4

Pancreas

The pancreas, sometimes referred to as the queen organ, plays a major role in digestion and metabolism. Two separate components accomplish these functions: the exocrine pancreas, which secretes powerful enzymes that break down carbohydrates, fat, and proteins; and the endocrine pancreas, made up of the islets of Langerhans, which elaborate insulin and glucagon, hormones that regulate the level of blood glucose.

Lying in its retroperitoneal position, with a temperament that is unpredictable, the pancreas continues to present major challenges to the surgeon. The pathophysiology of its inflammatory conditions is incompletely understood and their therapy inconclusive. Although pancreaticoduodenectomy and total pancreatectomy are now performed with a low mortality rate, the ability of these major operations to cure pancreatic cancer is disappointingly low.

ANATOMY

DEVELOPMENT OF THE PANCREAS

The pancreas develops as a dorsal and ventral bud from the foregut during fourth week of fetal life (Figure 4.1). The duct of the ventral pancreas joins the distal common bile duct. During gestation, the duodenum rotates clockwise in its long axis, and the ventral pancreas and common duct come to lie to the left of the duodenum and fuse with the dorsal pancreas. In the process of rotation, the ventral pancreas, which forms most of the head of the pancreas, encloses the superior mesenteric vessels, which come to lie between the uncinate process posteriorly and the pancreatic head anteriorly. Most of the duct that drains the dorsal pancreas joins the duct of the ventral pancreas to form the main pancreatic duct called the duct of Wirsung. The most medial portion of the duct of the dorsal pancreas becomes the accessory pancreatic duct—the duct of Santorini—and enters the duodenum about 1 in proximal to the entrance of the duct of Wirsung into the duodenum.

There was once a theory that the endocrine pancreas was derived from the neural crest of the embryo and that endocrine cells migrated to the abdomen along with the sympathetic chain and with the cells that comprise the adrenal medulla. There is now conclusive evidence derived from studies in molecular genetics that the endocrine cells derive from endoderm cells of the primitive embryonic foregut. The genes for insulin, glucagon, and somatostatin are expressed in the foregut at the site where the future diverticulum forms. The same is true for exocrine cells, although the genes for exocrine enzymes are expressed a little later. Furthermore, the mesenchyma surrounding the primitive endoderm cells, from which the pancreas form, exerts significant influence on differentiation of the pancreas. In the absence of mesenchyme—which is required for differentiation into exocrine cells—the endoderm cells differentiate only into endocrine cells.

SURGICAL ANATOMY

The pancreas is a retroperitoneal organ consisting of two distinct functional units, exocrine and endocrine pancreas. The exocrine pancreas is comprised of acini and ducts, while the endocrine pancreas comprises approximately 1 million islets of Langerhans interspersed among the exocrine glands and ducts throughout the pancreas. The endocrine pancreas constitutes approximately 1% of the total organ. The surgical anatomy is shown in Figure 4.2.

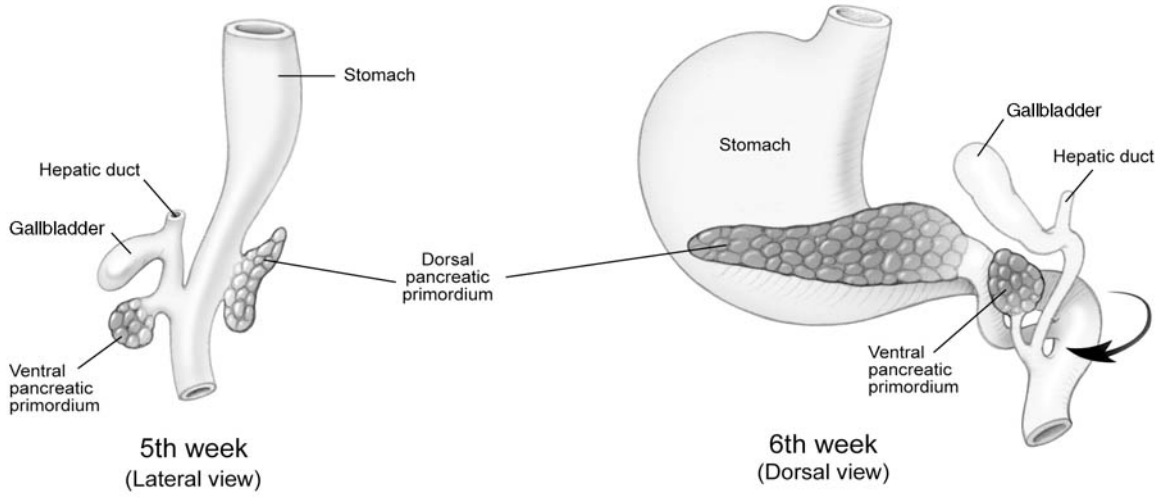


FIGURE 4.1. Development of the pancreas from the dorsal and ventral bud of the foregut. Lateral view at week 5 shows development of the ventral pancreas and biliary tree from the ventral bud. The dorsal view at week 6 shows how, with rotation of the duodenum clockwise, the ventral pancreas and common duct come to lie posteriorly and fuse with the dorsal pancreas.

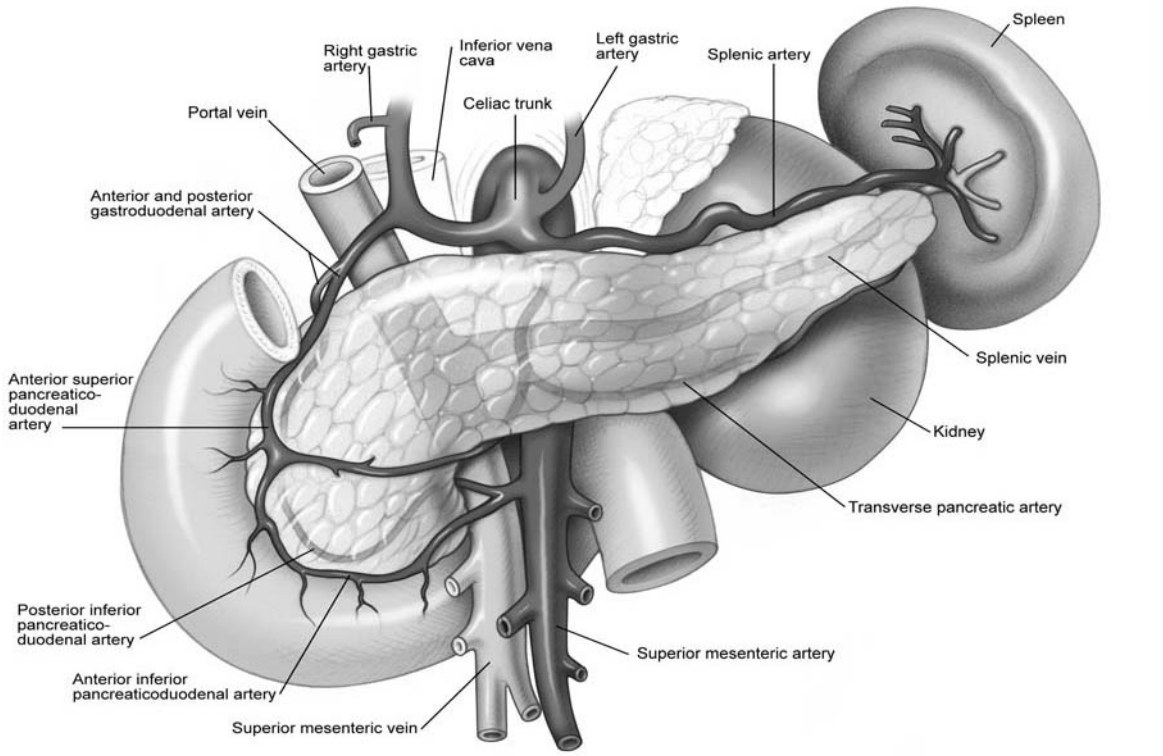


FIGURE 4.2. Surgical anatomy of the pancreas. The head of the pancreas lies in the concavity of the C-loop of the duodenum, from which the body and tail extend to the left upper quadrant. Blood supply to the head of the pancreas is from branches of the gastroduodenal artery, while that to the body and tail is primarily from branches of the splenic vessels. Behind the neck of the pancreas lies the junction of the superior mesenteric and splenic veins, forming the portal vein. Other important posterior relations of the pancreas include the left kidney, left renal vessels, and the left adrenal gland. (Adapted from Warren KW, Jenkins RL, Steele GD. Atlas of Surgery of the Liver, Pancreas, and Biliary Tract. Norwalk, CT: Appleton & Lange; 1991.)

Anatomic Relationships of the Pancreas

The pancreas lies transversely in the retroperitoneum across the upper abdomen, extending from the pancreatic head in the C-loop of the duodenum medially to the tail, which is closely related to the hilum of the spleen. Its anatomic relationships are as follows:

1. Anteriorly, the lesser sac and the stomach.
2. Medially, the C-loop of the duodenum.
3. Laterally, the splenic hilum.
4. Posteriorly, from right to left: The inferior vena cava (IVC) lies deep slightly to the right of the second portion of the duodenum and, more medially, the aorta. The left renal vein enters the IVC after running immediately behind the body, neck, and head of the pancreas from the left kidney. The superior mesenteric artery (SMA) and vein (SMV) run behind the head of the pancreas but anterior to the uncinate process. The SMV joins the splenic vein, which runs along the superior edge of the pancreas to form the portal vein (PV); the PV runs superiorly behind the head to the porta hepatis. The inferior mesenteric vein joins the splenic vein to the left and behind the neck of the pancreas. On the extreme left and more deeply lie the kidney with its hilar structures and the left adrenal gland.

Anatomic Points of Surgical Importance

Three salient points of pancreatic anatomy and its relationships are particularly important for the surgeon:

1. The tail of the pancreas is closely related to the hilum of the spleen. Care must be taken not to injure the pancreas when hilar vessels are divided in splenectomy.
2. No veins enter the anterior surface of the SMV and PV. Thus, an avascular window can be dissected behind the head of the pancreas and anterior to the PV and SMV. The dissection of this window, sometimes referred to as the portal tunnel, is a critical step in determining resectability during pancreaticoduodenectomy.
3. A substituted hepatic artery arises from the SMA rather than from the celiac axis in approximately 5%–10% of the population. To avoid inadvertent injury, the presence or absence of a substituted hepatic artery should be determined early in the dissection during pancreaticoduodenectomy.

Blood Supply

The arterial supply of the pancreas is derived from branches of the celiac axis and the superior mesenteric artery (SMA). The head of the pancreas shares its blood supply with the duodenum. The major blood supply to the head comes from the anterior and posterior pancreaticoduodenal arteries, which form arcades of vessels just inside the C-loop of the duodenum. These arteries originate from the gastroduodenal artery (a branch of the hepatic artery) and from the SMA, respectively. The body and tail of the pancreas are supplied by the superior and inferior pancreatic arteries, branches of the SMA, and branches of the splenic and left gastroepiploic arteries. Venous drainage corresponds to the arterial supply and eventually flows into the portal vein. The blood supply is shown in Figure 4.2.

Lymphatic Drainage

The head of the pancreas drains into nodes in the pancreaticoduodenal groove and then into subpyloric, portal, mesocolic, mesenteric, and aortocaval nodes. The body and tail of the pancreas drain into retroperitoneal and splenic hilar nodes, and to the celiac, mesenteric, and paraaortic nodes.

Innervation

The vagus and sympathetic nerves provide the principal extrinsic innervation. The preganglionic fibers of both the parasympathetic (celiac branches of the vagus) and sympathetic (the greater and lesser splanchnics) systems terminate in the celiac ganglia. Postganglionic vagal fibers are peptidergic as well as cholinergic and include neurons containing CCK, somatostatin, CGRP, neuropeptide Y, and gastrin-releasing peptide. Sensory innervation is via unmyelinated C-fibers containing substance P and CGRP.

MICROSCOPIC ANATOMY

Exocrine Pancreas

The exocrine pancreas is made up of grape-like glands called acini. These acini drain into ductules that join each other to make progressively larger ductules and ducts, which eventually drain into the main or accessory pancreatic ducts (Figure 4.3). The acinus is made up of polyhedral cells sitting on a basement membrane. The apical surfaces of these cells have microvilli and face the lumen of the acinar gland. The nuclei of acinar cells are located basally, and their cytoplasm contains several types of organelles. The rough endoplasmic reticulum (RER) and Golgi bodies are particularly prominent. Other structures in the cytoplasm include mitochondria, condensing vacuoles, numerous secretory granules, and lysosomes. The secretory granules are contained within cytoplasmic membranes and are transported to the apical membrane. The cytoplasmic membrane of the granules fuses with the apical membrane to initiate the process of exocytosis, by which the secretory proteins (proenzymes) are delivered to the acinar lumen. This intracellular transport or trafficking system of proteins is shown in Figure 4.4.

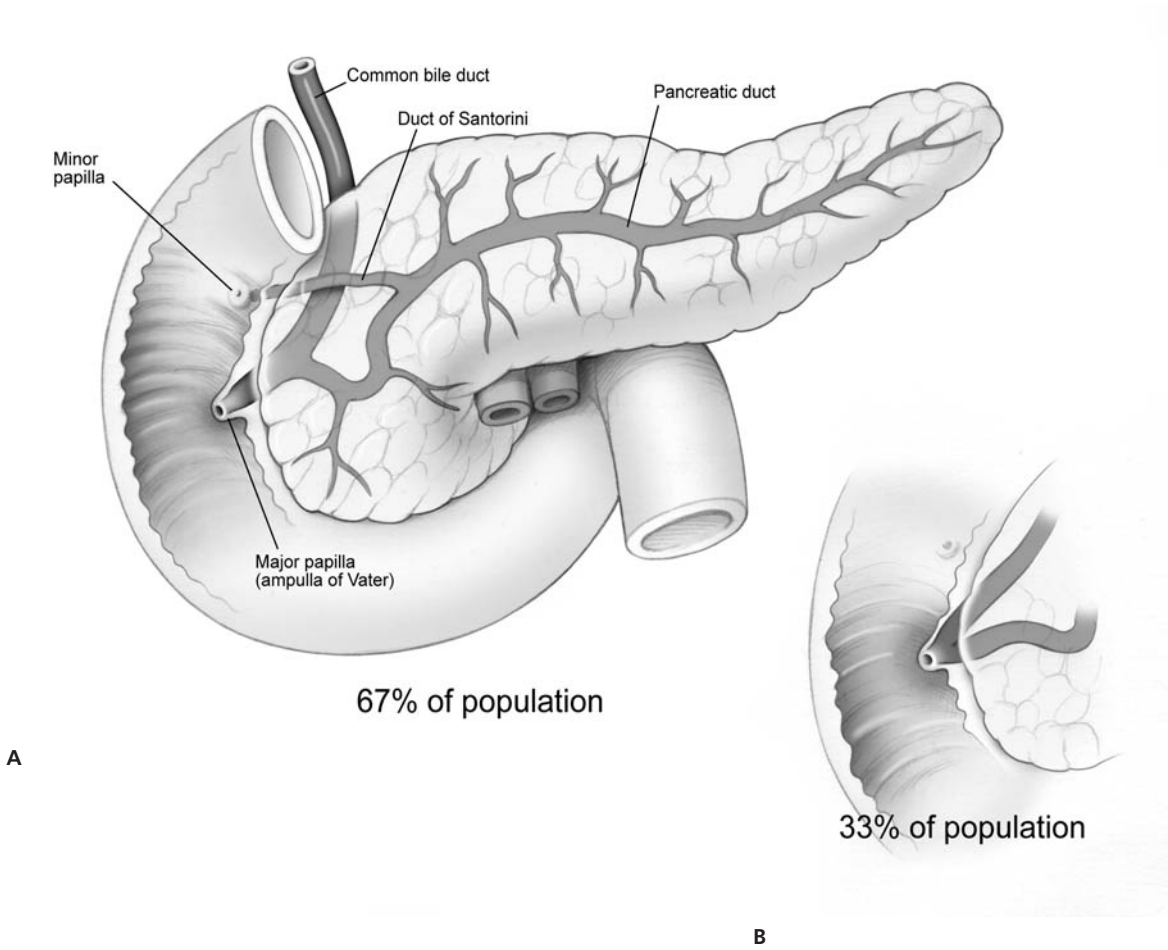


FIGURE 4.3. Pancreatic ductal system. The main pancreatic duct (the duct of Wirsung) joins the distal common bile duct to form a common channel (0.5–1.0 cm in length) before emptying into the duodenum at the major papilla (ampulla of Vater). The duct of Santorini drains separately into the duodenum at the minor papilla 1.0–1.5 cm proximal to the ampulla of Vater. (A) This common channel pattern is seen in 67% of the population. (B) In the remaining third of the population, no common channel exists and the two ducts drain into the ampulla separately.

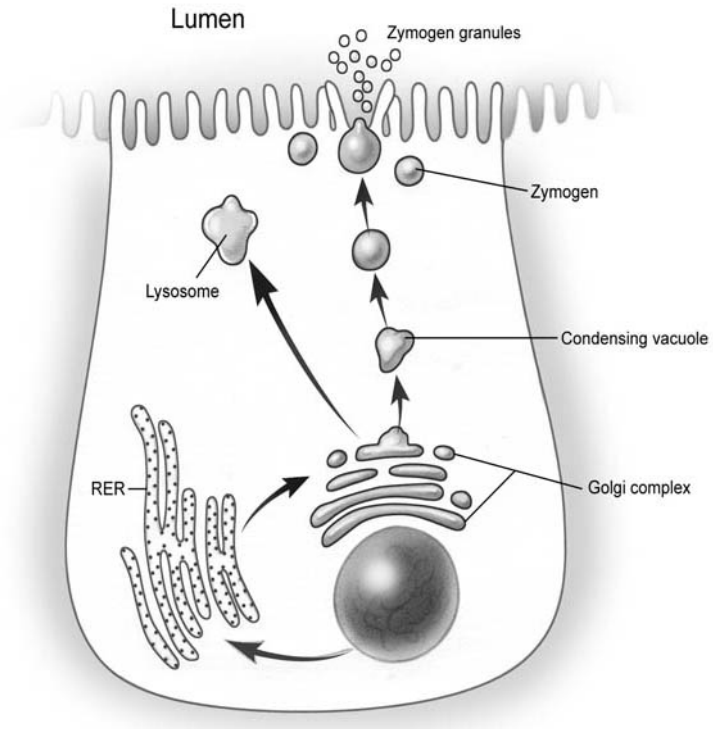


FIGURE 4.4. Intracellular trafficking of proteins.

Structure of Islets of Langerhans

The islet of Langerhans is made up of four types of cells: (1) glucagon-secreting alpha cells, (2) insulin-secreting beta cells, (3) somatostatin-secreting delta cells, and (4) pancreatic polypeptide (PP)-secreting cells. The beta cells comprise 80% of the islet cells. The islet architecture is designed to facilitate islet portal circulation (Figure 4.5). The beta cells comprise a central core; the three other cell types are arranged as a mantle surrounding the central core of beta cells. Arterial blood is delivered to the beta-cell core, from which venules carry the blood to the peripheral alpha, delta, and PP cells. This portal circulation allows for local paracrine influences between the cells. The islets are innervated with intrinsic neurons, which are cholinergic and peptidergic, and extrinsic neurons, which are cholinergic, peptidergic, and adrenergic.

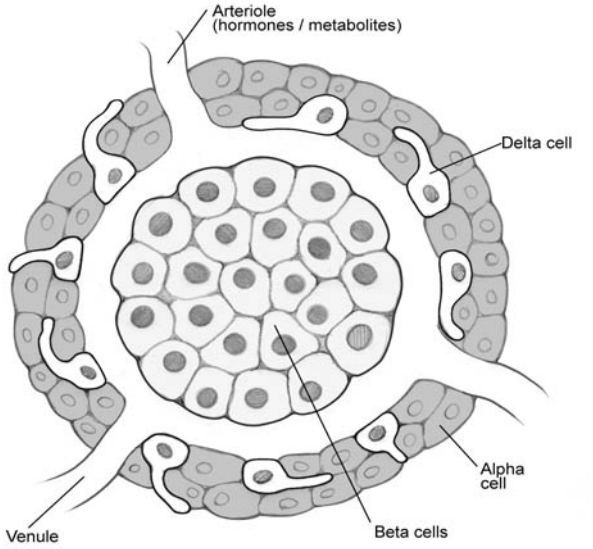


FIGURE 4.5. Structure of the islet of Langerhans. The islet of Langerhans consists of an inner core of insulin-secreting beta cells surrounded by a mantle of glucagon-secreting alpha cells interspersed with somatostatin-secreting delta cells and pancreatic polypeptide (PP)-secreting cells. The PP-secreting cells are few in number, located primarily in the outer layer, and some are located within nerves. Arterioles enter the core of the islet, from which venules carry the blood to the peripheral alpha, delta, and PP cells, thus establishing a portal circulation.

PHYSIOLOGY

EXOCRINE PANCREAS

Composition of Pancreatic Juice

The exocrine secretion of the pancreas consists of water, bicarbonate, and enzymes. Pancreatic juice is alkaline due to its bicarbonate content and typically has a pH of 8.2. Bicarbonate secretion is mainly derived from ductal cells, while enzyme secretion comes from acinar cells. Table 4.1 lists the major secretory products of the exocrine (and endocrine) pancreas and their normal function. The proteolytic enzymes are secreted as proenzymes or zymogens and remain in this inactive form until they reach the duodenum, where, by the action of the mucosal enzyme enterokinase, they are converted into active enzymes.

$$\text{TRYPSINOGEN} \xrightarrow{\text{ENTEROKINASE}} \text{TRYPSIN}$$

$$\text{TRYPSIN} \xrightarrow{\text{TRYPSIN}} \text{TRYPSIN}$$

$$\text{CHYMOTRYPSINOGEN} \xrightarrow{\text{TRYPSIN}} \text{CHYMOTRYPSIN}$$

$$\text{PROCARBOXYPEPTIDASE} \xrightarrow{\text{TRYPSIN}} \text{CARBOXYPEPTIDASE}$$

To ensure that these potent active enzymes are not generated within the pancreatic duct, pancreatic juice contains trypsin inhibitors.

Secretory Process

Bicarbonate Secretion

Bicarbonate is secreted primarily by ductal cells through catalytic conversion of carbon dioxide and water by carboxypeptidase.

$$CO_2 + H_2O \xrightarrow{\text{CARBOXYPEPTIDASE}} H_2CO_3 \longrightarrow HCO_3 + H^+$$

The bicarbonate so generated is then secreted into pancreatic ductules, while the H^+ crosses the basolateral membrane to enter the circulation.

Pancreatic Protein (Enzyme) Synthesis and Secretion

Pancreatic proenzymes are synthesized by ribosomes on the rough endoplasmic reticulum. The careful process of packaging and intracellular trafficking described above (Figure 4.4) then ensues to deliver these proteins to the apical membrane. Here, by the process of exocytosis, they

TABLE 4.1. Essentials: Exocrine and Endocrine Pancreas

Exocrine pancreas
- Constitutes 99% of pancreas
- Functional unit: Acinus
- Secretory products
  - H_2O + bicarbonate: pH >8
    - Main stimulant: Secretin
  - Proenzymes
    - Converted to active enzymes by enterokinase and pepsin
      - Trypsinogen
      - Chymotrypsinogen
      - Procarboxypeptidase

Main stimulants: Vagus, CCK

Endocrine pancreas
- Constitutes 1% of pancreas
- Functional unit: Islet of Langerhans
- Cell composition: A, B, D, and PP cells
- Secretory products
  - Insulin: Released from B cells in response to hyperglycemia and insulinotropic gut peptides (GLP, GIP, CCK, secretin)
  - Glucagon: Released from A cells in response to hypoglycemia, sympathomimetics, enteral amino acids, CCK, GIP, glucocorticoids
  - Somatostatin: Released from D cells; exerts inhibitory control on A and B cells
  - Pancreatic polypeptide: Released from PP cells under cholinergic neurocrine regulation

Abbreviations: A, alpha cells; B, beta cells; CCK, cholecystokinin; D, delta cells; GLP, glucagon-like peptide; GIP, gastric inhibitory peptide; PP, pancreatic polypeptide cells.

are secreted into the acinar lumen to be carried down ductules to the pancreatic duct and then into the duodenum. Lysosomal hydrolases are also synthesized by ribosomes on the rough endoplasmic reticulum. These powerful activating enzymes are immediately packaged separately and transported to the lysosomes in the cytoplasm of the acinar cell. In this way, they are segregated from the proenzymes to ensure that activation of the latter does not occur within the acinar cell.

Synthesis of pancreatic proenzymes is stimulated by a number of gastrointestinal peptides and by acetylcholine secreted at cholinergic nerve terminals. The major stimulant of the synthesis and release of pancreatic proenzymes is CCK, although a number of other peptides also have similar effects. The latter peptides include neurotensin, PACAP, secretin, and VIP.

Summary of Mechanisms that Protect the Pancreas from Autodigestion

The pancreas is normally protected from autodigestion by the powerful enzymes it secretes in three ways:

1. The proteolytic enzymes are secreted as inactive proenzymes (zymogens) and must reach the duodenum before they are activated by enterokinase. Once trypsin is generated, it also promotes activation of proezymes.
2. The proenzymes are packaged into membrane-bound organelles and transported within the acinar cell to the apical membrane segregated from lysosomal enzymes, which are similarly packaged into lysosomes.
3. Trypsin inhibitors are synthesized and secreted with the proenzymes to ensure that premature activation of proenzymes within the pancreas does not occur.

Regulation of Pancreatic Exocrine Secretions

Complex interaction between nerves and humoral agents regulates pancreatic secretion. Separate mechanisms regulate basal secretion, stimulation, and inhibition of pancreatic secretion. The mechanisms that regulate pancreatic secretion are summarized in Figure 4.6.

Basal Pancreatic Secretion

The pancreas secretes small amounts of proteins (proenzymes) and bicarbonate under basal (fasting) conditions. The amount of basal secretion tends to increase with the migrating motor complex (MMC). Somatostatin exerts inhibitory tone on the action of intrapancreatic CCK-ergic neurons to regulate low levels of basal secretion. The mechanism is depicted in Figure 4.7. Administration of monoclonal somatostatin antibodies to fasting rats causes a significant increase in basal pancreatic secretion. This enhanced basal secretion is blocked by specific CCK-A receptor antagonist, suggesting a key role for intrapancreatic CCK in basal secretion.

Stimulation of Bicarbonate Secretion

The most powerful stimulant of pancreatic bicarbonate secretion is the hormone secretin. Secretin is released from the duodenum mainly by means of acid entering the duodenum. The amount of secretin released and the amount of bicarbonate secreted is directly proportionate to the amount of acid load in the duodenum. Another stimulant of secretin release from the duodenum is luminal fat.

The action of secretin on pancreatic cells is direct, via the secretin receptor. Binding of secretin to its receptor activates adenylate cyclase, resulting in the generation of cyclic adenosine monophosphate (cAMP), which acts as the intracellular messenger.

The action of secretin on water and bicarbonate secretion is amplified by CCK. This synergistic interaction is likely to be important physiologically, since the main releaser of secretin, that is, acid, also releases CCK.

Stimulation of Pancreatic Enzyme Secretion

Pancreatic enzyme secretion is stimulated both by neural and humoral mechanisms.

Neural Mechanisms Direct vagal as well as regional reflexes stimulate pancreatic enzyme secretion.

Vagal Stimulation The vagus-mediated cephalic phase of pancreatic secretion in humans and experimental

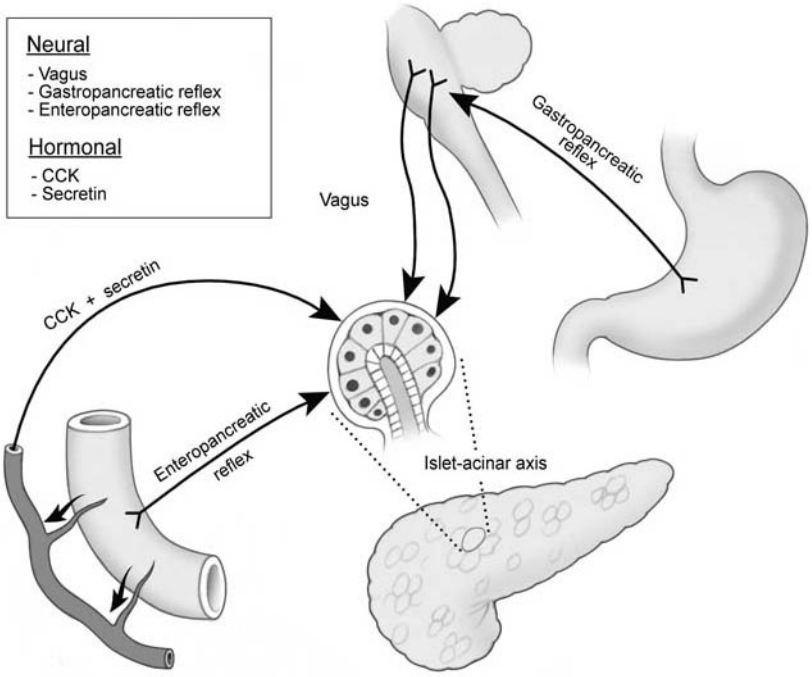


FIGURE 4.6. Regulation of pancreatic exocrine secretion. Neural regulation of exocrine pancreatic secretion involves direct vagal pathways as well as reflex pathways from both the stomach (gastropancreatic reflex) and duodenum (enteropancreatic reflex). Hormonal control is by the pancreatic peptides CCK and secretin. Enzyme secretion is stimulated largely by vagal mechanisms and CCK, while water and bicarbonate secretion is primarily under the control of the hormone secretin.

animals results in low-volume pancreatic secretion that is high in enzyme content. The final event of vagal stimulation at the level of the acinar cells is activation of cholinergic, muscarinic receptors (M3) with resultant generation of intracellular cyclic guanosine monophosphase (cGMP) and calcium. However, vagal stimulation of the acinar cell is not as simple as once thought. It is blocked not only by cholinergic nicotinic and muscarinic receptor antagonists, but also by specific CCK-A receptor antagonist. The action of CCK-A receptor antagonist appears to be on intrapancreatic CCK-ergic neurons, because the inhibition is seen in the isolated, vascularly perfused preparation of rat pancreas where duodenal CCK is excluded. A proposed mechanism is shown in Figure 4.8.

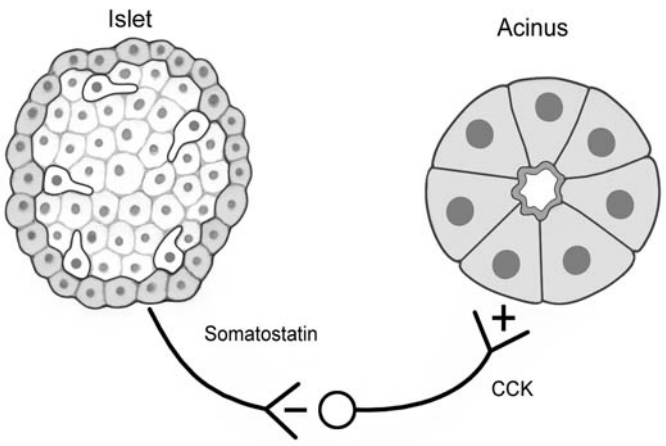


FIGURE 4.7. Regulation of basal pancreatic secretion. Basal pancreatic secretion is regulated by the interaction of stimulatory CCK-ergic and inhibitory somatostatin-ergic intrapancreatic neurons, indicating an important islet-acinar axis.

Reflex Pathways Antral distention elicits pancreatic enzyme secretion by activation of an *antropancreatic reflex*, that is, a long vagovagal reflex. The antropancreatic reflex is an important component of the gastric phase of pancreatic secretion. Food entering the duodenum stimulates not only the release of agonist peptides but also another reflex mechanism, the *enteropancreatic reflex*.

Humoral Mechanisms A number of peptides stimulate pancreatic enzyme secretion. These peptides may be hormones (e.g., CCK, secretin, neurotensin) or neurocrine agents (e.g., GRP, PACAP).

Cholecystokinin CCK is released from I cells of the duodenum primarily by protein digest, fat, and acid. (For a more complete discussion of CCK, see Chapter 5). CCK is the most important mediator of the intestinal phase of pancreatic secretion. Its action on pancreatic secretion is mediated via the CCK-A receptor, which is present on acinar cells, intrapancreatic neurons, and cholinergic afferent neurons. At low physiological levels, CCK stimulates pancreatic enzyme secretion by acting on afferent cholinergic pathways originating from the gastroduodenal mucosa. At higher doses, CCK may act directly on acinar cells or on intrapancreatic neurons to stimulate enzyme secretion. In humans, pancreatic enzyme secretion in response to CCK stimulation, particularly to low doses, is inhibited by atropine. Similarly, pancreatic enzyme secre-

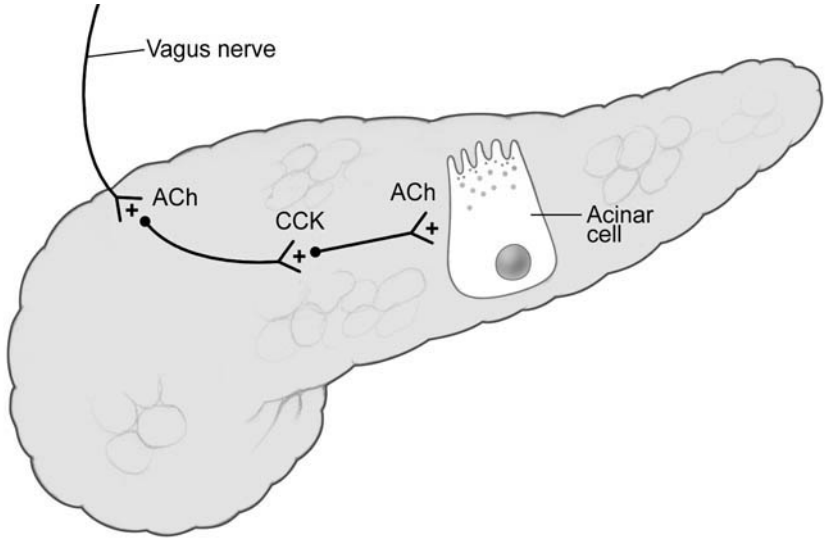


FIGURE 4.8. Vagal stimulation of pancreatic secretion. The mechanism by which the vagus stimulates pancreatic secretion involves preganglionic cholinergic neurons acting on CCK-ergic intrapancreatic interneurons, which, in turn, act on muscarinic cholinergic neurons. Thus, vagal stimulation of pancreatic secretion can be inhibited both by anticholinergic drugs and by CCK-A antagonists.

tion in response to food can be blocked completely by atropine. These observations suggest that CCK action on the pancreas is dependent on cholinergic mechanisms.

Other Humoral Stimulants of Enzyme Secretion A number of other peptides—including PACAP, GRP, and neurotensin—stimulate pancreatic enzyme secretion in vitro and in vivo. To what extent these peptides are important in physiologic control of pancreatic enzymes in humans is unknown. The action of GRP, the mammalian analogue of bombesin, is partly or wholly mediated through the release of CCK.

Inhibition of Pancreatic Secretion

A number of peptides are known to inhibit exocrine pancreatic secretion. These include somatostatin (SS), pancreatic polypeptide (PP), peptide YY (PYY), neuropeptide Y (NPY), pancreastatin, and glucagon. The action of these peptides is indirect through the activation of inhibitory intrapancreatic neurons. None of these peptides exert inhibitory action in vitro in the isolated acinar preparation. The tonic inhibitory role that somatostatin plays in basal pancreatic secretion was discussed earlier. It is likely that the main source of somatostatin in the pancreas is the delta cells of the islets of Langerhans, from which the peptide would diffuse out in a paracrine manner to inhibit acinar cells. Because somatostatin is also found in intrapancreatic neurons, the importance of a neural source of somatostatin cannot be excluded.

ENDOCRINE PANCREAS

The interplay between insulin and glucagon is responsible for maintaining blood sugar levels under normal and adverse circumstances. Thus, the control of secretion of these two peptides is critical.

Insulin Release

Insulin release is regulated by: (1) islet innervation, (2) circulating insulinotropic gut hormones, and (3) local paracrine and neurocrine mechanisms.

Islet Innervation

Splanchnic nerve stimulation causes glucagon release and inhibits insulin release, a response necessary for hypoglycemic crisis situations.

Circulating Insulinotropic Gut Hormones

These include glucagon-like peptide (GLP), gastric inhibitory peptide (GIP), cholecystokinin (CCK), and secretin. These peptides are released by nutrients (fat, proteins) in the gut. They amplify insulin release from the islets and are responsible for the observation that insulin response to an ingested meal is greater than the response to intravenously administered nutrients, known as the incretin effect.

Local Paracrine and Neurocrine Mechanisms

Somatostatin secretion from the delta cells of the islets exerts inhibitory control on insulin release. Under all conditions, the major stimulant of insulin secretion is glucose. The amino acids leucine and arginine are also stimulants. Inhibitory regulation of insulin is accomplished not only by somatostatin but also by the alpha-adrenergic effect of catecholamines.

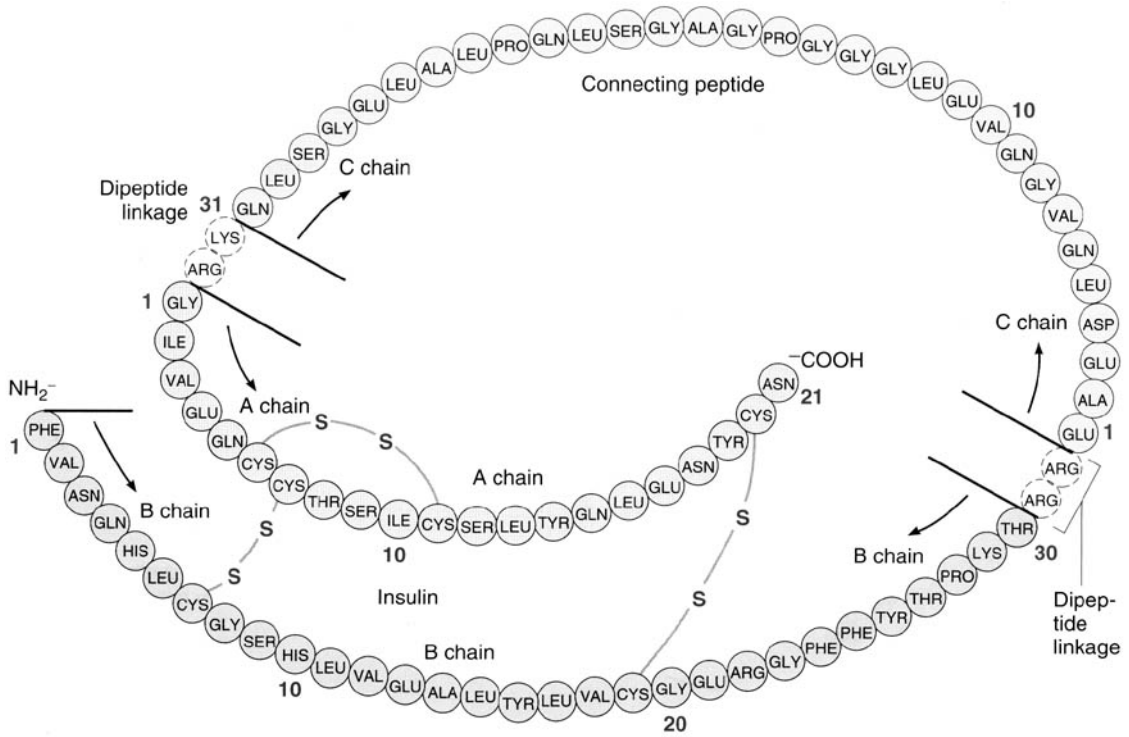


FIGURE 4.9. Structure of human insulin C-peptides and insulin molecules connected at two sites by disulfide links. (Reprinted with permission from Greenspan FS, ed. Basic and Clinical Endocrinology. 6th ed. Los Altos, CA: Lange Medical Publications; McGraw-Hill Companies 2001.)

Glucagon Release

Glucagon secretion is increased by both sympathetic and parasympathetic stimulation. Hypoglycemia is a potent releaser of glucagon, as are several amino acids (e.g., arginine, alanine). The gastrointestinal peptides CCK and GIP, as well as glucocorticoids, also release glucagon. Glucose exerts inhibitory regulation over glucagon. Somatostatin and gamma-aminobutyric acid (GABA) also inhibit glucagon secretion.

BIOCHEMICAL STRUCTURES

Insulin

Insulin is a 51-amino acid peptide consisting of A- and B-chains connected by two disulfide bonds (Figure 4.9). It is the result of posttranslational processing of pre-proinsulin into proinsulin and then into insulin. Proinsulin is converted into insulin by splitting off the C-peptide and, hence, every molecule of endogenously secreted insulin is accompanied by the release of a molecule of C-peptide. The presence of elevated levels of proinsulin or C-peptide in the blood, therefore, indicates an overproduction of endogenous insulin, a useful indicator in distinguishing the presence of insulinoma from that of factitious hyperinsulinism.

Glucagon

Glucagon, a single-chain peptide of 29 amino acids, also is derived from the processing of a large precursor molecule secreted by alpha cells. Besides glucagon, this proglucagon molecule contains glycentin-related peptide, glucagon-like peptide 1 (GLP-1), and GLP-2.

PATHOPHYSIOLOGY

ACUTE PANCREATITIS

It is generally agreed that, no matter what the primary etiology in acute pancreatitis might be, the final common event is activation of pancreatic proenzymes into nascent enzymes within the pancreas itself. Once pancreatic parenchymal damage occurs as a result of autodigestion, acute inflammatory cell infiltration begins and is accompanied by the release of cytokines, which further aggravates the inflammatory reaction.

Theories Regarding Initiation of Pancreatitis

What is not generally agreed upon is the mechanism by which pancreatic enzymes are activated within the pancreas. Several of the proposed explanations can be grouped into three theories: (1) secretory block resulting in intracellular activation of enzyme; (2) either bile or duodenal secretion refluxes into the pancreatic duct, causing activation first within the pancreatic ductal system; and (3) damage of pancreatic tissue by toxic or ischemic mechanisms.

Secretory Block Theory

The chapter described above how the intracellular transport of proenzymes in zymogen granules from the Golgi apparatus to the apical membrane is carefully segregated from lysosomal enzymes in lysosomes. An attractive theory popularized by Steer and colleagues that acute pancreatitis arises from a secretory block preventing exocytosis and leading to protein accumulation within the cytoplasm of acinar cells.[1] This leads to fusion of zymogen granules with lysosomes, leading in turn to activation of proenzymes. Also, zymogen granules take an abnormal path to the basolateral membrane and become discharged into the intercellular space. The presence of activated enzymes in the interstitial tissue causes tissue damage and inflammation, resulting in infiltration with activated neutrophils and macrophages and generation of cytokines. These cytokines include TNF-alpha, interleukin-1 beta (IL-1 beta), IL-6, IL-8, and intercellular adhesion molecule-1 (ICAM-1). The stage is then set not only for local inflammation but also for distant damage to organs such as the lung. Intracellular activation has been demonstrated in experimental pancreatitis caused by cerulein or by a choline-deficient diet. It has yet to be demonstrated in human pancreatitis.

Reflux Theory

Experimental pancreatitis can be caused by injection of bile (particularly infected bile) or bile salts into the pancreatic duct. Because approximately 67% of individuals have a common channel pattern, it is possible that a stone obstructing the ampulla of Vater could lead to reflux of bile into the pancreatic duct. Conversely, passage of a stone into the duodenum may temporarily leave the ampulla patulous, allowing duodenal fluid to reflux into the pancreatic duct. Duodenal fluid, of course, contains enterokinase, which could activate the proenzymes within the pancreas.

Pancreatitis occurs as a complication of endoscopic retrograde cholangiopancreatography (ERCP), with an approximate 1% incidence. The mechanism for this type of pancreatitis is not known, although excessive pressure of injection rather than postprocedure reflux of bile or duodenal juice is the probable cause.

Direct Damage of Pancreas

Toxic or ischemic damage of the pancreas may cause acute pancreatitis. One of the mechanisms proposed for alcohol-induced pancreatitis is acetaldehyde toxicity. Alcohol is metabolized into acetaldehyde, which has been shown experimentally to damage the pancreas by leading to increased permeability of ductal epithelium, which allows pancreatic enzymes to escape into the interstitial tissue. Acetaldehyde can also serve as a substrate for generation of toxic-free oxygen radicals. Other possible but less likely mechanisms for alcohol-induced pancreatitis include direct toxic damage of acinar cells and stimulation of pancreatic secretion at a time when spasm of the sphincter of Oddi has been caused by the presence of alcohol in the duodenal lumen. Hypertriglyceridemias are also thought to cause pancreatitis by leading to generation of toxic metabolites.

Ischemia causes tissue damage and capillary permeability. Ischemic insult capable of causing pancreatitis is seen in shock, hypothermia, during cardiopulmonary bypass surgery or in diseases causing small-vessel abnormalities (e.g., lupus, other collagen diseases). Conditions that cause ischemia, particularly those with systemic effects, lead to massive catecholamine response releasing alpha-adrenergic constrictors, which accentuate ischemia and initiate necrosis.

Etiologic Factors in Acute Pancreatitis

Several known etiologic factors in acute pancreatitis probably share more than one of the pathogenetic mechanisms for in situ enzyme activation described above. Alcohol and gallstones account for over 90% of cases of acute pancreatitis in the United States.[2]

Gallstones

The most common cause of pancreatitis, gallstones account for 60% of all cases of acute pancreatitis seen. Approximately 5% of individuals with gallstones develop acute pancreatitis. The likelihood is increased in those with small stones, those with a long common channel, and those with choledocholithiasis. Intraoperative cholangiogram associated with reflux into the pancreatic duct increases the likelihood of acute pancreatitis.

The great majority of patients who develop gallstone pancreatitis are not found to have a stone impacted at the lower end of the CBD. The question then is, how do stones cause pancreatitis? The two possible mechanisms are: (1) bile reflux into the pancreatic duct while the stone is going through the sphincter; or (2) reflux of enterokinase-containing duodenal fluid through the sphincter, left patulous after passage of the stone.

Three types of biliary (gallstone) pancreatitis may be recognized, based on severity of clinical presentation:

1. Type A. Biochemical pancreatitis or hyperamylasemia is found without associated abdominal findings. The hyperamylasemia is transient, lasting no more than 24 to 48 h.
2. Type B. Hyperamylasemia with moderate pancreatitis is associated with abdominal signs, often lasting 4 to 7 days and not associated with respiratory or other organ failure.
3. Type C. Type C disease indicates severe pancreatitis with multiple organ failure.

It is now clear that biliary pancreatitis can be cured with cholecystectomy and, if present, removal of CBD stones, with an extremely low risk of future recurrence or development of chronic pancreatitis.

Alcohol

Alcohol is the second most common cause of acute pancreatitis overall, but the most common in the population of patients seen in county and city hospitals. An acute attack often follows an episode of binge drinking. Alcoholic pancreatitis varies in its severity, but alcohol is the cause of some of the most severe cases of pancreatitis. Following an initial acute attack, alcoholic pancreatitis has a greater propensity than biliary pancreatitis to cause recurrent attacks and lead to chronic pancreatitis.

Postoperative and Post-ERCP Pancreatitis

Operations on and around the pancreas are associated with a small but significant incidence of postoperative or postprocedure acute pancreatitis. Gastric and hepatobiliary operations are associated with the highest incidence following operations on the pancreas itself. Postoperative pancreatitis can be severe and is associated with significant mortality.

The overall incidence of post-ERCP pancreatitis is 1%, but the incidence is higher when extensive instrumentation or manipulation of the papilla is required. Endoscopic sphincterotomy is associated with acute pancreatitis in 3% to 4% of cases.[3]

Hyperlipidemia

A higher incidence of acute pancreatitis has been recognized in several types of hyperlipidemias, especially Types I, IV and V. Some patients have milky serum during an attack of acute pancreatitis, due to massive elevation of triglycerides. This phenomenon can be seen in individuals without familial hyperlipidemia, presumably secondary to severe acute pancreatitis. Hence, when familial hyperlipidemia is suspected, full investigation should await total resolution of the pancreatitis. Patients with familial hyperlipidemia show high serum triglyceride levels but normal cholesterol. Hyperlipidemia may be associated with some of the severest attacks of necrotizing pancreatitis.

Hypercalcemia

Both primary and secondary hyperparathyroidism may be associated with acute pancreatitis. Although the mechanism is unknown, calcium is not only a potent releaser of the peptides that stimulate the pancreas, but it is also the intracellular secondary messenger leading to synthesis and secretion of pancreatic enzymes.

Drugs

Several drugs are associated with acute pancreatitis. The most common are thiazide diuretics, corticosteroids, estrogens, azathioprine, angiotensin-converting enzyme (ACE), sulfonamides, and tetracycline.

Carcinoma of the Pancreas

Occasionally, carcinoma of the pancreas presents with an attack of acute pancreatitis, presumably because of pancreatic duct obstruction by the tumor.

Idiopathic Pancreatitis

No demonstrable cause is seen in a significant number of patients with acute pancreatitis.

Other Causes

Acute pancreatitis may follow trauma, organ transplantation, or infection with viruses such as mumps, Epstein-Barr, or coxsackie virus. Bacterial infection with *Campylobacter* and infestation with ascariasis and *Clonorchis sinensis* have also been associated with acute pancreatitis. The association of pancreas divisum with acute pancreatitis has not been supported by incidence studies in large groups of patients.

Evolution of the Clinical Picture

The evolution of the full clinical picture in severe acute pancreatitis is described below and in Table 4.2. Not all attacks are severe and mild attacks will not have the discernible phases described here.

Hypovolemic Phase

The first 24 h or more of an acute attack are characterized by variable degrees of hypovolemia, with hypovolemic shock developing in severe cases. Several causes of hypovolemia may be identified:

1. Sequestration of fluid. Fluid may be sequestered in and around the pancreas, in the retroperitoneal space, in the peritoneal cavity, and within intestinal lumen due to paralytic ileus.
2. Systemic vasodilatation. Vasodilatation may occur as a result of release into the circulation of vasoactive sub-

TABLE 4.2. Essentials: Clinical Course of Acute Pancreatitis

Hypovolemic phase
First 24 h, characterized by:
- Sequestration of fluid (hypovolemia)
- Systemic vasodilatation
- Abdominal pain, vomiting, fever
- Release of myocardial depressing factor
- Hypotension

Respiratory phase
Within 48–72 h, characterized by:
- Tachypnea
- Hypoxemia
- Acute respiratory distress syndrome (in severe cases)

Septic phase
Usually during second or third week
Septic complications may include:
- Infected necrosis
- Pancreatic abscess
- Infected pseudocyst
- Acute cholangitis

stances such as bradykinin. This leads to reduction in circulating volume.

3. Abdominal pain, vomiting, and fever.

4. Myocardial depressing factor. Hypovolemia may be aggravated by decreased cardiac output secondary to release of myocardial depressing factor (MDF) from the injured pancreas. In addition to its systemic effects, hypovolemia contributes to pancreatic necrosis. Hemorrhagic pancreatitis is not seen as frequently now as it was 20 to 30 years ago, possibly because of the preventive effect of aggressive volume resuscitation now practiced in the early stages of the disease.

Respiratory Phase

Acute respiratory distress syndrome (ARDS), as evidenced by tachypnea and hypoxemia, is a common feature of severe acute pancreatitis, usually seen within 48 to 72 hours of onset. The more severe the attack, the earlier the signs and symptoms of respiratory distress develop, and the sooner the patient requires assisted ventilation. Two factors are important in the development of respiratory failure:

1. Lung injury. Lung injury is believed to be caused by cytokines released from activated neutrophils and macrophages. The important cytokines that have been implicated include TNF-alpha, IL-1, IL-6, IL-8, and IL-10, and the intercellular adhesion molecule (ICAM-1). Phospholipase A_2 (PLA_2) released from the injured pancreas is one of the factors that activates macrophages and neutrophils. Other toxic substances released by the injured pancreas, such as free fatty acids, may also contribute.

2. Decreased diaphragmatic movement. Abdominal pain limits diaphragmatic excursion, and the mechanics of breathing become intercostal.

Respiratory failure is a bad prognostic sign but, thanks to excellent treatment in intensive care units, most patients with this complication now survive. Occasionally, respiratory failure may develop later in the course of the disease or recur after initial improvement. This type of clinical setback in the course of the disease is invariably associated with infected pancreatic necrosis.

Septic Phase

Not all patients with acute pancreatitis develop sepsis, even in the presence of pancreatic necrosis. The overwhelming number of patients who develop septic complication, however, have pancreatic necrosis. The septic phase usually occurs in the second or third week, although it may occur even in the first week. Four types of septic complications are seen:

1. Infected necrosis. Infection of the necrotic pancreas or peripancreatic fat is the most serious complication. It is more serious and occurs earlier (within the first 2 weeks) than other types of septic complications. Infected necrosis is often associated with respiratory and other organ failure and may carry a mortality as high as 30%.[4] The source of bacterial infection is the gut, as evidenced experimentally by significant reduction in infection when either the gut is sterilized or the pancreas is mechanically shielded from the colon.

2. Pancreatic abscess. Abscess, a walled-off collection of pus in or around the pancreas, usually occurs after the second week. In a large study from Bittner and colleagues,[5] the average time to surgery from onset of pancreatitis was 2 weeks for infected necrosis and 5 weeks for pancreatic abscess.

3. Infected pseudocyst. This complication tends to occur late and represents infection of preexisting pseudocyst. The clinical course is neither as severe nor as fatal as infected necrosis or pancreatic abscess.

4. Acute cholangitis. This complication, which occurs when the CBD is obstructed, is seen almost exclusively in patients with biliary pancreatitis. The clinical picture is characterized by fever, chills, jaundice, increased pain, and mental obtundation.

Development of Other Complications

Several other complications are possible.

Pseudocysts

The wide utilization of CT scan has demonstrated that pseudocysts form in over 50% of patients with severe acute pancreatitis. Most of these cases resolve spontaneously.

Pseudocysts represent a collection of fluid associated with loss of integrity of a pancreatic duct.

Pseudocysts that do not resolve spontaneously proceed to form mature wall and become clinically significant when they persist beyond 4 to 6 weeks or achieve a size of 5 cm or more. Pseudocysts also become clinically significant if they: (1) perforate, causing peritonitis or pancreatic ascites; (2) erode into a blood vessel, causing a pseudoaneurysm that might rupture freely into the peritoneal cavity or into an adjacent viscus; or (3) compress an adjacent organ, either the CBD or duodenum, to cause obstruction.

Hemorrhage

Life-threatening hemorrhage occurs in 1% to 2% of patients with severe acute pancreatitis.[2] This complication may be associated with acute pseudocyst as described above, or it may occur in the absence of a pseudocyst.

Metabolic Complications

1. Hypocalcemia. A sign of severe pancreatitis, hypocalcemia may be caused by removal of calcium from circulation as calcium soaps, parathyroid hormone dysfunction, and increased deposition in bone due to increased calcitonin activity.

2. Hyperglycemia. A transient picture of hyperglycemia and glycosuria may be seen. An attack of acute pancreatitis is unlikely to lead to diabetes unless major necrosectomy has to be done. In patients with greater than 50% necrosectomy, more than 50% develop diabetes.

Hepatobiliary Complications

A mild picture of hepatocellular dysfunction or obstructive jaundice may occur. Acalculous cholecystitis occurs infrequently, usually at the time oral feeding is started. Although extremely rare, portal vein or hepatic artery thrombosis may occur, causing severe hepatobiliary and systemic dysfunction.

Gastrointestinal Complications

1. Upper GI bleeding. Bleeding may complicate the development of erosions or peptic ulcer or represent rupture of a pseudoaneurysm due to pseudocysts into the upper GI tract. It may also indicate bleeding from gastric varices due to splenic vein thrombosis, although this is rare in acute pancreatitis.

2. Bowel necrosis. Bowel necrosis leading to perforation, fistula formation, or stricture is a well-known complication. The transverse colon is at most risk.

3. Bowel obstruction. Bowel obstruction may occur due to compression from pseudocysts, adhesion formation, or development of stricture.

Vascular Complications

Several vascular complications may develop in acute pancreatitis:

1. Massive hemorrhage during acute attack. This uncommon complication represents necrosis and vascular wall digestion by nascent pancreatic enzymes during the early course of severe acute pancreatitis. Bleeding has occurred from the gastroduodenal, pancreaticoduodenal, or other pancreatic vessels. Still other vessels that may be involved include the hepatic, gastric, or even the splenic arteries.

2. Pseudoaneurysm formation. This complication can develop either as a result of partial damage to the wall of an artery or secondary to the erosion of a pseudocyst into an adjacent vessel. The latter is more serious because hemorrhage invariably follows.

When a pseudocyst erodes into a vessel, it suddenly enlarges, becomes pulsatile, and causes increased pain. This erosion, in essence the formation of a thin-walled pseudoaneurysm, causes bleeding in one of three ways: (1) free bleeding into the abdominal cavity; (2) erosion into adjacent viscus, leading to gastrointestinal hemorrhage; or, rarely, (3) bleeding back into the pancreatic duct in the presence of significant communication between the pseudocyst and the main pancreatic duct. In the latter case, bleeding occurs into the duodenum through the ampulla of Vater, a condition known as hemosuccus pancreaticus.

3. Left-sided portal hypertension and gastric varices. Splenic vein thrombosis sometimes complicates the course of acute pancreatitis. This condition leads to venous hypertension in the area drained by the splenic vein and, therefore, results in splenomegaly and gastric varices. Gastric varices may bleed, leading to upper gastrointestinal hemorrhage.

4. Portal vein thrombosis. An uncommon complication, portal vein thrombosis may contribute to ascites, sometimes present in acute pancreatitis.

CHRONIC PANCREATITIS

Although chronic pancreatitis can follow acute pancreatitis, two epidemiologic observations suggest that the two diseases are different. First, patients with chronic pancreatitis are, on average, 10 years younger than patients with acute pancreatitis. Second, alcohol is the cause of chronic pancreatitis in 70% to 80% of cases.[6] Other causes of acute pancreatitis (e.g., gallstones, hyperlipidemia, drugs) are infrequently associated with chronic pancreatitis.

Pathogenesis

The common final physical event in the pathogenesis of chronic pancreatitis appears to be the development of

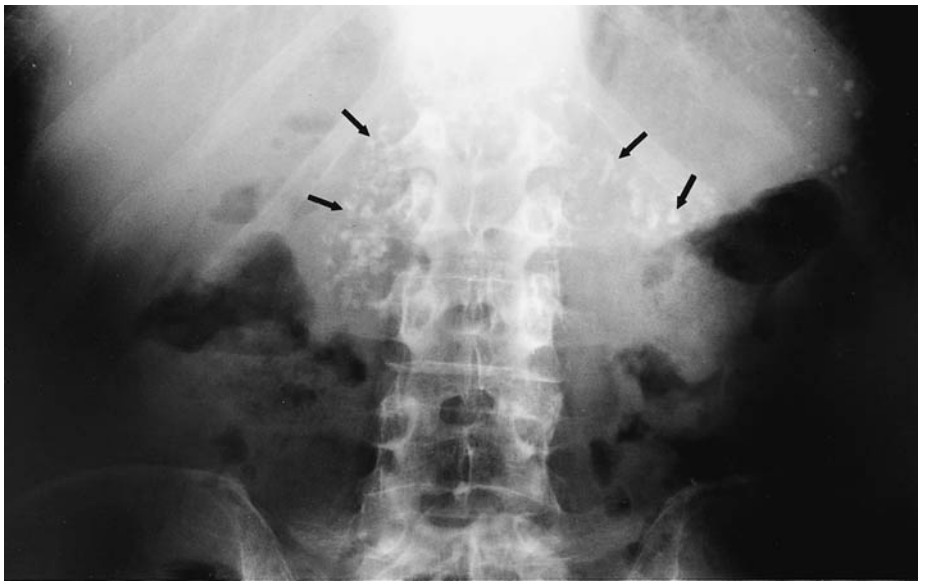


FIGURE 4.10. The common final physical event in the pathogenesis of chronic pancreatitis is the development of viscous pancreatic juice, leading to formation of protein plugs and secondary calcification (arrows), visible on x-ray. (Courtesy of Henry I. Goldberg, MD.)

viscous pancreatic juice, which subsequently leads to formation of protein plugs and secondary calcification (Figure 4.10). Two theories have been advanced:

1. Direct action of alcohol on the exocrine pancreas. This theory proposes that alcohol causes an increase in secretion of pancreatic proteins (enzymes) and a decrease in secretion of water, bicarbonate, and trypsin inhibitors.
2. Decreased secretion of pancreatic stone protein (lithostatin). The proposal is that chronic pancreatitis is associated with a lowered concentration of pancreatic stone protein. In patients with chronic pancreatitis, the concentration of pancreatic stone protein has been reported to be lowered, thus allowing calcium crystals and proteins to precipitate. Pancreatic stone protein (14,000-Da protein) is normally secreted in pancreatic juice and functions to prevent precipitation of calcium to form stones.

The essential features of this pathophysiology are summarized in Figure 4.11. Progression of disease includes:

1. Progressive inflammation and ductal injury, leading to progressive fibrosis, ductal obstruction, and stricture formation.
2. Calcification of proteinaceous plugs.
3. Progressive destruction of functional exocrine and endocrine pancreas, leading to pancreatic exocrine insufficiency (steatorrhea) and diabetes.
4. Development of pain, which gradually becomes intractable.

Etiologic Factors in Chronic Pancreatitis

Alcohol

The leading cause of chronic pancreatitis, alcohol accounts for 70% to 80% of all cases. National statistics in England and Wales have shown a close and direct correlation between the per capita consumption of alcohol and the incidence of hospital discharges for chronic pancreatitis. Between 1960 and 1988, both alcohol consumption and the incidence of chronic pancreatitis doubled in England and Wales.[7]

Familial Pancreatitis

Familial pancreatitis, a rare familial condition with Mendelian dominant inheritance, may lead to cancer in up to 25% of family members.

Tropical Pancreatitis

Seen in young people in the tropics, this form of chronic pancreatitis is thought to be caused by the combination of malnutrition and the presence of toxins in the diet (cassava and sorghum).

Hyperparathyroidism

Hyperparathyroidism is a rare cause of chronic pancreatitis.

Biliary Tract Disease

Although there is no clear evidence that chronic pancreatitis is caused by biliary tract disease, chronic

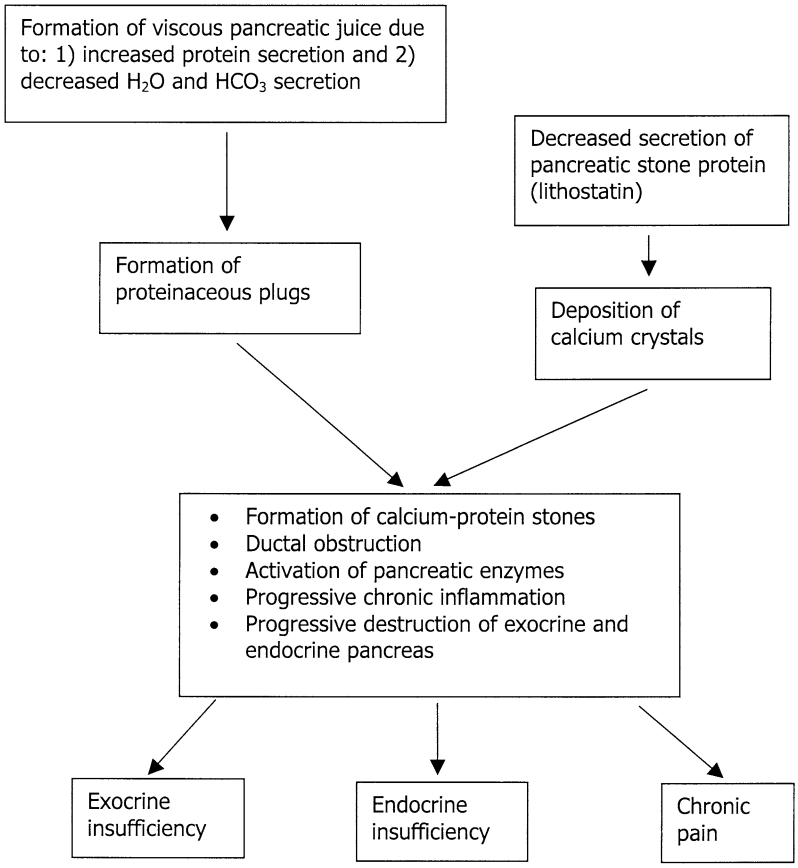


FIGURE 4.11. Essential features in the pathophysiology of chronic pancreatitis include formation of viscous pancreatic juice and decreased secretion of lithostatin, leading to exocrine and endocrine insufficiency and pain.

pancreatitis itself can lead to biliary disease due to stasis and stone formation in the common bile duct.

Obstructive Causes

Chronic pancreatic ductal obstruction from any cause may lead to chronic pancreatitis. Obstruction can be caused by post-traumatic or post-acute pancreatitis stricture, neoplasia, and perhaps also pancreas division, in which the entrance of the main pancreatic duct is strictured.

Cystic Fibrosis

Tenacious pancreatic juice is associated with defective chloride and water secretion in this congenital disease.

Idiopathic Causes

No cause is known in as many as 20% of patients with chronic pancreatitis.

Morphological Changes

A variety of morphological changes occur in the pancreas (Figure 4.12A), from minimal to end-stage fibrosis and destruction of the exocrine pancreas. Chronic inflammation is superimposed with acute necrosis. Single or multiple strictures of the pancreatic ducts may develop, and ducts may be obstructed with proteinaceous plugs or calculi. In the investigation of patients with chronic pancreatitis using ERCP or CT or MRI scans, two forms of chronic pancreatitis are recognizable depending on the size of the main pancreatic duct:

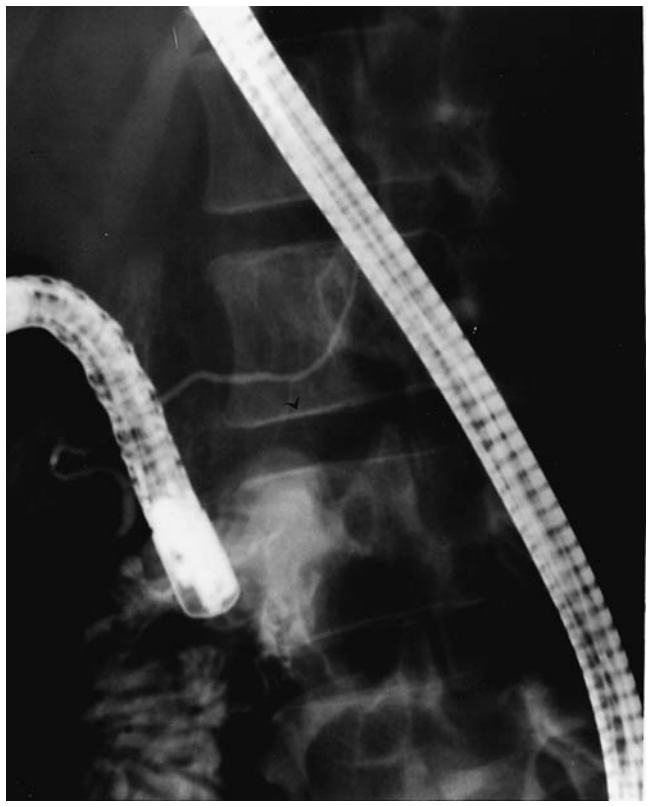
1. Small duct disease, in which no significant dilatation of the pancreatic duct occurs (Figure 4.12B); and
2. Large duct disease, in which the pancreatic duct is dilated (>6 mm) uniformly or in parts, with intervening fibrosis giving the impression of a chain of lakes (Figure 4.12C).

As discussed later, these two morphological types have a significant impact both on the choice and outcome of surgical treatment.

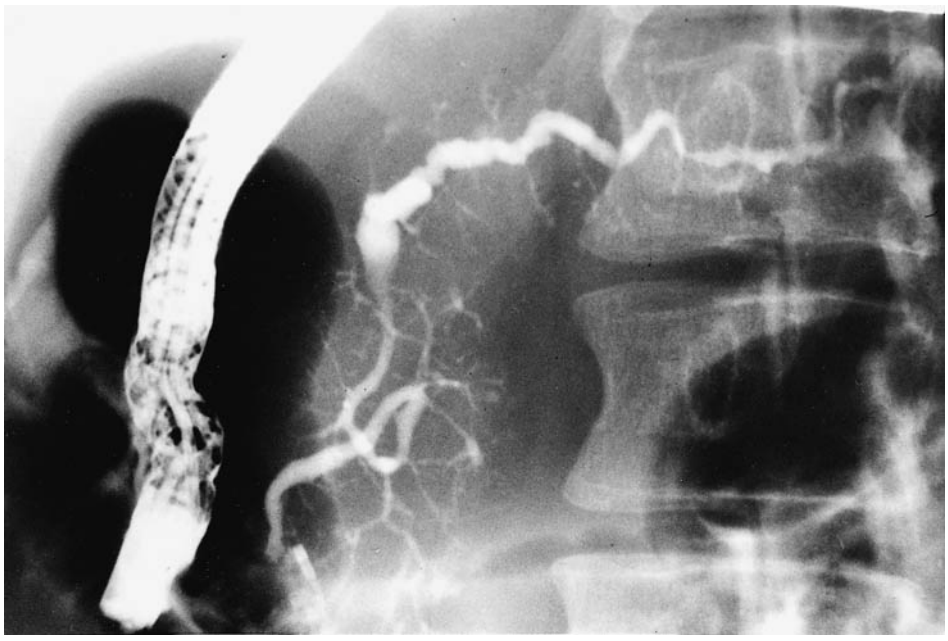
Functional Disturbances in Chronic Pancreatitis

Pain

Pain from chronic pancreatitis, the most important symptom, is present in more than 90% of patients.

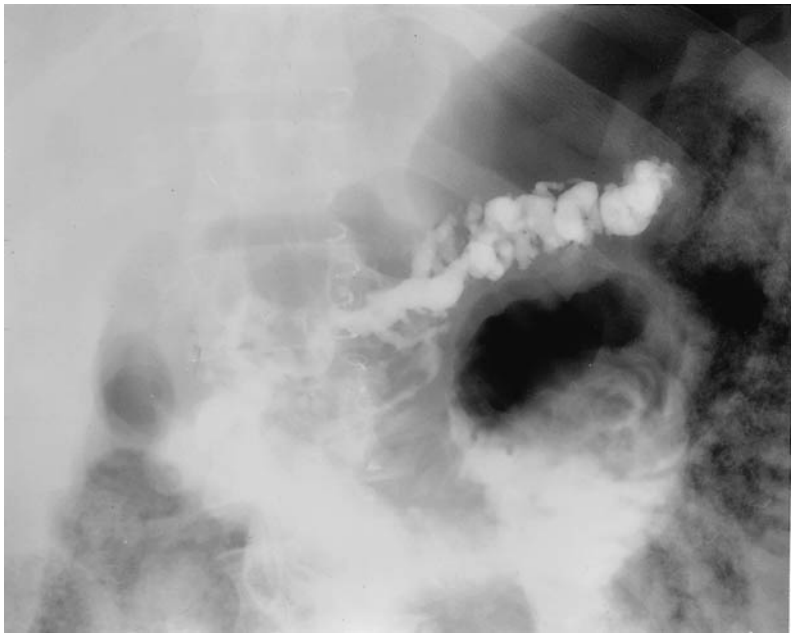


A



B

FIGURE 4.12. (A) In comparison with a normal pancreatic duct, (B) endoscopic appearance of small duct chronic pancreatitis demonstrates minimal dilatation (diameter <6 mm), tortuosity, and irregular contour of the main pancreatic duct and side branches. (C) Endoscopic appearance of large duct disease is characterized by pancreatic duct dilatation of >6 mm with intervening fibrosis and chain of lakes appearance. (Courtesy of Henry I. Goldberg, MD.)



C

FIGURE 4.12. *Continued*

Immunohistochemical studies of pancreata with chronic pancreatitis have demonstrated the presence of large amounts of calcitonin gene-related peptide and serotonin. CGRP-containing neurons are the sensory neurons, and the increased accumulation of CGRP is believed to be related to increased pain sensation. Other mechanisms may also operate.

Exocrine Pancreatic Insufficiency

Most patients have decreased secretion of pancreatic enzyme. Some develop overt steatorrhea, which results when pancreatic enzyme secretion is inadequate to provide complete digestion of fat and protein. Large quantities of fat are secreted in the stool, which becomes greasy and foul-smelling. Stools typically float in the toilet bowl, and may be difficult to flush. With the failure in fat digestion, variable deficiencies of the fat-soluble vitamins (A, D, E, K) may develop. Weight loss may be significant.

Endocrine Insufficiency

Diabetes develops in most patients with severe chronic pancreatitis lasting more than 10 to 15 years. The incidence of diabetes is dramatically increased by resective surgery. Patients with total pancreatectomy, in particular, are likely to have "brittle" diabetes and are susceptible to sudden death. Hence, it is important to consider concomitant islet cell transplantation when total pancreatectomy is the treatment of choice. Recent advances in islet cell transplantation, both in islet harvesting techniques and specific immunosuppression, are very promising.

Other Complications of Chronic Pancreatitis

Chronic Pseudocyst

More than two-thirds of pseudocysts requiring surgical management are associated with chronic pancreatitis. Pseudocysts are a feature of the clinical picture of chronic pancreatitis in 25%–30% of cases. They may be single or multiple, and a communication to the main pancreatic duct is identified by ERCP in at least 50% of pseudocysts larger than 5 cm in diameter. Important complications of pseudocyst include: (1) free rupture, which occurs when the pseudocyst communicates with the pancreatic duct, and results in pancreatic ascites; (2) erosion into adjacent vessel, which leads to formation of pseudoaneurysm and hemorrhage; (3) distal common duct obstruction; and (4) duodenal obstruction.

Portal Hypertension

Splenic vein thrombosis may cause left-sided portal hypertension and gastric varices. This complication can lead to upper GI hemorrhage.

Biliary Obstruction

CBD obstruction, due to fibrosis and stricture of the intrapancreatic portion of the CBD, leads to obstructive jaundice.

Intestinal Obstruction

The duodenum and transverse colon are susceptible to obstruction. The latter may mimic carcinoma.

Carcinoma of the Pancreas

There is no convincing evidence that chronic pancreatitis causes pancreatic cancer. The two conditions, however, may coexist. It is estimated that 4% of patients with chronic pancreatitis develop pancreatic cancer within 20 years of the onset of the pancreatitis.[8]

CLINICAL MANAGEMENT

ACUTE PANCREATITIS

Although no major breakthrough has occurred in our understanding of the etiology and pathogenesis of acute pancreatitis, significant advances in management of the disease have improved survival. Clinical management (Table 4.3) is guided by answering the following four critical questions: (1) Is this acute pancreatitis and what is the cause (i.e., diagnosis)? (2) How severe is the attack (i.e., severity assessment)? (3) Is pancreatic necrosis present? (4) Is pancreatic sepsis present?

Diagnosis

Clinical Features

Upper abdominal pain radiating to the back in the region of L1 is a predominant feature of acute pancreatitis. The pain often develops 2 to 3 h after ingestion of a large fatty meal or alcohol. Nausea and vomiting are frequent. Abdominal pain tends to get worse in the supine position and improves when the patient sits up and leans forward. When the attack is severe, the clinical picture is that of the acute abdomen. Because of the retroperitoneal location of the pancreas, however, abdominal rigidity is not as marked as in the case of a ruptured viscus. Severe cases may be associated with hypovolemic shock, anuria, and respiratory failure. In the rare occurrence of retroperitoneal hemorrhage, blood may track along fascial planes and produce discoloration of the flank (Cullen's sign) or around the umbilicus (Grey-Turner's sign). Low-grade fever is common. The differential diagnosis includes perforated peptic ulcer, acute cholecystitis, appendicitis, mesenteric infarction, ruptured ectopic pregnancy, and myocardial infarction.

Laboratory Investigation

A complete blood count should be obtained. The white blood count is elevated, sometimes above 20,000 cells/hpf. Elevated serum amylase, present in more than 90% of patients on admission, is the most helpful finding. The amylase levels are highest in the first 8 to 24 hours and tend to be higher in biliary pancreatitis. Serum amylase may not be elevated in very severe disease or in patients with preexisting chronic pancreatitis. The elevation in acute pancreatitis starts to fall within 24 h and may return to normal within 48 to 96 h.

TABLE 4.3. Essentials: Management of Acute Pancreatitis

Diagnosis
- Clinical features: Abdominal pain, peritoneal signs, nausea and vomiting, fever, hypovolemia, hypotension, anuria, respiratory failure, Cullen's sign, Grey-Turner's sign (if hemorrhagic)
- Laboratory: Leukocytosis, hyperamylasemia, hypocalcemia
- Imaging studies:
  - Abdominal ultrasound: Assesses biliary tree, may show pancreatic enlargement or fluid collection
  - Abdominal CT scan: Best method to assess pancreatic inflammation, necrosis

Assessment of severity
- Clinical criteria: Ranson, Imrie (Glasgow), or APACHE II (see Table 4.4)
- CT criteria: Grades A to E

Initial therapy
- Volume and electrolyte (calcium) resuscitation
- Prevention of aspiration (nasogastric suction)
- Respiratory support: Endotracheal intubation, assisted ventilation
- Pain control

Subsequent management
- Intravenous antibiotics in severe disease
- Nutritional support
- Monitoring for pancreatic necrosis (CE-CT)
- If necrosis exists, rule out pancreatic infection (FNA: Gram stain, culture, and sensitivity)
- If biliary pancreatitis exists, perform early endoscopic sphincterotomy, followed later by cholecystectomy

Management of complications
- Infected necrosis: Surgical debridement and drainage
- Pancreatic abscess: Surgical debridement and drainage
- Infected pseudocyst: Percutaneous catheter drainage
- Pancreatic hemorrhage: Attempt angiographic control; if unsuccessful, operative control
- Cholangitis: Endoscopic drainage, followed by definitive biliary tract disease treatment, if present

Abbreviations: CE, contrast-enhanced; CT, computerized tomography; FNA, fine-needle aspiration cytology.

Hyperamylasemia may be seen in several nonpancreatic conditions; important among these are perforated peptic ulcer, mesenteric infarction, and ruptured ectopic pregnancy. It is rare for serum amylase levels to be elevated more than three times the normal level in these nonpancreatic causes of hyperamylasemia. Measuring urinary amylase is important because its level tends to stay elevated longer and rules out renal failure as a cause of hyperamylasemia. When low urinary amylase level is associated with high serum amylase level but serum creatinine is normal, the condition of macroamylasemia should be suspected. The serum lipase level is more specific than serum amylase and tends to stay elevated longer. It has a sensitivity and specificity of 90% and is the best test when uncertainty exists. Other tests necessary for severity assessment include blood glucose, liver function tests, blood urea nitrogen, serum albumin, and arterial oxygen saturation.

Imaging Studies

Abdominal ultrasound is an important early examination in acute pancreatitis to assess for gallstones, the presence of which is highly suggestive of biliary pancreatitis. Its ability to assess the severity of pancreatitis is severely limited by gas in the intestine. Nevertheless, ultrasound identifies most significant fluid collections in and around the pancreas.

Plain films of the abdomen (supine, upright, and decubitus) are useful to rule out perforated viscus. Specific findings that support the presence of pancreatitis are a dilated, fluid-filled stomach, duodenum, and ileus; and a dilated, air-filled transverse colon—sometimes a cut-off sign when gas is seen in the ascending and descending but not in the transverse colon. Occasionally, a sentinel loop of jejunum is seen, which represents localized ileus in a loop of bowel adjacent to the inflamed pancreas.

CT scan of the abdomen, the best imaging study both to diagnose and to estimate the severity of acute pancreatitis, should be delayed until circulating volume is restored to avoid renal failure. CT scan is most useful when enhanced by intravenous injection of a bolus of contrast agent. If the diagnosis of acute pancreatitis is evident, contrast-enhanced CT (CE-CT) is usually delayed 48 to 72 h, at which time severity of disease can be properly evaluated.

TABLE 4.4. Clinical Scoring to Assess Severity of Acute Pancreatitis

Ranson criteria
0–2 = mild, 3–5 = moderately severe, >5 = very severe
On admission
- Age >55 years
- WBC ≥16,000
- Blood glucose >200 mg/dL
- LDH >300 IU/L
- SGOT >250 μm/dL

During initial 48 hours
- Hematocrit fall >10%
- Arterial oxygen saturation (P_aO_2) <60 mm Hg
- BUN rise >5 mg/dL
- Serum Ca^{++} <8 mg/dL
- Fluid sequestration >6000 mL

Imrie (Glasgow) criteria
On Admission
- Age >55 years
- WBC >15,000
- Blood glucose >10 nmol/L
- Serum urea >16 mmol/L (no response to IV fluids)
- Arterial oxygen saturation (P_aO_2) <60 mm Hg

During initial 48 h
- Serum calcium <2 mmol/L
- Serum albumin <32 g/L
- LDH >600 μ/L
- Aspartate aminotransferase/alanine aminotransferase >100 μm/L

APACHE II scoring
Acute physiology score = total points (0–4) for each of 12 variables:

Temperature:	0 = 36.0°–38.4°; 4 = <30.0° or >40.9°
Mean arterial pressure:	0 = 70–109; 4 = <50 or >159
Heart rate:	0 = 70–109; 4 = <40 or >179
Respiratory rate:	0 = 12–24; 4 = <6 or >49
FiO_2:	0 = >70; 4 = <55
Arterial pH:	0 = 7.33–7.49; 4 = <7.15 or >7.69
Serum sodium:	0 = 130–149; 4 = <111 or >179
Serum potassium:	0 = 3.5–5.4; 4 = <2.5 or >6.9
Serum creatinine:	0 = 53–129; 4 = ARF >305
Hemoglobin (g/L):	0 = 100–153; 4 = <67 or >200
WBC (per mm^3):	0 = 3.0–14.9; 4 = <1.0 or >39.9
Glasgow coma score (GCS):	Actual points

Abbreviations: APACHE II, acute physiology and chronic health evaluation; BUN, blood urea nitrogen; Ca^{++}, ionized calcium; FiO_2, fraction of inspired oxygen; IV, intravenous; LDH, lactate dehydrogenase; SGOT, serum glutamic-oxaloacetic transaminase; WBC, white blood cell.

Severity of Pancreatitis

Determining the severity of pancreatitis is a key step in management. It is best done by a combination of clinical and CT criteria. A useful practice is to obtain a clinical score within 48 h of admission and a CT scan within 72 h if the pancreatitis is severe. Routine use of these methods has facilitated comparison of various treatments in various centers.

Clinical Criteria

Three clinical criteria are in use: Ranson, Imrie (Glasgow), and the APACHE II scores (Table 4.4). Any of these three may be used, the important point being that the same criteria must be used over time.

When the Ranson criteria are used, a score of 2 or lower indicates mild pancreatitis, 3 to 5 moderately severe pancreatitis, and above 5 very severe pancreatitis. The mortality rate rises with the severity score.

CT Criteria

The severity of pancreatitis on CT scan has been graded as follows:

1. Grade A (score = 0): normal pancreas (Figure 4.13A).
2. Grade B (score = 1): pancreatic enlargement (Figure 4.13B).
3. Grade C (score = 2): grade B plus inflammation in the peripancreatic tissue (Figure 4.13C).
4. Grade D (score = 3): phlegmon and one fluid collection (Figure 4.13D).
5. Grade E (score = 4): phlegmon and two or more fluid collections (Figure 4.13E).

CE-CT scan is the best way to follow the course of severe pancreatitis that does not resolve, while ultrasonography is reserved to follow the course of any fluid collection.

Diagnosis of Pancreatic Necrosis

Pancreatic and peripancreatic necroses are the most important predisposing factors for pancreatic sepsis. Necrosis is associated with mortality rates of 5% to 20%, but virtually all patients with pancreatitis who do not have necrosis survive.[4] If patient does not improve in the first 2 weeks of the disease, it is critical that he or she be evaluated for pancreatic necrosis to determine whether any necrotic tissue is infected.

Numerous methods have been used in the attempt to confirm an early diagnosis of pancreatic necrosis. Most tests are based on serum concentrations of various indicators, including elevations in poly-[C]-specific ribonuclease (RNA-ase), alterations of alpha-1-protease inhibitor and alpha-2 macroglobulin, and decreases in complement factor C_3 and C_4. Unfortunately, none of these serum markers provide accurate diagnosis. Imaging with ultrasound and ^{111}In white-cell scan are likewise unsatisfactory.

The best available method at present is CE-CT, which correctly identifies the presence of necrosis in 90% of patients with severe pancreatitis. When a bolus of contrast is rapidly injected during CT scanning of the pancreas, vascularized pancreatic tissue is enhanced while areas of necrosis show as perfusion defects (Figure 4.14). The presence of pancreatic necrosis should lead to the next important question: Is the necrosis infected? Infected necrosis is more common than abscess formation.

Diagnosis of Sepsis in Acute Pancreatitis

1. Infected necrosis. The most serious complication of necrosis is infection. Mortality rates double when necrosis becomes infected. Once necrosis occurs, the likelihood of infection is as high as 50% to 70%.[4] Infection tends to occur within 1–2 weeks of onset of acute pancreatitis.

A clinical picture of deteriorating symptoms such as spiking fever, tachycardia, high leukocytosis with a shift to the left, and diminishing oxygen saturation should indicate the presence of infected necrosis. Unless diagnosis is made rapidly and treatment instituted, the patient becomes progressively confused and mentally obtunded. Septic shock with multiple organ failure and death may ensue. This type of end-stage deterioration can be prevented by regular follow-up of the sick patient with CE-CT and, when necrosis is diagnosed, fine-needle aspiration (FNA) for bacteriological studies.

CE-CT may demonstrate air bubbles associated with areas of poor or no perfusion, which is a late finding. Once CE-CT demonstrates necrosis, a CT-guided FNA is indicated to obtain aspirate for culture and sensitivity and for an examination with a Gram stain slide. CT- or ultrasound-guided FNA has proven to be safe and nearly always diagnostic. The finding of bacteria on Gram stain or culture indicates the need for surgical debridement.

2. Pancreatic abscess and infected pseudocyst. A pancreatic abscess probably results from infection of localized necrosis that undergoes liquefaction (Figure 4.15). It typically develops later than infected necrosis, often from 3 to 5 weeks after the acute attack. Pancreatic abscess develops in 1% to 4% of all patients with acute pancreatitis. The systemic manifestations of sepsis tend to be milder than those of infected necrosis. Another cause of pancreatic abscess is secondary infection of a preexisting pseudocyst. Diagnosis is established by CT or ultrasound scan with FNA to identify the infecting agent.

3. Acute cholangitis. Acute cholangitis accompanying acute pancreatitis is nearly always caused by CBD obstruction due to a gallstone. It is theoretically possible that obstruction of the distal CBD may be caused by edema in the head of the pancreas or an acute pseudocyst, leading to ascending cholangitis. Symptoms are fever with chills, abdominal pain, jaundice, and changes in the level of consciousness.

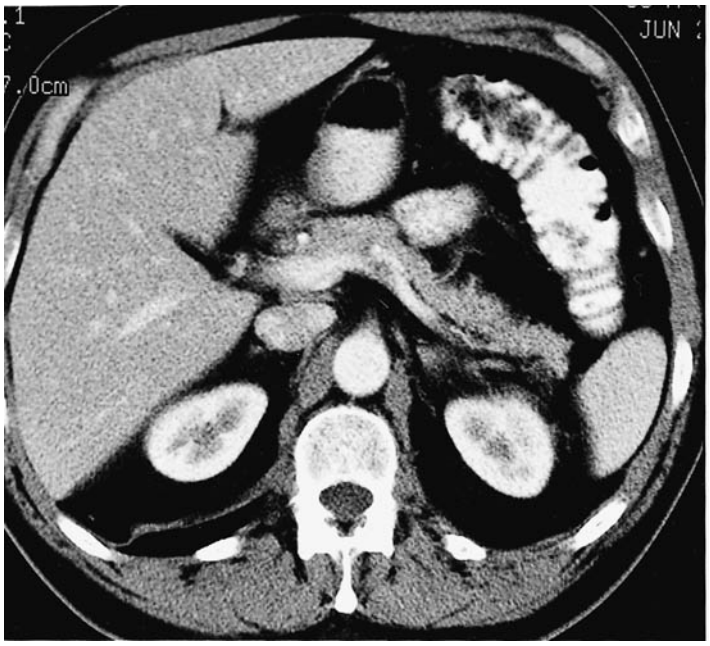
Ultrasonography usually shows stones within the gallbladder, rarely within the CBD, and modest dilatation of the extrahepatic biliary tree. Emergent ERCP may be required for diagnostic and therapeutic purposes.

General Treatment

Initial Therapy

Therapy in the first 24 to 48 h—the so-called hypovolemic phase of acute pancreatitis—is directed at volume resuscitation, prevention of aspiration, treatment of established or impending respiratory failure, and alleviation of pain.

1. Volume and electrolyte resuscitation. Patients with a severe attack of acute pancreatitis require major volume resuscitation that may need to be monitored by central venous pressure or pulmonary artery catheterization and urine output using a Foley catheter. The goal of therapy is to restore an adequate circulating volume and urine output (>50 mL/h) as quickly as possible. Such an aggressive approach to volume resuscitation is likely to prevent



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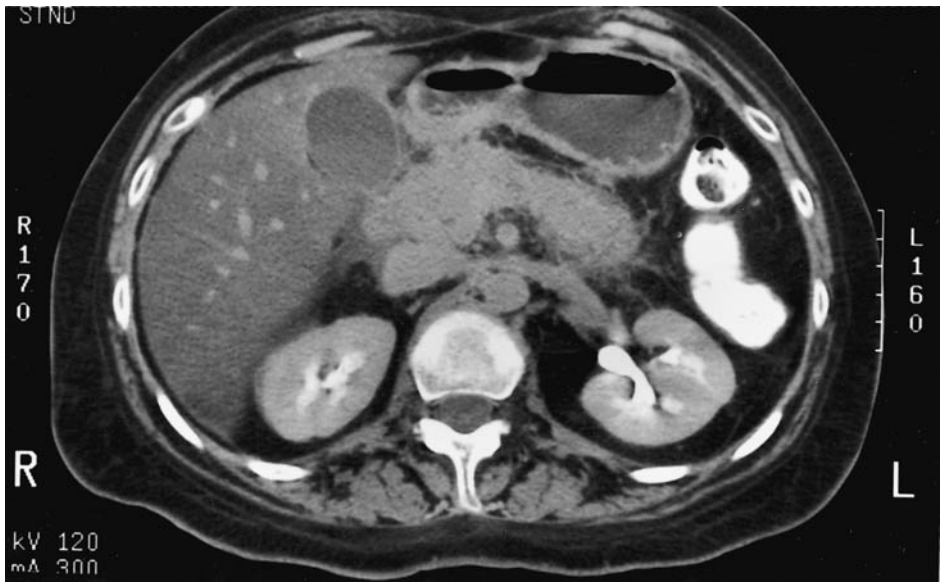
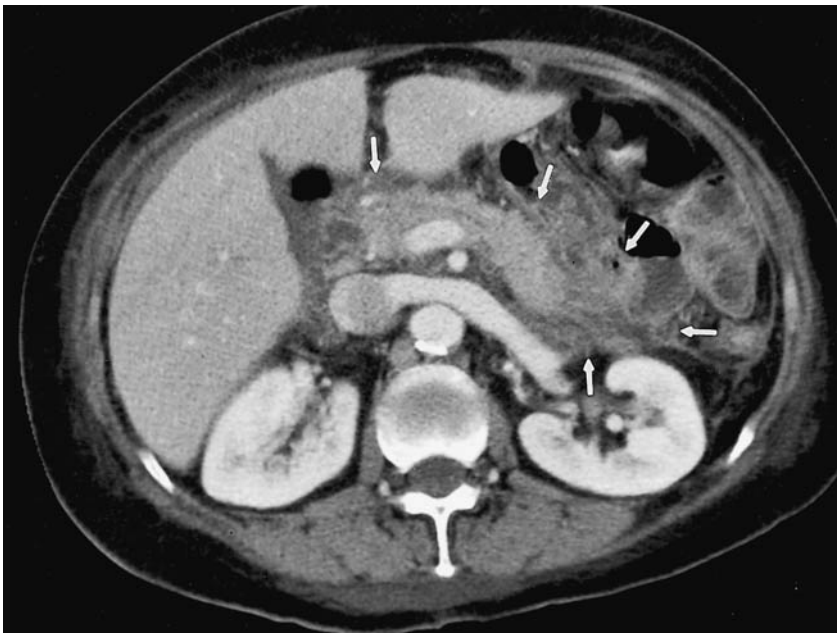


B

FIGURE 4.13. CT criteria for grading the severity of pancreatitis (A) compared with the normal pancreas. (B) Pancreatic enlargement with no fluid accumulation demonstrates grade B acute pancreatitis. (C) Grade C severity in acute pancreatitis includes enlargement of the pancreas and inflammation (arrows) in the peripancreatic tissue. (D) Pancreatic phlegmon with one fluid collection (arrows) demonstrates grade D disease and, (E) with two or more fluid collections (letter F), grade E disease. The pancreatic head is also enlarged (letter P). (Courtesy of Henry I. Goldberg, MD.)

(Continued)

C



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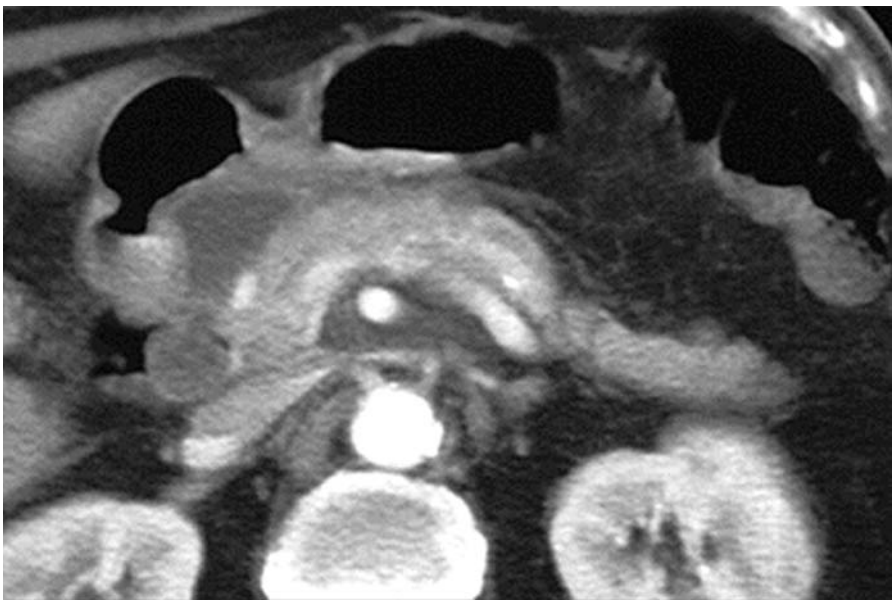

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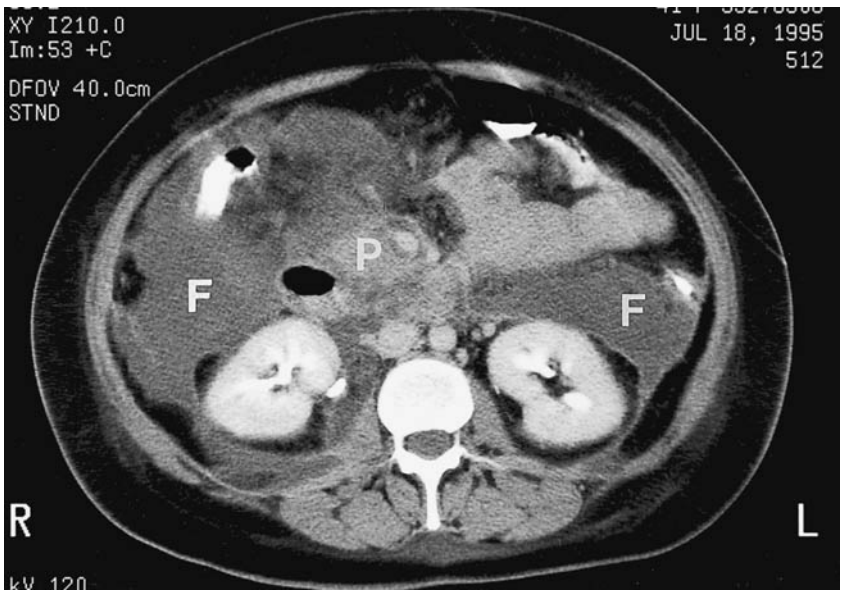

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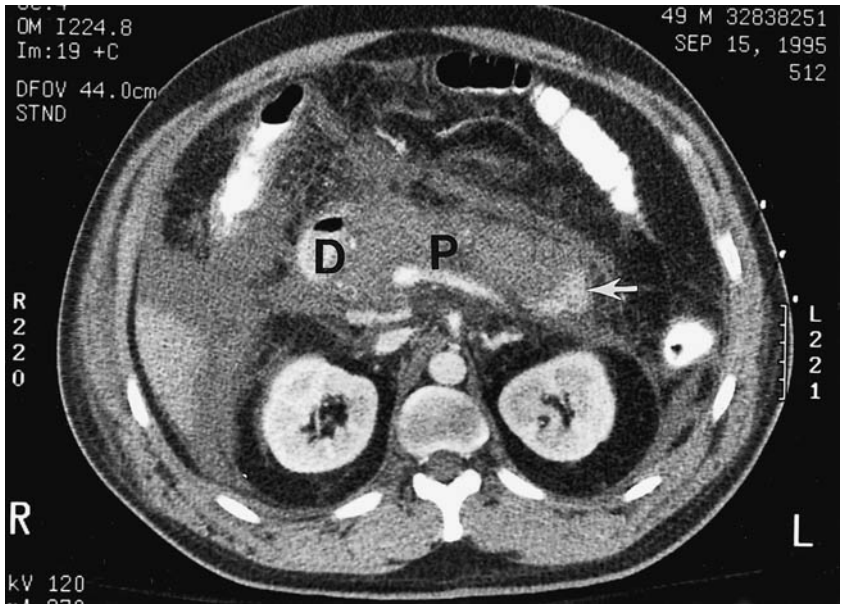

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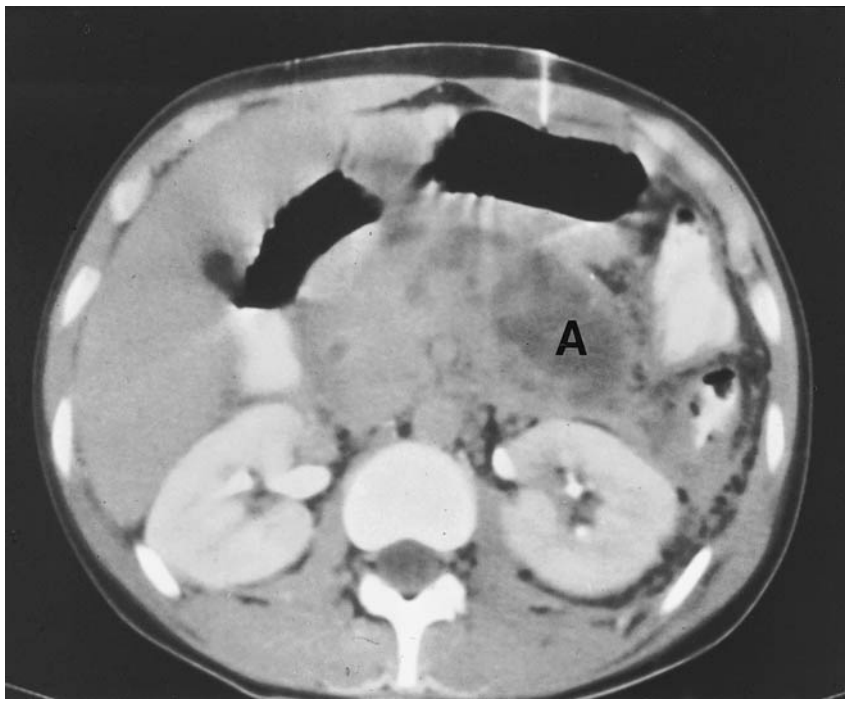


B

FIGURE 4.14. CE-CT scan demonstrates the presence of necrosis in severe pancreatitis. (A) A bolus of contrast is rapidly injected during CT scanning of the pancreas, enhancing vascularized pancreatic tissue (arrow) while areas of necrosis show as darker perfusion defects (letter P). The duodenum (letter D) marks the border with the necrotic head of the pancreas. (B) Even more extensive pancreatic necrosis is shown, with a large confluence of poorly perfused areas suggesting the presence of pancreatic abscess (letter A). (Courtesy of Henry I. Goldberg, MD.)

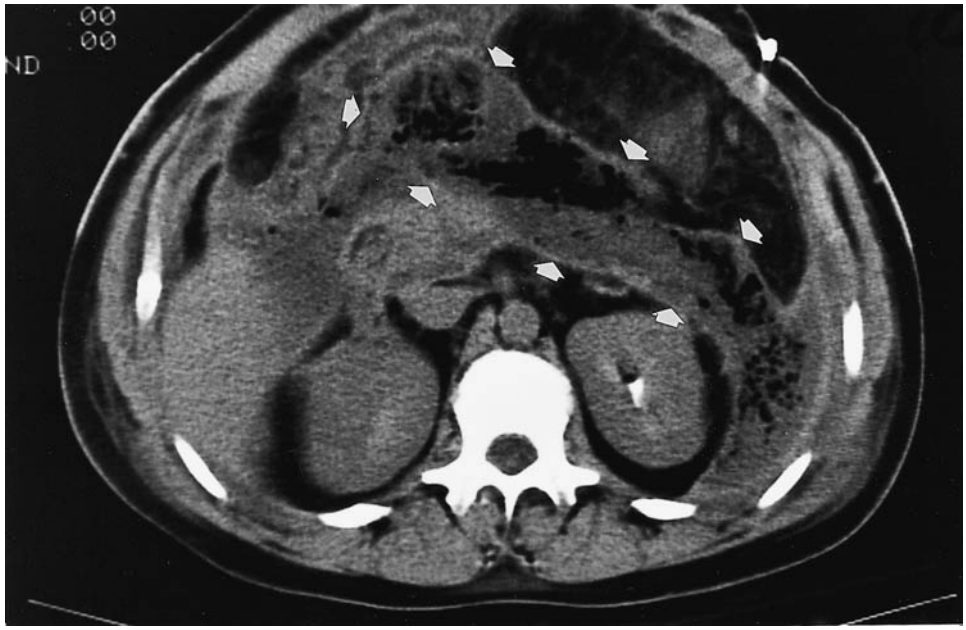


FIGURE 4.15. Pancreatic abscess with air fluid level and air bubbles (arrows) as demonstrated by CT scan may be a result of infection of localized necrosis that undergoes liquefaction in acute pancreatitis. (Courtesy of Henry I. Goldberg, MD.)

pancreatic ischemia and subsequent hemorrhage. Most patients can be adequately resuscitated with crystalloids, although colloids may be necessary in cases of hypovolemic shock. Transfusion of blood is used only if the hematocrit is low (<25%).

Serum calcium and magnesium levels should be measured and, if low, both should be corrected with the administration of calcium gluconate and magnesium sulfate, respectively. Occasionally, persistent hyperglycemia may develop. Hyperglycemia need not be treated unless ketosis develops.

2. Prevention of aspiration. Aspiration is an important complicating factor in severe acute pancreatitis. A nasogastric tube should be inserted in the patient to decompress the stomach. Gastric decompression is the more important reason for the use of nasogastric suction, but it also reduces pancreatic secretion by limiting duodenal acidification. Early intubation of the patient with respiratory failure and/or mental obtundation is another important strategy to prevent aspiration.

3. Respiratory support. Most patients can be supported with the administration of oxygen without intubation. Endotracheal intubation is necessary if arterial oxygen tension cannot be maintained above 60 mm Hg or if the patient has to work too hard to breathe and demonstrates a high respiratory rate (>30/min) for several hours or days.

4. Pain control. Rapid control of pain is best achieved with the intravenous administration of morphine or meperidine HCl (Demerol®). Theoretically, opiates should be avoided because they produce spasm of the sphincter of Oddi. Nevertheless, these drugs are the most effective in controlling the pain of acute pancreatitis.

Subsequent Therapy

If the patient's condition fails to improve within 72 to 96 h, not only must the initial treatment described above be continued, but additional therapeutic interventions must be considered, including prevention of sepsis, nutritional support, and peritoneal lavage.

1. Antibiotics. Prophylactic use of antibiotics was once considered ill-advised because it might possibly promote infection with resistant organisms and fungi. Recently, however, the use of prophylactic antibiotics in patients with severe pancreatitis has been condoned for two reasons. First, liberal use of CE-CT and FNA studies has shown that pancreatic necrosis is subsequently frequently infected with enteric organisms, suggesting that a preventive strategy may be valid. Second, recent experimental and clinical studies have shown that infection in acute pancreatitis can be prevented with antibiotics. In a recent controlled trial reported from the Netherlands by Luiten et al, selective gut decontamination with norfloxacin, colistin, and amphotericin B significantly reduced mortality rates (from 35%–22%) and the need for laparotomy in severe acute pancreatitis.[9] Other studies have shown that broad-

spectrum antibiotics given intravenously can significantly reduce infectious complications and mortality rates in severe acute pancreatitis. These studies suggest that antibiotics with good penetration into pancreatic juice are a better choice.[10,11] While no conclusive prospective trials are available, antibiotics such as clindamycin and ofloxacin are likely to be useful. Prophylactic antibiotics should be used judiciously and only in severe acute pancreatitis. Their use increases the incidence of systemic fungal infection.

2. Nutritional support. Parenteral hyperalimentation should be started if the patient is unable to take oral nutrition within 3 to 5 days and a protracted clinical course appears likely.

3. Therapeutic peritoneal lavage. Although pancreatic lavage is very effective in controlling pain, its therapeutic efficacy is still in doubt. Earlier studies showed that patients improved faster but developed sepsis with greater frequency after the initial improvement following peritoneal lavage. At present, therefore, therapeutic peritoneal lavage is rarely used.

4. Pharmacologic suppression of pancreatic inflammation. Several agents have been tried because of the obvious theoretical usefulness they appeared to have. Glucagon inhibits pancreatic and gastric secretion and increases pancreatic blood flow. Trasylol prevents activation of trypsin. Somatostatin suppresses pancreatic secretion directly and indirectly through inhibition of stimulant hormones. Unfortunately, prospective clinical trials with each of these three agents have failed to show therapeutic advantage. Indeed, once pancreatitis develops, no pharmacologic intervention to limit inflammation appears to work.

Specific Surgical Treatment

Treatment of Necrotizing Pancreatitis

Indications for Surgery Surgical intervention is indicated in severe necrotizing pancreatitis in two circumstances: (1) when infected necrosis is diagnosed, usually based on CE-CT and FNA; and (2) when the patient's condition deteriorates, despite the inability to establish the presence of infection.

Goals of Surgery The goals of surgery are threefold: (1) to remove all dead and liquefied pancreas, peripancreatic fat, and retroperitoneal tissue; (2) to establish adequate drainage of the lesser sac with or without continuous irrigation; and (3) to create a tube gastrostomy and feeding jejunostomy.

Procedure A large vertical midline or bilateral subcostal incision is usually needed. The lesser sac is opened and all dead tissue removed by blunt dissection with the finger or laparotomy sponges. Formal pancreatic resection is to be avoided because it has an unacceptably high mortality rate. When the extent of necrosis is too massive to manage in one procedure, subsequent second look operations are scheduled. As many as four or five operations may be needed, in which case the surgeon must decide whether to pack the abdomen open or close it. Some have used a zipper to allow easy reentry.

Once debridement is satisfactorily accomplished, the lesser sac should be drained with two or three large, soft sump tubes to establish closed-suction drainage. An alternative method is to strategically place two sump drains in the lesser sac (Figure 4.16) and use continuous irrigation postoperatively.

Provision of a tube gastrostomy avoids the need for prolonged use of a nasogastric tube. Construction of a feeding jejunostomy is advisable in the event of protracted duodenal ileus.

Outcome The mortality rate is high, especially when more than one operation is needed and when complications such as hemorrhage or small- or large-bowel fistula supervene. In a 1991 review of surgical treatment and the mortality rate in pancreatic necrosis and sepsis, D'Egidio and Schein reported the following outcomes: The mortality rate of patients treated with necrosectomy and lavage in 216 patients was 23%. However, when resection, necrosectomy, and drainage were performed in 516 patients, the mortality rate was 38%.[12] Necrosectomy without formal pancreatic resection and with continuous postoperative irrigation of the lesser sac appeared to provide the best outcome.

Treatment of Pancreatic Abscess

A pancreatic abscess that develops in the course of severe pancreatitis differs from a pseudocyst that becomes secondarily infected. In the latter, percutaneous tube drainage may prove satisfactory. True pancreatic abscess is not adequately managed with percutaneous catheters because it usually contains infected debris and dead tissue that cannot be drained with tube suctioning. Abdominal exploration with formal debridement and drainage is necessary.

Therapeutic Strategies in Biliary Pancreatitis

The simple classification of biliary pancreatitis given earlier provides useful guidelines for the therapeutic approach (Table 4.5). Type A patients have hyperamylasemia but no abdominal signs or any detectable inflammation of the pancreas. These patients are best treated with laparoscopic cholecystectomy and operative cholangiogram done on an urgent basis, usually when the hyperamylasemia subsides, which generally happens within 24 to 48 h.

Patients with Type B biliary pancreatitis have significant abdominal findings. On conservative treatment, the

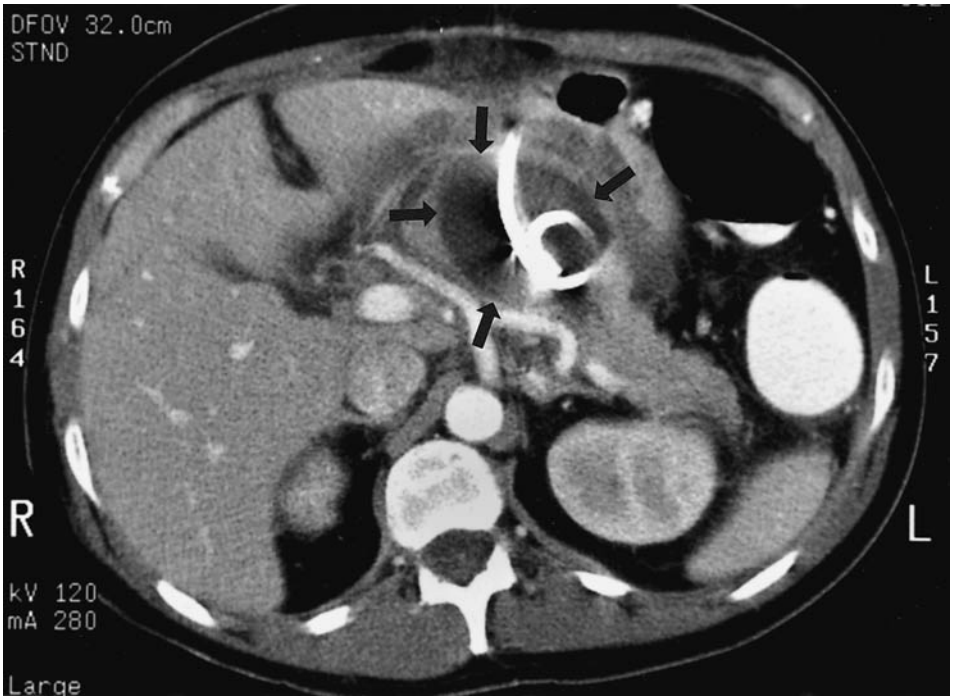


FIGURE 4.16. Necrotizing pancreatitis may be treated with surgical debridement and drainage, followed by strategic placement of two sump drains in the lesser sac to provide continuous irrigation postoperatively. The CT scan illustrates a large necrotic cavity (arrows) containing two drains (bright tubular structures). (Courtesy of Henry I. Goldberg, MD.)

abdominal findings usually resolve within 5 to 7 days. In the past, such patients were discharged home for readmission 6 to 8 weeks later for cholecystectomy. Unfortunately, acute pancreatitis, sometimes with fatal consequences, recurred too often during the waiting period. It is now generally accepted that patients with Type B biliary pancreatitis should have cholecystectomy and operative cholangiogram as soon as abdominal signs subside but during the same admission.

TABLE 4.5. Biliary Pancreatitis: Management Strategies

Classification	*Features*	*Treatment*
A	▪ Hyperamylasemia only ▪ No peritoneal signs	Urgent cholecystectomy and operative cholangiogram
B	▪ Hyperamylasemia ▪ Mild/moderate peritoneal signs ▪ Ranson score <3	▪ Allow peritoneal signs to subside ▪ Cholecystectomy during same admission
C	Severe pancreatitis ± multiple organ failure	▪ Endoscopic sphincterotomy within 3–5 days ▪ Definitive operation when condition is optimal

Patients with Type C biliary pancreatitis present more of a challenge because of the significant mortality. It was once advocated that these patients should be operated upon within 48 hours. This approach was associated with high morbidity and mortality. Treatment of this type of pancreatitis has been revolutionized by the advent of endoscopic sphincterotomy, which, in severe cases, if performed within 72 h, reduces morbidity and mortality. Rapid resolution of pancreatitis often follows, at which time definitive surgery can be performed.

Treatment of Acute Pseudocyst

Not all acute pseudocysts require specific treatment. As mentioned above, most cysts that develop in the course of acute pancreatitis resolve spontaneously. The indications for intervention and the nature of intervention are described below:

1. Rapid enlargement. When acute pseudocysts enlarge rapidly to 6 cm or more, especially when the enlargement is associated with increased pain, ultrasound- or CT-guided catheter drainage may be prudent to prevent spontaneous rupture.

2. Persistence of pseudocyst. Any pseudocyst 6 cm or more in size that persists for 8 weeks or longer after formation, especially if associated with symptoms, is an indi-

cation for internal drainage (cyst-gastric or cyst-enteric). A well-formed mature cyst wall is needed to create the anastomosis.

3. Infected pseudocyst. An infected pseudocyst must first be distinguished from pancreatic abscess. The infected pseudocyst may be treated by percutaneous catheter drainage and, if that fails, by operative external drainage. Pancreatic abscess, however, nearly always requires debridement and external drainage, accompanied by institution of appropriate antibiotic therapy.

4. Pseudocyst hemorrhage. Pseudocyst hemorrhage is usually due to erosion of an adjacent vessel and the formation of a pseudoaneurysm or cyst-aneurysm. This development usually causes acute worsening of pain. The cyst-aneurysm may rupture into the free peritoneal cavity, causing an acute abdomen and hypovolemic shock, or into an adjacent viscus, causing upper or lower gastrointestinal hemorrhage. Angiography is immediately indicated after resuscitative measures are instituted. Angiographic control of bleeding with metal coils (Gianturco) or embolization is the most expedient and often successful mode of therapy (Figure 4.17). When angiographic control is unsuccessful, abdominal exploration is necessary to accomplish either transcystic ligation of the bleeder and/or ligation of the feeding vessel.

5. Obstruction. Infrequently, a pseudocyst may obstruct an adjacent organ, usually the duodenum or common bile duct. Obstruction may be successfully resolved by cyst-duodenal or cyst-jejunal drainage. Rarely will a bypass procedure be necessary.

CHRONIC PANCREATITIS

Clinical Presentation

Abdominal pain is the main presenting symptom of chronic pancreatitis. The pain, often in the epigastrium or the left subcostal region, typically radiates to the back in the T12–L1 region. The pain waxes and wanes and, with time, may become persistent and lead to narcotic addiction. Weight loss can be severe. Steatorrhea occurs in advanced disease and may lead to malabsorption of fat-soluble vitamins (A, D, E, K). Sometimes, this chronic disease is punctuated with intermittent acute attacks requiring hospitalization.

Patients are referred for surgical treatment, either because of the severity and unresponsiveness of pain, or because a complication has developed. Obstructive jaundice occurs in 5% to 10% of patients. Pseudocysts may present as an abdominal mass or are discovered by imaging techniques in the investigation of worsening pain. Other less frequent complications include development of pancreatic ascites or bleeding gastric varices. The essentials of managing chronic pancreatitis are summarized in Table 4.6.

Investigation

The objectives of investigation are to establish the diagnosis, to evaluate the degree of pancreatic dysfunction, to assess the severity of pancreatic damage, to detect complications, and to assess the status of the pancreatic duct. Studies include biochemical analysis, pancreatic function tests, x-ray, and other imaging studies.

Biochemical

Serum amylase levels are usually normal unless the pancreatitis becomes acutely exacerbated or a pseudocyst develops. Liver function tests are assessed to rule out common bile duct obstruction. Prothrombin time should be assessed, particularly in the presence of steatorrhea, which can lead to vitamin K malabsorption.

Pancreatic Function

1. Endocrine pancreas. The status of pancreatic endocrine function should be assessed by performing fasting and 2-h postcibal blood glucose levels. A glucose tolerance test is rarely needed.

2. Exocrine pancreas. Exocrine pancreatic function studies are limited in establishing diagnosis and are usually useful only when the diagnosis is suspected and imaging studies are negative. The two more popular tests measure duodenal bicarbonate and enzyme secretion: one in response to a meal (the Lundh test), the other in response to intravenous secretin with or without cholecystokinin. These tests are cumbersome to perform and difficult to standardize. Pancreatic enzymes (trypsin and chymotrypsin) can also be measured in the blood or feces. Pancreatic enzyme action can also be measured indirectly by the N-benzoyl-tryosyl-p-aminobenzoic acid (NBT-PABA; bentiromide) breath test.

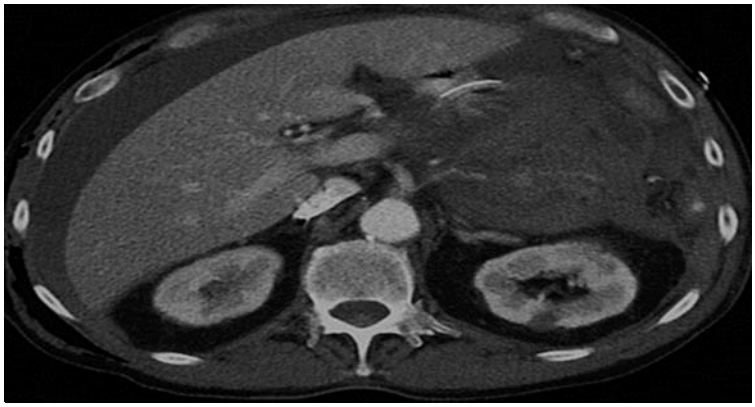
Plain Abdominal X-Ray

Speckled pancreatic calcification or calcium stones within the pancreas provide strong confirmatory evidence of chronic pancreatitis (see Figure 4.10).

Imaging Studies

1. Ultrasonography. This study can assess the size and texture of the pancreas and presence or absence of pancreatic duct dilatation and pseudocysts. Its major value, however, may be assessment of the biliary tract for associated pathology.

2. Computed tomography. CT is the most sensitive and specific imaging study for diagnosing chronic pancreatitis. CT examination evaluates the presence of calcifications,



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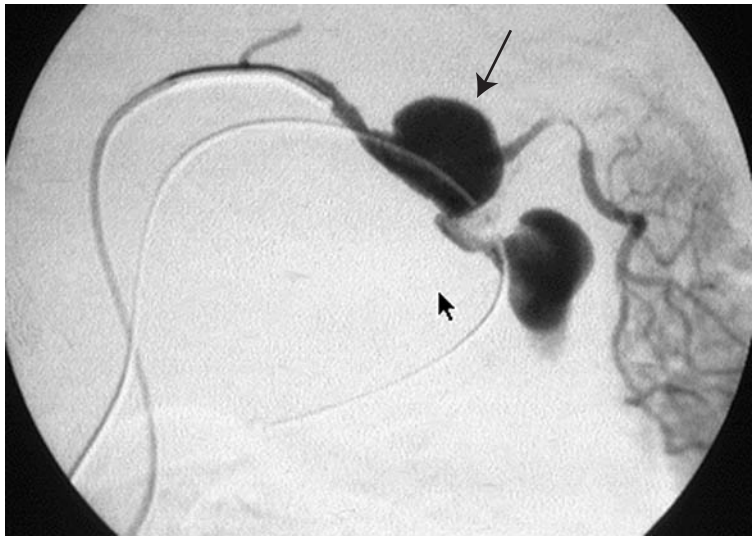

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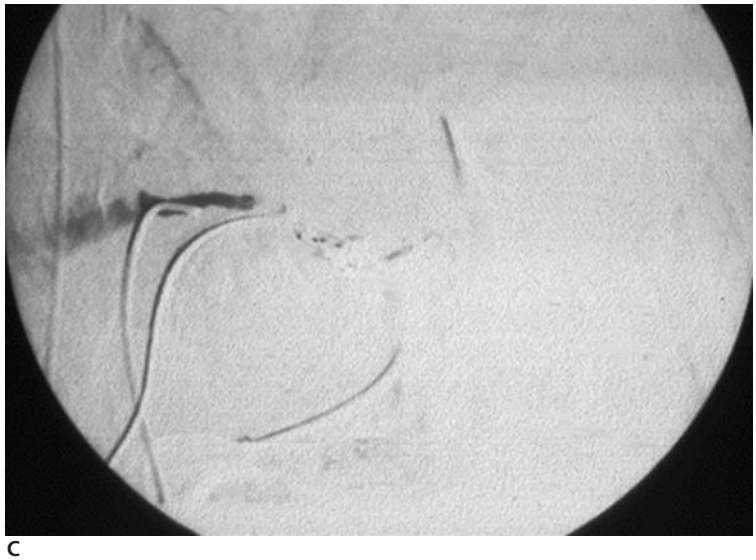


C

FIGURE 4.17. Pseudocyst hemorrhage can be treated with angiography. (A) The CT scan shows a large area of hemorrhage (arrows) in the region of the lesser sac. With metal coils (Gianturco), the bleeding pseudoaneurysm of the splenic artery (B, arrow) was embolized to control bleeding (C). (Courtesy of Henry I. Goldberg, MD.)

TABLE 4.6. Essentials: Management of Chronic Pancreatitis

Diagnosis
- Clinical
  - Chronic abdominal pain
  - Recurrent back pain (T12–L1)
  - History of alcoholism
  - Diarrhea, weight loss
- Laboratory
  - Serum amylase may be intermittently elevated
  - Pancreatic function tests
- Imaging
  - Plain abdominal films (calcification)
  - Ultrasound (PD: Dilatation, pseudocysts, gallstones)
  - CT scan (PD: Dilatation, pseudocysts, calcification)
  - ERCP: Most reliable and diagnostic study (pancreatic ductal anomalies, dilatation, chain of lakes, stones, pseudocysts)

Treatment
- Conservative
  - Abstinence from alcohol
  - Pain control
  - Patient education, counseling
  - Pancreatic enzyme therapy if steatorrhea present
  - Dietary restriction of fat and large meals
  - Vitamin E supplementation
  - Control of diabetes if present
- Endoscopic
  - Sphincterotomy and stone extraction
  - Dilatation of stenotic proximal duct
  - Stenting
- Surgical indications
  - Intractable pain
  - Pancreatic pseudocysts
  - Biliary obstruction
- Procedures (see Table 4.8)

Abbreviations: CT, computerized tomography; ERCP, endoscopic retrograde cholangiopancreatography; PD, pancreatic duct.

dilated pancreatic duct, and pseudocysts (Figure 4.18). It is also the best way to rule out the presence of pancreatic cancer. Helical CT provides even better images than traditional CT scans.

3. Endoscopic retrograde cholangiopancreatography. ERCP is not only the most reliable way to diagnose chronic pancreatitis, but it is also the best way to visualize pancreatic ductal anatomy, providing key information in surgical decision making. Pancreatic ductal abnormality may be mild and involve only peripheral ductules (Figure 4.12B). Or it may involve the main pancreatic duct, which may be dilated, sometimes with chain-of-lakes deformity when the duct is intermittently dilated between sites of stricture or impacted stones (Figure 4.12C). ERCP also assesses the presence or absence of common bile duct obstruction or other biliary tract pathology.

4. Angiography. Angiography is used only when there is either bleeding or suspicion of portal vein and splenic vein thrombosis. The latter information can be obtained more easily with the use of CE-CT scan or Doppler ultrasonography.

Management

Conservative Management

Most patients undergo medical management for years before they are eventually referred to surgery. Several aspects of conservative management are important.

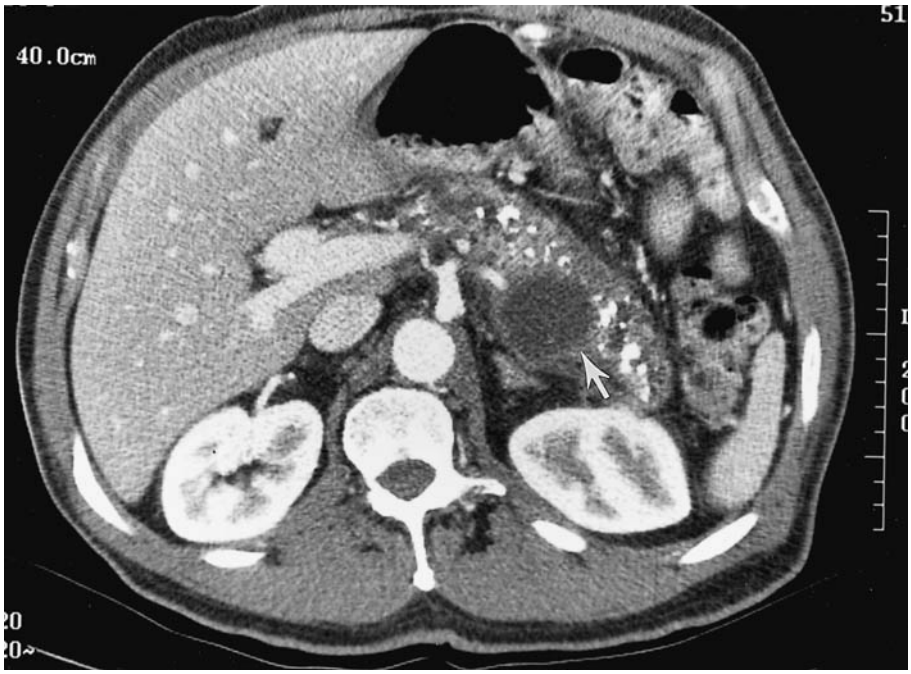


FIGURE 4.18. Chronic pancreatitis is best diagnosed with CT scan, which reveals the presence of calcifications, dilatated pancreatic duct, and pseudocysts (arrow). (Courtesy of Henry I. Goldberg, MD.)

1. Abstinence from alcohol. This important aspect of management is also the most difficult to institute. Patient education, counseling, group support, and psychiatry are all helpful.

2. Pain control. The cause of pain in chronic pancreatitis is unknown. Opioid drugs are invariably required and, with chronic use, addiction becomes a problem. Percutaneous celiac axis blockade with alcohol or phenol has proved disappointing. Three plausible causes for the pain have been described:

a. Ductal hypertension. Intraoperative measurements of pressure in dilated ducts have been shown to be elevated. The rationale for pancreatic drainage to ameliorate pain is based on reduction of ductal pressure. Unfortunately, many patients with pain do not have dilated ducts.

b. Perineural inflammation. In many specimens examined, perineural inflammation is striking. Recent studies with immunohistochemistry also show an increase in CGRP- and substance P-containing sensory neurons.

c. Peripancreatic inflammation. Chronic inflammation extending to the retroperitoneum is probably an important cause of back pain.

3. Pancreatic enzyme therapy. The finding that duodenal trypsin inhibits the release of CCK-releasing peptide and, thereby, secretion of CCK has led to the use of oral pancreatic enzyme supplements in chronic pancreatitis. The theory is that pancreatic stimulation is reduced, leading to pain relief. Unfortunately, the therapeutic effect on pain relief is sporadic. Pancreatic enzyme therapy, however, does play an important role in the treatment of steatorrhea.

4. Diet. Restriction of fat and large meals is useful in reducing pain. Vitamin supplements, especially fat-soluble vitamins, are also useful.

5. Control of diabetes. Appropriate measures are needed to control diabetes, when present, with either insulin or oral hypoglycemics.

Endoscopic Management

Advances in interventional endoscopy have provided a new alternative to surgical therapy. In addition to sphincterotomy, endoscopic procedures include sphincterotomy extraction of stones from the pancreatic duct, dilatation, and stenting of strictures. Good judgment and superior technical expertise are required. So far, anecdotal reports suggest that, under the right circumstances, these procedures result not only in relief of pain but also in some recovery of pancreatic endocrine function.[13]

Surgical Management

This section discusses the surgical options for treatment of chronic pancreatitis and its complications. Complications of surgery are listed in Table 4.7.

TABLE 4.7. Surgical Complications in Chronic Pancreatitis

Exocrine pancreatic insufficiency and steatorrhea
Diabetes mellitus
Pseudocyst formation
Pancreatic ascites
Hemorrhage due to vascular erosion, usually due to pseudocyst
Splenic vein thrombosis and gastric varices
CBD obstruction and obstructive jaundice
Duodenal obstruction
Carcinoma?

Abbreviation: CBD, common bile duct.

Intractable pain is the most common indication for surgery. Pancreatic pseudocysts and their complications are a second important indication. Biliary obstruction occurs in a significant percentage of patients but is severe or complete in only 5% to 10%.[6] Other complications that may require surgical intervention include bleeding gastric varices from splenic vein thrombosis, duodenal or colonic obstruction, pancreatic ascites, and sometimes, suspicion of pancreatic cancer.

Principles of Surgical Therapy

1. The goals of surgery must be clearly explained to the patient. They include alleviating pain and bypassing or removing complications. Reversal of loss of pancreatic exocrine or endocrine function cannot be promised.

2. Pancreatic drainage procedures are based on the premise that ductal obstruction leads to distension and pain; therefore, the presence of dilated pancreatic duct is necessary to embark on a pancreatic drainage procedure.

3. Resecting procedures are indicated when disease is largely confined to one region and the pancreatic duct is not dilated. Any amount of pancreatic resection increases the incidence of postoperative diabetes.

4. A well-planned procedure should be executed only by an expert pancreatic surgeon after a thorough investigation that includes proper imaging studies and ERCP to provide information on the pancreatic duct and biliary tree.

5. The operative procedure with the greatest chance of success must be selected.

6. Continued use of alcohol or addicting drugs by the patient is a relative contraindication for elective surgery.

Surgical Options for Treatment of Chronic Pancreatitis The two surgical options are pancreatic drainage and resection, various procedures for which are summarized in Table 4.8. In general, pancreatic drainage is reserved for cases in which the pancreatic duct is larger than 7 mm in diameter.

TABLE 4.8. Surgical Options in Treatment of Chronic Pancreatitis

Type of procedure	*Comments*
Pancreatic drainage procedures (require PD >7 mm)	
Longitudinal pancreaticojejunostomy (Peustow)	Relieves pain in 70%
End-to-side pancreaticojejunostomy (DuVal)	Relieves pain in 40%
Pancreaticogastrostomy	Infrequently performed
Sphincteroplasty	Low success rate
Pancreatic resection procedures	
Distal pancreatectomy	Rarely indicated
Near-total pancreatectomy (Child's)	Suboptimal
Pylorus-preserving pancreaticoduodenectomy	When disease is confined to the pancreatic head
Duodenum-preserving pancreatectomy	
▪ Beger procedure	▪ Excision of head and end-to-end pancreaticojejunostomy
▪ Frey procedure	▪ Excision of head and longitudinal pancreaticojejunostomy

Abbreviation: PD, pancreatic duct.

Pancreatic Drainage Procedures

1. Longitudinal pancreaticojejunostomy (the Peustow procedure). The lesser sac is opened through the gastrocolic ligament, and the pancreas is visualized from the head, at the duodenal C-loop, to the tail at the splenic hilum. The pancreatic duct can often be readily palpated; if not, intraoperative ultrasound helps in its identification. The duct is opened (filleted) along its entire length from tail to head, going as far as possible to the right of the superior mesenteric and portal veins and into the uncinate process. Any stones and sludge in the pancreatic duct are removed. A 40-cm retrocolic Roux-en-Y limb of jejunum is then fashioned and a side-to-side pancreaticojejunal anastomosis constructed along the entire length of the filleted pancreatic duct (Figure 4.19). Nonabsorbable sutures are used to construct the anastomosis between the opened Roux-en-Y jejunal limb and the pancreas, whose fibrosed capsule provides the necessary tissue of substance for the anastomosis.

Longitudinal pancreaticojejunostomy is a safe procedure with negligible mortality and morbidity rates. Long-term relief of pain has been reported in up to 70% of patients by several groups.[14]

2. End-to-side pancreaticojejunostomy (the DuVal procedure). Retrograde drainage of the pancreas into a Roux-en-Y limb of the jejunum is accomplished, following amputation of the tail of the pancreas and splenectomy (Figure 4.20). This procedure has not been as successful as longitudinal pancreaticojejunostomy, perhaps because multiple strictures and stones, often present in the duct in the head and body of the pancreas, prevent adequate drainage. Reported success in pain relief has been about 40%, and the procedure is not frequently used.[15]

3. Pancreaticogastrostomy. This procedure is used rarely and when the pancreatic duct has a single site of obstruction.

4. Sphincteroplasty. Transduodenal sphincteroplasty is useful only when the obstruction is in the area divided by sphincterotomy. When the operation was popular, temporary pain relief was achieved in 25% to 30%.

Pancreatic Resection

1. Distal pancreatectomy. This is a useful operation when disease involves only the body and tail. These circumstances rarely exist.

2. Near-total distal pancreatectomy (Child's procedure). This operation, which saves only a rim of pancreatic tissue along the duodenum, is only of historical importance. It does not have a high rate of success and can lead to postoperative diabetes.

3. Pylorus-preserving pancreaticoduodenectomy. When the main locus of disease is in the head of the pancreas and the major pancreatic duct is not dilated, pylorus-preserving pancreaticoduodenectomy is the operation of choice. The procedure also treats common bile duct obstruction if present. Pain relief has been accomplished in some 82% of reported cases.[16]

4. Duodenum-preserving resection of the head (the Beger procedure). The pancreas is divided over the superior mesenteric vein and the head of the pancreas cored out. The body of the pancreas is drained with a Roux-en-Y limb of jejunum to create an end-to-end anastomosis (Figure 4.21).

5. Frey procedure. This is another variant of duodenum-preserving resection of the pancreatic head, combined with longitudinal pancreaticojejunostomy (Figure 4.22). The Frey procedure addresses the difficulty of draining adequately with longitudinal pancreaticojejunostomy along the head of the pancreas when it is enlarged and the locus of major disease.

6. Total pancreatectomy. Total pancreatectomy inevitably creates total exocrine and endocrine insufficiency and is, therefore, used as a last procedure when

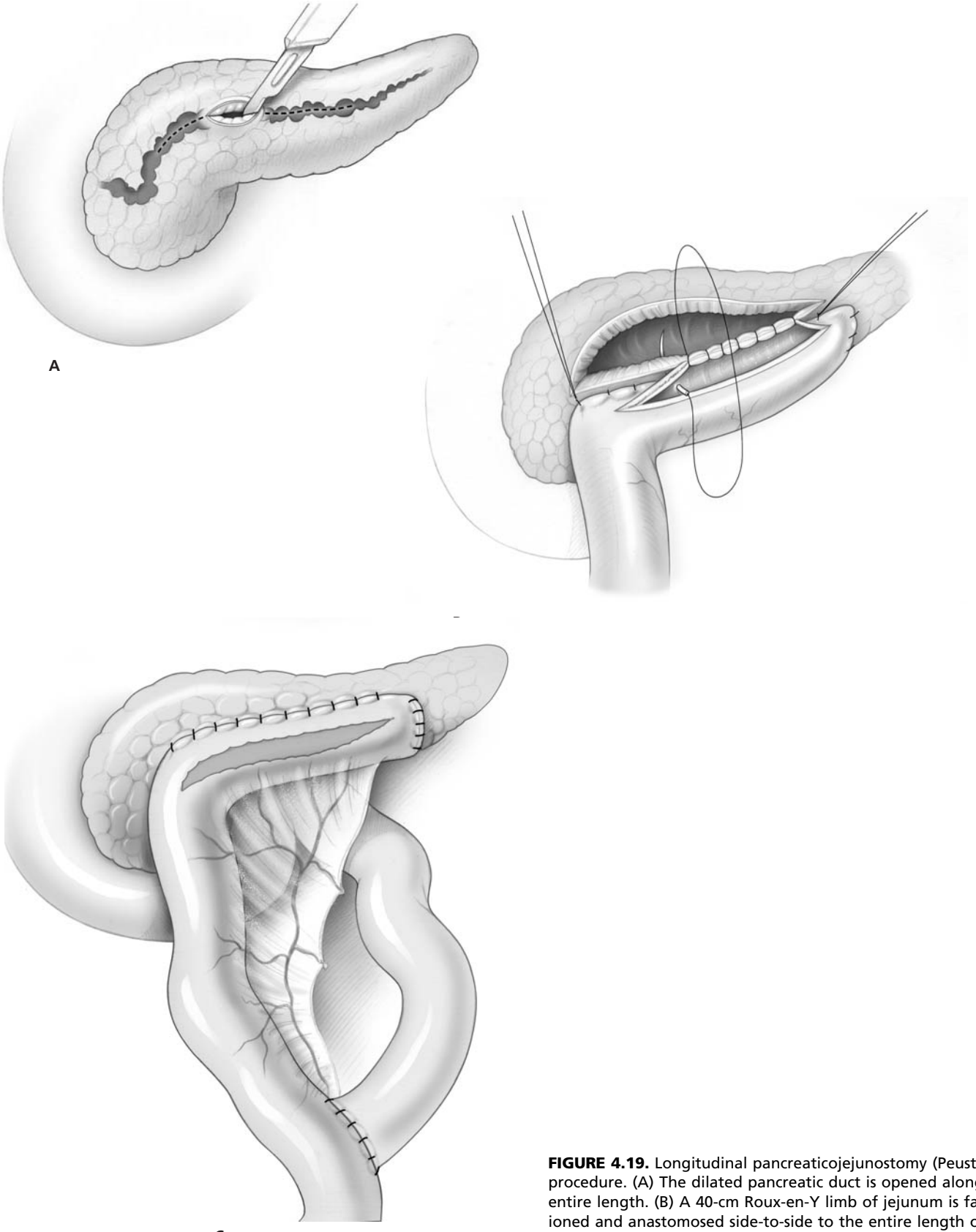


FIGURE 4.19. Longitudinal pancreaticojejunostomy (Peustow) procedure. (A) The dilated pancreatic duct is opened along its entire length. (B) A 40-cm Roux-en-Y limb of jejunum is fashioned and anastomosed side-to-side to the entire length of the filleted pancreatic duct. (C) The completed procedure is shown. (Adapted from Warren KW, Jenkins RL, Steele GD. Atlas of Surgery of the Liver, Pancreas, and Biliary Tract. Norwalk, CT: Appleton & Lange; 1991.)

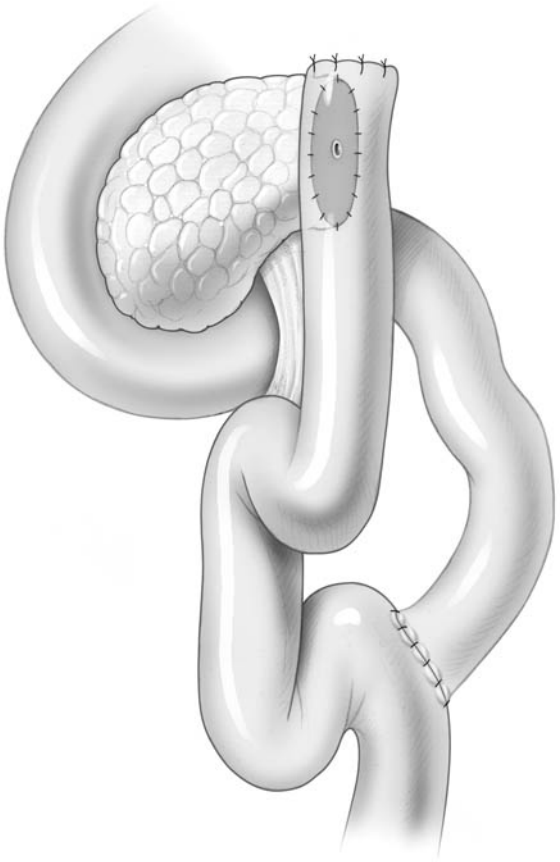
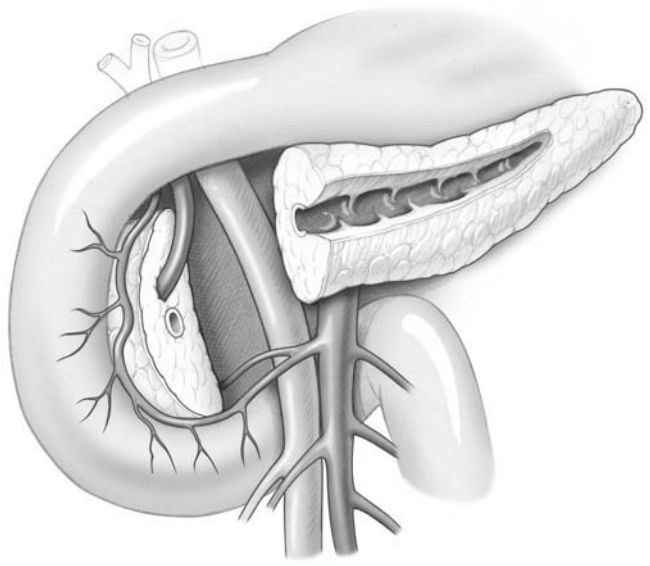


FIGURE 4.20. End-to-side pancreaticojejunostomy (DuVal) procedure. Following distal pancreatectomy, the cut edge of the pancreas is anastomosed end-to-side with a Roux-en-Y limb of jejunum. (Adapted from Warren KW, Jenkins RL, Steele GD. Atlas of Surgery of the Liver, Pancreas, and Biliary Tract. Norwalk, CT: Appleton & Lange; 1991.)



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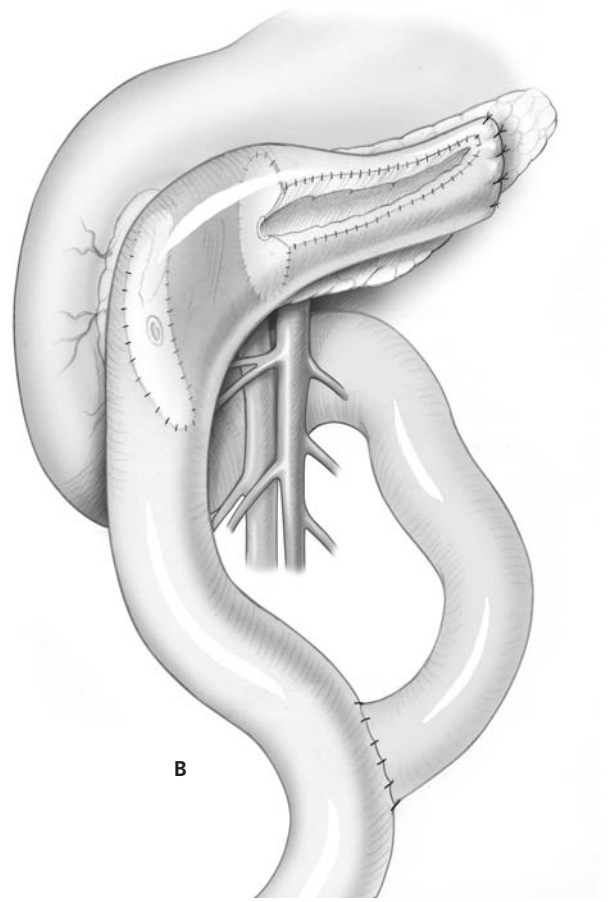

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FIGURE 4.21. Duodenum-preserving resection of the head of the pancreas (Beger procedure). (A) The pancreas is divided over the superior mesenteric vein and the head of the pancreas excised. The pancreatic duct is opened longitudinally along the body and tail. (B) A Roux-en-Y limb of jejunum is then anastomosed to the cut end of the residual head and the body and tail of the pancreas.

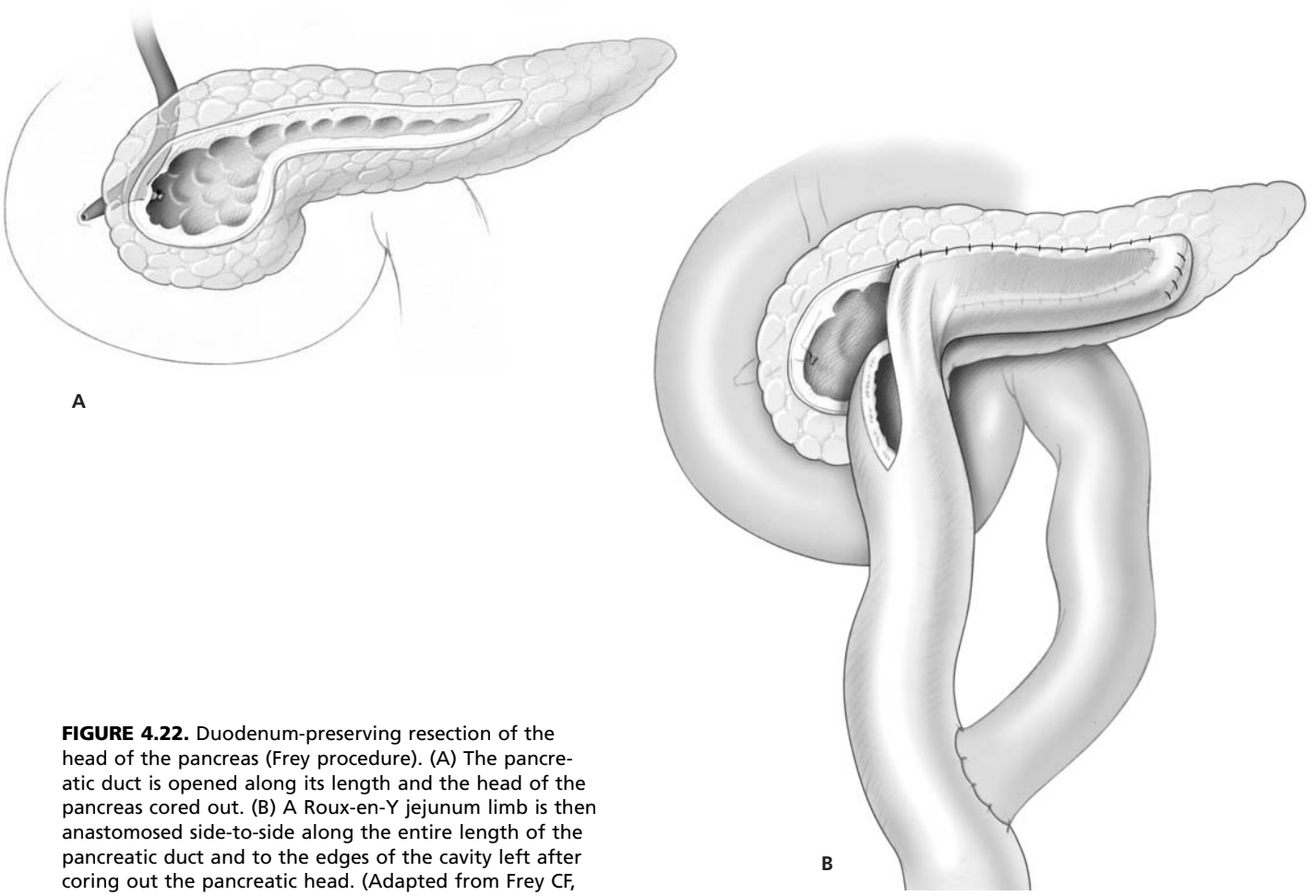


FIGURE 4.22. Duodenum-preserving resection of the head of the pancreas (Frey procedure). (A) The pancreatic duct is opened along its length and the head of the pancreas cored out. (B) A Roux-en-Y jejunum limb is then anastomosed side-to-side along the entire length of the pancreatic duct and to the edges of the cavity left after coring out the pancreatic head. (Adapted from Frey CF, Smith JG. Description and rationale of a new operation for chronic pancreatitis. Pancreas 1987;2:701–707.)

pancreaticoduodenectomy and distal resection fail. Even with total pancreatectomy, complete pain relief is achieved in only 65% to 80% of patients.[1]

Choice of Procedure in Chronic Pancreatitis Different procedures are indicated depending on the location of major disease and whether or not the pancreatic duct is dilated.

1. Uniformly dilated pancreatic duct. When the pancreatic duct is uniformly dilated, the procedure of choice is longitudinal pancreaticojejunostomy. When the major locus of disease is the head of the pancreas, causing it to be bulky and thickened, and the duct within the head cannot be adequately drained, the Frey procedure may be more suitable.

2. Small pancreatic duct. The choice of procedure in this situation depends on the main locus of disease. For disease located mainly in the body and tail, distal pancreatectomy is indicated. For disease located mainly in the head, either pylorus-preserving pancreaticoduodenectomy or the Beger procedure may be selected. If the CBD is obstructed, the former procedure is indicated.

When subtotal resection fails, total pancreatectomy is considered as a last resort. This operation may be associated with brittle diabetes and longterm sudden death. Transplantation of the patient's own islet cells into the liver may offer a solution to this vexing problem.

Outcome in Chronic Pancreatitis

It is estimated that about 50% of patients with chronic pancreatitis die of their disease or of problems associated with alcoholism, diabetes, infection, or suicide within 20 to 25 years. Surgical treatment results in significant pain relief in about 75% of patients. Long-term results depend more on the patient's habits of drinking alcohol and using drugs than on the type of surgery performed.

PANCREATIC NEOPLASMS

Classification

Pancreatic neoplasms may be benign or malignant and may be derived from ductal cells, acinar cells, islet cells, or

TABLE 4.9. Classification of Pancreatic Neoplasms

Cell of origin	*Benign*	*Malignant*
Ductal cell	Adenoma Cystadenoma	Adenocarcinoma Cystadenocarcinoma
Acinar cell	Acinar cell adenoma Acinar cystadenoma	Acinar cell carcinoma Acinar cystadenocarcinoma
Mesenchymal cell	Fibroma Leiomyoma	Fibrosarcoma Leiomyosarcoma
Islet cell	Insulinoma Glucagonoma Gastrinoma Somatostatinoma VIPoma Islet adenoma	Insulinoma Glucagonoma Gastrinoma Somatostatinoma VIPoma Nonfunctioning islet cell carcinoma

mesenchymal cells. A working classification is given in Table 4.9.

Adenocarcinoma of the Pancreas

Adenocarcinoma accounts for 90% of pancreatic malignancy. The tumor is located in the head of the pancreas in two-thirds of cases. Unlike gastric cancer, the incidence of pancreatic cancer has been rising and now accounts for about 1 patient per 10,000 of the American population.[8] It is twice as common in men as in women. Dietary and occupational factors are believed to be associated with the higher incidence and include smoking; obesity, high-fat and high-protein diet; and exposure to benzidine, beta-naphthalene, and ethylene chloride. Mutation of K-ras genes is found in more than 85% of cases. Mutations of the $p16^{INK4}$ gene on chromosome 9p21 is also seen in pancreatic cancer. Surgical resection is the only hope for cure, but even then only 5% to 10% of patients survive for 5 years.[17] The essentials of management are summarized in Table 4.10 and pathological staging of pancreatic cancer is given in Table 4.11.

TABLE 4.10. Essentials: Cancer of the Pancreas

Clinical
- Pancreatic malignancies are 90% adenocarcinoma
- Clinical picture depends on tumor location
  - Head
    - Painless jaundice (>90%)
    - Weight loss and pain (>66%)
    - Hepatomegaly, sometimes Courvoisier's sign
  - Body and tail
    - Pain, weight loss
    - Migratory thrombophlebitis (5%–10%)

Diagnosis
- Ultrasound
  - Dilated biliary tree
  - Hypoechoic pancreatic mass in some cases
- CT scan
  - Visible mass if >2 cm
  - Dilatation of extrahepatic biliary tree
  - Liver and lymph node metastasis if present
  - Arterial phase may show hepatic artery invasion
  - CT-guided needle biopsy not recommended
- ERCP
  - May show biliary dilatation and pancreatic duct obstruction or encasement
  - Needle biopsy, brush cytology, pancreatogram possible
  - Biliary drainage with stent possible

Management: See algorithm, Figure 4.26

Long-term outcome
- Five-year survival after pancreaticoduodenectomy: 12%
  - Diploid tumors: 40%
  - Aneuploid tumors: <10%
  - Periampullary: 21%–56%

Abbreviations: CT, computerized tomography; ERCP, endoscopic retrograde cholangiopancreatography.

TABLE 4.11. TMN Staging of Exocrine Pancreatic Cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Source: Reprinted with permission from the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, Sixth Edition (2002) published by Springer-Verlag New York, www.springer-ny.com.

Clinical Presentation

The classical presentation depends on the location of the tumor. Tumors in the head of the pancreas tend to present earlier and are often associated with painless obstructive jaundice. Adenocarcinoma of the body and tail presents late, often with pain and weight loss but without jaundice. Migratory thrombophlebitis (Trousseau's sign) is seen in 5% to 10%, more commonly with adenocarcinoma of the body and tail.

In adenocarcinoma of the head of the pancreas, jaundice is present in more than 90% of patients; weight loss and abdominal pain are seen in more than two-thirds. Typically, abdominal pain radiates to the back in the region of T12–L1. Hepatomegaly is detectable in some 80% of patients, and the gallbladder may be palpable (Courvoisier's sign). Anorexia, nausea, and vomiting are also common.

Diagnosis

Abdominal ultrasonography is usually the first diagnostic test to be obtained. It shows extrahepatic obstruction with dilated common bile duct and gallbladder in more than 75% of patients. A hypoechoic pancreatic mass may or may not be seen. Abdominal CT is then obtained, and a mass is usually visible if the tumor is larger than 2 cm in diameter (Figure 4.23). Dilatation of the extrahepatic biliary tree is also seen. CT may show the presence of hepatic metastasis and regional lymphadenopathy. The arterial phase of dynamic CT scan is shown in Figure 4.24.

In the past, a direct diagnostic approach with CT-guided fine-needle aspiration biopsy was advocated. This procedure, however, is now known to cause peritoneal and abdominal wall tumor spread and is recommended only in patients in whom abdominal exploration is not contemplated. Magnetic resonance imaging (MRI) provides no advantage over CT, but endoscopic ultrasound may detect lesions less than 2 cm in diameter more reliably than CT.

ERCP is often performed and is indispensable in patients with obstructive jaundice in whom neither tumor nor stone is visualized. It facilitates the performance of needle aspiration biopsy, brush cytology, and pancreatogram when the findings are equivocal. Visualization of the pancreatic duct is possible in over two-thirds of patients (Figure 4.25). ERCP also allows the placement of a drainage stent to provide relief of obstructive jaundice.

Use of these imaging techniques has increased resectability rates from less than 25% to over 75%.[18]

Treatment

An algorithm showing how treatment should be managed for carcinoma of the head of the pancreas is given in Figure 4.26. The options depend on several factors, including resectability, the presence of metastasis, and whether or not the tumor can be visualized.

Inoperable Tumor Pancreatic cancer is inoperable if it is associated with clinical evidence of ascites or distant metastasis. Inoperability may also be indicated with imaging studies that demonstrate the presence of liver or abdominal metastasis and invasion of the portal vein. In these latter circumstances, metastasis and portal vein involvement should be confirmed by laparoscopy.

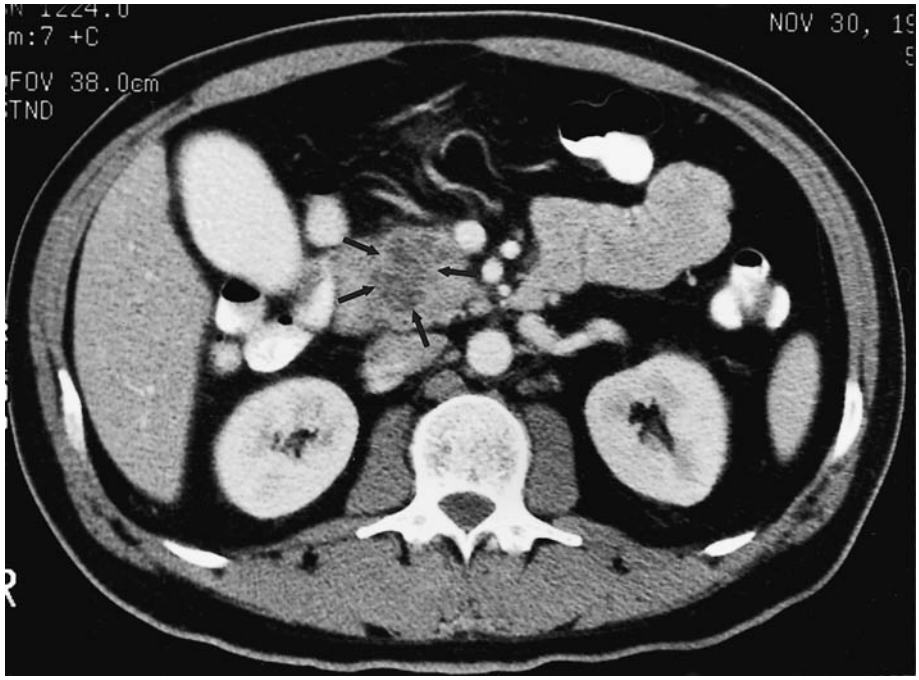


FIGURE 4.23. Abdominal CT can usually demonstrate pancreatic cancer if the mass is larger than 2 cm in diameter (arrows). (Courtesy of Henry I. Goldberg, MD.)

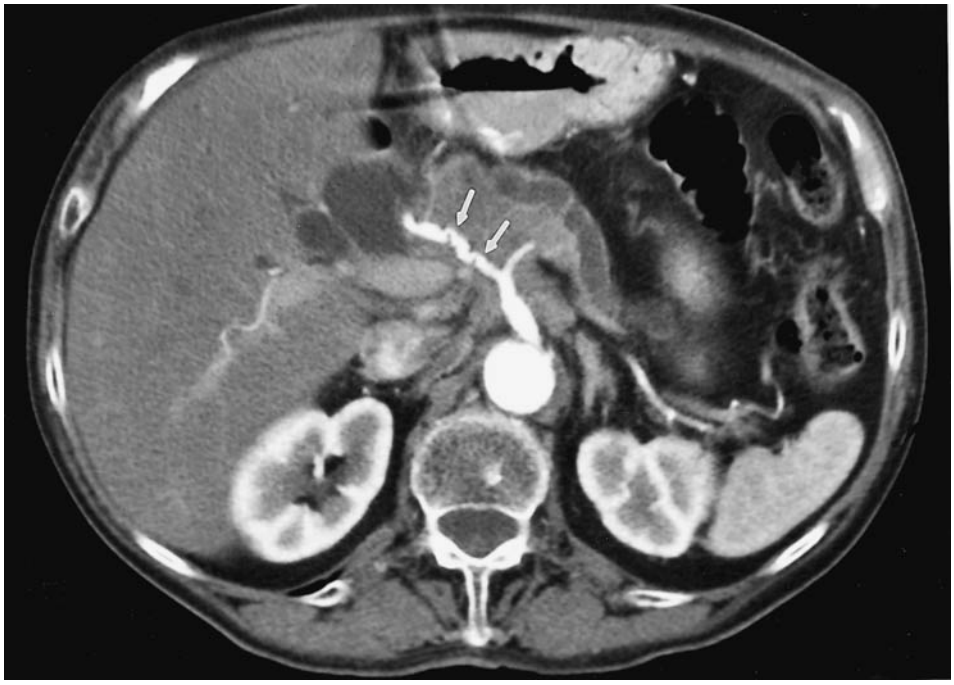


FIGURE 4.24. The arterial phase of dynamic CT scan may provide information about hepatic artery invasion (arrows) as well as portal vein involvement. (Courtesy of Henry I. Goldberg, MD.)

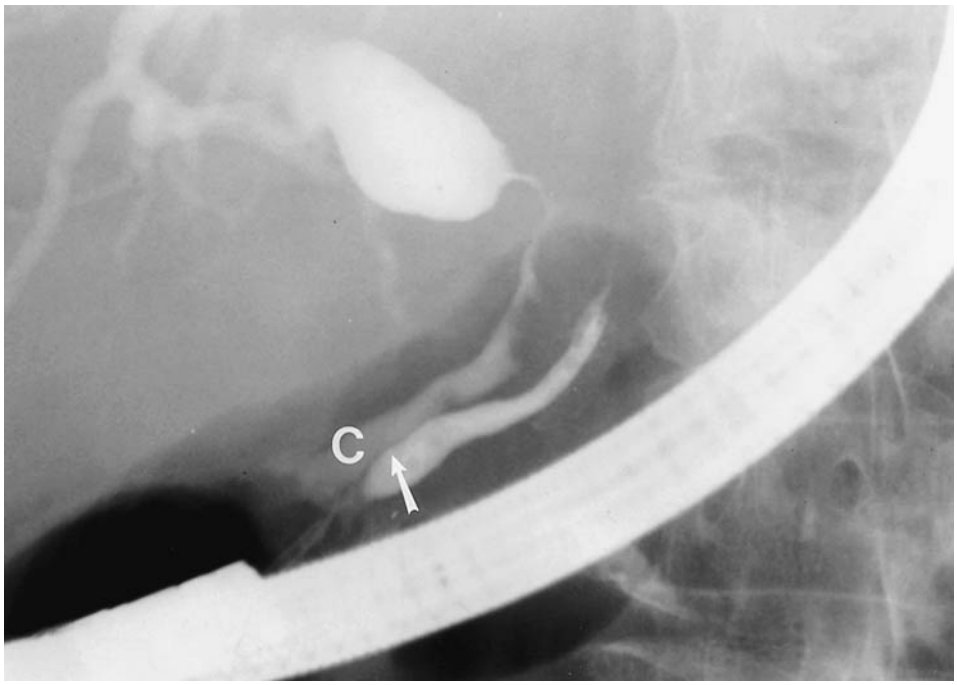


FIGURE 4.25. ERCP is useful in investigating pancreatic disease. The pancreatic duct can be visualized in more than two-thirds of patients. The usual findings are pancreatic duct obstruction or encasement (arrow). In this case, the common bile duct (C) is also obstructed. (Courtesy of Henry I. Goldberg, MD.)

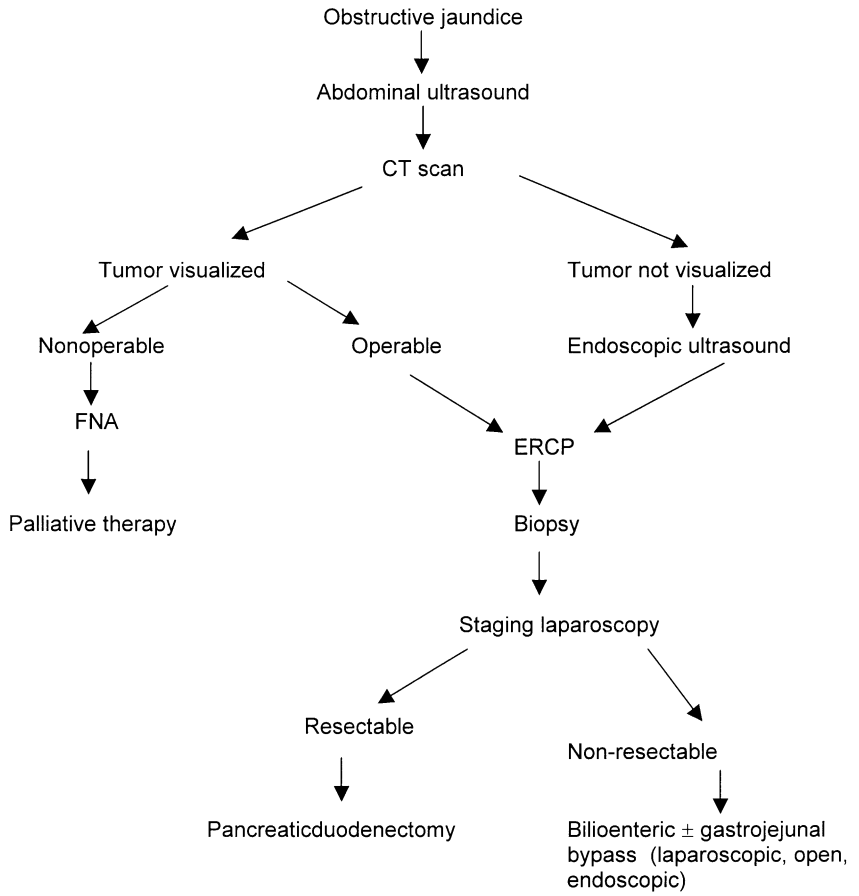


FIGURE 4.26. Algorithm for management of carcinoma of the head of the pancreas. *Abbreviations*: CT, computed tomography; FNA, fine needle aspiration; ERCP, endoscopic retrograde cholangiopancreatography.

If a patient's tumor is deemed nonresectable, palliation may be obtained with endoscopic or transhepatic biliary drainage using expandable stents or with operative biliary and gastric bypass performed either laparoscopically or with open abdominal operation. Although endoscopic and surgical bypass are equally effective in the short term, surgical bypass is associated with a lower incidence of recurrent jaundice and cholangitis. Following biliary bypass alone, 15% to 20% of patients develop duodenal obstruction.[19] Another advantage of surgical palliation is that gastric bypass can be done in addition to biliary bypass. Radiation and chemotherapy are relatively ineffective in providing palliation and, in any individual patient, the benefits must be compared with the side effects.

Resectable Tumor Patients with no demonstrable hepatic metastasis or other evidence of spread are candidates for pancreaticoduodenectomy. Resectability is determined during surgical exploration when the following are demonstrated:

1. The portal and superior veins are not invaded by tumor, and a tunnel can be developed anterior to these vessels and behind the head of the pancreas.
2. The tumor is not fixed to surrounding organs.
3. The transverse mesocolon is free of invasion.
4. No hepatic metastasis is demonstrated by palpation and intraoperative ultrasound.
5. There is no tumor deposit in lymph nodes that cannot be encompassed in en bloc excision.

Surgical Procedures Three types of resection are possible: the classic Whipple pancreaticoduodenectomy (Figure 4.27), pylorus-preserving pancreaticoduodenectomy, and total pancreatectomy. Regional pancreatectomy, in which the portal vein is resected and replaced with a vein graft, has not improved survival.

Although there is concern about the adequacy of resection when pylorus-preserving pancreaticoduodenectomy is performed, this operation is associated with better nutritional status than the classic Whipple procedure. Postoperative delayed gastric emptying, however, is more common. The macrolide antibiotic erythromycin is useful in improving gastric emptying after pancreaticoduodenectomy.

Total pancreatectomy has no survival advantage and is associated with a higher mortality rate and a higher incidence of brittle diabetes than the Whipple procedure. Its use may be indicated, however, in the following clinical situations:

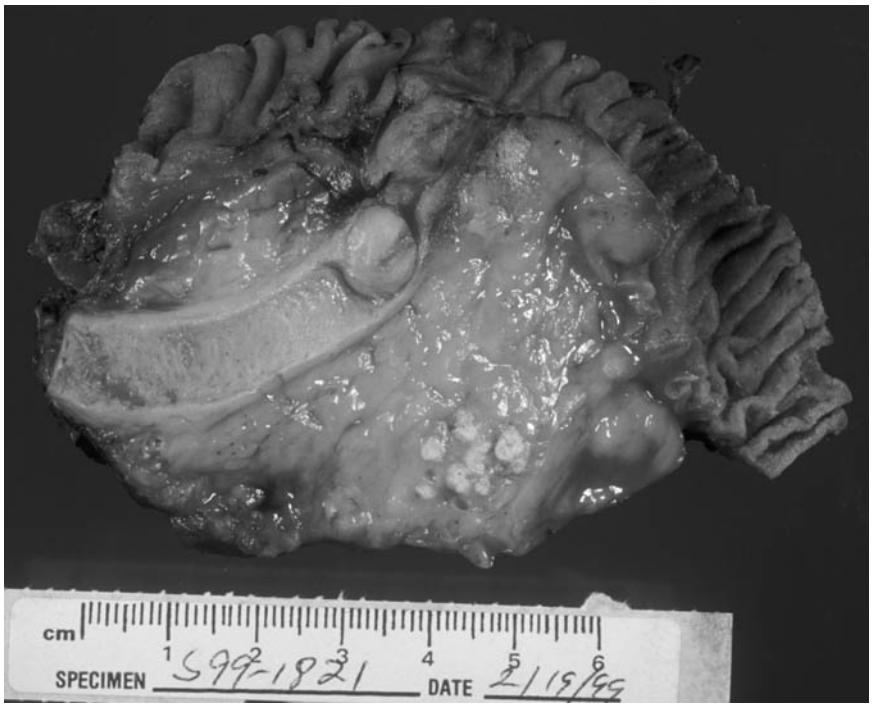


FIGURE 4.27. A Whipple resection specimen of ampullary carcinoma shows a polypoid lesion in the ampullary region obstructing the common bile duct. (Courtesy of Linda D. Ferrell, MD.)

1. The pancreas is so friable that it is unsuitable for anastomosis.
2. Frozen section reveals the presence of tumor at the resection line.
3. Diffuse involvement of the entire pancreas is present.
4. The patient already has insulin-dependent diabetes.

The operative mortality rate for pancreaticoduodectomy is now below 5% and in some centers below 2%, but this low mortality rate appears to be achieved only in hospitals where significant numbers of these procedures are performed.

Long-Term Outcome

The 5-year actuarial survival rate after pancreaticoduodenectomy is 12%.[17] The prognosis is better in small, well-differentiated and node-negative tumors, and the DNA content of the tumor cells has a significant implication. The 5-year survival rate of patients whose tumor cells are diploid is nearly 40% but less than 10% in those with aneuploid cells.

The 5-year survival rate is higher in periampullary tumors (21%–56%) than in tumors of the head of the pancreas.[8] Among periampullary tumors, duodenal tumor has the best prognosis.

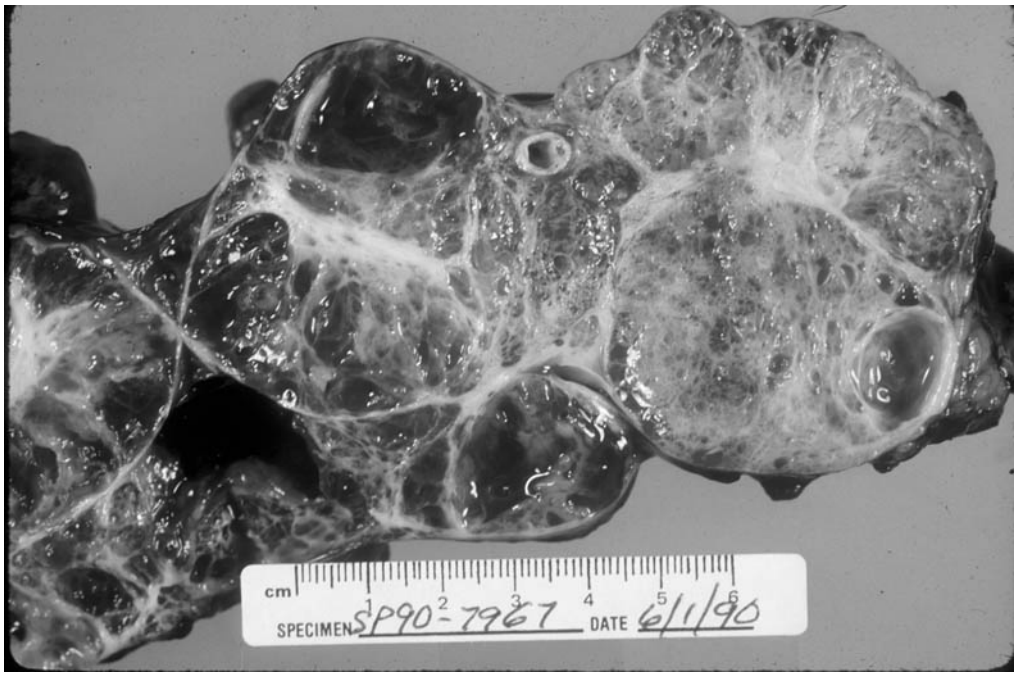
The overall prognosis of pancreatic cancer is dismal; only 10% of patients are alive 12 months after the diagnosis is made.[17]

Cystic Neoplasms of the Pancreas

Cystic neoplasms of the pancreas account for 1% of all pancreatic cancers and for 10% of all cystic lesions of the pancreas (Figure 4.28). They may be mucinous (50%), cystadenoma (30%), and neuroendocrine (20%). A resected specimen of mucinous cystadenoma is shown in Figure 4.29. They can develop without eliciting many symptoms, and the only symptom they do produce is usually vague upper abdominal pain. They frequently grow to large sizes and can reach 25 cm in diameter.

The important clinical challenge is distinguishing the cystic neoplasms from benign pseudocysts (Figure 4.30). A history of pancreatitis, increased serum amylase levels, and CT findings of pancreatitis are helpful in suggesting the diagnosis of benign pseudocyst. When presumed pseudocysts recur after cyst-gastric or cyst-enteric drainage, a cystic neoplasm must be excluded. The best strategy is to routinely obtain biopsy samples of the wall of a pseudocyst when a drainage procedure is being performed.

All cystic tumors of the pancreas are potentially malignant and should be resected.



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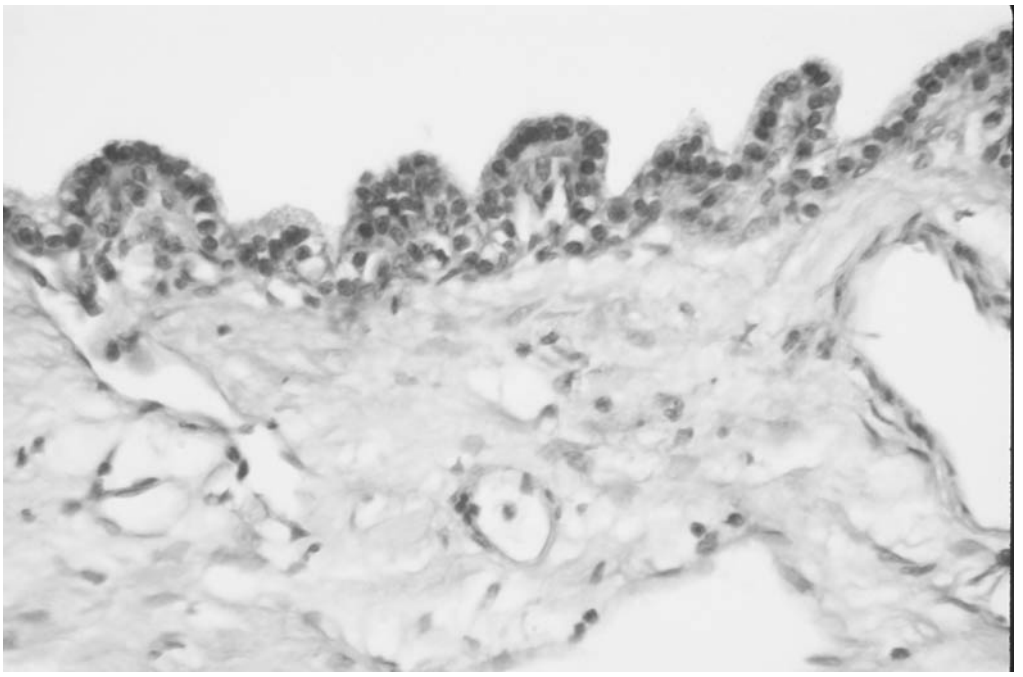

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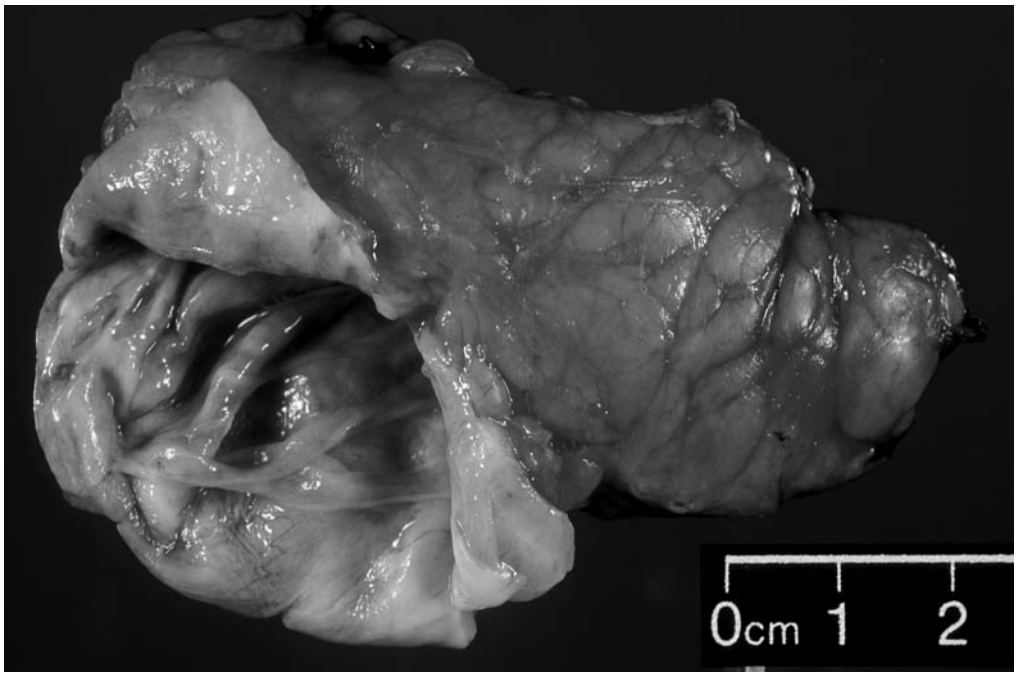
FIGURE 4.28. (A) Gross appearance of serous cystadenoma, also known as microcystic adenoma. (B) The typical microscopic feature is glycogen-containing cuboidal epithelial cells lining the wall of the cysts. The tumor tends to occur in the tail of the pancreas and is often benign. (Courtesy of Linda D. Ferrell, MD.)



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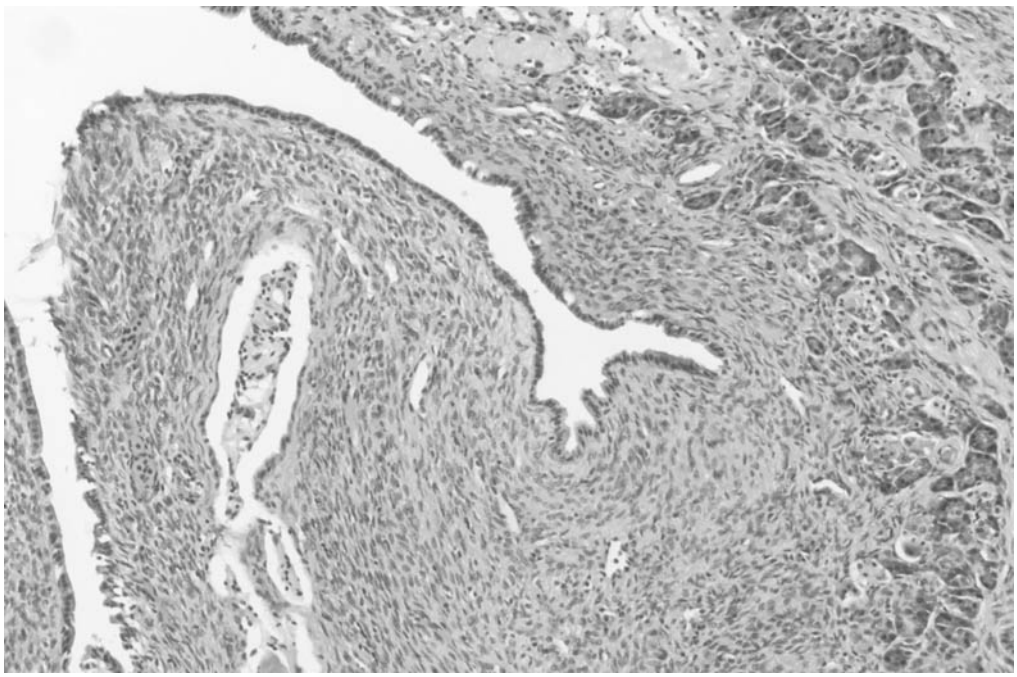

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FIGURE 4.29. (A) Pancreas resection specimen from a large mucinous cystadenoma was opened to show the trabeculated cyst lumen. (B) Microscopically, the cyst wall shows ovarian-type stroma. This rare tumor tends to occur more commonly in women. (Courtesy of Linda D. Ferrell, MD.)

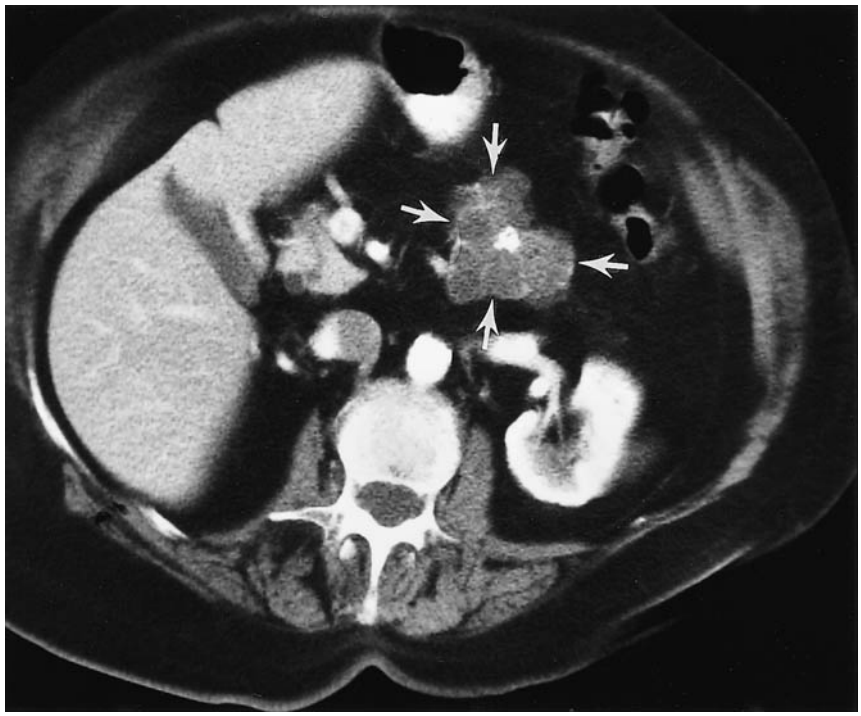

FIGURE 4.30. Cystic neoplasm. In patients with a history of pancreatitis, increased serum amylase levels, and CT findings characteristic of pancreatitis, such lesions are suggestive of benign pseudocyst. Neoplasm can be ruled out definitively with biopsy. These cystic neoplasms have septa and some have central calcification (arrows). (Courtesy of Henry I. Goldberg, MD.)

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