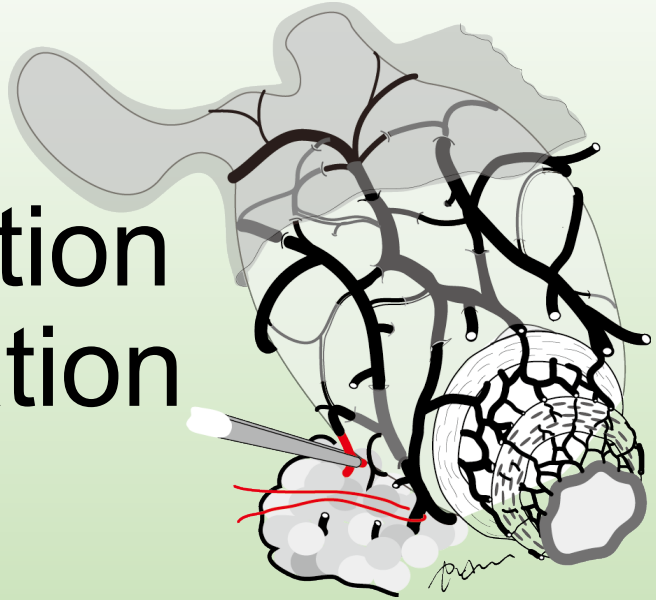
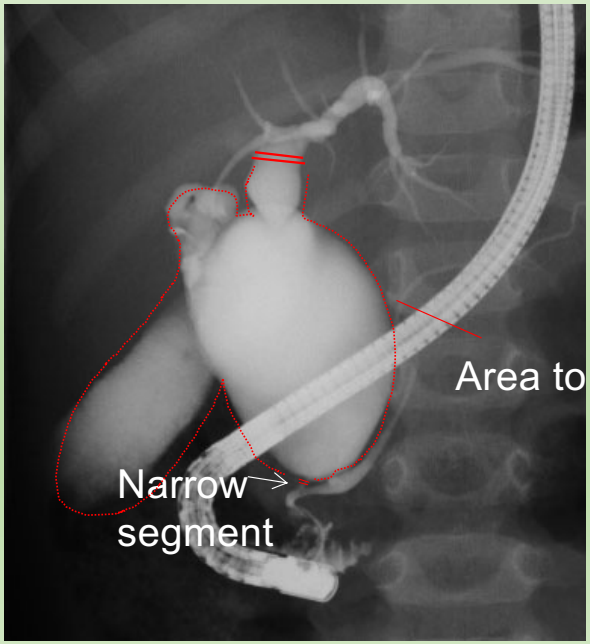
Atlas of Pancreaticobiliary Maljunction & Congenital Biliary Dilatation





Japanese Study Group on Pancreaticobiliary Maljunction (JSGPBM)
Scientific Committee

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Preface

Pancreaticobiliary maljunction (PBM) was discovered as a malformation accompanying choledochal cysts. In Japan, where choledochal cysts are common, the concept of PBM is widespread, but it seems unfamiliar in other countries where choledochal cysts are rare. However, the term “choledochal cyst” includes various entities of congenitally dilated bile ducts with or without PBM. Almost all choledochal cysts seen in Asia have localized dilatation of the bile duct and PBM, where PBM plays a major role in pathophysiology. In countries outside Asia, the frequency of choledochal cysts without PBM is relatively high, leading to confusion when discussing “ choledochal cysts”. We felt it necessary to differentiate this type with PBM from other types without PBM and defined the common type with PBM in Asia as “congenital biliary dilatation”.

PBM is also observed in patients without bile duct dilatation. Gallbladder cancers arise at an extraordinarily high frequency in these non-dilated PBM patients. However, the definition of non-dilatation has been unclear. We have developed ultrasonographic criteria for bile ducts of normal diameter, which we present here.

In this Atlas, we attempt to demonstrate clear and precise explanations of PBM and congenital biliary dilatation and hope this Atlas will help people unfamiliar to this field. The contents of the Atlas are free to use providing the source (JSGPBM Atlas of PBM & CBD) is cited.

September 2022
Editor-In-Chief, Kenitiro Kaneko

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Advanced

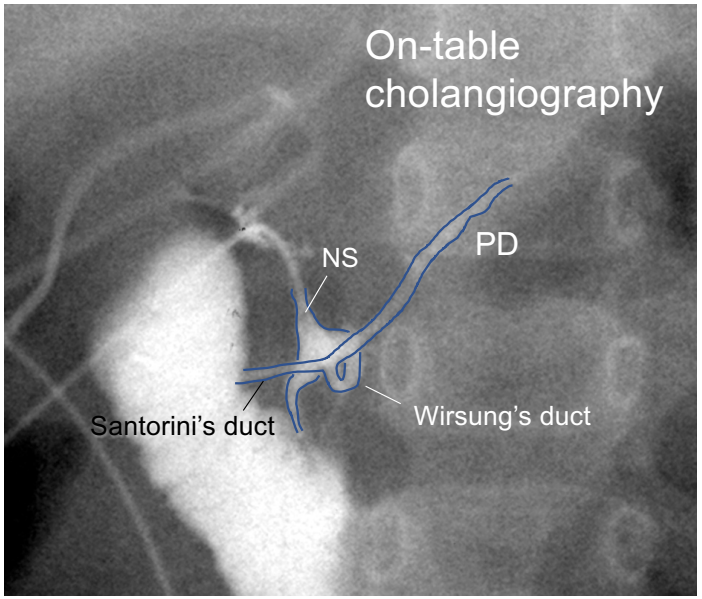
PBM seemingly complicated and rare type of PBM

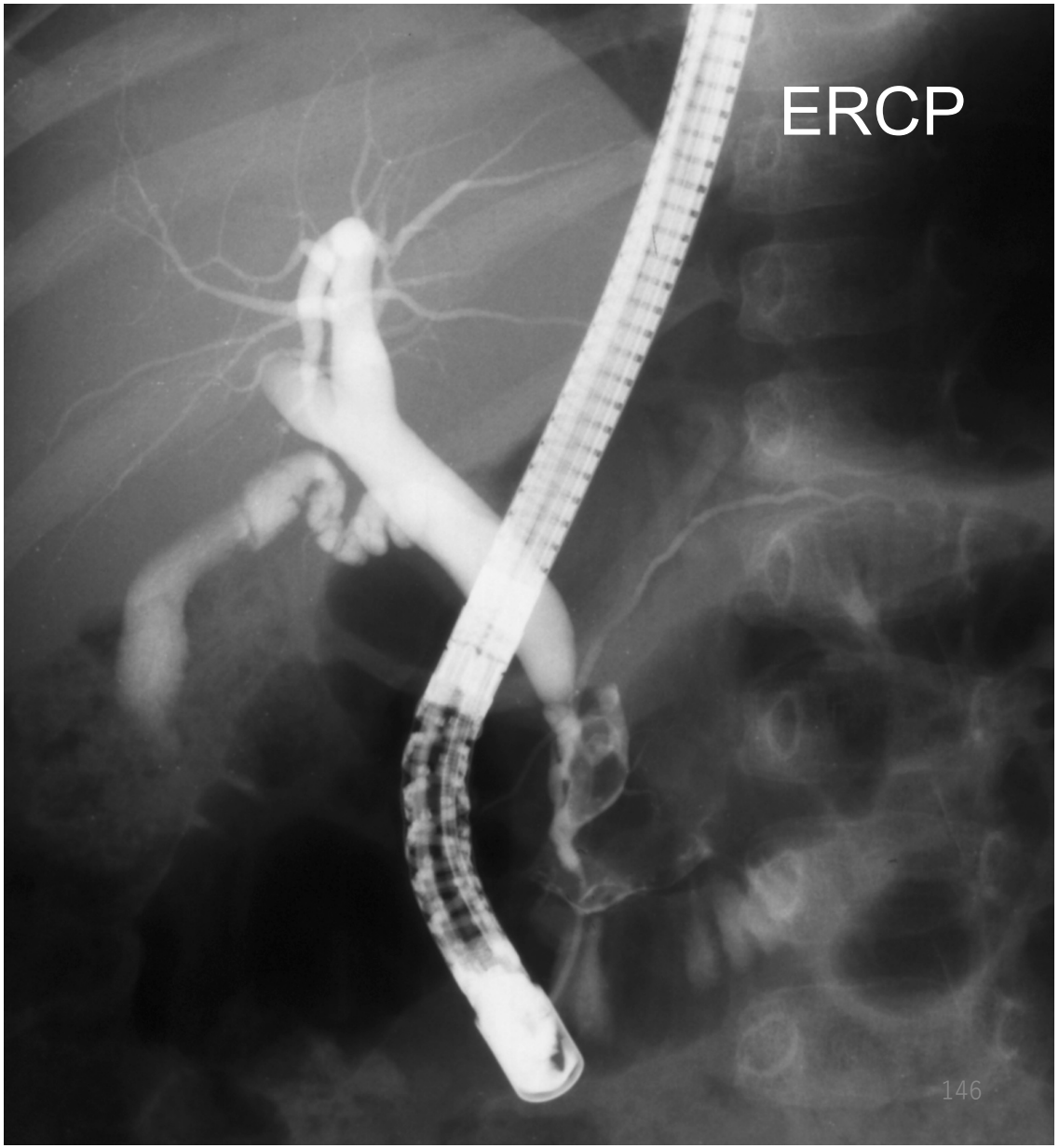
First version, September 2024

Case 44 Protein plugs complicate PBM

A 3-year old girl developed abdominal pain and vomiting, and jaundice after five days.
Protein plugs compacted in the common channel caused its dilatation, complicating the appearance of PBM.

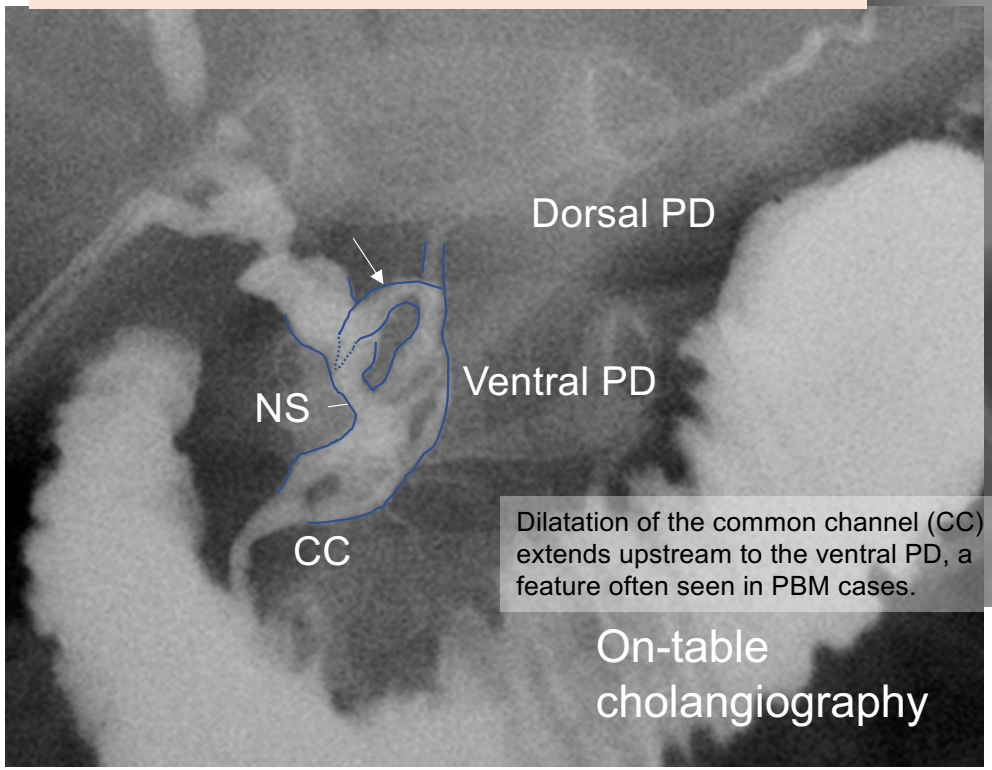
She underwent BD resection after her symptoms subsided.
On-table cholangiography showed the disappearance of the protein plugs, which disclosed the structure of PBM.
The dilatation of the common channel had completely disappeared.

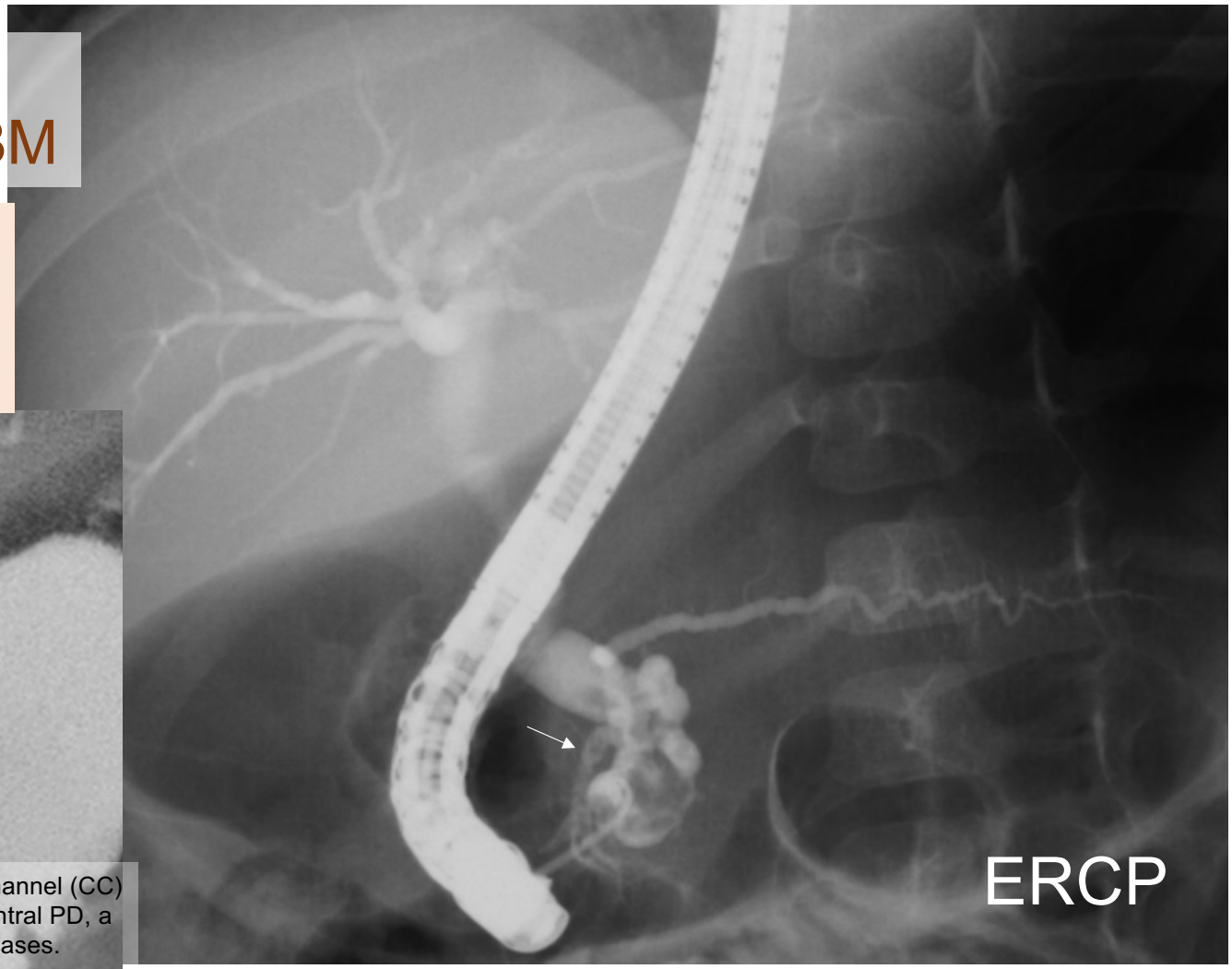




Case 45 Protein plugs complicate PBM

A 1-year-old girl developed acholic stool, abdominal pain, and jaundice with elevated serum levels of hepatobiliary enzymes .
Protein plugs compacted in the common channel complicated the appearance of PBM.
Most of the plugs had disappeared by the time of surgery.





Arrows indicate the same PD branch

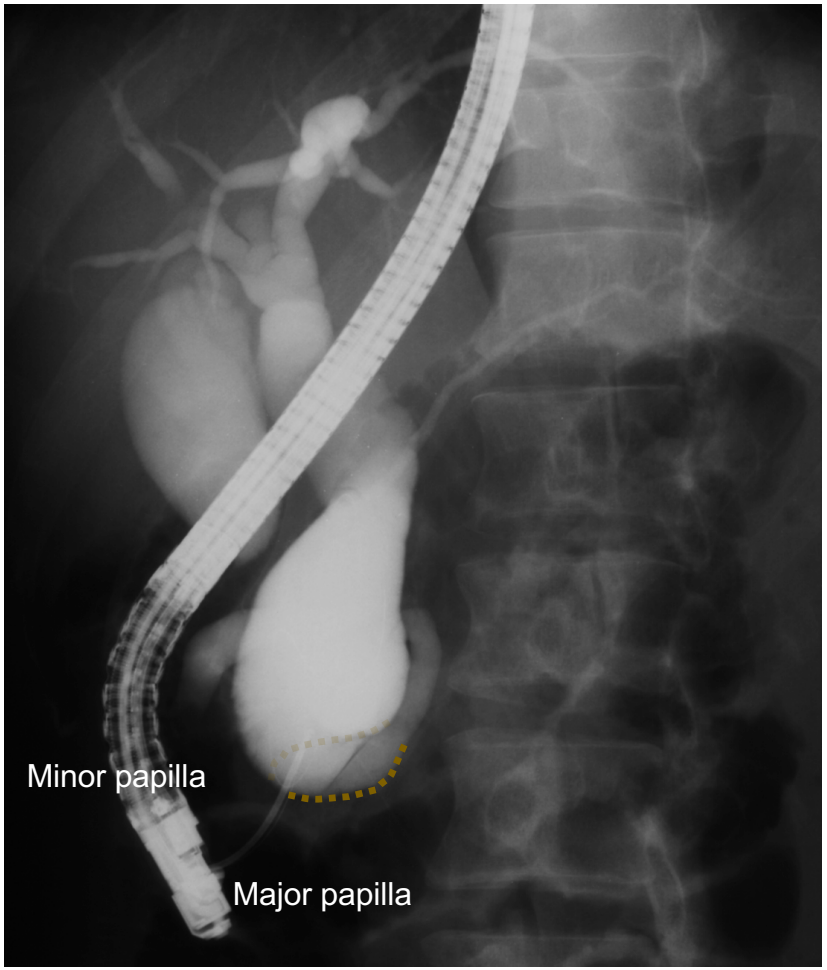
Case 46

Main (ventral) pancreatic duct forms the cyst bottom

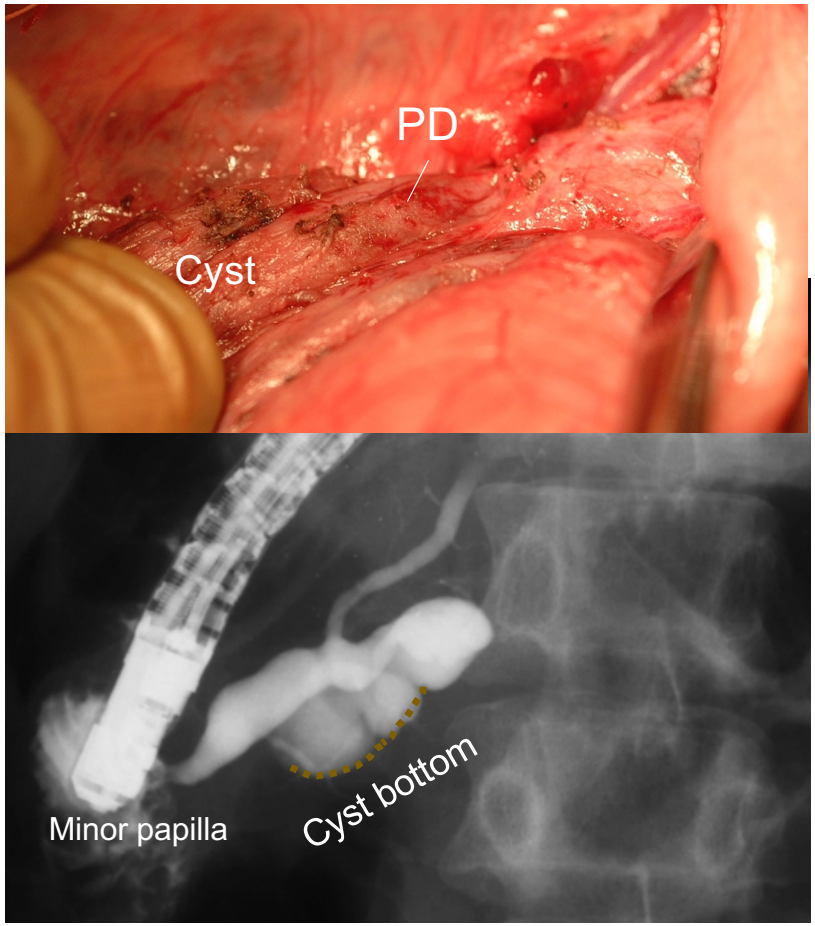
A female in her 20s developed abdominal pain with hyperamylasemia caused by protein plugs.

Because the narrow segment, which the cyst was expected to have, was not found during surgery, ERCP was performed to disclose the relationship with PD.

The guidewire through the main papilla was observed running along the bottom of the cyst.



Dotted line indicates where the cyst bottom was composed of the PD



Pancreatography through the minor papilla after cyst excision

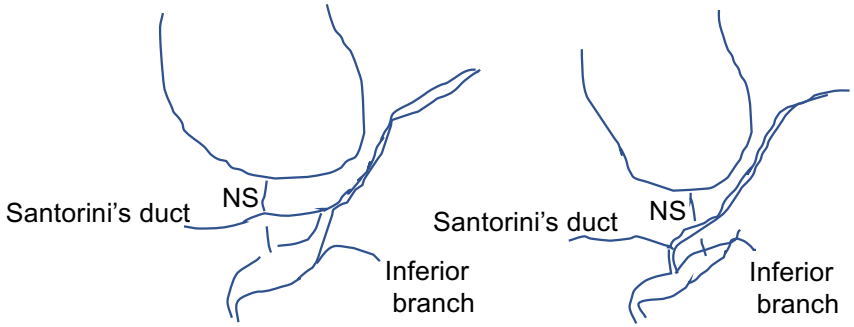
Case 47

Rare type
Bile duct joins the inferior branch of the PD

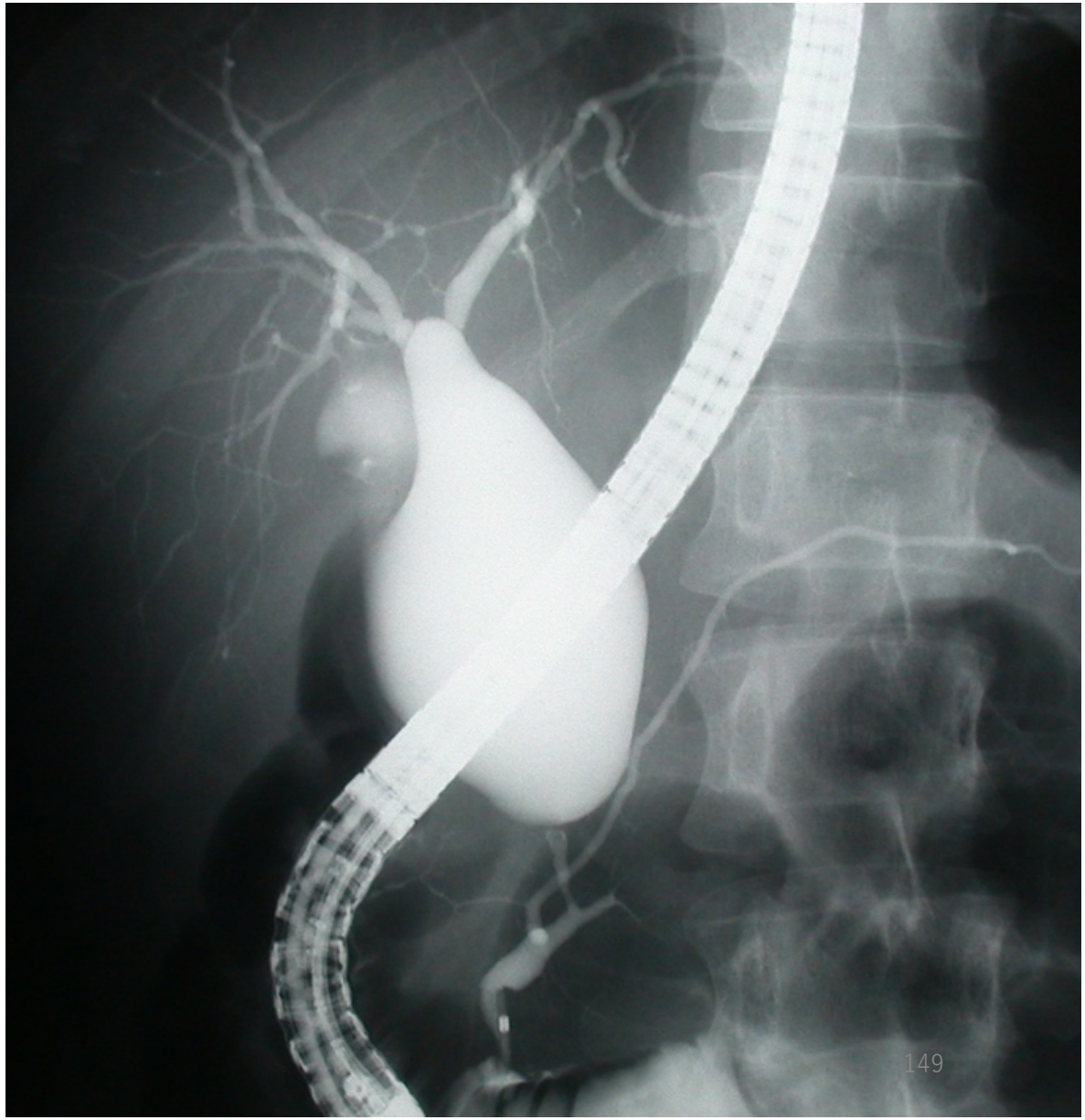
A male in his 20s.
Ultrasonography detected a dilated BD during a medical checkup.

Type Ia congenital biliary dilatation.

- **The BD joins the inferior branch of the PD**
  This case supports Matsumoto's theory that PBM is a malformation in which the choledochus misconnects with the ventral PD or its branches outside the duodenal wall (see p158).



Normal　　This case

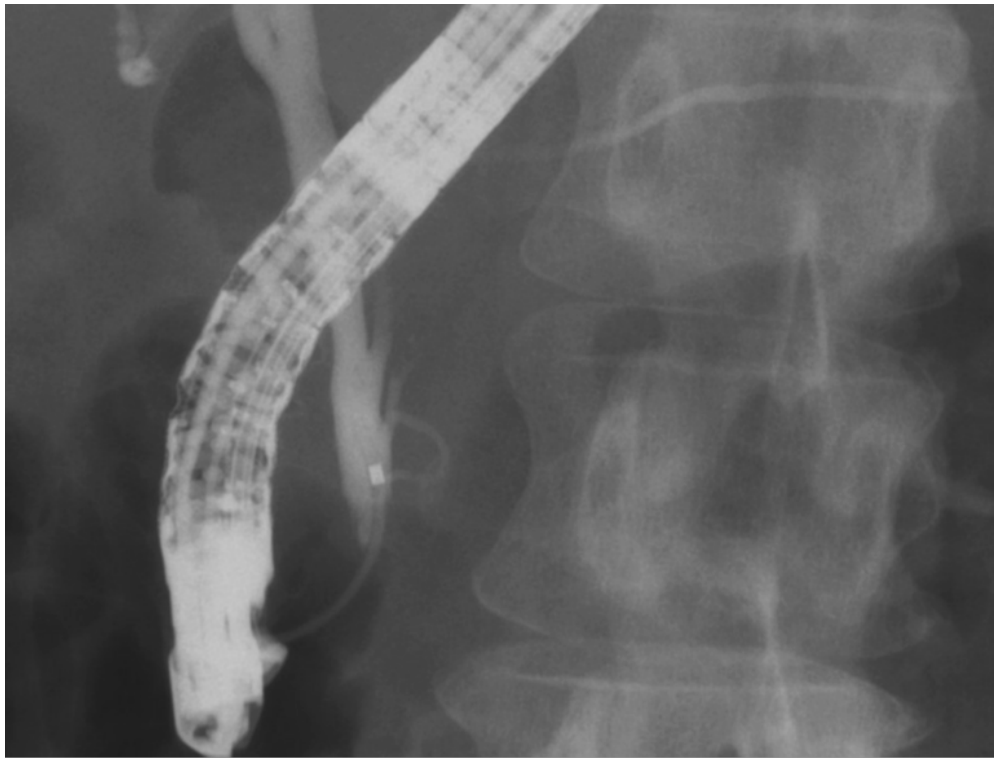


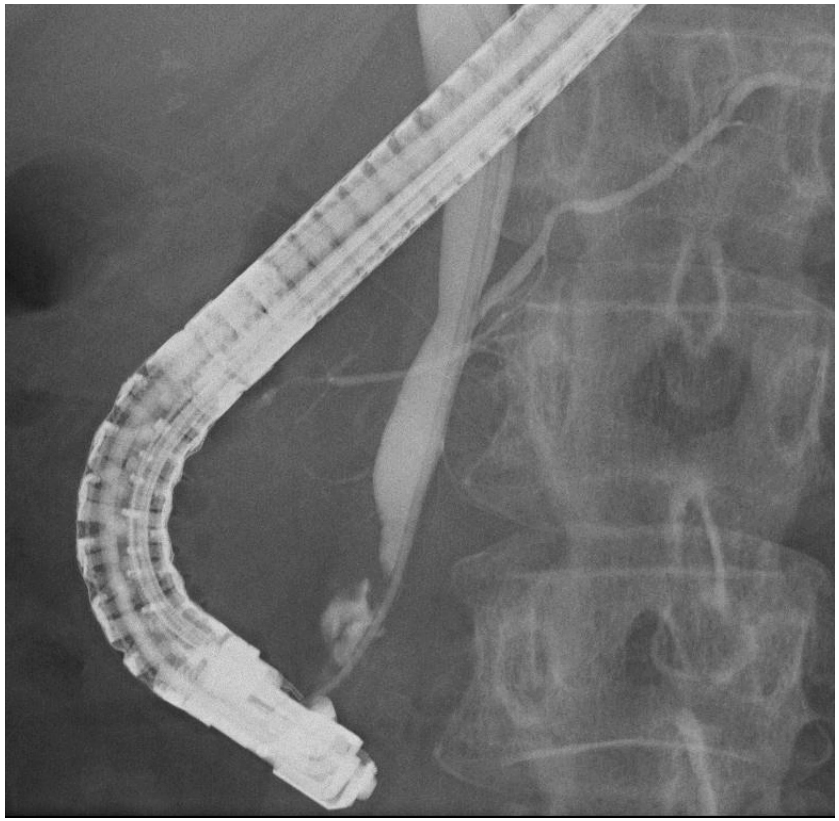
Advanced

Common channel and narrow segment

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Is the common channel a pancreatic duct or a bile duct?





PD branches arising from the common channel indicate that it is a pancreatic duct

Dilated common channel composed of both PD and BD

Proposed by Ando H, in 1999

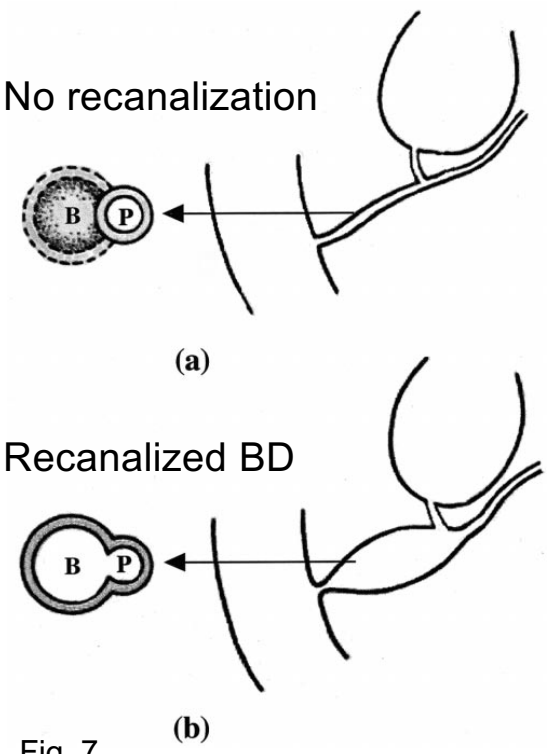
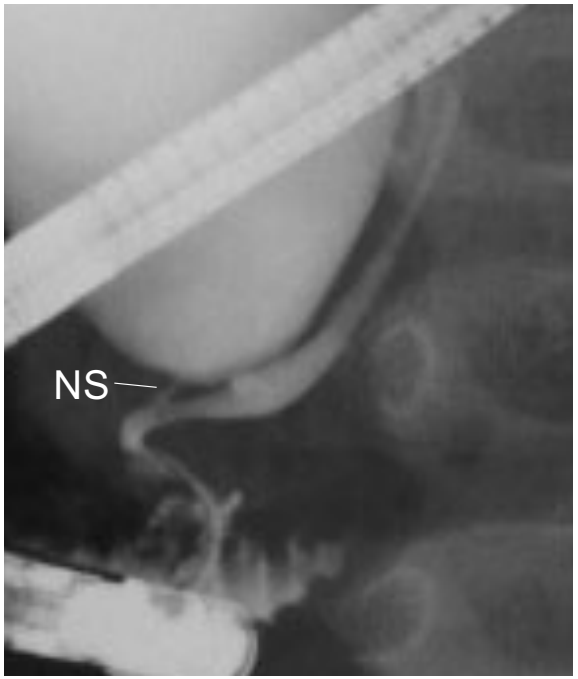
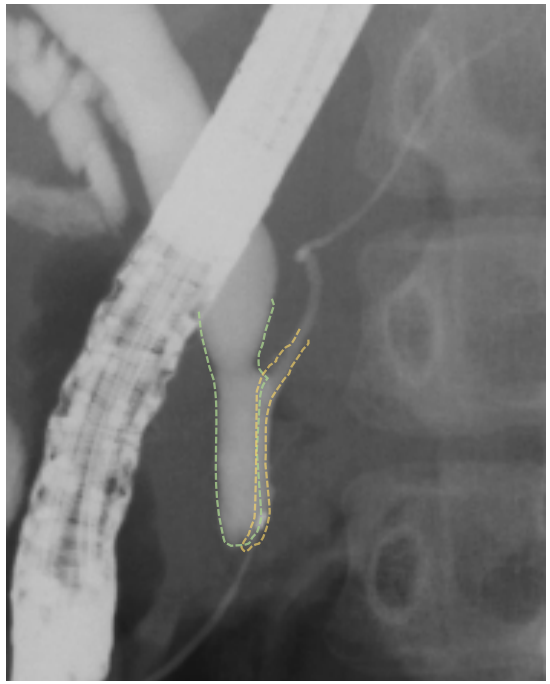


Fig. 7

Ando H, Kaneko K, Ito F, Seo T, Harada T, Watanabe Y.
Embryogenesis of pancreaticobiliary maljunction inferred from development of duodenal atresia.
J Hepatobiliary Pancreat Surg. 1999;6(1):50-54



PD alone



BD + PD

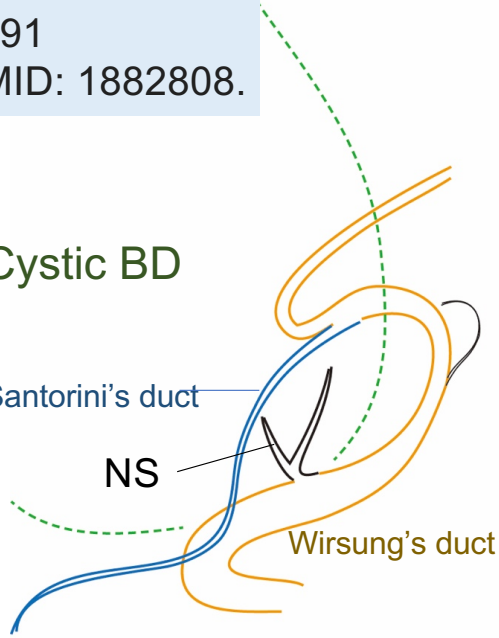
Case from *Basic Section* See p44.

NS is a branch of the PD

Histopathological demonstration

Suda K, Matsumoto Y, Miyano T. Narrow duct segment distal to choledochal cyst. *Am J Gastroenterol*. 1991 Sep;86(9):1259–63. PMID: 1882808.

Case 9



ERCP in a 1-year-old girl.
Vomiting and elevated pancreatic enzymes.

NS is one branch of the PD

Radiological demonstration

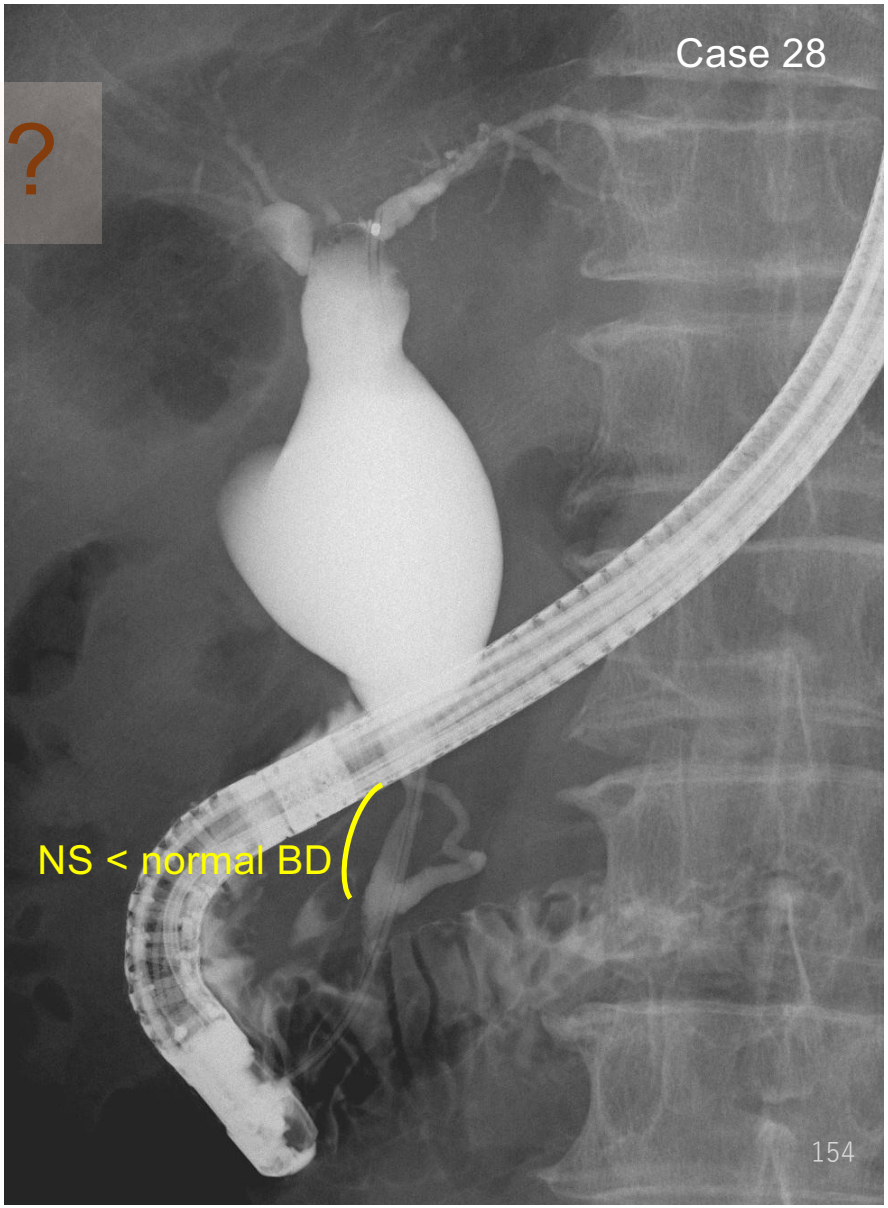


Matsumoto's theory of PBM embryogenesis:
PBM results from the BD misconnecting with the ventral PD or its branches (see p158).

Is NS really a PD branch?

In some cases of type Ic fusiform dilatation, the narrowed portion beneath the dilated BD may be considered a normal BD rather than a narrow segment (NS).
There is no abrupt narrowing in these cases.

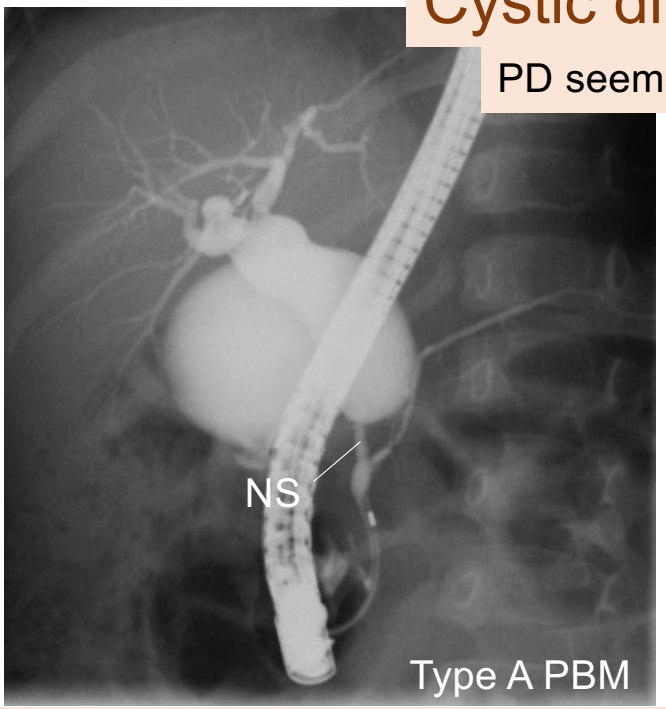
- JSGPBM classification (see p33): **Type B (non-stenotic type)** rather than Type A (stenotic type)
- The BD should be resected completely down to the PD using fluoroscopy with clips (see next page and p73).



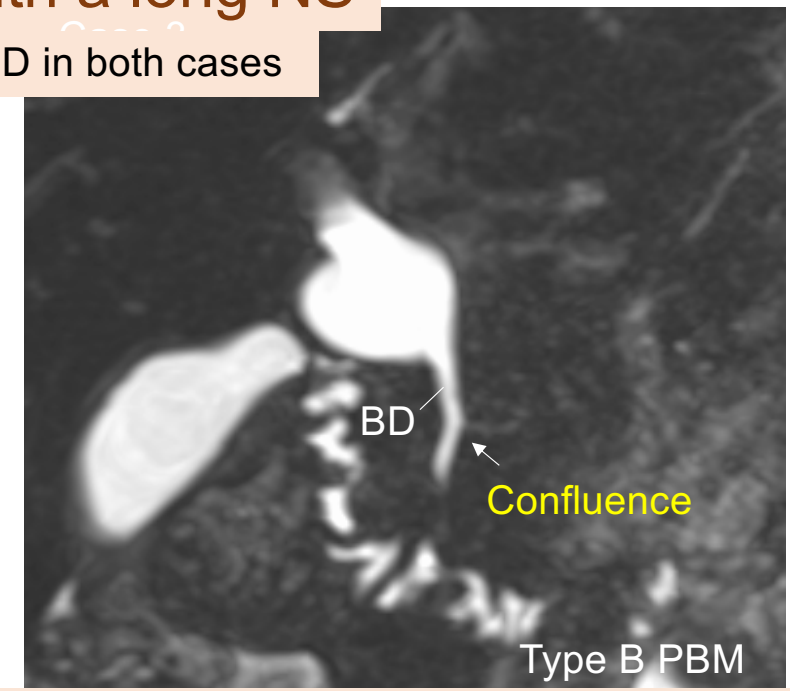
Is NS really a PD branch?

Cystic dilatation with a long NS

PD seems to enter the BD in both cases

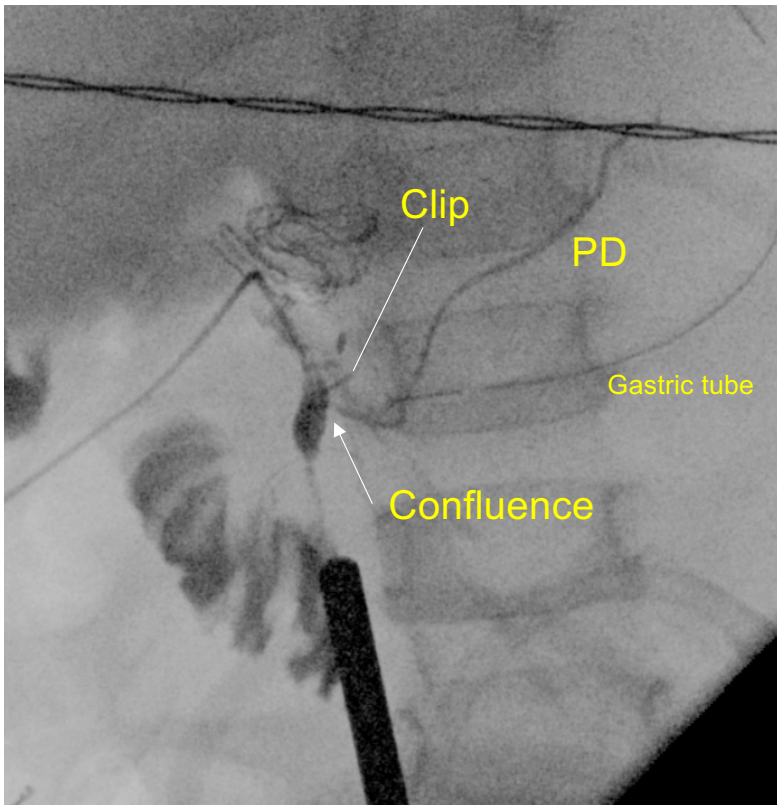


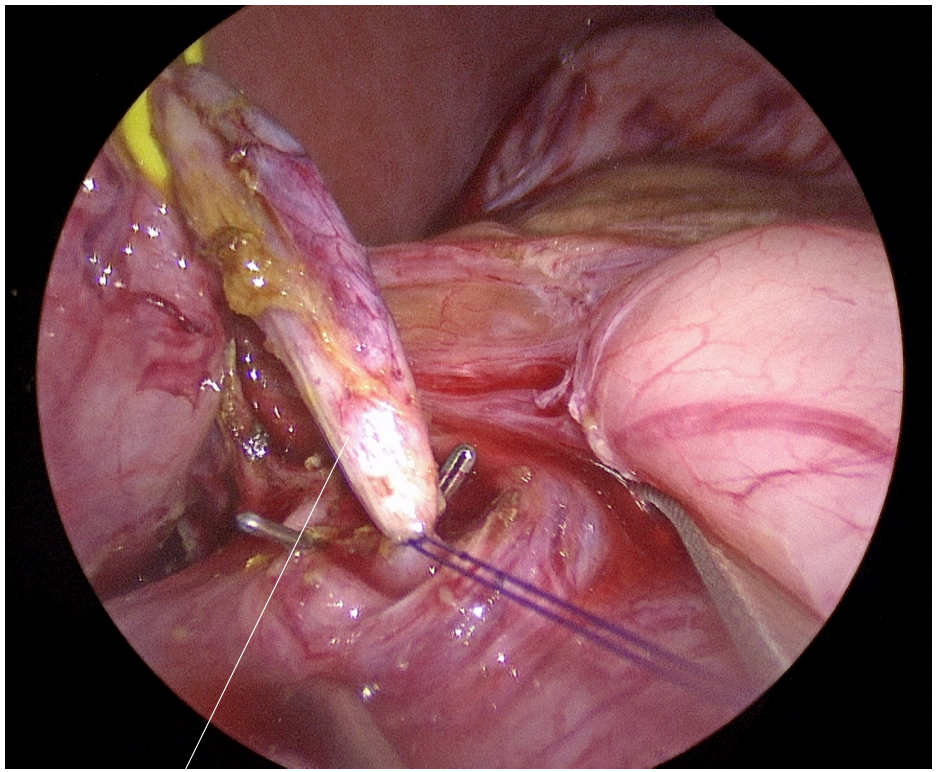
A 1-year-old child.
Vomiting, with elevated serum liver enzymes and amylase.
The BD was resected at the obvious NS.



A 3-year-old girl.
Abdominal pain, vomiting, and elevated serum liver and biliary enzymes.
No abrupt narrowing was identified, requiring dissection down to the PD using fluoroscopy with clips (see next page).

Surgery confirmed the absence of a true NS.
The BD was resected just above the PD using fluoroscopy with clips.

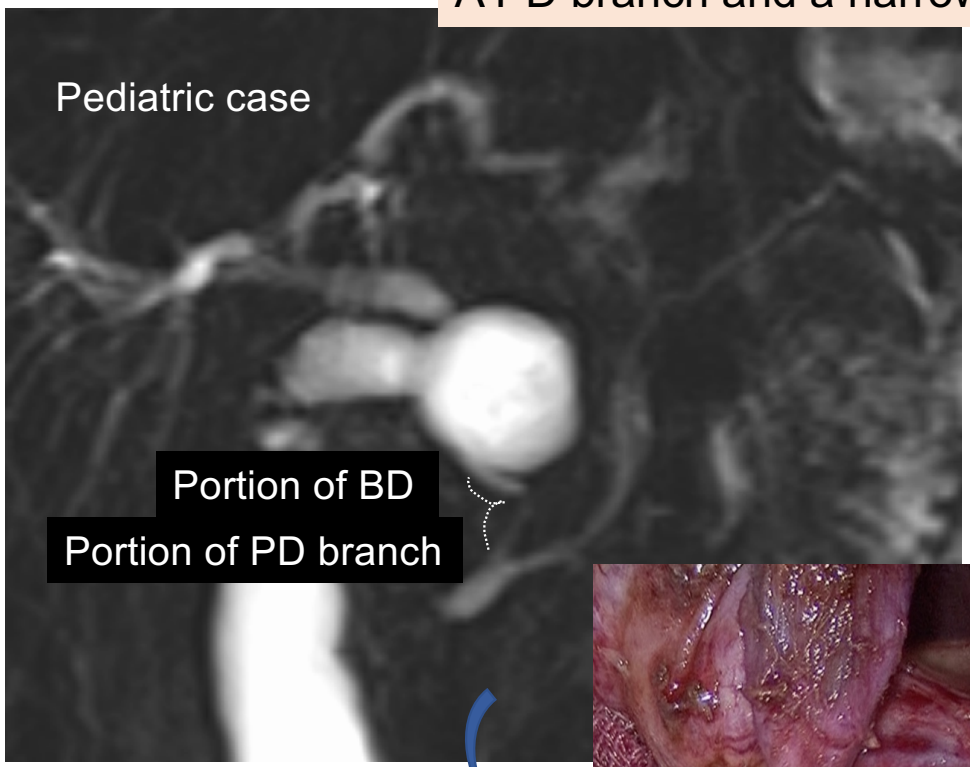


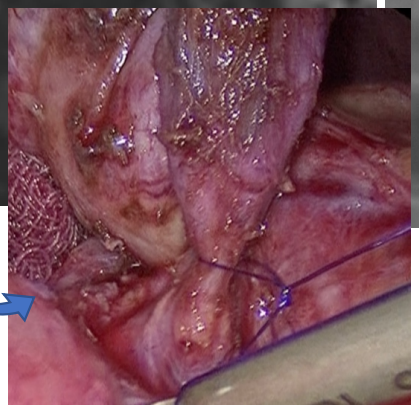


The narrowing portion on MRCP was actually a normal BD.

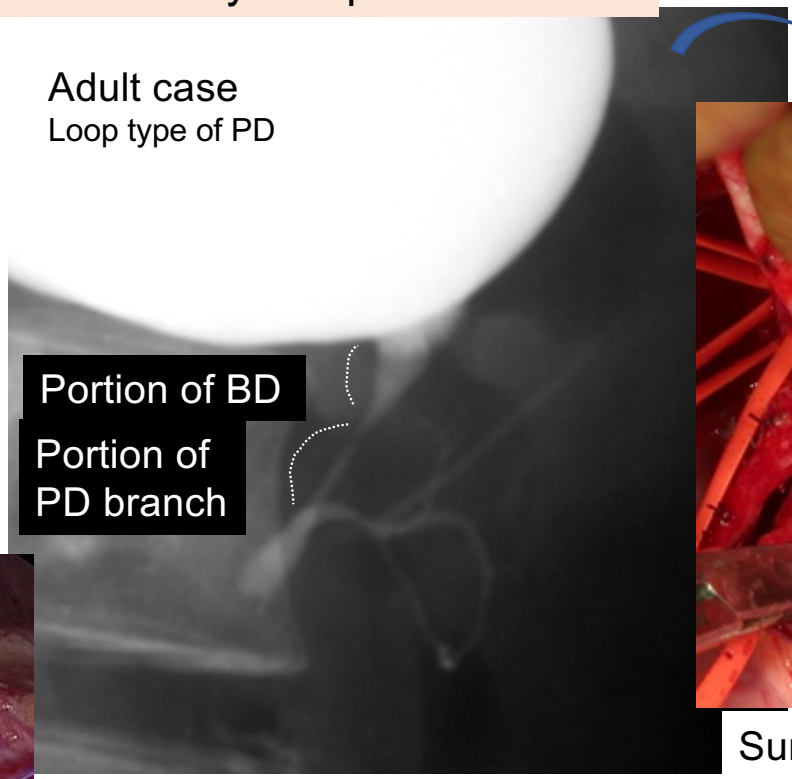
Is NS really a PD branch?

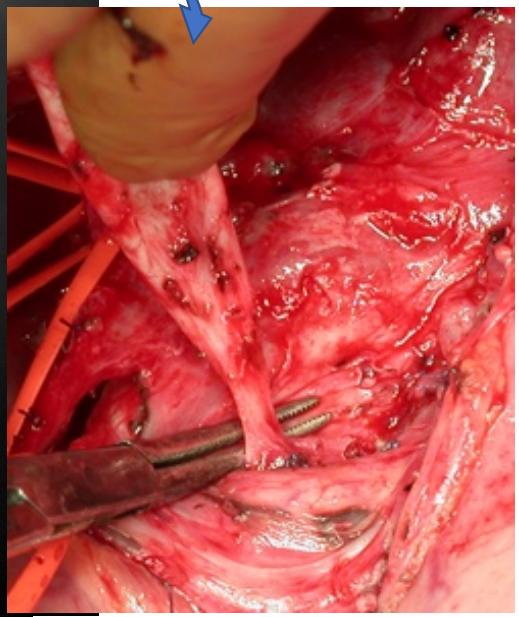
A PD branch and a narrowed BD may compose the NS





Surgery-confirmed NS

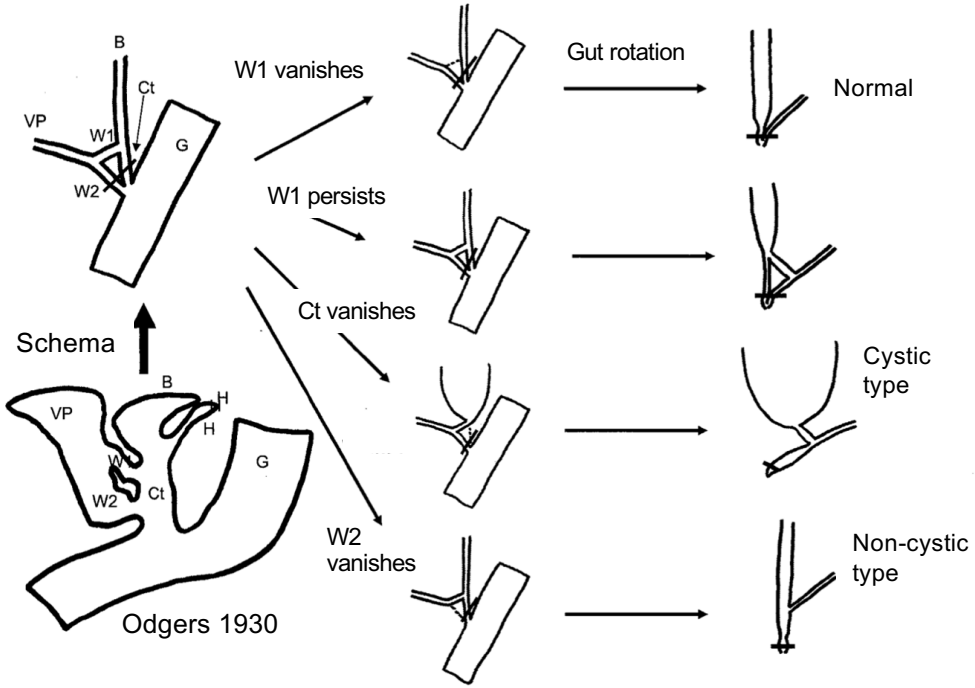




Surgery-confirmed NS

Matsumoto's theory of PBM embryogenesis:
PBM is a malformation in which the choledochus misconnects with the ventral PD or its branches outside the duodenal wall (see next page).

PBM embryogenesis



Cited from Itaru Oi. *Tokyo Women's Medical University Journal* 2008;78:55-60.

Oi's theory of PBM embryogenesis in 1977

Estimation based on Odgers's embryogenesis of PD (1930)

W1, Left ventral pancreas duct; W2, right VP duct; Ct, terminal choledochus

Two classic theories

Confluence site of the BD and ventral PD in congenital biliary dilatation



Cited from Yoshiro Matsumoto. *Nippon Shokakibyo Gakkai Zasshi* 1986;19:614-23.

Matsumoto's theory of PBM embryogenesis in 1986

Based on the fact that the BD never enters the dorsal PD in PBM

He proposed that PD branches arising from the common channel (CC) on cholangiopancreatography (see p151) indicated that the CC was functionally a pancreatic duct. He estimated that PBM is a malformation in which the choledochus misconnects with the ventral PD or its branches outside the duodenal wall.

See Cases 9* and 47**.

PBM embryogenesis

Ando H, Kaneko K, Ito F, Seo T, Harada T, Watanabe Y. Embryogenesis of pancreaticobiliary maljunction inferred from development of duodenal atresia. *J Hepatobiliary Pancreat Surg.* 1999;6(1):50-4*

Congenital duodenal atresia and stenosis

Disorder of recanalization from the solid stage

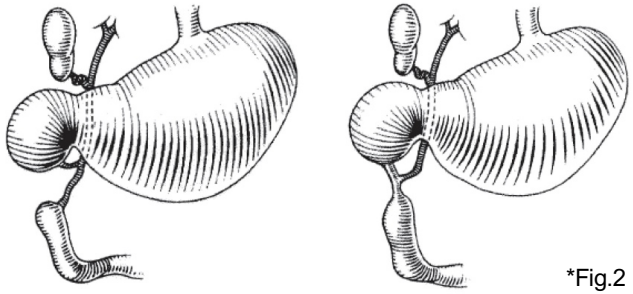
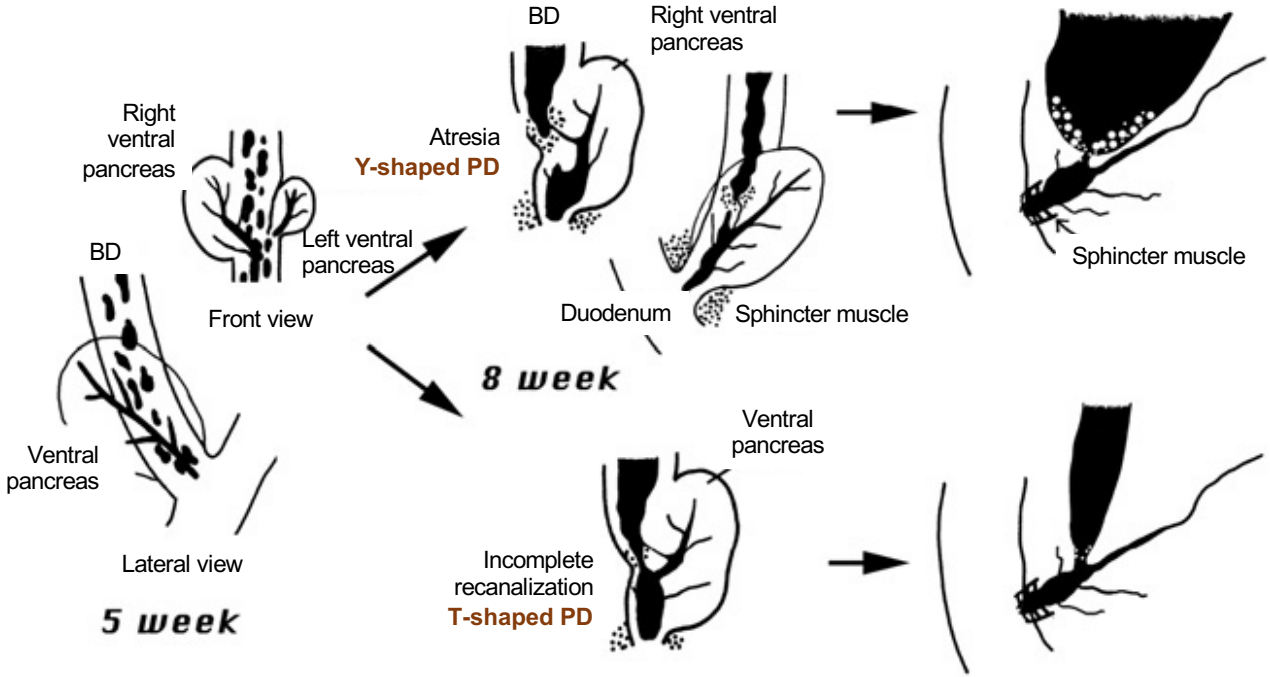


*Fig.2

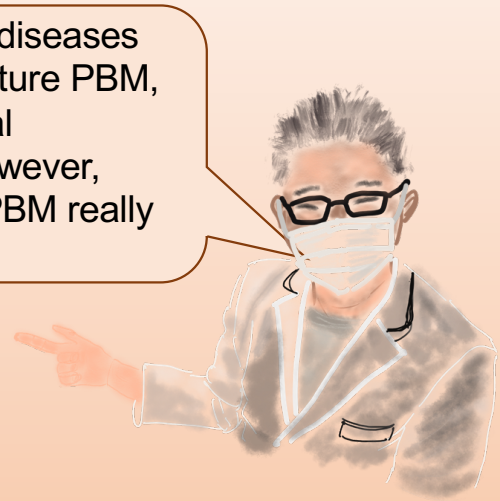
Atresia
Y-shaped BD

Stenosis
T-shaped BD



Cited from Hisami Ando. *Tando (Biliary Tract)*. 2008;22175–80.

Inferred from the embryogenesis of congenital duodenal atresia and stenosis, the BD passes through a solid stage during its development, similar to the duodenum, whereas the PD does not experience a solid stage.



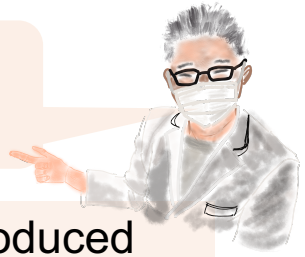
Advanced

What causes biliary dilatation?

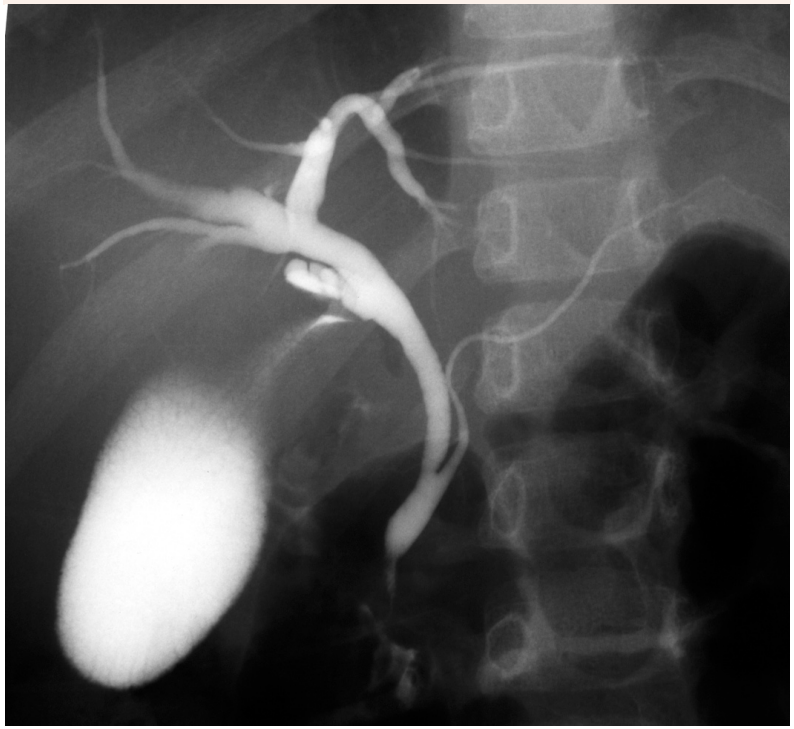
First version, September 2024

Regurgitation of pancreatic juice does not cause biliary dilatation

When the idea of PBM became popular in Japan, it was thought that bile duct injury due to pancreatobiliary reflux was the cause of dilatation

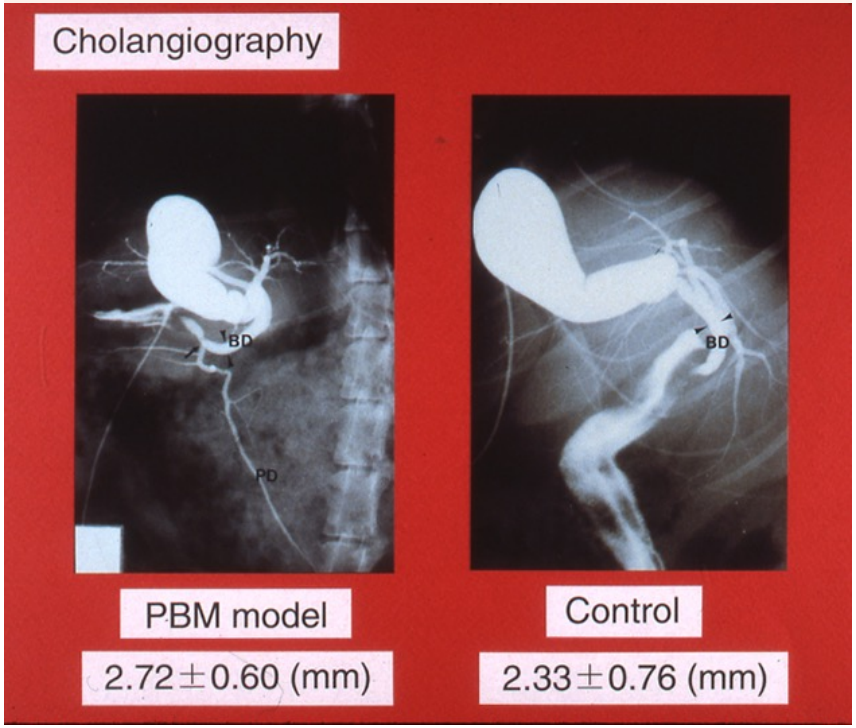


Non-dilated type of PBM exists



Pediatric case of non-dilated PBM
The common channel is dilated but the BD is not.

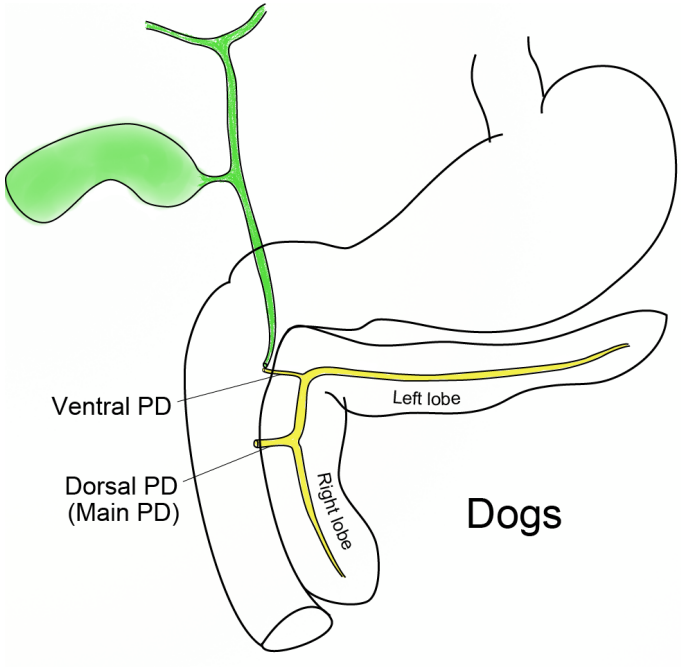
Cystic dilatation was not produced in animal PBM models



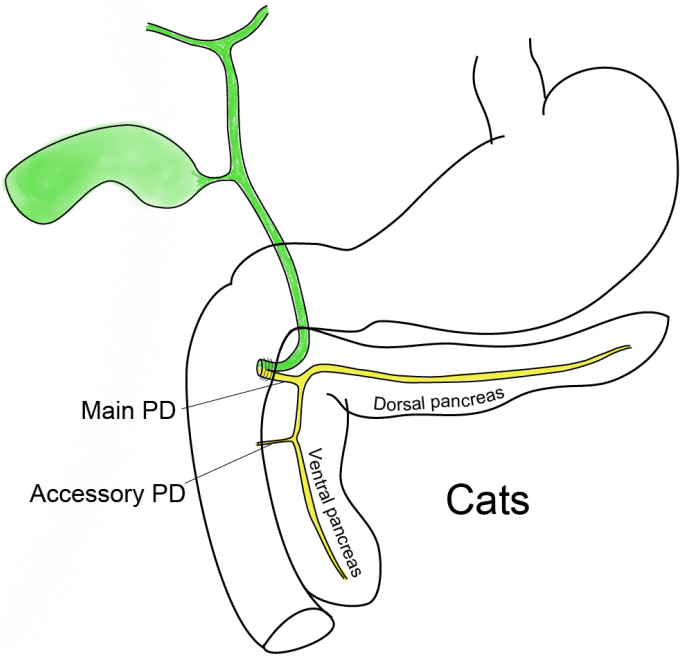
Cat model of PBM
The BD did not dilate.
Kaneko K, et al. *J Surg Res.* 1996;60:115-21.

Pancreatobiliary anatomy differs among animals

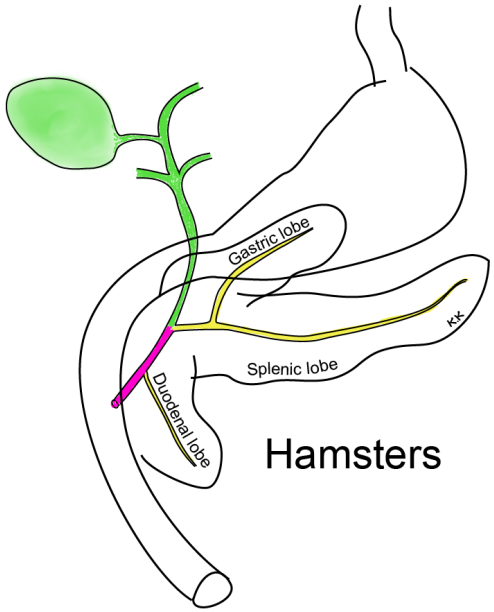
BD joins the accessory PD



Similar to human anatomy



PBM is normal in rodents, goats, and sheep.



The cause may be the narrow segment (NS)

Dilatation related with NS length — Ando H. *Jpn J Surgery.* 1983;84:1174–85
Increased intraductal pressure due to NS — Davenport et al. *J Pediatr Surg.* 2005;40:331–5



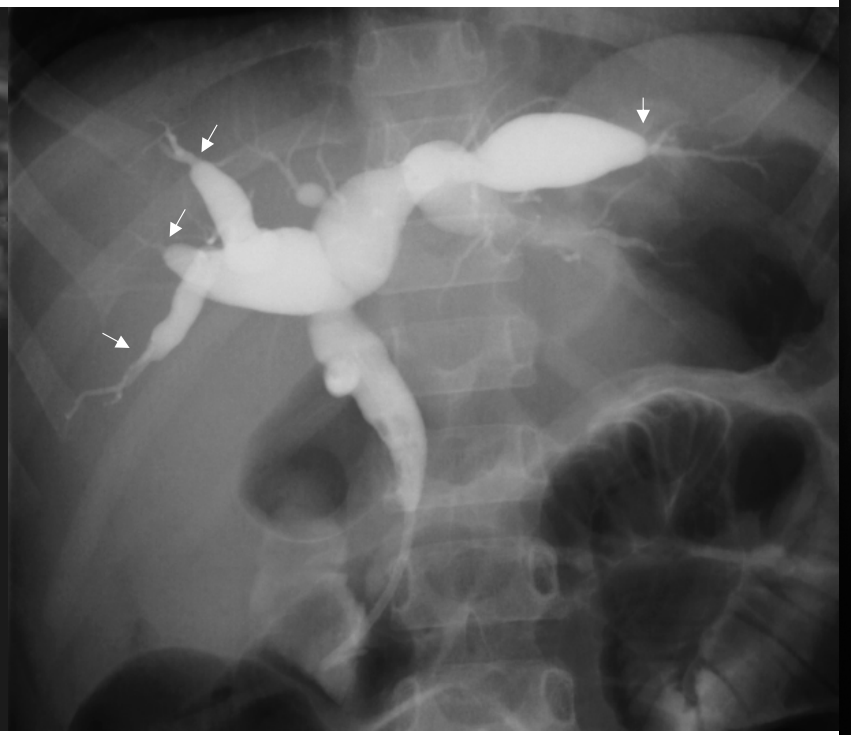
No NS | Slight constriction | Thick NS | Thin NS

The NS alone cannot explain characteristic dilatation

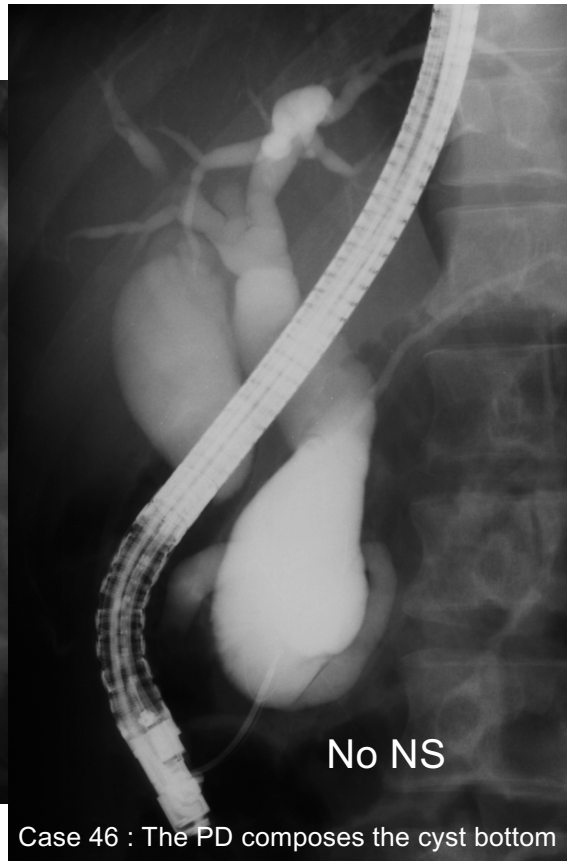
Increased ductal pressure cannot cause limited dilatation (see p11).



Localized dilatation



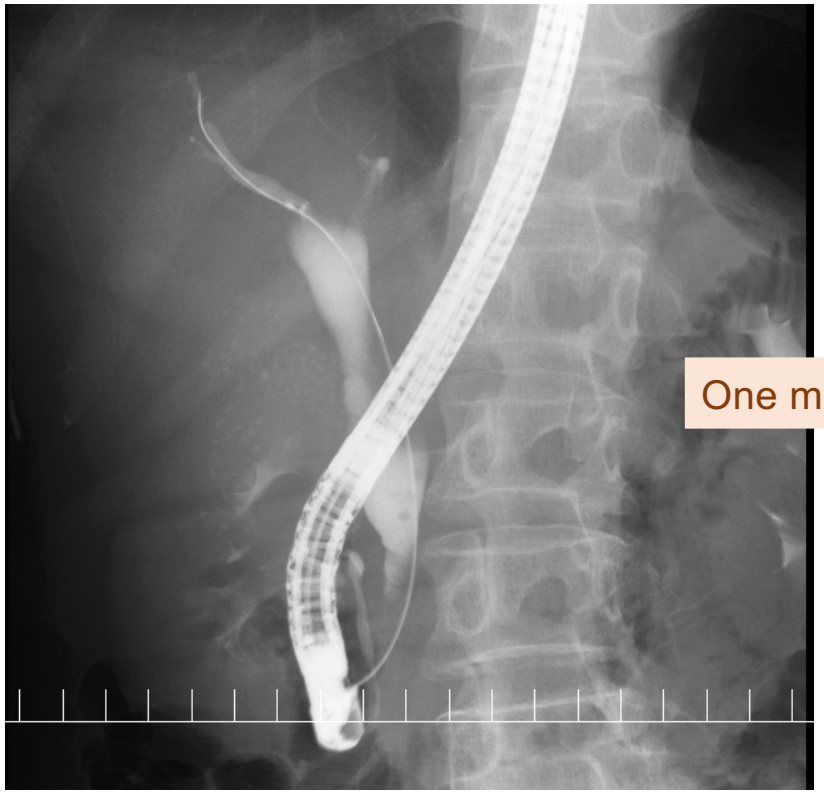
Localized dilatation
Intrahepatic bile ducts are more dilated



Case 46 : The PD composes the cyst bottom

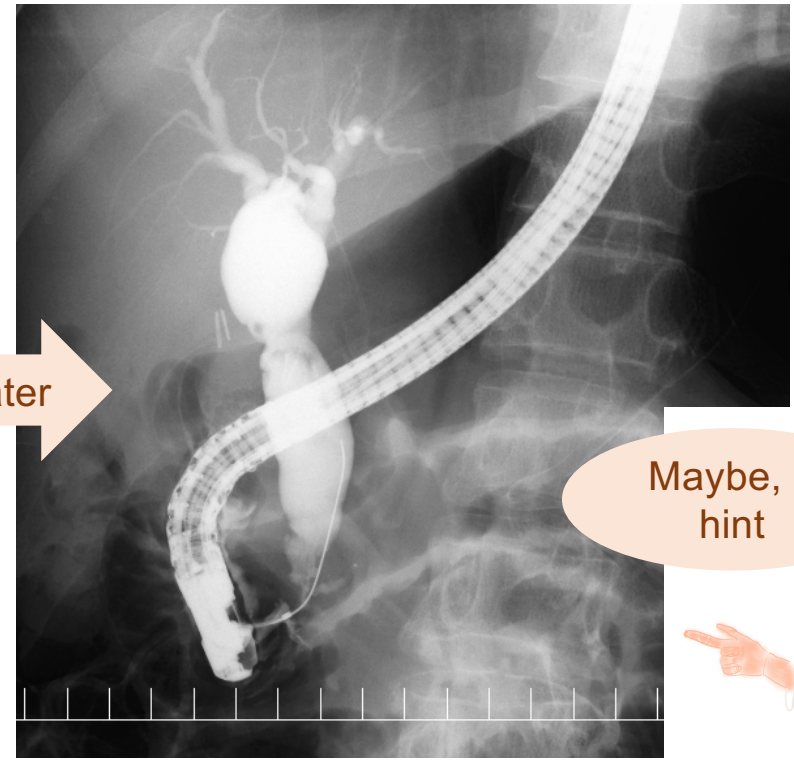
Acquired localized BD dilatation

Chronic intermittent increase in intraductal pressure



A male in his 50s with bile duct stones

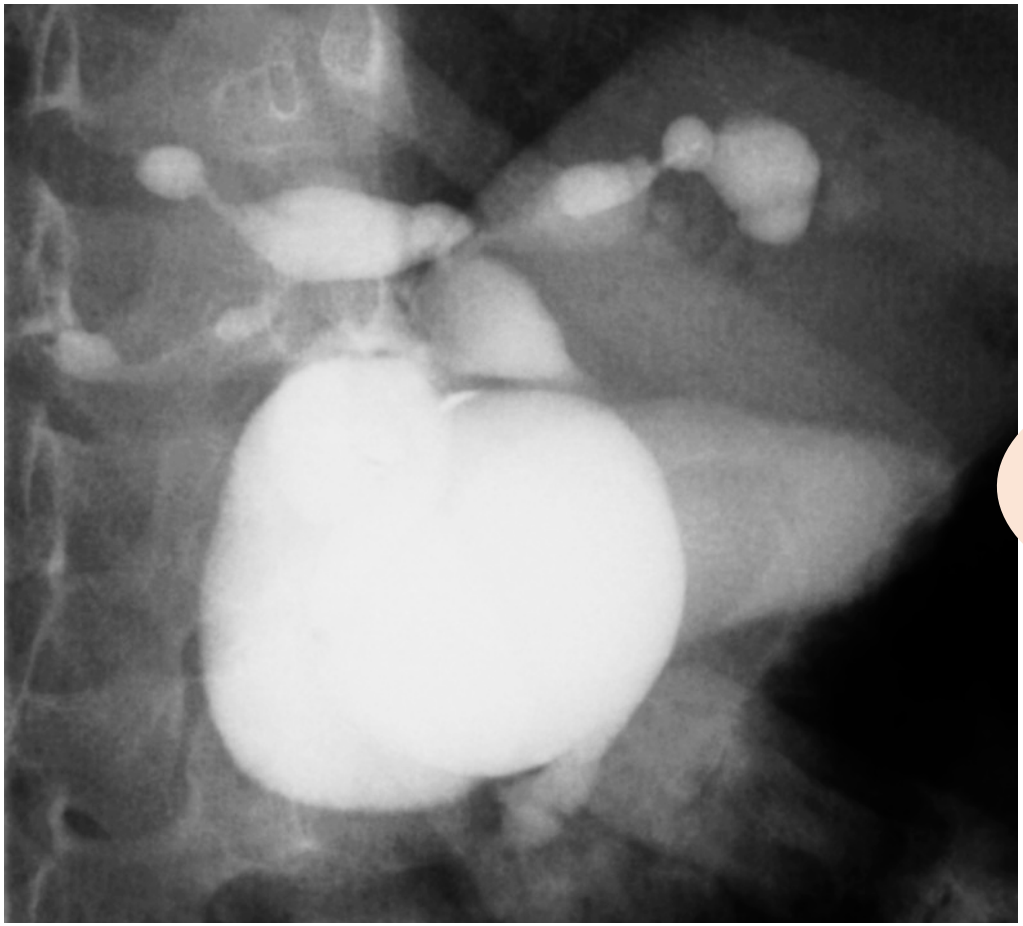
One month later

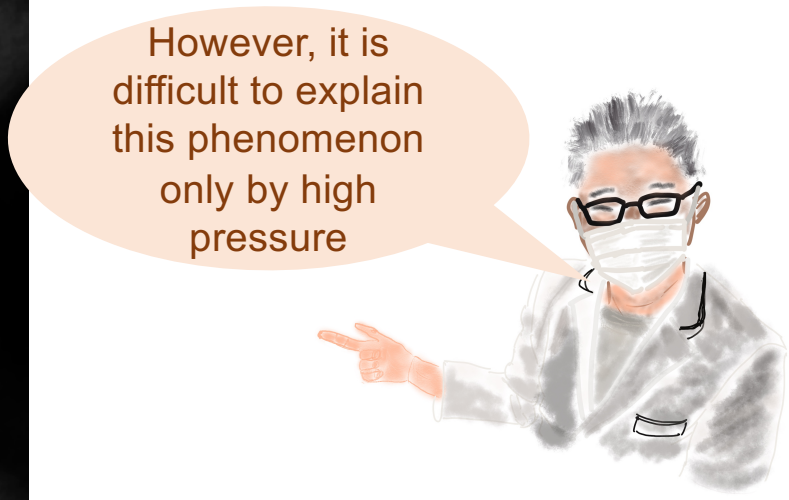




The common hepatic duct became larger but the upstream BDs did not dilate.

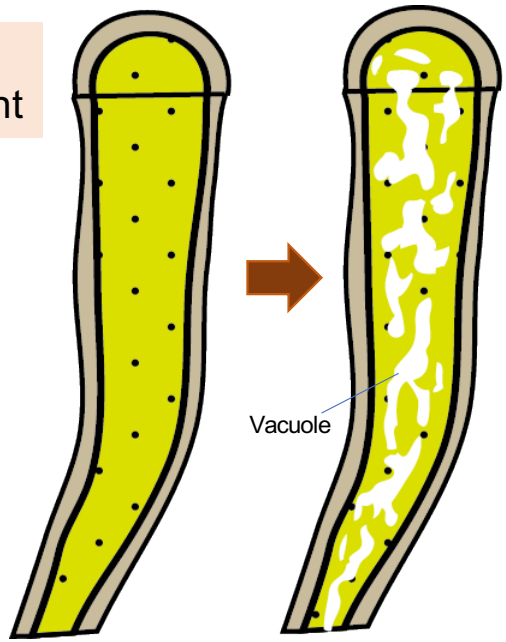
Peripheral cystic dilatation of intrahepatic BDs





Yotuyanagi's etiological theory in 1936
Localized dilatation in congenital biliary dilatation

Normal
BD development

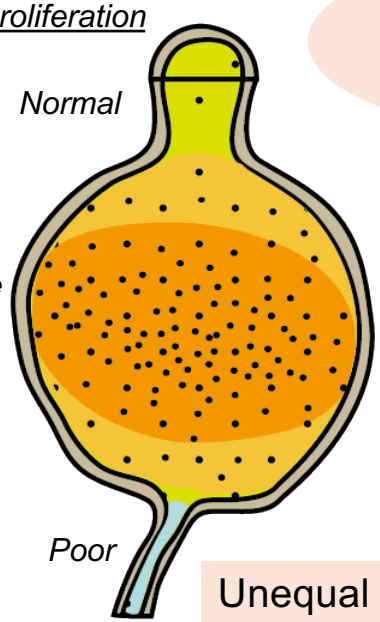


Biliary epithelia
occlude the lumen

Solid stage

Recanalization

Epithelial proliferation



Solid stage

Yotuyanagi referred to Kodumi and Kodama's paper, which first described PBM as an etiology in 1916.



Yotuyanagi stressed both localized dilatation and the narrow segment. He pointed out that the NS alone cannot explain localized dilatation. His theory explains simultaneous existence of both.

Unequal epithelial proliferation

Yotuyanagi S. Contributions to the aetiology and pathogeny of idiopathic cystic dilatation of the common bile-duct with report of three cases; A new aethiological theory based on supposed unequal epithelial proliferation at the stage of the physiological epithelial occlusion of the primitive choledochus. *Gann* 1936;30:601–52.

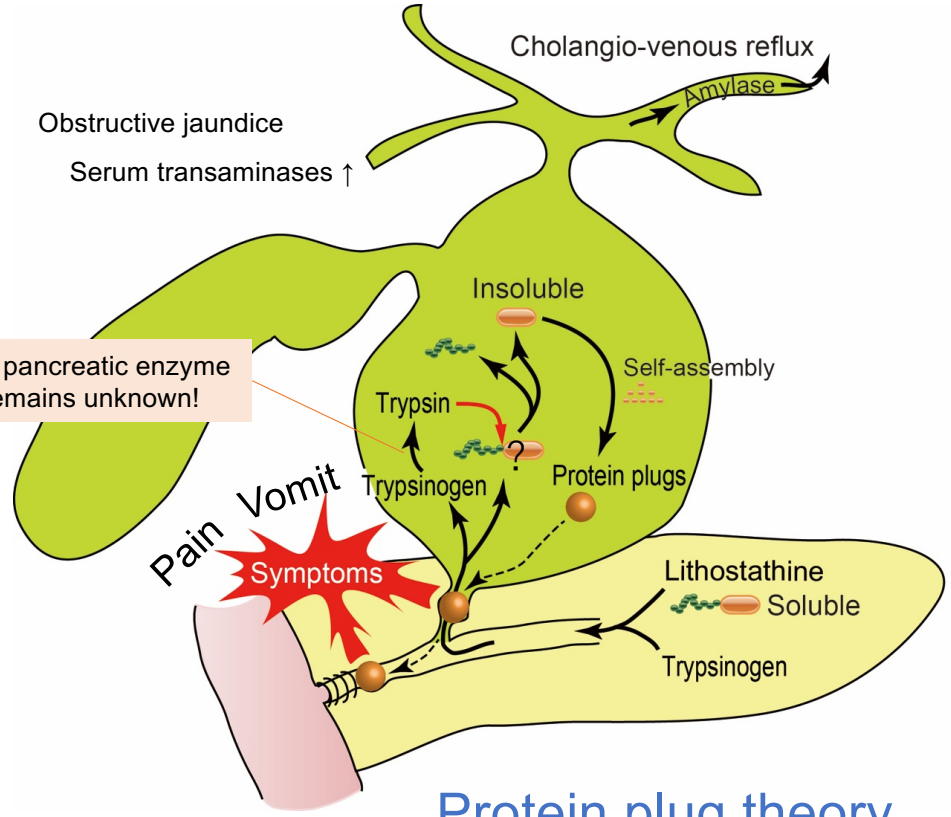
Advanced

Pathophysiology in pediatric patients

Mechanism of protein plug formation

First version, September 2024

Symptomatology in childhood (see *Basic Section*, p20–25)



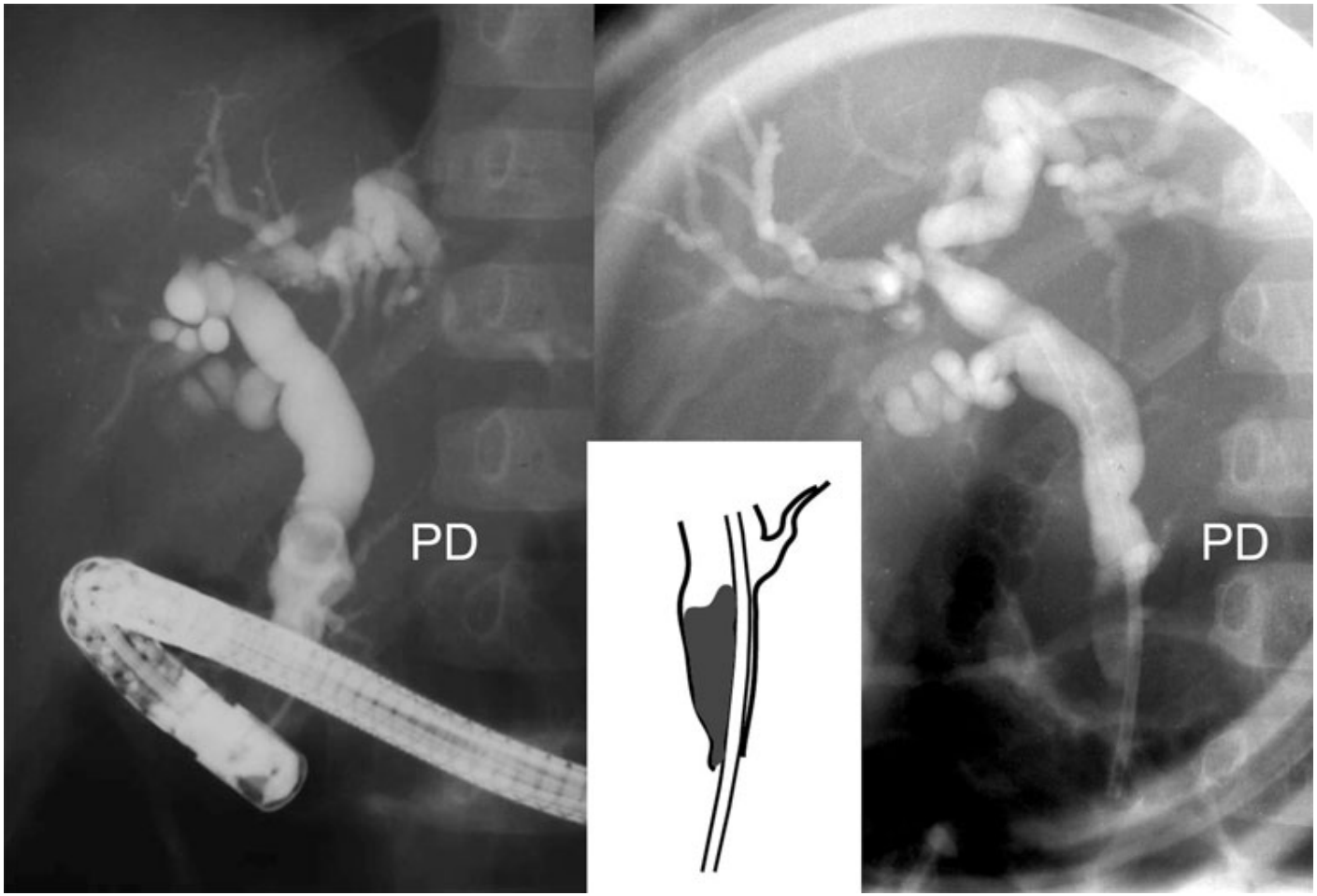
Protein plug theory



Fragile protein plugs occlude the narrow segment or the common channel, producing a transient increase in intraductal pressure and causing the symptoms

Findings supporting the protein plug theory

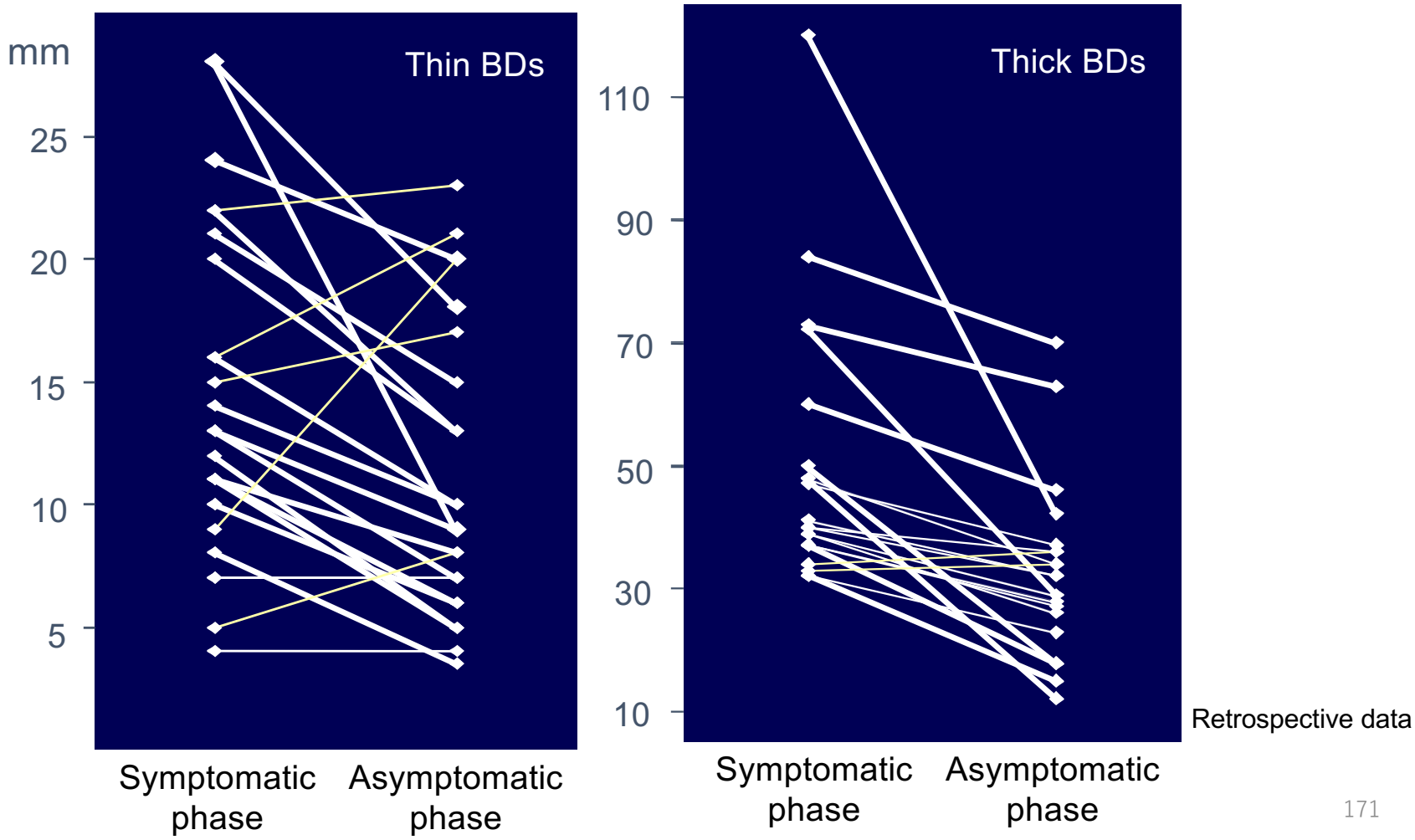
Endoscopic drainage promptly relieves persistent or exacerbated symptoms



Tsuchiya H, Kaneko K, Itoh A, Kawashima H, Ono Y, Tainaka T, Murase N, Ando H. Endoscopic biliary drainage for children with persistent or exacerbated symptoms of choledochal cysts. *J Hepatobiliary Pancreat Sci.* 2013 ;20(3):303-6. doi: 10.1007/s00534-012-0519-5. PMID: 22581057.
Fig. 1

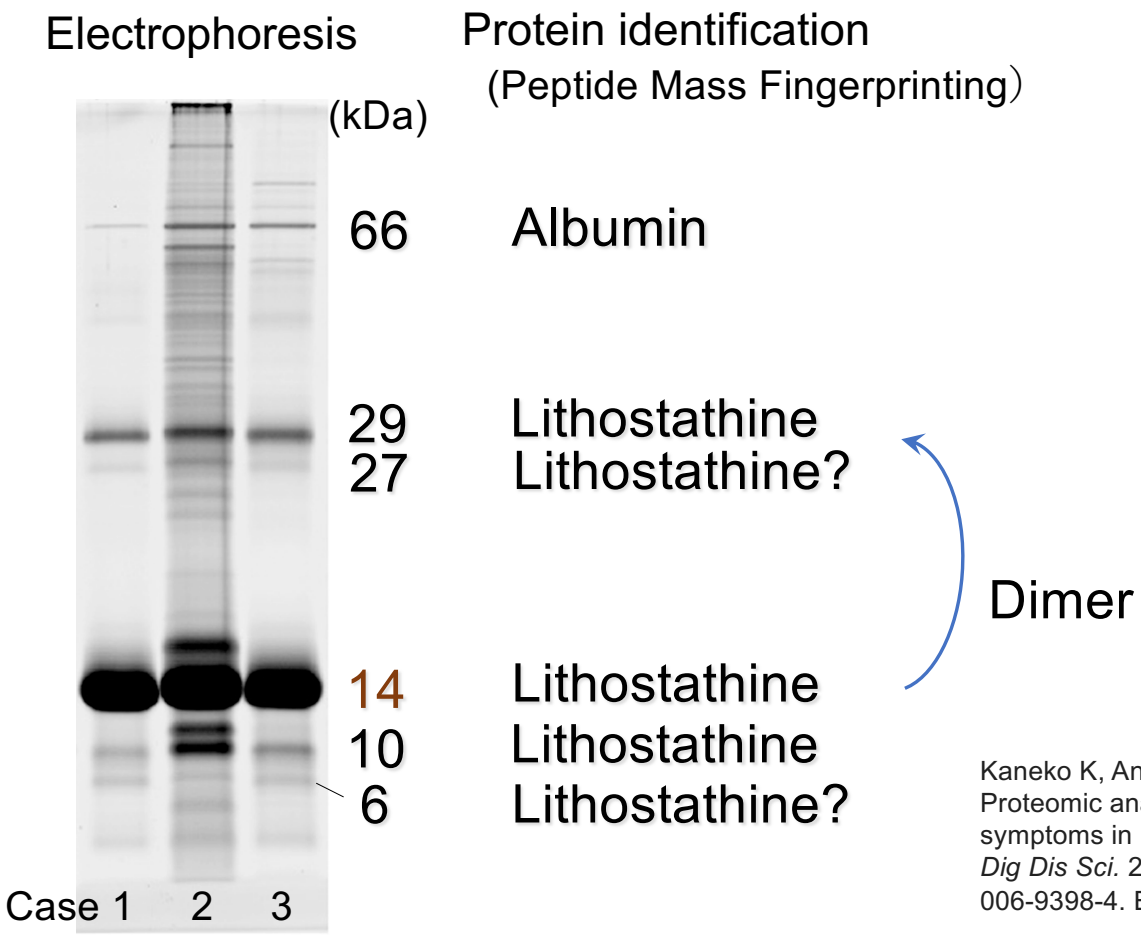
Findings supporting the protein plug theory

The common bile duct diameter is larger during the symptomatic phase



Retrospective data

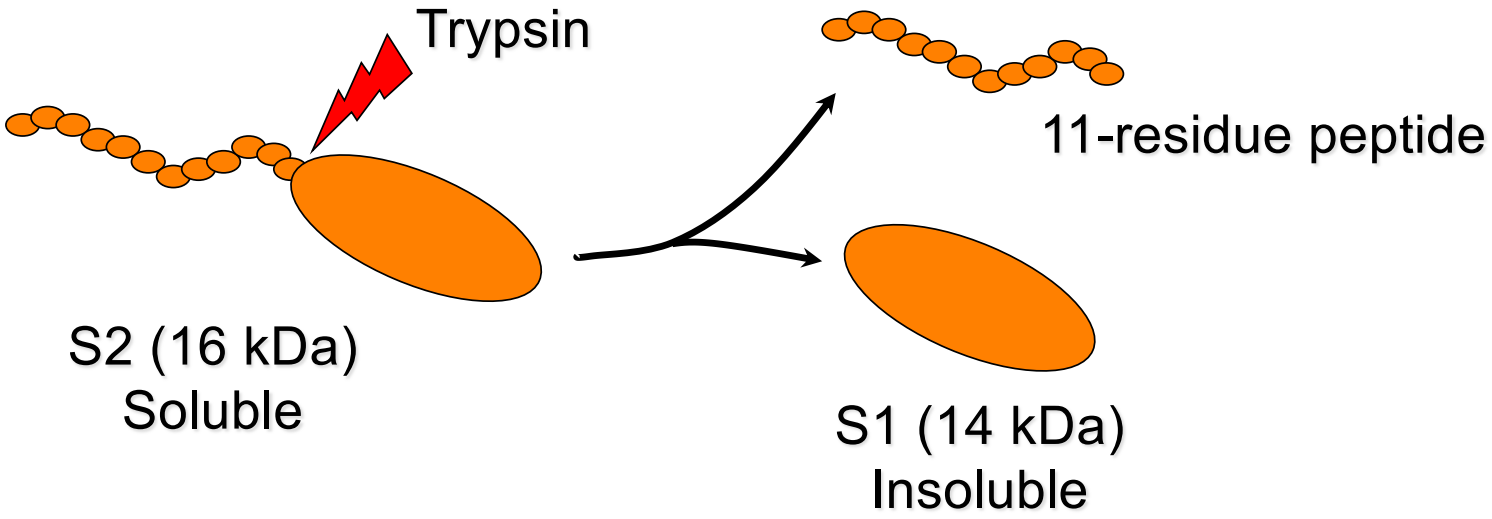
Protein plugs are composed of lithostathine



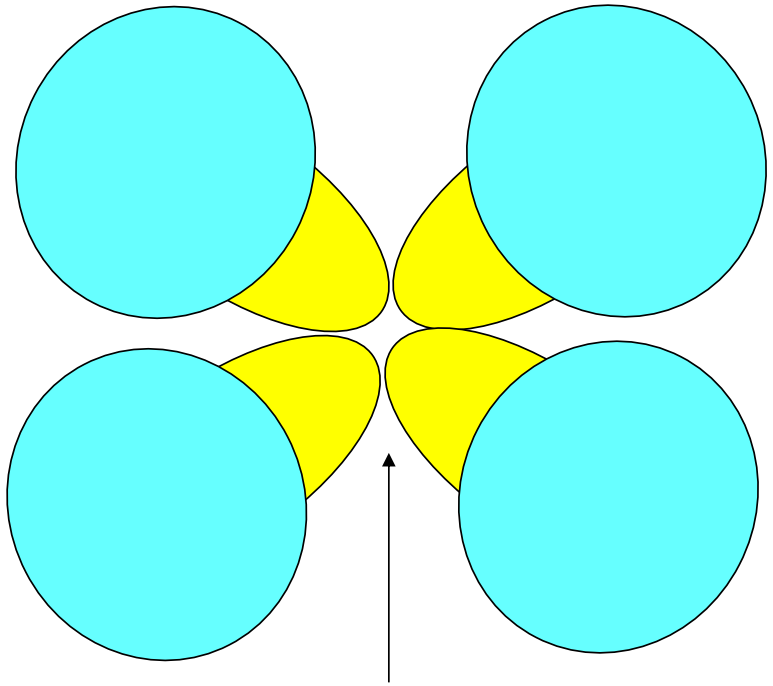
Kaneko K, Ando H, Seo T, Ono Y, Tainaka T, Sumida W. Proteomic analysis of protein plugs: causative agent of symptoms in patients with choledochal cyst. *Dig Dis Sci.* 2007;52(8):1979-86. doi: 10.1007/s10620-006-9398-4. Epub 2007 Apr 6. PMID: 17415647.

Lithostathine

- It is a soluble 144-amino acid glycoprotein secreted by pancreatic acinar cells.
- It accounts for 5%–10% of proteins in pancreatic juice, though its function remains unknown.
- It has many other names, such as pancreatic stone protein (PSP).



Lithostathine S1 forms tetramers by lateral hydrophobic interactions

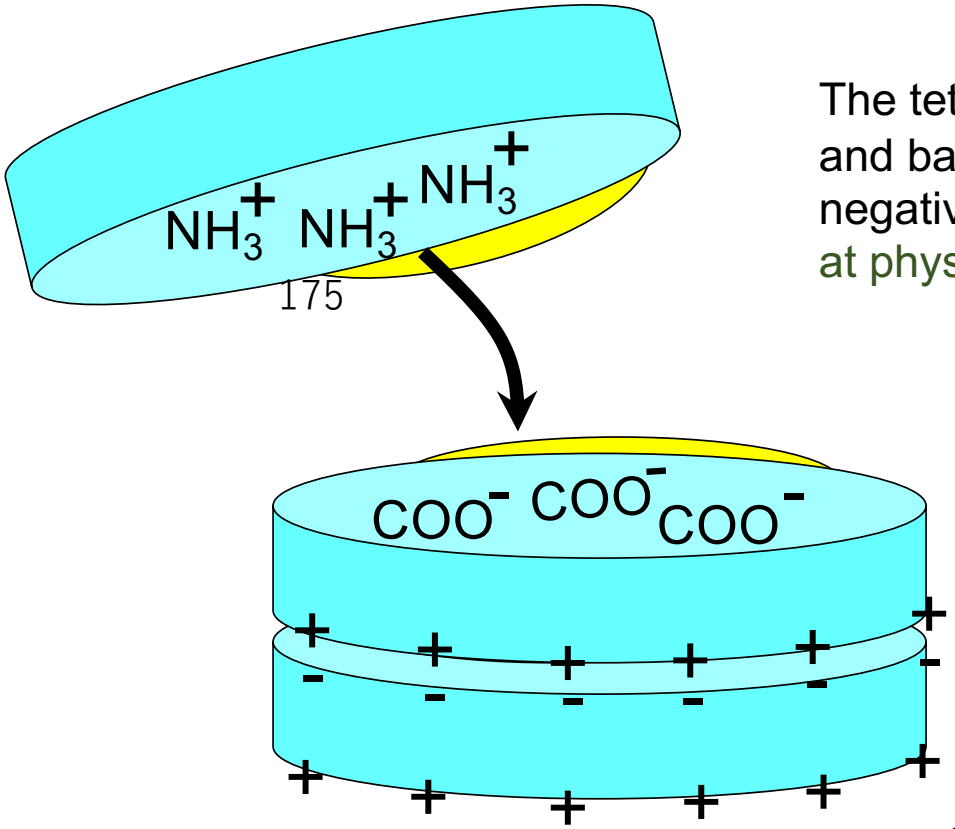


Hydrophilic

Hydrophobic

Gregoire, et al. *EMBO J.* 2001;20:3313–3321

Tetramers self-assemble by longitudinal electrostatic interactions

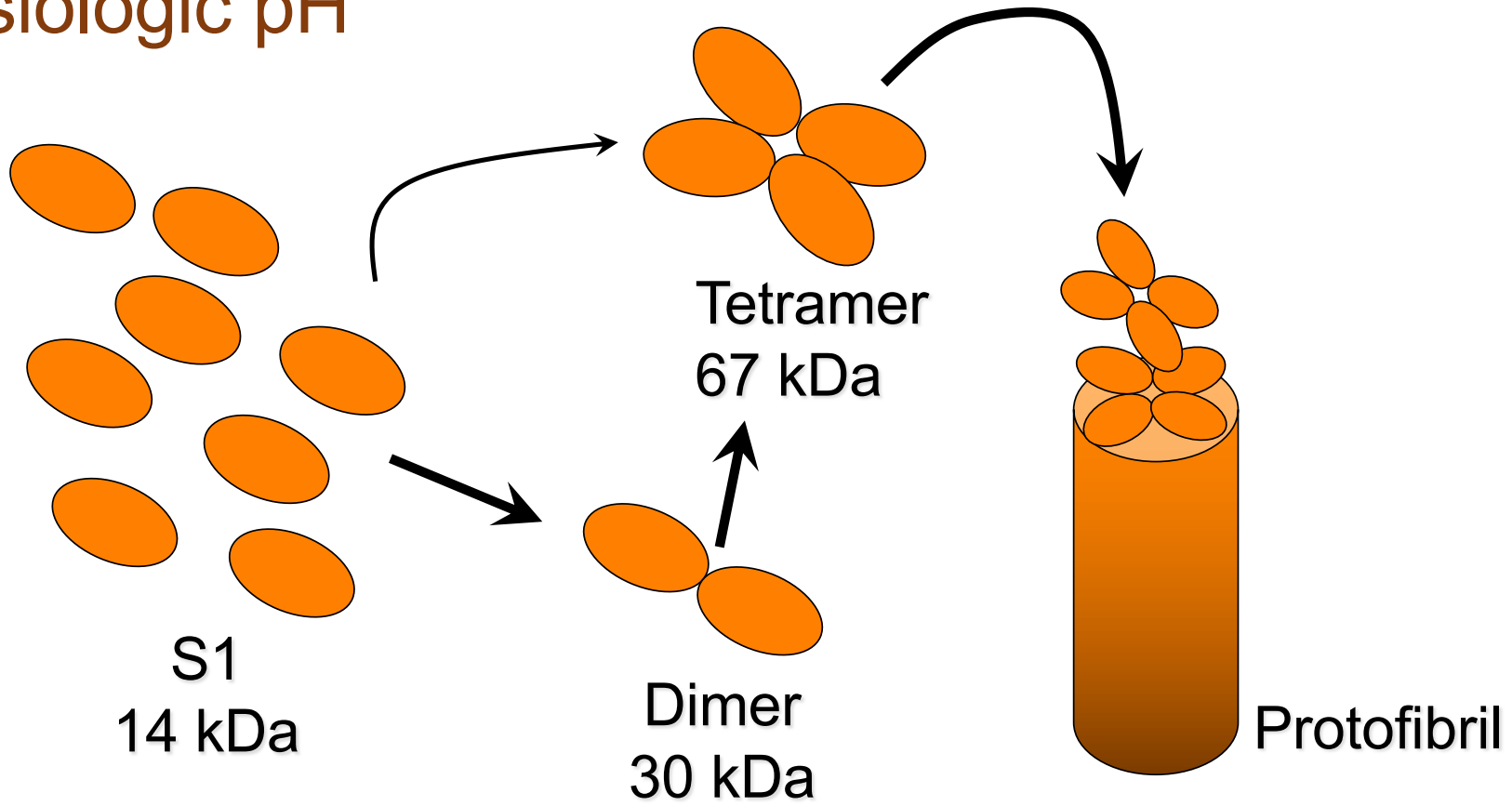


The tetramer has acidic residues on one side and basic residues on the other, contributing negative and positive charges, respectively, at physiologic pH.

Low pH	Physiologic pH	High pH
$-NH_3^+$	$-NH_3^+$	$-NH_2$
-COOH	$-COO^-$	$-COO^-$

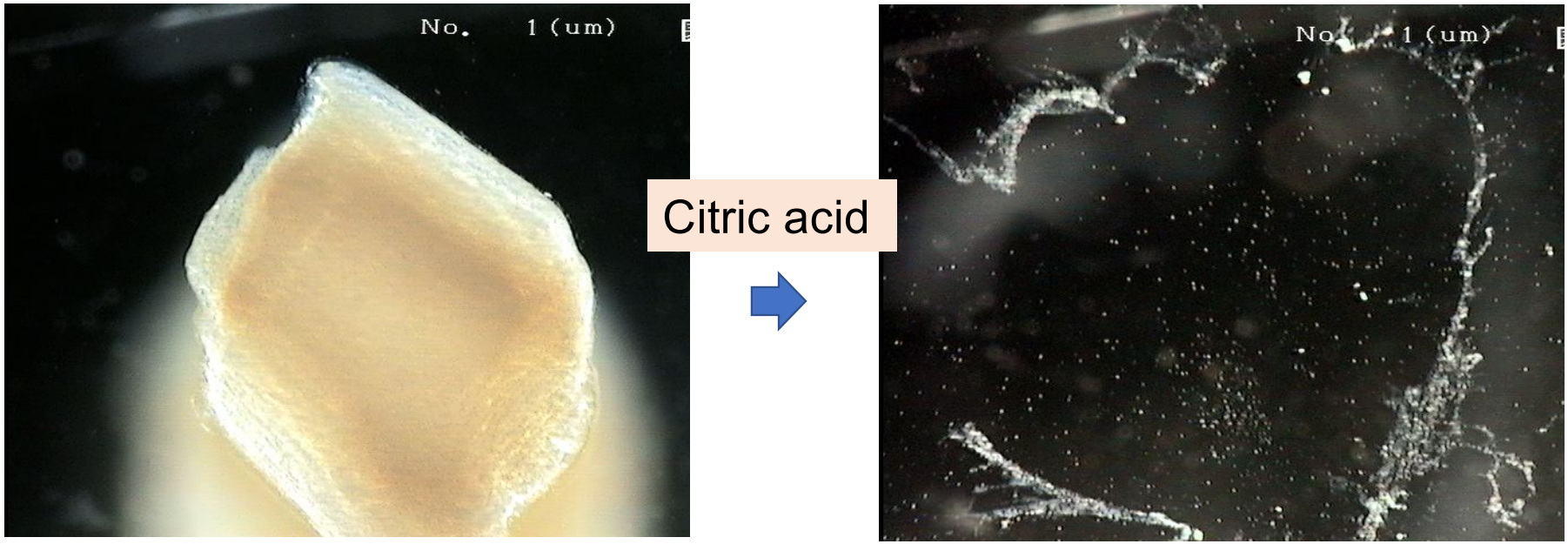
Gregoire, et al. *EMBO J* 2001;20:3313–3321

Cleaved lithostathine (S1) self-assembles into protofibrils at physiologic pH



Gregoire, et al. *EMBO J* 2001;20:3313–3321

Acidic and basic solutions dissolve protein plugs



Proof that electrostatic interactions work only at physiologic pH

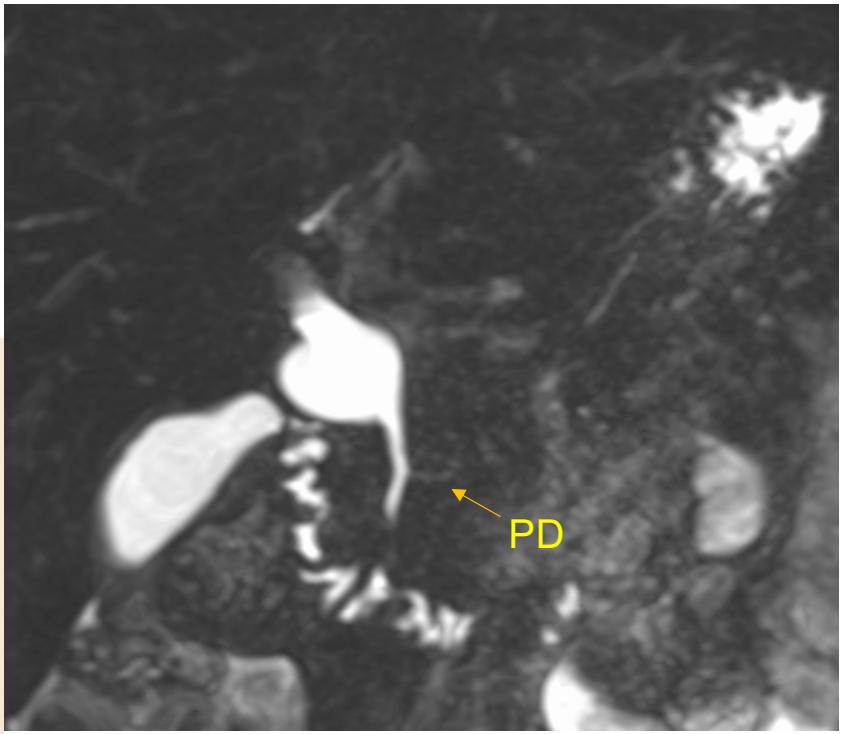
Kaneko K, Ono Y, Tainaka T, Sumida W, Ando H.
Acidic and basic solutions dissolve protein plugs made of lithostathine complicating choledochal cyst/pancreaticobiliary maljunction.
Dig Dis Sci. 2009;54(7):1475–80. doi: 10.1007/s10620-008-0503-8. Epub 2008 Nov 7. PMID: 18989781.

Where do protein plugs form?

Case 4 from *Basic Section* (see p28)

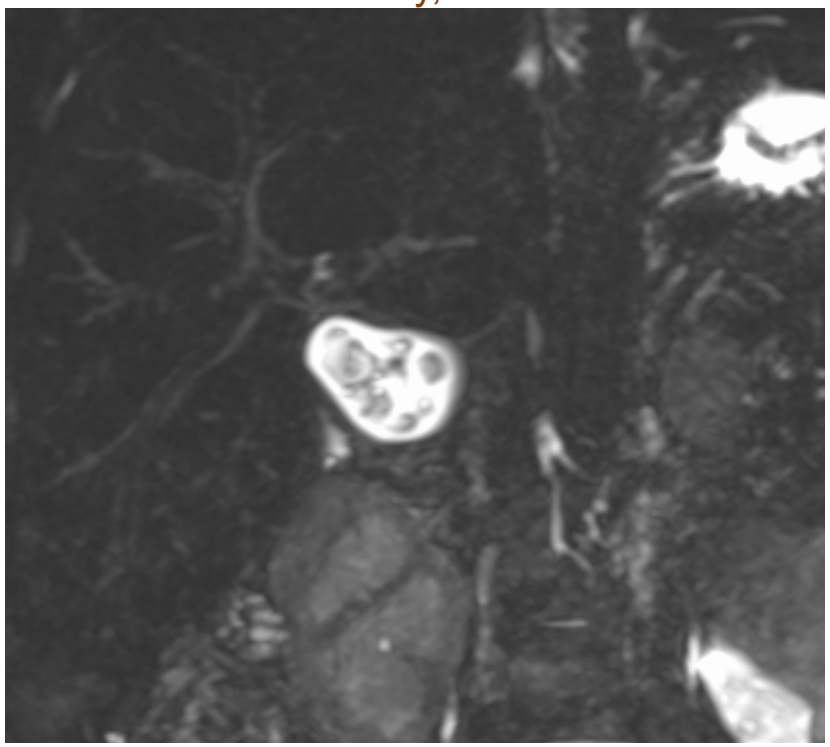
- A pediatric case with abdominal pain and vomiting.
- Elevated serum liver and biliary enzymes.
- No elevation of serum pancreatic enzymes.

Protein plugs are often found in the dilated common channel. However, plugs are formed as well in cases without common channel dilatation, as demonstrated here. Most plugs are presumed to form in the dilated BD or the gallbladder, where bile stagnates.



No dilatation of the common channel

Probably, here



Multiple filling defects on the dorsal side of the choledochus



Advanced

Pathophysiology in pediatric patients

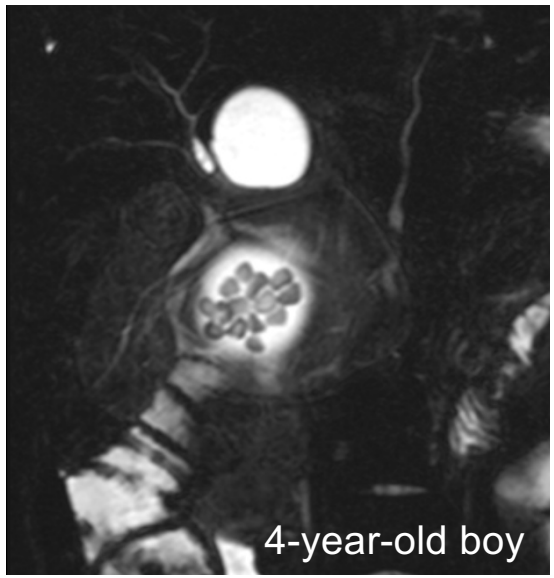
Symptomatology besides protein plugs

First version, September 2024

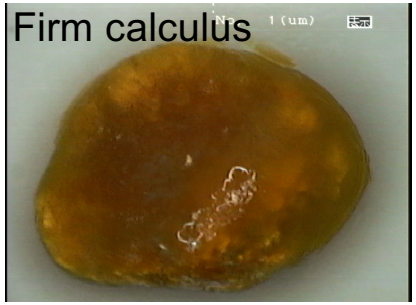
Symptomatology besides protein plugs

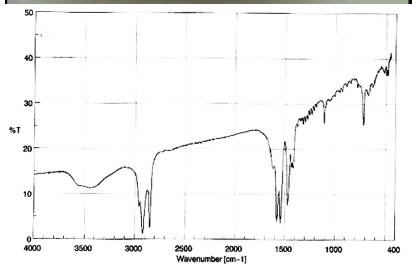
The protein plug theory explains symptoms in most pediatric cases. However, there are a few exceptions.

- Fatty acid calcium stones causing occlusion, but extremely rare
- Early onset in neonates and early infants



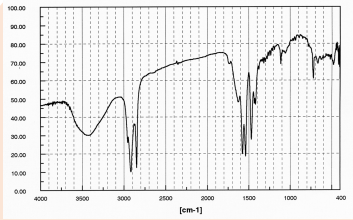
Uniformly shaped filling defects, a feature of gallstones different from nonuniform shape of protein plugs (compare with p178)



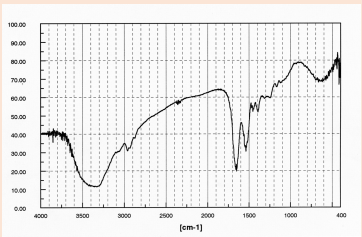


Infrared absorption spectrometry identifying fatty acid calcium

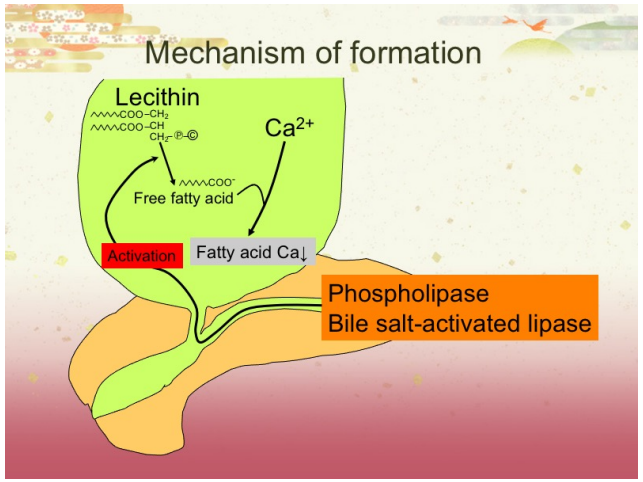
cf. Spectra of standard materials



Fatty Acid Calcium

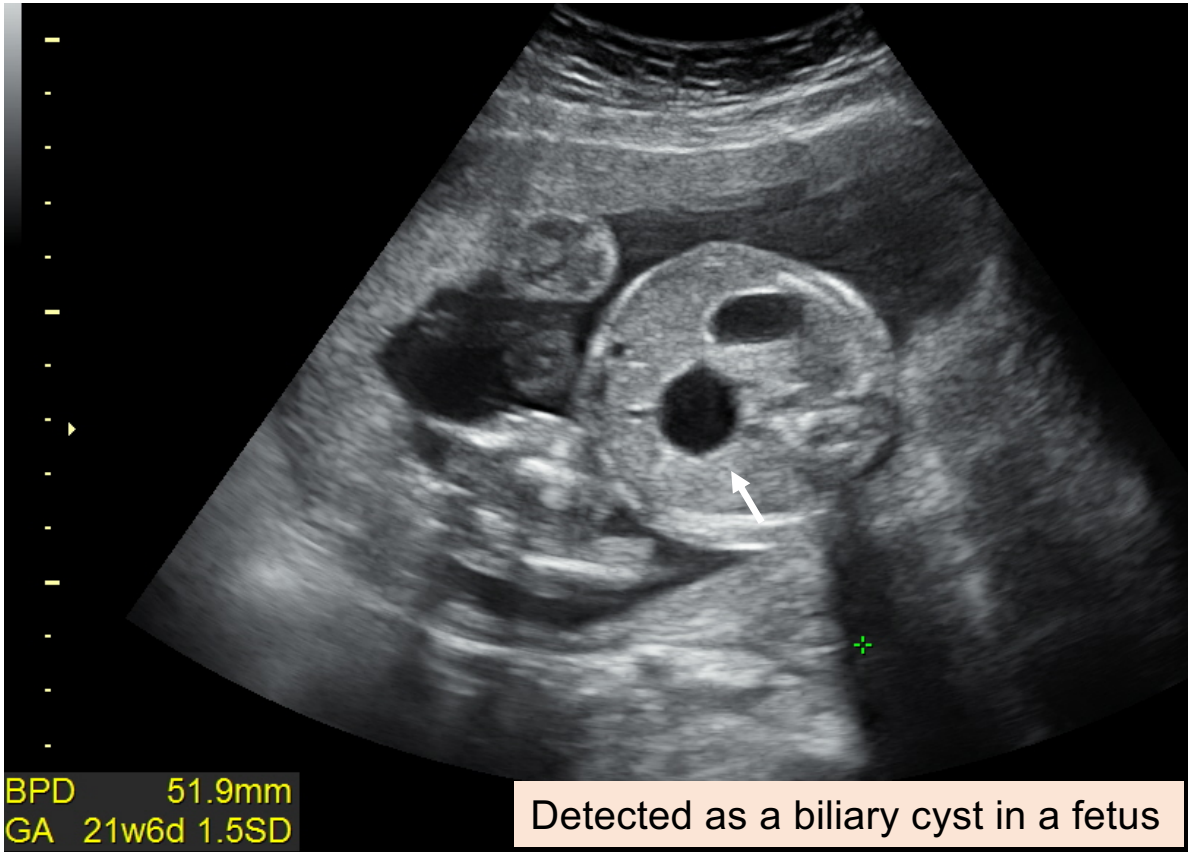


Protein

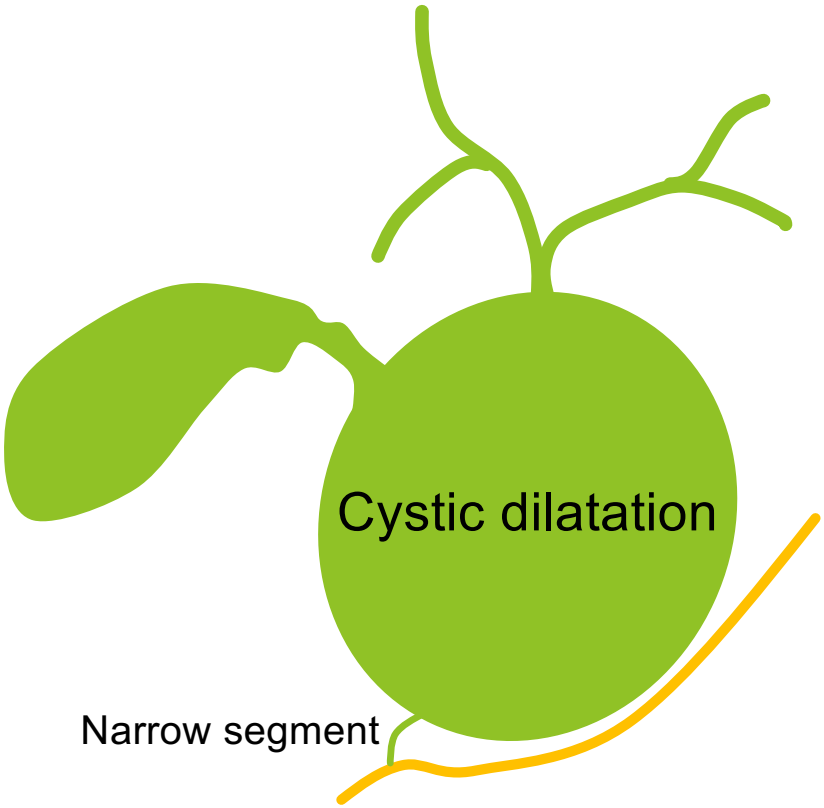


Kaneko K, Ono Y, Tainaka T, Sumida W, Ando H.
Fatty acid calcium stones in patients with pancreaticobiliary maljunction/choledochal cyst as another cause of obstructive symptoms besides protein plugs.
J Pediatr Surg. 2008 Mar;43(3):564-7. doi: 10.1016/j.jpedsurg.2007.11.004.
PMID: 18358304.

Onset in neonates and early infants



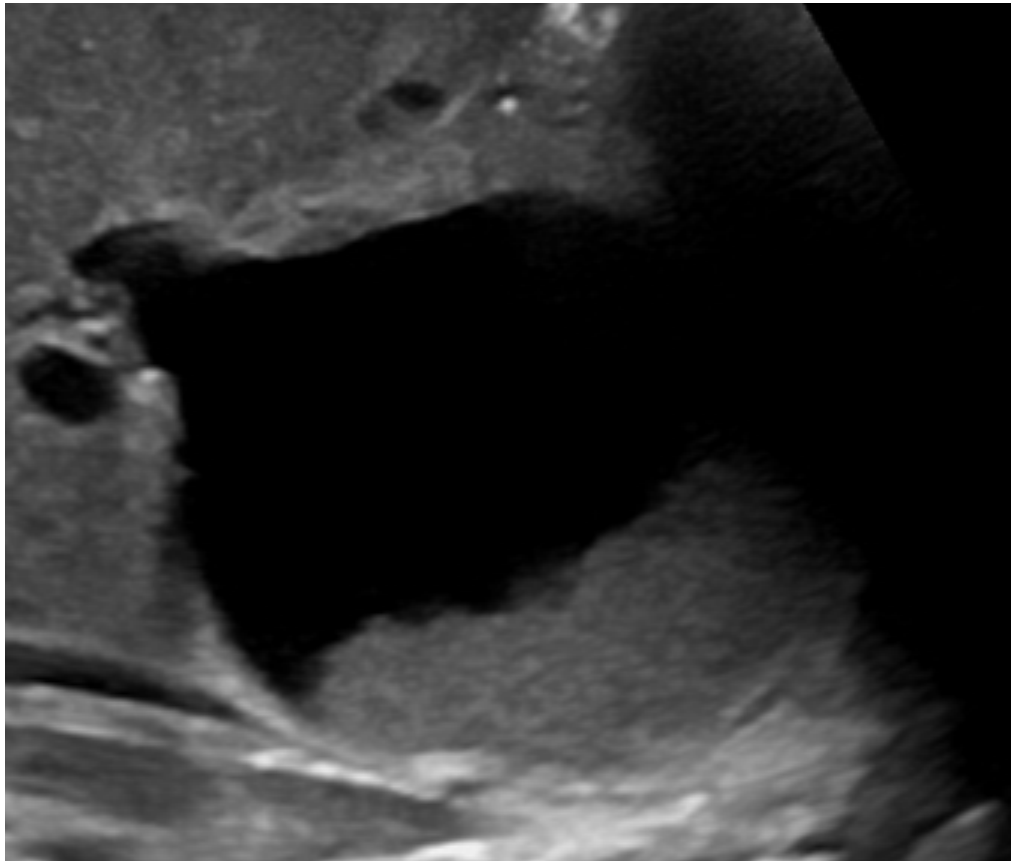
Detected as a biliary cyst in a fetus

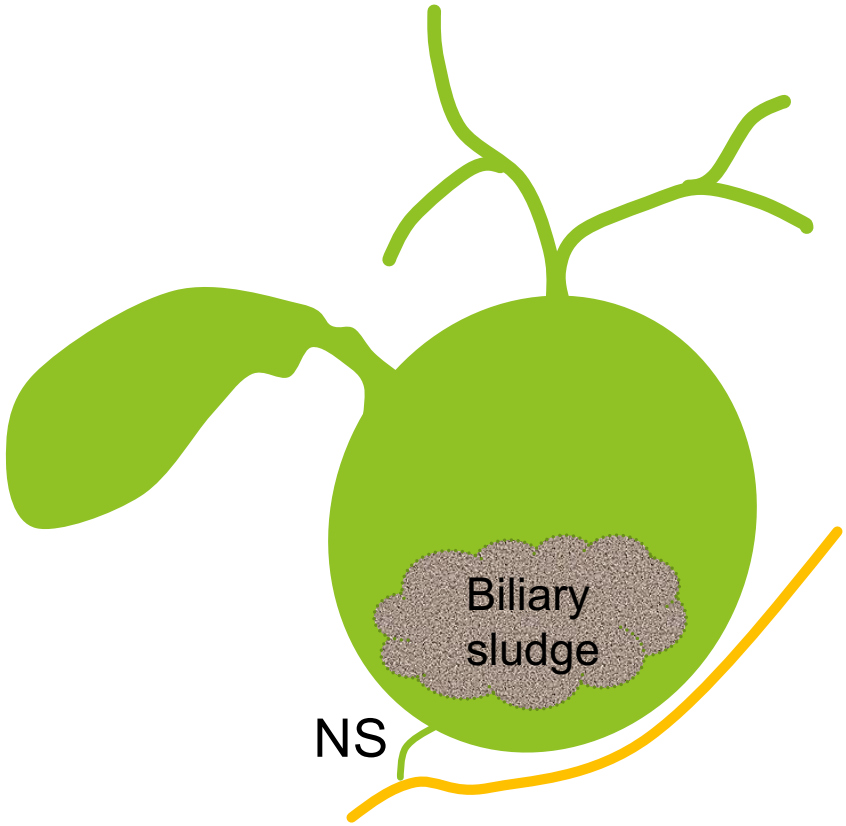


Almost all cases are of the cystic type with an NS

These biliary cysts are indistinguishable from cystic biliary atresia (type I cyst and IIId) even after birth (see *Expert Section*).

Debris appears in the cyst before symptoms occur

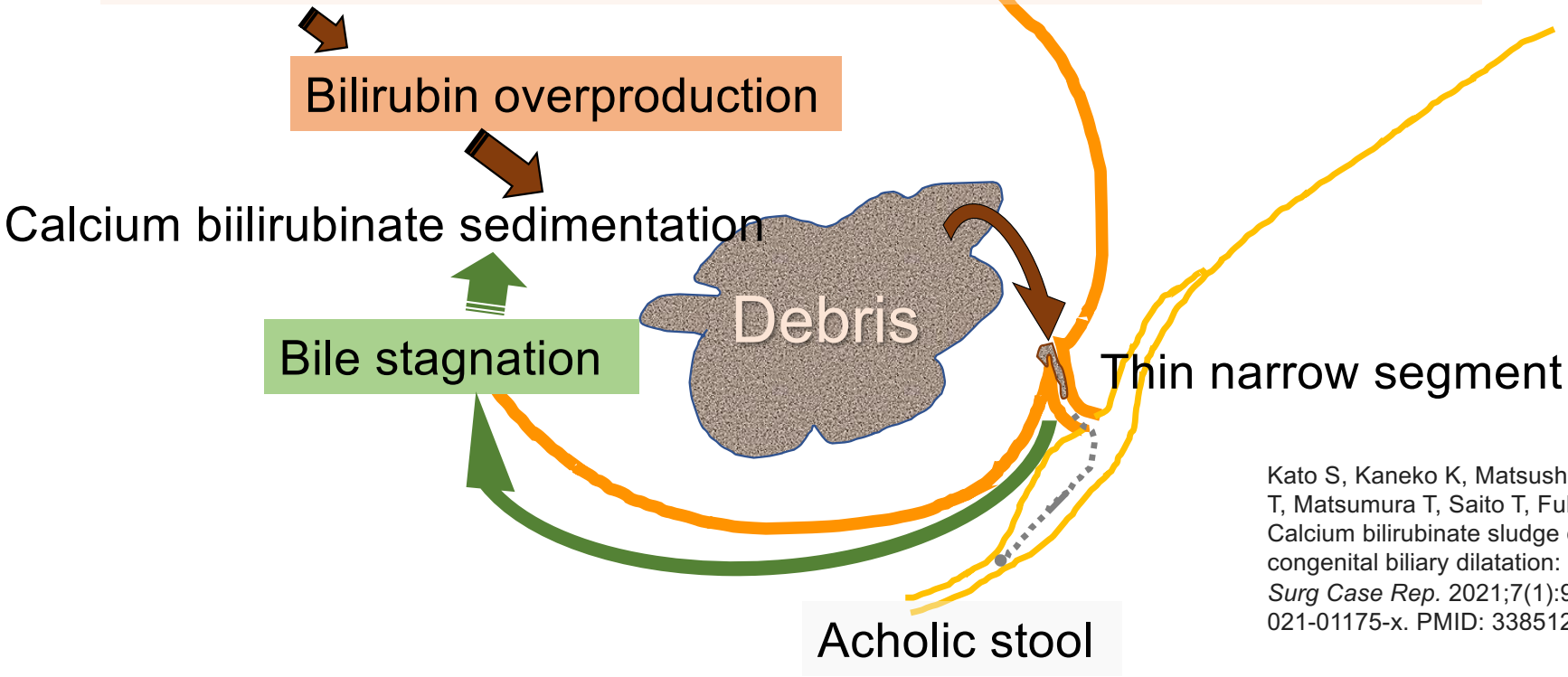




Infrared absorption spectrometry shows that the sludge is composed of calcium bilirubinate.

Proposed mechanism of early onset

Accelerated **hemolysis** due to neonatal hematologic features
- Physiological **polycythemia** of red blood cells (RBCs)
- High percentage of **HbF** RBCs with a **shorter life span**



Kato S, Kaneko K, Matsushita N, Kurahashi S, Osawa T, Matsumura T, Saito T, Fukami Y, Komatsu S, Sano T. Calcium bilirubinate sludge causes early onset of congenital biliary dilatation: a report of two cases. *Surg Case Rep.* 2021;7(1):92. doi: 10.1186/s40792-021-01175-x. PMID: 33851282; PMCID: PMC8044275.