Abdominal pain, and exocrine and endocrine pancreatic insufficiency are the leading symptoms of chronic pancreatitis. For the majority of patients, however, pain is the decisive symptom, causing much discomfort in their daily lives. Thus, the medical management of chronic pancreatitis has three aims: treatment of pain as well as of exocrine and endocrine pancreatic insufficiency.

**Pain in Chronic Pancreatitis**

**General**

The cause of pain in chronic pancreatitis is uncertain. There are at least two, not necessarily mutually exclusive, hypotheses under investigation [1]. Bockman et al. [2] showed that in chronic pancreatitis perineural inflammation disrupted perineural neural sheaths, and hypothesized that the exposure of the unprotected nerves to bioactive substances triggers pain. A second hypothesis is that painful chronic pancreatitis is caused by increased pancreatic ductal and parenchymal pressure, producing a compartment syndrome that induces ischemia; this hypothesis is supported by experimental studies by Karanjia et al. [3, 4]. They showed increased interstitial and perfusion pressures and decreased blood flow in cases of feline chronic pancreatitis [3]. These abnormalities were reversed substantially by surgical incision of the gland and draining of the pancreatic duct, but were affected minimally by stenting the pancreatic duct [4]. Thus, incision of the gland rather than ductal drainage may be more important in relieving pain, and reducing pancreatic secretion will reduce pressure and alleviate pain [1]. Further studies are required.

More than three decades ago, Ammann [5] postulated a close correlation between pain relief and severe exocrine pancreatic insufficiency, the so-called burn-out of chronic pancreatitis. Since then, this hypothesis has been questioned in several studies. All groups agree that there is an inexorable march toward calcification and exocrine and endocrine pancreatic insufficiency. However, the association between the cessation of pain and onset of calcification and exocrine and endocrine pancreatic insufficiency is controversial.

Ammann’s group has claimed that pain decreases with increasing duration of the disease [5–9]. In one long-term study, 85% of 145 patients with chronic pancreatitis felt no more pain after 4.5 years (median) duration of the disease [8]. In another series in which the interval between the onset of alcohol-induced chronic pancreatitis and pain relief was compared in a surgically and a nonsurgically treated patient group, the curves were virtually parallel: pain relief was obtained in about 50% within 6 years and in more than 80% within 10 years from the onset of illness [10].

The reports from Zürich are at variance with the studies from Japan and Germany. Miyake et al. [11] found that only 48.2% of patients with chronic pancreatitis became free of pain within 5 years, and 66–73% after more than 5 years. That meant that every third or fourth patient still suffered from relapsing pain attacks even after a longer observation time. Our group [12] reported that the incidence of relapsing pain attacks decreased during the observation period, but more than half of patients (53%) still suffered from relapsing pain attacks even after more than 10 years observation [12].

At present, the course of pain in alcoholic and idiopathic chronic pancreatitis remains to be clarified. Layer et al. [13] investigated a group of patients with idiopathic chronic pancreatitis who had never consumed alcoholic beverages during their lifetime. They found that patients with early-onset pancreatitis (onset at <35 years of age) have initially and thereafter a long course of severe pain, whereas patients with a late-onset pancreatitis (onset at >35 years) have a mild and often painless course. Both forms differ from alcoholic pancreatitis, with an equal gender distribution and a much slower rate of calcification. In contrast, our group found that the course of pain is the same in alcohol- and non-alcohol-induced chronic
pancreatitis [14]. Even when we divided the nonalcoholic group into teetotalers and patients with little alcohol consumption, and compared separately their course of pain with that of alcoholics, there were no differences concerning pain relief among the three groups [15]. Further studies are required [16].

**Pain Decrease and Progressing Exocrine and Endocrine Pancreatic Insufficiency**

The Swiss group repeatedly observed a pain decrease as exocrine and endocrine pancreatic function declined [5–7, 9]. Similarly, Girdwood et al. [17] reported from South Africa that pain decreased as exocrine pancreatic function deteriorated.

On the contrary, groups from Denmark and Germany have reported the opposite. Thorsgaard Pedersen et al. [18] from Copenhagen found no correlation between pain and exocrine pancreatic function. Our group from Göttingen [12] used the secretin-pancreozymin test and fecal fat analysis to evaluate exocrine pancreatic insufficiency, whereas the Swiss group had used only indirect pancreatic function tests (i.e., chymotrypsin measurements) to evaluate exocrine pancreatic insufficiency [8]. We used a clear-cut grading of the severity of exocrine pancreatic insufficiency: mild impairment was defined as reduced enzyme output; moderate, as a decreased bicarbonate concentration along with reduced enzyme output but normal fecal fat excretion; and severe impairment was equated with an abnormal secretin-pancreozymin test plus steatorrhea. At the end of observation period, 141 (45%) of 311 patients with painful chronic pancreatitis had severe exocrine pancreatic insufficiency. The majority of them (81/144; 57%) still suffered from pain attacks.

We also studied the course of pain in correlation to endocrine pancreatic insufficiency. Endocrine pancreatic insufficiency was classified as absent, moderate (diabetes mellitus treated only by diet plus/minus oral medication), and severe (requiring insulin). At the end of the observation time, 117 (38%) patients were classified as having severe endocrine pancreatic insufficiency. The majority of them (69/117; 59%) still suffered from pain attacks [12, 19].

Thus, according to our results, the progression of exocrine and endocrine pancreatic insufficiency has limited influence, if any, on the course of pain in chronic pancreatitis.

**Pain Decrease and Development of Morphological Changes of the Pancreas (Pancreatic Calcifications and/or Duct Abnormalities)**

The Swiss group [7, 8] showed an increased incidence of pancreatic calcifications, which in turn was associated with pain decrease. However, later on, the same group [20] reported a regression of pancreatic calcifications in a long-term study of patients with chronic pancreatitis. Thus, the prognostic role of pancreatic calcifications concerning the course of pain is unclear.

Furthermore, the Swiss results are at variance with those of two other studies. Malfertheiner et al. [21] found that 89% of patients had pain despite pancreatic calcifications (as observed using computed tomography), and 39% experienced very intense pain. In our study, freedom from pain was significantly higher among the calcification group as compared to the noncalcification group. However, the majority of patients with pancreatic calcifications (56%) still had relapsing pain attacks [12].

The correlation between pain and pancreatic duct changes or pressure in the duct system is also not clear. Ebbehøj et al. [22, 23] measured percutaneous or intraoperative pancreatic tissue fluid pressure and found a significant correlation with pain in patients with chronic pancreatitis but not with the endoscopic retrograde cholangiopancreatography (ERCP) results (i.e., the regional pressure tended to be highest in the region of the pancreas with the largest and not with the smallest duct diameter). Jensen et al. [24] found no correlation between pancreatic duct changes and pain. Warshaw et al. [25] found no pain relief in spite of a patent anastomosis detected by ERCP in two of ten of their patients, 1 year after a lateral pancreaticojejunostomy.

Two investigations have confirmed the nonparallel relationship between changes in the pancreatic duct and pain relief. Malfertheiner et al. [21] found severe pain in only 62% of patients who had advanced pancreatic duct changes, demonstrated by ERCP. We found no significant correlation between pancreatic duct abnormalities detected by ERCP and pain in 88 patients with chronic pancreatitis [12]. Severe pancreatic duct abnormalities – as defined by the Cambridge classification [26] – were present in 42 patients, but only 16 (31%) of these became free of pain. Despite a normal pancreatic duct in 14 patients, 10 (71%) of them suffered from persisting pain [12].

Thus, morphological changes such as pancreatic calcifications or pancreatic duct abnormalities are not necessarily helpful in making a prognosis of chronic pancreatitis or predicting the course of pain.