The pancreas was one of the last organs in the abdomen to receive the critical attention of anatomists, physiologists, physicians, and surgeons. It was first referred to as the "finger of the liver" in the Talmud, written between 200 BC and 200 AD. Galen named it (though Ruphos, circa 100 AD, should probably be credited), and thought the pancreas served to support and protect blood vessels. Vesalius considered the organ a cushion for the stomach. Little further information was available until Wirsung demonstrated the pancreatic ducts of humans in 1642 and de Graaf discovered pancreatic secretion from the pancreatic fistula of dogs in 1664.

The digestive action of pancreatic secretions was discovered almost 200 years later. Eberle in 1834, Purkinje and Pappenheim in 1836, and Valentin in 1844 observed the emulsification of fat, proteolytic activity, and digestion of starch, respectively, by pancreatic juice and extracts. Bernard subsequently demonstrated the digestive action of pancreatic juice on sugar, fats, and proteins, using secretions from pancreatic fistula preparations.

Kuhne introduced the term enzyme and isolated trypsin in 1876. The concept of enzymes led shortly to the identification of pancreatic amylase and lipase. In 1889, Chepovalnikoff, a student of Pavlov, discovered enterokinase in the duodenal mucosa, an enzyme that is essential for activation of the proteolytic enzymes. Another of Pavlov's students, Dolinsky, stimulated pancreatic secretion by instilling acid into the duodenum in 1895. This led to the discovery of secretin by Bayliss and Starling, which proved to be not an enzyme but the first hormone to be identified.

The histologic structure of the pancreas was first described in 1869 by Langerhans. Shortly thereafter, Heidenhain characterized the periodic postprandial changes that occurred in the histology of the canine pancreas. He found that as the granular regions of cells disappeared after feeding, the enzyme activity in pancreatic juice increased; he concluded that the granules contained the precursors of the digestive enzymes.

Pancreatic disease was rarely recorded before the 19th century. Friedreich wrote the first systematic description of pancreatic diseases in 1875. The description of acute pancreatitis by Fitz in 1889 remains a classic. Although Fitz suggested surgery for pancreatitis, surgery for pancreatic neoplasms and other diseases did not become popular until the 1930s, when it did so mainly as a result of the work of Whipple and Brunschwig.

ANATOMY

The pancreas is a soft, elongated, flattened gland 12 to 20 cm in length. The adult gland weighs between 70 and 110 g. The head lies behind the peritoneum of the posterior abdominal wall and has a lobular structure. The pancreas is covered with a fine connective tissue but does not have a true capsule. The head of the pancreas is on the right side and lies within the curvature of the duodenum. The neck, body, and tail of the pancreas lie obliquely in the posterior abdomen, with the tail extending as far as the gastric surface of the spleen.
The second and third duodenum curvatures lie around the head of the pancreas. The anterior surface of the head of the pancreas is adjacent to the pylorus, the first part of the duodenum, and the transverse colon. The posterior surface abuts the hilus and medial border of the right kidney, the inferior vena cava and the right renal vessels, the right gonadal vein, and the right crus of the diaphragm.

The uncinate process is a prolongation of pancreatic tissue of variable size and shape. It projects off the lower part of the head of the pancreas, extending upward and to the left. The uncinate
process lies anterior to the aorta and inferior vena cava and is covered superiorly by the superior mesenteric vessels that emerge below the neck of the pancreas. There is much variation in the uncinate process, which may even be absent altogether.

The neck of the pancreas is a constricted part of the gland extending from the head of the pancreas toward the left, joining the head with the body of the pancreas. It is 1.5 to 2.0 cm long and 3.0 to 4.0 cm wide. Posterior to the neck of the pancreas lies the confluence of the portal vein with the superior mesenteric and splenic veins. Anteriorly it is covered in part by the pylorus and peritoneum of the lesser sac. The neck extends to the right as far as the anterosuperior pancreaticoduodenal artery from the gastroduodenal artery.

The body of the pancreas runs toward the left side, anterior to the aorta. It is retroperitoneal and held against the aorta by the peritoneum of the lesser sac. The anterior surface of the body is covered by peritoneum of the omental bursa that separates the stomach from the pancreas. The antrum and body of the stomach and the transverse mesocolon contact the body anteriorly. Posterior to the body of the pancreas are the aorta, the origin of the superior mesenteric artery, the left crus of the diaphragm, the left kidney, the left adrenal gland, and the splenic vein. The midline part of the body overlies the lumbar spine, which makes this area of the pancreas most vulnerable to abdominal trauma.

The body passes laterally and merges with the tail of the pancreas without a discernible junction point. The tail is relatively mobile, its tip usually reaching the hilus of the spleen. With the splenic artery and vein, the tail is contained between the two layers of the splenorenal ligament. The splenocolic ligament attaches the splenic flexure of the colon to the spleen and brings it near the tail of the pancreas. The relationship of the pancreas to important structures in the posterior abdomen is seen in Figure 53-2.
The distal end of the common bile duct, the duodenum, and the head of the pancreas form a unit. The common bile duct is located to the right of the gastroduodenal artery in the posterior wall of the duodenum. The bile duct passes through the substance of the pancreatic head, usually to join with the main pancreatic duct for some distance to reach the duodenal papilla (Fig. 53-34).
Figure 53-3  Anatomic arrangement of the pancreatic duct system. A, The most common arrangement. Most of the pancreatic secretion empties into the duodenum along with bile through the major papilla. The proximal portion of the embryonic dorsal pancreatic duct remains patent in about 70% of adults and empties through the accessory papilla. B, Pancreas divisum. The embryonic dorsal and ventral ducts fail to fuse. Most of the pancreatic secretion empties through the accessory papilla. Only pancreatic secretions from the uncinate process and part of the head of the pancreas (which are derived from the embryonic ventral pancreas) drain through the duodenal papilla.
The main pancreatic duct (of Wirsung) begins near the tail of the pancreas. It is formed from anastomosing ductules draining the lobules of the gland. It courses left to right and is enlarged by additional ducts. Through the tail and body, the duct lies midway between the superior and inferior margins and slightly posterior. The main duct turns caudal and posterior on reaching the head of the pancreas. At the level of the major papilla, the duct turns horizontally to join usually with the common bile duct (see Fig. 53-3A). This short common segment is the ampulla of the bile duct, which terminates in the duodenal papilla.

The relationship of the common bile duct and the duct of Wirsung at the papilla is complex. The ducts may open separately at the ampulla and have an interposed septum or may have a common channel. A common channel for bile and pancreatic secretion is ordinarily formed by the absence of a septum between the biliary and pancreatic ducts as they approach the ampulla of Vater. In adults studied by endoscopic retrograde cholangiopancreatography (ERCP), the length of the common channel averages 4.5 mm, with a range of 1 to 12 mm. In various series, more than two thirds of patients had some degree of a common channel.

The accessory pancreatic duct of Santorini is frequently present and usually communicates with the main duct (see Fig. 53-3A). The accessory duct lies anterior to the bile duct and usually drains into the minor papilla, which lies proximal to the ampulla of Vater in the second duodenum. The accessory duct is patent in 70% of autopsy specimens. In about 10% of individuals there is no connection between the accessory duct and the main duct. A number of variations in the two pancreatic ducts may be encountered.

The greatest diameter of the main pancreatic duct is in the head of the pancreas, and the duct gradually tapers, progressing to the tail of the pancreas. The main duct ranges from 3.1 to 4.8 mm in the head of the pancreas and tapers to 0.9 to 2.4 mm in the tail. Specific normal limits of pancreatic duct diameter in the head (4 to 5 mm), body (3 to 4 mm), and tail (2 to 3 mm) are generally accepted. However, studies have shown an increase in pancreatic duct size with age and pancreatic disease.

CIRCULATION

The pancreas has a rich circulation derived from branches of the celiac and superior mesenteric arteries. The head of the pancreas and surrounding duodenum are supplied by two pancreaticoduodenal arterial arcades. They are formed by the anterior and posterior superior pancreaticoduodenal arteries from the hepatic branch of the celiac artery that join a second pair of anterior and posterior inferior pancreaticoduodenal arteries.

The gastroduodenal artery arises off the common hepatic branch of the celiac artery. It divides to form the anterior and posterior superior pancreaticoduodenal arteries. The anterior superior pancreaticoduodenal artery lies on the surface of the pancreas. It provides branches to the anterior surface of the duodenum, proximal jejunum, and pancreas. The artery enters the substance of the pancreas and, on the posterior surface, joins the anteroinferior pancreaticoduodenal artery from the superior mesenteric artery. The anteroinferior pancreaticoduodenal artery arises from the
superior mesenteric artery by the inferior margin of the pancreatic neck. The posteroinferior pancreaticoduodenal artery arises from the gastroduodenal artery. Its course is visible on the posterior surface of the pancreas, and branches may join with branches of the gastroduodenal artery or with a branch of the dorsal pancreatic artery. It passes posterior to the pancreatic portion of the bile duct. At the neck, the dorsal pancreatic artery usually arises from the splenic artery. From this, a right branch supplies the head and usually joins the posterior arcade. It also gives off one or two left branches that pass through the body and tail of the pancreas, often making connections with branches of the splenic artery and a more distal connection with the splenic or the left gastroepiploic artery. All major arteries lie posterior to the ducts.

The course of the splenic artery is posterior to the body and tail and loops above and below the superior margin of the pancreas. It gives off the dorsal pancreatic artery, which usually joins one of the posterior superior arcades after giving off the inferior pancreatic artery.

The caudal pancreatic artery arises from the left gastroepiploic artery or from a splenic branch at the spleen. It joins with branches of the splenic and great pancreatic arteries and other pancreatic arteries.

In general, the venous drainage of the pancreas is similar to the arterial blood supply. It flows into the portal venous system, which is formed by the joining of the superior mesenteric and splenic veins at the confluence behind the neck of the pancreas. The portal vein lies behind the pancreas and in front of the inferior vena cava, with the common bile duct to the right and the hepatic artery to the left. The splenic vein originates at the hilum of the spleen and curves behind the tail of the pancreas and below the splenic artery, to the right along the posterior surface of the pancreas. The pancreatic veins drain the neck, body, and tail of the pancreas and join the splenic vein. The pancreaticoduodenal veins lie close to their corresponding arteries and empty into the splenic or portal veins. Because of the close anatomic relationship of the splenic vein with the pancreas, inflammatory or neoplastic diseases involving the pancreatic body and tail can lead to splenic vein occlusion. This in turn can result in retrograde venous drainage toward the splenic hilum and then, by way of flow through the short gastric and left gastroepiploic veins, can create gastric varices.

LYMPHATIC DRAINAGE

The lymphatics, in general, drain the surface network of lymph toward regional nodes and are formed near the larger blood vessels. The superior lymphatic vessels run along the upper border of the pancreas closely with the splenic blood vessels. Those on the left side of the body and tail empty into nodes in the splenic hilum. Those on the right side of the body and the pancreatic neck empty into nodes near the upper border of the head. They also receive tributaries from the anterior and posterior pancreatic surfaces. The inferior lymphatic vessels run with the inferior pancreatic artery. Those that drain the lower left side of the body and tail drain toward nodes in the splenic hilum. The remaining regions of the neck and body drain toward the right.

Lymphatic vessel drainage of the pancreatic head is composed of an anterior system and a posterior system. These vessels generally occupy the grooves between the head of the pancreas and the duodenum, near the pancreaticoduodenal blood vessels. Each drainage system (anterior and posterior) also has superior and inferior drainage systems. In addition, a set of lymphatics also
drains the upper portion of the head, lying on the superior border. The lymphatic drainage of the
head of the pancreas and duodenum eventually flows into the celiac and superior mesenteric
groups of pancreatic nodes and into the cisterna chyli. The lymphatics of the tail drain into splenic
hilar nodes. The lymphatics of the body pass to the pancreaticosplenic nodes lying along the
superior border, which drain into celiac nodes. Lymphatics of the upper head of the pancreas pass
through subpyloric nodes. Inferiorly, lymphatics drain into retropancreatic and antepancreatic
nodes, which then drain into superior mesenteric nodes.

INNERVATION

The visceral efferent innervation of the pancreas is through the vagi and splanchnic nerves by way
of the hepatic and celiac plexuses. The efferent fibers of the vagi pass through these plexuses
without synapsing and terminate in parasympathetic ganglia found in the interlobular septa of the
pancreas. The postganglionic fibers innervate acini, islets, and ducts. The bodies of the neurons of
the sympathetic efferent nerves originate in the lateral gray matter of the thoracic and lumbar spinal
cord. The bodies of the postganglionic sympathetic neurons are located in the great plexuses of
the abdomen. Their postganglionic fibers innervate only blood vessels. The autonomic fibers, both
efferent and afferent, are located in proximity to the blood vessels of the pancreas. Little is known
about the distribution of the visceral efferent fibers in humans. They probably run through the
splanchnic nerves to the sympathetic trunks and rami communicantes and through spinal nerves
and ganglia. The vagi also carry some visceral afferent fibers.

HISTOLOGY AND ULTRASTRUCTURE

The pancreas is a compound, finely nodular gland that is grossly similar to but less compact than
the salivary glands. It is surrounded by fine connective tissue but does not have a fibrous tissue
capsule. The lobules are visible on gross examination and are connected by connective tissue
septa that contain the blood vessels, nerves, lymphatics, and excretory ducts (constituting about
18% of this organ). The gland is a mixed exocrine (about 80%) and endocrine (about 2%) organ
(Fig. 53-4). The endocrine portion consists of the islets of Langerhans, which are spherical
clusters of light-staining cells scattered throughout the pancreas (see Chapter 1). The exocrine
portion consists of numerous dark-staining acini composed of tubular and spherical masses of cells,
which are the subunits of the lobule. Silicone casts of the duct lumen formed by retrograde
injection indicate that the tubular portions of the acini are extensive and that the exocrine cells are
arranged primarily as curved, branching tubules that anastomose and end blindly (Fig. 53-5).
Figure 53-4  Histologic section of human pancreas obtained at autopsy shows dense-staining acinar cells and a light-staining islet of Langerhans just left of the center of the field. A small duct is visible on the left side of the illustration (9 o'clock position). Hematoxylin-eosin stain; ×140.
The lumen of the acinus is the origin of the secretory duct and contains centroacinar cells, which are unique to the pancreas. These cells are pale staining in histologic sections and smaller than the acinar cells. The lumen of the acinus leads into the intralobular ducts, which are covered by low columnar epithelial cells similar in appearance to the centroacinar cells. These ducts are nonstriated and anastomose to form the interlobular ducts, which are lined by a columnar epithelium (see Fig. 53-4). Goblet cells and occasional argentaffin cells also are present. The interlobular ducts anastomose to become the main pancreatic duct. The larger ducts have a somewhat thick wall consisting of connective tissue and elastic fibers. Acinar, ductal, and islet cells can be distinguished by monoclonal antibodies specifically reactive with these cell types.
Acinar cells are tall, pyramidal or columnar epithelial cells, with their broad bases on a basal lamina and their apices converging on a central lumen (Fig. 53-6). In the resting state, numerous eosinophilic zymogen granules fill the apical portion of the cell. The basal portion of the cells contains one or two centrally located, spherical nuclei and extremely basophilic cytoplasm. The Golgi complex lies between the nucleus and zymogen granules and can be seen as a clear, nonstaining region (see Fig. 53-6).

Figure 53-6  Photomicrograph of a human acinus, showing acinar and centroacinar cells. The acinar cell ergastoplasm, Golgi complex, and zymogen granules can be easily identified. Formalin stain, osmium fixation. Epon-embedded section, toluidine blue stain; ×3200.  (From Bloom W, Fawcett DWA: Textbook of Histology, 11th ed. Philadelphia, WB Saunders, 1986. Courtesy of Susumu Ito, MD.)

The acinar cells undergo cyclic changes in morphology in response to feeding and digestion. After a large meal, the zymogen granule content of the cells is depleted. This apparently occurs by a decrease in both the size and the number of granules. After depletion of the granules, the Golgi apparatus may be observed at the apex of the cell and appears more extensive than in the resting state. The reductions in size and number of granules occur with a substantial increase in pancreatic enzyme secretion (see Chapter 54).
The subcellular structure of the acinar cells can be visualized at the electron-microscopic level (Fig. 53-7). The acinar cell has several short, slender microvilli about 0.2 µm in length that extend into the lumen of the acinus. The lumen typically contains flocculent electron-dense material, which presumably is the secreted digestive enzymes. Thin filaments form the axis of the microvilli as well as a network beneath the apical plasmalemma. These microfilaments apparently play a structural role because their disruption causes expansion of the acinar lumen and loss of microvilli. Adjacent cells are joined at the apical surface by electron-dense intercellular junctions. Tight junctions form a belt-like band around the apical end of the cell and are produced by the apposition of the external membrane leaflets of neighboring cells. These junctions prevent the reflux of secreted substances from the duct into the intercellular space. Gap junctions are distributed on the lateral cellular membranes and are formed by the apposition of larger, disk-shaped membrane plaques. They allow communication between cells. Below the junctions, the lateral cell borders are relatively straight and have a few, small interdigitations. Pancreatic lateral cell membranes display unique antigenic determinants that are not found on apical cell membranes.
The nucleus usually is spherical, about 6 µm in diameter, with one or more nucleoli in the interior and patches of dense heterochromatin along the inner nuclear membrane. Numerous conspicuous nuclear pores are located at regions where the lightly stained euchromatin makes contact with the nuclear membrane. These pores presumably are the sites where messenger and transfer RNAs are transported out of the nucleus into the cytoplasm. Binucleate cells also are seen occasionally.

Mitochondria are elongate, cylindrical structures that may appear oval in cross-section and may contain well-developed cristae and many matrix granules. They occur throughout the cytoplasm, among the granular endoplasmic reticulum or zymogen granules, and adjacent to the basolateral cell border. The cytoplasmic matrix occupies about 45% of the cell volume.

Granular endoplasmic reticulum (see Fig. 53-7) occupies about 20% of the cell volume and fills most of the basal region of the acinar cells, although small amounts also occur in the apical region adjacent to and among the zymogen granules. This reticulum is composed of numerous parallel cisternal membranes covered with closely spaced attached ribosomes, giving the structures a granular appearance. On the basis of studies with laboratory animals, the ribosomes of the granular endoplasmic reticulum have been found to be the site of protein synthesis.

The Golgi complex is located between the nucleus and the mass of zymogen granules present in the resting gland (see Fig. 53-7). It consists of flattened, membranous sacs as well as small vesicles or vacuoles that contain flocculent electron-dense material. The Golgi sacules have been distinguished from other intracellular vesicles by enzyme cytochemistry and by immunohistochemistry using antienzyme and antireceptor antibodies. The Golgi complex is believed to play an important role in the transport of secretory proteins and the formation of zymogen granules. The mechanisms by which these processes occur are still unresolved.

The secretory granules of the pancreas usually are divided into two types, electron-lucent condensing vacuoles and electron-dense zymogen granules. The condensing vacuoles are typically seen in the vicinity of the Golgi complex and, on the basis of autoradiographic data, are believed to be precursors of the zymogen granules. They are membrane-bound vesicles slightly larger than zymogen granules and much less numerous, occupying only about 2% of the cytoplasm. Zymogen granules also are spherical, membrane-bound vesicles, slightly less than 1 mm in diameter, filled with electron-dense material that apparently represents the digestive enzymes (see Fig. 53-7).
Studies of the chemical composition of the zymogen granules have shown that they contain about 12 to 15 different digestive enzymes, which make up about 90% of the granule protein. Each granule apparently contains the entire complement of secreted digestive enzymes, because labeled antibodies to several different enzymes have been located over single zymogen granules from different cells. Individual zymogen granules can differ markedly in the concentration of specific digestive enzymes contained within the granules. The digestive enzymes within the granules are apparently not in solution or suspension but in a solid-state array, which exhibits specific binding between the enzymes themselves and between the enzymes and the granule membrane. Isolated zymogen granules are stable at slightly acid pH; at alkaline pH, they release their enzymes into solution. This behavior may account for the solubilization of digestive enzymes within the alkaline duct lumen.

Along the basal surface of the acinar cells, but not extending between adjacent cells, is a thin basal lamina, below which are collagen fibers and a rich capillary network. Efferent nerve fibers, derived from the sympathetic and parasympathetic systems, penetrate the basal lamina and terminate adjacent to the acinar cells.

The centroacinar cells (Fig. 53-8) and duct cells have electron-lucent cytoplasm containing few cytoplasmic organelles or specializations. They typically contain free ribosomes and small, round mitochondria. They contain virtually no granular endoplasmic reticulum and, therefore, are not active in protein synthesis for secretion. Farther down the ducts, the cells contain more mitochondria, but they are never associated with invaginations of the basolateral surface as occur in the transporting ductal epithelium of the salivary glands. Both centroacinar and duct cells apparently secrete bicarbonate and water. Carbonic anhydrase, the enzyme responsible for formation of bicarbonate, has been demonstrated in the epithelium.
Figure 53-8  Electron micrograph of a centroacinar cell (C) and several acinar cells (A). Note the electron-lucent cytoplasm, scattered mitochondria, and lack of other membranous organelles in the centroacinar cell. L, lumen of the acinus. ×9000.  (Courtesy of Susumu Ito, MD.)

The islets of Langerhans number about 1 million in the human pancreas and consist of anastomosing cords of polygonal endocrine cells (see Fig. 53-4). Each islet is about 0.2 mm in diameter, much larger than an acinus, and separated from the surrounding exocrine tissue by fine connective tissue fibers, which are continuous with those of the exocrine gland.
Each islet is surrounded and penetrated by a rich network of capillaries lined by a fenestrated endothelium. The capillaries are arranged in a portal system that conveys blood from the islets to acinar cells (Fig. 53-9). This insula-acinar portal system consists of afferent arterioles that enter the islet, form a capillary glomerulus, and leave the islet as efferent capillaries passing into the exocrine tissue. A parallel arterial system supplies blood directly to the exocrine pancreas (see Fig. 53-9), and yet this portal system permits the local action of islet hormones, especially insulin, on the exocrine pancreas. Acinar cells surrounding islets of Langerhans, termed peri-insular acini, are morphologically and biochemically different from acini situated farther away (tele-insular acini). Peri-insular acini have larger cells, nuclei, and zymogen granule regions and different ratios of specific digestive enzymes.

Figure 53-9  Schematic diagram of the insuloacinar portal system, illustrating the dual blood supply to the exocrine pancreas. (From Goldfine ID, Williams JA: Receptors for insulin and CCK in the acinar pancreas: Relationship to hormone action. Int Rev Cytol 85:1, 1983.)

Although the acinar cell secretes several different digestive enzymes in the exocrine pancreas, each cell type in the endocrine pancreas appears to secrete a single hormone. The four major types of cells found are B cells, A cells, D cells, and PP cells. B cells (beta cells), the most
numerous (50% to 80%), secrete insulin. Alpha cells or alpha cells (5% to 20%) secrete glucagon. PP (pancreatic polypeptide) cells (10% to 35%) secrete pancreatic polypeptide. D cells (5%) secrete somatostatin. Other rare cell types occur in the islet. In humans, the islets are subdivided into units, each of which exhibits a central aggregation of B cells surrounded by varying numbers of peripherally located cells that secrete the other hormones.