CHAPTER 11

History of chronic pancreatitis

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This international symposium on the Medical and Surgical Treatment of Chronic Pancreatitis has brought together more than 45 international thought leaders and specialists in chronic pancreatitis. Organized by David Adams, Peter Cotton, Horacio Rilo, and Nicholas Zyromski, the symposium includes thought leaders in medicine, surgery, psychology, physiology, pharmacology, and genetics. The goals of this symposium were to exchange ideas, to give thought to important unresolved issues in the medical and surgical treatment of chronic pancreatitis, and to plan future research.

The history of chronic pancreatitis is beautifully described in two outstanding books [1, 2]. The modern era is generally thought to date back to 1946, when Comfort and associates described the clinical course, pathology, and treatment of chronic relapsing pancreatitis and confirmed an association with excessive alcohol use [3]. Since then, the early features and natural history of chronic pancreatitis have been well described [4, 5]. There have been numerous efforts to classify and stage chronic pancreatitis [6–13] starting with the 1963 Marseille Meeting [6]. A listing of etiologic risk factors associated with chronic pancreatitis – the TIGAR-O Classification System – was outlined in 2010 [13]. This article defined chronic pancreatitis as "A continuing inflammatory disease of the pancreas characterized by irreversible morphologic changes that typically cause pain and/or permanent loss of function" [13].

Regarding etiologies of chronic pancreatitis, there has been considerable interest in tropical calcific pancreatitis [14], early- and late-onset idiopathic pancreatitis [15], autoimmune pancreatitis [16–19], and genetic predispositions [13, 20–28]. The association between chronic pancreatitis and pancreatic cancer has been firmly established [29]. The effect of alcohol and smoking on the development and severity of chronic pancreatitis has been well described [30, 31].

The pathophysiology of chronic pancreatitis initially focused on the importance of protein plugs within pancreatic ducts [32] and components of these plugs including GP2 [33]. More recently, emphasis has been placed on the activation of pancreatic stellate cells such as by ethanol [34, 35], the concept that sequential episodes of necrosis leads to fibrosis [3, 36, 37], and the sentinel acute pancreatitis event (SAPE) hypothesis model, which outlines the importance of metabolic and oxidative stress in the development of acute pancreatitis and the importance of activation of stellate cells which leads to fibrosis [22].

A variety of imaging techniques including abdominal ultrasound, CT scan, MRI, ERCP, and endoscopic ultrasound are now in use to support a diagnosis of chronic pancreatitis but thus far have not achieved sufficient accuracy to confirm a diagnosis of early chronic pancreatitis [13, 38–41].

Pancreatic function tests utilizing intravenous secretin with collection of pancreatic juice initially via a gastroduodenal tube and more recently via an endoscope have been utilized to identify a decrease in exocrine pancreatic function [41–43]. Fecal elastase test [44] has been shown to be significantly decreased in moderate to severe chronic pancreatitis but not mild chronic pancreatitis. The ^{13}C-mixed triglyceride breath test has been shown to be an accurate alternative to fecal fat quantification to detect fat maldigestion and to evaluate the effect of enzyme therapy on fat digestion [45].

The importance of pancreatic juice in digesting fat was demonstrated in 1856 by Bernard [46]. It was

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established by DiMagno and associates in 1973 that steatorrhea does not occur until lipase output from the pancreas was 10% or less of normal [47]. The importance of curbing gastric acid output among patients who fail to respond to pancreatic enzymes replacement was established in 1977 [48]. Ways to improve efficiency of enzyme replacement therapy has recently been established [49].

In 1988, an analysis of nerves in chronic pancreatitis revealed evidence of edema in the nerve bundle and loss of barrier function by the perineural sheath [50]. In recent years, the neurobiology of pain in chronic pancreatitis has come under intense investigation [51–55]. In a recent randomized controlled trial, pregabalin reduced pain among patients with chronic pancreatitis [56].

Despite advances in our understanding of the neurobiology of chronic pancreatitis and despite numerous articles that report efficacy with a variety of treatments, effective therapies to relieve the pain of chronic pancreatitis are lacking. There have been two recent studies that have evaluated the efficacy of antioxidant therapy [57, 58]. One carried out in India mostly among patients with tropical pancreatitis reported a reduction in pain compared to the placebo [57]. The second among patients predominately with alcoholic chronic pancreatitis did not find a reduction in pain [58]. The use of pancreatic enzymes to reduce pain has been associated with uncertain benefit [59, 60]. Extracorporeal shock-wave lithotripsy of pancreatic calculi has been reported to decrease pain but has not been subjected to randomized prospective trials involving control patients who did not undergo shock-wave lithotripsy [61, 62]. Endoscopic ultrasound-guided celiac plexus block has not proven to be beneficial [63, 64]. Endoscopic therapy has been reported to relieve pain in chronic pancreatitis [65], but randomized prospective trials have suggested that surgical therapy is superior to endoscopic therapy for long-term pain reduction [66–68]. Several randomized prospective trials have compared surgical techniques to relieve pain associated with chronic pancreatitis and have determined that pain relief is comparable among the various techniques that were compared [69–75]. Total pancreatectomy with islet autotransplantation is now carried out in numerous medical centers. It has been pointed out that a multicenter registry will be very important to advance our knowledge of the efficacy of this technique and that well-designed clinical trials will be required to validate the benefit [76].

Despite a large number of recent articles on the diagnosis and treatment of chronic pancreatitis, many important questions remain unanswered, and many areas of research need to be addressed. Several are as follows:

- We need to be able to make an accurate diagnosis of early chronic pancreatitis. This will make possible the planning of randomized prospective trials on treatment options before the disease becomes firmly entrenched. It will also allow us to distinguish patients with early chronic pancreatitis from those with a chronic pain syndrome. Proteomic analysis of pancreatic fluid has identified candidate proteins that are being evaluated as possible biomarkers of early chronic pancreatitis [77].
- We need to have a better understanding of the natural history of chronic pancreatitis. At the present time, early intervention which may be ineffective may be altering the natural history of the disease such that it becomes impossible to distinguish changes in structure, function, and clinical features caused by the therapy itself versus the natural history of chronic pancreatitis. The Dutch Pancreatitis Study Group has undertaken a long-term prospective study of patients with chronic pancreatitis with active collaboration of 33 hospitals to study the natural history of the disease and the impact of treatment strategies [78].
- We need to have a better understanding of the impact of genetic mutations and ways to prevent and treat acute pancreatitis associated with these mutations.
- We need to improve our studies on the treatment of pain with emphasis on uniform criteria for the evaluation of pain and standardized reporting of patient outcomes [79, 80].
- We need rigorously designed controlled clinical trials to assess outcomes of treatment. Studies are needed to compare treatment alternatives such as medical versus surgical strategies.
- We need studies on the quality of life among patients with chronic pancreatitis and the impact of the disease on employment and other life domains affected by chronic pancreatitis [81].
- We need to identify new treatments of pain. New treatments may become available as a result of our better understanding of the neurobiology of pain.
- We need a better understanding of stellate cell function. A goal of this research would be to find ways to prevent and/or eliminate pancreatic fibrosis.

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