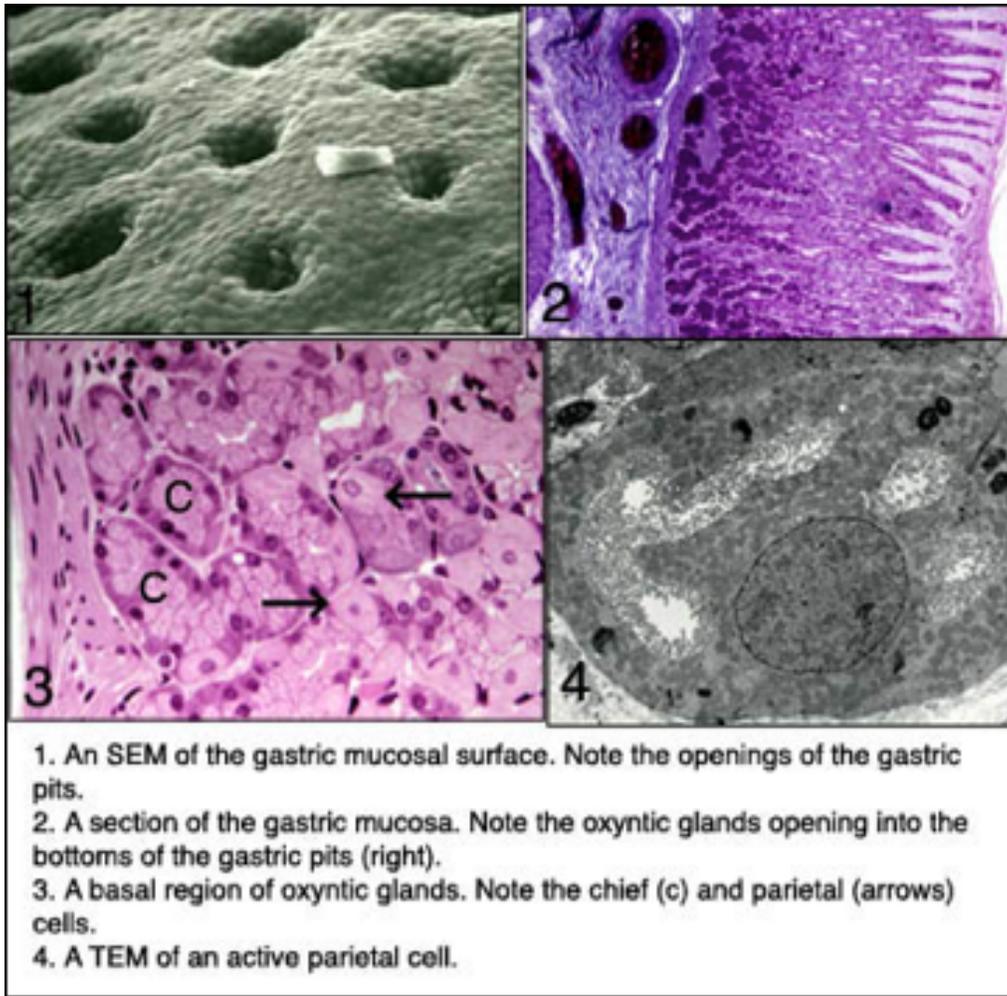


## Stomach



The stomach forms an expanded portion of the tubular digestive tract between the esophagus and small intestine. In humans, the stomach is divided into the cardia, a short region where the esophagus joins the stomach; the fundus, a dome-shaped elevation of the stomach wall above the esophagogastric junction; the corpus, the large central part; and the pylorus, a narrow region just above the gastrointestinal junction. The digestive functions of the stomach involve mechanical and chemical breakdown of ingested materials.

### Mucosa

The mucosa of the empty stomach has numerous folds or ridges called rugae that mostly disappear when the stomach is filled or stretched. The gastric lining epithelium is simple columnar and begins abruptly at the junction with the wet stratified squamous epithelium of the esophagus and ends just as abruptly at its junction with intestinal epithelium. The lining epithelium has a similar structure throughout the stomach and consists of secretory columnar cells that collectively form a secretory sheet. The neutral mucin produced by the surface epithelium is secreted continuously and forms a mucous film that helps protect the mucosa from the acid/pepsin in the gastric lumen and lubricates the surface. The apices of the columnar cells are held in close apposition by tight junctions, and the lateral cell membranes

show numerous desmosomes. Scattered, stubby microvilli are present on the apical surfaces, and numerous discrete mucin granules fill the apical cytoplasm. Granular endoplasmic reticulum is present in the basal cytoplasm, and well-developed Golgi complexes occupy the supranuclear region. The gastric mucosa contains about 3 million minute tubular infoldings of the surface epithelium that form the gastric pits or foveolae, which are lined by the same simple columnar epithelium that covers the surface. The epithelial cells on the surface are replaced every 4 to 5 days. New cells are derived from a small population of relatively undifferentiated cells located in the bottoms of the gastric pits. Cells from this region gradually migrate upward along the walls of the gastric pit to replace the cells of the surface epithelium. Three types of glands occur in the gastric mucosa: cardiac, gastric (oxyntic), and pyloric.

### **Cardiac Glands**

The cardiac glands begin immediately around the esophageal orifice and extend about 3.4 cm along the proximal stomach. They attain their greatest depth near the esophageal-gastric junction. Here, the tubular glands branch freely and appear to be aggregated into lobule-like complexes by the surrounding connective tissue of the lamina propria. Near the junction with the fundus, the cardiac glands show less branching, the distinct grouping disappears, and the thickness of the glandular area decreases. For the most part, cardiac glands are simple branched tubular glands that open into the overlying gastric pits. The depth of the gastric pit and the length of the cardiac gland are approximately equal. The secretory units consist mainly of mucous cells, but occasional parietal cells are present and appear to be identical to those of gastric glands. A number of endocrine cells of undetermined nature also are present.

### **Gastric (Oxyntic) Glands**

The gastric (oxyntic) glands are the most abundant glands in the stomach (about 15 million) and are found along the entire corpus of the stomach. They are mainly simple branched tubular glands. The glands run perpendicular to the surface of the mucosa, and one or several glands may open into the bottom of each gastric pit. The gastric glands are about four times as long as the pits into which they open. Each gland contains mucous neck cells, parietal cells, chief (zymogen) cells, and endocrine cells. Mucous neck cells occur primarily in the upper regions of the gastric glands, where the glands open into the gastric pits. The cells often appear to be sandwiched between other cell types, and their irregular shape is characteristic. Some have broad apices and narrow bases; others show narrow apices and wide bases. The nucleus is confined to the base of the cell, surrounded by basophilic cytoplasm. Secretory granules fill the apical cytoplasm. Unlike the mucous cells that line the gastric surface and gastric pits, mucous neck cells produce an acidic mucin. Although most numerous in the central area of the gastric glands, parietal cells also are scattered among mucous neck cells in the upper parts of the gland. They are large, spherical cells whose bases often appear to bulge from the outer margin of the glands into the lamina propria. In routine sections, parietal cells are distinguished by their acidophilic cytoplasm. Each cell contains a large, centrally placed nucleus and numerous mitochondria and is characterized by intracellular canaliculi. Mitochondria make up nearly 40% of the parietal cell volume and account for the eosinophilia in hematoxylin and eosin stained preparations. The canaliculi are invaginations of the plasmalemma that form channels near the nucleus and open at the apex of the cell into the lumen of the gland. Numerous microvilli project into the lumina of the intracellular canaliculi, their number and length varying according to the secretory activity of the cell. Immediately

adjacent to each canaliculus, a series of smooth cytoplasmic membranes forms small tubules and vesicles that make up a tubulovesicular system. The tubulovesicular membranes are rich in a unique hydrogen, potassium ATPase, which acts as a proton pump in the stimulated parietal cell. The membranes also contain potassium and chloride ion channel proteins. Secretion of hydrochloric acid occurs along the cell membrane that lines the canaliculi. During stimulation of parietal cells, the tubulovesicular membranes diminish, canalicular microvilli become more abundant, and canaliculi elongate; during acid inhibition, the reverse occurs. Following parietal cell stimulation, actin microfilaments polymerize, and their interaction with myosin promotes the movement and fusion of tubulovesicular with canalicular membranes, resulting in the increased canalicular membrane area containing hydrogen, potassium-ATPase and ion channel proteins. Parietal cells contain abundant carbonic anhydrase, which catalyzes the joining of carbon dioxide to water, forming carbonic acid ( $\text{H}_2\text{CO}_3$ ). Carbon dioxide and water diffuse into the cell from adjacent capillaries. Once formed,  $\text{H}_2\text{CO}_3$  immediately dissociates into hydrogen ions ( $\text{H}^+$ ) and bicarbonate ions ( $\text{HCO}_3^-$ ). Hydrogen ions are actively pumped into the lumen of the canaliculus, and bicarbonate ions pass back into the bloodstream of the gastric mucosa to cause an increase in pH known as the alkaline tide. Ion channels promote the movement of potassium and chloride ions into the canalicular lumen. The hydrogen, potassium-ATPase moves the potassium ion back into the parietal cell in exchange for hydrogen ion. The net result of this activity is the formation of hydrochloric acid in the canalicular lumen. Water enters the canaliculi osmotically driven by the movement of ions. The increase in canalicular membrane surface area during parietal cell stimulation makes these events possible. In addition to hydrochloric acid, parietal cells of the human stomach secrete a glycoprotein, gastric intrinsic factor, which complexes with dietary vitamin B12; the complex is absorbed in the distal small intestine. A deficiency of intrinsic factor results in decreased absorption of vitamin B12, an essential vitamin for the maturation and production of red blood cells. Lack of this vitamin results in pernicious anemia and is a condition often associated with atrophic gastritis.

Parietal cell stimulation is initiated and modulated by the vagus nerve during the cephalic phase of digestion in response to taste, smell, sight, chewing or even the thought of food. This activity results in the release of acetylcholine from postganglionic cholinergic muscarinic neurons that act to stimulate both parietal and ECL (enterochromaffin-like) cells. During the gastric phase of digestion, stomach distension, the presence of proteins and amino acids, stimulates G-cells within the pyloric mucosa to secrete gastrin, which also targets parietal and ECL cells. The histamine released by stimulated ECL cells acts synergistically with both gastrin and acetylcholine to enhance parietal cell secretory activity. These physiologic agonists (gastrin, histamine, acetylcholine) attach to individual transmembrane receptors in the parietal cell plasmalemma. Somatostatin from adjacent D cells in the pyloric mucosa acts on neighboring G cells to inhibit gastrin release and thereby inhibit parietal cell activity.

Chief (zymogen) cells are present mainly in the basal half of the gastric glands and in routine sections are distinguished by their basophilia. The cells contain abundant granular endoplasmic reticulum in the basal cytoplasm, well-developed Golgi complexes in the supranuclear cytoplasm, and apical zymogen granules, features that characterize cells involved in protein (enzyme) secretion. Chief cells secrete pepsinogen, a precursor of the enzyme pepsin that reaches its optimal activity at pH 2.0. The acid environment in the gastric lumen is created by the parietal cells. Pepsin is important in the gastric digestion of protein, hydrolyzing proteins into peptides.

Also scattered within the bases of the gastric glands are endocrine cells, peptide/amine-producing cells that contain specific granules enclosed by smooth membranes. The

polarization of these cells suggests that they secrete into the bloodstream or intercellular space rather than into the lumina of gastric glands. The gastrointestinal hormones somatostatin, glucagon, pancreatic peptide, histamine, and the amine 5-hydroxytryptamine (5-HT, serotonin) have been identified in the endocrine cells of the gastric glands. Gastric A cells produce glucagon which stimulates hepatic glycogen degradation and increases blood glucose levels.

### **Kinetics of the Gastric (Oxyntic) Glands**

Pluripotent stem cells located in the region where a gastric gland joins the bottom of a gastric pit (the isthmus) divide to maintain themselves as well as give rise to several committed cell types: pre-pit, pre-mucous neck, pre-parietal, and pre-endocrine. Chief cells are derived from mucous neck cells

through a pre-zymogenic stage. All pit cells migrate in the direction of the gastric lumen to become gastric lining epithelial cells and are eventually exfoliated into the lumen in about 5 days. Mucous neck cells, however, migrate inward toward the base of the gastric glands and in about 2 weeks become pre-chief (zymogenic) cells. As fully differentiated chief cells form, they migrate to occupy the bottom of the gastric glands and remain active for up to 6 months. Thereafter, they are either lost by necrosis and shed into the lumen or, if apoptosis occurs, phagocytosed by adjacent chief cells or macrophages entering the area. Endocrine cells also arise at the isthmus and migrate toward the base of the glands where they are abundant. Their turnover time is about 3 months. In contrast, differentiating parietal cells migrate in both directions with about equal numbers migrating toward either the gastric lumen or the bottoms of the gastric glands. They have a turnover rate of about 60 days and, if they become necrotic, are lost by extrusion into the lumen of the gland. If the parietal cells become apoptotic, neighboring cells or macrophages phagocytose them.

### **Pyloric Glands**

The pyloric glands are confined to the distal 4 or 5 cm of the stomach. They are simple or branched tubular glands composed of mucous cells similar in appearance to mucous neck cells of the fundic region. An occasional parietal cell may be present. The pyloric glands empty into gastric pits that are about the same length as the glands. Numerous endocrine cells, mainly G cells, are present. These unicellular endocrine glands produce gastrin, the peptide hormone that stimulates acid secretion by the parietal cells in the remainder of the stomach. Endocrine cells that produce somatostatin (D cells) and serotonin (5-HT) are present in large numbers in the pyloric glands also. Thus, in addition to the exocrine function of mucus production, pyloric glands have important endocrine functions as well. The serotonin produced increases gut motility whereas somatostatin acts to inhibit the secretion of adjacent endocrine cells.

### **Lamina Propria**

The lamina propria of the stomach is obscured by the close approximation of the glands in the gastric mucosa. It consists of a delicate network of collagenous and reticular fibers that surrounds and extends between the glands and gastric pits. The lamina propria contains numerous capillaries. Numerous lymphocytes, some plasma cells, eosinophils, and mast cells are found within the lamina propria. Lymphatic nodules also may occur.

## **Muscularis Mucosae**

The muscularis mucosae consists of an inner circular, an outer longitudinal and, in some places, an additional outer circular layer of smooth muscle. Slips of smooth muscle extending into the lamina propria form a loose network around individual glands and extend to the gastric lining epithelium. The contraction of these smooth muscle cells acts to compress the contained gastric glands. The muscularis mucosae gives additional mobility to the gastric mucosa.

## **Submucosa**

The submucosa consists of a coarse connective tissue rich in mast cells, eosinophils, and lymphatic cells. This layer contains lymph vessels and the larger blood vessels. Parent vessels originating from the celiac axis pierce the stomach wall at the lesser and greater curvatures and supply smaller branches that run about the circumference of the stomach within the submucosa. Smaller branches of the submucosal vessels enter the mucosa to provide its vascular supply.

## **Muscularis Externa**

The muscularis externa may consist of three layers of smooth muscle: outer longitudinal, middle circular, and sometimes an inner oblique layer in the body and fundic regions. Strong contractions of the muscle wall of the stomach create a churning action that contributes mechanically to the breakdown of ingested material. In the pylorus, the middle circular layer thickens to form the pyloric sphincter, which is thought to aid in controlling the emptying of the stomach. Isotonic contents act to stimulate whereas fats inhibit gastric emptying. High hydrogen ion concentrations in the proximal duodenal lumen also inhibit gastric emptying.

## **Serosa**

A thin layer of loose connective tissue covers the muscularis externa and is covered on its outer aspect by the mesothelial lining of the peritoneal cavity, the visceral peritoneum, forming a serosa.