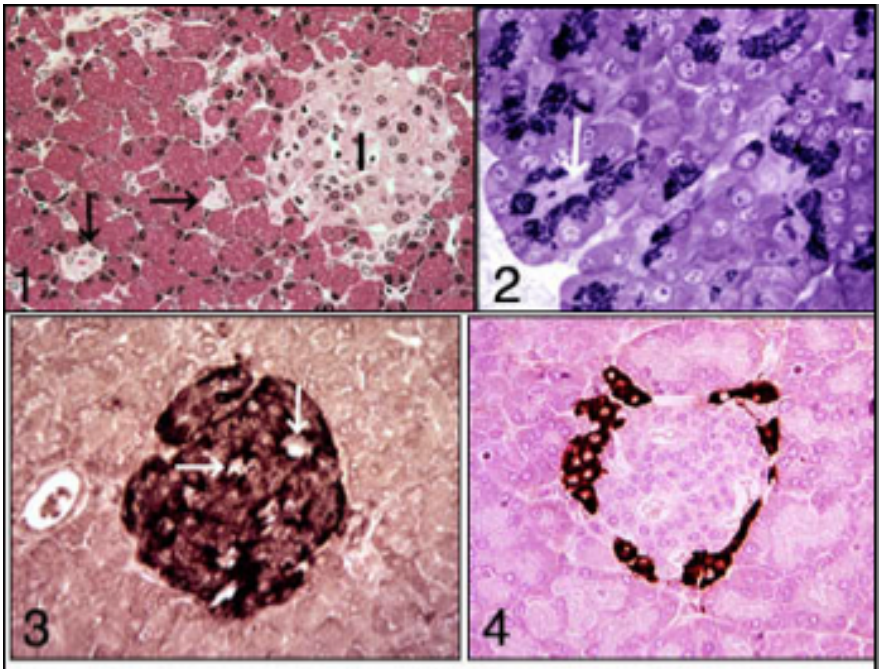
Pancreas



1. A region of pancreas showing an islet (I), pancreatic acini, and elements of the intralobular duct system (arrows).
2. Pancreatic acini. Note the centroacinar cells (arrow) within the acinus to the left.
3. A section of pancreas treated immunohistochemically to demonstrate insulin (black). Note the intense staining reaction next to capillaries (arrows)
4. A section of pancreas treated immunohistochemically to demonstrate glucagon (black).

The pancreas is the second largest gland associated with the gastrointestinal tract. In humans it is a retroperitoneal organ, 20 to 25 cm long, extending transversely from the duodenum across the posterior abdominal wall to the spleen. Macroscopically it consists of a head that lies in the C-shaped curve of the duodenum, a slightly constricted neck, and a body that forms the bulk of the pancreas. It lacks a definite capsule but is covered by a thin layer of areolar connective tissue that extends delicate septa into the substance of the pancreas and subdivides it into numerous small lobules. Blood vessels, nerves, lymphatics, and excretory ducts course through the septa. The major excretory duct runs the length of the pancreas, collecting side branches along its course. The major pancreatic duct and its branches have the general appearance of a fish backbone and gives some internal structural support to this gland. The pancreas consists of an exocrine portion, which elaborates numerous digestive enzymes and bicarbonate, and an endocrine portion, whose secretions are important in carbohydrate metabolism. Unlike the liver, the exocrine and endocrine functions of the pancreas are performed by different groups of cells.

Exocrine Pancreas

The exocrine pancreas is a large, lobulated, compound tubuloacinar gland in which the secretory units are tubular or flask-shaped. A delicate network of reticular fibers surrounds each secretory unit and forms the supporting stroma. Each acinus consists of a single layer of

large pyramidal cells whose narrow apices border on a lumen, while their broad bases lie on a thin basement membrane. A single, spherical nucleus is located near the base of the acinar cell, and one or more nucleoli may be present. The basal and perinuclear cytoplasm is filled with granular endoplasmic reticulum and mitochondria. Extensive Golgi complexes occupy the supranuclear region and are associated with forming zymogen granules. Mature zymogen granules are large, spherical, homogeneous structures that are limited by a membrane and often fill the apical cytoplasm. The pancreatic acinar cell, as indicated by its morphology, is actively involved in the synthesis and release of proteins (enzymes). Digestive enzymes of the pancreas are synthesized in the granular endoplasmic reticulum of the acinar cell and pass through the cisternae of this organelle to reach the Golgi complex in small transport vesicles. Precursors of the enzymes are packaged into zymogen granules by membranes of the Golgi complex. The granules then are liberated into the apical cytoplasm, where they accumulate. When the enzymes are to be released from the cell, the granules migrate to the apical cell membrane and discharge their contents into the acinar lumen by exocytosis. The contents of the granules also may be discharged into fine secretory canaliculi that lie between adjacent acinar cells and are continuous with the acinar lumen. Pancreatic acinar cells secrete elastase, amylases, endopeptidases (lipases, trypsin, and chymotrypsin) that cleave central peptide bonds, and exopeptidases (carboxypeptidases A and B) that cleave terminal peptide bonds. Together these proteolytic enzymes cleave proteins in the intestinal lumen into peptide fragments that then are reduced to amino acids prior to absorption. Deoxyribonuclease and ribonuclease also are produced by pancreatic acinar cells and digest deoxyribonucleoprotein and ribonucleoprotein, respectively. Pancreatic amylase breaks down starch and glycogen to disaccharides, and pancreatic lipase cleaves fat micelles into fatty acid and glycerol.

Duct System

An extensive duct system permeates the pancreas. At their beginnings, the ducts extend into the acini and are interposed between the acinar cells and the lumen. Ductal cells within the pancreatic acini are called centroacinar cells and appear as flattened, light-staining cells with few organelles.

The wall of the short initial segment of the duct system formed by centroacinar cells is continuous outside the secretory unit with intercalated and intralobular ducts. These ducts are tributaries of the interlobular ducts found in the loose connective tissue between lobules; the transition between ducts is gradual. The epithelial lining begins as simple squamous in the intercalated ducts, increases in height to cuboidal in the intralobular ducts, and is columnar in the interlobular ducts. Scattered goblet cells and endocrine cells also are found in the ductal system. The cells lining the ducts stain lightly, and organelles are not prominent in their cytoplasm. Desmosomes are scattered along the lateral cell surfaces, and tight junctions unite the apices of adjoining cells. The apical surfaces bear microvilli. A scanty connective tissue consisting mainly of reticular fibers supports the intercalated and intralobular ducts. The interlobular and major secretory ducts are contained within the interlobular septae and thus are surrounded by a considerable amount of fibroconnective tissue. The interlobular ducts drain into the primary and accessory pancreatic ducts. The primary duct runs the length of the pancreas, increasing in size near the duodenum, where it runs parallel to the common bile duct, with which it often shares a common opening at the greater duodenal papilla. The sphincter of the papilla controls the openings of both ducts. An accessory duct may lie proximal to the main duct and opens independently into the duodenal lumen. Secretion by the exocrine pancreas is under nervous and hormonal control. Two polypeptide hormones, secretin and

cholecystokinin, are released from cells of the intestinal mucosa and influence exocrine pancreatic secretion. Secretin, elaborated by S cells in the mucosa of the duodenum and proximal jejunum, stimulates the ductal system of the pancreas to secrete a large volume of fluid that is rich in bicarbonate. In the intestinal lumen, this alkaline secretion neutralizes the acid chyme from the stomach and deactivates the gastric enzyme pepsin, whose optimal activity occurs at a low pH (2.0). It also establishes the neutral to alkaline conditions needed for the optimal activity of pancreatic enzymes. Cholecystokinin, elaborated by I cells in the duodenal and jejunal mucosa, stimulates secretory units of the pancreas to synthesize and release pancreatic (digestive) enzymes. The proteolytic enzymes are secreted as inactive precursors (zymogens) that, in part, are converted to their active forms by enterokinase, an enzyme from the intestinal mucosa. Pancreatic amylase and lipase are said to be secreted in their active forms. Cholecystokinin also stimulates the gallbladder to contract, thereby adding bile to aid in neutralizing the intestinal contents and providing bile acids that act as emulsifying agents in the breakdown of neutral fats.

Endocrine Pancreas

Scattered among the pancreatic acini are irregular, elongate masses of pale-staining cells called the pancreatic islets (of Langerhans), which make up the endocrine portion of the pancreas. In humans they number about 1 million. The islets are separated from the surrounding exocrine pancreas by a delicate investment of reticular fibers, and as with all endocrine glands, the islets have a rich vascular supply. In ordinary tissue sections, the islets appear to be composed of a homogeneous population of pale polygonal cells, but with special stains and in electron micrographs, several distinct cell types can be identified. The majority of cells are alpha and beta cells.

Alpha cells make up about 20% of the islets and generally are located at the periphery of the islet. They contain large, dense, spherical granules that are limited by a membrane. Mitochondria are long and slender with a typical internal structure. A few profiles of granular endoplasmic reticulum are scattered about the cytoplasm, and Golgi bodies usually are found near the nucleus. They contain secretory granules with diameters of about 250 nm. Alpha cells produce the peptide hormone glucagon. Glucagon is released in response to hypoglycemia and acts on the liver to convert glycogen into glucose, stimulates hepatic gluconeogenesis from amino acids, and stimulates adipose tissue to release fatty acids that are in turn metabolized by the liver to produce keto acids. The net effect of glucagon secretion is that blood levels of glucose, free fatty acids and ketones increase. Thus, glucagon functions as a major fuel-mobilizing hormone.

Beta cells form about 78% of the islet cells and tend to locate near the center of the islet. Their secretory granules are smaller than those of alpha cells. Beta cell granules contain small, dense crystals that give them a distinctive appearance. The granular endoplasmic reticulum is less extensive and the Golgi complexes are more distinctive than in alpha cells. Beta cells produce insulin, released in response to hyperglycemia, which acts on the plasmalemma of various cell types, especially liver, muscle, and fat cells, to facilitate the entry of glucose into the cell and thus lower blood glucose. Insulin also stimulates fat synthesis, inhibits lipolysis, and stimulates the movement of amino acids into cells and their assembly into proteins. The net effect of insulin is opposite that of glucagon. Insulin acts as a fuel storage hormone and decreases blood levels of glucose, free fatty acids, and ketones.

Several other types of endocrine cells are present in small numbers in the islets. Delta cells secrete the hormone somatostatin, which inhibits hormone secretion by adjacent alpha and

beta endocrine cells within the pancreatic islet. Pancreatic polypeptide, secreted by PP cells, inhibits the pancreatic acinar secretion of enzymes and bicarbonate secretion by the ductal system. Endocrine cells of the kind found in the islets, including alpha and beta cells, also are scattered within the ducts and acini of the exocrine pancreas. The number of different endocrine cells may vary according to their locations in the head or body of the pancreas and may relate to the different origins of these two parts. There is considerable species variation in the distribution of cells within the islets. In humans, beta cells tend to be located centrally, while alpha, delta, and PP cells are concentrated at the periphery of the islets.

Islet cells are intimately associated with surrounding capillaries, and the secretory granules often appear to be located near the cell membrane that is adjacent to the vasculature. Secretory granules are released from islet cells by exocytosis into the surrounding blood vessels. The endothelium of the islet capillaries contains numerous fenestrations to facilitate entry of secretory products into the vasculature. In contrast, the endothelium of capillaries of the exocrine pancreas is not fenestrated.

A significant proportion of the arterial blood enters the pancreas via small interlobular and intralobular arteries that first supply the islets. Arterioles derived from these arteries give rise to capillaries at the periphery of the islets, in the region of the alpha, delta, and PP-cells. The capillaries then run centrally within the islet, after which they supply adjacent acinar cells of the exocrine pancreas. Thus, the pancreatic islet cells can interact with each other and influence the function of the exocrine pancreas as well.