Spontaneous Flow of Bile Through the Human Pancreatic Duct in the Absence of Pancreatitis: Nature's Human Experiment

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Case Report

One hundred years ago E. L. Opie proposed two distinct hypotheses to address the pathogenesis of gallstone-induced pancreatitis. These hypotheses appear mutually exclusive. The first predicts that impediment to the flow of pancreatic juice causes pancreatitis (the pancreatic duct obstruction hypothesis), whereas the second predicts that bile flow into the pancreatic duct behind an impacted gallstone would trigger the onset of acute pancreatitis (the common-channel hypothesis). One of the more convincing arguments against the latter hypothesis is the observation that bile, when experimentally perfused through the pancreatic duct of dogs, does not induce pancreatitis. This experimental situation had spontaneously developed in the patient we describe here: a biliopancreatic fistula had permitted the continuous flow of bile through a large portion of the pancreas, which was associated with cholangitis but had apparently never led to pancreatitis. This patient's case would suggest that in humans, just as in experimental animals, bile flow through the pancreatic duct is not necessarily involved in the onset of gallstone-induced pancreatitis and lends further support to Opie's pancreatic duct obstruction hypothesis.

Introduction

A century ago, Eugene Opie proposed two different hypotheses to explain the pathogenesis of gallstone-induced pancreatitis. His earlier hypothesis predicted that an impacted gallstone at the papilla would obstruct the outflow from the pancreatic duct and that pancreatic secretion in the presence of this impediment would trigger the onset of pancreatitis [1]. In a subsequent report from the same year of 1901, Opie proposed what later became known as his "common-channel hypothesis", and suggested that behind the impacted stone at the papilla, bile would flow from the bile duct into the pancreatic duct and that this biliopancreatic reflux would trigger the disease onset [2]. Interestingly, Opie based both of his hypotheses on careful autopsy observations and later performed animal studies to support them with experimental evidence. The common-channel hypothesis (as opposed to the soon-forgotten pancreatic duct obstruction hypothesis) became immediately popular because bile-stained necrotic pancreatic tissue is not an uncommon finding either at autopsy or in surgical specimens of the pancreas from patients with severe gallstone-induced pancreatitis.

One of the most convincing arguments against the common-channel hypothesis as a cause of gallstone-induced pancreatitis is the experimental observation that bile, when perfused without unphysiological pressure through the pancreatic duct of dogs, does not induce pancreatitis [3,4]. For obvious reasons this experimental study cannot be repeated in man and therefore little is known about the effect of continuous bile flow through the human pancreatic duct. Here we report the case of a young woman in whom a congenital biliopancreatic fistula permitted just such a continuous flow of bile through the pancreas. This had to be surgically corrected to prevent recurrent cholangitis, but had never caused pancreatitis.

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Bibliography
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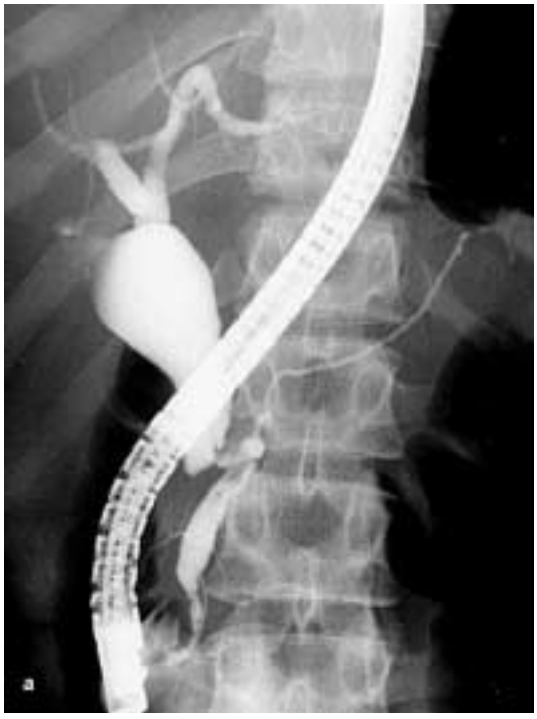
Table **1** Blood test findings on admission

Test	*Normal limits*	*Admission levels*
Erythrocyte sedimentation rate (ESR)	< 8 mm/h	42 mm/h
Alkaline Phosphatase	60–170 U/l	216 U/l
Gamma-glutamyl transferase (γ-GT)	< 28 U/l	81 U/l
Bilirubin	< 1.2 mg/dl	6.94 mg/dl (= 118.7 µml/l)
Conjugated	< 0.3 mg/dl	5.21 mg/dl (= 89.0 µmol/l)
Lipase	< 190 U/l	88 U/l
Creatinine	< 1.2 mg/dl	0.7 mg/dl (= 61.9 µmol/l)
Full blood count, electrolytes, and coagulation studies		Levels within normal limits

Case report

A 16-year-old girl was admitted because of upper abdominal pain that had lasted for 5 days and was associated with intermittent fever and chills. On physical examination she had jaundiced sclerae but no other signs of liver disease. Clinical chemistry findings on admission (Table **1**) indicated biliary obstruction, but serum values for amylase and lipase activity were normal. On abdominal ultrasound a cystic dilatation of the common bile duct (20 mm maximum diameter) was found but no gallstones were observed. The pancreas was visualized without difficulty and appeared normal in size, shape, and echogenic texture. After contrast filling of the pancreatic duct on endoscopic retrograde cholangiopancreatography (ERCP), the common bile duct was found to branch from the pancreatic duct in the body of the pancreas instead of draining into the duodenum at the papilla; filling of the pancreatic duct occurred via the common channel (Figure **1**). This indicated a biliopancreatic fistula with complete drainage of bile from the common bile duct through a large portion of the pancreas. Although the common bile duct was cystically dilated because of a narrowing at its junction with the pancreatic duct the intrahepatic bile ducts were of normal caliber. The main pancreatic duct, as well as its side branches were completely normal and without evidence of recurrent or chronic pancreatitis.

After ERCP, the serum lipase level increased to a maximum of 2.780 U/l but this hyperlipasemia resolved within 3 days and was not associated with clinical signs or symptoms of pancreatitis. In the absence of endoscopic options to prevent further episodes of cholangitis, the patient underwent surgery during which the gallbladder was removed, the cystically dilated common bile duct was separated from the pancreatic duct in the body of the pancreas and resected, and biliary drainage was restored by an hepaticojejunostomy. Neither inspection nor palpation of the pancreas gave evidence of acute or chronic pancreatitis and postoperative recovery was uneventful. On a follow-up visit after 1 year, the patient was well, reported no abdominal symptoms, and the laboratory findings, including gamma-glutamyl transferase, bilirubin, and serum lipase, were completely normal.



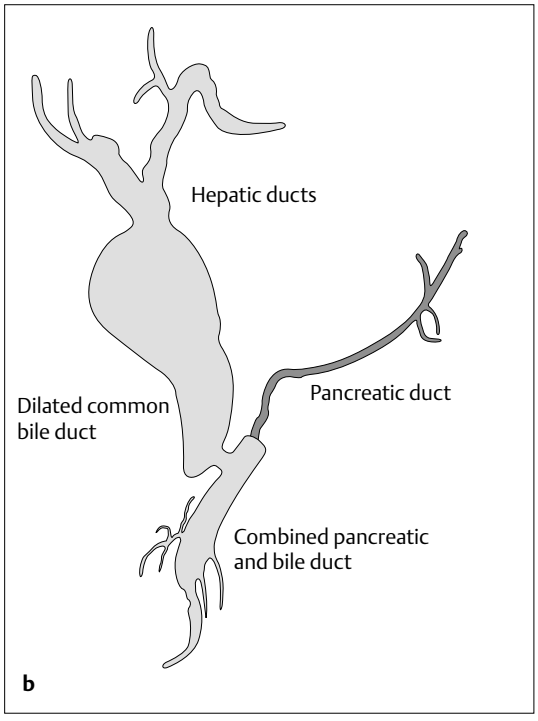


Figure **1** **a** Endoscopic retrograde cholangiopancreatography (ERCP) radiograph of the patient. Note that a cystically dilated common bile duct drains into the main portion of the pancreatic duct, and thus bile continuously flows through a large portion of the pancreas. Neither the main pancreatic duct nor its side branches show any morphological evidence of recurrent or chronic pancreatitis. **b** Schematic diagram of **a**.

Discussion

The pathologist Eugene Opie is credited with the first reports in which the pathogenesis of gallstone-induced pancreatitis was systematically addressed and a pathophysiological hypothesis, based on autopsy observations as well as animal experiments, was proposed. Interestingly, his observations led to two mutually exclusive concepts which he published consecutively in the same year of 1901. His first study suggested that impediment of the flow of pancreatic secretions, because of an impacted gallstone at the duodenal papilla, would trigger pancreatitis [1]. The second study implicated the formation of a communication between the bile duct and the pancreatic duct at the papilla as the triggering event, because bile would flow from the biliary tract into the pancreas and thus induce the onset of the disease [2]. Since bile-stained necrotic pancreatic tissue can occasionally be found in specimens obtained either at autopsy or during surgery of patients with gallstone-induced pancreatitis, the latter hypothesis became highly popular and the former was soon forgotten. Not long after Opie's initial report, his conclusions were challenged with a number of arguments. Pressure in the pancreatic duct is generally much higher than in the bile duct [5–7] and therefore pancreatic juice would be expected to flow into the biliary tract rather than bile to flow into the pancreas. Only long after the initiating phase of pancreatitis would the pressure gradient reverse and bile, indeed, flow into the pancreas, particularly if the duct and organ integrity had been compromised by pancreatic necrosis. While this would easily explain a bile-stained pancreas at surgery, it would have to be regarded as a consequence of pancreatitis rather than its triggering event. A second argument is the length of the common outlet of the pancreatic and the bile ducts at the papilla. Not only do some patients with pancreatitis have completely separate duodenal orifices for the pancreatic and bile ducts [8], in others the communication between these ducts is much too short to permit bile to flow into the pancreas behind an impacted stone [9]. A third argument is the observation that bile within the pancreatic duct of animals is harmless if perfused without the unphysiological pressure that is required to disrupt ductal integrity [3,4].

Several of the above arguments could be, and have been, experimentally tested in animal studies [10–12] whose results have refuted the common-channel hypothesis. A number of human observations have also supported the alternative hypothesis of duct obstruction [13,14]. The effect of bile perfusion on the human pancreas, on the other hand, is very difficult to assess, and studies in humans to address this question cannot be performed for obvious ethical reasons. In this context, the patient presented here is an experiment of nature.

Because of a congenital abnormality, her bile duct did not drain into the duodenum at the papilla but had a junction with the pancreatic duct that had permitted the continuous flow of bile through a large portion of the pancreatic duct for all of her life. This abnormal junction between the pancreatic and the bile ducts within the pancreas would be expected to permit the reflux of pancreatic juice into the biliary tract, to weaken the bile duct wall, and thus to result in its dilatation [15,16]. The resulting malformation would formally be classified as a choledochal cyst type Ic according to Todani et al. [17]. Intermittent jaundice and fever are known to occur as a result of recurrent cholangitis, and in our patient such an episode of cholangitis had led to hospital admission. The continuous flow of bile through the pancreatic duct had not, however, led either to episodes of acute pancreatitis or to the development of chronic pancreatitis. Neither imaging techniques, nor laboratory tests, nor direct surgical inspection could produce any evidence of pancreatic disease.

Other factors that have been discussed in the context of a hypothetical bile reflux into the pancreas are intraductal pressure and bacterial contamination [18,19]. The presence of the latter must be assumed in our patient because cholangitis had prompted hospital admission. Clinical pancreatitis, however, did not develop even during the flow of presumably infected bile through the pancreas. The last factor on the list of potential triggering events would be increased intraductal pressure. This might have occurred during the ERCP of our patient because the biliary tract had to be filled with contrast agent via the pancreatic duct and across the narrowing at the choledochal–pancreatic duct junction. The elevated serum activities of amylase and lipase following ERCP would, indeed, suggest that increased intraductal pressure had either impaired the barrier function of the ductal epithelium or damaged the acinar cells directly. While intraductal pressure elevation can thus be confirmed as a potential triggering event for pancreatic damage or pancreatitis, it is not a component of Opie's common-channel concept, but it is the critical factor in his duct obstruction hypothesis.

In this patient, neither the continuous flow of bile through the pancreatic duct for over 15 years, nor its presumed and intermittent contamination with bacteria had induced pancreatitis, and these two considerations, taken together, lend further support to the duct obstruction hypothesis of gallstone-induced pancreatitis that E.L. Opie proposed just over a century ago. It also confirms in humans the previous experimental observation that bile, when perfused through the pancreatic duct, and even when contaminated with bacteria, is not necessarily a predisposing factor for the development of pancreatitis.

References

[1] Opie EL. The relation of cholelithiasis to disease of the pancreas and to fat-necrosis. Johns Hopkins Hosp Bull 1901; 12: 19–21
[2] Opie EL. The etiology of acute hemorrhagic pancreatitis. Johns Hopkins Hosp Bull 1901; 12: 182–188
[3] White TT, Magee DF. Perfusion of the dog pancreas with bile without production of pancreatitis. Ann Surg 1960; 151: 245–250
[4] Robinson TM, Dunphy JE. Continuous perfusion of bile and protease activators through the pancreas. JAMA 1963; 183: 530–533
[5] Mann FC, Giordano AS. The bile factor in pancreatitis. Arch Surg 1923; 6: 1–30
[6] Elliott DW, Williams RD, Zollinger RM. Alterations in the pancreatic resistance to bile in the pathogenesis of acute pancreatitis. Ann Surg 1957; 146: 669–682
[7] Menguy RB, Hallenbeck GA, Bollman JL, Grindlay JH. Intraductal pressures and sphincter resistance in canine pancreatic and biliary ducts after various stimuli. Surg Gynecol Obstet 1958; 106: 306–320
[8] Sterling JA. The common channel for bile and pancreatic ducts. Surg Gynecol Obstet 1954; 98: 420–424
[9] DiMagno EP, Shorter RG, Taylor WF, Go VLW. Relationship between pancreaticobiliary ductal anatomy and pancreatic ductal histology. Cancer 1982; 49: 361–368

[10] Senninger N, Moody FG, Coelho JC, van Buren DH. The role of biliary obstruction in the pathogenesis of acute pancreatitis in the opossum. Surgery 1986; 99: 688 – 693
[11] Lerch MM, Saluja AK, Rünzi M, Dawra R et al. Pancreatic duct obstruction triggers acute necrotizing pancreatitis in the opossum. Gastroenterology 1993; 104: 853 – 861
[12] Lerch MM, Saluja AK, Dawra R et al. Acute necrotising pancreatitis in the opossum: earliest morphologic changes involve acinar cells. Gastroenterology 1992; 103: 205 – 213
[13] Lerch MM, Weidenbach H, Hernandez CA et al. Pancreatic outflow obstruction as the critical event for human gall stone induced pancreatitis. Gut 1994; 35: 1501 – 1503
[14] Hernandez CA, Lerch MM. Sphincter stenosis and gallstone migration through the biliary tract. Lancet 1993; 341: 1371 – 1373
[15] Ryckman FC, Noseworthy J. Neonatal cholestatic conditions requiring surgical reconstruction. Semin Liver Dis 1987; 7: 134 – 154
[16] O'Neill JA Jr. Choledochal cysts. Curr Probl Surg 1992; 29: 361 – 410
[17] Todani T, Watanabe Y, Narusue M et al. Congenital bile duct cysts: classification, operative procedures, and review of thirty seven cases including cancer arising from choledochal cyst. Am J Surg 1977; 134: 263 – 269
[18] Arendt T, Nizze H, Stuber E et al. Infected bile-induced acute pancreatitis in rabbits. The role of bacteria. Int J Pancreatol 1998; 24: 111 – 116
[19] Arendt T. The pathogenesis of acute biliary pancreatitis: a controversial issue. Part I. The concept of biliopancreatic reflux. Gastroenterol J 1989; 49: 50 – 53