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Multiple cysts in the hepatic hilum and their pathogenesis

A suggestion of periductal gland origin

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Summary. Multiple serous cysts involving only the hepatic hilum and larger portal tracts were found incidentally in 8 autopsy cases with several underlying liver diseases. The cysts were mostly small in size, and did not communicate with the lumena of the biliary tree. The lining of the cysts consisted of a single layer of columnar or cuboidal epithelium and the surrounding fibrous tissue was scanty. These were not associated with polycystic disease of the kidneys or cystic dilatation of the biliary tree. Cysts were absent in the liver parenchyma and an association with von Meyenburg complexes was rare. In the vicinity of the cysts there were many lobules of the glands which are physiologically present in the periductal connective tissue of the large intrahepatic bile ducts. It was noted that some of these glandular elements around the cysts disclosed varying degrees of cystic luminal dilatations. Almost all patients with such cysts had severe portal hypertension and over a half had occluding thromboemboli in the portal veins. These results lead us to propose the hypothesis that multiple cysts involving the hepatic hilum and the larger portal tracts are derived from the periductal glands in close association with an intrahepatic circulatory disturbance of the portal venous system.

Key words: Hepatic cyst – Peribiliary gland – Protal hypertension

Several types of hepatic cysts are known (De Bakey and Jordan 1982; Gibson and Sobin 1978; Ishak and Sharp 1979; Sherlock 1981). Some are considered to be congenital biliary cysts and are further subdivided into multiple and solitary varieties. Other cystic lesions include cystic dilatation of biliary tree, cystic papillary adenoma or carcinoma and parasitic cysts. The majority of these cystic lesions of the liver are known to have distinct clinicopathologic features.

Recently we have found multiple serous cystes in the hepatic hilar con-

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nective tissue of a HBsAg-positive cirrhotic liver. To our knowledge, cystic lesions limited to the hepatic hilum have not been reported in the English and Japanese literatures. This experience prompted us to survey such cystic lesions in our recent autopsy cases, and we found another 7 cases. Here we report the index case and describe the pathology of these other cystic lesions. Terada (1984) has recently found that there are excretory glands connecting with biliary tree in the connective tissue of the hepatic hilum and larger portal tracts where the hepatic, segment and area ducts of Healey's classification (1953) are present. The causal relation of the multiple serous cysts to periductal glands and the pathological differentiation of the multiple cysts in the present study from other types of hepatic cysts (Gibson and Sobin 1978) are discussed.

Report of a progenitor case

A 49-year-old male, teacher, was admitted to the Kaga Central Hospital, Kanazawa, Japan, in October 1980 for progressive anorexia, abdominal distension and oedema of the lower extremities. He did not report alcohol abuse or drug addiction. His past medical history revealed subtotal gastrectory for gastric ulcer at 46 years of age. On admission, a fluid wave in the abdomen and bilateral leg oedema were noted. The main abnormal data were (normal values in parenthesis): RBCs, 309×10^4/cum; platelets, 6.9×10^4/cumm; hemoglobin, 11.4 g/dl; serum protein, 6.4 g/dl with albumin 2.2 g/dl and globulin 4.2 g/dl; serum iron, 43 μg/dl (60 to 200 μg/dl); SGOT, 53 IU/l (<40); hepatitis B surface antigen in serum, positive; rheumatoid factor in serum, positive; C reactive protein in serum, positive; occlut blood in feces, positive. A diagnosis of decompensated liver cirrhosis was made. After admission he became drowsy and abdominal distension became conspicuous despite treatment with Lasix. Jaundice appeared and he died of hepatic coma in January 1981.

At autopsy the liver (950 g) showed a macronodular cirrhosis with cholestasis. A small solitary hepatocellular carcinoma (0.7×0.9 cm) without intra- and extrahepatic metastases was found incidentally in the right hepatic lobe. The portal vein trunk and its intrahepatic

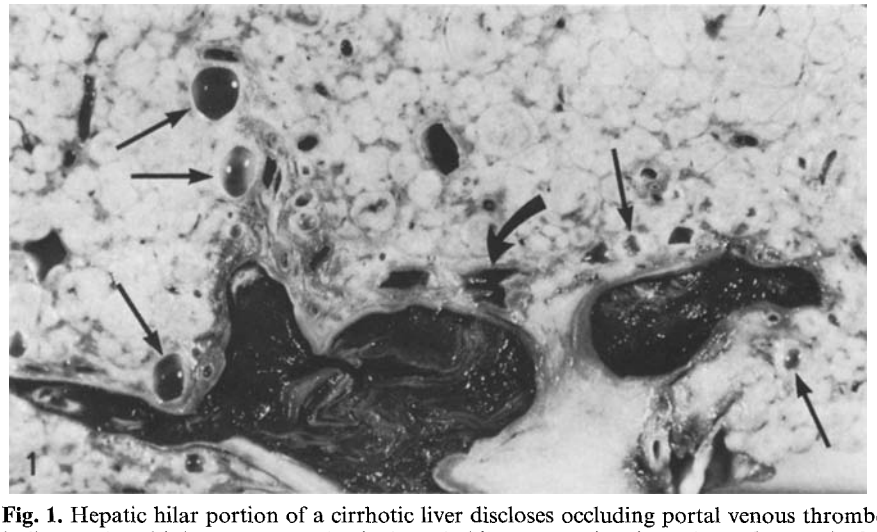

Fig. 1. Hepatic hilar portion of a cirrhotic liver discloses occluding portal venous thromboembolism and multiple serous cysts in the hepatic hilar connective tissue (*straight arrow*). Curved arrow denotes the intrahepatic biliary tree

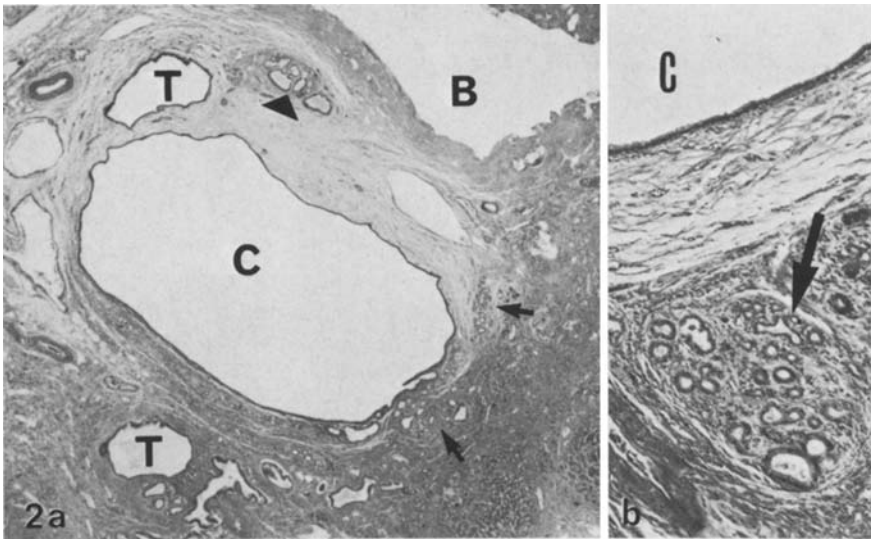

Fig. 2. a Thin-walled serous cyst (*C*) adjacent to the hepatic duct (*B*). Macroscopic cyst (*C*) and periductal glands (*arrow*) are intermixed. Microcystic dilatations of the periductal glands (arrow head) and intermediate-sized cysts (*T*) are also seen. HE., × 35. **b** Macroscopic cysts (*C*) lined by columnar epithelium is surrounded by thin fibrous layer. *Arrow:* periductal glands. HE., × 80

tributaries were occluded by recent thromboemboli (Fig. 1). It was noted that thin-walled cysts varying from less than a millimeter to 0.7 cm in diameter were found in the hepatic hilum and larger portal tracts (Fig. 1). They were ovoid or round and contained a serous, colourless fluid. There were no cystic lesions in the hepatic parenchyma and smaller portal tracts, and cystic dilatation of biliary tree was not present. The kidneys and pancreas failed to reveal cystic lesions.

Histologically, the lining epithelium of the cysts was composed of the cuboidal or columnar cells and surrounding fibrous tissue was scanty (Fig. 2). Some of the cysts were adjacent to the large intrahepatic bile duct, and lobules of the periductal glands (Terada 1984) were seen here and there between the cysts (Fig. 2). Some components of the glands showed microcystic dilatation. Furthermore, there were many transitional-sized cysts from macroscopic cysts to microscopic dilatations of the periductal elements (Fig. 2). There were no echinococcal cysts in the liver or other organs. The spleen (350 g) showed chronic passive congestion and oesophageal varices were seen.

Materials and methods

The following autopsy livers were collected from our recent autopsy cases which were all adults: normal livers (terminal congestion, 10 cases), chronic hepatitis (4 cases), fulminant hepatitis (4 cases), liver cirrhosis (17 cases), hepatocellular carcinoma with liver cirrhosis (21 cases) and chronic hepatitis (3 cases), primary biliary cirrhosis (Nakanuma and Ohta 1979) (fibrotic stage: 4 cases, cirrhotic stage: 4 cases), idiopathic portal hypertension (Okuda et al. 1982) with patent intrahepatic and extrahepatic portal venous system (2 cases), extrahepatic portal hypertension with occluding thromboembolism of the portal veins (6 cases), cholecystolithiasis (9 cases) and extrahepatic bile duct obstruction caused by stone or carcinoma (4 cases). The progenitor case, mentioned above, was also included in these materials. As for controls, three autopsy cases of adult polycystic livers were used.

Several liver slices including hepatic hilum were examined macroscopically in all cases and many tissue sections including the cysts, large bile ducts and large portal veins, were taken for histological examination. Routine stains were performed using paraffin sections.

Results

The multiple serous cysts which were present only in the hepatic hilum and larger portal tracts were found in 8 autopsy cases. The underlying diseases included liver cirrhosis, hepatocellular carcinoma with liver cirrhosis or chronic hepatitis, primary biliary cirrhosis, and extrahepatic portal hypertension (Table 1). The cysts were not found in normal liver, fulminant hepatitis, cholecystolithiasis and extrahepatic bile duct obstruction. Clinical features related to these cysts were unclear. All but one were middle to old aged ed males. All but one disclosed oesophageal varices, reflecting severe portal hypertension. Five cases revealed occluding portal venous thromboembolism.

Pathology of the cysts: they were round or ovoid in shape and their walls were thin. They were located in the center and/or periphery of the hepatic hilus and larger portal tracts (Figs. 1 and 3). The size of these cysts ranged from 2 cm to 0.2 cm. They were not green-colored, and did not communicate with lumena of the biliary tree. The microscopic features of these cysts and their relation to the periductal glands were identical

Table 1. Presentation of 8 autopsy cases with multiple cysts in the hepatic hilum and larger portal tracts

Case	Age (years)	Sex	Pathology of the liver (weight)	HBsAg in liver alcoholism	Esophageal varices	Ascites (ml)	Weight of spleen (g)	Thromboembolism of portal vein
1	49	M	LC+small HCC (950 g)	+/−	+	5,000	350	+*
2	68	M	LC+HCC (1300 g)	+/−	+	6,000	130	+
3	73	M	CAH+HCC (1360 g)	−/−	−	0	140	−
4	56	M	LC (975 g)	−/−	+	9,200	485	+
5	40	M	LC (940 g)	−/+	+	1,000	500	−
6	76	F	PBC** (590 g)	−/−	+	0	250	−
7	65	M	EPH (470 g)	−/−	+	1,500	100	+
8	75	M	EPH (800 g)	−/−	+	1,800	510	+

LC: liver cirrhosis, HCC: hepatocellular carcinoma, +*: tumor embolism, CAH: chronic active hepatitis, PBC**: primary biliary cirrhosis (fibrotic stage), M: male, F: female, EPH: extrahepatic portal hypertension, +: positive, −: negative

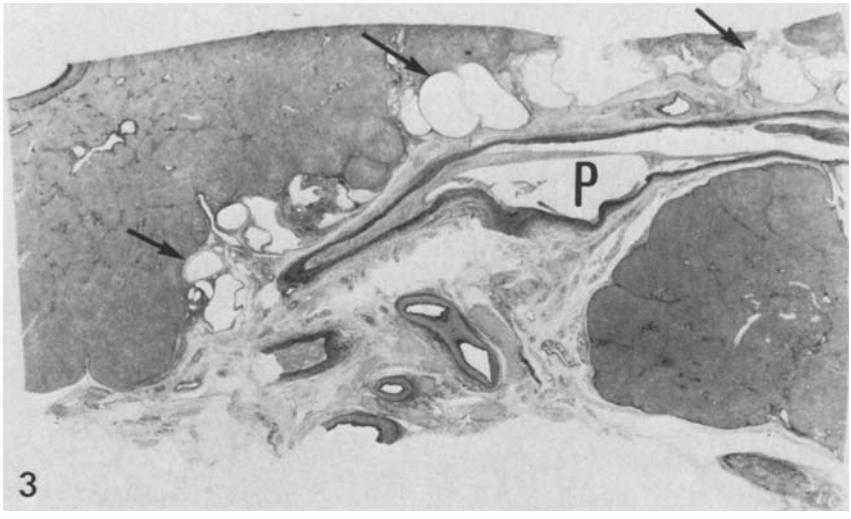

Fig. 3. There are many cysts (straight arrow) at the periphery of the hepatic hilum. P: recanalized portal vein. Case 7. Elastica van Gieson stain. ×35

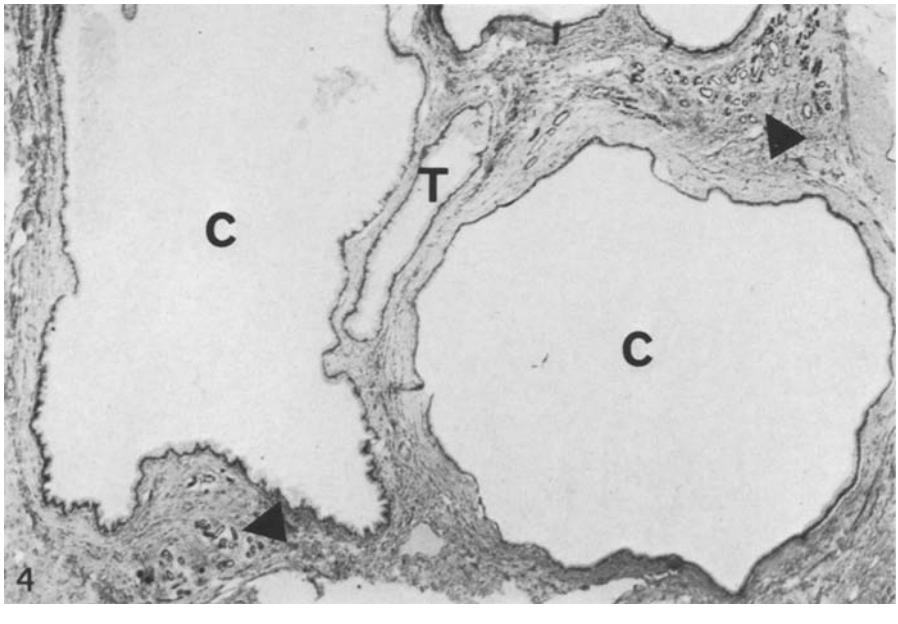

Fig. 4. Macroscopic cysts (*C*), transitional-sized cysts (*T*) and periductal glands (*arrow head*) are intermixed. Case 6. HE., ×35

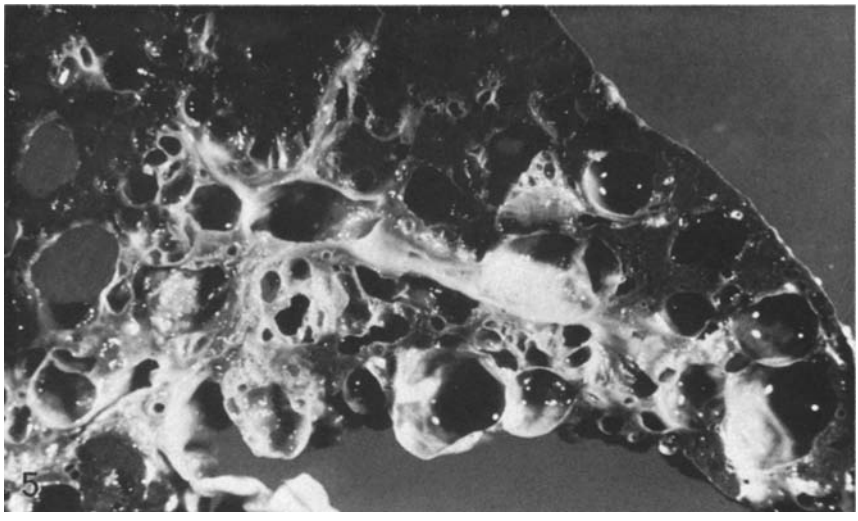

Fig. 5. Numerous cysts are seen in the cut surface of adult polycystic liver. Variable-sized cysts are studded in the hepatic parenchyma as well as in hepatic hilum and large to medium sized portal tracts.

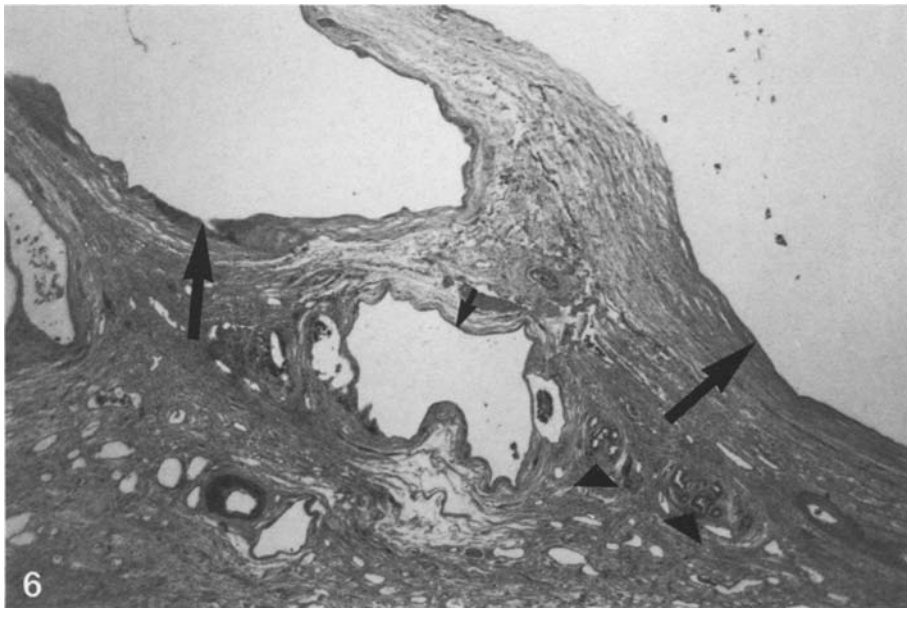

Fig. 6. Macroscopic (*large arrow*) and microscopic cysts (*small arrow*) are seen in the large portal tract. There are lobuli of periductal glands (*arrow head*) between cysts. Adult polycystic disease. HE., ×35

Table 2. Comparison of pathologic features of the liver between

	The test cases of multiple hilar cysts	Adult polycystic disease
Underlying liver disease	Present	Absent
Cysts in parenchyma and small portal tracts	Absent	Numerous
Cysts in heptatic hilium and large portal tracts	Number: variable Size: small	Numerous Small–large
Microcystic dilatation of periductal glands	Present	Present
Von Meyenburg complex	Rare	Consistent

to those of the index case (Fig. 3). Von Meyenburg complexes (Ishak and Sharp 1979; Gibson and Sobin 1978) were present focally in the hepatic parenchyma of case 7, but absent in the remaining 7 cases. The kidneys did not show polycystic of dysplastic changes. Pancreatic cysts were absent. The livers of 3 patients with adult polycystic disease (APCD) came from two females (75 and 60 years) and one male (67 years) cases, and all suffered from chronic renal failure. Numerous cysts were seen within the hepatic parenchyma as well as the hepatic hilum and larger portal tracts (Fig. 5). In comparison with the multiple hilar cysts the cysts of APCD were numerous and large. As in the multiple cysts of the present study, there were intermingled lesions of the cysts and lobuli of the periductal glands (Fig. 6), and microscopic dilatations of some elements of the periductal glandular lobuli were also seen in the hepatic hilum and larger portal tracts in APCD. All 3 livers with APCD showed von Meyenburg complexes here and there. The main differences in liver pathology between APCD and the presented cases are shown on Table 2.

Discussion

The multiple cysts in the hepatic hilum and larger portal tracts, "multiple hilar cysts", were compared with other previously reported hepatic cysts (De Barkey and Jordan 1982; Ishak and Sharp 1979). Solitary cysts, either unilocular or multilocular, are larger in size and clearly differ from the multiple hilar cysts, which were mostly small. There are many differences between the multiple hilar cysts and APCD. An association with von Meyenburg complexes is frequent in APCD but rare in the multiple hilar cysts. APCD is, further, inherited as an autosomal dominant character, predominant in females, not associated with severe portal hypertension, frequently associated with polycystic kidneys with chronic renal failure and occasionally with cysts in other organs, and has virtually normal hepatic functions and hepatic parenchymal histology except for lobular atrophy. However, the histology of the cystic lesions and the pericystic structures in the hepatic hilum and larger portal tracts were virtually identical in these two cystic conditions.

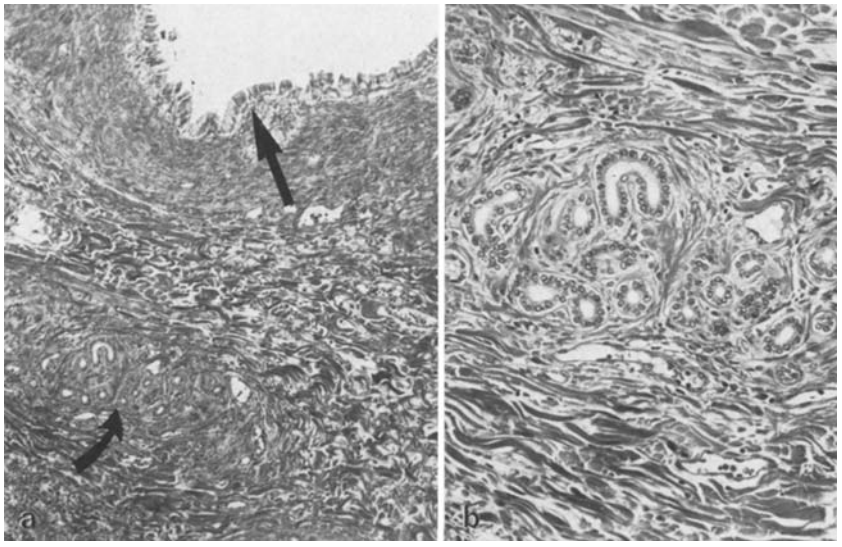

Fig. 7. a Intrahepatic large bile duct (*straight arrow*) and their periductal glands (*curved arrow*) of a normal liver. HE., ×70. **b** Periductal glands of branched tubuloalveolar pattern. High power picture of **a**. HE., ×135

There are two types of congenital cystic dilatations of the intrahepatic biliary tree, that is, multiple ductal dilatations (Ishak and Sharp 1979; Nakanuma et al. 1982) and localized sac-like dilatation (De Barkey and Jordan 1982). In addition, there are also cystic and cylindrical dilatations of the intrahepatic bile ducts, containing many stones, in hepatolithiasis (Terada 1984). They all differ from multiple hilar cysts. Traumatic pseudocyst, parasitic cysts and neoplastic cysts including cystadenoma and dermoid tumor are very different from the present cysts.

Masuko and Popper (1964) made the first description of glandular structures around the large intrahepatic bile ducts. Our recent study (Terada 1984) further disclosed that these glands communicated with ductal lumena through their ducts and that they are scattered in the periductal tissue of the hepatic, segment and area ducts of Healey's classification (1953) in the normal liver (Fig. 7). It was noted in the present study that the multiple hilar cysts were found exclusively in the hepatic hilum and larger portal tracts, where the periductal glands are physiologically present. The cysts were not seen within the duct walls themselves, the hepatic parenchyma, or the smaller portal tracts where the periductal glands are absent. Histologically, the cysts were closely intermixed with lobuli of the periductal glands and variable-sized microscopic dilatations were frequently seen within the areas of periductal glands. Thus, it seems reasonable to assume that the multiple cysts in the hepatic hilum and larger portal tracts are the results of cystic dilatation of the periductal glandular elements. These cysts appear to be retention cysts like those seen in glandular systems of other organs. (Okudaira 1982).

There have been several reports concerning with a possible causal relationship between circulatory disturbance in the liver and several biliary tract abnormalities (Balabaud et al. 1983; Ohta and Nakanuma 1983; Popovsky et al. 1979). Popovsky et al. (1979) reported that von Meyenburg complexes and simple bile cysts occurred in the liver from a patients with polyarteritis nodosa involving intrahepatic arteries and from monkeys treated by artificial occlusion of the hepatic arteries. They proposed that hepatic ischaemia is one of the factors causing von Meyenburg complexes and bile cysts. Balabaud et al. (1983) have noted, in rats treated with a portacaval shunt, that the lumen of the biliary tree was dilated and its lining epithelia became hyperplastic and grew into the ductal wall. They thought that increased hepatic arterial blood flow following a portacaval shunt led to these abnormalities. Our previous paper (Ohta and Nakanuma 1983) showed that presinusoidal portal hypertension in man (e.g. idiopathic portal hypertension) was on occasion associated with morphological changes in the intrahepatic biliary tree, and alternatively, diseases of the intrahepatic biliary tree, for example, primary biliary cirrhosis, were sometimes associated with severe presinusoidal portal hypertension. In the present study, severe portal hypertension was seen in almost all patients with multiple hilar cysts and about a half of them disclosed an occluding portal venous thromboembolism. Thus, it seems possible to consider that disturbance of portal venous blood flow in the liver causes morphological alterations of the periductal glandular elements, their luminal dilatation and the subsequent formation of micro- and macroscopic cysts in the hepatic hilum and larger portal tracts. If so, the multiple hilar cysts may be of an acquired origin and thereby should be distinguished from a group of congenital biliary cysts.

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