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The pain of chronic pancreatitis: a persistent clinical challenge

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Abstract

The pain of chronic pancreatitis represents a major challenge to those working in the field, including pain specialists, gastroenterologists and surgeons. This article describes the different aetiologies of chronic pancreatitis and lists the models for the pathogenesis of pain, including novel ideas such as the role of the immune system in the modulation of pain. The patient profile in chronic pancreatitis is discussed along with the social impact of the disease in relation to alcohol misuse.

The range of treatment strategies including medical, endoscopic and surgical approaches are evaluated. Common analgesic regimes and their limitations are reviewed.

The pain of chronic pancreatitis remains refractory to effective treatment in many cases and further study and understanding of the underlying pathophysiology are required.

Keywords

Pancreatitis, chronic, pain, neuropathic, opioid

Introduction

Pain medicine presents many clinical challenges, particularly in the accurate diagnosis of complex pain syndromes and in establishing the efficacy of pharmacological interventions, interventional pain procedures, surgical procedures and psychological therapies. A multi-modal approach, not just in terms of pharmacology, but in relation to all treatment strategies, is routinely employed to combat the symptoms of patients with chronic pain disorders. Huge strides have been made in the specialty of pain medicine in the past few decades, but consistently effective treatment for some of the more complex pain syndromes still proves to be elusive. The pain of chronic pancreatitis fits into this category. Much work has been, and continues to be, done on furthering our understanding of this condition. Chronic pancreatitis is a debilitating, painful condition that necessitates the patient encountering a range of medical and surgical specialists, resulting in a variety of medical and surgical interventions. Despite the multitude of treatments used in chronic pancreatitis, the impact of the disease may persist for the patient's lifetime after diagnosis.

In the UK the annual incidence of chronic pancreatitis is 1 in 100,000 with a prevalence of 3 in 100,000.[1] It affects males more than females (4:1) and has an average age at onset of 40 years. Alcohol-related disease is an increasing problem in the UK population and, as alcohol use is the commonest (but not the only) cause of chronic pancreatitis, there may be greater demands made on pain services in the management of pancreatic pain in the near future. It is also reasonable to predict that the number of women affected will rise and that the average age at onset of the condition will fall. Chronic pancreatitis, and the pain associated with it, threatens to be the hidden 'pain time-bomb' that has gone under the medical community's radar when considering all of alcohol-related disease.

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Table 1. Cambridge classification of chronic pancreatitis

Grade	ERCP	Ultrasound/CT
1. Normal	Quality study Whole gland visualized without abnormalities	
2. Equivocal	Fewer than three abnormal branches	One sign only from Main duct >4 mm Gland enlarged 2× normal Cavities >10 mm
3. Mild	Fewer than three abnormal branches	Two or more signs from Irregular ducts Focal acute pancreatitis Parenchymal heterogeneity
4. Moderate	Abnormal main duct and branches	Two or more signs from Duct wall echoes increased Irregular head/body contour
5. Marked	Abnormal main duct and branches	One or more signs from Large cavities >10 mm Gross gland enlargement > 2× normal Intraductal filling defects or calculi Duct obstruction, stricture or gross irregularity Contiguous organ involvement

CT: computed tomography; ERCP: endoscopic retrograde cholangiopancreatography.

Definition and classification

Acute pancreatitis is defined as an acute condition typically presenting with abdominal pain usually associated with raised pancreatic enzymes in blood or urine due to inflammatory disease of the pancreas. Chronic pancreatitis has been defined as a continuing inflammatory disease of the pancreas characterized by irreversible morphological changes.[2] These changes typically cause pain and loss of exocrine and endocrine pancreatic function.

Several systems of classification of chronic pancreatitis have been used, the most widely used being the Marseille classification of 1963[3,4] with revisions in 1984[5] and 1988[6] and the Cambridge classification of 1984.[2] The Marseille system distinguishes acute from chronic pancreatitis. The diagnosis of chronic pancreatitis requires permanent histological irregularity with persistent pain, with clinical and functional impairment of pancreatic function being the key features. The Cambridge classification (see Table 1) uses imaging results from ultrasound, computed tomography (CT) and endoscopic retrograde cholangiopancreatography (ERCP) to grade the severity of the disease.

Classification

The Marseille–Rome classification of pancreatitis is as follows[7]:

- Acute pancreatitis
- Chronic calcifying pancreatitis (see Figure 1)
- Chronic obstructive pancreatitis
- Chronic inflammatory pancreatitis

Aetiology

In the UK and the rest of the developed world alcohol misuse is the commonest and most important aetiological factor. It is estimated that 60–70% of patients with chronic pancreatitis have a history of alcohol use preceding the onset of the disease. Many patients have had excessive alcohol intake but others give histories detailing mild to moderate intake. It is not known what is a 'safe' level of alcohol consumption in regard to the development of chronic pancreatitis. Clearly, alcohol misuse is an important and potentially preventable trigger for chronic pancreatitis, but there are many other causes for the development of chronic pancreatitis and patients often complain that there is an assumption from the health professionals that their chronic pancreatitis is a result of alcohol.[8,9]

The common causes of chronic pancreatitis are as follows:

- alcohol
- gall stones
- pancreatic duct strictures
- cystic fibrosis
- chronic renal failure
- hypercalcaemia
- hyperlipidaemia
- autoimmune

- smoking
- pancreatic trauma
- hereditary/genetic pancreatitis
- idiopathic.

The TIGAR-O risk factor classification system[10] (Figure 2) was developed by the Midwest Multicenter Pancreatic Study Group to organize, study and determine the risk of factors that are probably associated with the development of chronic pancreatitis. This system introduces the concept of risk modifiers rather than discrete aetiologies. There may be more than one factor at play in any one patient. The interaction of different aetiological factors contributes to the heightening of the risk of developing chronic pancreatitis.

Pathogenesis of chronic pancreatitis

There have been several theories postulating the mechanisms for tissue damage in chronic pancreatitis.

Oxidative stress theory

Braganza[11] proposed that overactivity of hepatic mixed-function oxidases precipitates pancreatic disease. Secretion of oxidized compounds into bile leads to the contamination of pancreatic ducts. Oxidative damage occurs to acinar and ductal cells. If this damage is repeated and prolonged, inflammation and fibrosis will result.

Toxic–metabolic theory

Bordalo et al[12] put forward the theory that the intracellular metabolism of the acinar cell is impaired by the direct toxic effects of alcohol. Fatty degeneration, cellular necrosis and fibrosis are a result of cytoplasmic lipid accumulation within the acinar cells. It is thought that fatty acid ethyl esters, which result from pancreatic alcohol metabolism, are the toxic substances rather than the alcohol itself. However, not all chronic alcoholics develop acute or chronic pancreatitis (10–20%).[13] It seems that there is an interaction of environmental factors, linked to genetics, that magnifies the effects of alcohol. The serine protease inhibitor Kazal type 1 (SPINK-1) mutation is present in a large number of patients with chronic pancreatitis, who may otherwise have been categorized as having idiopathic chronic pancreatitis.[14] Activated trypsin is counteracted by pancreatic secretory trypsin inhibitor, which is encoded for by SPINK-1. Mutations of this gene result in a loss of efficacy of this protein and the development of chronic pancreatitis. CFTR (cystic fibrosis transmembrane conductance regulator) mutations have also been implicated in the development of chronic pancreatitis.

Other toxins and metabolic conditions are associated with the development of chronic pancreatitis. Smoking is a very important independent risk factor, distinct from alcohol use. Maisonneuve and colleagues[15] demonstrated that the progression of the disease, especially the development of calcification and diabetes, was accelerated in smokers independent of alcohol consumption. Smokers with chronic pancreatitis also have higher pain scores than non-smokers with chronic pancreatitis.[16,17] Hypercalcaemia and chronic renal failure are important causes of chronic pancreatitis through 'toxic–metabolic' mechanisms.

The stone and duct obstruction theory

Sarles drew attention to the consideration of acute and chronic pancreatitis as different diseases with differing pathological processes.[18] In acute pancreatitis tissue damage is secondary to uncontrolled activation of trypsin, leading to autodigestion of pancreatic tissue. The pattern of tissue damage is different in chronic pancreatitis. Alcohol alters exocrine function in the pancreas leading to increased formation of stones (Figure 3) and protein plugs. Over time, these stones within pancreatic ducts lead to scarring, ulceration, obstruction, stasis, atrophy and fibrosis.

Necrosis–fibrosis theory

This theory, unlike the stone and duct obstruction theory, requires the existence of previous recurrent attacks of acute pancreatitis. Inflammatory changes with necrosis lead to scarring in the peri-ductular areas. The ductules become obstructed and stasis of pancreatic fluid leads to stone formation. Atrophy and fibrosis follow on from severe obstruction. Support for this theory comes from work by Ammann and Muellhaupt,[19] who studied prospectively 254 patients after a first episode of alcoholic pancreatitis. The development of chronic pancreatitis was related to the severity and frequency of further episodes of acute pancreatitis. The genetic mechanism for hereditary pancreatitis is now better understood. A single gene mutation encoding for trypsinogen means that the activated protein cannot be inactivated. Autodigestion of pancreatic parenchymal tissue ensues with consequent acute pancreatitis. With recurrent attacks of acute pancreatitis, the majority of patients with hereditary pancreatitis develop chronic pancreatitis, adding credence to the necrosis–fibrosis theory.

Sentinel acute pancreatitis event hypothesis

Whitcomb and Schneider[20] have proposed this theory, which emphasizes the importance of the 'sentinel

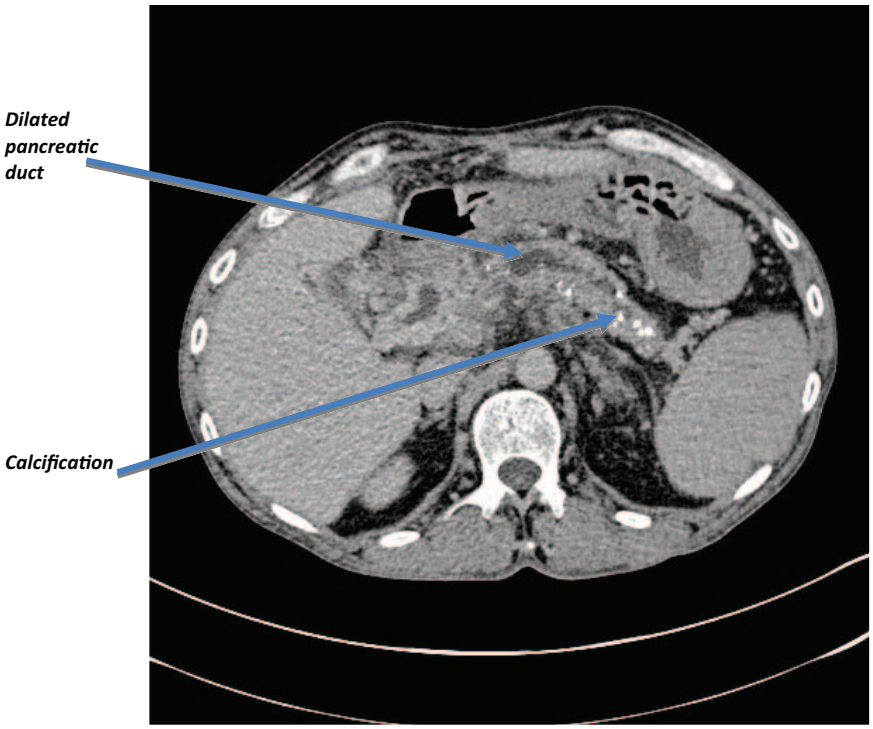

Figure 1. Pancreatic duct dilatation and calcification.

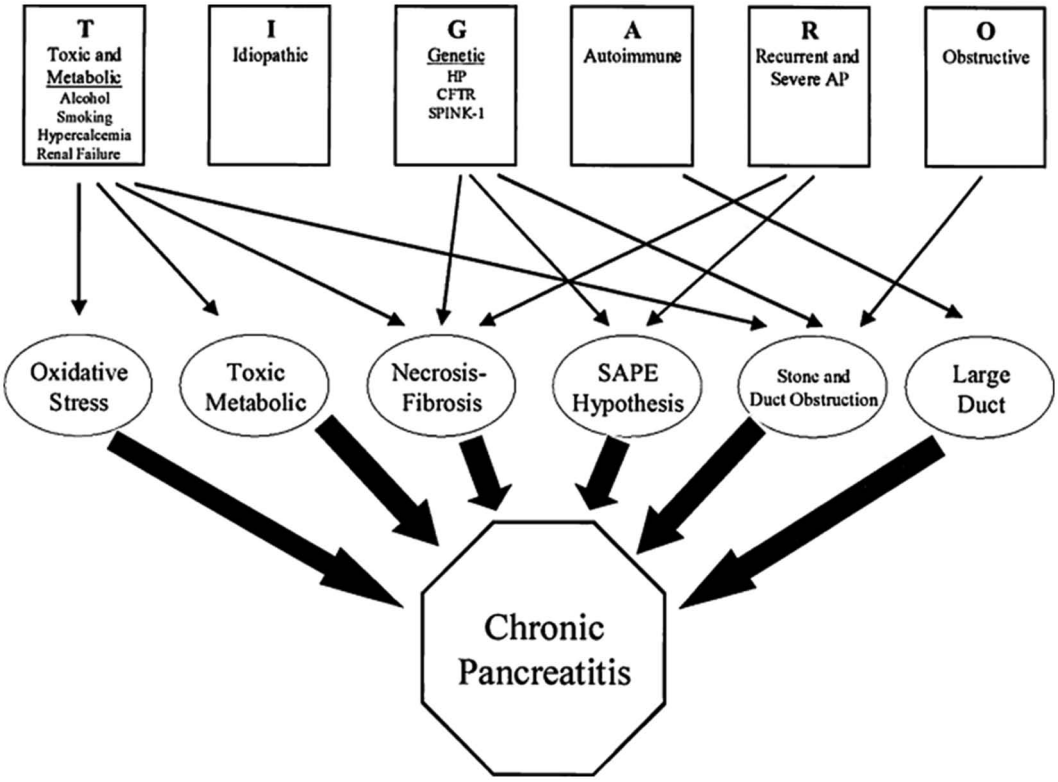

Figure 2. TIGAR-O Risk factor classification system.
Reproduced from Stevens T, Conwell DL and Zuccaro G. Pathogenesis of chronic pancreatitis: an evidence-based review of past theories and recent developments pathogenesis of chronic pancreatitis. *Am J Gastroenterol* 2004; 99: 2256–2270 with permission from Nature Publishing Group.[10]

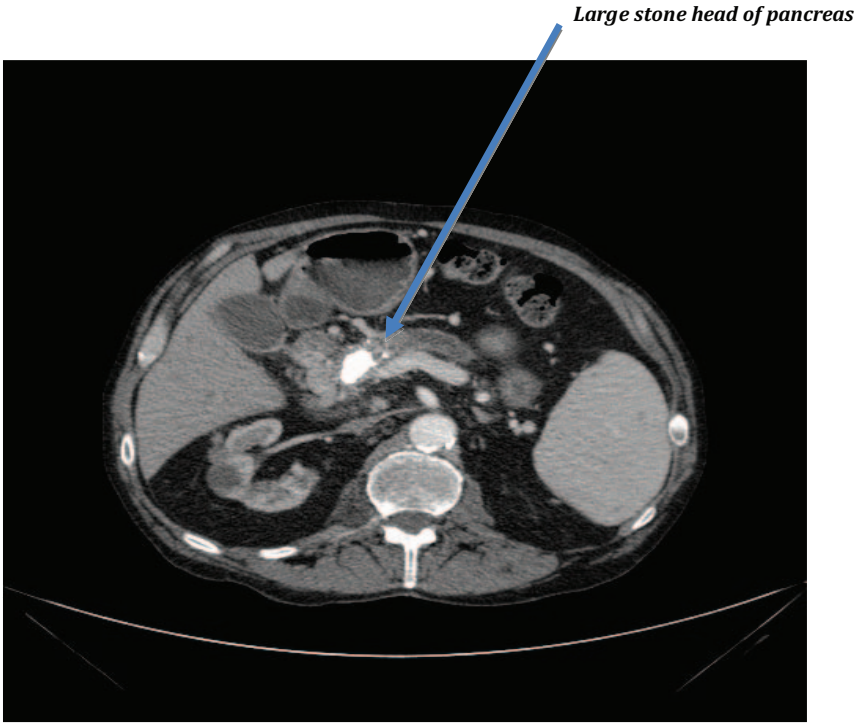

Figure 3. Large stone in the head of the pancreas.

event', that is the first episode of acute pancreatitis as a result of unregulated trypsin activation. The sentinel event produces a massive inflammatory response divided into early and late phases. Inflammatory cells and cytokines, such as transforming growth factor (TGF)-β1, tumour necrosis factor (TNF)-α, interleukin (IL)-1, IL-6 and platelet-derived growth factor (PDGF) predominate in the early phase. Cells promoting fibrosis, including stellate cells, constitute the late phase. If there is no further exposure to inciting factors, such as alcohol or oxidative stress, the pancreas should heal and recover. However, if those triggers persist, activated stellate cells will be directly stimulated by cytokines, alcohol and oxidative stress to deposit collagen leading to fibrosis and chronic pancreatitis. The sentinel acute pancreatitis event hypothesis goes some way towards unifying the other theories and describes a common pathway for the many different causes of chronic pancreatitis. The sentinel event is important in that it could be the time at which aggressive therapeutic interventions are instituted to prevent further progression of pancreatic disease.

Pathogenesis of pain in chronic pancreatitis

Pain is the predominant symptom in chronic pancreatitis; 80–90% of patients present with pain as the primary symptom either at the first attack of acute pancreatitis or as the main reason for hospital readmissions in the following months and years, as the disease progresses to what could be defined as chronic pancreatitis.

Anatomical causes for pain in chronic pancreatitis have been postulated for many years. Chronic pancreatitis can be divided simplistically into large or small duct disease. Large or dilated ducts are the result of obstruction from stones or fibrosis. The obstructions can occur within the pancreatic ducts, at the ampulla, as well as the result of extrapancreatic causes such as bile duct stenosis and duodenal stenosis. Pancreatic duct hypertension and associated ischaemia are described as a compartmental model of pain.[21] Endoscopic stone removal and surgical decompression procedures such as lateral pancreaticojejunostomy will result in pain relief in the majority of patients. Unfortunately, further work has shown that there is poor correlation between relief of obstruction and improvement in pain scores.[22,23] Anatomical and morphological changes do not differ between those individuals with painful pancreatitis and those with painless pancreatitis.[24] Anaparthy and Pasricha[25] published an interesting review entitled 'Pain and chronic pancreatitis: is it the plumbing or the wiring?', which explored not only empirical approaches aimed at relieving obstruction but also neuronal or 'wiring' causes for persistent pain in chronic pancreatitis.

As pancreatic fibrosis worsens, pseudocysts of the pancreas can cause severe pain in chronic pancreatitis.

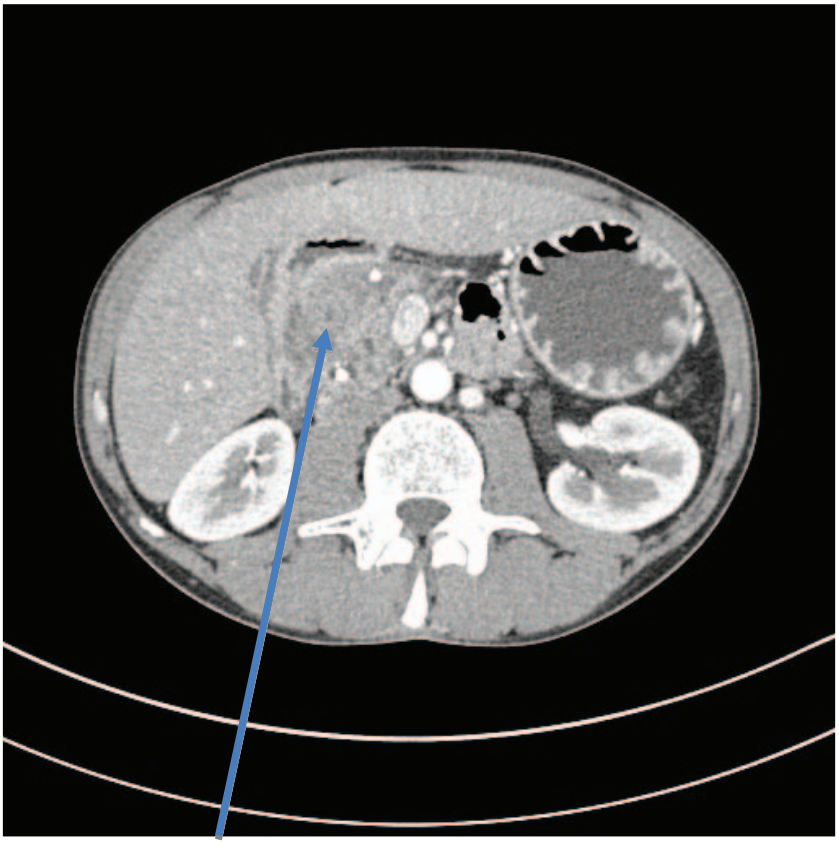

Figure 4. Inflammatory mass at head of pancreas.

Undoubtedly, neuronal tissues within the pancreas and within adjacent structures are affected by the inflammatory process. Recurrent episodes of pancreatic inflammation (see Figure 4) will involve adjacent structures such as the biliary system, duodenum, stomach and spleen. Current concepts in the pathogenesis of pain in chronic pancreatitis regard neuronal damage leading to peripheral sensitization and resultant central sensitization as fundamental to the development of persistent, often refractory pain in chronic pancreatitis.

In the periphery, multiple local mediators such as prostanoids, bradykinin, serotonin, tachykinins and other unknown compounds sustain and contribute to the peripheral sensitization seen in chronic pancreatitis. Enhanced activity in potassium channels and transient receptor potential vanilloid 1 (TRPV1) has been demonstrated in a rat model of chronic pancreatitis.[26,27] Nerve growth factor, important in nociceptive sensitization, has increased pancreatic expression in chronic pancreatitis. Trypsin may have direct effects on sensory neurons via the protease-activated receptor 2 (PAR-2). PAR-2 activation has been shown to result in TRPV1 receptor sensitization through capsaicin-evoked release of calcitonin gene related peptide (CGRP).[28] In addition to changes in the periphery, the central nervous system is altered by prolonged and repeated attacks of pain in chronic pancreatitis. Dimcevski and colleagues[29] measured electroencephalography traces in patients with chronic pancreatitis, who received electrical stimulation of the oesophagus, stomach and duodenum via an endoscope. They recorded changes in the limbic system and in cortical centres such as the anterior cingulate cortex. They concluded that chronic pancreatitis leads to changes in cortical projections of the nociceptive system. Further understanding of these processes may lead to a more targeted approach in terms of the choice of analgesic therapies.

Fregni and colleagues[30] have taken this concept further. They note that total pancreatectomy fails to relieve pain in up to 30% of chronic pancreatitis patients,[31] and use this as support for the notion that there must be a role for a pancreas-independent mechanism in the unremitting pain seen in chronic pancreatitis. They hypothesize that, in addition to anatomical and neuronal factors modulating pain, the immune system is involved in a 'salutogenic' mechanism perpetuating cycles of inflammation and ongoing pain – a salutogenic response being modulation of the immune response by centres in the brain. Therefore, one could

enhance the function of the immune system to promote healing of the inflamed pancreas. What might occur instead is that abnormal immune processes, linked to brain-mediated mechanisms, sustain the visceral inflammation and prolong the duration of pain. This process is ultimately a maladaptive brain response and they consider that fresh approaches to treating the pain of chronic pancreatitis are necessary. They propose that transcranial magnetic stimulation needs further evaluation as a treatment option in the management of chronic pancreatitis.[32] The author encourages all readers of this article to read Fregni's paper for a fresh approach to the pathophysiology of pain in chronic pancreatitis.

Does the pain of chronic pancreatitis fit into the pattern of other visceral pain?

Visceral pain has five important characteristics:[33]

1. It is not evoked from all viscera.
2. It is not linked to injury.
3. It is referred to as the body wall.
4. It is diffuse and poorly localized.
5. It involves intense motor and autonomic reactions.

The pain of chronic pancreatitis certainly demonstrates all of the features of visceral pain. The pain is not always linked to new injury, and 'flare-ups' do not necessarily mean a new bout of pancreatic inflammation. The pain of chronic pancreatitis is commonly referred to the abdominal wall, in more than one location. The features of pain in chronic pancreatitis are consistent and reproducible across a range of patients with the condition. Pain arises in the epigastrium, usually radiating to the back. Radiation to the right or left hypochondrium is common. Patients describe the pain as severe, constant and unremitting. It is the pain that never leaves them. Some describe it as 'gnawing', 'grinding' or 'toothache'. It is usually worse after food and associated with post-prandial nausea and vomiting. Patients with chronic pancreatitis often avoid regular meals for fear of the pain associated with eating. They therefore have the combined problems of malabsorption associated with exocrine insufficiency and the anxiety they suffer at the prospect of food precipitating a bout of pain. Unsurprisingly, many patients with chronic pancreatitis are malnourished. Autonomic and motor symptoms commonly occur in addition to nausea. Sweating, bowel spasm, palpitations, abdominal bloating and muscle spasms are all associated symptoms in chronic pancreatitis.

In addition to the constant background pain, patients universally describe an 'extra' pain. It may be described as the 'bad' pain that comes unexpectedly, without warning, 'out of the blue'. If patients are unable to control this pain with their usual analgesic regime, the end result is usually a hospital admission. Patients with chronic pancreatitis use graphic words to describe the pain they experience; 'burning', 'ripping', 'bursting', 'stabbing', 'relentless', 'crushing', 'jolting', 'electric-shock' and 'hot poker' are all adjectives the author has heard when taking histories from patients. Areas of hyperalgesia and allodynia can be demonstrated in those patients who have had surgery, but also in those awaiting surgery. It is the author's assertion that chronic pancreatitis displays some of the features of somatic pain, as well as some of visceral pain, but the neuropathic component of pain in chronic pancreatitis is often under-diagnosed and under-treated. The characteristics of the severe, sudden, unexpected pain experienced by all patients with chronic pancreatitis are indistinguishable from those seen in many other neuropathic pain syndromes. Detailed history-taking and specific questions looking for, in particular, neuropathic symptoms are essential in guiding therapy.

Patient profile in chronic pancreatitis

Although not universal, the following are common features in patients who suffer over many years from pain and the associated symptoms of chronic pancreatitis:

- A history of alcohol abuse in the majority of these patients.
- Multiple previous hospital admissions.
- Social/marital/employment difficulties.
- Depression/anxiety.
- Poor sleep pattern.
- They usually have a 'favourite' opioid.
- They usually have a favourite route of administration (intramuscular).
- Polypharmacy is common.

It is a condition that becomes all encompassing. It dominates all aspects of daily life and impacts not only on the patient's life but also on the lives of their friends and family. Repeated attendance at hospital means that this group of patients is often well known to the medical and nursing staff caring for them.

The hospital environment, and the degree of security it provides, becomes a safe haven for many patients with chronic pancreatitis. Everyday life for the patient with chronic pancreatitis can become unbearable not just because of pain but because of the multi-factorial impact the disease has on a patient's life. Unemployment, financial difficulties, broken or strained personal relationships, social isolation, poor housing, and ongoing drug and alcohol misuse all contribute to a 'toxic' mix

of hardship. There will be significant impairment of health-related quality of life in this group of patients. The degree of impairment is directly associated with the severity of symptoms.[34,35] Hospital readmissions for pain episodes are common in the patient with chronic pancreatitis. Clearly pain is a predominant symptom but it may not always be the primary reason for a patient with chronic pancreatitis seeking the sanctuary of a hospital bed.

Treatment strategies for the pain of chronic pancreatitis

Lifestyle changes

Alcohol. If there is a history of alcohol misuse then alcohol abstinence is essential. Even those patients who have other causes for chronic pancreatitis are strongly advised to avoid alcohol consumption.

Smoking. All patients with chronic pancreatitis should be encouraged and given support to stop smoking. Smoking is an independent risk factor for chronic pancreatitis, and it accelerates its progression and worsens the perception of pain.

Diet. Detailed dietary advice should be given. Chronic pancreatitis leads to malabsorption of fatty foods and many associated micronutrients (vitamin E, riboflavin, choline, magnesium, copper, manganese and sulphur).[36] Low-fat diets, vitamin supplements and antioxidant therapies are all recommended in chronic pancreatitis.

Support groups. Many patients with chronic pancreatitis have complex social and marital/relationship situations because of the impact of ongoing chronic disease. They can often become isolated socially, and peer support groups can be invaluable in helping patients with the difficulties that arise from their symptoms. Patients often share knowledge as to the best analgesics available or new treatments they have tried. Chronic pancreatitis is a condition with no clear-cut reliable treatment strategies and most patients have tried many different therapies. The shared experience of patients with chronic pancreatitis can help fellow patients and their doctors alike.

Medical therapy in chronic pancreatitis

Medical therapy in chronic pancreatitis involves numerous strategies to alleviate the symptoms and physiological impact of the disease. Many drugs are given alongside analgesics to combat exocrine and endocrine disorders, nutritional deficiencies and concomitant gastrointestinal symptoms (e.g. nausea, bloating). Non-pharmacological interventions, such as endoscopic sphincterotomy, insertion of pancreatic duct stents and removal of pancreatic stones, also come within the category of medical therapy (see Table 2).

Analgesic medications used in chronic pancreatitis. The World Health Organization (WHO) analgesic ladder[37] provides a logical and consistent framework for the initiation of analgesic medication in the management of the pain of chronic pancreatitis. Although this guideline was published in 1986 and was designed primarily for the management of cancer pain, its simplicity and flexibility are useful in the management of chronic pancreatitis.

There are many analgesic drugs used in the management of chronic pancreatitis and some examples are shown in Table 3. The range of drugs used and the choice of individual practitioners will vary from institution to institution. The fact that there is no universal agreement on the ideal analgesic regime is common to many chronic pain syndromes.

If the WHO ladder is used as a starting point, then patients rapidly ascend its steps, as the majority of patients with chronic pancreatitis have moderate or severe pain. In primary care, patients will commonly be started on a paracetamol–opioid combination therapy by their general practitioner. In the UK several of these preparations are available, the most frequently used being co-codamol (paracetamol 500 mg/codeine 30 mg; two tablets given four times daily). Tramadol is

Table 2. Medical treatment strategies in chronic pancreatitis

Expectant (non-specific) therapy	Analgesics Antidepressants Anxiolytics Antiemetics
Suppress secretion	PPIs and H_2-blockers Pancreatic enzymes Octreotide
Relieve obstruction	ERCP (sphincterotomy) Stents Elimination of stones
Modify neural transmission	Coeliac plexus block (EUS or CT guided) BITS
Reduce oxidative stress	Vitamin and antioxidant therapy Allopurinol

BITS: bilateral thoracoscopic splanchnicectomy; CT: computed tomography; ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasound; PPI: proton pump inhibitor.

Table 3. Examples of analgesics used in chronic pancreatitis

Analgesic group	Examples
Simple analgesics	Paracetamol Aspirin NSAIDs
Weak opioids	Codeine Dihydrocodeine Tramadol Buprenorphine
Strong opioids	Morphine Oxycodone Pethidine Fentanyl Methadone Hydromorphone
Antidepressants	Amitriptyline Nortriptyline Fluoxetine Paroxetine
Gabapentinoids	Gabapentin Pregabalin
NMDA receptor antagonists	Ketamine S-Ketamine

NMDA: *N*-methyl-d-aspartate; NSAID: non-steroidal anti-inflammatory drug.

regularly given in the primary care setting at a dose of 50–100 mg four times daily. Patients who present with painful attacks to hospital via emergency units or through direct referrals almost universally require strong opioids (intravenous morphine or intravenous oxycodone) to overcome the acute painful episode. The once common practice of regular intramuscular injections of pethidine to control such episodes is less prevalent. It is a practice that is ineffective in controlling pain, promotes a 'ritualization' of opioid-seeking behaviour, risks the onset of norpethidine toxicity and requires repeated injections owing to the short half-life of pethidine. Early conversion to the oral route for the administration of opioids is recommended.

In patients with chronic pancreatitis it needs to be determined during the initial phase of an attack of severe pain whether it is truly an acute-on-chronic attack of pain, secondary to inflammation in the pancreas, or a 'flare-up' of pain seen commonly as part of the chronic nature of the disease. Ammann and Muellhaupt described two typical patterns of pain in alcoholic chronic pancreatitis.[19] The type A pain pattern is observed in acute relapsing pancreatitis. It is short lived and episodes last fewer than 10 days separated by long pain-free intervals of several months to a year. Nearly all of these patients require hospitalization. Type B pain pattern is characterized by prolonged periods of persistent pain that may last for months. This pain is exacerbated by severe, worsening pain superimposed on the background pain. These patients usually present to hospital but unless there are new complications developing, such as acute inflammation, pseudocysts, cholestasis, bowel obstruction or worsening ductal hypertension, lengthy hospital stay is inadvisable. The patient requires adequate analgesia and this can be provided at home by primary care. It is a common pattern in patients with chronic pancreatitis to have repeated hospital admissions, purely for inadequate analgesia, when there is no acute illness. This 'revolving door' behaviour is one of the biggest challenges in the pain management of patients with chronic pancreatitis.

Oral maintenance regime. Polypharmacy is common in patients with chronic pancreatitis. Some patients attend more than one hospital for their in-patient admissions. This may be a combination of the district general hospital and the tertiary referral centre or teaching hospital. Chronic pancreatitis patients also attend their general practitioner's surgery regularly and there is a high risk that multiple prescribers can add new analgesic medications, without stopping others. Undesirable drug interactions can occur and the cumulative effects of several different drugs in the same category (e.g. opioids) can lead to significant and potentially dangerous side-effects such as sedation and respiratory depression. Constipation is an important side-effect in any patient on long-term opioids. It can confuse the clinical picture in chronic pancreatitis by worsening abdominal pain and bloating. Conversely, many patients, despite opioid use, still experience diarrhoea as a result of the malabsorption commonplace in chronic pancreatitis. All opioid-related side-effects should be monitored regularly and specific questions should be asked at regular out-patient or primary care consultations.

The approach in establishing an oral analgesia maintenance regime in the patient with chronic pancreatitis should emphasize simplicity and safety. *One* drug should be chosen from each drug category, a multi-modal approach should be used, adjuncts should be used appropriately and medical therapy should be maximized (e.g. enzyme supplementation, proton pump inhibitors, diabetic control, octreotide, antioxidants). The decision to embark on long-term use of strong opioids should be taken only when other measures have failed or are inadequate. The use of immediate-release opioid preparations should be restricted to 'breakthrough' pain only and should be kept to a minimum. The use of these preparations leads to peaks and troughs in the plasma concentration of the opioid. If episodes of breakthrough pain are becoming more severe or more frequent, the dose of the long-acting medication should be reviewed first. The majority of the opioid dose should be administered in a slow- or

modified-release formulation. The use of strong opioids in chronic pancreatitis is controversial and undoubtedly carries risk in a group of patients, many of whom have had a history of alcohol or drug misuse. There is a risk of addiction or opioid-seeking behaviour developing. There is the additional danger of accidental overdose of prescribed medication if it is taken in combination with alcohol or other recreational drugs. Close monitoring of drug dose and avoidance of dose escalation help to minimize this risk. In the case of strong opioids, it is strongly recommended that there is a single prescriber (usually the general practitioner), that the dispensing of the drug by the pharmacist is monitored to avoid stockpiling and there are strong lines of communication between hospital specialists and general practitioners to maintain consistency of prescriptions.

Most strong opioids are effective in chronic pancreatitis and oxycodone; morphine and fentanyl are the most commonly used in the UK. Oxycodone has increased in popularity in the past decade and possibly confers some advantages in chronic pancreatitis. It has high oral bioavailability and activity at κ-opioid receptors as well as μ-receptors and thus may be more effective for visceral and neuropathic pain. Staahl et al have demonstrated an advantage of oxycodone over morphine in an experimental model of visceral pain in chronic pancreatitis.[38,39] There is a scarcity of evidence in this area and there is still huge interindividual variation in deciding which opioid is most effective. Modified-release oxycodone (Oxycontin*)* is the author's first drug of choice because of the high level of tolerability observed in the majority of patients with chronic pancreatitis at the Royal Liverpool University Hospital. When converting to a long-term maintenance dose it is the easiest and quickest opioid to titrate. This is an opinion based on personal observation and experience and it must be emphasized that published clinical data supporting this view are scant. Opioid rotation is necessary in many patients with chronic pancreatitis especially if opioid-induced hyperalgesia develops. It is important to distinguish this phenomenon from opioid tolerance.[40] After many years of illness, chronic pancreatitis patients have usually tried every strong opioid on the market.

Antineuropathic agents. It is the author's assertion that the predominant pain in chronic pancreatitis, the pain that causes the most distress and precipitates a hospital admission, is neuropathic in origin. There is a growing body of evidence to suggest that peripheral and central sensitization of the pain in chronic pancreatitis are important in magnifying the pain of chronic pancreatitis and that spinal cord and cortical reorganization occurs. Allodynia and hyperalgesia can be demonstrated in chronic pancreatitis. Therefore, the use of antineuropathic agents, such as pregabalin, gabapentin and amitriptyline, is strongly recommended in chronic pancreatitis. Olesen's group demonstrated in a randomized controlled trial that pregabalin reduces pain in chronic pancreatitis.[41,42] Not only will this help to alleviate neuropathic symptoms, it is the author's experience that the use of pregabalin or gabapentin stabilizes opioid usage and delays or prevents dangerous dose escalation and opioid-induced hyperalgesia.

Increasingly, the use of ketamine as an option in the management of pancreatic pain is being considered. Bouwense and colleagues demonstrated that hyperalgesia in chronic pancreatitis can be modulated by the use of an infusion of S-ketamine.[43] Ketamine has been used in many chronic pain states[44] and also in cancer pain. More specific work on the use of this drug in chronic pancreatitis needs to be undertaken and could provide a fruitful area for research. It may prove to be a particularly useful drug in situations in which opioids have become ineffective or side-effects are troublesome. It might have a role in those patients who have exhausted the full range of medical and surgical options, including nerve ablations and complete or partial resections of the pancreas.

Non-pharmacological therapies

Neural interruption. The main approaches to blocking the neuronal transmission of pain in chronic pancreatitis are either bilateral thoracoscopic splanchnicectomy (BITS) procedure or coeliac plexus block.

BITS. In 1947 Reinhoff and Baker[45] first described pain relief in patients with calcific pancreatitis following BITS and splanchnicectomy for hypertension. This operative approach necessitated multiple rib resections. Morbidity from this procedure was high and postural hypotension was troublesome, in addition to associated diarrhoea and intercostal neuralgia. Cuschieri et al reported the thoracoscopic approach to the splanchnic nerves in 1994.[46] It was reported that pain relief was observed in three out of five patients after 8 months of follow-up. There have been many papers looking at the efficacy of BITS in the chronic pancreatitis population. Baghdadi and colleagues[47] performed a review collating the results of 16 papers: 302 patients had splanchnicectomies, 202 had bilateral procedures and 100 had unilateral procedures. At 6 months, 90% of patients had pain relief, 75% had pain relief between 6 and 15 months and 49% of patients had some relief between 15 months and 5.7 years. However, 12.9% of patients required further pain interventions. BITS may be useful in some patients to provide a pain-free or -reduced period. It is unlikely that this period will last longer than 18 months, with 46% of patients having relief at this point but only 20% at 5 years. In many patients severity of disease is an unfavourable predictor for outcome

after BITS. Maher et al showed that outcome is worse if the patient has had previous pancreatic surgery.[48]

Coeliac plexus block. Numerous approaches to blocking the coeliac plexus have been undertaken and described in the world literature. These include direct blockade at the time of pancreatic surgery, transcutaneous approach using anatomical landmarks, CT-guided and endoscopic ultrasound (EUS)-guided coeliac plexus block.

Gress and colleagues[49] showed that EUS-guided coeliac plexus block provides more persistent pain relief than CT-guided block and that it can be a safe and effective technique in managing the pain of chronic pancreatitis. However, patients younger than 45 years and those who have had previous pancreatic surgery do not fare so well. Separate reviews by Kaufman et al in 2010 and Puli et al in 2009 demonstrated that EUS-guided coeliac plexus block can be effective in treating pain in chronic pancreatitis.[50,51] Both reviews showed that EUS-guided coeliac plexus block was more effective in treating the pain of pancreatic cancer (72.54% to 80.12%) than the pain of chronic pancreatitis (51.46% to 59.4%).[50,51] The reasons for chronic pancreatitis patients having worse pain relief than cancer patients after EUS-guided coeliac plexus block are not clear. There are undoubtedly anatomical differences between the two distinct pathological processes. Life expectancy in the cancer group is shorter than in the chronic pancreatitis group and patients' expectations from a pain intervention may be different. The chronic pancreatitis patients will have experienced pain for a longer period of time than the cancer patients and consequently peripheral sensitization, central sensitization and cortical reorganization processes may have combined to create a 'hard-wired' pain pathway that is more resistant to a neuroablative technique.

The consistent feature of nerve blocks in chronic pancreatitis is that temporary relief is certainly achievable in a sizeable number of patients. Some patients will get no relief and severity of disease and previous surgery are good predictors for failure of the block. In the vast majority (80%) of patients who have a good result from a nerve block, this effect is time limited and unlikely to last beyond 18 months. There is morbidity associated with these blocks with common side-effects being postural hypotension and diarrhoea.

Endoscopic therapies in chronic pancreatitis. Pancreatic duct hypertension is thought to be a major contributory factor in the pathogenesis of pain in chronic pancreatitis. Consequently, endoscopic therapies are aimed at improving ductal drainage and so alleviating the pain of chronic pancreatitis. Endoscopic retrograde cholangiopancreatography is performed via this route, which can used for a range of procedures, namely pancreatic sphincterotomy, dilation of strictures, placement of stents and stone extraction. Large impacted stones can be treated by extracorporeal shock wave lithotripsy prior to endoscopic stone removal. EUS can be used to guide coeliac plexus block. Endoscopic interventions are certainly less invasive and have a shorter recovery period than surgery. Endoscopic procedures do not work well in patients with small duct chronic pancreatitis but have been shown to be effective in patients with large duct disease. Pain relief may not always be achieved or may be short lived. Multiple repeat procedures may be necessary before effective relief is achieved. Rösch and colleagues published a multi-centre long-term follow-up study showing that two-thirds of patients experienced long-term (2–12 years) pain relief after ductal decompression procedures while 24% of patients had subsequently undergone surgery following their endoscopic procedure.[52] More recently, Cahen and colleagues[53] have shown that, after a 5-year follow-up period, pain relief was superior (80% vs 38%) in patients undergoing surgical decompression rather than endoscopic procedures for pancreatic duct obstruction. In addition, 47% of patients in the endoscopy group eventually underwent surgery.[53] In patients with large duct disease, who have severe pain that is resistant to pharmacological therapies, endoscopic intervention should be considered before surgery is undertaken. However, a significant proportion of these patients are likely to require surgical intervention at a later stage.

Surgical treatment of the pain of chronic pancreatitis. Many operations have been described for the treatment of pain and complications of chronic pancreatitis. They can be divided into decompression and drainage procedures and resection procedures. The primary indication for surgical intervention in chronic pancreatitis is severe, unremitting pain that is resistant to other measures. Examples of the commonly used surgical procedures in the management of chronic pancreatitis are shown in Table 4.

Drainage procedures are performed when there is a widely dilated main pancreatic duct (>6–7 mm) and the most commonly performed operation is longitudinal pancreaticojejunostomy (the modified Puestow procedure). Short-term pain relief is achieved in up to 80% of patients with pain relief persisting for more than 2 years in 60% of patients.[54]

Resection procedures may be considered in patients in whom a drainage procedure is likely to be technically difficult or unsuccessful. This group of patients often has small duct disease (diameter of main pancreatic duct <6 mm). The clinical features listed below may be present and influence the decision-making process when considering a pancreatic resection.

Table 4. Surgical procedures performed in chronic pancreatitis

Decompression/drainage operations	Resection procedures
Longitudinal pancreaticojejunostomy (modified Puestow procedure)	Whipple procedure (pancreaticoduodenectomy)
Lateral pancreaticojejunostomy	Beger procedure (duodenum-preserving pancreatic head resection)
Lateral pancreaticoduodenectomy	Frey procedure (resection of the pancreatic head with longitudinal pancreaticojejunostomy)
Pancreatic pseudocyst drainage	Total pancreatectomy and islet cell autotransplant Distal pancreatectomy

1. Intractable pain that is resistant to other therapies.
2. Small duct disease.
3. The pancreatic head is enlarged.
4. There is a suspicion of malignant change.
5. Previous pancreaticojejunostomy has failed.

The choice of resection procedure is dependent on the individual surgeon or institution involved. Superior results are obtained when there is either complete or partial resection of the pancreatic head.[55] Strate and colleagues[56] reported on the long-term (9 years) follow-up of 74 patients who had been randomized to have either the Beger procedure or the Frey procedure. They found that there was no difference in outcome between the two groups in regard to mortality, quality of life, pain, or exocrine or endocrine insufficiency. Yin and colleagues[57] concluded that the Beger procedure was superior to the Frey in terms of number of patients achieving good pain relief, whereas the Frey procedure achieved significantly lower post-operative morbidity. Familiarity with a chosen surgical technique and accumulated expertise within the team of surgeons, anaesthesiologists, nurses and other support staff undoubtedly have the greatest bearing on the outcome and success of any particular operation. The operation of choice in the author's institute is the Beger procedure. In patients who have undergone partial pancreatectomy and experienced little pain relief total or completion pancreatectomy remains a surgical option of last resort. Owing to the complete loss of insulin production, the patient is wholly reliant on insulin replacement therapy. Tight glycaemic control is difficult to achieve and can be a source of serious long-term morbidity and mortality. Recent innovations have included the application of enhanced recovery principles, familiar in colorectal surgery, to pancreatic surgery. Enhanced recovery after surgery involves extensive pre-operative counselling and information, carbohydrate loading, goal-directed fluid therapy, less use of drains and nasogastric tubes, minimally invasive surgical techniques, epidural analgesia, early mobilization, early institution of oral fluids and diet, less use of opioid analgesia and coordinated discharge planning.[58] Early indications are that length of stay is shortened and post-operative morbidity is reduced by adherence to an evidence-based approach to peri-operative care in pancreatic surgery. Despite improvements in peri-operative care, surgery for chronic pancreatitis is a major undertaking that will involve complex surgery, a lengthy hospital stay and the risk of associated post-operative complications. The rehabilitation period after surgery can be difficult and includes a period of adjustment to a reduced dose of opioid analgesia or complete cessation of the drug. This period needs to be managed carefully, especially if the patient had been taking high doses of opioid analgesia before surgery. Altered endocrine function will necessitate a period of adjustment and education in self-administering subcutaneous insulin. There may be ongoing post-surgical pain from a large wound and the associated drain sites. Chronic wound pain may occur months or years after surgery. Although many patients improve after surgery, a significant number do not. Patients who have a poor result after surgery express regret at having subjected themselves to a major surgical procedure that has given them no tangible benefit and perhaps made their symptoms worse. Extensive pre-operative counselling, before the decision to undergo surgery is made, is essential to clarify the risks and benefits of surgery and to identify those patients who might not improve.

Conclusion

Chronic pancreatitis, and the pain associated with it, is a complex clinical syndrome that has a devastating effect on those who suffer from it. It can be described as a group of disorders, with diverse aetiologies and multiple pathological processes, leading to the anatomical and physiological destruction of normal pancreatic function. Despite the numerous causes and multiple theories of pathogenesis, the common feature throughout a diverse group of patients is pain; pain that some describe as unbearable, relentless and all consuming. It is a pain that dominates every aspect of the life of a patient with chronic pancreatitis. It is a disease process that commonly leads to multiple hospital admissions,

associated complications (diabetes, malnutrition, pseudocysts) and possible major therapeutic interventions such as nerve blocks, endoscopic drainage procedures and complex surgery. Life expectancy in chronic pancreatitis is shortened and there is an increased risk of developing pancreatic cancer. Reliance on opioid analgesics is commonplace and, in many cases, essential. Long-term use of opioids is not without risk in itself. Immune function can be impaired; endocrine and associated sexual dysfunction can occur. Constipation, sedation and respiratory depression are well-recognized risks. Accidental overdose and other physical accidents are a real concern especially in those patients who have ongoing drug or alcohol problems. Opioid-seeking behaviour is seen in this group of patients and close monitoring of opioid usage as well as consistent prescribing is fundamental to preserving patient safety. The increasing incidence of all alcohol-related diseases is likely to lead to a major public health crisis. Alcohol-related chronic pancreatitis could contribute significantly to that crisis by increasing demand on hospital services in particular. The future magnitude and impact of an increasing incidence of chronic pancreatitis are difficult to predict but should not be ignored.

There is a wide range of treatments available to ameliorate the symptoms of chronic pancreatitis. Primary-care physicians, gastroenterologists, anaesthesiologists, pancreatic surgeons, pain specialists, nurses and psychologists all have important roles to play in its management. A multi-disciplinary approach is fundamental to improving treatment and outcome in this field.

There is still much to learn about the pathology underlying the development of chronic pancreatitis and in particular the pathogenesis of the pain that is the dominant feature of this crippling disease. There is a huge body of work investigating all aspects of chronic pancreatitis but unfortunately still no consistently successful, unified treatment strategy that effectively eliminates the pain and suffering of chronic pancreatitis.

The answer to the persistent clinical challenge of chronic pancreatitis lies in the basic science underlying the disease. Further understanding of the complex pathophysiological processes leading to the disorder will bring us closer to the answer. Fundamental to this process will be greater exploration of the role that the central nervous system has in generating, modulating and magnifying the pain of chronic pancreatitis. Unlocking the secrets of cortical centres that undergo reorganization in response to chronic pancreatitis is an avenue of research that needs further exploration. The breakthrough in the pursuit of the solution to the pain of chronic pancreatitis has not yet occurred.

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