Alcohol and the pancreas

Alcohol abuse predisposes to acute and chronic pancreatitis, both of which carry a substantial risk of serious complications and even death. The various hypotheses for pancreatic damage are discussed, together with the management of alcoholic pancreatitis and the role of operative intervention.

In developed countries alcohol is the second commonest cause of acute pancreatitis (up to 36% of cases) and the commonest cause of chronic pancreatitis (60–90% of cases) (Spanier et al, 2008). Although an association between alcohol abuse and pancreatic injury was reported as early as 1878 (Apte et al, 1997), the precise mechanism remains unknown. The link between alcohol abuse and development of pancreatitis is clear-cut: 10% of alcohol abusers (>80 g daily intake) develop acute pancreatitis and 75% of autopsies on alcohol abusers show signs of chronic pancreatitis (Apte et al, 1997). Some of the difficulty in assessing the incidence of alcoholic pancreatitis relates to the reliability of patients reporting their true alcohol consumption, and likewise the differences in incidence between one country and the next.

This article reviews the threefold effects of alcohol on the pancreas and describes the diseases that can result.

Alcoholic injury to the pancreas

Direct damage to acinar cells

Most alcohol is metabolized in the liver by an oxidative system, but some is metabolized in the pancreas (Apte et al, 1997). As the concentration of ethanol increases, oxidative mechanisms are replaced by a non-oxidative pathway leading to the transient formation of fatty acid ethanol esters (Chowdhury and Gupta, 2006). Fatty acid ethanol ester synthesis is much greater in the pancreas than in the liver (Pandol and Raraty, 2007; Frossard et al, 2008). Fatty acid ethanol esters have been linked to pancreatic cellular disruption, intracellular digestive enzyme activation and necrosis, possibly through elevated intra-cellular calcium concentrations (Fortunato et al, 2006; Criddle et al, 2007). Excessive cytosolic calcium can also trigger the release of cytokines, thereby contributing to systemic inflammatory response syndrome and multiple organ failure.

Acinar cell necrosis is a key feature of pancreatitis, and the severity of acute pancreatitis correlates with the degree of cell necrosis (Fortunato et al, 2006). With regard to chronic pancreatitis, fatty acid ethanol esters also promote pancreatic fibrosis by inhibiting degradation of extracellular matrix proteins (Criddle et al, 2004; Chowdhury and Gupta, 2006). In addition, alcohol increases both the synthesis of digestive enzymes (Apte et al, 1997) and the fragility of zymogen granules; both mechanisms result in autodigestion of the pancreas.

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Alteration to pancreatic juice

Alcoholic pancreatitis is associated with an increase in the protein concentration of pancreatic juice and thus formation of protein plugs within the small excretory ducts (the ductal plug theory) (Gullo, 2005; Chowdhury and Gupta, 2006). Ethanol also stimulates basal pancreatic secretion and will therefore elevate intraluminal pressure in the pancreatic ductal tree (Sári et al, 2004). The plugs contain two pancreatic digestive enzymes and two pancreatic secretory proteins; as these plugs enlarge and calcify they block the pancreatic ducts and lead to fibrosis (Apte et al, 1997). The exact mechanism of increased protein concentration is not known, nor is it clear whether this is the cause or the effect of pancreatic injury.

Effect on the sphincter of Oddi

The action of alcohol on the sphincter of Oddi is controversial, various studies reporting that it can have both stimulating and relaxing properties. The obstruction-hypersecretion theory is based on the fact that ethanol can induce spasm of the sphincter of Oddi, with oedema of the papilla of Vater and increased pancreatic secretion (Sári et al, 2004; Siqin et al, 2009). Partial obstruction would increase pressure in the pancreatic duct and allow pancreatic juice to enter the pancreatic parenchyma, while oedema might permit bile reflux, which is a known trigger for acute pancreatitis (Apte et al, 1997). Alcohol could further affect the sphincter of Oddi either by stimulating secretion of cholecystokinin and motilin or via the parasympathetic nervous system. This neurohumoral hypothesis is supported by the fact that pancreatic duct obstruction and bile reflux are common features of pancreatitis from a variety of different sources (Siqin et al, 2009).

A contrary mode of action of alcohol has been identified in some studies showing that ethanol relaxes the sphincter of Oddi, allowing pancreatic juice to flow into the duodenum and thus protecting the pancreas from damage by elevated intraductal pressure during an acute

attack (Sári et al, 2004). Yet relaxation of the sphincter could also permit reflux of bile-activated enzymes or other substances from the duodenum back into the pancreatic duct and thus lead to pancreatitis – the duodenal-pancreatic reflux.

Acute-to-chronic progression

Two main hypotheses account for the progression from acute to chronic inflammation: first, the 'necrosis-fibrosis' sequence in which acute episodes lead to irreversible pancreatic damage (which may remain subclinical) and second, alcohol acting as a 'susceptibility and progression factor' that modifies the inflammatory, immune and fibrosing responses (Gukovsky et al, 2008). The element of progression could be explained by alcohol impairing the recovery from acute pancreatic injury.

Acute alcoholic pancreatitis

A disease on the increase

Over the last 50 years the incidence of all causes of pancreatitis has been increasing. Whether this is a true increase (Tinto et al, 2002) or just better detection of the disease (Yang et al, 2008) is uncertain. The relative incidence of gallstone pancreatitis and alcoholic pancreatitis differs widely both between countries and between men and women: biliary pancreatitis has a female predominance, while alcoholic pancreatitis is commoner in men (Spanier et al, 2008). The incidence of gallstone (and idiopathic) pancreatitis increases with age, whereas alcoholic disease is maximal in men aged 35–44 years and in women aged 25–34 years, suggesting a greater susceptibility in women despite the lower overall incidence (Yang et al, 2008).

Although alcoholic pancreatitis is becoming more common in Britain, the proportion of severe attacks remains constant, which implies better recognition of mild cases. This increase has not conclusively been linked to an increase in total alcohol consumption; patterns of drinking may also play a part (Tinto et al, 2002; Yang et al, 2008). In Britain at least, binge drinking has become more common in men under 26 years of age over the last 15 years, and there is evidence that the amount of alcohol consumed in the week before presentation with pancreatitis determines the severity of the attack (Yang et al, 2008). High alcohol consumption over a short period is an independent risk factor for a severe attack (Yang et al, 2008).

Does alcohol protect against gallstones?

Previous epidemiological studies have suggested that biliary disease is decreased by alcohol consumption (Kurtin et al, 1991; Thijs et al, 1991). The following mechanisms have been suggested:

1. Chronic ethanol exposure induces changes in the concentration and solubilization of cholesterol
2. Chronic ethanol exposure could be linked with decreased intestinal uptake of cholesterol
3. Ethanol may inhibit absorption of water by the gallbladder and alter the composition of biliary lipids.

Conflicting data come from studies showing reduced alcohol use in patients with symptomatic gallstones, suggesting that there is no causal relationship between alcohol consumption and gallstones (Thijs et al, 1991). Thus a clear history of alcohol abuse in a patient with acute pancreatitis does not preclude concomitant gallstones, which should be sought in the usual fashion.

Management of acute pancreatitis

Management depends on the likely aetiology and the severity of pancreatitis, as assessed by one of the multifactorial scoring systems (e.g. Ranson or Glasgow criteria, APACHE II) or by computed tomography (UK Working Party on Acute Pancreatitis, 2005). In general, three of every four attacks of acute pancreatitis are self-limiting, while the fourth is severe and can lead to complications and death (Corfield et al, 1985). Prompt recognition of more complex cases should be the focus of initial management, and severe disease should be managed in a critical care environment, where organ insufficiency be detected and corrected (Bang et al, 2008).

Besides supportive treatment – intravenous fluids and analgesics plus supplemental oxygen and nutritional support as needed – there is no specific therapy of proven value (Apte et al, 1997). As acute pancreatitis is strongly linked with calcium concentrations in the acinar cell, calcium channels could be a target for pharmacological intervention (Criddle et al, 2004; Bang et al, 2008). Prophylactic antibiotics are not beneficial, unless there are signs of infection or necrosis; likewise no clear value has been shown with gut decontamination. Enteral nutrition may preserve gut mucosal function and limit the inflammatory response (Powell et al, 2000). However, the benefit of enteral nutrition is not universally accepted, nor is the optimal method of delivery (nasogastric or nasojejunal tube) (UK Working Party on Acute Pancreatitis, 2005).

In terms of radiological investigation, current recommendations are that patients should have an ultrasound scan within 24 hours of admission, with contrast-enhanced computed tomography (spiral or multislice) being reserved for those with severe disease, in whom it will show the extent of pancreatic necrosis (UK Working Party on Acute Pancreatitis, 2005) (*Figure 1*). Given that at least half of severe pancreatitis is related to gallstones, there is a case for urgent computed tomography within 24 hours of diagnosis to detect patients who may benefit from urgent endoscopic retrograde cholangiopancreatiogram, i.e. within 72 hours of the onset of symptoms (Gurusamy et al, 2005). Urgent endoscopic retrograde cholangiopancreatiogram is only recommended for severe pancreatitis secondary to gallstones and for patients with acute cholangitis, jaundice or a dilated common bile duct. Sphincterotomy should be per-

formed whether or not stones are found in the bile duct; it should prevent bile reflux up the pancreatic duct (Sári et al, 2004; UK Working Party on Acute Pancreatitis, 2005; Siqin et al, 2009).

For alcoholic acute pancreatitis, treatment should include firm advice to stop drinking. Brief interventions such as group sessions focussing on abstinence can reduce alcohol consumption after one-to-four sessions (Apte et al, 2009). This relatively simple therapeutic approach may reduce both the frequency and the ferocity of recurrent alcoholic pancreatitis. Clear warnings should be given to abusers of alcohol about the likely outcome if they continue to drink, including the risk of progression to chronic pancreatitis.

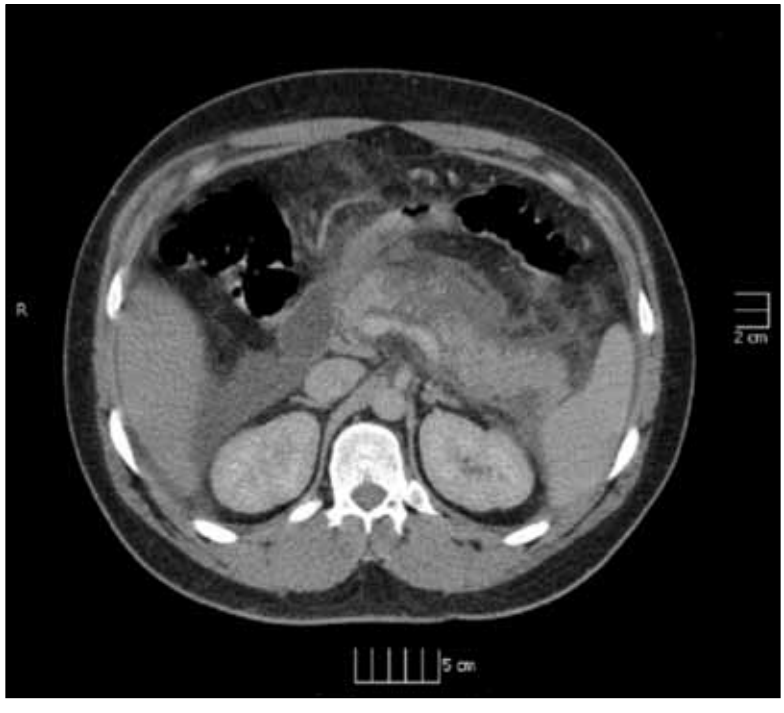
Chronic pancreatitis

Pathogenesis

Chronic pancreatitis is an inflammatory process leading to the progressive and irreversible destruction of exocrine and endocrine glandular pancreatic parenchyma, which is replaced by fibrotic tissue (Spanier et al, 2008). Four stages of disease progression are recognized:

1. Preclinical stage with either absent or non-specific symptoms
2. Recurrent episodes of acute inflammation without definite evidence of chronic pancreatitis on imaging
3. Recurrent episodes with intermittent or constant pain in between plus evidence of chronic pancreatitis on imaging (duct dilatation, pancreatic calcification) and impairment of exocrine function
4. Reduction in frequency and intensity of pain, with absence of acute flare-ups but progressive exocrine and endocrine insufficiency causing maldigestion and diabetes.

Figure 1. Transverse computed tomography scan showing marked peripancreatic inflammation and fluid collections within the pancreatic bed and lesser sac. Lack of enhancement within the body of pancreas suggests necrosis (in a 23-year-old man with acute severe alcoholic pancreatitis).



The risk of developing the disease increases with the amount and duration of consumption of alcohol: it is estimated that drinking more than 80 g alcohol per day for a minimum of 6–12 years is required to produce symptomatic disease (Chowdhury and Gupta, 2006). Two aetiological questions are unexplained: why only a minority of alcoholics suffer from pancreatitis and why some heavy drinkers develop cirrhosis of the liver or neurological disease instead (Spanier et al, 2008). Genetic mechanisms could explain this differential susceptibility (Jalleh et al, 1991), while dietary factors may also play a part: malnutrition, diets rich in fat and protein, and cassava consumption have been postulated as causes of chronic pancreatitis (Gullo, 2005; Chowdhury and Gupta, 2006; Criddle et al, 2007). Between 80 and 95% of alcohol abusers smoke and this habit is associated with both an earlier age of diagnosis and increased pancreatic calcification (Gullo, 2005; Spanier et al, 2008).

Clinical features

The typical patient with chronic alcoholic pancreatitis is a man of about 40 years who started drinking to excess when he began working some 20 years earlier (Gullo, 2005). Some patients present with an attack of acute pancreatitis and then sustain further attacks with increasing frequency but diminishing severity until they have pain on a daily basis. In others the disease is insidious, and by the time of clinical presentation (usually with deep-seated pain in the epigastrium) there are already features of chronic pancreatitis on imaging. Deteriorating exocrine function leads to steatorrhoea within 5–10 years of diagnosis of chronic pancreatitis. Ultimately the progressive fibrosis of the parenchyma involves the islet cells as well and leads to diabetes.

The pain of chronic pancreatitis is likely to be multifactorial: entrapment of the idiopancreatic nerve fibres, irritation of the coeliac plexus by peripancreatic inflammation, release of pain-producing substances within the gland, pressure from pseudocysts and compartment syndrome from oedema and fibrosis within the pancreatic 'capsule' (Jalleh and Williamson, 1992). Longitudinal studies indicate the eventual relief of pain as ongoing organ failure becomes absolute after a median period of 10 years, but sometimes the process of 'burn out' is both prolonged and incomplete.

In the authors' experience the single most useful imaging modality is abdominal computed tomography (*Figures 2* and *3*), which is more sensitive than plain X-ray in showing pancreatic calcification and can demonstrate additional features such as pseudocyst, dilatation of the main pancreatic duct, biliary stricture and involvement of the main blood vessels; there may be

thrombosis of the splenic vein, and less often the main portal vein, and occasional pseudoaneurysms of the splenic and pancreaticoduodenal arteries. Magnetic resonance imaging will show similar appearances on axial 'cuts' plus delineation of the pancreatic duct, bile duct and adjacent arteries and veins. Endoscopic retrograde cholangiopancreatiogram provides a sensitive means of scoring the changes in the pancreatic ductal tree associated with pancreatitis of increasing severity. Endoscopic ultrasonography, visceral angiography and on-table pancreatography (*Figure 4*) are other techniques of potential value in particular circumstances.

Management

Non-operative

Treatment starts with firm advice to abstain from alcohol completely; 'social' drinking is hard to control in someone accustomed to either a steady large intake or binges (Apte et al, 2009). Adequate pain relief should in theory help to curb intake in patients who drink to overcome their pain. Weight loss is a constant feature of end-stage pancreatitis, partly because food will often exacerbate the pain. Thus nutritional support and control of exocrine (and endocrine) insufficiency are important parts of the general care of a patient with chronic pancreatitis. Administration of pancreatic enzymes to inhibit pancreatic exocrine secretion is of limited value in patients with established chronic pancreatitis. Likewise the results of pancreatic denervation – either by percutaneous coeliac plexus block or thoracoscopic splanchnicectomy – are generally disappointing (Fleming and Williamson, 1995).

Indications for operation

There are three main indications for operative treatment in chronic pancreatitis. The commonest reason is intractable pain, but here the surgeon is faced with a conundrum: a major pancreatic resection may be unwise in a patient who is continuing to drink heavily, especially if it precipitates the need for insulin therapy. On the other hand, it is generally better to intervene before the patient becomes addicted to opiate drugs since a prolonged craving for pethidine or morphine may jeopardize the outcome of a potentially successful operation.

The second indication for operation is one or more 'obstructive' complications of the disease: pseudocyst formation, bile duct stricture causing persistent or recurrent jaundice, duodenal stenosis and potentially portal hypertension. In the authors' experience, although splenic vein thrombosis is quite a common feature in patients with left-sided pancreatitis, haemorrhage from the consequent oesophagogastric varices is rare. In general terms, the

Figure 2. Computed tomography scan in a 46-year-old man with chronic alcoholic pancreatitis: large pseudocyst within head of pancreas (thick arrow) containing focus of calcification. Note the distended gallbladder (thin arrow) (with incidental stone) caused by early bile duct obstruction.

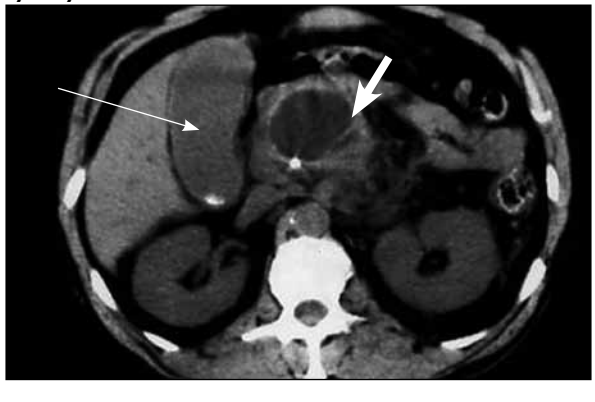


Figure 3. Two separate pseudocysts (arrows) contained within the head of pancreas in a 48-year-old man with chronic alcoholic pancreatitis.

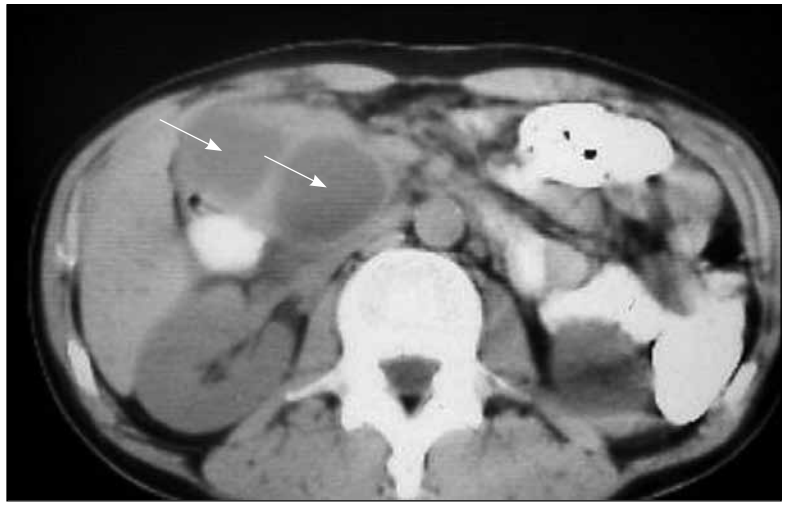
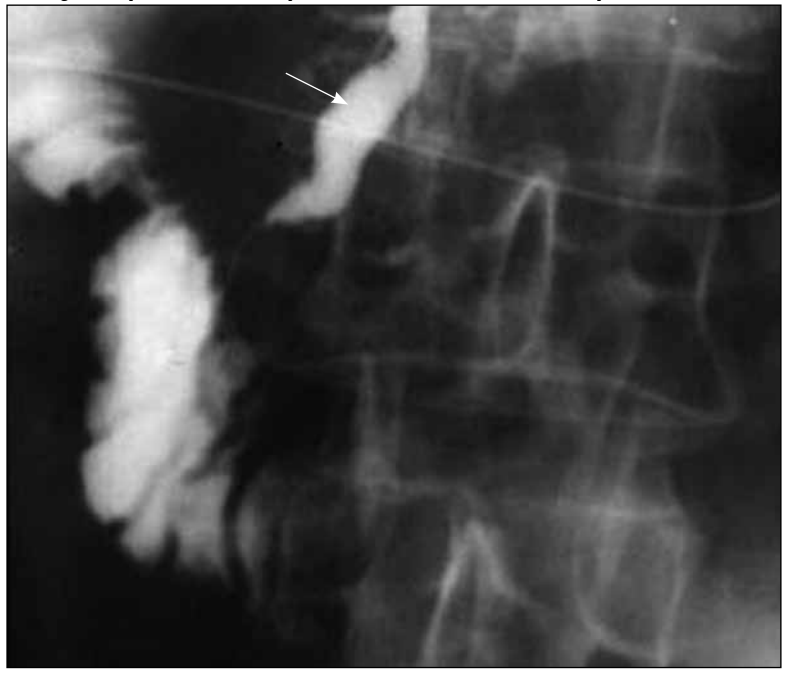


Figure 4. On-table pancreatogram obtained by cannulation of pancreatic duct in neck of pancreas after distal hemipancreatectomy. The grossly dilated duct (arrow) in the head of pancreas was drained into a Roux loop of jejunum, i.e. distal resection plus proximal drainage. The patient was a 41-year-old man with chronic alcoholic pancreatitis.



pseudocysts of acute pancreatitis are loculated collections of fluid rich in amylase that arise outside the gland (often in the lesser sac) and seldom communicate with the main pancreatic duct. By contrast, the pseudocysts of chronic pancreatitis are intrapancreatic in site, associated with parenchymal destruction and communicating with the ductal tree in up to half the cases (Grace and Williamson, 1993; Usatoff et al, 2000).

The third indication for operative intervention in chronic pancreatitis is the suspicion of cancer, which can arise in one of two clinical scenarios. Some patients present with relatively painless obstructive jaundice which mimics carcinoma of the head of the pancreas, especially if alcohol intake has been modest and there is no evidence of calcification. Sophisticated imaging cannot always differentiate between inflammatory and neoplastic mass, so resection of the pancreatic head may be the best expedient. Other patients have a cystic mass that could be neoplastic especially if irregular in shape and without a history of pancreatitis.

Surgical interventions

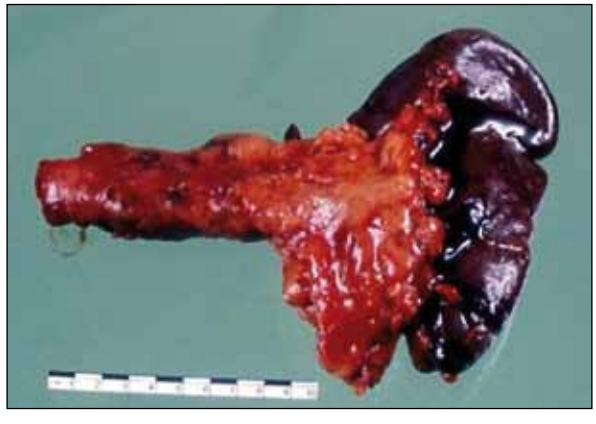
The most attractive operation for chronic pancreatitis is a drainage procedure, since it is safer than pancreatic excision and can achieve good pain relief without any (further) impairment of pancreatic function. External drainage of pseudocyst is generally unsatisfactory because of the frequency of communications between cyst and main pancreatic duct and thus the risk of chronic fistula to the skin. Internal drainage to a Roux loop of jejunum is an appropriate means of draining the pancreatic duct and/or associated pseudocyst (*Figure 5*). A long duct-to-jejunum anastomosis (longitudinal pancreaticojejunostomy Roux-en-Y) should provide permanent drainage of a dilated ductal tree. Rather like a fasciotomy, the long incision in the pancreas may decompress hypertensive parenchyma as well as duct and perhaps contribute to pain relief. Bile duct obstruction can be managed in one of two ways. If it is associated with an inflammatory mass, resection of the pancreatic head can relieve both pain and jaundice. In patients with end-stage disease and portal vein occlusion, hepaticojejunostomy is the only reasonable alternative; biliary stenting is inappropriate for persistent bile duct stricture caused by a benign condition.

If there is no obvious target to drain, pancreatic resection becomes appropriate. For disease predominantly in the head of pancreas, pancreatoduodenectomy may be the best option (Stapleton and Williamson, 1996). The pylorus can be preserved unless there is concomitant duodenal stenosis. An alternative option is Beger's operation in which the head of the pancreas is 'shelled out', leaving a rim of glandular tissue within the duodenal loop and creating a Roux loop for anastomosis to the pancreatic duct. A lesser – and simpler – variant is Frey's operation, in which longitudinal pancreaticojejunostomy is combined with a limited 'coring out' of inflammatory tissue surrounding the ducts in the head of pancreas.

Patients with persistent disease of the body and tail of pancreas are best served by a distal pancreatectomy, which will usually incorporate splenectomy (*Figure 6*) (Hutchins et al, 2002). In some patients with less severe inflammation and a patent splenic vein, conservative distal pancreatectomy may be appropriate; the pancreas is slowly separated from the splenic artery and vein, with division of numerous vascular twigs but preservation of the main trunks together with the spleen (Aldridge and Williamson, 1991). In general, distal hemipancreatectomy seems more likely to produce insulin-requiring diabetes than proximal hemipancreatectomy (Jalleh and Williamson, 1992). In patients with severe and generalized chronic pancreatitis who are already on insulin, total pancreatectomy may be appropriate, but it is a major undertaking. More often, total pancreatectomy is carried out as a second-stage procedure when pain recurs

Figure 5. Operative photograph in 37-year-old man with chronic alcoholic pancreatitis. Large pseudocyst (arrow shows thick 'rim') has been opened in head of pancreas before cystjejunostomy Roux-en-Y.

Figure 6. Conventional distal pancreatectomy specimen comprising body and tail of pancreas plus spleen (chronic alcoholic pancreatitis in 51-year-old man).



after a lesser resection. Good results can be anticipated in 70–80% of patients undergoing some form of pancreatectomy for chronic pancreatitis (Fleming and Williamson, 1995).

Conclusions

Although alcoholic pancreatitis is a disease on the increase, the exact causative mechanisms of pancreatic damage are not fully understood. The management of acute alcoholic pancreatitis is conservative, while operative management should be considered in chronic pancreatitis. It should be stressed that all operations on the pancreas carry appreciable risk, but a procedure that abolishes or greatly reduces pain is particularly worthwhile in terms of social rehabilitation. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Mechanisms of alcoholic injury to the pancreas include: direct damage to acinar cells, alterations to pancreatic juice and an effect on the sphincter of Oddi.
- The increasing incidence of acute alcoholic pancreatitis probably reflects national patterns of alcohol consumption.
- As no specific treatment of acute alcoholic pancreatitis has proven efficacy, the management remains primarily supportive.
- Chronic pancreatitis, which is generally related to persistent drinking, presents with pain and progressive organ dysfunction.
- Indications for operation in chronic pancreatitis are: intractable pain, one or more obstructive symptoms and suspicion of cancer. Options include drainage of pseudocyst or dilated duct or pancreatic resection tailored to the extent of disease.