

## Introduction to Pancreatic Disease: Chronic Pancreatitis

*Elham Afghani*

*Division of Gastroenterology, Cedars-Sinai Medical Center*

*Los Angeles, CA 90048*

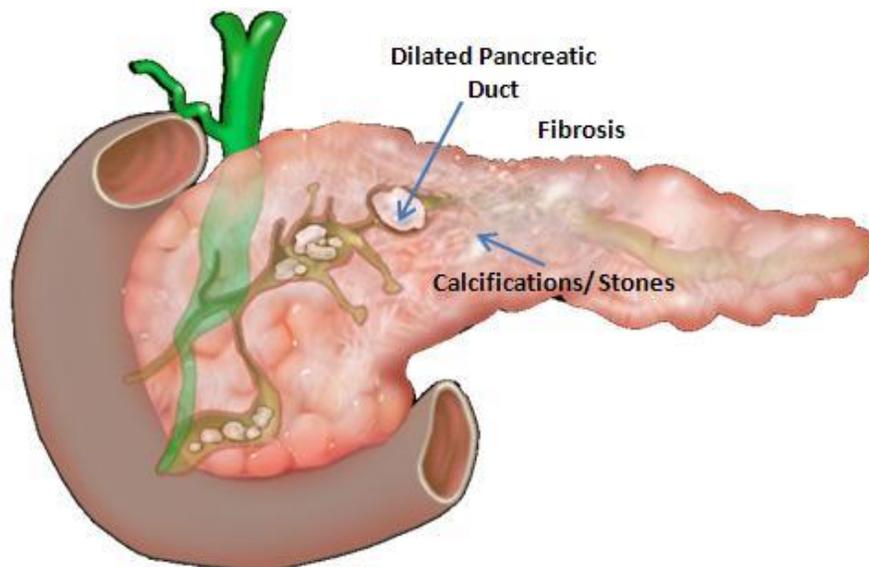
*e-mail: Elham.Afghani@cshs.org*

Version 1.0, December 16, 2014 [[DOI: 10.3998/panc.2015.3]

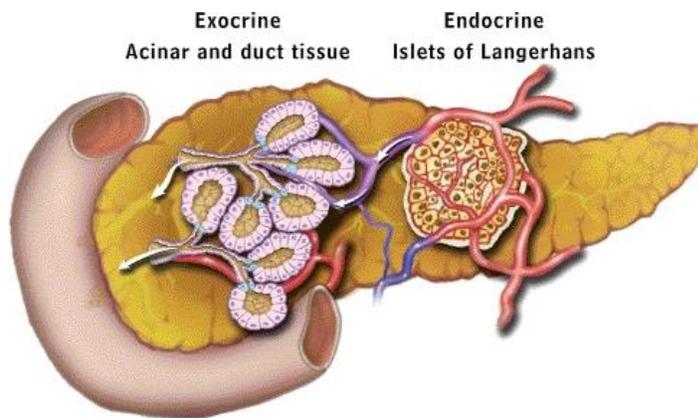
### 1. What is chronic pancreatitis?

Chronic pancreatitis is a long-standing inflammatory disease which leads to scarring of the pancreas and irreversible changes. Chronic pancreatitis results in abdominal pain and, in some cases, results in diabetes and fatty stools that are large and bulky. Calcification, which is another sign of chronic inflammation, can develop throughout the pancreas. These calcifications are like stones that are within the tissue itself, or within the pancreatic duct (**Figure 1**).

In the normal pancreas, there are three types of pancreatic cells: 1) acinar cells, which produce pancreatic digestive enzymes; 2) ductal cells lining pancreatic ducts, which secrete a watery fluid to carry the digestive enzymes into the intestine; and 3) endocrine cells present in the islets of Langerhans, which secrete insulin and other hormones (**Figure 2**). As the pancreas begins to scar and more than 90% of the tissue is destroyed over time (often over many years) patients develop fatty stools and fat malabsorption because they do not produce enough digestive enzymes; and diabetes due to loss of insulin producing cells.



**Figure 1. Features of chronic pancreatitis.** Chronic pancreatitis is progressive inflammatory process in the pancreas that causes fibrosis (scarring of tissue), calcifications or stones, and dilated pancreatic duct. Adapted from Gorelick F, Pandol, SJ, Topazian M. *Pancreatic physiology, pathophysiology, acute and chronic pancreatitis*. Gastrointestinal Teaching Project, American Gastroenterological Association. 2003.



**Figure 2. Cells of the pancreas.** The pancreas has two types exocrine cells which include acinar and ductal cells; and endocrine cells present in the islets of Langerhans. The exocrine portion of the pancreas makes up 85% of the pancreas. Adapted from Gorelick F, Pandol SJ., Topazian M. *Pancreatic physiology, pathophysiology, acute and chronic pancreatitis*. Gastrointestinal Teaching Project, American Gastroenterological Association. 2003.

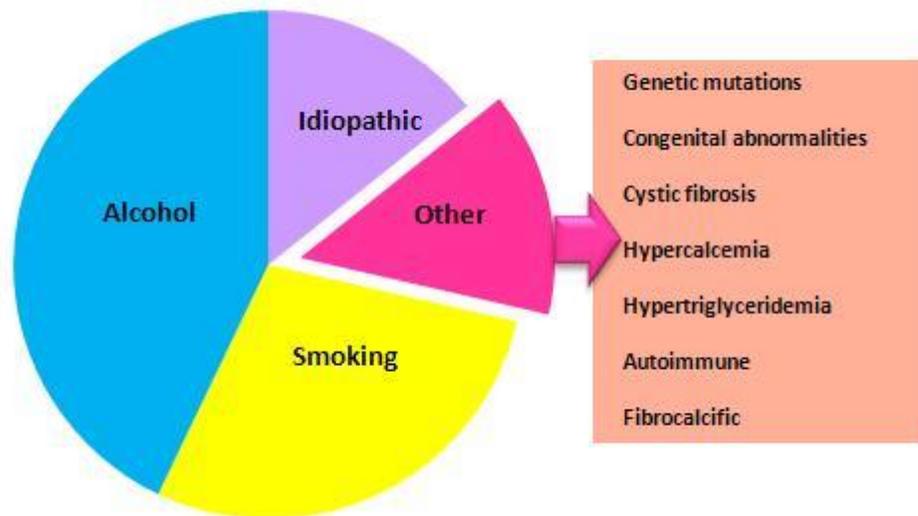
The incidence of chronic pancreatitis ranges from 4.4 to 11.9 per 100,000 per year, with a higher incidence in Japan compared to the United States. (6, 22, 23). Men are up to 1.5 times more likely to have chronic pancreatitis compared to women in the United States (22). The incidence may be higher in other countries. In 2009, there were 19,724 admissions for chronic pancreatitis in the United States, and associated with annual hospitalization costs of \$172 million (16). The incidence has been increasing which may be due to improved diagnostic techniques or increased use of alcohol worldwide but more so in the developing countries, such as India and China (7). The incidence of chronic pancreatitis is less in children. The age at presentation varies with etiology. Hereditary pancreatitis has a peak age at 10 to 14 years (11), juvenile idiopathic chronic pancreatitis at 19 to 23 years, alcoholic chronic pancreatitis at 36 to 44 years, and senile idiopathic chronic pancreatitis at 56 to 62 years (9, 13).

## 2. What causes chronic pancreatitis?

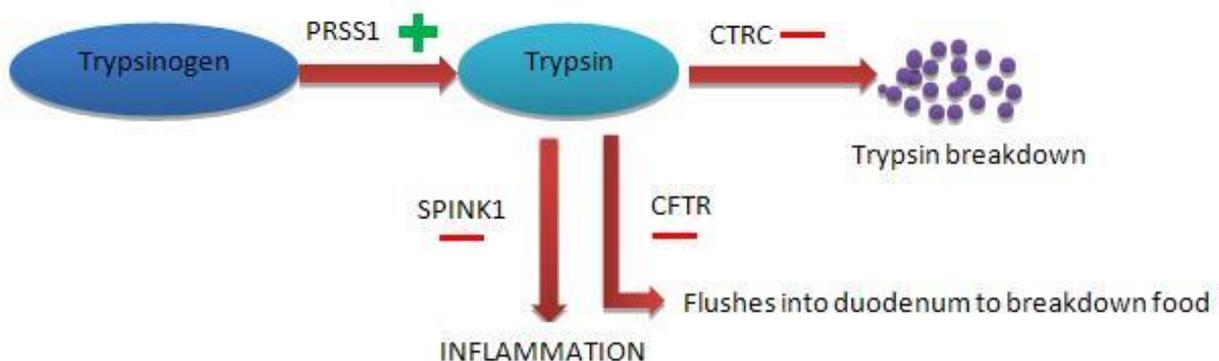
**Figure 3** shows the causes of chronic pancreatitis. Alcohol abuse and smoking are the most common causes of chronic pancreatitis. Heavy alcohol use, which means 4-5 drinks per day of alcohol over years, increases the risk of developing chronic

pancreatitis (8, 21). However even lesser amounts of alcohol can change the structure of the pancreas. Alcohol and smoking together increase the risk of chronic pancreatitis as they often coexist. However recently, it has been found that smoking is independent risk factor for chronic pancreatitis. Those who smoke less than one pack per day have a 2 fold risk of chronic pancreatitis, those who smoke more than one pack per day have a 3 fold risk (2), and those with more than 35 smoking pack year history (which is equal to the number of packs per day times the years) have a 13 fold risk of chronic pancreatitis (21). Continued smoking after the development of chronic pancreatitis speeds up the progression of the disease (19). It also further increases the risk of pancreatic cancer.

Chronic pancreatitis usually results from recurrent attacks of acute pancreatitis. In addition to alcohol abuse, other causes of acute recurrent pancreatitis include high levels of calcium or triglycerides in the blood, genetic mutations, and congenital abnormalities of the pancreas. Genetic mutations and cystic fibrosis can cause acute recurrent pancreatitis or may cause chronic pancreatitis without prior acute pancreatitis. These are also likely the causes of chronic pancreatitis in children. Hereditary pancreatitis due to genetic mutations is a rare cause of chronic pancreatitis.



**Figure 3: Causes of chronic pancreatitis.** The most common cause of chronic pancreatitis in the United States is alcohol and smoking. Other causes include genetic mutations, cystic fibrosis, hypercalcemia (or elevated calcium levels in the blood), hypertriglyceridemia (or elevated levels of triglycerides in the blood), autoimmune, or idiopathic, meaning that the cause is still unknown. Fibrocalcific pancreatitis, also known as tropical pancreatitis, is more common in India.



**Figure 4: Mechanism of gene mutations causing pancreatitis.** Trypsinogen is a precursor, meaning that it is an inactive form of an enzyme, called trypsin. It becomes activated. A gain of function mutation in PRSS1, is associated with premature and continued activation of trypsinogen into trypsin. Trypsin is flushed into the duodenal to allow for food digestion by bicarbonate rich fluid. A loss of function in CFTR prevents adequate formation of bicarbonate fluid, therefore increasing the amount of trypsin around the pancreas. Trypsin can also cause injury or inflammation of the pancreas. This is usually prevented by normal functioning SPINK1, a pancreatic secretory trypsin inhibitor. However, if there is a loss of function in SPINK1, then trypsin is free to cause inflammation. Trypsin is broken down by one form of the enzyme called chymotrypsin. The gene responsible for this enzyme is CTCR. A loss of function of CTCR prevents trypsin breakdown, therefore allowing more trypsin to cause tissue injury.

In the recent years, there has been more research that has found new genes that may be associated with the development of chronic pancreatitis. These genes include PRSS1, CFTR, SPINK1, and CTCR. A gain of function (which occurs in PRSS1)

or a loss of function (which occurs in SPINK1, CTCR, and CFTR) leads to either the premature activation of the enzymes that digest the pancreas (trypsin) or prevents it breakdown (20). (**Figure 4**).

Cystic fibrosis affects 1 in 3000 births in people of North European descent (15). Some people with cystic fibrosis may have pancreatic exocrine insufficiency while other will have a working pancreas, also known as pancreas sufficient. Those who are pancreas sufficient may go on to develop chronic pancreatitis, with or without discrete attacks of pancreatitis

Congenital abnormalities of the pancreas may become apparent either in childhood or in adulthood. These abnormalities include annular pancreas, which is an abnormal development of the pancreas during development while in the womb. Pancreas divisum is another abnormality. This abnormality is present in 10% of the population. The significance of pancreas divisum is unknown since most patients with this do not have symptoms or go on to develop chronic pancreatitis. One study showed that those with pancreas divisum and chronic pancreatitis had a genetic mutation, more commonly CFTR gene mutation, suggesting that pancreas divisum by itself does not cause pancreatitis (3).

Other causes of chronic pancreatitis in adults and children include autoimmune pancreatitis and fibrocalcific pancreatitis, also known as tropical pancreatitis, which is more common in India.

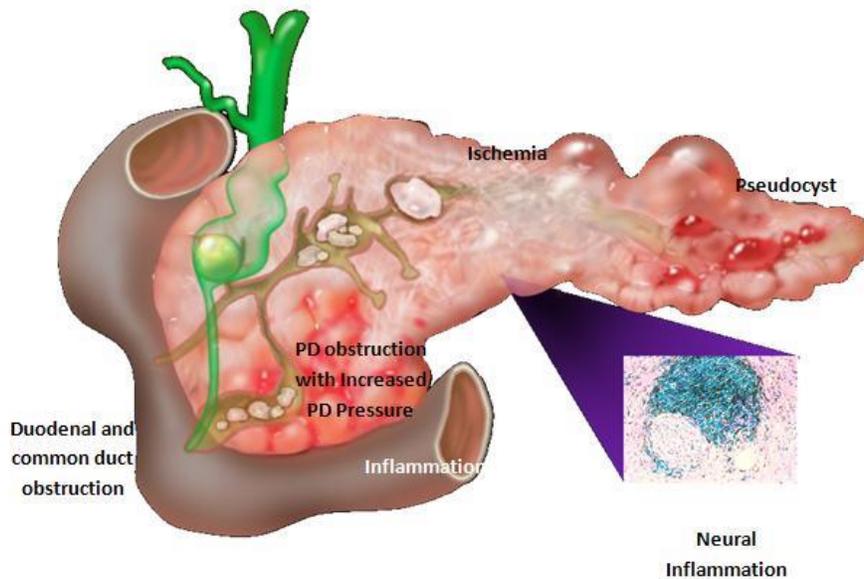
### 3. What are the symptoms of chronic pancreatitis?

Symptoms of chronic pancreatitis include abdominal pain, nausea, vomiting, weight loss, diarrhea, and diabetes. Abdominal pain is the most common presenting symptom. The abdominal pain is typically epigastric and radiates to the back. Pain may come and go or occur at all times, but is worse after eating. **Figure 5** shows the various potential causes of abdominal pain in chronic pancreatitis. However, there are other possible causes of abdominal pain other than chronic pancreatitis. These are shown in **(Figure 6)**. Children with chronic pancreatitis may have abdominal pain that comes and goes. They will also have vomiting.

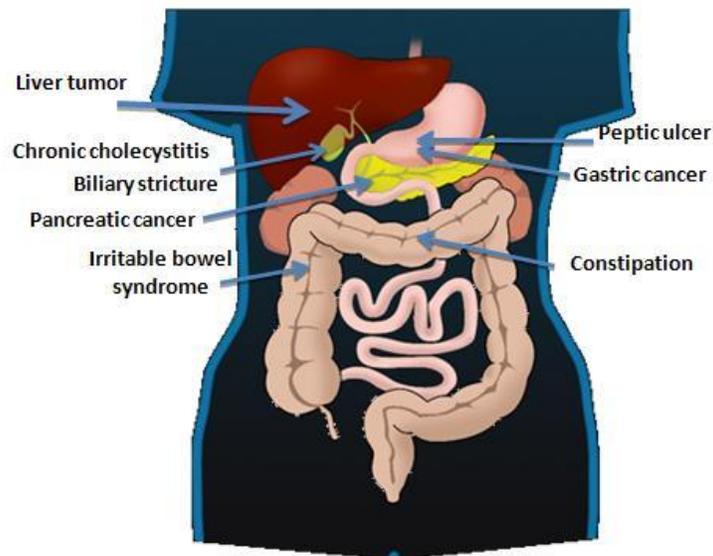
Due to the lack of pancreatic enzymes that are being released by the pancreas, patients may have fatty stool that is oily appearing and foul smelling. This is known as exocrine pancreatic insufficiency and is mainly due to a shortage of pancreatic lipase which is necessary for fat digestion. Patients may also develop diabetes that is due to the loss of pancreatic tissue and cells that produce insulin, also known as islets of Langerhans. This is known as endocrine insufficiency. Patients with alcohol induced chronic pancreatitis develop exocrine insufficiency approximately 4.8-5.5 years after the onset of chronic pancreatitis (1). Patients with hereditary chronic pancreatitis will develop exocrine insufficiency at a younger age (18). Patients with chronic pancreatitis have a 4% risk of developing pancreatic cancer over 20 years (10). However the risk of pancreatic cancer is also dependent on the cause of chronic pancreatitis. For example, smokers with chronic pancreatitis will develop pancreatic cancer earlier than nonsmokers (12, 17).

### 4. How is chronic pancreatitis diagnosed?

Chronic pancreatitis is diagnosed by a combination of symptoms and imaging tests, including CT or "CAT" scans and MRIs. CT scans can show calcifications and dilated ducts that occur with chronic pancreatitis. However CT scan is a poor test for diagnosing mild chronic pancreatitis. MRI can show abnormalities in the duct, but is not a good test for finding calcifications. Another test that may be done is an endoscopic ultrasound (EUS). This is an endoscopic procedure which uses ultrasound to examine the pancreas at close range. An endoscope is a thin, flexible tube that is passed into the mouth and esophagus, down to the stomach and the small bowel. The pancreas is right next to the stomach and small intestine so that the examination can be much more accurate. EUS looks at the pancreas, the pancreatic duct, and the common bile duct. It can find subtle changes within the pancreas.



**Figure 5. Causes of Pain in chronic pancreatitis.** This figure shows the various factors that may contribute to the pain of chronic pancreatitis. Obstruction of the pancreatic duct by strictures or stones may cause increased pressures within the duct. Ischemia of the pancreas occurs as a result of chronic inflammation, which can cause pain. Obstruction of the duodenum or common bile duct may worsen acute episodes. Inflammation of the nerves also causes pain. Various treatment modalities are targeted to these different factors. Adapted from Gorelick F, Pandol SJ, Topazian M. *Pancreatic physiology, pathophysiology, acute and chronic pancreatitis*. Gastrointestinal Teaching Project, American Gastroenterological Association. 2003.



**Figure 6. Other causes of abdominal pain that may be confused with chronic pancreatitis.** The most common diseases that can cause similar pain as that of chronic pancreatitis includes chronic cholecystitis, biliary strictures, pancreatic cancer, irritable bowel syndrome, peptic ulcer disease, gastric cancer, and constipation, which worsens with certain pain medications. Adapted from Gorelick F, Pandol SJ, Topazian M. *Pancreatic physiology, pathophysiology, acute and chronic pancreatitis*. Gastrointestinal Teaching Project, American Gastroenterological Association. 2003.

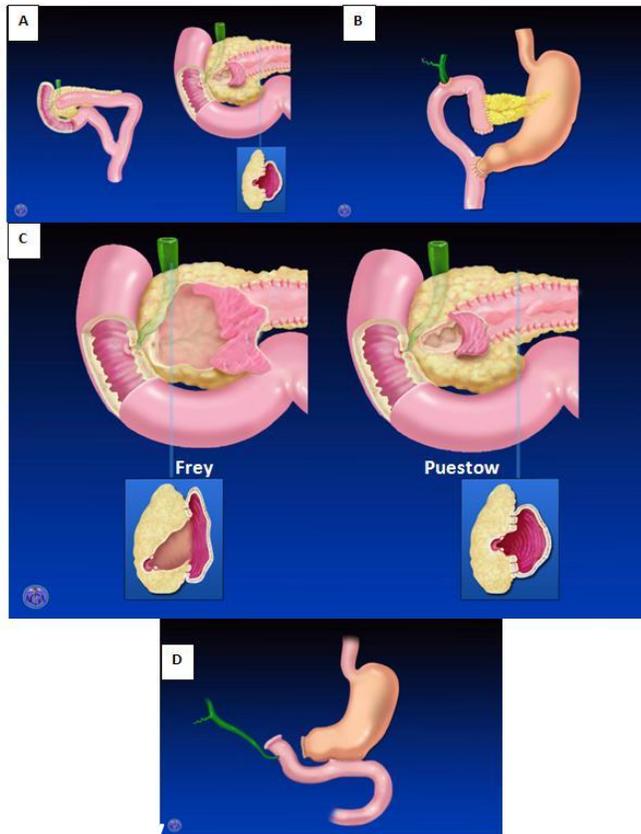
However, certain features or subtle changes may occur as a result of normal aging rather than chronic pancreatitis. Therefore, a scoring system evaluating a number of abnormalities is more useful for diagnosing chronic pancreatitis in order to separate those with aging pancreas from those with chronic pancreatitis. Another procedure which may help in visualizing the pancreatic duct is an endoscopic retrograde cholangiography, or ERCP. This also involves an endoscope that is passed into the mouth and into the small bowel. It is a side viewing scope which will allow access into the bile duct and pancreatic duct. ERCP may also be used to remove stones in the pancreatic duct and treatment for strictures of the duct. ERCP is typically reserved for therapeutic purposes. Both the EUS and ERCP are excellent for diagnosing severe disease; however these tests are invasive procedures and may lead to complications. The risk of EUS alone is the same as a standard upper endoscopy whereas the risk of ERCP has higher risk of post-ERCP pancreatitis.

Another way of to help make the diagnosis of the chronic pancreatitis is to check the pancreatic function. As indicated early, disease progression is accompanied by loss of function of the pancreas. There are two types of methods for doing this; 1) indirect methods involving collections of blood or stool, and 2) a direct methods which are more invasive. These tests are often used to determine exocrine pancreatic insufficiency. Direct pancreatic function test consists of giving an intravenous dose of hormones known to stimulate secretion of digestive enzymes and fluid from the pancreas. With administration of hormones secretions from the pancreas are collected in the small bowel with an endoscope. The collected fluid is analyzed to determine pancreatic digestive enzymes and bicarbonate which is secreted by duct cells. This test usually takes 60 minutes to perform and is not performed at every hospital. Indirect tests are simpler but less accurate. The most common is to measure fecal elastase, an

enzyme which is resistant to digestion and normally appears in the stool.

## **5. What is the treatment of chronic pancreatitis?**

Chronic pancreatitis is difficult to treat. Treatment is typically geared at symptoms and the cause of symptoms. The first step is the management of pain. Alcohol and smoking cessation will help prevent further damage to the pancreas. Pain medications are also often used to treat the pain. Non-narcotic medications are better in the long term as they do not have the complications of narcotic medications. However, narcotic medications are used for more severe pain. Narcotic medication side effects will worsen the pain of chronic pancreatitis over time. These side effects include constipation, dependency, and depression. One type of medication that has been shown to have good response in patients with chronic pancreatitis is pregabalin. Pancreatic enzymes are also effective in the treatment of chronic pancreatitis. These are also used in patients with pancreatic exocrine insufficiency but have also been successful in some without exocrine insufficiency to reduce the pain associated with chronic pancreatitis. Pancreatic enzymes help with the digestion of proteins, fat, and carbohydrates, which is otherwise affected in chronic pancreatitis. The inability to digest proteins, fats and carbohydrates leads to what is called maldigestion and weight loss. Pancreatic enzymes should be taken with meals instead of before or after. The success of the enzymes is measured by improvement of symptoms, and increase in weight. Side effects of pancreatic enzymes are rare but can include abdominal bloating, gas, hyperglycemia (14), and fibrosing colonopathy, which was primarily seen in children with cystic fibrosis receiving high dose pancreatic enzymes (4).



**Figure 7: Surgical therapy for chronic pancreatitis.** A. Puestow or lateral pancreaticojejunostomy. The pancreatic duct is filleted open and a loop of bowel is attached to allow for drainage of the pancreas. B. Whipple or pancreaticojejunostomy. The head of the pancreas and part of the small bowel is removed. This can be used to treat pancreatic tumors and chronic pancreatitis that is located only in the head of the pancreas. C. Frey procedure combines Puestow with removal of part of the pancreatic head. This is shown in comparison to the Puestow. D. Total pancreatectomy removes the entire pancreas, along with a part of the small bowel and spleen. Adapted from Gorelick F, Pandol SJ, Topazian M. *Pancreatic physiology, pathophysiology, acute and chronic pancreatitis*. Gastrointestinal Teaching Project, American Gastroenterological Association. 2003.

Endoscopic therapy is another treatment. This is geared towards treating strictures or duct obstruction which may cause pain. This therapy involves dilating and/or stenting a stricture in the pancreatic or biliary duct. Endoscopic therapy can also remove stones that may be causing obstruction. However, repeated endoscopic therapy is often required in most patients. Nerve blocks are also performed to manage the pain associated with chronic pancreatitis. This is either done endoscopically (through the stomach) or percutaneously (through the skin). However only 55% of patients will have pain relief after the procedure (5) and the pain relief is short-lived, and may require repeat procedures.

Surgical therapy includes surgically relieving duct obstruction or removing parts of the diseased pancreas. Surgical therapies are usually considered after medical and endoscopic therapies have failed. One procedure, known as the modified Puestow or lateral pancreaticojejunostomy, opens the pancreas at the pancreatic duct and attaches a loop of bowel to the open pancreatic duct (**Figure 7a**). Another procedure is known as the pancreaticoduodenostomy or Whipple procedure, which completely removes the head of the pancreas along with a portion of the small bowel (**Figure 7b**). A Frey procedure is a combination of the Puestow along with partial removal of the pancreatic head (**Figure 7c**). Another option may

be a distal pancreatectomy which will also involve removal of the spleen. This may be suitable for patients with disease in the tail of the pancreas. The last surgical option is total pancreatectomy. Often total pancreatectomy is done with saving the islets of Langerhans. This is called total pancreatectomy with autoislet transplantation (**Figure 7d**). This involves removing the entire pancreas in addition to the spleen and part of the small bowel and connecting the stomach directly to

the small bowel. The islets are removed from the pancreas and given back to the patient by placing them in the liver where they live and function normally. The goal of autoislet transplantation is to prevent the diabetes that would result by removing the entire pancreas. The combination of total pancreatectomy and autoislet transplantation is only performed in specialized centers, and usually for intractable pain.

## 6. References

1. **Ammann RW.** The natural history of alcoholic chronic pancreatitis. *Intern Med* 40(5): 368-375, 2001. [PMID: 11393404](#)
2. **Andruilli A, Botteri E, Almasio PL, Vantini I, Uomo G, Maisonneuve P, ad hoc Committee of the Italian Association for the Study of the Pancreas.** Smoking as a cofactor for causation of chronic pancreatitis: a meta analysis. *Pancreas* 39: 1205-1210, 2010. [PMID: 20622705](#)
3. **Bertin C, Pelletier AL, Vullierme MP, Bienvenu T, Rebours V, Hentic P, Maire F, Hammel P, Vilgrain V, Ruzsneiowski P, Levy P.** Pancreas divisum is not a cause of pancreatitis by itself but acts as a partner of genetic mutations. *Am J Gastroenterol* 107: 311-317, 2012. [PMID: 22158025](#)
4. **Fitzsimons SC, Burkhart GA, Borowitz D, et al.** High-dose pancreatic enzyme supplementation and fibrosing colonopathy in children with cystic fibrosis. *N Engl J Med* 336: 1283-89, 1997. [PMID: 9113931](#)
5. **Gress F, Schmitt C, Sherman S, Ciaccia D, Ikenberry S, Lehman G.** Endoscopic ultrasound guided celiac plexus for managing abdominal pain associated with chronic pancreatitis: a prospective single center experience. *Am J Gastroenterol* 96: 409-16, 2001. [PMID: 11232683](#)
6. **Hirota M, Shimosegawa T, Masamune A, Kikuta K, Hamada S, Kihara Y, Satoh A, Kimura K, Tsuji I, Kuriyama S, Research Committee of Intractable Pancreatic Diseases.** The sixth nationwide epidemiological survey of chronic pancreatitis in Japan. *Pancreatol* 12:79–84, 2012. [PMID: 22487515](#)
7. Global Status Report on Alcohol and Health 2011. Available at: [http://www.who.int/substance\\_abuse/publications/global\\_alcohol\\_report/en/index.html](http://www.who.int/substance_abuse/publications/global_alcohol_report/en/index.html). Accessed on December 17, 2014
8. **Kristiansen L, Gronbaek M, Becker U, Tolstrup JS.** Risk of pancreatitis according to alcohol drinking habits: a population-based cohort study. *Am J Epidemiol* 168:932–937, 2008. [PMID: 18779386](#)
9. **Layer P, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMagno EP.** The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology* 107:1481-7, 1994. [PMID: 7926511](#)
10. **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 Eng J Med* 328: 1433-1437, 1993, [PMID: 8479461](#)
11. **Lowenfels AB, Maisonneuve P, DiMagno EP, Elitsur Y, Gates LK Jr, Perrault J, Whitcomb DC.** Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. *J Natl Cancer Inst* 89:442-6, 1997. [PMID: 9091646](#)
12. **Lowenfels AB, Maisonneuve P, Whitcomb DC, Lerch MM, DiMagno EP.** Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. *JAMA* 286: 169-170, 2001 [PMID: 11448279](#)
13. **Mullhaupt B, Truninger K, Ammann R.** Impact of etiology on the painful early stage of chronic pancreatitis: a long-term prospective study. *Z Gastroenterol* 43:1293-301, 2005. [PMID: 16315124](#)
14. **O'Keefe SJ, Cariem AK, Levy M.** The exacerbation of pancreatic endocrine dysfunction by potent pancreatic exocrine supplements in patients with chronic pancreatitis. *J Clin Gastroenterol* 32:319-23, 2001. [PMID: 11276275](#)
15. **O'Sullivan BP, Freedman SD.** Cystic fibrosis. *Lancet* 373:1891–1904, 2009. [PMID: 19403164](#)
16. **Peery A.F, Dellon E.S, Lund J, Crockett S.D, McGowan C.E, Bulsiewicz W.J, Gangarosa L.M, Thiny M.T, Stizenberg K, Morgan D.R, Ringel Y, Kim H.P, Dibonaventura M.D, Carroll C.F, Allen J.K, Cook S.F, Sandler R.S, Kappelman M.D, Shaheen N.J.** Burden of gastrointestinal disease in the United States: a 2012 update. *Gastroenterology* 143: 1179-878, 2012. [PMID: 22885331](#)

17. **Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezilli R.** Pancreatic cancer in chronic pancreatitis: aetiology, incidence, and early detection. *Best Pract Res Clin Gastroenterol* 24: 349-358, 2010. [PMID: 20510834](#)
18. **Rebours V, Boutron-Ruault MC, Schnee M, Ferec C, Le Marechal C, Hentic O, Maire F, Hammel P, Ruzsneiowski P, Levy P.** The natural history of hereditary pancreatitis: a national series. *Gut* 58(1): 97-103, 2009. [PMID: 18755888](#)
19. **Talamini G, Bassi C, Falconi M, Sartori N, Vaona B, Bovo P, Benini L, Cavallini G, Pederzoli P, Vantini I.** Smoking cessation at clinical onset of chronic pancreatitis and risk of pancreatic calcifications. *Pancreas* 35: 320-326, 2007. [PMID: 18090237](#)
20. **Whitcomb DC.** Genetic aspects of pancreatitis. *Ann Rev Med* 61: 413-424, 2010. [PMID: 20059346](#)
21. **Yadav D, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA, Bishop MD, Baillie J, Sherman S, DiSario J, Burton FR, Gardner TB, Amann ST, Gelrud A, Lawrence C, Elinoff B, Greer JB, O'Connell M, Barmada MM, Slivka A, Whitcomb DC, North American Pancreatic Study Group.** Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Arch Intern Med* 169:1035–1045, 2009. [PMID: 19506173](#)
22. **Yadav D, Timmons L, Benson JT, Dierkhising RA, Chari ST.** Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. *Am J Gastroenterol* 106:2192–2199, 2011. [PMID: 21946280](#)
23. **Yang AL, Vadavkar S, Singh G, Omary MB.** Epidemiology of alcohol-related liver and pancreatic disease in the United States. *Arch Intern Med* 168:649–656, 2008. [PMID: 18362258](#)