ACUTE PANCREATITIS

MICHAEL PARKER provides an overview of the pancreas, its function and assessment, as well as the appropriate treatments for pancreatitis and their rationale.

Acute pancreatitis is a common emergency with potentially devastating consequences, but recognising symptoms early and good nursing and clinical assessment can benefit patients. Familiarity with the pathophysiology of the pancreas can provide an understanding of why acute pancreatitis can develop as well as its clinical presentation.

Acute pancreatitis is pancreatic inflammation due to auto-digestion. The condition is believed to develop when injury to the pancreatic duct allows proteolytic pancreatic enzymes to be activated prematurely in pancreatic tissue. The inflammatory response this initiates produces varying degrees of pancreatic oedema, fat necrosis and haemorrhage. Toxic enzymes are released into the bloodstream that can damage blood vessels and vital organs.

Most episodes are mild and self-limiting but up to a fifth of patients have attacks that can be fatal (Wilson et al 1990). The overall mortality rate of acute pancreatitis is between 5 and 10 per cent (Banks 1997, Banerjee et al 1995) but can increase to 35 per cent or more if complications develop (Banerjee et al 1995, Ranson 1993). In view of this, an underlying cause is usually sought so that appropriate treatment can be administered and recurrent episodes prevented.

In Europe and the US, gallstones and alcohol excess are the most common cause of acute pancreatitis, accounting for between 64 and 80 per cent of cases (Neoptolemos et al 1984). Figures suggest that in the UK gallstone disease is twice as likely as alcohol excess to be the cause (Beckingham and Bornman 2001).

Drugs, metabolic abnormalities, viral infections, trauma and various other rarer causes are implicated in up to 10 per cent of cases, and in between another 10 and 20 per cent of cases no abnormality is detected despite comprehensive investigations and biochemical screening. In these cases patients are conventionally classified as having acute idiopathic pancreatitis (Venu et al 1989).

THE PANCREAS AND ITS FUNCTIONS
The word pancreas comes from the Greek meaning ‘all flesh’. It is a long gland, which, because it resembles a bunch of grapes, is described as racemose: from the Latin word for a bunch of grapes, racemus.

It is situated behind the stomach, stretching from the duodenum to the spleen (Dorland 1994) (Fig. 1), and it has been described as the ‘hermit’ or ‘hidden organ’ of the abdomen because of its location behind the peritoneum (Gore 1994). Its location also makes it virtually impossible to palpate so life threatening lesions often go undetected until they encroach on other nearby structures such as the intestines.

The pancreas is portioned into three – the head, body and tail – and feeds into two pancreatic ducts: the principle duct, or duct of Wirsung, and the accessory duct, or duct of Santorini. These eventually join the common bile duct (CBD) and ultimately the duodenum (Fig. 1).

EXOCRINE AND ENDOCRINE ROLES
The pancreas has roles as both an exocrine and endocrine gland. Exocrine cells form 98 per cent of pancreatic tissue and consist of small clusters called acini (Tortora et al 1996), collectively known as acinar cells. The acinar cells make digestive enzymes in their inactive state (Box 1).

As well as being a protein digesting enzyme in its own right, trypsin is the catalyst for activating the other enzymes in the pancreas.

When trypsin is activated, there is a cascade of all the other enzymes and this results in auto-digestion and consequently...
produces symptoms of acute pancreatitis. The acini stop this from occurring by producing trypsin inhibitor.

The endocrine function of the pancreas is due to about a million small clusters of cells, known collectively as the islets of Langerhans (Fig. 1). The islets are richly vascularised, which allows the hormones they secrete to enter the circulation readily. They comprise only between 1 and 2 per cent of the total mass of the pancreas but they receive approximately 15 per cent of the total pancreatic blood volume (Guyton and Hall 1996).

The islets have three types of of cell, alpha, beta and delta (Fig. 1), which secrete glucagons, insulin and somatostatin respectively under the control of parasympathetic or sympathetic neurones. Cellular damage caused by acute pancreatitis can therefore affect blood sugar control.

**ALPHA CELLS**

Alpha cells produce glucagons, which maintain normoglycaemia through the process of glycogenolysis, the biochemical process by which glycogen is broken down into glucose, an important source of energy, and gluconeogenesis, the process by which glucose is synthesised from non-carbohydrate sources, such as amino acids, when carbohydrates are scarce. Both processes occur mainly in the liver and kidneys.

Hyperglycaemia lowers plasma glucagon levels and hypoglycaemia elevates them. Hyperglycaemia is induced by the ingestion of proteins and the presence of stressors such as infection, burns, tissue infarction and major surgery (Tortora et al 1996).

**BETA CELLS**

Beta cells produce insulin, which is responsible for controlling carbohydrate, protein and fat metabolism. It binds with cell receptors located throughout the body, thereby increasing cell membrane permeability to glucose, amino acids, and potassium, magnesium and phosphate ions, thereby reducing blood glucose levels (Kirkhorn 1995).

**Box 1. Digestive enzymes made by acinar cells**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Function</th>
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<tbody>
<tr>
<td>Trypsinogen</td>
<td>Converted into its active form, trypsin, in the duodenum, where it digests proteins</td>
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<tr>
<td>Chymotrypsinogen</td>
<td>Converted into its active form, chymotrypsin, also in the duodenum, where it also digests protein</td>
</tr>
<tr>
<td>Carboxypeptidase</td>
<td>Breaks down peptide bonds in proteins</td>
</tr>
<tr>
<td>Pancreatic lipase</td>
<td>Breaks down fats into glycerol and fatty acids</td>
</tr>
<tr>
<td>Pancreatic amylase</td>
<td>Digests starch into glucose, maltose and dextrin, and hydrolyses glycogen to yield glucose</td>
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DELTA CELLS
Delta cells secrete somatostatin, which performs many inhibitory functions: it inhibits growth hormone, thyroid stimulating hormone, insulin, the glucagon and various gastrointestinal hormones, as well as secretions from acinar cells (Amirata et al 1994). A synthetic analogue of somatostatin, called octreotide, is available and may prove beneficial in treating acute pancreatitis.

PATHOPHYSIOLOGY
Apart from mechanical factors, such as gallstones passing through the ampulla of Vater, the dilated part of the CBD where it is joined by the pancreatic duct, or cannulation during endoscopic retrograde cholangiopancreatography, little is known about how pancreatitis begins (Banks 1998, Beckingham and Bornman 2001). The early stages of acute pancreatitis are characterised by interstitial oedema in the pancreatic parenchyma and necrosis of the peripancreatic fat. The disease can progress to coagulation necrosis of pancreatic glandular elements and the surrounding fatty tissue, a condition described as necrotising pancreatitis (Gorelick 1995).

Premature activation of pancreatic enzymes is believed to be the central event in the pathogenesis of acute pancreatitis (Gorelick 1995). Banks (1998) however argues that the extent of the damage that auto-digestion causes is uncertain, and suggests that the early process of pancreatitis is incompletely understood because it is too difficult to access the organ and obtain biopsy specimens. In addition, most patients who seek clinical advice have already passed beyond the initial stage of the disease.

Nevertheless, in the absence of any other theory, Gorelick (1995) can provide a feasible sequence of events: once activated, trypsin can activate many other enzymes and this leads to the auto-digestion of pancreatic tissue as well as the systemic effects caused by circulating enzymes. These include vaso-dilatation, increased capillary permeability, resulting hypovolaemia, and disseminated intravascular coagulation (Gorelick 1995). In the most severe cases, the result is circulatory collapse, renal insufficiency and respiratory failure.

Despite the incomplete understanding of what starts to activate the enzymes, it is thought that predisposing factors include acute obstruction of the pancreatic duct, exposure to toxins or venoms, and ischaemia (Tortora et al 1996).

CLINICAL PRESENTATION
The manifestations of acute pancreatitis vary greatly depending on the severity of attack. Some patients are almost asymptomatic; others are in extreme distress with multiple and fatal organ failure (Wyatt et al 2001).

The hallmark of acute pancreatitis is a continuous, boring, epigastric pain, sometimes mistaken for an orthopaedic pain (Haycraft et al 1998). It often occurs between 24 and 48 hours after the ingestion of a heavy, fatty meal or the heavy use of alcohol (Brozenec 1998).

The pain is usually poorly localised, is often worse when patients are supine and radiates to the back in approximately half of cases (Beckingham and Bornman 2001, Haycraft 1998, Ruth-Sahd 1996). This is because the pancreas is located in the retroperitoneal space.

The pain can be accompanied by nausea, vomiting or pyrexia (Beckingham and Bornman 2001, Ruth-Sahd 1996). In contrast to the often abrupt onset of pain that accompanies perforation of an abdominal viscus, it increases in severity to a peak within between 30 and 60 minutes of pain onset or exposure to the predisposing factor, and then remains steady for many hours or days (Ruth-Sahd 1996).

THE DISEASE PROCESS
The cause of pancreatitis is multifactorial. The two most common theories are alcoholism in men and biliary tract disease in women over the age of 50 (Beckingham 2001).

Alcoholic pancreatitis is believed to result from the inflammatory effects of alcohol on the pancreas and its ducts. Supporting this belief is the ‘aftershave lotion theory’, so named because aftershave, which contains alcohol, smart when it enters the eye. According to the theory, alcohol can be expected to have a similar irritating effect on the sphincter of Oddi in the biliary tract, which prevents the reflux of duodenal contents, thereby putting it into spasm and obstructing secretion flow (Gorelick 1993).

This seems plausible but caution should be used when making comparisons between the membrane of the eye and the sphincter of Oddi in defining the cause of acute pancreatitis because they are different tissues that react differently to alcohol.
The inflammatory effects of alcohol are known, however, to damage the acini. This changes their secretory function and increases their enzyme and protein production (Holt 1993).

Acinar secretions become viscous, gluttonous and thickened by evaporation or absorption, and calcium carbonate precipitates resulting in ductal stone formation (Holt 1993). This leads to secretion obstruction and the degeneration and fibrosis of acini cells. Alcohol also may decrease muscle tone in the sphincter of Oddi causing reflux and premature activation of enzymes (Hadjak et al 1994).

There is no evidence that a single drinking bout in an otherwise abstemious person will lead to pancreatitis (Gorelick 1993). Researchers believe that it takes between five and 10 years of drinking several litres of spirits or the equivalent a day to cause pancreatitis (Healthman and Bullock 1996).

Beckingham and Bormman (2001) suggest that alcohol induced pancreatitis symptoms usually start 12 hours after an episode of binge drinking, but there is no reference to average daily intake of alcohol in their study, nor is it stated that the 12 hours post-binge is strictly applicable to known drinkers.

In biliary tract disease, obstruction of the biliary ducts (Fig. 1) can lead to increased pressure and rupture of the pancreatic duct. It can also cause reflux of bile and duodenal contents into the pancreas, leading to premature activation of enzymes and consequent auto-digestion.

The same model of bile activating pancreatic enzymes prematurely is used to describe gallbladder disease in women. Women are affected by this four times as often as men and it appears that pregnancy, obesity and diabetes are important predisposing factors (Burkitt et al 1998).

In gallbladder disease a stone leaves the CBD and becomes lodged in the main pancreatic duct outlet. The bile backs up in the CBD and enters the duct of Wirsung.
Box 2. Criteria for identifying severe pancreatitis early

'Severe pancreatitis' with a high risk of major complications or death is defined by the presence of three or more of the following features.

On presentation:
> age > 55 years (non-gallstone pancreatitis) or > 70 years (gallstone pancreatitis)
> leucocyte count > 16,000 x 10^9/L
> blood glucose > 10mmol/L (if not diabetic)
> lactate dehydrogenase > 350iu/L
> serum glutamic oxaloacetic transaminase levels > 100uL

Within 48 hours of presentation:
> haematocrit decrease by > 10 per cent
> serum urea increase by > 10mmol/L despite adequate intravenous therapy
> hypocalcaemia: corrected serum concentrations of calcium < 2mmol/L
> low arterial oxygen partial pressure: PO2 < 8kpa or 60mmHg
> metabolic acidosis: base deficit > 4mEq/L
> estimated fluid sequestration > 6L

(Ranson 1995)

Box 3. Modified Glasgow scoring system

The modified Glasgow scoring system is a prognostic tool used to assess patient morbidity and mortality early. It has a sensitivity of 68 per cent and a specificity of 84 per cent, and is particularly popular in the UK. Criteria to be identified within 48 hours of presentation. Severe disease is present if more than three factors are detected.

> age > 55 years
> white cell count > 15 x 10^9/L
> blood glucose > 10mmol/L
> urea > 16mmol/L
> arterial oxygen partial pressure < 8.0kpa
> albumin < 32g/L
> calcium < 2mmol/L
> lactate dehydrogenase > 600U or iu/L

(Imrie 1975)

activating the enzymes, which start to digest the pancreas.

PATIENT ASSESSMENT

Patients typically present with severe, constant, epigastric pain radiating into the centre of the back, with associated vomiting. They can be distressed due to the pain, sweating and pyrexial, and can show signs of hypovolaemia due to third space fluid loss. If there are signs of hypovolaemia, urgent fluid resuscitation should be initiated. Abdominal tenderness is likely to be worst in the epigastrium. A blush discolouration in the loins, known as the Grey-Turner's sign is not seen immediately but develops a few days after hypovolaemia and so is not a diagnostic tool in early presentation.

CRITERIA

Ranson's criteria provide valuable information about the severity of the acute inflammatory process using 11 factors (Box 2), but the simplified eight-risk factor system with modified Glasgow criteria, for use within the first 48 hours, is more widely used (Box 3). The modified Glasgow criteria is the easiest and quickest way to evaluate the severity of pancreatitis, and to ensure that patients are admitted to appropriate high dependency or intensive therapy units.

Mortality is between about 10 and 20 per cent when there are between three and five signs present, and 50 per cent when there are six or more signs (Banks 1997).

A third set of criteria, Apache 11, has high sensitivity and specificity in differentiating mild from severe pancreatitis, but it is time consuming and involves using a computer to ascertain values (Banks 1997). It is therefore rarely used.

Another method of investigation that is becoming more popular is computed tomography (CT) scanning. Days, even hours after an acute pancreatitis attack, CT scanning may offer better indications of prognosis than the more commonly used scoring systems and can show inflammation, fluid collection and changes consistent with necrosis. In general, the more complex the symptoms revealed by CT scans, the more likely patients will suffer a complicated course (Forsmark 2000) (Fig. 2). Other, more commonly used investigations and their rationales are listed in Box 4.

TREATMENT

Oxygen delivery and fluid resuscitation

Providing adequate oxygen is essential when treating patients in hypovolaemic shock. The effectiveness of oxygen delivery should be judged against patients' arterial oxygen partial pressure reading and titrated as necessary.

Close monitoring should be adopted to establish the effectiveness of tissue perfusion, with particular attention paid to
pulse, blood pressure, capillary refill and general cognitive state. It should be noted, however, that in the initial stage of hypovolaemic shock, and to some degree in compensated hypovolaemic shock, the body often remains within normal physiological parameters (Adomat 1992).

References in the literature to how often observations should be made are limited; most texts simply acknowledge that they take place. But frequency could start at a rate of once every five minutes and be adjusted according to clinical condition.

Intravenous (IV) access is essential for administering fluids and analgesia, and should be gained as early as possible.

Two wide-bore, 14-16g peripheral lines should preferably be inserted in the left and right antecubital fossae (American College of Surgeons 1993). Intravenous fluids should be given in accordance with the level of hypovolaemic shock (Wyatt 2001).

The inflammatory exudates around the pancreas resemble those of internal burns and consequently fluid may be sequestered into the retroperitoneal and peritoneal spaces. It is of paramount importance that this fluid is replaced.

Choice of replacement fluid – blood, crystalloid or colloid – should be based on haemodynamic state and the results of tests to ascertain levels of haemoglobin, haematocrit and serum albumin.

Resuscitation, however, is usually with crystalloid (Beckingham and Bornman 2001) but colloids may be required to restore circulating volume. Fluid resuscitation is monitored by ensuring that urine output exceeds 30 mL/h.

Some texts advocate using normal saline to prevent hypotension and maintain sufficient hydration (McCance and Huether 1997) but others advocate IV fluids with electrolyte replacement such as Hartmann’s fluid (Ruth-Sahd 1996).

The volume of fluid being administered and rate of administration should be determined by blood pressure, central venous pressure and urine output, and patients should have indwelling urinary catheters to measure involuntary production of urine (Ruth-Sahd 1996).

### Box 4. Commonly used investigations and their rationales

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>Oxygen saturations</td>
<td>Patients can show signs of hypoxia resulting from hypovolaemia due to third space fluid loss</td>
</tr>
<tr>
<td>Blood glucose concentration</td>
<td>If insulin production has decreased, patients can be expected to have higher circulating blood glucose levels because glucose can no longer enter muscle and adipose tissue</td>
</tr>
<tr>
<td>Serum amylase</td>
<td>Amylase is an enzyme secreted by the pancreas. Serum concentrations are grossly elevated in patients with acute pancreatitis. Test results are usually available within an hour but have low specificity; normally less than 70 per cent (Gorelick 1995). It should be noted that other conditions can also cause rises in serum amylase: perforated viscus, renal insufficiency and salivary gland inflammation. Amylase is a small molecule that is rapidly cleared by the kidneys, so large serum concentrations tend to be short lived</td>
</tr>
<tr>
<td>Serum lipase</td>
<td>Testing serum lipase is the test of choice, and can give results as quickly as serum amylase tests (Agarwal 1990). The simultaneous determination of amylase and lipase offers a sensitivity and specificity of between 90 and 95 per cent for detecting acute pancreatitis in patients presenting with acute abdominal pain (Calvien 1989). Serum lipase takes longer to clear from the bloodstream than amylase so is a more useful ‘historical’ indicator</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>This is used to rule out pleural effusion. Acute respiratory distress syndrome is common in severe attacks of acute pancreatitis (Burkitt et al 1998)</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Pancreatitis can cause gross fluid and electrolyte disturbances including hypocalcaemia. Electrocardiograms should therefore be taken to ensure that patients are in sinus rhythm (Burkitt et al 1998)</td>
</tr>
<tr>
<td>Arterial blood gas sampling</td>
<td>In the absence of insulin, large quantities of fatty acids are released into the circulation following the breakdown of stored triglycerides. This raises the volume of fatty acids in the liver. These are converted into acetoacetic acid, which cannot be metabolised and causes metabolic acidosis. Patients can show signs of hyperventilation as they try to ‘blow off’ carbon dioxide. Pancreatitis also reduces levels of bicarbonate, the body’s natural buffer. This causes blood pH to drop to as low as 7, which can be fatal.</td>
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**Morphine sulphate versus pethidine**

Assessing and treating pain in patients with pancreatitis is vital. The most common method of assessing pain is using the
Box 5. Aims and objectives

When you have read the article you should be able to answer the following questions:

> Where is the pancreas situated in the abdomen?
> Why has the pancreas been described as a hermit?
> Name the principle pancreatic duct
> Name the accessory pancreatic duct
> Exocrine cells form what percentage of the pancreatic tissue?
> What is the active form of trypsinogen?
> The endocrine function of the pancreas comprises around one million small clusters of cells, known collectively as what?
> What do alpha cells secrete?
> What do beta cells secrete?
> What to delta cells secrete?
> What mechanical factors are said to cause acute pancreatitis?
> Name the two most common causes of acute pancreatitis
> What clinical signs would you expect to see in patients with acute pancreatitis?
> What sign may be seen in patients with pancreatitis a few days after onset?
> Name the two predictor systems used to identify morbidity and mortality rates in patients with acute pancreatitis
> What analgesic is recommended for the treatment of acute pancreatitis?
> What other drug mentioned is also available for treating pain in patients with acute pancreatitis?

You should also:

> be able to identify the main functions of the pancreas as an endocrine and exocrine gland
> be aware of the altered pathophysiology in patients with acute pancreatitis
> know the two most common causes of acute pancreatitis
> know the most common presenting complaints of patients with acute pancreatitis
> understand what investigations are needed and why
> understand the use and implications of the relevant predictive scoring systems
> understand the drug therapy to treat acute pancreatitis.

However, the 'pethidine is better than morphine sulphate' debate is based on a common misconception that pethidine does not affect the sphincter of Oddi. In fact, like all opioids it can increase smooth muscle tone and so reduce biliary and pancreatic secretions and so increase bile duct pressure. This can lead to biliary spasm and constriction of the sphincter of Oddi (Pasero 1998).

There is no research evidence for using pethidine over morphine in patients with pancreatitis (Paulson 2002). Morphine, however, is better than pethidine for severe pain management in terms of duration (British National Formulary 2003), and repeated administration of pethidine can result in the accumulation of its metabolite, norpethidine, which causes increased central nervous system irritability and possibly seizures (Paulson 2002).

FUTURE OPTIONS FOR ANALGESIA

More research into analgesic treatment is needed, but preliminary clinical trials suggest that the long acting somatostatic analogue, octreotide, can reduce pancreatitis pain that is unrelieved by opioids.

Octrerotide, like somatostatin, is believed to work by suppressing the pancreatic secretions that cause auto-digestion. It is given every 12 hours subcutaneously and has few adverse effects (Pasero 1998).

The value of antibiotics in severe acute pancreatitis has been discussed for many years. Controlled trials suggest that there is a probable role for their use in preventing complications related to sepsis (Golub et al 1998). Current evidence shows that imipenem is better than other drugs such as quinolones, which cannot penetrate pancreatic tissue (Bass et al 1998).

To reduce discomfort, patients should be given nil by mouth, have nasogastric tubes placed on free drainage inserted, and be administered antiemetics such as cyclizine (Wyatt 2001).

CONCLUSION

Acute pancreatitis is a life threatening condition with high mortality and morbidity rates. Patients typically present with severe epigastric pain that radiates to the back. They may be vomiting or at least complain of nausea. Depending on the severity of the attack, patients can also display signs of hypovolaemia that needs urgent fluid resuscitation.
Patients should receive oxygen, and routine blood tests should be taken. Levels of serum amylase and serum lipase should be tested to enable diagnosis of acute pancreatitis within between 90 and 95 percent specificity and sensitivity.

Routine chest X-rays, electrocardiograms and arterial blood gas sampling should be sought to rule out pleural effusion, cardiac arrhythmias and metabolic acidosis. Urinary catheters should be placed in situ, and urine output readings should be taken hourly. Urine output should not fall below 30mL/h.

Intravenous opiates should be given for pain, although the drug of choice usually depends on the preferences of individual clinicians. Patients should be given nil by mouth, prescribed antiemetics and have nasogastric tubes inserted.

Patients who score highly on the Ranson’s or modified Glasgow criteria should be moved to high dependency or intensive therapy units for close monitoring.

References
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