Objectives

After studying this chapter you should be able to:

1. Describe the macroscopic and microscopic anatomy of the pancreas and relate these to its function.

2. Describe the components of exocrine function of the pancreas and apply this knowledge in understanding the pathological conditions of acute and chronic pancreatitis and cystic fibrosis.
sphincter muscle relaxes and allows the pancreatic juice and bile into the small intestine. The control of the sphincter of Oddi is discussed in Chapter 7. Exocrine dysfunction of the pancreas may be due to disorders of the pancreas itself, or to blockage of the main ducts which prevents the exocrine secretions reaching the duodenum. Duct blockage may also result in impaired bile flow from the liver and so cause jaundice.

In the small intestine, pancreatic juice, bile, and the juices secreted by the walls of the intestines, mix with the fluid (chyme) arriving from the stomach. Pancreatic juice provides most of the important digestive enzymes. In addition, by virtue of its HCO$_3$- content, it helps to provide the appropriate pH in the intestinal lumen for the enzymes to act on their nutrient substrates. The functional importance of the pancreas to the digestive processes can be illustrated by the problems arising in an individual suffering from chronic pancreatitis, a condition in which pancreatic tissue is destroyed.

**Introduction**

The pancreas contains exocrine tissue which secretes pancreatic juice, a major digestive secretion, and endocrine tissue which secretes the hormones insulin and glucagon. The hormones are important in the control of metabolism and their roles in the absorptive and postabsorptive metabolic states will be discussed in Chapter 9. This chapter will be mainly concerned with the exocrine secretions of the pancreas, their functions, and the mechanisms whereby the secretory processes are controlled.

Pancreatic juice finds its way into the duodenum via the pancreatic duct which opens into the duodenum at the same location as the common bile duct (see Chapter 1). Entry of both pancreatic juice and bile into the duodenum is controlled by the sphincter of Oddi. The smooth muscle of the sphincter is contracted between meals so that the junction is sealed. When a meal is being processed in the gastrointestinal tract, the sphincter muscle relaxes and allows the pancreatic juice and bile into the small intestine. The control of the sphincter of Oddi is discussed in Chapter 7. Exocrine dysfunction of the pancreas may be due to disorders of the pancreas itself, or to blockage of the main ducts which prevents the exocrine secretions reaching the duodenum. Duct blockage may also result in impaired bile flow from the liver and so cause jaundice.

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**Chronic pancreatitis Box 1**

**Chronic pancreatitis**

A forty-year-old man who had been a heavy drinker for many years, went to see his general practitioner. He had made two previous visits over the past year due to his experiencing recurrent episodes of abdominal pain. Although the pain had been intermittent at first, it was now continuous. The patient also said that he had lost a considerable amount of weight since his last visit. Upon enquiry the pain was described to originate in the epigastrium, and to radiate through to the back. In appearance the patient was very thin and the doctor noticed that he was mildly jaundiced. The doctor arranged for the patient to be admitted to hospital for a few days for tests so that his condition could be diagnosed. He was submitted to an x-ray examination, and serum and urine analyses were performed. The patient's stools were collected over three days. These were seen to be pale-coloured and bulky, indicating a high fat content (steatorrhoea). He was told to abstain from food the next morning so that a glucose tolerance test could be performed. The patient's response to secretin was also tested. This involved an injection of secretin (1 CU/kg body weight) and continuous aspiration of the duodenal contents until the water and bicarbonate output had returned to the initial level.

The blood tests showed a reduced serum pancreatic isoamylase, but increased bilirubin and alkaline phosphatase. The glucose tolerance test showed an abnormally high and prolonged rise in serum glucose, and urine analysis confirmed the presence of glycosuria (glucose in the urine), indicating that the patient was diabetic. The secretin test indicated a decreased pancreatic secretory response as manifest by a low level of HCO$_3$- secretion. The presumptive diagnosis was chronic pancreatitis. The patient was prescribed pethidine to control the pain. He was advised to abstain completely from alcohol, and to try to eat regular meals.

Examination of the details of this case gives rise to the following questions:

1. Is the primary defect in chronic pancreatitis known? What might the x-ray have revealed? What could be the cause of the condition in this patient?
2. How are the exocrine and endocrine functions of the pancreas impaired in chronic pancreatitis? How is this condition diagnosed? What did the high faecal fat content indicate? What is the basis of a) the secretin test, b) the glucose tolerance test? Why has diabetes mellitus developed in this patient? Why was the patient jaundiced? Why were the patient’s serum bilirubin and alkaline phosphatase abnormally high?
3. What are the main physiological consequences of this disease and how can the condition be treated or managed?

We shall address these questions in this chapter.
Anatomy

The pancreas is an elongated gland which lies in the abdominal cavity. It can be divided into three regions: the head, the body and the tail (Figs 5.1 and 5.2). The head is an expanded portion that lies in the C-shaped region of the duodenum to which it is intimately attached by connective tissue, and which is connected by a common blood supply. The body and tail extend across the midline of the body toward the hilum of the spleen. The pancreatic duct (duct of Wirsung) extends through the long axis of the gland to the duodenum. Pancreatic juice empties from this duct into the duodenum via the ampulla of Vater. In some individuals there is also an accessory pancreatic duct. Bile in the common bile duct from the liver also enters the duodenum at the ampulla of Vater.

Exocrine tissue

The exocrine units of the pancreas are tubuloacinar glands which are organised like bunches of grapes, in a similar manner to the units in the salivary glands (Fig. 5.3). These exocrine units surround the islets of Langerhans, the endocrine units of the pancreas. A thin layer of loose connective tissue surrounds the gland. Septa extend from this layer into the gland, dividing it into lobules, giving it an irregular surface. Larger areas of connective tissue surround the main ducts and the blood vessels and nerve fibres that penetrate the gland. Small mucous glands situated within the connective tissue surrounding the pancreatic duct secrete mucus into the duct.

Endocrine tissue

The endocrine units, or islets of Langerhans, are most numerous in the tail region of the pancreas. They consist of clusters of cells which are surrounded by the pancreatic acini (Fig. 5.3). The islets vary considerably in size. As with all endocrine tissue, the hormones they produce are secreted into the blood. The major
endocrine cell types present are α, β, D, and PP cells which secrete glucagon, insulin, somatostatin, and pancreatic polypeptide, respectively (for more information see Chapters 8 and 9). Different types of endocrine cells can be distinguished under the electron microscope by the different appearance of the granules within them. The islet cells have the general features of APUD cells (see Chapter 1). In addition there are a few (less than 5%) small ‘clear’ cells with as yet no clearly defined function.

Glucagon and insulin, the hormones produced by the α and β cells respectively are taken up by the local blood vessels to act systemically. Somatostatin acts locally in a paracrine manner to inhibit the secretion of the α and β cells, as well as the exocrine secretions of the acinar and duct cells. Pancreatic polypeptide acts in a paracrine manner to inhibit the exocrine secretions of the pancreas.

Oxygenated blood is supplied to the pancreas by branches of the coeliac and superior mesenteric arteries. The blood drains from the pancreas via the portal vein to the liver. The acini and ducts are surrounded by separate capillary beds. Some of the capillaries that supply the islets converge to form efferent arterioles, which then enter further capillary networks around the acini. This arrangement is important for the paracrine control of pancreatic exocrine secretion.

Cholinergic preganglionic fibres of the vagus nerve enter the pancreas. These synapse with postganglionic cholinergic nerve fibres which lie within the pancreatic tissue and innervate both acinar and islet cells. Postganglionic sympathetic nerves from the coeliac and superior mesenteric plexi innervate the pancreatic blood vessels as well as the acinar and duct cells.

**Histology of the exocrine tissue**

Figure 5.3 shows the structure of a pancreatic lobule. The exocrine units of the pancreas, or pancreatons, each consist of a terminal acinar portion and a duct (Fig. 5.4). The duct that drains the acinus is known as an intercalated duct. These empty into larger intralobular ducts. The intralobular ducts in each lobule drain into a larger interlobular duct which empties the secretions of that lobule into still larger ducts, and the latter converge into the main collecting duct, the pancreatic duct.

The acinus is a rounded structure consisting of mainly pyramidal epithelial cells (Fig. 5.4). These cells secrete the digestive enzymes of the pancreatic juice. They display polarised features which are common to secretory cells (Fig. 5.3). The nucleus of the acinar cell is situated at the base of the cell. The cytoplasm in the basal region can be stained with haematoxylin or basic dyes due to the presence of rough endoplasmic reticulum, the site of production of the digestive enzymes. Small mitochondria are situated throughout the cell. The apical portion of the cell contains the Golgi apparatus, and numerous zymogen granules which contain the pancreatic enzymes or enzyme precursors. The apical region therefore stains with acid dyes such as eosin. Microvilli extend from the apical surface of the acinar cell into the lumen. The apical poles of neighbouring cells are joined by tight junctions, known as zonulae adherens. These junctions separate the fluid in the lumen of the acinus from the fluid in the intercellular spaces that bathes the basolateral surfaces of the cells. The tight junctions are impermeable to macromolecules, such as digestive enzymes, in the luminal fluid, but permit the exchange of water and ions between the
Pancreatic juice

Composition of pancreatic juice

The pancreatic juice entering the duodenum is a mixture of two types of secretion, an enzyme-rich secretion and an aqueous alkaline secretion. If the ducts are ligated near the acini, which results in acinar cells degeneration, the secretion of the alkaline component of the juice is largely unaltered, but the secretion of enzymes is markedly reduced. This indicates that the enzymes are secreted by the acinar cells, and the alkaline fluid by the duct cells. The alkaline secretion originates largely from the centroacinar cells and the duct cells of the intralobular and small interlobular ducts. These relationships are illustrated in Figure 5.4.

Alkaline secretion

Composition

The cells of the upper ducts secrete an isotonic juice which is rich in bicarbonate but contains only traces of enzymes. There is a continuous resting secretion of this juice, but it can be stimulated up to 14-fold during a meal. It contains Na\(^+\), K\(^+\), HCO\(_3\)\(^-\), Mg\(^2+\), Ca\(^2+\), Cl\(^-\) and other ions, present in concentrations similar to those of plasma. It therefore resembles an ultrafiltrate of plasma. It is alkaline by virtue of its high HCO\(_3\)\(^-\) content.
Functions

The pancreatic juice arriving in the duodenum is mixed with the chyme by contractions of the smooth muscle of the small intestine. The function of the alkaline pancreatic secretion, together with the other alkaline secretions (bile and intestinal juices) that act in the small intestine, is to neutralise the acid chyme arriving from the stomach. This is important for several reasons: i) the pancreatic enzymes require a neutral or slightly alkaline pH for their activity, ii) the absorption of fat depends on the formation in the intestinal lumen of micelles, a process which only takes place at neutral or slightly alkaline pH values, iii) it protects the intestinal mucosa because excess acid in the duodenum can damage the mucosa and lead to the formation of ulcers.

Cellular mechanism of secretion

The mechanisms involved in the production of intracellular HCO₃⁻ in the centroacinar and upper duct cells depend on the formation in the intestinal lumen of micelles, a process which only takes place at neutral or slightly alkaline pH values, iii) it protects the intestinal mucosa because excess acid in the duodenum can damage the mucosa and lead to the formation of ulcers.

Defect and causes

Now we can ask what the primary defect in chronic pancreatitis might be and how the use of x-rays can reveal it. We can also ask what is the likely cause of the condition in this patient.

The primary malfunction in chronic pancreatitis is probably defective ductal secretion of bicarbonate and water which results in a high protein concentration in the pancreatic juice in the ducts. This results in the precipitation of protein, and the formation of protein plugs, and consequently dilatation of the proximal ducts. The effect of blockage of the ducts is the generation of a high pressure in the ducts which causes pain. Secondary back pressure may lead to disruption of the integrity of the ductal epithelium and result in destruction of the pancreatic tissue. This can lead to an inflammatory and fibrotic process in and around the pancreatic tissue. This in time leads to pancreatic insufficiency. Fibrosis around the autonomic nerves which surround the pancreas may result in back pain, which is a common feature of this condition.

Chronic pancreatitis is characterised by progressive functional damage to the pancreas, with or without evidence of inflammation. There is permanent destruction of pancreatic tissue, and exocrine and endocrine pancreatic insufficiency usually follows. However, owing to the tremendous reserve of pancreatic tissue, the insufficiency may be subclinical and tests of pancreatic function may be necessary to reveal it. The histopathology indicates irregularly distributed fibrosis, reduced number and size of islets of Langerhans, and variable obstruction of pancreatic ducts of all sizes. Protein precipitation initially occurs in the lobular and interlobular ducts, leading to the formation of plugs that calcify by surface accretion. Concentric lamellar protein precipitates appear in the major pancreatic ducts and these subsequently also calcify to form stones. A specific protein, called stone protein, a normal constituent of pancreatic juice, which has a high affinity for Ca²⁺, appears to be the major protein present in pancreatic stones. The calculi contain calcium bicarbonate or hydroxyapatite (calcium phosphate and calcium bicarbonate). The stones can be seen in x-rays (see Fig. 5.5). Foci of acinar ectasia are present, and acinar atrophy, chronic inflammation, and fibrosis, in areas of ductal obstruction. These, together with stricture formation due to peri ductal fibrosis eventually lead to ductal ecleasia. The chronic inflammation may extend to adjacent organs, causing constriction of the duodenum, stomach antrum, common bile duct, or transverse colon. Central epigastric pain is a common feature of chronic pancreatitis and is due to referred pain from the embryological foregut. Fibrosis and inflammation around the pancreas may involve the coeliac plexus of autonomic nerves resulting from the chronic pain that may accompany this condition.

In 90 per cent of patients with chronic pancreatitis there is a history of excessive alcohol intake. However the incidence of the disease is low, being approximately 30 per 100000 in the United Kingdom. Onset is usually in middle age. The disease is approximately three times more common in males than females. Affected patients are presumably susceptible to pancreatic damage by alcohol, although the genetic mechanism is poorly understood. Rare autosomal dominant inherited forms of the disease have been described. Most alcoholic patients already have sustained permanent structural and functional damage to the pancreas by the time of their first attack of abdominal pain. Moreover the morphological changes seen in chronic pancreatitis are evident at post mortem examination in many alcoholics who had no symptoms of pancreatic disease during life. Asymptomatic alcoholics often exhibit abnormal exocrine function when subjected to the secretin test. It is not precisely known how alcohol causes chronic pancreatitis. It may promote pancreatic duct obstruction through causing precipitation of proteins that are secreted by the pancreatic tissue.
are illustrated in Figure 5.6. The initial intracellular step involves the reaction of CO₂ and water. Secreted H⁺ ions react with HCO₃⁻ ions in the blood perfusing the gland and this generates CO₂, some of which diffuses into the duct cell. More than 90% of the HCO₃⁻ in pancreatic juice is derived from blood CO₂. In the cell the CO₂ combines with intracellular water to generate carbonic acid, in a reaction which is catalysed by carbonic anhydrase II, an enzyme present in the centroacinar and upper duct cells. The carbonic acid dissociates to give HCO₃⁻ and H⁺. Whilst bicarbonate is being secreted from the luminal membrane by Cl⁻/HCO₃⁻ exchange, and the H⁺ ions are secreted into the blood. Thus for every HCO₃⁻ ion that is secreted into the duct lumen one H⁺ ion is secreted into the blood. Therefore the blood flowing through the pancreas becomes transiently acid when it is secreting HCO₃⁻. The H⁺ ions in the blood help to neutralise the ‘alkaline tide’ produced during a meal by the secreting stomach (see Chapter 3), by combining with plasma HCO₃⁻ to produce CO₂. In post-surgical conditions where the patient has been provided with a draining pancreatic fistula, the pancreatic juice drains to the outside and the patient incurs considerable losses of HCO₃⁻. A pancreatic fistula that is in direct communication from the main pancreatic duct to the skin does not contain significant quantities of activated enzymes. However if the fistula communicates from the duodenum to the skin then the digestive enzymes are active and can cause a significant amount of skin excoriation and damage. This will result in considerable management problems until the fistula closes. Loss of HCO₃⁻ results in a metabolic acidosis. This is usually compensated for by renal and respiratory mechanisms. Fluid and electrolyte losses, however, can be more difficult to manage because the patient may have a restricted oral intake. Replacement via intravenous infusion is necessary.

The exchange mechanism in the centroacinar and upper duct cells, whereby HCO₃⁻ is secreted in exchange for Cl⁻, obviously depends on the presence of Cl⁻ in the fluid in the lumen. Cl⁻ flux out of the cell into the lumen is via a chloride conductance channel known as the cystic fibrosis transmembrane conductance regulator (CFTR) which is regulated by cyclic AMP. Immunocytochemical studies using fluorescent antibodies against the CFTR have shown that it is localised to the apical region of centroacinar and intralobular duct cells. The CFTR is coupled to the HCO₃⁻/Cl⁻ exchanger. Failure of this secretory mechanism is seen in cystic fibrosis (see below). It results in a high concentration of protein in the pancreatic ducts which can block the lumen. This results in secondary pancreatic damage; a process similar to that which occurs in chronic pancreatitis.

The Cl⁻ channel is present in clusters in the apical plasma membranes. When the gland is stimulated (by secretin or by an increase in cAMP), the channel clusters disaggregate (see Fig. 5.6) increasing the number of open channels. The channel is regulated in two ways: i) via phosphorylation and dephosphorylation by protein kinase A and a phosphatase respectively, which serves as a molecular switch involved in the gating of the channel, and ii) via activation of the channel by hydrolysis of ATP and other nucleotides.
The main features of the ion transport relationships in the pancreatic duct cell are shown in Figure 5.6. It has been observed, using electron microscopy, that when the cell is not being stimulated it contains numerous tubulovesicles in its apical cytoplasm. The membranes of these vesicles contain proton pumps which are ATPases. When the cell is stimulated, the tubulovesicles are translocated to the basolateral surface and their membranes fuse with the basolateral plasma membrane. Thus the proton pumps are incorporated into the membrane. Then H⁺ ions are actively pumped out of the cell into the interstitial fluid in the lateral spaces, and from there they diffuse into the plasma. Electron microscope studies have shown that stimulation of secretion involves a change in the shape of the cell. This is associated with expansion of the basolateral plasma membranes as the membrane of the vesicles fuse with it. The fusion of the membranes is an active process that derives its energy from the breakdown of ATP which is catalysed by the ATPase of the pumps.

Cl⁻ ions are secreted by the cells into the lumen via the CFTR (see above). Na⁺ and K⁺ ions reach the pancreatic juice by the paracellular route (between the cells), travelling down the electrochemical gradient. Water flows down the osmotic gradient (created by the ion transport) either transcellularly or paracellularly, from the lateral spaces. A Na⁺/K⁺-ATPase pump in the lateral borders of the cell transports Na⁺ out of the cell and this maintains a low intracellular concentration and high extracellular concentration of Na⁺ ions. A Na⁺/H⁺ exchange mechanism also operates at the basolateral pole of the cell to keep the intracellular pH stable, but this mechanism is probably not activated during secretion.

The bicarbonate concentration in the pancreatic juice that enters the duodenum ranges from 25 to 150 mM. The electrolyte composition of the juice varies with the flow rate. Figure 5.7 shows the changes in concentrations of HCO₃⁻ and Cl⁻ ions with increasing rates of flow. There is a reciprocal relationship between the concentrations of the two ions. The concentration of HCO₃⁻ increases with increasing flow rate and the concentration of Cl⁻ decreases. The sum of the concentrations of the two ions is kept constant by the action of the ion exchange pumps. As the HCO₃⁻ concentration increases, the juice becomes more alkaline.

The changes in the ionic composition of the juice with rate of flow are due to the presence of transport systems in the membranes of the duct cells. The primary alkaline juice secreted at the tops of the ducts is modified as it passes down the ducts by transport systems in the cells lower down in the extralobular ducts, and in the main ducts. At high flow rates the time the juice spends in contact with the cells is not sufficient for appreciable modification via HCO₃⁻/Cl⁻ exchange and other processes to take place. Therefore the composition of the juice produced at high flow rates resembles that of the primary secretion more closely than juice secreted at low flow rates.

**Fig. 5.7**
Variation in the composition of pancreatic juice with respect to Cl⁻ and HCO₃⁻, with rate of flow.

**Fig. 5.8**
Plain abdominal X-ray taken from a baby with cystic fibrosis. The meconium stool has obstructed the bowel and can be seen in the caecum (A). The proximal small bowel loops have dilated (B) and are filled with gas.
Cystic fibrosis

In the autosomal recessive inherited disorder known as cystic fibrosis the biochemical lesion is a defect in cyclic AMP-regulated chloride conductance via the CFTR. The defect is manifest in epithelial cells of the wet surfaces of the gastrointestinal tract, the respiratory tract, the reproductive tract, and the sweat glands. In the pancreas the defect in the CFTR is associated with defective secretion of bicarbonate and water. This leads to the formation of inspissated protein plugs which obstruct the proximal intralobular ducts. Reduced fluid secretion in the gastrointestinal tract results in mucous plugging of the intestinal lumen, and, in severe neonatal cases, gastrointestinal obstruction can develop. This is known as meconium ileus (Fig. 5.8). The same process of mucous plugging results in blockage of the bronchioles. This leads to recurrent respiratory infection and, later to respiratory failure.

Pancreatic enzymes

The enzymes released from the pancreatic acinar cells comprise the major enzymes involved in the digestion of foodstuffs. Many of these are secreted as inactive precursors. The acinar cells contain zymogen granules, which are the locus of storage of enzyme or enzyme precursor protein. The enzyme precursors produced by the acinar cells include those of the proteolytic enzymes, trypsin, chymotrypsin, carboxypeptidase and elastase, and that of phospholipase A. Lipase, α-amylase, ribonuclease, and deoxyribonuclease are secreted as active enzymes. The release of enzymes as inactive precursors ensures that the activated enzymes do not autodigest the pancreatic tissue.

Secretion of enzymes and precursors: cellular mechanisms

The mechanism of secretion in the acinar cell is illustrated in Figure 5.9. This scheme was first discovered by Palade in the 1970s. He was awarded a Nobel prize for the work. The enzymes or precursors are synthesised on the rough endoplasmic reticulum of the cell. The molecules are then released into the cisternae of the endoplasmic reticulum. Buds containing the enzymes or enzyme precursors break off the cisternal membranes and the buds coalesce in the region of the Golgi complex to form ‘condensing vacuoles’. The vacuoles migrate towards the luminal membrane. If the cells are stained for zymogen the vacuoles can be seen to be more and more densely stained as they approach the

Fig. 5.9
Mechanism of enzyme secretion in the acinar cell.
surface. At the luminal membrane the membranes which surround the ‘zymogen’ granules fuse with the cell membrane and the vesicles break open to release their contents, a process known as exocytosis. The different enzymes are packaged together in each zymogen granule and they are probably released together in constant proportions. The zymogen granule membrane is rapidly recycled from the surface membrane.

It is exocytosis, rather than the synthesis or sequestration of the enzyme proteins which is under physiological control by hormones and neurotransmitters. Exocytosis is triggered by an increase in intracellular Ca$^{2+}$. The rise in intracellular Ca$^{2+}$ when the cell is stimulated is via influx from the extracellular spaces or release from intracellular stores.

### Activation of enzyme precursors

The enzyme precursors secreted by the acinar cells are activated in the lumen of the duodenum and jejunum. Trypsinogen is converted to trypsin plus a short peptide, in a reaction catalysed by enteropeptidase, an enzyme present in the brush border of the epithelial cells of the small intestine. Once a small amount of activated trypsin has been formed it can catalyse the conversion of more trypsinogen to trypsin. Trypsin is a powerful proteolytic enzyme which can convert chymotrypsinogen, procarboxypeptidase, proelastase and prophospholipase A to their activated forms. Thus once a small amount of trypsin is formed a catalytic chain reaction occurs (Table 5.1).

### Acute pancreatitis

Acute pancreatitis is a disease in which the pancreatic tissue is destroyed by digestive enzymes. The physiological mechanisms underlying acute pancreatitis are incompletely understood. They probably involve abnormal release of enzymes (into the ducts) where they become activated in some way. The consequence of this is autodigestion of the pancreatic tissue.

The pancreas normally secretes a polypeptide known as Kazal inhibitor, that inhibits any small amounts of activated trypsin which may find its way into the ducts, by complexing with it. Another factor, enzyme Y, which is activated by traces of active trypsin degrades zymogen, exhibiting a protective function. The alkaline pH (8.0–9.5) and low Ca$^{2+}$ concentration in pancreatic secretions promote the degradation rather than the activation of trypsinogen. In acute pancreatitis activated trypsin and other enzymes are present in the ducts of the pancreas. Trypsin then proteolytically activates more trypsinogen and other proteolytic enzyme precursors (chymotrypsinogen, proelastase, and procarboxypeptidase) and prophospholipase A.

The active enzymes digest the pancreatic tissue. When the walls of the acini on the surface of the pancreas are digested, the enzymes leak into the abdominal cavity and a generalised peritonitis results. In 5% of cases the condition is extremely serious and the blood vessels are digested by pancreatic elastase with the formation of a haematoma. This haematoma is also digested by the enzymes and ischaemia results. The condition is then known as haemorrhagic necrotising pancreatitis which has an 80% mortality rate.

It is not known how activated digestive enzymes appear in the pancreatic ducts in acute pancreatitis, but it may be due to reflux of intestinal chyme containing activated enzymes, into the pancreatic duct. The condition is often associated with the presence of gallstones in the bile ducts. Ultrasonography may demonstrate gallstones or a swollen pancreas (Figs 5.10 and 5.11, page 86). It is likely that small gallstones lodge at the ampulla of Vater and splint the sphincter of Oddi. This process may allow duodenal juice containing activated enzymes to reflux into the pancreatic duct.

The diagnosis of acute pancreatitis depends on the presence of high concentrations of $\alpha$-amylase in the blood. This occurs because this enzyme, together with others, leaks from the necrotic tissue into the blood. $\alpha$-Amylase is also high in the urine because it is not reabsorbed adequately in the tubules. Hypocalcaemia may also be present. This is partly due to loss of albumen, with bound Ca$^{2+}$, in the protein-rich exudate. This exudation also causes a rise in the haematocrit due to loss of plasma.

### Control of secretion

The control of the exocrine secretion of the acinar and duct cells of the pancreas is via peptides such as the hormones secretin and CCK, and somatostatin which acts mainly as a paracrine factor, and via neurotransmitters.

### Hormonal control

The major hormones involved in stimulating secretion are secretin, which stimulates the secretion of the alkaline aqueous component, and cholecystokinin (CCK) which stimulates the secretion of the enzyme component. These hormones are produced by the APUD cells in the duodenal mucosa (see Chapter 1) in response to food constituents in the duodenal chyme (see below). As secretion of the two components of pancreatic juice is controlled by separate regulatory mechanisms, the composition of the juice entering the duodenum can
Pancreas: Exocrine Functions

Chronic pancreatitis Box 3

Impairment of functions

Both exocrine and endocrine secretions of the pancreas are impaired in chronic pancreatitis.

The blockage of the secretory ducts and loss of acinar tissue leads to a decrease in secretion of both alkaline juice and enzymes. The low alkaline secretion from the pancreas in chronic pancreatitis leads to i) impaired enzyme activity which results in malabsorption and weight loss, ii) impaired micelle formation which leads to steatorrhoea (high fat content in the stools), iii) in some cases duodenal ulceration, a consequence of the high acidity.

Destruction of islet tissue in chronic pancreatitis can lead to decreased secretion of the hormones insulin and glucagon, both of which are involved in the control of glucose metabolism. Insulin lowers the blood glucose by increasing the uptake of glucose into tissues (see Chapter 9), whilst glucagon increases blood glucose by stimulating glucose release from the liver. Thus the two hormones have opposite effects on blood glucose concentration. Insulin is normally released from the pancreas in response to an increase in blood glucose during a meal.

The glucose tolerance test measures the insulin response to ingestion of a glucose solution (100g glucose in 100ml of water). It involves measuring the blood glucose levels at intervals after the glucose load. The insulin response is impaired early in chronic pancreatitis: the time taken for the blood glucose to return to normal is prolonged due to hormone insufficiency caused by damage to the islet tissue. Early in the course of the disease, the rise in plasma glucose may still appear normal because there is a concomitant impairment of glucagon release from the pancreas. However, overt diabetes eventually develops in many patients with chronic pancreatitis. Some develop hypoglycaemia after their regular insulin injection owing to a combination of glucagon deficiency, their irregular eating habits (often due to the continuous pain), and malnutrition. Brittle diabetes is sometimes seen after total pancreatectomy and in chronic pancreatitis. This is presumed to be due to the severe impairment of glucose metabolism resulting from the loss of both insulin and glucagon function.

Epigastric pain that radiates through to the centre of the back is a common feature of chronic pancreatitis. It occurs because of damage to the pancreas itself, and inflammation or fibrosis of the surrounding tissue (see Case history, page 80).

Chronic progressive jaundice may also be seen in chronic pancreatitis. This is due to fibrosis around the lower end of the common bile duct as it passes through the head of the pancreas. The fibrosis prevents the access of bile to the small intestine and results in a raised serum bilirubin because of reflux of bile constituents into the systemic circulation. Raised serum alkaline phosphatase is also seen as this enzyme is released by damaged cells lining the biliary tree. In chronic pancreatitis, however, there may also be coexisting alcoholic liver disease. This makes it difficult to determine whether the jaundice is primarily due to disease of the pancreas or to underlying cirrhosis of the liver. A liver biopsy and histological assessment of the tissue may be required in this circumstance.

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Table 5.1
Activation of enzyme precursors in the small intestine

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Active enzyme</th>
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</thead>
<tbody>
<tr>
<td>Trypsinogen</td>
<td>enterokinase, trypsin + peptide</td>
</tr>
<tr>
<td>Chymotrypsinogen</td>
<td>trypsin + peptide</td>
</tr>
<tr>
<td>Proelastase</td>
<td>trypsin + peptide</td>
</tr>
<tr>
<td>Procarboxypeptidase</td>
<td>trypsin + peptide</td>
</tr>
<tr>
<td>Prophospholipase A</td>
<td>trypsin + peptide</td>
</tr>
</tbody>
</table>

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Octreotide is an octapeptide which contains the tetrapeptide sequence which is known to be essential for somatostatin activity. Somatostatin itself, when injected, has a short half life (less than 4 minutes). However, octreotide injected subcutaneously, has a half life of approximately 100 minutes and its action is therefore relatively long-lasting. This is important in the clinical setting as somatostatin is only effective if given as a continuous infusion, whereas analogues such as octreotide are effective if given as a bolus two or three times per day.

Nervous control

The nervous control of pancreatic secretion is via both parasympathetic and sympathetic nerves. Stimulation of cholinergic fibres in the vagus nerve enhances the rate of secretion of both enzyme and alkaline fluid. Stimulation of the sympathetic nerves inhibits secretion, mainly by reducing the blood flow to the gland (via vasoconstriction of the arterioles) which decreases the volume of juice secreted. However, stimulation of the sympathetic nerves to the pancreas depresses the enzyme content of the secretion as well as the volume of juice secreted.

Control of secretion during a meal

The control of the secretion of pancreatic juice during a meal depends on the volume and composition of the food. Ingested material present at different locations vary with respect to its enzyme protein content. It can contain between 1% and 10% protein.

CCK and gastrin compete for the same receptor on the acinar cell. CCK, gastrin and acetylcholine all increase enzyme protein synthesis and secretion via i) increase in phosphatidylinositol turnover and ii) increase in intracellular Ca^{2+} concentration (Fig. 5.12). Secretin and VIP act on the acinar cell to increase the intracellular levels of cAMP. This increase in cAMP by secretin and VIP potentiates the effect of CCK, gastrin and acetylcholine. Thus the enzyme secretion is greater when the two types of secretogogue are acting together.

Somatostatin

Somatostatin, which is present in D cells in the islets of Langerhans of the pancreas, is a powerful inhibitor of pancreatic secretion. It acts in a paracrine manner to inhibit the release of the exocrine alkaline and enzyme secretions, as well as the pancreatic hormones insulin and glucagon. In addition it inhibits the release of a number of gastrointestinal hormones, including CCK, secretin, and gastrin. Circulating somatostatin probably augments the actions of the locally released hormone. It originates from a number of sites in the body, including various locations in the gastrointestinal tract. Pancreatic somatostatin is predominantly the teradecapeptide form, S-14. The release of this hormone is stimulated by CCK, gastrin and secretin.

Analogues of somatostatin such as octreotide are used clinically to inhibit pancreatic enzyme secretion in acute pancreatitis, and following pancreatic surgery.

Fig. 5.10
Ultrasound scan of the biliary tree, showing a calcified stone in the common bile duct (A) which is dilated around the stone. The adjacent gallbladder is also seen (B).

Fig. 5.11
CT scan of the same patient as Fig. 5.10, showing the calcified stone at the lower end of the common bile duct (A) lying within a swollen head of the pancreas (B). The kidneys (C) and spleen (D) are also visible.
within the gastrointestinal tract affects the control of the secretions in different ways. The control during a meal can accordingly be divided into three phases (see Chapter 1) according to the location of the food or chyme; i) the cephalic phase, due to the approach of food or the presence of food in the mouth, ii) the gastric phase, when food is in the stomach, and iii) the intestinal phase when food material is in the duodenum.

Cephalic phase
The sight and smell of food, or other sensory stimuli associated with the impending arrival of food, elicit increased pancreatic secretion via a ‘conditioned’ reflex. The presence of food in the mouth stimulates secretion via a ‘non-conditioned’ reflex. The control during this phase is therefore nervous. It is mediated by impulses in cholinergic fibres in the vagus nerve. The juice secreted is mainly the enzyme-rich secretion, containing very little \( 	ext{HCO}_3^- \).

In response to vagal stimulation, the acinar cells also secrete kallikreins, which catalyse the production of bradykinin, a vasodilator. This results in increased blood flow to the pancreas, and increased volume of secretion. The mechanism involved in this effect is similar to that which occurs in the control of salivary secretion which is described in Chapter 2.

Gastric phase
The presence of food in the stomach stimulates the secretion of pancreatic juice via a hormonal mechanism. Activation of chemoreceptors in the walls of the stomach by peptides, and the activation of mechanoreceptors, causes the release of the hormone gastrin from G cells, into the local circulation. Stimulation of cholinergic nerves is also involved in this phase of control. During the gastric phase the secretion of both the enzyme-rich and the alkaline components of pancreatic juice is increased.

Intestinal phase
The intestinal phase of control is probably the most important phase of the response to food. Food material in the duodenum stimulates both the alkaline and the enzyme-rich components of pancreatic juice. The alkaline component of pancreatic juice is secreted in response mainly to acid in the duodenal contents. Acid stimulates the release of secretin from APUD cells in the walls of the intestine and this hormone stimulates the duct cells to secrete the alkaline fluid. This is a feedback control mechanism which helps to control the pH of the duodenal contents.

Physiological consequences, treatment and management

The main consequences of malabsorption and diabetes mellitus are malnutrition and weight loss. Lack of alkaline secretion can lead to alkalosis because the alkaline tide in the blood which results from gastric acid secretion (see Chapter 3) is normally partially neutralised by an ‘acid’ tide which results from the secretion of alkaline juice. However, in chronic pancreatitis, the alkalosis is normally compensated by respiratory and renal mechanisms.

Complications of chronic pancreatitis include pancreatic necrosis, haemorrhage, acute pseudocysts, and pancreatic abcesses. Treatment is usually non-surgical in uncomplicated chronic pancreatitis. The need for complete abstention from alcohol is emphasised. Pain relief is initially via aspirin treatment, and then, if necessary, via opiates. Nutritional support in the form of simple nutrients (amino acids, glucose, fatty acids) may be advised. Oral pancreatic extract can be prescribed to replace the pancreatic enzymes. Usually the extract is enriched with lipase as the secretion of this enzyme tends to decrease more rapidly than that of proteolytic enzymes. The enzyme preparation can be administered together with antacids or the anti-ulcer drug cimetidine to reduce the acid production by the stomach as this inactivates the enzymes. Alternatively the pancreatic enzyme preparation can be administered in the form of granules within which the enzymes are enclosed in a pH-dependent polymer. The protective coating dissolves only when the pH is more alkaline than 6.0, i.e. not in the stomach but hopefully in the duodenum or upper jejunum.

The metabolic complications of diabetes are discussed in Chapter 9. If diabetes is present it is treated with insulin.
The enzyme-rich juice is released during the intestinal phase in response to fat and peptides in the food. The fats and peptides cause the release of CCK from the walls of the duodenum into the blood. CCK stimulates the acinar cells to secrete enzymes. Trypsin in the duodenum inhibits the release of enzymes via inhibition of CCK release. This is another feedback control mechanism, which limits the quantity of enzymes present in the intestines, and may have some protective function.

Secretin exerts a permissive effect on the secretion of enzymes; it does not stimulate enzyme secretion on its own, but it enhances the effect of CCK. Likewise CCK exerts a permissive effect on the secretion of the alkaline fluid by secretin. Stimulation of the vagus nerve causes the release of mainly the enzyme-rich secretion, but if the vagi are sectioned, the alkaline secretion elicited in response to secretin is reduced by 50%, indicating a functional overlap between the effects of vagal stimulation and secretin. Thus the vagal mechanism may enhance the effect of secretin.

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**Self-assessment case study: cystic fibrosis**

A twelve-year-boy who was suffering from cystic fibrosis was taken to the outpatient clinic for his regular checkup. His condition had been diagnosed soon after birth and he had both pancreatic and respiratory tract involvement. He had been asked to bring a sample of his stool. This was pale-coloured, poorly formed, and oily in appearance. It was sent to the laboratory for analysis to assess his pancreatic function. His exocrine pancreatic insufficiency was being treated with a pancreatic enzyme preparation and the anti-ulcer drug cimetidine.

After studying this chapter you should be able to suggest the answers to the following questions:

1. What is the inherited defect in this condition?
2. How is the defect manifest in the pancreas? What abnormalities of pancreatic function result from this pathology?
3. Why is the child being treated with an enzyme preparation? What are the problems with having to give such a preparation by mouth. Why is the boy being treated with cimetidine? Would you expect enteric coated preparations to be more effective than a powder? Would you expect bicarbonate by mouth to be helpful? Would you expect any abnormalities in the acid bases status of this patient?
4. Why was the boy’s stool pale-coloured? What tests would be performed on the sample?

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**Self-assessment questions**

1. What exocrine cell types are present in the pancreas? What is the composition of each type of juice secreted?
2. Can you describe the cellular mechanisms involved in the secretion of alkaline pancreatic juice? How is the CFTR involved in this process?
3. Can you describe the cellular mechanisms of secretion of pancreatic enzymes? What part of this process is under physiological regulation by hormones?
4. How is the secretion of each component of pancreatic juice controlled by food in a) the mouth, b) the stomach, c) the duodenum?