Chronic Pancreatitis

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Plan of lecture

- **Chronic** Pancreatitis : etiology and pathogenesis;
- **Chronic** Pancreatitis: diagnosis;
- **Chronic** Pancreatitis : treatment.

Basis of this lecture – [A]- Medscape: Author **Jason L Huffman, MD** Gastrointestinal Associates PC; Jason L Huffman, MD is a member of the following medical societies: American Association for the Study of Liver Diseases, American College of Gastroenterology, American Gastroenterological Association, American Medical Association, American Society for Gastrointestinal Endoscopy, Texas Medical Association Coauthor(s)

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History [A]

For most patients with chronic pancreatitis, abdominal pain is the presenting symptom. Either the patient's age or the etiology of the disease has some influence on the frequency of this presentation. Ninety-six percent of those with early onset idiopathic pancreatitis present with abdominal pain, compared with 77% with alcohol-induced disease and 54% with late-onset idiopathic chronic pancreatitis.

Clinically, the patient experiences intermittent attacks of severe pain, often in the midabdomen or left upper abdomen and occasionally radiating in a bandlike fashion or localized to the midback. The pain may occur either after meals or independently of meals, but it is not fleeting or transient and tends to last at least several hours. Unfortunately, patients often are symptomatic for years before the diagnosis is established; the average time from the onset of symptoms until a diagnosis of chronic pancreatitis is 62 months. The delay in diagnosis is even longer in people without alcoholism, in whom the average time is 81 months from the onset of symptoms to diagnosis.

The natural history of pain in chronic pancreatitis is highly variable. Most patients experience intermittent attacks of pain at unpredictable intervals, while a minority of patients experience chronic pain. In most patients, pain severity either decreases or resolves over 5-25 years. Nevertheless, ignoring pain relief with the expectation that the disease eventually will resolve itself is inappropriate. In alcohol-induced disease, eventual cessation of alcohol intake may reduce the severity of pain. Variability in the pain pattern contributes to the delay in the diagnosis and makes determining the effect of any therapeutic intervention difficult.

Other symptoms associated with chronic pancreatitis include diarrhea and weight loss. This may be due either to fear of eating (eg, postprandial exacerbation of pain) or due to pancreatic exocrine insufficiency and steatorrhea.

Physical Examination [A]

In most instances, the standard physical examination does not help to establish a diagnosis of chronic pancreatitis; however, a few points are noteworthy.During an attack, patients may assume a characteristic position in an attempt to relieve their abdominal pain (eg, lying on the left side, flexing the spine and drawing the knees up toward the chest).

Occasionally, a tender fullness or mass may be palpated in the epigastrium, suggesting the presence of a pseudocyst or an inflammatory mass in the abdomen. Patients with advanced disease (ie, patients with steatorrhea) exhibit decreased subcutaneous fat, temporal wasting, sunken supraclavicular fossa, and other physical signs of malnutrition.

Diagnostic Considerations [A]

Some patients with cystic neoplasms have undergone cyst-enteric anastomoses, only to develop malignancy later. Consider a cystic neoplasm in any patient without a clinical history of pancreatitis, even if no septa, solid component, or rim calcification is present on the imaging study. Although aspiration of the cyst fluid and measurement of its viscosity, carcinoembryonic antigen (CEA), cancer antigen (CA) 19-9, and other factors are helpful in differentiating the various types of cysts, surgical resection of the cyst is the standard of care in a good surgical candidate.

Groove pancreatitis is a unique form of segmental pancreatitis in which the inflammatory process is confined to the groove between the duodenum and the common bile duct, without necessarily involving the entire head of the pancreas. [10]

Differential Diagnoses [A]

Ampullary Carcinoma
Cholangitis
Cholecystitis
Chronic Gastritis
Community-Acquired Pneumonia (CAP)
Crohn Disease
Intestinal Perforation
Mesenteric Artery Ischemia
Myocardial Infarction
Pancreatic Cancer
Peptic Ulcer Disease

Approach Considerations [A]

Blood tests

Serum amylase and lipase levels may be slightly elevated in chronic pancreatitis; high levels are found only during acute attacks of pancreatitis. In the later stages of chronic pancreatitis, atrophy of the pancreatic parenchyma can result in normal serum enzyme levels because of significant fibrosis of the pancreas, resulting in decreased concentrations of these enzymes within the pancreas.

Although low concentrations of serum trypsin are relatively specific for advanced chronic pancreatitis, they are not sensitive enough to be helpful in most patients with mild to moderate disease. Laboratory studies to identify the causative factors of chronic pancreatitis include serum calcium and triglyceride levels. When common etiologies are not found, research protocols are available to test for genetic mutations in cationic trypsinogen and *CFTR.*

Fecal tests

Because maldigestion and malabsorption do not occur until more than 90% of the pancreas has been destroyed, steatorrhea is a manifestation of advanced chronic pancreatitis. Neither qualitative nor quantitative fecal fat analysis can detect early disease. Assays of fecal chymotrypsin and human pancreatic elastase 1 have the same limitations but are useful in confirming advanced chronic pancreatitis with exocrine insufficiency.

The clinical practice guidelines for the diagnostic cross-sectional imaging and severity scoring of chronic pancreatitis were released in October 2018 by the Working Group for the International Consensus Guidelines for Chronic Pancreatitis. [12] Computed tomography (CT) is often the most appropriate initial imaging modality to evaluate suspected chronic pancreatitis (CP); it depicts most of the changes in pancreatic morphology.

CT is also indicated to exclude other potential intra-abdominal pathologies that present with symptoms similar to those of chronic pancreatitis, but CT cannot exclude a diagnosis of CP and cannot exclusively diagnose early or mild CP. Magnetic resonance imaging (MRI) and MR cholangiopancreatography (MRCP) are superior and are indicated especially in patients in whom no specific pathologic changes are seen on CT.

Secretin-stimulated MRCP is more accurate than standard MRCP to identify subtle ductal changes. Secretin-stimulated MRCP should be performed after a negative MRCP if there is still clinical suspicion of CP. Secretin-stimulated MRCP can provide assessment of exocrine function and ductal compliance.

Endoscopic ultrasound (EUS) can also be used to diagnose parenchymal and ductal changes mainly during the early stage of CP. There are no known validated radiologic severity scoring systems for CP, but a modified Cambridge Classification has been used for MRCP. A new and validated radiologic CP severity scoring system is needed that is based on imaging criteria (CT and/or MRI), including glandular volume loss, ductal changes, parenchymal calcifications, and parenchymal fibrosis.

Pancreatic Function Tests [A]

Direct tests

These tests are the most sensitive and can be used to detect chronic pancreatitis at its earliest stage; however, they are somewhat invasive, labor intensive, and expensive.

Determination in duodenal aspirates

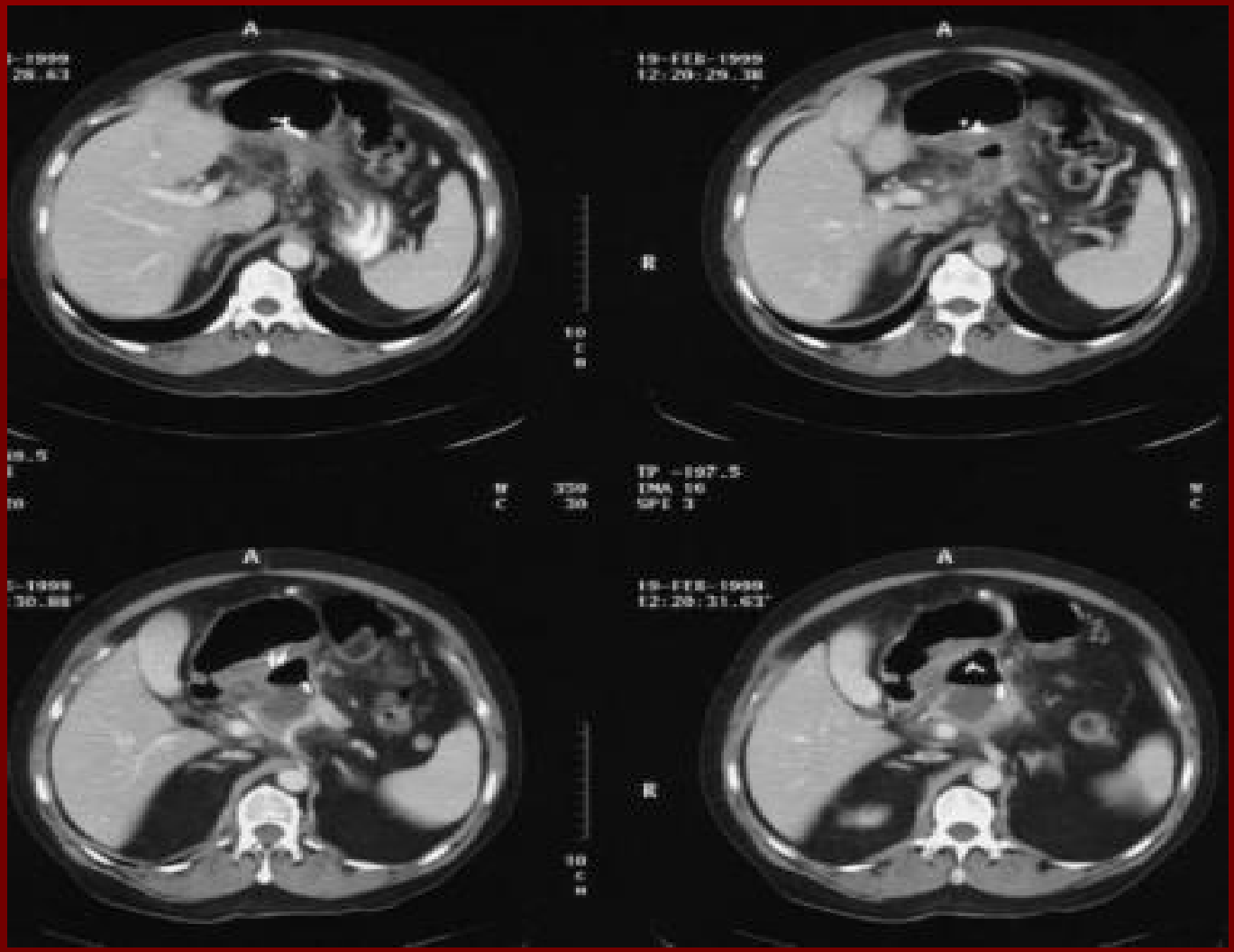
Intubation of the duodenum usually is performed with a Dreiling tube, which allows for separate aspiration of the gastric and duodenal contents. The methodology varies depending on the specific laboratory; however, exogenous secretin with cholecystokinin (CCK) is used to achieve maximal stimulation of the pancreas. The output of pancreatic bicarbonate, protease, amylase, and lipase then is measured in the duodenal aspirates.

This test currently is available only in specialized centers. While the greatest sensitivity can be obtained in prolonged infusions of a secretagogue to uncover a decreased pancreatic secretory reserve, it is impractical for general clinical use.

- *Determination in pancreatic juice*
- This test generally is performed in conjunction with ERCP. The pancreatic duct is freely cannulated, an exogenous secretagogue is administered as above, and the pancreatic juice then is aspirated out of the duct as it is produced. The output of pancreatic bicarbonate, protease, amylase, and lipase are measured.
- **Indirect tests**
- Noninvasive tests of pancreatic function have been developed for detecting chronic pancreatitis. In principle, these tests work via oral administration of a complex substance that is hydrolyzed by a specific pancreatic enzyme to release a marker substance. The intestine absorbs the marker, which then is measured in the serum or urine. These tests are capable of detecting moderate to severe chronic pancreatitis. The presence of renal, intestinal, and liver disease may interfere with the accuracy of these tests. Neither currently is freely available in the United States.

- **Radiography and CT Scanning**
- Hallmarks of chronic pancreatitis that can be detected on advanced imaging studies include calcifications, pancreatic duct dilatation, chronic pseudocysts, focal pancreatic enlargement, and biliary ductal dilatation. [13]
- **Abdominal radiography**
- Pancreatic calcifications, often considered pathognomonic of chronic pancreatitis, are observed in approximately 30% of cases. Paired anteroposterior (AP) and oblique views are preferred because the vertebral column otherwise could obscure small flecks of calcium. The calcifications form within the ductal system—initially in the head, and later in the body and tail, of the gland. Calcium deposition is most common with alcoholic pancreatitis, hereditary pancreatitis, and tropical pancreatitis; however, it is rare in idiopathic pancreatitis.

- **CT scanning**
- The advantage of CT scanning is that interpretation of pancreatic CT images is relatively intuitive. However, although CT scanning excels at depicting the morphologic changes of advanced chronic pancreatitis described above, the subtle abnormalities of early to moderate chronic pancreatitis are beyond its resolution, and a normal finding on this study does not rule out chronic pancreatitis.
- CT scan studies are indicated to look for complications of the disease and are useful in planning surgical or endoscopic intervention. The sensitivity and specificity of CT scanning are 80% and 85%, respectively. (See the images below.)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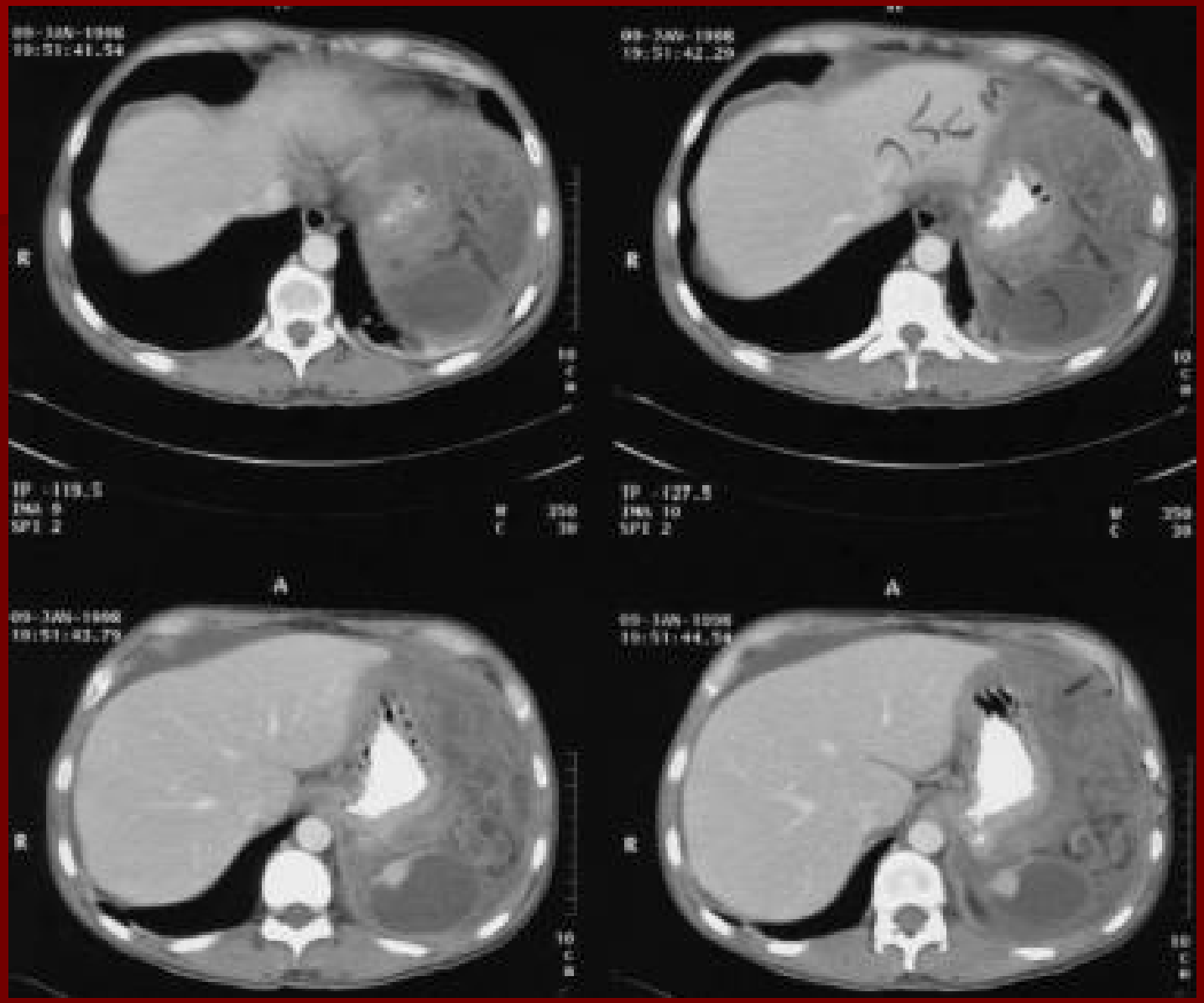
Chronic pancreatitis. CT scans of the abdomen following an endoscopic transgastric pseudocystogastrostomy. Note that 2 stents are placed through the stomach and into the pseudocyst. Before undertaking this type of endoscopic intervention, the endoscopist must be confident that a cystadenoma has not been mistaken for a pseudocyst.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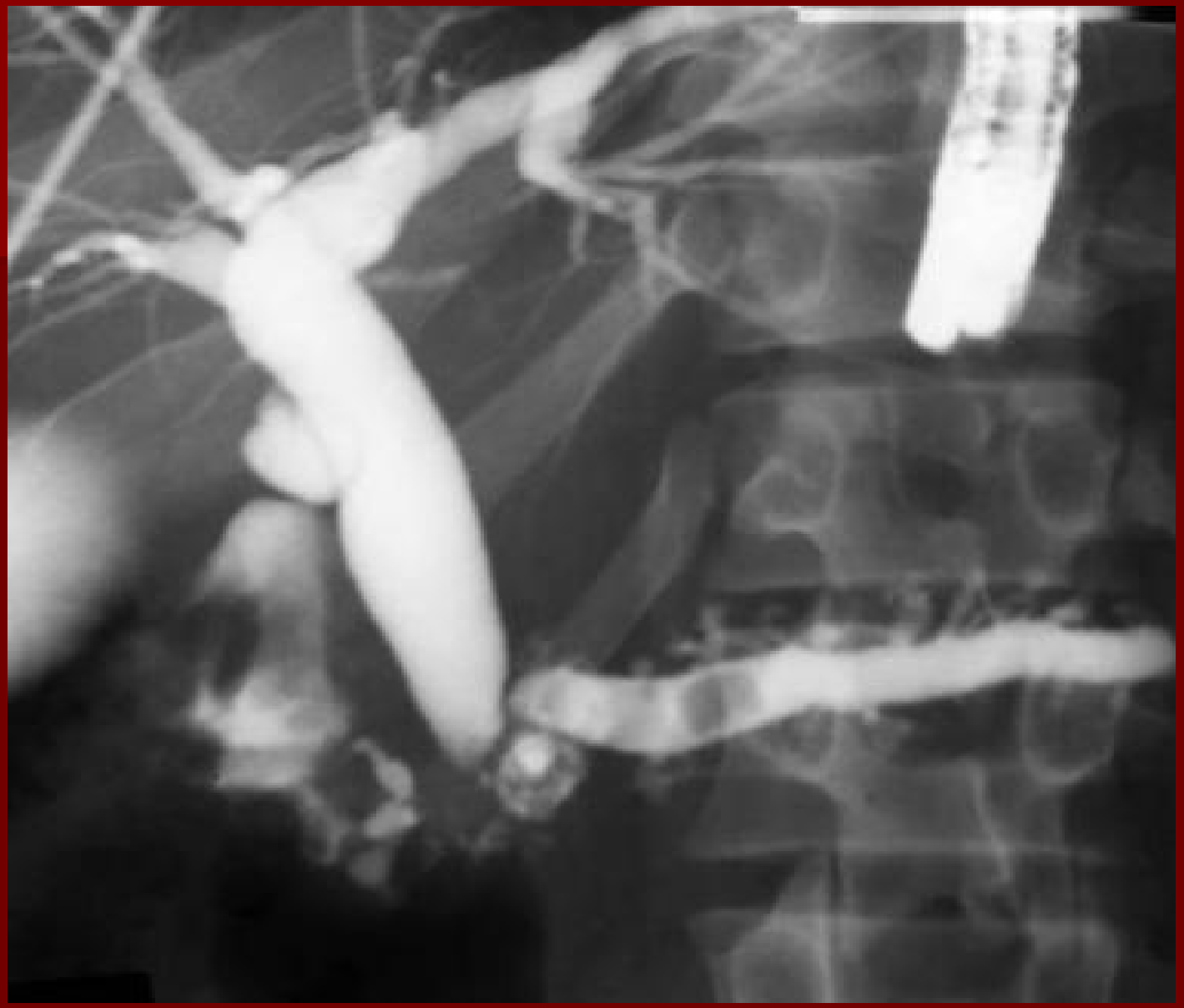
- Chronic pancreatitis. This patient developed abdominal pain several weeks after being accidentally hit with a baseball bat. A CT scan showed a large splenic hematoma, and the patient underwent a splenectomy. His postoperative course was notable for recurrent pain, abdominal distension, and elevation of serum amylase levels over the course of 2-3 months. This repeat CT scan shows postsurgical changes in the left upper quadrant and a large fluid collection.
- **Endoscopic Retrograde Cholangiopancreatography**
- ERCP, demonstrated in the image below, provides the most accurate visualization of the pancreatic ductal system and has been regarded as the criterion standard for diagnosing chronic pancreatitis. One limitation of ERCP, however, is that it cannot be used to evaluate the pancreatic parenchyma, and histologically proven chronic pancreatitis has been documented in the setting of normal findings on pancreatogram.

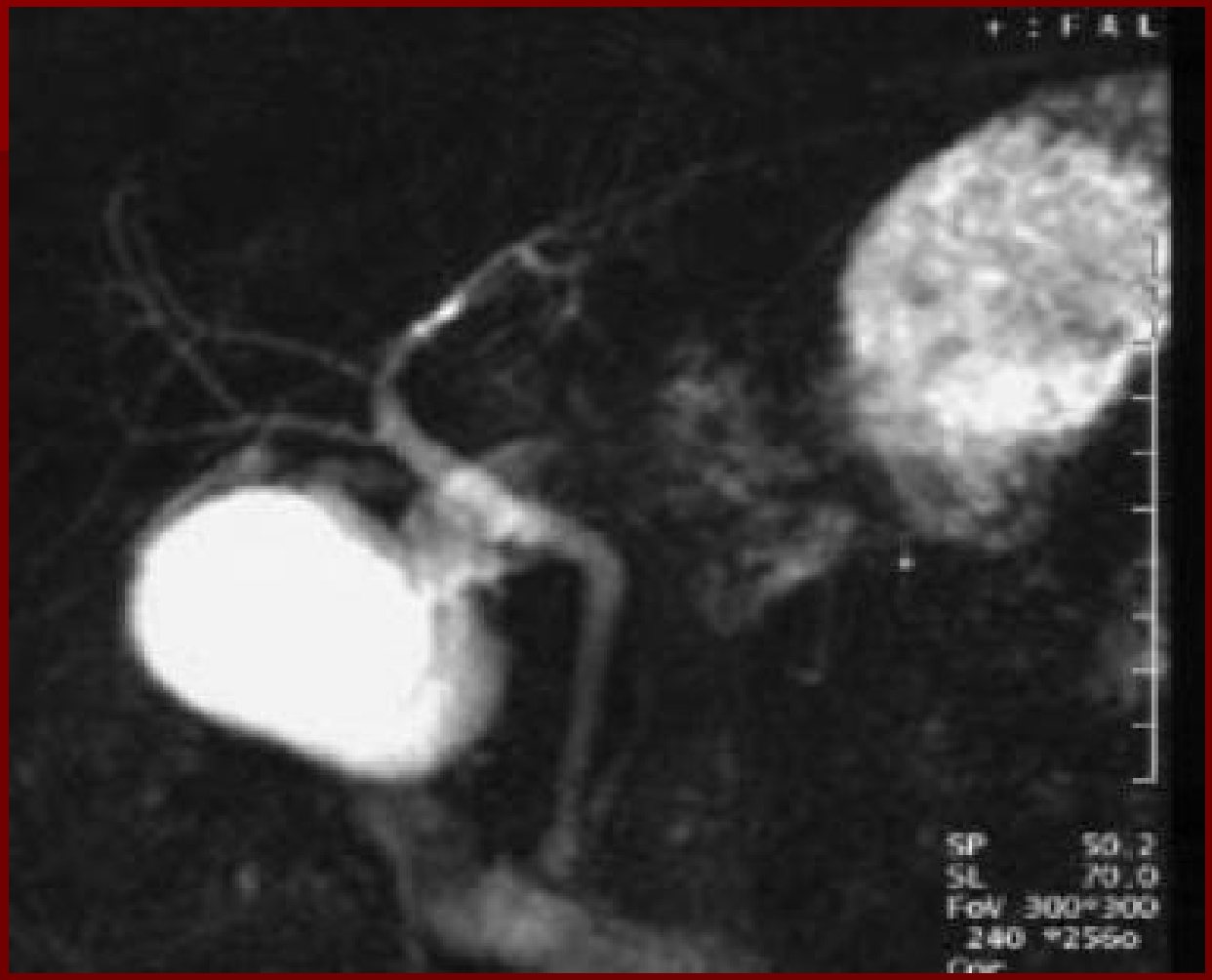


This endoscopic retrograde cholangiopancreatography (ERCP) shows advanced chronic pancreatitis. The pancreatogram has blunting of the lateral branches, dilation of the main pancreatic duct, and filling defects consistent with pancreatolithiasis. The cholangiogram also shows a stenosis of the distal bile duct and a dilated biliary tree.

Pancreatograms can be interpreted and classified according to several schemes, such as the Cambridge criteria. A comparison of ERCP scoring with direct pancreatic function tests demonstrated good correlation. However, pancreatography tended to show significantly more severe changes.

The problems with ERCP are that it is invasive and expensive, requires complete opacification of the pancreatic duct to visualize side branches, and carries a risk (operator-dependent) of pancreatitis.

- **Magnetic Resonance Cholangiopancreatography**
- MRCP, demonstrated in the image below, provides information on the pancreatic parenchyma and adjacent abdominal viscera, and MRCP uses heavily T2-weighted images to visualize the biliary and pancreatic ductal system. The use of secretin during the study enhances the quality of the pancreatogram. Accuracy is improving, and MRCP is relatively safe, reasonably accurate, noninvasive, fast, and very useful in planning surgical or endoscopic intervention.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Chronic pancreatitis. This magnetic resonance cholangiopancreatography (MRCP) shows a healthy biliary system. The pancreatic ductal system is not well visualized. A subsequent endoscopic retrograde cholangiopancreatography (ERCP [not pictured]) showed pancreas divisum, with no evidence of a communication with the pseudocyst. The endoscopic features were ideal for an endoscopic transgastric pseudocystogastrostomy.

Endoscopic Ultrasonography [A]

Although studies suggest that endoscopic ultrasonography (EUS) may be the best test for imaging the pancreas, it requires a highly skilled gastroenterologist. [14] Eleven sonographic criteria have been developed that identify characteristic findings of chronic pancreatitis. The most predictive endosonographic feature is the presence of stones. Other suggestive features include the following:

- Visible side branches
- Cysts
- Lobularity
- An irregular main pancreatic duct
- Hyperechoic foci and strands
- Dilation of the main pancreatic duct
- Hyperechoic margins of the main pancreatic duct

Before 2001, three or more of these criteria on EUS were used to diagnose chronic pancreatitis. However, subsequent data has suggested the use of five or more criteria to have higher specificity, rather than sensitivity, to diagnose chronic pancreatitis. In general, the presence of five or more of these features is considered highly suggestive of chronic pancreatitis.

EUS may be as sensitive and specific as tube tests for mild and advanced disease, especially when combined with fine needle aspiration or Tru-Cut biopsy.

Histologic Findings [A]

In the early stages of chronic pancreatitis, the parenchyma exhibits an increase in connective tissue around the ducts and between the lobules. The degree of inflammation is minimal to moderate, consisting mostly of T lymphocytes, and a patchy, focal process unevenly affects the pancreas. With increasing severity, the connective tissue progresses between the acini, which gradually become distorted and tend to disappear. In advanced disease, fibrous tissue replaces the acinar tissue, and the pancreas becomes contracted, small, and hard. The islets of Langerhans are relatively spared until very late in the disease process.

Patients can have severe histopathologic changes of chronic pancreatitis despite normal findings on imaging studies. In patients undergoing resection of the pancreas for chronic pancreatitis, focal necrosis is found in 11.9% of cases and segmental fibrosis is observed in approximately 40% of cases.

In chronic calcific pancreatitis, plugs of precipitated protein develop within the ductal system. While they may be observed in all types of chronic pancreatitis, in alcoholic and tropical forms these plugs tend to evolve into calculi by deposition of calcium within them. The calcified pancreatic calculi are distributed irregularly, affecting ducts of various sizes, and may be associated with ulcerations of the ductal epithelium. Periductal connective tissue may encroach into the lumen and cause ductal stenoses, creating the "chain of lakes" pancreatogram appearance observed in advanced chronic calcific pancreatitis.

- **Approach Considerations** [A]

The goals of medical treatment are as follows:

Modify behaviors that may exacerbate the natural history of the disease

Enable the pancreas to heal itself

Determine the cause of abdominal pain and alleviate it

Detect pancreatic exocrine insufficiency and restore digestion and absorption to normal

Diagnose and treat endocrine insufficiency

The benefit of antioxidants in the early stages of chronic pancreatitis is still controversial. Most patients can be managed medically. Even in patients with asymptomatic pseudocysts, relatively few develop serious complications (eg, bleeding, infection) requiring urgent surgery, and half will never require surgical intervention.

- **Inpatient care** [A]

The need for hospitalization and further inpatient management of patients with an attack of chronic pancreatitis depends on the severity of the disease.

Patients with mild pancreatitis are kept on nothing by mouth and administered intravenous (IV) fluid hydration. Narcotic analgesics generally are required for pain control. Nutritional supplementation is recommended in patients with malnutrition and in patients who are not able to take oral medication after a long hospitalization.

A small percentage of patients with severe pancreatitis may become critically ill, especially early in the natural history of recurrent acute or chronic pancreatitis. Intensive care management is required, and the clinician must look for developing complications, such as shock, pulmonary failure, renal failure, gastrointestinal bleeding, and multiorgan system failure.

Surgical care [A]

Intervention is indicated when an anatomical complication that is correctable by a mechanical intervention exists. Generally, this is an acquired abnormality, such as one of the following:

Pancreatic pseudocyst

Abscess

Fistula

Ascites

Fixed obstruction of the intrapancreatic portion of the distal common bile duct

Stenosis of the duodenum with gastric outlet obstruction

Variceal hemorrhage due to splenic vein thrombosis

Depending on the individual case, the appropriate intervention may involve endoscopic, radiologic, or surgical techniques.

Radiologic evaluation and drainage [A]

Prior to percutaneous drainage, performing pancreatography is important in order to understand the anatomy of the pancreatic ductal system and plan appropriate treatment. If a communication exists between the pancreatic ductal system and the pseudocyst, percutaneous drainage may create a persistent pancreaticocutaneous fistula, especially if the duct has a stricture downstream from the site of the disruption.

If the anatomy of the pseudocyst does not lend itself to transpapillary, transgastric, or transduodenal endoscopic drainage, then percutaneous drainage under ultrasonographic or CT scan guidance is an option. Transgastric pseudocyst drainage has been used to treat pancreatic pseudocysts successfully, but a high failure rate has been reported.

Consultations

Successful treatment of alcoholism and tobacco addiction requires a team approach, including the involvement and expertise of a chemical dependency counselor and a psychologist trained in cognitive therapy. In patients with uncontrolled abdominal pain, early referral to a pain management specialist may allow better pain control.

Behavior Modification [A]

Cessation of alcohol consumption and tobacco smoking are important. In early stage alcohol-induced chronic pancreatitis, lasting pain relief can occur after abstinence from alcohol, but in advanced stages, abstinence does not always lead to symptomatic improvement. Patients continuing to abuse alcohol develop either marked physical impairment or have a death rate 3 times higher than do patients who abstain.

Recommending abstinence from alcohol usually is not sufficient; the physician must use available resources for evaluation and treatment of alcohol and chemical dependency. Successful treatment requires a team approach, including the involvement and expertise of a chemical dependency counselor and a psychologist trained in cognitive therapy.

Tobacco smoking is a strong and independent risk factor for chronic alcoholic pancreatitis. Because much of the reported excess morbidity and mortality in these patients is related to smoking tobacco, patients also need to overcome their tobacco addiction.

Pharmacologic Alleviation of Abdominal Pain [A]

A number of factors may contribute to the pain in chronic pancreatitis, and the principal mechanisms of pain may change with the course of the disease. Sources of pain can include the following:

Acute disease with inflammation and pseudocyst formation may be superimposed on chronic disease

Obstruction of the pancreatic duct by strictures or stones may cause increased duct pressure and pain

Pancreatic ischemia, with decreased pancreatic oxygenation and a decreased tissue pH, caused by a compartment syndrome may cause pain that is relieved by duct decompression

Pancreatic nerves become enlarged, lose some of their cellular sheath, and are inflamed

Obstruction of the duodenum or biliary tract may worsen with acute episodes and improve with time

Diagnostic tests may be necessary to identify an anatomic explanation for the pain and to plan appropriate treatment. If no anatomic explanation for abdominal pain can be found, medical therapy can be attempted. This therapy includes pain control with analgesic agents and a trial of noncoated pancreatic enzymes.

Exogenous pancreatic enzymes and CCK [A]

The impetus for using exogenous pancreatic enzymes to reduce pain begins with the hypothesis that stimulation of the pancreas by food causes pain. Cholecystokinin (CCK) is one of the possible mediators of this response.

CCK releasing factor (CRF) typically is secreted into the duodenum. During the interdigestive period, proteolytic enzymes within the pancreatic juice rapidly degrade CRF. After a meal, the proteolytic enzymes are occupied with digesting dietary proteins, and enough CRF escapes to bind to duodenocytes, which stimulates CCK release, in turn stimulating pancreatic secretion.

In severe chronic pancreatitis with exocrine insufficiency, CCK levels may be high because proteolytic enzymes are low. When pancreatic enzyme supplements are administered in high doses, degradation of CRF is restored and the stimulus for CCK release is reduced.

This hypothesis is supported by one report that a CCK-receptor antagonist reduces pain in patients with chronic pancreatitis. The digestive products of a meal and the CCK-releasing factor stimulate CCK release from the duodenal mucosa. CCK acts directly on the pancreatic cells and indirectly through neural pathways to stimulate the pancreas. Through unknown mechanisms, such stimulation has been hypothesized to cause pain.

When exogenous pancreatic enzymes are taken with a meal, CCK-releasing factors are degraded and CCK release in response to a meal is reduced, as indicated by the smaller CCK response. This decreases pancreatic stimulation and pain. Any benefit from this treatment is likely limited to nonalcoholic patients with early chronic pancreatitis and requires the use of uncoated preparations.

Clinical trials investigating the benefits of this approach have provided mixed results. While four trials using enteric-coated enzyme preparations demonstrated no effect, these studies may have been flawed if the coating failed to release the enzymes into the feedback-sensitive portion of the duodenum. Two studies using non–enteric-coated tablets have demonstrated a reduction in pain compared with placebo. Female patients and those with idiopathic chronic pancreatitis appear to respond best.

Celiac ganglion blockade [A]

If conventional medical therapy is unsuccessful and the patient has severe, intractable pain, celiac ganglion blockade can be considered. [1]

This approach tries to alleviate pain by modifying afferent sensory nerves in the celiac plexus, using agents that anesthetize, reduce inflammation, or destroy nerve fibers.

In a study in which alcohol injections were administered, 12 of 23 patients obtained complete pain relief, and 6 of 23 patients obtained partial pain relief. However, the mean pain-free interval was only 2 months; the longest pain-free interval was only 4 months. Repeated blocks generally were not effective.

Because of the risks of paralysis resulting from a transverse myelopathy and catastrophic hemorrhage resulting from injury to major abdominal vasculature, the use of alcohol blocks should be restricted to patients with intractable, severe pain due to terminal pancreatic cancer.

Percutaneous or endoscopic celiac nerve blocks with either alcohol or steroids have had only limited success in chronic pancreatitis and should be considered an unproven therapy.

Pharmacologic Restoration of Digestion and Absorption [A]

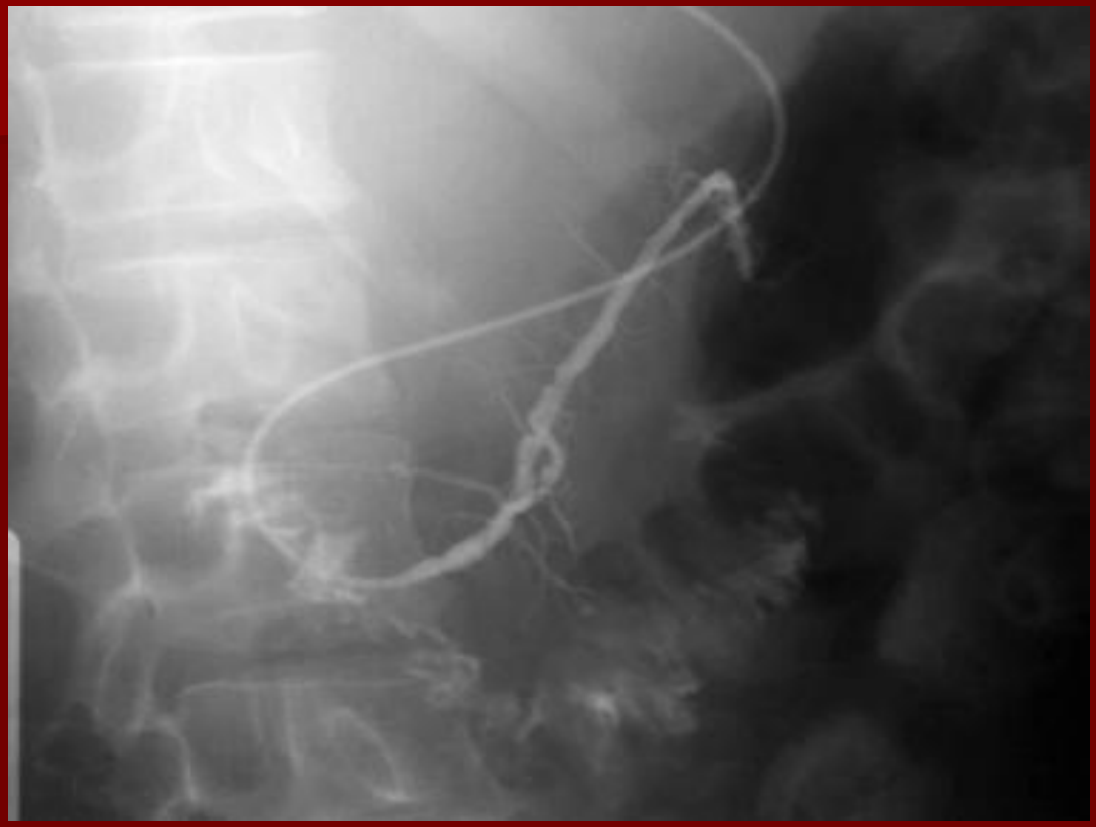
Although reduced fat intake is often recommended in patients with chronic pancreatitis, the clinical benefit is unknown. Indeed, the efficiency of fat absorption in dogs increases with increased fat intake. Whether humans have a similar response is unknown.

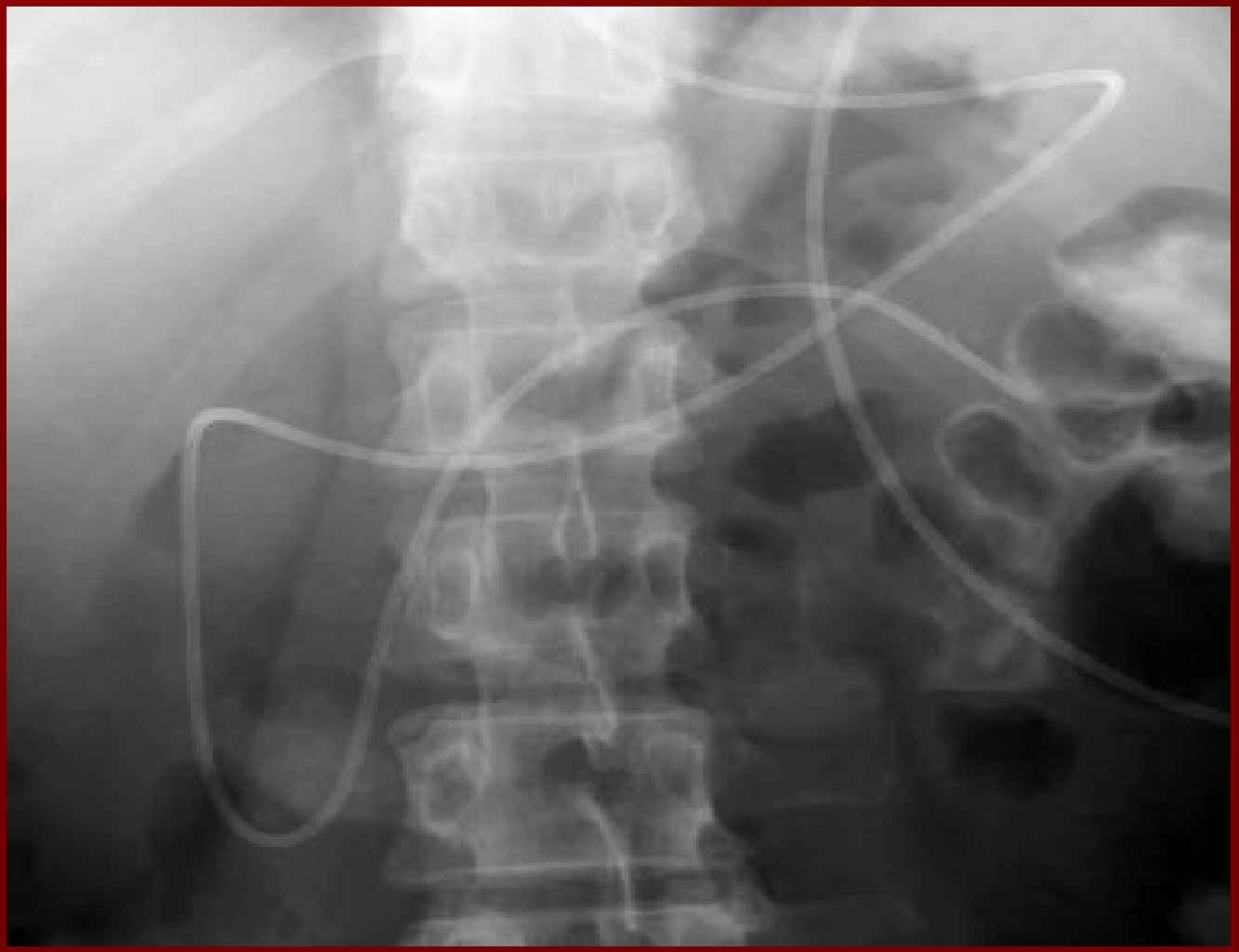
Medium chain triglycerides are directly absorbed by the small intestine without a requirement for digestion by lipase or micellar solubilization. To supply lipids and calories, medium-chain triglycerides can be used in patients with severe fat malabsorption. There is occasionally sufficient loss of fat-soluble vitamins to cause disease.

Enteric-coated preparations protect lipase from inactivation by gastric acid. Uncoated preparations are often less costly and adequate to relieve steatorrhea. Reducing gastric acid secretion may enhance the effectiveness of uncoated preparations. Enzyme preparations with high lipase content are available and recombinant lipase preparations will probably soon be marketed. Some of the recombinant enzymes are resistant to acidic denaturation. To provide adequate mixing with food, enzymes should be ingested during and just after a meal.

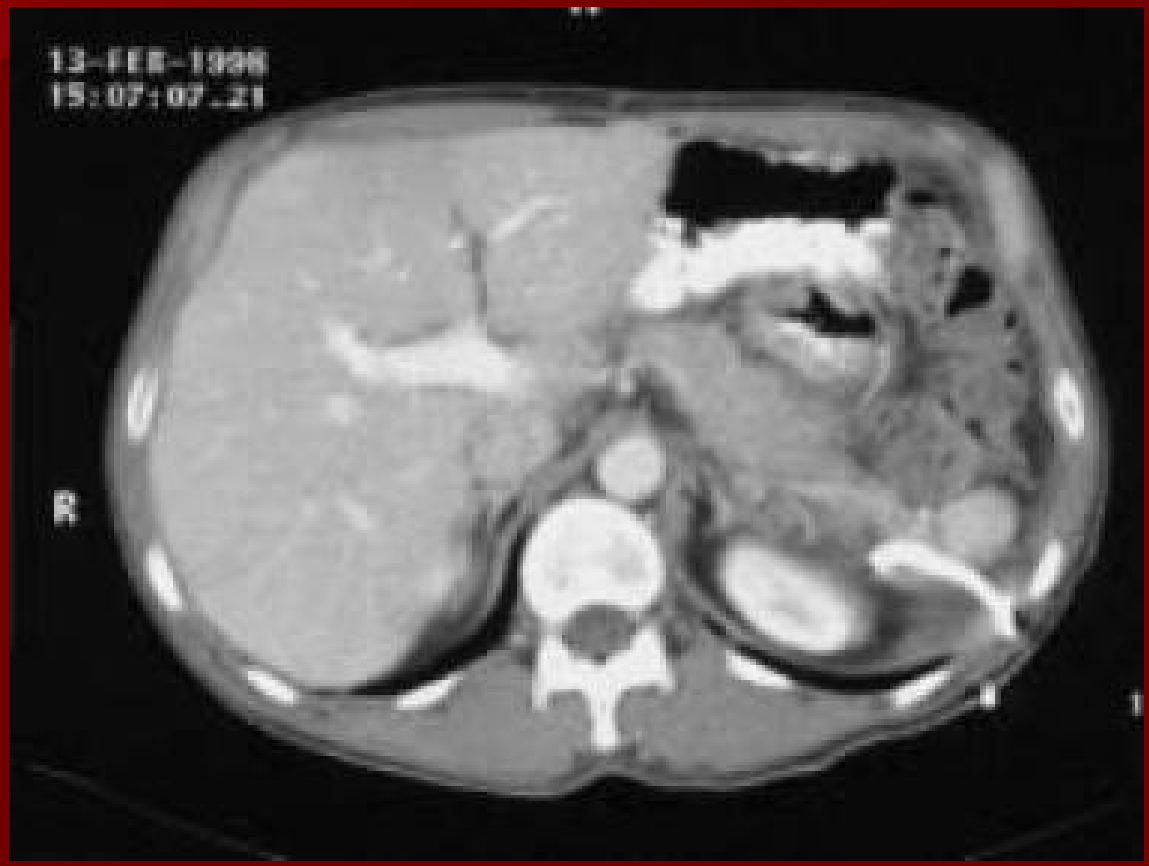
The most serious adverse effects (ie, colonic strictures) were observed with coated preparations that contained high concentrations of enzymes. In recent years, this adverse effect has not been seen, probably due to a reformulation of enzyme preparations.

Chronic pancreatitis. A nasopancreatic tube courses through the esophagus, stomach, and duodenum and into the pancreatic duct. Externally, the end of the tube is attached to a suction bulb to decompress the ductal system and monitor its function on a daily basis. In contrast to patients treated with transpapillary stents, none of these patients ever has failed to return for a follow-up appointment. In addition, while stent obstruction and subsequent infection can occur with transpapillary stents, the author has not observed this complication while using nasopancreatic tubes.





- Chronic pancreatitis. Nine days after placement of a nasopancreatic tube, a pancreatogram obtained via the tube showed that the disruption had healed (see the above image). The tube then was removed.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Chronic pancreatitis. This follow-up CT scan (see the above 2 images) shows a percutaneous tube in the left upper quadrant that was used to drain a fluid collection. It was removed after 4 weeks. The patient returned to work, regained his weight, and had no recurrence of abdominal pain or signs of a recurrent pancreatic leak.

At best, endoscopic treatment can offer pain relief in up to 60% of well-selected patients after 5 years of follow-up care. The one report with long-term follow-up included 1018 patients treated at 8 different centers who were followed for an average of 5 years. Obstruction of the pancreatic duct was due to strictures (47%), stones (18%), or strictures plus stones (32%). Patients were treated using various endoscopic techniques.

At the end of follow-up, 60% had completed the endoscopic therapy, while 16% were still undergoing some form of endoscopic therapy and 24% had undergone surgery. Pain relief (based upon a structured questionnaire) was achieved in 65% of patients on intention-to-treat analysis. Pancreatic function did not improve. The techniques involved can be technically challenging, and complications have been described. Currently, it should be performed only in centers with expertise in this area on carefully selected patients.

- Endoscopic therapy may be beneficial in chronic pancreatitis in any of the following situations:
- Papillary stenosis
- Pancreatic duct strictures
- Pancreatic duct stones
- Pancreatic pseudocysts

Papillary stenosis

In a subset of patients with chronic pancreatitis, the papillary sphincter pressure and pancreatic ductal pressure are increased. In appropriately selected patients, a pancreatic duct sphincterotomy will facilitate drainage and reduce ductal pressures and may help to alleviate pain.

Pancreatic duct strictures

Suitable candidates for endoscopic therapy are patients with a dominant distal pancreatic stricture and upstream ductal dilatation. The procedure involves placing a guidewire through the stricture into the proximal duct, performing a pancreatic sphincterotomy, dilating the stricture, and placing a stent. While technical success is achieved in more than 90% of patients, nearly 20% will have a complication and less than two thirds of patients will benefit clinically. Pain relief correlates with a reduction in the diameter of the duct by more than 2mm. Patients with recurrent pancreatitis are more likely to benefit than are those with chronic daily pain.

The stricture rarely disappears, and the stent invariably clogs; therefore, repeated procedures are required to exchange the stent. Prolonged or inappropriate stenting can injure the pancreatic duct.

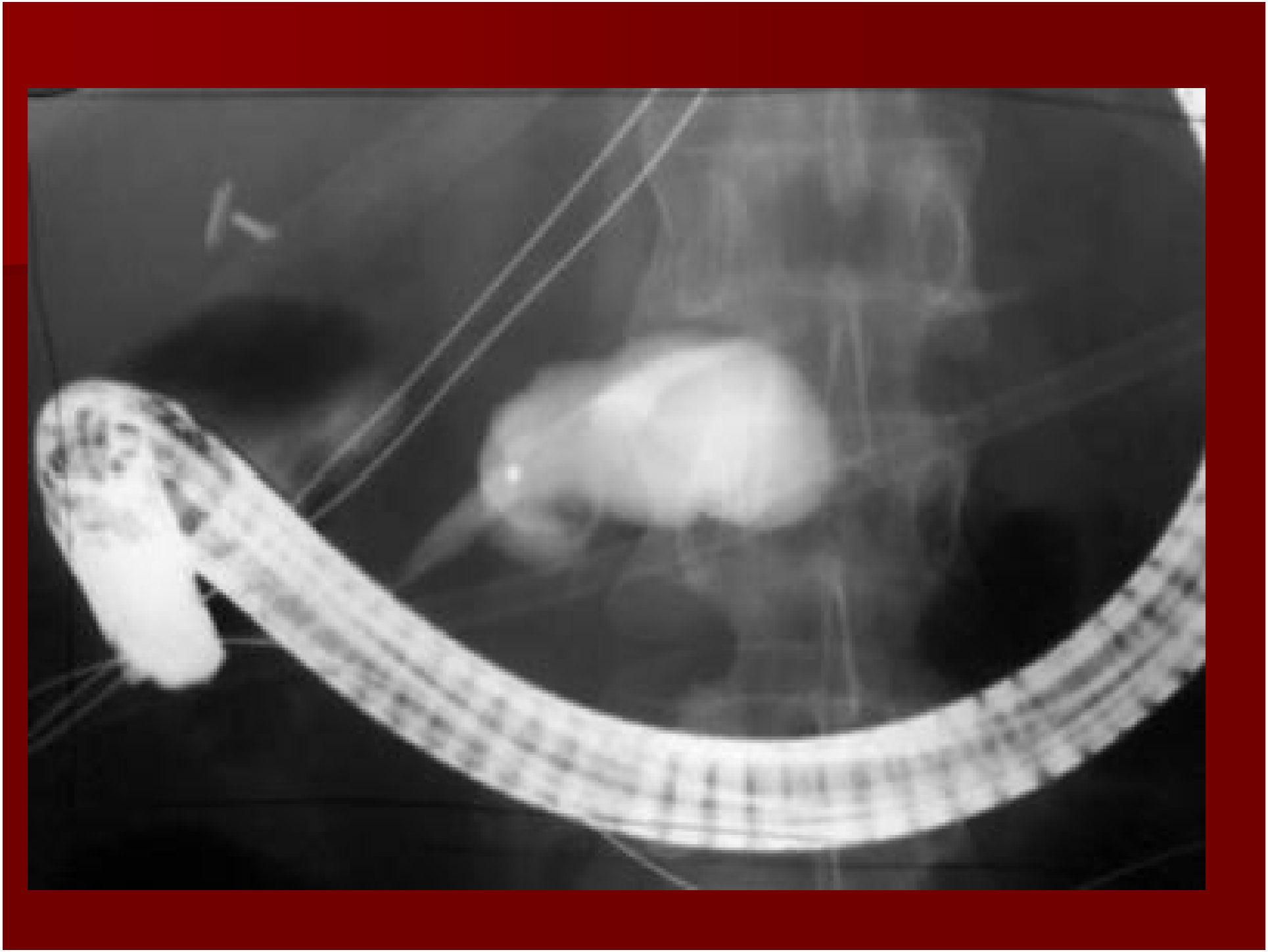
Pancreatic duct stones

While pancreatic duct stones are a sequelae of chronic pancreatitis, they also may be responsible for recurrent acute pancreatitis or exacerbations of chronic pain related to ductal obstruction and increased ductal pressure. Stones usually form proximal to the ductal strictures and usually require a pancreatic duct sphincterotomy and stricture dilation to enable their extraction. In addition to various endoscopic techniques, extracorporeal shockwave lithotripsy often is necessary to break up impacted or large stones into smaller pieces suitable for removal.

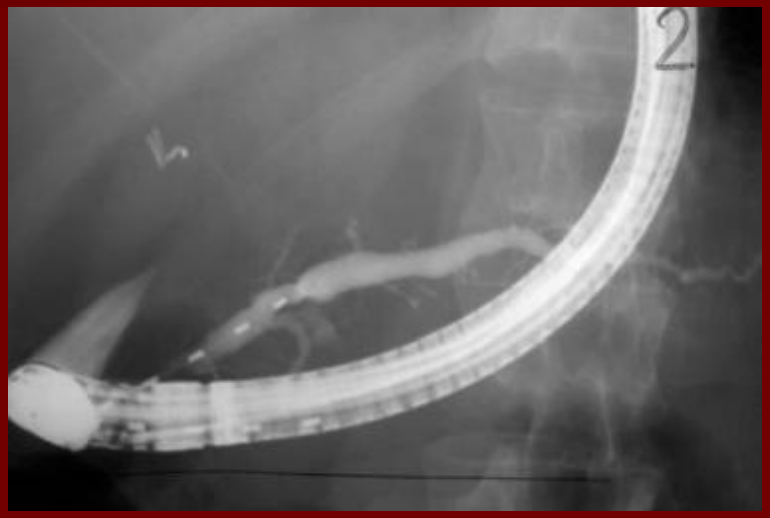
Technical success is achieved in approximately 60% of patients and complications occur in 20%. Approximately 70% of patients report improvement in their symptoms.

Pancreatic pseudocysts

Advances in interventional endoscopy now enable endoscopic treatment of many pseudocysts. In the appropriate clinical setting, obtain a pancreatogram to determine whether the pancreatic duct communicates with the pseudocyst. Ideally, communicating pseudocysts found in the head or body can be treated with transpapillary stents (see the images below), with a success rate of 83% and a complication rate of 12%.



This pancreatogram shows a pseudocyst communicating with the main pancreatic duct in a patient with chronic pancreatitis and recurrent abdominal pain. He was treated endoscopically with a transpapillary stent placed into the pancreatic duct.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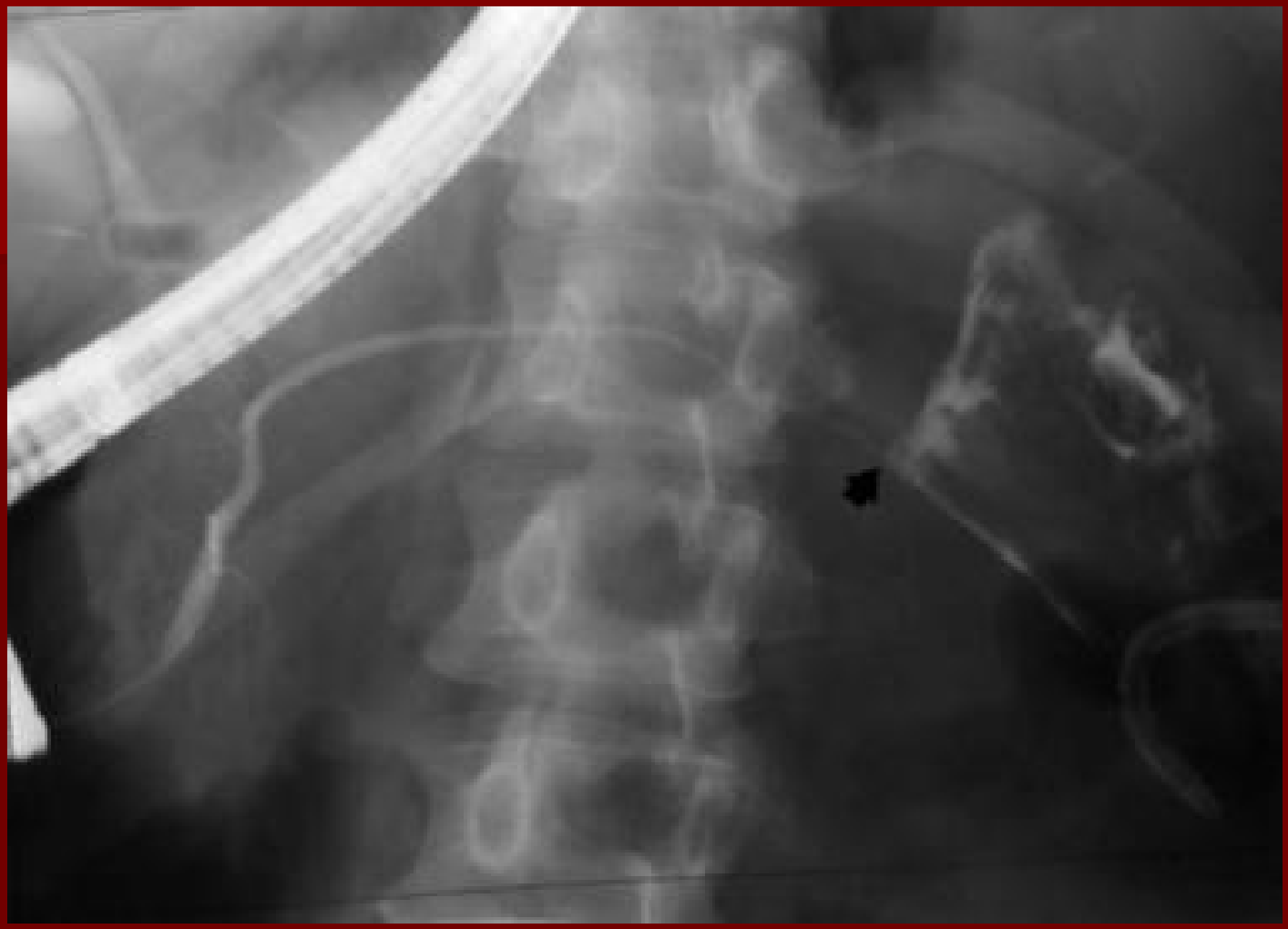
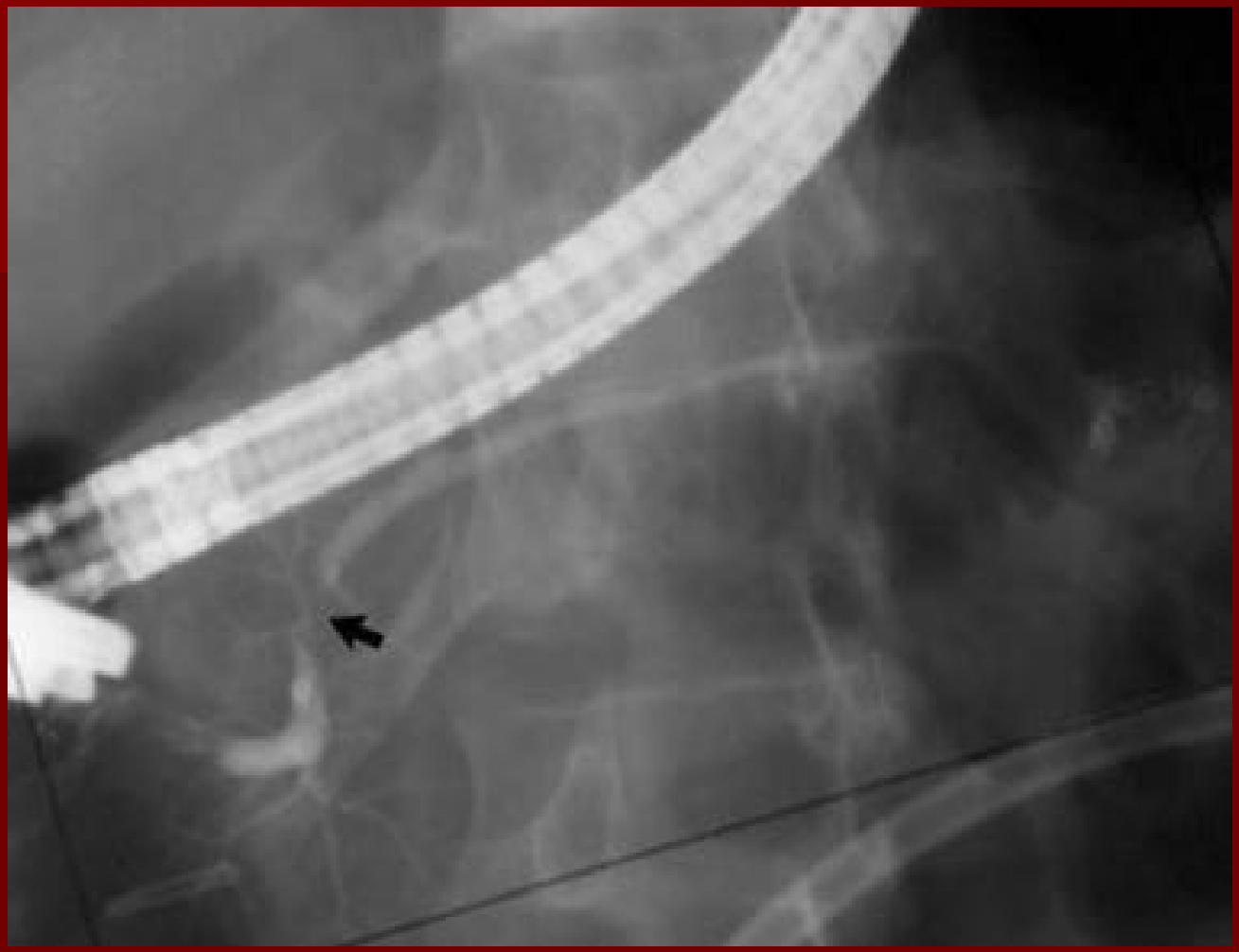
- Four weeks after placement of a transpapillary stent, a patient with a pseudocyst communicating with the main pancreatic duct (chronic pancreatitis with recurrent abdominal pain) had not had a recurrence of pain. The CT scan showed resolution of the cyst, and the follow-up pancreatogram showed marked improvement. Transpapillary stenting of the pancreatic duct should be reserved for patients with established chronic pancreatitis.
- Noncommunicating pseudocysts that bulge into the foregut and have a mature wall less than 1 cm thick are treatable by endoscopic transduodenal or transgastric pseudocystostomy. The success rate is 85%, with a 17% complication rate. The transduodenal approach has fewer complications and recurrences than the transgastric approach. The long-term success rate of the initial procedure is reported at 62%.

- **Surgical Therapy** [A]
- The choice of operation depends on the clinical problem and the preoperative assessment of the abnormality. In general, the approach aims either to improve pancreatic duct drainage or to resect the diseased organ. Data suggest that surgical drainage of the pancreatic duct is more effective than endoscopic drainage in patients with obstruction of the pancreatic duct due to chronic pancreatitis.
- **Pancreatic duct drainage**
- In patients with a dilated pancreatic duct, a Roux-en-Y side-to-side pancreaticojejunostomy is indicated. The operative mortality rate is about 3%, and pain relief is obtained in approximately 75% of patients (patients' cases were followed for a mean of 8 y). Pancreatic dysfunction progresses similarly in surgical and nonsurgical groups, suggesting that drainage procedures do not affect the natural evolution of the disease significantly. The long-term result for pain relief is reported in 42% of patients.

- **Pancreatic resection** [A]
- If the disease is limited to the head of the pancreas, a Whipple operation (pancreaticoduodenectomy) can produce good results. In patients with intractable pain and diffuse disease with nondilated ducts, a subtotal or total pancreatectomy can be offered; however, the pancreatic function and quality of life are impaired after these procedures, and the operative mortality rate of total pancreatectomy is about 10%. Pain is treated successfully in approximately 70% of cases. (See the images below.)



Chronic pancreatitis. This patient had a persistent postoperative leak from the site of a distal pancreatectomy. In the mid-1990s, the author sought to facilitate enteric drainage using transpapillary stents placed into the pancreatic duct. While this changed the fluid dynamics in favor of healing the disrupted duct, some patients developed complications from this technique.



- Chronic pancreatitis. The persistent postoperative leak from the site of a distal pancreatectomy has healed at 1-month follow-up (see the image above). However, after 4 weeks of transpapillary stenting, the pancreatogram now shows a stent-induced stenosis near the surgical genu (arrow). Based on this experience, the author stopped using pancreatic stents in this setting.
- **Total pancreatectomy and islet autotransplantation**

In 46 patients undergoing near-total pancreatectomy, pain relief occurred in 82% (resolved in 39% and improved in 43%). Although 51% were insulin independent initially, this decreased to 34% (one third) from 2-10 years after transplantation.

In selected patients, the long-term morbidity caused by diabetes following total pancreatectomy can be avoided. Doing so involves harvesting the islets from the resected pancreas and injecting them into the portal system, which then lodges them in the liver. Increasing severity of pancreatic fibrosis correlates positively with poor recovery of islets (< 300,000) and insulin dependence.

- **Diet**
- A diet low in fat and high in protein and carbohydrates is recommended, especially in patients with steatorrhea. The degree of fat restriction depends on the severity of fat malabsorption; generally, an intake of 20 g/day or less is sufficient. Patients who continue to suffer from steatorrhea following fat restriction require medical therapy.
- Clinically significant protein and fat deficiencies do not occur until over 90% of pancreatic function is lost. Steatorrhea usually occurs prior to protein deficiencies, since lipolytic activity decreases faster than proteolysis.
- Specific recommendations include a daily diet of 2000-3000 calories, consisting of 1.5-2 g/kg of protein, 5-6 g/kg of carbohydrates, and 20-25% of total calories consumed as fat (about 50-75g) per day.
- Malabsorption of the fat soluble vitamins (A, D, E, and K) and vitamin B-12 may also occur. Oral supplementation of these enzymes is recommended.

- **Medication Summary**
- **Analgesics, Other**
- **Class Summary**
- Initial therapy consists of acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs). For severe, refractory pain, narcotic analgesics often are required, starting with the least potent agents and progressing to more potent formulations as necessary.
- **Acetaminophen (Acephen, Cefotan, Mapap, Tylenol, FeverAll, Aspirin Free Anacin)**
-
- Acetaminophen is the drug of choice for pain in patients with documented hypersensitivity to aspirin or NSAIDs, those with upper GI disease, and those who are taking oral anticoagulants.

- **Opioid Analgesics**
- **Hydrocodone and acetaminophen (Vicodin, Lorcet, Lortab, Norco, Zolvit)**
-
- This drug combination is indicated for moderate to severe pain.
- **Acetaminophen with codeine (Tylenol-3)**
- This drug combination is indicated for treatment of mild to moderate pain.
- NSAIDs have analgesic, anti-inflammatory, and antipyretic activities. Their mechanism of action is not known, but they may inhibit cyclooxygenase activity and prostaglandin synthesis. Other mechanisms may exist as well, such as inhibition of leukotriene synthesis, lysosomal enzyme release, lipoxygenase activity, neutrophil aggregation, and various cell membrane functions.

- **Naproxen (Naprosyn, Aleve, Naprelan, Anaprox)**
-
- Naproxen is indicated for relief of mild to moderate pain. It inhibits inflammatory reactions and pain by decreasing the activity of cyclooxygenase, which results in a decrease in prostaglandin synthesis.
- **Diclofenac (Voltaren, Cataflam, Cambia, Zipsor)**
-
- These NSAIDs inhibit prostaglandin synthesis by decreasing cyclooxygenase activity and by decreasing the formation of prostaglandin precursors.
- **Ketorolac**
-
- Ketorolac is an intravenously administered NSAID and a very powerful analgesic. It inhibits prostaglandin synthesis by decreasing the activity of the enzyme cyclooxygenase, which results in decreased formation of prostaglandin precursors. In turn, this results in reduced inflammation.

- **Ibuprofen (Advil, Motrin, Caldolor)**
-
- Ibuprofen is usually the drug of choice for the treatment of mild to moderate pain, if no contraindications exist. It inhibits inflammatory reactions and pain by decreasing the activity of the enzyme cyclo-oxygenase, resulting in inhibition of prostaglandin synthesis.
- **Celecoxib (Celebrex)**
- Celecoxib inhibits primarily cyclooxygenase-2 (COX-2). COX-2 is considered an inducible isoenzyme; it is induced during pain and inflammatory stimuli. Inhibition of COX-1 may contribute to NSAID GI toxicity. At therapeutic concentrations, celecoxib does not inhibit the COX-1 isoenzyme; thus, GI toxicity may be decreased. The increased cost of celecoxib must be weighed against the benefit of avoidance of GI bleeds. Seek the lowest dose of celecoxib for each patient.

- **Hormones**
- Hormones can be used for the reduction of pancreatic exocrine secretion.
- **Octreotide (Sandostatin)**
- **Octreotide has an 8–amino acid sequence containing the active portion of somatostatin. In a study, subcutaneous injection of octreotide 3 times daily at 200mcg provided pain relief in 66% of patients. Note that 35% of the control group also experienced pain relief.**
- **Antidepressants, TCAs**
- In addition to alleviating coexistent depression, tricyclic antidepressants may ameliorate pain and potentiate the effects of opiates.
- **Amitriptyline hydrochloride**
- This agent is an analgesic for certain chronic and neuropathic pain.

- **Clomipramine (Anafranil)**
- **Clomipramine is a dibenzazepine compound belonging to the family of TCAs. The drug inhibits the membrane pump mechanism responsible for the uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons.**
- Clomipramine affects serotonin uptake while it affects norepinephrine uptake when converted into its metabolite desmethylclomipramine. It is believed that these actions are responsible for its antidepressant activity.
- **Doxepin (Silenor)**
- **Doxepin increases the concentration of serotonin and norepinephrine in the CNS by inhibiting their reuptake by presynaptic neuronal membrane. It inhibits histamine and acetylcholine activity and has proven useful in the treatment of various forms of depression associated with chronic pain.**
- **Nortriptyline (Pamelor)**
- Nortriptyline has demonstrated effectiveness in the treatment of chronic pain.
- **Desipramine (Norpramin)**
- **This is the original TCA used for depression. These agents have been suggested to act by inhibiting the reuptake of noradrenaline at synapses in the central descending pain-modulating pathways located in the brainstem and spinal cord.**

- **Pancreatic Enzyme Supplements**
- These are used as dietary supplementation to aid digestion in patients with pancreatic enzyme deficiency. Several preparations are available. The aim is to provide at least 30,000 units of lipase. Because the cost of different preparations is variable, consider the unit price of the enzyme supplement based on the lipase content.
- Uncoated pancrelipase is used to treat painful chronic pancreatitis based on the following rationale. Serum CCK levels are higher in patients with severe chronic pancreatitis, ductal or parenchymal hypertension is believed to cause pain, increased CCK levels stimulate pancreatic secretion (which increases ductal hypertension and exacerbates pain), and exogenous pancreatic enzyme supplements trigger a negative feedback inhibition.
- **Pancrelipase (Creon, Pancreaze, Ultresa, Viokace, Zenpep)**
- **Pancrelipase assists in the digestion of protein, starch, and fat. Nonenteric-coated products are used for pain caused by pancreatitis (ie, Viokace) in combination with a proton pump inhibitor. The enteric-coated products may be used for the restoration of digestion and absorption.**

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