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Does Endoscopic Therapy Favorably Affect the Outcome of Patients Who Have Recurrent Acute Pancreatitis and Pancreas Divisum?

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INTRODUCTION

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Endoscopic therapy for pancreas divisum (PD) in patients presenting with idiopathic pancreatitis (IP) is widely practiced among clinicians who perform endoscopic retrograde cholangiopancreatography (ERCP). But what is the evidence that the benefits of endoscopic therapy outweigh the risks?

At the November 2003 Annual Meeting of the American Pancreatic Association held in Chicago, Ill, Drs Eugene DiMagno of the Mayo Clinic and Glen Lehman of Indiana University debated this topic. They and their colleagues have submitted their arguments in writing. I hope you will find that this is an important contribution to the world's literature on this subject.

IDIOPATHIC PANCREATITIS IN PATIENTS WITH PD AND NORMAL DUCTS: THE CASE FOR ENDOSCOPIC THERAPY

Drs Evan L. Fogel, Tamas G. Toth, and Glen A. Lehman

Congenital anomalies and variants of the pancreas are seen in approximately 10% of the general population and are therefore not uncommon at ERCP. The term *congenital anomaly* indicates that during embryological maturation, there has been atypical development, and in the final analysis, an abnormality occurred which by implication may cause some disability, limitation, or disease. Developmental alterations that are generally of limited clinical importance might be best termed congenital variants. Although many congenital anomalies and variants of the pancreas are found coincidentally at endoscopy, surgery, or autopsy, a portion of these are clinically significant and cause symptoms in childhood or adulthood. Pancreas divisum is the most common congenital pancreatic anatomical variant occurring in approximately 7% of autopsy series (range, 1%–14%). The condition is least frequent in Asians (1%–2%)[1,2] and was reported to occur in 2% in 1 black population series.[3] The frequency of finding this condition varies greatly among ERCP series, depending on the population studied (frequency of pancreatitis patients) and the vigor with which complete pancreatography is pursued.

The ventral pancreas represents 2% to 20% of the pancreatic parenchymal mass. Fusion of the ventral and dorsal ductal system occurs in just more than 90% of individuals, although variations in patency of the accessory duct (of Santorini) occur. The variations of anatomy grouped under the heading of PD have been described and illustrated previously.[4] In incomplete PD, a small branch of the ventral duct communicates with the dorsal duct. Fifteen percent of PD cases are of the incomplete type.[5–7] The clinical implications of incomplete PD remain the same as for complete PD, except that modest to full visualization of the dorsal duct may occur via vigorous major papilla contrast injection. In reverse divisum, there is an isolated small segment of dorsal pancreas which drains through the minor papilla. The bulk of the pancreas drains via the main pancreatic duct via the major papilla. This occurs when the duct of Santorini does not connect with the genu of the main pancreatic duct. Reverse divisum is of no physiological significance but serves as a frustration to the endoscopist when cannulating the minor papilla in hopes of visualizing the entire pancreas. The latter may also serve as a setting for the rare case of pancreatic cancer which does not involve the main duct.

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ERCP and Clinical Relevance

Pancreas divisum has clinical relevance from the following 3 main standpoints. (1) The small ventral duct must be differentiated from various forms of main pancreatic duct cutoff, such as in pancreatic cancer. (2) At ERCP, only the ventral pancreas portion of the pancreas can be viewed via standard major papilla cannulation. Thus, incomplete ductography results and the dorsal pancreas remain unevaluated unless minor papilla cannulation is performed. (3) In a portion of PD patients, the minor papilla orifice is so small that excessively high intrapancreatic dorsal ductal pressure occurs during active secretion which may result in inadequate drainage, ductal distension, pain, or pancreatitis.[8–11] Pancreas divisum is seen in a disproportionate frequency of IP patients in most series (see Table 1).[8,9,11–16] This increased incidence in comparison with general populations adds to its pathophysiological significance.[15] Acute pancreatitis severity tends to be mild, but pseudocysts,[17,18] calculi,[19] and other more severe complications[20,21] are occasionally seen. It has been speculated that even low-grade intraductal hypertension makes the pancreas more prone to injury from alcohol, trauma, and drugs.[22] If ductal obstruction occurs, the problem is relative stenosis of the minor papilla rather than PD per se. As a consequence, some authorities prefer to call this condition the *dominant dorsal duct syndrome*.[23,24]

Most PD patients have no pancreatic symptoms throughout their lifetime; therefore, this anatomy appears to only be a condition, which predisposes the individual to the above events. Such a low frequency of symptoms manifestation has stirred great controversy as to whether PD and its associated small minor papilla orifice are ever a cause of obstructive pancreatitis.[13,25–28] Because it is estimated that less than 5% of PD patients ever develop pancreatic symptoms, the silent majority may statistically overshadow cause-and-effect relationships.

Very rarely, the ventral pancreas will be abnormal, whereas the dorsal duct remains normal.[29,30] In up to one third of cases with PD, no pancreatic duct can be identified connecting to the major papilla.[5] In such cases, the entire ventral portion of the pancreas generally drains cephalad through a branch of the dorsal duct. Because the ductal systems described by Wirsung, Santorini, and others generally refer to ductal systems without PD, these eponyms do not readily apply to PD and will not be used here.[31]

TABLE 1. Pancreas Divisum Associated With Acute Recurrent Pancreatitis

	Prevalence		
Author, y	**ARP (%)**	**Controls (%)**	***P***
Cotton,[9] 1980	26	4	<0.05
Richter et al,[12] 1981	12	3	<0.005
Delhaye et al,[13] 1985	8	6	NS
Brenner et al,[14] 1990	13	5	<0.05
Bernard et al,[8] 1990	50	5	<0.001
Morgan et al,[15] 1999	49	12	<0.001
Fischer et al,[16] 2005	19	6	<0.05

ARP indicates acute recurrent pancreatitis; NS, not significant.

Clinical Management of PD Patients

Coincidental Finding

When PD is detected in the setting of common duct stones, sclerosing cholangitis or other liver parenchymal conditions, and the patient has no computed tomography (CT) scan abnormality of the pancreas nor clinical history of pancreatitis, the PD ductal anatomy is clearly coincidental and can be ignored. Indeed, in the setting of a common duct stone, PD is probably an asset; serious gallstone pancreatitis is probably not possible, as gallstone obstruction at the major papilla will only block the small ventral duct, and major papilla sphincterotomy may be performed more aggressively because, again, only a small portion of the pancreas may be disturbed. In rare cases, the minor papilla is on the cephalad rim of the longitudinal fold to the major papilla.[32] This must be recognized to avoid injury during standard biliary sphincterotomy.

Symptomatic Patients

Patients with PD and mild or infrequent bouts of pancreatitis can generally be managed with appropriate medical therapy, which may include a low-fat diet, analgesics, anticholinergics, and pancreatic enzyme supplements. Such therapy appears to be of some symptomatic benefit, although it does not directly address the underlying ductal anatomy. It is controversial whether persons with mild symptoms should have aggressive therapy in hopes of preventing progression to more advanced disease. At this point, we favor a conservative approach, although the correct degree of aggressiveness is uncertain.

Patients with recurrent pancreatitis associated with clinically significant disability warrant thorough evaluation of the dorsal pancreas and minor papilla. We generally evaluate the dorsal pancreas and perform minor papilla therapy in patients having 2 or more bouts of pancreatitis or 1 bout of severe pancreatitis.

Methods to Evaluate for Pathologic Minor Papilla Narrowing

In a patient with IP and a finding of PD at ERCP or magnetic resonance cholangiopancreatography (MRCP), it has been suggested that the stenotic minor papilla orifice is the etiology for the clinical presentation. Although an abnormal dorsal ductogram clearly suggests that chronic pancreatitis (CP) is already evident, most patients have normal dorsal pancreatograms. There are multiple methods to evaluate for minor papilla narrowing and/or factors which suggest that minor papilla stenosis is present. Some of these factors are valuable as clinically diagnostic tools, yet others are only suggestive in a retrospective manner, such as in the resected pancreatic specimen.

Noninvasive Methods

Simple noninvasive methods which would identify patients with pathological minor papilla narrowing are

needed. Such tools would ideally selectively identify candidates for invasive therapy. A standard CT scan of the pancreas may identify dilation of the dorsal duct and/or changes of CP, which are confined to the dorsal area of the pancreas. More commonly, the CT scan just shows nonspecific prominence of the pancreatic head. The normal pancreas shows dilation of the main pancreatic duct over a 5- to 10-minute interval after intravenous secretin stimulation.[33] Using transcutaneous ultrasonography to monitor dorsal duct diameter, Warshaw et al[24] and Tulassay et al[33] observed that patients with pancreatic outlet obstruction may have dorsal duct dilation which persists for greater than 15 minutes. The precise criteria for a positive test remain undefined. Other series have attempted to correlate the dorsal duct response on the secretin ultrasound test with clinical evidence of pancreatitis or dorsal ductography findings.[34,35] Correlation has been poor, but this is not the main clinical issue. Warshaw et al[24] has appropriately correlated the outcome of therapy with ultrasound findings and showed a moderate correlation. Patients with a positive, abnormal test had a 90% chance of obtaining clinical relief with minor papilla therapy, whereas patients with normal tests (ie, no abnormal dilation) had a 40% chance of obtaining relief if minor papilla therapy was still performed. Confirmation of these results is needed from other centers.

Additionally problematic are patients with CP because they may have hyposecretory exocrine function and may not dilate their dorsal duct, despite significant minor papilla narrowing. If obesity or overlying gas precludes standard transcutaneous ultrasonography, the test can be performed under endoscopic ultrasonography observation or even CT scan observation. The role of MRCP for this indication is undergoing investigation.

Diagnostic ERCP

Diagnostic ventral and dorsal ductography may provide additional clues. An abnormal dorsal ductogram (dilation and/or CP changes) in combination with a normal ventral duct suggests pathological minor papilla narrowing. However, in our experience, dorsal duct dilation is a relatively uncommon finding. Lindstrom and Ihse[34] found an abnormal dorsal duct (without ventral abnormality) in 5 of 27 patients. On occasion, a cystic dilation of the very terminal portion of the dorsal duct ("Santorinicele") may be seen, as originally noted by Eisen et al.[36] In such cases, commonly, the minor papilla orifice is pinpoint in size and has a weblike surface. This especially may occur when the minor papilla is located in a diverticulum. Pain provocation during dorsal ductography occasionally occurs and is of uncertain significance. Presence of a Santorinicele has been suggested by some investigators to imply a stenotic minor papilla.

Special/Therapeutic ERCP Techniques

Even in the setting of normal ventral and dorsal ductography, evidence for CP can be obtained by collection of pure pancreatic juice, especially from the dorsal duct. A secretin-stimulated bicarbonate concentration of less than 105 MEq/L and pancreatic juice volume of less than 3 mL/min support a diagnosis of CP.

Manometry of the minor papilla has been performed infrequently. Normal minor papilla basal pressures have not been defined. Nevertheless, it is interesting to speculate that if a basal pressure of more than 40 mm Hg is abnormal for the major papilla, use of this number for the minor papilla may be appropriate because the pancreas presumably does not want to secrete against an excessively high barrier at either orifice. Our own limited experience with use of a standard 5F triple lumen manometry catheter (over a 0.018 guidewire) in previously untreated minor papillae has almost invariably shown very high basal sphincter pressures of more than 200 mm Hg.[37] Staritz and Meyer zum Buschenfelde[38] studied PD patients and showed that the group had high intraductal basal pressures in the dorsal duct compared with accessory duct pressures (minor papilla cannulation) in nondivisum patients (with patent major papilla orifices). He did not report, however, whether his patients were symptomatic or not. These studies need to be repeated with small-caliber (perhaps 3F) catheters which measure both intraductal and intrapapillary (intrasphincter) pressure. Once a guidewire has been passed into the dorsal duct, observation of the degree of resistance to passage of a 3F, 4F, or 5F catheter may be a gauge of the degree of minor papilla narrowing. This is not standardized but may have extrapolations to intraoperative observations used by surgeons to evaluate sphincter patency.

Lastly, trial therapy of enlarging the orifice of the minor papilla may give clinically helpful observations. Patients with daily or at least weekly symptoms can be observed after minor papilla dilation, stenting, or sphincterotomy for therapeutic response. A response to such therapy strongly implies that the minor papilla was previously too narrow. Short-term observations are difficult because a placebo effect may be present. Patients with bouts of pancreatitis occurring infrequently (perhaps 1 to 2 times per year) may require several years of observation before determining the benefits of trial therapy. Such long intervals of trial stenting are not recommended.

Intraoperative Patency Determination: Historically, the surgeon determined patency of the minor papilla by assessing the resistance to passage of a 0.75-mm-diameter lacrimal probe into the minor papilla. This, of course, requires laparotomy and duodenotomy. Endoscopic cannulation of most minor papillae with guidewires greater than 0.021-in diameter is usually difficult. The standard 0.035-in-diameter guidewire is 0.89-mm diameter. It is understandable how surgeons have reached these criteria for minor papilla evaluation. Warshaw and colleagues[24] found that patients with minor papilla narrowing by lacrimal probe patency had a high probability of response to therapy, whereas patients with patent minor papilla by lacrimal probe patency had a low probability of responding to minor papilla sphincteroplasty. Unfortunately, most studies have not addressed whether CP changes restricted to the dorsal pancreas were identified.

Histology

There are very limited data available from cutting core (eg, Tru-cut) needle biopsies of the pancreas in benign conditions. Separate dorsal and ventral biopsies have not been

reported. In resection specimens, differences in dorsal and ventral pancreas histology have been noted (ie, CP restricted to the dorsal gland).[22,39]

The numerous tests and observations noted above have received only limited assessment, and their sensitivity and specificity have largely been undefined. Collection of large series of PD patients to assess these tests remains a problem. In addition, finding a pathologically tight minor papilla does not guarantee that minor papilla therapy will be clinically effective.

Surgical Minor Papilla Sphincterotomy and Sphincteroplasty

Endoscopic management must be evaluated against the background of available surgical management methods. Published adult surgical results of minor papilla therapy are listed in Table 2.[14,24,40–48] Most surgeons also include a cholecystectomy and major papilla sphincteroplasty, thereby making pathophysiological interpretation less precise. Wedge sections of the minor papilla have shown fibrosis or inflammation in one third of specimens.[23,44] Ectopic pancreatic tissue and small neuroendocrine tumors have occasionally been found obstructing the minor papilla.[22] Where patient categorization is detailed, it is evident that patients with attacks of acute recurrent pancreatitis (ARP) are generally improved with such minor papilla therapy. In contrast, patients with established CP or those with chronic continuous pain have a lower response to such therapy. The largest series published by Warshaw et al[24] indicates that the response to ultrasound-monitored secretin stimulation tests and the clinical history help to sort out responders. In this series, 19 (90%) of 21 patients with recurrent attacks of pain and a positive secretin test had symptomatic improvement, whereas 3 (21%) of 14 patients with continuous pain and a negative secretin response had benefit from sphincteroplasty. Similarly, if the minor papilla was stenotic, as evidenced by difficult passage of a 0.75-mm lacrimal probe, the patient was more likely to benefit from the surgery. Surgical sphincterotomy series and sphincteroplasty series seem to have similar outcomes. Overall, if appropriate patients are selected, surgical responses appear excellent. Reporting of complications from surgery has not been standardized, but the morbidity rate is approximately 10%, and postoperative deaths have occurred.

Endoscopic Minor Papilla Dilation and Stenting

The minor papilla orifice may be opened endoscopically by dilation, stenting,[49–55] or sphincterotomy.[56–67] Dilation may be achieved by passage of a tapered-tipped dilating catheter (5F–10F size) over a guidewire or by passage of a small diameter, 4- to 6-mm balloon.[68] There is significant concern that balloon dilation may provoke tissue disruption and serious pancreatitis; therefore, these techniques are generally not recommended.

Stenting has been applied to the minor papilla on a therapeutic trial (short-term) and long-term basis. In patients who are having daily pain, placement of a transpapillary decompressing stent will serve as a therapeutic trial (ie, did

TABLE 2. Selected Series of PD: Surgical Therapy of Minor Papilla

		ARP			Pain Alone‡			CP§					Mean Follow-up
Author, y	Total (n)	Patients Improved (%)†	n	Patients Improved (%)	n	Patients Improved (%)	n	Patients Improved (%)	Restenosis	Major Complications	Deaths	Months
Warshaw et al,[24] 1990	88	77	43	82	45	56	0	0	7/88	1/88	0	53
Brenner et al,[14] 1990	13	54	10	70	3	0	0	0	0/13	0/13	0	18
Cooperman et al,[41] 1982	4	75	4	75	0	0	0	0	1/4	NG	0	14
Bragg,[42] 1988	4	100	3	100	1	100	0	0	0/4	NG	0	21
Rusnak et al,[43] 1988	4	75	NG	—	NG	—	NG	—	1/4	0/4	0	~48
Madura,[23] 1986	32	75	11	82	19	68	2	0	NG	3/32	0	31
Britt et al,[45] 1983	5*	60	4	75	0	0	1	0	1/5	NG	0	21
Russell et al,[46] 1984	7	71	NG	—	NG	—	NG	—	1/7	NG	0	8
Gregg et al,[47] 1983	19	53	NG	—	NG	—	NG	—	1/19	1/19	1	NG
Keith et al,[48] 1989	22*	86	13	100	8	75	1	0	1/22	2/22	0	53
Total	198	74	88	83	76	59	4	0	13/166 (8%)	7/178 (4%)	0.5%	29

All series used sphincteroplasty, except Keith et al,[48] who did sphincterotomy alone.
*Plus 1 patient who failed minor papilla identification at laparotomy.
†Includes patients graded excellent, good, and fair (if more than 50% improved and off narcotics).
‡Pain suggestive of pancreatic origin (generally epigastric with back radiation) without serological, ultrasound, CT scan, or ductographic evidence of pancreatitis.
§Some patients had heavy alcohol ingestion history.
NG indicates not given.

duct decompression resolve pain?). In patients having only episodic pain or pancreatitis, perhaps 1 or 2 times a year, short-term stenting (1–2 months) trials are of no benefit. Lans et al[53] reported a prospective randomized trial comparing long-term dorsal duct stenting to continued conservative therapy for PD patients presenting with idiopathic recurrent pancreatitis. The stents (3–7-cm long with multiple side holes) were exchanged every 3 to 4 months and were left in place for 1 year. Control patients had statistically significantly more hospitalizations, emergency department visits, and pancreatitis episodes than did treated patients. Overall, 90% of stented patients were improved, compared with 11% of controls ($P < 0.05$). Benefit generally persisted over a mean 24-month follow-up period after stent removal. More recently, the same group presented preliminary data[54] evaluating PD patients who had presented to their institution between 1995 and 2002 for evaluation of ARP (n = 83), CP (n = 38), or chronic abdominal pain alone (n = 48). Stents were exchanged at 6- to 12-week intervals for 24 to 48 weeks, with follow-up of 13 weeks to 36 months. In the ARP group, 53% had no further episodes of pancreatitis, and an additional 13% had a 50% reduction in frequency of ARP. Therapy was less effective in the other 2 groups. Only 21% of the CP patients reported complete pain relief, and 16% reported a 50% improvement, whereas the patients with pain only noted 13% complete and 10% partial responses. Post-ERCP pancreatitis rates were disappointingly high: 29.4% of ARP, 23.7% of CP, and 25.0% of pain-only patients.

The potential adverse effects of prolonged pancreatic stenting are numerous and include stent occlusion[69] or migration,[70,71] pancreatitis, pancreatic duct perforation, and pseudocyst formation. A major concern in treating minor papilla stenosis with long-term stenting is the induction of ductal and parenchymal changes indicating or simulating CP.[72] A portion of such changes are not reversible during medium-term follow-up.[73,74] Placement of 5F polyethylene stents in the normal dog pancreas over a 2- to 4-month interval has shown very worrisome induction of ductal and periductal changes of chronic fibrosis, inflammation, and atrophy.[75] Because of these observations, we strongly discourage use of long-term polyethylene stents in patients with normal-appearing pancreatograms.

Endoscopic Minor Papilla Sphincterotomy

For many years, endoscopic sphincterotomy had received limited application for opening the minor papilla. The term *papillotomy* may actually be preferred, as a true sphincter may not be present. Cotton[57] reported the first such sphincterotomy, and subsequently, several small series with brief follow-up have been published. Early attempts to treat PD patients by minor papilla snare papillectomy have been abandoned. Some series are only in abstract form or are combined with other therapies which make delineation of treatment outcome difficult. Two techniques have generally been used: (1) minipapillotome or standard papillotome (generally wire guided) to make a 4- to 6-mm incision in approximately the 10- to 12-o'clock position, after initial dilation of the orifice to 5F to 7F; or (2) placement of a small diameter, 3F to 5F plastic stent, and then perform a needle-knife cut, generally in the 10-o'clock position to a depth of 3 to 4 mm and a height of 4 to 6 mm, using the stent as a guide. Unfortunately, the landmarks for determining the appropriate depth and height of the cuts have not been precisely defined, except in Santorinicele patients where unroofing of the bulbous segment is the goal. From our experience in more than 500 cases, we prefer to use the stent and needle-knife technique,[60] with placement of a stent without an internal flange, promoting spontaneous passage.[74]

Table 3 shows that when using a global pain score method, approximately 75% of idiopathic ARP (IARP) patients are improved after endoscopic therapy. After minor papilla therapy, patients typically have fewer pancreatitis attacks and hospitalizations. These patients have typically been found to have normal dorsal ductograms at ERCP. In

TABLE 3. Selected Series of Endoscopic Minor Papilla Therapy for PD

Author, y	Therapy	Mean Follow-up (mo)	ARP		Pain Only		CP	
			n	% Improved	n	% Improved	n	% Improved
Soehendra et al,[58] 1986	MiES	3	2	100	0	—	4	75
Liguory et al,[59] 1986	MiES	24	8	63	0	—	0	—
McCarthy,[50] 1988	Stent	21	19	89	0	—	0	—
Lans et al,[53] 1992	Stent	30	10	90	0	—	0	—
Lehman et al,[60] 1993	MiES	22	17	76	23	26	11	27
Coleman et al,[61] 1994	MiES/stent	23	9	78	5	0	20	60
Sherman et al,[64] 1994	MiES	28	0	—	16	44	0	—
Kozarek et al,[62] 1995	MiES/stent	20	15	73	5	20	19	32
Ertan,[55] 2000	Stent	24	25	76	0	—	0	—
Heyries et al,[63] 2002	MiES/stent	39	24	92	0	—	0	—
Linder,[54] 2003	Stent	NG (range, 3–36)	83	66	48	23	38	37
Bierig,[65] 2006	MiES	19	16	94	7	43	16	38
Linder,[67] 2003	MiES	NG (range, 1–120)	38	58	12	0	4	25
Borak,[66] 2005	MiES	44	62	89	29	69	23	43
Total		25	328	77	145	33	135	41

MiES indicates minor papilla sphincterotomy; NG, not given.

contrast, in patients with CP changes of the dorsal duct or those with pain suggestive of pancreatic origin but no other documented evidence of pancreatic disease, approximately one half of patients experienced some pain reduction, but only one quarter of the group had at least a 50% pain improvement. Recent preliminary reports have demonstrated similar results. Bierig and colleagues[65] reviewed 41 PD patients who underwent successful minor papilla endoscopic therapy at their institution from 2000 to 2005. With a mean follow-up of 19 months (range, 1–54), 26 patients (63%) had clinical improvement: 15 (94%) of 16 with ARP, 6 (38%) of 16 with CP, and 3 (43%) of 7 with pain alone. Two others had resolution of dorsal duct leak and resolution of minor papilla bleeding, respectively. The South Carolina group[66] evaluated similar groups of patients and defined *clinical success* as improvement or resolution of symptoms, without requiring 2 or more repeat ERCPs or pancreatic surgery. Follow-up data (median, 44 months; range, 14–75) were available in 114 patients who underwent minor papilla therapy for PD between 1997 and 2003. Clinical success was achieved in 89% (55/62) of patients with ARP, 43% (10/23) with CP, and 69% (20/29) with pain only. Linder and colleagues[67] evaluated 54 symptomatic PD patients who underwent minor papilla sphincterotomy at their institution from 1990 to 2001. Follow-up was for 1 month to 10 years. Using the same criteria for improvement as their minor papilla stent trial (53), no further episodes of pancreatitis were noted in 47% (18/38) of patients in the ARP group, and a reduction in frequency of pancreatitis was noted in 11% (4/38) of these ARP patients. Only 1 of 4 CP patients had a partial response, with no patient reporting complete pain relief. None of 12 patients with abdominal pain alone benefited from minor papilla sphincterotomy. In each of these 3 preliminary studies, the authors concluded that minor papilla therapy was most effective for patients with ARP (and a normal or nearly normal dorsal ductogram), with less impressive results seen in patients with established CP or pain only. Whether patients with known causes for pancreatitis—alcohol, hypertriglyceridemia, cystic fibrosis, etc—and PD benefit from minor papilla therapy is unknown.

The overall reported response rate to minor papilla endoscopic therapy (stenting with or without sphincterotomy) mirrors the surgical sphincteroplasty results in similar patient categories. The short-term complication rate for endoscopic minor papilla sphincterotomy appears to be similar to endoscopic major papilla sphincterotomy, although experience remains limited, and reports have come only from experienced centers. When endoscopic sphincterotomy is done, post-ERCP pancreatitis rates are lower when temporary, protective pancreatic duct stents are placed.[63] A recent meta-analysis evaluating the role of these protective pancreatic stents placed via the major papilla demonstrated a significant reduction in pancreatitis rates in high-risk patients.[76] The risk-benefit ratio should be carefully reviewed with potential therapy patients. The restenosis rate for any therapy for the minor papilla is estimated to be 10% to 20%, although methods of calibration of restenosis are uncertain. Our experience agrees with that of Kozarek et al,[62] in that patients who have restenosis after endoscopic sphincterotomy also restenose after sphincteroplasty. Trials of injection of long-acting steroids around the sphincterotomy site showed a trend toward less restenosis (23% vs. 15%), but this was not statistically significant.[77] High-grade strictures of the terminal 10 mm of the dorsal duct are estimated to occur in 2% to 3% of patients. These are particularly problematic because the narrowing extends beyond the duodenal wall and a pancreatic head resection or a Puestow drainage procedure may be required. Lifelong follow-up will be needed for both surgical and endoscopic treatments. Endoscopic techniques seem preferable because laparotomy is avoided. Because similar techniques are now being applied to children,[78,79] long-term outcomes are especially important in this group. As with pancreatic stenting, pancreatic sphincterotomy should be restricted to large centers with extensive experience in therapeutic ERCP. Further randomized trials comparing various therapeutic alternatives are awaited.

Summary

Overall, we believe that PD should be considered an etiologic factor in previously unexplained acute pancreatitis. The increased incidence of this congenital anomaly in patients with IP, findings of CP confined to the dorsal ductal system at ERCP or in resected specimens, and response to endoscopic or surgical therapy supports this belief. On the other hand, in patients where changes of CP are identified in both the ventral and dorsal systems, the finding of PD is clearly incidental, and a careful search should be made for an alternative etiologic factor. Furthermore, evidence now supports the role for endoscopic therapy in patients with IP, PD, and a normal dorsal ductogram, as outlined above. Indeed, although isolated dorsal changes of CP may support a causative role, patients with a normal duct respond better to minor papilla therapy. In more than 300 patients reported in the literature to date, three quarters of these patients have typically noted reduced global pain scores and fewer subsequent pancreatitis attacks and hospitalizations. Patients with idiopathic recurrent pancreatitis and established changes of CP at dorsal ductography do less well. Results of large, prospective studies with longer follow-up (ie, >10 years) are awaited. Methods to select patients who are likely to respond to invasive therapy need refinement; perhaps secretin-enhanced Magnetic Resonance Pancreatography may play a role. Clinicians and endoscopists are strongly encouraged to be cautious and conservative with this patient group until stronger data indicate optimal management schemes.

IDIOPATHIC PANCREATITIS IN PATIENTS WITH PD AND NORMAL DUCTS: THE CASE AGAINST ENDOSCOPIC THERAPY

Drs Matthew J. DiMagno and Eugene P. DiMagno

Centuries before the discovery that the pancreas is a physiologically significant secretory organ, Claudius Galenus (approximately AD 130–200) recognized that the pancreas contained duct structures, as did Andreas Vesalius ("*de humani corporis fabrica," 1543)*.[80] Vesalius, however, as

quoted by Schirmer,[80] metaphorically described the function of the pancreas as a *pulvinaris* or protective cushion for the stomach and vascular structures. *Pulvinaris* is the Latin word used for the cushion seats or couches the gods rested on at feasts.

In homineautem hoccorpus magis album quam rubrum cernitur, venae portae, arteriarum et nervorum ramis inibi attensum, ut illorum divaricatio inferori membrane omenti duntaxat suffulta, reddatur securior, utque ventriculo etiam instar substerniculi ac pulvinaris subjiciatur.

In humans, this body (the pancreas) is perceived as more white than red, and extends to the portal vein and the branches of the arteries and nerves, which are in that place, where it (on one hand) spreads under the fatty under membrane, and in so far, lays a foundation for (these structures), which are made more secure, (but also) certainly spreads under and attaches to the stomach, resembling a substratum or cushion seat for it.

Clearer understanding of pancreatic duct anatomy occurred in 1641 when Moritz Hoffman[80,81] discovered the "duct of Wirsung" in a Rooster pancreas. One year later, in 1642, Wirsung[81,82] reported this finding in the human pancreas. Later, others identified additional pancreatic anatomical structures and normal variations. The discoveries of the pancreatic accessory duct, the papilla duodeni major (ampulla of Vater) and PD have been attributed to Giovanni Domenico Santorini (1681–1737), Abraham Vater (1684–1751), and Joseph Hyrtl (1810–1894), respectively, but as reviewed by Stern,[31] each of these structures had been observed and reported by multiple anatomists during the 17th century. In 1859, Hyrtl[83] coined PD when he observed "*Ein Pancreas Divisum*" at autopsy of a newborn child whose pancreas displayed nonfusion of the embryonic ventral and dorsal duct systems. Whether this entity had clinical significance, specifically related to pancreatitis, however, was not seriously considered until the 1970's, when endoscopists, using ERCP, increasingly identified this variant anatomy during life. Even now, it is controversial if PD causes pancreatitis. Our aim is to clarify this controversy for clinicians so our patients will be managed appropriately.

The analysis of the association of PD to pancreatitis is difficult because authors use different terminology for pancreatitis and likely enter different subsets of patients into their studies. The most common term investigators use is IARP. In our opinion, IARP is a misnomer because this assignation does not consider that this condition is CP from the initial presentation of symptoms. Use of IARP arose because patients with early onset idiopathic CP have recurrent episodes of painful attacks during their early course of the disease when hallmarks of CP are not present. The natural history of early onset idiopathic CP[84] is an initial presentation with pain; followed by recurrent attacks of pain at variable intervals of months to years. Detection of the hallmarks of CP (calcification, diabetes, and malabsorption) occurs years later. In support of the premise that IARP is CP, consider that in endoscopic studies up to 53% of patients with recurrent pancreatitis had evidence of CP.[4,9,12,85] Therefore, in this paper, we will use the term IP and include within this term the diagnoses of acute and chronic IP made by others.

Two other points deserve consideration/clarification. First, the perceived benefits of endoscopic therapies should be tempered by evidence that many of these patients who do not undergo invasive therapy have a benign clinical course,[8,51,86] consistent with IP. Second, investigators frequently perform invasive endoscopic and surgical treatments on patients with abdominal pain who have little evidence of pancreatitis. Appreciation of the natural history of idiopathic CP and inclusion into studies of only patients with a definitive diagnosis of pancreatitis would greatly advance the analysis of the effects of invasive procedures in IP.

Objective

Management of patients with PD and pancreatitis depends upon answers to several important questions. Is there a causal relationship between pancreatitis and PD? Do interventional therapies prevent recurrent attacks of pancreatitis? Do interventional therapies expose patients to significant risk, abrogating the Hippocratic Oath to first-and-foremost "do not harm." Thus, our objectives are to discuss the association of PD with IP, the hypothesis that PD causes pancreatitis[9,47,87] and that endoscopic therapy prevents recurrent attacks of pancreatitis. In addition, the discussion includes alternative explanations for IP in PD (eg, association with *CFTR* dysfunction and/or mutation),[88,89] recent evidence-based assessments for performing endoscopic therapy (pro and con),[90–92] ERCP complications and diagnostic pitfalls,[93] and a summary. The following case report illustrates some of these issues including the long time interval between some attacks of pain and evidence of CP 15 years after the initial attack of pain, characteristic of IP. In addition, sphincterotomy failed to prevent recurrent painful attacks.

Case Report

A 26-year-old woman presented in 1990 with recurrent episodes of pancreatitis, characterized as epigastric abdominal pain associated with more than 3-fold elevation in serum amylase and lipase. She experienced her first attack at age 11, followed by attacks at ages 18 (twice), 24, and 26. She underwent cholecystectomy at age 24, which revealed no evidence of cholelithiasis. In March 1990 (age 26), interpretation of an ERCP was that it showed PD, but otherwise, the ducts were of normal appearance (Fig. 1), and she underwent surgical sphincterotomy of the minor papilla. She had no further attacks for 2 years until March 1992 when she experienced recurrent pain associated with a more than 4-fold elevation of serum lipase. At a subsequent ERCP (Fig. 2) in 1994 (age 30), there was no evidence of stricturing at the orifice of the dorsal duct. There was, however, evidence of CP of the dorsal and ventral ducts.

Hypothesis

The rationale for performing endoscopic therapy in patients with IARP with PD and normal ducts derives from

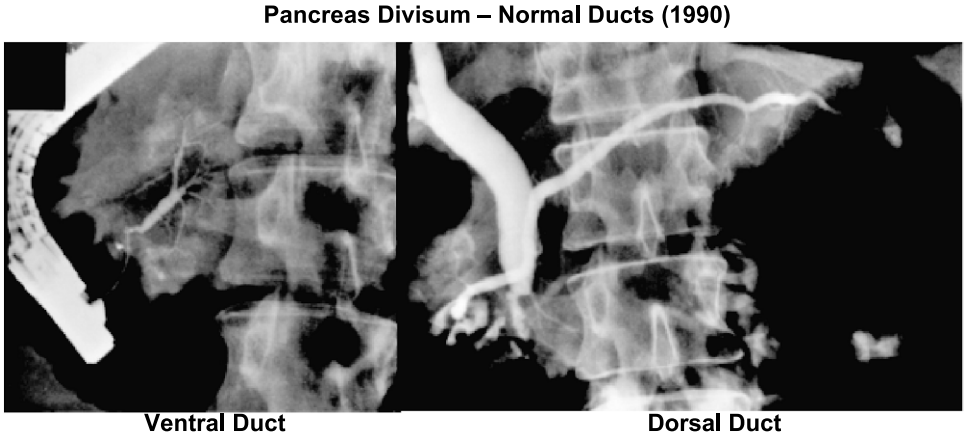

FIGURE 1. Endoscopic retrograde cholangiopancreatography conducted in March 1990 (age 26) showed PD but otherwise normal-appearing ventral (left) and dorsal (right) ducts.

the hypothesis that obstruction of the minor papilla causes pancreatitis.[9,47,87] If this hypothesis is correct, the prevalence of PD in pancreatitis should be greater than the prevalence of PD in the general population, dilatation of the dorsal duct system should be present if there is a functionally significant obstruction of the dorsal duct, and disease should only develop in the dorsal duct.

Association Between PD and IP

What is the true prevalence of PD in persons without and with pancreatitis? How accurate is the detection of PD by ERCP? Is the prevalence of PD in patients with pancreatitis greater than in the general population? Answers to these critical questions are necessary to determine if there is an association between PD and pancreatitis.

General Comments About the Literature Review and Statistical Methods

Autopsy, ERCP, and magnetic resonance cholangiopancreatography (MRCP) have been used to assess the prevalence of PD in the general population and in patients with pancreatitis. We included in our analysis only manuscripts we could personally review. We did not rely upon secondary reports. References in languages other than English were used only if we could translate the manuscripts (Latin and German). In 8 non-English publications, we extracted information primarily from the abstract because only the abstract was written in English[59,94–98] or the full article was not available,[99,100] but in the former instance, we used interpretable data tables present in the manuscript.[59,98] With these restrictions, we reviewed 23 autopsy,[3,80,81,101–120] 41 ERCP,[8,9,12–14,25,41,45,47,59,85–87,94,95,97–99,120–143] and 13 MRCP[96,98,100,137,144–152] studies (Appendices 1–8, Fig. 3).

Studies among the 3 methods of assessing prevalence of PD are heterogeneous and therefore not amenable to standard meta-analysis. Nevertheless, to obtain some measure of possible differences among the methods for assessing PD prevalence, we calculated the 95% CIs by assuming an α level of less than 0.05 to be significant at the $P < 0.05$ level (Fig. 3). Data derived from these analyses we present in the text as mean % (95% CI).

General Comments About Methods to Diagnose PD

Perhaps, the strongest data to determine the true prevalence of PD in the general population are from autopsy studies. Unlike most endoscopic studies, the objective of autopsy studies was to classify normal variations of human pancreatic ducts and structures and not to determine if there was a relation between PD and IP. Indeed, 91% (21/23) of autopsy studies were completed before clinicians claimed an association between PD and pancreatitis, and with the

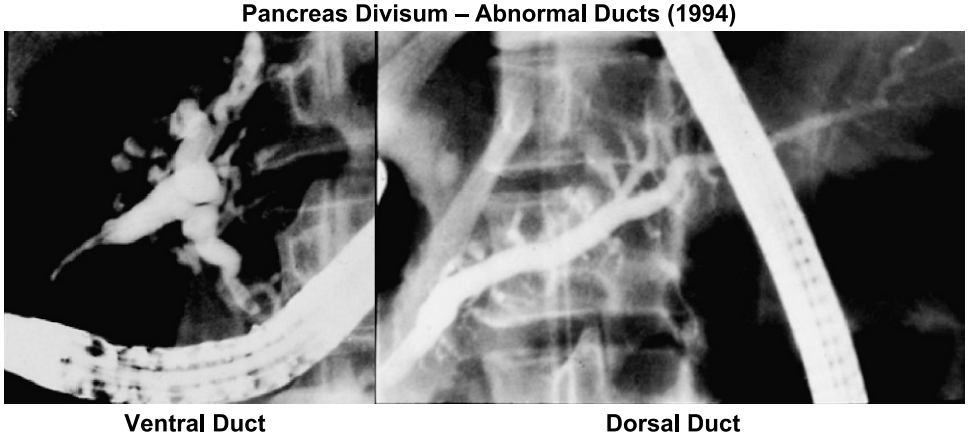

FIGURE 2. A subsequent ERCP conducted in 1994 (age 30) showed interval development of CP with dilated ventral (left) and dorsal (right) ducts.

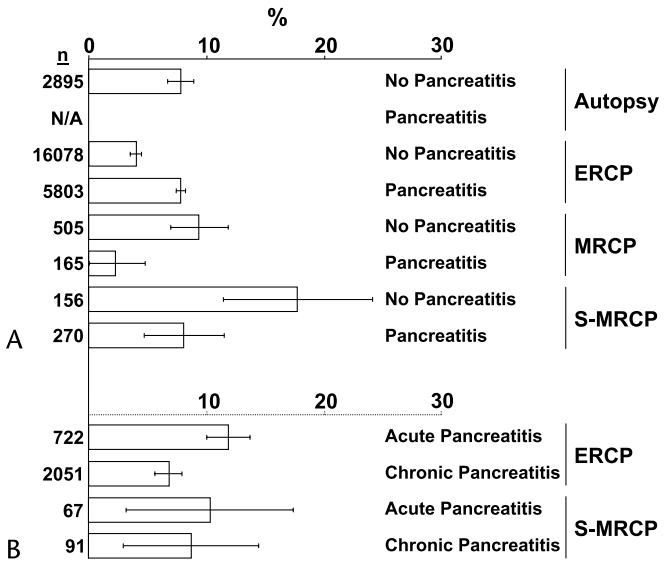

FIGURE 3. Prevalence of PD. Bars represent mean PD as % total cases (n), and error bars are 95% confidence intervals (CIs). A, The prevalence of PD without or with pancreatitis reported in autopsy, ERCP, MRCP, and secretin-MRCP (S-MRCP) studies. B, The prevalence of PD with acute and CP reported in ERCP and S-MRCP studies.

exception of a recent study,[120] PD was not mentioned in the publication title. Hence, autopsy studies lack referral bias (eg, patients referred after unsuccessful ERCP have PD as frequently as 50% [14/28][147]) and technical bias (eg, failure to access and inject the dorsal duct) inherent in endoscopic studies. Magnetic resonance cholangiopancreatography, however, may be preferable to assess the prevalence of PD because it minimizes iatrogenic complications and referral bias and pitfalls associated with failed cannulation and injection of the dorsal duct present in ERCP studies. In addition, advances in fast magnetic resonance technology, phased array coils, and use of secretin have increased image resolution. Secretin improves the rate of cannulating the dorsal duct during ERCP[151] and improves the visibility of the dorsal duct during MRCP.[148,149,154–156]

Prevalence of PD in the populations of persons without pancreatitis (assumed to be the general population) varies among the 3 different types of studies (no pancreatitis in Fig. 3A, Appendices 1–4). The prevalence of PD in persons without pancreatitis was *significantly higher* in the autopsy, S-MRCP, and MRCP studies than in the ERCP studies. In autopsy studies (Fig. 3A, Appendix 1), the prevalence of PD is 7.8% (95% CI = 6.8–8.8; 226 of 2895 autopsies). The prevalence of PD in patients without pancreatitis tested by S-MRCP[98,146–151] (Fig. 3A, Appendix 3) is 17.9% (95% CI = 11.9–24.0; 28 of 156 S-MRCPs) and by standard MRCP studies[96,100,137,144–147,152] (Fig. 3A, Appendix 4) is 9.3% (95% CI = 6.8–11.8; 47 of 505 MRCPs). By contrast, in ERCP studies[8,9,12,13,25,45,59,85,126,129,131–133] (Fig 3A, Appendix 2), the prevalence of PD in patients without pancreatitis is significantly less, 4.1%, (95% CI = 3.8–4.4; 661 of 16078 ERCPs).

Thus, from the autopsy studies, the prevalence of PD in the general population approximates 8%, indicating that endoscopists performing ERCPs underrecognize the prevalence of PD in patients without pancreatitis. Analysis of the MRCP studies suggests that the prevalence of PD in the general population is higher than 8%. Interpretation of the MRCP data, however, is tempered by the limitation that MRCP "cannot completely exclude a connection between the dorsal and ventral ductal system (incomplete PD) due to limited spatial resolution"[157] and may overestimate the prevalence of PD. With this understanding, based on S-MRCP data (Fig. 3, Appendix 3), it is likely that the prevalence of PD in the general population approximates 10% to 18%. The 10% prevalence arises by assuming that detection of PD is correct only in the 89% (67 of 75) of PD diagnoses subsequently confirmed by ERCP.[98,146–151] The 18% prevalence of PD arises by assuming that all 75 PD diagnoses were correct, including the 8 of 75 cases that had no confirmatory ERCP.[98,148]

Prevalence of PD in Persons With Pancreatitis

In this analysis, we relied upon ERCP and MRCP studies to determine the prevalence of PD in IP because autopsy data on the prevalence of PD in pancreatitis are sparse. The cumulative data analyses of ERCP studies supporting[8,9,12,45,59,85,138] or refuting[13,25,126,129,131–133,136] a greater incidence of PD in pancreatitis (Fig. 3A, Appendix 2) reveal a statistically significant difference in the prevalence of PD in patients with pancreatitis versus those without pancreatitis (7.6 [95% CI = 7.0–8.3] vs. 4.1 [95% CI = 3.8–4.4]). This finding, however, is of questionable clinical significance for several reasons. The ERCP prevalence data for PD in pancreatitis patients is not statistically different compared with prevalence of PD in the general population of autopsy studies (7.6% vs. 7.8%). The prevalence of PD in patients without pancreatitis is *statistically lower* in ERCP versus autopsy (4.1 [95% CI = 3.8–4.4] vs. 7.8% [95% CI = 6.8–8.8]; Fig. 3A). Furthermore, although the prevalence of PD in patients with pancreatitis was similar in the S-MRCP studies (8.1% [95% CI = 4.9–11.4]) and ERCP studies, the prevalence of PD in patients with pancreatitis in the S-MRCP studies was much lower than in persons without pancreatitis (8.1% [95% CI = 4.9–11.4] vs. 17.9% [95% CI = 11.9–24.0]; Fig. 3A, Appendix 3). The accuracy of ERCP prevalence data for PD in pancreatitis is also questionable because 8 studies[86,95,125,127,134,138,141,143] lack any control population but were nonetheless included in the analysis for completion. Hence, these data further emphasize that endoscopists underestimate the prevalence of PD in the general population leading to the doubtful conclusion that the prevalence of PD is increased in patients with pancreatitis.

Prevalence of PD in Acute and CP

Some make the claim that the prevalence of PD is only increased in patients with acute IP. As noted earlier, we hold the distinction between acute and chronic IP spurious. Nevertheless, to investigate any potential differences of PD prevalence in these subsets of patients with acute pancreatitis

and CP, we analyzed 6 of the 41 ERCP studies and 2 of the 7 S-MRCP studies that separated pancreatitis into acute or chronic disease (Fig 3B, Appendices 5–6). Among these studies, the prevalence of PD in acute pancreatitis and CP varies between 6.8% and 12% (Fig. 3B, Appendices 5–6). The only apparent significant difference among the acute pancreatitis and CP groups is the apparent increase in the prevalence of PD in acute pancreatitis compared with CP with ERCP (12.0 [95% CI = 9.7–14.4] vs. 6.8% [95% CI = 5.7–7.9]). On closer analysis, however, the increased PD prevalence in acute pancreatitis in the 5 ERCP studies shown (Appendix 5) is directly attributable to 2 publications that are from the same investigators.[8,129] Hence, our interpretation of the data is that most of the studies (3/5) show no increase in the prevalence of PD in acute pancreatitis compared with autopsy studies. Furthermore, the data from the largest endoscopic series of patients with PD (n = 304) illustrate that the frequency of PD is similar in acute pancreatitis and CP (6.9%) when compared with all the patients who underwent ERCP (n = 5357).[13] One explanation for the contrasting observations in the 2 studies claiming an increased prevalence of PD[8,127] (Appendix 5) in acute pancreatitis[13,25,126] is that Sahel et al[129] overestimated the prevalence of PD because they obtained only a ventral duct pancreatogram in most cases (a dorsal duct pancreatogram was performed in only 34% of patients by Sahel et al[129] vs. 60% by Delhaye et al[13]) and assumed a PD was present only on the appearance of the ventral duct. Secondly, Sahel et al[129] likely underreported the prevalence of PD in patients without pancreatitis because they did not carry out a diligent search for PD. Endoscopists believe that PD is a cause of pancreatitis and very carefully search for PD in patients with a history of pancreatitis but fail to visualize both duct systems as assiduously when doing procedures in patients without a history of pancreatitis.

In summary, according to autopsy and MRCP studies, the overwhelming evidence is that the prevalence of PD in the general population is approximately 8%. By contrast, in ERCP studies, the prevalence of PD in patients without IP (general population) is approximately 4%, whereas the prevalence of PD in IP patients is approximately 8%. Endoscopists interpret these data as showing an increased prevalence of PD in IP. These combined data, however, point to a more realistic if not inescapable conclusion that endoscopists underrecognize PD in the general population and that there is no association between PD and IP.

Does Dilatation of the Dorsal Duct Occur in PD?

If the hypothesis is true, dilatation of the dorsal duct system should be present if there is a functionally significant obstruction of the dorsal duct. Most patients with PD, however, do not have a dilated dorsal duct[44,46,127,129,158] even when pancreatitis is associated with PD.[159] Thus, proponents of the PD causing pancreatitis hypothesis claim that the flow rate approximately 2 L/d of pancreatic juice through the dorsal duct into the duodenum decreases and intraductal volume increases without increasing intraductal pressure above the threshold that causes ductal dilatation. Investigators interpreted results of 1 recent uncontrolled surgical study as showing that reduction in pancreatic duct and sphincter pressures after sphincteroplasty predicted a good outcome.[160] However, diagnostic tests for assessing the presence of functional obstruction are not specific (secretin induced duct dilatation detected by US/MRCP is "abnormal" in 50% of normal controls[35] and does not differ in patients with or without PD,[147,148]) and/or results of standardized tests (sphincter manometry) do not correlate with symptoms or predict response to intervention.[159]

Does Pancreatitis Associated With PD Develop Exclusively in the Dorsal Duct System?

If pancreatitis associated with PD is due to obstructed flow of pancreatic juice through the dorsal duct, pancreatitis should reside only within the parenchyma drained by the dorsal duct system. Several studies indicate that this is not so. Although Cotton[27,161] demonstrated that patients with PD may have normal histology of the ventral pancreas, pooled data from endoscopic,[5,8,12,25,27,29,30,47,52,87,136,162–165] magnetic resonance imaging,[138] and autopsy[93,119] data (Appendix 7) indicate that ventral duct pancreatitis is present in up to 11.8% cases with PD and is the only duct affected in 4.2% of cases with PD. During clinical follow-up,[138,164] many patients with isolated ventral duct pancreatitis will develop dorsal duct pancreatitis.

In addition, patients with PD and recurrent pancreatitis have histological evidence of CP in tissue drained by the dorsal and ventral duct systems, underscoring the point that IARP is an inaccurate label. For example, Madura et al[160] reported that of 74 patients with PD and symptoms suggestive of pancreaticobiliary disease who had a surgical sphincteroplasty, 41.5% had histological evidence of inflammation and/or fibrosis in the accessory papilla, and 43.4% had inflammation and/or fibrosis in the ventral system, including the transampullary septum and the major papilla in 20%. The prevalence of inflammation and/or fibrosis in the ventral system in this study may be an underestimate because biopsies were not performed in all patients and because there was a small representation of ventral and dorsal pancreas histology. Results of this study and the findings of CP in both dorsal and ventral ducts in our patient (Fig. 2) indicate that in patients with IP and PD, a factor other than PD is responsible for pancreatitis. Although a weak argument might be that pancreatitis originates in the dorsal pancreas and subsequently spreads to the ventral pancreas, presence of pancreatitis in the dorsal and ventral pancreas raises questions about the rationale of endoscopic/surgical intervention for IP with PD, particularly as these interventions cause significant morbidity and even death.[92,166–168]

Alternative Explanations for IP With PD-Role of *CFTR* Mutations

Two recent studies[88,89] provide compelling evidence that aberrant functioning of the cystic fibrosis transmembrane conductance regulator (*CFTR* is present in some patients with IP and PD and may be the cause of IP. First, Choudari et al[88] tested for the 13 common *CFTR* gene mutations and found that they were present in 22% (8/37) of those with PD and IP

and in 0% (0/20) in patients with PD and no pancreatitis (P = 0.02, 22% vs. 0%). The prevalence of *CFTR* gene mutations in patients with PD and IP was remarkably similar to the 19% (19/96) prevalence of *CFTR* gene mutations in all IP patients. Correspondingly, the 0% prevalence of *CFTR* gene mutations in patients with PD and no IP was similar to the prevalence of 3.5% (7/198) in controls without pancreatitis and 2.6% (2/78) in controls with pancreatitis of known cause (eg, gallstones, hypertriglyceridemia, etc). These data correlate with the landmark observations of an increased prevalence of *CFTR* gene mutations in IP by Sharer et al and Cohn et al[169,170] and illustrate that IP patients with and without PD have a similar prevalence of *CFTR* gene mutations. Therefore, collectively, these data indicate that in patients with IP and PD, predisposing factors (eg, *CFTR* gene mutations) other than PD are necessary for pancreatitis to develop. More importantly, PD is unnecessary for pancreatitis to occur in patients with *CFTR* gene mutations. The data of Choudari et al[88] are even more impressive because these investigators likely underestimated the true prevalence of *CFTR* mutations in IP. For example, Bishop et al,[171] using exhaustive gene identification methods, showed that the frequency of *CFTR* gene mutations in patients with IP classified as acute or chronic disease was 34% and 50%, respectively.

Equally provocative, similar conclusions may be drawn from the study of Gelrud et al[89] who showed that *CFTR* dysfunction (determined by nasal potential difference testing) associates with PD and IP. Twelve patients with PD and IP had an intermediate value of nasal epithelium *CFTR* function in response to isoproterenol, between values for normal controls (P = 0.001) and those with classic cystic fibrosis (CF) (P < 0.0001) who had pancreas sufficiency or insufficiency (Fig. 4). In addition to substantiating the clinical association of aberrant *CFTR* function with IP and PD, Gelrud et al[89] also provided insight on endoscopic therapy and the rarity of this condition. The 12 patients with IP and PD had 2 to 5 ERCPs, 10 of 12 had endotherapy (stent/sphincterotomy), and 8 had a cholecystectomy. Despite the extent of these endoscopic and surgical interventions, only 2 of 10 who underwent endoscopic and/or surgical interventions had resolution of symptoms. Although the reported therapeutic component of this study was not randomized or controlled, the results do not support invasive therapy (which is further addressed below). Secondly, the authors point out that only a few patients with both PD and IP could be found at 3 institutions, indicating that this is not a common problem. Thus, these findings cast further doubt on the controversial hypothesis that PD triggers IP and raise serious questions about the rationale for endotherapy in those rare patients with IP and PD.

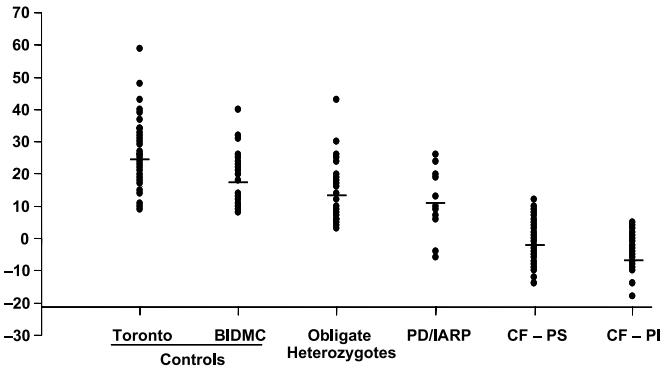

FIGURE 4. Nasal transepithelial potential difference measurements. Direct measurement of *CFTR* function in nasal epithelium in response to isoproterenol, a stimulator of cyclic-adenosine monophosphate–mediated chloride secretion through *CFTR*. Groups studied include controls from Toronto (n = 50) and Beth Israel Deaconess Medical Center (BIDMC, n = 19), obligate *CFTR* heterozygotes (n = 16), patients with PD and IARP (PD/IARP, n = 12), and CF patients with pancreatic sufficiency (CF-PS, n = 56) or insufficiency (CF-PI, n = 39). Figure modified from Gelrud et al.[89] P < 0.0001, among groups; P < 0.02 or less, each group versus controls.

Evidence-Based Literature Reviews of Endotherapy in IP With PD

Evidence-based reviews of endotherapy in IP with PD and normal ducts substantiate flawed characteristic(s) in every study including small sample size, referral bias, population heterogeneity (IP, pancreatic-type pain without objective evidence of pancreatitis), short duration, high endoscopic placebo effect, patients lost to follow-up, absence of a control group, blinding, and randomization. Major flaws of many studies are that the response to endoscopic interventions is used to substantiate a causal relationship between PD and pancreatitis[167] and that patients classified as having a good to excellent response in one series may have sought and received care elsewhere for less than satisfactory results. These flaws occur because no diagnostic test reliably predicts the "symptomatic response" to dorsal duct decompression. Thus, investigators who use endoscopic interventions do not establish a causal relationship between PD and pancreatitis and cannot predict the likelihood of a symptomatic response.

The poor design of the studies also relates to inadequate understanding of the natural history of IP. In this regard, 4 points warrant emphasis. Many patients with IP have long intervals between attacks. For example, after surgery on the minor papilla, symptoms recur after 1 to 2 years.[52] Hence, short-term studies are of little value to assess results of interventions. Second, patients with IP and PD who undergo invasive therapies frequently require multiple surgeries and/or endoscopic interventions.[51] Third, patients with IP and PD who do not undergo invasive therapies appear to have a benign clinical course.[8,51,86] When the diagnoses of PD and acute pancreatitis appear firm, morbidity is low. For example, Bernard et al[8] reported that 50% of 58 patients with a single or recurrent attacks of IP had PD, and all IP patients had a mild clinical course: "In no instance was PD-associated idiopathic AP (acute pancreatitis) severe from a clinical point of view. The generally recurrent painful episodes were always well tolerated with neither loss of weight nor deterioration in general condition." Fourth, a high "placebo effect" occurs after either interventional or medical treatment of patients with pancreatitis or presumed pancreaticobiliary pain. That is, merely intervening by either doing a sham procedure or administrating a placebo drug reduces

attacks of pain (particularly if pain is not pancreatic). For example, Wilcox[172] noted an endoscopic placebo response rate of 38% in patients with type 2 and 3 sphincter of Oddi dysfunction (SOD), and we previously noted a similar placebo response rate when we tested the effect of octreotide in patients who had CP and severe pain (type B).[173] In situations where a therapeutic response is noted, Cooperman et al[174] pointed out that it remains unclear "Whether this represents a satisfactory result, stabilization of the disease, symbiosis between patient and symptoms, or fear of admitting persistent symptoms…" Hence, to determine whether endoscopic therapy is effective requires properly randomized and controlled trials of treatment versus no treatment.

In an evidence-based review, Mark et al[90] stated that no study met criteria set for review (a controlled study with a minimum of 25 patients per treatment arm). Yet, he placed a fair amount of emphasis upon a small, randomized controlled trial by Lans et al.[53] These investigators showed that ERCP + stenting of the dorsal duct for 1 year (n = 10) versus ERCP alone (n = 9) decreased the incidence of painful attacks in patients with IP (7:1) and hospitalization (7:0) and was associated with increased subjective improvement (9:1). A similar conclusion was reached by 2 retrospective, single arm studies. Kozarek et al[62] showed that endoscopic therapy with ERCP in 39 patients (stent [n = 13], sphincterotomy [n = 4], stent + sphincterotomy [n = 22]) decreased the frequency of painful attacks in patients with IP from 2 to 0.3 per year ($P < 0.02$) and Lehman et al[60] showed that ERCP and sphincterotomy in 52 patients decreased the frequency of attacks of IARP from 9.1/year to 1.0/year ($P < 0.02$). Among the deficiencies of the Lans et al[53] study were a very small sample size, short duration (<1 year) and lack of masking the patients or investigators. Deficiencies of the Kozarek et al[62] and Lehman et al[60] (before and after in same patients) studies included the lack of considering the natural history of pancreatitis (long intervals between attacks and high placebo effect) and the uncontrolled and retrospective nature of the studies. Another major problem is that the diagnosis of pancreatitis, particularly in the Lans et al[53] study, is questionable because the patients had pancreatic pain with minimal amylase elevations and no other indicators of pancreatitis (Table 4). Mark et al[90] note the very significant limitations of these studies by stating the "…evidence is sparse and largely uncontrolled…," but he surprisingly claims the study by Lans et al[53] as fair and "…suggests that ERCP treatment reduces hospitalizations and emergency room visits …".

Another weak endorsement of endoscopic therapy for PD, possibly reflecting the biases of endoscopists rather than an unbiased evaluation of available data, is the National Institutes of Health consensus panel[92] conclusion "…that ERCP treatment with stent or sphincterotomy decreases recurrent…pancreatitis and reduces pain…a single trial (supports)…but further research is warranted." In contrast, Clain and Pearson[91] in their evidence-based assessment challenged the concept that PD is a cause of pancreatitis and provided a more logical conclusion. First, they pointed out that studies inconsistently demonstrate an increased incidence of IP in PD and evidence of dorsal duct obstruction. Secondly, there is a lack of properly randomized and controlled trials of treatment versus no treatment. They summarized by challenging the assumption that treatment of PD requires accessory papillotomy and stenting and indicated that there may be other explanations for pancreatitis (as outlined in a recent review).[175]

TABLE 4. Diagnostic Criteria for IP Used by Endoscopic Studies

Study	Criteria for Diagnosis of IP
Lans et al[53]	1. >2 episodes of abdominal pain 2. >2 fold elevation of serum amylase
Kozarek et al[62]	Not provided
Lehman et al[60]	1. >2 discrete attacks of abdominal pain 2. abnormal serum amylase or lipase and/or CT scan or ultrasound changes of acute pancreatitis

Diagnostic criteria for IP used in endoscopic studies analyzed by Mark et al[90] in a recent evidence-based review of endotherapy in IP with PD.

ERCP Complications and Diagnostic Pitfalls

Complications of ERCP (and endotherapy) are not trivial and occur in up to 50% of cases.[60,176] Immediate complications include pancreatitis in 5% to 7% (20% in SOD with normal bilirubin), hemorrhage, perforation, death[92,166–168] as occurred in 1 patient in the present series, and a 30-day mortality rate of 5.8% observed in a recent prospective study of complications in 1177 ERCPs.[168] Delayed complications include papillary stenosis,[167] stent-induced dorsal duct changes (in up to 50%),[60,176] and conversion of a presumed dysfunction of the dorsal duct to a mechanically/organically altered duct resembling CP, for which the prevention is avoiding unnecessary ERCP. Even surgery for PD carries a significant risk of complications. Madura et al[160] reported that complications occurred in 34.8% of patients, including 1 death, and more than 44.6% of patients underwent 2 or more surgeries/procedures.

An important pitfall of ERCP is that findings may be misinterpreted as PD. A shortened ventral duct interpreted as PD may be a "false PD"[177] attributable to other pathophysiological causes,[93,123,177–179] including a fibrotic stricture (from alcoholic and CF-related pancreatitis) or pseudocyst in CP, previous pancreatic trauma, partial pancreatectomy, or tumor (Table 5). In situations where "false PD" is suspected, S-MRCP (or endoscopic ultrasonography or CT) may be a better test rather than attempting ERCP cannulation of the dorsal duct, which may carry a substantial risk of pancreatitis. In addition, it is important to realize that a confounding factor in detecting PD is that the dorsal duct does not communicate with the duodenum in 29% to 90% (627/1102; mean, 56.9 [95% CI = 54.0–59.8]; Appendix 8) of humans without known pancreatic disease[80,81,102,103,111–114,116–118,180] and may end blindly in cul-de-sac. Secretin-MRCP or EUS with secretin may be useful to differentiate between dorsal duct blind termination and patency through the accessory papilla.

Review for Case Report

To obtain data pertinent to our case report, we reviewed 24 patients with PD (9 evaluated by E.P. DiMagno, the

TABLE 5. Factors Contributing to Endoscopic Appearance of PD

Case Series	Explanation for ERCP Findings of PD
Thal et al[178]	Calcification/fibrotic stricture (1)
Belber and Bill[123]	"Pathologic obstruction" (7) [>3 due to carcinoma]
Warshaw and Cambria[177]	Pseudocyst (2), fibrotic stricture (5), anomalous duct system (1)
Sharma[179]	Carcinoma (3), trauma (2), pancreatitis with pseudocyst (1)
Kamisawa et al[93]	Fibrotic stricture (1)

Numbers inside parentheses and brackets indicate the number of patients with condition.

remainder was evaluated by other gastroenterologists). The Mayo Foundation Institutional Review Board approved this study. Of the 24 patients, 8 (33%) had pancreatitis, but only 2 of the 8 (25%) had IP—both these patients underwent sphincterotomy of the accessory papilla without resolution of symptoms. The causes of pancreatitis were hypercalcemia (n = 1), hyperlipidemia (n = 1), gallstones (n = 1), and alcohol (n = 2), and 1 patient had pancreatitis involving both ducts. The diagnoses of patients with PD but no pancreatitis were gallstones (n = 5), chronic pain syndrome (n = 3, 1 with salivary hyperamylasemia), sclerosing cholangitis (n = 2), pancreatic cancer (n = 2), metastases to the pancreas (n = 2; alveolar cell cancer, breast cancer), primary biliary cirrhosis (PBC) (n = 1), and an enlarged pancreas due to nonfusion of dorsal and ventral pancreas (n = 1). To underscore the risks of endotherapy, 1 post-ERCP death occurred due to hemorrhagic pancreatitis.

From this small but consecutive series of patients with PD, we conclude that referral centers with expertise in pancreatic disease may encounter a high proportion of patients with PD (33% in our series), but most patients will have pancreatitis due to other causes (75%) rather than IP. The 25% prevalence of IP among all cause of pancreatitis in this small series of PD is remarkably similar to approximately 20% rate of IP in our much larger study of the natural history of pancreatitis,[84] suggesting that the prevalence of IP in PD patients with pancreatitis is no greater than in the overall population of patients with pancreatitis. Thus, patients assumed to have IP due to PD should be assessed carefully by reviewing the patient's history and all data for previous episodes of presumed pancreatitis. This review is necessary to determine the validity of the diagnosis of pancreatitis, to exclude causes of pancreatitis such as *CFTR* mutation, gallstones, alcohol, metabolic abnormalities, and previous ERCP/treatment, and to exclude other problems that may explain the symptoms,[175] including but not limited to chronic pain syndrome, pancreatic cancer, metastases, irritable bowel, or radiculopathies.

Summary

Endoscopists and surgeons generally agree that caution should be exercised in evaluating and managing patients with IP and PD, but not always for the same reasons. Arguments against endotherapy are numerous (see Table 6).

1. Pancreas divisum is not more frequent in patients with IP and thus does not cause IP. Because the prevalence of PD is so similar between the general population and persons with IP, enthusiasm for generating new data to disprove this conclusion in a well-designed study using noninvasive tests may be quenched by the required size and expense of the study. For example, by assuming a PD prevalence of 8% in the general population and 12% in persons with IP, more than 900 persons per group would be required to generate enough power to show a statistically different PD prevalence ($P < 0.05$) between these 2 groups. An even more daunting sample size of 3940 persons per group would be necessary to show a significant difference if 10% is assumed to be the prevalence of PD in the general population and 12% in persons with IP.
2. There is increasing evidence that IP with PD is caused by *CFTR* gene mutations and other yet undiscovered genetic abnormalities, metabolic abnormalities (hyperlipidemia, hypercalcemia), or alcohol. These data also indicate that PD likely represents an incidental finding and does not cause pancreatitis.
3. In some patients, the erroneous interpretation of the presence of PD at endoscopy may be due to a fibrotic stricture secondary to CP or obstruction of the ventral duct by pancreatic cancer.
4. Endoscopic therapy does not benefit patients and instead causes pancreatitis and its associated complications, including death.

Because of these concerns and because the prevalence of IP and PD is so low, there is no clear justification for the widespread use of endoscopic therapy for patients with IP and PD. Validation of endoscopic therapy for patients with IP and PD requires undertaking a properly randomized and controlled clinical trial of treatment versus no treatment in carefully selected patients with PD and IP who do not have *CFTR* (or other) gene mutations, which in 1 recent study was associated with multiple procedures in the same patient and a lack of a "clinical response."[87] Results of such a trial are mandatory to determine if there is any potential benefit for

TABLE 6. Summary: Arguments Against Endotherapy For IP in PD

1. Hypothesis not supported.
   The prevalence of PD is not increased in IP.
   Pancreatitis in ventral duct system of PD patients, indicating other causes of pancreatitis.
2. Alternate hypothesis is more specific; IP develops in PD only if *CFTR* dysfunction/gene mutations.
3. Diagnosis of PD may be inaccurate; fibrotic stricture/tumoral obstruction of ventral duct resembles PD at ERCP.
4. IP with PD is uncommon and does not support widespread use of endotherapy.
5. Patients with IP and PD have a benign clinical course without endotherapy.
6. Endotherapy for IP in patients with PD has not been proven; existing studies are flawed.
7. Endotherapy exposes patients to unnecessary risk and abrogates Hippocratic Oath dictum to first-and-foremost "do not harm."

endoscopic and surgical therapies and to determine if benefit overrides risks (complications) associated with invasive procedures. In the meantime, we advise trainees, endoscopists, surgeons, and gastroenterologists to avoid interventional treatments to manage IP patients with PD.

Conclusions

Is endoscopic therapy indicated in IP in patients with PD and normal (or abnormal) ducts? No!

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COMMENTS AND CONCLUSIONS

Dr Jamie S. Barkin

There is truth to both sides of this discussion. I agree with Varshney and Johnson[181] that patients with PD should be divided for therapeutic approach, as he has suggested. Group 1 are those patients with minimal symptoms whose source of symptoms should be reevaluated and not assumed to be related to pancreatic disease. Group 2 are those patients with documented ARP, who have been reported to have a 75% response to endoscopic or surgical therapy for the minor ampulla although it is markedly less in my experience. One must exclude all other possible sources of ARP. Group 3 are those patients with CP in the dorsal duct, who respond to endoscopic or surgical therapy, but less so than group 2, approximately 40% to 60%, and group 4 are those patients with so-called chronic pancreatic pain without pancreatitis, who respond to invasive therapy in the range of placebo effect.

Patients with or without PD may develop a secondary process, which presumably causes narrowing of the sphincter of Santorini. This has possible pathological significance only in patients with PD because it causes pancreatic outflow obstruction. In persons with normal duct configuration, drainage will presumably be diverted through the sphincter of Oddi. This so-called sphincter of Santorini dysfunction (SSD) is similar to patients with SOD. The group with SOD that responds best to sphincterotomy either surgically or endoscopically are those patients with abdominal pain with elevated liver function tests, dilated common bile duct, and delayed drainage of the common bile duct at ERCP. All are indicative of relative obstruction of the sphincter of Oddi (SOD) whether it is functional or structural. This concept is similar to the relative obstruction of the sphincter of Santorini (SSD) seen in some patients with PD. We should carefully select our patients for therapy for SSD excluding other causes of ARP or CP, and limit intervention to patients in Varshney's group 3 and possibly group 2.

CONCLUDING REMARKS

Dr William M. Steinberg

There you have the debate of 2 schools of thought from authorities coming from leading institutions. Leading endoscopists continue to pursue aggressive endoscopic therapy on the minor papilla for PD and IP, and leading nonendoscopic pancreatologists question the premises and complications of this therapy. My own opinion is that the natural history of acute pancreatitis in each patient is so variable that one cannot make judgments as to the efficacy of treatment with short-term follow-up of 1 to 3 years. Each patient needs to be their own control to determine efficacy of treatment.[182] You, the reader, after reading this debate, are left to decide whether the benefits of endoscopic therapy outweigh the obvious risks.

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APPENDIX 1. Autopsy: Prevalence of PD

Study, y	Description	Total	No PD	PD	% PD	Comments
Schirmer,[80] 1893	Routine necropsies	104	93	11	10.6	11 PD; of these, 4 dorsal duct only.
Helly,[101] 1898	Routine necropsies	50	47	3	6.0	3 PD; of these, 1 dorsal duct only.
Charpy,[102] 1898	Routine necropsies	30	28	2	6.7	
Opie,[103] 1903	Routine necropsies	100	90	10	10.0	10 PD; 4 additional minute anastomotic twig between dorsal and ventral ducts.
Baldwin,[81] 1911	Random	76	66	10	13.2	100 autopsies; only 76 for purposes of ductal anatomy.
Clairmont and Hadjipetros,[104] 1920	Routine necropsies	50	44	6	12.0	6 PD; of these, 4 dorsal duct only.
Cameron,[105] 1924	Nonpancreatic cause of death	100	94	6	6.0	
Keyl,[106] 1925	Routine necropsies	121	115	6	5.0	6 PD; of these, 4 dorsal duct only.
Schmieden and Sebening,[107] 1927	Not stated	35	34	1	2.9	
Schwarz,[108] 1926	Routine necropsies	64	56	8	12.6	8 PD; of these, 3 dorsal duct only.
Mehnen,[109] 1938	Gallstone disease (112)	449	431	18	4.0	Emphasis on CBD and ventral duct anatomy to gallstones; 4 dorsal duct main duct (Wirsung absent or rudimentary), uncertain if dorsal duct searched for.
Näätänen,[110] 1941	No pancreatic, biliary, duodenal disease	100	4	96	4.0	
Rienhoff,[111] 1945	No pancreatic disease	100	89	11	11.0	
Hjorth,[112] 1947	Gallstone (22) & nonpancreatic disease	100	92	8	8.0	
Kleitsch,[113] 1955	Routine necropsies	33	30	3	9.1	
Birnstingl,[114] 1959	No pancreatic disease	150	143	7	4.7	Only 1 papilla injected; thus, prevalence of PD a minimal value.
Millbourn,[115] 1960	No pancreatic disease	200	185	15	7.5	15 PD; of these, 6 dorsal duct system only. Not included in the 15 PD are 2 cases of minute anastomosis between ductal systems.
Berman et al,[116] 1960	Biliary & pancreatic disease No analysis regarding PD & pancreatitis	130	123	7	5.4	143 autopsies but 130 for analysis.
Dawson and Langman,[117] 1961	Not stated	120	107	13	10.8	13 PD; of these, 9 large dorsal duct (embryonic type); 4 small/independent dorsal duct (group 4).
Hand,[118] 1963	No pancreatic or biliary disease	50	43	7	14.0	7 PD; of these, 1 dorsal duct only.
Smanio,[3] 1969	Not stated	200	171	29	14.5	
Sigfúussen et al,[119] 1983	Random	330	301	29	8.8	29 PD; of these, 8 dorsal duct only.
Stimec et al,[120] 1996	Random	203	191	12	5.9	
Mean % PD					8.4	
SD % PD					3.5	
Sum		2895	2669	226		
Mean pooled % PD					7.8	
SE					0.5	
95% CI					6.8–8.8	

All identified autopsy studies included. Information gathered from primary sources only.
CBD indicates common bile duct.

APPENDIX 2. ERCP: Prevalence of PD in Patients With and Without Pancreatitis

	All Cases				No Pancreatitis				All Pancreatitis				
Study, y	Total	No PD	PD	% PD	Total	No PD	PD	% PD	Total	No PD	PD	% PD	Comments
Phillip et al,[121] 1974	666	648	18	2.7									Dorsal duct not injected; 1 CF patient. No pancreatitis patients.
Varley et al,[122] 1976	102	99	3	2.9									Limited clinical data. 102/500 pancreatograms selected for study based on technical quality and normal pancreatic status (at autopsy, surgery or subsequent ERCP). Aim was to establish normal standards of ductal morphology.
Rösch et al,[87] 1976	1850	1787	63	3.4									Prevalence data only. Dorsal duct cannulated in ~30%.
Gregg et al,[47] 1977	1100	1067	33	3.0									Dorsal duct cannulated in 4/33 PD patients.Incomplete data on pancreatitis for PD group. No pancreatitis data provided in those with normal anatomy.
Belber and Bill,[123] 1977	195	188	8	4.1									Prevalence data only. No dorsal duct injection obtained (only attempted in 6).
Salmon,[124] 1978	500	485	15	3.0									All ERCP cases. Data interpreted from text & Table 9, based on a total of 800 cases. Clinical data of PD cases not available.
Katon et al,[125] 1978	28	28	0	0					28	28	0	0	No control group. Patients referred for nonalcoholic (idiopathic) pancreatitis.
Mitchell et al,[126] 1979	449	428	21	4.7	329	312	17	5.2	120	116	4	3.3	Determined pancreatitis incidence in groups with normally-and nonfused duct systems. 4 patients had pancreatitis based on clinical data and were classified as acute pancreatitis.
Cotton,[9] 1980	810	763	47	5.8	633	615	18	2.8	177	148	29	16.4	Most patients appeared to have CP but data incomplete. CP diagnosed by imaging and functional tests.
Tulassay and Papp,[85] 1980	2410	2379	33	1.4	2032	2020	12	0.6	378	357	21	5.6	Dorsal duct not injected. Diagnosis of "CP" included pancreatic cysts and cancer.
Richter et al,[12] 1981	519	493	26	5.0	394	383	11	2.8	125	110	15	12.0	Pancreatitis group is heterogenous, likely composed of CP patients.
Thompson et al,[127] 1981	850	839	11	1.3									Prevalence data only. 3/11 PD patients had CP and others had chronic abdominal pain. Pancreatitis not discussed for those with normal anatomy.
Cooperman et al,[41] 1982	314	293	21	6.7									Prevalence data only. Pancreatitis not discussed for those with normal anatomy.
Hamilton et al,[128] 1982	31	31	0	0					31	31	0	0	No control group. Patients referred for precominantly nonalcoholic acute pancreatitis (25/31), without known CP, and ≤3 attacks of pain. 12/30 diagnosed with CP. Limited clinical data for PD patients.
Sahel et al,[129] 1982	812	771	41	5.0	610	580	30	4.9	202	191	11	5.4	The dorsal duct was only cannulated in 15/44 patients diagnosed with PD.
Keith et al,[130] 1982	480	475	5	1.0									Prevalence data only; pancreatography not performed in many cases and underestimates true prevalence of PD.

(Continued on next page)

APPENDIX 2. (Continued)

	All Cases				No Pancreatitis				All Pancreatitis				
Study, y	Total	No PD	PD	% PD	Total	No PD	PD	% PD	Total	No PD	PD	% PD	Comments
Britt et al,[45] 1983	152	143	9	5.9	94	92	2	2.1	58	51	7	12.1	No dorsal duct injection in PD patients. Diagnosis made by presence of truncated ventral duct on pancreatogram.
Ott and Rösch,[131] 1983	2389	2249	140	5.9	1788	1686	102	5.7	601	563	38	6.3	
Buhler et al,[99] 1983	500	478	22	4.4									
Feller,[86] 1984	73	98	5	6.8					73	98	5	6.8	No control group. Patients referred for IP with single (n = 28) or recurrent (n = 45) attacks of pain. Duct strictures (CP) in some but unclear number.
Delhaye et al,[13] 1985	5357	5053	304	5.7	5225	4972	253	4.8	741	690	51	6.9	Dorsal pancreatogram obtained in 60% of PD patients.
Oi,[94] 1985	6000	5970	30	0.5									Article in Japanese. Limited information extracted from extract. Cases of PD were confirmed by dorsal pancreatogram.
Liguory et al,[59] 1986	1808	1721	87	4.8	1395	1341	54	3.9	326	293	33	10.1	Data extracted from Table 1 in manuscript. Further interpretation limited by language barrier. Control group composed of chronic abdominal pain and hepatobiliary disease. Diagnosis of pancreatitis included cancer.
Sugawa et al,[132] 1987	1529	1488	41	2.7	926	899	27	2.9	603	589	14	2.3	
Agha and William,[133] 1987	450	440	10	2.2	288	284	4	1.4	212	206	6	2.8	No pancreatogram for 50/500 patients. Limited clinical data; patients had known or suspected pancreatic disease.
Venu et al,[134] 1989	116	105	11	9.5					116	105	11	9.5	No control group. Patients referred for IP with ≥2 attacks of pain. Prevalence of PD in forms of pancreatitis unclear. Diagnoses included tumors (4), cholelithiasis (8), choledochocele (4), PD (11), SOD (?17), ? CP (pancreatic duct dilation).
Bernard et al,[8] 1990	1825	1688	137	7.5	1360	1283	77	5.7	465	405	60	12.9	
Brenner et al,[14] 1990	336	313	23	6.8	250	238	12	4.8	86	75	11	12.8	
Burtin et al,[25] 1991	1049	987	62	5.9	754	712	42	5.6	292	272	20	6.8	
Brown et al,[135] 1993	92	78	14	15.2									Prevalence data only. Limited clinical data. Study of children suspected of having pancreatic or biliary disease.
Barthet et al,[136] 1995	411	393	18	4.4					411	393	18	4.4	No control group. Compared natural history of chronic calcifying pancreatitis in PD vs fused duct pancreas.
Stimec et al,[120] 1996	610	596	14	2.3									Prevalence data only, no clinical data.
Bret et al,[137] 1996	108	102	8	5.6									Prevalence data only, no clinical data.
Guitron et al,[97] 1998	50	48	2	4.0									Abstract only. Study of children suspected of having pancreatic or biliary disease. Prevalence data only.
Eisendrath et al,[138] 2000	542	480	62	11.4					542	480	62	11.4	No control group. Aim to determine prevalence of isolated ventral disease in CP.

APPENDIX 2. (Continued)

Zoepf et al,[139] 2001	700	674	26	3.7								Prevalence data only, limited clinical data. Patients suspected of having pancreatic or biliary disease. 700 patients identified of 2925 patients; 350 had juxtapapillary duodenal diverticulum, and 350 were matched controls.
Poddar et al,[140] 2001	72	69	3	4.2								Prevalence data only. Limited clinical data. Study of children suspected of having pancreatic or biliary disease.
Kaw and Brodmerkel,[141] 2002	126	117	9	7.1					126	117	9	7.1	No control group. Patients referred for IP manifesting as recurrent attacks of pain. PD confirmed by dorsal duct injection.
Kim et al,[142] 2002	4097	4087	10	0.2								Prevalence data only. Nationwide, Korean prospective study. 10 additional incomplete PD not included in table.
Coyle et al,[143] 2002	90	72	18	20.0					90	72	18	20.0	No control group. Patients referred for evaluation of IP with 1 attack (n = 24) or ≥2 attacks (n = 66) of pain and included pancreatic cancer (8), CP (18). 50% already had cholecystectomy. Those with preexisting structural evidence of CP were excluded.
Kamisawa et al,[95] 2005	34	29	5	14.7					34	29	5	14.7	Abstract only. No control group. Patients referred for IP. 11 with normal ducts had an accessory duct that did not directly communicate with duodenum.
Mean % PD				5.2				3.5				8.3	
SD % PD				4.2				1.9				5.2	
Sum	39,632	38,222	1413		16078	15417	661		5803	5360	443		
Mean pooled % PD				3.6				4.1				7.6	
SE				0.1				0.2				0.3	
95% CI				3.4–3.7				3.8–4.4				7.0–8.3	

Information was collected from primary sources only. The general pancreatitis group contains patients with acute pancreatitis, CP irrespective of etiology and in a few instances pancreatic cysts or tumors. (It was attempted but proved to be impossible to establish more precise diagnostic categories due to use of different diagnostic criteria and diagnostic labels.) To further complicate diagnosis, the dorsal duct was frequently not cannulated.

APPENDIX 3. S-MRCP: Prevalence of PD in Patients With and Without Pancreatitis

	All Cases				No Pancreatitis				All Pancreatitis				
Study, y	**Total**	**No PD**	**PD**	**% PD**	**Total**	**No PD**	**PD**	**% PD**	**Total**	**No PD**	**PD**	**% PD**	**Comments**
Manfredi et al,[146] 2000	115	101	14	12.2									Prevalence data only, limited clinical data. Patients had CP or suspected pancreatic disease. ERCP comparison limited.
Matos et al,[147] 2001	279	249	30	10.8	54	48	6	11.1	135	122	13	9.6	Patients referred for suspected pancreatic disease. Data from control group and pancreatitis (idiopathic acute & chronic). No prior ERCP but subsequent ERCP confirmed diagnosis of PD.
Petersein et al,[148] 2001	110	99	11	10.0	30	21	9	30.0	80	78	2	2.5	340 MRCP cases. 110 cases selected for secretin injection due to question of CP or incomplete ductal visualization. ERCP performed in 4/11 PD patients and confirmed diagnosis. Clinical data incomplete; pancreatic cancer and CP grouped together.
Hellerhoff et al,[149] 2001	95	82	13	13.7	59	48	11	18.6	23	21	2	23.0	Patients primarily referred for pancreatic disease. Incomplete clinical data; data only for 84/95 patients. ERCP confirmed diagnosis of PD.
Hellund et al,[98] 2002	20	17	3	15.0	13	11	2	15.4	7	6	1	14.3	Data extracted from table of 20 patients but limited by inability to translate into English. Pancreatitis group contains those with pancreatic cancer and strictures, but not SOD (n = 7). ERCP performed in 2/3 PD patients.
Manfredi et al,[150] 2002	15	13	2	13.3					15	13	2	15.0	Children with IP and at least 3 attacks of pain. 10 had ERCP findings of CP; however, the characteristics of the PD patients is unclear. ERCP confirmed diagnosis of PD.
Khalid et al,[151] 2003	10	8	2	20.0					10	8	2	20.0	Retrospective study of IARP. ERCP confirmed diagnosis of PD.
Mean % PD				13.6				18.8				11.4	
SD % PD				3.3				8.1				5.9	
Sum	644	569	75		156	128	28		270	248	22		
Mean pooled % PD				11.6				17.9				8.1	
SE				1.3				3.1				1.7	
95% CI				9.2–14.1				11.9–24.0				4.9–11.4	

Information was collected from primary sources only. The general pancreatitis group contains patients with acute pancreatitis, CP irrespective of etiology, and in 2 instances, pancreatic cysts or tumors. (It was attempted but proved to be impossible to establish more precise diagnostic categories due to use of different diagnostic criteria and diagnostic labels.)

APPENDIX 4. Standard MRCP: Prevalence of PD in Patients With and Without Pancreatitis

	All Cases				No Pancreatitis				All Pancreatitis				
Study, y	**Total**	**No PD**	**PD**	**% PD**	**Total**	**No PD**	**PD**	**% PD**	**Total**	**No PD**	**PD**	**% PD**	**Comments**
Soto et al,[144] 1995	37	33	4	10.8	26	23	3	11.5	11	10	1	9.1	Referred for ERCP for biliary or pancreatic disease. 8% of MRPs poor quality. Pancreatitis group includes cancer. ERP compared leading to detection of 2 additional PD cases (1 each per group, not included in table). Dorsal duct only in 2 cases.
Bret et al,[137] 1996	310	285	25	8.1									Primarily referred for ERCP for biliary or pancreatic disease. Limited clinical information. 42 MRPs nondiagnostic. ERP comparison performed for 108 patients.
Hatano et al,[96] 1998	56	55	1	1.8									Abstract data only. Diseases and cancers of hepatobiliary & pancreas systems. ERP or PTC comparison.
Ueno et al,[145] 1998	162	158	4	2.5									Limited clinical data. Patients diagnosed with heterogenous pancreatic disease based on clinical examination or diagnostic testing. ERP comparison for 98 (and all PD) patients, revealing 5 additional PD cases.
Calvo et al,[100] 1999	37	35	2	5.4									Abstract data only. Referred for biliary or pancreatic dz. ERCP comparison.
Manfredi et al,[146] 2000	115	108	7	6.1									Limited clinical data. Patients had CP or suspected pancreatic disease. Prevalence of PD in subsets of pancreatitis unclear. ERCP comparison limited.
Matos et al,[147] 2001	279	256	23	8.2									Patients referred for suspected pancreatic disease. No prior ERCP; ERCP confirmed diagnosis of PD. Pancreatogram and text suggest diagnosis of 7 PD made only with S-MRCP.
Mortelé et al,[152] 2004	633	586	47	7.4	479	435	44	9.2	154	151	3	1.9	Incomplete clinical data; none for 248 patients. Large number of poor quality studies in absence of secretin. Pancreatitis group contains CP, pancreatic cysts, pancreatic malignancy.
Mean % PD				6.4				10.4				5.5	
SD % PD				3.2				1.7				5.1	
Sum	1587	1474	113		505	458	47		165	161	4		
Mean pooled % PD				7.1				9.3				2.4	
SE				0.6				1.3				1.2	
95% CI				5.9–8.4				6.8–11.8				0.1–4.8	

Information was collected from primary sources only. Additional studies were identified but not included in the above analyses because of inability to extract specific data from S-MRCP studies (Table 6)[148–151]. The general pancreatitis group contains patients with acute pancreatitis, CP irrespective of etiology, and in one instance, pancreatic cysts or tumors. (It was attempted but proved to be impossible to establish more precise diagnostic categories due to use of different diagnostic criteria and diagnostic labels.)

APPENDIX 5. ERCP: Prevalence of PD in Patients With Acute and CP

	Acute Pancreatitis				CP				
Study, y	**Total**	**No PD**	**PD**	**% PD**	**Total**	**No PD**	**PD**	**% PD**	**Comments**
Mitchell et al,[126] 1979	43	43	0	0.0	77	73	4	5.2	Determined pancreatitis incidence in groups with normally and nonfused duct systems. 4 patients had pancreatitis based on clinical data and were classified as acute pancreatitis.
Sahel et al,[129] 1982	39	31	8	20.5	163	160	3	1.8	The dorsal duct was only cannulated in 15/44 patients diagnosed with PD.
Delhaye et al,[13] 1985	335	310	25	7.5	406	380	26	6.4	Dorsal pancreatogram obtained in 60% of PD patients.
Bernard et al,[8] 1990	162	117	45	27.8	303	288	15	5.0	
Burtin et al,[25] 1991	143	134	9	6.3	149	138	11	7.4	
Barthet et al,[136] 1995					411	393	18	4.4	No control group. Compared natural history of chronic calcifying pancreatitis in PD vs fused duct pancreas.
Eisendrath et al,[138] 2000					542	480	62	11.4	Only CP. Focus on prevalence of isolated ventral pancreatitis in CP.
Mean % PD				12.4				5.2	
SD % PD				11.4				3.5	
Sum	722	635	87		2051	1912	139		
Mean pooled % PD				12.0				6.8	
SE				1.2				0.6	
95% CI				9.7–14.4				5.7–7.9	

APPENDIX 6. S-MRCP: Prevalence of PD in Patients With Acute and CP

	Acute Pancreatitis				CP				
Study, y	**Total**	**No PD**	PD	**% PD**	**Total**	**No PD**	**PD**	**% PD**	**Comments**
Matos et al,[147] 2001	67	60	7	10.4	68	62	6	8.8	Patients referred for suspected pancreatic disease. No prior ERCP but subsequent ERCP confirmed diagnosis of PD.
Hellerhoff,[149] 2001					23	21	2	8.7	Patients primarily referred for pancreatic disease. Incomplete clinical data, data only for 84/95 patients. ERCP confirmed diagnosis of PD.
Mean % PD				10.4				8.8	
SD % PD								0.1	
Sum	67	60	7		91	83	8		
Mean pooled % PD				10.4				8.8	
SE				3.7				3.0	
95% CI				3.1–17.8				3.0–14.6	

APPENDIX 7. Pancreatograms: Pancreatitis in Isolated or Both Ducts in PD

		Pancreatitis				
Study, y	**PD (n)**	**All PD Cases (n)**	**Both Ducts (n)**	**Ventral Duct (n)**	**Dorsal Duct (n)**	**Comments**
Rösch et al,[87] 1976	63	12	3	5	4	
Gregg et al,[47] 1977	33	15	0	1	1	
Richter et al,[12] 1981	26	15	2	(Incomplete data)	(Incomplete data)	Alcohol related
Sigfússon,[119] 1983	29	2	>2 (Incomplete data)	(Incomplete data)	(Incomplete data)	Autopsy study
Cotton et al,[27] 1985	50	>17 (Incomplete data)	(Incomplete data)	3	14	Alcohol related
Brinberg et al,[162] 1988	1	1	0	1	0	Alcohol related
Saltzberg et al,[30] 1990	1	1	0	1	0	
Benage et al,[5] 1990	120	43	5	0	18	Alcohol related
Bernard et al,[8] 1990	137	60	15	0	0	
Siegel et al,[52] 1990	31	31	2	(Incomplete data)	(Incomplete data)	
Burtin et al,[25] 1991	62	20	7	3	3	5 cases for both ducts possibly ventral only
Grech et al,[29] 1992	1	1	0	1	0	
Barthet et al,[136] 1995	18	18	6	3	9	Alcohol related
Sanada et al,[163] 1995	1	1	0	1	0	
Ianitti et al,[164] 1998	1	1	0	1	0	
Takeda. et al,[165] 1999	1	1	0	1	0	
Eisendrath et al,[138] 2000	62	62	32	6	24	5 with dorsal duct had no ventral injection. Alcohol related
Kamisawa et al,[93] 2005	1	1	1	0	1	Autopsy study Alcohol related
Total	638	302	75	27	74	
Mean % Total		47.3	11.8	4.2	11.6	
SE		2.0	1.3	0.8	1.3	
95% CI		43.5–51.2	9.3–14.2	2.7–5.8	9.1–14.1	

APPENDIX 8. Autopsy Studies: Dorsal Duct Patency in Cadavers With Fused Duct Anatomy

	Dorsal Ducts		
Study, y	**Total (n)**	**Patent Duodenal Orifice (n)**	**% Patency**
Schirmer,[80] 1893	104	85	81.7
Charpy,[102] 1898	30	9	30.0
Opie,[103] 1903	100	79	79.0
Baldwin,[81] 1911	50	45	90.0
Rienhoff,[111] 1945	85	62	72.9
Howard and Jones,[180] 1947	150	54	36.0
Hjorth,[112] 1947	100	29	29.0
Kleitsch,[113] 1955	33	23	69.7
Birnstingl,[114] 1959	150	102	68.0
Berman et al,[116] 1960	130	43	33.1
Dawson and Langman,[117] 1961	120	64	53.3
Hand,[118] 1963	50	32	64.0
Mean % (single study)			
SD (single study)			58.9
21.9			
Sum	1102	627	
Mean % (pooled studies)			56.9
SE			1.5
95% CI			54.0–59.8