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Congenital Anomalies of the Pancreas and the Extrahepatic Bile Ducts

Pancreaticobiliary maljunction (PBM) is frequently associated with congenital choledochal cyst, but differs with regard to its embryonic cause and clinical features. It is thought to develop as a misarrangement of the embryonic connections in the pancreaticobiliary ductal system, with the terminal bile duct joined to one of the ducts of the ventral pancreas. The clinical aspects of these anomalies of the pancreaticobiliary ductal system are intermittent abdominal pain, relapsing acute pancreatitis, jaundice, cholangitis, and gallbladder cancer. Coexistence of pancreas divisum complicates a diagnosis of pancreaticobiliary maljunction, so it is very important to understand the diagnostic criteria of pancreas divisum for correct diagnosis of pancreaticobiliary maljunction. Surgical treatment for congenital choledochal cyst with relative stricture in the upper portion of the biliary tract should be performed with care to avoid postoperative cholangitis.

Pancreaticobiliary Maljunction

Definition

PBM is a congenital anomaly in which the junction of the pancreatic duct and biliary duct is located outside the duodenal wall (Fig. 2.1a); in the normal pancreaticobiliary junction, the main pancreatic duct (MPD,

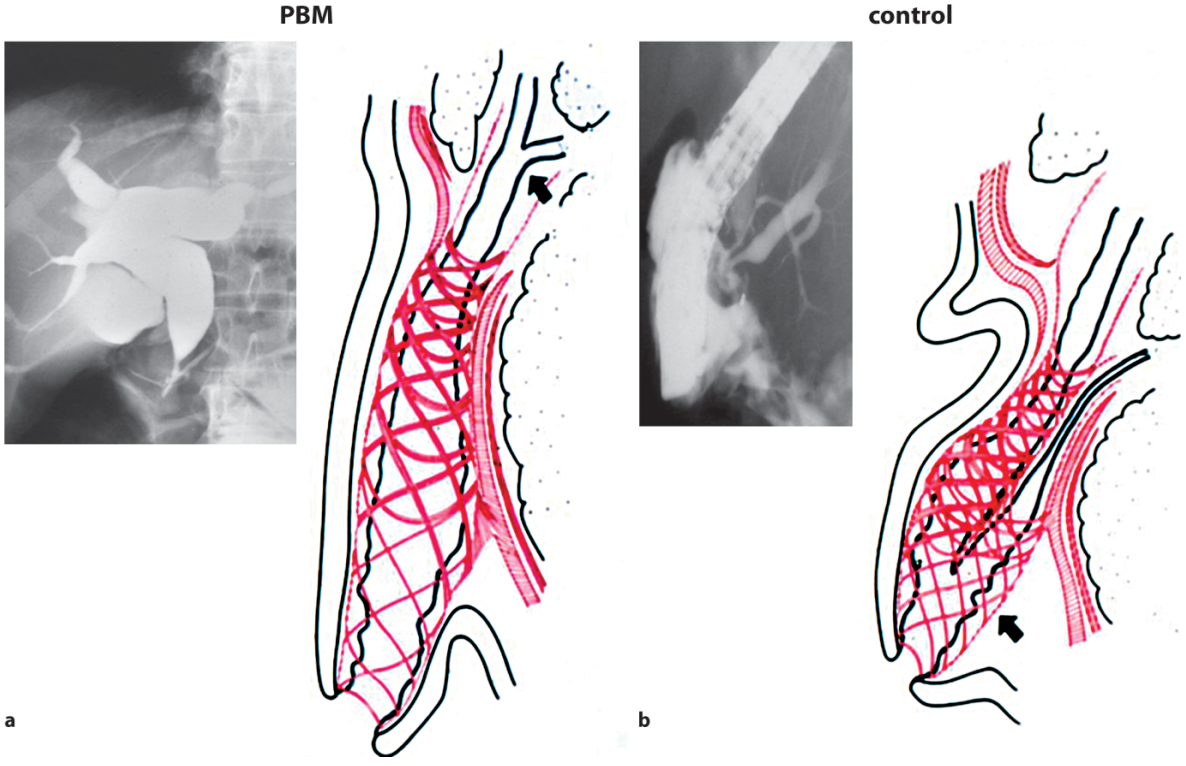

Figure 2.1

b Diagram showing the sphincter muscle at the end of the common bile duct and the main pancreatic duct in controls, and **a** in patients with pancreaticobiliary maljunction (PBM)

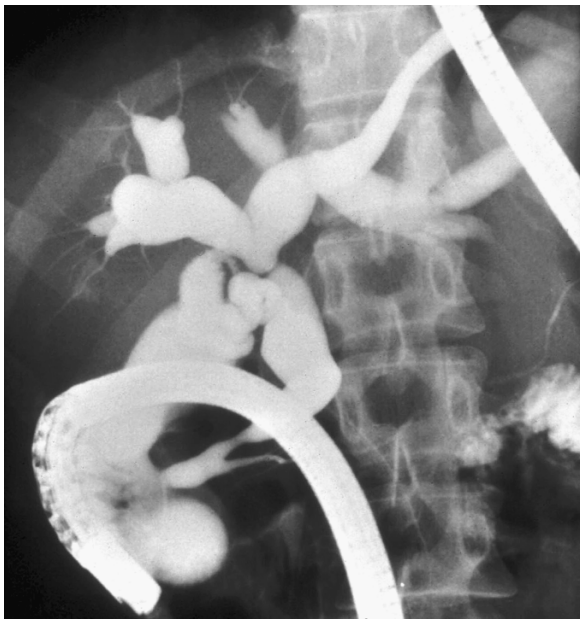

Figure 2.2

PBM is almost always seen in patients with congenital choledochal cyst or congenital biliary dilatation

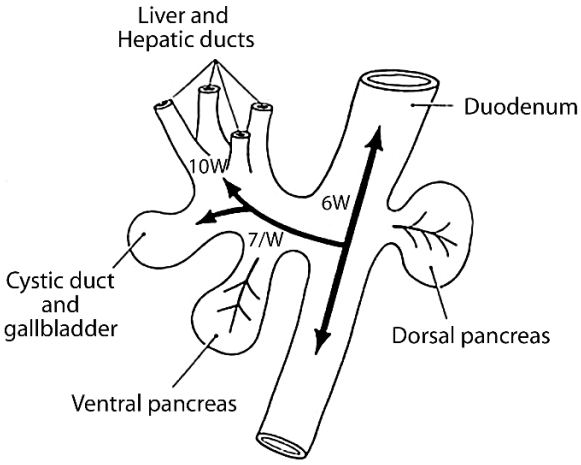

Figure 2.3

The process of normal development of hepatobiliary system and pancreas

Wirsung's duct) joins with the common bile duct (CBD) inside the muscle layer of the duodenum to form the ampulla of Vater (Fig. 2.1b). PBM is almost always seen in patients with congenital choledochal cyst or congenital biliary dilatation (Fig. 2.2). However, it may occur independently of any other developmental anomaly in the CBD.

Embryology of the Hepatobiliary System and Pancreas in Normal Human Development

Akin [1] described the process of normal development of the hepatobiliary system and pancreas (Fig. 2.3). The extrahepatic bile duct system and the ventral anlage (primordium) of the pancreas arise from the hepatic diverticulum, which is first visible on the ventral surface of the anterior intestinal portal of the embryo early in the 4th week of gestation. By late in the 4th week, the ventral anlage of the pancreas arises from the base of the hepatic diverticulum itself, and the dorsal anlage of the pancreas arises directly from the dorsal side of the duodenum almost opposite the liver primordium. By the beginning of the 5th week, the pancreatic duct, as well as the gallbladder, cystic duct, and CBD, are demarcated, and during the 5th week, the proximal portion of the hepatic diverticulum elongates but does not increase greatly in diameter, in contrast to the tremendous growth of the distal end. During this stage, the future CBD system is in an incomplete or solid cord state. By the 6th week, the ventral primordium has been carried away from the duodenum by elongation of the proximal part of the diverticulum. During the 7th week, duodenal torsion brings the two pancreatic primordia side by side, and the smaller, ventral primordium fuses with the proximal part of the dorsal pancreas. No solid stage seems to occur in the pancreatic ducts. Reestablishment of the lumen of the hepatic diverticulum commences with the CBD in the 6th week of gestation, and progress slowly to the distal portion; the lumen extends into the cystic duct by the 7th week. During the 8th week, the proximal portion of the diverticulum is usually absorbed into the intestinal wall, so that the CBD and the pancreatic duct enter the duodenum side by side. That is, the point of junction of the pancreatic duct and CBD recede to the level of the submucosa from the common bile duct orifice, with the elongation of the papilla of Vater, and with increasing thickness of the duodenal wall. The muscle fibers of the sphincter of Oddi are derived directly from the mesenchyme around the CBD during the 11th week of gestation. In short, during the normal course of development of the hepatobiliary system and the pancreas, the MPD joins to the CBD to form a "common channel" (the ampulla of Vater), and the common channel moves inside the muscle layer of the duodenum after the 12th week of gestation.

PBM Hypothesis

Alons-Lej et al. [2] and Yotuyanagi [3] described the narrowed duct segment distal to the biliary cyst as a "narrow part of the terminal bile duct" (Fig. 2.4a). Babbitt [4] described it as a long common channel that was thought to arrest the normal inward migration of the choledochopancreatic junction [5] (Fig. 2.4b), similar to the occurrence of congenital biliary atresia.

We clarified that the long common channel actually represents Wirsung's duct system [6], based on a radiological and anatomical analysis of patients with PBM. Figure 2.5 shows small radicles that were thought to be branches of the pancreatic duct arising from the so-called long common channel. Figure 2.6 shows a huge choledochal cyst in a surgical specimen associated with gall bladder carcinoma that invades the duodenum; the junction of the MPD and the CBD was situated external to the muscle layer of the duodenum, a condition that is referred to as PBM, thus forming an extended common channel. Also in this case, the minute orifice was found macroscopically in the narrowed duct segment (Fig. 2.6) and was identified microscopically as a small duct from the pancreatic parenchyma; these small pancreatic ducts were derived from the ventral pancreas, based on the distribution of islets with pancreatic-polypeptide-positive (PP) cells (PP islets) [7].

In conclusion, both the long common channel and narrowed duct segment originate from pancreatic duct. Anatomical and radiological analyses of the junction of the pancreatic duct with the bile duct show that there are variations in the location of the union of the terminal bile duct with ventral pancreatic duct system, as shown in Fig. 2.7 [8].

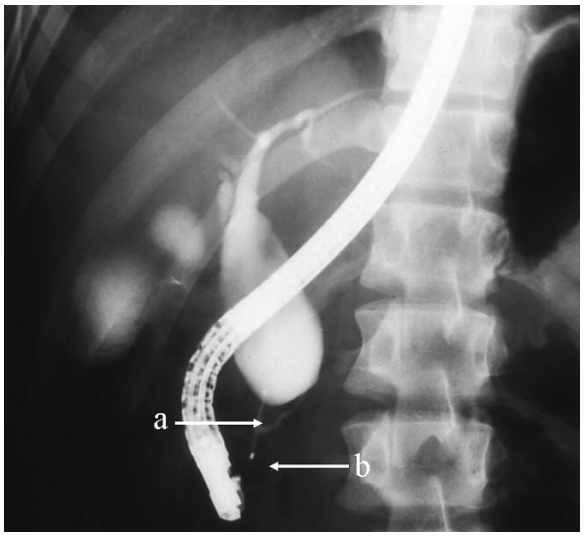

Figure 2.4

Narrow part of the terminal bile duct (a) and a long common channel (b)

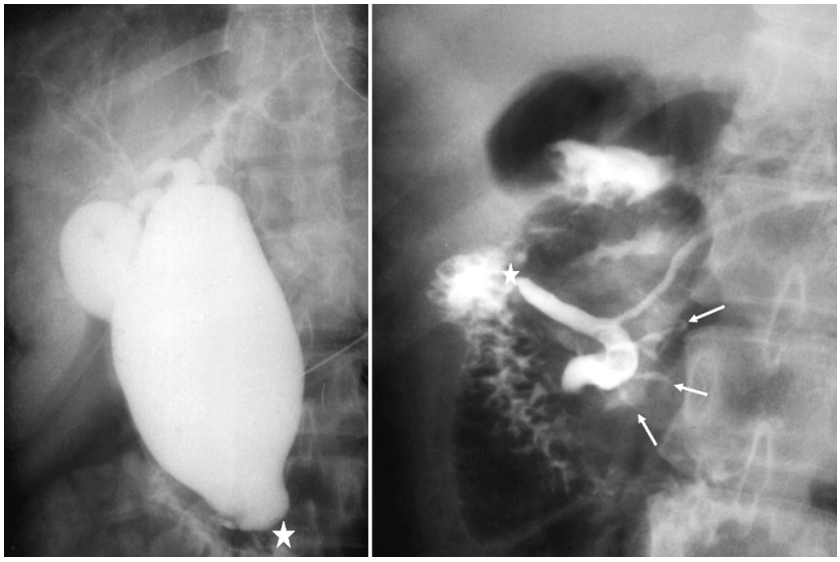

Figure 2.5

Small radicles that were thought to be branches of the pancreatic duct arise from so-called long common channels (*arrows*)

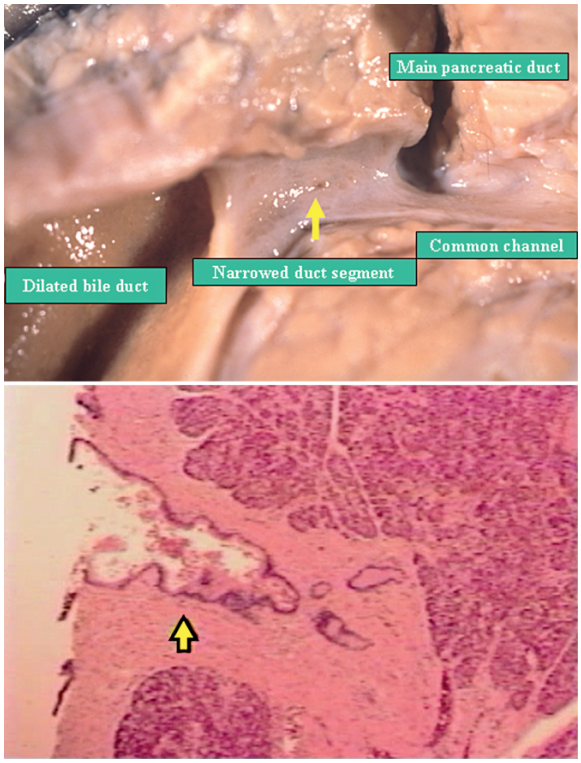

Figure 2.6

The junction of the main pancreatic duct and the common bile duct, in this case is situated external to the muscle layer of the duodenum and minute orifice, and can be found macroscopically in the narrowed duct segment and identified microscopically as a small duct from the pancreatic parenchyma

Carcinogenesis in PBM

The number of reports of biliary malignancies with PBM has recently increased. Among the 130 cases of gallbladder cancer seen in our institute in the past 20 years, 55 had concomitant PBM; the incidence is thought to be extremely high (Table 2.1). Many studies of biliary carcinogenesis in PBM have been reported, such as an assessment of the cell proliferative activity [9] and various oncogenes and tumor-suppressor genes in the epithelium of the biliary ductal system in PBM patients [10]. Kato and Mizuno [11] reported that the mixing of pancreatic juice and bile in PBM resulted in the production of various harmful substances in the biliary tract, such as activated pancreatic enzymes, lysolecitin, and some mutagens, of which mutagens in particular were thought to be involved in the development of biliary tract cancer. They identified mutagenic substances in the mixture of bile and pancreatic juice, and estimated that the substances had a molecular weight of 1500–3500 (as assessed by gel chromatography) and were complexes of low-molecular-weight stable substances containing amino acids and peptides (as assessed by gas chromatography and mass spectrometry). Accordingly, the mixture of bile and pancreatic juice due to reciprocal reflux in PBM very likely plays an important role in biliary carcinogenesis.

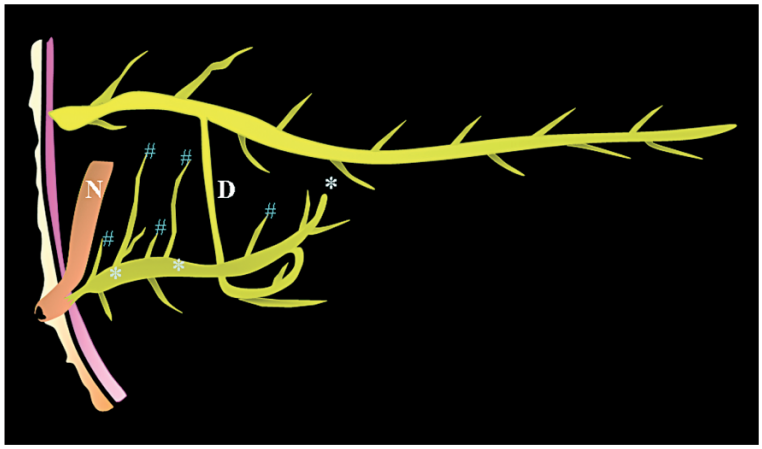

Figure 2.7

There are variations in the location of the union of the terminal bile duct with the ventral pancreatic duct system

Table 2.1. Clinical review of 250 patients with pancreaticobiliary maljunction. CCDB Congenital cystic dilatation of the common bile duct, *GB* gallbladder, *CB* common bile duct, *IHB* intrahepatic bile duct, *GBX* carcinoma of gallbladder, *CBX* carcinoma of common bile duct, *IHBX* carcinoma of intrahepatic bile duct

	Without CCDB		With CCDB			
			Infant-type cyst		Adult-type cyst	
	Men (*n*=29)	Women (*n*=64)	Men (*n*=3)	Women (*n*=9)	Men (*n*=47)	Women (*n*=98)
None (*n*=56)	8	16	3	5	11	13
Stones						
GB (*n*=44)	9	25	0	0	3	7
CB (*n*=52)	0	0	0	2	17	33
IHB (*n* =17)	0	0	0	0	5	12
Cancer						
GBX (*n* =55)	9	22	0	1	5	18
CBX (*n* =14)	3	1	0	1	2	7
IHBX (*n* =12)	0	0	0	0	4	8

Mechanism of Pancreatic Juice Reflux into the Biliary Tract in PBM

The reason why PBM is abnormal may possibly be explained more clearly by the reconstruction study of Suda et al. [12], as shown in Fig. 2.1. In the controls, the CBD and the MPD penetrate the muscle layer of the duodenum obliquely and parallel to each other, and form a junction in the submucosal layer just before opening into the duodenum. The angle of the ductal junction is therefore very sharp. The sphincter of Oddi, which surrounds both ducts and the common channel, normally consists of three sections: the sphincter choledochus, the sphincter pancreaticus, and the sphincter ampullae [13]. Of these, the sphincter muscle at the distal end of the choledochus (sphincter choledochus) is the best-developed. It regulates the outflow of bile and prevents free communication between the bile and pancreatic ducts.

In the case of PBM, however, the junction of the ducts is situated external to the muscle layer of the duodenum, thus forming an extension to the muscularis propria of the duodenum, thus forming an extended common channel [14]. The angle of the ductal junction is less sharp in these patients than in control cases. The well-developed sphincter muscle is situated in the submucosal layer, as in controls, but it mainly surrounds the common channel (sphincter ampullae); the sphincter choledochus is extremely hypoplastic. The anatomical findings suggest the possibility of the communication between the ducts in cases of PBM. As the intraductal pressure of the pancreatic duct is normally higher than that of the bile duct [15], reflux of pancreatic juice may occur into the bile duct and could lead to nonsuppurative chronic inflammation of the bile duct.

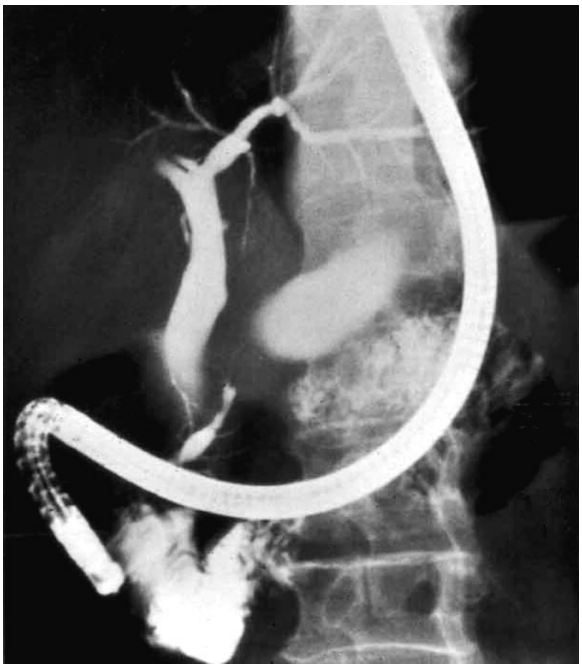

Figure 2.8

A case of isolated dorsal pancreatitis associated with pancreas divisum, the branch fusion seemed to be composed of an inferior branch of the ventral pancreatic duct and an inferior branch of the dorsal pancreatic duct

Pancreas Divisum

Definition

In the pancreas divisum, the parenchyma of the ventral pancreas and the dorsal pancreas are separated as a double pancreas. Recently, however, the term pancreas divisum has been used widely to describe two

ductal systems, the ventral pancreatic duct and the dorsal pancreatic duct, which do not unite or communicate and separately drain to the two duodenal papillae [16]. In this condition, pancreatic juice from the dominant dorsal moiety flows out only through the minor papilla, in which the outlet is notably small in most cases. This raises the question of whether this variation plays a role in the development of pancreatic pain or pancreatitis. The clinical relevance of pancreas divisum has been argued repeatedly [16]. Figure 2.8 shows an example of isolated dorsal pancreatitis associated with pancreas divisum. This condition strongly suggests inadequate drainage from the minor papilla.

Branch Duct Fusion of the Ventral and Dorsal Pancreatic Ducts

A case of fusion via two so-called inferior branches between the ventral pancreatic duct and dorsal pancreatic duct was studied based on the organogenesis of the pancreas [17], as shown in Fig. 2.8. Radiologically, branch fusion seems to be composed of an inferior branch of the ventral pancreatic duct and an inferior branch of the dorsal pancreatic duct. By mapping the locations of PP islets in material obtained by pancreaticodudenectomy, however, the branch was identified as a branch of the dorsal pancreatic duct. Thus fusion between two inferior branches was not established, but was found to consist of an inferior branch of the dorsal pancreatic duct connected with the ventral pancreatic duct.

Identification of the Originating Primordium of the Pancreas

Fusion of the "ventral" and "dorsal" pancreata can be distinguished [18] according to the distribution of PP islets [19], selectively in the ventral pancreas. In some cases both pancreata can be identified macroscopically. There are two further distinct characteristic differences. One is the shape of the islets; those in the ventral pancreas, which include abundant PP cells, are irregular, in contrast to the neatly round or oval-shaped islets found in the dorsal pancreas (Fig. 2.9). The other is the distribution of fatty infiltration in the pancreas. There is more fat in the dorsal pancreas than in the ventral pancreas [18]. The ventral primordium forms the posterior part of the head of the pancreas, completely or partially surrounding the CBD and the uncinate process. However, the dorsal bud forms the remaining ventral parts of the head, the isthmus, the body, and the tail of the pancreas. The fusion line between both pancreata has no defined border, but it is the so-called "locus minoris resistantiae" and it is the easiest "pathway" for a duodenal diverticulum to penetrate the pancreas.

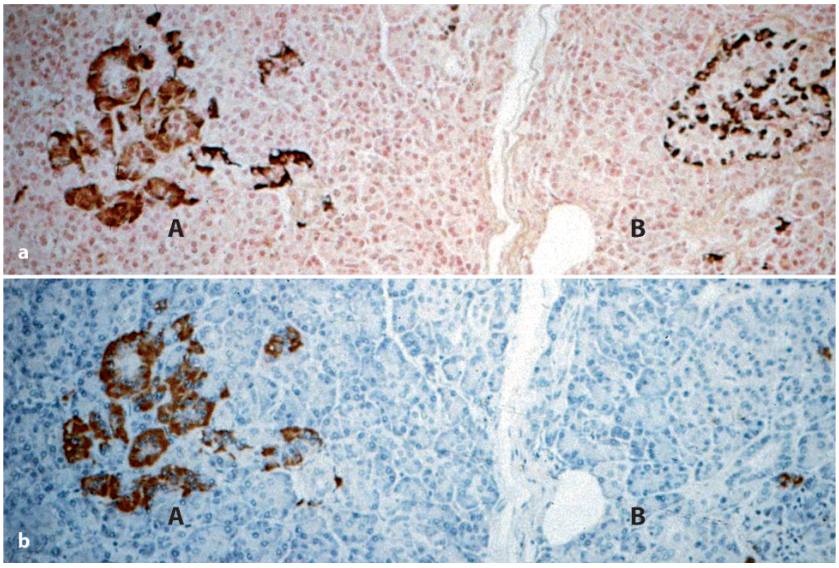

Figure 2.9

a Grimerius staining. **a** Irregular-shaped islet in the ventral pancreas. **b** Round-shaped islet in the dorsal pancreas. **b** Immunohistochemical staining for pancreatic polypeptide. **a** Islet of the ventral pancreas contains many pancreatic-polypeptide-positive (PP) cells. **b** Islet of the dorsal pancreas containing only a few PP cells

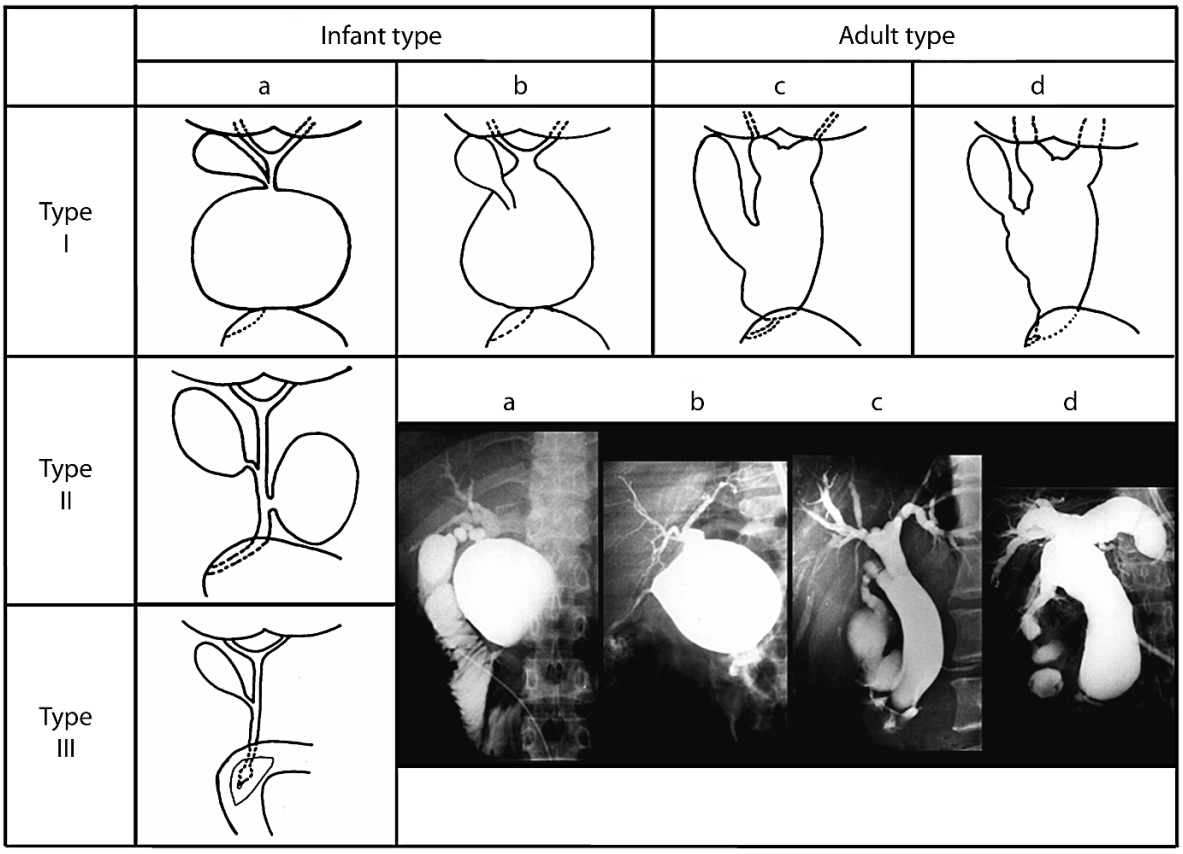

Figure 2.10

Classification of congenital cystic dilatation of the common bile duct

Congenital Cystic Dilatation of the CBD

Definition and Classification

Congenital cystic dilatation of the CBD (CCDB) has been classified into three types by Alonso-Lej et al. [2]: type I, congenital cystic dilatation of the CBD; type II, congenital diverticulum of the CBD; type III, congenital choledochocele. In addition, it was proposed that the criteria for the diagnosis of CCDB should be: (1) the intrahepatic tree is usually normal, (2) the biliary tree above the cystic dilatation of the CBD is somewhat dilated secondary to the obstructive factor in the distal choledochus, (3) the cystic dilatation of the CBD proper begins and ends sharply, and (4) the terminal CBD is frequently narrowed. However, recent advances in diagnostic techniques for biliary disease disclosed that there were many cases of choledochal cyst that dilated into the intrahepatic bile duct. We thus classified CCDB into two subtypes: "infant type" and "adult type," based on the anatomic location and clinical features [20]. Infant-type cysts are typically large cysts of the choledochus and occur most commonly in infancy and childhood. Adult-type cysts are fusiform dilatations of the biliary tract, and occur most commonly in adults (Fig. 2.10). Gallstones were seen in most of the patients with adult-type cysts.

Relative Stricture in the Upper Portion of the Biliary Tract

Definition and Classification

Stricture in the upper portion of the biliary tract is a localized reduction in the caliber of the bile duct proximal to the common hepatic duct. When biliary dilatation is present in a bile duct that continues to the strictured lesion, the caliber of the strictured portion can become larger than that of the normal bile duct; such strictures are called relative strictures.

The location of the biliary strictures is observed at the following six sites in the upper portion of the bili-

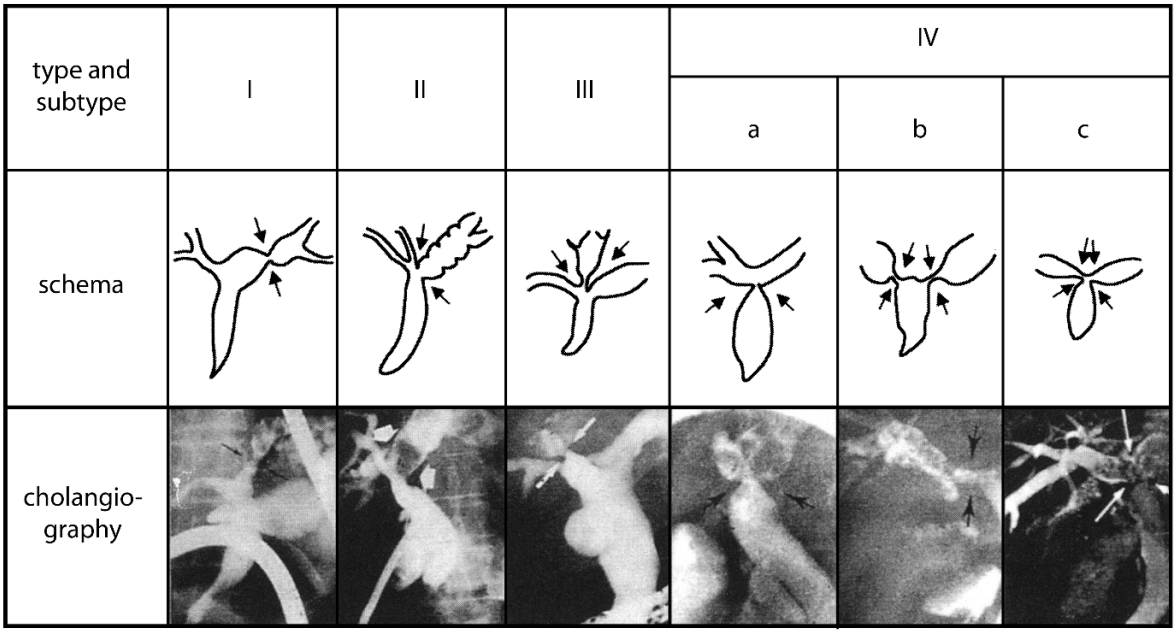

Figure 2.11

Classification of relative biliary strictures based on the anatomical location of the stricture

ary tract, and they are classified into four groups according to the anatomical location of the stricture (Fig. 2.11) [21].

1. Type I: the site of stricture is the region where the left hepatic duct enters the intrahepatic portion in the lateral segment of the liver. This type of stricture occurs with the highest frequency and is associated with intra- and extrahepatic bile duct dilatation.
2. Type II: this type of stricture is present at the root of the left hepatic duct. The liver parenchyma extends to the strictured lesion, and the entire left hepatic duct including the strictured lesion is within the liver.
3. Type III: this type of stricture is present at the region where the intrahepatic bile ducts in the anterior segment or the superior area of the anterior segment of the right hepatic lobe join the right hepatic duct. They are located immediately beneath the hepatic capsule where the bile duct enters the hepatic parenchyma. Both intra- and extrahepatic bile duct dilatations are observed in this stricture type.
4. Type IV-a: this stricture is present at the upper portion of the common hepatic duct, and dilatations in the common hepatic duct and the hepatic duct proximal to the stricture are also present.
5. Type IV-b: this stricture is present in the bilateral hepatic ducts.
6. Type IV-c: this type of stricture is located at the region encompassing the upper portion of the common hepatic duct and the confluence of the bilateral hepatic ducts.

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