

# Chronic pancreatitis

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## Abstract

Chronic pancreatitis is distinguished by structural and functional criteria. Alcohol is the major aetiological factor, but other causes (for example including hereditary pancreatitis) must be considered. Abdominal pain is the usual presenting feature, but chronic pancreatitis is clinically silent in many patients. The pathogenesis of chronic pancreatitis is incompletely understood. Diagnosis is usually made on imaging (computed tomography, magnetic resonance cholangiopancreatography, endoscopic ultrasound). Complications include exocrine and endocrine insufficiency, obstructive jaundice, duodenal obstruction, left-sided portal hypertension, and the development of pancreatic cancer. Overall management is difficult and depends upon symptoms, morphological characteristics and complications. Treatment options include medical, endoscopic, and surgical strategies; the latter is reserved for patients with complications. Early involvement of a specialist centre in the care of patients with complicated chronic pancreatitis is important and should be encouraged.

**Keywords** Chronic pain; chronic pancreatitis; exocrine insufficiency; Frey procedure; pancreas

Chronic pancreatitis is characterized by a continuous, prolonged inflammatory process of the pancreas with irreversible morphological changes of fibrosis and stricture formation, resulting in pancreatic exocrine and endocrine insufficiency. It usually presents with abdominal pain, but may be painless. The clinical course is also variable. The intensity of pain may range from low to severe even in patients with little evidence of parenchymal or ductal disease on imaging; complex morphological changes may give rise to minimal or extensive symptoms.

## Pathophysiology

Most patients with chronic pancreatitis have had one or more attacks of acute pancreatitis resulting in inflammatory change and fibrosis, but some patients have a more insidious onset. The molecular and biochemical mechanisms causing the fibrosis and destruction of the pancreatic parenchyma are largely unknown, but four theories have attracted attention.

- Toxic-metabolic; a direct effect of alcohol combined with poor nutrition.

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- Oxidative stress; over-activity in hepatic detoxification enzymes (mixed-function oxidases) that generates free-radical oxidant by-products that are secreted in bile and cause damage to the pancreatic parenchyma by reflux up the pancreatic duct.
- Ductal obstruction and stone formation; an increase in protein secretion with abnormal insoluble forms of protein, combined with an increase in ductal permeability to calcium, resulting in formation of 'protein plugs' and intraductal deposition of calcium.
- Necrosis-fibrosis; the characteristic fibrosis evolves from the recurrent cycles of inflammation and necrosis seen after repeated attacks of acute pancreatitis.

Each hypothesis is undermined by oversimplification; it is likely that a combination of factors is responsible because none accounts for the heterogeneity of clinical phenotypes. Within the pancreas, T-cell-activated cytotoxic cells and activated pancreatic stellate cells are thought to have a key role. T-cells contribute to the chronic inflammatory process and the degree of lymphocytic infiltration correlates with pain severity. Stellate cells are stimulated by various factors (for example oxidative stress, transforming growth factor- $\beta$ , platelet-derived growth factor). After stimulation, they transform into myofibroblasts and proceed to produce several components of the extracellular matrix, resulting in fibrosis.

Pathogenesis of the severe pain that is a major feature of chronic pancreatitis is incompletely understood, but three theories have emerged:

- Increased pressure in the main pancreatic duct.
- Parenchymal oedema causing a compartment syndrome.
- The neuronal inflammatory mediator hypothesis, where inflammatory mediators (derived largely from infiltrating lymphocytes) are responsible for increased signals along the axons of pain-sensitive neurons.

## Incidence

The annual incidence in Western Europe is about five new cases per 100,000 population. The male:female ratio is 7:1 and the average age of onset is between 36 years and 55 years.

## Aetiology

### Alcohol

Alcohol is responsible for 70–80% of cases of chronic pancreatitis (Table 1). There is no uniform threshold for the toxic effects of alcohol on the pancreas, but the quantity and duration of alcohol consumption correlate with the development of chronic pancreatitis. There is little evidence that the type or pattern of consumption is important. It has been suggested that ingestion of 150–200 ml of >40% ethanol per volume daily for 10–15 years is needed for clinically significant chronic pancreatitis to develop, but one can assume a patient has alcohol-induced disease if they give a history of heavy use of alcohol. Emerging evidence suggests that the pancreas of one individual may be significantly more sensitive to alcohol than that of another, and that unidentified genetic factors may be responsible for this difference.

### Idiopathic

In the UK, the next commonest cause is idiopathic, accounting for 20–30% of cases (Table 1). Epidemiological evidence suggests that idiopathic chronic pancreatitis is a distinct entity, and these

## Causes of chronic pancreatitis

### Main causes (90–95%)

Alcohol 70–80%  
Idiopathic 20–30%

### Less common causes (5–10%)

Tropical  
Hypercalcaemia  
Hyperlipidaemia  
Hereditary pancreatitis  
Gallstones  
Pancreatic tumours  
Pancreatic divisum

**Table 1**

patients resent the label of ‘alcoholic’. Idiopathic chronic pancreatitis affects equal numbers of men and women, and delayed progression of endocrine and exocrine insufficiency is observed.

### Other causes

Fewer than 10% of patients with chronic pancreatitis have one of these less common causes. Hereditary pancreatitis is being increasingly recognized and must be suspected in patients with a family history of pancreatitis or diabetes. It is inherited as an autosomal dominant condition with penetrance of 80%, with >80% of affected individuals developing clinical disease before the age of 20 years. The activation of trypsin appears to be an important step in the initiation of pancreatitis, therefore failure of mechanisms that prevent inappropriate activation of trypsin could lead to pancreatitis. Point mutations have been identified in the cationic trypsinogen gene (*PRSS1*) located on chromosome 7; example mutations are named R122H, N291 and A16V. The R122H mutation results in the elimination of a failsafe self-destruct mechanism, which prevents the rapid accumulation of large concentrations of active trypsin in the pancreas. Mutations in the serine protease inhibitor, Kazal type-I (*SPINK1*), also known as ‘pancreatic secretory trypsin inhibitor’, have also been described. Hereditary pancreatitis carries a substantially increased risk of pancreatic cancer (Figure 1).

## Clinical features

### History

Abdominal pain is the principal presenting feature of chronic pancreatitis. Usually, patients have had pain for months or years before seeking help. This pain, while typically deep, boring and radiating to the back, can be highly variable, ranging from mild to severe. Characteristically, it is eased by sitting upright or by drawing the knees up into the ‘jackknife’ position. Food consumption may exacerbate the pain, resulting in avoidance and consequential weight loss. Initially, abstinence from alcohol improves the episodic attacks but, as the disease progresses, the pain becomes more chronic, developing a more persistent pattern, and the beneficial effects of abstinence from alcohol are reduced. Assessment of pain in alcoholic patients can be challenging because of their manipulative personalities and dependency; other surrogate markers may be more helpful:

- loss of sleep
- interference with work or family responsibilities
- hospital admissions.



**Figure 1** Resection specimen showing pancreatic adenocarcinoma (arrow) arising within hereditary chronic pancreatitis. Ductal calcification and cyst formation are also seen.

Pancreatic insufficiency characteristically develops 10–15 years after the onset of pancreatitis and is progressive. Exocrine insufficiency results in deficiency of protein and fat. Steatorrhea with loose, grey, foul-smelling stools that are difficult to flush away is common. The nutritional status of alcoholic patients is frequently poor and awareness of thiamine deficiency (and Wernicke’s encephalopathy) is important. Endocrine insufficiency resulting in diabetes develops over time and is ultimately dependent on insulin. The medium-to-long-term effects of diabetes (for example ischaemic heart disease, nephropathy, retinopathy, peripheral vascular disease) are less likely to be clinically significant than in other diabetic patients because of the shorter life expectancy associated with chronic pancreatitis.

### Clinical examination

Physical examination may not reveal specific features. Weight loss and malnutrition may be clinically apparent and can be monitored with serial measurements. Erythema *ab igne* on the epigastrium or back represents attempts to relieve the pain by the application of topical heat. Anaemia, jaundice, ascites and splenomegaly may be detected. Signs of liver stigmata and failure should be looked for in alcoholic patients (although cirrhosis in patients with chronic pancreatitis is surprisingly rare).

## Diagnosis and investigation

Diagnosis in the early stages of chronic pancreatitis can be difficult compared to an advanced stage where it is much more obvious. The principal differential diagnosis is pancreatic cancer, although other causes of pain (Table 2) should also be considered (particularly if presentation is early).

### Laboratory tests

*Blood tests* are, in general, unhelpful; serum amylase, lipase and elastase are usually normal even during an acute painful exacerbation. Other blood tests that should be done are routine haematology, clotting screen and routine biochemistry (including bone and lipid profile) as a baseline.

### Differential diagnosis of chronic pancreatitis

Pancreatic cancer  
Upper abdominal cancer  
Peptic ulceration  
Cholelithiasis  
Irritable bowel syndrome  
Mesenteric vascular disease  
Endometriosis

**Table 2**

*Liver function tests* may be deranged, indicating biliary obstruction; thrombocytopenia may suggest thrombosis of the splenic vein.

*Urine tests* should include glucose and glycosylated haemoglobin.

*Genetic sequencing with appropriate counselling* is involved in the investigation of suspected hereditary pancreatitis.

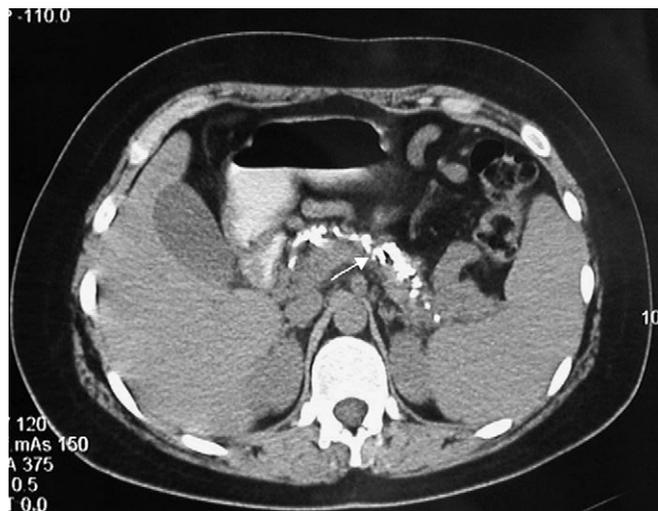
*Pancreatic exocrine function tests* should be done, but they do not differentiate chronic pancreatitis from pancreatic cancer. Faecal elastase is the preferred test.

### Imaging

The diagnosis is almost always made on imaging. Plain radiography may show pancreatic calcification. Transabdominal ultrasound may show enlargement of the pancreas, duct dilatation and pseudocysts (see below).

*Computed tomography (CT)* is the principal investigation (Figure 2). Multislice, contrast-enhanced, pancreatic-specific protocols can provide considerable information:

- size, outline and shape of the gland
- changes in parenchymal attenuation
- pancreatic duct dilatation and calculi
- dilatation of the bile duct
- fluid collections (including pseudocysts; see below)
- gastrointestinal or vascular involvement.



**Figure 2** Computed tomography scan showing heavy ductal calcification of the pancreas in chronic pancreatitis (arrow).

The disadvantages of contrast-enhanced CT include the inability to detect the subtle early changes of chronic pancreatitis and to define the degree of ductal abnormality.

*Magnetic resonance cholangiopancreatography (MRCP)*: traditionally, endoscopic retrograde cholangiopancreatogram (ERCP) was used for ductal assessment, but this has diminished with the increasing availability of MRCP with three-dimensional rendering of the main pancreatic duct. This method gives detailed information regarding dilatation and narrowing of the duct, as well as intraductal filling defects. Secretin stimulation during MRCP gives functional information. ERCP should be used only rarely in the diagnostic setting because of its attendant complications. Indications include cases where MRCP has failed to image the duct or in the delivery of interventional techniques (for example stone removal, stricture dilation, stent insertion).

*Endoscopic ultrasound (EUS)* has a vital diagnostic role because it is extremely sensitive in detecting the early pathological changes of chronic pancreatitis. EUS is the investigation of choice if chronic pancreatitis is suspected but not proven. EUS-guided fine-needle aspiration cytology is useful for the diagnosis of chronic pancreatitis and also for helping to exclude pancreatic cancer, although it may be difficult to obtain a good sample from an indurated gland.

### Diagnostic criteria

**Ultrasonography:** pancreatic stones, evident by intra-pancreatic hyper-reflective echoes with acoustic shadows behind.

**Contrast-enhanced CT:** pancreatic atrophy, calcifications and main pancreatic duct dilatation.

**Endoscopic ultrasound (EUS):** parenchymal features (gland atrophy, hyperechoic foci, hyperechoic stranding, cysts, lobularity) and ductal features (narrowing, dilatation, irregularity, calculi, sidebranch dilatation, hyperechoic walls).

ERCP is rarely used for diagnosis only. Features are irregularity of the main and side pancreatic ducts with stones or protein plugs.

Histology is the 'gold standard' and observed features are irregular fibrosis with destruction and loss of exocrine parenchyma.

### Treatment

The aims of treatment are to establish a diagnosis, and to manage symptoms and complications (Table 3) medically or surgically. Chronic pancreatitis predisposes to pancreatic cancer and this diagnosis should be considered in patients with exacerbation of pain or development of obstructive jaundice.

### Important factors

Pain is a major problem for most patients and analgesics are required during acute exacerbations as well as continuously (albeit usually at a lower dose) in a minority of patients. Pain intensity frequently necessitates opiate analgesia, which is effective in the initial stages of the disease, but becomes less so as the disease progresses or consumption continues. With escalating opiate doses, more side-effects are experienced and the risk of addiction becomes a problem. Pancreatic enzyme supplements, particularly uncoated preparations in large doses, can reduce pain in some patients. Acute exacerbations requiring hospital admission should be managed by resting the intestine and providing supplemental nutrition. Neurolysis in the form of coeliac plexus block or thoracoscopic splanchnicectomy can

## Complications of chronic pancreatitis

Complication	Comment	Treatment
Intractable pain	In a minority of patients	Consider neurolytic intervention; surgical drainage or resection if indicated
Pancreatic insufficiency	Exocrine and endocrine	Pancreatic enzyme supplements and diabetic therapy
Pseudocyst	Usually mature and connected to the ductal system, so resolution is unlikely	Endoscopic or surgical drainage
Duodenal stenosis or colonic stricture	Intestinal obstruction	Surgical drainage if does not resolve
Haemorrhage	Erosion of the splenic artery causing pseudoaneurysm or variceal bleeding	Surgical or endoscopic control; angiography or embolization may be useful for post-procedural bleeding
Pancreatic cancer	Risk of cancer increased by 5–10-fold	Consider suitability for resection
Pancreatic ascites	From ductal disruption or ruptured pseudocyst	Optimize nutrition, octreotide and drainage; pancreatic duct stenting; surgery if persistent
Portal hypertension	Thrombosis of the splenic vein (although high intake of alcohol may cause hepatic cirrhosis)	Supportive
Inflammatory mass in the head of the pancreas	May cause recurrent attacks of pain	Consider resection
Biliary obstruction	15% of patients	Initially managed with stenting, but surgery is usually required
Pancreatic ductal stricture and stones	Likely to cause symptoms and benefit from intervention	Endoscopic or surgical drainage

**Table 3**

provide good short-term relief of pain, but inevitably pain recurs and repeat procedures are often necessary. The decision to embark upon surgical or radiological intervention for intractable pain is difficult, and the advice of a pain specialist and clinical psychologist is essential (see below).

Exocrine failure with resulting deficiencies in fat, protein and vitamins is improved with pancreatic enzyme supplementation; preparations containing gastric acid-resistant enteric-coated microspheres (which facilitate delivery to the duodenum) seem to be the most effective. Despite the enteric coating, it is advisable for them to be taken with meals and a proton pump inhibitor is also usually prescribed. An adequate dose is determined by stool size and frequency, and varies from 30,000 units to 200,000 units of lipase per adult per day. The starting dose is usually 20,000 with each meal and 10,000 units with a snack. A reduction in daily intake of fat can help reduce steatorrhoea. Reasons for treatment failure include:

- poor compliance
- an inadequate prescription
- excessive heating of the supplements if mixed with food
- an incorrect diagnosis.

Endocrine failure tends to be progressive and insulin is usually required. Compared to patients with idiopathic diabetes, hypoglycaemia occurs more easily because of the lack of endogenous glucagon. Near-perfect control should be strived for in alcoholic patients with a poor calorific intake (to avoid infective and microvascular complications) but otherwise, higher glucose levels should be accepted to avoid hypoglycaemia.

Pseudocysts are peripancreatic fluid collections that have been present for more than 4 weeks. They are often seen in

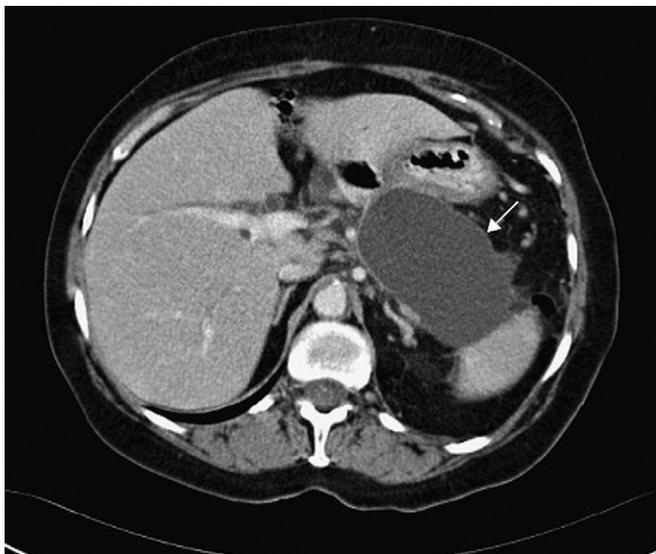
chronic pancreatitis, and can become infected or cause local effects such as:

- biliary obstruction (see below)
- duodenal obstruction
- gastric compression
- pain.

Pseudocyst drainage must be done if any of these features are detected. Percutaneous aspiration or drainage risks an external pancreatic fistula or infection, and internal drainage is preferable. Assessment by CT or endoscopic ultrasound is important (Figure 3). Endoscopic cyst-gastrostomy can usually be done using ERCP-type stents if the cyst is applied to the stomach. This is ideally carried out under guidance by endoscopic ultrasound to avoid vessels in the cyst wall. Alternatively, a laparoscopic approach can be used. Open drainage may be necessary if the cyst is not in contact with the stomach or duodenum, by cyst-gastrostomy or cyst-jejunostomy using the most dependent part of the cyst. Resolution of the cyst is successful in 80–90% of cases if a successful communication is established. Biliary obstruction occurs in about 15% of patients with chronic pancreatitis and may be due to pseudocysts or pancreatic parenchymal fibrosis affecting the lower common bile duct. ERCP and placement of a biliary stent can relieve jaundice in the short term but, for patients with fibrosis, most eventually require choledochoduodenostomy or choledochojejunostomy.

### Endoscopic management of the pancreatic duct

Pancreatic ductal strictures can be dilated and stones removed endoscopically. Ideally this should be combined with extracorporeal shockwave lithotripsy to the ductal stones. Although the



**Figure 3** Computed tomography scan showing pseudocyst (arrow) in chronic pancreatitis; treatment was pancreatic cyst-jejunostomy.

benefits of treating ductal hypertension with stenting are well documented, endoscopy has no benefits over surgery and should be reserved for less fit patients.

#### Medical management

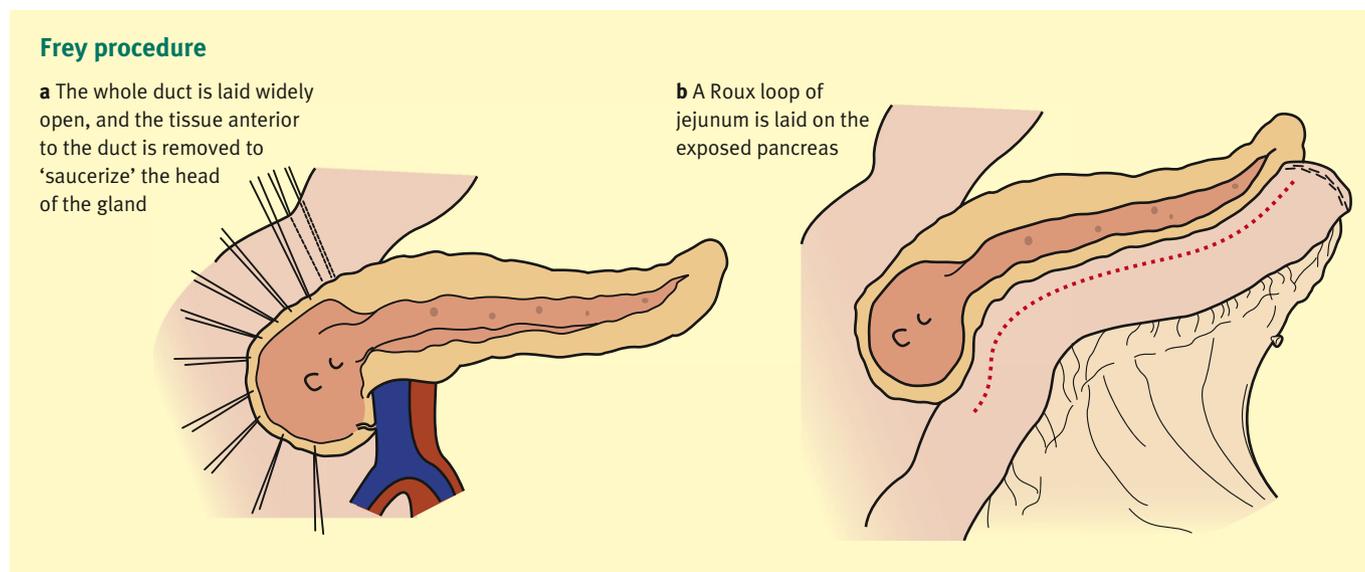
**Psychological support:** patients with a definitive diagnosis have usually undergone many investigations and had numerous hospital admissions (often under different clinicians) in relation to the predominant symptom of abdominal pain. These individuals must be offered understanding and an explanation of their condition, and overall management should be in a specialist unit. Patients without complications can be cared for expectantly. Attention should be paid to the underlying cause of pancreatitis, particularly abstinence from alcohol. Psychiatric and psychological support may be required if alcohol addiction is present. It is not uncommon for individuals taking excessive alcohol to suffer from chronic abdominal pain in the absence of chronic

pancreatitis. Establishing that there is no evidence of chronic pancreatitis in these patients is helpful.

#### Open surgery

Surgical management of chronic pancreatitis is reserved for patients with complications (Table 3). Some patients with chronic pancreatitis benefit from major surgery, but expectant therapy is adequate for most patients. Surgery to treat intractable pain or to preserve pancreatic function depends on the calibre of the main duct and the distribution of disease in the pancreas; the appropriate selection of these patients is paramount. A patient with pain and a dilated pancreatic duct (>7 mm in diameter) ± ductal calculi is likely to benefit from drainage, which works by decompressing the pancreatic duct or by relieving the pancreatic capsular hypertension.

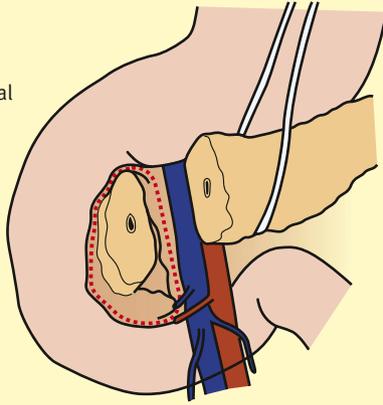
The commonest drainage procedure, lateral pancreaticojejunostomy (a modified Puestow or Partington–Rochelle procedure), involves exposure of the gland, opening of the entire length of the pancreatic duct to the ampulla of Vater, and anastomosis to a Roux-en-Y loop of jejunum. This procedure has disadvantages. Pancreatic head tissue is left *in situ*. If this is inflammatory, as it often is, a neuroinflammatory pain is likely to persist, and biliary obstruction or thrombosis of the portal vein can develop. A better result can be obtained if part of the head is excised in addition to the lateral pancreaticojejunostomy (as described by Frey; Figure 4). Alternatively, a duodenum-preserving resection of the head of the pancreas, as described by Beger, may be done (Figure 5). This is a similar procedure, but with a more extensive resection of the head of the pancreas, has similar results to the Frey procedure in terms of pain relief and therefore has no distinct advantages. These duodenum-preserving resectional procedures provide good relief from recurrent attacks of pain and are superior to pancreaticoduodenectomy, which is required only rarely for chronic pancreatitis (usually if pancreatic cancer is suspected). Distal pancreatectomy may be carried out for disease confined to the tail of the pancreas and this is the only one of these procedures which may be attempted laparoscopically if the degree of inflammation is minimal. Total pancreatectomy



**Figure 4**

### Beger procedure

**a** The head of the pancreas is excised within the duodenal loop, leaving sufficient pancreas to maintain the blood supply to the duodenum; the bile duct is drained



**b** The reconstruction with pancreatic duct and bile duct anastomoses

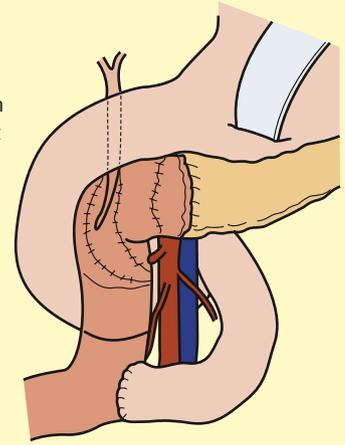


Figure 5

relieves pain in only about 50% of individuals with constant pain because autonomic pathways are damaged; it renders the patient a brittle diabetic and is rarely indicated. If total pancreatectomy is unavoidable in a patient with good glucose tolerance, islet auto-transplantation (using a portal vein catheter) should be considered.

#### Complications of surgery and outcome

Overall, surgical mortality should be 1–2%, particularly for the Frey and Beger procedures. Overall, surgical morbidity is 5–20%. In addition to surgical complications, patients with chronic pancreatitis are at risk of other complications (Table 3) and some of these account for deaths. Patients with chronic pancreatitis have a 5-year survival of 70% and 10-year survival of 40%. Patients are exposed to the inherent risks associated with diabetes and suboptimal nutrition; many alcoholic patients have a significant intake of tobacco, and smoking-related deaths are higher than in the general population. Long-term follow-up is necessary after the initial diagnosis to address pain management and pancreatic endo/exocrine insufficiency. The progressive nature of

chronic pancreatitis ensures that assessment for medical or surgical intervention is likely to be needed more than once. ◆

#### FURTHER READING

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