REVIEW

Etiological Relationships between Choledochal Cyst and Anomalous Junction of the Pancreaticobiliary Ductal System

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Abstract

The etiology of choledochal cyst has been investigated by clinicians and pathologists primarily of Germany, Austria, United States, United Kingdom, and Japan from the end of the last century, but Japanese investigators contributed greatly to the study of the relationship between choledochal cyst and anomalous junction of the pancreaticobiliary ductal system. Heid (1893) is considered to be the first to document choledochal cyst associated with anomalous pancreaticobiliary junction, but it was probably Kozumi *et al.* (1916) that first evaluated anomalous junction in relation to the etiology of choledochal cyst. Yotsuyanagi (1936), who is noted for his work on the etiological studies of choledochal cyst, attached particular importance to anomalous junction and attempted to establish a relationship between dysplasia of the primordial common bile duct and its anomalous junction with the pancreatic duct. It is no exaggeration to say that this area was led by Japanese investigators even after the introduction of Babbitt's anomalous junction theory (1968). In this review, etiological theories of choledochal cyst and their changes with time were discussed separately for those before and after the advent of Babbitt's anomalous junction theory (1968) with particular reference to the causative relationship between anomalous junction and choledochal cyst. Although there is as yet no definite answer to this problem, the theories advanced to date are considered to be summarized as the following three major

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lines of thought: 1) bile duct dilatation and anomalous junction are both congenital dysplasia occurring simultaneously during the embryonic development, 2) bile duct dilatation is a secondary change induced by influx of pancreatic juice into the biliary tract due to anomalous pancreaticobiliary junction, and 3) bile duct dilatation is induced secondarily by stenosis of the distal bile duct, which is a part of complex anomaly of the pancreaticobiliary system. Which of these etiological mechanisms is more important than others must still be clarified, but these three factors are considered to be interrelated with one another in the etiology of choledochal cyst.

Key words: choledochal cyst, etiology, anomaly, pancreaticobiliary ductal system

Introduction

Choledochal cyst is considered to have been first described by Vater *et al.*¹ (1723). The reports of the disease were sporadic thereafter, but their number increased rapidly from the latter half of the 19th century to the beginning of this century with increased references being made to its etiology. Hypotheses of the etiologic process of choledochal cyst may be generally classified into 1) those based on congenital anomaly (congenital anomaly theories), 2) those based on weakness of the wall of the biliary tract (wall weakness theories), 3) those based on obstruction of the biliary tract (obstruction theories), and 4) those based on both weakness of the wall and obstruction of the biliary tract (dual theories).

Anomalous junction of the pancreatic duct and the biliary tract was already noted at the beginning of this century as a dysplasia of the pancreaticobiliary ductal system associated with choledochal cyst.²⁻¹⁴

Although this anomaly was suggested to be an important clue to the etiology of choledochal cyst by some authors,^{8,14} no conclusive observation was made concerning the causative relationship between the two conditions. Babbitt¹⁵ (1968) was probably the first to theoretically explain the causative relationship between choledochal cyst and anomalous junction of the pancreaticobiliary ductal system on the basis of pathophysiologic evaluation of the latter.

He presented the theory that pancreatic juice flowing into the biliary tract due to the intraluminal pressure gradient between the pancreatic duct and the biliary tract induces cholangitis and, together with a high secretion pressure of pancreatic juice, causes dilatation of the common bile duct. When the dilatation is severe, obstruction is considered to occur due to edema, valve-like mechanism, or fibrosis in the distal bile duct. Babbitt theory, which is based on the assumption that anomalous junction of the pancreaticobiliary ductal system is at the basis of weakness of the wall and ob-

struction of the biliary tract, can be categorized as a dual theory.

While Yotsuyanagi theory¹⁴ (1936), which is supported by a number of investigators, maintains that dysplasia of the primordial common bile duct occurring during the embryonic development is the etiological basis of choledochal cyst, Babbitt theory assumes the presence of primary anomalous junction of the pancreaticobiliary ductal system and secondary development of choledochal cyst. Since anomalous junction is associated with influx of pancreatic juice into the bile duct in most patients with choledochal cyst, this theory also gained a wide support. However, as clinical and experimental studies were accumulated since the introduction of Babbitt theory, doubts have been raised about the role of anomalous junction of the pancreaticobiliary ductal system in the etiology of choledochal cyst.

While the etiological process of choledochal cyst has yet to be established, this chapter summarizes major etiologic theories presented to date by various investigators and presents the author's personal view on the causative relationship of this condition with anomalous junction of the pancreaticobiliary ductal system.

Etiological theories of choledochal cyst (mainly those before Babbitt)

Detailed reviews concerning the etiology of choledochal cyst was made already during the first half of this century by investigators such as Kuru⁷ (1913), Kozumi *et al.* (1916), Kremer¹⁶ (1919), Zipf¹⁷ (1922), McWhorter¹⁸ (1924), Yotsuyanagi¹⁴ (1936), and Shallow *et al.*¹⁹ (1943). The theories advocated by these authors may be classified into 1) those based on congenital anomalies, 2) those based on weakness of the wall of the biliary tract, 3) those based on obstruction of the biliary tract, and 4) those based on dual causation (weakness of the wall and obstruction of the biliary tract). Various etiologic theories have been presented also in the second half of this century by authors including Alonso-Lej *et al.*,²⁰ but they can also be classified into the above 4 categories; Babbitt theory is no exception.

Each of these categories are discussed below.

A. Congenital anomaly theories

These theories assume that some dysplasia of the primordial common bile duct occurring during the embryonic development causes congenital dilatation in the common bile duct. Premature babies born with choledochal cyst reported by Heiliger²¹ (1910) are often cited as the evidence of these theories.

Zipf¹⁷ considered that cystic dilatation of the bile duct develops from congenital mild dilatation in the presence of congenital or acquired distal bile ductal obstruction. Flechenmacher²² (1919), Budde⁹ (1920), Schurholz¹³ (1929), Erdély²⁴ (1928) and Winternitz²⁵ (1928) speculated that diverticular projections in the wall of the primordial common bile duct grow into cystic dilatations.

Dreesmann²⁶ (1908), Heiliger²¹ (1910), Seeliger²⁷ (1916), Krabbel²⁸ (1924), Lange²⁹ (1927), Giezendanner³⁰ (1929) and Ravitch³¹ (1958) also supported the congenital anomalous theory, but did not elaborate on the nature of the primary dysplasia.

Yotsuyanagi¹⁴ (1936) presented the most detailed and logical of the congenital anomaly theories from the embryological and anatomicopathological viewpoints, and his theory is still supported by a large number of investigators today. According to this theory, epithelial growth of the primordial common bile duct becomes uneven for some reason in early embryonic development. If the epithelial growth is insufficient in the lower portion but excessive in the upper portion of the biliary tract, stenosis results in the lower bile duct and dilatation develops in the upper bile duct during the following period of recanalization. Bile stasis due to the stenosis promotes the dilatation of the upper bile duct, resulting in cystic enlargement. Biliary atresia and Alonso-Lej type II choledochal cyst may also be explained by this theory.

B. Wall weakness theories

These theories are based on the assumption that weakness of the wall of the biliary tract, mostly considered to be congenital, is responsible for choledochal cyst. Authors such as Lavenson³² (1909), Kremer¹⁶ (1919), Zipf¹⁷ (1922) and Neugebauer³³ (1924) emphasized immaturity and weakness particularly of the muscle in the construction of the wall, and Dreesmann²⁶ (1908) noted hypoplasia of elastic fibers. Wagner³⁴ (1918) suggested "sackartige Anlage" developing in the common bile duct, and Budde⁹ (1920) suggested ectopic development of pancreatic tissue in the wall of the common bile duct, as causing weakness of its wall, leading to localized dilatation of the common bile duct. Authors such as Russell³⁵ (1897), Goldammer³⁶ (1907), Weiss³⁷ (1909), Heiliger²¹ (1910), Mayesima⁶ (1912), Bolle³⁸ (1922) and Kolb³⁹ (1924) also emphasized the importance of weakness or reduction in the tonus of the wall of the biliary tract in the development of choledochal cyst, but did not discuss the mechanism of weakening the wall in details.

C. Obstruction theories

A number of investigators ascribed choledochal cyst to congenital or acquired bile ductal obstruction. Heid² (1893), Böhm⁴⁰ (1914), Seeliger²⁷ (1916) and McWhorter¹⁸ (1924) indicated congenital stenosis of the distal biliary tract, and Böhm considered that this stenosis results from persistence of the physiological epithelial occlusion of the primordial common bile duct preventing its recanalization. The most frequently documented causes of bile ductal obstruction are unusual course of the biliary tract, its kinking, and valve-like changes of the biliary mucosa. Russell³⁵ (1897), Arnolds⁴ (1906), Wettwer⁴¹ (1907), Ebner⁴² (1909), Schloessmann⁵ (1911) and Budde⁹ (1920) ascribed dilatation of the bile duct to the increase in the intraluminal pressure due to

unusual course and kinking of the distal biliary tract. Rostowzew³ (1902), Weiss³⁷ (1909), Konitzky⁴³ (1888), Clairmont⁴⁴ (1911) and Sternberg⁴⁵ (1911), on the other hand, considered that unusual course and kinking of the distal biliary tract induce secondary development of the valve-like mechanism, which causes its obstruction. In contrast, Bakes⁴⁶ (1907), Reel⁴⁷ (1922) and Neugebauer⁴⁸ (1924) suggested the primary presence of valve-like folds in the distal biliary tract.

Although the above authors regarded morphological factors as responsible for bile ductal obstruction, others sought for their causes among functional factors. Rostowzew⁸ and Ebner⁴² suggested reflex spasm of the sphincter of Oddi, and Rolleston⁴⁸ (1905) indicated neuromuscular incoordination (achalasia) as causing obstruction. Weber⁴⁹ (1934) supported Rolleston's view⁴⁸ and, speculating that this neuromuscular incoordination is caused by autonomic neurodysplasia, further suggested that choledochal cyst should be named megalocholedochus on the assumption of its etiological analogy with megacolon, megaloesophagus, and megaloureter, whose etiology was not established at his time. Saltz *et al.*⁵⁰ (1956) considered that narrowing of the distal biliary tract is caused by defect of intramural neurons as in Hirschsprung disease from morphological similarities of the two conditions. However, they carried out no pathological evaluations.

Cholangitis, gall stones, trauma, and pregnancy have been suggested as acquired factors in bile ductal obstruction.

Edgeworth⁵¹ (1895), Russell³⁵ (1897) and Lavenson³² (1909) regarded catarrhal cholangitis, and Raynaud *et al.* (1879) and Seyffert⁵⁹ (1888) regarded choledocholithiasis, as causing biliary stenosis. Kremer¹⁶ presented a trauma theory on the basis of his experience of the condition after abdominal trauma. Concerning pregnancy, Goldammer³⁶ (1907) suggested compression of the biliary tract by the uterus of pregnancy and McWhorter¹⁸ suggested that postpartum kinking of the biliary tract can induce its obstruction.

D. Dual theory (wall weakness and obstruction)

A dual theory is considered to have been first presented by Ebner¹³ (1909), and authors such as Zipf¹⁷ (1922), Gross⁵⁴ (1933) and Alonso-Lej²⁰ (1959) supported this theory. In addition, many authors including Lavenson³² (1909), Bolle³⁸ (1922), Neugebauer³³ (1924) and Kasai⁵⁶ (1967) suggested that both weakness of the wall and obstruction of the biliary tract are needed for the development of choledochal cyst, though they did not define their theories as dualistic.

Ebner⁴² considered defect of elastic fibers to be responsible for the weakness of the wall as suggested by Dreesmann,²⁶ and agreed with Rostowzew³ that obstruction is caused by congenital or acquired kinking of the biliary tract. However, he also considered that inflammation and spasm of the sphincter of Oddi may cause temporary

obstruction. Zipf¹⁷ speculated that choledochal cyst results when congenital and acquired factors such as kinking, valve-like changes, spasm, and infection of the distal bile duct are added to inherent predisposing factors of dilatation of the bile duct.

Alonso-Lej²⁰ considered that weakness of the wall is congenital and that obstruction is more often congenital but can also be acquired. He further suggested uneven epithelial growth of the primordial common bile duct as the cause of congenital wall weakness and obstruction, a theory essentially the same as Yotsuyanagi's.

The etiologic theories advanced before Babbitt¹⁵ (1968) reported an etiologic relationship between choledochal cyst and anomalous junction of the pancreaticobiliary ductal system were reviewed above. However, most of these theories lacked embryological, anatomical, or physiological evidence and were no more than speculations. As a result, a single author often presented two or more theories, and the intention of the reports were sometimes difficult to understand. Of the 4 categories of the etiological theories, the congenital anomaly theories, particularly Yotsuyanagi's theory and dual theories appear to be feasible and logical.

Since Yotsuyanagi's theory is based on detailed organogenic observations of the biliary system and provides logical explanation of the etiological process of this disease, it is still supported widely by investigators today. Ascribing the etiologic root of choledochal cyst to uneven epithelial development of the primordial common bile duct, this theory may also be valid in accounting for the etiology of not only Alonso-Lej type I but also diverticular (type II) choledochal cyst as well as biliary atresia. Although the origin of the intrahepatic bile duct is different from that of the primordial common bile duct, cystic dilatation of the intrahepatic bile duct may also be explained similarly by epithelial dysplasia. However, questions remain in this theory concerning the assumptions that epithelial growth is always excessive in the hepatic side of the common bile duct and insufficient on the duodenal side and that excess and insufficient epithelial growth occurs simultaneously in continuous sites. It appears more likely that excess and insufficient epithelial growth occurs separately at different sites. Yotsuyanagi also documented instances of anomalies of the pancreatic duct such as abnormal length of the ductus pancreatico-biliosus (considered to be anomalous junction). Moreover, he made an interesting suggestion that these anomalies are related to epithelial dysplasia of the distal biliary tract.

Dual theories also appear to be well-founded. Many investigators ascribed weakness of the biliary wall to congenital predisposition and bile ductal obstruction to congenital or acquired factors. Kato⁵⁶ (1972) experimentally demonstrated the validity of the dual theory. He succeeded in producing cystic dilatation of the common bile duct in young dogs by transpapillary curettage of the middle portion of the common bile duct followed by its ligation at the papillary region after 3 days but observed no cystic dilatation after curettage or ligation of the bile duct alone. He considered that

wall weakness of the bile duct is a result of degeneration of submucosal elastic fibers. The weakness of the wall was first related to elastic fibers by Dreesmann²⁶ (1908). However, Kasai⁵⁵ indicated from detailed examination of human neonatal and fetal bile ducts that the appearance of elastic fibers tends to be delayed in the middle to distal portion of the common bile duct as compared with the hepatic duct, gall bladder, and cystic duct, and considered that cystic dilatation may occur primarily in the middle portion of the common bile duct if such a delay is accompanied by distal bile ductal obstruction. Ikeda *et al.* (1983), who also examined the bile duct in fetuses and infants, reported that there are no demonstrable elastic fibers in the bile duct until about 1 years after birth and suggested that cystic dilatation may develop if biliary obstruction occurs during this period. In fact, successful production of cystic dilatation in the common bile duct or in the extrahepatic portion of the bile duct was reported by Spitz⁵⁸ (1977) after ligation of the common bile duct in neonatal sheep and by Miyano *et al.*⁵⁹ (1978) and Nakashima⁶⁰ after ligation and transection of the common bile duct in young rats. Moreover, in all these studies, the procedures resulted in mild and diffuse dilatation of the entire biliary system in mature animals, suggesting that the immature bile duct with weaknesses in mural construction such as the lack of elastic fibers readily develops cystic dilatation in the presence of increased intraluminal pressure.

Unusual course, kinking, and valve-like changes in the distal bile duct are frequently referred to in obstruction theories and dual theories as possible causes of bile ductal obstruction, but they are considered to be direct consequences of anomalous junction or secondary changes due to biliary dilatation. Bile ductal obstruction, which is often regarded as a result of inflammation or dysfunction of the distal bile duct, may also be derived from the pathophysiology of anomalous junction of the pancreaticobiliary ductal system.

Etiological relationship between choledochal cyst and anomalous junction (mainly after Babbitt's report)

Since the report of Heid² (1893), simultaneous presence of choledochal cyst and anomalous junction of the pancreaticobiliary ductal system has been demonstrated by Rostowzew³ (1912), Arnolds⁴ (1906), Schloessmann⁵ (1916), Mayesima⁶ (1912), Kuru⁷ (1913), Kozumi *et al.*⁸ (1916), Budde⁶ (1920), Sato¹⁰ (1920), Fukuda¹¹ (1922), Fukamachi,¹² Feyrter¹³ (1929), Yotsuyanagi¹⁴ (1936), Taybi⁶¹ (1967) and Babbitt¹⁵ (1968) by autopsy and cholangiography. However, only 5 authors, namely Kuru,⁷ Kozumi *et al.*,⁸ Yotsuyanagi¹⁴ and Babbitt,¹⁵ appear to have noted some etiological relationship between the two conditions. On the basis of the autopsy findings that bile ductal obstruction such as kinking and stenosis, which were considered to be important

etiologic factors in choledochal cyst at that time, was absent near the duodenal opening of the common bile duct, but that pancreas accessorium was attached to the bile duct showing cystic dilatation, Kuru⁷ suggested that drainage of the accessory pancreatic duct (considered to be a conduit originating from the pancreas accessorium) into the common bile duct may have etiological significance. Unfortunately, he failed to demonstrate the communication between the accessory pancreatic duct and the common bile duct. Kozumi *et al.*⁸ considered that chance occurrence of uncommon choledochal cyst with equally uncommon anomalies of the bile duct and pancreatic duct (considered to be anomalous junction of the two ducts) is unlikely, and speculated that bile stasis due to kinking of the common bile duct associated with physiological rotation of the stomach and the duodenum during the embryonic development is the primary cause of cystic dilatation of the bile duct. They also suggested that this kinking of the common bile duct is more likely in the presence of anomalous junction of the pancreaticobiliary system. According to Yotsuyanagi,¹⁴ abnormal length of the ductus pancreaticobilius (considered to be anomalous junction) is caused either by secondary factors associated with the advancement of bile duct dilatations or congenital anomalies, and the etiological process based on congenital anomalies can be explained by his own theory. That is, uneven epithelial development in the biliary system results in formation of stenosis in a distal portion of the primordial common bile duct. This prevents normal anastomosis between the pancreatic duct from the ventral pancreas and the common bile duct at this site, resulting in anomalous junction of the two ductal systems. Thus, Kozumi *et al.*⁸ and Yotsuyanagi¹⁴ attempted to explain the etiological relationship between anomalous junction choledochal cyst on the basis of abnormal organogenesis of the pancreaticobiliary system.

By contrast, Babbitt¹⁵ assumed the inherent presence of anomalous junction due to pancreaticobiliary dysplasia and speculated that influx of pancreatic juice into the bile duct in the presence of this anomaly induces cholangitis, which, together with increased secretion pressure of pancreatic juice, leads to dilatation of the common bile duct. He regarded the high amylase activity in the content of the bile duct as an important ground of this theory. He further suggested that if dilatation of the bile duct advances, obstruction develops in the distal bile duct due to edema, valve-like changes, or fibrosis, and resultant bile stasis aggravates dilatation of the bile duct.

As Babbitt's theory was introduced to Japan by Komi⁶² (1975), it aroused interest in anomalous junction of the pancreaticobiliary ductal system associated with choledochal cyst, and with rapid improvements in imaging techniques such as PTC and ERCP, anomalous junctions were studied widely. As these studies showed that choledochal cyst is frequently complicated by anomalous junction of the pancreaticobiliary ductal system and often demonstrated high amylase levels in the contents of the bile duct, Babbitt's theory appeared to have gained wide acceptance. However, with further ad-

vancements of studies, instances of choledochal cyst unaccompanied by anomalous junction⁶³⁻⁶⁶ and anomalous junction with no or only slight bile duct dilatation were reported, raising questions about the causative relationship between choledochal cyst and anomalous junction and urging reevaluation of Babbitt's theory.

Among experimental studies, models of anomalous junction of the pancreatobiliary ductal system were produced by investigators such as Ikeda^{67,68} (1977), Kato⁶⁹ (1980), Okawa *et al.*,⁷⁰ Miyano *et al.*⁷¹ (1981), Tsuge⁷² (1984) and Oguchi⁷³ (1986) for pathological and biochemical evaluations. Ikeda *et al.*^{67,68} lead pancreatic juice into the biliary tract by pancreatobiliary shunt operation using a catheter in young dogs and confirmed histological changes primarily of disruption of the mucosa, cell infiltration, and fibrosis in the wall of the biliary tract resembling those observed in clinical cases. However, dilatation of the biliary tract was reportedly mild.

Kato⁶⁹ performed pancreaticholecystostomy in adult dogs and observed injuries in the wall of the biliary tract nearly identical to those described by Ikeda *et al.* Of these changes, however, Kato particularly noted damages of elastic fibers. Cystic dilatation as well as spindle-shaped dilatation was observed grossly. Okawa *et al.*⁷⁰ observed similar histological changes in the wall of the biliary tract in adult as well as young dogs after pancreaticholedochostomy and reported epithelial proliferation after a long-term follow-up of one year. Bile duct dilatation was columnar with no differences in its morphology between adult and young dogs, but cystic dilatation was noted exceptionally in one adult dog. Okawa *et al.*⁷⁰ also examined the mechanism of activation of pancreatic enzymes that entered the biliary tract in the presence of anomalous junction. Miyano *et al.*⁷¹ performed choledochopancreaticostomy in young dogs, and reported the above-mentioned histological changes after a short follow-up and epithelial proliferation after a long follow-up. In this model, however, biliary dilatation was no more than spindle-shaped. Tsuge⁷² carried out a repeat study of pancreaticholedochostomy of Okawa *et al.*⁷⁰ in young dogs and obtained similar results. Oguchi⁷³ performed pancreaticholecystostomy in adult dogs as did Kato⁶⁹ and reported the histological findings of enlargement of the glandular lumen with inflammatory cell infiltration and a gross finding of columnar dilatation of the bile duct.

To summarize the above observations, when pancreatic juice is led to the biliary tract, columnar or spindle-shaped dilatation develops within weeks to months, but it does not progress further, rarely assuming a cystic morphology. Histologically, early injury of the epithelium and elastic fibers of the bile duct are remarkable, but hyperplastic and metaplastic changes develop gradually in the epithelium with no progression of the damage in submucosal tissues.

Dilatations of the common bile duct produced in pancreaticholedochostomy or choledochopancreaticostomy, which are more analogous to clinical pancreatobiliary anomalies and those induced by simple perfusion of pancreatic juice in the common

bile duct were both mild and showed no differences. This indicates that the primary causes of bile duct dilatation are irritants such as pancreatic enzymes acting on the wall of the biliary tract and hydrodynamics of the influx of pancreatic juice. Miyano *et al.*⁷¹ morphologically classified clinical bile duct dilatations into two types, namely type I with cystic appearance and type II with spindle-shaped appearance, and suggested from experimental observations that the etiology of type II dilatation can be explained by influx of pancreatic juice. Oguchi⁷³ histologically classified clinical bile duct dilatations into the glandular lumen-forming type and fibrosis type, and reported that the former type is observed in only columnar dilatation while the latter is observed in both columnar and cystic dilatations. However, because of the experimental finding that only columnar dilatation with glandular proliferation could be induced, he considered that influx of pancreatic juice into the bile duct due to anomalous pancreaticobiliary junction is involved in the development of the glandular lumen-forming type dilatation. These experimental findings indicate that influx of pancreatic juice into the biliary tract alone causes columnar or spindle-shaped dilatation but not cystic dilatation of the bile duct, but left the etiology of cystic dilatation associated with anomalous junction of the pancreaticobiliary ductal system yet to be clarified.

As mentioned earlier, Kato⁵⁶ (1972) performed epithelial ablation of the middle portion and ligation of the lower portion of the common bile duct and showed formation of cystic dilatation at the site of epithelial ablation. Furthermore, Spitz⁵⁸ (1977), Miyano *et al.*⁵⁹ (1978) and Nakashima⁶⁰ (1986) produced cystic dilatation by ligation of the bile duct in neonatal sheep and young rats. These findings suggest that cystic dilatation develops readily if intrabiliary pressure increases during the period when the construction of the bile duct wall is still immature. This observation, indicating that the presence of accidental bile ductal obstruction occurring while the bile duct wall is immature can alone induce cystic dilatation of the bile duct, is convenient to explain the etiology of choledochal cyst unaccompanied by anomalous pancreaticobiliary junction. Although Spitz⁵⁸ did not refer to the relationship between his experimental results and anomalous pancreaticobiliary junction, Miyano *et al.*⁷¹ considered that congenital stenosis of the distal bile duct immediately above the pancreaticobiliary junction is primarily responsible for cystic dilatation (Miyano's type I) and that the influx of pancreatic juice has only minor effects. Nakashima^{60,74} also considered that the development of cystic dilatation of the bile duct at the sites of congenital and acquired abnormalities is triggered by stenosis of the distal bile duct primarily due to anomalous junction, but that cause of columnar and spindle-shaped dilatation can be explained by influx of pancreatic juice into the bile duct due to anomalous junction.

Ando⁷⁸ (1983) studied the relationship of the width and length of the stenotic portion in the distal bile duct with the maximum transverse diameter of the bile duct in cholangiographic images obtained in 44 children with choledochal cyst. The maxi-

mum transverse diameter of the bile duct correlated with the length, but not the width, of the stenotic portion in the distal bile duct. He also confirmed these clinical observations experimentally. From these findings, Ando considered that dilatation of the common bile duct is caused by increased resistance to the bile flow due to stenosis rather than by weakness of the wall of the bile duct exposed to pancreatic juice. Referring also to the cause of stenosis associated with anomalous pancreaticobiliary junction, he suggested that, because no abnormalities are observed in the dorsal pancreatic duct in patients with choledochal cyst,⁵⁴ some abnormality causing anomalous junction occurs before the 6th week of the embryonic development, when the ventral pancreas rotates to merge with the dorsal pancreas, and disturb recanalization of the common bile duct, which begins in the 6th week of the embryonic development, resulting in stenosis in the distal bile duct.

Citing the results of the above studies using anomalous junction models and bile duct ligation models, and supporting the view of Oi *et al.*⁶⁴ (1977) that abnormal organogenesis of the ventral pancreas and associated dysplasia of the distal common bile duct give rise to anomalous pancreaticobiliary junction and stenosis of the distal common bile duct, Nakanishi *et al.*⁷⁶ (1983) suggested that the degree of stenosis of the distal bile duct associated with anomalous junction determines the morphology of the biliary dilatation. If the anomaly is Kimura's type II, in which the common bile duct joins the pancreatic duct, stenosis is severe and the stasis is sufficient to induce cystic dilatation, but if type I, in which the pancreatic duct joins the common bile duct, stenosis is mild and biliary dilatation is spindle-shaped at the maximum. They also referred to cholangitis and injury of intramural elastic fibers due to influx of pancreatic juice as possible causes of the weakness of the bile duct wall.

The morphology of dilatation of the common bile duct is considered to be dependent on the degree of stenosis of the distal bile duct and becomes cystic if the stenosis is severe but columnar if the stenosis is mild (Miyano *et al.*,⁷⁹ 1979). Moreover, the dilatation is more often cystic if the area of stenosis is long, but columnar if it is short (Ando,⁷⁶ 1983). On the basis of these observations, Todani *et al.*⁷⁸ (1984) suggested that the severity of stenosis of the distal bile duct are affected by secondary changes induced by influx of pancreatic juice into the bile duct.

As shown in the above review, the etiological relationship between anomalous pancreaticobiliary junction and choledochal cyst has been aggressively studied especially by Japanese investigators since the report of Babbitt. The findings established through these studies may be summarized as below.

- (1) Anomalous junction is a dysplasia occurring in the organogenic process of the pancreaticobiliary ductal system.
- (2) Choledochal cyst is accompanied by anomalous junction in nearly 100% of the case.

- (3) Since the pancreatic duct and common bile duct are anastomosed outside the duodenal wall beyond the range of the control of the sphincter of Oddi, pancreatic juice flows into the bile duct according to the pressure gradient.
- (4) Pancreatic juice in the bile duct damages the biliary epithelium and submucosal tissues, inducing weakness of the biliary wall.
- (5) Perfusion of pancreatic juice in the bile duct alone causes columnar or spindle-shaped bile duct dilatation, but not cystic dilatation.
- (6) Anomalous junction of the pancreaticobiliary ductal system is often associated with some form of stenosis in the distal bile duct.
- (7) Although stenosis of the distal bile duct is generally considered to be due to dysplasia, the possibility of its secondary induction by actions of pancreatic juice cannot be excluded.
- (8) Cystic dilatation results when bile ductal obstruction occurs while the biliary wall is still immature.
- (9) The severity of this obstruction determines the degree of the resulting bile duct dilatation.

Although no conclusion has been reached as for the etiological relationship between anomalous pancreaticobiliary junction and dilatation of the bile duct, a summary of the findings obtained to the present day may be useful. First, even when congenital biliary dilatation is present with anomalous junction, as suggested by Kozumi and Yotsuyanagi, the conditions of choledochal cyst are considered to be modified secondarily by stenosis of the distal bile duct or influx of pancreatic juice into the bile duct. Babbitt's view that choledochal cyst is caused secondarily by the influx of pancreatic juice into the biliary tract¹⁴ appeared to be reasonable and may account for mild dilatation such as the columnar type and spindle-shaped type, but it does not sufficiently explain the process of cystic dilatation. Miyano,^{69,71} Ando,⁷⁶ and Nakashima *et al.*^{60,74} considered stenosis of the distal bile duct associated with anomalous pancreaticobiliary junction to be primarily responsible for bile duct dilatation and suggested that elevation in the intrabiliary ductal pressure due to stenosis while the wall of the biliary tract is still immature causes bile duct dilatation. This theory conveniently explains the development of various morphological changes of the bile duct ranging from no dilatation to columnar or spindle-shaped dilatation and, eventually, cystic dilatation by combination of various degrees of stenosis and weakness of the bile duct wall. However, a role of pancreatic juice flowing into the biliary tract in this process cannot be excluded. As experiments indicated, stenosis of the distal bile duct is unlikely to be a result of inflammatory changes due to exposure to pancreatic juice; it is more reasonably regarded as based on congenital dysplasia associated with anomalous pancreaticobiliary junction.

Thus, bile duct dilatation may be a congenital condition due to dysplasia of the pancreaticobiliary system including anomalous junction or an acquired condition in-

duced by influx of pancreatic juice into the biliary tract or caused secondarily by stenosis of the distal bile duct. These three factors are considered to be involved in an inter-related manner rather than independently in dilatation of the bile duct.

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