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TOPIC HIGHLIGHT

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Pain management in chronic pancreatitis

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Abstract

Abdominal pain is a major clinical problem in patients with chronic pancreatitis. The cause of pain is usually multifactorial with a complex interplay of factors contributing to a varying degree to the pain in an individual patient and, therefore, a rigid standardized approach for pain control tends to lead to suboptimal results. Pain management usually proceeds in a stepwise approach beginning with general lifestyle recommendations. Low fat diet, alcohol and smoking cessation are encouraged. Analgesics alone are needed in almost all patients. Maneuvers aimed at suppression of pancreatic secretion are routinely tried. Patients with ongoing symptoms may be candidates for more invasive options such as endoscopic therapy, and resective or drainage surgery. The role of pain modifying agents (antidepressants, gabapentin, pregabalin), celiac plexus block, antioxidants, octreotide and total pancreatectomy with islet cell auto transplantation remains to be determined.

Key words: Chronic pancreatitis; Pain; Endoscopy; Endoscopic ultrasound; Pancreas

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INTRODUCTION

Chronic pancreatitis remains an enigma in the field of gastroenterology. Challenges can be encountered in defining the etiology and pathogenesis, in securing the diagnosis, and finally in providing adequate therapy. Chronic pancreatitis is a common problem, but the exact prevalence is unclear. Many patients suffering from chronic abdominal pain may indeed have unrecognized chronic pancreatitis. The prevalence in the developed world is reported from 0.4% to 5%[1].

In the western world alcohol abuse is the overwhelming etiologic factor. Of patients with chronic pancreatitis, 60% to 70% have 6 to 12 years history of heavy consumption of alcohol (150-175 g/d)[2]. Less common, but important etiological factors to consider, are ductal obstruction (from tumors and strictures), autoimmune, hypercalcemia, hyperlipidemia, toxins, and genetic. In a small number of cases, there is no identifiable causative factor and the pancreatitis is deemed idiopathic. It should not be surprising in view of this array of etiologic factors that there exist uncertainties in both diagnosis and ultimately treatment of chronic pancreatitis. Adding to the perplexity of this clinical situation are the multiple treatment options that can be provided by primary care physicians, gastroenterologists, interventional endoscopists, and surgeons. Despite the evolution of new medications and tools in the last two decades no clear consensus has emerged on the management of chronic pancreatitis. Most reports are either anecdotal or collected experiences of a single approach.

It is the purpose of this review to discuss the different modalities that are currently being used for the treatment of pain in chronic pancreatitis and to attempt to integrate them in a patient centered comprehensive approach.

PATHOPHYSIOLOGY OF PAIN IN CHRONIC PANCREATITIS

At least 85% of patients with chronic pancreatitis

develop pain at some point during the course of their disease. Painless chronic pancreatitis is rare, and more commonly late in the natural history of idiopathic chronic pancreatitis[3]. The frequency, severity and other characteristics of pain in chronic pancreatitis have a major impact on its management, the number of treatments, and the choice between medical and surgical interventions.

Several hypotheses exist as to the basis for pain in chronic pancreatitis; however, the exact mechanism is still not completely known. Possible mechanisms for pain include acute inflammation of the pancreas, increased pressure within the ductal system and parenchyma, neuritis, recurrent ischemia of the parenchyma; intra-pancreatic causes such as acute pseudocysts; and extra-pancreatic causes such as common bile duct or duodenal stenosis[4,5]. The relative contribution of each factor is unknown.

THERAPY OF PAIN IN CHRONIC PANCREATITIS

Medical therapy

Nonspecific supportive therapy: The first line in pain management is the use of medical therapy. The initial step of medical therapy usually is nonspecific supportive treatment. Supportive therapy is aimed at treating the concurrent symptoms and not the underlying factors in pain causation. Analgesic drugs are still the most commonly adopted method for pain relief. The obvious problem with this method of treatment is that patients often become dependant on heavy narcotic use. Most patients with chronic pancreatitis have their pain treated with analgesics on an episodic or continuing basis. Although the use of narcotics for the treatment of chronic pancreatitis is widespread, there are no controlled trials testing their efficacy as compared to the other modalities. Time intervals and doses of drug application must be adapted to the individual pain pattern. Although reluctance to use of narcotics is understandable, it should not be withheld if the treatment would otherwise not lead to adequate pain control[6].

There may be significant psychiatric, psychological, or psychosomatic contributions to the pain syndrome in these patients. Many physicians and surgeons use antidepressant medications as concomitant therapy, acknowledging the difficulty in assessing the psychological contributors to patients' pain syndrome. The benefits are anecdotal and variable in any individual experience and have never been rigorously assessed. It has been suggested that the natural path of chronic pancreatitis is toward progressive glandular insufficiency and calcification, and with the eventual 'burnout' would come spontaneous remission of pain[7]. There is a school of thought against conservative therapy. Pain is endured until burnout. This theory sheds light on the uncertainty regarding the duration of clinical pain, and if burnout is indeed a certainty and not solely a proposed hypothesis[8,9]. In conclusion, a strategy of waiting for spontaneous pain relief is not reliable and may be unreasonable advice for the patient with persistent or frequent severe pain.

Pancreatic enzymes: The presumed mechanism for pain relief after the administration of oral pancreatic enzymes is thought to involve the negative feedback inhibition to the pancreas. A cholecystokinin (CCK)-releasing peptide in the duodenum is normally denatured by pancreatic trypsin. In chronic pancreatitis, damage to acinar cells results in decreased secretion of pancreatic trypsin and consequently insufficient denaturing of the CCK-releasing peptide. This then leads to the potentiation and increased release of CCK, which causes pancreatic pain related to an increase in pancreatic enzyme output. When pancreatic enzymes are administered orally, there is more complete denaturing of the CCK-releasing peptide, thereby diminishing the release of CCK[10,11]. The results of studies examining the use of pancreatic enzymes that are administered orally to treat the pain of chronic pancreatitis have been variable, in part because of a high placebo response rate of over 35%, the potential for exogenously administered digestive enzymes to be inactivated by gastric acid and pancreatic proteases, and the lack of efficacy of enteric coated preparations[12-16].

In one of the earliest double-blind randomized trials of pancreatic enzymes, Isakson *et al* showed the pain relieving effect of oral enzyme preparations in a proportion of patients with chronic pancreatitis[16]. They took 19 patients with chronic pancreatitis, and treated them for 1 wk with a granulated pancreatic enzyme preparation (Pankreon®; five times daily 7.5 mL) or placebo and vice versa. Pain was evaluated using an analog scale and by questioning. A 30% pain reduction was seen after treatment with pancreatic extract compared to placebo. Fifteen of the nineteen patients had less pain during the week of treatment with pancreatic extracts. These results could not be confirmed by Halgreen, who conducted a 4-wk double-blind cross-over study with pancreatic enzymes (Pancrease®) in 20 chronic pancreatitis patients. There was no significant pain reduction[17]. In a placebo-controlled, double-blind, crossover study, pancrelipase (Viokase), in a dose of six tablets taken four times per day for one month, significantly reduced pain in 75% of patients with mild-to-moderate disease[15]. The best response was in young women with idiopathic chronic pancreatitis, whereas patients with advanced disease, including those with steatorrhea, had no response.

Of the 6 randomized trials published to date two studies using a non-enteric coated enzyme preparation reported benefit and four studies using an enteric-coated capsule showed no effect on pain in chronic pancreatitis. The conflicting study results led to investigators questioning the mechanism of negative feedback inhibition in the proximal small bowel[18]. As noted, the presumed mechanism for pain relief with administration of oral pancreatic enzymes is thought to involve feedback inhibition of the exocrine pancreas by the

degradation of CCK-releasing peptide in the duodenum. The administered enzymes would need to release activated serine proteases into the duodenum. This is much more likely with the non-enteric coated than the enteric-coated preparations, and hence the suspicion that the former are more effective. A meta-analysis of the six randomized, double-blind, placebo-controlled trials for the treatment of chronic pancreatitis with pancreatic enzymes showed no benefit in improving pain. The pooled estimate of the percentage of patients per study who preferred enzymes relative to placebo was 52% (95% confidence interval 45%-60%). This was not statistically different from 50%. Thus, this analysis demonstrates no significant benefit of pancreatic enzyme therapy to relieve chronic pancreatitis-associated pain[19]. It should be noted that this meta-analysis combines studies using enteric-coated and studies using non enteric-coated preparations. In that way, the potential benefit of non enteric-coated enzymes may have been negated by the lack of positive effect with non-enteric-coated preparation. The role of oral pancreatic enzymes in reducing pain in chronic pancreatitis, therefore, remains unclear. Additional studies are required to establish the effectiveness of this modality of treatment and to define whether certain subsets of pain: chronic *versus* intermittent pain; patients with or without exocrine insufficiency; alcoholic *versus* idiopathic pancreatitis; minimal *versus* extensive pancreatic duct changes; are more likely to benefit from enzyme therapy than others. Non-enteric coated enzymes are certainly safe and reasonable to try before considering more invasive or risky therapies.

Octreotide: Cholecystokinin-receptor antagonists or somatostatin analogues, such as octreotide, have been postulated to work on the negative feedback inhibition as well as hypertension of the pancreatic duct due to outflow obstruction. Inhibition of pancreatic secretion using somatostatin might, therefore, be effective in reducing pain in chronic pancreatitis. Octreotide is a synthetic somatostatin-analogue with an increased half-life, higher potency and the possibility of subcutaneous application. Experimental data suggest that octreotide increases the contractibility of the sphincter of Oddi, while somatostatin decreases it. This has, however, not consistently been demonstrated[20]. Normally, the release of cholecystokinin from specific intestinal cells is regulated by a cholecystokinin-releasing peptide in the proximal small intestine that is luminally active and trypsin-sensitive[13]. In chronic pancreatitis, exocrine insufficiency may lead to increased cholecystokinin-mediated stimulation of the pancreas. Theoretically, this process could be interrupted by the administration of cholecystokinin-receptor antagonists, or somatostatin. In a multicenter pilot study, octreotide, in a dose of 200 μg administered subcutaneously three times per day for 4 wk, reduced pain scores by 25% or more in 65% of patients with severe chronic pancreatitis[21]. On the other hand in a randomized, prospective, double-blind, placebo-controlled study conducted in Europe [100 mg subcutaneously (*sc*) every 8 h] administered to 10 patients for only 3 d was no more effective than placebo in relieving pain in chronic pancreatitis[22]. In a second study[23], octreotide (100 mg *sc* every 8 h for 3 wk) administered to six patients in a nonblinded fashion provided relief of pain in some but not all patients. In a third study[24], octreotide was administered to 84 patients for 4 wk in a randomized, prospective, double blind trial and showed a trend toward benefit at the highest dosage used (200 mg *sc* every 8 h). However, this effect did not reach statistical significance in this dose-ranging study. The longevity of the possible benefit was not established. Clearly further studies are needed before the use of octreotide can be widely adopted.

Antioxidant therapy: Bhardwaj *et al*[25] reported a decreased micronutrient intake (Vitamin E, riboflavin, choline, magnesium, copper, manganese and sulphur) in patients with chronic pancreatitis. This was due to diet modifications due to pain, as well as to a lower caloric intake. This points to the possibility that micronutrients deficiency may contribute to increased oxidative stress. In a comparison between patients with chronic pancreatitis and acute pancreatitis, the antioxidant profiles appeared to be different. Patients with chronic pancreatitis had significantly lower plasma concentrations of selenium, Vitamins A and E, beta-carotene, xanthine, beta-cryptoxanthine and lycopene in comparison with patients with recurrent acute pancreatitis[26]. Cullen *et al*[27] reported a decrease in antioxidant enzyme expression in pancreatic cells from normal pancreas to chronic pancreatitis to pancreatic cancer. Another observation concerning antioxidants is the altering of antioxidant status in chronic pancreatitis patients, which is worsened in patients with diabetes mellitus[28]. A 1-year clinical trial with 10 patients studied the effect of food supplementation using a complex containing l-methionine, beta-carotene, Vitamins C and E and organic selenium[29]. This resulted in a significant decrease in the intensity of pain as well as in days of hospital admission. Based on a placebo-controlled trial, followed by a retrospective cross-sectional study in 94 patients, some authors recommend antioxidant therapy consisting of supplements of methionine, Vitamin C and selenium[30].

Based on the observations that activation of oxygen free radicals can cause metabolic changes leading to pancreatic ischemia, antioxidant treatment with allopurinol seems a valid option. A trial with 13 patients with chronic pancreatitis investigated the effect of allopurinol on pain in a cross-over double-blind, randomized treatment trial[31]. Allopurinol, which is believed to reduce oxidative stress by inhibiting xanthine oxidase and thereby preventing the formation of oxygen derived free radicals, was given to 13 patients with pain occurring at least three times each week. Allopurinol was not effective in reducing pain or improving activities of daily living compared to placebo. In contrast, others showed that addition of allopurinol or dimethyl sulfoxide to intramuscular pethidine hydrochloride significantly

enhanced the efficacy of the analgesic regime[32]. This report suggests that removing oxygen free radicals in chronic pancreatitis may result in a beneficial therapeutic effect. The results of the most recent randomized trial presented only in abstract form showed that the combination of selenium, Vitamin C, β-carotene, Vitamin E, and methionine was significantly better in controlling pain compared to placebo[33]. In summary, there are conflicting data about the effectiveness of antioxidant therapy. A few trials show potential benefit, but further research is needed before it can become standard of therapy.

Endoscopic therapy

Endoscopists have shown that they can overcome pancreatic duct obstruction caused by ampullary stenosis, strictures, or stones. However, there have been no published validated guidelines for defining significant obstruction, and methodology for assessing patients before treatment and then judging the efficacy of that treatment. It should be noted though that the alternative to endoscopy, surgical sphincterotomy and sphincteroplasty, have already proven to be less efficient[34,35]. These interventions are hardly ever used now. This may also be due to the more acceptable rate of complication with endoscopic procedures, in conjunction with stent placement and stone extraction. For the present, the decision to perform endoscopy is based partially on subjective judgments that include assessment of the need for long-term narcotic therapy, marked diminution of the quality of life because of intractable pain, or major nutritional consequences of pain. When major pain episodes cannot be controlled by major, but acceptable maintenance analgesics, intervals of narcotics, or reasonable and brief periodic hospitalizations, a trial of interventional therapy can be justified. Among three recent studies involving stent therapy in 98 patients, at times associated with other interventional therapies such as lithotripsy and/or sphincterotomy[36-38], two studies[36,38] reported amelioration of pain and one did not[37].

The ideal treatment for patients with pancreatic-duct stones, dilated pancreatic ducts, and pain is not known. The stones can be easily removed coincidently with the performance of a surgical-drainage procedure, such as pancreaticojejunostomy. Alternatively, however, they can be fragmented by extracorporeal shock-wave lithotripsy (ESWL) and removed endoscopically after sphincterotomy of the pancreatic duct. Stones can be cleared by this approach in roughly 80 percent of patients, and approximately 50% of these have long-term relief of their symptoms[39,40]. Dumonceau *et al* conducted a randomized trial comparing pain relief after extracorporeal shock wave lithotripsy alone *versus* in combination with endoscopic drainage of the main pancreatic duct in patients with painful calcified chronic pancreatitis. Two years after trial intervention, 10 (38%) and 13 (45%) patients of the ESWL alone and ESWL combined with endoscopy group, respectively, had presented pain relapse. In both groups, a similar and significant decrease was seen after treatment in the number of pain episodes/year (mean decrease 3.7 episodes). There was no difference between the treatment groups and the treatment costs per patient were three times higher in the ESWL combined with endoscopy group compared with the ESWL alone group[41]. The claims for the efficacy of stone removal for pain relief should be considered in context with the observations that the presence or absence of stones does not necessarily correlate with the existence of pain. In the absence of randomized prospective trials comparing stone ablation either with placebo or with surgical decompression, it is difficult to assess the results of pancreatic stone removal.

An alternative involves the use of endoprostheses or stents placed in the pancreatic duct endoscopically. Reports indicate that 30%-76% of patients receiving such stents had symptomatic improvement over a period of 14 to 36 mo of observation[42-46]. Cremer *et al*[42], for example, noted initial improvement of symptoms in 94% of patients who were so treated for pancreatic-duct strictures and upstream ductal dilatation. In that group of patients, 53% remained free of symptoms over a mean follow-up period of 36 mo. Similarly, Grimm *et al*[43] showed that 57% of their patients were symptomatically improved by this treatment over a mean follow-up period of 19 mo. Although these results seem encouraging, a criticism is that most of the data reported to date were from relatively short term, nonrandomized studies. The issue is further complicated by the fact that pancreatic-duct stents may not be entirely harmless; for example, they may cause further pancreatic duct changes and potentiation of chronic pancreatitis[47-49]. Endoprosthesis occlusion and migration also seem to be relatively common.

Analyzing all the endoscopic modalities taken together it is usual to find a report of 80%-90% complete stone clearance and good immediate pain relief[47]. The long term results were not as favorable in the larger series. Delhaye *et al*[39] found that of 123 patients, only 60% experienced complete or partial pain relief during 14 mo follow-up. So far there are two randomized control trials comparing endoscopic therapy with surgery[50,51]. The study from Dite *et al* randomized 72 patients with large duct chronic pancreatitis to endoscopic therapy *versus* surgical lateral pancreaticojejunostomy. In addition, 68 patients were treated with endoscopy or surgery based on patient preference. The results between the randomized and nonrandomized study groups are similar. After 5 years of follow-up only 14% of the patients treated by endoscopy were pain free compare with 36% in the surgery group. The latest randomized controlled study comparing endoscopy with surgery (lateral pancreaticojejunostomy) enrolled 36 patients. The results are strikingly similar to the previous study. Pain was absent in 16% of patients treated with endoscopy and 40% in patients treated with surgery. Based on these trials it appears that surgery provides better pain relief compared to endoscopy, but even surgery fails to provide substantial pain relief in more than half of the patients[51].

Endoscopic treatment may have a place in the prevention of acute relapsing pancreatitis, more so than treatment of the pain of chronic pancreatitis. To avoid this potential problem, some have suggested that endoscopically placed pancreatic-duct stents should be used only for relatively short periods. This serves as a screening procedure, to identify those patients most likely to benefit from surgical drainage[42,45,52]. At present, endoscopically placed stents should be considered an unproved, but potentially useful approach to the treatment of chronic pancreatitis.

Kozarek and Traverso[53] have analyzed collected experiences and indicate that the likelihood of symptomatic improvement with combination endotherapy is reported to be 50%-85% at 15 to 25 mo. Successful pain relief has been correlated anecdotally with stone removal and subsequent decrease in diameter of the pancreatic duct. As a rule, the focus is on stones in the main duct and the morbidity of side-branch stones has not been defined. Better selection of patients for endotherapy may be helpful in order to maximize results. Due to its low degree of invasiveness, however, endotherapy can be offered as a first-line treatment, with surgery being performed in case of failure and/or recurrence.

Nerve blockade

Although this modality is thought to be medical management, it may be administered *via* endoscopic or interventional radiological means. Although widely used, there have been relatively few formally reported experiences with nerve blocks for long-term therapy of chronic pancreatitis. Leung *et al*[54] studied the use of celiac block in 23 patients with chronic pancreatitis. Twelve of the 23 had complete analgesia, whereas six had partial relief. There was no effect in five patients. The mean pain-free period in the chronic pancreatitis patients was only 2 mo, and the longest 4 mo. Benefit was least in patients with previous pancreatic surgery and repeat blocks were unhelpful.

Because of possible concerns about potential irreversible nerve injury, including very rare anecdotes of paraplegia from neurolytic agents, injection of steroids for the treatment of chronic pancreatitis has been recommended, instead of the use of alcohol injected into the celiac plexus (principally used in the treatment of cancer pain)[55,56]. In one study, steroid injection provided relief of pain (lasting two mo) in only 4 of 16 patients[57]. Eleven of the 12 patients who did not obtain relief were narcotic dependent, whereas none of the four who obtained relief were narcotic dependent. This finding emphasizes the complexity of treating pain in a population of patients with chemical dependencies and other abnormal psychological and psychosomatic behavior. In another report[58], which investigated the mode of delivering the nerve block, only 2 of 8 patients with a CT-guided celiac plexus block experienced relief of pain compared with 6 of 14 who were treated by endoscopic ultrasonography-guided celiac plexus block with 10 mL of bupivacaine. The benefit from endoscopic ultrasonography-guided celiac plexus block seemed to persist longer that CT-guided block. More importantly, paraplegia has not been described after endoscopic ultrasonography-guided celiac plexus block, probably because of the anterior transgastric approach taken during endoscopic ultrasonography-decreasing or even eliminating the risk of nerve or spinal cord injury. The same group of investigators more recently published their prospective experience with endoscopic ultrasonography-guided celiac plexus block with steroids in 90 patients with pain resulting from chronic pancreatitis[59]. A significant improvement in pain score occurred in 55% of the patients. The benefit persisted beyond 12 wk in 26% of patients and beyond 24 wk in only 10%. Younger patients (< 45 years) and patients with previous pancreatic surgery for chronic pancreatitis did not appear to benefit from the block.

The current evidence indicates that endoscopic ultrasonography-guided celiac plexus block is safe and well tolerated, with excellent temporary results in some patients. Unfortunately, reliable predictors of success are lacking. In the absence of long-term studies with follow-up in patients with chronic pancreatitis whose pain is chronic, the role of endoscopic ultrasonography-guided celiac plexus block should be limited to treating flares of chronic pain in patients with otherwise limited therapeutic options.

Surgical treatment

Duval pioneered efforts to treat the pain of chronic pancreatitis by surgical means in the 1950s with trans-duodenal sphincteroplasty and with caudal pancreato-jejunostomy (the Duval procedure). The results of this procedure were fraught with variable and usually poor results, perhaps only helping some of those patients with true recurrent acute pancreatitis[60]. A more extensive drainage procedure, lateral pancreatojejunostomy, described by Puestow and Gillesby[61] and subsequently modified by Partington and Rochelle[62], was applied to the subset of patients with dilated main pancreatic duct and became the first surgical treatment widely considered to be effective for pain in this disease. At that time, however, its application was hampered because there was no way to determine preoperatively if a patient with chronic pancreatitis had the dilated ducts required for this procedure because neither ERCP nor CT was available until the 1970s. Thus, at exploration an intraoperative pancreatogram was used to select who would be candidates for lateral pancreatojejunostomy. In those without dilated ducts, the remaining options were to perform a sphincteroplasty (which was largely abandoned because of its failure) or to do nothing further. In the 1960s, surgeons began performing pancreatic resections for chronic pancreatitis, initially distal pancreatectomies (with poor results) and later distal subtotal (95%) resections, which were relatively more effective for pain, but rendered most patients diabetic[63]. Proximal resections of the head of the pancreas (i.e. Whipple procedures) were not widely applied until the 1980s, when the associated operative morbidity and mortality fell substantially[64-66].

Patients whose pain persists in spite of aggressive noninvasive treatment should undergo endoscopic retrograde pancreatography to define the caliber and morphologic characteristics of their pancreatic ducts. Depending on the population being studied, up to half of these patients may have dilated ducts, frequently with areas of stricture-the "chain of lakes" or "string of pearls" appearance; the remainder have either ducts of normal caliber (2 to 4 mm in diameter) or small ducts that may lack side branches-the "tree in winter" appearance[67,68]. Ducts larger than 8 mm in diameter can be successfully decompressed by an internal surgical-drainage procedure, such as a longitudinal pancreaticojejunostomy (the modified Puestow procedure)[60,62], but smaller ducts are not amenable to internal surgical drainage or resection.

Like most surgical procedures currently in use, those for chronic pancreatitis gradually became part of the armamentarium without undergoing rigorous testing and were never compared against medical treatment or no treatment. The vast majority of patients are still operated on when they continue to have intractable pain despite medical treatment. There are very few controlled trials in the surgical literature on this disease. The two randomized controlled studies comparing surgery with endoscopic therapy are discussed in the endoscopic therapy section. Surgical options include decompression/drainage operations, pancreatic resections, and denervation procedures. As with endoscopic interventional therapy, objective transferable criteria for the need for surgical intervention have not been developed or agreed upon.

Decompression/drainage operations: At present, the ultimate role of these various invasive approaches to the treatment of patients with large-duct, symptomatic chronic pancreatitis has not been established. Given the information available at the present time, most physicians recommend longitudinal pancreaticojejunostomy for patients with pain and dilated ducts. This operation may also retard the progression of exocrine and endocrine insufficiency[69,70]. Surgical decompression of the obstructed main pancreatic duct was for a long time the gold standard[71]. Drainage procedures today are most commonly side to side pancreaticojejunostomy. This particular procedure preserves parenchymal function. Longitudinal pancreaticojejunostomy is also used based on the concept the ductal obstruction leads to distention and that this in turn gives rise to pain and should thus be favored if the duct is widened. Ebbehoj *et al*[72] were able to show a relationship between the degree of pain and intrapancreatic pressure. Pancreatic pressure was measured by a percutaneously placed needle preoperatively, postoperatively, and one year after pancreatic duct drainage. Patients whose pressure decreased after surgery and remained low were pain free, whereas those with recurrent pain had increased pressure.

Theoretically, any procedure that improves drainage, either by improving flow into the jejunum or stomach, might be expected to relieve pain. Pancreatic decompression results in immediate and lasting pain relief in a high proportion (80%-90%) of patients with non-alcoholic chronic pancreatitis[73]. These procedures have been less successful with alcoholic chronic pancreatitis with pain relief averaged at 60%[74]. Although early good results have also been reported after a lateral pancreaticojejunostomy in patients with alcoholic pancreatitis, when these patients are followed for 5 years only 38%-60% of them continue to be pain free[75]. These operations are predicated upon the presence of a widely dilated main pancreatic duct (generally taken as > 6 to 7 mm) and the presumption that the dilated ducts imply an abnormally high pressure in the duct system[75] and in the pancreatic parenchyma[72,76]. The operation most commonly performed is a variant of the Puestow procedure, which is actually the Partington-Rochelle modification (lateral pancreaticojejunostomy)[62].

Many of the studies of lateral pancreatico-duodenectomy find that short-term pain relief is achieved in about 80% of patients and that the operation can be performed with a very low morbidity and mortality (0%-5%). Although the short-term studies shine a positive light on the procedure, long-term follow-up studies show that pain not uncommonly recurs. As time goes by, pain recurs, perhaps related to progression of the pancreatic injury and fibrosis. Pain relief for greater than two years is achieved in only 60% of patients[77,78]. Strategies for salvage in patients with persistent or recurrent pain after drainage procedures include redoing or extending the pancreatojejunostomy and resection procedures[79]. Of patients undergoing pancreatic duct drainage procedures, 25%-66% require concomitant biliary or gastric drainage, because of functionally significant obstruction of the bile duct or duodenum[80,81]. Biliary or duodenal strictures have been reported to be more likely in patients with large-duct disease than in their counterparts without dilated ducts[81].

The only reported attempt made to compare pancreatic duct drainage with no intervention in the management of pain is that of Nealon and Thompson[70]. In a series of 143 patients with chronic pancreatitis, 85% of the 87 patients who were treated by pancreatic duct decompression achieved pain relief, whereas pain abated spontaneously in only 1.3% of the 56 nonoperative patients. The study was not randomized, however, the principal criterion to determine candidacy for the operation was the presence of a dilated pancreatic duct. Thus, what the study actually reports is the outcome of pancreatojejunostomy in patients with dilated ducts *versus* the natural history of patients with chronic pancreatitis and no duct dilation. The study also found that deterioration of pancreatic function was slower in their patients with dilated ducts than in those with small ducts. Although this effect was ascribed by the investigators to the protection or relief afforded by the surgical drainage procedure, the cause and effect relationship is uncertain because of the differences in the patient population.

The consensus, albeit based on evidence from collected experiences, states that pancreatic duct decompression *via* lateral pancreatojejunostomy (a Puestow-type operation) can be accomplished with low associated morbidity and mortality and that pain relief will be achieved in the

majority of patients. For most experienced pancreatic surgeons, it is the preferred surgical treatment option in patients whose main pancreatic duct measures 6 mm or more because of its simplicity, safety, and benefits, including the advantage that remaining pancreatic tissue and function are at least not compromised further by loss from resection.

Drainage of pancreatic pseudocysts provides another form of pancreatic decompression in conjunction and even in continuity with a lateral pancreatojejunostomy when the main duct is also dilated. Up to 39% of patients undergoing lateral pancreaticojejunostomy have evidence of pseudocysts disease at the time of surgery[82]. Pseudocysts are found in about 25% of patients with chronic pancreatitis and have a much lower rate of spontaneous resolution than those that are a consequence of an attack of acute pancreatitis[82-84]. They can be the source of pain indistinguishable from that of the underlying chronic pancreatitis. In one study, surgical drainage resulted in complete short-term pain relief in 96% of 55 patients, and 53% remained pain free after a median follow-up of 11 years[84]. Endoscopic drainage of pseudocysts into the stomach or duodenum may be an alternative, especially in patients who do not have associated duct dilation. Studies directly comparing surgical with endoscopic drainage of pseudocyst are lacking.

It should also be mentioned that there are numerous variations of the previously mentioned operations. Frey *et al*[85,86] combined a coring out of the pancreatic head with a lateral pancreaticojejunostomy. In his series, the pain relief after 5 years was complete or improved in 87% of cases. There is also one randomized series of patients comparing the Beger and Frey procedure[86-90], with no difference in decrease of pain, but less morbidity with the Frey procedure.

Resection procedures: The therapeutic principle of resection is based on the assumption that pain in chronic pancreatitis is predominantly caused by inflammation. This inflammation then becomes the nidus for qualitative and quantitative changes of nerve fibers. This is especially seen in the clinical scenario of normal sized ducts and masses of the head of the pancreas. Thirty percent of patients with chronic pancreatitis develop inflammatory enlargement of the pancreatic head with subsequent obstruction of the pancreatic duct, and sometimes also of the common bile duct and duodenum. In these cases a pancreaticoduodenectomy, "Whipple procedure", has been the procedure of choice for a long time, as it provides reasonably effective pain relief. These resections, however, have both immediate postoperative morbidity and long-term morbidity. Insulin dependent diabetes mellitus has an increase in the incidence from 20% preoperatively to 60% in the years that follow[81]. Also, postgastrectomy complications detract significantly from the overall quality of life. The long-term mortality rate and quality of life after this procedure in patients with chronic pancreatitis has not always been encouraging, and in some studies disappointing[71]. Distal pancreatectomy alone had poor results unless the disease is largely confined to the body and tail of the gland, e.g. with an occlusion of the mid-pancreatic duct or with a pseudocyst in the tail. By contrast, resection of the pancreatic head by either a conventional or pylorus-preserving pancreaticoduodenectomy will provide pain relief in up to 85% of patients, even if the disease extends into the distal pancreas. In order to deal with these undesirable consequences of the Whipple procedure, surgeons turned to the pylorus preserving pancreaticoduodenectomy (PPPD) and the "Beger procedure"[88-91]. Russel[92], in studying the results of preservation of the duodenum in total pancreatectomy compared with those of standard pancreaticoduodenectomy, found no difference in pain relief between the results of the two operations. He noted that 13 (14%) of the 32 still had severe pain after duodenum preserving total pancreatectomy, and that six required major analgesics. The purported benefits of better postoperative nutritional status and glucose control in the duodenum-preserving procedure were addressed in two randomized trials[93,94].

Frey and Amikura have recently reported a surgical modification that combines removing part of the anterior segment of the pancreatic head with longitudinal duct anastomosis to the jejunum[86]. A randomized trial[87] found little difference between the Frey procedure and the duodenum-preserving resection of the pancreatic head as described by Beger and Buchler[95].

Noteworthy in recent years has been the very low operative morbidity and mortality of pancreatic resection, which may be one reason for the larger numbers of patients with benign disease being referred for surgical treatment. In a recent series of 231 pancreatic resections, the most frequent indication being chronic pancreatitis, the operative mortality was 0.4%[66]. McLeod *et al*[96] studied the morbidity of the Whipple operation. Although the study focused on resections for neoplasms, the observations pertain as well to those for chronic pancreatitis and show satisfactory digestion, weight maintenance, and activity level in the great majority of patients. A study of quality of life after pancreatic resections found that diabetes and its complications had the greatest negative influence on everyday well-being[97].

Distal pancreatectomy[98] has a very limited role in management of pain, and only in patients with non-dilated pancreatic duct and pseudocysts involving the tail of the pancreas does this procedure seem to be associated with a good outcome[99]. Keith *et al*[100], analyzed the results of 80% distal pancreatectomy, pancreaticoduodenectomy and total pancreatectomy. After an average follow-up of 5 years, 9 years, and 6 years, respectively, he found that four of five patients after pancreaticoduodenectomy required narcotics. Thirteen of 32 patients had complete pain relief after 80% distal pancreatectomy. Finally total pancreatectomy is usually reserved as a last resort following a failed partial pancreatic resection.

Resection of pancreatic tissue results in the loss of

some exocrine and endocrine function and increases the possibility or hastens the onset of fat malabsorption and diabetes. Whereas only 20% of normal pancreatic tissue is required for clinically adequate function, the pancreas already damaged by chronic pancreatitis may have substantially reduced reserves even before resection. Because of the complete lack of insulin and glucagon after total pancreatectomy, very brittle diabetes may ensue and can be the source of considerable morbidity and even mortality. In an attempt to lessen these adversities, autotransplantation of either part of the organ[101] or of islet tissue[102] has been described. In the latter study, Farney *et al* obtained insulin independence in 20% of 24 patients at a mean follow-up of 5.5 years. A more extensive experience with islet cell autotransplantation was reported by the Minnesota group in 1995 comprising 48 patients[103]. Forty-seven of the 48 patients had small duct chronic pancreatitis. Only one postoperative death resulted, but 25% of patient's encountered complications. There were 8 deaths in the follow-up period, none apparently attributable to the operation. In follow-up, from 1 mo to 17 years, 39% of patients reported that pain was resolved, and 61% still had some degree of pain. Twenty of 39 evaluable patients (51%) had initial (less than 1 mo) insulin independence, but this dropped to 15 patients (38%) beyond 1 mo. A more recent European experience of 13 patients indicated sustained insulin independence in 5 of 9 surviving patients (4 late deaths) from 9 to 48 mo after surgery[104]. The latest studies suggest improvement in both the areas of brittle diabetes and in pain control. Rodriquez *et al*[105] recruited 22 patients who underwent pancreatectomy and autologous islet cell transplantation. All patients demonstrated C-peptide and insulin production indicating graft function. Forty-one percent were insulin dependent, and 27% required minimal amount of insulin or a sliding scale. Eighty-two percent no longer required analgesics postoperatively and 14% experienced a decrease in need for narcotics. Their success was attributed due to the provision of pancreatectomy and islet cell transplantation earlier in the course of the disease. Clayton *et al*[106] followed 40 patients who had pancreatectomy followed by islet cell transplantation. At 2 years post-transplant, 18 patients had a median HbA1c of 6.6% (5.2%-19.3%), fasting C-peptide of 0.66 ng/mL (0.26-2.65 ng/mL), and required a median of 12 (0-45) units of insulin per day. At 6 years, these figures were 8% (6.1%-11.1%), 1.68 ng/mL (0.9-2.78 ng/mL) and 43 U/d (6-86 U/d), respectively. The majority of patients (68%) no longer require opiate analgesia. Finally, Gruessner *et al*[107] performed 112 islet autotransplants at the time of total pancreatectomy. They found that islet autotransplants, at the time of total pancreatectomy in patients who had not had previous operations on the body and tail of the pancreas, were associated with > 70% of the recipients achieving complete insulin independence. In contrast, a previous distal pancreatectomy or a Puestow drainage procedure was associated with complete insulin independence in < 20%. Islet autotransplantation offers a valuable addition to surgical resection of the pancreas, as a treatment for chronic pancreatitis; and even in cases in which insulin independence is not achieved, the potential beneficial effects of C-peptide make the procedure worthwhile, particularly in early disease.

Many studies on pancreatic resection and even those on drainage procedures show that up to 15% of patients undergoing these surgical treatments for treatment of pain due to chronic pancreatitis will be found to have pancreatic cancer[7,79,99,108] and it has been shown that a chronic pancreatitis is in fact, a small, but real risk factor in the development of pancreatic cancer[109]. This is an important consideration to keep in mind during the diagnostic work-up and choice of operation. The morphology of the pancreas by CT imaging and by cholangiopancreatography may fail to discriminate between cancer and chronic pancreatitis. Cytological confirmation by fine-needle aspiration is helpful when positive, but the true diagnosis may become known only with resection (10% of cases). This consideration in some cases may determine the treatment strategy.

Surgical denervation: Most of the sensory nerves returning from the pancreas pass through the celiac ganglion and splanchnic nerves. It is hypothesized that interruption of these fibers may lessen pain. Mallet-Guy[110] reported an experience with 215 patients over 30 years whose principal treatment for pain was by sensory denervation. These patients first underwent abdominal exploration to document the absence of pancreatic ductal dilation or pseudocysts and to correct any associated biliary pathology; this was immediately followed by resection of the greater splanchnic nerve and celiac ganglion through a left translumbar approach. Although excellent long-term results are reported (90% of patients were pain-free, with 60% followed for more than five years), the heterogeneity of the patient population and the simultaneous use of biliary diversion procedures in many cases precludes meaningful conclusions. This treatment has not been widely accepted.

The celiac block can be done during laparotomy or percutaneously, usually from the back. The placement of the injection can be done simply by using anatomical landmarks or by checking the position with an imaging modality: fluoroscopy, scout X-ray films, ultrasonography, computed tomography, or at angiography. A nerve block with 25 mL of 50% alcohol on each side should be preceded by a positive diagnostic block with long acting local anesthesia, carried out at least 1 d earlier. The method aims at blockage of the splanchnic nerves before they reach the celiac plexus[111].

Stone and Chauvin reported on 15 patients with chronic pancreatitis who had previous unsuccessful operative procedures for pain[112]. Denervation was accomplished with a transthoracic left splanchnicectomy with concomitant vagotomy, and all 15 patients had immediate pain control. Five later suffered recurrent pain, but were successfully treated with a right splanchnicectomy. The long-term outcomes are not

known. The advent of thoracoscopic surgery has made this procedure more attractive, and a few small series have reported its feasibility and early results[113,114]. Maher *et al* recently reported on 15 patients with chronic pancreatitis, mostly idiopathic, with chronic pain measured by visual analogue pain scale[115]. Unilateral thoracoscopic splanchnic nerve resection in eight patients and bilateral in seven patients resulted in significant decreases in pain frequency and intensity, as well as in narcotic consumption. Overall, 80% of patients had good results or were improved, with a mean follow-up of 16 mo. A controlled trial comparing this procedure to other surgical options or to medical treatment is needed. Of note, pancreaticoduodenectomy and duodenum-preserving resection of the pancreatic head may well confer pain relief at least in part through denervation.

CONCLUSION

Pain is the most difficult to treat symptom of chronic pancreatitis. The current approach is largely based on data from studies of suboptimal quality and expert opinions. At present, a step wise strategy is recommended starting with life style modifications such as alcohol abstinence and low fat diet, then moving to high dose non-coated pancreatic enzymes and oral analgesic therapy. In patients with dilated main pancreatic duct unresponsive to medical therapy, endoscopy or decompressive surgery should be considered. Patients with debilitating pain, non-dilated pancreatic duct and inflammatory masses may be candidates for resective surgery. The role of pain modifying agents (antidepressants, gabapentin, pregabalin), celiac plexus block, antioxidants, octreotide and total pancreatectomy with islet cell auto transplantation remains to be determined.

REFERENCES

1 **Feldman M**, Friedman L, Brandt L. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. 8th ed. Philadelphia: Saunders, 2006: 1271-1300
2 **Sarles H**, Sahel J, Staub JL, Bourry J, Laugier R. Chronic Pancreatitis. In: Howat HT, Sarles H, editors. The exocrine pancreas. Philadelphia: WB Saunders, 1979: 402-439
3 **Ammann RW**, Buehler H, Muench R, Freiburghaus AW, Siegenthaler W. Differences in the natural history of idiopathic (nonalcoholic) and alcoholic chronic pancreatitis. A comparative long-term study of 287 patients. *Pancreas* 1987; **2**: 368-377
4 **Bradley EL 3rd**. Pancreatic duct pressure in chronic pancreatitis. *Am J Surg* 1982; **144**: 313-316
5 **Makrauer FL**, Antonioli DA, Banks PA. Duodenal stenosis in chronic pancreatitis: clinicopathological correlations. *Dig Dis Sci* 1982; **27**: 525-532
6 **Andren-Sandberg A**. Pain relief in pancreatic disease. *Br J Surg* 1997; **84**: 1041-1042
7 **Ammann RW**, Akovbiantz A, Largiader F, Schueler G. Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients. *Gastroenterology* 1984; **86**: 820-828
8 **Lankisch PG**, Seidensticker F, Lohr-Happe A, Otto J, Creutzfeldt W. The course of pain is the same in alcohol- and nonalcohol-induced chronic pancreatitis. *Pancreas* 1995; **10**: 338-341
9 **Warshaw AL**. Pain in chronic pancreatitis. Patients, patience, and the impatient surgeon. *Gastroenterology* 1984; **86**: 987-989
10 **Owyang C**, Louie DS, Tatum D. Feedback regulation of pancreatic enzyme secretion. Suppression of cholecystokinin release by trypsin. *J Clin Invest* 1986; **77**: 2042-2047
11 **Layer P**, Jansen JB, Cherian L, Lamers CB, Goebell H. Feedback regulation of human pancreatic secretion. Effects of protease inhibition on duodenal delivery and small intestinal transit of pancreatic enzymes. *Gastroenterology* 1990; **98**: 1311-1319
12 **Dobrilla G**. Management of chronic pancreatitis. Focus on enzyme replacement therapy. *Int J Pancreatol* 1989; **5** Suppl: 17-29
13 **Andren-Sandberg A**. Theory and practice in the individualization of oral pancreatic enzyme administration for chronic pancreatitis. *Int J Pancreatol* 1989; **5** Suppl: 51-62
14 **Mossner J**, Secknus R, Meyer J, Niederau C, Adler G. Treatment of pain with pancreatic extracts in chronic pancreatitis: results of a prospective placebo-controlled multicenter trial. *Digestion* 1992; **53**: 54-66
15 **Slaff J**, Jacobson D, Tillman CR, Curington C, Toskes P. Protease-specific suppression of pancreatic exocrine secretion. *Gastroenterology* 1984; **87**: 44-52
16 **Isaksson G**, Ihse I. Pain reduction by an oral pancreatic enzyme preparation in chronic pancreatitis. *Dig Dis Sci* 1983; **28**: 97-102
17 **Halgreen H**, Pedersen NT, Worning H. Symptomatic effect of pancreatic enzyme therapy in patients with chronic pancreatitis. *Scand J Gastroenterol* 1986; **21**: 104-108
18 **Mossner J**, Wresky HP, Kestel W, Zeeh J, Regner U, Fischbach W. Influence of treatment with pancreatic extracts on pancreatic enzyme secretion. *Gut* 1989; **30**: 1143-1149
19 **Brown A**, Hughes M, Tenner S, Banks PA. Does pancreatic enzyme supplementation reduce pain in patients with chronic pancreatitis: a meta-analysis. *Am J Gastroenterol* 1997; **92**: 2032-2035
20 **Uhl W**, Anghelacopoulos SE, Friess H, Buchler MW. The role of octreotide and somatostatin in acute and chronic pancreatitis. *Digestion* 1999; **60** Suppl 2: 23-31
21 **Toskes PP**, Forsmark CE, Demeo MT. A multicenter controlled trial of octreotide for the pain of chronic pancreatitis. *Pancreas* 1993; **8**: 774
22 **Malfertheiner P**, Mayer D, Buchler M, Dominguez-Munoz JE, Schiefer B, Ditschuneit H. Treatment of pain in chronic pancreatitis by inhibition of pancreatic secretion with octreotide. *Gut* 1995; **36**: 450-454
23 **Scmalz MJ**, Soerger KH, Johanson JF. The effect of octrotide acetate, sandostatin, on the pain of chronic pancreatitis. *Gastroenterology* 1992; **102**: A290
24 **Toskes PP**. Medical management of chronic pancreatitis. *Scand J Gastroenterol Suppl* 1995; **208**: 74-80
25 **Bhardwaj P**, Thareja S, Prakash S, Saraya A. Micronutrient antioxidant intake in patients with chronic pancreatitis. *Trop Gastroenterol* 2004; **25**: 69-72
26 **Morris-Stiff GJ**, Bowrey DJ, Oleesky D, Davies M, Clark GW, Puntis MC. The antioxidant profiles of patients with recurrent acute and chronic pancreatitis. *Am J Gastroenterol* 1999; **94**: 2135-2140
27 **Cullen JJ**, Mitros FA, Oberley LW. Expression of antioxidant enzymes in diseases of the human pancreas: another link between chronic pancreatitis and pancreatic cancer. *Pancreas* 2003; **26**: 23-27
28 **Quilliot D**, Walters E, Bonte JP, Fruchart JC, Duriez P, Ziegler O. Diabetes mellitus worsens antioxidant status in patients with chronic pancreatitis. *Am J Clin Nutr* 2005; **81**: 1117-1125
29 **De las Heras Castano G**, Garcia de la Paz A, Fernandez MD, Fernandez Forcelledo JL. Use of antioxidants to treat

pain in chronic pancreatitis. *Rev Esp Enferm Dig* 2000; **92**: 375-385
30 **Salim AS**. Role of oxygen-derived free radical scavengers in the treatment of recurrent pain produced by chronic pancreatitis. A new approach. *Arch Surg* 1991; **126**: 1109-1114
31 **Banks PA**, Hughes M, Ferrante M, Noordhoek EC, Ramagopal V, Slivka A. Does allopurinol reduce pain of chronic pancreatitis? *Int J Pancreatol* 1997; **22**: 171-176
32 **McCloy R**. Chronic pancreatitis at Manchester, UK. Focus on antioxidant therapy. *Digestion* 1998; **59** Suppl 4: 36-48
33 **Bhardwaj P**, Grag PK, Saray A, Acharya S. Antioxidant Supplementation for Pain Relief in Chronic Pancreatitis: A Randomized Placebo Controlled Double Blind Trial. *Gastroenterology* 2007; **132**: A51
34 **Dreiling DA**, Greenstein RJ. The sphincter of Oddi, sphincterotomy and biliopancreatic disease. *Am J Gastroenterol* 1979; **72**: 665-670
35 **Bagley FH**, Braasch JW, Taylor RH, Warren KW. Sphincterotomy or sphincteroplasty in the treatment of pathologically mild chronic pancreatitis. *Am J Surg* 1981; **141**: 418-422
36 **Smits ME**, Badiga SM, Rauws EA, Tytgat GN, Huibregtse K. Long-term results of pancreatic stents in chronic pancreatitis. *Gastrointest Endosc* 1995; **42**: 461-467
37 **Ashby K**, Lo SK. The role of pancreatic stenting in obstructive ductal disorders other than pancreas divisum. *Gastrointest Endosc* 1995; **42**: 306-311
38 **Kozarek RA**, Ball TJ, Patterson DJ, Brandabur JJ, Traverso LW, Raltz S. Endoscopic pancreatic duct sphincterotomy: indications, technique, and analysis of results. *Gastrointest Endosc* 1994; **40**: 592-598
39 **Delhaye M**, Vandermeeren A, Baize M, Cremer M. Extracorporeal shock-wave lithotripsy of pancreatic calculi. *Gastroenterology* 1992; **102**: 610-620
40 **Neuhaus H**. Fragmentation of pancreatic stones by extracorporeal shock wave lithotripsy. *Endoscopy* 1991; **23**: 161-165
41 **Dumonceau JM**, Costamagna G, Tringali A, Vahedi K, Delhaye M, Hittelet A, Spera G, Giostra E, Mutignani M, De Maertelaer V, Deviere J. Treatment for painful calcified chronic pancreatitis: extracorporeal shock wave lithotripsy versus endoscopic treatment: a randomised controlled trial. *Gut* 2007; **56**: 545-552
42 **Cremer M**, Deviere J, Delhaye M, Baize M, Vandermeeren A. Stenting in severe chronic pancreatitis: results of medium-term follow-up in seventy-six patients. *Endoscopy* 1991; **23**: 171-176
43 **Grimm H**, Meyer WH, Nam VC, Soehendra N. New modalities for treating chronic pancreatitis. *Endoscopy* 1989; **21**: 70-74
44 **Huibregtse K**, Schneider B, Vrij AA, Tytgat GN. Endoscopic pancreatic drainage in chronic pancreatitis. *Gastrointest Endosc* 1988; **34**: 9-15
45 **Geenen JE**, Rolny P. Endoscopic therapy of acute and chronic pancreatitis. *Gastrointest Endosc* 1991; **37**: 377-382
46 **Burdick JS**, Hogan WJ. Chronic pancreatitis: selection of patients for endoscopic therapy. *Endoscopy* 1991; **23**: 155-159
47 **Kozarek RA**. Pancreatic stents can induce ductal changes consistent with chronic pancreatitis. *Gastrointest Endosc* 1990; **36**: 93-95
48 **Gulliver DJ**, Edmunds S, Baker ME, Paine S, Baillie J, Cotton PB, Rice RP. Stent placement for benign pancreatic diseases: correlation between ERCP findings and clinical response. *AJR Am J Roentgenol* 1992; **159**: 751-755
49 **Freedman SF**, Venu RP. Can pancreatic stent placement lead to chronic pancreatitis. *Gastroenterology* 1993; **104**: A304
50 **Dite P**, Ruzicka M, Zboril V, Novotny I. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. *Endoscopy* 2003; **35**: 553-558
51 **Cahen DL**, Gouma DJ, Nio Y, Rauws EA, Boermeester MA, Busch OR, Stoker J, Lameris JS, Dijkgraaf MG, Huibregtse K, Bruno MJ. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. *N Engl J Med* 2007; **356**: 676-684
52 **Siegel JH**, Ben-Zvi JS, Pullano W, Cooperman A. Effectiveness of endoscopic drainage for pancreas divisum: endoscopic and surgical results in 31 patients. *Endoscopy* 1990; **22**: 129-133
53 **Kozarek RA**, Traverso LW. Endoscopic treatment of chronic pancreatitis: An alternative to surgery? *Dig Surg* 1996; **13**: 90
54 **Leung JW**, Bowen-Wright M, Aveling W, Shorvon PJ, Cotton PB. Coeliac plexus block for pain in pancreatic cancer and chronic pancreatitis. *Br J Surg* 1983; **70**: 730-732
55 **Pap A**, Nauss LA, Di Magno EP. Is percutaneous celiac plexus block PCPB associated with pain relief in chronic pancreatitis? A comparison among analgesic, alcohol and steroid PCPB. *Pancreas* 1990; **5**: 725
56 **Wallace MB**, Hawes RH. Endoscopic ultrasound in the evaluation and treatment of chronic pancreatitis. *Pancreas* 2001; **23**: 26-35
57 **Busch EH**, Atchison SR. Steroid celiac plexus block for chronic pancreatitis: results in 16 cases. *J Clin Anesth* 1989; **1**: 431-433
58 **Gress F**, Schmitt C, Sherman S, Ikenberry S, Lehman G. A prospective randomized comparison of endoscopic ultrasound- and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain. *Am J Gastroenterol* 1999; **94**: 900-905
59 **Gress F**, Schmitt C, Sherman S, Ciaccia D, Ikenberry S, Lehman G. Endoscopic ultrasound-guided celiac plexus block for managing abdominal pain associated with chronic pancreatitis: a prospective single center experience. *Am J Gastroenterol* 2001; **96**: 409-416
60 **Duval MK Jr**. Caudal pancreatico-jejunostomy for chronic relapsing pancreatitis. *Ann Surg* 1954; **140**: 775-785
61 **Puestow CB**, Gillesby WJ. Retrograde surgical drainage of pancreas for chronic relapsing pancreatitis. *AMA Arch Surg* 1958; **76**: 898-907
62 **Partington PF**, Rochelle RE. Modified Puestow procedure for retrograde drainage of the pancreatic duct. *Ann Surg* 1960; **152**: 1037-1043
63 **Frey CF**, Child CG, Fry W. Pancreatectomy for chronic pancreatitis. *Ann Surg* 1976; **184**: 403-413
64 **Grace PA**, Pitt HA, Tompkins RK, DenBesten L, Longmire WP Jr. Decreased morbidity and mortality after pancreatoduodenectomy. *Am J Surg* 1986; **151**: 141-149
65 **Crist DW**, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality, and survival after the Whipple procedure. *Ann Surg* 1987; **206**: 358-365
66 **Fernandez-del Castillo C**, Rattner DW, Warshaw AL. Standards for pancreatic resection in the 1990s. *Arch Surg* 1995; **130**: 295-299; discussion 299-300
67 **Frey CF**. Why and when to drain the pancreatic ductal system. In: Beger HG, Buchler M, Ditschuneit H, Malfertheiner P, editors. Chronic pancreatitis: research and clinical management. Berlin: Springer-Verlag, 1990: 415-425
68 **Nagata A**, Homma T, Tamai K, Ueno K, Shimakura K, Oguchi H, Furuta S, Oda M. A study of chronic pancreatitis by serial endoscopic pancreatography. *Gastroenterology* 1981; **81**: 884-891
69 **Nealon WH**, Townsend CM Jr, Thompson JC. Operative drainage of the pancreatic duct delays functional impairment in patients with chronic pancreatitis. A prospective analysis. *Ann Surg* 1988; **208**: 321-329
70 **Nealon WH**, Thompson JC. Progressive loss of pancreatic function in chronic pancreatitis is delayed by main pancreatic duct decompression. A longitudinal prospective analysis of the modified puestow procedure. *Ann Surg* 1993; **217**: 458-466; discussion 466-468
71 **Eckhauser FE**, Knol JA, Mulholland MW, Colletti LM. Pancreatic surgery. *Curr Opinion Gastroenterol* 1996; **12**: 448-456
72 **Sharma AK**, Pande GK, Sahni P, Nundy S. Surgery for

nonalcoholic chronic pancreatitis. *World J Surg* 1998; **22**: 236-239; discussion 239-240
73 **Mannell A**, Adson MA, McIlrath DC, Ilstrup DM. Surgical management of chronic pancreatitis: long-term results in 141 patients. *Br J Surg* 1988; **75**: 467-472
74 **Sato T**, Miyashita E, Yamauchi H, Matsuno S. The role of surgical treatment for chronic pancreatitis. *Ann Surg* 1986; **203**: 266-271
75 **Jalleh RP**, Aslam M, Williamson RC. Pancreatic tissue and ductal pressures in chronic pancreatitis. *Br J Surg* 1991; **78**: 1235-1237
76 **Ebbehoj N**, Borly L, Bulow J, Rasmussen SG, Madsen P. Evaluation of pancreatic tissue fluid pressure and pain in chronic pancreatitis. A longitudinal study. *Scand J Gastroenterol* 1990; **25**: 462-466
77 **Holmberg JT**, Isaksson G, Ihse I. Long term results of pancreaticojejunostomy in chronic pancreatitis. *Surg Gynecol Obstet* 1985; **160**: 339-346
78 **Bradley EL 3rd**. Long-term results of pancreatojejunostomy in patients with chronic pancreatitis. *Am J Surg* 1987; **153**: 207-213
79 **Markowitz JS**, Rattner DW, Warshaw AL. Failure of symptomatic relief after pancreaticojejunal decompression for chronic pancreatitis. Strategies for salvage. *Arch Surg* 1994; **129**: 374-379; discussion 379-380
80 **Prinz RA**, Aranha GV, Greenlee HB. Combined pancreatic duct and upper gastrointestinal and biliary tract drainage in chronic pancreatitis. *Arch Surg* 1985; **120**: 361-366
81 **Warshaw AL**. Conservation of pancreatic tissue by combined gastric, biliary, and pancreatic duct drainage for pain from chronic pancreatitis. *Am J Surg* 1985; **149**: 563-569
82 **Munn JS**, Aranha GV, Greenlee HB, Prinz RA. Simultaneous treatment of chronic pancreatitis and pancreatic pseudocyst. *Arch Surg* 1987; **122**: 662-667
83 **Warshaw AL**, Rattner DW. Timing of surgical drainage for pancreatic pseudocyst. Clinical and chemical criteria. *Ann Surg* 1985; **202**: 720-724
84 **Lohr-Happe A**, Peiper M, Lankisch PG. Natural course of operated pseudocysts in chronic pancreatitis. *Gut* 1994; **35**: 1479-1482
85 **Frey CF**, Smith GJ. Description and rationale of a new operation for chronic pancreatitis. *Pancreas* 1987; **2**: 701-707
86 **Frey CF**, Amikura K. Local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy in the management of patients with chronic pancreatitis. *Ann Surg* 1994; **220**: 492-504; discussion 504-507
87 **Izbicki JR**, Bloechle C, Knoefel WT, Kuechler T, Binmoeller KF, Broelsch CE. Duodenum-preserving resection of the head of the pancreas in chronic pancreatitis. A prospective, randomized trial. *Ann Surg* 1995; **221**: 350-358
88 **Buchler MW**, Friess H, Bittner R, Roscher R, Krautzberger W, Muller MW, Malfertheiner P, Beger HG. Duodenum-preserving pancreatic head resection: Long-term results. *J Gastrointest Surg* 1997; **1**: 13-19
89 **Beger HG**, Krautzberger W, Bittner R, Buchler M, Limmer J. Duodenum-preserving resection of the head of the pancreas in patients with severe chronic pancreatitis. *Surgery* 1985; **97**: 467-473
90 **Beger HG**, Muchler M. Duodenum-preserving reaction of the head of the pancreas in chronic pancreatitis with inflammatory mass in the head. *World J Surg* 1990; **14**: 83-87
91 **Traverso LW**, Longmire WP Jr. Preservation of the pylorus in pancreaticoduodenectomy. *Surg Gynecol Obstet* 1978; **146**: 959-962
92 **Russel RCG**. Indications for surgical treatment in chronic pancreatitis. In: Standards in Pancreatic Surgery. Berger HG, Cuchler M, Malfertheiner P, editors. Berlin: Springer-Verlag, 1983: 350-357
93 **Buchler MW**, Friess H, Muller MW, Wheatley AM, Beger HG. Randomized trial of duodenum-preserving pancreatic head resection versus pylorus-preserving Whipple in chronic pancreatitis. *Am J Surg* 1995; **169**: 65-69; discussion 69-70
94 **Klempa I**, Spatny M, Menzel J, Baca I, Nustede R, Stockmann F, Arnold W. Pancreatic function and quality of life after resection of the head of the pancreas in chronic pancreatitis. A prospective, randomized comparative study after duodenum preserving resection of the head of the pancreas versus Whipple's operation. *Chirurg* 1995; **66**: 350-359
95 **Bloechle C**, Izbicki JR, Knoefel WT, Kuechler T, Broelsch CE. Quality of life in chronic pancreatitis--results after duodenum-preserving resection of the head of the pancreas. *Pancreas* 1995; **11**: 77-85
96 **McLeod RS**, Taylor BR, O'Connor BI, Greenberg GR, Jeejeebhoy KN, Royall D, Langer B. Quality of life, nutritional status, and gastrointestinal hormone profile following the Whipple procedure. *Am J Surg* 1995; **169**: 179-185
97 **Petrin P**, Andreoli A, Antoniutti M, Delina Z, Corrado DL, Bruno B, Luigi G, Sergio P. Surgery for chronic pancreatitis: What quality of life ahead? *World J Surg* 1995; **19**: 398
98 **Andren-Sandberg A**, Wagner M, Tihanyi T, Lofgren P, Friess H. Technical aspects of left-sided pancreatic resection for cancer. *Dig Surg* 1999; **16**: 305-312
99 **Rattner DW**, Fernandez-del Castillo C, Warshaw AL. Pitfalls of distal pancreatectomy for relief of pain in chronic pancreatitis. *Am J Surg* 1996; **171**: 142-145; discussion 145-146
100 **Keith RG**, Saibil FG, Sheppard RH. Treatment of chronic alcoholic pancreatitis by pancreatic resection. *Am J Surg* 1989; **157**: 156-162
101 **Rossi RL**, Soeldner JS, Braasch JW, Heiss FW, Shea JA, Watkins E Jr, Silverman ML. Long-term results of pancreatic resection and segmental pancreatic autotransplantation for chronic pancreatitis. *Am J Surg* 1990; **159**: 51-57; discussion 57-58
102 **Farney AC**, Najarian JS, Nakhleh RE, Lloveras G, Field MJ, Gores PF, Sutherland DE. Autotransplantation of dispersed pancreatic islet tissue combined with total or near-total pancreatectomy for treatment of chronic pancreatitis. *Surgery* 1991; **110**: 427-437; discussion 437-439
103 **Wahoff DC**, Papalois BE, Najarian JS, Kendall DM, Farney AC, Leone JP, Jessurun J, Dunn DL, Robertson RP, Sutherland DE. Autologous islet transplantation to prevent diabetes after pancreatic resection. *Ann Surg* 1995; **222**: 562-575; discussion 575-579
104 **Oberholzer J**, Triponez F, Mage R, Andereggen E, Buhler L, Cretin N, Fournier B, Goumaz C, Lou J, Philippe J, Morel P. Human islet transplantation: lessons from 13 autologous and 13 allogeneic transplantations. *Transplantation* 2000; **69**: 1115-1123
105 **Rodriguez Rilo HL**, Ahmad SA, D'Alessio D, Iwanaga Y, Kim J, Choe KA, Moulton JS, Martin J, Pennington LJ, Soldano DA, Biliter J, Martin SP, Ulrich CD, Somogyi L, Welge J, Matthews JB, Lowy AM. Total pancreatectomy and autologous islet cell transplantation as a means to treat severe chronic pancreatitis. *J Gastrointest Surg* 2003; **7**: 978-989
106 **Clayton HA**, Davies JE, Pollard CA, White SA, Musto PP, Dennison AR. Pancreatectomy with islet autotransplantation for the treatment of severe chronic pancreatitis: the first 40 patients at the leicester general hospital. *Transplantation* 2003; **76**: 92-98
107 **Gruessner RW**, Sutherland DE, Dunn DL, Najarian JS, Jie T, Hering BJ, Gruessner AC. Transplant options for patients undergoing total pancreatectomy for chronic pancreatitis. *J Am Coll Surg* 2004; **198**: 559-567; discussion 568-569
108 **Lankisch PG**, Lohr-Happe A, Otto J, Creutzfeldt W. Natural course in chronic pancreatitis. Pain, exocrine and endocrine pancreatic insufficiency and prognosis of the disease. *Digestion* 1993; **54**: 148-155
109 **Lowenfels AB**, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, Dimagno EP, Andren-Sandberg A, Domellof L. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. *N Engl J Med* 1993;

328: 1433-1437
110 **Mallet-Guy PA**. Late and very late results of resections of the nervous system in the treatment of chronic relapsing pancreatitis. *Am J Surg* 1983; **145**: 234-238
111 **Ischia S**, Ischia A, Polati E, Finco G. Three posterior percutaneous celiac plexus block techniques. A prospective, randomized study in 61 patients with pancreatic cancer pain. *Anesthesiology* 1992; **76**: 534-540
112 **Stone HH**, Chauvin EJ. Pancreatic denervation for pain relief in chronic alcohol associated pancreatitis. *Br J Surg* 1990; **77**: 303-305
113 **Worsey J**, Ferson PF, Keenan RJ, Julian TB, Landreneau RJ. Thoracoscopic pancreatic denervation for pain control in irresectable pancreatic cancer. *Br J Surg* 1993; **80**: 1051-1052
114 **Cuschieri A**, Shimi SM, Crosthwaite G, Joypaul V. Bilateral endoscopic splanchnicectomy through a posterior thoracoscopic approach. *J R Coll Surg Edinb* 1994; **39**: 44-47
115 **Maher JW**, Johlin FC, Pearson D. Thoracoscopic splanchnicectomy for chronic pancreatitis pain. *Surgery* 1996; **120**: 603-609; discussion 609-610

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