CHRONIC PANCREATITIS: NEW INSIGHTS IN ETIOLOGY
Michelle A. Anderson, MD, MSc

Chronic pancreatitis is a persistent inflammatory condition of the pancreas characterized by recurrent episodes of abdominal pain with variable patterns of intensity and duration. Although there are numerous etiologies for pancreatitis (Figure 1), there is uniformity in the progressive fibrotic damage to the pancreatic parenchyma seen among all patients that eventually results in irreversible morphologic and functional impairment. It has been estimated that the prevalence of chronic pancreatitis in the United States is roughly 50/100,000 persons and the annual incidence ranges from 5 to 12/100,000 persons. Chronic pancreatitis has profound effects on patient’s quality of life frequently necessitating hospitalization for pain control or complications from the disease process. In one recent study on the burden of the disease in the United States, authors found that there had been 19,724 admissions nationwide in 2009 with a principal diagnosis of chronic pancreatitis resulting in a mean length of stay of 5.1 days and mean hospital charges of $28,634. This same study noted that there had been 78 deaths among these admissions pointing toward the gravity of this disease. In a similar study, researchers found that pancreatitis ranked 8th among all digestive diseases in years of potential life lost before age 75 with an average of 12.3 years lost per death among the average patient with chronic pancreatitis who dies from his or her disease. Clearly, if we are to make progress toward symptom control and treatment we need to improve our understanding of the pathogenesis of the disease and our ability to diagnose the correct etiology at the soonest time point.

Alcohol and Chronic Pancreatitis
In industrialized civilizations, alcohol is the most common cause of chronic pancreatitis. As recently as 2003, alcohol was reported to be the underlying etiology in more than 70% of all chronic pancreatitis cases. Although excessive alcohol use remains the most cause of chronic pancreatitis, recent epidemiologic studies suggest that alcoholism accounts for no more than 45% of cases in the United States today. Moreover, as a medical community we have made tremendous progress in our understanding of the pathogenesis of alcohol-related pancreatitis. For instance, we now know that disease risk is directly related to alcohol dose and that the average male incurs a significant risk (Odds ratio, 3.1) when his consumption reaches a threshold of approximately 35 drinks per week.

So how does one explain this apparent reduction in the prevalence of alcohol-induced chronic pancreatitis? In part, there has been a reduction in alcohol consumption in some areas of Western society but this has been quite minor and not large enough to explicate the shifts in etiologies we are seeing. Instead, many experts believe that medical advancements in our understanding of the pathogenesis of chronic pancreatitis have allowed us to more accurately assign an etiology to a given patient thereby reducing the proportion of patients labeled as having “alcoholic chronic pancreatitis” and reallocating those patients into more appropriate diagnostic bins. Much of this has occurred coincident with genetic testing becoming clinically accessible and covered by third party payors. Finally, the efforts of multicenter cooperative groups such as the North American Pancreatitis Study Group (NAPS), have allowed for a much better understanding of the multifactorial nature of the disease, its epidemiology and the impact of tobacco on disease risk.

Understanding the Effects of Tobacco Use in Chronic Pancreatitis
The detrimental effects of smoking on the pancreas have been reported for many decades. Since the prevalence of smoking increases with alcohol consumption, it has been difficult to adequately control for confounding in population-based studies. However, a recent large, prospective, case-control study from the NAPS-2 research group has accomplished this by comparing pancreatitis risk between patients with idiopathic chronic pancreatitis to control subjects. The NAPS-2 study enrolled 539 patients who met pre-defined criteria for chronic pancreatitis from 19 academic and community practices across North America. Patients completed detailed questionnaires which included information on tobacco and alcohol use. The study also included 695 control subjects who completed similar surveys. Surprisingly, heavy or “at-risk” alcohol use was actually more common in the control group than in the patients with idiopathic chronic pancreatitis (12.2% versus 5.2%, p<0.02) while there were no differences in age, gender or race. The most important finding from the study was that the frequency of tobacco use was significantly higher among patients with idiopathic CP (p<0.05) and that smoking was an independent risk factor for CP even after controlling for age, sex, BMI and alcohol intake (Table 1). Studies such as this have estimated that the attributable risk of smoking, or the reduced incidence that would occur if the population were entirely unexposed to this risk, is 25%!

The damaging effects of smoking do not end with the onset of the disease. Recent studies have shown that continued...
tobacco use makes acute pancreatitis more likely to progress to chronic pancreatitis and to advance the rate of progression of chronic pancreatitis. In one study involving patients from Italy, authors found that patients with idiopathic chronic pancreatitis who never drank but who did smoke were more than 2 times more likely to develop pancreatic calcifications after a mean follow-up of 5.8 ± 6.7 years than patients who did not smoke (HR=2.09; 95% CI 1.07-4.10) and in a shorter interval (median time from onset to calcification in years for smokers versus non-smokers was 2 years versus 13 years). In the same study, heavy smoking, defined as tobacco use > than 20 cigarettes per day, was associated with the development of diabetes (HR 3.94, 95% CI, 1.14-13.6). In contrast, there appear to be clear benefits to smoking cessation in this population. In a study from Verona, Italy researchers found that subjects who had ceased smoking at the time of being diagnosed with chronic pancreatitis were no more likely to develop pancreatic calcifications than their never-smoked counterparts (OR 0.56, 95% CI 0.2-1.4) in contrast to patients who continued to smoke (OR 1.76, 95% CI 1.1-2.8 for 1 pack per day smokers).8

Despite the ever-increasing and overwhelming evidence of the harmful effects of tobacco on the pancreas, the association between smoking and chronic pancreatitis is often under recognized by physicians. Even among experts practicing at tertiary care centers, smoking was cited as a risk factor for pancreatitis in less than 50% of cases in which patients had self-reported regular tobacco use suggesting that all of us need to consider this in our evaluation of these patients.9 This is especially true considering that numerous studies have shown that physician advice and counseling can have profound effects on tobacco cessation rates.

### Table 1: Multivariate LR Comparison of Tobacco Use Among Idiopathic CP versus Controls NAPS2

<table>
<thead>
<tr>
<th>Smoking Category</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever smoked</td>
<td>1.65</td>
<td>1.08-2.52</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.80</td>
<td>1.10-3.05</td>
</tr>
<tr>
<td>≥ 1 pack per day</td>
<td>1.87</td>
<td>1.10-3.12</td>
</tr>
</tbody>
</table>

### Figure 2: Autoimmune Pancreatitis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Jaundice</td>
<td>• Serum IgG4*</td>
<td>• Prednisone 40 mg/day x 4-6 weeks</td>
</tr>
<tr>
<td>• Mass</td>
<td>• ANA</td>
<td>• Taper 5 mg/1-2 weeks</td>
</tr>
<tr>
<td>• Abd pain</td>
<td>• Imaging</td>
<td>• Azathioprine for failures or relapse</td>
</tr>
<tr>
<td>• Pancreatitis</td>
<td>• BX</td>
<td></td>
</tr>
<tr>
<td>• Other organ</td>
<td>• HISORt</td>
<td></td>
</tr>
<tr>
<td>involvement</td>
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*X=ULN=140. IgG4≥280 mg/dL are 99% specific but only 53% sensitive (Ghazale, et al. AJG 2007)

### Genetic Mutations and Chronic Pancreatitis – Taking the Complex and Making it Simple

In 1996, Whitcomb and colleagues identified the cationic trypsinogen gene (PRSS1) as the gene responsible for hereditary pancreatitis.10 This discovery and subsequent work showed that mutations in this gene result in a “super”-trypsin molecule which is more resistant to degradation due to the fact that the point at which it should be cleaved to undergo inactivation has been altered. More recent studies have shown that this mutated trypsin also exhibits increased autoactivation and greater zymogen stability all of which equate to active trypsin being around in the pancreas where it shouldn’t be longer than it should. Interestingly, although the hereditary pancreatitis gene is inherited as an autosomal dominant gene, it only exhibits about 80% penetrance so not everyone who gets the gene gets the disease. This is fortunate since there appears to be a fairly significant risk of pancreatic cancer associated with this disease which has been estimated at approximately 40% lifetime risk.11

Once one understands the paradigm of mutation leading to inappropriate activated trypsin shown by the PRSS1 gene model, all of the other gene mutations become easier to understand. For example, the serine protease inhibitor Kazal type 1 (SPINK1) gene encodes a protein which acts as a scavenger to inhibit proteases (hence the name) of which trypsin is one. The purpose of this protein is to rid the pancreas of prematurely activated trypsin. Mutations in this gene lead to a loss-of-function rather than the gain-of-function that we saw with the PRSS1 gene and result in the loss of one of the body’s protective mechanisms against pancreatitis. It then would follow that mutations in this gene would not be sufficient in and of themselves to result in pancreatitis in most cases since one would still need activated trypsin and since there are redundant protective mechanisms. Indeed, that is exactly what is seen clinically. That is, patients with mutations in the SPINK1 gene typically require
Cystic fibrosis (CF) is the most common inherited disorder in Caucasians in the United States. CF is caused by loss-of-function mutations in the CF transmembrane conductance regulator (CFTR) gene and more than 1,000 different mutations have been described. Its function in the pancreas is to dilute and alkalinize the pancreatic protein secretions. When mutations occur and this doesn’t happen, protein plugs form in ductules leading to pancreatic injury, premature activation of trypsin and pancreatitis. Interestingly, it appears that the particular mutations associated with the forms of CF which result in pancreatic disease phenotypes are not the same as those that result in pulmonary forms of disease. Moreover, unlike the pulmonary-predominant phenotype in which both alleles must be mutated to produce clinically-evident disease (recall that CF is an autosomal recessive disorder), patients with pancreatic-specific mutations can present with acute recurrent or chronic pancreatitis with a single mutated allele or as compound heterozygotes.

Two additional genes which have recently been implicated in chronic pancreatitis are the calcium-sensing receptor gene (CASR) and the chymotrypsinogen C gene (CTRC). Mutations in both of these genes result in a loss-of-function. Table 2 summarizes the five genes which have been widely accepted to play a role in chronic pancreatitis as well as their chromosomal location and function. All five of these genes can be tested for clinically using a simple blood draw although patients should undergo formal genetic counseling from trained personnel prior to testing and upon receiving the results. The highest yield for genetic testing occurs in patients with a family history of pancreatic or pulmonary disease, those with early-onset of disease and in those with associated disorders in their families such as pancreatic cancer, cystic fibrosis or infertility. Although there are no gene-directed therapies currently available, there are a few drugs currently in development for patients with CFTR mutations. In addition, there are indirect benefits to genetic testing such as limiting further testing in the search for additional causes, cancer risk ascertainment in the case of hereditary pancreatitis and reproductive disease risks in the case of CFTR carrier state.

### Table 2: Chronic Pancreatitis-associated Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome Location</th>
<th>Encoded Protein</th>
<th>Normal Function</th>
<th>Mutation Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRSS1</td>
<td>7q35</td>
<td>Cationic Trypsinogen</td>
<td>Digests Protein</td>
<td>Gain in Fxn</td>
</tr>
<tr>
<td>SPINK1</td>
<td>5q31.2</td>
<td>Serine protease inhibitor Kazal type 1</td>
<td>Scavenges activated trypsin in pancreas</td>
<td>Loss of Fxn</td>
</tr>
<tr>
<td>CFTR</td>
<td>7q31.2</td>
<td>Cystic Fibrosis transmembrane conductance regulator</td>
<td>Dilutes and alkalinizes pancreatic secretions</td>
<td>Loss of Fxn</td>
</tr>
<tr>
<td>CTRC</td>
<td>1p32</td>
<td>Chymotrypsinogen C</td>
<td>Highly specific for digesting trypsin</td>
<td>Loss of Fxn</td>
</tr>
<tr>
<td>CASR</td>
<td>3q13.3</td>
<td>Calcium-sensing Receptor</td>
<td>Controls electrolyte movement across acini</td>
<td>Loss of Fxn</td>
</tr>
</tbody>
</table>

LPSP – lymphoplasmocytic sclerosing pancreatitis, IDCP – idiopathic ductcentric pancreatitis.

*Other organs: Biliary, retroperitoneal, renal or salivary.


A second “hit” in the form of an environmental factor such as smoking or alcohol or a congenital abnormality such as pancreas divisum before they have clinical manifestations of chronic pancreatitis. A fascinating exception to this has been the description of tropical pancreatitis in patients who carry a particular variant of the SPINK1 gene N34S which is strongly associated with the disease.12,13

Autoimmune Pancreatitis: How to Recognize It

Autoimmune pancreatitis (AIP) is a form of chronic pancreatitis that most commonly presents with obstructive jaundice and may present with signs or symptoms of acute or chronic pancreatitis (Figure 2). Because these patients frequently have an associated mass in the head of the pancreas, they are often confused as having pancreatic cancer and undergo Whipple procedures or attempted Whipple procedures only to find fibrosclerosing pancreatitis on pathology. Because this variation of chronic pancreatitis is highly responsive to steroid treatment, it is important to consider this diagnosis in the evaluation of patients who present with a compatible constellation of findings. Unfortunately, moving from speculation to certain diagnosis is often quite difficult. Several different diagnostic criteria have been proposed although none are 100% sensitive. Most of these involve serum testing for gammaglobulin subclasses and ANA. Patients with AIP typically have serum IgG4 levels > 140 although levels may be elevated in other conditions such as pancreatic cancer, primary biliary cirrhosis, COPD, Sjogren’s disease and chronic pancreatitis from other etiologies. In one study IgG4 levels > 280 (2x the upper limit of normal) were 99% specific but only 53% sensitive for AIP.14 Other key diagnostic findings include characteristic imaging findings such as a diffusely enlarged pancreas with a rim described as a “halo” sign or a loss of pancreatic borders resulting in a pancreas with a classic “sausage” appearance. On ERCP or MRCP, the pancreatic duct of patients with AIP will differ from other patients with chronic pancreatitis from other etiologies in the appearance of diffusely irregular stric-
tories and a beaded appearance. Of course, histology showing characteristic lesions (either lymphoplasmacytic sclerosing pancreatitis with more than 10 IgG4 positive cells per high power field or idiopathic duct-centric pancreatitis without IgG4 cells) can establish the diagnosis although achieving adequate tissue through non-invasive means can be difficult.

Recent studies have shown that there appear to be two distinct forms of AIP. (Table 3) Type 1 AIP is the lymphoplasmocytic sclerosing form of pancreatitis and is part of a systemic IgG4-positive disease process. This form is associated with other organ involvement including the thyroid (autoimmune thyroiditis), kidneys (interstitial nephritis), salivary glands (Sjogren’s syndrome), lungs and skin (vitiligo). Patients with type 1 AIP rarely have associated inflammatory bowel disease as do patients with type 2 or idiopathic ductentric AIP. Although both types of AIP are initially responsive to steroid therapy, patients with type 1 AIP are much more likely to suffer a relapse and require steroid-sparing therapies such as azathioprine than patients with type 2 AIP.15

Conclusions
There appear to be real shifts in the etiologies of chronic pancreatitis in Western society. In part, these have arisen due to changes in the epidemiology of the disease with deceased alcohol use and more accurate diagnosis. A greater impact has occurred through correct etiology classification which in turn has been enabled at least in part through the availability and application of genetic testing, an understanding of the role of tobacco on disease risk and recognition of the entity of autoimmune pancreatitis. The importance of multicenter cooperative studies to accomplish the scale of studies needed to address important questions in chronic pancreatitis risk, diagnosis and treatment cannot be overestimated and were at the center of the advancements described herein. If we are to make further strides in this disease, similar studies will be needed.

Clinically, these studies have taught us that we need to encourage smoking cessation in all patients with pancreatitis from those presenting with acute pancreatitis to those with an initial diagnosis of chronic pancreatitis and to keep encouraging it. Given our growing understanding of the role of genetics in chronic pancreatitis, this is something that all gastroenterologists should consider when evaluating patients with pancreatitis particularly those patients who are young or who have a family history of pancreatic disease. Finally, although autoimmune pancreatitis is a rare form of chronic pancreatitis, it is the only form that is responsive to medical therapy and so being vigilant to this as a possible diagnosis may make a critical difference in the care of your patient.

REFERENCES