa et al. 1983).

The histological evidence that there are no remarkable changes in the arteries, even in regions showing marked atrophy, indicates that arterial blood flow is only of minor importance for the maintenance of liver parenchyma in IPH. According to these findings, it seems reasonable that the intrahepatic circulation in IPH is largely maintained by the portal system. Therefore, the decrease of portal blood flow is a main etiologic factor for the development of liver atrophy and the deterioration of liver function. There is no progression to cirrhosis in most cases of IPH. Some investigators include Miyake's type-B' cirrhosis in the IPH classification because it is a type of hepatic fibrosis or incomplete cirrhosis (Shikata, 1981). There are also cases which are very difficult to categorize. Apparently, type-B' cirrhosis behaves quite differently from IPH cases showing liver histology involving round fibrous enlargement of the portal area. Type-B' cirrhosis might progress to liver cirrhosis, whereas IPH with round-shaped portal fibrosis never progress to cirrhosis.

The pathogenesis and clinical significance of portal sclerosis in IPH are not clear. It is easier to regard phlebosclerosis as a secondary process, that is, in response to blood stasis and increased blood pressure (Mochcowitz, 1959). It is possible that aging and the prolonged clinical course are contributory factors in the progression of portal sclerosis; however, another possibility is that some injurious factor(s) acts on the portal vein to damage the vessel wall, as described by Banti (1898, 1910). This portal phlebosclerosis was considered by Mikkelsen et al. (1965) and Nayak et al. (1969) to be the primary phenomenon affecting either the intra- or extra-hepatic portal veins. Irrespective of whether the lesion is primary or secondary, it seems reasonable to infer that a progression of the sclerotic lesion of the portal veins causes a decrease in portal blood flow resulting in parenchymal atrophy.

Furthermore, an extension of the sclerotic changes may result in occlusion of the venous lumen. The tendency for secondary thrombi to develop due to mechanical injury and/or blood stasis because of the increased portal pressure may create a vicious cycle and result in the formation of multi-layered plaque and, finally, occlusive thrombi.

Oclusive fresh red thrombi around the porta hepatis at autopsy could have formed near the terminus when the portal blood flow was reduced. However, some of these occlusive thrombi were partially organized with recanalization, and there was one case in which a portal thrombus caused an intestinal infarction. Such occlusive thrombi would further reduce the vascular lumen and increase the vascular resistance.

Irrespective of whether it represents a primary triggering mechanism, the thrombo-phlebosclerosis can further reduce the portal vascular bed and induce a parenchymal atrophy due to an insufficient supply. In some cases this results in a marked decrease of liver weight, a marked atrophy of one lobe or a secondary extrahepatic portal obstruction (Fig. 13).
Fig. 13. A hypothesis of the histological changes in a liver with IPH. Whether the phlebosclerosis of the portal system is secondary or primary, the development of the portal sclerosis is the main contributory factor in producing the parenchymal atrophy and liver cell dysfunction. Some cases finally develop a decrease of liver weight, marked atrophy of one lobe, or secondary extrahepatic portal obstruction.

All the morphological evidence suggests that the gross parenchymal changes occurring in IPH are secondary to portal circulatory insufficiency. Parenchymal atrophy in IPH occurred gradually, therefore hyperplasia or regeneration in other parts of the liver were not obvious. However, it seems probable that atrophy in some parts was compensated for by regeneration of an other part, especially in the hilar region. Little importance has been attached to parenchymal regeneration in the IPH liver. However, the IPH liver seems to be a condition in which parenchymal atrophy and regeneration are occurring simultaneously. Cases with a normal liver weight seem to indicate that the parenchymal atrophy in the subcapsular region is well compensated for by hyperplasia of another region with a normal blood supply. Failure of this compensatory parenchymal regeneration due to an insufficient blood supply could be the main factor responsible for the decrease of liver weight and deterioration of liver function.

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References


IDIOPATHIC PORTAL HYPERTENSION


