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The Surgical Management of Chronic Pancreatitis

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1. Introduction

Chronic pancreatitis (CP) has been defined as a continuing inflammatory disease of the pancreas characterized by irreversible morphological changes, often associated with pain and with the loss of exocrine and endocrine function which may be clinically relevant (Clain JE Surg Clin North Am 1999). Pain is the principal cause of intractability and together with pancreatic insufficiency may have a significantly deleterious effect on a patient's quality of life as well as their ability to work and contribute to society, often leading to loss of their social support network (Lankisch PG Digestion 1993). Progressive disease may culminate in severe and disabling symptoms requiring narcotic analgesia and frequent hospital admission with a consequent impact on health resources (Bornman PC W J Surg 2003; Braganza JM The Lancet 2011). The incidence and prevalence of disease has not been well documented however it is considered uncommon in Europe and the USA. This is in contrast to data available from South India where a prevalence of 114-200/100 000 people has been documented. Alcohol is the leading cause in western developed countries and some developing countries such as Brazil, Mexico and South Africa while idiopathic disease predominates in Asia and the subcontinent (Braganza JM The Lancet 2011; Garg PK J Gastroenterol Hepatol 2004).

Despite extensive study, the pathogenesis of chronic pancreatitis and the mechanisms which result in the development of pain remain poorly understood. As a result, treatment strategies have been largely empirical and based on symptoms, management of clinically evident exocrine and endocrine dysfunction and gross morphological abnormalities. Modalities employed have included medical support (with analgesics, anti-diabetic medication, pancreatic enzyme replacement, nutrient support and steroids in autoimmune disease), interventional endoscopy and surgery. The role of surgery has been primarily to relieve pain refractory to medical therapy, to address complications and to resect suspected or confirmed neoplastic disease (Bornman PC S Afr Med J 2010). The causes of pain in CP are likely multifactorial and proposed factors include excessive oxygen-derived free radicals, tissue hypoxia and acidosis, inflammatory infiltration accompanied by an influx of pain transmitted substances into damaged nerve ends and the development of pancreatic ductal and tissue fluid hypertension (Bornman PC W J Surg 2003). Surgical intervention for the relief of pain focuses primarily on the latter two proposed mechanisms. Two distinct principles have been applied in the development of

procedures to address these mechanisms. Resection of diseased pancreatic tissue, in particular inflamed tissue within the head of the pancreas containing altered neural tissue and diseased ducts, considered the “pacemaker of disease” (Beger HG World J Surg 1990) and drainage of the pancreatic ductal system, in order to relieve ductal and parenchymal tissue hypertension. Removal of sufficient pancreatic tissue as to result in effective and durable relief of symptoms must however be balanced against the desire to avoid surgically related morbidity and mortality as well as to prevent post-operative pancreatic functional insufficiency. This has led to the development of less extensive resections and hybrid procedures which attempt to combine the advantages while avoiding the disadvantages of each approach.

This chapter will describe the theories around the pathophysiology of pain in chronic pancreatitis, discuss the rationale and indications for surgical intervention and detail the procedures currently available. It will also review the literature guiding the choice of these procedures for the relief of pain.

2. Pathophysiology of pain in chronic pancreatitis

The pathophysiology of CP is complex and remains poorly understood, with a number of theories having been put forward. Together with this, understanding of the mechanisms leading to the development of pain has also remained largely theoretical, confounded to a large extent by small and to some degree poorly designed studies, which have at times been contradictory. Furthermore, it is likely that the cause of pain is multi-factorial and may vary during the course of the disease (Bornman PC W J Surg 2003). To date, the most predominant theories regarding genesis of pain in CP have included:

2.1 Morphological pancreatic ductal changes resulting in obstruction and pancreatic ductal and tissue hypertension

In large duct chronic pancreatitis, changes in the composition of pancreatic fluid occur including an increase in free oxygen radicals and secretion of enzymes and calcium but a concomitant decrease in serine protease inhibitor Kazal type 1 (SPINK1), bicarbonate and citrate. (Sarles H Dig Dis Sci 1986). These changes are followed by precipitation of proteins such as lactoferrin and altered levels of pancreas related secretory stress proteins (including pancreatitis associated protein and pancreatic stone protein) (Singh SM W J Surg 1990; Graf R J Surg Res 2006). Glycoprotein plugs are formed which later become calcified leading to calcific disease with associated parenchymal fibrosis. Calcified protein plugs or calculi damage the ductal epithelium further and contribute to stasis thereby facilitating further stone formation. These changes are believed to begin in the side ducts but progress to involve the main pancreatic duct (PD) with the development of pancreatic duct strictures and obstruction (PDSO) as a consequence of fibrosis or calculi. Ductal hypertension follows with associated dilatation (Nagata A Gastroenterology 1981). Together with ductal hypertension, pancreatic tissue pressure may become elevated, particularly in areas of calcification (Okazaki K Gastroenterology 1986; Manes G Int J Pancreatol 1994; Jalleh RPBr J Surg 1991). The exact mechanism of elevated PTP in CP has not been proven, however it has been speculated that it may be a reflection of obstructed pancreatic side ducts rather than main PD obstruction. This situation may be aggravated by the development of perilobular fibrosis and a fibrotic peripancreatic capsule, resulting in a compartment syndrome like

scenario with consequent tissue ischaemia and acidosis. (Karanjia ND Br J Surg 1994). While PDSO with ductal and tissue hypertension have not been consistently demonstrated in CP, nor a definite correlation shown with the development of pain (Novis BH Dig Dis Sc 1985; Manes G Int J Pancreatol 1994; Ugljesic M Int J Pancreatol. 1996; Bornman PC W J Surg 2003), surgical drainage procedures have been documented to reduce pancreatic tissue pressures (PTP), while a significant association between recurrence of pain and subsequent elevation of PTP has been shown. (Ebbehøj N Scand J Gastroenterol. 1990). On the other hand, ductal dilatation has been observed in the absence of ductal obstruction giving rise to the suggestion that dilatation may also be related to parenchymal destruction; this is supported by the association between duct dilatation and pancreatic insufficiency (Jensen AR Scand J Gastroent 1984). Thus, while PDSO is likely an important factor in generating pain, there are likely factors other than main pancreatic duct abnormalities that can also be implicated (Bornman PC W J Surg 2003). Furthermore, the role of side duct obstruction in the genesis of pain has not yet been clearly defined; it may be that side branch disease contributes to the development of an inflammatory mass in the pancreatic head which is recognised as important in driving the disease process (the so called “pacemaker” of disease) (Beger HG World J Surg 1990).

2.2 Interaction between the processes of inflammation and damaged neural structures

Histological studies have shown that there is invasion of neural tissue by inflammatory cells associated with chronic pancreatitis. This is accompanied by disruptions in the perineural sheaths which expose the internal neural compartments to the inflammatory response (Bockman DE Gastroenterol 1988). In addition, there are increased amounts of pain transmitted substances, pain modulators and nerve growth factors and receptors in enlarged / damaged pancreatic nerve structures, which appear to correlate with the intensity and frequency of pain (Büchler M Pancreas 1992, Zhu ZW Dig Dis Sci 2001, McMahon SP Nat Med 1995, Friess H Ann Surg 1999). Surgical resection of a pancreatic inflammatory mass effectively removes the pain stimulus together with the altered / damaged neural structures.

2.3 Toxin metabolism and generation of excessive oxygen derived free radicals resulting in electrophilic stress and inflammation

Acinar cells and proliferated islets of Langerhans are known to express cytochrome P450 (CYP) mono-oxygenases which metabolise xenobiotics (substances foreign to a living organism), often utilizing glutathione & catalysed by glutathione transferases. (Foster JR J Pathol 1993). There may however be adverse consequences to these metabolic reactions with the generation of reactive oxygen species (ROS) and toxic xenobiotic metabolites. Prevention of cellular injury relies on defences against ROS and xenobiotic metabolites; these defences include: selenium dependant glutathione peroxidase, glutathione transferases, glutathione and ascorbic acid. These varied properties make the pancreas a versatile yet vulnerable xenobiotic metabolizing organ (Braganza JM JOP 2010; Foster JR. Toxicology of the exocrine pancreas. In: General and applied toxicology 2009). Inhaled xenobiotics (such as cigarette smoke, occupational volatile hydrocarbons and petrochemicals) that pass through the pulmonary circulation represent the biggest threat by striking the pancreas through its rich

arterial supply (Braganza JM Lancet 2011). When the acinar cell's defence mechanisms are insufficient to meet the increased oxidant load from ROS and xenobiotic metabolites, electrophilic stress results (Braganza JM Digestion 1998; Braganza JM JOP 2010; Foster JR. Toxicology of the exocrine pancreas. In: General and applied toxicology 2009). Dietary insufficiency of micronutrients and ascorbic acid may predispose to this (Braganza JM Digestion 1998). Electrophilic stress in turn results in pancreastasis, the failure of apical exocytosis in the acinar cell (Sanfey H Ann Surg 1984; Leung P Antioxid Redox Signal 2009). Enzymes (both newly synthesised & those stored in zymogen granules) not able to be released apically, are released via the basolateral membrane into the interstitium, lymphatics and bloodstream (Cook LJ Scand J Gastroenterol 1996). Entrance of enzymes and free radical oxidation products into the interstitium causes mast cell degranulation, resulting in local inflammation, activation of nociceptive axon reflexes and fibrosis. (Cook LJ Scand J Gastroenterol 1996; Braganza JM Digestion 1998). This inflammatory response is potentiated by cytokines produced by the damaged acinar cell as a result of activated signaling cascades caused by the release of ROS. (Leung P Antioxid Redox Signal 2009).

2.4 Fibrosis as a result of pancreatic stellate cell activation in the necrosis-inflammation-fibrosis sequence and sentinel acute pancreatitis events

Pancreatic stellate cells play a central role in the fibrotic process associated with chronic pancreatitis (Stevens T Am J Gastroenterol 2004). This is particularly relevant in the necrosis-inflammation-fibrosis sequence, the most widely accepted hypothesis in the pathogenesis of chronic pancreatitis (Bornman PC in Chronic pancreatitis. Hepatobiliary and pancreatic surgery – a companion to specialist surgical practice. 2009). Initially this hypothesis held that fibrosis developed as a stepwise progressive process from recurrent bouts of acute pancreatitis (Comfort MW Gastroenterology 1946; Kloppel G Hepatogastroenterol 1991). An alternative theory suggested that alcohol might be directly toxic to the acinar cell through a change in cellular metabolism (toxic-metabolic theory). Alcohol was purported to produce cytoplasmic lipid accumulation within the acinar cell, leading to fatty degeneration, cellular necrosis and eventual fibrosis (Bordalo O Am J Gastroenterol 1977). More recently the theory of a sentinel acute pancreatitis event (SAPE) has been proposed. This theory hypothesizes that stimulation of the pancreatic acinar cell by alcohol or oxidative stress activates trypsin which results in a sentinel acute pancreatitis event. This is followed by a dual phase chronic inflammatory response, with the early phase characterised by a pro-inflammatory cell infiltrate including macrophages and lymphocytes. Cytokines released during the early phase also attract a later anti-inflammatory cellular infiltrate comprising pro-fibrotic cells, including stellate cells. These cells, once attracted, are activated by lipid peroxidation products (caused by excess ROS) and mast cell degranulation products, and are considered "primed"; continued stimulation by cytokines (in particular TGF- β 1) produced by acinar cells, inflammatory cells or the stellate cells themselves as a result of oxidative stress, alcohol or recurrent acute pancreatitis, cause these activated stellate cells to deposit collagen, resulting in fibrosis and the features of chronic pancreatitis (Whitcomb DC Best Pract Res Clin Gastroenterol 2002). The transient formation of fatty acid ethanol esters and the role of macrophages and lymphocytes in pancreatic tissue destruction are also thought to be integral to this process (Pandol SJ Pancreatology 2007). It is suggested that the contractive potential and perivascular location of the stellate cells results in fibrosis that leads to microvascular ischaemia and pain (Wells RG Gastroenterol 1998).

2.5 Primary duct hypothesis

This theory suggests a primary immunological attack on ductal epithelium leading to inflammation and scarring of ductal architecture. This may have specific relevance in autoimmune pancreatitis. (Cavallini G. *Ital J Gastroenterol* 1993).

Once inflammation becomes established in CP, patients may enter a phase of stable disease with the histological features of acinar loss, mononuclear cell infiltrate and fibrosis (Shrikhande SV *Br J Surg* 2003). Subsequent progression to end stage disease is characterised by loss of all secretory tissue, disappearance of inflammatory cells and intense fibrosis. This may be accompanied by loss of pancreatic function together with diminished pain, the so-called “pancreatic burn-out syndrome”; this phenomenon is however not a universal outcome in patients with CP, thereby confounding potential treatment strategies (Girdwood AH *J Clin Gastroenterol* 1981; Amman RW *Gastroenterol* 1984; Lankisch PG *Digestion* 1993).

Complications of CP related to inflammation and fibrosis may develop which can alter the course of disease as well as clinical presentation. These include

1. Biliary obstruction

This is common in advanced disease, particularly when there calcification and an inflammatory mass in the head. Obstruction may be transient when related to oedema during acute flaring of disease or more permanent when occurring as a result of a fibrotic stricture or mass effect from an adjacent pseudocyst. .

2. Duodenal obstruction

This may be the result of peri-duodenal fibrosis or from the mass effect provided by a pseudocyst.

3. Development of a pseudocyst / pancreatic ascites

Pancreas related fluid collections or pseudocysts occur in 30-40% of patients with CP and are thought to be the consequence of either ductal obstruction or pancreatic necrosis with ductal disruption (D'Egidio A *BJS* 1991). Typically cysts communicate with the pancreatic ductal system which shows gross morphological abnormalities. Postnecrotic peripancreatic collections occur only rarely, usually as a consequence of an acute on chronic attack of pancreatitis. Pseudocysts in CP are usually located either near the head when they are mostly intra-pancreatic or in the lesser sac. Pseudocysts in CP are less likely to spontaneously resolve than those associated with acute disease as they have usually matured by the time of presentation and typically communicate with the pancreatic ductal system. Pancreatic ascites occurs when there is rupture of a pseudocyst or duct into the peritoneal cavity (Bornman PC in *Hepatobiliary and pancreatic surgery – a companion to specialist surgical practice*. 2009).

4. Gastro-intestinal bleeding, related to

a. Portal hypertension

Portal hypertension may develop in up to 10% of patients as a result of venous compression or thrombosis. Splenic vein thrombosis may result in segmental portal hypertension giving rise to gastric and oesophageal varices, although frank variceal bleeding in this setting is

uncommon (Bornman PC in Hepatobiliary and pancreatic surgery – a companion to specialist surgical practice. 2009).

b. Pseudoaneurysms

Enzyme rich fluid collections may erode into vascular structures resulting in false aneurysms with bleeding into the cyst and pancreatic duct, peritoneum or retroperitoneum.

3. Rationale and indications for surgical intervention

Surgery is indicated in chronic pancreatitis for the relief of pain, to manage complications and to resect confirmed or suspected neoplastic disease (Bornman PC S Afr Med J 2010). Two theoretical principles underlie the rationale for surgery to alleviate pain in CP. The first utilises the ductal / parenchymal tissue hypertension and inflammatory-neural theories on the pathogenesis of pain in CP. It postulates that surgical decompression of the main pancreatic duct will alleviate interstitial hypertension thereby improving parenchymal perfusion and acidosis (Patel AG Gastroent 1995) with consequent reduction of inflammatory stimulation and influx of mediators into damaged nerves (Salim AS HPB Surg 1997). The second principle focuses on removal of pathologically inflamed parenchyma together with altered neural tissue in particular that within the head, which is considered the “pacemaker” of disease. Emphasis has also been placed on the importance of addressing diseased side ducts, thereby limiting the possibility of recurrence (Beger HG World J Surg 1990).

The objectives of surgery for pain in CP are effective and durable relief of symptoms while preserving endocrine and exocrine function, thereby restoring the patient’s quality of life. The potential for morbidity and mortality as well as recurrence should be low. Based on these objectives and the principles outlined above, a number of procedures have been developed. Essentially, these procedures fall into a spectrum covering three broad categories. At one end of the spectrum are drainage procedures which focus on decompressing the main pancreatic duct by establishing a new pancreatic-enteric communication which bypasses any native obstruction to pancreatic outflow. At the other end of the spectrum are resectional procedures which aim to remove diseased ductal and neural tissue within chronically inflamed parenchyma. Over time, a number of modified and hybrid procedures have evolved which attempt to retain the advantages while limiting the disadvantages of both the former 2 categories.

Little data exists to guide decision making regarding the optimal timing of surgery to alleviate pain in CP. There are two schools of thought. The first suggests that conservative non-surgical management should be pursued for as long as possible in order to avoid morbidity and side effects that may be associated with surgical intervention, in particular pancreatic insufficiency. They argue that the long term outcome of surgery is no different from medical management, and that the “pancreatic burn-out syndrome” is likely responsible for pain relief observed after surgery (Amman RW gastroenterol 1984). In contrast to this, others have argued that pain relief is better when surgical drainage is carried out earlier rather than later (Nealon WH Ann Surg 1993). It also remains controversial whether surgery can delay the natural course of the disease in terms of deterioration in pancreatic function (Warshaw AL Gastroenterol 1980; Nealon WH Ann Surg 1993; Jalleh RP Ann Surg 1992). Both arguments appear to have merit. While it seems

foolhardy to offer surgical intervention with its attached risk of morbidity and even mortality in patients whose symptoms might be controlled by medical means, it seems equally unreasonable to persist with a conservative approach in anticipation of pain relief, delaying surgery until narcotic addiction has developed and the outcomes from surgery may be worse (Warshaw AL *gastroenterol* 1984). In the absence of good evidence to guide decision making, it seems most appropriate that the decision regarding timing of surgery be individualized on a patient to patient basis. Surgical intervention should be performed only once an adequate trial of medical therapy has failed to control symptoms and the patient has been counseled regarding the risks and benefits of both modalities.

Patients referred for surgery for relief of intractable symptoms of CP should be evaluated by experienced clinicians working in a high volume, multi-disciplinary environment. All other treatment options should have been exhausted or considered not appropriate. Cross sectional imaging should be conducted to clearly delineate pancreatic morphology and detect local complications or features suggestive of neoplastic disease. The presence of portal hypertension, particularly as a result of portal or superior mesenteric vein thrombosis should be noted, as this may preclude surgical intervention (Bornman PC *S Afr Med J* 2010). With careful patient selection and modern surgical strategies, surgery may offer effective pain relief in over 90% of patients at 5 year follow up (Beger HG *Ann Surg* 1989).

In considering intervention for complications of CP, the clinical picture is paramount in decision making. Biliary obstruction may be asymptomatic, detected only biochemically or during imaging for other indications. In addition, there may be transient jaundice as a result of oedema during acute flares of the disease. The above are not indications for intervention. It must be remembered that once the biliary system has been entered, either percutaneously, endoscopically or surgically, this once sterile system should be considered contaminated with the risk of sepsis developing should obstruction recur in the future. On the other hand, persistent biliary obstruction of sufficient duration may result in secondary biliary cirrhosis, atrophy and deterioration in hepatic function. (Abdallah A *HPB* 2007). Obstruction longer than 4 weeks should arouse concern and warrants intervention. Decompression by means of endoscopic stenting should only be considered as a temporary bridge to surgery, in acute cholangitis or where patient factors preclude surgery (Bornman PC *S Afr Med J* 2010). Duodenal obstruction on the other hand typically represents either advanced fibrosis or a clinically significant pseudocyst, neither of which are likely to resolve before progression or further complications develop. Intervention is therefore indicated. Pseudocysts in CP are less likely to resolve than their acute counterparts and thus more often require drainage. The indications for drainage are the presence of symptoms or complications. Although size alone is not a criterion for intervention, cysts larger than 6cm are more likely to be symptomatic and require treatment (Bornman PC *S Afr Med J* 2010). Percutaneous procedures are generally not favoured for these lesions due to an increased risk of failure, introducing sepsis or creating an external fistula. Endoscopic drainage is associated with a success rate of 65-95% and a low complication rate and is preferred to surgery due to its less invasive nature. (Beckingham IJ *Br J Surg* 1997). Strict morphological criteria are required however, relating to cyst maturity, intra-luminal bulging, wall thickness (less than 10mm) and vascularity, particularly in the presence of portal hypertension. To this end, careful cross sectional imaging and endoscopic ultrasound are important adjuncts in assessing patients for this modality of treatment. Transmural drainage may be transduodenal or transgastric depending on the best route into the cyst while transpapillary drainage is an

alternative option when communication with the pancreatic duct can be demonstrated. Surgery is indicated when endoscopic intervention fails or is not appropriate due to cyst morphology or patient factors. Surgical drainage of a pseudocyst may also be employed as part of an intervention planned for treatment of pain or additional complications. Pancreatic ascites is an uncommon but serious complication of CP which is managed in the first instance with paracentesis, nutritional support and endoscopic stenting of the pancreatic duct (Kozarek RA *Gastrointest Endosc Clin North Am* 1998; Bornman PC in *Hepatobiliary and pancreatic surgery – a companion to specialist surgical practice* 2009). Use of a somatostatin analogue remains controversial. Surgery is reserved for failures of conservative treatment. Bleeding from gastric varices related to segmental portal vein thrombosis is uncommon, thus the authors recommend intervention only once there is proven bleeding from gastric varices. Haemorrhage related to a pseudoaneurysm is best dealt with via selective angiography and embolisation due to the hazards of surgery in this setting. Surgery is reserved for failure of angiographic treatment.

4. Surgery for chronic pancreatitis – Drainage procedures

For many years longitudinal pancreaticojejunostomy (LPJ) as described by Partington and Rochelle in 1960 was the favoured surgical option in the treatment of chronic pancreatitis. This involves entering and laying open of the pancreatic duct followed by a splenic preserving pancreaticojejunostomy without resection of the pancreatic tail (Partington PF, Rochelle REL. *Ann Surg* 1960). This procedure is relatively simple in comparison to many of the other available operations and has a low mortality and morbidity with maximal pancreatic tissue preserved. Pain relief in the short term approximates 75% but there is frequently recurrence in the long term (Bachmann K *Best Pract and res Clin Gastro* 2010). This is thought to be due to incomplete decompression of the main pancreatic duct, particularly in the head. There remains a residual inflammatory mass containing altered nerve fibres (Pessaux P *Pancreas* 2006) as well as obstructed second and third order ducts causing ongoing intraductal hypertension (Markowitz JS *Arch Surg* 1994). Current indications for this procedure are isolated dilatation of the pancreatic duct greater than 7mm or where the duct has a “chain of lakes” appearance without an inflammatory mass in the head (Yekebas EF *Ann Surg* 2006). Where the duct is undilated (less than 3mm) a longitudinal V-shaped excision of the ventral pancreas combined with a longitudinal pancreaticojejunostomy has been described (Izbicki JR *Ann Surg* 1998, 227). This may be particularly useful when a sclerosing form of chronic pancreatitis results in so called small duct disease (Bachmann K *Best Pract and res Clin Gastro* 2010). Good results with pain relief in 89% of patients and comparable morbidity of 19.6% have been reported (Yekebas EF *Ann Surg* 2006).

5. Surgery for chronic pancreatitis – Resectional procedures

With recognition that inflamed, fibrotic tissue containing damaged neural structures within the pancreatic head is critical in the generation of symptoms, pancreaticoduodenectomy became the gold standard in surgical treatment against which other procedures were measured. It has been assumed that outcomes concerning pain and quality of life are better than simple drainage procedures performed in isolation, however clear evidence of this in randomized trials is lacking.

In the modern era, pylorus preservation as in a Pylorus Preserving Pancreaticoduodenectomy (PPPD) has been shown to result in less pain and nausea and improved quality of life when compared with the traditional Whipples pancreaticoduodenectomy (Mobius C Langenbecks Arch Surg 2007). This procedure can be performed with a mortality of 5-10% and morbidity of 20-40% and improves pain and quality of life in both the short and long term in up to 90% of patients (Bachmann K Best Pract and res Clin Gastro 2010). There are however a number of disadvantages relating to the sacrifice of functional pancreatic parenchyma and the non-diseased duodenum and common bile duct. The loss of natural bowel continuity and reduced endocrine and exocrine function result in side effects and reduced quality of life (Izbicki JR Ann Surg 1998 (228); Koninger J Surgery 2008). In order to allow organ preservation and reduce adverse effects, duodenum preserving resections of the pancreatic head (DPPHR) were developed. The Beger procedure was introduced in 1980 and was the first to include these principles (Beger HG Chirurg 1980). It consists of a subtotal resection of the head following transection of the pancreas above the portal vein. The Pancreas is then drained by an end-to-side or end-to-end pancreaticojejunostomy using a Roux-en-Y loop. Physiological gastroduodenal passage and CBD continuity are therefore preserved. This procedure could be performed with low mortality (0-3%) and morbidity (15-32%) and long term pain relief in 75-95% of patients (Izbicki JR Ann Surg 1995, Buechler MW J Gastrointest Surg 1997, Frey CF Ann Surg 1994). The Frey procedure (Frey CF Pancreas 1987) subsequently combined an LPJ (as described by Partington and Rochelle) with a limited duodenum preserving excision of the head. Following exploration of the main pancreatic duct well into both the head and the tail, the head is cored out leaving a small cuff of parenchyma along the duodenal wall. This results in a lesser resection of the head than that described by Beger. In further contrast to the Beger operation, the pancreas is not divided over the SMV/portal vein complex making it an easier operation to perform. Care is taken not to enter the CBD. Drainage of the resection cavity within the head and from the opened main pancreatic duct within the body and tail is obtained with an LPJ using a Roux-en-Y loop (Frey CF Pancreas 1987). Good results have been obtained with substantial pain relief in more than 85% of patients while mortality is less than 1% and morbidity 9-39% (Izbicki JR Ann Surg 1995, Izbicki JR Ann Surg 1998, Beger HG Ann Surg 1989). Endocrine & exocrine function are well preserved and the operation may control complications such as CBD stenosis, duodenal stenosis and internal pancreatic fistulas. The Frey operation is currently the most widely performed operation for patients with an inflammatory mass in the head together with pancreatic duct dilatation while the Beger procedure is reserved for patients where the main pancreatic duct is not dilated (Bornman PC S Afr Med J 2010).

Two further modifications of the above procedures have been described. The Hamburg operation employs subtotal excision of the pancreatic head including the uncinate process (a more extensive resection than the Frey operation but comparable to Beger's procedure) together with a V-shaped excision of the ventral aspect of pancreas into the pancreatic duct. Pancreatic-enteric continuity is re-established with an LPJ using a Roux-en-Y loop (comparable to the Partington-Rochelle and Frey reconstructions). This operation combines aspects of the Frey and Beger procedures, without transection of gland over SMV/portal vein. The extent of resection is customized to pancreatic morphology while the V-shaped excision creates a trough-like new ductal system allowing better drainage of ductal side branches (Izbicki JR Ann Surg 1998, 227, Bachmann K Med Sci Monit 2008). In the Berne operation, an extensive duodenum-preserving resection of the head is performed (as in the

Beger procedure), but without division of pancreas anterior to superior mesenteric / portal vein complex and without laying open the pancreatic duct in the body and tail. In biliary obstruction a longitudinal opening may be made in the CBD within the cavity created in the pancreatic head. Drainage of the cavity is achieved with a pancreatic-enteric anastomosis to small bowel in a Roux-en-Y reconstruction similar to the reconstructions described above. Results of the Berne procedure are comparable to the other duodenum preserving resections (Gloor B Dig Surg 2001).

Little comparative data is available to guide choice between the various available procedures in CP. Four randomized controlled trials have been conducted comparing PPPD with DPPHR, with 2 providing long term follow up (table 1). In the short to medium term,

| | Follow up | Procedure | Mortality | Morbidity | Pain free | Pain relief | Better QOL | Endocrine function | Exocrine function | Weight gain |
|--------------|-----------------|---------------------|-----------|-----------|-----------|-------------------|---------------------|---|--|-----------------|
| Buchler 1995 | 6 months | | | | | | | Glucose tolerance at 150min | Pancreolauryl test: pre- vs post-op | |
| | | PPPD (n=20; FU 15) | 0 | 4 | 6 | 4 | 8 | 130mg/dL | 2.05µg/mL (0.48-6.6) vs 1.13µg/mL (0.4-87) | 1.9+/- 1.2kg |
| | | Beger (n=20; FU 16) | 0 | 3 | 12 | 3 | 12 | 88mg/dL | 2.7µg/mL (0-8.25) vs 1.4µg/mL (0-4.41) | 4.1+/- 10.9kg |
| | | P value | NS | NS | <0.05 | Not stated | NS | <0.01 | NS | <0.05 |
| Klempa 1995 | 36 to 60 months | | | | | | | New onset IDDM | Steatorrhea; enzyme substitution | |
| | | PPPD (n=21; FU 20) | 1 | 5 | | 14 | | 6 | 20/20 | Mean 4.9kg |
| | | Beger (n=22; FU 20) | 0 | 4 | | 20 | | 2 | 3/4 | Mean 6.4Kg |
| | | P value | NS | NS | | <0.05 | | Not stated | <0.05 | not stated |
| Izbicki 1998 | 12 - 36 months | | | | | | | Insulin dose or Glucose tolerance: improved vs worsened | Abnormal faecal chymotrypsin, pancreolauryl test | Median (range) |
| | | PPPD (n=30; FU 30) | 0 | 16 (53%) | | 28; 18.1 (0-37.5) | 85.7 (71.4-100); 13 | 0 vs 6 | 7 | 6.7kg (3.1-9.2) |
| | | Frey (n=31; FU 31) | 1 | 6 (19%) | | 26; 6.1 (0-40) | 57.1 (33.3-100); 21 | 3 vs 2 | 1 | 1.9kg (0-6.3) |
| | | P value | NS | <0.05 | | NS; not stated | <0.05; <0.05 | Not stated | Not stated | Not stated |
| Farkas 2006 | 12 months | | | | | | Prof rehab | New onset DM | Stool elastase: pre- vs post op | |

| | Follow up | Procedure | Mortality | Morbidity | Pain free | Pain relief | Better QOL | Endocrine function | Exocrine function | Weight gain |
|-----------------------------------|-------------------|-----------------------|------------------------------------|-----------|-----------|-------------------|--|---|--|--------------|
| | | PPPD (n=20; FU 20) | 0 | 8 | 18 | 2 | 11/17 | 3 | 128 +/- 29µg/g vs 122.2 +/- 23 µg/g | 7.8+/- 0.9kg |
| | | Berne (n=20; FU 20) | 0 | 0 | 17 | 3 | 14/18 | 0 | 124.3 +/- 33µg/g vs 132.7 +/- 39µg/g | 3.2+/- 0.3kg |
| | | P value | NS | <0.05 | NS | NS | NS | NS | NS | <0.05 |
| Muller 2008 (FU of Buchler 1995) | 14 years | | | | | Median pain score | EORTC QLQ 30 - global health status (s.d.) | Presence of IDDM; new onset DM | Enzyme substitution | |
| | | PPPD (n=20; FU=14) | 5 | | | 0 | 58.3 (34.2) | 11; 6/9 | 8/14 | |
| | | Beger (n=20; FU= 15) | 5 | | | 0 | 65.0 (22.3) | 7; 4/11 | 8/15 | |
| | | P value | NS- Mortality unrelated to surgery | N | | S N | S, part from greater appetite loss in PPPD group | 0.128; 0.327 | NS | |
| Strate 2008 (FU of Izbiccki 1998) | median of 7 years | | | | | Pain score | EORTC Global quality of life | Presence of DM or abnormal glucose tolerance test | Abnormal faecal chymotripsin | |
| | | PPPD (n=30; FU 23) | 4 | | | 18.75 (0-75) | 50 (0-100) | 15/23 | 22/23 | |
| | | Frey (n=30; FU 24) | 6 | | | 17.5 (0-100) | 58.35 (0-83.4) | 13/23 | 18/21 | |
| | | P value | | | | 0.821 | 0.974 | 0.672 | 0.335 | |
| | | 3 patients lost to FU | | | | | | | 3 patients did not attend for assessment | |

QOL= quality of life; pre-op= pre-operative; post-op= post-operative; FU= follow up; PPPD= pylorus preserving pancreaticoduodenectomy; NS= not significant; IDDM= insulin dependant diabetes mellitus; DM= diabetes mellitus; Prof rehab= professional rehabilitation; EORTC= European Organisation for Research and Treatment of Cancer; QLQ= Quality of Life Questionnaire; s.d= standard deviation

Buchler MW Am J Surg 1995

Klempa I Chirurg 1995

Izbicki JR Ann Surg 1998; 228

Farkas G Langenbecks Arch Surg 2006

Muller MW Br J Surg 2008

Strate T Gastroenterology 2008

Table 1. Outcomes of Pylorus preserving pancreaticoduodenectomy (PPPD) vs duodenum preserving pancreatic head resection (DPPHR)

| | Follow up | Procedure | Mortality | morbidity | Pain relief | QOL | Endocrine function | Exocrine function | Weight gain |
|----------------------------------|--------------------------------|---|-----------|---------------------------------|------------------------------|--------------------------------------|--|--|---------------|
| Izbicki 1995 | Mean 1.5 yrs (6-24 months) | | | | Pre-op vs post-op pain score | Prof rehab; post-op global QOL score | worsened DM control; new onset DM; newly abnormal Oral GTT | New faecal chymotrypsin/ Pancreolauryl test abnormality on post-operative FU | |
| | | Beger (n=20) | 0 | 6 | 62.25; 3 | 14; 28.6 | 2; 0; 1 | 2 | 6.7 +/- 2.1kg |
| | | Frey (n=22) | 0 | 2 | 61.50; 4 | 15; 28.6 | 0; 0; 1 | 2 | 6.4 +/- 2.5kg |
| | | P value | NS | <0.05 | NS | NS; NS | Not stated | NS | Not stated |
| Strate 2005 (FU of Izbicki 1995) | Median 8.5 yrs (72-144 months) | | | | | Less fatigue with Beger | | | |
| | | | | Pancreas related repeat surgery | Pain score | global QOL score; Prof rehab | Presence of DM | Abnormal faecal pancreatic elastase | |
| | | Beger (n=38; FU= 26) | 8 | 3 | 11.25 (0 - 75) | 66.7 (0-100); 16 | 14/25 | 22/25 | |
| | | Frey (n=36; FU=25) | 8 | 0 | 11.25 (0 - 99.75) | 58.35 (0-83.4); 11 | 15/25 | 18/23 | |
| | | P value | NS | 0.08 | 0.679 | 0.476; NS | 0.774 | 0.157 | |
| Köninger 2008 | 6 months and 2 years | 7 patients lost to FU (Beger 4, Frey 3) | | | | | 1 patient declined testing | 3 patients declined testing | |
| | | | | | | EORTC QLQ-C30, QLQ-PAN26 scores | | | |

| | Follow up | Procedure | Mortality | morbidity | Pain relief | QOL | Endocrine function | Exocrine function | Weight gain |
|--|-----------|---|-----------|-----------|-------------|------------------------------|--------------------|-------------------|-------------|
| | | Beger (n=32; FU=30 and 26) | | 6 | | 65.6 +/- 24.8, 63.9 +/- 23.7 | | | |
| | | Berne (n=33; FU=32 and 29) | | 7 | | 71.3 +/- 21.6, 75.8 +/- 15.7 | | | |
| | | P value | | >9,9 | | 0.371, 0.037 | | | |
| | | Patients analysed on intention to treat; but 8 in Beger and 6 in Berne groups had technique converted | | | | | | | |

QOL= quality of life; pre-op= pre-operative; post-op= post-operative; GTT= glucose tolerance test; FU= follow up; NS= not significant; DM= diabetes mellitus; Prof rehab= professional rehabilitation; EORTC= European Organisation for Research and Treatment of Cancer; QLQ= Quality of Life Questionnaire
Izbicki JR Ann Surg 1995
Strate T Ann Surg 2005
Koninger J Surgery 2008

Table 2. Comparisons of duodenum preserving resections of the pancreatic head.

there was evidence for significant benefit of DPPHR over PPPD in terms of morbidity (2 trials), pain relief (2 trials), quality of life (1 trial), endocrine function (1 trial), exocrine function (1 trial) and weight gain (2 trials). In addition, 2 trials showed a benefit for DPPHR in terms of operating time while hospital stay and requirement for blood transfusion were improved in 1 trial each. A Cochrane review on short term outcomes concluded that there was benefit for DPPHR in respect of quality of life and professional rehabilitation, exocrine insufficiency, weight gain, hospital stay and intra-operative blood replacement. There was also a trend towards reduced post-operative diabetes (Diener MK Ann Surg 2008). However, in the 2 studies examining long term outcomes, it was seen that many of the short term clinical benefits described above were not maintained. Proposed reasons for this were study error related to the small population sizes studied and that pancreatic gland burn-out might be delayed by DPPHR (Muller MW Br J Surg 2008). Nevertheless, at 14 year follow up there remained a trend towards better endocrine function, while there was significant benefit in terms of appetite, subjective feeling of well being and mean period of employment after surgery for patients undergoing DPPHR (Muller MW Br J Surg 2008). Thus, while short term results favour DPPHR over PPPD in CP, long term results appear equivalent and probably reflect the natural course of the disease.

Only 2 randomized trials have compared different DPPHR procedures, with 1 trial undergoing long term follow up (table 2). The first trial compared the Beger and Frey procedures with no significant differences being found in the short term apart from a benefit for the Frey operation in terms of morbidity. After a median of 8.5 years, all variables had comparable outcomes while almost all patients were noted to be exocrine insufficient (Izbicki JR Ann Surg 1995; Strate T Ann Surg 2005). The second study compared the Beger and Berne procedures, suggesting a benefit for the Berne operation in terms of operation time and hospital stay. Results were analysed on intention to treat basis however, including 8 out of 32 (Beger procedure) and 6 out of 33 (Berne procedure) patients who had their operations altered for technical reasons. When patients were analysed per protocol ie only those who underwent their assigned procedure, only the difference in operating times remained significant.

More extensive pancreatic resections such as total or near total distal pancreatectomy offer only short term relief and are associated with significant mortality and morbidity, often as a result of markedly reduced pancreatic function. They have largely been abandoned with their main role being as salvage procedures for complications relating to previous surgical interventions (including anastomotic leakage, pancreatic fistula and intractable pain following previous adequate resection or drainage surgery).

6. Surgery for the complications of chronic pancreatitis

Surgery for the complications of CP should be individualized to cater to a patient's specific morphology and clinical presentation.

6.1 Biliary obstruction

Choledocho-duodenostomy or hepatico-jejunostomy using a Roux-en-Y loop are the preferred procedures to resolve isolated biliary obstruction although the former may result in enteric reflux and a sump-like syndrome. Cholecysto-enterostomy has been associated

with poor results and has fallen into disfavour. A Hepatico-jejunostomy may be included in the Roux loop used to drain the pancreatic duct in dedicated drainage, resection or hybrid procedures performed to relieve pain. Alternatively, the CBD may be opened within the surgically created cavity in the pancreatic head during the Berne procedure.

6.2 Duodenal obstruction

Surgical relief of obstruction related to a fibrotic stricture involves duodenal mobilization by Kocher's manoeuvre with division of all fibrotic tissue. Should this be insufficient to restore patency, duodeno-duodenostomy or a gastro-jejunostomy may be considered, although the latter may be associated with biliary reflux. Where biliary obstruction co-exists in the presence of duodenal obstruction together with an inflammatory mass in the head, two options exist: PPPD or gastric bypass with a gastro-jejunostomy as part of the Roux drainage limb in a DPPHR.

6.3 Development of a pseudocyst

The choice of surgical procedure is dictated by the location of the pseudocyst and its proximity to a section of bowel suitable for drainage. Cyst-gastrostomy, cyst-duodenostomy and cyst-jejunostomy may all be employed depending on individual patient characteristics. Distal pancreatectomy may be employed for segmental disease within the body/tail together with an associated pseudocyst (Bornman PC S Afr Med J 2010). Surgery for pancreatic fistulae / ascites entails either a roux-en-Y jejunostomy to the fistula tract or an appropriate resection.

6.4 Gastro-intestinal bleeding, related to

a. Portal hypertension

Patients who have bled from gastric varices related to segmental portal hypertension as a consequence of splenic vein thrombosis can usually be managed with distal pancreatectomy.

b. Pseudoaneurysms

Where angiographic embolisation has failed to control a bleeding pseudoaneurysm vascular control may be achieved using a Frey-type procedure in preference to a more extensive resection which may be hazardous under these circumstances, while bleeding from the tail can usually be dealt with safely by means of a distal pancreatectomy (Bornman PC S Afr Med J 2010).

Surgery for suspected malignancy should utilize either a pancreatoduodenectomy or distal pancreatectomy depending on tumour location and should be performed in keeping with the oncological principle of clear resection margins.

7. Conclusion

The pathophysiology of chronic pancreatitis is complex and as yet incompletely understood, confounding attempts at effective management strategies. The clinical picture is dominated by progressive pain which may become intractable and pancreatic endocrine and exocrine

dysfunction which may severely impact on a patient's quality of life. Surgery aims to relieve ductal and tissue hypertension related to obstruction in the main and side branch ducts while also removing inflamed and fibrotic parenchymal tissue containing diseased nerve fibres. Duodenal preserving pancreatic head resections, usually combined with drainage of the main pancreatic duct, achieve both objectives with short and long term relief of pain in approximately 90% of patients at 5 year follow up. By preserving some parenchymal tissue these procedures attempt to limit pancreatic functional insufficiency. With acceptable morbidity and mortality figures, they have evolved as the surgical procedure of choice for the majority of patients with pain refractory to medical treatment. Surgery for complications of CP should be individualized while resection for neoplastic disease should be performed according to oncological principles, ensuring a clear margin of resection. More extensive resections should generally only be performed as salvage procedures for complications of previous surgery. Patients requiring surgery for chronic pancreatitis should be evaluated and treated by experienced surgeons in high volume centres utilizing a multi-disciplinary approach. Prior to undergoing surgery for pain, patients should have completed an adequate trial of medical therapy and been thoroughly counseled regarding the risks of surgery and its likely outcomes.

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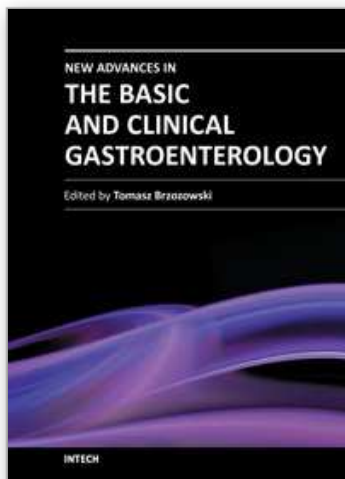
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The purpose of this book was to present the integrative, basic and clinical approaches based on recent developments in the field of gastroenterology. The most important advances in the pathophysiology and treatment of gastrointestinal disorders are discussed including; gastroesophageal reflux disease (GERD), peptic ulcer disease, irritable bowel disease (IBD), NSAIDs-induced gastroenteropathy and pancreatitis. Special focus was addressed to microbial aspects in the gut including recent achievements in the understanding of function of probiotic bacteria, their interaction with gastrointestinal epithelium and usefulness in the treatment of human disorders. We hope that this book will provide relevant new information useful to clinicians and basic scientists as well as to medical students, all looking for new advancements in the field of gastroenterology.

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