The Pancreas

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The pancreas is a mixed gland with an exocrine (secretion of digestive enzymes) and endocrine (release of insulin and glucagon for blood glucose control) functions. In this book, we will focus on the digestive function of the pancreas.

5.1 Macroscopic Anatomy

5.1.1 Shape and Structure

Pancreatic regions The pancreas is a retroperitoneal organ that can be divided into four anatomical regions:

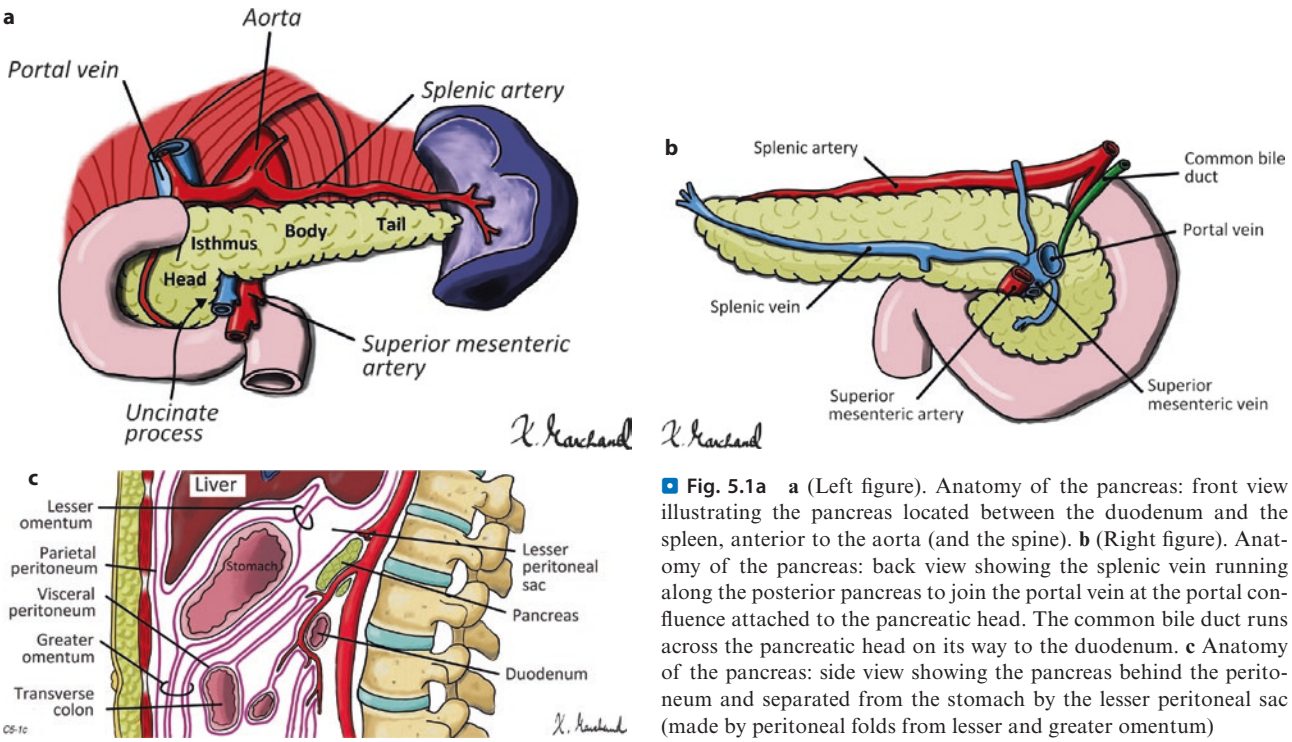
The *head*, including the uncinate process, is located in a vertical position to the right of the aorta and the spine; it intimately abuts the duodenal wall (surgical resection of the pancreatic head will therefore involve resection of the duodenum during the Whipple procedure) and is close to the superior mesenteric vein and artery (common sites of neoplastic invasion in pancreatic head cancers) (◘ Fig. 5.1a, b).

The *isthmus, body, and tail* of the pancreas are in a horizontal position and extend from in front of the spine (at the level of D12–L1) and the abdominal aorta to the spleen. This position in front of the spine makes the pancreas vulnerable to abdominal trauma by anterior compression (e.g., car accident with blunt impact on the steering wheel).

The anterior portion of the pancreas is covered by posterior peritoneum and is separated from the posterior wall of the stomach by the lesser peritoneal sac (or omental bursa) formed by peritoneum folds from lesser and greater omentum (◘ Fig. 5.1c). The retroperitoneal position of the pancreas explains why pain tends to radiate to the back when it is caused by pancreatic lesions. The anterior surface of the pancreatic neck is intimately attached to the duodenal bulb; a peptic ulcer from the bulb of the duodenum can penetrate to the pancreas (known as a boring ulcer) and lead to abdominal pain radiating to the back as well as pancreatitis.

Pancreatic ducts The pancreas is a solid organ containing the main and accessory pancreatic ducts, as well as the common bile duct.

The *main (or major) pancreatic duct (also known as the duct of Wirsung)* drains secretions from the exocrine pancreas to the duodenum. The duct traverses from the



◘ **Fig. 5.1a** **a** (Left figure). Anatomy of the pancreas: front view illustrating the pancreas located between the duodenum and the spleen, anterior to the aorta (and the spine). **b** (Right figure). Anatomy of the pancreas: back view showing the splenic vein running along the posterior pancreas to join the portal vein at the portal confluence attached to the pancreatic head. The common bile duct runs across the pancreatic head on its way to the duodenum. **c** Anatomy of the pancreas: side view showing the pancreas behind the peritoneum and separated from the stomach by the lesser peritoneal sac (made by peritoneal folds from lesser and greater omentum)

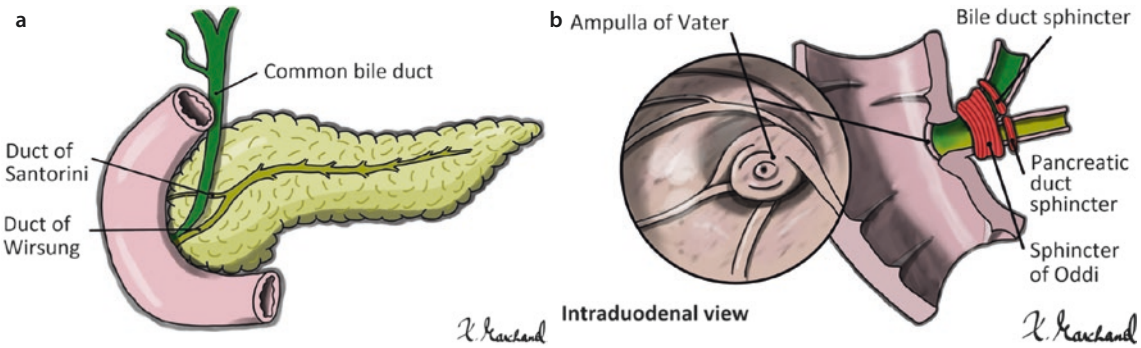
tail to the head of the pancreas, meeting with the distal bile duct at the level of the major papilla (also known as the ampulla of Vater) within the middle of the second portion of the duodenum. A smaller *accessory duct (duct of Santorini*: embryological remnant and atrophic in 30% of normal adults) connects the middle portion of the duct of Wirsung to the upper duodenum via the minor papilla (◘ Fig. 5.2a).

The *ampulla of Vater*, where end up pancreatic secretions drained by the main pancreatic duct and biliary secretions from the common bile duct, includes a sphincter, the *sphincter of Oddi (S0)*, to regulate the delivery of these secretions into the duodenum. The SO is comprised of three sphincter rings: a pancreatic sphincter specific to the pancreatic duct, a biliary sphincter dedicated to the bile duct, and a distal sphincter common to both ducts (. Fig. 5.2b). A sphincterotomy can be performed during interventional endoscopy to facilitate biliary interventions such as the extraction of stones from the common bile duct.

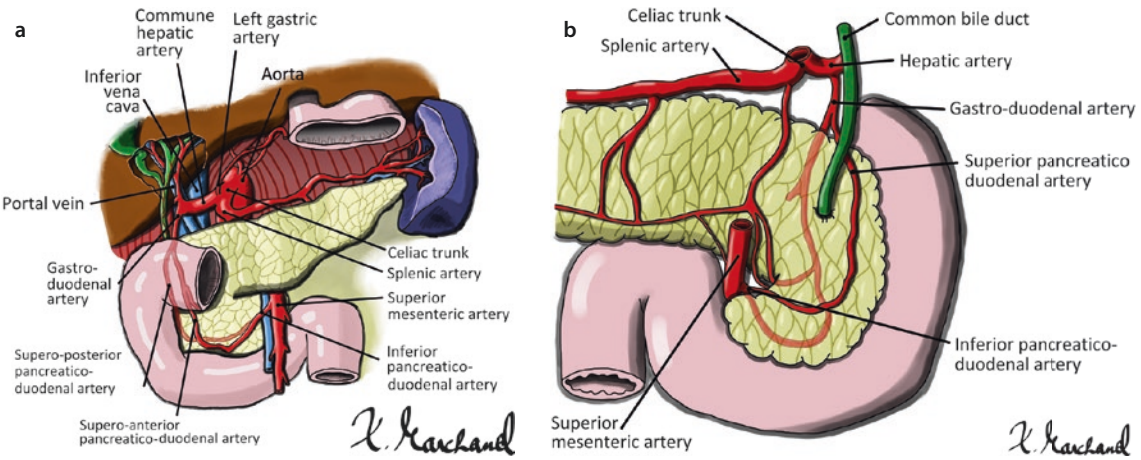
The *common bile duct* runs vertically through the pancreatic head, carrying bile from the liver to the duodenum; an inflammatory or tumoral lesion of the pancreatic head can obstruct the bile duct and impair bile evacuation, leading to jaundice.

5.1.2 Vascular Supply

Arteries Blood supply to the pancreas comes from two major arteries emerging from the aorta: the celiac trunk (CT) and the superior mesenteric artery (SMA). These vessels arise from the aorta at the height of vertebrae T12 and L1, respectively) (◘ Fig. 5.3).



◘ **Fig. 5.2** **a** (Left figure): Pancreatic ducts. **b** (Right figure): Ampulla of Vater and sphincter of Oddi



◘ **Fig. 5.3** Arterial supply to the pancreas. On the left figure, the anterior view shows the celiac trunk emerging from the aorta and its three branches: (1) the left gastric artery (going to the stomach), (2) the splenic artery which, on its way to the spleen, gives arteries to the corporeo-caudal pancreas, (3) the common hepatic artery dividing into (**a**) the proper hepatic artery (going to the liver and gallbladder) and (**b**) the gastroduodenal artery, from which originates the superior pancreaticoduodenal artery irrigating the cephalic pancreas. On the right figure, the posterior view shows the superior mesenteric artery which, in the direction of the small intestine, gives rise to the inferior pancreatico-duodenal artery to also supply the cephalic pancreas

The pancreatic gland to the right of the aorta is supplied by a vast anastomotic network that links the celiac and mesenteric circulations. This dual supply ensures continuous vascularization of the pancreas and reduces the risk of ischemic damage to the pancreas. The common hepatic artery (also called hepatic artery, one major branch of the CT) gives birth to the gastroduodenal artery (GDA) which is at the origin of the superior pancreaticoduodenal artery that links with the inferior pancreaticoduodenal artery (first branch of the SMA) to vascularize the pancreatic head and the uncinate process.

The pancreatic gland located on the left side of the aorta receives its vascular supply via the splenic artery (one of the three branches of CT) which runs along the body and tail of the pancreas and divides into smaller pancreatic arteries all along this route.

Veins Venous blood from pancreatic tail and body drains into the splenic vein. At the pancreatic head, veins run along the branches of superior and inferior pancreaticoduodenal arteries and drain into the superior mesenteric vein. The junction of the superior mesenteric vein to the splenic vein (known as the portal confluence), forming the portal vein, is done behind the head of the pancreas.

Lymphatics Lymphatic drainage of the pancreas follows the main arterial vessels. Lymphatic vessels from body and tail of the pancreas drain to lymph nodes located along the splenic vein. Lymphatics from cephalic pancreas drain to lymph nodes of the hepatic hilum.

5.1.3 Innervation

The pancreas is innervated by the parasympathetic (via the vagus nerve) and sympathetic (through splanchnic nerves) systems. Vagal efferent nerves terminate, within the pancreatic tissue, at parasympathetic nodes whose postganglionic fibers innervate acini, islets of Langerhans, and pancreatic ducts. Sympathetic axons from neural bodies of the thoracic spinal cord synapse with neurons of abdominal plexus (e.g., celiac node) whose postganglionic fibers run along the arterial vessels to reach the pancreas.

Little is known about pancreatic afferent nerves. They probably travel through splanchnic nerves, crossing the main plexus ganglions to reach the spinal cord, and then the brain. Celiac node infiltration (done during ultrasound endoscopy) with a local anesthetic agent (such as xylocaine) is used to reduce pain from pancreatic cancer.

5.2 Microscopic Anatomy

Most pancreatic tissue is devoted to exocrine functions, with acinar cells and ducts comprising more than 85% of the pancreatic tissue. This exocrine activity aims to synthesize and secrete enzymes, water, and bicarbonates that are transported through the pancreatic ducts to the duodenum to participate in the digestion of the ingested nutrients. The endocrine function of the pancreas relies on the islets of Langerhans, which represent only 2% of pancreatic parenchyma, to ensure the synthesis and secretion of the hormones insulin and glucagon released into the bloodstream to regulate carbohydrates metabolism.

The histological appearance of the pancreas can be seen in ◘ Fig. 5.4.

5.2.1 Acini

The cells responsible for synthesis and secretion of pancreatic enzymes are grouped together in a spherical anatomical unit called an acinus. The acinar cell has a pyramidal shape, with a wide and basophilic (bluish coloration on hematoxylin and eosin stain) basal portion, and a narrow and acidophilic (pinkish coloration due to the presence of many zymogen grains that store pancreatic proenzymes waiting to be secreted in the duodenum) apical portion. The basal portion of the acinar cell is in contact with the blood vessels and nerves regulating pancreatic function, while the apical portion opens onto a duct through where enzymes can be released.

Each acinar cell has a general function and synthesizes all pancreatic enzymes (amylase, lipase, etc.). The morphology of the acinar cell varies with meals. After food ingestion, the membrane of the zymogen grains fuses with the apical membrane of the acinar cell to allow exocytosis of pancreatic enzymes from the cell to the duct lumen. This massive release produces a depletion of zymogen grains which is followed by an increase in the synthesis activity by the acinar cells to replace enzymatic stocks that have been secreted.

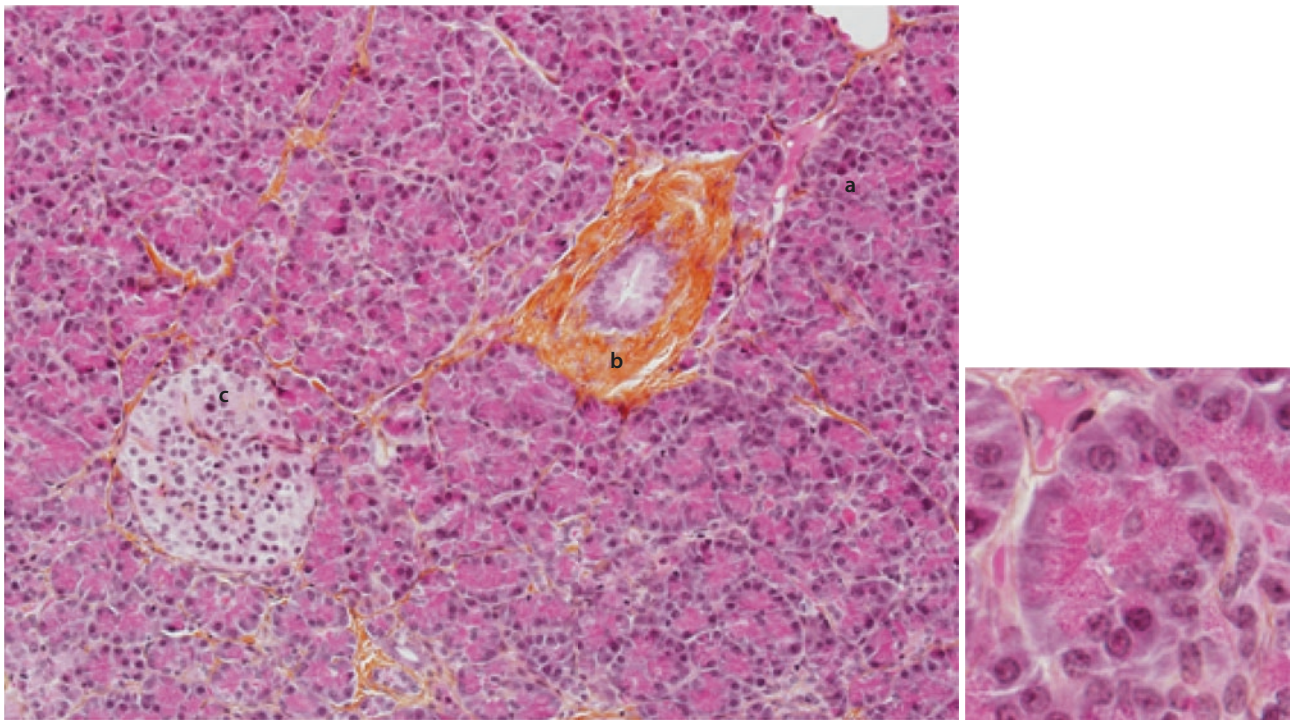


Fig. 5.4 **Left**: histological appearance (on H&E stain) of a normal pancreas with acini **(A)**, pancreatic ducts **(B)** and islets of Langerhans **(C)**. **Right**: at higher magnification, pancreatic cells with their acidophilic secretory granules are grouped in an acinus around a central canaliculus where enzymes will be secreted

5.2.2 Ducts

Acinar cells are grouped in circle around a central opening receiving their secreted enzymes and forming a canaliculus where enzymes will flow to peripheral canaliculi draining into larger ducts leading to the central main pancreatic duct (duct of Wirsung). Pancreatic enzymes will then travel to the duodenum lumen where they will be activated to participate in nutrients digestion.

The canaliculi are lined by cylindrical cells duct cells that secrete H_2O and HCO_3^- in the duct lumen.

5.2.3 Islets of Langerhans

There are about 1 million islets of Langerhans in the human pancreas (2% of pancreatic mass). Each one measures approximately 0.2 mm in diameter and is therefore larger than an acinus. The islets are surrounded by a connective tissue sheath but communicate with the systemic circulation where hormones are released. Each islet is made up of four major types of endocrine cells: beta cells are the most numerous (50–80%) and secrete insulin, alpha cells (5–20%) secrete glucagon, PP cells (10–35%) the pancreatic polypeptide, and D cells (5%) somatostatin. In contrast to the acinar cell which has a general activity and synthesizes all pancreatic enzymes, each endocrine islet cell has a specific function and produces only one type of hormone.

5.3 Embryology

5.3.1 Normal Development

The fetal pancreas begins to develop around the fourth week of gestation when the embryo measures only 4 mm. Initially, from the endoderm of the primitive duodenum, two buds are formed in an antero-posterior axis, one ventral and one dorsal. The dorsal (or posterior) bud will form the body and tail of the pancreas, while the anterior ventral bud will form the head of the pancreas and the uncinate process (as well as the bile ducts and liver) (Fig. 5.5a). At about the sixth week, begins a process of rotation along the vertical axis of the digestive tract, bringing the ventral bud to the right (pulled by the hepatic bud that will develop in the right hypochondrium), while the dorsal bud will move to the left (Fig. 5.5b). The proximal potion of the ventral bud passes from behind to be positioned under the dorsal bud. Toward the seventh week, the ventral and dorsal buds merge together. The distal portion of the dorsal

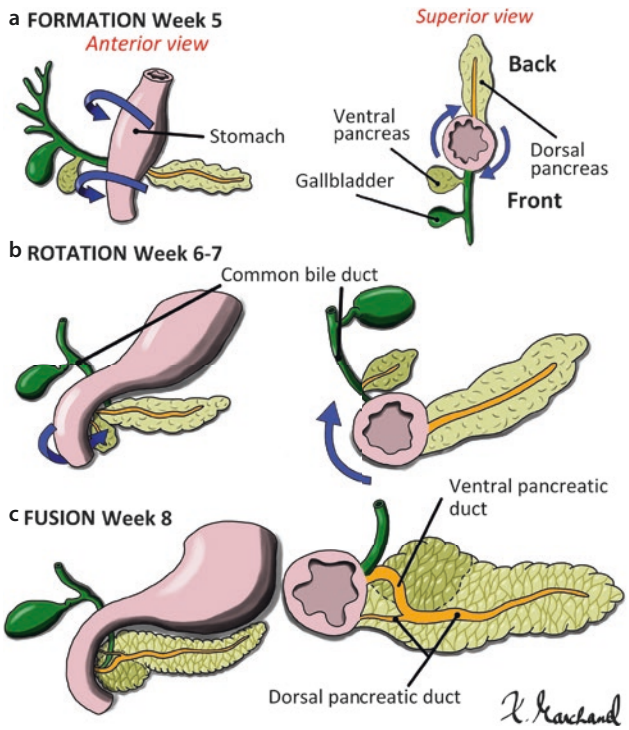


Fig. 5.5 Pancreas development in the embryo: **a** from the endoderm of the primitive duodenum, two buds are formed in an anterior-posterior axis, one ventral and one dorsal; **b** a rotation, along the vertical axis of the digestive tract, brings the ventral bud to the right (pulled by the hepatic bud which will develop in the right hypochondrium) and the dorsal bud will move to the left. The proximal portion the ventral bud passes from behind to be situated beneath the dorsal bud; **c** at around the seventh week of gestation, a merger occurs between the two buds, ventral and dorsal, as well as between their ducts that will form the main pancreatic duct (Wirsung's duct)

duct will connect to the ventral duct to form the main pancreatic duct (of Wirsung) (Fig. 5.5c). The remainder of the proximal dorsal duct will form the accessory duct (of Santorini; atrophic in 30% adults) which drains into the duodenum via the minor papilla.

5.3.2 Developmental Abnormalities

Several abnormalities in the development of the pancreas may occur (Fig. 5.6).

Pancreas divisum (Fig. 5.6a) is the result of a lack of union between the ducts of the ventral and dorsal pancreas during the fusion of the two embryonic buds. The pancreatic head (born from the ventral pancreas) drains its secretions toward the duodenum via the.

Wirsung's duct and the Vater's ampulla, while the corporeo-caudal pancreas (issued from the dorsal pancreas) will drain its secretions via the Santorini's duct and the minor ampulla. This congenital anomaly is found in 5–10% of autopsies or pancreatography examinations (ERCP, MRI). Most individuals with pancreas divisum are asymptomatic and have normal pancreatic exocrine function. Some authors have proposed that pancreas divisum can cause some forms of pancreatitis. They hypothesized that the minor ampulla is too small to allow an easy flow of secretions from corporeo-caudal pancreas, leading to an excess pressure within the duct and secondary pancreatitis; they proposed sphincterotomy of the minor ampulla as a form of treatment for this anomaly. The association between pancreas divisum and risk of pancreatitis remains controversial. More recently, it has been suggested that pancreas divisum is a risk factor for pancreatitis when it is combined to other risk factor, such as the hyperviscosity of the pancreatic juice seen in cystic fibrosis.

Annular pancreas (Fig. 5.6b) is an uncommon variant (1 in 20,000 births) where pancreatic tissue persists around the duodenum from the rotation that has brought the ventral bud into its final position. This pancreatic tissue surrounding the second portion of the duodenum (at the level of the major ampulla) may cause

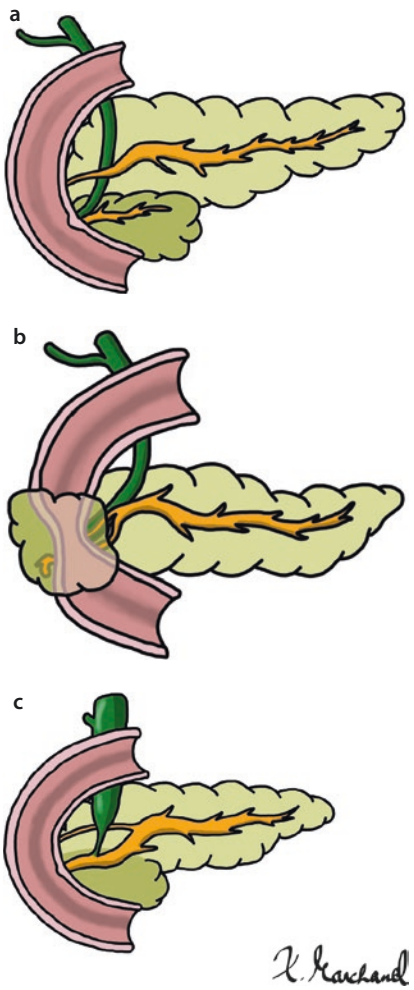


Fig. 5.6 Developmental abnormalities: **a** pancreas divisum; **b** annular pancreas; **c** abnormally implanted bile duct

partial or complete obstruction of the duodenum. Annular pancreas can be associated with other congenital anomalies (such as Down's syndrome, duodenal atresia, tracheoesophageal fistula, cardiac abnormalities, etc.). In symptomatic cases, treatment is provided by bypass surgery (e.g., gastrojejunostomy) to allow food to avoid duodenal obstruction and come out of the stomach into the intestine. The annular pancreas may occasionally be revealed in an adult who experiences obstructive symptoms (pain, nausea, vomiting, bloating) during episodes of pancreatitis produced by the inflammatory swollen pancreatic ring.

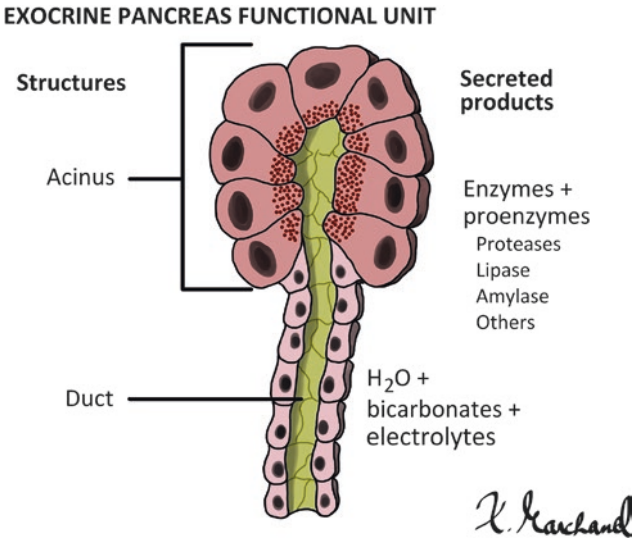
Ectopic pancreas (also known as heterotopic or accessory or aberrant pancreas) refers to the presence of pancreatic tissue outside of its normal location, in various sites of the digestive tract (mostly in submucosal surfaces of the stomach, duodenum, or jejunum). Present in up to 10% of autopsies, the ectopic pancreas is usually asymptomatic and is identified incidentally during digestive endoscopy (showing a small submucosal lesion with a central umbilication) or on imaging studies. Clinical manifestations of the ectopic pancreas include cystic dystrophy of the duodenal wall (CDDW, also known as groove pancreatitis or paraduodenal pancreatitis) where pancreatic secretions, unable to drain from their acini due to the absence of functional excretory ducts in the ectopic pancreas, accumulate to form walled-off fluid collections within the duodenopancreatic region that can result in duodenal obstruction, jaundice, or pancreatitis.

Complete pancreatic agenesis is a rare phenomenon that may be associated with other developmental abnormalities and which usually results in death in utero or at birth. Incomplete and segmental agenesis can occur and is usually asymptomatic (incidental finding in MRI or CT abdominal imaging).

Congenital cysts of the pancreas are relatively rare. They may be solitary or multiple and may occasionally be associated with other development abnormalities or certain genetic diseases (polycystic kidney disease, etc.). Unlike pancreatic pseudocysts (consequence of inflammatory fluid accumulation during pancreatitis), congenital cysts have an epithelial lining capable of fluid secretion. Congenital cysts can be found in the newborn, child, or adult. Large cysts can cause symptoms by compressing adjacent digestive or biliary structures and can then require surgical treatment.

5.4 Secretion

The pancreatic exocrine secretory apparatus is made up of two functional units: the acinus and the ductule (◘ Fig. 5.7). The acinus is a spherical grouping of acinar cells secreting enzymes for the intestinal digestion of



◘ **Fig. 5.7** Functional units of the exocrine secretory pancreas: acinus and duct

carbohydrates (amylase), lipids (lipase), and proteins (trypsin, elastase, etc.) of the diet. The ducts are lined with an epithelium of cells that secrete large quantities of bicarbonate (to neutralize gastric acid arriving in the duodenum) and water (to transport enzymes from the acinus to the duodenum). Every day, 1.5–2 liters of pancreatic juice is released into the duodenum.

5.4.1 Acinar Cell

The acinar cell synthesizes and secretes pancreatic enzymes involved in the digestion of food (glycolytic, lipolytic, proteolytic enzymes), as well as other proteins which have various roles in pancreatic homeostasis. This cell, therefore, is very rich in organelles involved in protein synthesis, such as rough endoplasmic reticulum (RER), Golgi apparatus, condensation vacuoles, and zymogen granules.

Like all exocrine proteins, pancreatic enzymes, after nucleic acid transcription from DNA to RNA in the cell nucleus, are synthesized in the cytoplasm: messenger RNAs, helped by ribosomal and transfer RNAs, enter the reticulum endoplasmic (RER) where nucleic acids will be translated into amino acids; posttranslational modifications that occur in RER and Golgi apparatus allow newly made proteins to acquire their final tertiary and quaternary structures; once their synthesis is completed, the pancreatic enzymes are stored in very dense zymogen granules that accumulate at the apex of the cell, waiting for secretion out of the cell. See ◘ Fig. 5.8.

Stimulation of the acinar cell (through mechanisms to be discussed shortly) leads to migration of zymogen granules to the apical membrane of the cell where the membranes of the cell and granules will fuse to deliver,

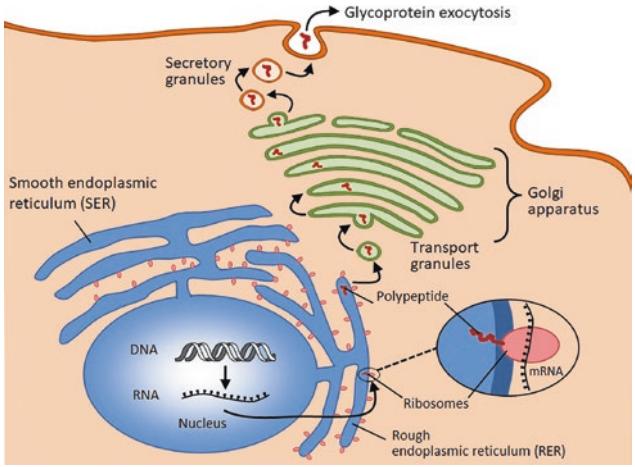


Fig. 5.8 Protein synthesis in the acinar cell. After transcription in the nucleus of DNA into RNA, translation of nucleic acids into amino acids (3 nucleic acids = 1 amino acid) occurs in the endoplasmic reticulum to form a polypeptide protein sequence that will be submitted to subsequent transformations during its maturation through the Golgi apparatus toward its storage in secretion vesicles (zymogen granules) while waiting for exocytosis to be transported outside of the cell

Table 5.1 Products of the acinar cell

Proenzymes	Enzymes	Nonenzyme products
Chymotrypsinogens (A, B)	Amylase	Bradykinin
Kallikreinogen	Sterol esterase	Ions: Na+, Cl^-, Ca^{2+}
Procarboxypeptidases (A, B)	Lipase	Glycoprotein 2 (GP2)
Phospholipases (l, ll)	DNase	Lithostatin
Proelastase	RNase	Monitor peptide
Mesotrypsin	Lysosomal enzymes	Pancreatitis-associated protein (PAS)
Trypsinogens (1, 2, 3)	Unknown	Trypsin inhibitor

via a secretion process called exocytosis, the granule content into the lumen of the acinus, and then pancreatic ductules.

The acinar cell indiscriminately synthesizes all digestive enzymes. However, the relative concentration of enzymes can vary according to the ingested diet (e.g., increase in lipase content if high-fat diet). The main proteins synthesized and secreted by acinar cells are listed in Table 5.1. In humans, proteases account for 90% of the total enzymatic content (amylase 7%, lipase 2.5%, nuclease <1%). The predominance of proteolytic enzymes is probably an adaptation to the carnivorous nature of man since its origin. Pancreatic secretion therefore includes: (a) proteolytic enzymes of two main types, (1) endopeptidases (which cleave proteins at specific peptide bonds within the polypeptide) such as chymotrypsin, trypsin, kallikrein, and elastase and (2) exopeptidases (which cleaves peptide bonds at the carboxyterminal end of the polypeptide) such as carboxypeptidases A and B; (b) a glycolytic enzyme, amylase, to hydrolyze starch and complex carbohydrates; (c) lipolytic enzymes such as lipase, esterases, and phospholipases; (d) enzymes involved in hydrolysis of nucleic acids, DNase and RNase; and (e) nonenzymatic products, such as trypsin inhibitor, procolipase, etc.

If proteolytic and lipolytic enzymes were synthesized in an active form, they would constitute a great threat to the pancreas (and to any human tissue since we are largely made up of proteins and lipids). These enzymes are therefore synthesized and secreted as inactive proenzymes that remain harmless as long as they have not been activated (see ▶ Sect. 5.4.4). Activation of proenzymes into active enzymes occurs in the duodenum by trypsin (itself secreted as inactive trypsinogen). In case of premature activation of trypsin within the pancreas, an additional protection mechanism involving a trypsin-inhibiting protein can intervene to avoid pancreatic acinar cell damage.

5.4.2 Ductal Cell

Cuboidal cells make up the epithelium of the ductules that originate at the acinus border (see Fig. 5.7) and will merge and grow until they reach the main pancreatic duct of Wirsung.

The main functions of ductal cells and the ducts they form are (1) to ensure an anatomical route to transport pancreatic enzymes to the duodenum, (2) to provide water facilitating movements of pancreatic secretions in ducts lumen, and (3) to secrete bicarbonates to neutralize acidic gastric chyme poured into the duodenum. The ductal cell (Fig. 5.9) is equipped with secretory mechanisms that ensure high concentrations and high flow rates of electrolytes:

- HCO_3^- is secreted at the apical membrane via an ion channel and a Cl^-/HCO_3^- pump. Intracellular availability of HCO_3^- is provided by cytoplasmatic carbonic anhydrase (transforming CO_2 and H_2O to HCO_3^-), as well as by an HCO_3^-/Na^+ carrier located on the basolateral membrane (promoting the entry of HCO_3^- into the cell).
- Cl^- is secreted out of the cell by a CFTR channel (cystic fibrosis transmembrane regulator) (hence the

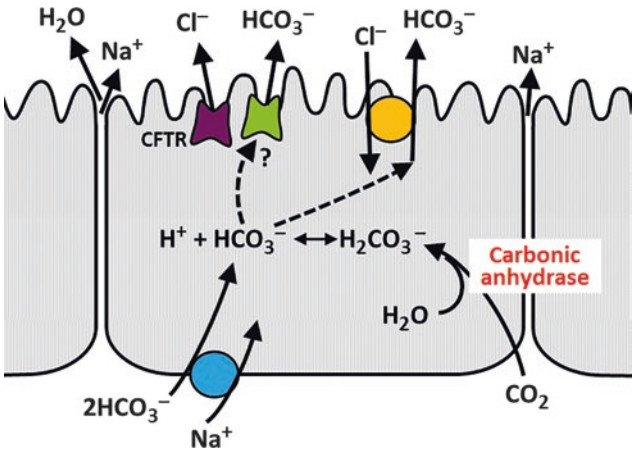


Fig. 5.9 Duct cell secretion. HCO_3^- is secreted at the apex of the cell by various mechanisms (channels, pumps). Secreted HCO_3^- is manufactured inside the cell (carbonic anhydrase) or is transported there (Na^+/HCO_3^- carrier on basal membrane). Cl^- is secreted through a CFTR channel. Na^+ diffuses, with H_2O, through paracellular spaces toward the pancreatic duct

pancreatic damage in cystic fibrosis discussed in the ▶ Sect. 5.9 of this chapter).

- Na^+ and H_2O pass into the canaliculus passively, following electrochemical and/or concentration gradients, by diffusion through intercellular junctions.

Circulating secretin and neuronal acetylcholine are the main stimuli for duct cell secretion.

5.4.3 Regulation of Pancreatic Secretion

Pancreatic secretion is essential for assimilation of food: pancreatic enzymes (lipase, amylase, etc.) are essential for chemical digestion of nutrients; bicarbonates are necessary for neutralization of acidic gastric chyme to optimize enzymatic digestion, micellar formation, etc. (as described in ▶ Chap. 3).

Pancreatic secretion is regulated by neurohormonal mechanisms. Parasympathetic control mechanisms are provided by the vagus nerve, secondary intrapancreatic neurons, and pancreatic reflexes. The sympathetic system may influence blood circulation to the pancreas and otherwise has a limited role in the regulation of pancreatic secretion. The hormones cholecystokinin (CCK) and secretin are essential for pancreatic postprandial stimulation (◘ Fig. 5.10).

Pancreatic secretion is activated by meal. Three phases of secretion can be distinguished:

1. The cephalic phase of pancreatic secretion occurs before meal ingestion and when seeing and smelling food stimulates vagal efferences synapsing with intrapancreatic secondary neurons to induce cells secretion through various neurotransmitters including acetylcholine, VIP (vasoactive intestinal polypeptide), and GRP (gastrin releasing peptide).
2. The gastric phase of pancreatic secretion results from distension of the stomach by meal. Gastric distension activates acinar cells by vago-vagal reflexes, and this effect is abolished by vagotomy. It can be reproduced experimentally with distension by a balloon and is therefore independent of chemical stimuli such as gastric acid or meal contents.
3. The intestinal phase of pancreatic secretion is the most important. It is triggered when the gastric chyme reaches the duodenum to induce the release of hormones secretin and CCK into the blood (as shown in ◘ Fig. 5.11).

- *Secretin:* Acidity of the gastric chyme stimulates S-cells located in duodenal mucosa. These endocrine cells, responsible for synthesis and secretion of secretin, are activated by H^+ ions contained in duodenal luminal fluids and release their hormone into the blood circulating to the pancreas. Secretin acts mainly on pancreatic duct cells to activate the secretin receptor located on the basal membrane and its intracellular second messenger cyclic AMP (◘ Fig. 5.10 left). Secretin also acts on the acinar cell to potentiate the effect of CCK on enzyme secretion (◘ Fig. 5.10 right).
- *CCK:* Fatty acids and amino acids from the meal induce the release into circulation of CCK from I-cells of the duodenal mucosa. Activation of the I-cell is due to a direct cell stimulation by the nutrients, to a paracrine action of CCK-RP (CCK-releasing peptide) secreted by endocrine cells of the duodenal mucosa, and by "monitor peptide," a stimulatory agent contained in pancreatic secretions (◘ Fig. 5.12).

Serum CCK acts on specific CCK receptors (CCK-R2) to activate acinar cell secretion of pancreatic enzymes (via the second messenger intracellular Ca^{2+}). Although CCK receptors on the acinar cell basal membrane are well demonstrated in many experimental animal models, they are hardly identifiable in humans where CCK is probably acting on vagal afferent branches to stimulate acinar cells through intermediary neurotransmitters such as acetylcholine, VIP, and GRP (◘ Fig. 5.10). CCK effect on enzyme secretion is potentiated by secretin.

During the intestinal phase, inhibitory mechanisms of pancreatic secretion are also elicited. When trypsin no longer has food substrate to digest, it breaks down

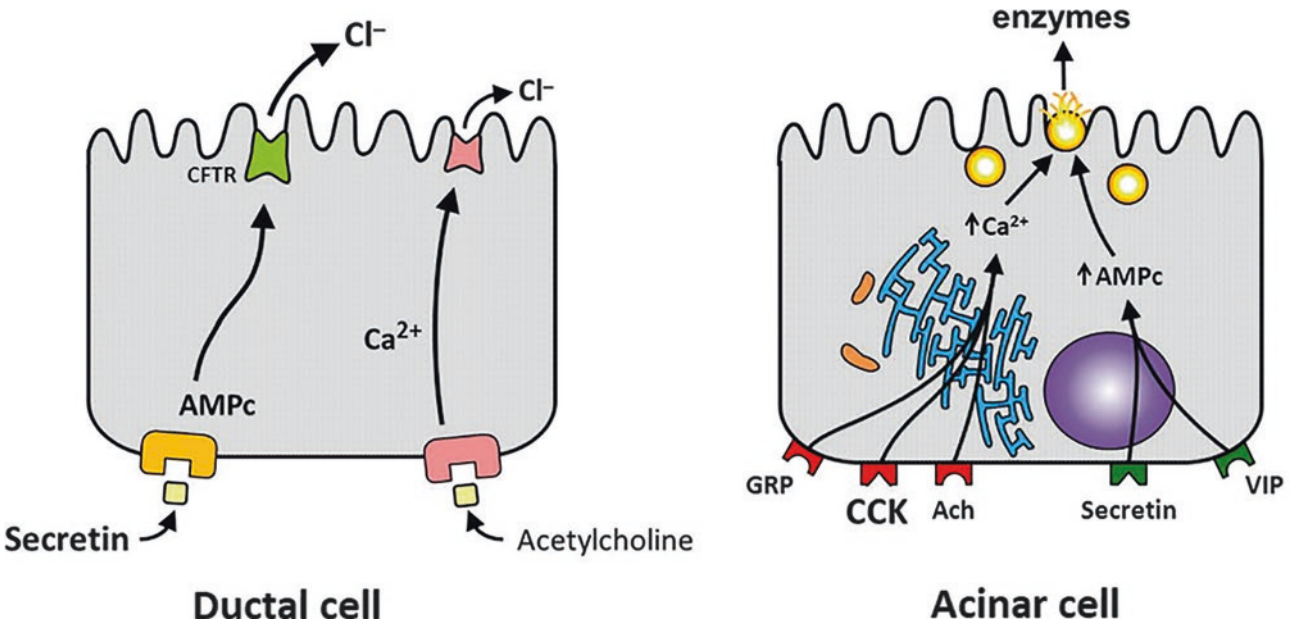


Fig. 5.10 Stimulation of ductal and acinar cells. On the left, the duct cell is stimulated by circulating secretin and neuronal acetylcholine to secrete bicarbonates and ions. On the right, enzymatic secretion of the acinar cell is stimulated by circulating CCK and cholinergic neurotransmitters; CCK stimulation is potentiated by secretin

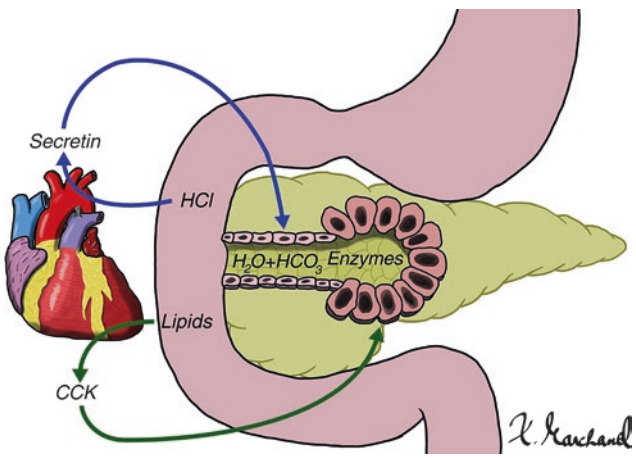


Fig. 5.11 Pancreatic secretion is activated by duodenal hormones secretin and CCK released into the circulation by the gastric chyme reaching the duodenum

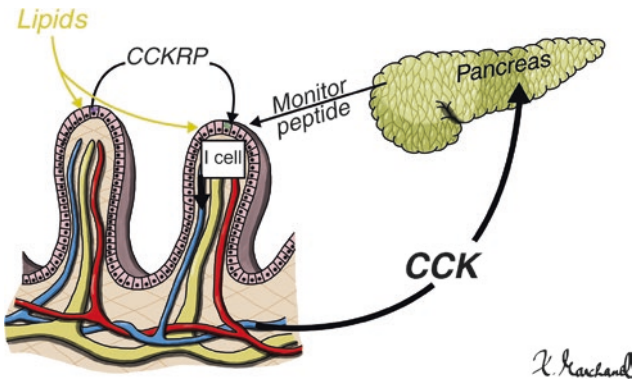


Fig. 5.12 Postprandial release of CCK from I-cell is due to (1) a direct action of diet lipids on the I-cell, (2) CCK-releasing peptide issued from duodenal mucosa, and (3) "monitor peptide" contained in pancreatic secretions

CCK-RP as well as monitor peptide, so that they can no longer stimulate the release of CCK.

5.4.4 Activation of Pancreatic Proenzymes

Pancreatic proteolytic enzymes necessary for digestion of food proteins are secreted in the pancreas in the form of inactive proenzymes to prevent self-digestion of the pancreas. Inactive proenzymes are transformed to active enzymes (chymotrypsinogen/chymotrypsin, trypsinogen/trypsin, proelastase/elastase, etc.) after cleavage, by trypsin, of their inactivation peptide situated at the NH_2 terminal end of the molecule. This activation of pancreatic proenzymes by trypsin takes place in the duodenum after inactive pancreatic trypsinogen has been transformed into active trypsin by the enzyme enterokinase produced by intestinal mucosa (Fig. 5.13).

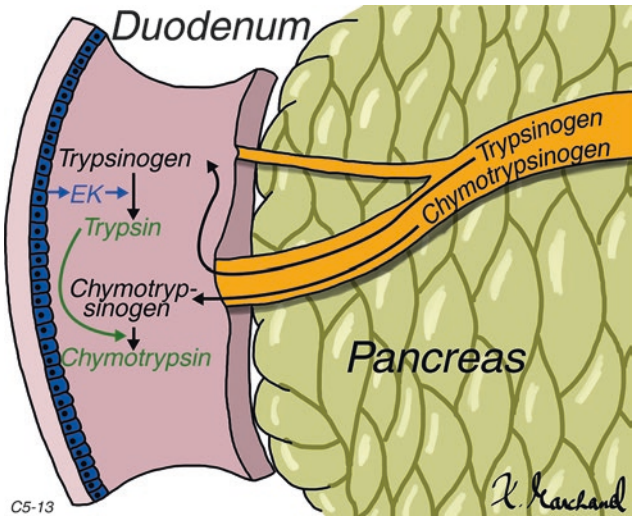


Fig. 5.13 Pancreatic proteolytic enzymes are secreted as inactive proenzymes. Enterokinase (EK) contained in the intestinal brush border transform inactive trypsinogen into active trypsin which will then transform inactive pancreatic proenzymes into activated enzymes

Activation of pancreatic enzymes (and hence pancreatic digestion of nutrients) can therefore be affected in case of enterokinase deficiency (e.g., villous atrophy with celiac disease; see ► Chap. 3).

5.5 Motility/Sensitivity

The sphincter of Oddi (SO) relaxes to allow the passage of the pancreatic (and biliary) secretions into the duodenum. CCK, while stimulating pancreatic secretion and gallbladder contraction, relaxes SO.

Impaired SO relaxation can increase pancreatic duct pressure and lead to pancreatic pain. Impaired relaxation may be due to a fibrous ampulla (for instance, after passage of a biliary stone) or to a neurological dysfunction equivalent to esophageal achalasia ("achalasia of Oddi," which remains however a much debated clinical entity). Rome IV classification (see ► Chap. 4) of functional GI disorders includes SO dysfunction affecting the pancreas or the bile ducts (see ► Chap. 6).

The pancreatic gland seems sensitive to increased intraductal pressure. Pancreatic pain sensation is transmitted mainly by sympathetic afferences traveling through abdominal nodes to the medulla and the brain. Infiltration of the celiac node by pharmacological agents such as lidocaine can, in some cases, relieve pancreatic pain.

5.6 Inflammation Disorders

5.6.1 Acute Pancreatitis

(a) Definition and Generalities

Acute pancreatitis is a common condition, with an incidence up to 38 cases per 100,000 population. It is defined as an acute inflammation, of variable intensity, of the pancreas. In most cases, it is a benign self-limited condition with edema and inflammation of the pancreas (manifested as a severe abdominal pain) that will heal without any anatomical or functional sequelae. In 10–20% of cases, acute pancreatitis is severe and leads to local complications (intra-abdominal fluid collections, abscesses, etc.) Systemic consequences (sepsis, end-organ failure with renal, respiratory insufficiency, etc.) are associated with up to 30% mortality. Severe pancreatitis is associated with important necrosis of the pancreatic parenchyma and can leave, after healing, functional sequelae such as exocrine and endocrine pancreatic insufficiency.

(b) Etiology of Acute Pancreatitis

Causes of acute pancreatitis are summarized in Table 5.2. Biliary pancreatitis and alcoholic pancreatitis account for more than 80% of cases of acute pancreatitis.

- ***Biliary pancreatitis or gallstone pancreatitis*** (40–60% of acute pancreatitis) occurs when a gallstone migrated through the cystic duct to the common bile duct becomes trapped (often transiently) within the ampulla of Vater causing obstruction of the Wirsung pancreatic duct. It is more frequent when the gallbladder contains small stones (>5 mm stones are more likely too large to enter the cystic duct) or biliary sludge (which contains micro-stones likely to migrate across the cystic duct to the common bile duct).
- ***Ethyl alcohol abuse*** is the second most common cause of acute pancreatitis (25–35% of cases). Patients, most often, have a history of chronic alcohol overuse and are more likely to demonstrate clinical and imaging features of chronic pancreatitis when they present with an acute episode of pancreatitis. The mechanism by which alcohol induces damage to the pancreas remains uncertain. It has been proposed that alcohol increases the concentration of pancreatic juice to cause protein plugs obstructing small pancreatic ducts. Alcohol has also been linked to early activation of trypsinogen, which can lead to pancreatic acini autodigestion. Direct toxicity of alcohol or one of its metabolites on pancreatic cells is also possible.

Table 5.2 Causes of acute pancreatitis

Obstructive	***Metabolic***	***Trauma***
Gallstones	Hypertriglyceridemia	
Neoplasia	Hypercalcemia	***Autoimmune***
Parasites		IgG4-mediated
Duodenal diverticulum	***Infectious***	Non IgG4-mediated
Annular pancreas	Viruses	
Choledocele	Bacteria	***Iatrogenic***
Others	Fungi	Post-ERCP
	Parasites	Postoperative
Toxic		
Ethyl alcohol	***Vascular***	***Controversial causes***
Methyl alcohol	Vasculitis	Pancreas divisum
Scorpion venom	Embolic	Dyskinesia of Oddi sphincter
Organophosphorus insecticides	Hypotension	
Medication		***Idiopathic***

5

Other causes of pancreatitis are more rare:

- ***Obstructive pancreatitis*** is due to a blockage of the pancreatic duct leading to increased intraductal pressure and pancreatitis upstream of the obstacle. Intraductal papillary mucinous neoplasm of the pancreas (IPMN) is the most common lesion. In these cases, the acute nature of pancreatitis is probably related to a sudden episode of obstruction caused by a mucin plug trapped within the pancreatic duct; pancreatitis secondary to slow duct obstruction by pancreas adenocarcinoma or ampullary tumor is more rare. In countries where parasitic infections such *Ascaris* or *Clonorchis* are endemic, these parasites can obstruct the pancreatic duct and induce acute pancreatitis.
- ***Drug-induced pancreatitis*** can usually be diagnosed after ruling out more common causes of pancreatitis and establishing an exposure to a drug known to be associated with pancreatitis [the causal association being more or less solid according to the number of cases reported and (but rarely available) to the documentation of recurrence of pancreatitis after reintroduction of the drug]. The most common drugs associated with acute pancreatitis are listed in Table 5.3. Pathological mechanisms are multiple: immunological (e.g., 6-mercaptopurine/azathioprine, 5-ASA), direct drug toxicity (thiazide diuretics), indirect toxicity from metabolites (e.g., valproic acid, DDI), ischemic (diuretics), and thrombotic (estrogens). Delay between exposure to medication and occurrence of pancreatitis is variable, 24 hours (e.g., acetaminophen, codeine, propofol) to more than 30 days (e.g., valproic acid, tamoxifen, hydrochlorothiazide, estrogens, DDI). Drug-induced pancreatitis is seldom severe and usually regresses when the responsible drug is discontinued.
- ***Metabolic*** causes of acute pancreatitis are recognized:

Table 5.3 Drugs classically associated with pancreatitis (alphabetical order)

Azathioprine	Mesalamine (5-ASA)
6-mercaptopurine	Metronidazole
Codeine	Pentamidine
Dapsone	Pravastatin
DDI (didanosine)	Procainamide
Enalapril	Sulfas
Estrogens	Sulindac
Furosemide	Tamoxifen
Hydrochlorothiazide	Tetracycline
INH (isoniazid)	Trimethoprim
Losartan	Valproic acid

- *Hypertriglyceridemia* can cause pancreatitis when triglyceride serum level exceeds 10 mmol/L as it can be seen in hereditary hyperlipidemia types 1, 2, and 5 or during certain conditions that may increase lipids serum level (alcohol abuse, pregnancy, use of estrogens, tamoxifen, glucocorticoids, etc.). Reducing serum triglycerides levels below 5 mmol/L helps to prevent the recurrence of pancreatitis. The physiopathological mechanism of hypertriglyceridemic pancreatitis is not completely understood. Chylomicrons (triglyceride-rich lipoprotein particles) present in the blood stream in cases of hypertriglyceridemia could occlude pancreatic capillaries leading to ischemia; in animal experimentation, it is possible to induce pancreatitis by perfusing the pancreas with high concentrations of free fatty acids (producing pro-inflammatory mediators?).
- *Hypercalcemia* (more than 3 mmol/L) is a (rare) cause of acute pancreatitis. The pathophysiological mechanism is unknown (premature activation of trypsinogen and calcium deposition within pancreatic ducts?). Underlying conditions include hyperparathyroidism, hypercalcemia associated to bone metastases, etc.

- ***Infectious agents*** that can cause pancreatitis including viruses (mumps, Coxsackie, hepatitis A or B, *Cytomegalovirus*, herpes zoster, Epstein-Barr, etc.), bacteria (*Mycoplasma*, *Legionella*, *Leptospira*, *Salmonella*), fungi (*Aspergillus*, *Candida albicans*), parasites (*Toxoplasma*, *Cryptosporidium*, *Ascaris*, *Clonorchis sinensis*).
- ***Ischemia-induced pancreatitis*** is usually of mild severity but sometimes can be severe. Causes include vasculitis (lupus, polyarteritis nodosa, etc.), atherosclerosis (thrombotic or embolic), or systemic hypoperfusion (hypovolemia secondary to hemorrhagic shock, intraoperative hypotension, sepsis, etc.).
- ***Iatrogenic pancreatitis*** is most often associated with retrograde cholangiopancreatography (ERCP). Hyperamylasemia (biochemical pancreatitis) can be found in more than 35% of patients after undergoing this endoscopic intervention, and clinical pancreatitis can be diagnosed in up to 5% of cases.
- ***Traumatic pancreatitis*** can be from penetrating (e.g., gunshot, stab wounds) or blunt where the pancreas is compressed against the spine (e.g., punch to the epigastrium, steering wheel impact during car accident, fall on bicycle handlebar).
- ***Acute pancreatitis in children***

  The most common causes of acute pancreatitis in children are, in descending order of frequency, abdominal trauma, idiopathic cases, genetic conditions involving the pancreas, infections, medications, and lithiasis.

  Diagnosis and treatment of pancreatitis in children follow the same cardinal rules as in adults.

(c) Physiopathology of Acute Pancreatitis

Acute pancreatitis results from self-digestion of the pancreatic gland by its proteolytic enzymes. This occurs during inappropriate intrapancreatic activation of trypsinogen in trypsin which surpasses the endogenous protection mechanisms of the acinar cell. Trypsin then activates other proenzymes co-located in the acinar cell, thereby inducing digestion of acinar cells and pancreatic tissue.

Necrosis of pancreatic tissue leads to an inflammatory reaction, locally at the pancreas as well as systemically via the release of pro-inflammatory (TNF; IL-1, IL-6, and IL-8; PAF; etc.) and anti-inflammatory cytokines (IL-2, IL-10, IL-11, etc.).

The local inflammatory reaction first manifests as edema of the pancreas and surrounding tissues (retroperitoneal pancreatic area, lesser peritoneal sac). In more severe cases, pancreatic necrosis with peripancreatic, retroperitoneal, or abdominal fluid collections can develop. When necrosis affects large vessels, hemorrhagic pancreatitis may occur, associated with hematomas in the pancreatic compartment or in the retroperitoneum.

The release of pro-inflammatory cytokines may be important enough to induce systemic complications such as acute respiratory distress syndrome (ARDS), renal failure, heart failure, shock, metabolic complications (e.g., hyper or hypoglycemia, metabolic acidosis, hypocalcemia, hypomagnesemia), etc.

Septic complications can occur later, generally after the second week of evolution of severe pancreatitis (fever in the early period of pancreatitis is rarely due to infection but rather to the inflammatory process). They result from infection of the necrotic pancreatic tissue, either by blood contamination or by translocation of intestinal bacteria (this explains the importance to administer enteral nutrition early in the course of pancreatitis, as it has been shown to maintain intestinal barrier integrity and decrease bacterial translocations and the risk of secondary pancreatic infections).

(d) Clinical Manifestations of Acute Pancreatitis

Abdominal pain, present in more than 90% of cases, has a fast onset, reaching its peak in the first hour, is constant, and can be very severe. It often lasts more than 24 hours and can extend over several days. Pain is perceived mainly in the epigastric area with transfixing radiation to the back; it frequently diffuses to the upper hemi-abdomen and can extend into the lower abdomen

if inflammatory collections are present in para-colonic gutters. Nausea and vomiting are common.

Findings on physical examination vary according to the severity of pancreatitis. In patients with benign acute pancreatitis, the clinical signs may be limited to epigastric tenderness only. In more severe pancreatitis, tachycardia, tachypnea, hypotension, and other signs of shock may be seen. Fever (37.5–39 °C) is frequent; it is related to the important inflammatory reaction prevailing during the first week of presentation and is uncommonly associated with an infection (which occurs later in the evolution of the pancreatitis). The abdomen may be distended because of paralytic ileus and its associated intestinal dilatation. Intestinal sounds are reduced. Palpation of the abdomen accentuates pain, especially in the epigastric region; abdominal rigidity and rebound tenderness (Blumberg's sign) are suggestive of peritoneal irritation.

In rare cases (1%), one may observe ecchymotic staining of one or both flanks (Grey-Turner's sign) or in the umbilical region (Cullen's sign) and witness of a necrotico-hemorrhagic pancreatitis which carries a poor prognosis. Subcutaneous nodules, red and tender, from 0.5 to 2 cm in diameter can be seen (often on the extremities but also on the trunk, scalp, or buttocks), corresponding to subcutaneous fat necrosis due to fat digestion by large circulating quantities of lipolytic enzymes.

The differential diagnosis of epigastric pain seen in pancreatitis include, among others, biliary colic, cholecystitis, perforated duodenal ulcer, mesenteric ischemia, intestinal obstruction, lower myocardial infarction, aortic dissection, etc.

(e) Diagnostic Evaluation of Acute Pancreatitis

***Blood tests*:** Amylase or lipase levels more than three times the upper normal limits are characteristic of acute pancreatitis. The level of both enzymes rises in parallel during the first 12 hours of pancreatitis and remains high from a few hours to a few days. The sensitivity of these two assays for the diagnosis of acute pancreatitis is similar (85–100%). There is no direct relationship between the rate of elevation of these enzymes and the severity of pancreatitis. Serum amylase has a shorter half-life and therefore decreases sooner after a pancreatitis episode compared to lipase. Hyperamylasemia is also not specific to the pancreas and can be encountered in several non-pancreatic conditions (such as parotitis, cholecystitis, intestinal perforation, mesenteric ischemia, renal failure, ectopic pregnancy, ovarian tumor, etc.). Given its low specificity, some laboratories have discontinued serum amylase dosage as a diagnostic test for pancreatitis and replace it with serum lipase due to its greater specificity (though not 100%) for pancreatitis.

Several other blood markers can be abnormal, without being specific for acute pancreatitis. Hyperleukocytosis is common. Elevated hemoglobin and hematocrit levels are indicative of hypovolemia in the vascular space at the expense of a "third-spacing" or fluid loss into the retroperitoneum; they can also decrease quickly in cases of hemorrhagic pancreatitis. Bilirubin, AST, ALT, and alkaline phosphatase may rise, especially in cases of biliary pancreatitis. Loss of circulating volume can lead to renal impairment with increased creatinine levels as well as electrolytes abnormalities. Some blood analyses can guide the etiological diagnosis (e.g., hypertriglyceridemia, hypercalcemia, high blood alcohol levels, etc.).

***Imaging*:** Multiple imaging modalities can be effective for the evaluation of acute pancreatitis and the techniques can often be complementary:

- *Abdominal X-ray* (flat plate) often appears normal in acute benign edematous pancreatitis. In a more severe pancreatitis, intestinal ileus characterized as a localized sentinel intestinal loop dilatation in the pancreas region or more diffuse intestinal distension is common; more rarely, intestinal or colonic wall edema and organ displacements (from inflammatory fluid accumulation) can be seen. Calcified gallstones can suggest a biliary etiology, while pancreatic calcifications sign an underlying chronic pancreatitis. Flat plate abdominal X-ray can be used to rule out visceral perforation (with free air in the abdomen) as a cause of the abdominal pain.
- *Chest X-ray*: atelectasis in the inferior segments of the lungs, pleural effusions, may occur. Pulmonary infiltrates, pericardial effusion, signs of heart failure, and ARDS are less common and usually associated with severe forms of acute pancreatitis.
- *Abdominal ultrasound* is the test of choice for asserting the presence of gallstone(s) when biliary pancreatitis is suspected; dilatation of the common bile duct (although found in only a minority of cases of biliary pancreatitis) is highly suggestive of an obstructing stone (sometimes, the stone can be seen). Ultrasound can also confirm inflammation of the pancreas and examine for pancreatic fluid collections; however, it is less sensitive for the identification of these finding compared to CT scan.
- *Scanner* (CT scan or computed tomography of the abdomen): CT scan is the imaging modality of choice for acute pancreatitis (see ◘ Fig. 5.14). It allows evidence (1) to make the diagnosis of pancreatitis, (2) to rule out other conditions with a similar clinical picture (e.g., perforation of a hollow viscus, mesenteric ischemia, etc.), (3) to assess the severity of pancreatitis (Balthazar's criteria), and (4) to identify complications (pseudocysts, abscesses, intestinal or biliary obstruction, etc.).

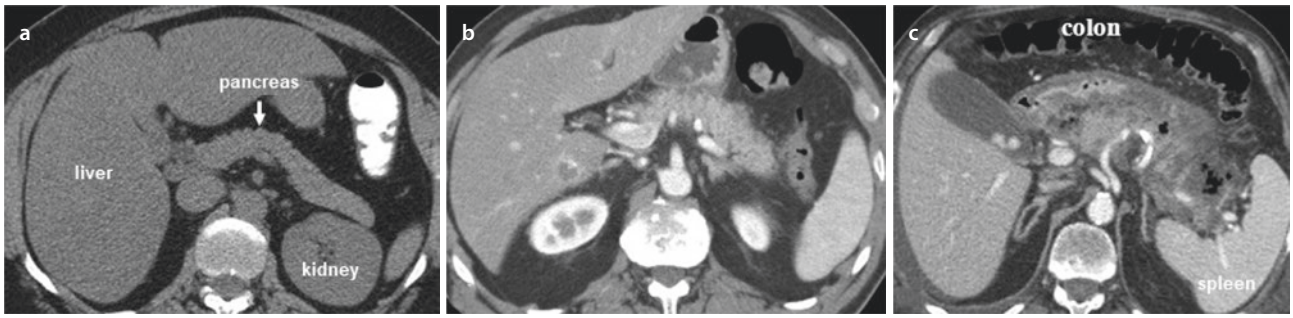


Fig. 5.14 CT scan of the abdomen and pancreatitis. **a** Normal pancreas. **b** Mild pancreatitis: edema of the gland and surrounding tissues; the pancreas is well perfused by the intravenous dye administered. **c** Severe pancreatitis: the pancreas is very edematous and necrotic with perfusion defects and air bubbles indicating abscesses

In benign self-resolving pancreatitis, CT scan performed within the first 48 hours of presentation is seldom useful, and it should not be prescribed routinely. Obtaining a CT scan in the first hours of pancreatitis should be limited to cases where the diagnosis is uncertain (e.g., to rule out perforated duodenal ulcer, aortic aneurysm, etc.).

In more severe pancreatitis, CT examination can be performed after 48–72 hours of evolution to evaluate the presence of pancreatic necrosis and other relevant complications. Edematous pancreatitis, recognizable by the good coloration of the gland, is always evolving favorably. Tissue digestion with significant necrosis of the pancreatic gland is characterized on CT scan by the lack of perfusion to necrotic tissue; clinical severity of acute pancreatitis is directly related to the extent of tissue necrosis.

- *Magnetic resonance imaging* (MRI): MRI is highly sensitive to detect choledocholithiasis. It is the only advantage of MRI (over CT scan) when used in the evaluation of acute pancreatitis.
- *Echo-endoscopy (EUS)* is highly sensitive for the evaluation of choledocholithiasis. It is seldomly used for this purpose in cases of acute pancreatitis as it is more invasive than MRI.
- *Endoscopic retrograde cholangiopancreatography (ERCP):* this endoscopic technique allows to visualize the bile duct or the pancreatic duct, but its complication rate (pancreatitis, infection, etc.) prohibits its general use in acute pancreatitis. It is the treatment of choice for choledocholithiasis, but its role in acute biliary pancreatitis is very limited. Stones trapped in the ampullary region, causing obstruction of the pancreatic duct and pancreatitis, will in a large majority (80–85%) of cases spontaneously pass into the duodenum within the first 24–48 hours of illness. The indication for ERCP (for biliary sphincterotomy and evacuation of gallstones) in acute biliary pancreatitis is limited to the case where persistent bile duct obstruction, especially with cholangitis, is suspected or confirmed.

(f) Assessment of Severity and Prognosis of Acute Pancreatitis

Early assessment of the severity of acute pancreatitis contributes to optimize treatment and prevent local and systemic complications.

Different clinical scoring systems have been developed to predict the severity of acute pancreatitis. The Ranson score is certainly the most popular (although more rarely used in nonspecialized units). It includes 11 variables that are collected during the first 48 hours of illness (Table 5.4). Mortality risk from acute pancreatitis increases significantly with the number of criteria present (Fig. 5.15). The APACHE-II and BISAP scores have also been suggested in the same context but are less commonly used due to their greater complexity. Other authors have suggested that simple markers, such as a CRP >150 mg/L at 48 hours after presentation, could help to predict the adverse evolution of a pancreatitis (and justify more aggressive therapies). In common practice, the importance of these predictive scores is however debated. In more than 80% of cases, pancreatitis resolves in less than 1 week.

Table 5.4 Ranson score (11 criteria) for acute pancreatitis

Criteria at arrival	Criteria after 48 hours
Age >55 years old if ROH, or >70 years if biliary cause	Ht decrease >10%
Leukocytes >16,000 × 10^6/L	Urea >2 mmol/L (in spite of liquids)
Blood glucose >11 mmol/L	Ca^+ < 2 mmol/L
LDH > 350 u/L	pO_2 < 60 mmHg
AST > 250 u/L	HCO_3^- deficit >4 mmol/L
	Liquid sequestration >6 L

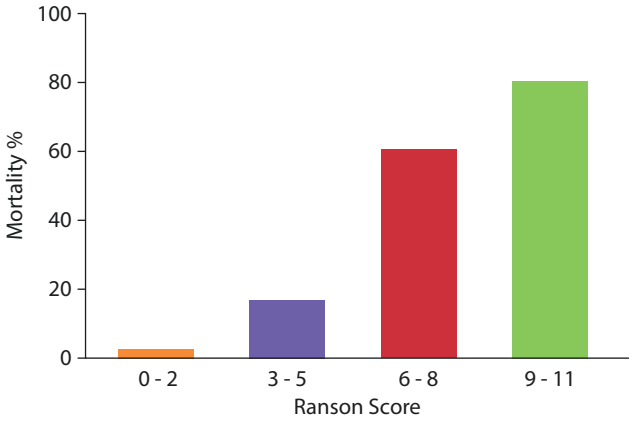


Fig. 5.15 Ranson score and mortality associated with acute pancreatitis. The majority of patients with severe pancreatitis have three to six criteria

Derived from CT scan findings, Balthazar radiological criteria also predict the severity of acute pancreatitis: severity of pancreatic/peripancreatic inflammation + pancreatic necrosis (areas with perfusion defects) in <30%, 30–50%, or >50% of the pancreatic gland = mortality rates of 3, 6, or 17% respectively.

5

(g) Complications of Acute Pancreatitis

Acute pancreatitis can be associated with local or systemic complications (Table 5.5).

- ***Fluid collections***, pancreatic as well as peripancreatic, are common. After 4 weeks, they can mature to become pseudocysts or encapsulated necrosis zones.
- ***Pseudocyst of the pancreas*** begins with an effusion of inflammatory fluid around the pancreas, especially in pancreatic retroperitoneum and at times extends to reach the para-colonic or pararenal gutters. These amylase (and lipase)-rich fluid collections may persist, and, after at least 6 weeks of evolution, become encapsulated by a fibro-inflammatory wall (hence the name pseudocyst, by comparison with a real cyst whose walls are lined with epithelial cells). The presence of pseudocysts is suspected when pain and/or elevated serum pancreatic enzymes persist following an acute episode of pancreatitis. Ultrasound or abdominal CT scan confirms the existence of pseudocyst(s).

Asymptomatic pseudocysts, regardless of their size, do not require treatment. Drainage is indicated when cysts are responsible for persistent pain, symptomatic compression of the digestive tract (such as biliary compression with jaundice or duodenal compression with gastric outlet obstruction and vomiting), or if the cyst becomes infected. Therapeutic intervention will also be required in presence of rare complications, such as intracystic hemorrhage (from arterial pseudoaneurysm) or pseudocyst rupture leading to pancreatic ascites with a very high amylase content.

Various interventions are available to drain a pseudocyst: percutaneous drainage is carried out under radiological imaging (US or CT scan); endoscopic drainage is done via the transgastric or transduodenal route; and surgical drainage evacuates the cystic content in the stomach (cystogastrostomy), or the duodenum (duodeno-cystostomy), or the intestine (on a Roux-en-Y intestinal loop).

- ***Sterile* vs *infected necrosis***. Necrosis of pancreatic tissue occurs early in the evolution of pancreatitis and is a determinant of pancreatitis severity. Pancreatitis is said to be necrotizing if more than 30% of the pancreatic tissue is not perfused on the CT scan of the abdomen realized with contrast dye. Necrotizing pancreatitis is generally more severe and is associated with more complications than edematous pancreatitis.

Pancreatic necrosis can be sterile or infected. It is rare for necrotic tissue to become infected before the second week of evolution of an acute pancreatitis. Leukocytosis or fever after 10 days of evolution must raise the suspicion of infected pancreatic necrosis. Diagnostic puncture, under radiological guidance or other, of the necrotic zone must be done with the aspirated liquid subjected to microbial study with gram staining and culture to determine the bacteria involved and tailor antibiotic therapy. Until recently, infected necrosis was treated by surgical debridement (often very morbid). We now prefer, in a stable patient without systemic failures, medical treatment with broad-spectrum antibiotics; if there is a suboptimal response or clinical deterioration of the patient's condition, minimally invasive debridement, by a surgical or endoscopic approach, is performed.

Table 5.5 Complications of acute pancreatitis

Local complications	Systemic complications
Fluid collection	Respiratory failure
Pseudocyst	Renal failure
Sterile necrosis	Shock
Infected necrosis	Hyperglycemia
Abscess	Hypocalcemia
Vascular	Intravascular coagulation
Thrombotic	Adipose necrosis
Hemorrhagic	

- ***Vascular complications.*** The splenic vein, running along the body of the pancreas, and the portal vein, being intimately connected to the pancreatic head, may be sites of reactive thrombosis related to peripancreatic inflammation. Thrombosis in these areas can lead to portal hypertension [central (portal vein thrombosis) or segmental (splenic vein thrombosis)] and, in some cases, result in esophageal or gastric varices which can be source of important GI bleedings (see ▶ Chap. 8). Prophylactic anticoagulation is a component of severe acute pancreatitis treatment in order to prevent thrombotic events.

  Rupture of vascular structures can cause bleeding in the abdomen (hemorrhagic pancreatitis), via the pancreatic duct (with "wirsungorrhagia"), or in a pseudocyst. These complications can be urgent and life-threatening. They are usually treated by radiological intervention (vascular embolization) or by (often morbid) surgery.
- ***Systemic complications.*** *V*arious organs can be affected in severe acute pancreatitis.

  Renal (prerenal) failure is common due to hypovolemia generated by severe vomiting or by loss if fluids to the "third space" in the pancreatic compartment. Shock, secondary to volume deficit, bleeding, sepsis, etc., may be lead to acute tubular necrosis requiring dialysis.

  Respiratory failure is a frequent complication in severe pancreatitis: atelectasis, pleural effusion, pneumonia, and acute respiratory distress syndrome (ARDS) are contributory. Increased oxygen supply, thoracocentesis, antibiotic therapy, and even ventilation may be necessary for treatment.

  Hyperglycemia, caused, among other things, by impaired insulin production due to islet cell necrosis, is possible. Hypocalcemia can occur as a result of calcium precipitation following fat saponification (chelation of calcium salts by free fatty acids, released due excess concentrations of lipase in circulation) which occurs mainly in the abdominal cavity (with the formation of yellowish droplets classically called "candle stains").

(h) Treatment of Acute Pancreatitis

No pharmacological treatment is recognized as effective for the treatment of pancreatic inflammation. The key principles for the treatment of patients with acute pancreatitis are early aggressive IV fluid resuscitation, analgesia, close monitoring, early identification and treatment of organ failure, and thrombosis prophylaxis.

(1) Early Days (Day 0–3)

- "*Pancreatic rest*" has always been the basic treatment (although empirical) for acute pancreatitis. Since the pancreas is active mainly during the postprandial period to secrete digestive enzymes, abstaining from oral food was proposed as the best way to minimize the production of pancreatic enzymes responsible for the autodigestion of pancreatic tissue.

  Recently, numerous studies focused on the risks of prolonged fasting and the benefit of early realimentation in patients with acute pancreatitis, and the strict and prolonged NPO diet is no longer recommended. Patients can often start within 24 hours of presentation with a clear fluid diet and progress to regular diet within 72 hours.
- *Intravenous fluid* replacement is necessary to compensate for a reduced oral intake as well as for losses resulting from vomiting or creation of a third space in the abdominal cavity (intra-abdominal or retroperitoneal). Hypovolemia is recognized as an unfavorable prognostic factor, and its aggressive treatment is essential. IV administration of several liters of fluid (lactate Ringer's) will be necessary on a daily basis, aiming to correct (1) hypotension, (2) plasma hematocrit, and (3) serum urea, and (4) maintain urine outcome greater than 0.5 mL/kg/h.
- *Analgesia* is often essential with opiates such as meperidine 50–75 mg i.m. q 3 h, hydromorphone 1–4 mg s.c. q 2–3 h, morphine 5–15 mg s.c. q 3–4 h, etc.
- *Thrombosis prophylaxis* is recommended.
- *Biological parameters* must be monitored to correct kidney failure, electrolytes disorders (serum urea, creatinine, sodium, potassium, bicarbonates), hypo- or hyperglycemia, as well as hypocalcemia.
- A *nasogastric tube* may be useful to relieve symptomatic nausea or vomiting (but is not essential or useful to improve pancreatitis outcome).

(2) Middays (Day 4–14)

- *Replacement feeding* is necessary after 3–5 days of fasting (for details, see ▶ Chap. 23). Enteral tube feeding, nasogastric or nasojejunal (more complex but possibly better tolerated), is preferred. If enteral feeding is not tolerated, parenteral nutrition will be required (but a small oral intake should be given to maintain intestinal mucosal integrity and prevent translocation of intestinal bacteria causing infection of necrotic tissues).
- *Fever* in the first 10–15 days of an acute pancreatitis episode is most often due to the inflammatory process and not infection.
- *Specific and particular considerations:*
  - With patients suffering from acute pancreatitis due to alcohol abuse, alcohol withdrawal syndrome may develop during the first days of hospitalization. Long-term management can be

facilitated with the support of specialty services such as addiction counselling, social work, psychiatry, etc.

- In biliary pancreatitis, the biliary stone responsible for the pancreatitis passes spontaneously in 80–85% of patients as the pancreatitis rapidly resolves. If pancreatitis persists, the possibility of a residual stone obstructing the pancreatic ampulla must be considered; MRI cholangiography or endosonography (EUS) may be useful before proceeding to an ERCP with sphincterotomy and stone extraction. The risk of gallstone pancreatitis recurrence is 20% in 1 month and 60% in 6 months; therefore, a cholecystectomy is required soon after the pancreatitis episode.
- In acute pancreatitis due to hypertriglyceridemia, lipid levels may decrease rapidly during the reduced oral intake period and fenofibrate treatment. In severe or persistent cases, plasmapheresis can be used to lower serum lipids levels and improve outcomes.
- Pancreatitis can be severe in 10–20% of cases. Close monitoring in a hospital setting or intensive care unit is warranted to prevent metabolic and respiratory complications.

(3) Late Days (Week 2–6)

Fever or clinical deterioration of the patient may be signs of infection of the necrotic tissues. Blood cultures and puncture of pancreatic or abdominal collections for culture of the collected liquids are essential. Medical treatment with antibiotics can be effective, but debridement with endoscopic, laparoscopic, or open surgical procedures may be required.

(4) Very Late Days (>6 Weeks)

Fluid collections are now encapsulated (pseudocysts), and, if symptomatic (compression of adjacent organs, pain, etc.), are amenable to drainage treatment.

The management of acute pancreatitis is summarized in Fig. 5.16.

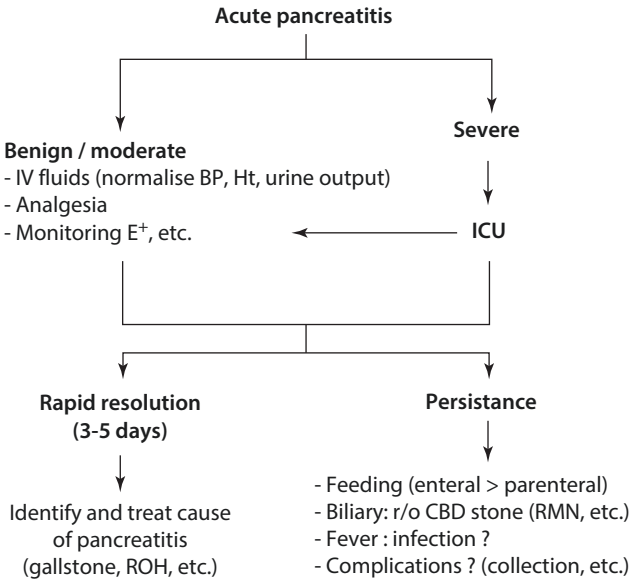


Fig. 5.16 Acute pancreatitis: initial treatment

5.6.2 Chronic Pancreatitis

(a) Definition and Generalities

Chronic pancreatitis is a chronic inflammatory disease of the pancreas that results in definitive structural and functional damage to the gland. This leads to a decline in exocrine and endocrine pancreatic secretory functions that become increasingly important over the course of disease progression and is often associated with chronic epigastric pain.

Stigmata of chronic pancreatitis are found in 5% of autopsies. The annual incidence of chronic pancreatitis is relatively low (3–9/100,000 population), and its prevalence is around 25/100,000 (and varies by the rate of chronic alcoholism in the population being studied). Chronic pancreatitis is a frequent cause of repeated hospitalizations, reduced quality of life, and death. Mortality and morbidity in subjects with chronic pancreatitis is related to various factors including complications from alcoholism, smoking, pancreatic cancer, or surgery.

(b) Pathology and Pathophysiology of Chronic Pancreatitis

On histology, chronic pancreatitis is characterized by fibrosis, dilated ducts, and protein precipitates in ducts lumen. Chronic inflammatory infiltration, with lymphocytes, plasma cells, and macrophages, often coexists with areas of acute pancreatitis characterized by edema, acute inflammation, and acinar cell necrosis. Histological damage is at first lobulated and heterogenous but will involve more and more pancreatic parenchyma over the progressive evolution of the disease. Calcifications develop from protein plugs formed within the ducts. Progressive replacement of acini, and later of the islets of Langerhans, by fibrosis explains the development of exocrine pancreatic insufficiency followed by diabetes.

In the obstructive forms of chronic pancreatitis, histological anomalies occur upstream of the obstruction and are more diffuse and homogenous. Ductal protein plugs, characteristic of others forms of chronic pancreatitis, are not present. Pancreatic tissue downstream of the obstructive lesion is spared.

The pathophysiological mechanism of chronic pancreatitis is unclear. Three main models are retained to date: (a) the work of J. C. Sarles suggested that the chronic ingestion of alcohol produces pancreatic secretions of reduced volume, rich in proteins and low in bicarbonate, which promotes the formation of protein plugs in the excretory ducts with progressive obstruction of the pancreatic ducts, leading to the atrophy and fibrosis of exocrine tissue found upstream of the obstruction. (b) A second model suggests a toxic effect of alcohol, or its derivatives, on exocrine pancreatic tissue and stellate cells is responsible for the fibrosis found in the pancreas. (c) The third model (necrosis-fibrosis) argues that repeated (clinical or subclinical) episodes of acute pancreatitis produce cellular necrosis that results in the disappearance of the pancreatic tissue and its replacement by fibrosis.

None of these models fully explains the development of chronic pancreatitis and, in particular, the fact that only a small proportion (about 5%) of alcoholics develops chronic pancreatitis. Other factors including exogenous (environmental) or endogenous (genetic predisposition) also probably contribute to the pathogenesis of the disease. It is now recognized that smoking is a very important cofactor in the development of alcoholic chronic pancreatitis. Certain genetic mutations, in particular SPINK 1 (see section on hereditary pancreatitis), have been associated with alcoholic or tropical chronic pancreatitis. A recent American-European study (Whitcomb, D. C., 2012) using GWAS technology (Genome Wide Association Study) which allows for the evaluation of the entire genome revealed an important association between chronic alcoholic pancreatitis and the gene encoding claudin 2 (CLDN2), a protein of acinar cells intercellular junctions. This gene is carried by the chromosome X, which could explain the strong preponderance of males in alcoholic chronic pancreatitis.

Table 5.6 Chronic pancreatitis: various causes are often identifiable by the presence or absence of calcifications (evaluated on imaging examinations)

With calcifications	Without calcification
Alcoholic	Metabolic
Tropical	Hypertriglyceridemia?
Genetic	Obstructive
Mutations PRSS1, CFTR, SPINK 1	Autoimmune
Metabolic	Postnecrotic
Hypercalcemia	Asymptomatic pancreatic fibrosis
Idiopathic	Chronic alcool
	Age
	Chronic kidney failure
	Diabetes
	Radiotherapy
	Idiopathic

(c) Etiology of Chronic Pancreatitis

Chronic pancreatitis may present in calcifying or non-calcifying forms (detectable in imaging examinations) and is each has been linked to several causes (Table 5.6).

Alcohol Alcohol abuse is responsible for 60–70% cases of chronic pancreatitis. The risk of developing the disease increases with amount of alcohol consumed. Although there is no lower risk threshold, in the majority of the cases, the consumption exceeded 150 g/day for a period of 5–10 years. However, only a small proportion (3–15%) of excess alcohol consumers will develop chronic pancreatitis. Smoking is now recognized as a major cofactor in the pathogenesis of alcoholic pancreatitis (and pancreatic cancer), and other factors were also mentioned such as genetic predisposition, diet rich in protein or fat, and antioxidant deficiency. Although the majority of heavy alcohol consumers do not develop clinical features of pancreatitis, autopsy and endosonography studies show morphological abnormalities of chronic pancreatitis in many of these individuals.

First clinical manifestation of alcoholic pancreatitis is often repetitive episodes of «acute» pancreatitis, on a background of morphological changes of chronic disease. Pancreatic calcifications are seen in about 60% of cases, and pancreatic insufficiency, exocrine and endocrine, occurs in 50% of patients after many years of evolution. In a small percentage of cases, the disease manifests with pancreatic insufficiency, calcified pancreas on imaging, and no abdominal pain. The prognosis for alcoholic-related chronic pancreatitis is poor, as these patients have reduced survival and poor quality of life. Stopping alcohol consumption can reduce disease progression and morbidity.

Tropical Calcifying chronic pancreatitis is common in tropical regions, particularly in the province of Kerala in southwest India. The cause is unknown, but genetic abnormalities have now been identified, and environmental factors (nutritional deficits, infections) have been mentioned. The disease is revealed clinically in most cases before the age of 40 years by abdominal pain associated with pancreatic insufficiency and severe malnutrition.

Hereditary/Genetic Chronic pancreatitis and recurrent pancreatitis have now been associated with various gene mutations including those encoding cationic pancreatic trypsinogen (PRSS1), trypsin inhibitor (SPINK 1), and membrane protein CFTR. The latter two are predisposing factors for pancreatitis, but are not sufficient alone to induce the disease.

- Cationic trypsinogen (encoded by the PRSS1 gene) is the major form of trypsinogen in the pancreas [the two other forms, anionic trypsinogen (PRSS2) and mesotrypsin (PRSS3) representing only 35%]. More than 20 PRSS1 mutations have been described. A single mutation is sufficient to produce the disease with autosomal dominant transmission. These mutations are responsible for hereditary pancreatitis by inactivating the trypsin self-degradation site.
- Trypsin inhibitor (encoded by the SPINK1 gene) is a 56-amino acid protein that specifically inhibits trypsin by binding to its active site. It is thus an internal defense system against inappropriate activation of trypsin in the acinar cell. Among the identified mutations of SPINK1, the two most common, N34S and P55S, are found in about 2% of the general population and are not able on their own to cause pancreatitis. On the other hand, the high frequency of these mutations (approximately 25%) in patient populations suffering from chronic idiopathic pancreatitis supports their association with pancreatic disease.
- CFTR (cystic fibrosis transmembrane conductance regulator) is a transmembrane protein of 1480 amino acids expressed in several epithelial cells of the respiratory tract, digestive tract, bile ducts, and pancreatic ducts to control ions exchange (in particular the secretion of chloride and bicarbonate). More than 1600 mutations in the CFTR encoding gene are known to modify to various degrees the synthesis or activity of the protein; they have been classified according to the resulting clinical phenotype as severe, moderate, or mild mutations. The association of two severe mutations abolishes the biological function of CFTR, and leads to cystic fibrosis of the pancreas (discussed in the ▶ Sect. 5.9).

  On the other hand, the association of a severe and a mild mutation leads to an atypical disease phenotype and has been found in cases of chronic or recurring pancreatitis of undetermined etiology. Heterozygote mutations and CFTR polymorphisms are common in European and American populations without necessarily leading to a clinical phenotype of chronic or recurrent pancreatitis; it is likely that other factors, environmental or genetic, must be combined with CFTR mutations to produce the clinical picture.

Identification of genetic abnormalities related to pancreatic disease is very contributive in the understanding of the disease physiopathology. Genetic variants associated to chronic pancreatitis can be classified into mechanistic pathways explaining their pathogenic effects: trypsin-dependent pathway (including PRSS1, PRSS2, SPINK1, CTRC genes) appears most important in pancreatitis physiopathology; misfolding of pancreatic enzymes (mutations in CPA1, CEL genes) is an apparent but rare mechanism; abnormal ductal secretion (CFTR, claudin 2, TPRV6 genes) is more and more confirmed as an important pathway in the genesis of chronic pancreatitis.

Metabolic Hypercalcemia is associated with the activation of trypsinogen and calcium deposition in the pancreatic ducts. The association between familial hyperparathyroidism and chronic pancreatitis is well recognized.

Hypertriglyceridemia is a classic cause of recurrent acute attacks of pancreatitis, but its relationship with chronic pancreatitis remains controversial.

Obstructive Chronic obstructive pancreatitis corresponds to a diffuse and homogenous atrophy of the exocrine pancreas upstream of a pancreatic duct blockage and associated with inter- and intralobular fibrosis. Various lesions may be responsible for ductal obstruction including neoplastic stenosis, inflammatory scar, pancreatic stone, papillary stenosis, etc. In some cases, correcting the blockage can restore the pancreatic function.

Obstructive pancreatitis caused by pancreas divisum? Pancreas divisum is an anatomical variant found in 4–11% of the population (see ▶ Sect. 5.3) and which has no clinical consequence in the majority of cases. The debate as to whether it is associated with a pancreatic pathology (acute recurrent pancreatitis or chronic pancreatitis) is still unresolved. In certain cases of pancreas divisum where the dorsal duct (of Santorini) is dilated upstream of the minor papilla, ductal hyperpressure leading to obstructive pancreatitis may probably be considered.

Autoimmune Pancreatitis (AIP) This inflammatory chronic pancreatitis occurs mainly in men (2:1) after the age of 50. Two types are recognized: AIP type 1 (which could be called IgG4 disease) is often associated with elevated serum IgG4. The pancreas is infiltrated with lymphocytes and plasma cells expressing IgG4. This form of pancreatic disease represents 5–6% cases of chronic pancreatitis. The disease may be limited to the pancreas or affect other organs, especially the bile ducts, salivary glands, and retroperitoneum. AIP type 2 has normal IgG4 levels, is restricted to the pancreas, and is associated

with chronic inflammatory bowel disease, Crohn's disease or ulcerative colitis.

Autoimmune pancreatitis can manifest as painful attacks of acute pancreatitis or by a painless obstructive jaundice due to an inflammatory mass in the head of the pancreas compressing the intrapancreatic portion of the bile duct. In this type of presentation, it is important to assess for the presence of a neoplastic lesion of the pancreas. Jaundice can also come from a biliary tract stenosis appearing like sclerosing cholangitis or a cholangiocarcinoma.

Imaging evidence of AIP includes a tumor-like mass (as discussed above) or a diffusely enlarged pancreas (typically having a "sausage" appearance). Serum hypergammaglobulinemia is present in 50–60% of cases, with elevated IgG4 levels (with a diagnostic sensitivity of 75–90% in AIP type 1).

A major diagnostic criterion for autoimmune pancreatitis is its rapid clinical and radiological response to corticosteroid treatment. Despite a complete response to corticosteroid therapy, 30–40% of patients will have a recurrence more or less later. This can be managed again with steroids or in some cases requires maintenance treatment with small doses of steroids or with thiopurine.

Chronic pancreatitis in children:

- Hereditary pancreatitis must be considered in any child with recurring episodes of unexplained pancreatitis or from the outset at the first episode if there is a family history of pancreatitis. PRSS1 gene, which codes for cationic trypsinogen, is most frequently involved.
- Between 30% and 70% of chronic pancreatitis case in children remains unexplained and is called idiopathic.
- Autoimmune pancreatitis, especially type 2 associated with inflammatory bowel disease, can occur in pediatric age.

(d) Clinical Presentation of Chronic Pancreatitis

The three clinical challenges associated with chronic pancreatitis are (1) *abdominal pain* from the sick pancreas, (2) *exocrine pancreatic insufficiency* due to the inability of the destroyed pancreas to produce digestive enzymes (amylases, lipases, etc.) in sufficient quantities to ensure digestion of ingested food, and (3) *endocrine insufficiency* by destruction of the islets of Langerhans and insufficient production of insulin to allow blood glucose homeostasis.

- ***Pain*** is the cardinal symptom of pancreatitis and the main reason for hospitalization and surgery in this population of patients. Chronic pain is present in 50–90% of subjects with chronic pancreatitis and is often a major impediment to their quality of life. It is felt in the epigastric area, throbbing, radiating to the back, and aggravated by meals.

  The natural history of this painful syndrome is variable. Pain can occur early or late in the evolution of the disease. It can present as intense but transient flare-ups which resorb completely or partially and leaving the patient asymptomatic between episodes or either with more or less intense chronic pain. In some cases, pain diminishes over time in parallel with the progressive destruction of the pancreatic parenchyma and appearance of exocrine pancreatic insufficiency.

  Pathophysiology of pain syndrome is not completely understood, but two main mechanisms seem to be at work: (1) increased pressure in pancreatic tissues and ducts (interventions, endoscopic or surgical, used to decompress and drain the pancreatic ducts may help in relieving pancreatic pain) and (2) perineural inflammation of sensory afferent fibers of the pancreas.
- ***Exocrine pancreatic insufficiency*** is revealed by steatorrhea (fatty stools). It is seen rather late in the evolution of the disease since pancreatic functional reserve is large and destruction of more than 90% of acinar cells is required before significant deficit in secreted enzymes occurs and results in maldigestion of dietary lipids and steatorrhea. Protein and carbohydrate maldigestion may be seen in advanced forms of the disease. Maldigestion of lipids occurs sooner because it is not only related to a reduction of lipase and colipase pancreatic input but also to a reduction in the secretion of bicarbonate, leading to acidification of duodenal pH and inactivation of bile salts and residual lipase.

  Maldigestion is revealed by frequent evacuation of oily stools that are pale and malodorous (steatorrhea), weight loss, and malnutrition. Proteolytic pancreatic enzymes are also necessary for digestion the R factor that binds dietary vitamin B12 (see ▶ Chap. 3), and thus vitamin B12 deficiency can sometimes occur.
- ***Endocrine pancreatic insufficiency***, through damage to the beta cells of the islets of Langerhans, is characterized by deficient insulin production. Diabetes is a late manifestation of chronic pancreatitis found in 40–80% of patients (half of them will need insulin). Glycemic control with insulin therapy is often difficult for these patients because of frequent hypoglycemic reactions (induced by insulin therapy) related to the concomitant damage to islets alpha cells that limits the production of serum glucagon (a pancreatic hormone which plays a compensatory role in glycemic equilibrium by increasing, if necessary, glucose blood levels lowered by insulin).

Congenital pancreatic insufficiency in children:

Isolated enzyme deficits mainly involving (intestinal) enterokinase or (pancreatic) lipase have been reported (but are very rare).

Lipomatosis with accumulation of adipocytes replacing the exocrine pancreatic tissue is known. Two entities can be distinguished: the syndrome of Shwachman-Diamond where a mutation of the SBDS gene on chromosome 7 induces exocrine secretory insufficiency is associated to hematological damage of central origin. The Johanson-Blizzard syndrome is characterized by exocrine pancreatic insufficiency associated with various malformations (aplasia of nose wings, deafness, skin aplasia, hypothyroidism, anal imperforation, etc.).

Pearson's syndrome, due to mitochondrial cytopathy secondary to a deletion of the mitochondrial genome, is associated with refractory sideroblastic anemia, exocrine pancreatic insufficiency, and deficient oxidative phosphorylation (resulting in metabolic crises with lactic acidosis).

5

(e) Diagnosis of Chronic Pancreatitis

The diagnosis is, in practice, most often made by an imaging evidence of anatomical changes suggestive of the disease or, more rarely, by a measure of pancreatic exocrine function.

Imaging Tests

- *Abdominal X-ray* is sometimes diagnostic in advanced forms of the disease since the typical pathognomonic pancreatic calcifications are common at this stage (Fig. 5.17).
- *Abdominal axial tomography (CT scan)* can detect pancreatic calcifications at an early stage of the disease, as it can reveal dilation of pancreatic ducts, inflammatory masses, or pseudocysts associated with the disease.
- *Cholangiopancreatography by resonance (MRCP or MRI)* may reveal more discreet morphological features.
- *Endoscopic retrograde pancreatography (ERCP)* has good sensitivity, but it is not used nowadays for diagnostic purposes given the invasiveness and risk of complications (post-ERCP pancreatitis, pseudocyst infection, etc.) of the procedure and the now established reliability and security of other diagnostic modalities.
- *Endosonography (endoscopic ultrasound, EUS)* is the most sensitive imaging test for detection of ductal or parenchyma abnormalities in the pancreas. However, the endoscopic procedure is invasive (usually performed under heavy sedation), requires a highly specialized technical expertise, and is less accessible compared to CT or MRI. In addition, chronic ingestion of alcohol is frequently associated with morphological changes of the pancreatic tissue that are asymptomatic and often difficult to differentiate from mild chronic pancreatitis.

Function Tests

- *Secretion tests.* The secretory function of the pancreas can be directly and precisely evaluated by using a tube positioned in the duodenum (or even in the pancreatic duct) to collect pancreatic secretions (obtained during various stimulations) to be ana-

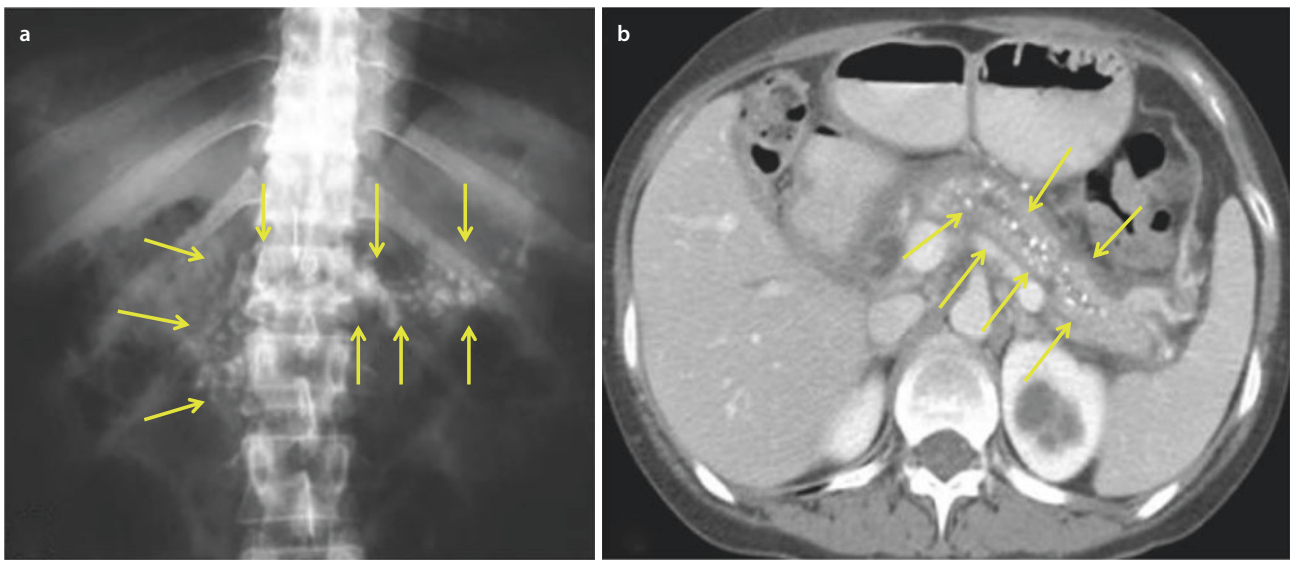


Fig. 5.17 Pancreatic calcifications seen in chronic pancreatitis on abdominal X-ray **a**, on abdominal CT scan **b**

lyzed for their ionic or enzymatic content. In presence of pancreatic insufficiency, the pancreatic secretion of bicarbonate in response to secretin injection is lowered, as is the secretion of pancreatic enzymes (trypsin, lipase, etc.) in response to CCK injection (or to a test meal ingestion).

Although considered as gold-standard procedures for the diagnosis of pancreatic insufficiency, these tubing tests for the measurement of the pancreatic function are invasive, relatively complex, tedious, and now usually replaced by imaging tests (although unable to assess pancreatic insufficiency, but they can confirm pancreatic disease).

- *Fecal fat* measurement [stool collection during 48–72 hours while the patient is consuming a high-fat (100 g per day) diet] confirms steatorrhea, but does not establish its origin (maldigestion due to pancreatic insufficiency or malabsorption by damage to the small intestine?).
- *Fecal elastase* or chymotrypsin dosage in the stool may in severe cases reveal low concentrations of these pancreatic enzymes and confirm pancreatic exocrine insufficiency.
- *Serum trypsinogen* levels (as well as serum lipase, although less specific) are often very low in severe pancreatic insufficiency.

(f) Treatment of Chronic Pancreatitis

It involves treatment of the causative or aggravating phenomenon and management of pain. Pancreatic insufficiency will be treated by replacement of the deficient secretion with enzyme supplements and insulin as needed. Treatment of chronic pancreatitis is summarized in Table 5.7.

Table 5.7 Chronic pancreatitis: manifestations/diagnosis/treatment

Manifestation	Diagnosis	Treatment
Abdominal pain	Imaging (confirms CP)	Stop ROH/smoking
		Pancreatic enzymes/ antioxidants
		Analgesics: • Acetaminophen-NSAIDs • Pregabalin-amitriptyline • Opiates
		Wirsung decompression: • Endoscopy • Surgery
		Celiac block
		Surgical resection
Exocrine insufficiency (steatorrhea)	Imaging (confirms CP)	Pancreatic enzymes: • Enterocoated/enteric release • Natural enzymes + PPIs
Endocrine insufficiency (diabetes)	Blood glucose	• Oral hypoglycemics • Insulin

Treatment of aggravating or causal phenomenon In alcoholic pancreatitis, total and definitive cessation of alcohol consumption is imperative. Even though chronic pancreatitis is an irreversible disease, stopping alcohol can not only improve the pain but can also slow disease progression toward pancreatic insufficiency. Multidisciplinary and specialized (medical, social, psychiatric, etc.) care for alcohol dependency is often essential for these patients.

Smoking, a recognized cofactor in the development of chronic pancreatitis, should be discouraged.

Pain management *Simple analgesics* such as acetaminophen, alone or in combination with nonsteroidal anti-inflammatory drugs, can be tried first

Opiate analgesics (codeine, oxycodone, hydromorphone, morphine, etc., in repeated oral doses or in oral sustained-release preparation or in skin patch) will often be necessary in face of an inadequate response to simple analgesics. The risk of narcotics addiction is obviously present since it is a chronic pain and a long-term treatment.

Antioxidants [vitamins, selenium (e.g., Stresstab Plus®)] may sometimes be effective and are a simple measure to try.

Calcium channels inhibitors (pregabalin, gabapentin) for the treatment of pancreatic pain (neuropathic?) can sometimes be useful.

P*ancreatic enzymes* administration for the reduction of pancreatic pain has physiological merit and is theoretically a logical therapeutic avenue (reducing pancreatic stimulation by providing an exogenous source of digestive enzymes). Although effective in animal experiments, it rarely seems a worthy solution in human practice; some literature suggests that the benefit would be better with natural enzymes than with enterocoated preparations (see below).

E*ndoscopic or surgical treatment* may be considered (see below) in cases where medical treatment of pain proves insufficient.

Treatment of exocrine pancreatic insufficiency Oral preparations of pancreatic enzymes (obtained from pig pancreas, freeze-dried and encapsulated) are available. To reduce steatorrhea, at least 30,000 IU (90,000 USP) of lipase should be administered with every meal, taken in divided doses at the beginning, middle, and near the end of the meal, to ensure better distribution of enzymes. Two formulations of pancreatic enzymes are available: the "natural" form, whose capsule is dissolved in the stomach (Viokase®), and the coated form with microgranules dissolving in the duodenum at noacidic pH (Creon®, Pancrease®). Since lipase is irreversibly inactivated by acid, natural unprotected enzymes preparations should be administered with a gastric acid inhibitor (PPI) to prevent enzyme inactivation by gastric acid. Preparations of enteric-release microgranules optimize the amount of enzymes available for nutrient digestion in the intestine and do not need to be protected from acid. However, they may dissolve distally in the small intestine and be unable to elicit duodenal feedback to inhibit postprandial pancreatic activity and reduce pancreatic pain (as discussed earlier).

Treatment of endocrine pancreatic insufficiency Diabetes associated with chronic pancreatitis can be difficult to manage since the concomitant glucagon deficiency can predispose persons to hypoglycemia. Some patients can respond to oral hypoglycemic medications, but the majority will require insulin therapy. Since pancreatic diabetes is associated with health complications, such as retinopathy, nephropathy, neuropathy, etc., appropriate glycemic monitoring is required for all patients.

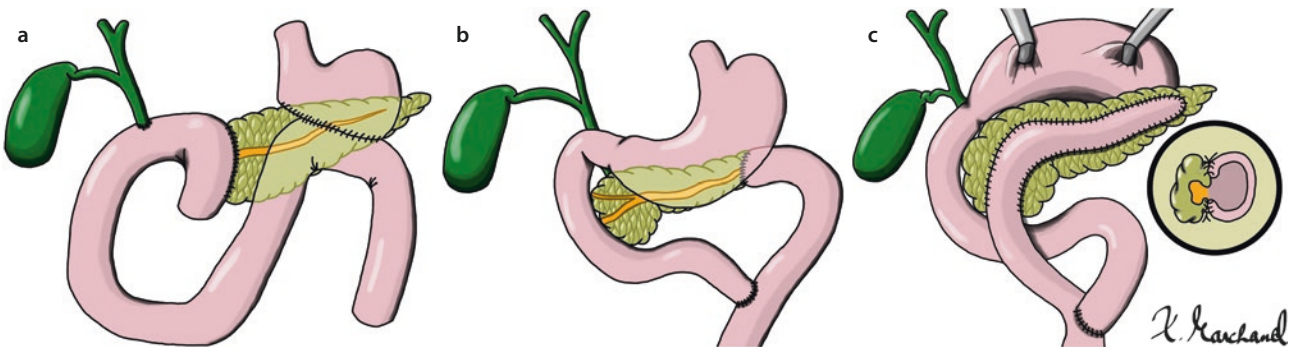
Endoscopic/surgical treatment of chronic pancreatitis In some cases, management of pancreatitis may benefit from endoscopic procedures or surgical procedures. The indication, as well as the execution of these techniques, which are often difficult and potentially highly morbid, must be entrusted to experts.

Endoscopic dilatation of pancreatic duct stenoses and/or extraction of pancreatic stones (with or without extracorporeal lithotripsy) can be done to improve function and/or pain. Endoscopy-guided drainage of pseudocysts, also a major cause of chronic pain, can be an effective treatment in selected cases. Celiac plexus blockade or neurolysis by injection, under endoscopic endosonographic vision, of corrosive alcohol or anesthetizing xylocaine solutions into the celiac plexus innervating the pancreas can also relieve pain, but the effect is unfortunately ephemeral.

Surgical treatment of chronic pancreatic pain can be done by resection of inflammatory masses or pseudocysts and/or by decompression of the pancreatic ducts and tissues. In the case of a dilated (hypertensive) pancreatic duct, it is possible to decompress the pancreatic gland via a lateral pancreaticojejunostomy (Puestow's procedure, or variants such as Frey's or Berger's procedures) which allows for a large surface drainage from the pancreatic duct opening along its entire length into an anastomosed intestinal loop. If the disease involves mainly the cephalic pancreas, a Whipple's duodenopancreatectomy may be necessary (this is one of the most complex interventions of modern surgery). In the case of a left-sided lesion, resection of the caudal pancreas (possibly with distal drainage of the remaining pancreas into an anastomosed intestinal loop according to Duval's procedure) may be done (see ◘ Fig. 5.18).

5.7 Tumor Disorders

Pancreatic tumors may be benign or malignant as shown in ◘ Table 5.8



◘ **Fig. 5.18** Surgical procedures for pancreatitis: **a** Whipple surgery involves resection of the pancreatic head and attached duodenum (and often includes the adjacent gastric antrum) and reconstruction using an intestinal loop to drain secretions from the remaining pancreas, from the bile duct, and to evacuate gastric contents; **b** in Duval operation (rarely performed now), the pancreatic tail is resected, and the remaining pancreas is anastomosed to an intestinal loop draining pancreatic secretions; **c** Puestow procedure is performed by opening the dilated pancreatic duct along its longitudinal axis and anastomosing it with an intestinal loop. This allows for secretions to be drained to the intestine and to decompress the pancreatic gland

5.7.1 Pancreatic Cancer/Adenocarcinoma

(a) General

Pancreatic adenocarcinoma is the second most common cancer of the digestive system. The prognosis is poor, with an average survival, all stages combined, of 25% at 1 year and 8% at 5 years. Its incidence is 9 per 100,000 population, with a slight predominance for males (1.3:1). It is uncommon before the age of 45, but risk gradually increases with age afterward; the average age at diagnosis is 71 years.

Environmental (lifestyle) factors associated with an increased risk of pancreatic cancer include alcoholism (via chronic pancreatitis; see Table 5.9), smoking, as well as excessive consumption of meat and fatty foods. The influence of tobacco smoking seems particularly harmful since the risk of developing pancreas adenocarcinoma by 70 years of age among persons with hereditary chronic pancreatitis is respectively of 40% or 20% in the presence or absence of smoking.

Genetic predispositions to pancreatic cancer are now recognized (Table 5.10). Recommendations for screening in these genetic forms of pancreatic cancer however do not yet make consensus. Some associations recommend screening from age 35 onward in patients with hereditary chronic pancreatitis and at 10 years less the age of the youngest afflicted member in the case of a subject where familial pancreatic cancer (defined as the occurrence of pancreatic cancer in two first-degree parents or in three parents) is suspected. Examination of the pancreas by magnetic resonance imaging (MRI) or endosonography can be used for screening.

Although ductal tissue only accounts for only 10–15% of the total pancreatic tissue (acinar 80%, endocrine 1–2%), 85–90% of pancreatic cancers are adenocarcinomas from duct origin. The majority of these tumors are found in the head of the pancreas (60–70%), 5–10% in the body, and 10–15% in the tail of the pancreas. These lesions progress by locoregional extension (invading adjacent structures, the retroperitoneum) and disseminates as metastasis to lymph nodes (peripancreatic, hilar, celiac) and the liver. Early invasion of essen-

Table 5.8 Primary tumors of the exocrine pancreas according to the World Health Organization

Benign lesions
Serous cystadenoma
Mucinous cystadenoma
Intraductal papillary mucinous adenoma
Mature cystic teratoma
Intermediate lesions (uncertain malignant potential)
Mucinous cystadenoma with moderate dysplasia
Intraductal papillary mucinous adenoma with moderate dysplasia
Solid pseudopapillary tumor
Malignant lesions
Ductal adenocarcinoma
Giant cell osteoclastic tumor
Serous cystadenocarcinoma
Mucinous cystadenocarcinoma
Intraductal papillary mucinous carcinoma
Acinar cell adenocarcinoma
Pancreatoblastoma
Solid pseudopapillary carcinoma
Other carcinomas

Table 5.9 Pancreatic cancer: risks and favoring factors

Subject	Cancer risk at 70
Normal	0.5%
Family history of pancreatic cancer (number of 1st degree relatives)	
1 Parent	1%
2 Parents	10%
3 Parents	40%
Chronic pancreatitis	4%
Hereditary pancreatitis	40%

Table 5.10 Genetic predisposition to pancreatic cancer

Clinical history	Gene	Relative risk
None	None	1
Breast-ovarian cancer	BRCA 1 and 2	2–10
FAMMM	P16 (CDKN2A)	10–25
Familial pancreatic cancer n: 1, 2, 3	Unknown	2, 6, 32
Hereditary pancreatitis	PRSS1	50–80
Peutz-Jeghers syndrome	STK11/LKB1	100–130
HNPCC	MLH1, MSH2 + others	4–8

FAMMM familial atypical multiple mole melanoma syndrome, *HNPCC*, hereditary nonpolyposis colorectal cancer syndrome (Lynch syndrome)

tial nearby structures (such as the portal vein and the superior mesenteric vein) is such that the majority of tumors cannot be surgically resected at the time of their diagnosis.

Unfortunately, pancreatic cancer is often characterized by a rapid and painful evolution.

(b) Clinical Presentation of Pancreatic Cancer

Pancreatic cancer commonly manifests by jaundice (in >50% of cases; due to obstruction of the intrapancreatic portion of the common bile duct), pain (often epigastric and radiating to the back; due to tumor invasion of nerves or peripancreatic structures or to pancreatitis upstream from an obstructed duct), and/or weight loss (due to malabsorption, postprandial abdominal pain that interferes with eating, or anorexia). Diarrhea with steatorrhea (obstruction of the pancreatic duct limiting enzymes delivery), de novo diabetes (mechanism uncertain), and symptoms of depression (mechanism unknown) may also be the initial clinical symptoms of pancreatic cancer. Symptoms appear however unfortunately late in the progression of pancreatic cancer, so that few (less than 10%) pancreatic lesions are resectable when discovered.

Physical examination is often of little help to make a diagnosis of pancreatic cancer. Jaundice is often due to a tumor of the head obstructing the intrapancreatic bile duct but too small to be appreciable via abdominal palpation. Large tumors (especially in the tail where they can progress without causing jaundice) may be palpable. In some cases, it is possible to palpate a distended gallbladder (Courvoisier's gallbladder distended by biliary obstruction usually related to a progressive malignant process since acute blockade by a stone will lead to pain and cholangitis before gallbladder can distend), or a hard metastatic nodule at the level of the umbilicus (Sister Marie-Joseph's nodule). Hepatomegaly, as ascites, is suggestive of metastatic diffusion. Cachexia, from either caloric deficit or neoplastic catabolic process, is a poor prognostic factor.

(c) Diagnosis of Pancreatic Cancer

Blood tests: jaundice (obstructive) is cholestatic, with elevated serum levels of conjugated bilirubin, alkaline phosphatase, and GGT.

Both serum pancreatic amylase and lipase may be mildly elevated, but this is not diagnostic.

Tumor marker CA19-9 is associated with pancreatobiliary cancers (86% sensitivity and 87% specificity). On the other hand, its usefulness is limited in the presence of cholestatic jaundice that can increase CA19-9 levels to very high values even in the absence of malignancy.

Imaging tests:

- *Abdominal ultrasound* is minimally invasive and is often one of the first imaging tests done. It can reveal enlarged bile ducts and gallbladder and less often identify the source the obstruction of the common bile duct (such as an infiltrating pancreatic mass). Hepatic metastases and/or ascites can also be detected.
- *Abdominal CT scan* (Fig. 5.19) with contrast is the most commonly used test to identify and evaluate a pancreatic cancer lesion and its extension and, most importantly, to assess its potential surgical resection. This examination can evaluate for the presence of distant metastases (liver, peritoneum, lymph nodes), as well as malignant invasion of the main vessels (celiac trunk, superior mesenteric artery, portal vein, superior mesenteric vein); all these items being radiological criteria for non-resectability of the lesion (however, up to 50% of pancreatic lesions deemed resectable with CT scan will be declared non-resectable at the time of surgery).
- *Magnetic resonance pancreatography (MRI)* has the advantage of avoiding iodine injection in an allergic patient or with renal failure. MRI with gadolinium contrast may be more sensitive for the identification and staging of pancreatic tumors; however, CT scan may be more accurate for identifying vascular invasion. MRI is increasingly being used to further characterize liver lesions suspicious for metastatic disease on CT scan.
- *Endoscopic retrograde cholangiopancreatography (ERCP)* may reveal a stricture of the common bile duct or the main pancreatic duct. It is primarily used for therapeutic decompression in cases of malignant biliary obstruction. Brushing samples can provide a cytopathological diagnosis.

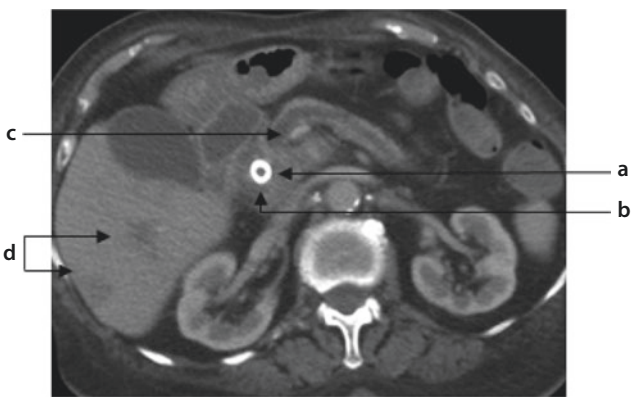


Fig. 5.19 Pancreatic adenocarcinoma on CT scan: **(a)** the pancreas head is replaced by a mass; **(b)** a plastic biliary stent (white plastic ring) for biliary decompression has been placed in the common bile duct; **(c)** the pancreatic duct is dilated on the obstacle; **(d)** metastases are present in the liver

- *Endosonography (endoscopic ultrasound, EUS)* is the most sensitive modality for the detection of tumors and evaluation for local extension to lymph nodes, vessels, adjacent organs, or ascites. Needle biopsy of the tumor can be performed to confirm the malignant nature of the lesion (useful in case of doubt or when precise histological diagnostic is needed to undertake treatment such as palliative chemotherapy). Moreover, a coeliac block (infiltration of xylocaine or alcohol) can be done to reduce abdominal pain.
- *Positron emission tomography (PET scan)* is of little use to reveal anatomical details and resectability of pancreatic lesions, but it may be of interest to demonstrate distant metastasis, to differentiate malignant from benign lesions, and to evaluate the response to neoadjuvant chemoradiotherapy.

Table 5.11 Treatment of pancreatic adenocarcinoma

Tumor	Frequency	Survival	Suggested treatment
Metastatic (liver)	60% of cases	6–12 months	Chemotherapy
Locally advanced (lymph nodes, vessels)	25%	9–12 months	Chemotherapy
Resectable	15%	15–55 months	Surgery + chemotherapy

(d) Treatment of Pancreatic Cancer

Curative treatment of pancreatic cancer requires complete surgical resection of the tumoral lesion and its lymph nodes. Unfortunately, curative surgery is possible in only 15–20% of patients at the time of diagnosis. Metastases or malignant infiltration of nearby structures are common contraindications to curative resection.

The type of surgical resection performed must be adapted to the site of the lesion. In case of a tumor in the head of the pancreas, Whipple's cephalic pancreatoduodenectomy, with or without pyloric preservation, is the procedure of choice but still remains a major and delicate surgical procedure (in expert centers, this can now be performed with reasonable morbidity and mortality rates). Survival at 5 years after surgery that was considered curative is limited historically to 10–20%; the role of adjuvant chemotherapy is now confirmed (median recurrence-free survival of 40% with FOLFORINOX).

Palliative treatment of cancer will unfortunately be the only possible therapeutic avenue for a large number of patients (see Table 5.11). Obstruction of the bile duct and/or duodenum can be managed by various surgical derivation procedures or, preferably, by a less morbid endoscopic approach allowing biliary and/or duodenal stenting.

Various palliative chemotherapy protocols have been studied (5-FU, gemcitabine, FOLFORINOX, Abraxane) in an attempt to improve patient survival. Gemcitabine since 1997 is a classical palliative treatment, recognized to provide a slight survival advantage at 1 year and above all a better quality of life with less pain and weight loss. FOLFORINOX (5-FU, irinotecan, oxaliplatin) appears more effective than gemcitabine, but its superior toxicity limits its use to patients in good general condition.

Pain is an important symptom in these patients. It can be managed by analgesic therapy with long-acting narcotics. Celiac ganglion neurolysis can be performed endoscopically (EUS; more rarely by surgical intervention or transcutaneously by X-ray guidance).

Since the obstruction of the pancreatic duct leads to impaired delivery of pancreatic enzymes and therefore to nutrient maldigestion, it is important to prescribe pancreatic enzyme preparations to these patients.

5.7.2 Cystic Tumors/Cysts

Cystic structures are found, often incidentally, in 3% of pancreatic imaging exams (CT scan, MRI, or ultrasound).

(a) Cysts and pseudocysts Nonneoplastic cysts of the pancreas include pseudocysts (extra-pancreatic liquid collections contained between various viscera and having fibro-inflammatory walls rather than epithelial walls like real cysts) or retention cysts [dilatation of a (secondary or primary) pancreatic duct by accumulation of pancreatic fluid upstream of a blockade] that may both occur in the context of pancreatitis (acute or chronic) and simple pancreatic cysts (congenital or acquired; usually of small size) most often discovered incidentally during an imaging exam.

(b) Cystic neoplasms Pancreatic cystic neoplasms account for only 10% of pancreatic neoplasms but for over 60% of cystic lesions of the pancreas identified during abdominal imaging. Of all lesions described in Table 5.12, serous cystadenoma, which accounts for about 30% of neoplastic cysts, is the only one with almost no malignant potential. All other lesions may transform into malignant lesions to variable degrees, so

Table 5.12 Cystic tumors of the pancreas

	Frequent (80%)	Rare (20%)
Benign	Serous cystadenoma	
Malignant potential	Mucinous cystadenoma	Pseudopapillary solid tumor
	IPMN	Cystic endocrine tumor
		Cystic duct adenocarcinoma
		Cystic acinar adenocarcinoma

that if there is any doubt about the nature of the lesion and its malignant potential, a surgical resection is indicated. Also, any symptomatic cystic lesion will have to be resected.

- ***Serous cystadenoma*** is a benign lesion found most often in women over 50 years of age. It is characteristically composed of multiple small honeycomb nests and can present a star shaped central calcification. When punctured, the aspirated cyst fluid is clear, serous, and nonviscous, contains no amylase and low CEA or CA 72-4, and is benign on cytopathology. The serous cystadenoma is common (30% of cystic pancreatic tumors), does not require follow-up, and should be resected only if >4 cm or symptomatic.
- ***Mucinous cystadenoma*** is the most common neoplastic cystic lesions of the pancreas. Surrounded by ovarian stroma, mucinous cystadenoma is found in women over 50 years of age, in the body or tail of the pancreas. On imaging, it presents a thick wall forming a single cyst containing some divisions by internal septa. When punctured (in EUS), the recovered liquid is clear, viscous, containing little amylase but high levels of CEA and CA 19-9. Surgical resection is clearly to be considered since in situ or invasive cancer is found in up to 17% of cases.
- ***Intraductal papillary mucinous neoplasm (IPMN)*** of the pancreas is most often found in the cephalic region and can be located either in the main pancreatic duct or in a side branch of it. This difference is important since IPMNs of the main duct have a much more malignant potential (15–40%) than those originating in collateral branches (10%).

Papillary tumors secrete significant amounts of mucin which can lead to obstruction and dilatation of the ducts upstream of the blockade. Duct dilatation is the major sign found by the different imaging methods that can highlight these lesions, either CT scan, MRI, or EUS.

IPMN incidence is equal in men and women and occurs at a median age of 65 years. It is symptomatic in 50–75% of cases, either by acute pancreatitis (by duct obstruction by mucin or the tumor) or epigastric abdominal pain associated with weight loss (caused by a lack of enzyme secretion due to duct obstruction).

Given the malignant potential of a main duct IPMN, the best treatment is complete surgical resection of the lesion (which can result in 5-year survivals up to 75%, if the lesion is not advanced at the time of resection). In the case of a collateral branch lesion (often of benign nature), it is agreed to perform surgical resection if the lesion is symptomatic, if it measures more than 3 cm, if it contains masses or nodules, or if it is associated with a main duct dilatation; otherwise, an imaging follow-up is recommended.

5.7.3 Neuroendocrine Tumors (NETs)

(a) General

NETs account for 1–10% of pancreatic tumors. They are histologically identifiable by their small round cells, and the German term *Karzinoide* (carcinoid-like) was first used to describe an intestinal tumor with the unique feature of behaving like a benign tumor clinically while having a malignant appearance microscopically. Carcinoid tumor of the intestine (which secretes serotonin leading to the carcinoid syndrome discussed in ▶ Chap. 3) was for long the prototype of these tumors containing secretory granules with neuroendocrine markers (chromogranin A, synaptophysin, etc.) and now identified as NETs. NETs can be found mainly in the pancreas (pNET) or intestine (iNET). Their granules contain various substances (serotonin, gastrin, insulin, etc. that can be released into circulation without regulation and induce typical clinical manifestations) which can be identified using electron microscopy (thanks to the size and density of the secretory granules) or by immunohistochemical staining markers (specific to each substance such as anti-gastrin or anti-insulin antibodies).

NETs can be nonsecretory (30–50% cases) or release into circulation large quantities of "hormonal" substances (such as insulin or gastrin) which leads to a clinical phenotype specific to this hormonal hypersecretion

(for instance, hypoglycemia if hyperinsulinemia or peptic ulcers if hypergastrinemia, etc.). The most common pNETs are insulinoma and gastrinoma; VIPoma and glucagonoma are less frequent, and somatostatinoma is rare.

NETs may be sporadic (80% cases) or associated with hereditary diseases such as the MEN-1 syndrome [multiple endocrine neoplasia type 1 with parathyroid, pituitary (often prolactinoma), and pancreatic tumors] or the rare phakomatoses (von Hippel-Lindau disease, Bourneville's tuberous sclerosis, von Recklinghausen neurofibromatosis).

NETs arise from neuroendocrine cells that are located throughout the body; however, NETs tend to occur mainly in the gastrointestinal tract, lungs, and pancreas (Table 5.13). All these lesions have a potential for malignancy and can therefore become metastatic (although it is rare in the case of insulinoma). Tumor evolution of NET is often less aggressive compared to adenocarcinoma, and patients survival may be prolonged for several years, even in the case of metastatic tumors.

(b) Phenotype and Clinical Presentation of NETs

Nonsecreting NETs (although this term may be inappropriate since the vast majority will secrete into circulation pancreatic polypeptide and/or chromogranin A, these substances do not have identifiable biological effects) may present, similarly to other pancreatic tumors with a pancreatic lesion, liver metastases, abdominal pain, impairment of general condition, etc.

Table 5.13 Neuroendocrine tumors

NET	Location	Secretions	Manifestations
"Carcinoid"	Ileum (30%)	Serotonin	Diarrhea
	Lung (25%)	Histamine	Bronchospasm
	Appendix (20%)	Kinins	Flushing
	Rectum (10%)	TGF-B	Fibrosis
Gastrinoma	Pancreas (50%) Duodenum (50%)	Gastrin	Ulcers Diarrhea Malabsorption
Insulinoma	Pancreas	Insulin	Hypoglycemia
VIPoma (WDHA, pancreatic cholera)	Pancreas	Vasoactive Intestinal Peptide	Diarrhea Achlorhydria Hypokalemia
Glucagonoma	Pancreas	Glucagon	Diabetes Rash Anemia
Somatostatinoma	Pancreas	Somatostatin	Steatorrhea Gallstones Diabetes
PPoma	Pancreas	Pancreatic polypeptide	None
ACTHoma	Adrenal gland Pancreas (10%)	ACTH	Cushing's syndrome
GRFoma	Lung (50%) Pancreas (30%)	Growth hormone releasing factor	Acromegaly
ECLoma	Stomach	Histamine	None

Secreting NETs are identified by the substance produced by the tumor and released into circulation:

- *Insulinoma* results in very high serum levels of insulin and manifests itself as hypoglycemic episodes. The tumor is usually pancreatic, unique, benign, and often easily resectable by enucleation.
- *Gastrinoma*, or Zollinger-Ellison syndrome (ZES), is due to tumoral gastrin hypersecretion resulting in an excessive secretion of HCl by gastric parietal cells causing a severe acido-peptic disease, often diarrhea (secretory volume exceeding the reabsorption capacities of the gut), and possibly malabsorption (lipase and bile salts inactivation by acid) (as discussed in ► Chaps. 2 and 3). Treatment of ZES aims to reduce the secretion of gastric HCl by PPIs (proton pump inhibitors usually needed at very high doses) to avoid the severe complications (even lethal) of this extraordinary hyperchlorhydria. The tumor is most often localized in the head of the pancreas (50% of the time) or in the duodenal wall (which thus requires a Whipple's cephalic pancreatoduodenectomy). In MEN type 1 (20% of cases), the tumors are often multiple and distributed throughout the pancreatic gland (prohibiting then surgical resection). Nodes and/or liver metastases are frequent.
- *VIPoma* [known as WDHA (watery diarrhea, hypokalemia, achlorhydria) syndrome, or pancreatic cholera, or Verner-Morrison syndrome before VIP was identified as the causal agent] is due to an exaggerated secretion of vasointestinal polypeptide which activates adenylate-cyclase of the enterocyte, thus inducing an intestinal secretion of electrolytes and H_2O that can be very severe. Watery stools, hypokalemia, and dehydration can make diarrhea look like cholera. VIP also inhibits the secretion of gastric HCl (achlorhydria of WDHA). The medical treatment of VIPoma relies on somatostatin analogues (e.g., octreotide) suppressing VIP release by the tumor, as well as inhibiting of the action of VIP on enterocytes to stop the severe (often lethal) diarrhea. Surgical resection of the tumoral lesion, if feasible, is indicated.
- *Glucagonoma* (presenting with diabetes, skin lesions, anemia, and sometimes constipation) and *somatostatinoma* (diarrhea/malabsorption, gallstones, diabetes) are more rare.

(c) Diagnosis of NET

Diagnosis of secretory NETs is achieved by confirming circulating excess "hormone" produced by the tumor. Measurement of plasma insulin or gastrin levels is readily available in most hospital laboratories; measurement of somatostatin or VIP is however limited to specialized laboratories.

Imaging for tumor localization uses the same tools as for adenocarcinoma, i.e., CT scan, MRI, endosonography, etc. Endocrine tumors usually contain somatostatin receptors, which allows imaging by nuclear scintigraphy (Octreoscan with isotopically labelled somatostatin analogue In^{111}octreotide) or by positron scintigraphy (PET scan with octreotide analogue dotatate labeled with Gallium ^{68}).

(d) Treatment of NET

Symptomatic treatment includes:

- Suppression of the biological action of the hypersecreted hormone (e.g., inhibition of gastric acid secretion with PPIs).
- Pharmacological suppression of the hypersecreted hormone (with somatostatin analogues such as octreotide).
- Suppression of "hormonal" hypersecretion through complete (if possible) or partial (debulking) surgical resection of the tumor.

Tumor progression of NET is usually much slower than that of other tumors, and the oncological prognosis is more favorable (survival of 10–20 years are observed, even in metastatic forms). Oncological treatment is provided by:

- Surgical resection of the primary tumor and its metastasis
- Control of tumor growth with somatostatin analogues
- Chemotherapy with classical streptozotocin (or temozolomide), or with new agents acting on tyrosine kinase (sunitinib) or on mTOR pathway (everolimus)

5.8 Function Disorders

The only pancreatic pathology that could be considered of functional origin is SO dyskinesia with secondary obstructive pancreatitis. Impaired relaxation of the sphincter of Oddi ("achalasia" of Oddi) in absence of a fibrous ampulla is however a much debated entity not recognized by all.

5.9 Miscellaneous

5.9.1 Cystic Fibrosis

Cystic fibrosis is an inherited condition that implies hyperviscosity of glandular and mucus secretions in various organs. Lung disease is usually the most serious complication of this disease which also affects the pancreas as well as other digestive organs such as the bile ducts and the small intestine.

(a) Etiopathogeny Cystic fibrosis is a genetic disease with autosomal recessive transmission and most frequently identified in Caucasians (1/2500 births). It is due to mutations in the CFTR gene (cystic fibrosis transmembrane conductance regulator) on chromosome 7, which alter the CFTR protein, an ion channel for the secretion of chloride through cell membranes (the efflux of Cl^- generates H_2O movement out of the cell). In respiratory and digestive tracts, the impaired secretion of Cl^- and, secondarily, H_20 leads to viscous and thick secretions.

(b) Physiopathology Mucus hyperviscosity leads to obstructive blockages in different organs:

- In the lungs, increased viscosity of pulmonary secretions leads to clogging of the airways by mucus plugs favoring pulmonary superinfection by different bacteria and progressive (and lethal) destruction of the lungs.
- In the pancreas, hyperviscosity of pancreatic juice leads to protein plugs preventing the flow of exocrine pancreatic secretions. This can cause recurrent acute pancreatitis as well as nutrients malabsorption via exocrine pancreatic insufficiency.
- In the small bowel, thick intestinal secretions may cause intestinal obstruction by meconium in the newborn. Dry stools that are difficult to externalize and require defecation efforts can cause rectal prolapse in infant. In adult, intestinal or colonic impactions by dry "stools" can occur.
- In the bile ducts, hyperviscosity of the bile can lead to obstructions in the hepatic ducts and an evolution toward secondary biliary cirrhosis.

(c) Diagnosis The diagnosis of cystic fibrosis is usually made in children using the sweat test which confirms high concentrations of sodium and chloride in skin sweat secretions. Several mutations of the CFTR gene are known, and prenatal genetic screening is available, as well as screening for individuals at risk of carrying a transmissible gene.

(d) Treatment of cystic fibrosis Life expectancy of patients with cystic fibrosis was previously very much reduced by pulmonary complications; in the absence of treatment, the average survival was 3–5 years. Over the last 50 years, life expectancy increased to 40–50 years. Even though there is no cure for cystic fibrosis, multidisciplinary management aiming to treat respiratory complications by pulmonary rehabilitation and antibiotics, preventing pancreatic and digestive tract conditions by enzyme supplements etc., improves quality of life and life expectancy of these patients. Lung transplantation is now possible for many patients, as well as pancreatic or liver transplantation if needed. Genetic therapies to correct the biochemical abnormalities responsible for this disease are still awaited.

PS: For complementary lectures on the pancreas, see ► Chaps. 16, 25, and 29.